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Reductive Removal of Trityl group from Tetrazoles via Indium, Zinc and Arene Catalyzed Lithiation

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Dedication

Thanks to the Almighty, who gave me courage, the will, the force to accomplish this memo , which no one cannot be made without its desire.

I dedicate this modest work which I hope useful:

To My father to my tender and wonderful mother, I hope that they will be always proud of me.

To my husband Fouad Abdennour who always supported me and has greatly contributed to the success of this work.
To my little angel YASSER IYED.

To my brothers Yacine, Anis and my sister Karima

To my friends,

To all person of my family.

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And finally thanks to all who have crossed my path.

Technical notes

During our work we used the following equipment:

Nuclear Magnetic Resonance spectrometry (NMR)

NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, or CD_3OD as solvent and TMS (δ= 0.00 ppm, ^{1}H) or $CDCl_3$ (δ= 77.0 ppm, ^{13}C), DMSO-d_6 (δ= 2.50 ppm, ^{1}H; δ= 39.75 ppm, ^{13}C), or CD_3OD (δ= 4.87 ppm, ^{1}H; δ= 49.0 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (J) in Hz.

Multiplicities are given as s: singlet, d: doublet, t: triplet, td: triplet of doublet, m: multiplet, ddd: doublet of doublet.

Infra-Red spectrometry

FT-IR spectra were recorded on a Nicolet Impact 400D spectrophotometer using KBr pellets.

Melting points

All melting points were measured in open end glass capillary tubes on a Buchi 535 melting point apparatus and are uncorrected.

Chromatography

Column chromatography was performed on silica gel 60 (35–70 mesh) or basic aluminum oxide (50–160 μm particle size). Deactivated silica gel was treated with 5% Et_3N in hexane, and the column was eluted with the same solvent mixture until the eluent was basic, as shown by pH paper.

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General Introduction

General Introduction

Tetrazoles are a class of heterocycles with a wide range of applications in medicinal chemistry and in material sciences. However, Sartans are a group of drugs that are effective in treating hypertension and heart failure. They block the renin-angiotensin system and they are among the most effective treatments for hypertension.[1]

Of the seven sartans that are used in clinical practice, five contain tetrazole moieties within their structures. The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these sartans.[2]

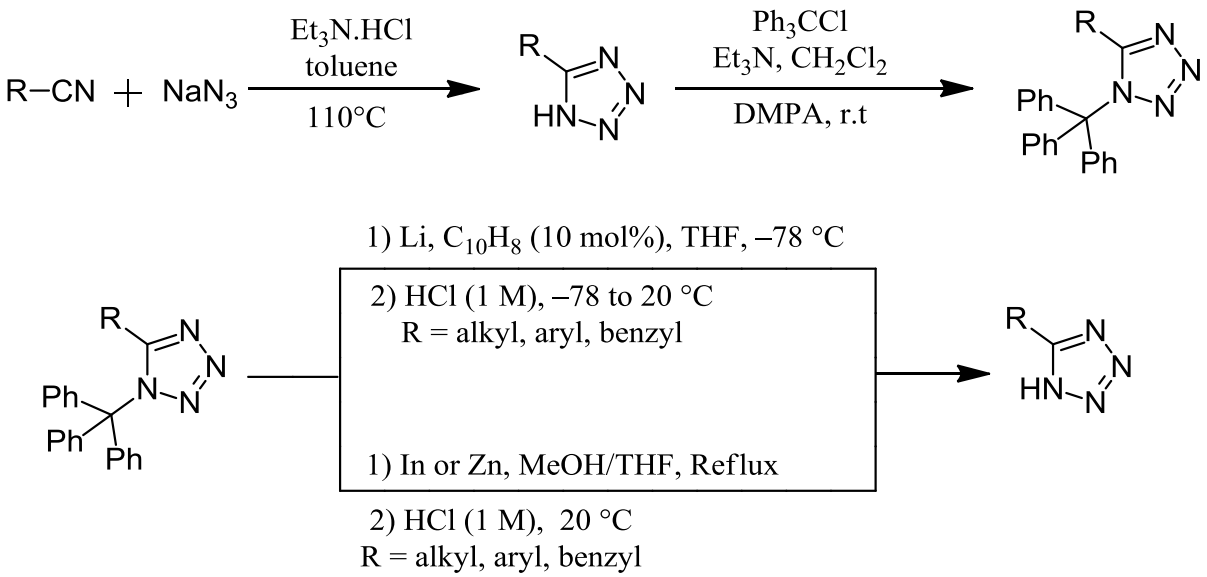
One group that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl) group, a very efficient protecting group for amines[3] and amino acids,[4] because its bulkiness causes the nitrogen atom to be much less reactive as a nucleophile. Simple treatment with an aqueous acidic solution can be used to remove the trityl protecting group,[3c] but some side-reactions have been observed under these conditions, such as elimination of tritylamine during detritylation of some tritylated amines.[5] Other procedures that have been shown to be efficient in detritylation processes include dissolving-metal reduction,[3c] reactions with molecular hydrogen catalyzed by palladium,[3c] reduction with sodium borohydride in the presence of mercury salts,[6] and reductive cleavage promoted by silanes[7] or low-valent titanium reagents.[8] Palladium catalysts in combination with poly(methylhydrosiloxane) have been shown to permit direct conversion of *N*-trityl amines into *tert*-butyl carbamates.[9]

The aim of this project is developing new methods to remove trityl unit from the nitrogen atom of several protected tetrazoles.

This project is composed of two essential parts as follows:

Part one concludes the introduction and presenting the importance of the heterocyclic compounds that contain tetrazole skeleton. Also this part is concluded from the point of view; synthesis, reactions and biological activities of tetrazoles and protected tetrazoles, after that we report the development of two novel efficient processes one for transforming a wide variety of nitriles into the corresponding tetrazoles in high yield, using a simple and safe protocol. And the other one is to protect tetrazoles wich is our starting materials.

Part two concludes our research of developing deprotection methods to remove the trityl group from the nitrogen atom of several protected tetrazoles using different electron transfer sources (lithium, indium and zinc). See the following general scheme below.



General scheme.

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Chapter 01: The 5-Substituted Tetrazoles

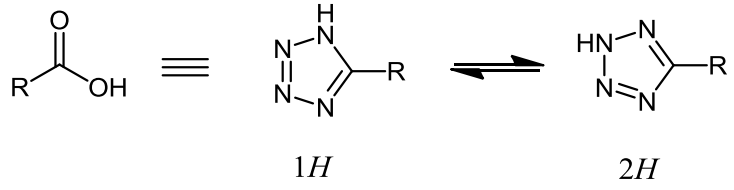
Introduction

Tetrazoles are a class of heterocycles with a wide range of applications which are currently receiving considerable attention,[1] therefore the literature on tetrazole is expanding rapidly. This functional group has a role in coordination chemistry as a ligand,[2,3,4] as well as in various materials sciences applications including photography and specialty explosives.[5] Extensive work has also been carried out in the field of medicinal chemistry, where tetrazoles are frequently used as metabolically stable surrogates for carboxylic acids.[6,7,8]

Less appreciated, but of enormous potential, are the many useful transformations that make tetrazoles versatile intermediates en route to substituted tetrazoles and especially to other 5-ring heterocycles via Huisgen rearrangement.[9,10] The prime reason for the scarcity of practical applications for these sophisticated tetrazole-based reactions is the lack of appealing synthetic routes to the key intermediates 5-substituted tetrazoles. Tetrazoles readily tolerate a wide range of chemical environments[1] and new uses for this unique family of heterocycles continue to emerge in both materials science, and pharmaceutical applications.

I.1. The 5-Substituted Tetrazoles

5-Substituted tetrazoles that contain a free N-H bond are frequently referred to as tetrazolic acids and exist in two tautomeric forms **(Figure 1)**.[1, 11,12]



1*H* 2*H*

Figure 1. Tetrazolic acids are bioisosteres of carboxylic acids.

The tautomerism is a rapid process in solution and individual tautomers can not be detected even at low temperature. The corresponding dipole moments are 5.63 D for the 1*H*-tautomer and 2.19 D for the 2*H*-form.[1] In the gas phase, the 2*H*-tautomer tends to be the dominant form, while in solution the 1*H*-tautomer is favored because of solvation effects.

Tetrazoles can be regarded as nitrogen analogues of carboxylic acids. The free N-H bond of tetrazoles makes them acidic molecules and both the aliphatic and aromatic heterocycles have pKa values similar to the corresponding carboxylic acids (4.5-4.9 vs 4.2-

4.4, respectively) due to the ability of the moiety to stabilize a negative charge by electron delocalization.[1]

Tetrazole nitrogens have a considerable amount of local electron density, which consequently leads to a wide range of stable metallic and molecular complexes.[13] Furthermore, the tetrazole ring possesses a strong electron-withdrawing inductive effect (-I) which surpasses the weak mesomeric effect (+ M), therefore, the ring is a deactivating group.[1]

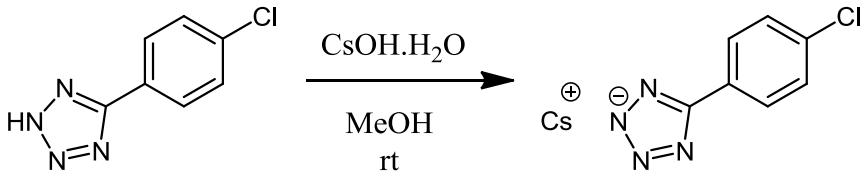
I.2. Chemical and Physical Properties

I.2.1. Aromaticity

The tetrazole ring is a 6π-azapyrrole-type system.[1,11] Reactivity of 5-substituted tetrazoles permits them to be classified as aromatic compounds.[1,14] In tetrazoles, two of the six π-electrons required by the Huckel rule are provided by the lone pair of one nitrogen while the remaining four π-electrons are provided by the other four atoms of the ring.

I.2.2. Tetrazolate anions: acidity

5-Substituted tetrazoles display an acidity comparable with the corresponding carboxylic acids.[1,15] One difference between the tetrazole ring and the carboxylic acid group is the annular tautomerism of the tetrazoles. Substituents at C-5 have effects similar to those for carboxylic acids, while in general, 5-aryltetrazoles **1** are stronger acids. The increased acidity is ascribed to an enhanced resonance stabilization in the 5-phenyltetrazole anion **2** relative to benzoate.[1b] The tetrazolate anions are easily generated with metal hydroxides and are stable in hot alcoholic and aqueous solutions **(Figure 2)**.[16,1]

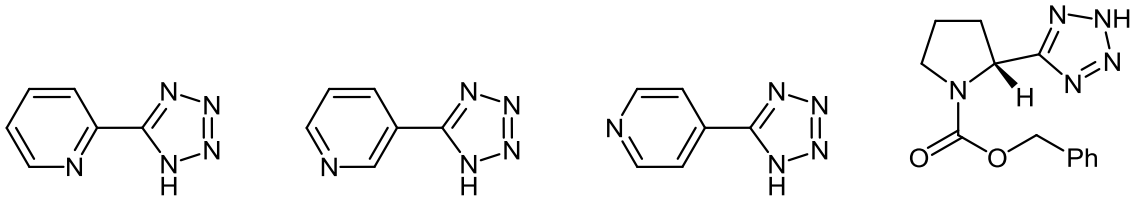


1 **2**

Figure 2. Example of a metal tetrazolate salt.

I.2.3. Solubility

5-Substituted tetrazoles are generally soluble in polar organic solvents such as ethyl acetate and DMSO, but under basic conditions they can be easily extracted into the water phase as a salt, like the carboxylic acid. Very polar tetrazole derivatives such as pyridinetetrazoles **3, 4** and **5** or pyrrolidine tetrazoles **6** are soluble in water therefore the extraction from water can be problematic **(Figure 3)**.



3 **4** **5** **6**

Figure 3.

I.3. Medicinal Chemistry of Tetrazoles

Tetrazoles are an increasingly popular functionality with wide ranging application. They have found use in coordination chemistry[16,17] and in various materials sciences applications including photography,[1,18] specialty explosives,[5] information recording systems[19] and agricultural composition.[20] In addition extensive work has been carried out in the field of medicinal chemistry.[1,9]

I.3.1. Action on central nervous system

Several tetrazole derivatives act on the central nervous system, the most prominent being compounds reported to possess analeptic activity. The standard drug in the area is leptazol (pentamethylenetetrazole) **7**. Leptazol produces hypothermia and this effect is probably the result of a direct effect of the drug on the thermoregulaiory mechanism in the hypothalamus, and not necessarily mediated by the release of a neurohumoral substance from the hypothalamus.[21] Leptazol was recommended as a more sensitive tool for detecting potential anti-convulsants.[22] Tetrazole derivatives possessing a methyl or ethyl group at position 5 and a substituent at position 1 having four to six carbon atoms are active as analeptics, [23] the more significant activity is obtained when 1,5-positions are bridged through a penta- or hepta-methylene chain.[24] An increase[25] or decrease[26] in the number of polymethylene carbons is not conducive for the activity. However, tetrazoles prepared from

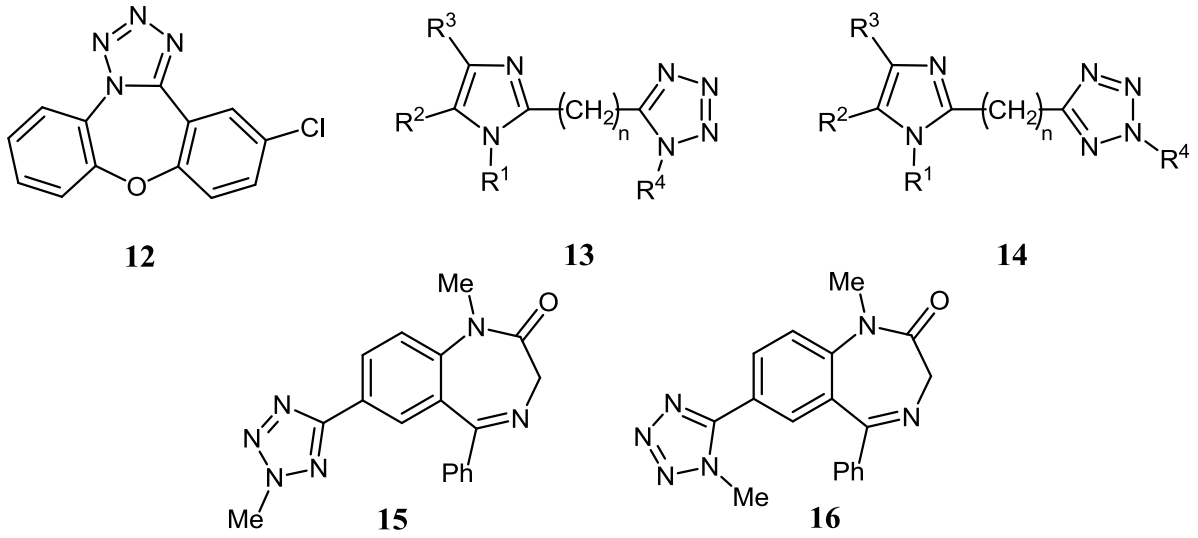
camphor and α-thujone and mixtures of α- and β-thujone are reported to be active analeptics.[27] „Camphor tetrazole" is claimed to be very potent in drogs,[28] and l-isobornyld-methyltetrazole is also reported to be active[29] **(Figure 4)**.

7 R= H **9** R= *i*-Pr
8 R= Me **10** R= *t*-Bu **11**

Figure 4.

The effect of substitution on carbons of pentamethylene bridge in **7** has also been examined.[23] The 8-methyl **8**, 8-isopropyl **9** and 8-*tert*-butyl **10** derivatives were more potent than **7** whereas there was drop in activity in the 8-*sec*-butyl or *tert*-pentyl analogues. The spiro analogue **11** was also claimed to be more active analeptic than **7.**[30] The analeptic activity of **7** was lost on quaternary salt formation.[23] The monochloro and dichloro substitution at position 6 in **7** increased the activity;[24] however, the bromo analogues were less active.

Of the actions of several other tetrazole derivatives showing central nervous system activity tetrazole analogues **12,**[31] **13** and **14**.[32] However, 1,3-dihydro-1-methy1-7-(2-methyltetrazol-5-y1)-5-phenyl-2*H*-1, 4-benzodiazepin-2-one **15** and 1,3-dihydro-1-methy1-7-(1-methyltetrazol-5-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one **16** were found to be inactive as sedative and anti-convulsants[33] **(Figure 5)**.



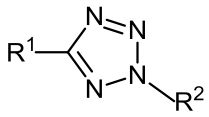
12 **13** **14**

15 **16**

Figure 5.

I.3.2. Anti-inflammatory activity

Maximum anti-inflammatory activity was found in those members of the series which have meta-halogenated aromatic substituents and a propionic acid residue at position 2 of the tetrazole ring **17**. The amides obtained from the corresponding acids have also been found to be active.[34] The quantitative structure-activity relationship in the series has been studied.[35] Substituted benzylidene derivatives **18** of 2-hydrazinocarbonylmethyl-5-phenyltetrazole are also reported to be active.[36] In addition, certain carbamido derivatives **19** are active as anti-inflammatory agents[37] **(Figure 6)**.



17 R^1= aryl; R^2= -$(CH_2)_n$COOH

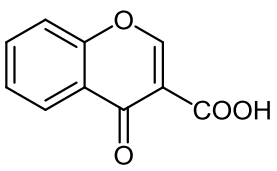
18 R^1= Ph; R^2= —CH_2–C(=O)—NH—N=CH—(C$_6$H$_4$)—X

19 R^1= Ph; R^2= —CH_2–C(=O)—NH—C(=O)—NHX

Figure 6.

I.3.3. Derivatives with anti-allergic activity

Several 3-(tetrazol-5-yl)chromones have been reported to be active as antiallergic.[38] In contrast to inactivity of **20**,[38] the tetrazole derivative **21** was active.[38] The inactivity of former was attributed to its weak acidity due to intra-molecular hydrogen bonding. In general, the analogues bearing a tetrazole group at C-3 were 2.5 times as active as compared with C-2 tetrazole-substituted chromones . The derivatives of **21** with substitutions at 6 and 8 positions were even more active **(Figure 7)**.



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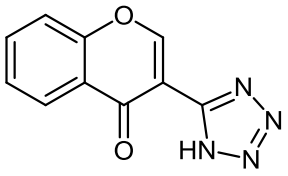
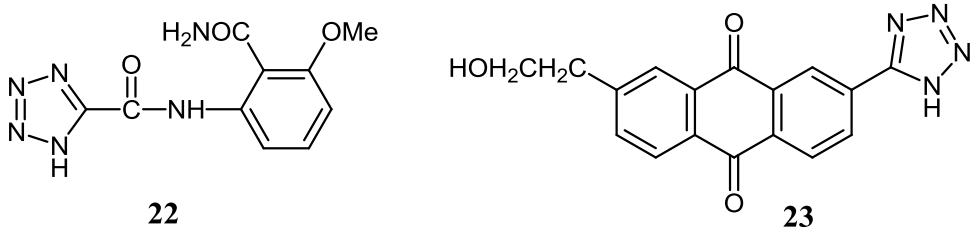


21

Figure 7.

There are several other patents[39] of assorted types of tetrazole derivatives which are claimed to possess anti-allergic activity. Among them may be mentioned the compounds **22**[39] and **23**[40] **(Figure 8)**.



22 **23**

Figure 8.

I.3.4. Cardiovascular activity

The 5-(4‴-methyl-1,1‴-biphenyl-2-yl)-tetrazole subunit has been used as a carboxylic acid mimic in the class of so called sartan derivatives **(Figure 9)**. Angiotensin II (AII) is the octapeptide responsible for the peripheral effects of the rennin-angiotensin system[43,44,45,46,47] which include the regulation of blood pressure and volume homeostasis. Lorsartan was the first nonpeptide angiotensin receptor antagonist to appear on the market[41,42,44,48] followed by Valsartan **(Figure 9)**. The 5-(4‴-methyl-1,1‴y-biphenyl-2-yl)-1*H*-tetrazole subunit has become ubiquitous in the most potent and bioavailable antagonists disclosed to date.[31]

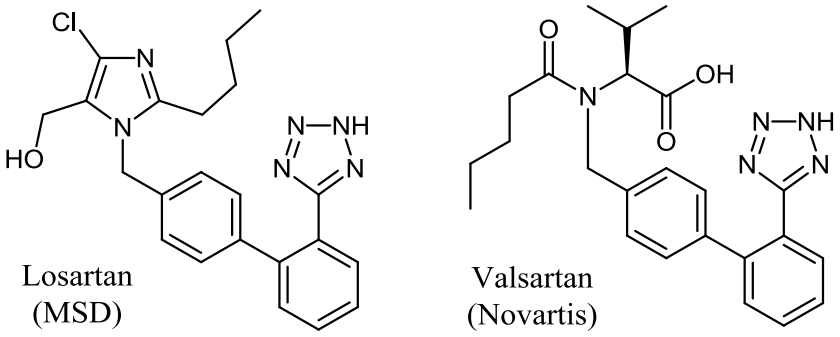


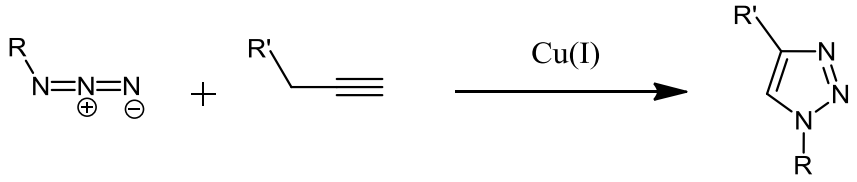
Figure 9. Sartans.

I.4. Synthesis of Tetrazoles

5-Substituted tetrazoles are usually obtained by the addition of azide ion to organic nitriles and many methods are reported in the literature.[1,8,49,50,51] Unfortunately, each of those protocols suffers from some disadvantages: the use of both toxic metals and expensive reagents, drastic reaction conditions, water sensitivity and possible presence of dangerous hydrazoic acid or other explosive sublimates.

I.4.1. The Huisgen 1,3-dipolar cycloaddition

The Huisgen 1,3-dipolar cycloaddition is the reaction of alkynes to azides to form 1,4-disubsituted-1,2,3-triazoles **(Scheme 1)**.[9] A notable variant of the Huisgen cycloaddition is the copper (I) catalyzed variant, in which organic azides and terminal alkynes are united to afford 1,4-regioisomers of 1,2,3-triazoles as sole products.[52] Huisgen was the first to understand the scope of this organic reaction. This cycloaddition is considered the cream of the crop of "click chemistry". The azide and alkyne functional groups are largely inert towards biological molecules and aqueous environments, which allows the use of the Huisgen 1,3-dipolar cycloaddition in target guided synthesis[53] and activity-based protein profiling.[54] The resulting triazole has similarities to the ubiquitous amide moiety found in nature, but unlike amides, is not susceptible to cleavage.



Scheme 1. Huisgen 1,3-dipolar cycloaddition of alkynes to azides.

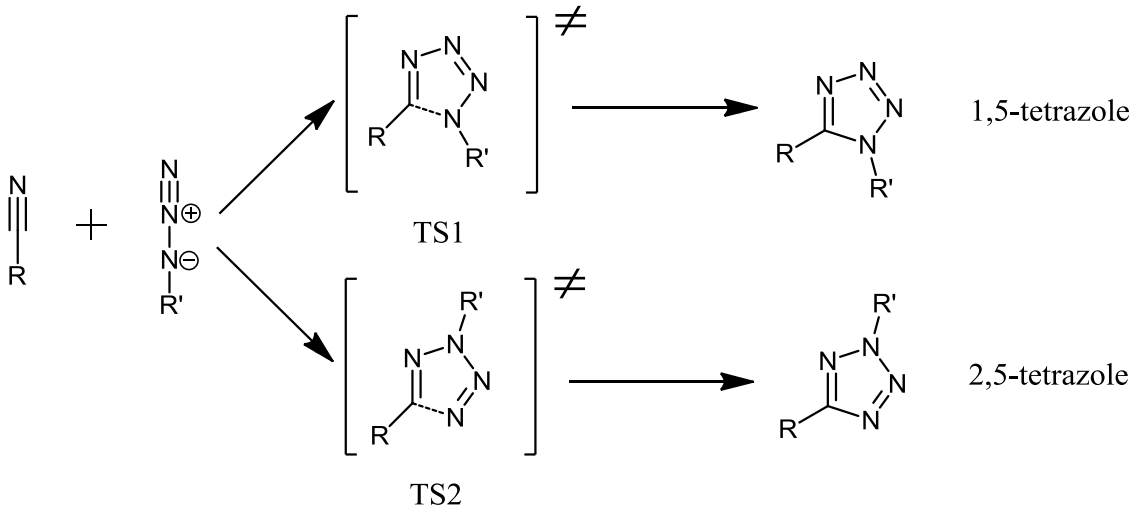
I.4.2. Synthesis of tetrazoles from nitriles with azides

Tetrazoles are generally prepared by the reaction of a hydrazoic acid source with a nitrile, in an inert solvent at high temperatures. They fall into three main categories: those that make use of tin or silicon azides, those that use strong Lewis acids[55,56] and those that are run in acidic media.[57] The few methods that seek to avoid hydrazoic acid liberation during the reaction by avoiding acidic conditions, require a very large excess of sodium azide.[58] In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents such as DMF. This is one of the solvent classes that process chemists would rather not use. The mechanism of the reaction of azide salts to nitriles is different for different azide species[59,60,61] and several possible reaction pathways can be envisioned.[62,63,64]

I.4.2.1. Neutral cycloaddition

A [2+3] cycloaddition is the most likely pathway for the bimolecular addition of non-ionic azides to nitriles.[61] In concerted cycloadditions, two different isomers of tetrazole, the

1,5- and the 2,5-disubstituted, can be formed. Generally the TS1 is the preferred transition state using electron-withdrawing substituents R **(Scheme 2)**.



Scheme 2. Neutral cycloaddition.

I.4.2.2. Anionic mechanism

In reactions where NaN_3 is added to nitriles in aprotic organic solvents, such as dimethylformammide (DMF), it has been found that yields are generally lower and higher temperature are required.[57,62] In theses cases, there are two possible mechanisms,[61] either a direct [2+3] cycloaddition or a two step-mechanism sequence wherein the azide first nucleophilically attacks the nitrile, followed by ring closure. In this context, Sharpless *et al.* have calculated the barriers of cycloaddition of the azide anion to nitrile.[61] As in the case of the neutral [2+3] cycloadditions, the barrier for anionic [2+3] cycloaddition decreases with increasing electron-withdrawing potential of the substituent on the nitrile. The geometry of the transition state of anionic reactions is more asymmetric than for neutral reactions. The $C_{nitrile}$-N_{azide} distance is significantly shorter than the $N_{nitrile}$-N_{azide} distance. The difference grows with the electron-withdrawing potential of the substituent and for very strong electron-withdrawing groups like RSO_2, an intermediate such as that shown in Figure 10 could be found. Despite the existence of this intermediate for the strongly activated nitriles, the $\Delta G^{\neq}$ of the transition state for the ring closing turns out to be identical to the $\Delta G^{\neq}$ for concerted [2+3] transition state. The two pathways have therefore essentially the same rate.[61]

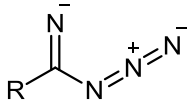
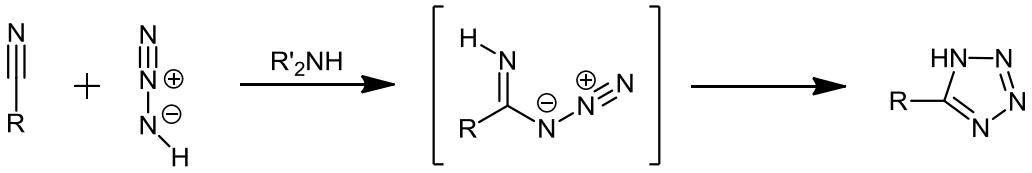


Figure 10.

I.4.2.3. Proton involvement

Koldobskii *et al.*[65] showed that protic ammonium salts of azide are competent dipoles; tetrabutylammonium azide does not work. When a proton is available, the nitrile is activated and the reaction is supposed to proceed via an intermediate instead of a direct [2+3] dipolar cycloaddition **(Scheme 3)**.[61]



Scheme 3.

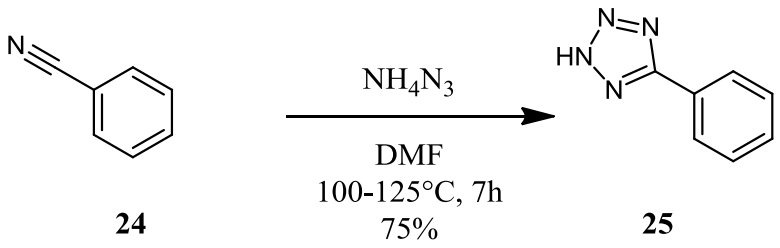
I.4.2.4. Hydrazoic acid

The acid-catalysed cycloaddition between hydrazoic acid and nitriles has long been one of the main routes to 5-substituted tetrazoles.[8,66] The first method to appear in the literature was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932.[67] This process is generally thought to occur by a concerted 1,3-dipolar cycloaddition mechanism, in which the nitrile acts as the dipolarophile toward the azide, which serves as the 1,3-dipolar species in the cycloaddition. Protonation of the tetrazolium anion upon workup provides the tetrazolic acid. In literature a two-step mechanism has also been reported.[68] However this standard procedure needs the direct addition of a large excess of dangerous and harmful hydrazoic acid. Hydrazoic acid itself is poisonous, extremely explosive, and has a low boiling point (37°C). Not many organic solvents are stable at the high temperatures that are necessary for this cycloaddition (sometimes as high as 130°C), and for this reason DMF is most commonly used for this purpose.[1,29]

I.4.2.5. Metal salt methods using sodium azide

I.4.2.5.1. Ammonium and trialkyl ammonium azides

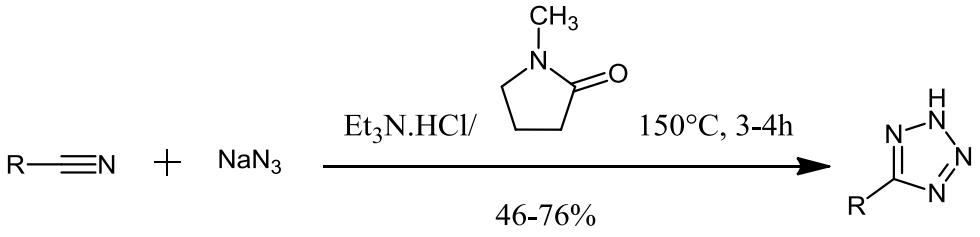
The reaction of nitriles with the ammonium and trialkyl ammonium azides in organic solvents such as dimethylformamide, has been found fifteen years ago by Lofquist and Finnegan[62] to be a general method to give good yields of 5-substituted tetrazoles. The reactive azide species is prepared *in situ* by reaction of sodium azide and the appropriate ammonium or trialkyl ammonium chloride **(Scheme 4)**. The proposed mechanism involves a nucleophilic attack of azide ion on the carbon of the nitrile group, followed by ring closure of the imino azide to form the tetrazole ring.[62] Electronegative substitution on the nitrile enhances the rate of the reaction. The solubility of the azide salt also influences the rate of reaction. The ammonium azides are soluble in dimethylformamide.



Scheme 4. Synthesis of 5-phenyltetrazole with ammonium azide.

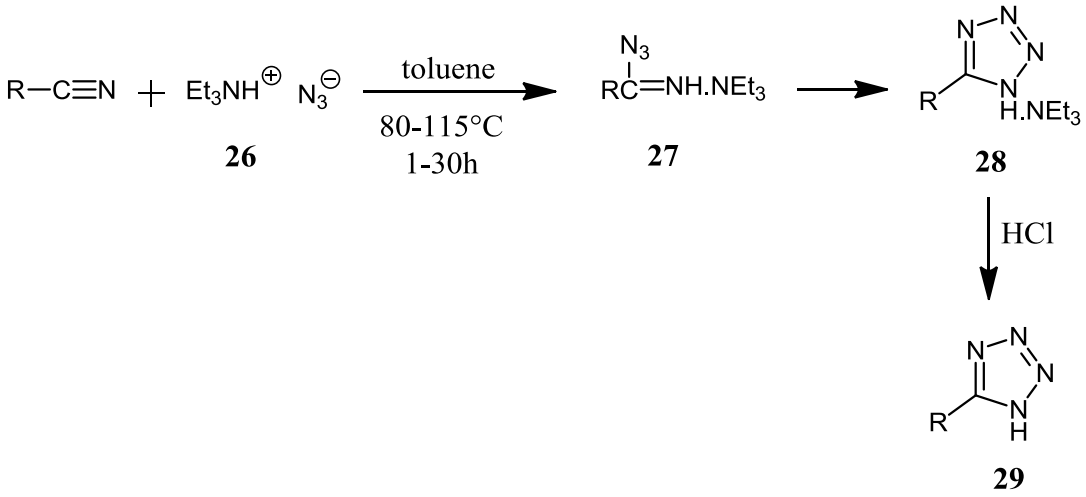
This methodology is not appropriate for the preparation of 5-thiosubstituted tetrazoles because they easily undergo irreversible decomposition to hydrazoic acid and thiocyanate at or near their melting points, which are, in several cases, quite close to the reflux temperature of DMF;[69] therefore using high temperature is not advisable in these cases. In addition this protocol for the synthesis of tetrazole rings is accompanied by the sublimation of explosive NH_4N_3.[70] The sublimation of explosive NH_4N_3 also occurs when other aprotic solvents instead of the DMF are used for the reaction.

Bernstein and Vacek showed that a combination of sodium azide and triethylammonium chloride is an useful alternative to synthesize tetrazoles when *N*-methylpyrrolidinone is used as a solvent instead of the DMF (shorter reaction times) **(Scheme 5)**.[71] DMF under heating and basic conditions partially decomposes and forms free nucleophilic amines which may react with starting nitriles which contain certain functional groups.[71] An alternative to eliminate the amine sources was found to be the use of 1-methyl-2-pyrrolidinone as solvent.



Scheme 5. Preparation of 5-substituted tetrazoles.

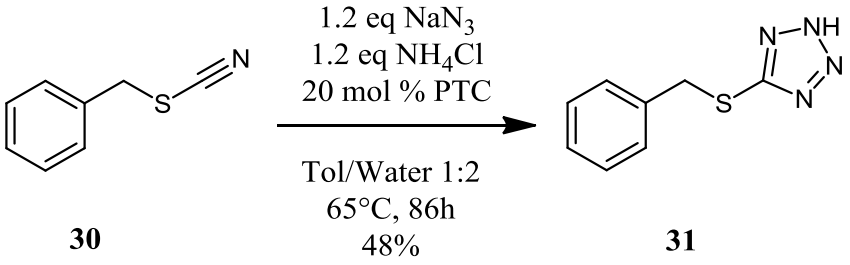
Koguro *et al.*, reported a variant by using triethyl amine hydrochloride in toluene.[72] In this procedure, the authors proposed that the intermediate complex [$Et_3N \cdot HN_3$] is first ionized as Et_3NH^+ and N_3^-, then, each of these react with the triple bond of the nitrile group to produce **28 (Scheme 6)**. When an aromatic solvent such as toluene is used, both the cation and the anion are not solvated, and the reaction thus proceeds smoothly.



26 **27** **28** **29**

Scheme 6. Synthesis of tetrazoles with triethylammonium azide.

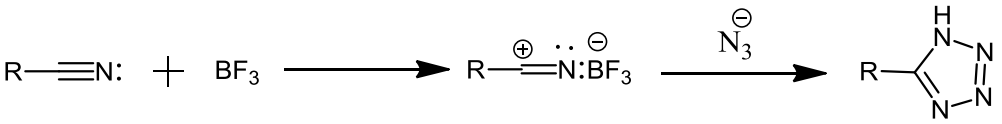
LeBlanc and Jursic recently reported a simple alternative for the method using sodium azide and ammonium chloride in DMF, by working under phase transfer conditions (PTC) **(Scheme 7)**.[73] Hexadecyltrimethylammoniumbromide was found to be the most useful catalyst. The ratio of water and toluene as well as the reaction temperature are important factors to obtain satisfactory yields. This methodology can be a good alternative to the simple use of sodium azide and amonium chloride[69] for the preparation of 5-alkylthio and 5-arylthiotetrazoles, which are activators for RNA and DNA synthesis. However this procedure requires long reaction times, which makes an application in an industrial scale up improbable.



Scheme 7. Synthesis of tetrazoles using PTC conditions.

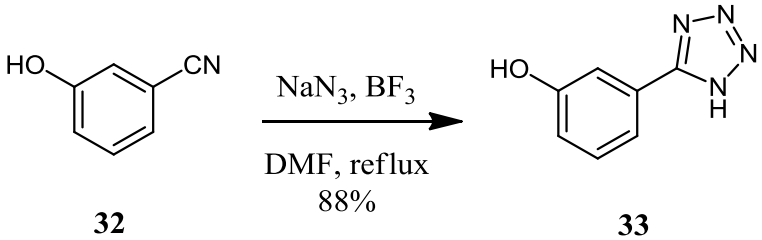
I.4.2.5.2. NaN_3 in the presence of Lewis acid

Finnegan and Lofquist reported in 1958 the study of the tetrazole formation in the presence of Lewis acids.[62] The proposed mechanism involves a nucleophilic attack of the azide ion on the carbon of nitrile group, followed by ring closure of the imino azide to form the tetrazole ring. Conditions which enhance or favour a δ^+ charge on the nitrile carbon, such as the cordination of a Lewis acid, increase the rate of the reaction **(Scheme 8)**.



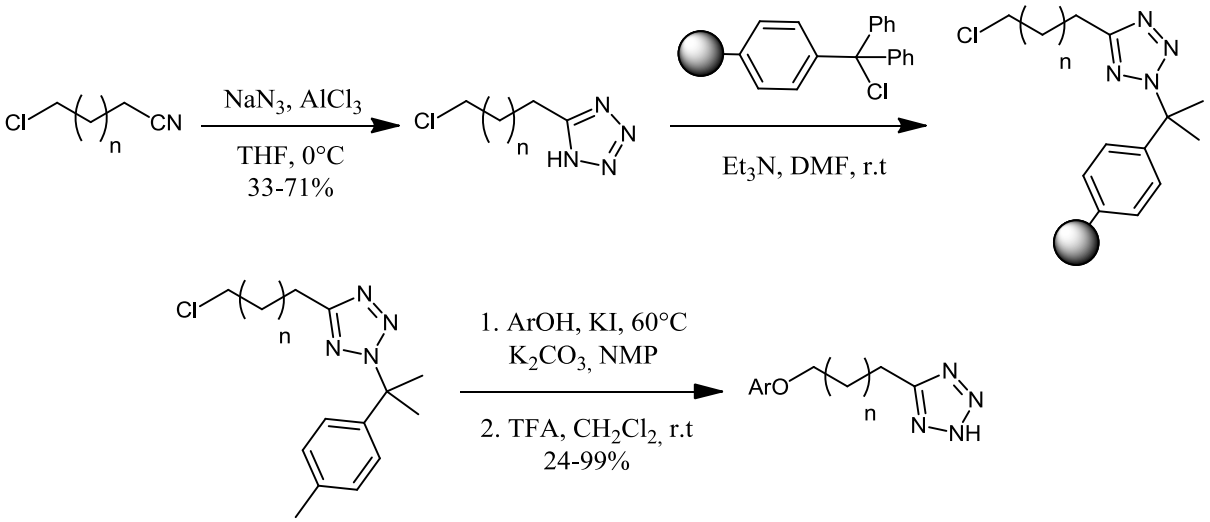
Scheme 8. Tetrazole formation in the presence of Lewis acid.

Nearly four decades later Shechter *et al*. reported the preparation of a few simple 5-(hydroxy-phenyl)tetrazoles by the addition of aryl nitriles with sodium azide in the presence of boron trifluoride **(Scheme 9)**.[74]



Scheme 9. Preparation of tetrazoles with NaN_3 in the presence of BF_3 as Lewis acid.

Recently the use of aluminum chloride as a Lewis acid catalyst for the generation of aliphatic tetrazoles with a relatively low yield has been reported.[75] The crude was protected as a resin-bound trityl derivatives, which was subjected to alkylation followed by cleavage from the solid support to generate the desired tetrazole derivatives **(Scheme 10)**.



Scheme 10. Tetrazole ring formation with NaN_3 in the presence of $AlCl_3$ as Lewis acid.

I.4.2.6. Sharpless methodology: The Click Chemistry approach

I.4.2.6.1. The Click Chemistry

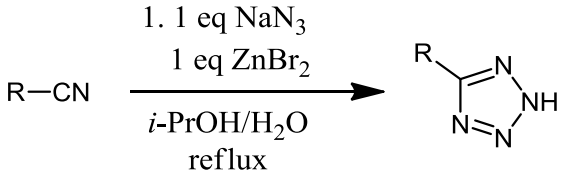
The term "Click Chemistry" was introduced by K. Barry Sharpless *et al*. in 2001.[76,77] "Click chemistry" is a modular approach that uses only practical and reliable reactions with readily available reagents. In several instances water is the ideal reaction solvent, providing the best yields and highest rates. Reaction work-up and purification uses benign solvents and avoids chromatography.

One of the "click approaches" is the copper-(I)-catalyzed 1,2,3-triazole formation from azides and terminal acetylenes as a particularly powerful linking reaction, due to its high degree of reliability and complete specificity of the reactants.

I.4.2.6.2. Synthesis of tetrazole rings

Sharpless *et al*. have reported a simple protocol for transforming a wide variety of nitriles into the corresponding 1*H*-tetrazoles, by using NaN_3 in the presence of Zn(II) salts in aqueous conditions **(Scheme 11)**.[61,63,78,79] This procedure shows a good level of generality, however, in the case of sterically hindered aromatic or alkyl inactivated nitriles, high temperatures (140-170°C) are required. They have not been able to achieve significant conversions of aromatic nitriles bearing an sp^3-hybridized substituent in the ortho position.[63] When the reaction is run at a concentration of (1 M) in sodium azide and (1 M) of $ZnBr_2$ a small amount of hydrazoic acid in the headspace above the reaction mixture is liberated.[78] Even at 100°C, release of hydrazoic acid is minimal. The exact role of zinc is not yet clear.[78]

The mechanism of the reaction has been controversial, with evidence supporting both a two-step mechanism and a concerted [2+3] cycloaddition.[61]



Scheme 11. Tetrazole ring formation with the Sharpless methodology.

The chief competing reaction is hydrolysis of the nitrile to primary amide; therefore with electron-poor nitriles, lowering the amount of zinc avoids significant formation of the amide byproduct. Other zinc salts such perchlorate and triflate also work; Zinc bromide is the best compromise between cost, selectivity and reactivity.

I.4.2.7. Tin- and silicon-mediated methods

Some of the newer methods for the preparation of 5-substituted tetrazoles involve the reaction of alkyl- or arylnitriles with safer organic soluble azides such as trialkyltin azide or trimethylsilylazide.[29,1,80]

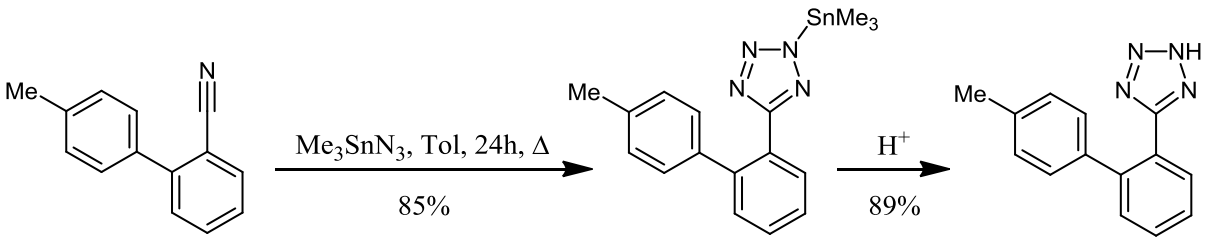
I.4.2.7.1. Trialkyltin azide

Methods for the tetrazole formation from organic-soluble reagents trimethylstannyl[81] or tri-*n*-butylstannyl azides[48,82] are more commonly utilized in larger scale than the sodium azide /ammonium salt protocols.

Duncia and Carini,[44] of DuPont, looking for a good alternative method to synthesize sartans[83] and using the biphenylnitrile **34** as a model system, discovered that both trimethyl- and *n*-butyltin azides react forming the trialkltin-tetrazole adducts. However, removal and disposal of stoichiometric (highly toxic) residual organotin at the end of the reaction is a major drawback of this methodology.[48]

Trialkyltin azide is typically prepared *in situ* from trialkyl chloride (volatile and toxic) and sodium azide, and has been shown to be effective in the synthesis of 5-substituted tetrazoles. Better yields are generally obtained compared to silicon-based azide reagents. The treatment of the starting nitrile **34** with trimethyl- or tri-*n*-butyltin azide[48] in toluene or xylene at refluxing gives the corresponding tetrazole. The insoluble tin-tetrazole adduct **35**

precipitates and when the reaction is finished, the product is simply filtered and dried. Subsequent acid hydrolysis yields the desired tetrazole **(Scheme 12)**.



34 **35** **36**

Scheme 12. Synthesis of sartans precursor using trimethyltin azide.

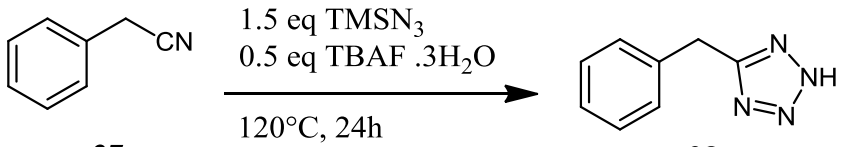
Higher temperature and/or longer reaction time are required using tri-*n*-butyltin reagent because of the more bulky character. An alternative to remove the tributyltin moiety, is to substitute the tin group with a trityl protecting group.

I.4.2.7.2. Trimethylsilyl azide

Trimethylsilyl azide has been reported to react with nitriles to give 5-substituted tetrazoles. [84] It is an attractive azide source due to its stability and relatively high boiling point (105°C). However, benzonitrile reacts with only very low conversion and *ortho*-substituted benzontriles fail to undergo the reaction.

I.4.2.7.2.1. $TMSN_3$ under solvent free conditions

Pizzo *et al*. recently reported the use of $TMSN_3$ in solvent free conditions.[85] Catalytic amount of tetrabutylammonium fluoride (TBAF) is used for the anionic activation of the silicon-nitrogen bond.[86] The use of TBAF has the advantage to activate the azide nucleophile and deprotects the *N*-silylated products. This catalytic system is relatively efficient and a wide range of tetrazoles are obtained in 1 to 48 hours at 85 to 120°C **(Scheme 13)**.

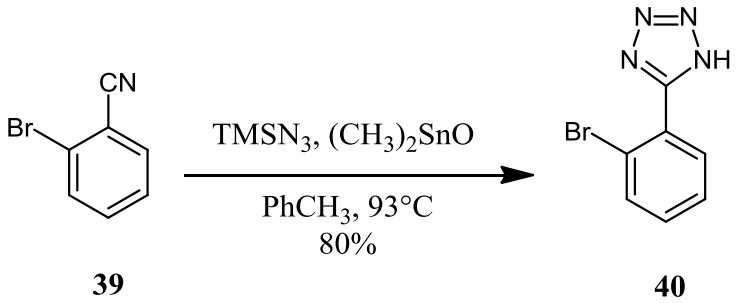


37 **38**

Scheme 13. Synthesis of tetrazoles with $TMSN_3$ in the presence of TBAF.

I.4.2.7.2.2. $TMSN_3$ in the presence of dibutyltin oxide as catalyst

The use of trimethlsilyl azide in the presence of a catalytic amount of dibutyltin oxide to convert nitriles into tetrazoles has been developed **(Scheme 14)**.[43,87,88]

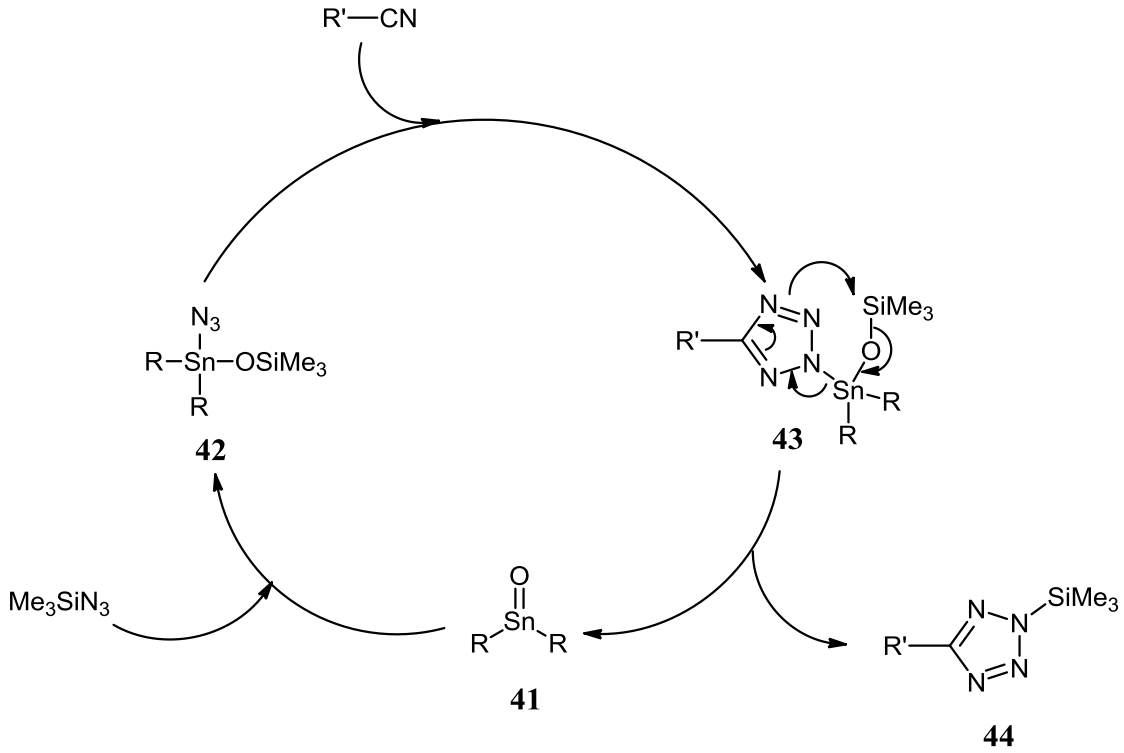


39 **40**

Scheme 14. Synthesis of tetrazoles with $TMSN_3$ in the presence of dibutyltin oxide as Catalyst.

In the general procedure the nitrile is treated in toluene at high temperature for 24 to 72 hours, with 2 equivalents of trimethylsilyl azide and 0.1 equivalent of dibutyltin oxide to provide the desired tetrazole. However in some cases, full conversion is obtained using in total 1 equiv of tin reagent and 5 equiv of $(TMS)N_3$ at 100°C **(Scheme 14)**.

The catalytic cycle involves the formation *in situ* of the dialkyl(*O*-trimethylsilyl) azidostannylhydrin **42** which reacts with the nitrile to give the N-(dialkyl (trimethylsloxy)stannyl)tetrazole **43** **(Scheme 15)**. The intermediate N-(dialkyl(trimethylsoloxy)stanyl)tetrazole **33** breaks down into the N-(trimethylsilyl)tetrazole **40** and the dialkyltin oxide **41** that carries on the catalytic cycle **(Scheme 15)**.[43]



Scheme 15.

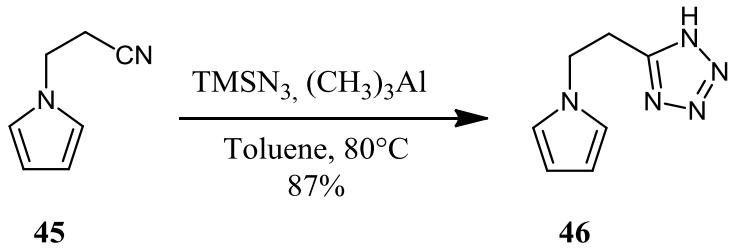
The trimethylsilyl azide as the azide source greatly reduces the hazard posed by *in situ* generation of hydrazoic acid and eliminates the possibility of the exposure to the toxic trialkyltin chloride used for the preparation of trialkyltin azide. However, at least two equivalents of trimethylsilyl azide are required for the reaction to run to completion and it is still difficult to separate the desired product from the stannane compounds. In addition the stannane compounds used in these reactions are generally highly toxic and require additional treatment of the waste water.

I.4.2.7.2.3. $TMSN_3$ in the presence of trimethyl aluminium

A method using trimethylsilyl azide was recently described by Lilly chemists Huff and Staszak,[55] who showed that an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene is an efficient combination to prepare 5-substituted tetrazoles **(Scheme 16)**. However, highly hindered nitriles resulted in poor conversion and the results are similar to those obtained using *n*-Bu_3SnN_3.

Roeder and Dehnicke[89] reported that trimethylaluminum when treated with trimethylsilyl azide forms a 1 to 1 complex at temperatures below 120°C which reacts to give

$(Me_2AlN_3)_3$ only at higher temperature. Therefore, it is likely that trimethylaluminum simply acts as a Lewis acid under these reactions and does not form $(Me_2AlN_3)_2$.

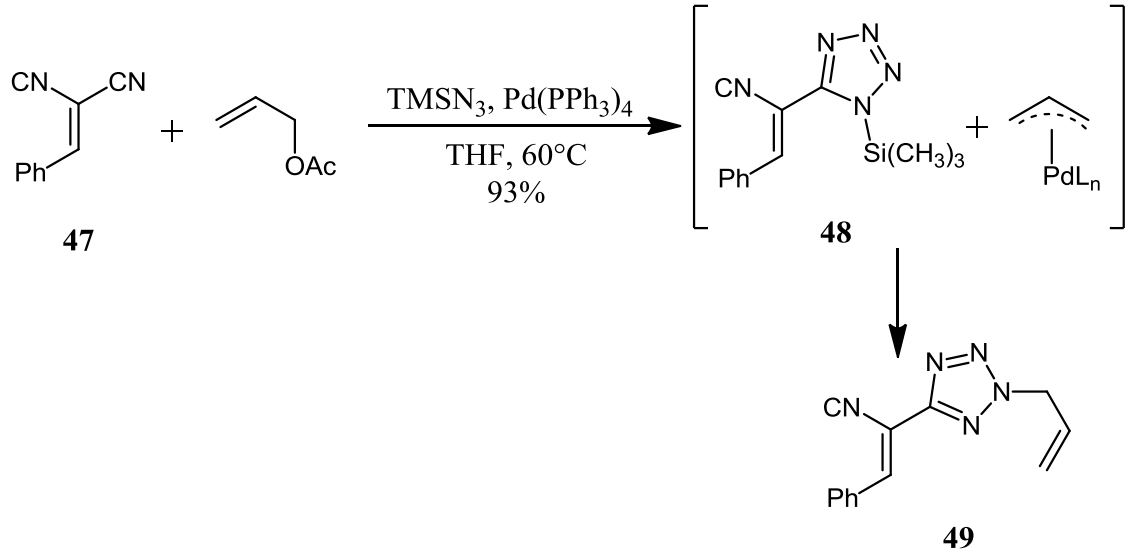


45 **46**

Scheme 16. Synthesis of tetrazoles with $TMSN_3$ in the presence of Me_3Al.

I.4.2.7.2.4. $TMSN_3$ in the presence of $Pd(PPh_3)_4$: Yamamoto methodology

Yamamoto *et al*. reported the synthesis of 2-allyltetrazoles starting from cyano compounds via the palladium-catalyzed three-components coupling reaction.[90] The *N*-silyl tetrazole **48**, derived from the cycloaddition reacts *in situ* with the π-allylpalladium species to provide the *N*-allylated product **48 (Scheme 17)**.



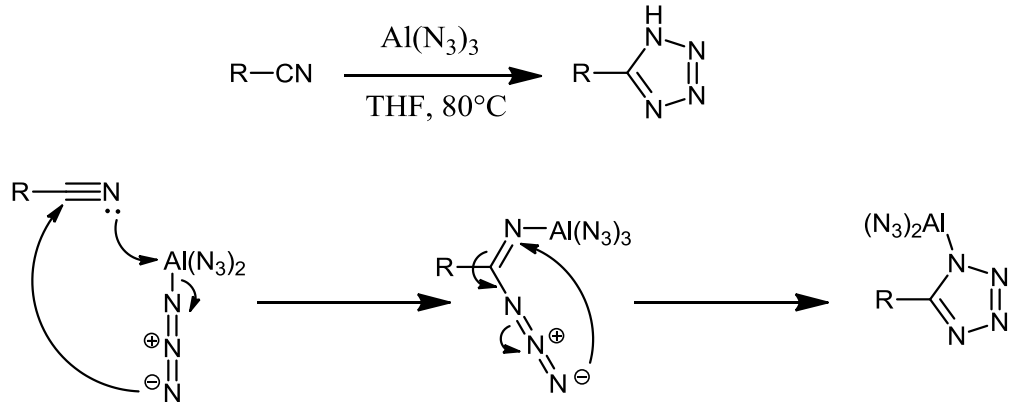
47 **48** **49**

Scheme 17. Preparation of 2,5-disubstituted tetrazoles.

I.4.2.8. Aluminum azide

Aluminum azides have already been reported by Wiberg and Michaud in a 1957 German patent.[91] The $Al(N_3)_3$ can be prepared by treatment of $AlCl_3$ with 3 equivalents of NaN_3 in THF at reflux.[91,92] However, using aluminum azide for the preparation of tetrazoles,

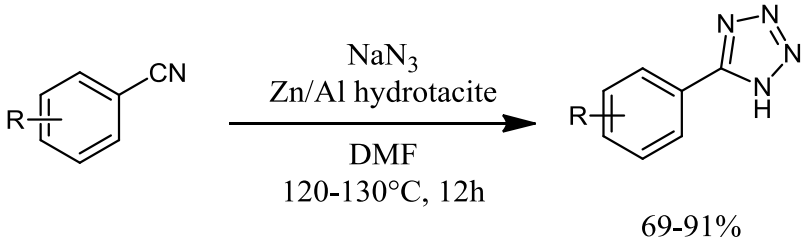
two moles of HN_3 are formed for every mole of product during the acidic quench of the reaction. The mechanism proposed proceeds through intramolecular delivery of N_3^- from $Al(N_3)_3$ complexed with the nitrile **(Scheme 18)**.



Scheme 18. Proposed mechanism fort the tetrazole formation with $Al(N_3)_3$.

I.4.2.9. Synthesis of 5-substituted tetrazoles using Zn/Al hydrotalcite catalyst

Katam *et al*. reported an alternative method to prepare tetrazole rings using Zn/Al hydrotalcite as heterogeneous catalyst[93] **(Scheme 19)**. The anionic [Zn-Al-Cl], with [Zn]/[Al] ratio of 3 to 1, is synthesized by co-precipitation at pH 9. This methodology requires relative high temperature and long reaction times in DMF, with the use of Zn which requires additional treatment of the waste water.



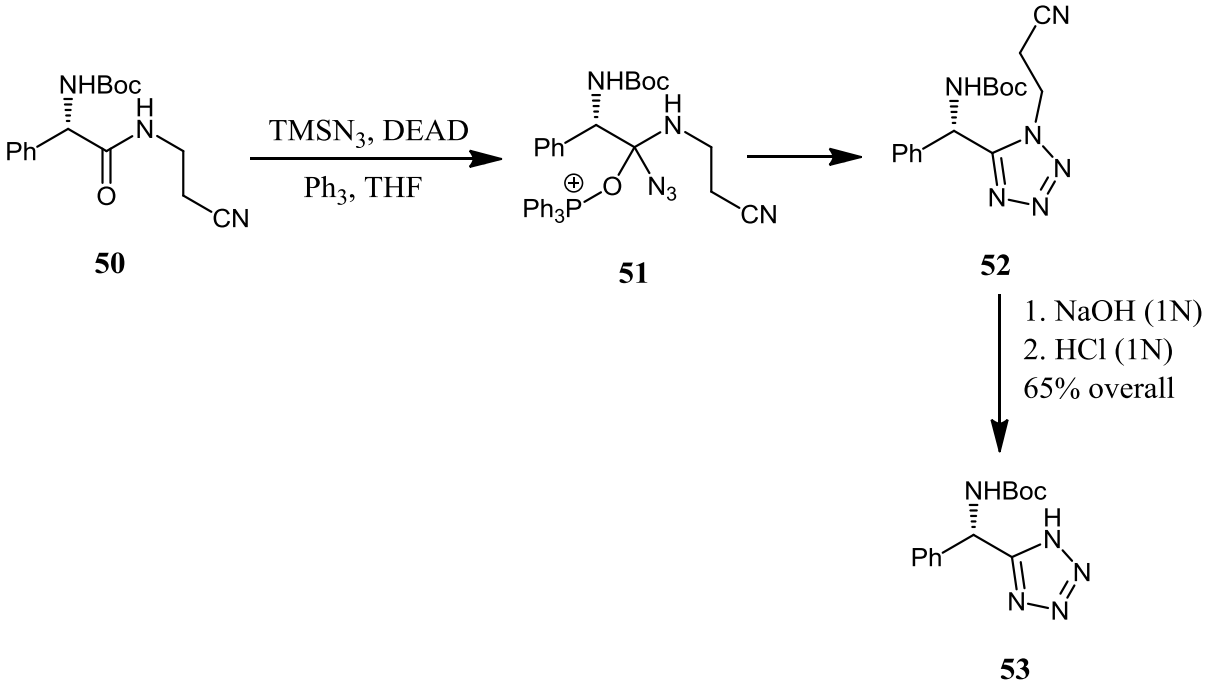
Scheme 19. Zn/Al hydrotalcite catalyzed synthesis of 5-substituted-tetrazoles.

I.4.3. Synthesis of tetrazoles with other methods

Several reports have appeared which make use of precursors other than nitriles to prepare 5-substituted-1*H*-tetrazoles. Short overviews of these methods are given herein.

I.4.3.1. From N-(cyanoethyl)amides

N-(Cyanoethyl)amides **50** reacts with trimethylsilyl azide to provide 1N-protected tetrazole **52 (Scheme 20)**. Removal of the N-cyanoethyl moiety of **52** with aqueous sodium hydroxide, followed by acidification, led to the free tetrazole **53** in relative good overall yield **(Scheme 20)**.[8]

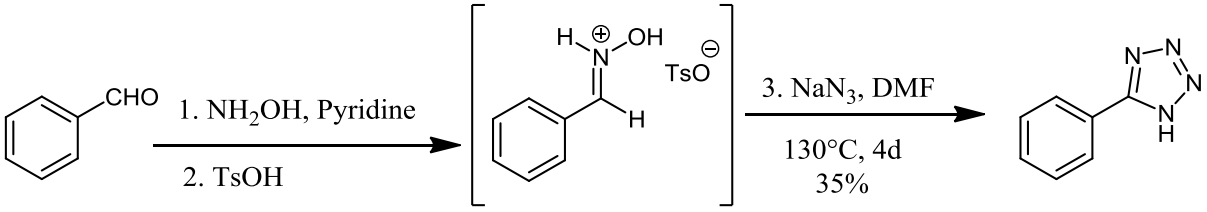


50 **51** **52** **53**

Scheme 20.

I.4.3.2. From oxime salts

An useful process for the preparation of 5-substituted-tetrazoles is the reaction of oxime salt **55** with sodium azide developed by Antonowa and Hauptmann.[94] In this procedure, benzaldehyde **54** may be directly transformed into the corresponding aryl tetrazole **56 (Scheme 21)**.



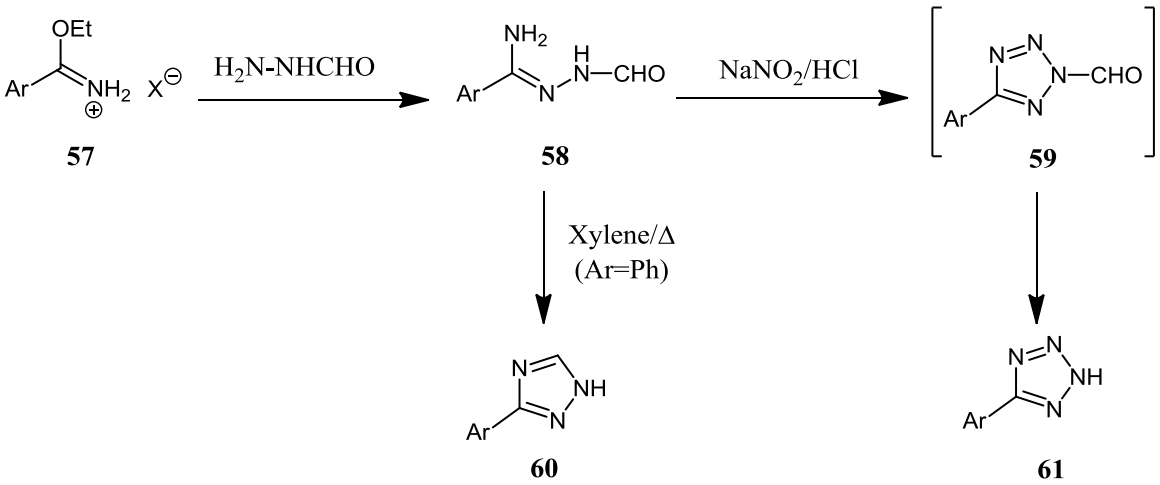
54 **55** **56**

Scheme 21. Synthesis of tetrazoles from oxime salts.

I.4.3.3. From imidate salt and imidoyl chlorides

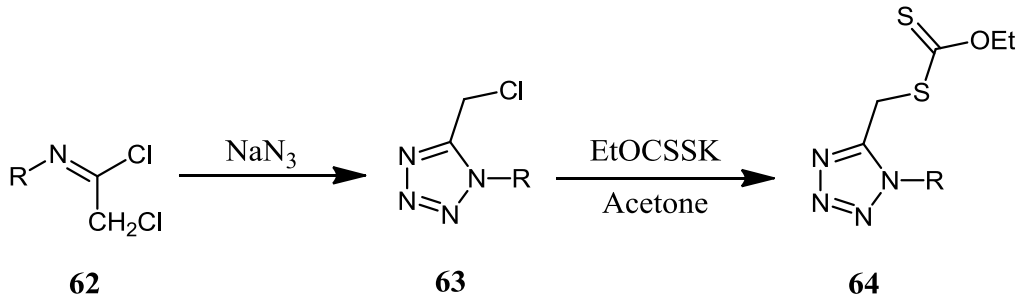
Zard *et al*. proposed an alternative method to prepare 5-substituted tetrazoles from imidate salts which does not involve azides.[95] The reaction of imidates **57** with *N*-formyl hydrazine is known to give 1,2,4-triazoles via the intermediate *N*-formyl amidrazones **58**.

However, by working at low temperature (0°C) the triazole formation can be avoided and indeed, in the presence of sodium nitrite and diluted HCl, the desired tetrazole **61** can be isolated in good yields **(Scheme 22)**. The triazole **60** can be isolated only upon heating in xylene.



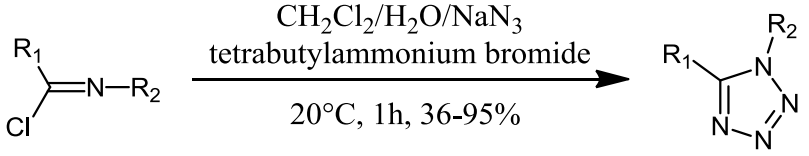
Scheme 22.

Few years later, Zard[96] proposed a method to prepare disubstituted tetrazoles. The reaction of imidoyl chloride **62** with sodium azide provides the 5-chloro methyl tetrazole **63** which is then treated with potassium *O*-ethyl xanthate in acetone to give the corresponding tetrazole xanthates **64 (Scheme 23)**.



Scheme 23.

Koldobskii *et al*. proposed the synthesis of 1,5-disubstituted tetrazoles under phasetransfer conditions from imidoyl chlorides by treatment with sodium azide **(Scheme 24)**.[97]



Scheme 24. Synthesis of tetrazoles from imidoyl chlorides.

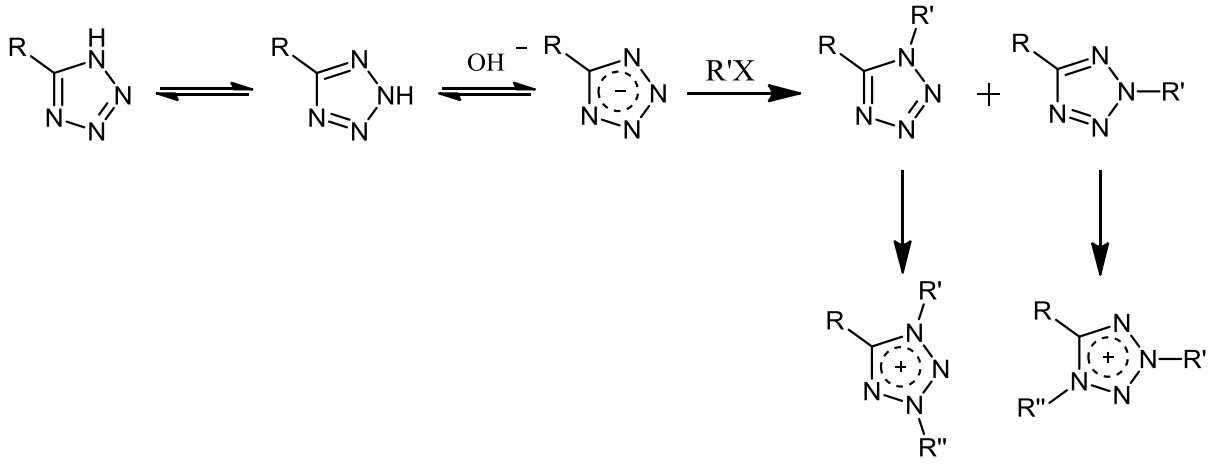
I.5. Reactivity of Tetrazoles

Reactivity of 5-substituted tetrazoles permits to classify them as aromatic compounds. The ring undergoes electrophilic substitution, is stable toward oxidation and, in general, the tetrazole ring remains unchanged during reduction of susceptible substituents.[1]

I.5.1. Reaction with electrophiles

Peculiarities of the π-electron system of the tetrazole ring is the availability of lone pairs of the nitrogens which allow these heteroatoms to be attacked by various electrophilic reagents.[1,98] Aside from the variety of alkyl substituents, many other groups can be introduced including acyl, imidoyl, silyl, phosphoryl, sulfonyl, aryl, vinyl and amino functions.[98]

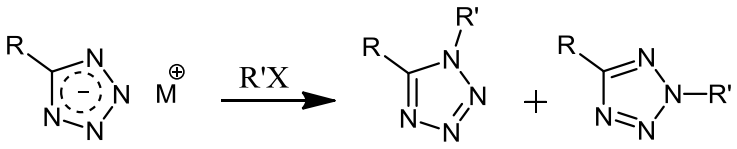
The most common nucleophile type reactions at the tetrazole nitrogens arise from the acidity of the ring N-H bond. The tetrazolic acids form stable anions when treated with bases and are more reactive than neutral tetrazoles towards electrophiles and alkylating agents **(Scheme 25)**.[98] The product is a mixture of 1*N*- and 2*N*-alkyl isomers, the relative proportions of which depend upon the conditions of the alkylation, the steric requirements of the alkylating agent and the influence of the 5-substituent. In general, electron-donating substituents at C-5 tend to favor 2*N*-alkylation.



Scheme 25. Reactions with electrophiles.

I.5.2. Alkylation of tetrazolate anion salts

Metal salts of 5-substituted tetrazoles undergo to alkylation on heating with alkyl halides in a wide range of solvents. The products are a mixture of 5-substituted 1*N*- and 2*N*-alkyl tetrazoles **(Scheme 26)**.[1]



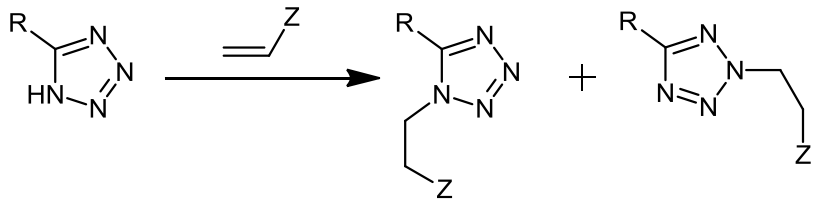
Scheme 26.

I.5.3. Acylation and alkylation of neutral tetrazoles

There are a variety of electrophilic substitutions on 5-substituted tetrazoles with reagents such as hydrazonoyl halides, electron-deficient vinyl systems and acyl halides.[49] These reactions are carried out in the presence of excess Et_3N used to promote loss of halide or hydrogen halide (generating nitrilimines or nitrile oxides) and involve the tetrazolate anion as the reactive tetrazole species.[1]

I.5.3.1. Michael reaction

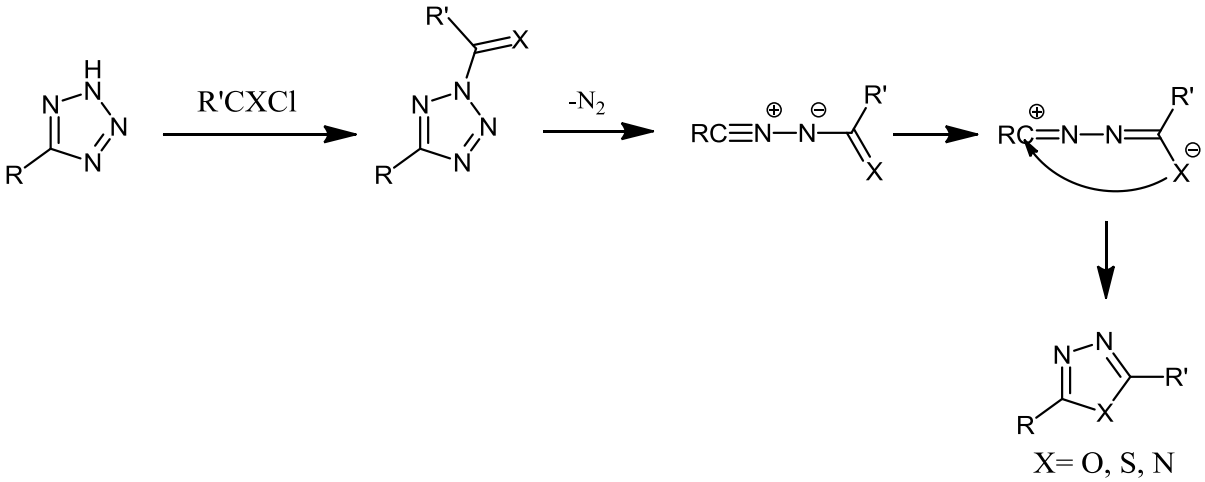
The Michael reactions of 5-substituted tetrazoles with electron-deficient vinyl systems give the 2-alkylated products in yields of about 50-80 % **(Scheme 27)**.[1]



Scheme 27. Michael reactions of 5-substituted tetrazoles.

I.5.3.2. Acylation

Electrophiles such as acyl halides and imidoyl halides attack the 5-substituted tetrazole ring at the N2-position which can give after thermal decomposition of the Huisgen product **(Scheme 28)**.



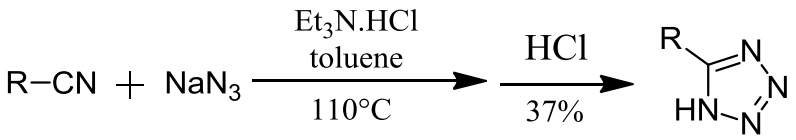
Scheme 28. Acylation of tetrazoles followed by thermal decomposition and Huisgen reaction.

I.6. Results and Discussion

I.6.1. Synthesis of tetrazoles

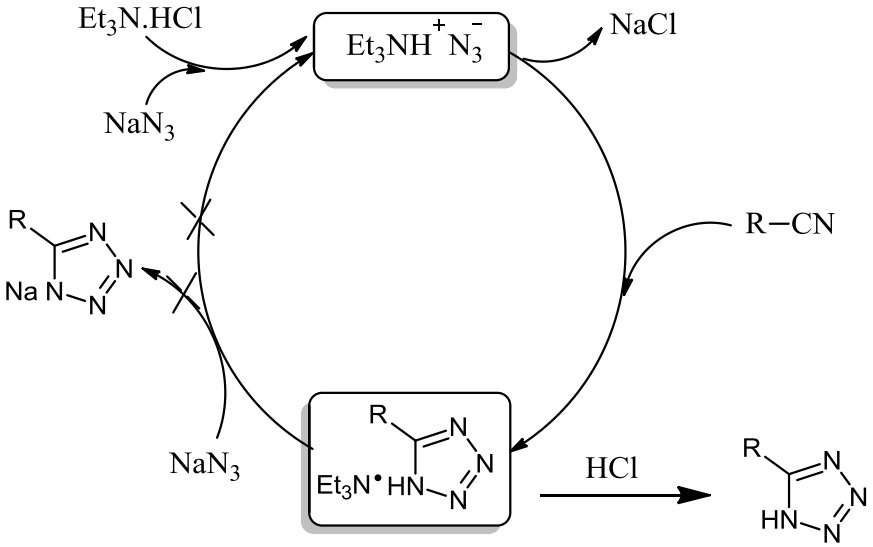
Tetrazole derivatives have attracted much attention as raw materials for medicine, agricultural chemicals, foaming agents, and in the automobile inflator industry. Especially in recent years, remarkable related development has been made in the medicinal field. Yet in order to use tetrazole compounds as starting materials in the fine chemicals field, compounds with high quality polyfunctional structures are required. However, a varsatile method for synthesizing many kinds of tetrazoles through safe and simple manipûlation had not been developed. In this work we have developed a novel synthetic method.

The method involves the reaction of nitrile with an inorganic azide, using an amine salt in an aromatic solvent in a facile workup procedure, to produce tetrazoles with higher purity in greater yield **(Scheme 29)**.



Scheme 29.

The mechanism of reaction



Scheme 30.

I.6.1.1. Synthesis of tetrazoles from aromatic nitriles

The reaction of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile, 2,2-diphenylacetonitrile and anthracene-9-carbonitrile with NaN_3 at 110°C in the presence of an amine salt for 24h yielding the desired tetrazoles **2b, 2k** and **2l** in excellent yield **(table 1; entries 1, 3 and 4)**. The corresponding 2-phenylacetonitrile requires shorter reaction times and provides the tetrazole **2c** in good yield using NaN_3 at 110°C for only 17 hours **(Table 1; entry 2)**.

Table 1 summarized the physical properties of products prepared as well as gotten yields.

Table 1: Synthesis of 5-substituted tetrazoles.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2b**	24	149-151	78
2	**2c**	17	123-124	63
3	**2k**	24	165-166	72
4	**2l**	24	215-216	75

Note: Yield after extraction and crystallisation.

The identification of compounds **2b, 2c, 2k** and **2l** has been established well by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data:

IR Spectroscopy

The IR spectrums of the gotten products showed strong absorption band characteristic of the amino group at υ_{N-H} (cm^{-1})= 2987; 3336, and a second strip of frequency toward 1046; 1053 cm^{-1} due to stretching of C=C. Function tetrazole is also verified by the presence of band at [2900-2917] cm^{-1} who corresponds to the C=N link.

^{1}H NMR Spectroscopy

Compound (2b)

The spectrum of this compound showed a singlet (s) absorption band for group CH_3 at 2.28 ppm. And aromatic protons appear at [6.98-7.69] ppm which multiplicity appears as follows:

- Two doublets (d): the first at 6.98 ppm with coupling constant *J*= 8.1 Hz, while the second at 7.12 ppm with coupling constant *J*= 7.9 Hz.

- Doublet of doublet of doublet (ddd) at 7.55 ppm with coupling constants *J*= 10.3, 5.8, 1.9 Hz.
- The other protons appear at [7.63-7.69] ppm as a multiplet (m) with integration 2H.

Compound (2c)

The spectrum of this compound was characterized by a multiplet (m) at [7.24-7.35] ppm. This multiplet was assigned for 5 aromatic protons. The spectrum also showed a singlet (s) peak at 4.28 ppm for CH_2.

Compound (2k)

The spectrum of this compound showed singlet band at 5.85 ppm belong to CH. Also this spectrum showed the multiplet (m) at [7.14-7.37] ppm due to the 10 aromatic protons.

Compound (2l)

Aromatic protons appear at [7.45-8.94] ppm which multiplicity appears as follows:

- Doublet (d) at 7.45 ppm with coupling constant *J*= 8.6 Hz with integration 2H.
- Two multiplet (m) first at [7.56-7.63] ppm with integration 4H and second at [8.23-8.31] ppm with integration 2H.
- Singlet (s) at 8.94 ppm with integration 1H.

The results of ^{1}H NMR of products **2b, 2c, 2k** and **2l** are summarized in **Table 2**.

Table 2: ^{1}H NMR for compounds **2b**, **2c**, **2k** and **2l**.

Compounds	CH	CH_2	CH_3	H_{arom}
2b	---	---	2.28, s, 3H	6.98, d, *J*= 8.1 Hz, 2H; 7.12, d, *J*= 7.9 Hz, 2H; 7.55, ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H; 7.63-7.69, m, 2H
2c	---	4.28, s, 2H	---	7.24-7.35, m, 5H
2k	5.85, s, 1H	---	---	7.14-7.30, m, 10H
2l	---	---	---	7.45, d, *J*= 8.6 Hz, 2H; 7.56-7.63, m, 4H; 8.23-8.31, m, 2H; 8.94, s, 1H

Notes: ^{1}HNMR: (300 MHz, DMSO-d_6).

^{13}C NMR Spectroscopy

Compound (2b)

The spectrum of this compound showed the expected peak for CH_3 at 20.7 ppm, the other aromatic carbons appear in the area [123.4-155.1] ppm.

Compound (2c)

The carbon of the group CH_2 fate to 29.0 ppm, the aromatic carbons appear at [127.1-155.3] ppm.

Compound (2k)

The spectrum showed the appearance of CH peak at 40.8 ppm. Also this spectrum showed 5 peaks at [128.6-160.0] ppm due to the 13 aromatic carbons.

Compound (2l)

The spectrum showed the aromatic carbons peaks at [120.6-150.1] ppm.

Table 3 summarized all results of ^{13}C NMR for compounds **1b, 1c, 1k** and **1l**.

Table 3: ^{13}C NMR for compounds **2b**, **2c**, **2k** and **2l**.

Compounds	CH	CH_2	CH_3	C_{arom}
2b	---	---	20.7	123.4-155.1
2c	---	29.0	---	127.1-155.3
2k	40.8	---	---	128.6-160.0
2l	---	---	---	120.6-150.1

Notes: ^{13}CNMR: (75 MHz, DMSO-d_6).

I.6.1.2. Synthesis of 5-substituted heteroaromatic tetrazole

Heteroaromatic nitriles such as picolinonitrile give the corresponding tetrazole **2f** in the presence of an amine salt and NaN_3 at 110°C for 24 hours at high temperature with good yield **(Table 4; entry 1)**. The main problem of this substrate is the high hydrophilicity of the corresponding product which makes difficult the purification with the common extraction procedure.

Table 4 summarized the physical properties of products prepared as well as gotten yields.

Table 4: Synthesis of heteroaromatic tetrazoles.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2f**	24	208-210	85

The structure of compound **2f** was inferred from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data.

^{1}H NMR Spectroscopy

The spectrum of this product showed two doublet of doublet of doublet (ddd), the first at 7.63 ppm with coupling constants *J*= 7.8, 4.8, 1.2 Hz, and the second at 8.79 ppm with coupling constants *J*= 4.8, 1.7, 0.9 Hz. And triply of doublet (td) at 8.08 ppm with coupling constant *J*= 7.8, 1.7 Hz. Also this spectrum showed a doublet of triplet at 8.22 ppm with coupling constant *J*= 7.9, 1.0 Hz.

The results of ^{1}H NMR for compound **2f** are illustrated in **Table 5**.

Table 5: ^{1}H NMR for compound **2f**.

Compound	H_{arom}
2f	7.63, ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H 8.08, td, *J*= 7.8, 1.7 Hz, 1H 8.22, dt, *J*= 7.9, 1.0 Hz, 1H 8.79, ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H

^{13}C NMR Spectroscopy

The spectrum showed the aromatic carbons peaks at [122.6-154.8] ppm.

I.6.1.3. Synthesis of tetrazoles from alkyl nitriles

The reaction of pivalonitrile, with NaN_3 at 110°C in the presence of an amine salt for 17h yielding the desired tetrazole **2d** in excellent yield **(table 6; entry 1).** The tetrazole **2e** is obtained under similar conditions for 30 hours **(Table 6; entry 2).**

Table 6 summarized the physical properties of products prepared as well as gotten yields.

Table 6: Synthesis of 5-substituted tetrazoles from alkyl nitriles.

Entry	Products	Time(h)	mp(°C)	Yield(%)
1	**2d**	17	208-210	90
2	**2e**	30	72-73	57

The structures of compounds **2d** and **2e** were inferred from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) data.

^{1}H NMR Spectroscopy

Compound (2d)

The spectrum of this compound showed presence of singlet (s) band at 5.85 ppm belongs to $3CH_3$.

Compound (2e)

The protons of this compound appear at [0.84-2.84] ppm which multiplicity appears as follows:

- Tow triplets (t): first at 0.84 ppm with coupling constant *J*= 6.8 Hz, and second at 2.84 ppm with coupling constant *J*= 7.6 Hz.
- Two multiplet (m): the first at 1.24 ppm with integration 16H, and the second at 1.65-1.68 ppm with integration 2H.

Table 7 summarized all results of ^{1}H NMR for compounds **2d** and **2e**.

Table 7: ^{1}H NMR for compounds **2d** and **2e**.

Compounds	CH_2	CH_3
2d	---	1.35, s, 9H.
2e	1.24, m, 16H 1.65-1.68, m, 2H, 2.84, t, *J*= 7.6 Hz, 2H	0.84, t, *J*= 6.8 Hz, 3H

^{13}C NMR Spectroscopy

Compound (2d)

In the spectrum of this compound we record the presence of three peaks: the first at 28.9 ppm corresponding to the three CH_3, the second at 30.3 ppm corresponding to alkyl C, and the third at 163.4 ppm corresponding to C of tetrazole ring.

Compound (2e)

In the spectrum of compound **2e** we observe:

- The carbon of function CH_3 appears at 13.9 ppm.
- The carbons CH_2 resonate in the area [22.2-31.3] ppm.
- The carbon C of tetrazole ring appears at 155.9 ppm.

The results of ^{13}C NMR for compounds **2d** and **2e** is illustrated in **Table 8**.

Table 8: ^{13}C NMR for compounds **2d** and **2e**.

Compounds	C	CH_2	CH_3
2d	30.3, 163.4	---	28.9
2e	155.9	22.2-31.3	13.9

I.6.1.4. Synthesis of tetrazoles in the presence of carbonyl groups

The treatment of 4,4-dimethyl-3-oxopentanenitrile with NaN_3 at 110°C in the presence of an amine salt for 30h yielding the corresponding tetrazole **2j** in very good yield **(Table 9; entry 1).**

Table 9: Synthesis of tetrazole **2j**.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2j**	30	152-154	85

^{1}H NMR Spectroscopy

The spectrum of this compound showed two singlets (s): the first at 1.18 ppm corresponding to protons of three CH_3, and the second at 4.41 ppm corresponding to the protons of CH_2.

Table 10 summarized all results of ^1H NMR for compound **2j**.

Table 10: ^1H NMR for compound **2j**.

Compound	CH_2	CH_3
2j	4.41, s, 2H	1.18, s, 9H

^{13}C NMR Spectroscopy

Spectral analysis of this compound shows the existence of:

- A signal at 25.8 ppm corresponding to the carbons of three CH_3, and other at 32.2 ppm corresponding to CH_2 group.
- A signal out to 209.8 ppm corresponding to the carbon of carbonyl.

- The carbon of tetrazole ring appears at 128.2 ppm, and the alkyl carbon fate at 44.0 ppm.

The assignment of the major ^{13}C NMR signals is summarized in **Table 11**.

Table 11: ^{13}C NMR for compound **2j**.

compound	**C**	**CH_2**	**CH_3**	**C-C=O**	**C=O**
2j	128.2	32.2	25.8	44.0	209.3

I.7. Conclusion

The application of sodium azide for the synthesis of 5-substituted tetrazoles is a new efficient process and offers several advantages over many of the previously published procedures, including a reduced environmental impact resulting from the elimination of toxic waste.[99,100]

The use of sodium azides as an azide source greatly reduces the hazard posed by *in situ* generation of hydrazoic acid and avoids formation. The reaction is suitable for use on a large scale as special care is not required when recycling waste water because the sodium is a non-toxic metal compared to tin organo-metallics. As dialkylaluminum chlorides are available in large quantities and are relatively inexpensive (they are produced for use in Ziegler-Natta catalysis), the reaction is also economically attractive.

In this chapter we have developed a noval synthetic method this method involves the reaction of nitrile with an inorganic azide, using an amine salt in an aromatic solvent in a facile workup procedure, to produce tetrazoles **2b**, **2c**, **2d**, **2e**, **2f**, **2j**, **2k** and **2l** with higher purity in greater yield. Our method has several advantages:

- The reaction produces no byproducts due to side reaction.
- The reaction takes place rapidly.
- Produces the products in excellent yield.

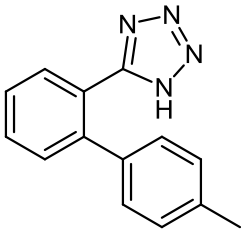
Another characteristic is its simple workup procedures, through which products of excellent purity can be easily isolated. Moreover, the amines and solvents used in the method can be recycled without additional troublesome treatment.

I.8. Experimental part

General procedure

The mixture of a nitrile (50 mmol), NaN_3 (65 mmol) and an amine salt (150 mmol) in an aromatic solvent (100 mL) was heated to 110°C for 17-30 h with stirring. After cooling, the product was extracted with water (100 mL). To the aqueous layer, 36% HCl was added dropwise to salt out the produced tetrazole. After filtration, the solid was dried under reduced pressure, yielding the tetrazole.

Synthesis of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

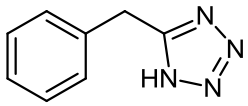


2b

Following the general procedure, the reaction of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile (3.94 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2b** as a brawn solid.

- **Yield**= 78% (3.76 g).
- **Mp**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH) , 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).

Synthesis of 5-benzyl-1H-tetrazole (2c)[102]

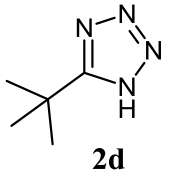


2c

Following the general procedure, the reaction of 2-phenylacetonitrile (2.350 ml, 50 mmol), NaN_3 (3.9 g, 65-150 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2c** as a white solid.

- **Yield**= 63% (2.5 g).
- **Mp**= 123-124°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).

Synthesis of 5-(tert-butyl)-1H-tetrazole (2d)[101]

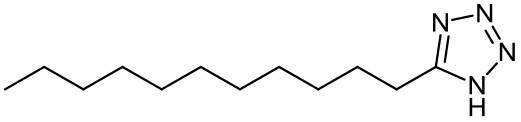


2d

Following the general procedure, the reaction of pivalonitrile (2.256 mL, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2d** as a white solid.

- **Yield**= 90% (2.82 g).
- **Mp**= 208-210°C.
- **IR (KBr):** 2977, 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

Synthesis of 5-undecyl-1H-tetrazole (2e)[103]

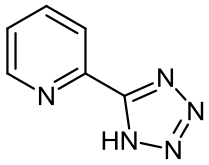


2e

Following the general procedure, the reaction of dodecanenitrile (2.214 mL, 50 mmol), NaN_3 (1.95 g, 32 mmol) and an amine salt (4.11 g, 75 mmol) in toluene at 110°C gave **2e** as a brawn solid.

- **Yield**= 57% (3.19 g).
- **Mp**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).

Synthesis of 2-(1H-tetrazol-5-yl)pyridine (2f)[101]

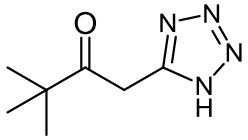


2f

Following the general procedure, the reaction of picolinonitrile (5.20 g, 50 mmol), NaN_3 (3.9 g, 65 mmol)) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2f** as a brawn solid.

- **Yield**= 85% (6.06 g).
- **Mp**= 208-210°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

Synthesis of 3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2j)[104]

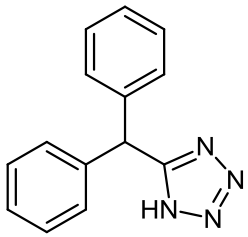


2j

Following the general procedure, the reaction of 4,4-dimethyl-3-oxopentanenitrile (6.25 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2j** as a orange solid.

- **Yield**= 85% (7.11 g).
- **Mp**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

Synthesis of 5-benzhydryl-1H-tetrazole (2k)[105]

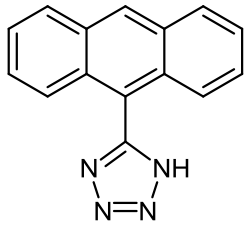


2k

Following the general procedure, the reaction of 2,2-diphenylacetonitrile (9.55 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2k** as a white solid.

- **Yield**= 72% (8.42 g).
- **Mp**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

Synthesis of 5-(anthracen-9-yl)-1H-tetrazole (2l)[102]



2l

Following the general procedure, the reaction of anthracene-9-carbonitrile (10.16 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22, 150 mmol) in toluene at 110°C gave **2l** as a green solid.

- **Yield**= 75% (1.85 g).
- **Mp**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

Chapter 02: Protection of Tetrazole Ring

Introduction

The problem of functional group incompatibility in the synthesis of complex organic structures has persisted since the pioneering research of Emil Fischer on the synthesis of carbohydrates. One of Fischer's enduring contributions to the development of organic chemistry was the notion that an otherwise reactive functional group could be temporarily renderer inert by appending a suitable protecting group with could then be later removed. Despite an intervening century of fabulous progress in synthetic methodology, the proliferation of protecting groups is a tacit acknowledgement that selectivity in functional group transformations remains a central and unsolved problem in organic synthesis. The problem is especially acute in the design and construction of polyfunctional molecules such as peptides, oligosaccharides, glycopeptides, glycolipids, nucleotides, and polyketides which often require a scaffold of protecting groups comparable in mass to the target itself.

There are 7 tactical considerations which define how effectively a protecting group will best fulfil its assigned strategic role of shielding a functional group from destruction (or reaction with another functional group):

1. The protecting group should be easily and efficiently introduced.
2. It should be cheap or readily available.
3. It should be easy to characterize and avoid such complications as the creation of new stereogenic centers.
4. It should be stable to chromatography.
5. It should be stable to the widest possible range of reaction conditions.
6. It should be removed selectively and efficiently under highly specific conditions.
7. The by-products of the deprotection should be easily separated from substrate.

II.1. Properties of a protective group

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being, developed for this purpose. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should form a derivative

(without the generation of new stereogenic centers) that can easily be separated from side products associated with its formation or cleavage. The protective group should have a minimum of additional functionality to avoid further sites of reaction. All things considered, no one protective group is the best. Currently, the science and art of organic synthesis, contrary to the opinions of some, has a long way to go before we can call it a finished and well-defined discipline, as is amply illustrated by the extensive use of protective groups during the synthesis of multifunctional molecules. Greater control over the chemistry used in the building of nature's architecturally beautiful and diverse molecular frameworks, as well as unnatural structures, is needed when one considers the number of protection and deprotection steps often used to synthesize a molecule.

II.2. Historical development

Since a few protective groups cannot satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and, indeed, are available. In early syntheses, the chemist chose a standard derivative known to be stable to the subsequent reactions. In a synthesis of callistephin chloride, the phenolic-OH group in **65** was selectively protected as an acetate.[106] In the presence of silver ion, the aliphatic hydroxyl group in **66** displaced the bromide ion in a bromoglucoside. In a final step, the acetate group was removed by basic hydrolysis. Other classical methods of cleavage include acidic hydrolysis (eq. 1), reduction (eq. 2) and oxidation (eq. 3) (**Figure 11).**

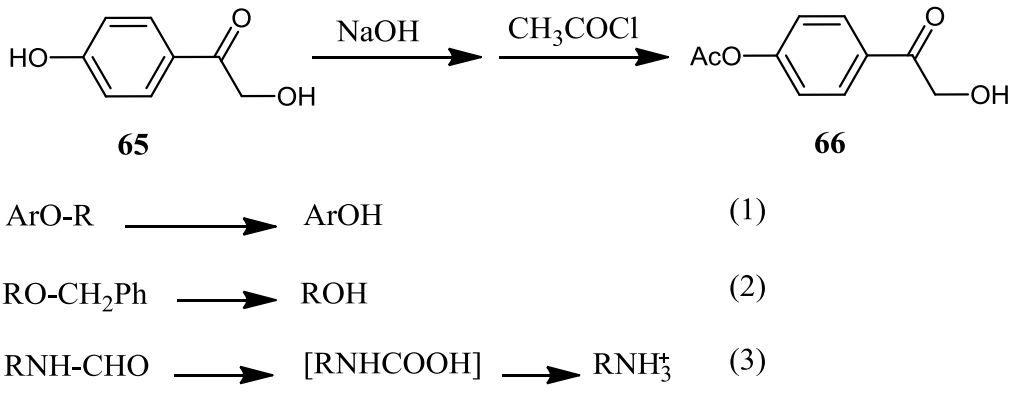


Figure 11.

Some of the original work in the carbohydrate area in particular reveals extensive protection of carbonyl and hydroxyl groups. For example, a cyclic diacetonide of glucose was

selectively cleaved to the monoacetonide.[107] A summary[108] describes the selective protection of primary and secondary hydroxyl groups in a synthesis of gentiobiose, carried out in the 1870s, as triphenylmethyl ethers.

II.3. Development of new protective groups

As chemists proceeded to synthesize more complicated structures, they developed more satisfactory protective groups and more effective methods for the formation and cleavage of protected compounds. At first a tetrahydropyranyl acetal was prepared,[109] by an acid-catalyzed reaction with dihydropyran, to protect a hydroxyl group. The acetal is readily cleaved by mild acid hydrolysis, but formation of this acetal introduces a new stereogenic center. Formation of the 4-methoxytetrahydropyranyl ketal[110] eliminates this problem.

Catalytic hydrogenolysis of an O-benzyl protective group is a mild, selective method introduced by Bergmann and Zervas[111] to cleave a benzyl carbamate (>NCO-$OCH_2C_6H_5$------>NH) prepared to protect an amino group during peptide syntheses. The method has also been used to cleave alkyl benzyl ethers, stable compounds prepared to protect alkyl alcohols; benzyl esters are cleaved by catalytic hydrogenolysis under neutral conditions.

Three selective methods to remove protective groups have received attention: "assisted", electrolytic, and photolytic removal. For examples illustrate "assisted removal" of a protective group. A stable allyl group can be converted to a labile vinyl ether group (eq. 4)[112] a β-haloethoxy (eq. 5)[113] or a β-silylethoxy (eq. 6)[114] derivative is cleaved by attack at the 3-substituent; and a stable *o*-nitrophenyl derivative can be reduced to the *o*-amino compound, which undergoes cleavage by nucleophilic displacement (eq. 7)[115] **(Figure 12).**

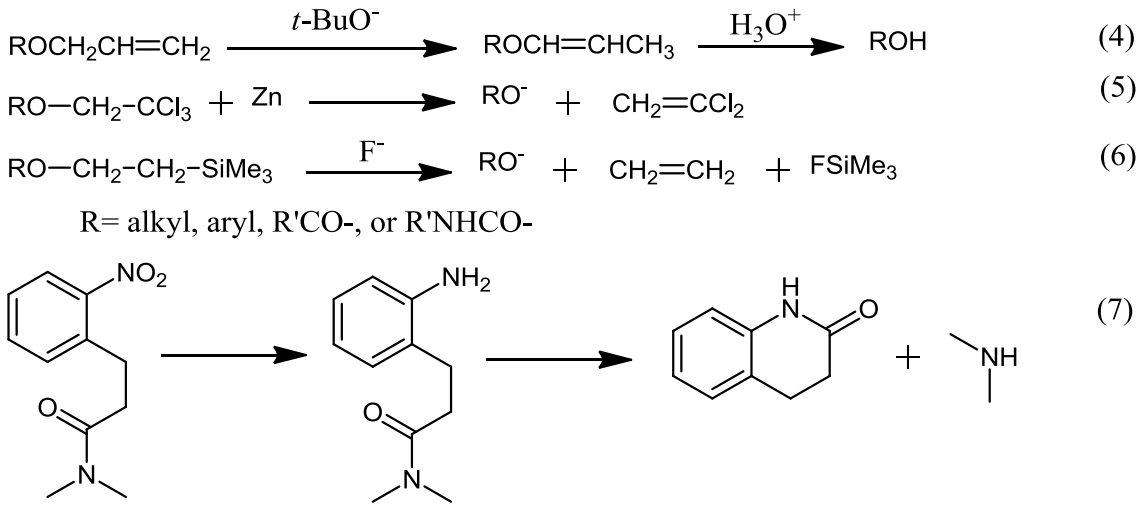


Figure 12.

The design of new protective groups that are cleaved by "assisted removal" is a challenging and rewarding undertaking.

Removal of a protective group by electrolytic oxidation or reduction is useful in some cases. An advantage is that the use and subsequent removal of chemical oxidants or reductants (eg., Cr or Pb salts; Pt- or Pd-C) are eliminated. Reductive cleavages have been carried out in high yield at -1 to -3 V, depending on the group; oxidative cleavages in good yield have been realized at 1.5-2 V. For systems possessing two or more electrochemically labile protective groups, selective cleavage is possible when the half-wave potentials, $E_{1/2}$, are sufficiently different; excellent selectivity can be obtained with potential differences on the order of 0.25 V. Protective groups that have been removed by electrolytic oxidation or reduction are described; a review article by Mairanovsky[116] discusses electrochemical removal of protective groups.[117]

Photolytic cleavage reactions (eg., of *o*-nitrobenzyl, phenacyl, and nitrophenylsulfenyl derivatives) take place in high yield on irradiation of the protected compound for a few hours at 254-350 nm. For example, the *o*-nitrobenzyl group, used to protect alcohols,[118] amines[119] and carboxylic acids,[120] has been removed by irradiation. In addition, the reader may wish to consult five review articles.[121]

One widely used method involving protected compounds is solid-phase synthesis (polymer-supported reagents). This method has the advantage of requiring only a simple workup by filtration such as in automated syntheses, especially of polypeptides, oligonucleotides, and oligosaccharides.

Internal protection, used by van Tamelen in a synthesis of colchicine, may be appropriate.[122]

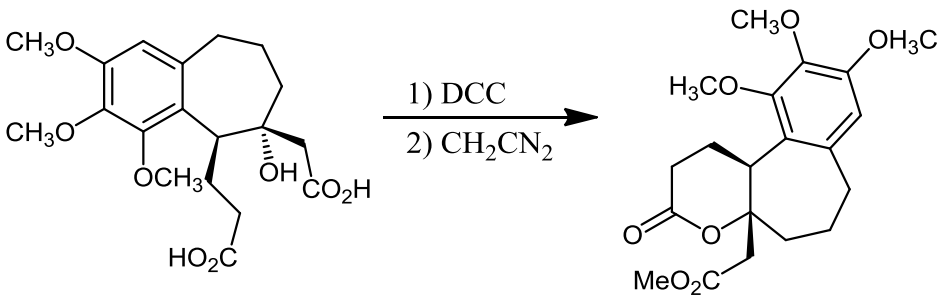


Figure 13.

II.4. The role of protecting groups in organic synthesis

When a chemical reaction has to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protecting groups (PG) have been, and are being, developed for this purpose. A protecting group must fulfil a number of requirements:

a) It must react selectively in good yield to give a protected substrate that is stable to the projected reaction.

b) The protecting group must be selectively removed in good yield by readily available and preferably non-toxic reagents that do not attack the regenerated functional group.

c) The protecting group should form a derivative (without the generation of new stereogenic centres) that can easily be separated from side products associated with its formation or cleavage.

d) The protecting group should have a minimum of additional functionalities to avoid further side reactions.

All things considered, no protecting group is the best. Currently, the science and art of organic synthesis has a long way to go before we can call it a finished and well-defined discipline, as it is amply illustrated by the extensive use of protecting groups during the synthesis of multifunctional molecules. Greater control over the chemistry used in the building of naturally occurring architecturally beautiful and diverse molecular frameworks, as well as unnatural structures, is needed when one considers the number of protection and deprotection steps often used to synthesize a molecule.

Chemists are often faced with the problem of having to use one or more protecting groups as part of a synthetic sequence. Having recognized that functional group protection is required, the chemist must decide: which protecting groups can be used and which one is most suitable for the task in hand.

A number of factors must be taken into account because the protecting group must be easily and selectively introduced at the desired site and in high yield.

Today, organic synthesis has reached a remarkable level of competence and even the complex molecules are accessible. The prerequisites for this success[179] are both the availability of a wide range of efficient synthetic methods[180] and reagents, and the fact that retrosynthetic analysis[181] can provide a framework for the design of a synthetic strategy leading to the desired product in the most efficient and logical way.

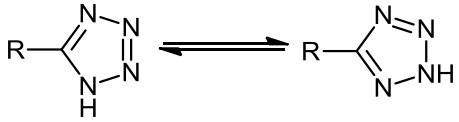
These strategies include tactics for the construction of the molecular framework, for the establishment of the absolute configuration of any stereocenter that is present, for the efficient formation of rings and for the reduction of the number of synthetic steps. The complex synthetic intermediates and products contain, in general, a multiplicity of functional groups, most of which must be blocked and, at an appropriate point in the synthesis, liberated. The correct choice of protecting groups is often decisive for the realization of the overall operation.

As a consequence of the great importance of protecting groups in organic chemistry, a multitude of blocking techniques has been developed for a wide range of functional groups. However, when giving a detailed description of successfully completed total synthesis, authors rarely comment on why they selected particular protecting group patterns. Similarly, in the monographs[182] and reviews concerning protecting group chemistry, the emphasis lies in the presentation of the various possibilities that exist for the blocking and deprotection of the function in question. Strategies that can be used to combine protecting groups in appropriate ways and that have proved their capability and reliability in complex synthesis have never been published or only for isolated cases. The protecting groups could be classified according to their liability for a more comprehensive treatment according to the functional group they block. This has the advantage that the sensitivity of the compounds to be protected and the required conditions can be accounted for in the planning of a synthesis.

Experience shows that the critical parameters are generally the stability and the cleavage of the protecting groups rather than their introduction. For most of the typically required functional groups, protecting groups are known that are labile under different, often alternative, conditions. Furthermore, unified concepts for the development of new blocking possibilities become clear as a consequence of this approach.

II.5. Protection of tetrazole ring

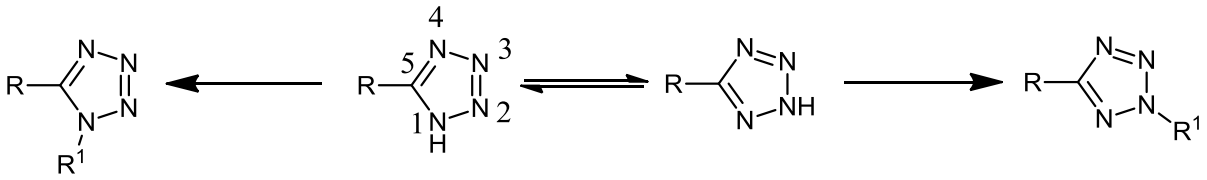
The tetrazole itself is an aromatic nucleus, which may exist in two tautomeric forms **(Figure 14)**.[1]



1H ***2H***

Figure 14. Tautomeric forms of 5-substituted tetrazoles.

Replacement of the tautomeric ring hydrogen leads to two possible type of disubstituted tetrazoles, namely the 1,5- and the 2,5-disubstituted tetrazoles, respectively the 1*N* and 2*N*-alkylated **(Scheme 31)**. The transformation of 5-substituted tetrazoles to *N*-substituted tetrazoles is fundamentally important for the preparative chemistry of tetrazoles.



Scheme 31. Structure and numbering of disubstiuted tetrazoles.

II.5.1. Chemical and Physical Proprieties of Disubstituted Tetrazoles

II.5.1.1. Physical properties

N-Unsubstituted tetrazoles are generally white solids where the hydrogen in the tetrazole ring provides intermolecular hydrogen bonding which influences the melting point. *N*-Unsubstituted tetrazoles tend to be moderately high-melting solids due to these intermolecular hydrogen bonding. Replacement of the ring NH hydrogen by a methyl causes in 1,5- and 2,5-disubstituted tetrazoles a low-melting point except where the 5-substituent itself is capable of forming hydrogen bonds (eg., OH or NH).[1] In molecules where hydrogen bonding is not possible, for example in the *N*-methyl disubstituted tetrazole series, the more polar 1,5-disubstituted form (high dipole moment) usually has a higher melting point or boiling point than the corresponding 2,5-disubstituted isomer (lower dipole moment) **(Figure 15)**. In general 1,5-disubstituted tetrazoles have a dipolar moment in the range of 5.0-5.90 D and the corresponding 2,5-derivatives have values of 2.4-2.7 D.[1]

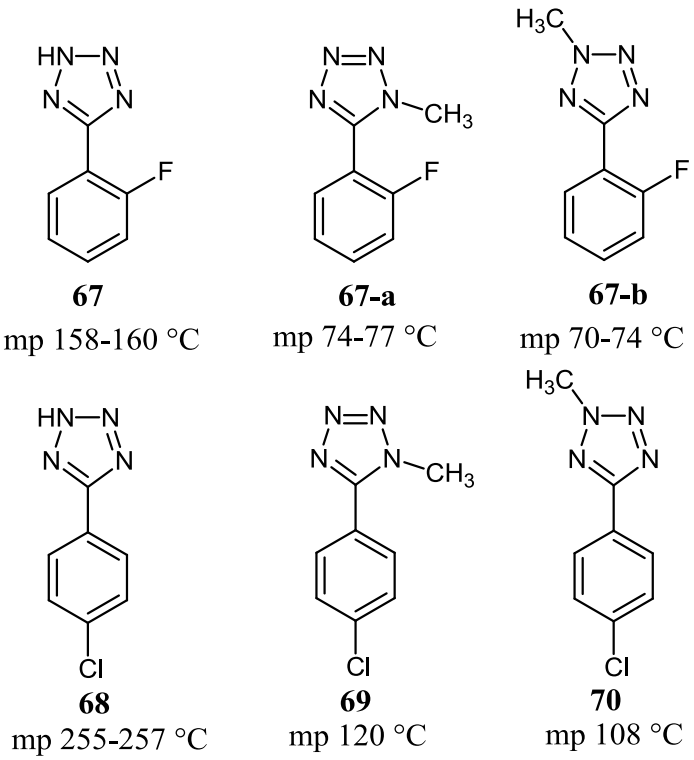


Figure 15. Examples of melting points of tetrazole series.

II.5.1.2. Solubility and chromatography

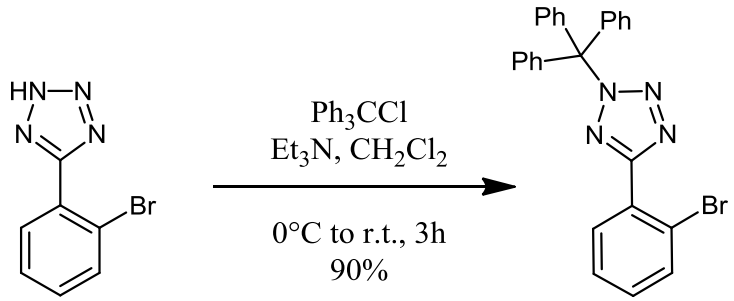
The solubility of tetrazoles is strongly influenced by the effect of carbon or nitrogen substituents on the charge distribution in the ring. In general, 2,5-disubstituted tetrazole, with low dipole moments, tend to be soluble in apolar organic solvents.[1] The different dipole moments usually ensure excellent separation of regio-isomers on silica gel columns with normal elution systems such as hexane/ethyl acetate 5:1.

II.5.2. Alkylation of Tetrazole Ring

Alkylation of 5-substituted tetrazoles is one of the most useful routes for the preparation of *N*-substituted derivatives due to the availability of various starting tetrazoles, alkylating agents and to the simplicity of the process.[32a,98,124] At the present time, introduction of an appropriate *N*-substituent into an already existing tetrazole cycle is the most common synthetic pathway to disubstituted tetrazoles.In almost all the cases alkylation of 5-substituted tetrazoles with alkyl halides give rise to mixtures of isomeric 1,5- and 2,5-disubstituted tetrazoles.[1,125] The position of substitution has been found to be sensitive to the steric requirements of the alkylating agent and to the C-5 substituent of tetrazole.[98,126] We report here some example of recent reported literatures for the alkylation of 5-substituted tetrazoles.

II.5.2.1. Alkylation of tetrazoles with Alkyl Halides

Triphenylmethyl (trityl) group is one common protecting group for tetrazole rings.[127] It is demonstrated that the alkylation of tetrazoles with triphenylchloromethane provides exclusively the N2-derivatives **(Scheme 32)**.[32a] The reaction is usually carried out in the presence of base and it is presumable that tritylation of 5-substituted tetrazoles follows S_N1 mechanism.

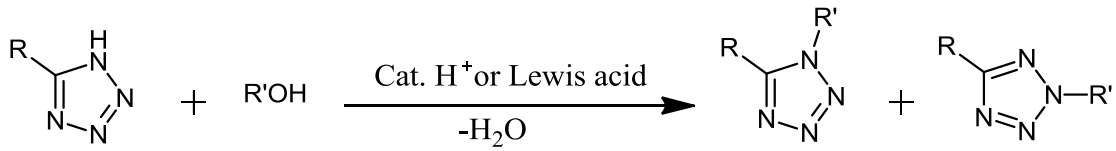


71 **72**

Scheme 32. Preparation of *N*-trityl-tetrazoles.

II.5.2.2. Alkylation of tetrazoles with alcohols

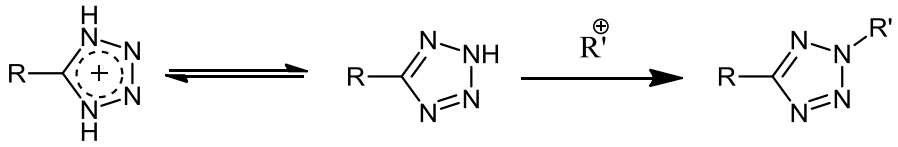
The alkylation of tetrazoles with alcohols can be performed under a variety of conditions.[124] Alcohols readily generate carbenium cations in the presence of acidic catalysts and react with *N*-unsubstituted tetrazoles yielding mixtures of 1N- and 2N-regioisomers. The reaction can be carried out in neutral organic solvents (dichloromethane, acetonitrile, chloroform) in the presence of catalytic amounts of sulphuric or a Lewis acid **(Scheme 33)**.



Scheme 33.

Formation of 2*N*-alkyl derivatives as the sole products has been reported for the reaction of 5-substituted tetrazoles with secondary and tertiary aliphatic alcohols such as *tert*-butyl alcohol in sulphuric acid media **(Scheme 34)**.[98,128,129,130] The reaction proceed at room temperature in high yields in relative short time (1-3 hours). In this acidic conditions the tetrazoles is partailly protonated to form the symmetrical 1H, 4H-tetrazolium cation, in the

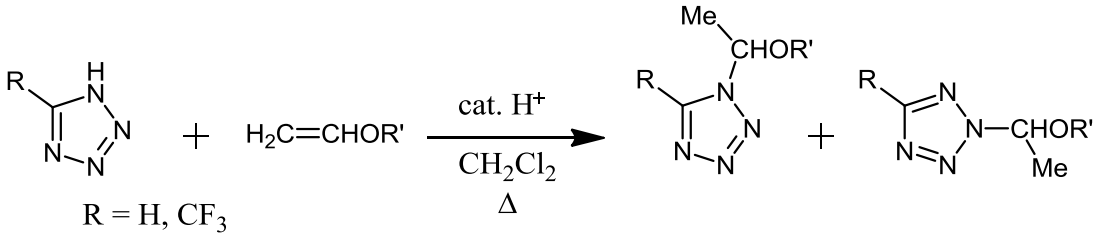
latter, only the atoms N2 and N3 are accessible for electrophilic attack whereas both N1 and N4 are blocked by the attached protons.



Scheme 34.

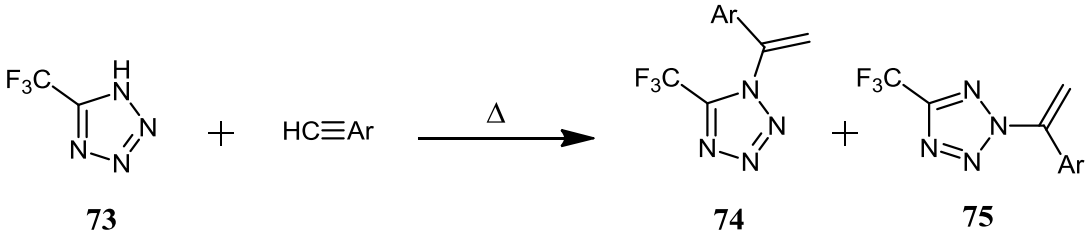
II.4.2.3. Alkylation of tetrazoles by addition of C-C multiple bonds

N-Unsbstituted tetrazoles react with vinyl ethers in acidic-catalyzed conditions. The tetrazole forms a bond with the α-carbon atom of the vinyl moiety **(Scheme 35)**. The *N*2-alkylated tetrazole is the predominantly formed products.



Scheme 35. Addition onto C=C bonds.

Addition onto the triple bonds in aryl acetilenes yields α-substituted *N*-vinyltetrazoles, but so far, only 5-trifluoromethyltetrazoles has been reported as 5-substituted starting material **(Scheme 36)**.



Scheme 36. Addition onto C≡C bonds.

II.5.3. Methylation of Tetrazole Ring

In the last years a wide variety of *N*-methyl-tetrazole derivatives has been reported from pharmaceutical companies as compounds with biological activities. In medicinal

chemistry they can find application in the treatment of pain and inflammation **76**,[131] obesity **77**,[132] HIV **78**,[133] diabete,[134] as anticancer[135] and antimicrobial agents.[136] More than 600 patent applications including *N*-methyl-tetrazole derivatives were published in the last ten years from pharmaceutical and agricultural companies and some example is shown in **(Figure 16)**.

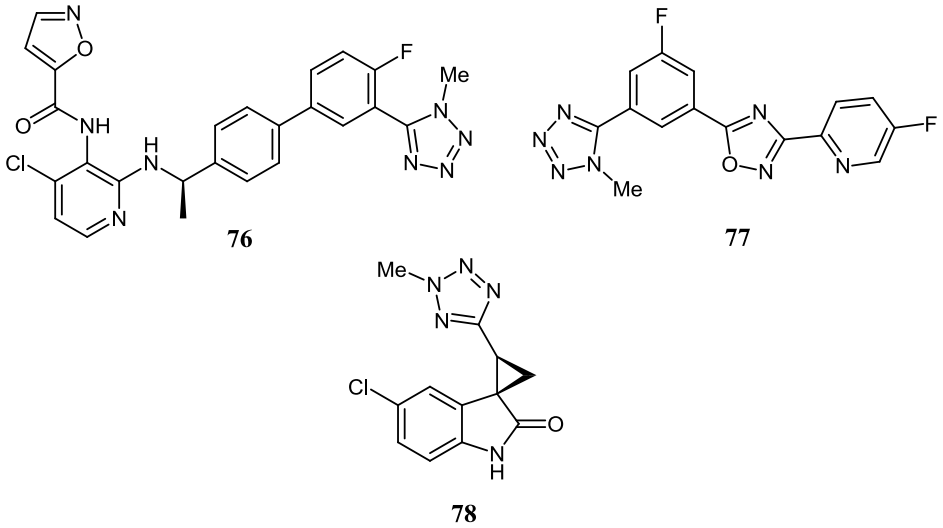


Figure 16. *N*-Methyl tetrazoles with biological activity**.**

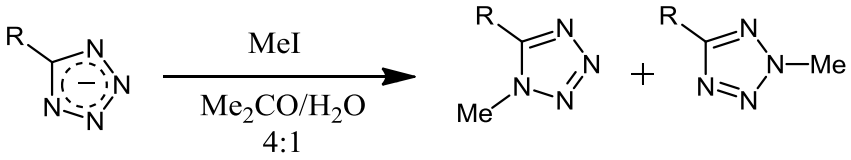
II.5.3.1. Methylation with dimethyl sulfate

Dimethyl sulphate[137] is a well known methylating agent for amines, phenols, alcohols, thiols and tetrazoles.[138,139] Typically, one methyl is removed more quickly than the other methyl group. The mechanism that typically occurs with dimethyl sulfate is an S_N2 reaction. Dimethyl sulfate is carcinogenic and toxic.[140] The toxicity of dimethyl sulfate is so extreme that some consider it a potential chemical weapon while is absorbed through the skin, mucous membranes and gastrointestinal tract. Since dimethyl sulfate is very toxic, other methylating reagents are often used. However, it is sometimes more appropriate to use dimethyl sulfate due to the effectiveness and affordability.

II.5.3.2. Methylation with methyl iodide

Methyl iodide is an excellent reagent for S_N2 substitution reactions and is a well known reagent used for methylation, like dimethyl sulfate, but is less hazardous and more expensive. Methyl iodide is a liquid with low boiling point (42.5°C) and there are some disadvantages to its use such as its toxic profile.[141] The substance can be absorbed into the body by inhalation of its vapor, by ingestion and through the skin. It is irritating to the eyes,

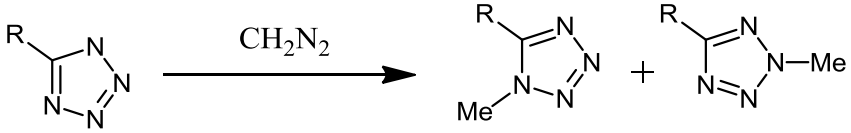
the skin and the respiratory tract and may cause effects on the central nervous system. Methylation of tetrazoles is normally carried out on the tetrazolate anion generated *in situ* by dissolution in an equimolar quantity of aqueous sodium hydroxide, with stoichiometric methyl iodide in acetone followed by heating at reflux for 3 to 18 hours **(Scheme 37)**[142] or in ethanol-water (1:1) under reflux for 12 hours[12] or with NaH in THF[143] among others.



Scheme 37. Methylation of tetrazole rings with MeI.

II.5.3.3. Methylation with diazomethane

Diazomethane is a well known methylating agent for carboxylic acids.[2] It react with 5-substituted tetrazoles to yield the corresponding disubstituted derivatives, 1*N*- and 2*N*-methyltetrazoles, in ratio close to that observed for alkylation of the respective tetrazolates with dimethylsulfate or methyl iodide[98] **(Scheme 38)**.



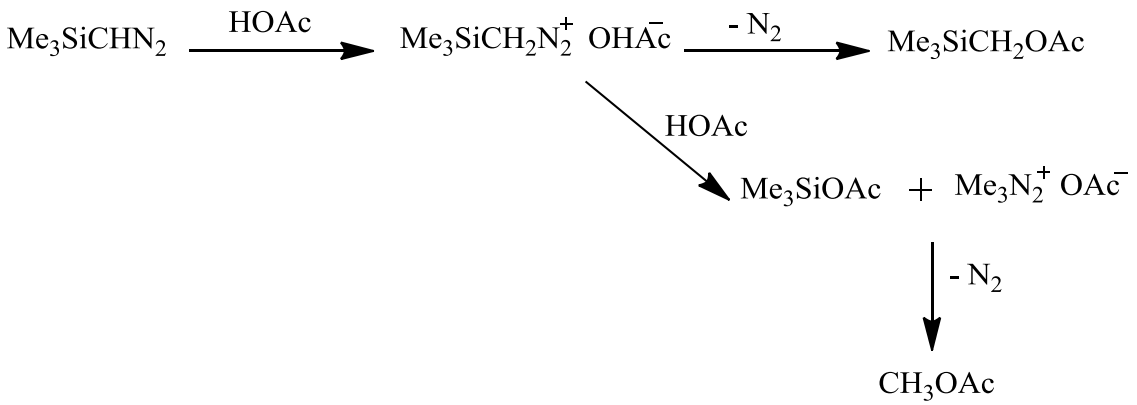
Scheme 38. Methylation of tetrazole ring with CH_2N_2.

A plausible explanation for such similarity is that the first stage of the process is a fast proton transfer from the NH-acidic heterocycles to a diazomethane molecule. Then, at the rate limiting step, the tetrazolate anion and protonated diazomethane form an ion pair.[98] The methylation of tetrazoles with diazomethane has the tendency to be currently rarely used because of its highly toxic and explosive nature. In addition, polyethylene may form as a byproduct of diazomethylation.[144]

II.5.3.4. Methylation with trimethylsilyldiazomethane

Trimethylsilyldiazomethane,[145] a greenish yellow liquid, is stable thermally and can be distilled at atmospheric pressure, is commercially available and is a safer alternative for diazomethane as methylatig agent. However the industrial use of this methylating agent is

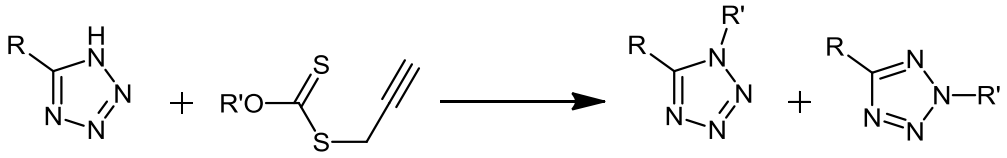
limitated by cost and by the fact that it forms numerous artifacts complicating spectra interpretation. Thus a reaction of this diazoalkane with water-free acetic acid in benzene at room temperature gave not only the expected trimethylsilylmethyl acetate but also methyl acetate and trimethylsilyl acetate **(Scheme 39)**.[146]



Scheme 39.

II.5.3.5. O-Alkyl-S-propargyl xanthates (dithiocarbonates)

Zard *et al*. reported recently esterification reagents capable of reacting with Nhacids as well[147] to methylate and benzylate 5-substituted tetrazoles **(Scheme 40)**. The methylation gives a 1 to 7 mixture of 1N- and 2N-substituted tetrazoles respectively, whereas the only reaction product detected in the benzylation is the corresponding 2-alkyl derivatives.

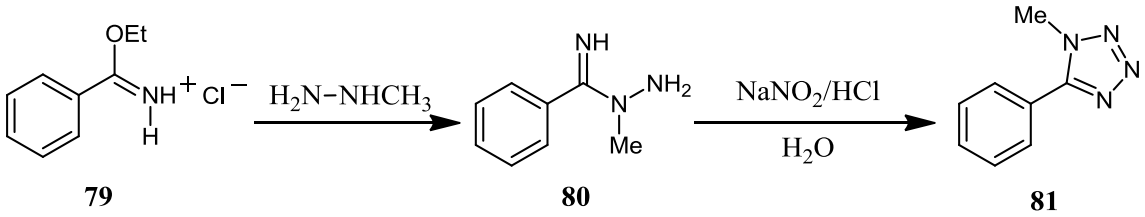


R' = Me, Bn

Scheme 40. Alkylation of tetrazoles with dithiocarbonates.

II.5.3.6. Synthesis of methyl-tetrazoles from imidates

In an extension work of Zard,[96] reaction of imidate hydrochloride salt with methyl hydrazine gives compound **80** which could be treated with sodium nitrite in diluted hydrochloric acid to give the 1*N*-methyl-5-phenyltetrazole in good yield. This approach is complementary to the direct methylation of the free tetrazole ring which leads to a mixture of isomers where the 2*N*-isomer dominates **(Scheme 41)**.



79 **80** **81**

Scheme 41. Synthesis of 1N-methyl-5-phenyltetrazoles from imidates

II.6. Results and Discussion

In the recent years, protection of N-H bonds in nitrogen-containing heterocycles by introduction of a triphenylmethyl (trityl) group has received increasing application.

In the course of our investigation towards the protection or alkylation of *N*-unsubstituted tetrazoles moiety, we demonstrate the possibility of using trityl group as a more accessible and cheaper tritylating agent to protect a variety of tetrazoles including *tert*-butyl-, benzyl-, alkyl- and aromatic derivatives.

The reaction smoothly proceeds in CH_2Cl_2 in the presence of Et_3N and 4-(dimethylamino)pyridine at r.t to get tritylated tetrazoles **1a-1l.** The 5-regioismer are generally more polar and they have a higher melting point. Therefore, the regioisomers can be distinguished with a high reliability and, generally, they can be isolated in good yields by simple chromatography on silica gel.

For the preparation of the ditritylated compound **1g**, the amounts of the reagents and solvents used were double those indicated above. In all cases the reaction was quenched with H_2O.

Table 12 summarizes the physical properties of products prepared as well as achieved yields.

Table 12: physical properties of protected tetrazoles.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**1a**	overnight	156-158	95
2	**1b**	overnight	180-184	67
3	**1c**	overnight	160-164	88
4	**1d**	overnight	132-136	69
5	**1e**	overnight	76-80	83
6	**1f**	overnight	126-128	85
7	**1g**	overnight	220-222	25
8	**1i**	overnight	172-174	69
9	**1j**	overnight	190-194	62
10	**1k**	overnight	164-166	61
11	**1l**	overnight	170-172	71

Note: Yield after extraction and crystallisation

The spectral data (IR, ^{1}H NMR, ^{13}C NMR and Element analysis) verified the structure of compounds **1a-1l**.

IR Spectroscopy

IR spectrums of all compounds showed disappearance of NH peak at 2987-3336 cm^{-1}.

^{1}H NMR Spectroscopy

Compound (1a)

The spectrum of this compound showed the presence of two multiplets (m), first at [7.13-7.47] ppm with integration 18H and second at [8.12-8.16] ppm with integration 2H.

Compound (1b)

The analysis of this spectrum showed a a singlet (s) absorption band for group CH_3 at 2.19 ppm and aromatic protons appear at [6.82-7.84] ppm which appears as three multiplets (m), first at [6.82-6.95] ppm with integration 9H, second at [7.17-7.40] ppm with integration 13H, third at [7.17-7.40] ppm with integration 1H.

Compound (1c)

The spectrum showed the singlet (s) at 4.28 ppm due to CH_2, the other aromatic protons appears as two multiplets (m) at [7.08-7.12] ppm and [7.23-7.37] ppm.

Compound (1d)

The spectrum of this product showed a singlet (s) at 1.94 ppm due to three CH_3 and a multiplet (m) at [7.01-7.26] ppm with integration 15H.

Compound (1e)

The protons of this compound appear at [0.87-7.36] ppm which multiplicity appears as follows:

- Tow triplet (t): first at 0.87 ppm with coupling constant J= 6.8 Hz, and second at 2.90 ppm with coupling constant J= 7.6 Hz.
- Three multiplets (m) two at [1.27-1.79] ppm corresponding to protons of CH_2 and the other at [7.07-7.36] ppm corresponding to aromatic protons.

Compound (1f)

The protons of this compound appear at [6.79-8.36] ppm which multiplicity appears as follows:

- Two multiplets (m): the first at [6.79-6.94] ppm with integration 15H, and second at [7.17-7.21] ppm with integration 1H.
- Triply of doublet (td) at 7.64 ppm with coupling constant *J*= 7.8, 1.6 Hz.
- Two doublet (d) one at 7.80 ppm with coupling constants *J*= 7.9 Hz and the other at 8.36 ppm coupling constants *J*= 4.4 Hz.

Compound (1g)

The spectrum of this product showed a singlet (s) at 6.82 ppm characteristic of the NH proton. The other aromatic carbons appear in the area [6.84-7.40] ppm.

Compound (1i)

The spectrum of this compound showed presence of singlet (s) band at 5.85 ppm belongs to CH_3 group. The aromatic protons appear at [7.09-7.38] ppm.

Compound (1j)

The spectrum of this compound showed two singlets (s): the first at 1.22 ppm corresponding to protons of three CH_3, and the second at 4.14 ppm corresponding to the protons of CH_2. Also this spectrum showed aromatic protons as multiplet at [7.10-7.35] ppm.

Compound (1k)

The spectrum of this compound showed singlet band at 5.88 ppm belong to CH. Also this spectrum showed the multiplet (m) at [7.13-7.38] ppm due to the 25 aromatic protons.

Compound (1l)

Aromatic protons appear at [7.45-8.94] ppm which multiplicity appears as follows:

- Doublet of doublet (dd) at 8.03 ppm with coupling constants *J*= 4.8, 4.2 Hz with integration 1H.
- Two multiplets (m) first at [7.23-7.45] ppm with integration 21H, and second at [7.40-7.73] ppm with integration 1H.
- Singulet (s) at 8.57 ppm with integration 1H.

The results of ^{1}H NMR of products are summarized in **Table 13**.

Table 13: ^{1}H NMR for tritylated tetrazoles.

Compounds	CH	CH_2	CH_3	H_{arom}
1a	---	---	---	7.13-7.47, m, 18H; 8.12-8.16, m, 2H
1b	---	---	2.19, s, 3H	6.82-6.95, m, 9H; 7.17-7.40, m, 13H; 7.81-7.84, m, 1H
1c	---	4.28, s, 2H	---	7.08-7.12, m, 6H; 7.23-7.37, m, 14H
1d	---	---	1.34, s, 9H	7.01-7.26, m, 15H
1e	---	1.27, m, 16H; 1.72-1.79, m, 2H; 2.90, t, *J*= 7.6 Hz, 2H	0.87, t, *J*= 6.8 Hz 3H	7.07-7.36, m, 15H
1f	---	---	---	6.79-6.94, m, 15H; 7.17-7.21, m, 1H, 7.64, td, *J*= 7.8, 1.6 Hz, 1H; 7.80, d, *J*= 7.9 Hz, 1H; 8.36, d, *J*= 4.4 Hz, 1H
1g	---	---	---	6.84-7.40, m, 30H
1i	---	---	2.56, s, 3H	7.09-7.12, m, 6H; 7.21-7.38, m, 9H
1j	---	4.17, s, 2H	1.22, s, 9H	7.10-7.35, m, 15H
1k	5.88, s, 1H	---	---	7.13-7.38, m, 25H
1l	---	---	---	7.23-7.45, m, 21H; 7.70-7.73, m, 1H; 8.03, dd, *J*=4.8, 4.2 Hz, 1H; 8.57, s, 1H

Notes: ^{1}HNMR: (300 MHz, $CDCl_3$).

^{13}C NMR Spectroscopy

In the spectrums of all compounds the signal of C-5 is located at about [150.1-166.2] ppm and aromatic carbons appears at [51.6-154.1] ppm.

The chemical shifts of the major peaks appeared in the spectrums are reported in **Table 14.**

Table 14: ^{13}C NMR fortritylated tetrazoles.

Compounds	C	CH	CH_2	CH_3	C=O	C_{arom}
1a	164.2	---	---	---	---	83.3 -150.8
1b	164.3	---	---	21.3	---	83.0-154.1
1c	164.6	---	32.0	---	---	83.0-141.5
1d	41.7; 162.1	---	---	30.0	---	82.8-141.5
1[e]	166.2	---	22.8-39.7	14.3	---	82.7-141.6
1f	150.1	---	---	---	---	51.6-143.6
1g	165.1	---	---	---	---	71.7-147.8
1i	162.1	---	---	11.4	---	82.8-141.5
1j	44.0; 162.1	---	32.2	25.8	209.3	82.8-141.5
1k	165.1	50.9	---	---	---	82.1-147.8
1l	162.6	---	---	---	---	83.7-147.0

Notes: $^{13}CNMR$: (75 MHz, $CDCl_3$).

Element analysis

The Element analysis of compounds **1d, 1e, 1f, 1g, 1i, 1j, 1k** and **1l** are reported in **Table 15.**

Table 15. Element analysis of compounds **1d, 1e, 1f, 1g, 1i, 1j, 1k** and **1l**

Compounds	Calcd			Found		
	C	H	N	C	H	N
1d	78.23	6.57	15.21	78.26	6.55	15.23
1[e]	79.79	8.21	12.01	79.76	8.22	12.03
1f	77.10	4.92	17.98	77.08	4.88	18.00
1g	82.22	5.48	12.29	82.22	5.46	11.24
1i	77.28	5.56	17.17	77.41	5.57	17.41
1j	76.07	6.38	13.65	76.09	6.37	13.68
1k	82.82	5.48	11.71	82.80	5.46	11.69
1l	83.58	4.95	11.47	83.55	4.91	11.50

II.7. Conclusion

The trityl (triphenylmethyl) group has been used to protect a variety of amines,[148] and especially amino acids in the synthesis of peptides[149] and cephalosporins.[150] Sartans area class of drugs those are effective in treating hypertension and heart failure. These drugs block the reninangiotensin system and represent one of the most significant therapeutic interventions available for the treatment of hypertension.[150] There are about seven sartans in clinical practice, of which five of them possess a tetrazole moiety in their structure. The protection and deprotection of the N-atom of the tetrazole moiety becomes essential during the synthesis of these sartan drugs.[151]

The role of the trityl group is to create steric hindrance around the nitrogen atom, which reduces the nucleophilicity of the latter.

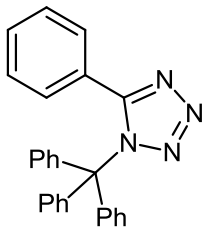
In this chapter we have prepared a wide variety of N-tritylated tetrazoles **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, **1g**, **1i**, **1j**, **1k** and **1l** with greater yields. The general protocols for the tritylation of tetrazole rings suffer from several disadvantages such as the high toxic profile of water waste and possible presence of byproducts. The reaction occurs long time at room temperature. A simple work-up procedure gives N-tritylated tetrazole derivatives which are generally separated by chromatography on silica gel.

II.8. Experimental part

General procedure

A solution of the corresponding tetrazoles (10.0 mmol) in CH_2Cl_2 (5 mL) was added to a solution of trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at r.t. and the mixture was stirred overnight. The reaction was then quenched with H_2O (5 mL) and extracted with EtOAc (3x15 mL) and the combined organic phases were washed with brine (5 mL) and dried (Na_2SO_4). After evaporation of the solvents, the resulting residue was purified by recrestalisation (hexane–EtOAc) affording the expected trityltetrazole.

Synthesis of 5-phenyl-1-trityl-1H-tetrazole (1a)[152]

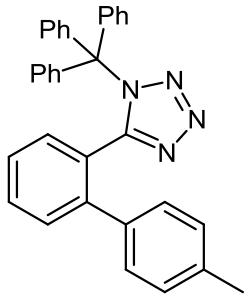


1a

Following the general procedure, the reaction of 5-phenyl-1*H*-tetrazole (0.46 g, 10 mmol), trityl chloride (0.78 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1a** as a White solid.

- **Yield**= 95% (3.69 g).
- **Mp**= 156-158°C.
- **IR (KBr):** 1491, 1447, 1189, 1026, 876, 762, 747, 729, 693 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 7.13-7.47 (m, 18H), 8.12-8.16 (m, 2H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 83.3 (C), 127.2 (2xCH), 127.7 (3xCH), 127.9 (6xCH), 128.9 (C), 130.5 (6xCH), 141.5 (CH), 145.3 (2xCH), 150.8 (3xC),164.2 (C).

Synthesis of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1H-tetrazole (1b)[153]

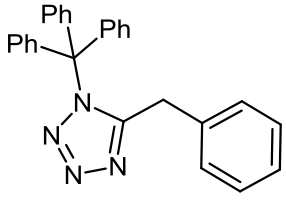


1b

Following the general procedure, the reaction of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole (1.47 g, 10 mmol), trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1b** as a white solid.

- **Yield**= 67% (3.21 g).
- **Mp**= 180-184°C.
- **IR (KBr):** 3056, 1445, 1028, 827, 748, 698, 640 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 2.19 (s, 3H), 6.82-6.95 (m, 9H), 7.17-7.40 (m, 13H), 7.81-7.84 (m, 1H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 21.3 (CH_3), 83.0 (C), 126.6, 127.4, 127.7, 128.1, 128.2, 128.3 (4C), 129.2, 129.3 (6C), 129.4, 130.4, 130.5, 130.8, 136.5 (23xCH), 138.3 (C), 141.4 (C), 142.4 (C), 147.0 (C), 154.1 (3xC), 164.3 (C).

Synthesis of 5-benzyl-1-trityl-1H-tetrazole (1c)[154]

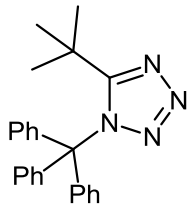


1c

Following the general procedure, the reaction of 5-benzyl-1*H*-tetrazole (1.47 g, 10 mmol), trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1c** as a white solid.

- **Yield**= 88% (3.54 g).
- **Mp**= 160-164°C.
- **IR (KBr):** 1530, 1252, 1073, 889, 733, 694 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 4.28 (s, 2H), 7.08-7.12 (m, 6H), 7.23-7.37 (m, 14H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 32.0 (CH_2), 83.0 (C), 126.8 (CH), 127.8 (3xCH), 128.1 (6xCH), 128.8 (2xCH), 129.1 (2xCH), 130.0 (6xCH), 137.0 (C), 141.5 (3xC), 164.6 (C).

Synthesis of 5-(tert-butyl)-1-trityl-1H-tetrazole (1d)[155]

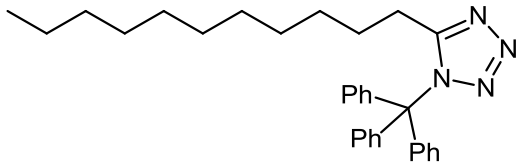


1d

Following the general procedure, the reaction of 5-(*tert*-butyl)-1*H*-tetrazole (0.63 g, 10 mmol), trityl chloride (1.4 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4 (dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1d** as a white solid.

- **Yield**= 69% (2.54 g).
- **Mp**= 132-136°C.
- **IR (KBr):** 3005, 2605, 1578, 1565, 1386, 1255, 1112, 1052, 899, 683, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 1.34 (s, 9H), 7.01-7.26 (m, 15H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 30.0 (3xCH_3),41.7 (C), 82.8 (C), 127.4 (3xCH), 127.8 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C).
- **Anal. Calcd for $C_{24}H_{24}N_4$:** C, 78.23; H, 6.57; N, 15.21. **Found:** C, 78.26; H, 6.55; N, 15.23.

Synthesis of 1-trityl-5-undecyl-1H-tetrazole (1e)[155]

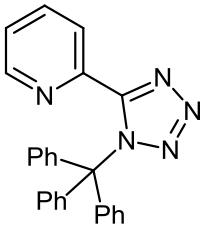


1e

Following the general procedure, the reaction of 5-undecyl-1*H*-tetrazole (0.63 g, 10 mmol), trityl chloride (1.4 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1e** as a Brawn solid.

- **Yield**= 83% (3.87 g).
- **Mp**= 76-80°C.
- **IR (KBr):** 2922, 2850, 1493, 1444, 747, 698 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 0.87 (t, *J*= 6.8 Hz, 3H), 1.27 (m, 16H), 1.72-1.79 (m, 2H), 2.90 (t, *J*= 7.6 Hz, 2H), 7.07-7.36 (m, 15H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 14.3 (CH_3), 22.8, 29.2, 29.4, 29.7, 29.8, 32.2, 39.7 (C), 82.7 (C), 127.9 (5xCH), 128.2, 128.4, 128.7, 129.9, 130.3 (6xCH), 141.6 (3xC), 166.2 (C).
- **Anal. Calcd for $C_{31}H_{38}N_4$:** C, 79.79; H, 8.21; N, 12.01. **Found:** C, 79.76; H, 8.22; N, 12.03.

Synthesis of 2-(1-trityl-1H-tetrazol-5-yl)pyridine (1f)[155]



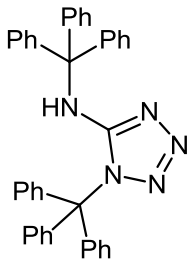
1f

Following the general procedure, the reaction of 2-(1*H*-tetrazol-5-yl)pyridine (1.47 g, 10 mmol), trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1f** as a pink solid.

- **Yield**= 85% (3.31 g).

- **Mp**= 126-128°C.
- **IR (KBr):** 1489, 1446, 1072, 747, 698 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 6.79-6.94 (m, 15H), 7.17-7.21 (m, 1H), 7.64 (td, *J*= 7.8, 1.6 Hz, 1H), 7.80 (d, *J*= 7.9 Hz, 1H), 8.36 (d, *J*= 4.4 Hz, 1H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 51.6 (C), 86.4 (CH), 122.6 (CH), 126.1 (CH), 127.0 (3xCH), 127.9 (6xCH), 128.2 (6xCH), 137.0 (3xC), 138.2 (C), 143.6 (C), 150.1 (CH).
- **Anal. Calcd for $C_{25}H_{19}N_5$:** C, 77.10; H, 4.92; N, 17.98. **Found:** C, 77.08; H, 4.88; N, 18.00.

Synthesis of N,1-dityrityl-1H-tetrazol-5-amine (1g)[155]

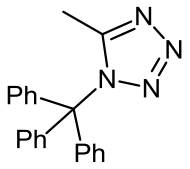


1g

Following the general procedure, the reaction of 1*H*-tetrazol-5-amine (0.85 g, 10 mmol), trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1g** and **1h** as a white solid.

- **Yield**= 25% (1.42 g).
- **Mp**= 220-222°C.
- **IR (KBr):** 1560, 1493, 1446, 1184, 881, 743, 696, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 6.82 (s, 1H), 6.84-7.40 (m, 30H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 71.7 (C), 82.1 (C), 125.9, 126.4, 126.8, 127.6, 127.8, 127.9, 128.0 (5C), 128.4 (6C), 129.0 (5C), 129.6 (6C), 130.1, 141.5 (30xCH), 144.8 (3xC), 147.8 (3xC), 165.1 (C).
- **Anal. Calcd for $C_{39}H_{31}N_5$:** C, 82.22; H, 5.48; N, 12.29. **Found:** C, 82.22; H, 5.46; N, 11.24.

Synthesis of 5-methyl-1-trityl-1H-tetrazole (1i)[155]

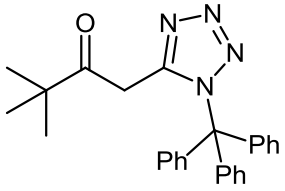


1i

Following the general procedure, the reaction of 5-methyl-1*H*-tetrazole (0.84, 10 mmol), trityl chloride (0.92 g, 11 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1i** as a white solid.

- **Yield**= 69% (2.25 g).
- **Mp**= 172-174°C.
- **IR (KBr):** 1507, 1492, 883, 748, 696, 635 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 2.56 (s, 3H), 7.09-7.12 (m, 6H), 7.21-7.38 (m, 9H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 11.4 (CH_3), 82.8 (C), 126.9 (3xCH), 128.1 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C).
- **Anal. Calcd for $C_{21}H_{18}N_4$:** C, 77.28; H, 5.56; N, 17.17. **Found:** C, 77.41; H, 5.57; N, 17.41.

Synthesis of 3,3-dimethyl-1-(1-trityl-1H-tetrazol-5-yl)butan-2-one (1j)[155]



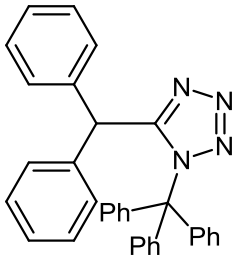
1j

Following the general procedure, the reaction of 3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (1.52 g, 10 mmol), trityl chloride (1.6 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1j** as a pink solid.

- **Yield**= 62% (2.55 g).
- **Mp**= 190-194°C.
- **IR (KBr):** 1714, 1445, 1057, 882, 752, 697 cm^{-1}.

- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 1.22 (s, 9H), 4.17 (s, 2H), 7.10-7.35 (m, 15H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 82.8 (C), 127.4 (3xCH), 127.8 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C), 209.3 (C=O).
- **Anal. Calcd for $C_{26}H_{26}N_4O$:** C, 76.07; H, 6.38; N, 13.65. **Found:** C, 76.09; H, 6.37; N, 13.68.

Synthesis of 5-benzhydryl-1-trityl-1H-tetrazole (1k)[155]

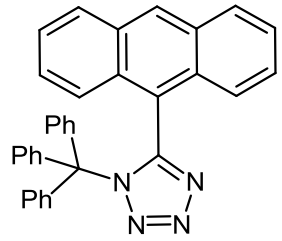


1k

Following the general procedure, the reaction of 5-benzhydryl-1*H*-tetrazole (2.36 g, 10 mmol), trityl chloride (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1k** as a Yellow solid.

- **Yield**= 61% (2.92 g).
- **Mp**= 164-166°C.
- **IR (KBr):** 1492, 1445, 1048, 748, 697, 639 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 5.88 (s, 1H), 7.13-7.38 (m, 25H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 50.9 (CH), 82.1 (C), 125.9, 126.4, 126.8, 127.4 (2C), 127.6 (4C), 127.8 (3C), 127.9, 128.1, 128.4 (6C), 129.0, 129.6, 130.1, 141.5, 144.0 (25xCH), 144.8 (C), 147.0 (2xC), 165.1 (3xC).
- **Anal. Calcd for $C_{33}H_{26}N_4$:** C, 82.82; H, 5.48; N, 11.71. **Found:** C, 82.80; H, 5.46; N, 11.69.

Synthesis of 5-(anthracen-9-yl)-1-trityl-1H-tetrazole (1l)[155]



1l

Following the general procedure, the reaction of 5-(anthracen-9-yl)-1*H*-tetrazole (1.39 g, 10 mmol), trityl chloride (1.47 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1l** as a Green solid.

- **Yield**= 71% (3.71 g).
- **Mp**= 170-172°C.
- **IR (KBr):** 1491, 1447, 1189, 876, 762, 747, 694 cm^{-1}.
- **^{1}HNMR: (300 MHz, $CDCl_3$):** δ= 7.23-7.45 (m, 21H), 7.70-7.73 (m, 1H), 8.03 (dd, *J*=4.8, 4.2 Hz, 1H), 8.57 (s, 1H).
- **^{13}CNMR: (75 MHz, $CDCl_3$):** δ= 83.7 (C), 125.6 (2xCH), 126.8 (2xC), 127.4 (2xC), 128.0 (3xCH), 128.1 (CH), 128.2 (6xCH), 128.6 (2xCH), 128.7 (2xCH), 130.4 (6xCH), 131.3 (C), 141.6 (2xC), 147.0 (3xC), 162.6 (C).
- **Anal. Calcd for $C_{34}H_{24}N_4$:** C, 83.58; H, 4.95; N, 11.47. **Found:** C, 83.55; H, 4.91; N, 11.50.

Chapter 03: Detritylation of protected tetrazoles by naphthalene-catalysed lithiation

Introduction

The importance of lithium derivatives continues to grow due to the versatility of these reagents in the synthesis of novel inorganic, organometallic, organic, and bioorganic compounds. This widespread use, together with the peculiar properties of lithium due to its small size, has led to a considerable interest in the generation, structures, and reactivity of organolithium compounds. The great volume of experimental and theoretical work makes lithium chemistry a branch of chemistry in itself.[156]

The replacement of hydrogen by lithium in an organic compound is a versatile method for preparing organolithium compounds. The general principle involved in this reaction is, on the one hand, the use of a relatively strongly acidic hydrocarbon (p*K*a ≤ 33) or the presence in the α- or β-position of a heteroatom that increases the kinetic and/or thermodynamic acidity of a particular hydrogen atom, and, on the other hand, the use of a strong base such as an organolithium compound or a lithium amide. However, this method is not available for a wide range of organic starting materials. Another important method for preparing organolithium derivatives is by lithium-halogen exchange. However, this method has some disadvantages because it is an equilibium process, which makes the reaction useful only for synthesizing organolithium compounds whose structure enables them to accommodate partial carbanionic character better than the starting organolithium compounds (usually commercially available alkyllithiums). Thus, it is particularly useful for preparing aryl- and 1-alkenyllithium derivatives from the corresponding iodo or bromo derivatives of arenes and alkenes; the corresponding chloro derivatives, however, usually give poor results. Moreover, coupling of the starting organolithium compound with the alkyl halide to give the Wurtz-type product cannot be ignored, although this disadvantage can be partly overcome by using two equivalents of the starting alkyllithium. Other methods for the preparation of organolithium derivatives, starting from other organometallic compounds, from sulfonylhydrazones, or by the addition of organolithium compounds to carbon-carbon multiple bonds, are of less general applicability.

Due to the above mentioned reasons, among the many different methods for preparing organolithium compounds,[157] the direct reduction of organic halides by treatment with lithium metal is the most direct and versatile procedure. However, the use of polylithiated organic compounds or their functionalized derivatives in organic synthesis has emphasized the need for new methods of preparing these intermediates,[158] which often cannot be obtained from

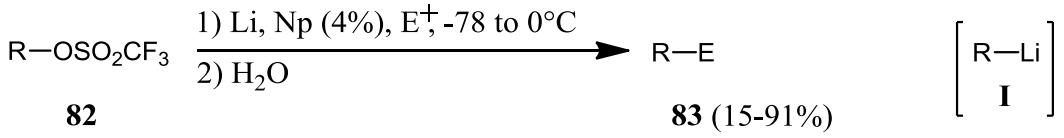
lithium metal alone. To this end, several methods have been described involving activation of the metal,[159] the most popular among these perhaps being to dissolve the lithium metal in a stoichiometric amount of certain arenes,[160] usually naphthalene (Np) or 4,4'-di-*tert*-butylbiphenyl (DTBB). An improvement on this method is the use of sub-stoichiometric amounts of the arenes,[161] this method also being used to prepare highly reactive metals.[162] In this way, some of the problems of obtaining by-products, arising from the reaction of arene anions, may be overcome. The reactivity of this mixture (lithium powder and a catalytic amount of an arene) is different and, in general, is much higher than that in other lithiation procedures. Investigation into the use of arenes as electron shuttles in the preparation of organolithium compounds has been an ongoing concern in these laboratories for some time now.[163] This chapter focuses on efforts made in the last few years to use this lithiation mixture for improving known processes and, perhaps more interestingly, to perform new lithiation processes, which are difficult or impossible to achieve by other methods.

III.1. Organolithium compounds from Non-Halogenated Materials

Although the reduction of halogenated compounds with lithium is the most direct way of preparing organolithium derivatives, in some cases the preparation of the appropriate halogenated starting material is difficult or impossible, or the presence of the halogen may even be unsuitable. To overcome this problem, certain functionalities other than halogen may be used as leaving groups in the process of organolithium derivative preparation.[164]

III.1.1. Reductive Carbon-Oxygen Cleavage

Alkyl triflates **82** are formally transformed into the corresponding alkyllithium **I** by a lithiation reaction catalyzed by naphthalene and these intermediates react *in situ*, under barbier-type conditions,[165] with various electrophiles such as aldehydes, ketones, imines, amides, or disulfides to give, after hydrolysis, the expected products **83**,[166] this method representing a new indirect transformation of alcohols into the corresponding organolithium derivatives **(scheme 42)**.

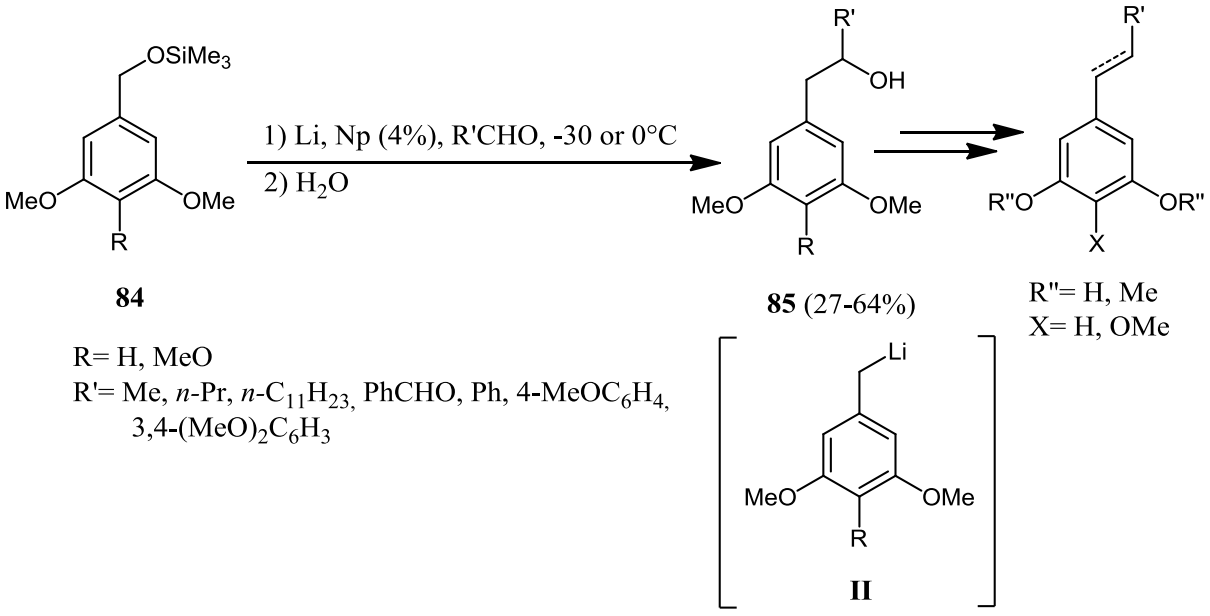


82 **83** (15-91%)

R= Me, Et, *n*-C_6H_{13}, $MeC{\equiv}C(CH_2)_2$
E^+= *t*-BuCHO, PhCHO, 4-$MeOC_6H_4CHO$, $Me(CH_2)_6CHO$, $(CH_2)_5CO$, $(c\text{-}C_3H_5)_2CO$, PhCOMe, 4-MeC_6H_4COPh, *n*-$C_8H_{17}CON(CH_2)_4$, $(PhCH_2S)_2$

Scheme 42.

O-Silylated benzylic alcohols **84** can be used as starting materials in the formal preparation of bynzyllithiums **II** through a naphthalene-catalyzed lithiation. Their reaction with aldehydes under Barbier-type conditions gives the expected 2-phenylethanol derivatives **85 (Scheme 43)**, which are easily transformed into several 5-substituted resorcinols such as olivetol, grevillol, dihydropinosilvine, pinosilvine, resveratrol, piceatannol, combretastatin, B-4 tetramethyl ether, or chrysotobibenzyl,[167] these compounds possessing a wide variety of biological activities.



84

R= H, MeO
R'= Me, *n*-Pr, *n*-$C_{11}H_{23}$, PhCHO, Ph, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$

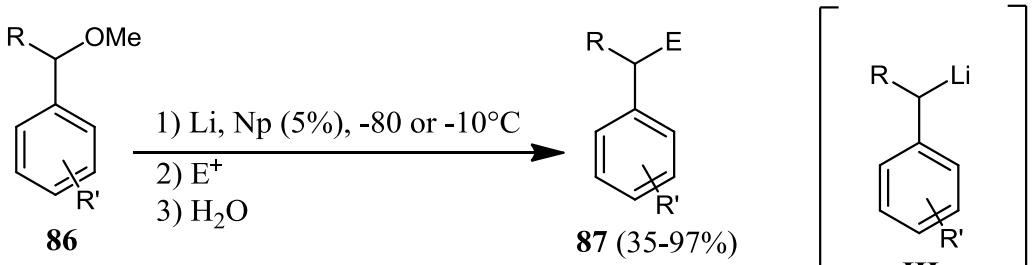
85 (27-64%)

R"= H, Me
X= H, OMe

Scheme 43.

Another possible means of preparing these benzyllithium derivatives has been reported.[158] in this case, several benzyl methyl ethers **86** can be used as starting materials, which are reduced using an excess of lithium and catalytic amount of naphthalene, leading to

the formation of the corresponding benzyllithium derivatives **III**. These then react with various electrophiles giving, after hydrolysis, the expected compounds **87 (Scheme 44).**

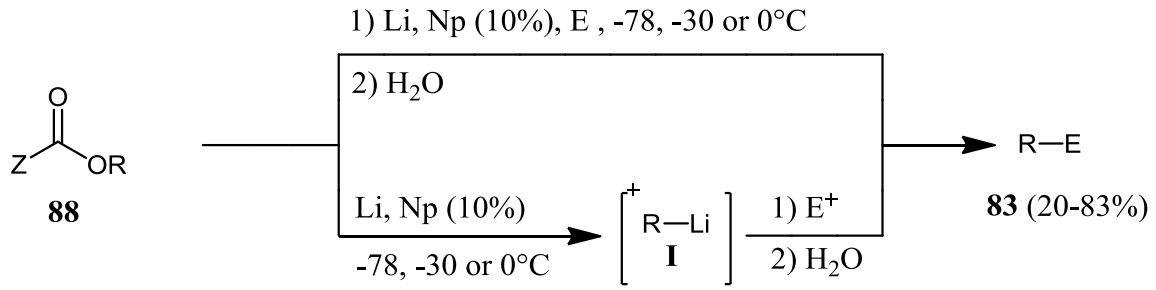


86 **87** (35-97%) **III**

R= H, Me
R'= Me, MeO, Me_2N, F
E= D_2O, MeI, *n*-BuBr, *t*-BuCHO, PhCHO

Scheme 44.

Benzyl or allyllithium derivatives can also be prepared from the corresponding pivalates, carbonates, or *O*-benzyl carbamates **88**.[169] Thus, their naphthalene-catalyzed reduction gives the expected organolithium compounds **I**, which either in a two-step reaction or under Barbier-type conditions, are trapped with electrophiles to yield after hydrolysis the expected products **83 (Scheme 45)**. Two aspects of these reactions must be pointed out: firstly, the reaction generally gives better yields under Barbier-type conditions, and secondly, when the reaction is performed using symmetrical carbonates only one of the two possible equivalents of the corresponding organolithium **I** is generated, probably due to decomposition of the allyl- or benzyllithium carbonate intermediate, yielding carbon dioxide and the corresponding lithium alcoholate.



88 **83** (20-83%)

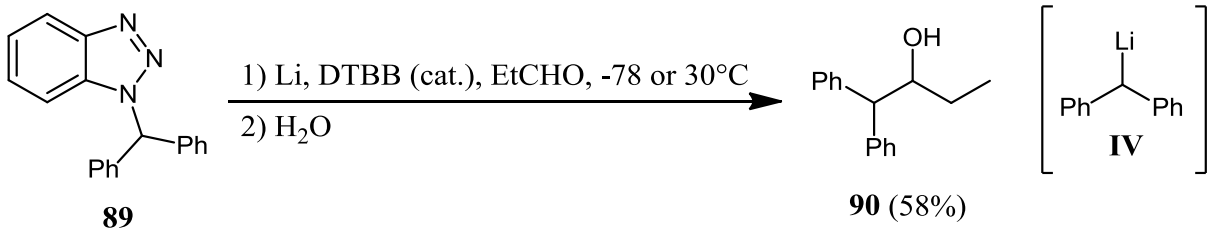
R= CH_2=$CHCH_2$, geranyl, Bzl, PhCHMe
Z= *t*-Bu, CH_2=$CHCH_2O$, *t*-BuCO, BzlO
E^+= Me_3SiCl, *i*-PrCHO, *t*-BuCHO, PhCHO, MeCO, Et_2CO, $(CH_2)_2CO$, Ph_2CO

Scheme 45.

III.1.2. Reductive Carbon-Nitrogen Cleavage

N-allyl and *N*-benzyl triflamide derivatives may be used as starting materials for preparing the corresponding allyl- or benzyllithium derivatives. Their reactions with lithium powder and a catalytic amount of naphthalene in the presence of electrophiles such as aldehydes and ketones give after hydrolysis, the expected products in 25-94% yield.[166] it is worthy of note that in this case, when the reaction is performed using *N*,*N*-diallyl triflamide, two equivalents of the expected allyllithium are generated.

Another nitrogen-containing functionality, playing the role of a leaving group in a reduction catalyzed by DTBB, is benzotriazole.[170] Reaction of the benzotriazole derivative **89** with an excess of lithium and a catalytic amount of DTBB in the presence of propionaldehyde gives, after hydrolysis, the expected 1,1-diphenyl-2-butyl alcohol **90**, as well as some diphenylmethane, probably due to the abstraction of a proton from the medium by the corresponding organoli-thium **IV (Scheme 46).**



89 **90** (58%)

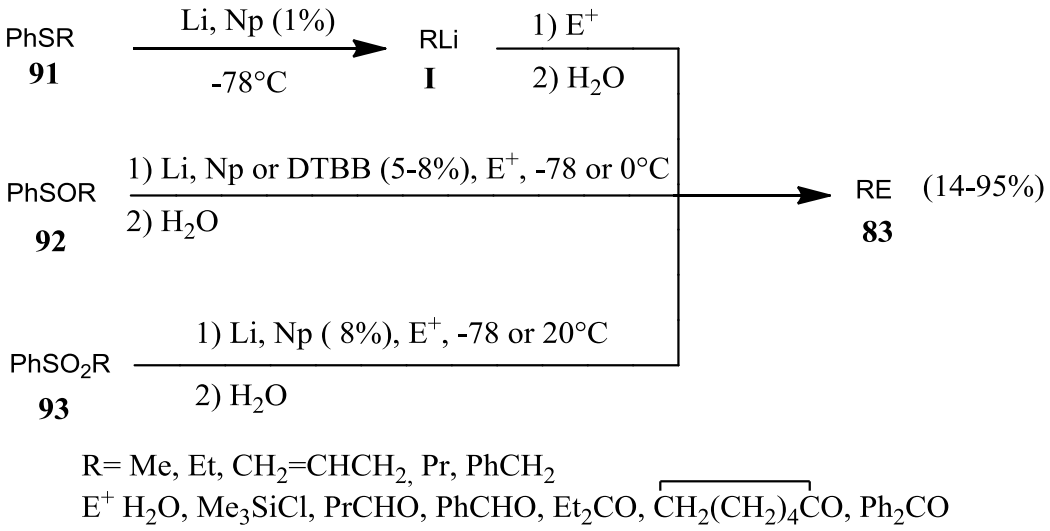
Scheme 46.

Finally, *N*-benzyl pivalamide, urea, or carbamate derivatives may be lithiated in naphthalene-catalyzed processes to give the corresponding benzyllithium intermediates of type **I**, which can be trapped in Barbier-type reactions with electrophiles such as aldehydes or ketones affording, after hydrolysis, the expected benzylic derivatives in 30-85% yield.[169]

III.1.3. Reductive Carbon-Sulfur Cleavage

Phenyl sulfides **91** react with lithium powder at low temperature in the presence of a catalytic amount of naphthalene to give the expected alkyllithium compounds **I**, which behave as usual towards electrophiles giving products **83**.[161h] This reaction has been recently applied to the synthesis of α-silylated organolithium intermediates.[171] When the same procedure is used with phenyl sulfoxides **92**[169] or phenyl sulfones **93**[169] it is necessary to work under

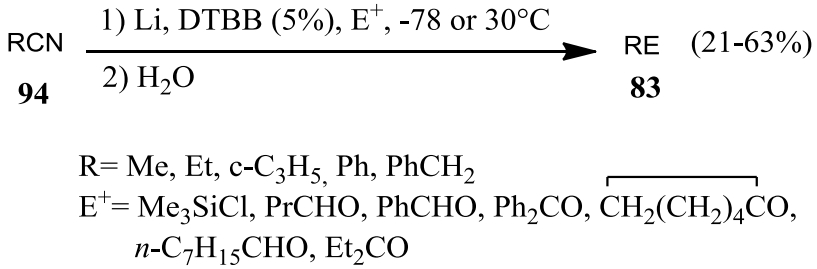
Barbier-type reaction conditions in order to avoid decomposition of the *in situ* generated organolithium compound even at low temperatures **(Scheme 47).**



Scheme 47.

III.1.4. Reductive Carbon-Carbon Cleavage

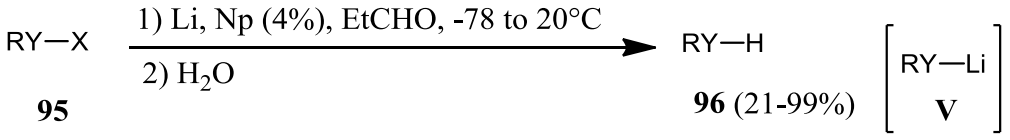
Nitriles **94** have been decyanated reductively using a DTBB catalysed lithiation and working under Barbier-type reaction conditions at low temperature, so the intermediate organolithium compound of type 2 prefers to react with the electrophile present in the reaction medium instead of reacting with the starting nitrile (α-deprotonation or addition to the cyano group) **(Scheme 48).**



Scheme 48.

III.1.5. Reductive Deprotections

A naphthalene-catalyzed lithiation process has been employed for the reductive deprotection of allyl-, benzyl-, and sulfonyl-substituted alcohols, amines and amides **95** at temperatures ranging from -78 to 25°C **(Scheme 49)**.[172] The chemoselective reductive deprotection of one group in the presence of other protecting groups has also been studied. For example, allyl benzyl ether derivatives can be reduced to the corresponding allyl alcohols without obtaining any benzyl alcohol. *N*-Substituted tosylamides can also be reduced, but the reaction does not proceed with the corresponding mesylamides. However, *N*, *N*-disubstituted mesylamides are reduced to give, after hydrolysis, the expected secondary amines. In the case of benzyl, allyl, or acyl sulfonamides, the reductive cleavage invariably leads to the corresponding benzyl or allyl amines or carboxamide derivatives, except in the case of *N*-substituted *N*-allyl mesylamides, where the corresponding *N*-substituted mesylamides are isolated in excellent yields. This methodology has recently been extended to sulfonyl aziridines, using DTBB as an electron shuttle, giving, after hydrolysis, the expected aziridine derivateves in 40-85% yield.[173]



Y= O, NH, NR, NBzl, NCOR, NCOR, NCO_2t-Bu, $NCONi$-Pr_2
R= Alkyl, CH_2=$CHCH_2$
X= CH_2=$CHCH_2$, Bzl, Ms, Ts

Scheme 49.

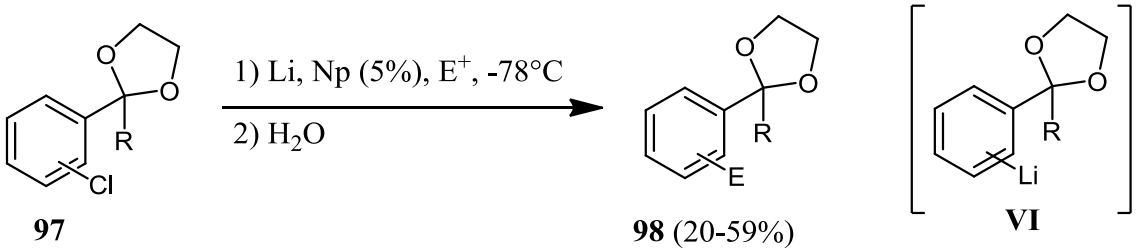
III.2. Preparation of Functionalized Organolithium Compounds

Functionalized nonstabilized organolithium derivatives[174] are interesting intermediates for the construction of organic structures due to the fact that their reactions with electrophiles usually lead directly to polyfunctionalized molecules. Their stability depends strongly on three factors: a) the type of functionality, b) the relative position between the functional group and the lithium atom, and c) the hybridization of the carbanionic atom.

III.2.1. Lithiation of Functionalized Halogenated Materials

1-(Benzyldimethylsilyl)naphthalene has been used as an electron shuttle in the lithiation of chlorobenzene and 9-chloroanthracene yielding the expected aryllithium derivatives.[174] A similar process has been used to prepare ketones from alkyl chlorides and carboxylic acids with yields rangcing from 18 to 97%, using in this case naphthalene as the catalyst for the lithiation step.[174]

Functionalized halogenated arenes have been submitted to naphthalene-catalyzed lithiations. Thus, lithiation of 2-(chlorophenyl)-1,3-dioxolanes **97** in the presence of carbonyl compounds gives, after hydrolysis, the expected benzylic derivatives **98** with masked carbonyl functionalities,[174] formally *via* the intermediate **VI (Scheme 50)**. When the reaction is performed with DTBB as electron shuttle, besides the chlorine/lithium exchange, a reductive opening of the heterocycle takes place, again highlighting the importance of choosing an appropriate arene as the catalyst.



97 **98** (20-59%) **VI**

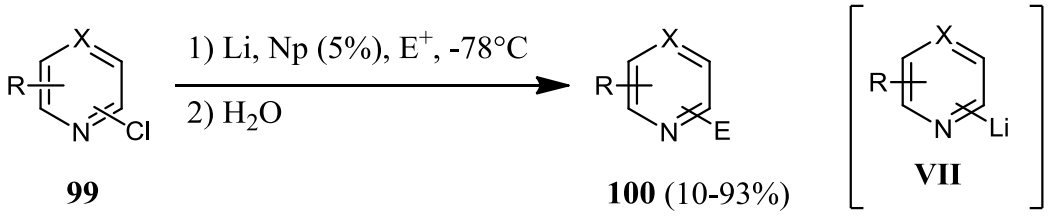
R= H, Me

E^+= *t*-BuCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe

Scheme 50.

Naphthalene-catalyzed lithiation of 2-(4-bromophe-nyl)butan-2-ol has been used to reduce the carbon-bromine bond to afford the corresponding 2-phenylbutan-2-ol, and in this way, to assign the absolute configuration of the starting bromo derivative.[174] In this process, the lithiation and subsequent reaction with water proceed without any racemization. Chlorinated azines **99** have been successfully lithiated by means of a naphthalene-catalyzed process.[174] The reaction proceeds under Barbier-type conditions *via* the intermediate **VII** and is compatible with all types of azines, such as pyridines, quinolines, pyrimidines, pyrazines, and 1,2,3-tria-zines, even those bearing methyl or methoxy substituents **(Scheme 51)**. When the reaction is carried out in the absence of an arene, a mixture of di-, tri-, and oligoazines is

formed initially, which can play the role of the catalyst for the lithiation reaction, therefore giving a lower yield than with the naphthalene-catalyzed process.

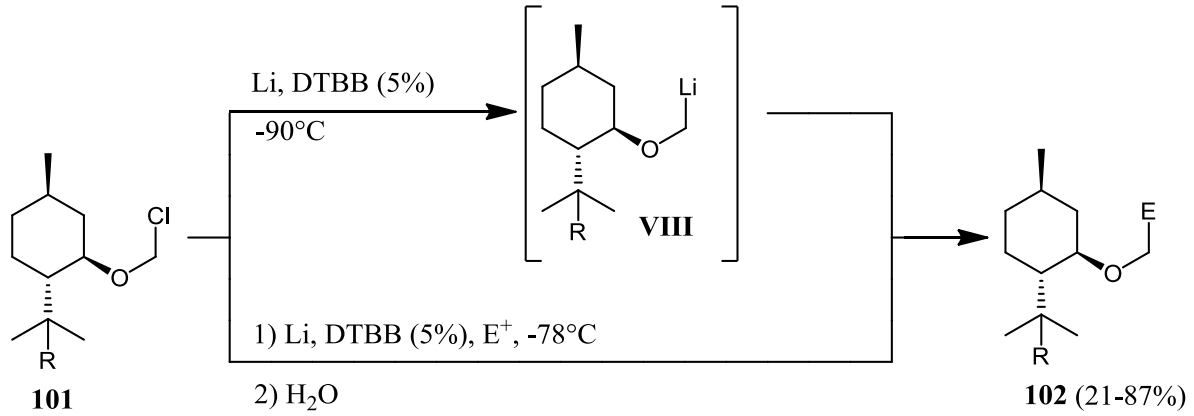


R= CH, N

E^+= *t*-BuCHO, PhCOMe, Et_2CO, PhCOMe, PhCH=NPh, PhCN

Scheme 51.

α-Functionalized organolithium compounds, the socalled ”carbenoids”, have been prepared from several chlorinated materials. Thus, the DTBB-catalyzed lithiation of chiral chloromethyl menthyl ethers **101** at -90°C gives the expected chiral carbenoids **VIII**, which can be trapped by reaction with various electrophiles **(Scheme 52)**. The same reaction can be performed at -78°C, although the electrophile must be present in order to avoid the corresponding α-elimination.[174] In the case of prostereogenic carbonyl compounds, the diastereomeric ratio never exceeds 65:35.



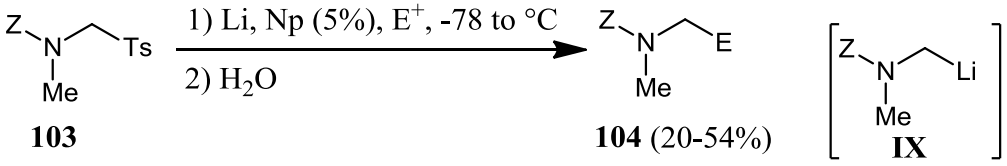
R= H, Ph

E^+= H_2O, D_2O, Me_3SiCl, *t*-BuCHO, PhCHO, Et_2CO, $(CH_2)_4CO$, PhCOMe, Ph_2CO, PhCH=NPh, DMF

Scheme 52.

III.2.2. Lithiation of Functionalized Sulfur Derivatives

As mentioned above, leaving groups other than halogens can be reduced to allow the preparation of organolithium compounds. One of these is the tosyl group, which can be used to generate α-functionalized organolithium intermediates through naphthalene-catalyzed reductive cleavage.[174] Thus, α-amidomethyl and α-aminomethyl sulfones **103** are reductively cleaved in a naphthalene-catalyzed reaction and the *in situ* formed α-functionalized organolithium intermediates **IX** are trapped by reaction with various electrophiles affording, after hydrolysis, the expected functionalized amides and amines **104**, respectively **(Scheme 53)**.



103 **104** (20-54%)

Z= Ph, *t*-BuOCO

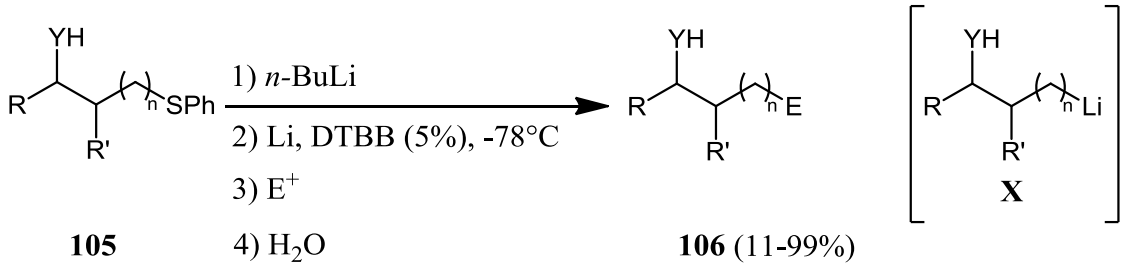
E^+= Me_3SiCl, *t*-BuCHO, PhCHO, Et_2CO, *i*-Pr_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe

Scheme 53.

An elegant process for obtaining organolithium compounds was introduced by Screttas *et al.*[161e] and involves the reductive cleavage of phenyl thioethers. This approach has recently been used under catalytic conditions to prepare β- and γ-functionalized[174] organolithium intermediates.

Thus, reaction of the corresponding β - or γ -functionalized phenyl thioethers **105** with *n*-butyllithium, followed by treatment with an excess of lithium powder and a catalytic amount of DTBB, affords the expected dilithium intermediates **X**, which are trapped by reaction with various electrophiles giving, after hydrolysis, the expected functionalized amines or alcohols **106 (Scheme 54)**. It must be pointed out that in the case of *trans*-(2-phenylsulfanyl)cyclohexanol, a mixture of *cis* and *trans* products is isolated after the reaction. The observed *cis:trans* ratio depends on the electrophile, from which it is concluded that the corresponding dilithiated intermediates of type **X** are not configurationally stable. When (*S*)-1-phenyl-(2-phenylsulfanyl)-propan-1-ol is lithiated and reacted with benzaldehyde, a ca. 1:1 mixture of both epimers is isolated. One important point merits comment: aliphatic and

nonsubstituted amines can be used as starting materials, which are not compatible with the other methodologies.



105 **106** (11-99%)

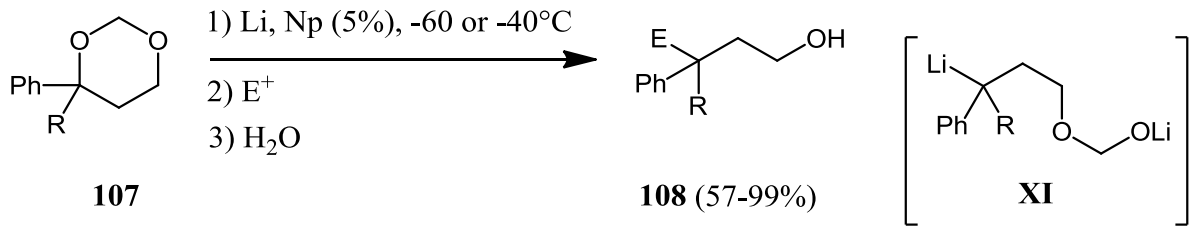
n= 0, 1
Y= NH, N*i*-Pr, NPh, O
R, R'= H, Me, *n*-C_6H_{13}, Ph; R-R'= $(CH_2)_4$
E^+= D_2O, *t*-BuCHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$

Scheme 54.

III.2.3. Reductive Opening of Heterocycles

An important route leading to functionalized organolithium compounds is the reductive opening of heterocycles.[174] In recent years, M. Yus and others have employed this strategy either to prepare new organolithium derivatives or to use them in novel syntheses.

Very recently, reductive cleavage of 4-phenyl-1,3-dioxane derivatives has been used in the preparation of γ-oxido-functionalized organolithium compounds.[174] Thus, naphthalene-catalyzed lithiation of 1,3-dioxane **107** gives the expected γ-functionalized benzyllithium derivatives **XI**, which may be trapped by reaction with various electrophiles to afford, after hydrolysis, the expected primary alcohols **108 (Scheme 55)**.

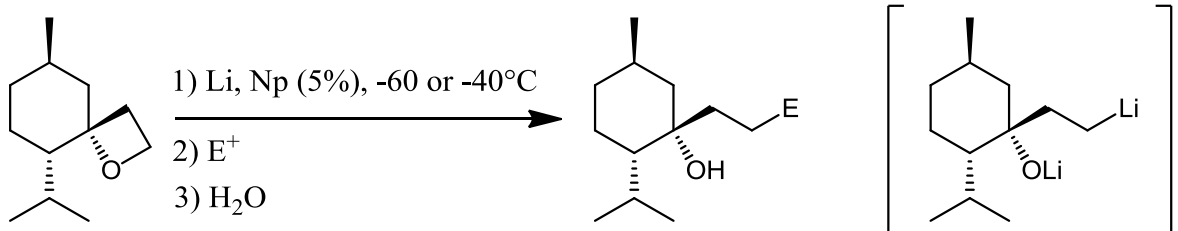


107 **108** (57-99%)

R= H, Me, Ph
E^+= H_2O, MeOD, Me_3SiCl, *n*-BuBr, *i*-PrBr, $C_6H_{13}Br$, *t*-BuCHO, Me_2CO, CO_2

Scheme 55.

It has been possible to prepare chiral γ-oxido-functionalized organolithium compounds from chiral oxetanes through a DTBB-catalyzed lithiation process.[174] The organolithium intermediate **XII** was reacted with various electrophiles giving, after hydrolysis, the expected chiral functionalized alcohols **110 (Scheme 56)**. Using prostereogenic carbonyl compounds, a ca. 1:1 mixture of epimers is isolated, which can be separated by chromatography.



109 **110** (57-98%) **XII**

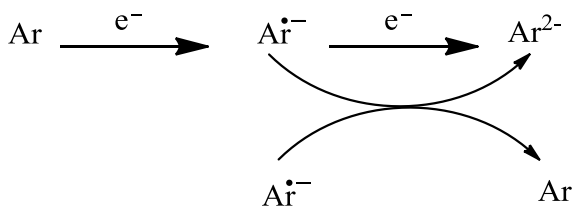
E^+= H_2O, D_2O, Me_3SiCl, *t*-BuCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, CO_2

Scheme 56.

III.3. Results and discussion

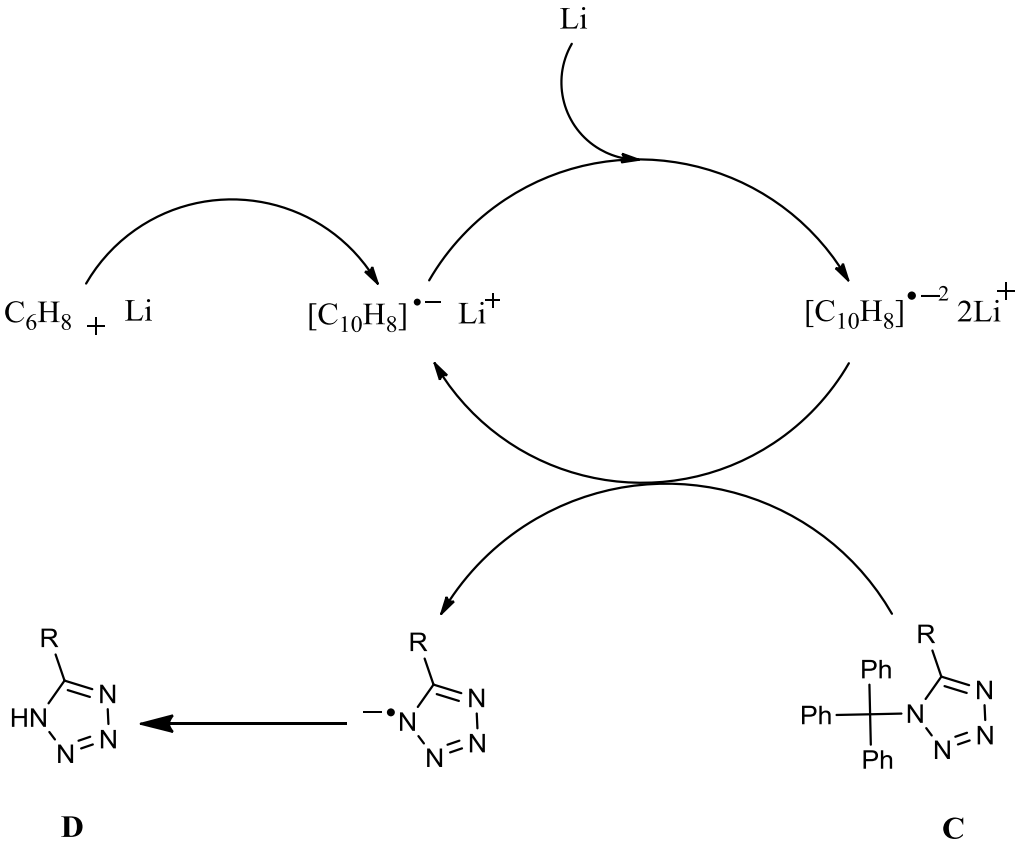
III.3.1. Activation of lithium by use of electron carriers

Among all methods for the activation of lithium, we will pay a special attention to the method of activation by means of an arene in substoichiometric amounts.[163] There are some aromatic hydrocarbons which are able to be reduced by addition of an electron; in this way, a radical-anion is generated. The latter presents an average lifetime longer than normal due to the possibility of delocalization of the negative charge. The addition of a second electron is even possible, which leads to a dianion species with a very high reducing power. The dianion can also be generated by disproportionation of the radical-anion, in which case the dianion would be obtained together with the starting arene. All these processes are represented in scheme 57.



Scheme 57.

One way to get very active lithium is to dissolve the metal in a stoichiometric amount of an arene,[160] using almost always tetrahydrofuran (THF) as solvent. As arenes, naphthalene ($C_{10}H_8$) and 4,4'-di-*tert*-butylbiphenyl (DTBB) are the most frequently used. In 1991, Prof. Miguel Yus and his co-workers found that it was possible to use a catalytic amount of the arene.[161h] The mechanism of this catalytic lithiation process is shown in scheme 58.



Scheme 58.

Lithium metal reacts with the arene affording the corresponding arene radical-anion. The latter then transfers an electron to the substrate C and the arene is regenerated and can enter the catalytic cycle again. Finally, the radical-anion species generated from C leads to the product D. The dianion of the arene can also perform the electron transfer to C instead of the arene radical-anion.

III.3.2. Reductive Cleavage of Tritylated tetrazoles via Naphthalene-Catalysed Lithiation

According to our previous experience in the reductive cleavage of trityl ethers,[176] we first tried to perform the detrytilation of 5-phenyl-1-trityl-1*H*-tetrazole **1a (Table 16, entry 1)** at –78 ºC. When a solution of **1a** in THF was added to a green suspension of an excess of lithium powder and a catalytic amount of naphthalene (1:0.2 molar ratio) in the same solvent at –78 ºC, the reaction mixture took a red colour which could be indicative of the formation of the trityl radical[177] and/or the trityl anion.[178] When the reaction was complete (TLC

monitoring), the hydrolysis with (HCl 1M) at the same temperature gave a mixture of corresponding tetrazole and triphenylmethane. The formation of the latter could be explained by protonation of the generated triphenylmethyllithium in the final hydrolysis step. The yield of 5-phenyl-1*H*-tetrazole was 97%. In order to seek for the optimum reaction conditions, The high yield 5-phenyl-1*H*-tetrazole didn't push us to look for other temperature or other catalyst. Other Tr-tetrazole **1d, 1e, 1i** aliphatic tetrazoles were submitted to the above mentioned detritylation process under the optimum reaction conditions (naphthalene catalysed lithiation at -78 ºC) and the results are indicated in **(Table 16, entries 4, 5, 9)** The aromatic tetrazoles **1k**, **1l** gave respectively a 84% and 75 % yield of the corresponding tetrazoles **(Table 16, entries 11, 12)**. The trityl group could chemoselectively be removed in the presence of benzyl group, which are also prone to undergo reductive cleavage by reaction with lithium. The expected detritylation product was 82% yield **(Table 16, entry 3)**.

Table 16 summarized the physical properties of products prepared as well as gotten yields.

Table 16: Reductive detrytilation of tetrazoles **1a-1l** by a naphthalene-catalysed lithiation.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2a**	3	215-216	97
2	**2b**	4	149-151	99
3	**2c**	3	123-124	82
4	**2d**	4	208-210	97
5	**2e**	3	72-73	81
6	**2f**	4	208-210	86
7	**2g**	4	212-214	93
8	**2h**	2.5	148-150	94
9	**2i**	2.5	138-140	93
10	**2j**	4	152-154	80
11	**2k**	2	165-166	84
12	**2l**	6.5	215-216	75

The structure of compound **2a-2l** was inferred from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and Element analysis) data.

IR Spectroscopy

The IR spectrums of the gotten products showed strong absorption band characteristic of the amino group at υ_{N-H} (cm^{-1})= 2977; 3336, and a second strip of frequency toward 1046; 1053 cm^{-1} due to stretching of C=C. Function tetrazole is also verified by the presence of band at [2900-2917] cm^{-1} who corresponds to the C=N link.

^{1}H NMR Spectroscopy

Compound (2a)

Aromatic protons of this product appear at [7.55-8.10] ppm as two multiplets (m), first with integration 3H and other 2H.

Compound (2b)

The spectrum of this compound showed a singlet (s) absorption band for group CH_3 at 2.28 ppm. And aromatic protons appear at [6.98-7.69] ppm which multiplicity appears as follows:

- Two doublets (d): the first at 6.98 ppm with coupling constant *J*= 8.1 Hz, while the second at 7.12 ppm with coupling constant *J*= 7.9 Hz.
- Doublet of doublet of doublet (ddd) at 7.55 ppm with coupling constants *J*= 10.3, 5.8, 1.9 Hz.
- The other protons appear at [7.63-7.69] ppm as a multiplet (m) with integration 2H.

Compound (2c)

The spectrum of this compound was characterized by a multiplet (m) at [7.24-7.35] ppm. This multiplet was assigned for 5 aromatic protons. The spectrum also showed a singlet (s) peak at 4.28 ppm for CH_2.

Compound (2d)

The spectrum of this compound showed presence of singlet (s) band at 5.85 ppm belongs to $3CH_3$.

Compound (2e)

The protons of this compound appear at [0.84-2.84] ppm which multiplicity appears as follows:

- Tow triplets (t): first at 0.84 ppm with coupling constant *J*= 6.8 Hz, and second at 2.84 ppm with coupling constant *J*= 7.6 Hz.
- Two multiplets (m): the first at 1.24 ppm with integration 16H, and the second at 1.65-1.68 ppm with integration 2H.

Compound (2f)

The spectrum of this product showed two doublet of doublet of doublet (ddd), the first at 7.63 ppm with coupling constants *J*= 7.8, 4.8, 1.2 Hz, and the second at 8.79 ppm with coupling constants *J*= 4.8, 1.7, 0.9 Hz. And triplet of doublet (td) at 8.08 ppm with coupling constant *J*= 7.8, 1.7 Hz. Also this spectrum showed a doublet of triplet at 8.22 ppm with coupling constant *J*= 7.9, 1.0 Hz.

Compound (2g)

The spectrum of this product showed the presence of singlet (s) at 6.56 ppm corresponding to NH group.

Compound (2h)

The spectrum of this product showed a multiplet (m) at [7.14-7.32] ppm corresponding to aromatic protons with integration 15H.

Compound (2i)

The spectrum of this product showed a singlet (s) at 2.46 ppm with integration 3H.

Compound (2j)

The spectrum of this compound showed two singlets (s): the first at 1.18 ppm corresponding to protons of three CH_3, and the second at 4.41 ppm corresponding to the protons of CH_2.

Compound (2k)

The spectrum of this compound showed singlet band at 5.85 ppm belong to CH. Also this spectrum showed the multiplet (m) at [7.14-7.37] ppm due to the 10 aromatic protons.

Compound (2l)

Aromatic protons appear at [7.45-8.94] ppm which multiplicity appears as follows:

- Doublet (d) at 7.45 ppm with coupling constant *J*= 8.6 Hz with integration 2H.
- Two multiplets (m) first at [7.56-7.63] ppm with integration 4H, and second at [8.23-8.31] ppm with integration 2H.
- Singulet (s) at 8.94 ppm with integration 1H.

The results of ^{1}H NMR of products **2a-2l** are summarized in **Table 17**.

Table 17: ^{1}H NMR for terazoles **2a-2l.**

Compounds	CH	CH_2	CH_3	H_{arom}
2a	---	---	---	7.55-7.62, m, 3H; 8.01-8.10, m, 2H
2b	---	---	2.28, s, 3H	6.98, d, *J*= 8.1 Hz, 2H; 7.12, d, *J*= 7.9 Hz, 2H; 7.55, ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H; 7.63-7.69, m, 2H
2c	---	4.28, s, 2H	---	7.24-7.35, m, 5H
2d	---	---	1.35, s, 9H	---
2e	---	1.24, m, 16H; 1.65-1.68, m, 2H; 2.84, t, *J*= 7.6 Hz, 2H	0.87, t, *J*= 6.8 Hz 3H	7.07-7.36, m, 15H
2f	---	---	---	7.63, ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H; 8.08, td, *J*= 7.8, 1.7 Hz, 1H; 8.22, dt, *J*= 7.9, 1.0 Hz, 1H; 8.79, ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H
2h	---	---	---	7.14-7.32, m, 15H
2i	---	---	2.46, s, 3H	---
2j	---	4.41, s, 2H	1.18, s, 9H	---
2k	5.88, s, 1H	---	---	7.14-7.30, m, 10H
2l	---	---	---	7.45, d, *J*= 8.6 Hz, 2H; 7.56-

				7.63, m, 4H; 8.23-8.31, m, 2H; 8.94, s, 1H

Notes: ^{1}HNMR: (300 MHz, DMSO-d_6).

^{13}C NMR Spectroscopy

Compound (2a)

The spectrum showed the aromatic carbons peaks at [122.6-154.8] ppm.

Compound (2b)

The spectrum of this compound showed the expected peak for CH_3 at 20.7 ppm, the other aromatic carbons appear in the area [123.4-155.1] ppm.

Compound (2c)

The carbon of the group CH_2 fate to 29.0 ppm, the aromatic carbones appear at [127.1-155.3] ppm.

Compound (2d)

In the spectrum of this compound we record the presence of three peaks: the first at 28.9 ppm corresponding to the three CH_3, the second at 30.3 ppm corresponding to alkyl C, and the third at 163.4 ppm corresponding to C of tetrazole ring.

Compound (2e)

In the spectrum of compound **2e** we observe:

- The carbon of function CH_3 appears at 13.9 ppm.
- The carbons CH_2 resonate in the area [22.2-31.3] ppm.
- The carbon C of tetrazole ring appears at 155.9 ppm.

Compound (2f)

The spectrum showed the aromatic carbons peaks at [122.6-154.8] ppm.

Compound (2g)

The spectrum showed the presence of one peak at 158.2 ppm corresponding to C-5 of tetrazole ring.

Compound (2h)

The spectrum showed the aromatic carbons peaks at [82.2-162.1] ppm.

Compound (2i)

The spectrum showed two peaks: the first at 8.4 ppm corresponding to CH_3 and second at 152.2 ppm corresponding to C-5 of tetrazole ring.

Compound (2j)

Spectral analysis of this compound shows the existence of:

- A signal at 25.8 ppm corresponding to the carbons of three CH_3, and other at 32.2 ppm corresponding to CH_2 group.
- A signal out to 209.8 ppm corresponding to the carbon of carbonyl.
- The carbon of tetrazole ring appears at 128.2 ppm, and the alkyl carbon fate at 44.0 ppm.

Compound (2k)

The spectrum showed the appearance of CH peak at 40.8 ppm. Also this spectrum showed 5 peaks at [128.6-160.0] ppm due to the 13 aromatic carbons.

Compound (2l)

The spectrum showed the aromatic carbons peaks at [120.6-150.1] ppm.

The assignment of the major ^{13}C NMR signals is summarized in **Table 18**.

Table 18: ^{13}C NMR for compounds **2a-2l**.

Compounds	**C**	**CH**	**CH_2**	**CH_3**	**C=O**	**C_{arom}**
2a	155.3	---	---	---	---	124.1-129.4
2b	155.1	---	---	20.7	---	123.4-141.5
2c	155.3	---	29.0	---	---	127.1-136.0
2d	30.3; 163.4	---	---	28.9	---	---
2e	155.9	---	22.2-31.3	14.3	---	---

2f	154.8	---	---	---	---	122.6-150.1
2g	158.2	---	---	---	---	---
2h	162.1	---	---	---	---	82.2-141.5
2i	152.2	---	---	8.4	---	82.8-141.5
1j	44.0; 128.2	---	32.2	25.8	209.3	---
1k	160.0	40.8	---	---	---	128.6-160.0
1l	150.1	---	---	---	---	120.6-138.3

Notes: ^{13}CNMR: (75 MHz, DMSO-d_6).

Element analysis

The Element analysis of compounds **2a-2l** are reported in **Table 19.**

Table 19. Element analysis of compounds **1b, 2c, 2e** and **2i.**

Compounds	**Calcd**			**Found**		
	C	**H**	**N**	**C**	**H**	**N**
2b	71.17	5.12	23.71	70.86	5.17	24.07
2c	59.99	5.03	34.98	60.05	4.80	36.21
2e	64.24	10.78	24.97	63.97	10.50	26.51
2i	28.57	4.80	66.64	28.77	4.70	71.13

III.4. Conclusion

In the last few years, we have been using an arene-catalyzed lithiation to prepare organolithium compounds under very mild reaction conditions. The use of an excess of lithium powder and a catalytic amount of an arene (naphthalene) allowed us to generate simple organolithium compounds starting from non-halogenated materials,[176] and functionalised organolithium compounds[176] by chlorine-lithium exchange or by ring opening of heterocycles.[176] Using this lithiation methodology, we have been able to achieve the reductive cleavage of carbon-nitrogen bonds in different substrates. We have recently described the reductive detritylation of trityl tetrazole by a naphthalene catalysed lithiation process.[176] In this chapter, we report the application of this lithiation methodology to the removal of the trityl group in several N-atom of the tetrazole **2a, 2b, 2c, 2d, 2e,2f, 2g, 2h, 2i, 2j, 2k** and **2l** moiety, which leads to the corresponding deprotected tetrazole under mild reaction conditions.

The reaction can be followed by a simple colour change: at the beginning (before adding the substrate to be lithiated), the reaction mixture shows the colour of the arene radical-anion (dark green for naphthalene) and, after addition of the starting material, the colour disappears and the mixture becomes again coloured at the end of the lithiation step, when the substrate has been consumed.

Some advantages of this methodology compared to the use of a stoichiometric amount of the arene are:

a) Yields are similar or better in the catalytic version.
b) Reaction times are far shorter.
c) Reactions are very clean and by-products resulting from the reaction of the arene radical anion with the electrophile are not normaly obtained.
d) The method avoids separation of significant amounts of the arene.

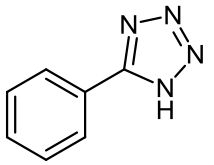
III.5. Experimental part

III.5.1. Reductive Cleavage of Tritylated tetrazoles 1a-1f and 1i-1l via Naphthalene-Catalysed Lithiation

General procedure

A solution of trityltetrazole (0.5 mmol) in THF (2 mL) was dropwise added to a green suspension of Lithium powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC. The reaction mixture turned to a dark red color after the addition of a few drops of the solution of trityltetrazole. After stirring at the same temperature, HCl (5 mL, 1M) was carefully added, the cooling bath was removed and the reaction mixture was stirred till it reached r.t. The mixture was extracted with EtOAc (3x15 mL) and the combined organic phases were washed with brine (5 mL), and then dried (Na_2SO_4). After evaporation of the solvents, the resulting residue was purified by column chromatography (basic aluminium oxide, hexane/ethyl acetate), affording the corresponding tetrazole.

5-phenyl-1H-tetrazole (2a)[152]

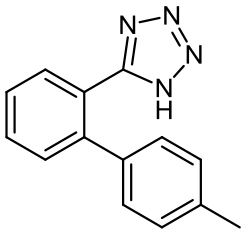


2a

Following the general procedure, the reaction of 5-phenyl-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2a** as a white solid.

- **Yield**= 97% (0.066 g).
- **Mp**= 215-216°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.55-7.62 (m, 3H), 8.01-8.02 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 124.1 (2xCH), 127.0 (C), 129.4 (CH), 131.3 (2xCH), 155.3 (C).

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

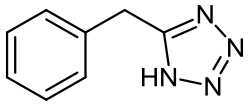


2b

Following the general procedure, the reaction of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2b** as a Brawn solid.

- **Yield**= 99% (0.089 g).
- **Mp**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH) , 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).
- **Anal. Calcd for $C_{14}H_{12}N_4$**: C, 71.17; H, 5.12; N, 23.71. **Found**: C, 70.86; H, 5.17; N, 24.07.

5-benzyl-1H-tetrazole (2c)[102]



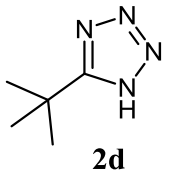
2c

Following the general procedure, the reaction of 5-benzyl-1-trityl-1*H*-tetrazole (0.12 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2c** as a white solid.

- **Yield**= 82% (0.028 g).
- **Mp**= 123-124°C.

- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).
- **Anal. Calcd for $C_8H_8N_4$**: C, 59.99; H, 5.03; N, 34.98. **Found**: C, 60.05; H, 4.80; N, 36.21.

5-(tert-butyl)-1H-tetrazole (2d)[101]

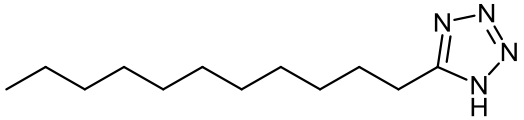


2d

Following the general procedure, the reaction of 5-(*tert*-butyl)-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2d** as a white solid.

- **Yield**= 97% (0.056 g).
- **Mp**= 208-210°C.
- **IR (KBr):** 2977, 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

5-undecyl-1H-tetrazole (2e)[103]



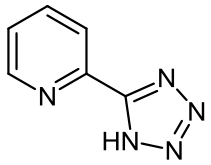
2e

Following the general procedure, the mixture of 1-trityl-5-undecyl-1*H*-tetrazole (0.23 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2e** as a Brawn solid.

- **Yield**= 81% (0.094 g).
- **Mp**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.

- **^{1}HNMR: (300 MHz, MeOD-d_4):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **^{13}CNMR: (75 MHz, MeOD-d_4):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).
- **Anal. Calcd for $C_{12}H_{24}N_4$**: C, 64.24; H, 10.78; N, 24.97. **Found**: C, 63.97; H, 10.50; N, 26.51.

Synthesis of 2-(1H-tetrazol-5-yl)pyridine (2f)[101]

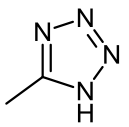


2f

Following the general procedure, the mixture of 2-(1-trityl-1*H*-tetrazol-5-yl)pyridine (0.19 g, 0.5 mmol) Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar at -78 ºC gave **2f** as a Brawn solid.

- **Yield**= 86% (0.06 g).
- **Mp**= 208-210°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

5-methyl-1H-tetrazole (2i)[102]

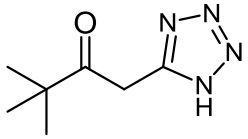


2i

Following the general procedure, the reaction of 5-methyl-1-trityl-1*H*-tetrazole (0.12 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (7 mL), under Ar at -78 ºC gave **2i** as a white solid.

- **Yield**= 93% (0.028 g).
- **Mp**= 138-140°C.
- **IR (KBr):** 3005 (NH), 2879 (CH_3), 2605 (C=N), 1578, 1565, 1112, 1052, 899, 683 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.46 (s, 3H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 8.4 (CH_3), 152.2 (C).
- **Anal. Calcd for $C_2H_4N_4$**: C, 28.57; H, 4.80; N, 66.64. **Found:** C, 28.77; H, 4.70; N, 71.13.

3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2j)[104]

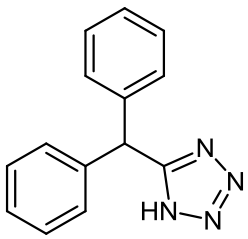


2j

Following the general procedure, the reaction of 3,3-dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one (0.20 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (7 mL), under Ar at -78 ºC gave **2j** as a Orange solid.

- **Yield**= 80% (0.065 g).
- **Mp**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

5-benzhydryl-1H-tetrazole (2k)[105]

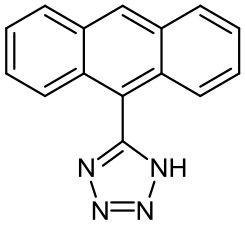


2k

Following the general procedure, the reaction of 5-benzhydryl-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (7 mL), under Ar at -78 ºC gave **2k** as a white solid.

- **Yield**= 84% (0.029 g).
- **Mp**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

5-(anthracen-9-yl)-1H-tetrazole (2l)[102]



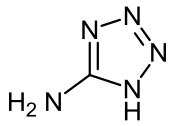
2l

Following the general procedure, the reaction of 5-(anthracen-9-yl)-1-trityl-1*H*-tetrazole (0.24 g, 0.5 mmol), Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (7 mL), under Ar at -78 ºC gave **2l** as a green solid.

- **Yield**= 75% (0.09 g).
- **Mp**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

III.5.2. Reductive Cleavage of double Tritylated Amino tetrazol

1H-tetrazol-5-amine (2g)[175]

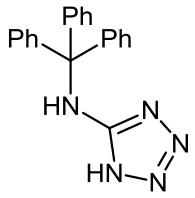


2g

To a solution of N,1-ditrityl-1*H*-tetrazol-5-amine (0.28 g, 0.5 mmol) in THF (2 mL), under Ar, at 0 ºC, *n*-BuLi was dropwise added until a red colour developed in the reaction mixture (0.45 mL of a 1.6 M solution of *n*-BuLi in hexane, 0.7 mmol). After stirring for 10 min, trimethylsilyl chloride was added until the red colour vanished (0.15 mL, 1.2 mmol). The reaction mixture was stirred for 10 min and it was then transferred dropwise via syringe to a green suspension of lithium powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar, at -78 ºC. The reaction mixture turned to a dark red colour. After stirring at the same temperature, HCl 1M (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The mixture was acidified with 2 M HCl (5 mL) and extracted with EtOAc (3×15 mL), the combined organic phases being discarded. The aqueous phase was basified with 2 M NaOH (5 mL) and extracted with dichloromethane (3×15 mL). The combined organic phases were dried over sodium sulfate. Evaporation of the solvents afforded a 93% yield of pure expected tetrazole **2g** as a white solid (0.055 g, 93%).

- **Yield**= 93% (0.055 g).
- **Mp**= 212-214°C.
- **IR (KBr):** 3399 (NH_2), 3192 (NH), 1636, 1263, 1044 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 6.56 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 158.2 (C).

N-trityl-1H-tetrazol-5-amine (2h)[155]



2h

To a solution of *N*,1-ditrityl-1*H*-tetrazol-5-amine (0.28 g, 0.5 mmol) in THF (2 mL), under Ar, at 0 ºC, *n*-BuLi was dropwise added until a red colour developed in the reaction mixture (0.45 mL of a 1.6 M solution of *n*-BuLi in hexane, 0.7 mmol). After stirring for 10 min. The reaction mixture was stirred for 10 min and it was then transferred dropwise via syringe to a green suspension of lithium powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL), under Ar, at -78 ºC. The reaction mixture turned to a dark red colour. After stirring at the same temperature, HCl 1M (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The mixture was acidified with 2 M HCl (5 mL) and extracted with EtOAc (3×15 mL), the combined organic phases being discarded. The aqueous phase was basified with 2 M NaOH (5 mL) and extracted with dichloromethane (3×15 mL). The combined organic phases were dried over sodium sulfate. Evaporation of the solvents afforded a 94% yield of pure expected tetrazol **2h** as a yellow solid.

- **Yield**= 94% (0.15 g).
- **Mp**= 148-150°C.
- **IR (KBr):** 3266 (NH), 1560, 1445, 757, 695, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.14-7.32 (m, 15H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 82.2 (C), 126.9-130.3 (15xCH), 141.5 (3xCH), 162.1 (C).

Chapter 04: Indium-mediated Cleavage of the Trityl Group from Protected 1H-Tetrazoles

Introduction

Since the successful introduction of magnesium metal in Grignard reactions for carbon-carbon bond formation, the utilization of other metals of the Periodic System for organic synthesis has received widespread interest and one of the latest additions is indium. Although indium was briefly used for synthetic purposes early in the 20th century,[183] studies of the utility of indium reagents for organic transformations have been carried out only very recently.[184] During the last decade, indium has emerged as a metal of high potential in organic synthesis because of certain unique properties that it possesses. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. Generally speaking, indium exhibits a low heterophilicity in organic reactions and thus oxygen- and nitrogen-containing functional groups are usually tolerated by organoindium reagents. Moreover, indium-assisted reactions display a low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity. However, although indium has been used extensively in carbonyl addition reactions,[185] its potential in other domains, including addition to other electron-deficient systems, has not yet been explored to any great extent.[186] Because indium closely resembles magnesium, zinc, and tin in several respects, including its first ionization potential, indium metal could also represent a suitable reagent for SET (single electron transfer) processes.

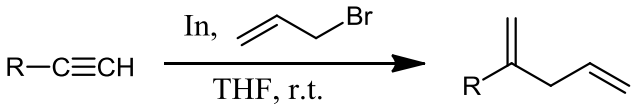
IV.1. Indium Metal and Its Halides in Organic Synthesis

IV.1.1. Allylation and Vinylation Reactions

IV.1.1.1. Regioselective Allylation of Alkynes

Allylmetallation of carbon-carbon triple bonds by allylmetal compounds is useful for the synthesis of 1,4-dienes. Although the carbometallation of activated alkynes, such as alkynyl ketones, proceeds readily with various allylmetal compounds,[187] the carbometallation of unactivated alkynes is not so easy and only a few metals have been successfully employed for this purpose.[188] Recently, a procedure has been reported for the allylation of alkynols using indium powder and allylic bromides in DMF at elevated temperature, leading to allylalkenols predominantly by anti Markovnikov addition.[189] However, the presence of a hydroxy functionality adjacent to the triple bond was found to be essential for facilitating this addition and thus the allylation of non-functionalized alkynes could only be accomplished in

low yields (12-28%), even at higher temperatures. Moreover, hydroxy-protected alkynes could not be allylated at all.[189] Nevertheless, the author's group has observed a very significant effect on the course of indium-mediated allylation reaction through a change of solvent and slight modification of the experimental conditions.[190] Thus, unactivated (non-functionalized and hydroxy-protected) alkynes have been found to undergo efficient allylation by Markovnikov addition simply by treating them with allyl bromide and indium metal in THF at room temperature **(Scheme 59)**.[190]



Scheme 59. Allylation of alkynes.

IV.1.1.2. Allylation of Aldehydes

A chiral indium-PYBOX complex **(Figure 17)** has been shown to be an effective catalyst for the enantioselective allylation of a variety of aldehydes, including aromatic, aliphatic, and α,β-unsaturated aldehydes, both in organic solvents and in ionic liquids[191] **(Scheme 60)**.

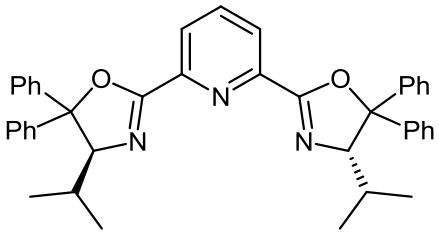
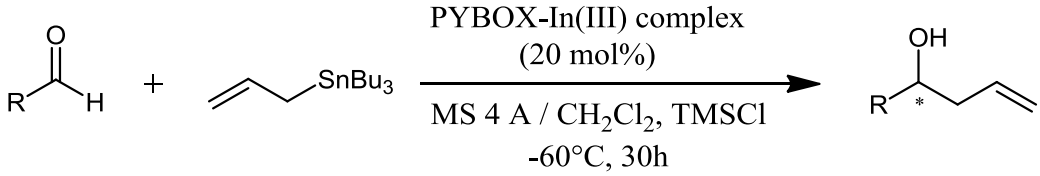


Figure 17. Chiral PYBOX ligand.

Allyltributylstannane is used as the allylating agent to afford the corresponding homoallylic alcohols. This protocol allows the recovery of the ligand without any racemization, which makes the cost of the chiral catalyst irrelevant. Furthermore, this reaction is highly chemoselective, taking place only with aldehyde functionalities even in the presence of keto groups.



Scheme 60. Indium-PYBOX-catalyzed allylation of aldehydes.

IV.1.1.3. Allylation of Ketones

Aromatic ketones have also been reported to undergo enantioselective allylation in the presence of chiral indium complexes.[192] Many methods for the enantioselective allylation of ketones in the presence of BINOL-indium or PYBOX-indium complexes have already been developed.[193] Despite all the progress achieved, the development of new approaches for this reaction is still in demand because of the reduced reactivities and lower binding affinities of ketones.[194] A ligand derived from (*S*)-picolinic acid *N*,*N*'-dioxide **(Figure 18)** in complexation with indium metal is used as the chiral catalyst together with tetraallyltin as the allylating agent **(Scheme 61)**.

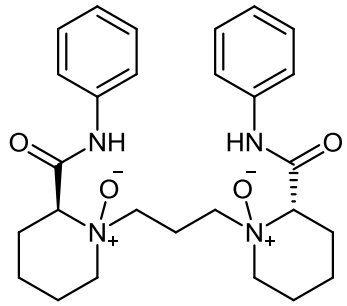
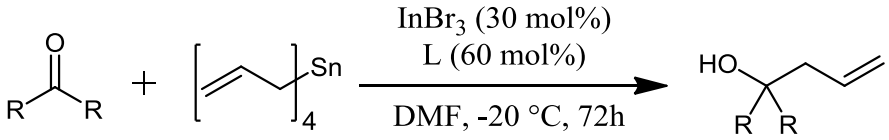


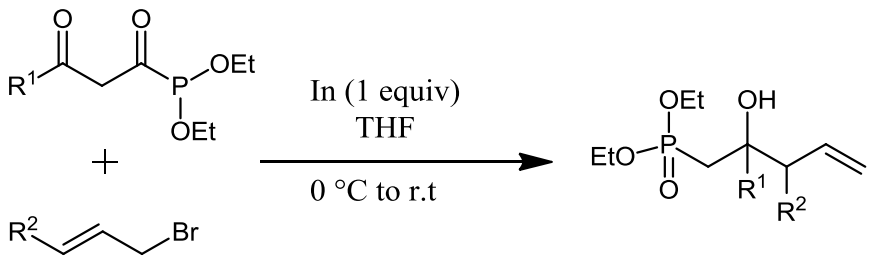
Figure 18. *N*,*N*'-Dioxide ligand.



Scheme 61. The enantioselective allylation of ketones.

IV.1.1.4. Allylation of β-Keto Phosphonates

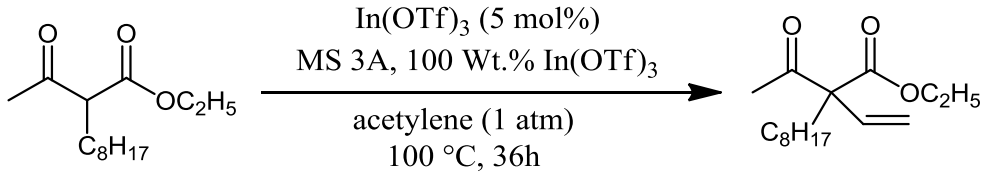
Allylation of β-keto phosphonates, which remains unsuccessful with Grignard reagents, has been reported to be successful in the presence of allylindium reagents[195] **(Scheme 62)**. Here, allylindium generated in situ reacts with the β-keto phosphonate without any catalyst.



Scheme 62. Indium-mediated allylation of β-keto phosphonates.

IV.1.1.5. Vinylation of β-Keto Esters

$In(OTf)_3$ has been shown to catalyze the vinylation of β-keto esters with acetylene gas to afford the corresponding α-vinylated keto esters[196] **(Scheme 63)**.



Scheme 63. In(OTf)3-catalyzed vinylation of β-keto esters.

In comparison with existing methods that utilize acetylene gas, which suffer from many problems such as the acidand base-sensitivity of acetylene, this method provides a highly practical protocol for the vinylation of keto esters, allowing the use even of welding-grade acetylene, which contains both acetone and water. Another feature of this method is the high atom efficiency. This method tolerates acid-sensitive groups and it is also applicable to substituted acetylenes.

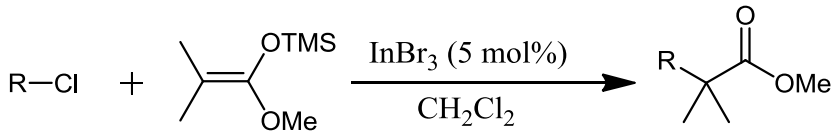
IV.1.2. Coupling Reactions

Coupling reactions to make new C-C bonds have always been a fascinating area of research in the field of organic synthesis. Indium or its salts have now emerged as valuable tools to fulfill these requirements. Indium and its compounds have thus functioned both as reagents and as catalysts in some carbon-carbon bond-forming reactions, such as allylation of carbonyl compounds,[197] Reformatsky reactions,[198] Aldol reactions,[199] Diels-Alder reactions,[200] Michael reactions,[201] Friedel-Crafts reactions,[202] and reductive coupling reactions.[203] More developments in such coupling reactions have taken place recently, with

indium salts having provided very reliable and practically useful alternatives to already available methods.

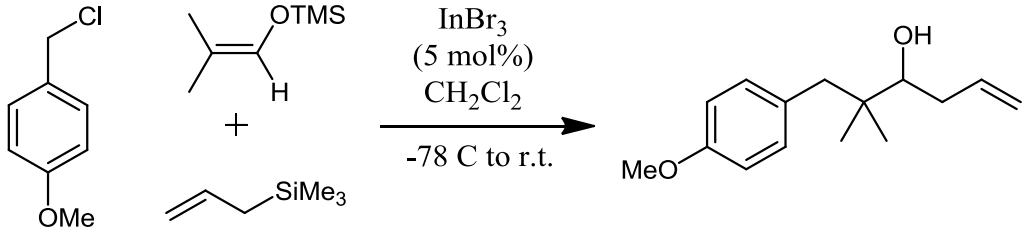
IV.1.2.1. Reactions of Alkyl Halides

Coupling reactions between alkyl chlorides and silyl enolates of various aldehydes to give α-alkylated carbonyl compounds are some of the interesting examples that have been reported in the recent past[204] **(Scheme 64)**.



Scheme 64. $InBr_3$-catalyzed couplings of alkyl halides with silyl enolates.

This method has the distinction of providing a good variety of substrates, and has attracted much interest in relation to the available methods catalyzed by zinc halides,[205] because these alkyl halides are much more weakly activated. Additionally, not much work has done with aldehyde-derived enolates because of their lesser nucleophilicity.[206] Another advantage of this method is that whereas most of the other previously reported methods use a halogenated solvent, it can give satisfactory yields in hexane as solvent, which is interesting as far as green chemistry is concerned. These indium halides can also catalyze three-component reactions of aldehyde enolates, alkyl chlorides, and allyl- or alkynylsilanes to afford homoallyl alcohols **(Scheme 65)**.

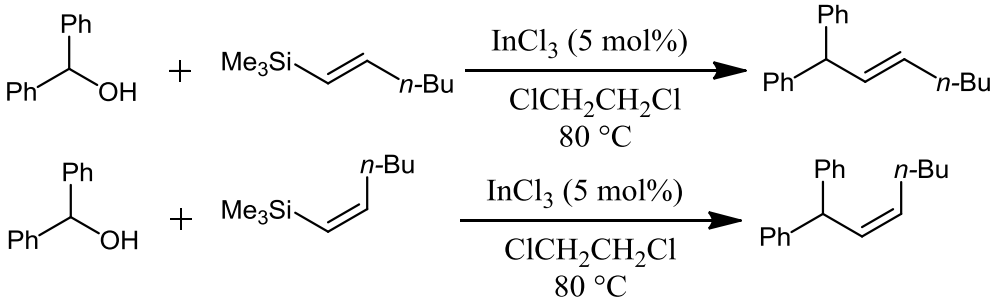


Scheme 65. $InBr_3$-catalyzed three-component reactions of aldehyde enolates, alkyl chlorides, and allylsilanes.

IV.1.2.2. Reactions of Alcohols

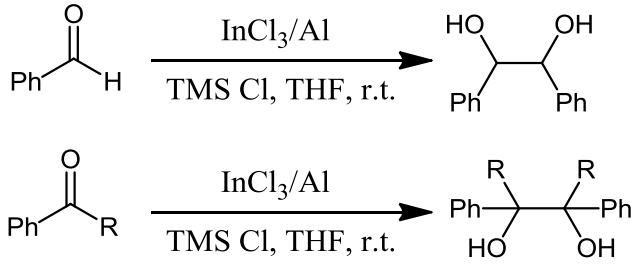
Indium(III) halides have also been reported to catalyze direct coupling reactions of alcohols (alkyl, benzylic or allylic) with alkenylsilanes **(Scheme 66)**.[207] These reactions are

important because of the fact that they successfully overcome the poor leaving ability of the hydroxy group. This report represented the first direct coupling of alcohols other than allylic alcohols with metallic nucleophiles, previous reports having been limited only to allylic alcohols.[208] Here, *cis*-alkenylsilanes give *cis* products and *trans*-alkenylsilanes give *trans* products.



Scheme 66. $InCl_3$-catalyzed coupling of alcohols with alkenylsilanes.

These indium(III) halides can also catalyze homocoupling reactions of various aromatic aldehydes, ketones, and imines[209] **(Scheme 67)**.



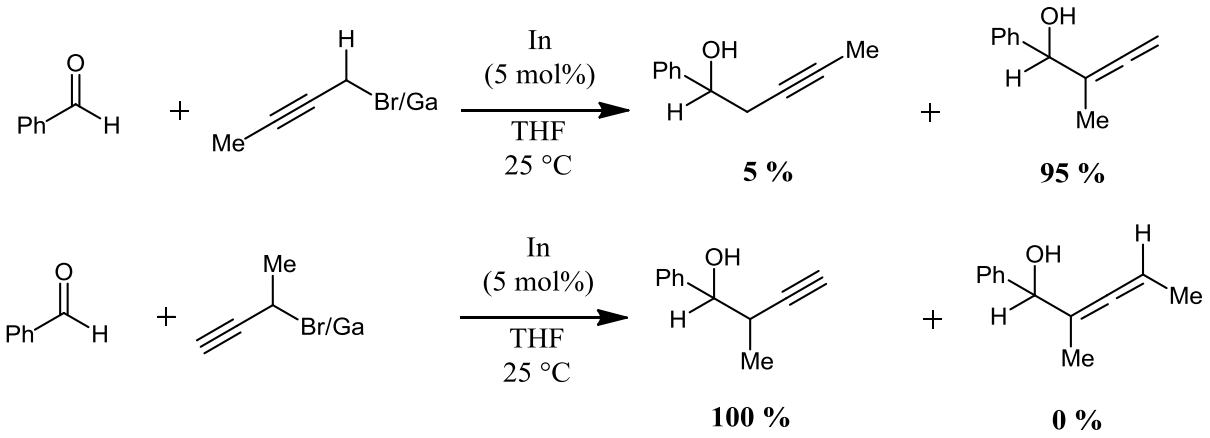
Scheme 67. $InCl_3$-catalyzed homocoupling of aldehydes and ketones.

IV.1.3. Addition and Condensation Reactions

IV.1.3.1. Addition of Carbonyl Compounds

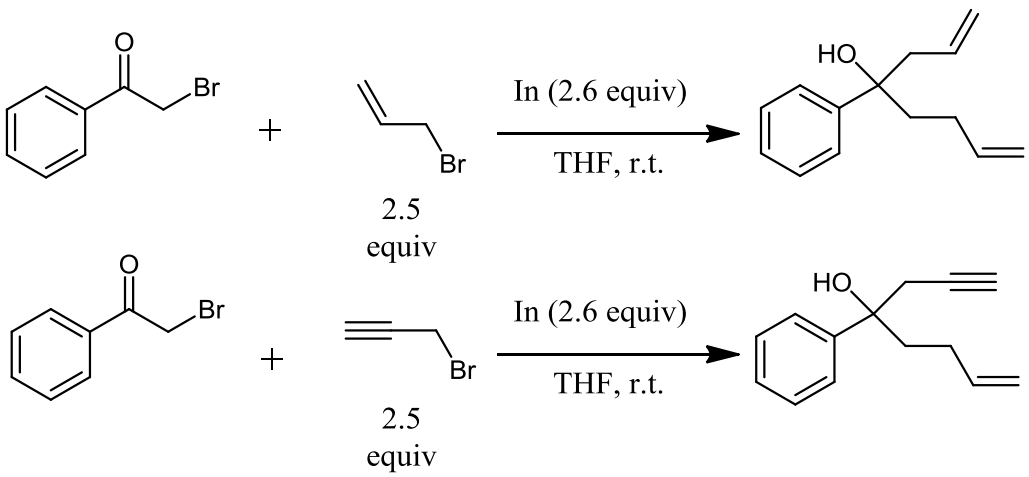
Regioselective additions of propargylgallium reagents to carbonyl compounds are a relatively unexplored area in relation to the use of propargylindium.[210] These reactions, which result in the formation of homopropargyl alcohols, has their own importance in the field of organic synthesis.[211] Although many methods have already been developed,[212] selective nucleophilic allenylations or propargylations of carbonyl compounds are still very desirable reactions to achieve. Recently, selective preparations either of homoallenyl alcohols or of homopropargyl alcohols through cat-In/InX3-mediated (X= F or Br) reactions between 3-

bromo-1-(trialkylsilyl)prop-1-ynes and various aldehydes have been reported.[213] This selectivity can also be achieved with propargylgallium in the presence of indium metal.[214] Depending on the substitution on the propargylgallium, selectivity between homopropargyl alcohols and homoallenyl alcohols can be achieved. A substituent at the γ-carbon atom of the propargylgallium reagent favors the formation of a homoallenyl alcohol, except in the case of a γ-trimethylsilyl substituent. Formation of homopropargylic alcohols is favored when a substituent is present at the α-carbon atom of the propargylgallium **(Scheme 68)**.



Scheme 68. Additions of organoindium species, generated in situ, to aldehydes.

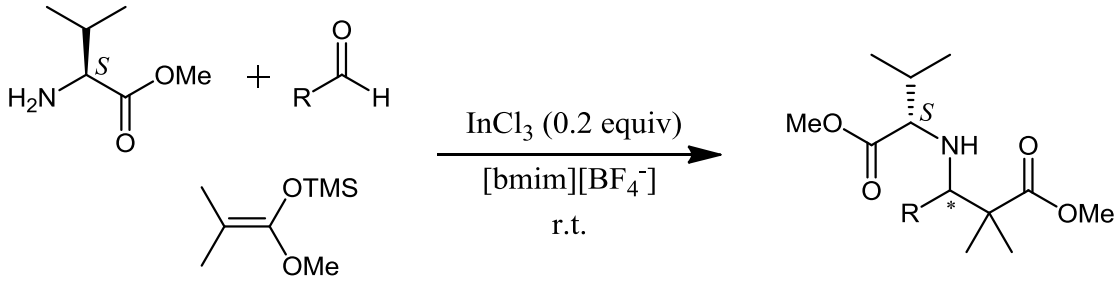
This method tolerates aromatic or aliphatic carbonyl compounds and the order of their reactivity is found to be in the order: aromatic aldehyde > aliphatic ketone > aromatic ketone. *vic*-Dipropargylated or *vic*-diallylated compounds have recently been prepared from phenacyl bromide through the use of propargylindium or allylindium reagents[215] **(Scheme 69)**.



Scheme 69. Indium-mediated diallylations.

IV.1.3.2. Mannich-Type Condensations of Aldimines

Indium(III) chloride has been reported to be an efficient catalyst for Mannich-type condensations of aldimines with silylenol ethers or silylketene acetals. With $InCl_3$, Mannich-type reactions in pure water, to afford various β-amino ketones, have been reported for the first time.[216] A symmetric version of the reaction with aromatic aldimines has also been reported.[217] L-Valine methyl ester has been used as a chiral auxiliary with enolate equivalents such as silylenol ethers or silylketene acetals. Rather than using a chiral catalyst, this method uses the chiral amine to generate a chiral imine, thereby producing a diastereomeric pair of products **(Scheme 70)**.



Scheme 70. $InCl_3$-catalyzed Mannich-type reactions for the synthesis of β-amino esters.

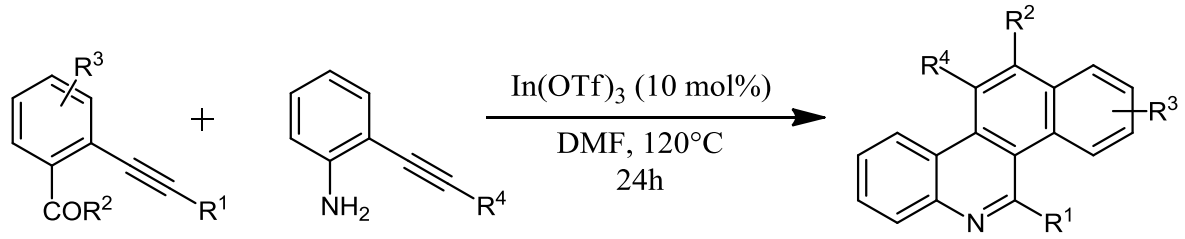
IV.1.4. Synthesis of Heterocycles

The synthesis of heterocyclic compounds has always been a fascinating field of research because these systems form the core structures of most of the available natural products of biological importance. Even DNA also contains heterocycles in its core structure. Among heterocyclic compounds, nitrogen heterocycles are of very great importance with respect to the synthesis of drug molecules.

IV.1.4.1. Synthesis of Phenanthridines

Because of their importance in pharmaceutical applications, the synthesis of phenanthridines is always of interest, but still only a small number of methodologies for their synthesis has been reported. [218] Electrophilic cyclization of phenylacetylenes with aldehyde or imino groups at their *ortho* positions is very familiar method for the synthesis of different phenanthridines. It has been reported recently that $In(OTf)_3$ can act as an efficient catalyst for the synthesis of phenanthridines through cyclizations of phenylacetylene-carbaldehydes with *ortho* alkynylanilines.[219] Phenylacetylene-carbaldehydes bearing electron-withdrawing groups

on their aromatic rings are better substrates than those with electron-donating groups **(Scheme 71)**.

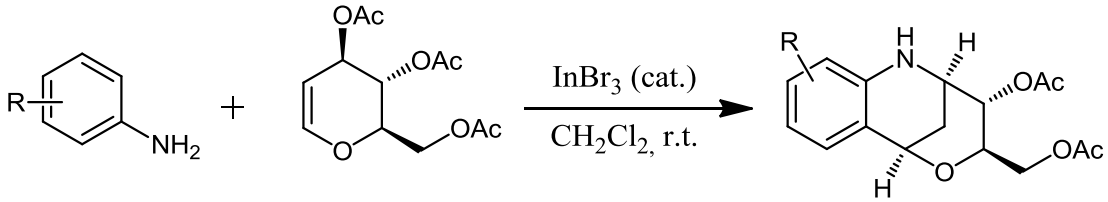


R^1= Ph, Bu; R^2= H; R^3= Me, F; R^4= H, Bu

Scheme 71. Reactions between phenylacetylene-carbaldehydes and *ortho*-alkynylanilines.

IV.1.4.2. Synthesis of Benzo-Fused Heterobicycles from D-Glucal

Many methods for the synthesis of different glycosides through Ferrier rearrangements of glucal with different nucleophiles have been reported. Different indium-catalyzed methods for glycosidation with different nucleophiles such as alcohols, phenols, thiols, etc. have also been reported. Extension of the same procedure to anilines as nucleophiles gave benzobicyclo compounds with high stereoselectivity[220] **(Scheme 72)**. It has been found that the 2,6-disubstituted anilines do not give the result. One of the important aspects of this method is that the reaction is also performable in water.



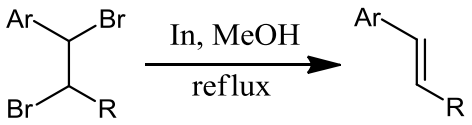
Scheme 72. $InBr_3$-catalyzed reaction of anilines with glucal.

IV.1.5. Miscellaneous Reactions

IV.1.5.1. Stereoselective Debromination of vic-Dibromides

The protection-deprotection of olefins through Bromination-debromination is an important process in organic synthesis. Although bromination generally proceeds smoothly and stereospecifically to give high yields of dibromides, debromination at a later stage in the synthesis often proves more difficult. This is primarily because the efficiency of the process is strongly dependent on the stereoselectivity of the debromination step and on the compatibility

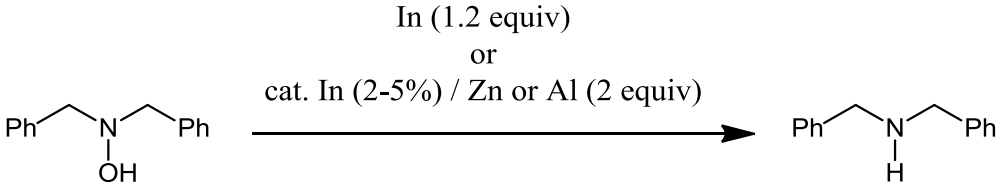
of the reagent with the carbon-carbon double bond formed and other functionalities present in the substrates. Many reagents,[221] including metals such as Zn, Mg, and Sm, have been reported in the literature to be effective in this reaction, but most of them are associated with limitations regarding selectivity and compatibility. It has been discovered[222] that aryl-substituted *vic*-dibromides undergo smooth debromination to produce the corresponding (*E*)-alkenes when treated with indium metal in MeOH **(Scheme 73)**.



Scheme 73. Indium-mediated debromination.

IV.1.5.2. Reduction of Hydroxylamines to Amines

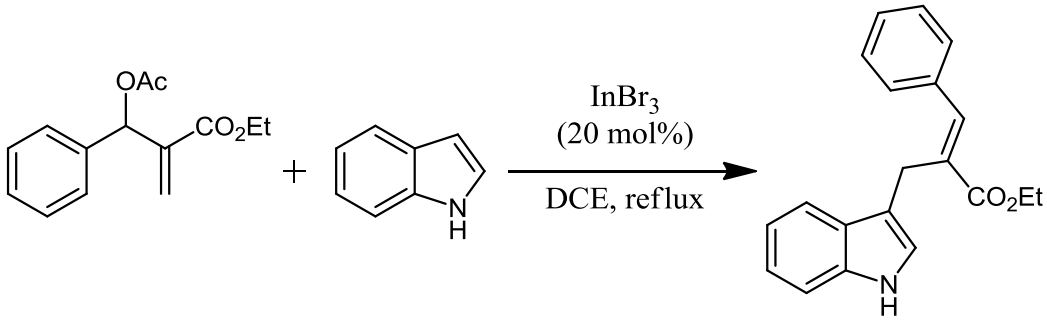
A novel and simple procedure for reduction of hydroxylamines to the corresponding amines by means of indium powder in aqueous media is reported. Applicability to one-pot reactions and isoxazolidine N-O bond reduction is also demonstrated. A catalytic version of the process using 2-5% In in the presence of other metals (Zn, Al) has been successfully developed **(Scheme 74)**.[223]



Scheme 74.

IV.1.5.3. C-Alkylation of Indoles

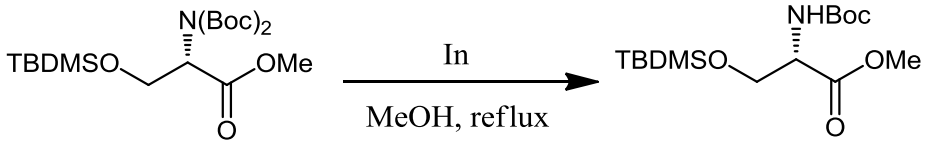
Functionalized indoles are very important synthetic intermediates. *C*-Alkylation of indoles with Baylis-Hilman acetates[224] is one method for introducing different functionalities and can be catalyzed by $InBr_3$[225] **(Scheme 75)**. Various substituted indoles also reacted smoothly to form the corresponding 3-substituted indoles.



Scheme 75. $InCl_3$-catalyzed *C*-alkylation of indoles.

IV.1.5.4. Cleavage of tert-Butoxycarbonyl Groups

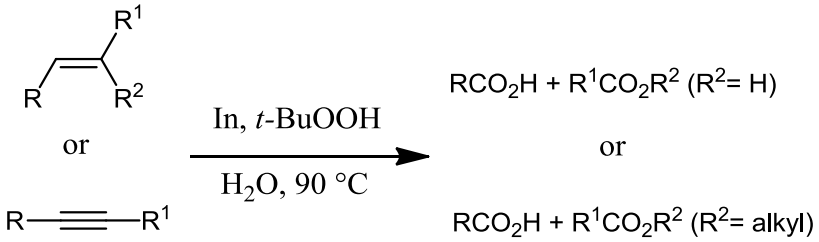
Protection and deprotection of amino groups is important in multistep synthesis, but selective removal of only one Boc group from a di-Boc-protected amine is very rare. Indium-mediated selective removal of only one Boc group from such a system has been reported[226] **(Scheme 76)**. One advantage of this method is that *N*-Boc-protected amines remain unaffected and it works only with *N*-$(Boc)_2$-protected amines to give mono-Boc-protected amines with complete retention of configuration.



Scheme 76. Indium-mediated cleavage of *tert*-butoxycarbonyl groups.

IV.1.5.5. Oxidative Cleavage of C-C Multiple Bonds by tert-Butyl Hydroperoxide

Oxidative cleavage of alkenes or alkynes to afford acids, aldehydes, and ketones is a very important reaction in organic chemistry. Even though several methods such as ozonolysis, treatment with OsO_4, etc. are available, these suffer from the toxicities of the reagents. A relatively inexpensive and safe method for the oxidative cleavage of C-C multiple bonds is very much in demand in organic synthesis. Oxidative cleavage of C-C multiple bonds in alkynes and alkenes with hydroperoxide to afford the corresponding acids or ketones has been achieved in the presence of catalytic amounts of $InCl_3$[227] **(Scheme 77).**

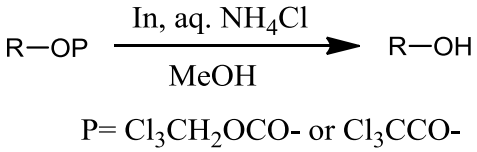


Scheme 77. $InCl_3$-catalyzed oxidative cleavage of C-C multiple bonds.

IV.1.5.6. Deprotection of trichloroethoxycarbonyl and trichloroacetyl groups

2,2,2-Trichloroethoxycarbonyl (Troc) and trichloroacetyl groups have been widely used as protecting groups in organic synthesis.[228-229] Though they are very useful protecting groups, only a few deprotection methods are available for their removal. The Troc group can be removed by zinc reduction,[228-230] electrolysis,[231] or alkenolysis.[232] In contrast, the trichloroacetyl group can be removed by ammonia[233] and alkali bases.[229] Since these conditions are not mild enough to accommodate several other functionalities, the development of a new mild method seemed worthwhile.

Valluri *et all*[234] describe a mild, chemoselective, and general method for the release of alcohols from the corresponding trichloroethoxycarbonate and trichloroacetate derivatives by refluxing the protected alcohols in the presence of indium powder and aq. NH_4Cl in methanol **(Scheme 78)**.

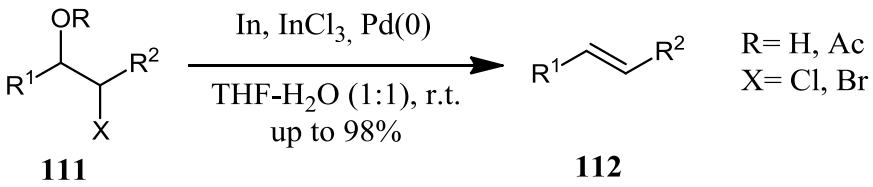


Scheme 78. Deprotection of Troc and trichloroacetyl groups using indium and aq. NH_4Cl.

IV.1.5.7. Reduction of Carbon-Halogen Bonds

The reduction of the carbon-halogen bond by indium metal in organic solvents leads to a mixture of organoindium species. [235] Various reactions in which the carbon-halogen bond is reduced by indium metal, including reduction of vicinal dibromides, aryl-substituted geminal dibromides and α-halo carbonyl compounds, reductive coupling of aryl and alkyl halides, or deprotection of trichloroacetyl and trichloroethoxycarbonyl-protected alcohols and amines, have been reviewed recently. [236] More recently, reductive elimination of halohydrins, such as chlorohydrin or bromohydrin, by indium metal was carefully investigated **(Scheme 79)**. It

was determined that the reaction required the addition of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.02 equiv) and indium(III) chloride (0.5 equiv); the reaction of the acyclic *syn*- and *anti*-halohydrins **111** afforded the corresponding (*E*)-olefins **112** exclusively. [237]



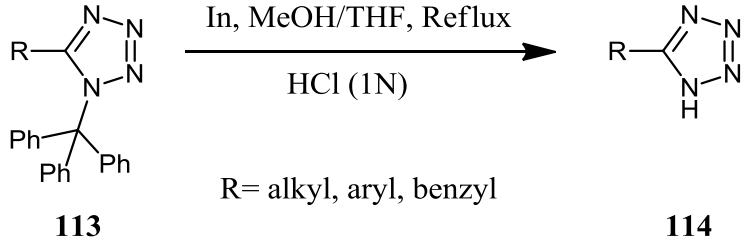
111 **112**

Scheme 79. Indium-mediated reductive elimination.

IV.2. Results and discussion

Indium and its salts have emerged as promising catalysts for effecting various functional group transformations in last two decades. There are a great number of reported reactions involving indium reagents; the versatility and the applicability of these reactions makes it a hot field to explore, and it attracts much interest from organic chemists. The development of indium reagents in C-C bond-formation reactions, coupling reactions, asymmetric synthesis in the presence of chiral-metal ligand complexes, etc. has made this field more attractive.

In the course of developing deprotection methods of many protecting groups, we attempt to remove the trityl unit using different electron transfer sources. Such as lithium, sodium, samarium and indium. The application of indium metal reductive removal of the trityl group from the nitrogen atom of several protected tetrazoles under mild reaction conditions is discussed in **Scheme 80**.



113 **114**

Scheme 80.

With the aim of determining the best reaction conditions for the removal of the trityl group bonded to the nitrogen in different tetrazoles, we took 5-phenyl-1-trityl-1*H*-tetrazole **1a** as the model compound. Unfortunately, no reaction occurred when tetrazole **1a** was treated with indium metal (1:1molar ratio) in a mixture of MeOH and THF (2:1 volume ratio) at 0°C for 24 hours. However, total conversion was observed when this reaction mixture was heated at reflux temperature for 26 hours, 5-phenyl-1*H*-tetrazole **2a** being isolated in 93% yield after column chromatography purification **(Table 20, entry 1).** In order to broad the scope of this indium-mediated detritylation, we applied the same reaction conditions to different 5-substituted tetrazoles. Detritylation of tetrazoles bearing aromatic (**1b** and **1j**) and benzylic (**1c** and **1i**) substituents at 5-position occurred also in high yields **(Table 20, entries 2, 3, 9 and 10).** Similar results were also obtained for aliphatic substituted tetrazoles. Thus, for compound

1d with a sterically demanding *tert*-butyl group at 5-position, detritylation produced 5-*tert*-butyl-1*H*-tetrazole in 92% yield **(Table 20, entry 4)**, meanwhile, in the case of tetrazole **1e** bearing a long linear aliphatic chain, the detritylated tetrazole **2e** was obtained in 81% yield **(Table 20, entry 5)**.

These reaction conditions were also highly effective in the detritylation of functionalised tetrazoles. For instance, tritylated tetrazole with a heteroaromatic 2-pyridyl substituent at 5-position gave 5-(2-pyridyl)-1*H*-tetrazole **2f** in 86% yield **(Table 20, entry 6).**

Even more interestingly, a double deprotection of ditritylated 5-amino substituted tetrazole **1g** was observed, leading to 5-amino-1*H*-tetrazole **2g** in 93% yield **(Table 20, entry 7)**. This methodology was also compatible with the presence of carbonyl groups. Detritylation of **1h** gave 1-(1*H*-tetrazole-5-yl)propan-2-one **2h** in 80% yield **(Table 20, entry 8).**

Once the reaction went to completion, final hydrolysis with 1M HCl led to the corresponding tetrazoles **114**.

Table 20 summarized the physical properties of products prepared as well as gotten yields.

Table 20: Indium-mediated Cleavage of the Trityl Group from Protected 1*H*-Tetrazoles **2a-2j**.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2a**	26	215-216	93
2	**2b**	21	149-151	96
3	**2c**	25.5	123-124	80
4	**2d**	22	208-210	92
5	**2e**	21	72-73	81
6	**2f**	23	208-210	86
7	**2g**	4	212-214	93
8	**2h**	20	152-154	88
9	**2i**	23	165-166	82
10	**2j**	20	215-216	77

The structure of compound **2a-2j** was confirmed from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and Element analysis) data. The results of spectroscopic data were sited in Chapter 3.

IV.3. Conclusion

The importance of indium metal and its salts has been well demonstrated through novel protocols for carbon-carbon bond formation, rearrangements, and a variety of useful reactions over the past decade.[138] Thus, the search for new indium derivatives for more improvement in organic transformations is of much current interest.[139]

In this chapter we have presented a very efficient method for the detritylation of protected tetrazoles using indium as an electron source. The methodology has proved to be useful for the removal of the trityl group from Tr-tetrazoles substituted on the carbon atom of the ring by aromatic, heteroaromatic, aliphatic or benzylic carbon chains, with in some cases sensitive functionalities like carbonyl and amino groups.

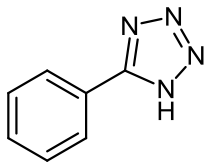
This method represents a good alternative to the commonly used detritylation procedures. Which are sensitive to air moisture and acidic conditions.

IV.4. Experimental part

General procedure

The mixture of trityltetrazole (0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) was heated at reflux temperature for 4-26h with stirring. After cooling, HCl (5 mL, 1M) was carefully added. The mixture was extracted with EtOAc (3x15 mL) and the combined organic phases were washed with brine (5 mL), and then dried (Na_2SO_4). After evaporation of the solvents, the resulting residue was purified by column chromatography (basic aluminium oxide, hexane/ethyl acetate), affording the corresponding tetrazole.

5-phenyl-1H-tetrazole (2a)[152]

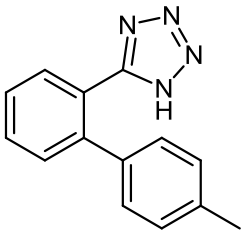


2a

Following the general procedure, the reaction of 5-phenyl-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2a** as a white solid.

- **Yield**= 93% (0.065 g).
- **Mp**= 215-216°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.55-7.62 (m, 3H), 8.01-8.02 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 124.1 (2xCH), 127.0 (C), 129.4 (CH), 131.3 (2xCH), 155.3 (C).

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

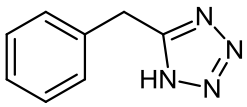


2b

Following the general procedure, the reaction of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2b** as a Brawn solid.

- **Yield**= 96% (0.085 g).
- **Mp**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH) , 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).
- **Anal. Calcd for $C_{14}H_{12}N_4$**: C, 71.17; H, 5.12; N, 23.71. **Found**: C, 70.86; H, 5.17; N, 24.07.

5-benzyl-1H-tetrazole (2c)[102]



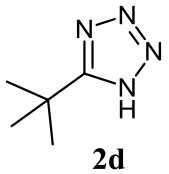
2c

Following the general procedure, the reaction of 5-benzyl-1-trityl-1*H*-tetrazole (0.20 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2c** as a white solid.

- **Yield**= 80% (0.063 g).
- **Mp**= 123-124°C.

- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).
- **Anal. Calcd for $C_8H_8N_4$**: C, 59.99; H, 5.03; N, 34.98. **Found**: C, 60.05; H, 4.80; N, 36.21.

5-(tert-butyl)-1H-tetrazole (2d)[101]

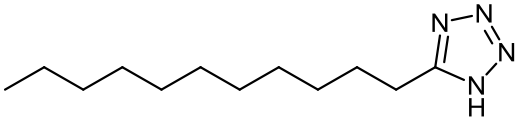


2d

Following the general procedure, the reaction of 5-(tert-butyl)-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2d** as a white solid.

- **Yield**= 92% (0.056 g).
- **Mp**= 208-210°C.
- **IR (KBr):** 2977 , 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

5-undecyl-1H-tetrazole (2e)[103]



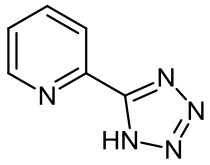
2e

Following the general procedure, the reaction of 1-trityl-5-undecyl-1*H*-tetrazole (0.23 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2e** as a Brawn solid.

- **Yield**= 81% (0.094 g).
- **Mp**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.

- **^{1}HNMR: (300 MHz, MeOD-d_4):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **^{13}CNMR: (75 MHz, MeOD-d_4):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).
- **Anal. Calcd for $C_{12}H_{24}N_4$**: C, 64.24; H, 10.78; N, 24.97. **Found**: C, 63.97; H, 10.50; N, 26.51.

Synthesis of 2-(1H-tetrazol-5-yl)pyridine (2f)[101]

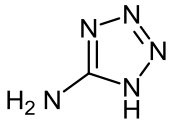


2f

Following the general procedure, the reaction of 2-(1-trityl-1*H*-tetrazol-5-yl)pyridine (0.19 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2f** as a Brawn solid.

- **Yield**= 86% (0.06 g).
- **Mp**= 208-210°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

1H-tetrazol-5-amine (2g)[175]



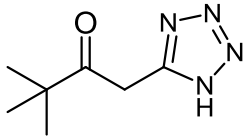
2g

Following the general procedure, the reaction of N,1-ditrityl-1*H*-tetrazol-5-amine (0.28 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2g** as a white solid.

- **Yield**= 93% (0.055 g).

- **Mp**= 212-214°C.
- **IR (KBr):** 3399 (NH_2), 3192 (NH), 1636, 1263, 1044 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 6.56 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 158.2 (C).

3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2h)[104]

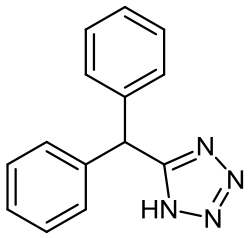


2h

Following the general procedure, the reaction of 3,3-dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one (0.20 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2h** as a Orange solid.

- **Yield**= 88% (0.07 g).
- **Mp**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

5-benzhydryl-1H-tetrazole (2i)[105]



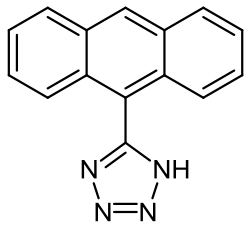
2i

Following the general procedure, the reaction of 5-benzhydryl-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2i** as a white solid.

- **Yield**= 82% (0.09 g).

- **Mp**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

5-(anthracen-9-yl)-1H-tetrazole (2j)[102]



2j

Following the general procedure, the reaction of 5-(anthracen-9-yl)-1-trityl-1*H*-tetrazole (0.24 g, 0.5 mmol) and In powder (70 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2j** as a green solid.

- **Yield**= 77% (0.092 g).
- **Mp**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

Chapter 05: Detritylation of protected Tetrazoles by Dissolving Zinc-Metal

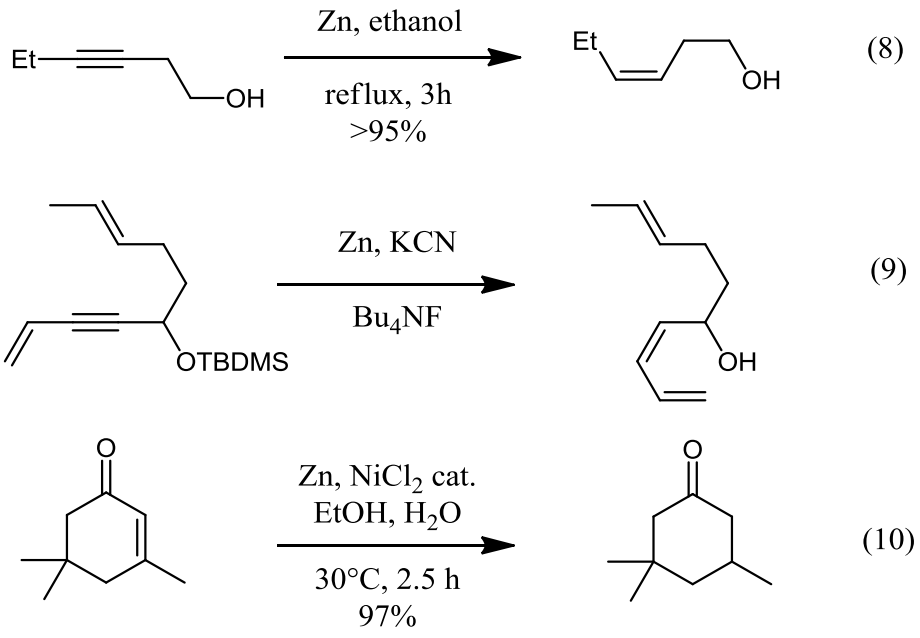
Introduction

The development of methods for sustainable, efficient, and selective synthesis of chemicals with higher values is one of the fundamental research objectives in modern chemistry. Especially, the reduction of waste and the reduction of energy demands are clearly the challenges for the future to use the steadily decreasing resources in a more efficient manner to create a sustainable society. Among all of the chemical methodologies considered thus far, heterogeneous, homogeneous, and biocatalyses offer an efficient approach to achieve this goal, which is underlined by the high impact of catalysis on industrial processes including bulk, fine agrochemicals and pharmaceuticals (~90%). In particular, metal catalysts are among the most successful examples of practical catalysis. Nevertheless, the use of most of the metals (eg., Pd, Rh, Ru, Ir) involved difficulties due to their low abundance, high price, or toxicit. Moreover, the current trend to establish a "greener" chemistry has initiated the search for more environmentally benign and sustainable alternatives. Hence, current research is focusing, on the one hand, on replacement with cheaper and low toxic metals and, on the other, on the discovery of new protocols with such metals. In this regard, the application of zinc can be of great interest because of its general abundance (twenty-fourth (0.0076%) in the earth crust) and high concentration in ores. For instance, one major mined source for zinc is the mineral Sphalerite, which contains significant amounts of zinc sulfide (~60% zinc concentration) and variable amounts of iron. In contrast to other metals, zinc is easily extracted from the minerals in high purity.

V.1. Reduction of Carbon-Carbon Multiple Bonds

Whereas isolated double bonds are rarely reduced by zinc, triple bonds are cleanly converted to alkenes using either ***Zinc/Copper Couple*** or ***Zinc Amalgam.***[240] A regio- as well as stereospecific reduction of a wide range of alkynic derivatives can be performed using zinc powder (eq 8**).**[241] The reduction of propargylic alcohols proves to be especially efficient (eq 9**).**[242] Also, the selective *cis* reduction of conjugated dienynes and trienynes proceeds well with Zn(Cu/Ag).[243] The presence of a leaving group at the propargylic position leads to the formation of allenes.[244] The conjugation of a double bond with an electron-withdrawing substituent considerably facilitates the reduction of the double bond.[245] The reduction of α**,** β-unsaturated ketones produces the corresponding saturated ketones.[246] Nickel catalysis allows

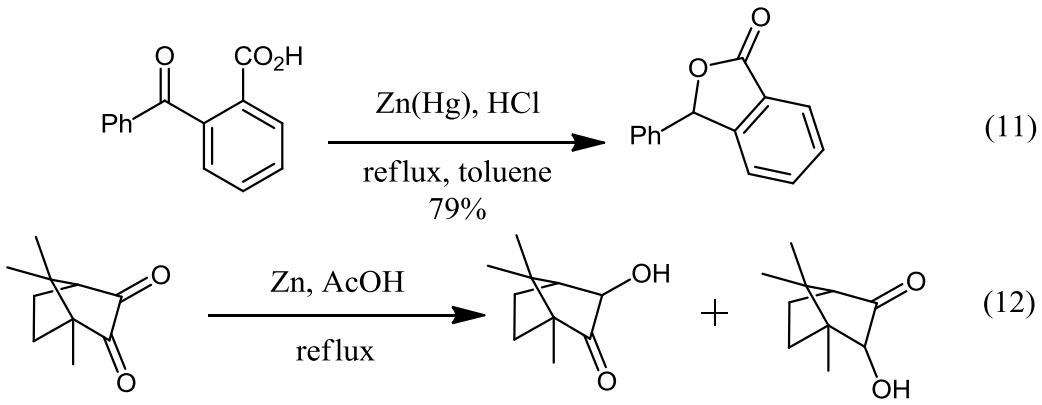
the reduction of unsaturated aldehydes, ketones, and esters in an aqueous medium under ultrasonic irradiation (eq 10)[247] (**Scheme 81).**



Scheme 81.

V.2. Reduction of Carbonyl Groups

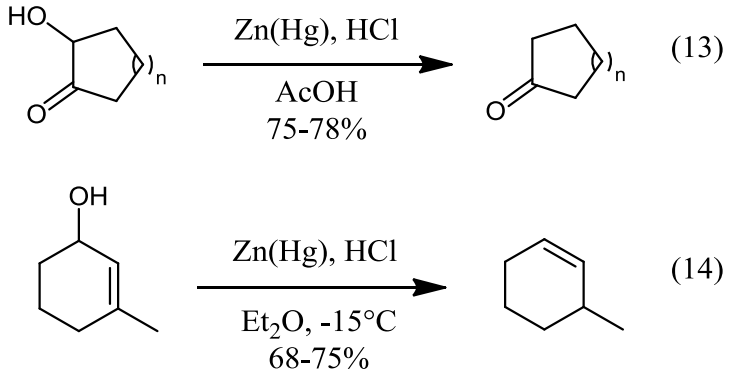
Zinc reduces ketones to either alcohols or to a methylene unit, depending on the reaction conditions and the nature of the substrate. For example, conjugation is required if reduction to a hydroxy group is desired. The reduction of aryl ketones provides benzylic alcohols (eq 11)[248] and α-diketones can be converted selectively to α-hydroxy ketones (eq 12)[249] (**Scheme 82)**.



Scheme 82.

V.3. Reduction of Carbon-Oxygen Bonds

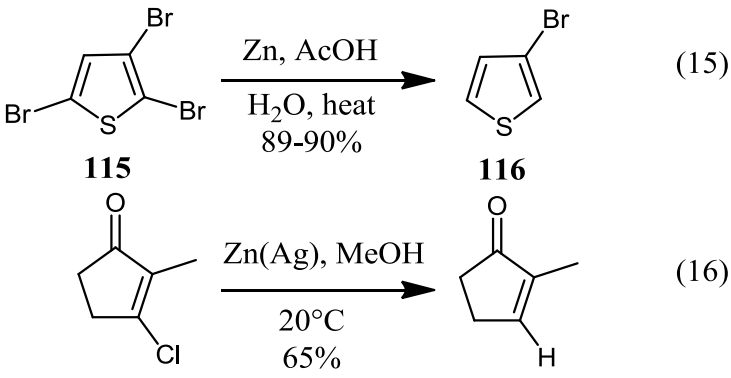
Carbon-oxygen bonds situated α to an unsaturation are easily reduced with zinc in an acidic medium. In the case of α-hydroxy ketones, ketones are obtained in good yields (eq 13).[250] A wide range of allylic or benzylic ethers, acetates, and alcohols are reduced with zinc (eq 14)[251-252] (**Scheme 83)**.



Scheme 83.

V.4. Reduction of Carbon-Halide Bonds

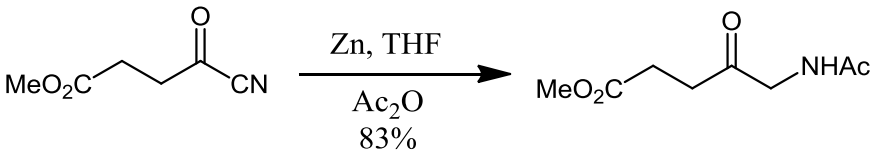
Alkyl and alkenyl halides are readily reduced with zinc under various reaction conditions. The reduction produces, as an intermediate, an organic radical which can undergo carbon-carbon bond formation (Barbier reaction)[253] or can be further reduced, usually under acidic conditions. Aliphatic iodides or bromides and benzylic chlorides react readily with ***Zinc-Acetic Acid,*** providing the corresponding hydrocarbon.[254] Although aromatic halides are reduced less easily, the tribromothiophene **115** is reduced selectively to the bromide **116** (eq 15).[254e-g] Various β-chloro enones are cleanly reduced to enones with ***Zinc/Silver Couple*** in methanol at r.t (eq 16)[254] (**Scheme 84)**.



Scheme 84.

V.5. Reduction of Carbon-Nitrogen Bonds

Aldimines and oximes are converted to amines, and various heterocycles bearing carbon-nitrogen double bonds are reduced with zinc under acidic conditions.[255] Cyanamides can be cleanly cleaved leading to amines[256a] and the zinc reduction of acylnitriles provides α-amino ketone derivatives[256b] (**Scheme 85)**. Aromatic amides can be reduced with zinc dust to aromatic aldehydes.[256c] Activated carbon-sulfur bonds α to a carbonyl group[257a-b] and sulfur ylides[257c-d] can be reduced with zinc.



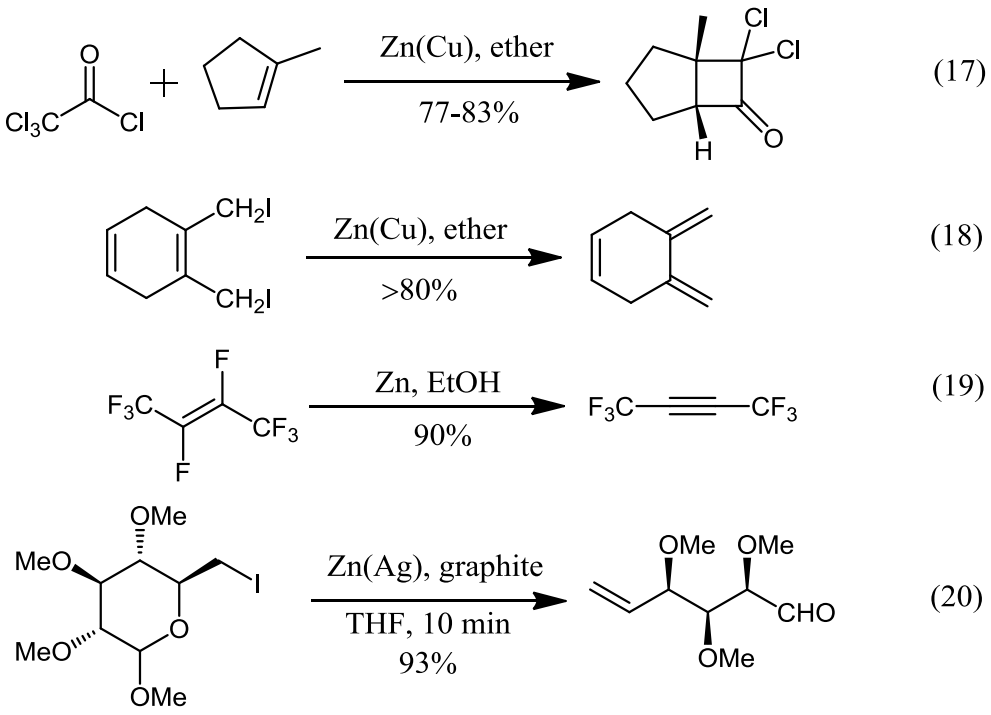
Scheme 85.

V.6. Reduction at Heteroatoms[261]

Nitrogen-oxygen bonds of oximes[258] nitro,[259] and nitroso[260] groups are readily reduced by zinc in acidic medium. Zinc in acetic acid has often been used for the workup procedure of alkene ozonolysis to afford aldehydes or ketones.[261] Sulfinates and thiols can be obtained selectively by the reduction of aromatic sulfonyl chlorides or disulfides.[262]

V.6.1. Dehalogenation and Related reaction[263]

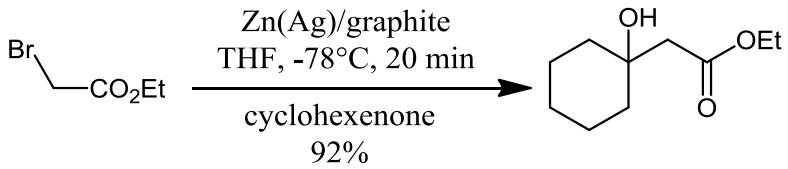
Zinc dust is a very efficient reducing agent for the dehalogenation of 1,2-dihalides or 1-halo-2-alkoxy derivatives, leading to alkenes. The reaction allows an access to highly reactive ketenes,[264] alkenes[265] or alkynes[266] not readily available by standard methods (eqs 17-19). The reduction of β-alkoxy halides using ***Zinc-Graphite*** proved to be especially interesting when applied to sugar derivatives (eq 20).[263a-267] The dehalogenation using zinc is such a straightforward and chemoselective reaction that several protecting groups have been devised which use this reaction as a deblocking step[268] (**Scheme 86)**.



Scheme 86.

V.6.2. The Reformatsky Reaction

The insertion of zinc into α halo esters produces zinc ester enolates which react readily with aldehydes or ketones, leading to aldol products. Historically, this reaction has been important since it allowed the first quantitative generation of an ester enolate. However, several modern synthetic methods for the stereoselective preparation of aldol products using metal enolates compete favorably with the Reformatsky reation.[269] The nature of the zinc activation has proved to be important for fast and quantitative zinc insertion. Remarkably, the Zn(Ag) couple on graphite reacts with ethyl bromoacetate at -78°C within 20 min,[270a] whereas Rieke zinc requires 1h at 25°C,[270b] as does zinc generated from the reaction of ***Zinc Chloride*** with ***Lithium*** under ultrasound irradiation[270c] (**Scheme 87)**.



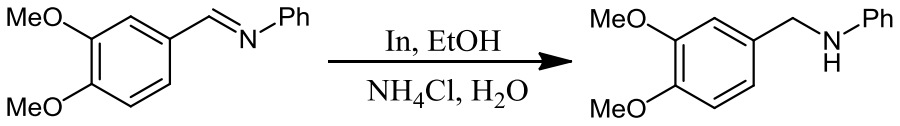
Scheme 87.

V.7. Dissolving metals

Dissolving metals have been used extensively as reducing agents for more than a century but today they have been partially displaced from the central field of organic synthesis by the use of other more selective methodologies, such as metal hydrides[269] and catalytic hydrogenations.[270] However, dissolving metals are still of interest for the selective reduction of specific polar functional groups (such as hindered cyclic ketones) and the reductive cleavage of some activated bonds.[271]

V.7.1. Reduction of Imines

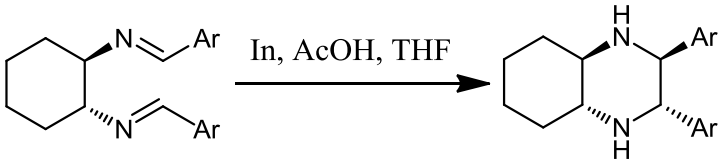
Imines are reduced by means of dissolving metals to give amines. The most common combinations are Na, Al and Mg in alcoholic solvent and Zn-NaOH.[272] More recently, the treatment of *N*-benzylideneaniline with In powder in ethanolic aqueous ammonium chloride gave a mixture of all the diamine isomers in good yield. Attempted extension of the reaction to the imine **117** resulted in the simple reduction of the C=N bond to the benzylic amine **118** (**Scheme 88)**.



117 **118**

Scheme 88.

However, the imine coupling could be carried out intramoleculary. Thus, treatment of the bis-imine **119** with In in THF in the presence of acetic acid gave decahydroquinoxaline **120** in good yield as a single diastereomer (**Scheme 89)**.

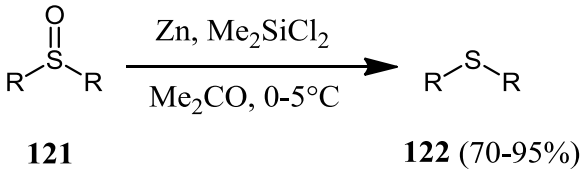


119 (Ar= 4-MeC_6H_4) **120** (80%)

Scheme 89.

V.7.2. Reduction of Sulfoxides

The reduction of sulfoxides has been reviewed extensively.[273] Many low-valent transition metals (Mo(II), Mo(III), Ti(II), V(II), W(II)) have been found to be effective in the deoxygenation of sulfoxides. Deoxygenation of sulfoxides **121** was also achieved using a combination of Zn and Me_2SiCl_2 in acetone as the reducing combination to give sulfides **122** (**Scheme 90)**.

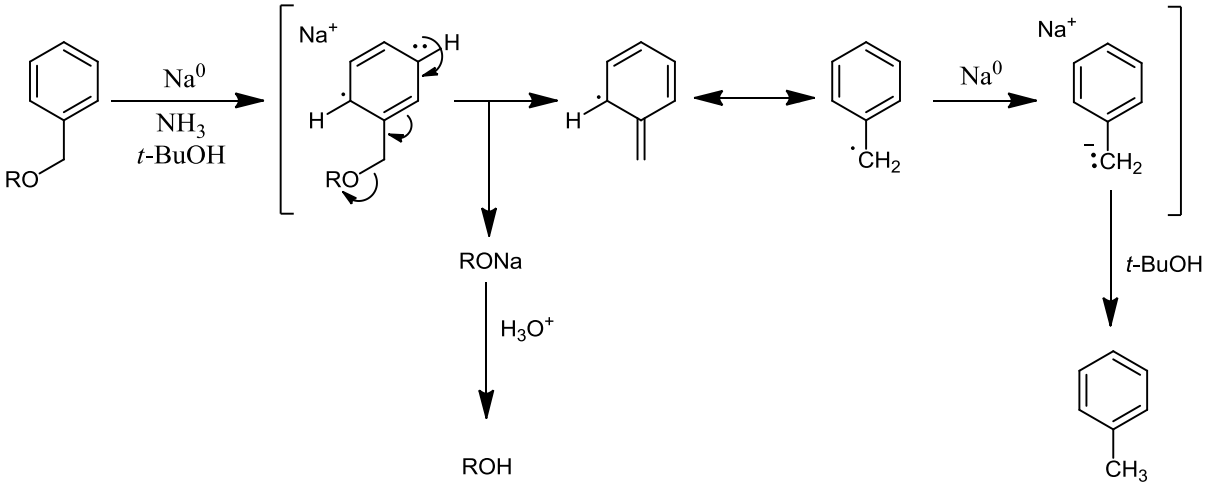


121 **122** (70-95%)

Scheme 90.

V.7.3. Protecting groups cleaved by dissolving metal reduction

Sodium or lithium in liquid ammonia cleave benzylic ethers and esters in the presence of a proton source to provide a pentadienyl anion expels an alkoxide or carboxylate leaving group **(Scheme 91)**. Aqueous acidic workup returns the carboxylic acid or alcohol and toluene. Many functional groups are anable to survive such powerful reducing conditions.



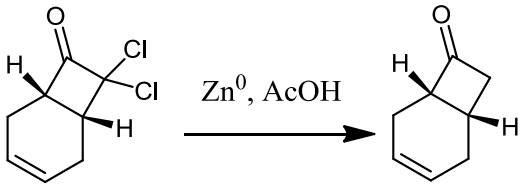
Scheme 91.

V.7.4. Reduction with Zinc

For many years, zinc has been an importent metal for reduction of organic molecules. The most common reducing medium is zinc dust in acetic acid or HCl. Zinc in acetic acid is a

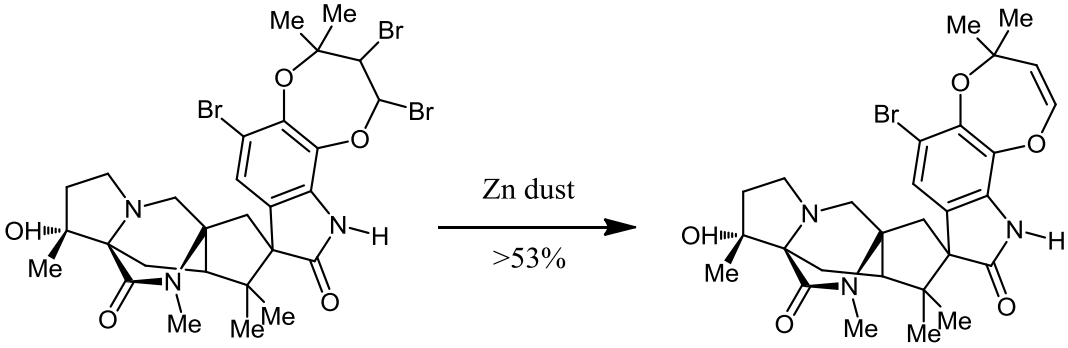
very effective reagent for reduction of α-haloketones, as with α,α-dichloro ketone **123,** which was converted to **124** (eq 21). Alkyl bromides and chlorides react with zinc and acetic acid very slowly when the halogen is not conjugated to a carbonyl. Reduction of primary iodides is relatively fast, and this method is commonly used to insert methyl groups in a synthetic target.

Another reaction is observed when a molecule contains two halogen atoms on adjacent carbon atoms (a vertical dihalide). Reductive dehalogenation to the alkene is a useful process, as seen in the conversion of **125** to **126** (eq 22) in >53% yield **(Scheme 92)**.



(21)

123 **124**

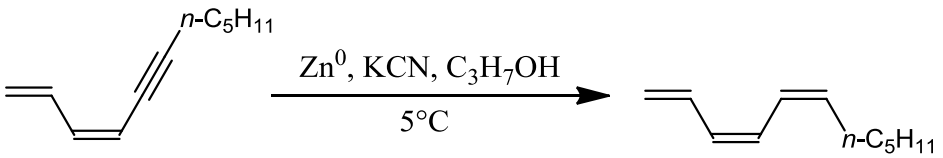


(22)

125 **126**

Scheme 92.

It was previously mentioned that zinc reduces alkynes to alkenes. Näf showed that reduction of alkyne **127** to conjugated cis alkene **128** occurred with zinc in the presence of potassium cyanide (KCN) **(Scheme 93)**.



127 **128**

Scheme 93.

V.8. Results and discussion

In this report we describe a novel and catalytic method for detritylation using zinc in a mixture of MeOH and THF (2:1 volume ratio) at reflux temperature. The procedure is highly selective to deprotect trityl tetrazoles leaving other functional groups antact. Trityl tetrazoles are deprotected in high yield (67-98%) within 3-19h of reaction time. Further, the cleavage also proceeded smoothly with a catalytic amount of Zn metal (1:1 molar ratio) in refluxing mixture of MeOH and THF (2:1 volume ratio).

Our methodology was successfully applied to the detritylation of protected tetrazoles **(Table 21, entries 1-10)**. Trityl group could easily be removed from an acyclic and a cyclic protected tetrazoles. 5-phenyl-1*H*-tetrazole **2a** was obtained in a very good yield **(Table 21, entry 1)**. Detritylation of two other protected tetrazoles bearing aromatic substituents **1b** and **1j** under the optimized reaction conditions gave the expected free tetrazoles **2b** and **2j** in 92 and 67% yield, respectively **(Table 21, entries 2 and 10)**. A tritylated tetrazole bearing a heteroaromatic 2-pyridyl substituent was also deprotected with very good results **(Table 21, entry 6)**. The benzylic substituents of protected tetrazoles were unaffected by these reaction conditions, leading to the expected deprotected tetrazoles **2c** and **2i** in 91 and 88% yield, respectively **(Table 21, entries 3 and 9).** The detritylation procedure was also effectively applied to tetrazoles **2d**, **2e** and **2g** wich were substituted on the carbon atom of the ring with aliphatic chains **(Table 21, entries 4, 5 and 7)**. Interestingly, compound which contains a keto-functionalized substituent, could be detritylated under our mild reaction conditions without affecting the carbonyl group. As a result, 3,3-dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one **2h** was isolated in 80% **(Table 21, entry 8)**.

Table 21: Cleavage of the Trityl Group from Protected 1*H*-Tetrazoles **2a-2j**.

Entry	Product	Time(h)	mp(°C)	Yield(%)
1	**2a**	3	215-216	92
2	**2b**	19	149-151	91
3	**2c**	12	123-124	75
4	**2d**	2	208-210	93
5	**2e**	11	72-73	94
6	**2f**	8	208-210	80
7	**2g**	11	138-140	84
8	**2h**	4	152-154	80

9	**2i**	13	165-166	88
10	**2j**	11	215-216	67

The structure of compound **2a-2j** was confirmed from spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and Element analysis) data. The results of spectroscopic data were sited in Chapter 3.

V.9. Conclusion

The development of a neutral alternative would extend the scope of the trityl protective group in peptide synthesis.[149] Recently, metal mediated reactions have attracted much interest in organic synthesis because of their high reactivity, stability and selectivity. Particularly, zinc metal has gained more popularity, owing to its unique reactivity and stability in aqueous media. However, there are no reports on the partial deprotection of trityl using zinc or indium metal.

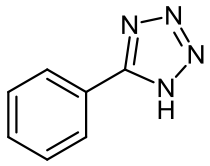
In this chapter we describe a new and efficient procedure for the selective removal of the trityl group from protected tetrazoles **1a-1j** using zinc metal under mild conditions which leads to the corresponding deprotected tetrazole.

V.10. Experimental part

General procedure

The mixture of trityltetrazole (0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) was heated at reflux temperature for 2-19h with stirring. After cooling, HCl (5 mL, 1M) was carefully added. The mixture was extracted with EtOAc (3x15 mL) and the combined organic phases were washed with brine (5 mL), and then dried (Na_2SO_4). After evaporation of the solvents, the resulting residue was purified by column chromatography (basic aluminium oxide, hexane/ethyl acetate), affording the corresponding tetrazole.

5-phenyl-1H-tetrazole (2a)[152]

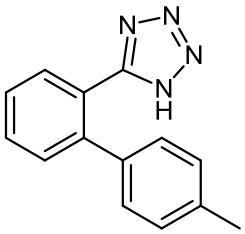


2a

Following the general procedure, the reaction of 5-phenyl-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2a** as a white solid.

- **Yield**= 92% (0.045 g).
- **Mp**= 215-216°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.55-7.62 (m, 3H), 8.01-8.02 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 124.1 (2xCH), 127.0 (C), 129.4 (CH), 131.3 (2xCH), 155.3 (C).

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

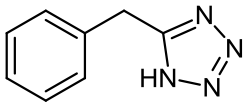


2b

Following the general procedure, the reaction of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole (0.19 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2b** as a Brawn solid.

- **Yield**= 91% (0.058 g).
- **Mp**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH), 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).
- **Anal. Calcd for $C_{14}H_{12}N_4$**: C, 71.17; H, 5.12; N, 23.71. **Found**: C, 70.86; H, 5.17; N, 24.07.

5-benzyl-1H-tetrazole (2c)[102]



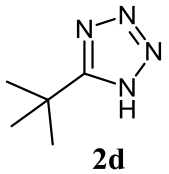
2c

Following the general procedure, the reaction of 5-benzyl-1-trityl-1*H*-tetrazole (0.20 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2c** as a white solid.

- **Yield**= 75% (0.03 g).
- **Mp**= 123-124°C.

- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).
- **Anal. Calcd for $C_8H_8N_4$**: C, 59.99; H, 5.03; N, 34.98. **Found**: C, 60.05; H, 4.80; N, 36.21.

5-(tert-butyl)-1H-tetrazole (2d)[101]

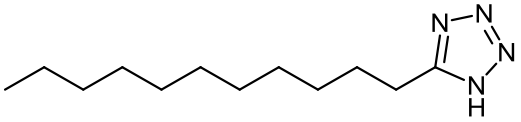


2d

Following the general procedure, the reaction of 5-(*tert*-butyl)-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2d** as a white solid.

- **Yield**= 93% (0.025 g).
- **Mp**= 208-210°C.
- **IR (KBr):** 2977, 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

5-undecyl-1H-tetrazole (2e)[103]



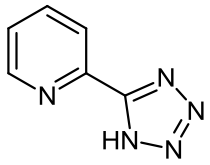
2e

Following the general procedure, the reaction of 1-trityl-5-undecyl-1*H*-tetrazole (0.23 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2e** as a Brawn solid.

- **Yield**= 94% (0.064 g).
- **Mp**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.

- **^{1}HNMR: (300 MHz, MeOD-d_4):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **^{13}CNMR: (75 MHz, MeOD-d_4):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).
- **Anal. Calcd for $C_{12}H_{24}N_4$**: C, 64.24; H, 10.78; N, 24.97. **Found**: C, 63.97; H, 10.50; N, 26.51.

Synthesis of 2-(1H-tetrazol-5-yl)pyridine (2f)[101]

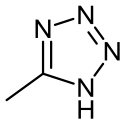


2f

Following the general procedure, the reaction of 2-(1-trityl-1*H*-tetrazol-5-yl)pyridine (0.19 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2f** as a Brawn solid.

- **Yield**= 80% (0.039 g).
- **Mp**= 208-210°C.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

5-methyl-1H-tetrazole (2g)[102]



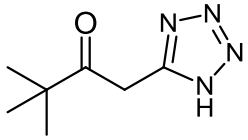
2g

Following the general procedure, the reaction of 5-methyl-1-trityl-1*H*-tetrazole (0.12 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2g** as a white solid.

- **Yield**= 87% (0.0013 g).

- **Mp**= 138-140°C.
- **IR (KBr):** 3005 (NH), 2879 (CH_3), 2605 (C=N), 1578, 1565, 1112, 1052, 899, 683 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 2.46 (s, 3H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 8.4 (CH_3), 152.2 (C).
- **Anal. Calcd for $C_2H_4N_4$**: C, 28.57; H, 4.80; N, 66.64. **Found:** C, 28.77; H, 4.70; N, 71.13.

3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2h)[104]

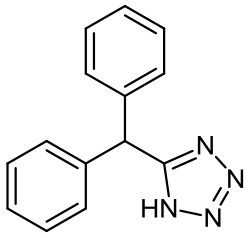


2h

Following the general procedure, the reaction of 3,3-dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one (0.20 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2h** as a Orange solid.

- **Yield**= 80% (0.032 g).
- **Mp**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

5-benzhydryl-1H-tetrazole (2i)[105]

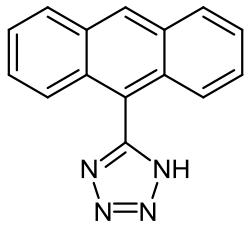


2i

Following the general procedure, the reaction of 5-benzhydryl-1-trityl-1*H*-tetrazole (0.23 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2i** as a white solid.

- **Yield**= 98% (0.063 g).
- **Mp**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

5-(anthracen-9-yl)-1H-tetrazole (2j)[102]



2j

Following the general procedure, the reaction of 5-(anthracen-9-yl)-1-trityl-1*H*-tetrazole (0.24 g, 0.5 mmol) and Zn powder (32 mg, 0.5 mmol) in MeOH/THF (6 ml/3 ml) gave **2j** as a green solid.

- **Yield**= 67% (0.04 g).
- **Mp**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **^{1}HNMR: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **^{13}CNMR: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

General Conclusion

General Conclusion

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Tetrazoles as a group of heterocyclic compounds are reported to possess a broad spectrum of biological activities such as antibacterial, antifungal, antiviral, analgesic, anti-inflammatory, antiulcer and antihypertensive activities. Also, 5-substituted-1*H*-tetrazoles can function as lipophilic spacers and carboxylic acid surrogates,[6,7,8] specialty explosives and information recording systems in materials ligands,[2,3,4] and precursors of a variety of nitrogen containing heterocycles in coordination chemistry.

The main objective of this work is the preparation of some new heterocyclic compounds which is tetrazoles and protected tetrazoles and developing an efficient method to remove the trityl group from protected tetrazoles.

This manuscript encloses five principal parts: In the first two parts, we have described the synthesis and protection of many tetrazoles using trityl chlirode as protecting group.

In the third part, we have reported the treatment of *N*-tritylated tetrazoles bearing aliphatic, aromatic, or heteroaromatic substituents (including functionalized ones) with lithium powder and a catalytic amount of naphthalene led to reductive removal of the trityl group to give excellent yields of the corresponding free tetrazoles without decomposition of the tetrazole ring. The detritylation process was successfully extended to several tetrazoles that are components of sartans, an interesting class of drugs. This method represents an efficient technique for deprotection of tritylated tetrazoles under non-acidic conditions.

Similarly, we have reported in two other parts, the reductive removal of trityl group from same *N*-tritylated tetrazoles according to reaction catalyzed by indium or zinc.

Our work opens a large perspective in the protection and deprotection of variety of functional groups such as triazoles, indoles and thioles groups using diffrent electron transfer sources.

Résumé de la thése

Introduction Générale

La chimie des composés azotés est la source privilégiée de nombreux sujets d'étude en chimie organique. L'atome d'azote est présent dans de nombreuses molécules naturelles d'intérêt pharmacologique et de très nombreuses méthodes ont été mises au point pour accéder aux composés azotés, notamment hétérocycliques. Quelques unes d'entre elles ont été explorées, à travers la chimie des tétrazoles.

Cet intérêt est encore stimulé par la mise en évidence des activités pharmacologiques variées que présentent la majorité de ces composés.

Parmi les différentes classes de ces composés, les tétrazole et les tétrazoles protégés qui jouent un rôle intéressant comme squelette de base pour la synthèse de beaucoup d'autres produits pharmacologiquement et biologiquement actifs où on les trouve comme: anti-inflammatoire[37], anti-allergique[38], antifongiques, antibactériens, anticancéreux. Leur intérêt dans la chimie médicinale est lointain pour venir à une fin**.**

La découverte de nouvelles réactions, capables de former plusieurs liaisons, en une seule étape, avec de bons rendements globaux, tout en respectant l'environnement, est donc devenue un défi important pour le chimiste organicien. Ainsi, les réactions de protéction et déprotéction, qui répondent à l'ensemble de ces critères, jouent un rôle innovateur et font l'objet d'une attention toute particulière.

L'objectif majeur de ces travaux de thèse est lié au réexamen et au développement des nouvelles méthodes de déprotéction des différents tétrazoles protégés par le trityl groupe en utilisant plusieurs métaux qui sont le lithium (Li), le zinc (Zn) et l'indium (In).

Notre thèse est constituée en cinq chapitres. Le premier chapitre est consacré à une revue bibliographique sur l'intérêt biologiques et les différentes méthodes de synthèse des tetrazoles, la première partie de ce travail sera consacrée à la synthèse du dérivé des tétrazoles. Le deuxième chapitre concerne la protéction des differents dérivés des tétrazoles.

Les trois autres chapitres sont consacrés pour un axe de recherche développé dans notre laboratoire, objet de la déprotéction des tétrazoles protégé par le lithium, le zinc et l'indium. Voir le schéma réactionnel général (general introduction page 2).

VI.1. Les tetrazoles

Les besoins recents en chimie organique de synthese appliquee focalisent les efforts des chercheurs au developpement de nouvelles voies efficaces et versatiles pour la preparation de molecules bioactives, en prenant en comptes en particulier les criteres economiques et environnementaux. Nous avons developpe une methode novatrice et ecologique pour la preparation de tetrazoles.[141,142] Ce groupe fonctionnel trouve des applications dans des domaines varies allant des materiaux aux explosifs, et est d'un interet tout particulier en chimie medicinale.[1]

Cette importance a conduit au développement de diverses methodes de preparation des tetrazoles, toutes presentant cependant des desavantages majeurs comme l'utilisation de reactifs toxiques ou explosifs, entre autres. La methode alternative que nous avons développé permet la formation de tetrazoles a partir de nitriles en utilisant des soduimes d'azides, qui possedent l'avantage d'etre des reactifs bon marche et non toxiques et permettent la preparation d'une large variete de tetrazoles de facon tres efficace, adaptable a l'echelle industrielle **(Schéma 29 Chapitre I)**.

VI.1.1. Définition

Les tétrazoles sont des composés hétérocycliques, le premier de la série est pentatomique, il comprend quatre atomes d'azote et a pour formule chimique CN_4H_2, avec une masse molaire de 70.05g/mole et une de densité 1.477g/ml. Les tétrazoles sont aussi nommés pyrrotriazoles.[274]

VI.1.2. Propriétés physiques et aspects thermodynamiques des tétrazoles

VI.1.2.1. Les points d'ébullition et de fusion des tétrazoles

Les points de fusion et d'ébullition d'un tétrazole se situent dans les intervalles respectifs suivants: [156-158°C] et [220±23°C],[275] ils diminuent de façon remarquable selon la substitution du tétrazole.

VI.1.2.2. La Solubilité des tétrazoles

La substitution d'un tétrazole au niveau du carbone ou de l'un des azotes du cycle, modifie ses propriétés physico-chimiques, entre autres; sa solubilité dans les solvants

organiques. Par exemple les tétrazoles substitués en position 2 et 5, sont solubles dans l'éthanol.[276] Les valeurs de la conductivité des sels de métaux alcalins et des sels d'ammonium du 5-phényl-tétrazole suggèrent aussi leur solubilité dans les solvants organiques. A de faibles concentrations (10-3M), ces sels se décomposent complètement dans les solvants organiques tels que l'acétonitrile (MeCN), le nitrométhane ($MeNO_2$) et le diméthyle sulfoxide (Me_2SO).[277]

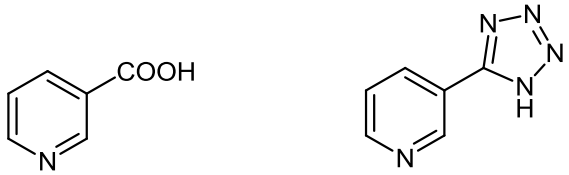
Les tétrazoles monosubstitués RCN_4H, comme leurs analogues les acides carboxyliques RCO_2H, sont très solubles dans l'eau et donc ne peuvent pas y cristalliser. Par contre, ils cristallisent très bien dans des solvants comme l'acétate d'éthyle, le mélange toluène-pentane. Les tétrazoles substitués 5-aryl sont, en général, facilement recristallisés dans les alcools.[277]

VI.1.3. Domaines d'applications et intèrêt des tétrazoles

VI.1.3.1. Les applications dans le domaine médical et biologique

De nombreux tétrazoles sont des composés biologiquement actifs, prenons l'exemple du 1,5-pentaméthylènetétrazole (appelé pentétrazole ou encore cardiazole), il est utilisé en médecine comme stimulant cardiaque et respiratoire et est également employé contre les empoisonnements aux barbituriques.[278]

Pour chaque acide carboxylique biologiquement actif, il existe un composé ayant la même structure spatiale, biologiquement actif ; dans lequel, le groupement carboxyl est remplacé par un fragment de substituant-5-yl.[278] Par exemple, le tétrazole analogue de l'acide nicotinique schématisé ci-dessous, a la propriété de réduire le taux de gras et de cholestérol dans le sang:



Acide nicotinique Tétrazole Analogue

Figure 19.

VI.1.3.2. Les applications dans le domaine de l'agriculture

En agriculture, les tétrazoles sont employés essentiellement comme régulateurs de croissance des herbicides, fongicides et plantes.[279] Leur action sur la croissance des plantes, peut les rendre, et ce par une légère modification de leur structure, des stimulateurs ou inhibiteurs de croissance.

Ainsi, le bis-tétrazolyl-dichlorométhane, est un inhibiteur de croissance de la laitue et de l'avoine:

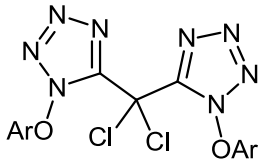
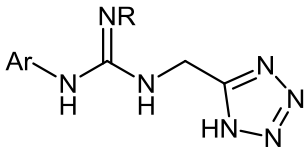


Figure 20.

VI.1.3.3. Les applications dans le domaine des édulcorants

Des substituants tétrazoles, d'acides carboxyliques, ont été introduits dans le domaine des édulcorants artificiels.[280] Une large gamme de tétrazol-yl-guanidines comme schématisé ci-après, a été brevetée, comme édulcorants.[281]



Tétrazol-yl guanidines

Figure 21.

VI.2. Protéction des Tétrazoles

Le but d'une protection est de préserver une fonction intacte. Ainsi, en protégeant une fonction on la préserve en l'empêchant de réagir. La fonction ainsi protégée n'est plus la fonction d'origine, elle ne réagit donc plus de la même façon vis-à-vis des différents réactifs. Il est alors possible de protéger une fonction réactive de façon de faire de nombreuses étapes d'aménagement fonctionnel sur d'autres parties de la molécule. Puis, lors d'une ultime étape de déprotection on récupère la fonction protégée précédemment. Il apparaît alors que les étapes de protection et de déprotection sont des étapes qui doivent se faire avec des rendements proches de 100%.

VI.2.1. Les Groupements Protecteurs

Le groupement protecteur est caractéristique d'une ou de plusieurs fonctions. Il est généralement utilisé en synthèse multi-étapes pour bloquer une fonction choisie, il doit résister aux conditions réactionnelles. Il peut également coexister avec un autre groupement orthogonal sur la même molécule, ce qui permet la protection/déprotection de façon sélective.

Un groupement protecteur devient très intéressant lorsqu'il est:

- Facile à greffer sur la fonction à protéger d'une part et facile à cliver d'autre part afin de retrouver la fonction originale avec des bons rendements.
- Stable dans les conditions de réactions ultérieures projetées.
- Facile à caractériser par les méthodes d'analyse (RMN, SM, IR, etc.).
- Stable vis-à-vis les techniques de séparation et de purification comme la chromatographie.
- Le coût de la réaction de protection et de déprotection d'un groupement ne doit pas être trop élevé.
- Le produit de la déprotection doit être facile à séparer du résidu de la protection.

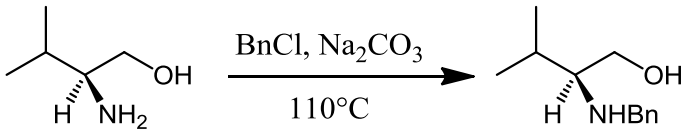
VI.2.2. Protection de la fonction amine

Plusieurs composés organiques biologiquement actifs contenant la fonction amine, ont fait l'objet de plusieurs travaux de protection/déprotection ces dernières années en synthèse organique.[282] Dans ce cadre, la conception de nouvelles méthodes douces et efficaces pour la protection/déprotection de la fonction amine devient une priorité.

VI.2.2.1. Alkyl amine R-NH-R'

Le groupement *N*-Bn est commodément clivé par hydrogénolyse par rapport l'éther benzylique.[283] La protection *N*-Bn est largement utilisé en synthèse organique vue la stabilité de ce motif dans diverses conditions réactionnelles (traitement acide/base et les catalyseurs nucléophiles).

Le groupement benzyle est introduit sélectivement sur la fonction amine de l'amino alcool **129** à l'aide du chlorure de benzyle en présence de carbonate de sodium.[284] (**Schéma 94).**

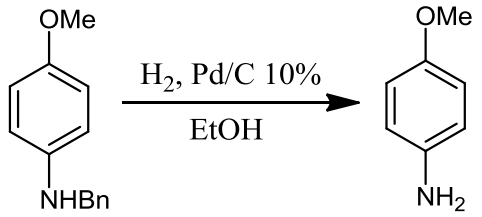


129 **130**

Schéma 94. Formation sélective de *N*-Bn *vs O*-Bn.

Clivage

Le groupement *N*-Bn peut être clivé par hydrogénolyse en présence de Pd/C dans EtOH **(Schéma 95)**.[285]



131 **132**

Schéma 95. Déprotection du groupement benzyle par hydrogénolyse.

VI.2.2.2. Carbamates

Les carbamates ont été employés pour la protection de la fonction amine. En effet, le doublet électronique libre porté par l'azote n'est pas réactif et est engagé en mésomérie avec le carbamate, il est alors possible de faire des aménagements fonctionnels sans un caractère nucléophile prononcé de l'amine.

VI.2.2.2.1. Le tert-Butyloxycarbonyle (N-Boc)

L'efficacité des carbamates *tert*-butyliques est due à leur stabilité dans diverses conditions réactionnelles comme les attaques nucléophiles, les traitements basiques modérés et l'hydrogénation catalytique.[286]

Heydari *et al*[287] ont développés une méthode efficace avec de bons rendements. La *N*-*tert*-butoxycarbonylation des amines primaires et secondaires est effectuée dans un milieu hétérogène en utilisant le di-*tert*-butyle dicarbonate en présence d'hétéropolyacide $H_3PW_{12}O_{40}$ **(Schéma 96)**.

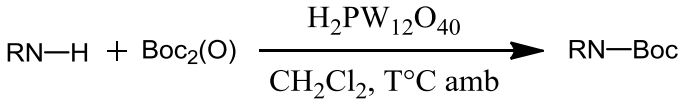
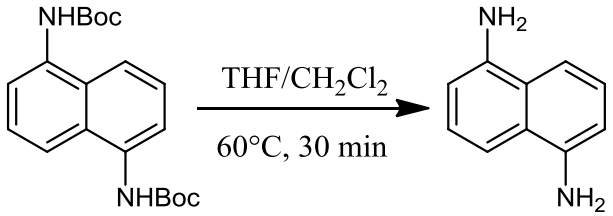


Schéma 96. *N-tert*-butoxycarbonylation sélective en présence de HPA ($H_3PW_{12}O_{40}$).

Clivage

La déprotection chimiosélective *N*-Boc est communément réalisé par un traitement acide et est accomplie rapidement en utilisant 5 équivalents de TFA à 60°C pendant 30 min.[288] **(Schéma 97)**. La sélectivité de cette méthode de déprotection *N*-Boc est approuvé par la préservation de l'éther OTBDMS.



133 **134**

Schéma 97. Déprotection *N*-Boc en présence de TFA.

VI.2.2.2.2. Le 9-Fluorenylmethyloxycarbonyle (N-Fmoc)

La forme carbamique *N*-Fmoc est largement utilisée pour la protection de la fonction amine en synthèse peptidique sur phase solide ou en solution, vu sa stabilité dans les conditions acides et son orthogonalité vis-à-vis les formes *N*-Boc et *N*-Cbz.[289]

La protection *N*-Fmoc d'amino acide qui possède une fonction amine secondaire est effectuée utilisant le Fmoc-Cl en excès (4,4 éq) dans un mélange du (dioxane/H_2O : 2/1) en présence du diisopropyléthylamine à température ambiante.[290] **(Schéma 98)**.

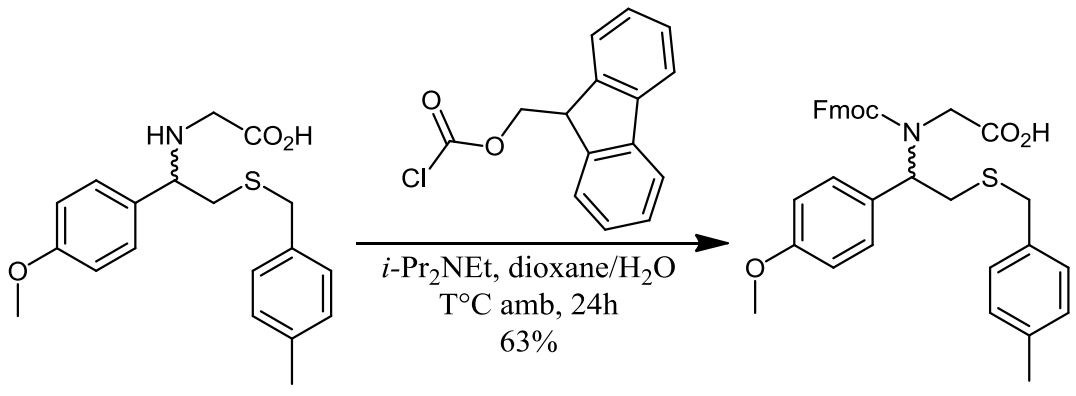


Schéma 98. Protection *N*-Fmoc dans un milieu basique.

Clivage

Le Fmoc est souvent stable dans les conditions d'hydrogénolyse. Cependant, il a été observé que dans des conditions particulières, il peut être clivé par traitement avec H_2/Pd/C, dans le mélange AcOH/MeOH.[291]

James *et al*[192] ont rapportés la déprotection du *N*-Fmoc en présence de 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) en quantité catalytique et le 1-octanethiole **(Schéma 99)**.

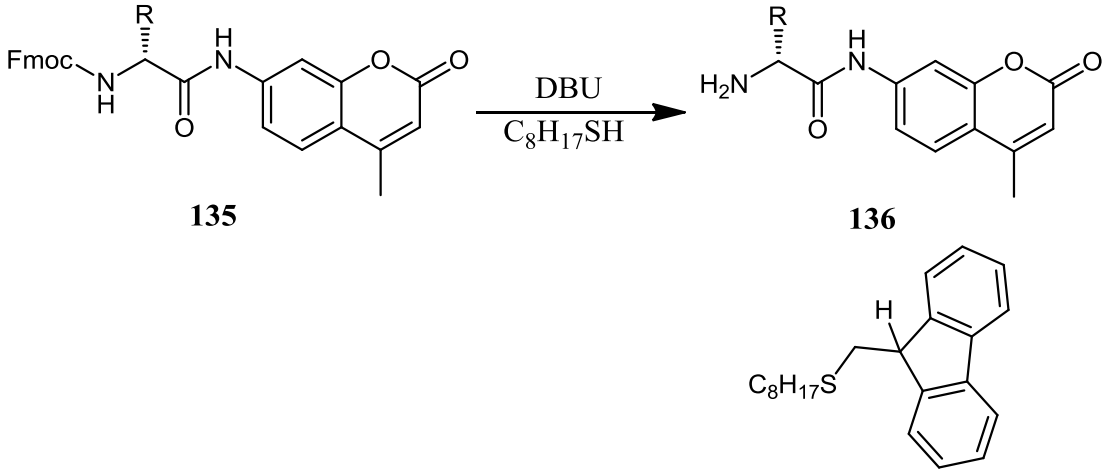


Schéma 99. Déprotection *N*-Fmoc en présence DBU/1-octanethiol.

VI.3. La déprotection des tétrazoles

VI.3.1. Par le Lithium

Behloul *et all.*[193a-c] Ont développé une méthode effecace de la déprotéction du groupement trityl dans les amines (eq 23),[193a] les alcools (eq 24)[193b] et les tetrazoles (eq 25)[193c] en utilisant le Li comme catalyseur en présence du naphthaléne à -78°C **(Schéma 100).**

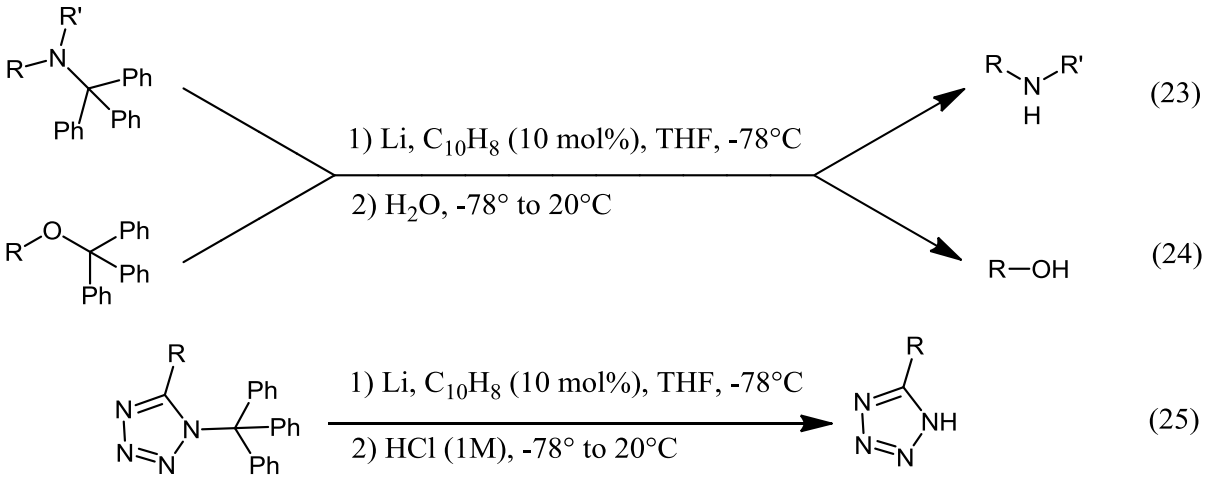


Schéma 100.

Ils ont appliqué aussi cette méthode pour la deprotection des autres groupements protécteurs comme le groupement silyl (eq 26)[293d] et le pivaloyl (eq 27)[293e] **(Schéma 101).**

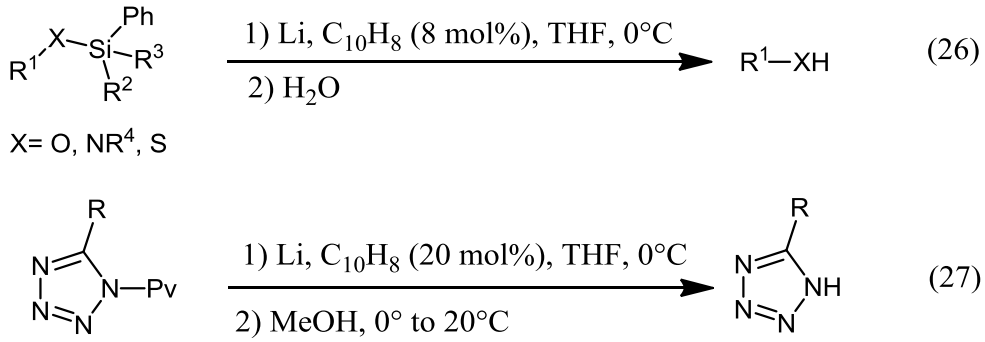
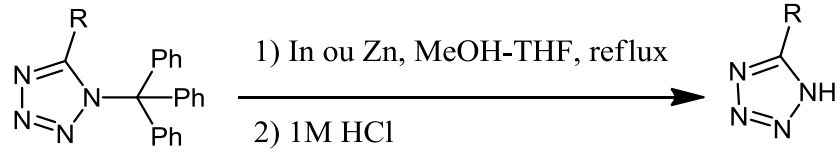


Schéma 101.

VI.3.2. Par l'indium et le Zinc

Behloul *et all*.[294] ont décrit la déprotéction des tétrazoles par l'indium et le zinc en présence d'un mélange MeOH/THF a reflux avec des très bons rendement **(Schéma 102)**.



R= alkyl, aryl, benzyl

Schéma 102.

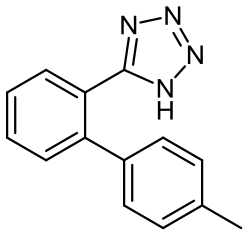
VI.4. Partie Expérimentale

VI.4.1. Synthése des tétrazoles

Mode opératoire général

Un mélange d'un nitrile (50 mmole), NaN_3 (65 mmole) et un sel d'amine (150 mmole) est chauffé à reflux dans un solvant aromatique (100 mL) pendant 17 a 30 heurs. Le mélange réactionnel est ensuite extrait par H_2O (100 mL). on additionne a la phase aqueuse HCl 36% goutte à goutte afin de faire précipiter le produit. Le solide formé est filtré, lavé avec H_2O et seché sous pression réduite pour donner un produit analytiquement pur. Tout les dérivés des tétrazoles sont connus et sont caractérisés par leur T_{fus}, IR et par RMN^{1}H et RMN^{13}C. Ces données sont en accord parfait avec les structures proposées.

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

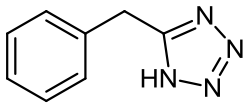


2b

A partir de 3.94 g de 4'-methyl-[1,1'-biphenyl]-2-carbonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 3.76 g de 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole sous forme d'un solide marron.

- **Rdt**= 78% (3.76 g).
- **T_{fus}**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH), 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).

5-benzyl-1H-tetrazole (2c)[102]

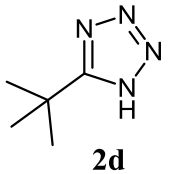


2c

A partir de 2.350 g de 2-phenylacetonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 2.5 g de 5-benzyl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 63% (2.5 g).
- **T_{fus}**= 123-124°C.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).

5-(tert-butyl)-1H-tetrazole (2d)[101]

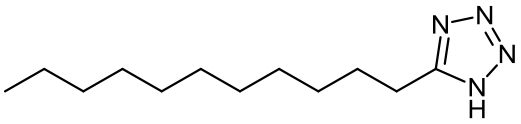


2d

A partir de 2.256 mL de pivalonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 2.82 g de 5-(*tert*-butyl)-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 90% (2.82 g).
- **T_{fus}**= 208-210°C.
- **IR (KBr):** 2977, 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

5-undecyl-1H-tetrazole (2e)[103]

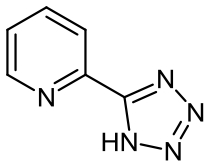


2e

A partir de 2.214 mL de dodecanenitrile, 1.95 g de NaN_3 et 4.11 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 3.19 g de 5-undecyl-1*H*-tetrazole sous forme d'un solide marron.

- **Rdt**= 57% (3.19 g).
- **T_{fus}**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).

2-(1H-tetrazol-5-yl)pyridine (2f)[101]

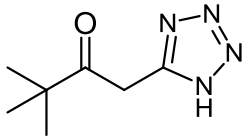


2f

A partir de 5.20 g de picolinonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 6.06 g de 2-(1*H*-tetrazol-5-yl)pyridine sous forme d'un solide marron.

- **Rdt**= 85% (6.06 g).
- **T_{fus}**= 208-210°C.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2j)[104]

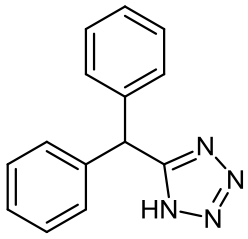


2j

A partir de 6.25 g de 4,4-dimethyl-3-oxopentanenitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 7.11 g de 3,3-dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one sous forme d'un solide orange.

- **Rdt**= 85% (7.11 g).
- **T_{fus}**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

5-benzhydryl-1H-tetrazole (2k)[105]

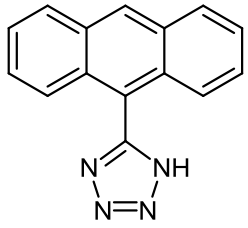


2k

A partir de 9.55 g de 2,2-diphenylacetonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 8.42 g de 5-benzhydryl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 72% (8.42 g).
- **T_{fus}**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

5-(anthracen-9-yl)-1H-tetrazole (2l)[102]



2l

A partir de 10.16 g de anthracene-9-carbonitrile, 3.9 g de NaN_3 et 8.22 g d'un sel d'amine dans le toluene, on obtient selon le mode opératoire 1.85 g de 5-(anthracen-9-yl)-1*H*-tetrazole sous forme d'un solide vert.

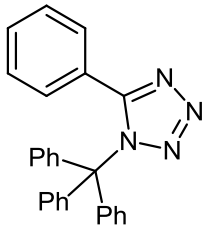
- **Rdt**= 75% (1.85 g).
- **T_{fus}**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

VI.4.2. Protection des tetrazoles

Mode opératoire général

Dans un bicol de 50 ml, on ajoute 10 mmole de tetrazole et 5 mL de CH_2Cl_2 sur un mélange de 3.1 g (11.0 mmole) de trityl chloride, 2.5 mL (17.6 mmole) de Et_3N, 92 mg (0.4 mmole) de 4-(dimethylamino)pyridine et 10 mL CH_2Cl_2. On laisse le mélange sous agitation magnétique à température ambiante pendant une nuit. On ajoute 5 mL d'eau distillé et on laisse le mélange sous agitation magnétique pendant 30min. Le mélange réactionnel est ensuite extrait par l'acétate d'éthyle. Les phases organiques réunies seront lavées avec une solution saturée de NaCl, séchées sur Na_2SO_4 et concentrées. Les produits bruts ont été purifiés par recristallisation dans un mélange (hexane/AcOEt) pour offrir les tetrazoles protégés avec 25-95% de rendements.

5-phenyl-1-trityl-1H-tetrazole (1a)[152]

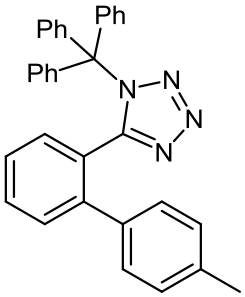


1a

A partir de 0.46 g de 5-phenyl-1*H*-tetrazole, 0.78 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.69 g de 5-phenyl-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 95% (3.69 g).
- **T_{fus}**= 156-158°C.
- **IR (KBr):** 1491, 1447, 1189, 1026, 876, 762, 747, 729, 693 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 7.13-7.47 (m, 18H), 8.12-8.16 (m, 2H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 83.3 (C), 127.2 (2xCH), 127.7 (3xCH), 127.9 (6xCH), 128.9 (C), 130.5 (6xCH), 141.5 (CH), 145.3 (2xCH), 150.8 (3xC),164.2 (C).

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1H-tetrazole (1b)[153]



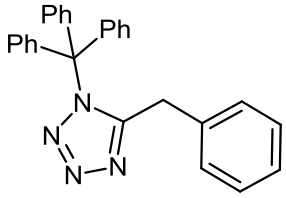
1b

A partir de 1.47 g de 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole, 3.1 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.21 g de 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 67% (3.21 g).
- **T_{fus}**= 180-184°C.
- **IR (KBr):** 3056, 1445, 1028, 827, 748, 698, 640 cm^{-1}.

- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 2.19 (s, 3H), 6.82-6.95 (m, 9H), 7.17-7.40 (m, 13H), 7.81-7.84 (m, 1H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 21.3 (CH_3), 83.0 (C), 126.6, 127.4, 127.7, 128.1, 128.2, 128.3 (4C), 129.2, 129.3 (6C), 129.4, 130.4, 130.5, 130.8, 136.5 (23xCH), 138.3 (C), 141.4 (C), 142.4 (C), 147.0 (C), 154.1 (3xC), 164.3 (C).

5-benzyl-1-trityl-1H-tetrazole (1c)[154]

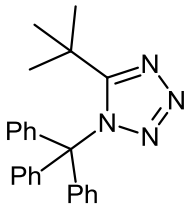


1c

A partir de 1.47 g de 5-benzyl-1*H*-tetrazole, 3.1 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.69 g de 5-benzyl-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 88% (3.54 g).
- **T_{fus}**= 160-164°C.
- **IR (KBr):** 1530, 1252, 1073, 889, 733, 694 cm^{-1}.
- **RM^{1}NH: (300 MHz, $CDCl_3$):** δ= 4.28 (s, 2H), 7.08-7.12 (m, 6H), 7.23-7.37 (m, 14H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 32.0 (CH_2), 83.0 (C), 126.8 (CH), 127.8 (3xCH), 128.1 (6xCH), 128.8 (2xCH), 129.1 (2xCH), 130.0 (6xCH), 137.0 (C), 141.5 (3xC), 164.6 (C).

5-(tert-butyl)-1-trityl-1H-tetrazole (1d)[155]

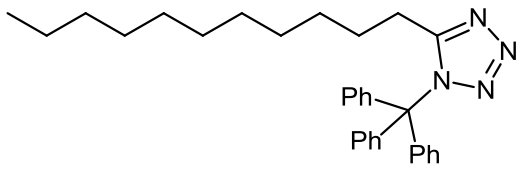


1d

A partir de 0.63 g de 5-(*tert*-butyl)-1*H*-tetrazole, 1.4 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 2.54 g de 5-(*tert*-butyl)-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 69% (2.54 g).
- **T_{fus}**= 132-136°C.
- **IR (KBr):** 3005, 2605, 1578, 1565, 1386, 1255, 1112, 1052, 899, 683, 632 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 1.34 (s, 9H), 7.01-7.26 (m, 15H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 30.0 (3xCH_3),41.7 (C), 82.8 (C), 127.4 (3xCH), 127.8 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C).
- **Anal. Calcd for $C_{24}H_{24}N_4$:** C, 78.23; H, 6.57; N, 15.21. **Found:** C, 78.26; H, 6.55; N, 15.23.

1-trityl-5-undecyl-1H-tetrazole (1e)[155]

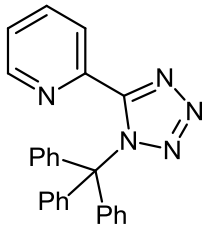


1e

A partir de 0.63 g de 5-undecyl-1*H*-tetrazole, 1.4 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.87 g de 1-trityl-5-undecyl-1*H*-tetrazole sous forme d'un solide marron.

- **Rdt**= 83% (3.87 g).
- **T_{fus}**= 76-80°C.
- **IR (KBr):** 2922, 2850, 1493, 1444, 747, 698 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 0.87 (t, *J*= 6.8 Hz, 3H), 1.27 (m, 16H), 1.72-1.79 (m, 2H), 2.90 (t, *J*= 7.6 Hz, 2H), 7.07-7.36 (m, 15H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 14.3 (CH_3), 22.8, 29.2, 29.4, 29.7, 29.8, 32.2, 39.7 (C), 82.7 (C), 127.9 (5xCH), 128.2, 128.4, 128.7, 129.9, 130.3 (6xCH), 141.6 (3xC), 166.2 (C).
- **Anal. Calcd for $C_{31}H_{38}N_4$:** C, 79.79; H, 8.21; N, 12.01. **Found:** C, 79.76; H, 8.22; N, 12.03.

Synthesis of 2-(1-trityl-1H-tetrazol-5-yl)pyridine (1f)[155]

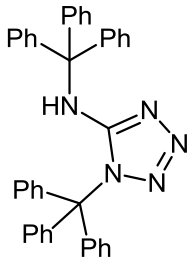


1f

A partir de 1.47 g de 2-(1*H*-tetrazol-5-yl)pyridine, 3.1 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.31 g de 2-(1-trityl-1*H*-tetrazol-5-yl)pyridine sous forme d'un solide rose.

- **Rdt**= 85% (3.31 g).
- **T_{fus}**= 126-128°C.
- **IR (KBr):** 1489, 1446, 1072, 747, 698 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 6.79-6.94 (m, 15H), 7.17-7.21 (m, 1H), 7.64 (td, *J*= 7.8, 1.6 Hz, 1H), 7.80 (d, *J*= 7.9 Hz, 1H), 8.36 (d, *J*= 4.4 Hz, 1H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 51.6 (C), 86.4 (CH), 122.6 (CH), 126.1 (CH), 127.0 (3xCH), 127.9 (6xCH), 128.2 (6xCH), 137.0 (3xC), 138.2 (C), 143.6 (C), 150.1 (CH).
- **Anal. Calcd for $C_{25}H_{19}N_5$:** C, 77.10; H, 4.92; N, 17.98. **Found:** C, 77.08; H, 4.88; N, 18.00.

N,1-dityrityl-1H-tetrazol-5-amine (1g)[155]



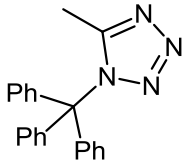
1g

A partir de 0.85 g de 2-(1*H*-tetrazol-5-yl)pyridine, 3.1 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 1.42 g de *N*,1-dityrityl-1*H*-tetrazol-5-amine sous forme d'un solide blanc.

- **Rdt**= 25% (1.42 g).

- **T_{fus}**= 220-222°C.
- **IR (KBr):** 1560, 1493, 1446, 1184, 881, 743, 696, 632 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 6.82 (s, 1H), 6.84-7.40 (m, 30H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 71.7 (C), 82.1 (C), 125.9, 126.4, 126.8, 127.6, 127.8, 127.9, 128.0 (5C), 128.4 (6C), 129.0 (5C), 129.6 (6C), 130.1, 141.5 (30xCH), 144.8 (3xC), 147.8 (3xC), 165.1 (C).
- **Anal. Calcd for $C_{39}H_{31}N_5$:** C, 82.22; H, 5.48; N, 12.29. **Found:** C, 82.22; H, 5.46; N, 11.24.

5-methyl-1-trityl-1H-tetrazole (1i)[155]

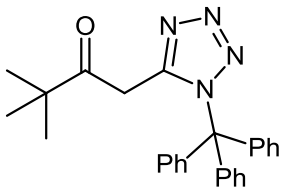


1i

A partir de 0.84 g de 5-methyl-1*H*-tetrazole, 0.92 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 2.25 g de 5-methyl-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 69% (2.25 g).
- **T_{fus}**= 172-174°C.
- **IR (KBr):** 1507, 1492, 883, 748, 696, 635 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 2.56 (s, 3H), 7.09-7.12 (m, 6H), 7.21-7.38 (m, 9H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 11.4 (CH_3), 82.8 (C), 126.9 (3xCH), 128.1 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C).
- **Anal. Calcd for $C_{21}H_{18}N_4$:** C, 77.28; H, 5.56; N, 17.17. **Found:** C, 77.41; H, 5.57; N, 17.41.

3,3-dimethyl-1-(1-trityl-1H-tetrazol-5-yl)butan-2-one (1j)[155]

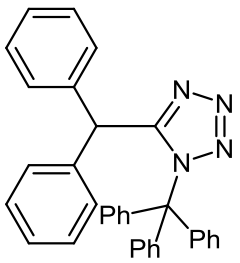


1j

A partir de 1.52 g de 3-dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one, 1.6 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 2.55 g de 5-methyl-1-trityl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 62% (2.55 g).
- **T_{fus}**= 190-194°C.
- **IR (KBr):** 1714, 1445, 1057, 882, 752, 697 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 1.22 (s, 9H), 4.17 (s, 2H), 7.10-7.35 (m, 15H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 82.8 (C), 127.4 (3xCH), 127.8 (6xCH), 130.3 (6xCH), 141.5 (3xC), 162.1 (C), 209.3 (C=O).
- **Anal. Calcd for $C_{26}H_{26}N_4O$:** C, 76.07; H, 6.38; N, 13.65. **Found:** C, 76.09; H, 6.37; N, 13.68.

5-benzhydryl-1-trityl-1H-tetrazole (1k)[155]



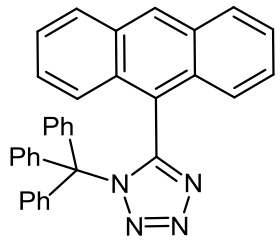
1k

A partir de 2.36 g de 5-benzhydryl-1*H*-tetrazole, 3.1 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 2.92 g de 5-benzhydryl-1-trityl-1*H*-tetrazole sous forme d'un solide jaune.

- **Rdt**= 61% (2.92 g).
- **T_{fus}**= 164-166°C.

- **IR (KBr):** 1492, 1445, 1048, 748, 697, 639 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 5.88 (s, 1H), 7.13-7.38 (m, 25H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 50.9 (CH), 82.1 (C), 125.9, 126.4, 126.8, 127.4 (2C), 127.6 (4C), 127.8 (3C), 127.9, 128.1, 128.4 (6C), 129.0, 129.6, 130.1, 141.5, 144.0 (25xCH), 144.8 (C), 147.0 (2xC), 165.1 (3xC).
- **Anal. Calcd for $C_{33}H_{26}N_4$:** C, 82.82; H, 5.48; N, 11.71. **Found:** C, 82.80; H, 5.46; N, 11.69.

5-(anthracen-9-yl)-1-trityl-1H-tetrazole (1l)[155]



1l

A partir de 1.39 g de 5-(anthracen-9-yl)-1*H*-tetrazole, 1.47 g de trityl chloride, 2.5 mL de Et_3N et 92 mg de 4-(dimethylamino)pyridine dans le CH_2Cl_2, et suivant le mode opératoire général, on obtient 3.71 g de 5-(anthracen-9-yl)-1-trityl-1*H*-tetrazole sous forme d'un solide vert.

- **Rdt**= 71% (3.71 g).
- **T_{fus}**= 170-172°C.
- **IR (KBr):** 1491, 1447, 1189, 876, 762, 747, 694 cm^{-1}.
- **RMN^{1}H: (300 MHz, $CDCl_3$):** δ= 7.23-7.45 (m, 21H), 7.70-7.73 (m, 1H), 8.03 (dd, *J*=4.8, 4.2 Hz, 1H), 8.57 (s, 1H).
- **RMN^{13}C: (75 MHz, $CDCl_3$):** δ= 83.7 (C), 125.6 (2xCH), 126.8 (2xC), 127.4 (2xC), 128.0 (3xCH), 128.1 (CH), 128.2 (6xCH), 128.6 (2xCH), 128.7 (2xCH), 130.4 (6xCH), 131.3 (C), 141.6 (2xC), 147.0 (3xC), 162.6 (C).
- **Anal. Calcd for $C_{34}H_{24}N_4$:** C, 83.58; H, 4.95; N, 11.47. **Found:** C, 83.55; H, 4.91; N, 11.50.

VI.4.3. La déprotection des tétrazoles

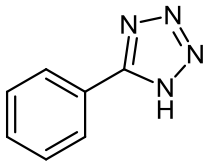
VI.4.3. Par le Lithium

VI.4.3.1. Déprotection des tétrazoles 1a-1f et 1i-1l

Mode opératoire général

Dans un bicol muni d'un agitateur magnétique sous Ar, on introduit (70 mg, 10.0 mmole) de lithium et (26 mg, 0.2 mmole) de naphthalene dans 5 mL de THF fraîchement distillé. Le mélange réactionnel est laissé sous agitation magnétique à température ambiante jusqu'a formation d'une suspension de couleur vert foncé. On refroidit le mélange à −78°C, On ajoute une solution de tétrazole protégé (0.5 mmole) dans THF (2 mL) en goutte à goutte pendant 15 min. On maintient le mélange réactionnel à la même température sous agitation magnétique pendant 2-6 heures. Après on ajoute 5 mL une solution d'acide chlorhydrique (1M), on laisse le mélange réactionnel sous agitation magnétique à température ambiante pendant 30 min. On extrait à l'AcOEt, les phases organiques sont réunies et séchées sur ($MgSO_4$). Après évaporation du solvant, le produit brut obtenu est purifié par chromatographie sur colonne d'oxide d'aluminium en utilisant l'éluant hexane/acétate d'éthyle (9/1).

5-phenyl-1H-tetrazole (2a)[152]

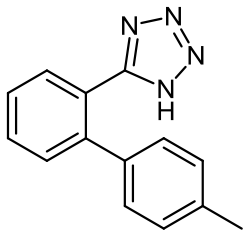


2a

Suivant le mode opératoire général, on obtient à partir de 0.19 g de 5-phenyl-1-trityl-1*H*-tetrazole, 0.066 g de 5-phenyl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 97% (0.066 g).
- **T_{fus}**= 215-216°C.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.55-7.62 (m, 3H), 8.01-8.02 (m, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 124.1 (2xCH), 127.0 (C), 129.4 (CH), 131.3 (2xCH), 155.3 (C).

5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-tetrazole (2b)[101]

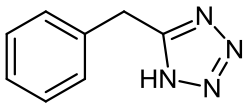


2b

Suivant le mode opératoire général, on obtient à partir de 0.19 g de 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1-trityl-1*H*-tetrazole, 0.089 g de 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole sous forme d'un solide marron.

- **Rdt**= 99% (0.089 g).
- **T_{fus}**= 149-151°C.
- **IR (KBr):** 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 2.28 (s, 3H), 6.98 (d, *J*= 8.1 Hz, 2H), 7.12 (d, *J*= 7.9 Hz, 2H), 7.55 (ddd, *J*= 10.3, 5.8, 1.9 Hz, 2H), 7.63-7.69 (m, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 20.7 (CH_3), 123.4 (CH), 127.6 (CH) , 128.7 (2xCH), 128.9 (CH), 130.5 (2xCH), 130.6 (CH), 131.1 (C), 136.3 (C),136.8 (C), 141.5 (C), 155.1 (C).
- **Anal. Calcd for $C_{14}H_{12}N_4$**: C, 71.17; H, 5.12; N, 23.71. **Found**: C, 70.86; H, 5.17; N, **24.07.**

5-benzyl-1H-tetrazole (2c)[102]



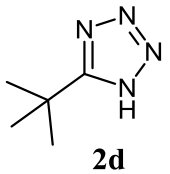
2c

Suivant le mode opératoire général, on obtient à partir de 0.12 g de 5-benzyl-1-trityl-1*H*-tetrazole, 0.028 g de 5-benzyl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 93% (0.028 g).
- **T_{fus}**= 123-124°C.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 4.28 (s, 2H), 7.24-7.35 (m, 5H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 29.0 (CH_2), 127.1 (CH), 128.7 (2xCH), 128.8 (2xCH), 136.0 (C), 155.3(C).

- **Anal. Calcd for $C_8H_8N_4$**: C, 59.99; H, 5.03; N, 34.98. **Found**: C, 60.05; H, 4.80; N, 36.21.

5-(tert-butyl)-1H-tetrazole (2d)[101]

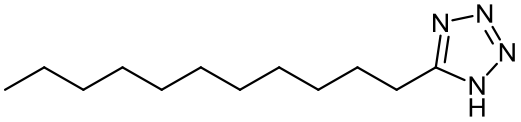


2d

Suivant le mode opératoire général, on obtient à partir de 0.23 g de 5-(*tert*-butyl)-1-trityl-1*H*-tetrazole de 5-(*tert*-butyl)-1*H*-tetrazole, 0.056 g de 5-benzyl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 92% (0.056 g).
- **T_{fus}**= 208-210°C.
- **IR (KBr):** 2977, 2986, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 1.35 (s, 9H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 28.9 (3xCH_3), 30.3 (C), 163.4 (C).

5-undecyl-1H-tetrazole (2e)[103]



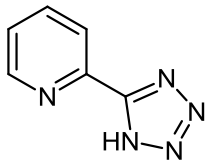
2e

Suivant le mode opératoire général, on obtient à partir de 0.23 g de 1-trityl-5-undecyl-1*H*-tetrazole, 0.094 g de 5-undecyl-1*H*-tetrazole sous forme d'un solide marron.

- **Rdt**= 81% (0.094 g).
- **T_{fus}**= 72-73°C.
- **IR (KBr):** 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.
- **RMN^{1}H: (300 MHz, MeOD-d_4):** δ= 0.84 (t, *J*= 6.8 Hz, 3H), 1.24 (m, 16H), 1.65-1.68 (m, 2H), 2.84 (t, *J*= 7.6 Hz, 2H).
- **RMN^{13}C: (75 MHz, MeOD-d_4):** δ= 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2C), 31.3 (10xCH_2), 155.9 (C).

- **Anal. Calcd for $C_{12}H_{24}N_4$**: C, 64.24; H, 10.78; N, 24.97. **Found**: C, 63.97; H, 10.50; N, 26.51.

Synthesis of 2-(1H-tetrazol-5-yl)pyridine (2f)[101]

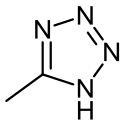


2f

Suivant le mode opératoire général, on obtient à partir de 0.19 g de 2-(1-trityl-1*H*-tetrazol-5-yl)pyridine, 0.06 g de 2-(1*H*-tetrazol-5-yl)pyridine sous forme d'un solide marron.

- **Rdt**= 86% (0.06 g).
- **T_{fus}**= 208-210°C.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.63 (ddd, *J*= 7.6, 4.8, 1.2 Hz, 1H), 8.08 (td, *J*= 7.8, 1.7 Hz, 1H), 8.22 (dt, *J*= 7.9, 1.0 Hz, 1H), 8.79 (ddd, *J*= 4.8, 1.7, 0.9 Hz, 1H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

5-methyl-1H-tetrazole (2i)[102]

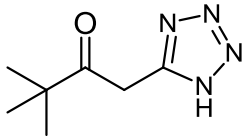


2i

Suivant le mode opératoire général, on obtient à partir de 0.12 g de 5-methyl-1-trityl-1*H*-tetrazole, 0.028 g de 5-methyl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 93% (0.028 g).
- **T_{fus}**= 138-140°C.
- **IR (KBr):** 3005 (NH), 2879 (CH_3), 2605 (C=N), 1578, 1565, 1112, 1052, 899, 683 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 2.46 (s, 3H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 8.4 (CH_3), 152.2 (C).
- **Anal. Calcd for $C_2H_4N_4$**: C, 28.57; H, 4.80; N, 66.64. **Found:** C, 28.77; H, 4.70; N, 71.13.

3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (2j)[104]

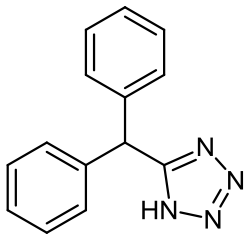


2j

Suivant le mode opératoire général, on obtient à partir de 0.20 g de 3,3-dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one, 0.065 g de 3,3-dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one sous forme d'un solide orange.

- **Rdt**= 80% (0.065 g).
- **T_{fus}**= 152-154°C.
- **IR (KBr):** 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 1.18 (s, 9H), 4.41 (s, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 25.8 (3xCH_3), 32.2 (CH_2), 44.0 (C-C=O), 128.2 (C), 209.3 (C=O).

5-benzhydryl-1H-tetrazole (2k)[105]

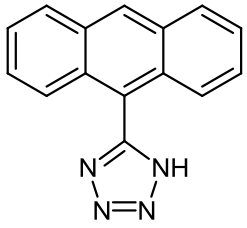


2k

Suivant le mode opératoire général, on obtient à partir de 0.23 g de 5-benzhydryl-1-trityl-1*H*-tetrazole, 0.029 g de 5-benzhydryl-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 84% (0.029 g).
- **T_{fus}**= 165-166°C.
- **IR (KBr):** 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 5.85 (s, 1H), 7.14-7.30 (m, 10H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 40.8 (CH), 128.6 (2xCH), 129.6 (4xCH), 129.9 (4xCH), 140.8 (C), 160.0 (2xC).

5-(anthracen-9-yl)-1H-tetrazole (2l)[102]



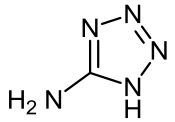
2l

Suivant le mode opératoire général, on obtient à partir de 0.24 g de 5-(anthracen-9-yl)-1-trityl-1*H*-tetrazole, 0.09 g de 5-(anthracen-9-yl)-1*H*-tetrazole sous forme d'un solide blanc.

- **Rdt**= 75% (0.09 g).
- **T_{fus}**= 215-216°C.
- **IR (KBr):** 2987, 2900, 1578, 1053, 735 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.45 (d, *J*= 8.6 Hz, 2H), 7.56-7.63 (m, 4H), 8.23-8.31 (m, 2H), 8.94 (s, 1H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 120.6 (2xCH), 124.8 (2xCH), 126.4 (2xC), 128.2 (CH), 129.2 (C), 130.8 (2xCH), 131.0 (2xCH), 138.3 (2xC), 150.1 (C).

VI.4.3.2. Déprotection des tétrazoles 1g et 1h

1H-tetrazol-5-amine (2g)[175]



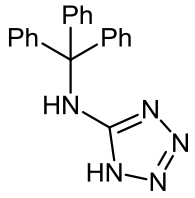
2g

Dans un bicol de 50 ml muni d'un agitateur magnétique sous Ar, on place 0.28 g (0.5 mmole) de N,1-ditrityl-1*H*-tetrazol-5-amine et 2 mL de THF, on maintient le mélange sous agitation a 0°C pendant 10min, puis 0.45 mL de *n*-BuLi que nous avons préparé (*n*-BuLi dans l'hexane) et 0.15 mL de trimethylsilyl chloride ont été ajouté. Après 3 min le mélange devient homogène de couleur rouge. On additionne ce mélange goutte à goutte au mélange de lithium (70 mg, 10.0 mmole) et de naphthalene (26 mg, 0.2 mmole) dans THF (5 mL). On refroidit le mélange à −78°C. On maintient le mélange réactionnel à la même température sous agitation magnétique pendant 2 heures. Après on ajoute 5 mL une solution d'acide chlorhydrique (1M), on laisse le mélange réactionnel sous agitation magnétique à température ambiante pendant 30 min. On extrait à l'AcOEt, les phases organiques sont réunies et séchées sur ($MgSO_4$). Après

évaporation du solvant, le produit brut obtenu est purifié par chromatographie sur colonne d'oxide d'aluminium en utilisant l'éluant hexane/acétate d'éthyle (9/1).

- **Rdt**= 93% (0.055 g).
- **T_{fus}**= 212-214°C.
- **IR (KBr):** 3399 (NH_2), 3192 (NH), 1636, 1263, 1044 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 6.56 (s, 2H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 158.2 (C).

N-trityl-1H-tetrazol-5-amine (2h)[155]



2h

Dans un bicol de 50 ml muni d'un agitateur magnétique sous Ar, on place 0.28 g (0.5 mmole) de N,1-ditrityl-1*H*-tetrazol-5-amine et 2 mL de THF, on maintient le mélange sous agitation a 0°C pendant 10min, puis 0.45 mL de *n*-BuLi que nous avons préparé (*n*-BuLi dans l'hexane) a été ajouté. On additionne ce mélange goutte à goutte au mélange de lithium (70 mg, 10.0 mmole) et de naphthalene (26 mg, 0.2 mmole) dans THF (5 mL). On refroidit le mélange à −78°C. On maintient le mélange réactionnel à la même température sous agitation magnétique pendant 2 heures. Après on ajoute 5 mL une solution d'acide chlorhydrique (1M), on laisse le mélange réactionnel sous agitation magnétique à température ambiante pendant 30 min. On extrait à l'AcOEt, les phases organiques sont réunies et séchées sur ($MgSO_4$). Après évaporation du solvant, le produit brut obtenu est purifié par chromatographie sur colonne d'oxide d'aluminium en utilisant l'éluant hexane/acétate d'éthyle (9/1).

- **Rdt**= 94% (0.15 g).
- **T_{fus}**= 148-150°C.
- **IR (KBr):** 3266 (NH), 1560, 1445, 757, 695, 632 cm^{-1}.
- **RMN^{1}H: (300 MHz, DMSO-d_6):** δ= 7.14-7.32 (m, 15H).
- **RMN^{13}C: (75 MHz, DMSO-d_6):** δ= 82.2 (C), 126.9-130.3 (15xCH), 141.5 (3xCH), 162.1 (C).

VI.4.4. Par l'indium et le Zinc

Un mélange de tétrazole protégé (0.5 mmole) et Zn ou In poudre (0.5 mmole) est chauffé à reflux dans un délange de MeOH/THF (6 mL/3 mL) pendant 2-19 heures. Après refroidissement, on ajoute 5 mL une solution d'acide chlorhydrique (1M), on laisse le mélange réactionnel sous agitation magnétique à température ambiante pendant 30 min. On extrait à l'AcOEt, les phases organiques sont réunies et séchées sur ($MgSO_4$). Après évaporation du solvant, le produit brut obtenu est purifié par chromatographie sur colonne. Tous produits sont connus et sont caractérisés par leur $T_{fus.}$, IR et par RMN^{1}H et RMN^{13}C. Ces données sont en accord parfait avec les structures proposées.

Les données spectroscopiques (IR, RMN ^{1}H, RMN ^{13}C) sont bien détaillées dans les chapitres 4 et 5.

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Abstract

This manuscript describes the reductive removal of trityl groups from *N*-protected tetrazoles, using indium, zinc and arene-catalysed lithiation processes.

Chapters 1 and 2 report the development of two efficient processes one for transforming a wide variety of nitriles into the corresponding tetrazoles in high yield, using a simple and sofe protocole, and other to protect tetrazoles wich is our starting materials.

Chapter 3 shows the deprotection of the trityl (triphenylmethyl) group, from tritylated tetrazoles using lithium powder and a catalytic amount of naphtalene to give corresponding free tetrazoles without decomposition of the tetrazole ring.

Chapter 4 describes the reductive cleavage of the same group from the same protected *N*-tetrazoles using indium as a source of free electron transfer which can show you a good method even in the presence of the air moister.

Chapter 5 In the latter case, deals with the deblocking of tetrazoles, protected with trityl group, respectively. Using in this case zinc as a dissolving metal in Methanol/THF, in the opposite of lithium; this methodology led to the removal of this group from different tetrazoles even in the presence of the proton source.

Keywords: Tetrazoles, protection, arene, lithiation, cleavage, zinc, indium, trityl.

Résumé

Les dérivés des tetrazoles présentent des propriétés biologiques et pharmaceutiques intéressantes. L'importance de ces produits organiques a éveillé un grand intérêt pour la synthèse et l'évaluation biologique de ces dérivés.

Motivés par l'activité biologique avérée de ces dérivés de composés, l'objectif du présent travail est la synthèse et la protéction des tétrazoles ainsi que le développement des nouvelles méthodes de la déprotection des différents tetrazoles protégés par le trityl en utilisant l'indium, le zinc et le lithium.

Ce manuscrit comprend cinq parties principales :

Dans les deux premières parties nous avons donné un large aperçu sur les méthodes les plus significatives de préparation et de protéction des dérivés de tétrazole, ainsi que leurs rôles dans le domaine thérapeutique. Nous avons présenté également, un rappel bibliographique sur la réactivité des tétrazoles et des tétrazoles protégés.

Dans la troisième partie, nous avons rapporté l'utilisation avec succès d'un nouveau catalyseur dans la déprotéction du groupement trityl. Il s'agit de lithium et une aréne qui ont été employé avec des quantités catalytiques pour accéder aux dérivés des tetrazoles correspondants avec des rendements généralement très bons.

De même, nous avons décrit en quatrieme et cinquieme parties, le cleavage des dérivés de tetrazoles selon une réaction catalysée par l'indium ou le zinc. Ces catalyseurs se sont avérés très efficace pour l'obtention des tetrazoles avec de très bons rendements.

Mots clés: Tétrazoles, protéction, aréne, lithiation, cleavage, zinc, indium, trityl.

الملخص

تندرج هذه الاطروحة ضمن مخطط اصطناعي لمركبات حلقية جديدة تحتوي على الرابطة (N-H) بالخصوص اليوريا الحلقية والسلفونيل يوريا، وايجاد طرق جديدة لتحضير هذه المركبات الجديدة مستمدة من مادة الكلوروسلفونيل ايزوسيانات والاقتصاد بهذه المادة.

حيث تضمن الجزء الاول والثاني العمل على المينات والاحماض الامينية التي تم تحويلها الى اليوريا والسلفونيل يوريا. وفي الجزء الثالث تم الاستعمال الجزئي للمركبات الحلقية التي تم الحصول عليها. هذا ولقد تم في الجزء الرابع عرض النتائج المستخلصة.

في الجزء الثالث تناولنا بالدراسة تحضير السلفونيل يوريا المشتقة من المادة الاولية والتي تحتوي على البنية الحلقية وفي الخ... المركبات الجديدة.

بالاضافة الى ما تقدم في الجزء الرابع والخامس تم تحضير مركبات جديدة من الكلوروسلفونيل يوريا و... بمردود يتراوح بين 70 و 70%.

الكلمات المفتاحية: كلوروسلفونيل ايزوسيانات، سلفونيل يوريا، يوريا حلقية، ...

Annex

SYNTHESIS

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Detritylation of Protected Tetrazoles by Naphthalene-Catalyzed Lithiation

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Dedicated to the honor of Prof. Francisco Foubelo García

Abstract: Treatment of N-tritylated tetrazoles bearing aliphatic, aromatic, or heteroaromatic substituents (including functionalized ones) with lithium powder and a catalytic amount of naphthalene led to reductive removal of the trityl group to give excellent yields of the corresponding free tetrazoles without decomposition of the tetrazole ring. The detritylation process was successfully extended to several tetrazoles that are components of sartans, an interesting class of drugs. The chemoselectivity between trityl–tetrazole and trityl–amine bond-cleavage reactions was also studied. This method represents an efficient technique for deprotection of tritylated tetrazoles under non-acidic conditions.

Key words: tetrazoles, deprotection, reductions

Sartans are a group of drugs that are effective in treating hypertension and heart failure. They block the renin–angiotensin system and they are among the most effective treatments for hypertension.[1] Of the seven sartans that are used in clinical practice, five contain tetrazole moieties within their structures. The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these sartans.[2] One group that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl) group, a very efficient protecting group for amines[3] and amino acids,[4] because its bulkiness causes the nitrogen atom to be much less reactive as a nucleophile. Simple treatment with an aqueous acidic solution can be used to remove the trityl protecting group,[3c] but some side-reactions have been observed under these conditions, such as elimination of tritylamine during detritylation of some tritylated amines.[5] Other procedures that have been shown to be efficient in detritylation processes include dissolving-metal reduction,[3c] reactions with molecular hydrogen catalyzed by palladium,[3c] reduction with sodium borohydride in the presence of mercury salts,[6] and reductive cleavage promoted by silanes[7] or low-valent titanium reagents.[8] Palladium catalysts in combination with poly(methylhydrosiloxane) have been shown to permit direct conversion of *N*-trityl amines into *tert*-butyl carbamates.[9]

The arene-catalyzed lithiation method for generating organolithium compounds has been a topic of our research activities for several years.[10,11] By treatment with an excess of lithium powder, some arenes [mainly naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB)] generate highly reactive radical anions and dianions that are efficient electron carriers that induce reductive cleavage of various carbon–heteroatom bonds in organic halides,[10,11] nonhalogenated materials,[12] or heterocycles,[13] leading to the corresponding organolithium compounds, including some functionalized examples.[14] This lithiation methodology permits reductive cleavage of C–N bonds in various organic compounds,[15] including detritylation of trityl amines by a naphthalene-catalyzed lithiation process.[16] The application of this lithiation procedure to the reductive removal of the trityl group from the nitrogen atom of several protected tetrazoles under very mild reaction conditions is discussed below.

We chose 5-phenyl-1-trityl-1*H*-tetrazole (**1a**) as a model substrate, and we attempted to detritylate this compound at –78 °C. When a solution of tetrazole **1a** in tetrahydrofuran was added to a green suspension of an excess of lithium powder and a catalytic amount of naphthalene (molar ratio 1:0.2) in tetrahydrofuran at –78 °C, the mixture turned red, possibly indicating the formation of a trityl radical[17] and/or a trityl anion.[18] When the reaction was complete, hydrolysis with 1 M hydrochloric acid at the same temperature gave the corresponding tetrazole **2a**, together with triphenylmethane (Table 1, entry 1). The latter was probably formed by protonation of the generated tritylllithium in the final hydrolysis step. The yield of the isolated 5-phenyl-1*H*-tetrazole was 97%.

Detritylation of two other protected tetrazoles bearing aromatic substituents (**1b** and **1l**) under the optimized reaction conditions gave the expected free tetrazoles **2b** and **2l** in 99 and 75% yield, respectively (Table 1, entries 2 and 12). A tritylated tetrazole bearing a heteroaromatic 2-pyridyl substituent was also deprotected with very good results (entry 6). The detritylation procedure was also effectively applied to tetrazoles **1d**, **1e**, and **1i**, which were substituted on the carbon atom of the ring with aliphatic chains, including a sterically hindered *tert*-butyl group (entries 4, 5, and 9). The benzylic substituents of protected tetrazoles **1c** and **1k** were unaffected by these reaction conditions, leading to the expected deprotected tetrazoles **2c** and **2k** in 82 and 84% yield, respectively (entries 3 and 11).

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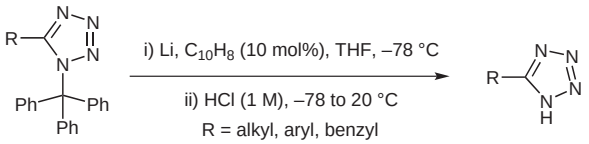
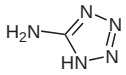
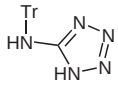
Table 1 Reductive Detritylation of Protected Tetrazoles **1** by a Naphthalene-Catalyzed Lithiation Process[a]



Entry	R	Time (h)	Product	Yield[b] (%)
1	Ph	3.0	**2a**	97
2	2-(4-MeC$_6$H$_4$)C$_6$H$_4$	4.0	**2b**	99
3	Bn	3.0	**2c**	82
4	*t*-Bu	4.0	**2d**	97
5	$(CH_2)_{10}$Me	3.0	**2e**	81
6	2-pyridyl	4.0	**2f**	86
7[c]	TrNH	4.0	 **2g**	93
8[d]	TrNH	2.5	 **2h**	94
9	Me	2.5	**2i**	93
10	CH_2CO*t*-Bu	4.0	**2j**	80
11	$CHPh_2$	2.0	**2k**	84
12	9-anthryl	6.5	**2l**	75

[a] All reactions were performed at –78 °C.
[b] Yield of isolated product after purification by column chromatography (basic Al_2O_3, hexane–EtOAc), based on starting material **1**.
[c] Compound **1g** was deprotonated with BuLi and treated with TMSCl before performing the naphthalene-catalyzed lithiation step.
[d] Compound **1g** was deprotonated with BuLi before performing the naphthalene-catalyzed lithiation step.

Our method could also be applied to the chemoselective deprotection of a trityl tetrazole in the presence of a trityl amine group. The starting material **1g** has an NH proton that is acidic enough to decompose the naphthalene radical-anion and dianion that act as lithiation agents in this process. To prevent this decomposition, substrate **1g** was deprotonated with butyllithium and treated with chloro(trimethyl)silane before performing the naphthalene-catalyzed lithiation step. This operation led to double detritylation of the starting material to give 1*H*-tetrazol-5-amine (**2g**) in 93% yield (Table 1, entry 7). However, when deprotonated **1g** was directly submitted to the lithiation step without previous treatment with chloro(trimethyl)silane, the trityl group on the tetrazole ring was selectively removed (entry 8). Therefore, the negative charge that appears on the tritylamino substituent after deprotonation with butyllithium effectively protects this group against reductive cleavage of the Tr–N bond.

Interestingly, compound **1j**, which contains a keto-functionalized substituent, could be detritylated under our mild reaction conditions without affecting the carbonyl group, which might have been expected to be reduced by the naphthalene radical-anion or dianion. As a result, 1-(1*H*-tetrazol-5-yl)acetone (**2j**) was isolated in 80% yield (Table 1, entry 10).[19]

In all cases, triphenylmethane, formed by protonation of tritylllithium in the final hydrolysis process, was easily separated from the deprotected tetrazoles by column chromatography.

The starting tritylated tetrazoles **1** were prepared by treatment of the corresponding tetrazoles with trityl chloride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine.

In summary, we have developed an efficient method for detritylation of protected tetrazoles by a naphthalene-catalyzed lithiation process. The method proved to be useful for the removal of trityl groups from *N*-trityltetrazoles containing aromatic, heteroaromatic, benzylic groups or optionally functionalized aliphatic groups. *N*-Tritytetrazoles containing a secondary *C*-tritylamino group can be selectively detritylated. This method represents a good alternative to the commonly used detritylation procedures, which require acidic conditions.

FT-IR spectra were recorded on a Nicolet Impact 400D spectrophotometer using KBr pellets. NMR spectra were recorded on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, or CD_3OD as solvent and TMS (δ = 0.00 ppm, ^{1}H) or $CDCl_3$ (δ = 77.0 ppm, ^{13}C), DMSO-d_6 (δ = 2.50 ppm, ^{1}H; δ = 39.75 ppm, ^{13}C), or CD_3OD (δ = 4.87 ppm, ^{1}H; δ = 49.0 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. Elemental analyses were performed by the Technical Services of the University of Alicante. Column chromatography was performed on silica gel 60 (35–70 mesh) or basic aluminum oxide (50–160 μm particle size). Deactivated silica gel was treated with 5% Et_3N in hexane, and the column was eluted with the same solvent mixture until the eluent was basic, as shown by pH paper. Naphthalene, TMSCl, and all the reagents used in the syntheses of the *N*-trityltetrazoles **1** were commercially available (Acros or Aldrich) and were used without further purification. Li powder was prepared according to a previously described procedure.[20] Commercially available BuLi was titrated with a 1 M solution of *s*-BuOH in xylene, with 1,10-phenanthroline as indicator.[21] Commercially available anhyd THF (99.9%, H_2O content ≤ 0.006%; Acros) was used as the solvent for all the lithiation reactions.

Tetrazoles 2a–l; General Procedure[22]
The mixture of the appropriate nitrile (50 mmol), NaN_3 (65 mmol), and Et_3N·HCl (150 mmol) in toluene (100 mL) was stirred at 110 °C for 17–30 h (**2b**, **2f**, **2k**, and **2l** for 24 h; **2c** and **2d** for 17 h; **2e** and **2j** for 30 h). The mixture was cooled to r.t. and extracted with H_2O (100 mL). The aqueous layer was acidified with 36% aq HCl and filtered. The resultant solid was washed with H_2O and dried under reduced pressure.

5-Phenyl-1*H*-tetrazole (2a)[23]
White solid; yield: 1.39 g (95%); mp 215–216 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.1 (2 × CH), 127.0 (C), 129.4 (CH), 131.3 (2 × CH), 155.3 (C).

5-(4′-Methylbiphenyl-2-yl)-1*H*-tetrazole (2b)[24]
Brown solid; yield: 1.84 g (78%); mp 149–151 °C.

IR (KBr): 3336, 2974, 2900, 1080, 1046, 879, 755 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.28 (s, 3 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.55 (ddd, *J* = 10.3, 5.8, 1.9 Hz, 2 H), 7.63–7.69 (m, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.7 (CH_3), 123.4 (CH), 127.6 (CH), 128.7 (2 × CH), 128.9 (CH), 130.5 (2 × CH), 130.6 (CH), 131.1 (C), 136.3 (C), 136.8 (C), 141.5 (C), 155.1 (C).

5-Benzyl-1*H*-tetrazole (2c)[25]
White solid; yield: 1.01 g (63%); mp 123–124 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.28 (s, 2 H), 7.24–7.35 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 29.0 (CH_2), 127.1 (CH), 128.7 (2 × CH), 128.8 (2 × CH), 136.0 (C), 155.3 (C).

5-*tert*-Butyl-1*H*-tetrazole (2d)[24]
White solid; yield: 1.14 g (90%); mp 208–210 °C.

IR (KBr): 2986, 2977, 2869, 1717, 1558, 1366, 1066, 1045, 1008 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.35 (s, 9 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.9 (3 × CH_3), 30.3 (C), 163.4 (C).

5-Undecyl-1*H*-tetrazole (2e)[26]
Brown solid; yield: 1.28 g (57%); mp 72–73 °C.

IR (KBr): 3225, 2914, 2848, 1545, 1471, 1074, 716 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.84 (t, *J* = 6.8 Hz, 3 H), 1.24 (m, 16 H), 1.65–1.68 (m, 2 H), 2.84 (t, *J* = 7.6 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.9 (CH_3), 22.2, 22.7, 27.0, 28.3, 28.6, 28.7, 28.9, 29.0 (2 C), 31.3 (10 × CH_2), 155.9 (C).

2-(1*H*-Tetrazol-5-yl)pyridine (2f)[24]
Brown solid; yield: 1.25 g (85%); mp 208–210 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.63 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 8.08 (td, *J* = 7.8, 1.7 Hz, 1 H), 8.22 (dt, *J* = 7.9, 1.0 Hz, 1 H), 8.79 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 122.6 (CH), 126.2 (CH), 138.3 (CH), 143.7 (C), 150.1 (C), 154.8 (CH).

1*H*-Tetrazol-5-amine (2g)[27]
White solid; yield: 0.79 g (93%); mp 212–214 °C.

IR (KBr): 3399, 3192, 1636, 1263, 1044 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 6.56 (s, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 158.2 (C).

***N*-Trityl-1*H*-tetrazol-5-amine (2h)**[28]
Yellow solid; yield: 2.95 g (90%); mp 148–150 °C.

IR (KBr): 3266, 1560, 1445, 757, 695, 633 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.32 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.2 (C), 126.9, 127.4, 127.8, 127.9, 128.0, 128.2, 128.4 (6 C), 128.8, 130.0, 130.3 (15 × CH), 141.5 (3 × CH), 162.1 (C).

Anal. Calcd for $C_{20}H_{17}N_5$: C, 73.88; H, 5.61; N, 21.51. Found: C, 73.92; H, 5.21; N, 22.60.

5-Methyl-1*H*-tetrazole (2i)[25]
White solid; yield: 0.78 g (93%); mp 138–140 °C.

IR (KBr): 3005, 2879, 2605, 1578, 1565, 1112, 1052, 899, 683 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.46 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 8.4 (CH_3), 152.2 (C).

3,3-Dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one (2j)[29]
Orange solid; yield: 1.43 g (85%); mp 152–154 °C.

IR (KBr): 2973, 2322, 1716, 1365, 1048, 1007, 728 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.18 (s, 9 H), 4.41 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 25.8 (3 × CH_3), 32.2 (CH_2), 44.0 (C–C=O), 128.2 (C), 209.3 (C=O).

5-(Diphenylmethyl)-1*H*-tetrazole (2k)[30]
White solid; yield: 1.70 g (72%); mp 165–166 °C.

IR (KBr): 3264, 2917, 1560, 1446, 743, 695, 632 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 5.85 (s, 1 H), 7.14–7.30 (m, 10 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 40.8 (CH), 128.6 (2 × CH), 129.6 (4 × CH), 129.9 (4 × CH), 140.8 (C), 160.0 (2 × C).

5-(9-Anthryl)-1*H*-tetrazole (2l)[25]
Green solid; yield: 1.85 g (75%); mp 215–216 °C.

IR (KBr): 2987, 2900, 1578, 1053, 735 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.45 (d, *J* = 8.6 Hz, 2 H), 7.56–7.63 (m, 4 H), 8.23–8.31 (m, 2 H), 8.94 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 120.6 (2 × CH), 124.8 (2 × CH), 126.4 (2 × C), 128.2 (CH), 129.2 (C), 130.8 (2 × CH), 131.0 (2 × CH), 138.3 (2 × C), 150.1 (C).

1-Trityl-1*H*-tetrazoles 1a–1l; General Procedure
A solution of the appropriate tetrazole **1** (10.0 mmol) in CH_2Cl_2 (5 mL) was added to a solution of TrCl (3.1 g, 11.0 mmol), Et_3N (2.5 mL, 17.6 mmol), and DMAP (92 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at r.t., and the mixture was stirred overnight. The reaction was then quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated at 15 Torr. The residue was purified by column chromatography (deactivated silica gel, hexane–EtOAc) to give the expected tetrazoles **1a–f** and **1i–l**.

For the preparation of the ditritylated compound **1g**, the amounts of the reagents and solvents used were double those indicated above.

5-Phenyl-1-trityl-1*H*-tetrazole (1a)[23]
White solid; yield: 3.69 g (95%); mp 156–158 °C.

IR (KBr): 1491, 1447, 1189, 1026, 876, 762, 747, 729, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.47 (m, 18 H), 8.12–8.16 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.3 (C), 127.2 (2 × CH), 127.7 (3 × CH), 127.9 (6 × CH), 128.9 (C), 130.5 (6 × CH), 141.5 (CH), 145.3 (2 × CH), 150.8 (3 × C), 164.2 (C).

5-(4′-Methylbiphenyl-2-yl)-1-trityl-1*H*-tetrazole (1b)[31]
White solid; yield: 3.21 g (67%); mp 180–184 °C.

IR (KBr): 3056, 1445, 1028, 827, 748, 698, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 6.82–6.95 (m, 9 H), 7.17–7.40 (m, 13 H), 7.81–7.84 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 83.0 (C), 126.6, 127.4, 127.7, 128.1, 128.2, 128.3 (4 C), 129.2, 129.3 (6 C), 129.4, 130.4, 130.5, 130.8, 136.5 (23 × CH), 138.3 (C), 141.4 (C), 142.4 (C), 147.0 (C), 154.1 (3 × C), 164.3 (C).

5-Benzyl-1-trityl-1*H*-tetrazole (1c)[32]
White solid; yield: 3.54 g (88%); mp 160–164 °C.

IR (KBr): 1530, 1252, 1073, 889, 733, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.28 (s, 2 H), 7.08–7.12 (m, 6 H), 7.23–7.37 (m, 14 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0 (CH_2), 83.0 (C), 126.8 (CH), 127.8 (3 × CH), 128.1 (6 × CH), 128.8 (2 × CH), 129.1 (2 × CH), 130.0 (6 × CH), 137.0 (C), 141.5 (3 × C), 164.6 (C).

5-*tert*-Butyl-1-trityl-1*H*-tetrazole (1d)[28]
White solid; yield: 2.54 g (69%); mp 132–136 °C.

IR (KBr): 3005, 2605, 1578, 1565, 1386, 1255, 1112, 1052, 899, 683, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 7.01–7.26 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0 (3 × CH_3), 41.7 (C), 82.8 (C), 127.4 (3 × CH), 127.8 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C).

Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.26; H, 6.55; N, 15.23.

1-Trityl-5-undecyl-1*H*-tetrazole (1e)[28]
Brown solid; yield: 3.87 g (83%); mp 76–80 °C.

IR (KBr): 2922, 2850, 1493, 1444, 747, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.27 (m, 16 H), 1.72–1.79 (m, 2 H), 2.90 (t, *J* = 7.6 Hz, 2 H), 7.07–7.36 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3 (CH_3), 22.8, 29.2, 29.4, 29.7, 29.8, 32.2, 39.7 (C), 82.7 (C), 127.9 (5 × CH), 128.2, 128.4, 128.7, 129.9, 130.3 (6 × CH), 141.6 (3 × C), 166.2 (C).

Anal. Calcd for $C_{31}H_{38}N_4$: C, 79.79; H, 8.21; N, 12.01. Found: C, 79.76; H, 8.22; N, 12.03.

2-(1-Trityl-1*H*-tetrazol-5-yl)pyridine (1f)[28]
Pink solid; yield: 3.31 g (85%); mp 126–128 °C.

IR (KBr): 1489, 1446, 1072, 747, 698 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.79–6.94 (m, 15 H), 7.17–7.21 (m, 1 H), 7.64 (td, *J* = 7.8, 1.6 Hz, 1 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 8.36 (d, *J* = 4.4 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 51.6 (C), 86.4 (CH), 122.6 (CH), 126.1 (CH), 127.0 (3 × CH), 127.9 (6 × CH), 128.2 (6 × CH), 137.0 (3 × C), 138.2 (C), 143.6 (C), 150.1 (CH).

Anal. Calcd for $C_{25}H_{19}N_5$: C, 77.10; H, 4.92; N, 17.98. Found: C, 77.08; H, 4.88; N, 18.00.

***N*,1-Ditrityl-1*H*-tetrazol-5-amine (1g)**[28]
White solid; yield: 1.42 g (25%); mp 220–222 °C.

IR (KBr): 1560, 1493, 1446, 1184, 881, 743, 696, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 6.84–7.40 (m, 30 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 71.7 (C), 82.1 (C), 125.9, 126.4, 126.8, 127.6, 127.8, 127.9, 128.0 (5 C), 128.4 (6 C), 129.0 (5 C), 129.6 (6 C), 130.1, 141.5 (30 × CH), 144.8 (3 × C), 147.8 (3 × C), 165.1 (C).

Anal. Calcd for $C_{39}H_{31}N_5$: C, 82.22; H, 5.48; N, 12.29. Found: C, 82.22; H, 5.46; N, 12.24.

5-Methyl-1-trityl-1*H*-tetrazole (1i)[28]
White solid; yield: 2.25 g (69%); mp 172–174 °C.

IR (KBr): 1507, 1492, 883, 748, 696, 635 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 7.09–7.12 (m, 6 H), 7.21–7.38 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4 (CH_3), 82.8 (C), 126.9 (3 × CH), 128.1 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C).

Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.17. Found: C, 77.41; H, 5.57; N, 17.41.

3,3-Dimethyl-1-(1-trityl-1*H*-tetrazol-5-yl)butan-2-one (1j)[28]
Pink solid; yield: 2.55 g (62%); mp 190–194 °C.

IR (KBr): 1714, 1445, 1057, 882, 752, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 4.17 (s, 2 H), 7.10–7.35 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8 (3 × CH_3), 32.2 (CH_2), 44.0 (C–C=O), 82.8 (C), 127.4 (3 × CH), 127.8 (6 × CH), 130.3 (6 × CH), 141.5 (3 × C), 162.1 (C), 209.3 (C=O).

Anal. Calcd for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.65. Found: C, 76.09; H, 6.37; N, 13.68.

5-(Diphenylmethyl)-1-trityl-1*H*-tetrazole (1k)[28]
Yellow solid; yield: 2.92 g (61%); mp 164–166 °C.

IR (KBr): 1492, 1445, 1048, 748, 697, 639 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.88 (s, 1 H), 7.13–7.38 (m, 25 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 50.9 (CH), 82.1 (C), 125.9, 126.4, 126.8, 127.4 (2 C), 127.6 (4 C), 127.8 (3 C), 127.9, 128.1, 128.4 (6 C), 129.0, 129.6, 130.1, 141.5, 144.0 (25 × CH), 144.8 (C), 147.0 (2 × C), 165.1 (3 × C).

Anal. Calcd for $C_{33}H_{26}N_4$: C, 82.82; H, 5.48; N, 11.71. Found: C, 82.80; H, 5.46; N, 11.69.

5-(9-Anthryl)-1-trityl-1*H*-tetrazole (1l)[28]
Green solid; yield: 3.47 g (71%); mp 170–172 °C.

IR (KBr): 1491, 1447, 1189, 876, 762, 747, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.45 (m, 21 H), 7.70–7.73 (m, 1 H), 8.03 (dd, *J* = 4.8, 4.2 Hz, 1 H), 8.57 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 83.7 (C), 125.6 (2 × CH), 126.8 (2 × C), 127.4 (2 × C), 128.0 (3 × CH), 128.1 (CH), 128.2 (6 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 130.4 (6 × CH), 131.3 (C), 141.6 (2 × C), 147.0 (3 × C), 162.6 (C).

Anal. Calcd for $C_{34}H_{24}N_4$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.55; H, 4.91; N, 11.50.

Reductive Cleavage of 1-Trityl-1*H*-tetrazoles 1a–1f and 1i–1l by Naphthalene-Catalyzed Lithiation; General Procedure
A solution of *N*-trityltetrazole **1** (1.0 mmol) in THF (2 mL) was added dropwise to a green suspension of Li powder (70 mg, 10.0 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture, which turned dark red after the addition of a few drops of the solution of tetrazole **1**, was stirred at –78 °C for the time indicated in Table 1. 1 M aq HCl (5 mL) was carefully added, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was then extracted with EtOAc (3 × 15 mL) and the organic phases were combined, washed with brine (5 mL), dried (Na_2SO_4), and concentrated at 15 Torr. The residue was purified by column chromatography (basic Al_2O_3, hexane–EtOAc), affording the corresponding free tetrazoles **2** in the following yields: **2a** (142 mg, 97%), **2b** (234 mg, 99%), **2c** (131 mg, 82%), **2d** (122 mg, 97%), **2e** (182 mg, 81%), **2f** (127 mg, 86%), **2i** (78 mg, 93%), **2j** (135 mg, 80%), **2k** (198 mg, 84%) and **2l** (185 mg, 75%).

Compounds **2a**, **2g**, and **2i** were commercially available, and compounds **2b**–**f**, **2h**, and **2j**–**l** were prepared by us (see above). All the compounds were characterized by comparison of their physical and spectroscopic properties with those of authentic samples.

Reductive Cleavage of *N*,1-Ditrityl-1*H*-tetrazol-5-amine (1g) by Naphthalene-Catalyzed Lithiation
A 1.6 M solution of BuLi in hexane (0.45 mL, 0.7 mmol) was added dropwise to a solution of tetrazole **1g** (186 mg, 0.5 mmol) in THF (2 mL) at 0 °C under argon until a red color developed. The mixture was stirred for 10 min then TMSCl was added until the red color vanished (0.15 mL, 1.2 mmol). The mixture was stirred for 10 min

and then transferred dropwise by syringe to a green suspension of Li powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture turned dark red and was stirred at –78 °C for the time indicated in Table 1. 1 M aq HCl (5 mL) was carefully added, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was then acidified with 2 M aq HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were discarded and the aqueous phase was basified with 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give the pure tetrazole **2g** [yield: 79 mg (93%)], which was characterized by comparison of its physical and spectroscopic properties with those of an authentic sample.

Monodetritylation of *N*,1-Ditrityl-1*H*-tetrazol-5-amine (1g) by Naphthalene-Catalyzed Lithiation

A 1.6 M solution of BuLi in hexane (0.45 mL, 0.7 mmol) was added dropwise to a solution of tetrazole **1g** (186 mg, 0.5 mmol) in THF (2 mL) under argon at 0 °C until a red color developed. The mixture was stirred for 10 min and then transferred dropwise by syringe to a green suspension of Li powder (50 mg, 7.2 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at –78 °C. The mixture turned dark red and was stirred at –78 °C for 2.5 h. 1 M aq HCl (5 mL) was then carefully added, the cooling bath was removed, and the reaction was stirred until it reached r.t. The mixture was acidified with 2 M aq HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were discarded and the aqueous phase was basified with 2 M NaOH (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried (Na_2SO_4), and concentrated to give the pure tetrazole **2h** [yield: 308 mg (94%)], which was characterized by comparison of its physical and spectroscopic properties with those of an authentic sample.

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Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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Indium-Mediated Cleavage of the Trityl Group from Protected 1*H*-Tetrazoles

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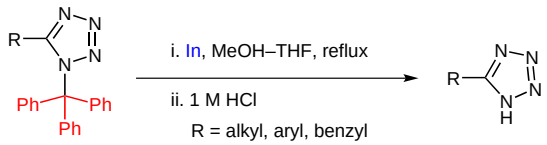
Dedicated to the memory of Prof. Manfred Schlosser



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Abstract On treatment with indium metal in MeOH–THF, trityl groups undergo reductive removal from 1*H*-protected tetrazoles (including aliphatic, aromatic, and heteroaromatic substituents), affording the corresponding free tetrazoles in excellent yields, without any decomposition of the tetrazole ring or reduction of any other group.

Key words tetrazole, indium, detritylation, cleavage

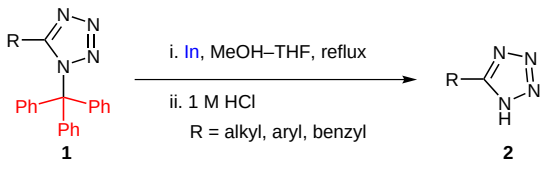
Indium metal is an excellent, useful reagent for a broad range of organic reductions.[1] Indium has a first electrode potential of 5.8 eV, which is similar to that of the alkali metals, such as sodium (5.1 eV) and lithium (5.4 eV), and much lower than that of zinc and magnesium.[2] Due to that, indium has demonstrated to be an excellent single-electron-transfer reducing reagent, and has been used for the removal of many protecting groups. For instance, Moody et al. reported the general reductive removal of 4-nitrobenzyl oxygen protecting group with this reagent. In this reaction, the nitro group is reduced first to give the corresponding aniline, which activates the benzilic carbon–oxygen bond towards the addition of an electron.[3]

In addition, reductive dehalogenations of α-halocarbonyl compounds with indium in the presence of a catalytic amount of sodium dodecyl sulfate in water were performed to afford the corresponding parent carbonyl compounds in excellent yields,[4] and 2,2,2-trichloroethyl carboxylates smoothly underwent deprotection to carboxylic acids and reductive monodechlorination to 2,2-dichloroethyl esters.[5] Furthermore, the selective cleavage of *tert*-butyldimethylsilyl ethers to give the corresponding alcohols by means of indium(III) chloride was also reported,[6] this methodology being also applied to the chemoselective deprotection of different functional groups in polyfunctionalized substrates.

On the other hand, in the world drug, there are more than six types of sartans, which display different biological activities. Some of them, such as candesartan, irbesartan, losartan, olmesartan, and valsartan, bear a tetrazol unit in their structures and have a variety of therapeutic targets like angiotensin II receptor blocker, lowering blood pressure, and playing a significant role in the progression of tissue damage in cardiovascular diseases.[7]

The protection and deprotection of the nitrogen atom of the tetrazole ring is a crucial operation during the synthesis of these sartans. One group that can be used to protect the tetrazole nitrogen is the triphenylmethyl (trityl) group.[8] Detritylation of tetrazole *N*-trityl-protected sartan derivatives to produce the free N–H bonds was carried out under different conditions: hydrogenolysis in the presence of Pt/C (5%)[9] or with aqueous NaOH in MeOH.[8] Surprisingly, in the last case, the removal took place without any side reaction and in excellent yields.

Our research group has already reported the removal of the trityl protecting unit in different functional groups using an arene catalyzed lithiation. All these reactions were performed at –78 °C in excellent yields.[10]



Equation 1

In the course of developing deprotection methods of many protecting groups, we attempt to remove the trityl unit using different electron-transfer sources, such as lithium, sodium, samarium, and indium.[10,11] The application of indium metal reductive removal of the trityl group from the nitrogen atom of several protected tetrazoles under mild reaction conditions is discussed below (Equation 1).

Table 1 Indium-Mediated Cleavage of the Trityl Group under Reflux from Protected 1*H*-Tetrazoles

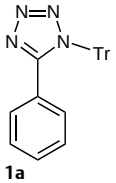
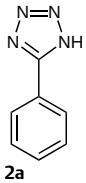
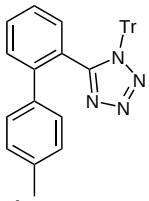
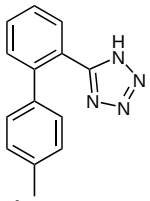
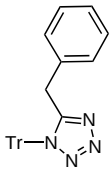
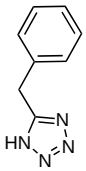
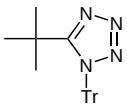
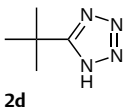
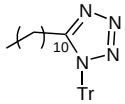
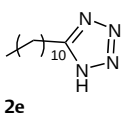
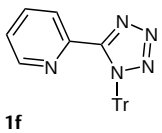
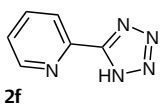
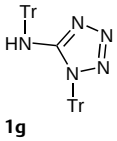
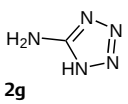
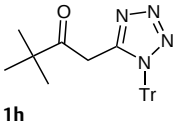
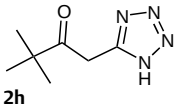
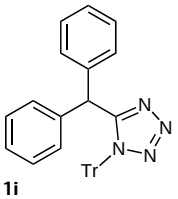
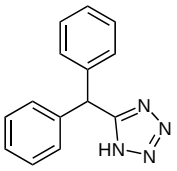
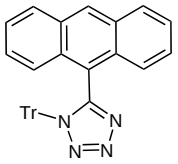
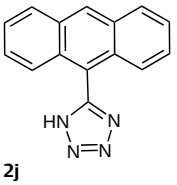
Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	26	 **2a**	93
2	 **1b**	21	 **2b**	96
3	 **1c**	25.5	 **2c**	80
4	 **1d**	22	 **2d**	92
5	 **1e**	21	 **2e**	81
6	 **1f**	23	 **2f**	86
7	 **1g**	4	 **2g**	93

Table 1 (continued)

Entry	Substrate	Time (h)	Product	Yield (%)[a]
8	 **1h**	20	 **2h**	88
9	 **1i**	23	 **2i**	82
10	 **1j**	20	 **2j**	77

[a] Yield of isolated product after purification by column chromatography (basic aluminum oxide, hexane–EtOAc), based on the starting material.

With the aim of determining the best reaction conditions for the removal of the trityl group bonded to the nitrogen in different tetrazoles, we took 5-phenyl-1-trityl-1*H*-tetrazole (**1a**) as the model compound. Unfortunately, no reaction occurred when tetrazole **1a** was treated with indium metal (1:1 molar ratio) in a mixture of MeOH and THF (2:1 volume ratio) at 0 °C for 24 hours. However, full conversion was observed when this reaction mixture was heated at reflux temperature for 26 hours, 5-phenyl-1*H*-tetrazole (**2a**) being isolated in 93% yield after purification by column chromatography (Table 1, entry 1). In the absence of indium, the cleavage did not take place under the same reaction conditions. On the other hand, indium was partially consumed during the reaction, before the acidic hydrolysis. In order to broaden the scope of this indium-mediated detritylation, we applied the same reaction conditions to different 5-substituted tetrazoles. Detritylation of tetrazoles bearing aromatic (**1b** and **1j**) and benzylic (**1c** and **1i**) substituents at the 5-position occurred also in high yields (Table 1, entries 2, 3, 9, and 10). Actually, compound **2b** is a direct precursor of the sartans.[9] Similar results were also obtained for aliphatic substituted tetrazoles. Thus, for compound **1d** with a sterically demanding *tert*-butyl group at the 5-position, detritylation produced 5-*tert*-butyl-1*H*-tetrazole in 92% yield (Table 1, entry 4). In the case of tetrazole **1e** bearing a long linear aliphatic chain, the detritylated tetrazole **2e** was obtained in 81% yield (Table 1, entry 5).

These reaction conditions were also highly effective in the detritylation of functionalized tetrazoles. For instance, tritylated tetrazole with a heteroaromatic 2-pyridyl substituent at the 5-position gave 5-(2-pyridyl)-1*H*-tetrazole (**2f**) in 86% yield (Table 1, entry 6). Even more interestingly, a double deprotection of ditritylated 5-amino-substituted tetrazole **1g** was observed, leading to 5-amino-1*H*-tetrazole (**2g**) in 93% yield (Table 1, entry 7). Comparing with the lithium arene catalyzed detritylation, this methodology seems to be superior, because previous deprotonation with *n*-butyllithium of tetrazole **1g** was not necessary. The starting material **1g** has an N–H bond which is acidic enough to decompose the naphthalene radical anion and dianion that act as lithiation agents. This is the reason why it has to be removed first, beforethe lithium–arene combination is used in these reductive reactions. This methodology was also compatible with the presence of carbonyl groups. Detritylation of **1h** gave 1-(1*H*-tetrazol-5-yl)propan-2-one (**2h**) in 88% yield (Table 1, entry 8), the removal of the trityl unit taking place without affecting the carbonyl group under these reductive reaction conditions.

The progress of the reactions was monitored in all cases by thin-layer chromatography. Once the reaction went to completion, final hydrolysis with 1 M HCl led to the corresponding tetrazoles **2**. After hydrolysis, the triphenylmethane and the tetrazole products were extracted with EtOAc and then easily separated by column chromatography.

The starting Tr-tetrazoles **1** were prepared by reaction of the corresponding tetrazole **2** with trityl chloride in the presence of triethylamine and a catalytic amount of 4-(dimethylamino)pyridine. Compounds **2a**,**g**,**i** are commercially available and **2b–f**,**h**,**j** were prepared by us.[12] All of these compounds were characterized by comparison of their physical and spectroscopic data with authentic samples.

In summary, in this paper we have presented a very efficient method for the detritylation of protected tetrazoles using indium as an electron source. The methodology has proven to be useful for the removal of the trityl group from Tr-tetrazoles substituted on the carbon atom of the ring by aromatic, heteroaromatic, aliphatic, or benzylic carbon chains, with, in some cases, sensitive functionalities like carbonyl and amino groups. The double detritylation of a Tr-tetrazole in the presence of a secondary Tr-amine was also observed. This method represents a good alternative to the commonly used detritylation procedures, which are sensitive to air moisture and acidic conditions.[13,14]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379933.

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(12) With the aim of trying to broaden the substrate scope, we tried to prepare some other tetrazoles functionalized with either ester or amide groups but, unfortunately, all our attempts were unsuccessful.

(13) **Typical Procedure**
In a typical procedure, a mixture of 5-phenyl-1-trityl-1*H*-tetrazole (**1a**, 0.230 g, 0.5 mmol) and indium powder (0.058 g, 0.5 mmol) in MeOH (6 mL) and THF (3 mL) was stirred at 78 °C for 26 h. Then the resulting mixture was cooled to r.t., hydrolyzed with 1 M HCl (2 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated (20 mbar). The resulting

residue was purified by column chromatography (silica gel, hexane–EtOAc) to yield 5-phenyl-1*H*-tetrazole (**2a**, 0,134 g, 93%) as a white solid, mp 215–216 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7. 55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 124.1 (2 × CH), 127.0 (C), 129.4 (CH), 131.3 (2 × CH), 155.3 (C).[10h]

(14) For all detailed procedures, see the attached Supporting Information.