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DEPARTMENT OF CHEMISTRY

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SUBMITTED IN PARTICAL FULFILLMENT OF REQUIREMENT
FOR DOCTORAT LMD IN ORGANIC CHEMISTRY

OPTION
ORGANIC SYNTHESIS

TITLE

Removal of Pivaloyl and trityl groups from Tetrazoles and alcohols via Indium, lithium chloride and arene catalyzed lithiation

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Sustained in……..

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 tender and wonderful parents, who always supported me and have greatly contributed to the success of this work.

To my husband Nassredine Lafalla, I hope that he will be always proud of me.
To my little angel HADJER ALAA.

To my brother Hamza, and my sisters Leila, Amina, Fouzia, Meriem.

To my friends,

To all person of my family.

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I would like to thank my dear friends: kenza, Meriem, Wafa, Zaynab, Faiza, Halima, Asma, Souad, Rachida who were always by my side, all the thanks words could not express my thanks and gratitude for their support to me.

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) and a Bruker AC-400 spectrometer (400 MHz for ^{1}H and 100 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), Fourrier BRUCKER DPX 250 (250 MHz for proton and 62.5 MHz for carbon 13) 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, dd: doublet of doublet.

Infra-Red spectrometry

FT-IR spectra were recorded on a Nicolet Impact 400D spectrophotometer and Fourrier Shimadzu FTIR-8201 PC 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.

CONTENTS

Chapter III: Removal of pivaloyl tetrazoles with arene catalysed lithiation and trityl ethers via indium and lithium chloride

GENERAL INTRODUCTION

General introduction

Fine chemicals includes all kinds of complex and multifunctional molecules, their synthesis generally require multi-step and sometimes in phases. The functional groups may react upon each other, as they can be competitive with respect to the same reagent, so their synthesis remains difficult to achieve.

The use of a protecting group it is necessary in organic synthesis? No, it should be avoided if possible. However, in synthesis multi-step, the use of one or more protecting groups is difficult to avoid.

Development of new and mild reactions and reagents for the protection of functional groups is of paramount research in the area of synthetic organic chemistry. A total synthesis of complex natural product always is benefited by mild reagents and efficient protocols for the protection as well as deprotection. Inspite, still there is an urge for new and specific protecting groups to realize the successful overall operation of the total synthesis.[1] 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 use of protecting groups in organic synthesis has made a significant growth in recent years, witnessing the many methods described in the literature on this subject. Environmental and economic considerations have been identified for academic and industrial research by designing own synthesis processes, selective, cost effective and easy to implement.

We are interested in the protection / deprotection under very mild reaction conditions of the amine function (tetrazoles) and hydroxyl function (alcohols). In connection with this process; we have perform the deprotection of pivaloylated tetrazoles with lithium and tritylated alcohols with indium and lithium chloride.

The first part of our work was interesting about a big class of heterocycles that has acquired immense importance in recent years which is the synthesis of tetrazoles using a simple and safe protocol, this function is metabolically stable and the close similarity between the acidic character of the tetrazole group and carboxylic acid group have inspired medicinal chemists to

synthesize substituted tetrazoles as potential medicinal agents. 5-Substituted-tetrazoles are reported to possess antibacterial,[2] antifungal,[3] antiviral,[4] analgesic,[5] anti inflammatory,[6] antiulcer[7] and antihypertensive[8] activities. Also, tetrazole moieties are important synthons in synthetic organic chemistry.[9]

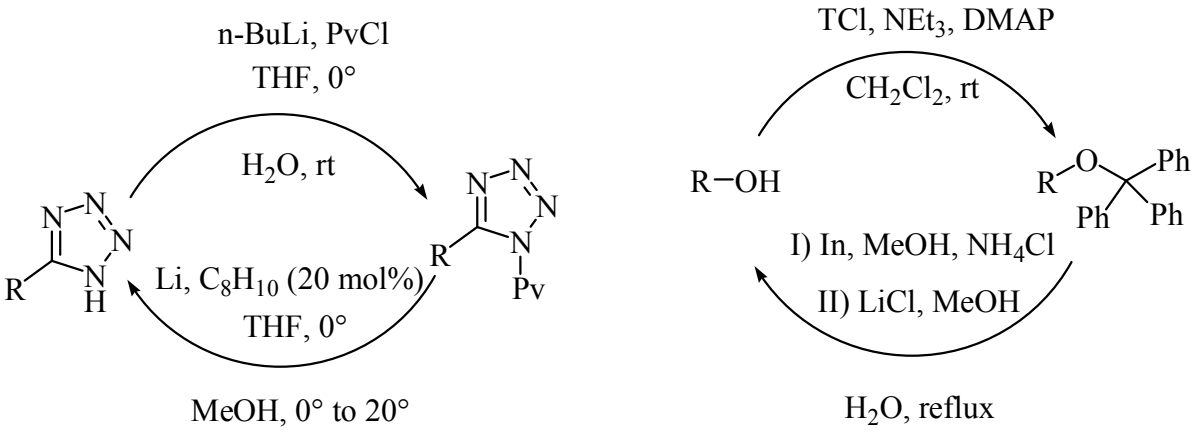
The second part of our work contains the protection of two big families: the hydroxyl groups with trityl chloride and amino protecting groups with pivaloyl chloride, many methods for the introduction of these two groups have been described in the literature. Hydroxyl group protection is important in the synthesis of some organic molecules. One way to protect hydroxyl groups is to transform the molecules to their corresponding trityl (Tr) ethers.
In general, the sterically least hindered alcohols are the most readily tritylated. A large number of tritylation methods exist for the introduction of the trityl group into a variety of alcohols. Due to its steric hindrance, trityl group finds a specific application and can be used for selective protection in different substrates such as selective protection of hydroxyl groups in nucleosides. On the other hand, trityl ethers show good stability in mild acidic or basic media which make them good candidates to be used in total syntheses of related targets.[10]

Several biologically active organic compounds containing the amine function have been the subject of several studies of protection in recent years in synthesis organic. In this context, the design of new gentle and effective protecting groups becomes a priority. The pivaloyl group is one of these protecting groups, is widely used in organic synthesis due to its easy introduction, stability under a variety of reaction conditions, and relatively easy removal to give the corresponding depivalated compounds.[11]
The third part includes our own and principal work using the most methodologies of deprotection which are metals. The removal was applied on C-N bond of pivalated tetrazoles with lithium; the same removal was applied on C-O bond of trityl ethers using indium and lithium chloride respectively.

In the last few years, the organic chemists have been using an arene-catalysed 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 (DTBB) allowed them to generate simple organolithium compounds starting from non-halogenated materials and functionalized organolithium compounds by chlorine lithium exchange or by ring-opening of heterocycles.[12]

Because of its particular importance in topical fields of research, Indium has 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. Indium has pronounced Lewis acid character and is also attractive because of their moderate stability.[13]

Our work is summarizing in this Figure



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CHAPTER I

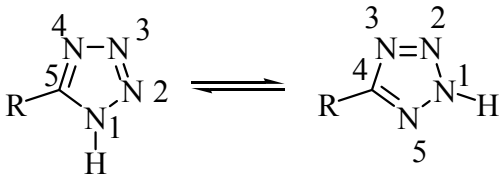
Synthesis of tetrazoles

I.1. Introduction

Tetrazoles have been extensively studied as a group of compounds because they are regarded as biologically equivalent to the carboxylic acid group and have been proven to be metabolically more stable. The development of the chemistry of tetrazoles has been largely associated with the wide use of these compounds in medicinal chemistry and in various materials science applications, including specialty explosives. Various publications describe tetrazoles as inhibitors of monoamine oxidase, antiviral activity, antibacterial activity, and as antagonists of cerebellum-specific GABAA receptors and angiotensin II. Some tetrazole derivatives have been prepared from carbohydrates and used as glycosidase inhibitors. Structural modifications have been undertaken to obtain compounds with different physicochemical properties, and subsequently with different pharmacodynamics and pharmacokinetic properties.[1]

I.2. Structure of Tetrazoles

The tetrazole ring has two tautomeric forms (**1**) and (**2**) .The numbering system of form (**1**) is used to number ring subtituents (as against tautomeric proton). The tetrazole ring is different from other azole systems insofar as it represents the functional group for a full series of carbazolic acid RCN_4H, full nitrogen analogoues of carboxylic acids RCO_2H (figure I.1).



1 **2**

Figure I.1. Structure of Tetrazoles.

I.3. Chemical & Physical Properties

I.3.1. Aromaticity

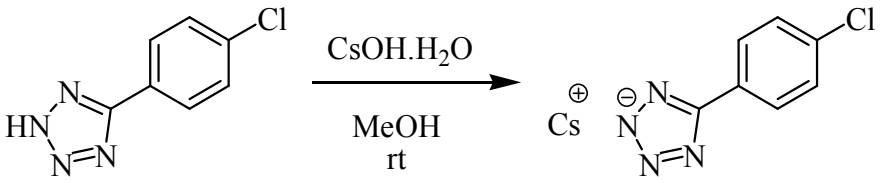
The tetrazole ring is a 6π-azapyrrole-type system.[2,3] Reactivity of 5-substituted tetrazoles permits them to be classified as aromatic compounds.[2,4] In tetrazoles, two of the six π-electrons required by the Huckel rule are provided by the lone pair of one nitrogen while the remaining four π-electrons are provided by the other four atoms of the ring.

I.3.2. 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 pyridine tetrazoles or pyrrolidine tetrazoles are soluble in water therefore the extraction from water can be problematic.

I.3.3. Tetrazolate anions: acidity

5-Substituted tetrazoles display acidity comparable with the corresponding carboxylic acids.[2, 5] 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 are stronger acids. The increased acidity is ascribed to enhanced resonance stabilization in the 5- phenyltetrazole anion relative to benzoate.[2] The tetrazolate anions are easily generated with metal hydroxides and are stable in hot alcoholic and aqueous solutions (figure I.2).[2,6]



3 **4**

Figure I.2. Example of a metal tetrazolate salt.

I.4. Application of Tetrazoles

People are more interested in heterocyclic compounds containing tetrazole rings in recent years because of their broad applications in different scientific research fields. As a good ligand, the nitrogen atoms from tetrazole rings can be coordinated with metallic ions to form various functional complexes. In medicinal chemistry, the tetrazole ring can act as a metabolically stable surrogate for a carboxylic acid group, and these compounds have various material science applications, including special explosives.

In 1994, the first member of Sartan's family, Losartan, was synthesized and applied to clinical treatments. After that, scientists have been decorating its molecular structure with chemical reactions on the mother nucleus to improve its curative effects of lowering blood pressure, prolonging its process, and decreasing its side effects. Losartan's outstanding

performance accelerated the emergence of other members of Sartan's family and mean while promoted the development of medicinal chemistry. These novel medicines can be used for the treatment of hypertension, heart failure, and kidney diseases.[7]

Until now, the angiotensin II acceptor depressant family has many members, such as Losartan, Irbesartan, Candesartan, Tasosartan, Valsartan, and Olmesartan. In these medicinal molecules, there is a normal 2-substituted biphenyl tetrazole unit, which is the important intermediate for preparing Sartan.

I.4.1. Biological importance of tetrazoles

- ***Antimicrobial activity***

Tetrazole ring is associated with potential antibacterial and antifungal activities. Some 5-substituted tetrazole derivatives have revealed strong growth inhibitory activity against Candida species. In an attempt to find new antifungal agents in the tetrazole series another group of workers have found some 1-(2,4-dihydroxyl thiobenzoyl)- tetrazoles as potential antifungal agents. Chemists have obtained some azole antimicrobial pharmacophore-based tetrazoles as potential antimicrobial agents. These compounds were able to display variable growth inhibitory effects on the tested Gram positive and Gram negative bacteria with special efficacy against the Gram positive strains. Meanwhile, some compounds exhibit moderate antifungal activity against Candida albicans and Aspergillusfumigatus.

Encouraged by the various biological activities of tetrazole and its derivatives, many methods carried out the synthesis of a novel series of 5-thiosubstituted tetrazole derivatives and visualize their antibacterial and antifungal properties. In another recent investigation the synthesis of some tetrazole derivatives was carried out and these compounds were screened for their antiamoebic and cytotoxic properties.

- ***Miscellaneous***

There is synthetic tetrazole analogue of nicotinic acid which is effective in high concentrations as a growth factor for Lactobacillus arabinosus and was found to be three to four times more potent than nicotinic acid in lowering serum cholesterol in man. Tetrazole analogue of a series of N-Phenyl anthranilic acids have been reported to possess anti-inflammatory activity in both pharmacological and clinical tests.

Tetrazoles are also reported to exhibit antihypertensive, antiallergic and antibiotic activity. Furthermore aminotetrazole derivative have been patented for their muscle relaxation, anti-inflammatory, antiarthritic, analgesic, ulcer therapeutics and cocediostatic properties.

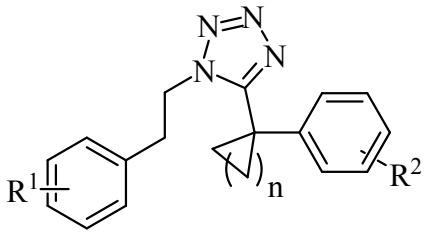
Tetrazole are used as plant growth regulators herbicides and fungicides in agriculture as stabilizers in photography and photoimaging and as explosives in rocket propellants. Some of the 1-substituted 1,2,3,4-tetrazole compounds have shown strong phytocidal activity. A series of perfluoro amides having 1H-1,2,4-tetrazole moiety as an acidic heterocycle have been reported to display highly significant insulin sensitizing property and thereby exhibit potent hypoglycemic activity. In addition some compounds bearing a 1H-tetrazole moiety in there skeleton have been found to be potent antihyperglycemic agents.

I.4.2. Pharmaceutical properties

Tetrazole itself does not exhibit pharmacological activity; however, many of its derivatives possess interesting biological activities and they are frequently used as metabolically stable surrogates for carboxylic acids, while tetrazoles generally offer a more favorable pharmacokinetic profile. [2,8,9,10,11]

Like their carboxylic acid analogues, tetrazoles exhibit a planar structure. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylate, which is an important factor in allowing the molecule to pass through cell membranes. Hydrogen bonding capability of tetrazolic anions with receptor recognition sites is a key interaction for enhanced binding affinity.

In addition, in the design of drug molecules, one advantage of tetrazoles over carboxylic acids is that they are resistant to many biological metabolic degradation pathways. Tetrazole derivatives have been investigated in areas as diverse as anti-arrhythmic agents (5), anti-diabetic agents, anti-cholesterol agents, antifungal agents, anti-allergic agents (7), neurodegenerative diseases (8-11) among others. Some examples are given in figures I.3-I.6.



n= 0, 1, 2, 3, 4
R^1= *p*-MeO-, *p*-Me-, *p*-F-
R^2= *p*-Cl-, -O-Me-

5

Figure I.3. Anti-arrhythmic agents.

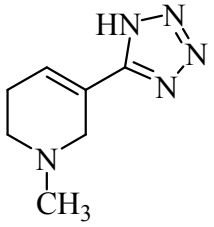


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Figure I.4. Muscarinic agonist.

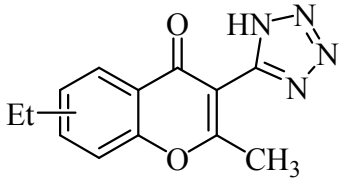

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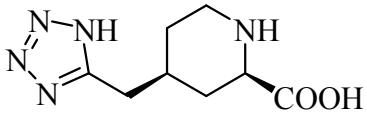
Figure I.5. Anti-allergenics



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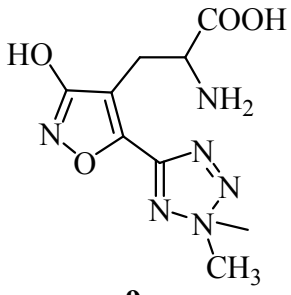

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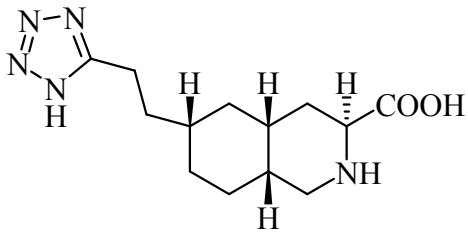

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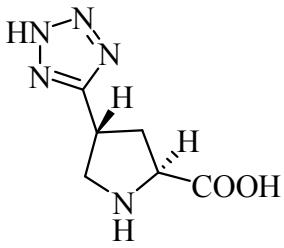

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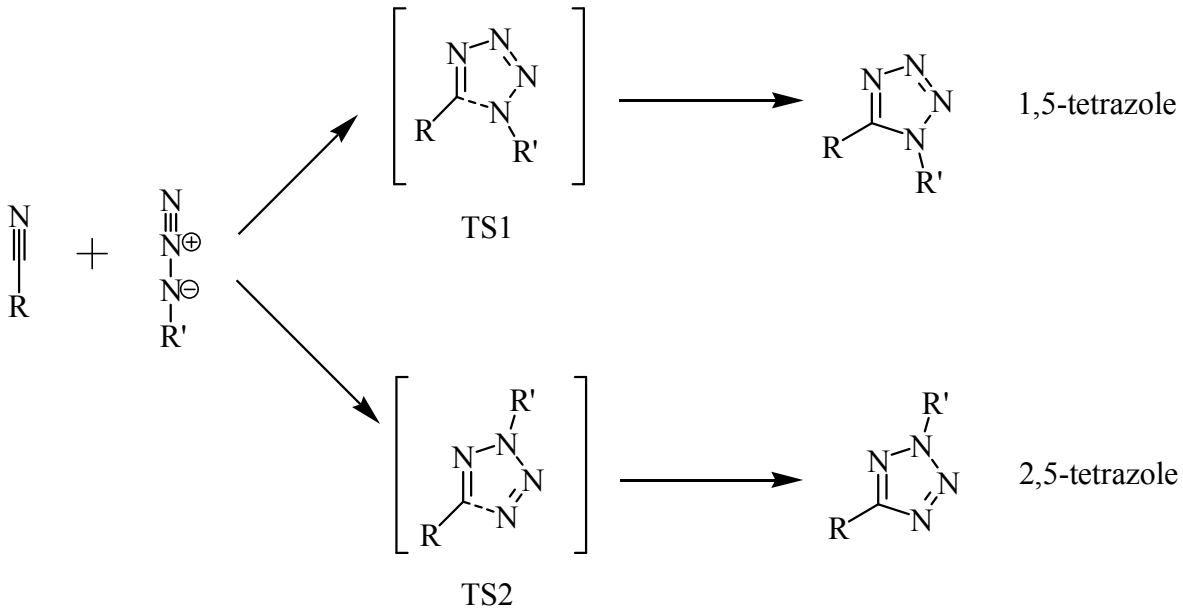
Figure I.6. Tetrazole derivatives with central nervous system activity.

I.5. Methods of Synthesis

I.5.1. Synthesis of tetrazoles from nitriles with azides

❖ ***Neutral cycloaddition***

A [2+3] cycloaddition is the most likely pathway for the bimolecular addition of non-ionic azides to nitriles.[12] 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-with drawing substituents R (Scheme I.1).



Scheme I.1

❖ ***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.[13,14] In theses cases, there are two possible mechanisms, 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. As in the case of the neutral [2+3] cycloadditions, the barrier for anionic [2+3] cycloaddition decreases with increasing electron with drawing 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 with drawing potential of the substituent and for very strong electron-with drawing groups like RSO_2, an intermediate such as that shown in figure I.7 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. [12]

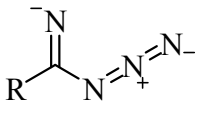
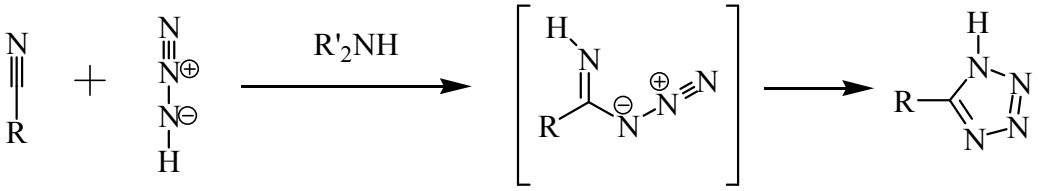


Figure I.7. Structure of the intermediate.

❖ ***Proton involvement***

Koldobskii *et al.*[15] 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 I.2).[12]



Scheme I.2

I.5.1.1. Hydrazoic acid

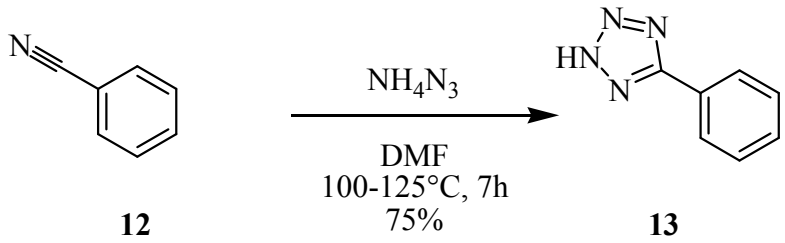
The acid –catalysed cycloaddition between hydrazoic acid and nitriles has long been one of the main routes to 5-substituted tetrazoles.[5,16] The first method to appear in the literature was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932.[17]

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.[18] 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. [19,20]

I.5.1.2. Metal salt methods using sodium azide

➢ **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[18] 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 I.3).



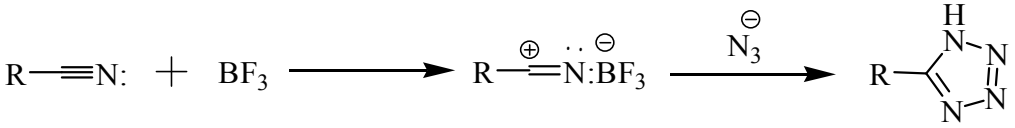
12 **13**

Scheme I.3

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[21]; therefore using high temperature is not advisable in these cases.

- **NaN_3 in the presence of Lewis acid**

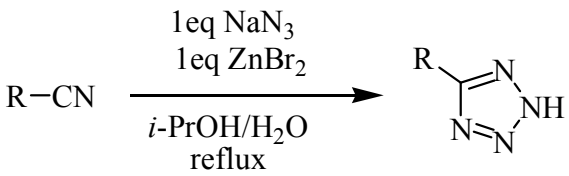
Finnegan and Lofquist reported in 1958 the study of the tetrazole formation in the presence of Lewis acids. The proposed mechanism involves a nucleophilic attack of azide ion on the carbon of nitrile group, followed by ring closure of the iminoazide to form the tetrazole ring. Conditions which enhance or favour a δ+ charge on the nitrile carbon, such as the coordination of a Lewis acid, increase the rate of the reaction (Scheme I.4).



Scheme I.4

I.5.1.3. Sharpless methodology

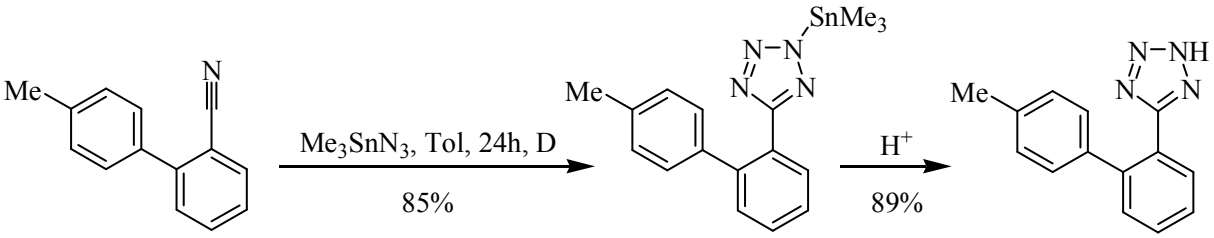
Sharpless *et al*. have reported a simple protocol for transforming a wide variety of nitriles into the corresponding 1H-tetrazoles, by using NaN_3 in the presence of Zn(II) salts in aqueous conditions (Scheme I.5).



Scheme I.5

I.5.1.4. Trialkyltin azides

The treatment of the starting nitrile **14** with trimethyl- or tri-*n*-butyltinazide[22] in toluene or xylene at refluxing gives the corresponding tetrazole. The insoluble tin-tetrazole adducts **15** precipitates and when the reaction is finished, the product is simply filtered and dried. Subsequent acid hydrolysis yields the desired tetrazole (Scheme I.6).

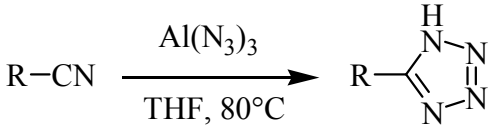


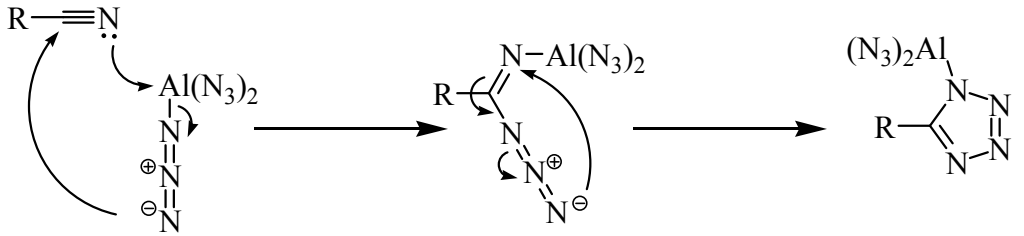
14 **15** **16**

Scheme I.6

I.5.1.5. Aluminum azide

Aluminum azides have already been reported by Wiberg and Michaud in a 1957 German patent. The $Al(N_3)_3$ can be prepared by treatment of $AlCl_3$ with 3 equivalents of NaN_3 in THF at reflux. 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 I.7).

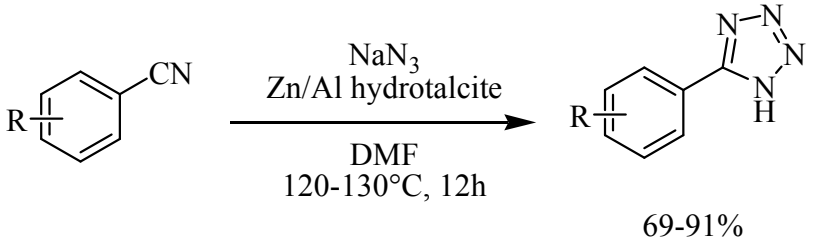




Scheme I.7

I.5.1.6. Synthesis of 5-substituted tetrazoles using Zn/Al hydrotalcite catalyst

Katam *et al*. reported alternative methods to prepare tetrazole rings using Zn/Al hydrotalcite as heterogeneous catalyst (Scheme I.8). 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.

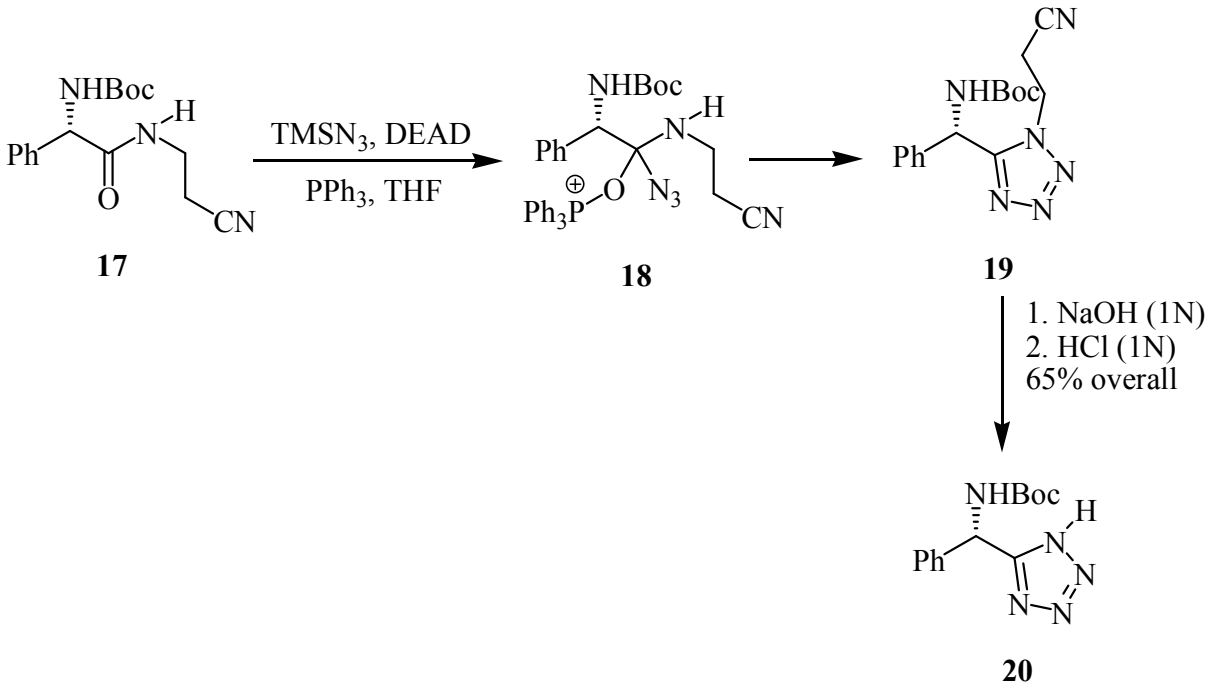


Scheme I.8

I.5.2. Synthesis of tetrazoles with other methods

I.5.2.1. From N-(cyanoethyl) amides

N-(Cyanoethyl) amides **17** reacts with trimethylsilyl azide to provide 1N-protected tetrazole **19** (Scheme I.9). Removal of the N-cyanoethyl moiety of **19** with aqueous sodium hydroxide, followed by acidification, led to the free tetrazole **20** in relative good overall yield.[23]

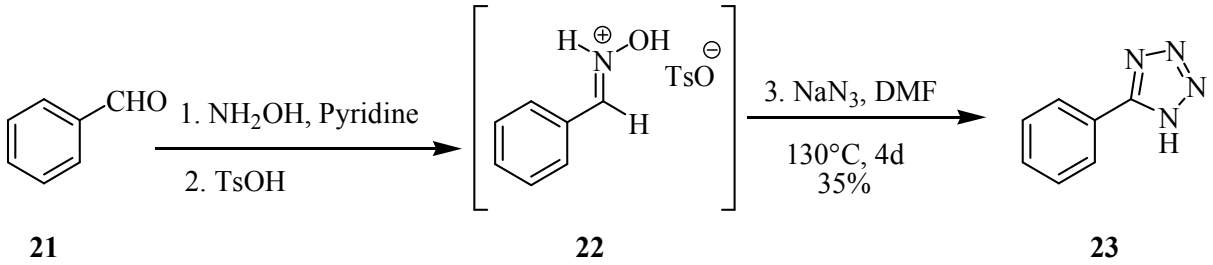


17 **18** **19** **20**

Scheme I.9

I.5.2.2. From oxime salts

An useful process for the preparation of 5-substituted-tetrazoles is the reaction of oxime salt **22** with sodium azide developed by Antonowa and Hauptmann. In this procedure, benzaldehyde **21** may be directly transformed into the corresponding aryl tetrazole **23** (Scheme I.10).

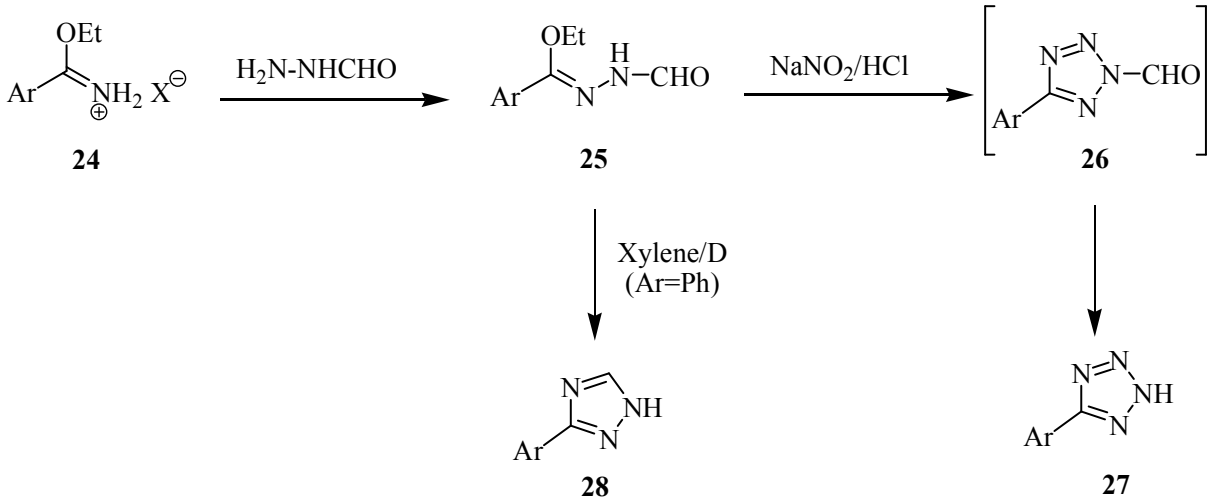


21 **22** **23**

Scheme I.10

I.5.2.3. 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. The reaction of imidates **24** with N-formylhydrazine is known to give 1,2,4-triazoles via the intermediate N-formylamidrazones **25**. 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 **27** can be isolated in good yields (Scheme I.11). The triazole **28** can be isolated only upon heating in xylene.[24]

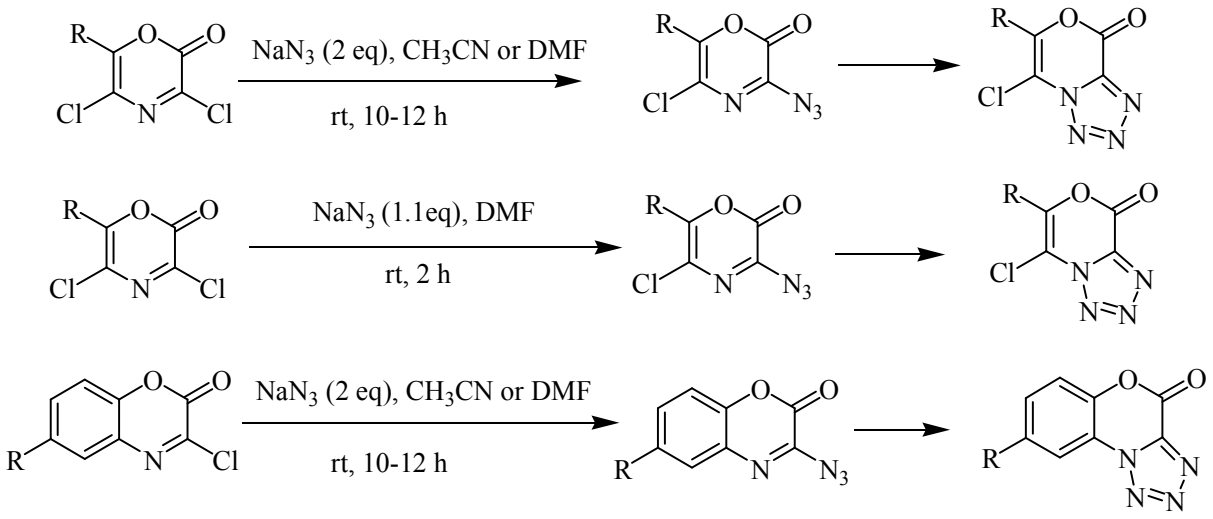


24 **25** **26** **28** **27**

Scheme I.11

I.5.2.4. From 3,5-dichloro-2H-1,4-benzoxazin-2-ones with diazocompounds

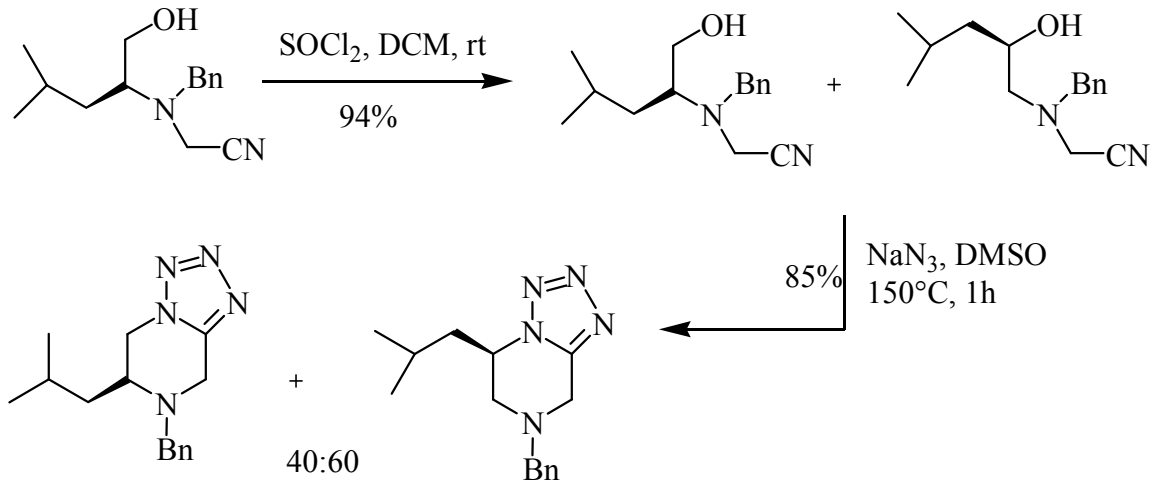
Bat-t P. Medaer *et al*. have reported a simple protocol for synthesis of new lH-tetrazoles in a typical procedure; the 3,5dichloro-2H-l,4-oxazin-2-ones and 3-chloro-2H-l,4-benzoxazin-2-ones are reacted with bifunctional reagents as sodium azide and diazocompounds in CH_3CN or DMF to yield bi(tri)cyclic tetrazolo- fused intermediates *via* an intramolecular cyclisation reaction by substitution of the imidoyl chloride function followed by ring closure *via* the azidoimino-tetrazolo equilibrium[25] (Scheme I.12).



Scheme I.12

I.5.2.5. From b-amino alcohols

F. Couty *et al*. reported recently that the chlorination ($SOCl_2$) of N-cyanomethyl b-amino alcohols derived from available b-amino alcohols was regio- and stereoselective and gave in high yields chlorinated amines.[26] These compounds were in turn converted into 2-cyano azetidines. They found that the treatment of these chlorides with sodium azide in DMSO at 150°C gave good yields of fused tetrazole–piperazines[27] (Scheme I.13).



Scheme I.13

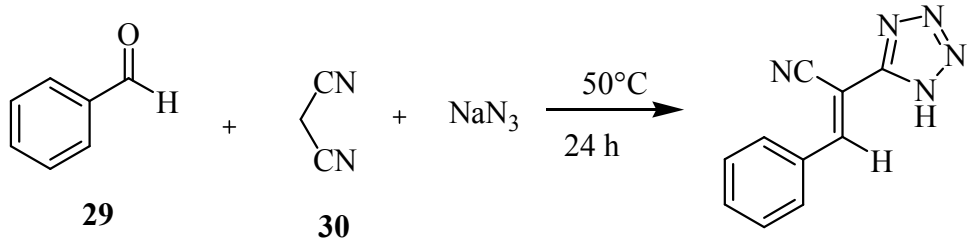
I.5.2.6. From a multi-component domino Knoevenagel condensation/1,3 dipolar cycloaddition reaction

Many protocols for the synthesis of 5-substituted 1H-tetrazoles have some disadvantages, such as the use of toxic metals, strong Lewis acid, expensive reagents, low yield, drastic reaction conditions, water sensitivity and the presence of hydrazoic acid, which is toxic and explosive. In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents, such as DMF. Recently, Sharpless *et al*. reported an improved preparation of tetrazoles by the reaction of nitriles and NaN_3 in the presence of Zn(II) salts in water. In the case of sterically hindered aromatic or deactivated alkyl nitriles, high temperature (140-170° C) and long reaction times are required. Thus, the development of a convenient and safe process for the preparation of new tetrazole derivatives is an interesting target for investigation. Despite continuous research for the synthesis of tetrazoles and development of new multi-component reactions, Z.N. Tisseh *et al*. reported a novel, facile, eco-friendly and one-pot process for synthesis of 5-substituted 1H-tetrazoles via a domino Knoevenagel condensation and 1,3 dipolar cycloaddition reaction.

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the three-component reaction of benzaldehyde **29**, malononitrile **30** and sodium azide as a simple model substrate was investigated in different solvents without any catalyst. The desired product was scarcely obtained in non-polar solvents (benzene, chloroforme) and even methanol and ethanol as a polar protic solvent failed to produce the desired 1H-tetrazole in good yield. It was found that water is the best solvent with respect to

reaction yield. This effect can be attributed to the strong hydrogen bond interaction at the organic-water interface, which stabilizes the reaction intermediate.[28]

They performed the model reaction using different quantities of reagents in water. The best result was obtained with a 1:1:2 ratio of benzaldehyde, malononitrile and sodium azide (Scheme I.14).

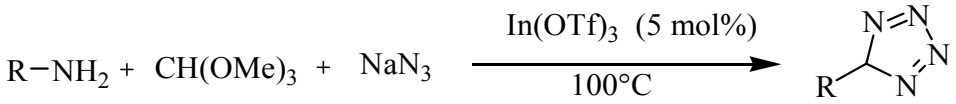


29 **30**

Scheme I.14

I.5.2.7. From indium triflate-catalyzed one-pot

A simple, efficient, and general method has been developed by D. Kundu *et al*. For the synthesis of 1-substituted-1H-1,2,3,4- tetrazoles via a three-component condensation of amine, trimethyl orthoformate, and sodium azide in presence of a catalytic amount of indium triflate under solvent-free conditions. The reaction proceeds smoothly to generate the corresponding 1-substituted tetrazoles. The reaction of aniline (2 mmol), trimethyl orthoformate (2.4 mmol), and sodium azide (2 mmol) was carried out in various solvents as well as neat in presence of different catalysts. The results revealed that $In(OTf)_3$ (5 mol %) was better suited to afford the tetrazole in excellent yield under neat conditions at 100 °C (Scheme I.15).[29]



Scheme I.15

I.6. Results and discussion

I.6.1. Synthesis of tetrazoles

The tetrazole moiety is present in several biologically active compounds, such as sartans, which are pharmaceuticals that are efficient for the treatment of several diseases like hypertension, kidney damage caused by diabetes, and heart failure. The synthesis of sartans generally requires protection and deprotection steps to the tetrazole ring.

According to the literature, the synthesis of the tetrazoles can be carried out according to several methods. In our case we have used a simple method wich is nitriles.

A variety of tetrazoles were prepared through respective reactions of sodium azide with corresponding nitriles in aromatic solvent in the presence of an amine salt. The mixture was heated to 110°C for 17-30 h with stirring. The product was extracted with water and the aqueous layer was acidified with HCl affording to the expected tetrazoles with higher purity in greater yield after filtration. Our method has several advantages: the reaction produces no byproducts due to side reaction; the reaction takes place rapidly, and 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 (Scheme I.16).

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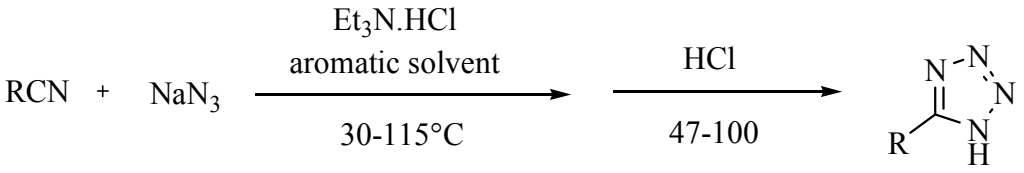
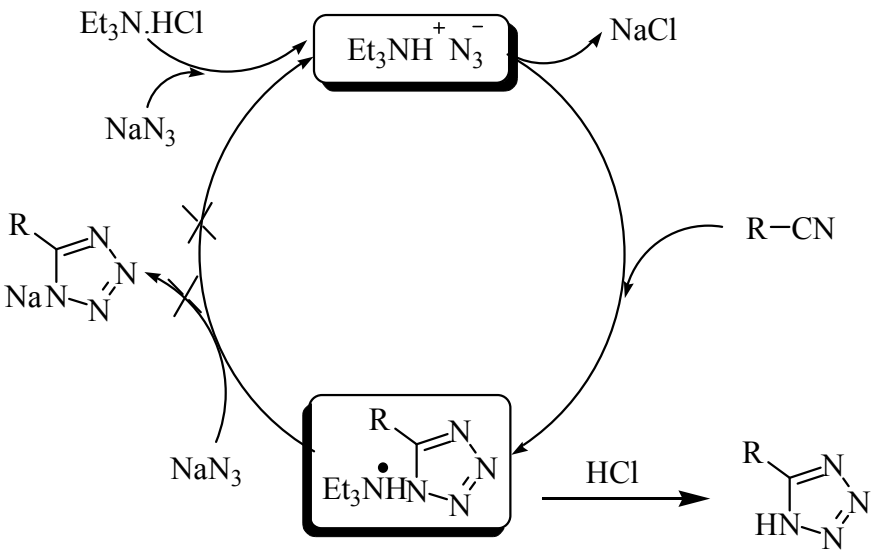


Scheme I.16

The mechanism of reaction



Scheme I.17

I.6.2. Synthesis of 5-substituted tetrazoles from nitriles

The simplicity of the synthesis of tetrazoles allowed us to synthesize several products have the same form with a difference in the radical which is varied between aromatic and alkyl nitriles.

The reaction of 4'-methyl-[1,1'-biphenyl]-2-carbonitrile and 2,2-diphenylacetonitrile as aromatic nitriles with NaN_3 at 110°C in the presence of an amine salt for 17-30h yielding the desired tetrazoles **2b, 2f** in excellent yield (Table I.1; entries 1, 4).

The reaction of nitriles bearing aliphatic groups like pivalonitrile with NaN_3 at 110°C in the presencs of an amine salt for 17h yielding the desired tetrazole **2c** in excelent yield (Table I.1; entrie 2). The tetrazole **2d** is obtained under similar conditions for 30 hours (Table I.1; entrie 3). The reaction conditions and the physical properties of synthetic products are summarizing in Table I.1.

Table I.1: Synthesis of 5-substituted tetrazoles from nitriles.

Entry	Product	R	Time (h)	Mp (°C)	Solvent	Yield (%)
1	**2b**	2-(4-MeC_6H_4)C_6H_4	17-30	149-151	Toluene	78
2	**2c**	*t*-Bu	17	208-210	-	90
3	**2d**	CH_2CO*t*-Bu	30	152-154	-	85
4	**2f**	$CHPh_2$	17-30	165-166	-	72

All tetrazole products were identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR and also by comparison with authentic samples.

IR Spectroscopy

Analysis of IR spectroscopic results of tetrazoles is in perfect agreement with those reported in the literature.

The IR spectrums of the all products showed strong absorption band characteristic of the NH function in 2987; 3336, and a second strip of frequency toward 1046; 1053 cm^{-1} due to stretching of C=C for aromatic rings. Tetrazole Function is also verified by the presence of band at [2900-2917] cm^{-1} who corresponds to the C=N link. Absorption between 1701-1716 cm^{-1} shows the presence of a carbonyl group for compound **2d.**

^{1}H NMR Spectroscopy

General appearance nuclear magnetic resonance spectra of the proton ^{1}H NMR present two types of signals, the first one corresponding to strongly deshielded protons (δ= [6.98-7.69] ppm), while the other may have an armored (δ= [1.18-4.41] ppm).

Compound (2b)

We note in the region of the strong field, the appearance of signal corresponding to the methylene group at 2.28 ppm. The protons of the aromatic ring are observed in the range [6.98-7.69] ppm whose multiplicity varies between 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. We have 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 showed a singlet (s) absorption band for group CH_3 with integration 9H at 1.35 ppm.

Compound (2d)

The spectrum showed the appearance of singlet signal at 1.18 ppm corresponding to three methylene group. Another singlet peak at 4.41 ppm corresponding to CH_2.

Compound (2f)

We note in the spectrum of this compound a singlet peak at 5.85 ppm corresponding to CH. Also the ten aromatic protons appear at [7.14-7.30] ppm as multiplet (m).

These results are summarizing in the Table I.2.

Table I.2: ^{1}H NMR for compounds **2b**, **2c**, **2d** and **2f**.

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	---	---	1.35, s, 9H	---
2d		4.41, s, 2H	1.18, s, 9H	---
2f	5.85, s, 1H	---	---	7.14-7.30, m, 10H

^{13}C NMR Spectroscopy

The signals located in high fields are those of methyl group; one methyl at 20.7 ppm for compound **2b** and three methyl at 28.9, 25.8 ppm for compounds **2c**, **2d** respectively. The appearance of CH and CH_2 peaks at 40.8, 32.2 ppm for compounds **2d**, **2f** respectively.

Spectral analysis of the compound **2d** prepared shows the existence of a weak magnetic field signal at 209.3 ppm corresponding to the carbonyl group. The aromatic carbons appear in the

usual area between [123.4 -130.6] ppm, whereas they appear in the interval [128.6-129.9] ppm for compounds **2b**, **2f** respectively.

These results are summarizing in the Table I.3.

Table I.3: The ^{13}C NMR for compounds **2b**, **2c**, **2d** and **2f**.

Compounds	CH	CH_2	CH_3	C_{arom}
2b	---	---	20.7	123.4-155.1
2c	---	29.0	28.9	---
2d	---	32.2	25.8	---
2f	40.8	---	---	128.6-160.0

I.7. Conclusion

Tetrazoles are a class of heterocycles with wide ranges of applications in medicinal chemistry and in material sciences Research on the preparation of tetrazoles has been conducted for more than 50 years. A tetrazole moiety is a 5-membered cyclic ring containing 4 nitrogen atoms and a carbon. Tetrazoles can be prepared from imidoyl chlorides, amidrazones, nitriles, nitrilium salts, and isonitriles. All of these reactions require the use of either an organic or inorganic azide (N_3^-) in the presence of a proton source.

The most common method of producing tetrazoles is through the reaction of a nitrile with an organic azide. However, inorganic azides are easily converted to hydrazoic acid (HN_3) through protonation. Hydrazoic acid is extremely dangerous due to its explosive nature and high toxicity and, for this reason; reactions with azide must be conducted with extreme caution. For these reasons, we have tried to use a simple method for the preparation of tetrazoles. The goal was to have a process that used sodium azide while limiting the possibility of forming the toxic and explosive hydrazoic acid.

In this chapter and with success we have prepared efficient process for transforming a wide variety of nitriles into the corresponding tetrazoles in high yield, using a simple and safe protocol.

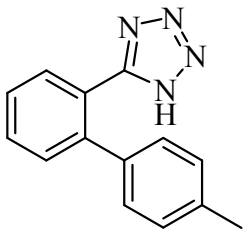
I.8. Experimental part

I.8.1. Synthesis of 5-substituted tetrazoles from nitriles

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'-methylbiphenyl-2-yl)-1*H*-tetrazole (2b)**

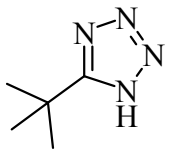


2b

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-(*tert*-butyl)-1*H*-tetrazole (2c)**

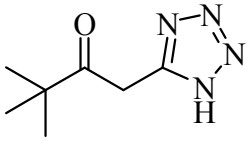


2c

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 **2c** 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 3,3-dimethyl-1-(1*H*-tetrazol-5-yl)butan-2-one (2d)**

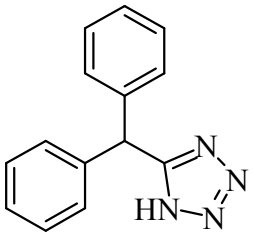


2d

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 **2d** as an 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-1*H*-tetrazole (2f)**



2f

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 **2f** 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).

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CHAPTER II

Protection of tetrazoles and alcohols

II.1. Introduction

Today, organic synthesis has reached a remarkable level of competence and even the complex molecules are accessible. The prerequisites for this success[1] are both the availability of a wide range of efficient synthetic methods[2] and reagents,[3] and the fact that retrosynthetic analysis[4] can provide a framework for the design of a synthetic strategy leading to the desired product in the most efficient and logical way. The protecting groups used influence the length and efficiency of the synthesis and are often responsible for its success or failure. A wide range of blocking groups is currently available for the different functional groups; however, an overall strategy combining these different masking techniques in an advantageous and reliable manner has never been proposed or at best only for individual cases.

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:

(a) Which protecting groups can be used?

(b) 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.

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 have 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.[5] Similarly, in the monographs[6] and reviews[7] 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.2. The role of protective groups in organic synthesis

II.2.1. 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.[8]

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 protective group is the best protective group. 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.2.2. Hydroxy protecting groups

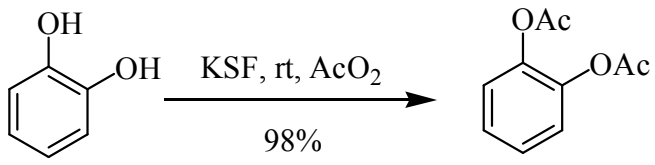
Protection and deprotection of alcohols have received attention in recent years not only because of their fundamental importance, but also for their role in multistep synthesis. High selectivity is frequently requested for a given hydroxy group in polyol chemistry, as well as simplicity and mildness in preparing and removing the specific function. Moreover, even when a substrate protects and deprotects efficiently, the reaction frequently needs quenching and products must be isolated from the reaction mixture and purified by suitable methods. For substrates that are particularly abile, these operations can cause further degradation. In these situations, the use of solid catalysts allows all the above-described operations to be performed in a more efficient way.[9]

II.2.2.1. Esters

- **Acetate esters**

The acetylation of alcohols represents an important reaction for the synthetic organic chemist; it is frequently used for derivatization and characterization of alcohols as well as for further transformations.

The acetylation of alcohols and phenols was performed at room temperature using acetic anhydride as acylating reagent in the presence of montmorillonites KSF and K10. Primary hydroxy groups react preferentially in the presence of secondary ones (although a small amount of diacetylated product is also formed—6% in the case of **31** (Scheme II.1).[10]



31 **32**

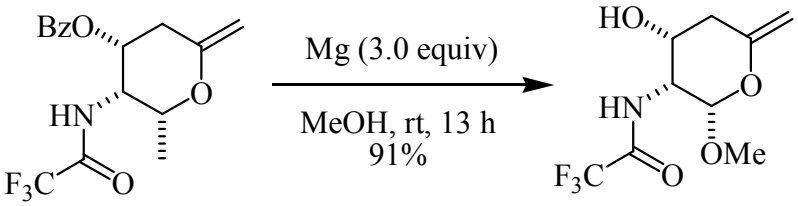
Scheme II.1

- **Benzoate esters (Bz)**

Acyl migration is less problematic with benzoates and it is reduced further still with *p*-methoxybenzoates. Nevertheless, migration is observed when there is a driving force as illustrated by the benzoate migration *en route* to *N*-acetyl neuraminic acid.[11]In this case the migration was thermodynamically driven by the greater stability of the equatorial benzoate in the product; however, under acidic conditions (25% HF in acetonitrile, 50°C, 24h), migration

of an axial benzoyl to an adjacent equatorial hydroxyl on a cyclohexane ring does not occur. Acyl migration decreases with the solvent polarity.[12]

The difference in the rate of benzoate and acetate solvolysis is sufficient to enable selective removal of acetates in the presence of benzoates. Typical conditions include magnesium methoxide in methanol[13], guanidine in the methanol-dichloromethane, and fluoroboric acid in methanol. Fluorine substitution on benzoyl groups increases hydrolytic lability[14](Scheme II.2).



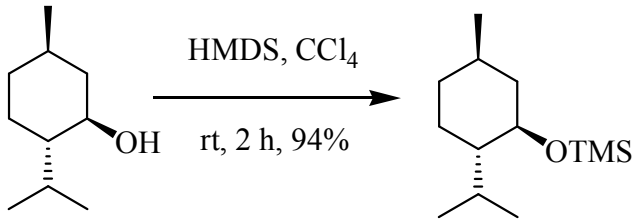
33 **34**

Scheme II.2

II.2.2.2. Silyl Ethers

- **Trimethylsilyl (TMS)**

Since the introduction of the *tert*-butyldimethylsilyl (TBS) group in 1968 and its use as a protecting group for alcohols in 1972, silyl protecting groups for alcohols have gained prominence as critical tools for the protection of alcohols in total synthesis. By altering the steric and electronic properties of the substituents on the silicon atom, reactivity and stability can be varied even though the same functional group (silyl ether) is being employed to mask the alcohol group. As a result, in many complex synthetic schemes, multiple alcohol groups can be protected as different silyl ethers and then selectively unmasked as needed. Numerous silylating methods can be utilized today; among them, trimethylsilylation is one of the most often used. Alcohols and phenols could be conveniently converted into the corresponding silyl ethers by treatment with hexamethyldisilazane (HMDS) in the presence of a natural kaolinitic clay treated with 2 M hydrochloric acid (Scheme II.3).[15]



35 **36**

Scheme II.3

Some of the silyl protecting groups of alcohols are represented in figure II.1.

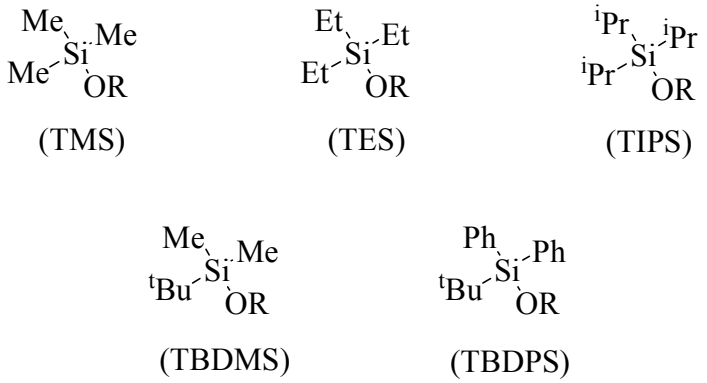
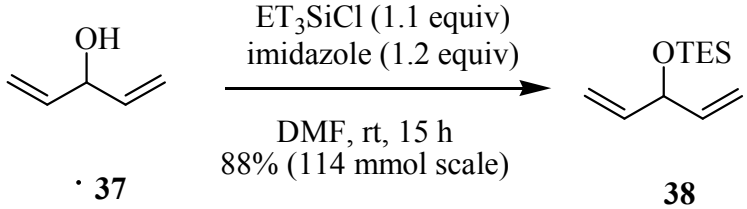


Figure II.1. Silyl protecting groups.

- **Triethylsilyl ethers (TES)**

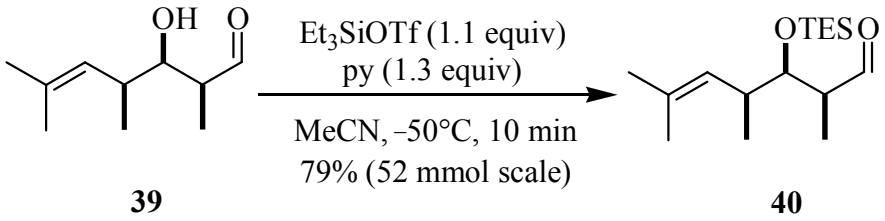
Formation

Three of the most common procedures for the formation TES ethers have been selected for their large scale preparative value. Triethylsilyl ethers are prepared by the reaction of the alcohol with chlorotriethylsilane in the presence of a catalytic amount of imidazole[16] (Scheme II.4) or DMAP.[17] Triethylsilyl triflate in the presence of pyridine[18] (Scheme II.5) or 2,6-lutidine[19] (Scheme II.6) can be used to protect β- hydroxy aldehydes, ketonnes[20], and esters. Chlorotriethylsilane and triethylsilyl triflate are commercially available.



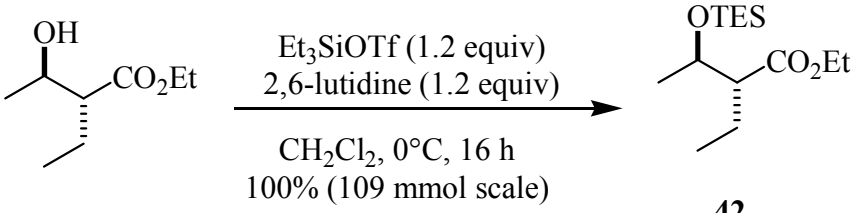
37 **38**

Scheme II.4



39 **40**

Scheme II.5

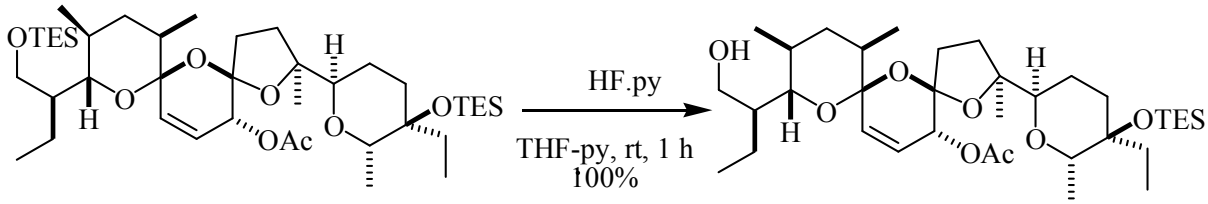


41 **42**

Scheme II.6

Cleavage

In a synthesis of the polyether ionophore antibiotic Salinomycin, a primary TES ether was cleaved in preference to a tertialy TES ether by using HF· pyridine complex at room temperature[21] (Scheme II.7).



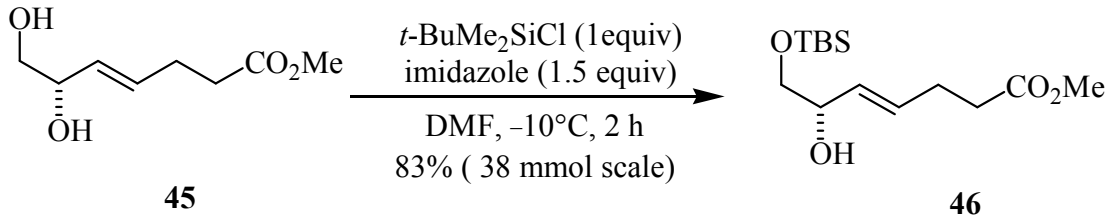
43 **44**

Scheme II.7

- ***Tert*-Butyldimethylsilyl ethers (TBS)**

Formation

The steric bulk of the *tert*-butyl group significantly diminishes the rate of silylation with *Tert*-Butyldimethylsilyl chloride (TBSCl, mp 86-89 °C, bp 125 °C) so convenient rates are best achieved by the addition of basic activators such as imidazoles or DMAP[22] and by using dipolar aprotic solvents such as DMF. Primary alcohols[23] react much faster than secondary alcohols but tertiary alcohols are inert (Scheme II.8).

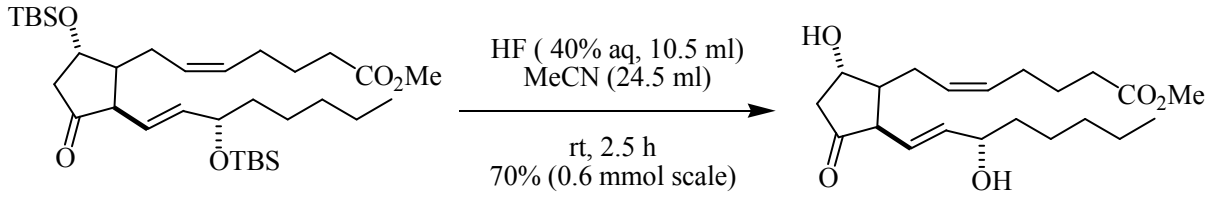


45 **46**

Scheme II.8

Cleavage

During a synthesis of sensitive Prostaglondin D derivatives, Newton and co-workers were not able to deprotect a bis-TBS ether (Scheme II.9) using aqueous acetic acid in the usual way but successful hydrolysis was accomplished using aqueous HF in acetonitrile conditions which are now widely used in synthesis. HF (pKa 3.45) is only slightly more acidic than formic acid (pK_a 3.75) and these conditions are mild enough to tolerate acetals, esters, and epoxides.[24,25]



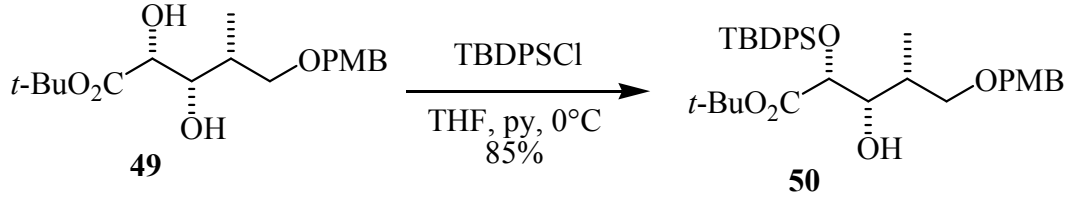
47 **48**

Scheme II.9

- ***Tert*-butyldiphenylsilyl ether (OTBDPS)**

Formation

The TBDPS is introduced by the reaction of an aliphatic hydroxyl with TBDPSCl in a pyridine medium (Scheme II.10), other reagents are used according to the functional groups of the molecule. The addition of $AgNO_3$ increases the rate of silylating reaction of the most acidic alcohol.

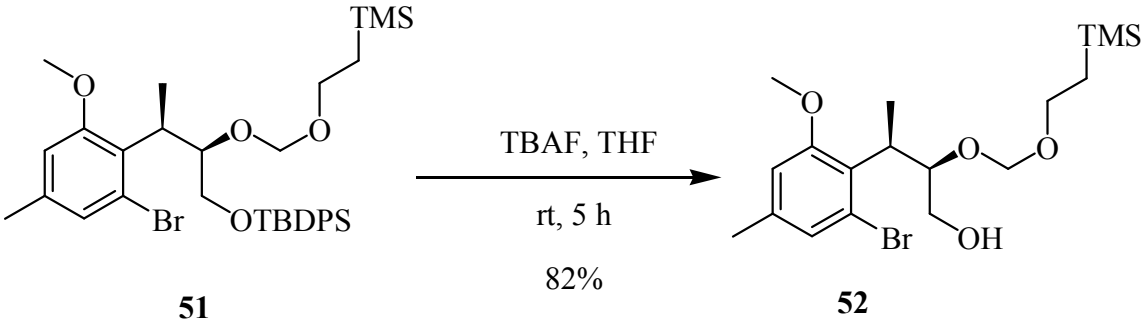


49 **50**

Scheme II.10

Cleavage

Such ethers is generally cleaved in an basic medium.[26] The TBDPS is cleaved selectively by *tetra*-butyl ammoniumfluoride[27] (Scheme II.11).

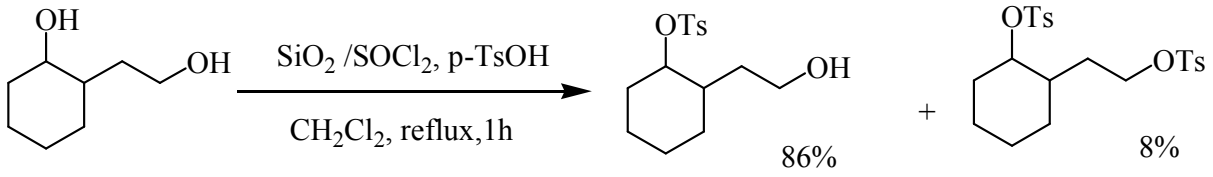


51 **52**

Scheme II.11

II.2.2.3. Tosylates

Tosylation of alcohols was used occasionally as a protective instrument in organic synthesis. Several alcohols were tosylated with *para*-toluene sulfonic acid in the presence of silica chloride ($SiO_2/SOCl_2$) in methylene chloride under reflux (Scheme II.12). Primary and secondary alcohols (except long-chain alcohols) afforded the products in very high yields.



53 **54** **55**

Scheme II.12

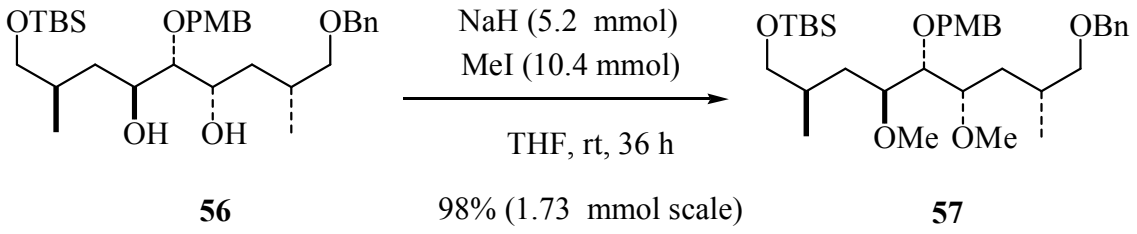
II.2.2.4. Alkyl ether

- **Methyl ether**

For simplicity there are few protecting groups that can top a methyl ether;of cource there is a price to pay: the condition required for deprotection are rather harsh and so comparatively few functional groups are compatible. Nevertheless there is niche for methyl ethers in the protection of hydroxy groups that must survive strongly basic or acidic conditions.

Methyl ethers are usually prepared by some variant of williamson ether synthesis in which an alcohol reacts with either iodomethane, dimethyl sulfate, or methyl triflate in the presence of a

suitable base. Simple aliphatic alcohols require stronger bases such as sodium hydride[28] (Scheme II.13).



56 98% (1.73 mmol scale) **57**

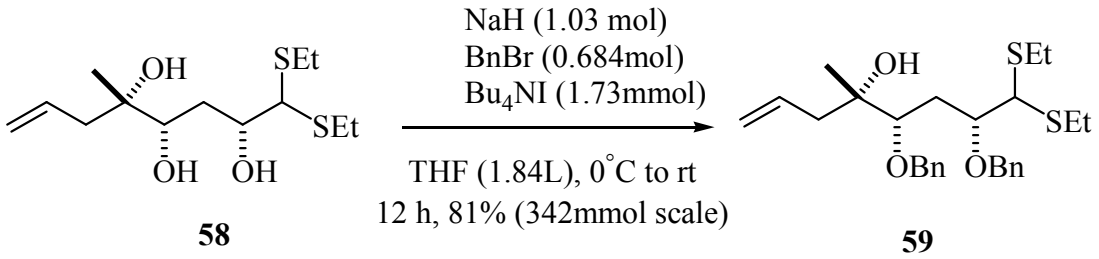
Scheme II.13

- **Benzyl ether**

Benzyl ethers are stable to a wide range of aqueous acidic and basic conditions and they are not readily attacked by most metal hydride reducing agents or mild oxidizing agents (pyridiniumchlorochromate, chromic acid, sodium periodate). As a group, the benzyl ethers can be cleaved by lewis -acids, dissolving metal reduction, oxidation and hydrogenolysis.

Formation

The alkylation of metal alkoxides with benzyl bromide or chloride is probably the most common method for preparing benzyl ethers. Since the metal alkoxide are usually generated with sodium hydride or potassium hydride, this method is incompatible with base-sensitive functional groups. In the (Scheme II.14) a catalytic amount of tetrabutylammonium iodide was added to accelerate the alkylation because iodide displaces bromide or chloride to give benzyl iodide *in situ* which is a much better alkylation agent. Iodide is then regenerated on alkylation of the benzyl iodide. [29]



58 **59**

Scheme II.14

Some of the benzylic protecting groups of alcohols are represented in figure II.2.

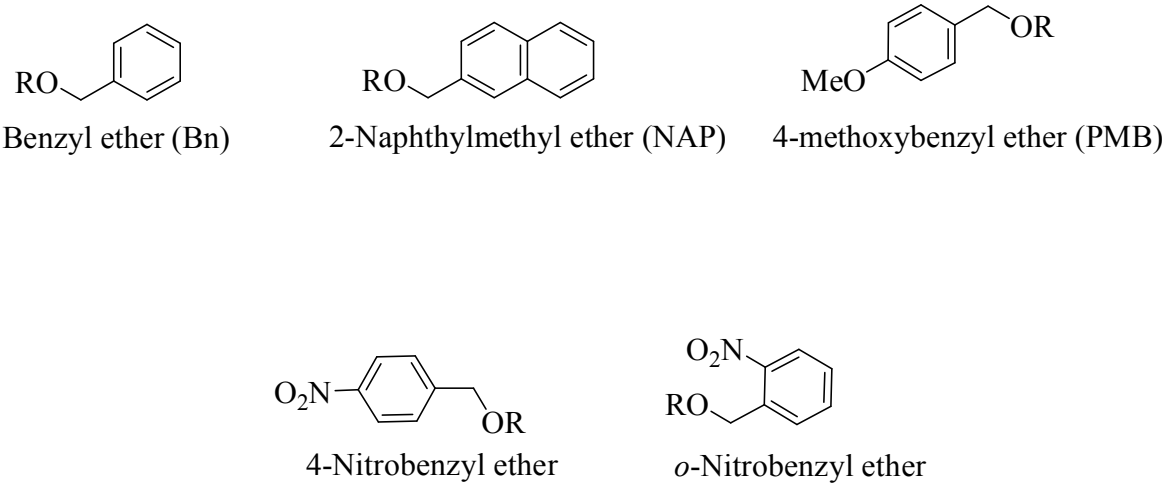


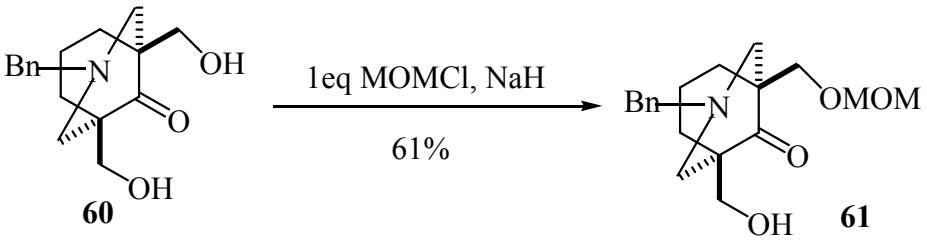
Figure II.2. Benzylic protecting groups.

- **Methoxymethyl ether (MOM)**

Methoxymethyl ether (MOM ether) is widely used as a protecting group of alcohols; it is easily introduced stable *via* conditions of deprotection of other protecting groups such as; the silyl, alkoxyacyl or the benzylic derivatives, as well as in the strongly basic or acidic conditions.

Formation

The MOM ether is generally introduced on the hydroxy using the chloro methyl ether in slightly basic medium (*i*-Pr_2NEt),[30] in the *mono*-protection of hydroxy diol **60** we must have a strong base like NaH (Scheme II.15).[31]

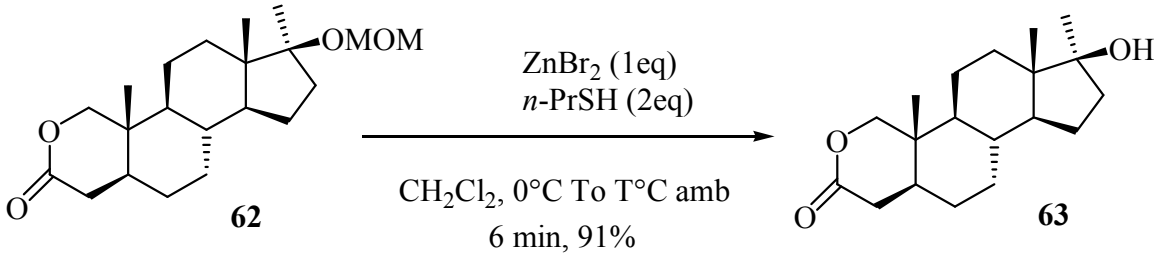


Scheme II.15

Cleavage

Various methods have been described for protection of the MOM ether, using Bronsted[32] acids and Lewis acids.[33] Synthetic applications of these methods are limited

because of the low selectivity of MOM deprotection in the presence of other hydroxy protecting groups and the reaction time is relatively long. A method of cleavage of the MOM ether of primary, secondary, tertiary alcohols and phenol has been described in the presence of zinc (II) bromide with n-propane-1-thiol (Scheme II.16).[34]The chemoselectivity of deprotection is designed successfully in the presence of other hydroxy protecting groups: TBDPS, Ac, Bn and PMB.



Scheme II.16

- **Methylthiomethyl ethers (MTM)**

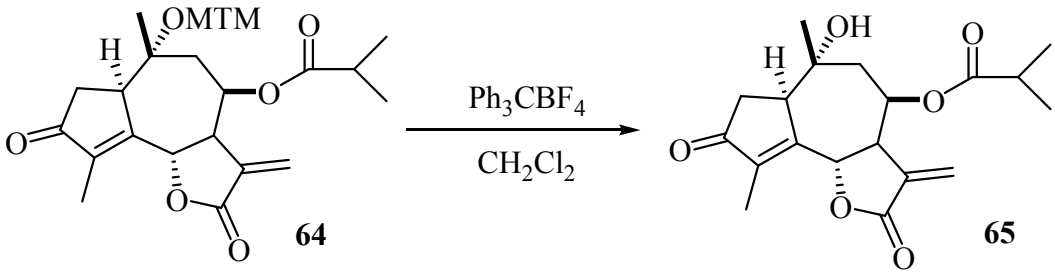
The methylthiomethyl ethers are quite stable in acidic conditions. Most ethers are stable under the conditions of deprotection of MTM ether, the disadvantage lies in the difficulty of introducing this group.

Formation

MTM is generally introduced by the use of (chloromethyl) (methyl) sulfane (CH_3SCH_2Cl) in the presence of the couple NaH / NaI in DMF.[35]

Cleavage

The MTM ether is cleaved in the presence of Ph_3CBF_4 in good yields, isobutyrate remains intact and without opening the heterocycles like dihydrofuran-2-(3H)-one in the molecule **65**[36](Scheme II.17).

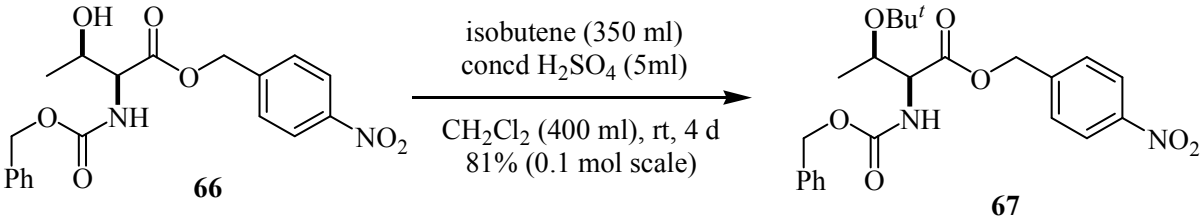


Scheme II.17

- ***Tert*-butyl ethers**

Formation

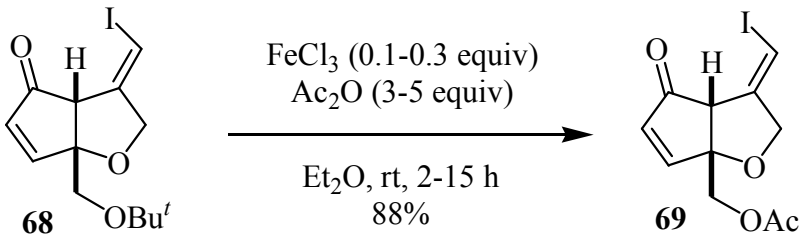
The traditional method for preparing *tert*-butyl ethers involves reacting a large excess of isobutene with a solution of the alcohol in dichloromethane in the presence of concentrated sulfuric acid, *p*-toluenesulfonic acid or phosphoric acid and the method is effective for protecting the side chain hydroxyl functions of serine, threonine and tyrosine (Scheme II.18). [37,38] A more convenient method involving use of Amberlyst H-15 resin in hexane as the acid catalyst deserves wider attention.



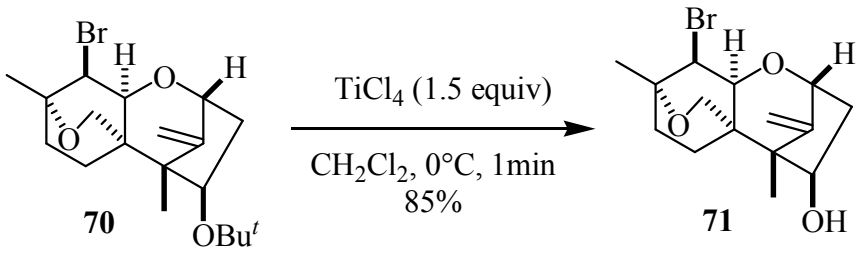
Scheme II.18

Cleavage

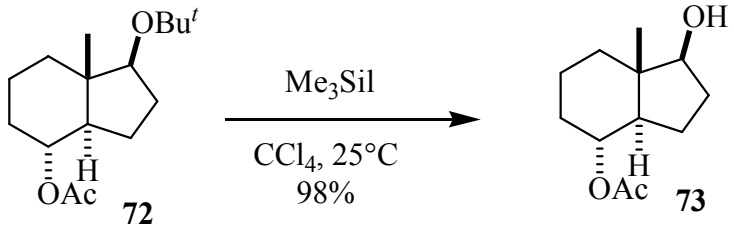
A wide range of lewis acids has been employed to cleave *tert*-butyl ethers but only a small selection of those used in various naturel product syntheses will be cited here. Thus 10% anhydride was used to cleave *tert*-butyl ether in good yield to give the corresponding acetate at a late stage in a synthesis of Didemnones A and B (Scheme II.19). Titanium tetrachloride has also been used to give the alcohol (Scheme II.20). During a synthesis of 1α,25-Dihydroxy-vitamin D (Scheme II.21), a group of Hofmann-LaRoche[39] found that iodotrimethylsilane accomplished the deprotection of a *tert*-butyl ether in the presence of a secondary acetate ester. The reaction is usually performed in tetrachloromethane or chloroform at 25°C for ≤10 min.[40]



Scheme II.19



Scheme II.20

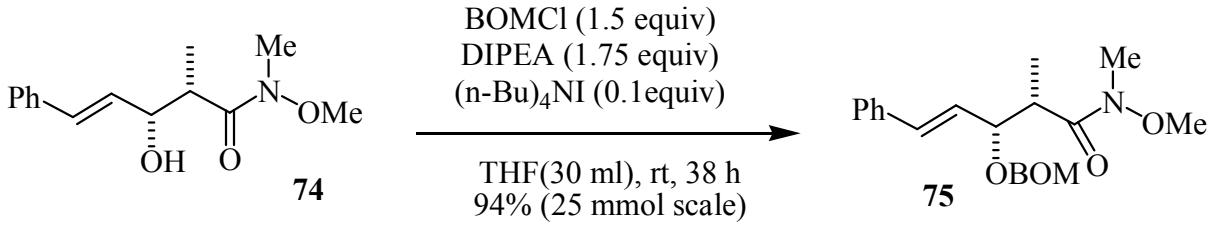


Scheme II.21

- **Benzyloxymethyl (BOM)**

Formation

Primary, secondary, and tertiary alcohols react with benzyl chloromethyl ether in the presence of *i*Pr$_2$NEt to give the BOM ethers in good yield. If the reaction requires acceleration, some tetrabutylammonium iodide (10%) may be added to the reaction mixture (Scheme II.22).[41]



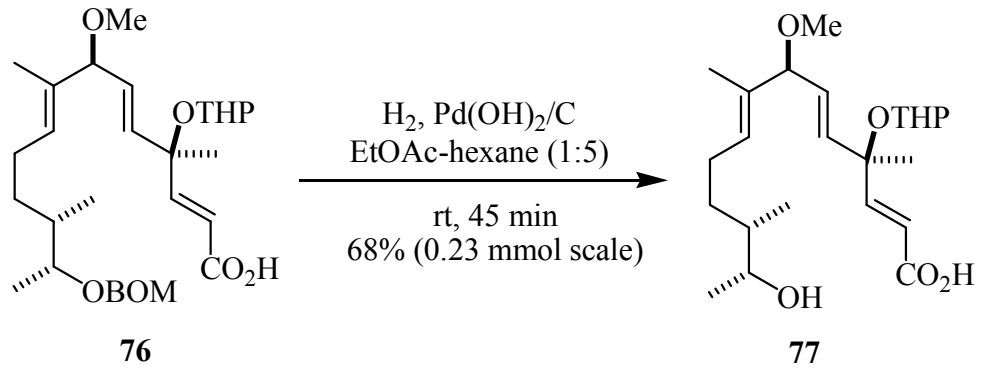
Scheme II.22

Cleavage

Benzyloxymethyl ethers are comparable in base stability to MOM. However, like benzyl ethers they can be removed by hydrogenolysis or Birch reduction. The advantage BOM ethers have over benzyl ethers is their easier preparation and easier removal. However, unlike benzyl ethers, they decompose in aqueous acid. The BOM group was introduced in

1975 by Stork and Isobe,[42] but it has not been as widely applied as MOM groups though its virtues are gaining in appreciation.

Hydrogenolysis of BOM ethers in the presence of alkenes is possible using Pearlman's catalyst [$Pd(OH)_2/C$].[43] For example a BOM group was removed from the macrolide precursor **76** in the presence of three alkene including a di-substitued alkene (Scheme II.23).



76 **77**

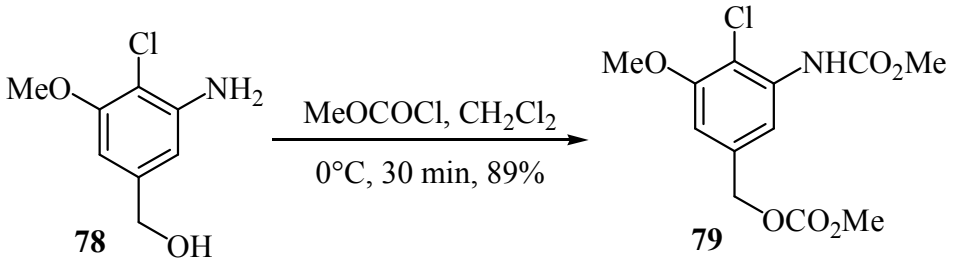
Scheme II.23

II.2.2.5. Carbonates

Carbonates are an important class of compounds having pharmacological and chimical importance.[44]They are used as alkylating agents in organic reactions, in medicinal chemistry and pharmaceutic.[45]

Formation

Methoxy carbonyl (OCO_2Me) is introduced into a hydroxyl using methyl chlorofomate without selectivity *via* the amine function[46] (Scheme II.24).



78 **79**

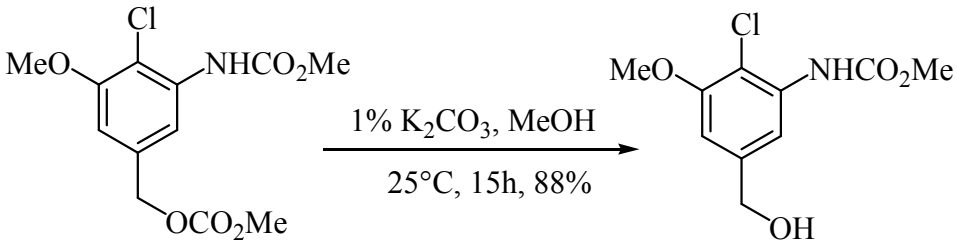
Scheme II.24

Cleavage

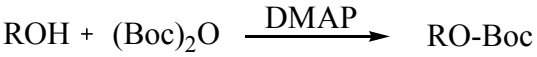
Carbonate is selectively deprotected in the presence of K_2CO_3[47] (Scheme II.25).

Other protecting groups in the form of carbonates are used for the protection of the hydroxyls such as the O-Fmoc, Cbz-O and O-Boc. Recently, various methods for introduction and cleavage of the O-Boc pattern have been described.

Tert-butoxycarbonylation hydroxide alcohols and phenols were carried out in the presence of DMAP[48] (Scheme II.26), the latter is used for the electrophilic activation of $Boc_2(O)$. In most cases, the acids such as TFA[49] allow deprotection of *tert*-butoxycarbonyl carbonate.



Scheme II.25

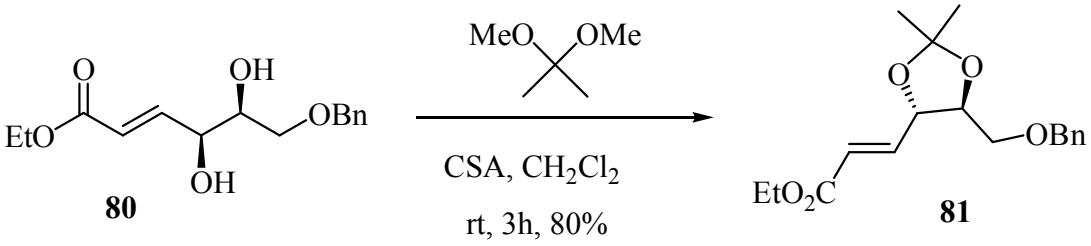


Scheme II.26

II.2.2.6. Protection of diol

- **1,2-diol**

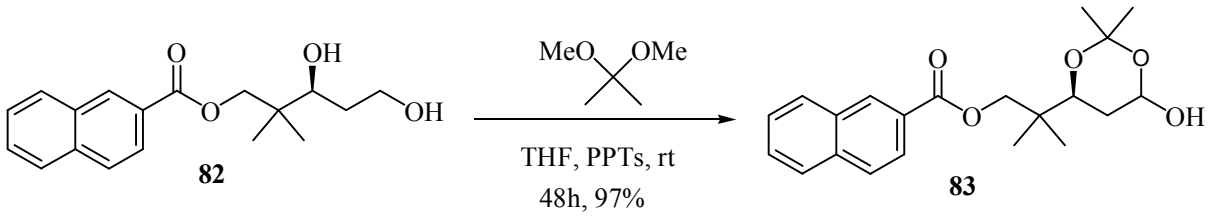
The protection of a diol 4S, 5S-dihydroxy of **80** is effected in the presence of camphorsulfonic acid (CSA) to yield 1,3-dioxolane (Scheme II.27).[50]



Scheme II.27

- **1,3-diol**

The two hydroxyl groups of a 3,5-dihydroxy are converted to 1,3-dioxane under the catalytic effect of para-toluene sulfonate, pyridinium (PPTS) (Scheme II.28).[51]

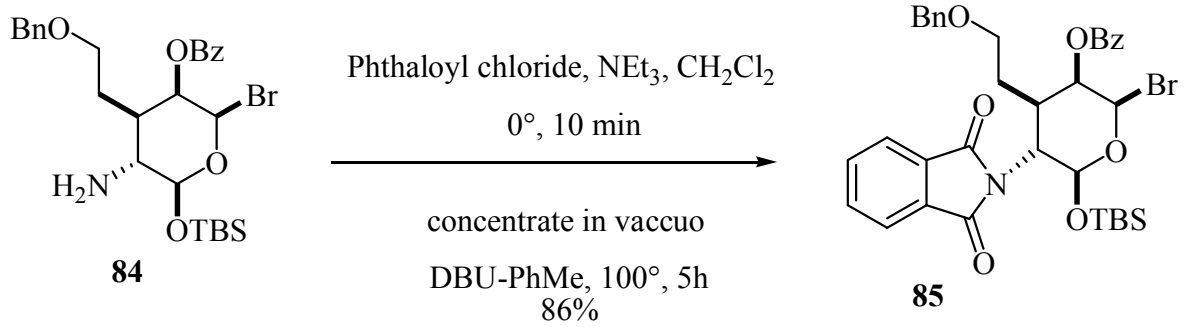


Scheme II.28

II.2.3. Amino protecting groups

II.2.3.1. Phthaloyl group

The phthalimide group is typically introduced by reaction of primary amine with phthalic anhydride in chloroform at 70°C for 4h (85-93% yield) or phthaloyl chloride in the presence of triethylamine (Scheme II.29). Phthalamides are especially useful in the protection of amino functions in aminoglycoside syntheses.



Scheme II.29

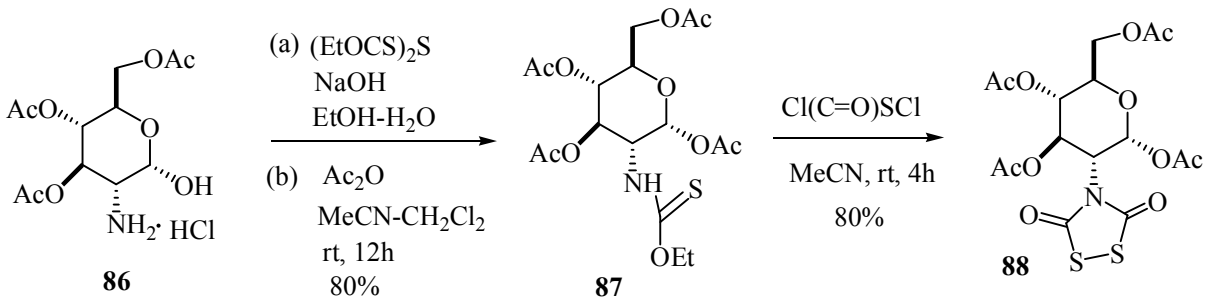
II.2.3.2. Dithiasuccinyl (Dts)

The dithiasuccinyl protection group was developed by Barany and Merrified for the use in peptide synthesis, though nowadays, it is more often deployed in aminoglycoside and glycopeptide synthesis. In peptide synthesis, the Dts group survives the strongly acidic conditions required to cleave *tert*-butyl and benzyl esters and carbamates.

Formation

Unfortunately, introduction of the *N*-Dts group requires two steps, the first being reaction of the amino group with-ethyl S-carboxymethyldithiocarbonate or *O,O*- diethyl trithiodicarbonate (Scheme II.30). The intermediate ethoxythiocarbonyl derivative is then

treated with chlorocarbonylsulfenyl chloride, whereupon chloroethane is extruded to give the *N*-Dts derivative.



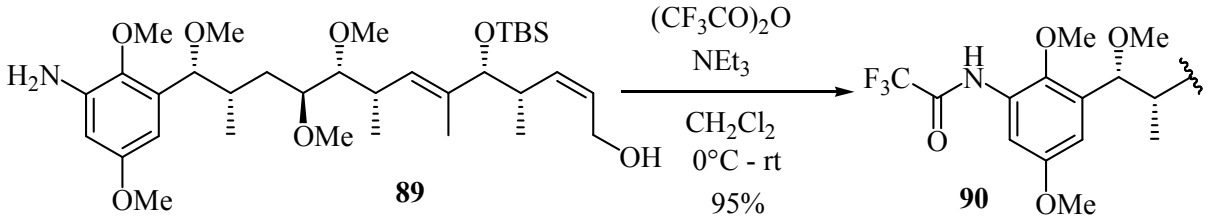
Scheme II.30

II.2.3.3.Trifluoroacetyl

Simple amide derivatives are usually worthless as protecting groups because the conditions required to remove them are harsh. A notable exception is the *N*-trifluoroacetyl group, which is exceptionally labile to basic hydrolysis and therefore useful in the protection of primary and secondary amines – a fact appreciated for some time by peptide chemists.

Formation

Selective trifluoroacetylation of primary amines in the presence of secondary amines can be accomplished by reaction with a stoichiometric amount of ethyl trifluoroacetate (bp 60-62 °C) in THF, acetonitrile or dioxane at 0 °C. The product is simply isolated by evaporation of the solvent and liberated ethanol. Perhaps the most common method entails acylation of the amine with trifluoroacetic anhydride in the presence of a suitable base such as triethylamine or pyridine in dichloromethane (Scheme II.31).



Scheme II.31

II.2.3.4. Carbamate

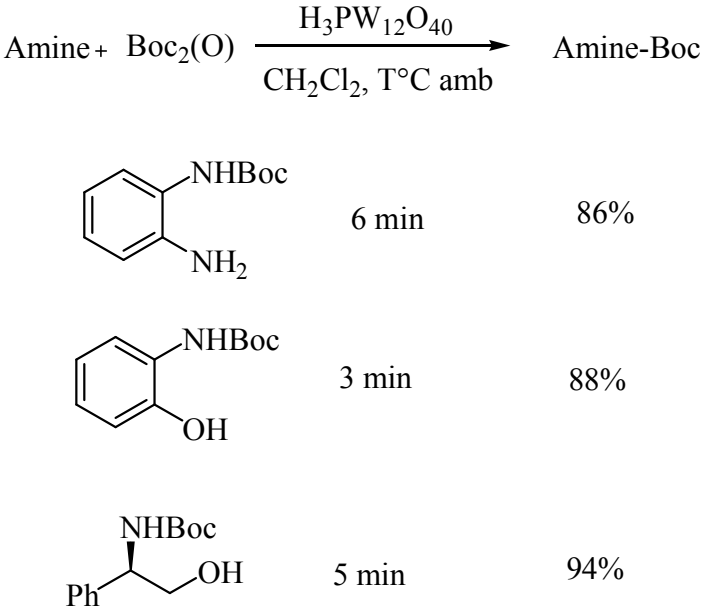
Carbamates have been used for the protection of the amine function. Indeed, the lone pair of electrons carried by the nitrogen is unreactive and is engaged in mesomerie with carbamate, it is then possible to make functional facilities without pronounced nucleophilic character of the amine.

- ***Tert*- butoxycarbonyl (N-boc)**

The effectiveness of *tert*-butyl carbamate was due to their stability under various reaction conditions as the nucleophilic attacks, moderate alkaline treatments and catalytic hydrogenation.[52]

Formation

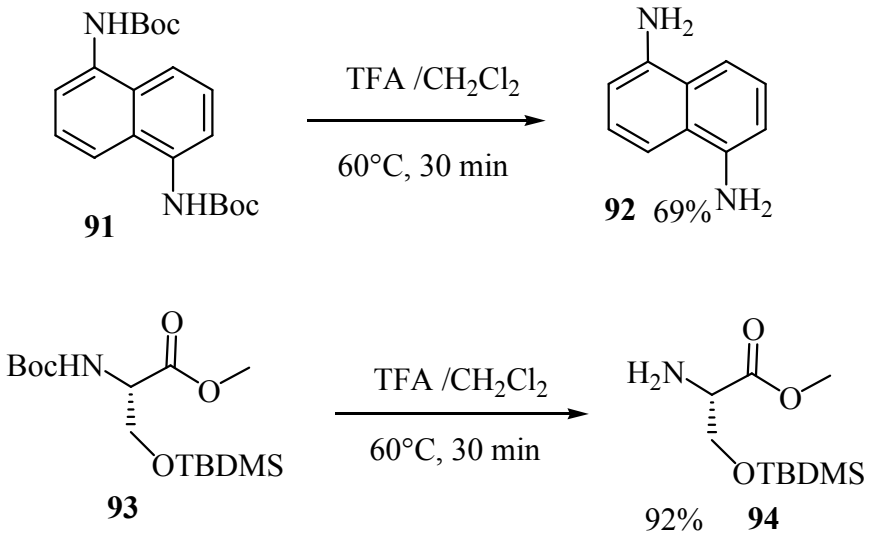
Heydari *et al*.[53] have developed an effective method with good yields. The N-tert-butoxycarbonylation of the primary and secondary amines is conducted in a heterogeneous medium using di-*tert*-butyl dicarbonate in the presence of heteropolyacid $H_3PW_{12}O_{40}$ (Scheme II.32).



Scheme II.32

Cleavage

Chemoselective deprotection of N-Boc is realised by acid treatment and is Quickly accomplished using 5 equivalents of TFA at 60 ° C for 30 min.[54] The selectivity of this method of N-Boc deprotection is approved by the preservation of the OTBDMS ethers (Scheme II.33).



Scheme II.33

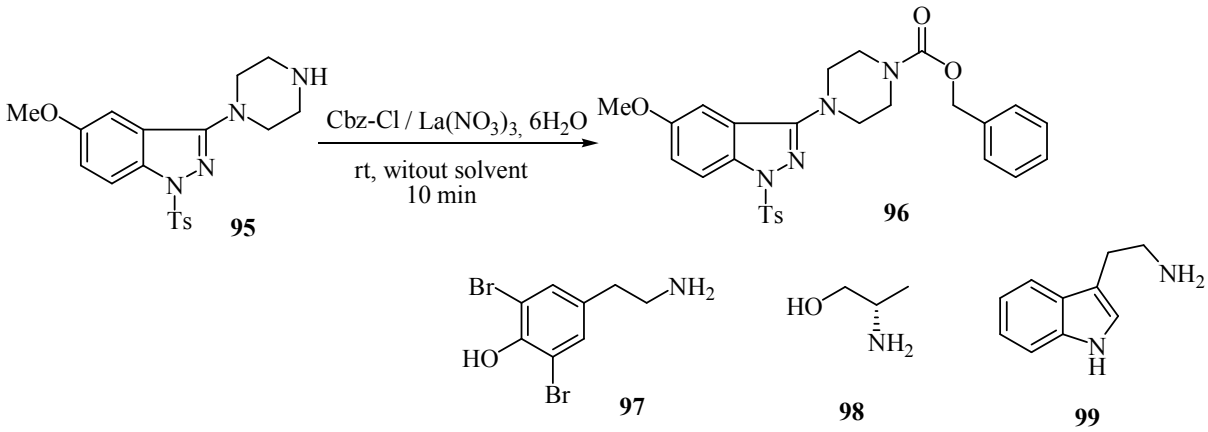
- **Benzyloxycarbonyl (Cbz)**

The benzyloxycarbonyl (Cbz) is a very useful group for the protection of amines in organic synthesis and particularly peptide synthesis, alkaloids and amino acids.[55,56]

Cbz pattern is very convenient in the protection of the amine function of polyfunctional molecules, it is due to his stability *via* various conditions acidic / basic and also his orthogonality vis-à-vis the other protecting groups.

Formation

The treatment of aliphatic amines (cyclic, acyclic), aromatic with benzyl chloroformate in the presence of lanthanium (III) nitrate hexahydrate (La $(NO_3)_3.6H_2O$) leads to the corresponding carbamates. The chemoselectivity of the N-benzyloxycarbonylation is performed in the presence of aliphatic alcohols and phenols.[57] (Scheme II.34).

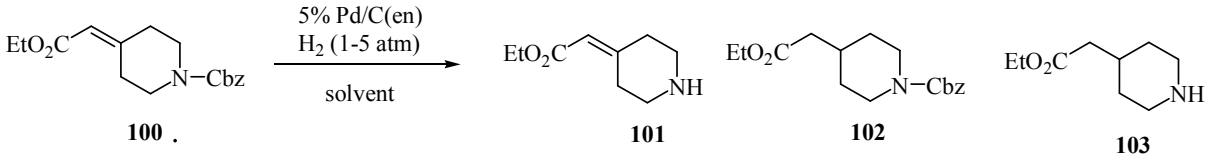


Scheme II.34

Cleavage

N-Cbz deprotection is commonly carried out in the catalytic hydrogenation conditions.[58]Hyd-

rogenolysis of benzyl 4-(2-ethoxy-2-Idene oxoethyl) piperidine-1-carboxylate **100** resulted in the deprotection of N-Cbz and secondary compounds **102** and **103** (Scheme II.35).[59]



100 . **101** **102** **103**

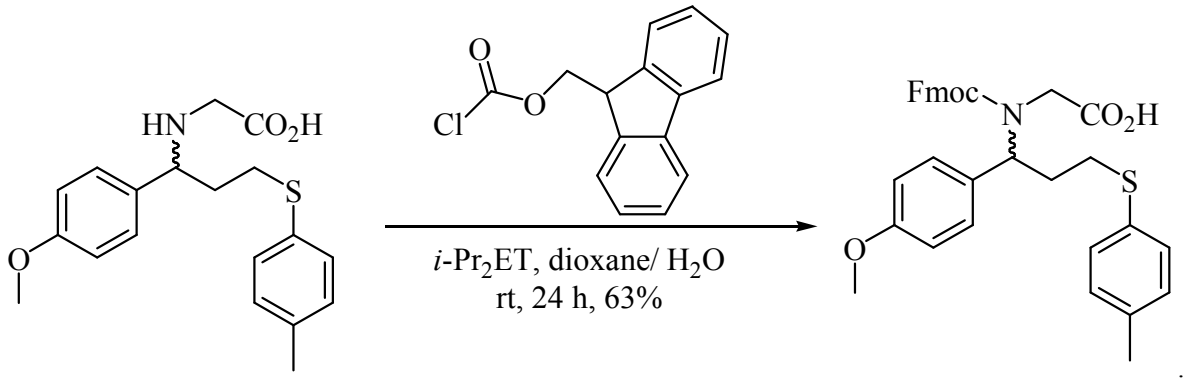
Scheme II.35

- **9-Fluorenylmethyloxycarbonyle (N-Fmoc)**

The carbamic form N-Fmoc is widely used for the protection of the amine function in peptide synthesis on solid phase or in solution, due to its stability in the acidic conditions and its orthogonality *via* Forms N-Boc and N-Cbz.[60]

Formation

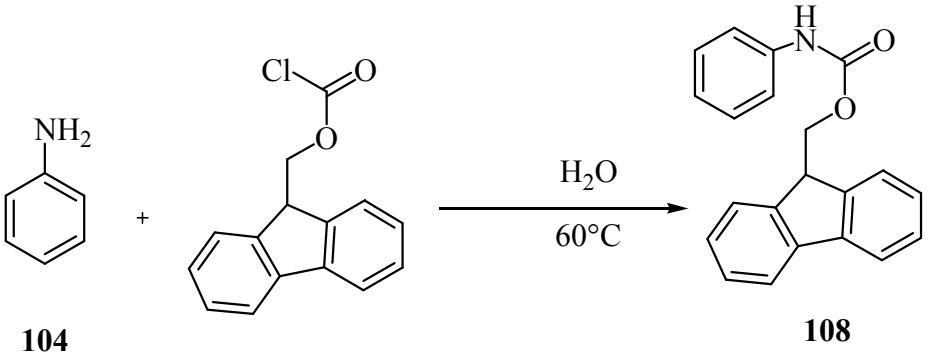
The protection N-Fmoc of amino acid with a secondary amine function is performed using the Fmoc-Cl in excess (4.4 eq) in a mixture (dioxane / H_2O: 2/1) in presence of diisopropylethylamine at room temperature (Scheme II.36).[61]

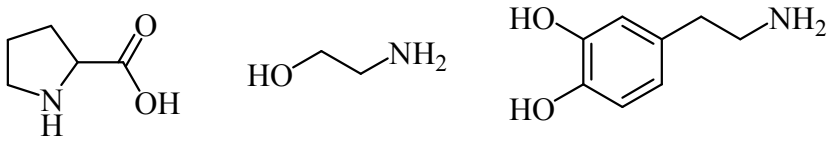


Scheme II.36

Recently, the protection by the 9-fluorenylmethyloxycarbonyl of series of aliphatic and aromatic amines, amino acids, amino alcohols is reported in an aqueous medium under mild conditions and in the absence of catalysts. The use of ethanol as a co-solvent is essential in the case of insoluble solutes in water.

This method proved to be chemoselective in the presence of moderate nucleophiles (Scheme II.37).[62]



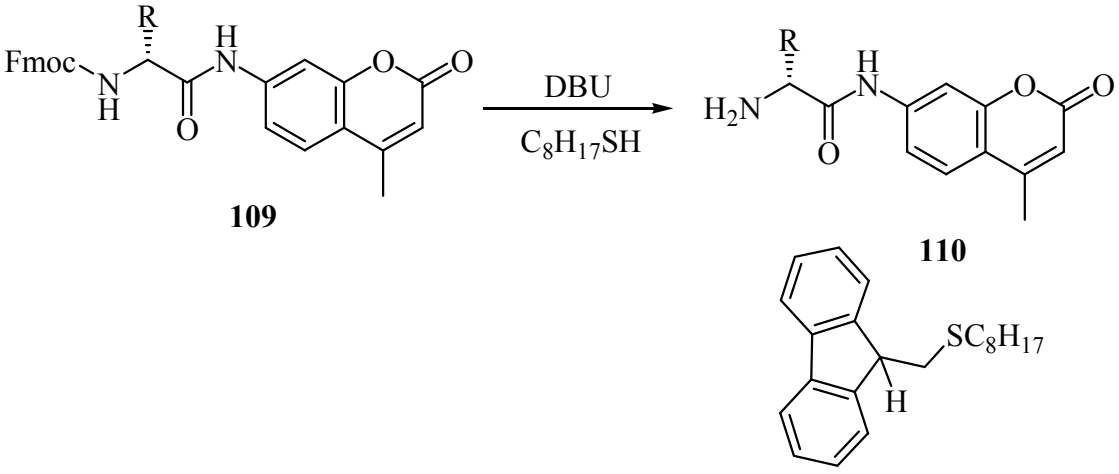


105 **106** **107**

Scheme II.37

Cleavage

The Fmoc is often stable under hydrogenolysis conditions. However, it has been found that under particular conditions, it may be cleaved by treatment with H_2 / Pd /C in AcOH / MeOH. James *et al*.[63] have reported the N-Fmoc deprotection in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) in a catalytic amount and 1-octanethiol (Scheme II.38).



109 **110**

Scheme II.38

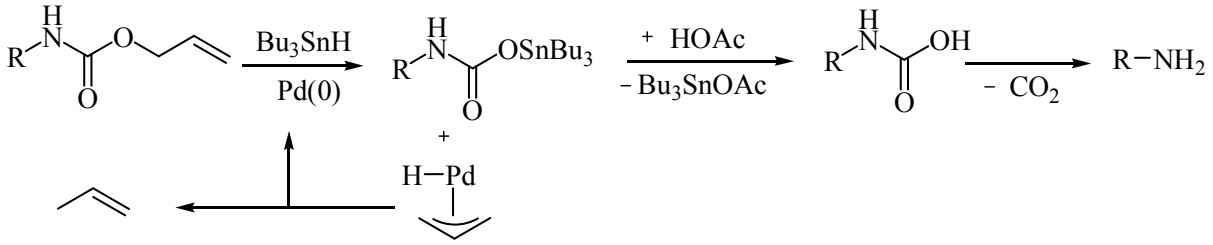
II.2.3.5. Allyloxycarbonyl (Aloc)

Formation

Aloc groups are introduced by *N*-acylation with commercially available allylchloroformate (bp 109-110 °C) under Schotten-Baummann conditions or diallyldicarbonate (bp 60 °C/7 Pa).

Cleavage

Reductive cleavage of Aloc groups can be accomplished under Pd(0)-catalysis using various hydride donors such as formic acids. Tributylstannane, phenylsilane, sodium borohydride or various borane-amine complexes. The reaction gives metal carbamate derivatives and propene as the primary products. With tributylstannane the reactions is usually conducted in the presence of acetic acids, in which case the intermediate tributylstannylcarbamate is converted to tributylstannyl acetate and the free carbamic acid under the reaction conditions as illustrated in (Scheme II.39). With silane and borane reagents, the amine is only liberated after aqueous workup.



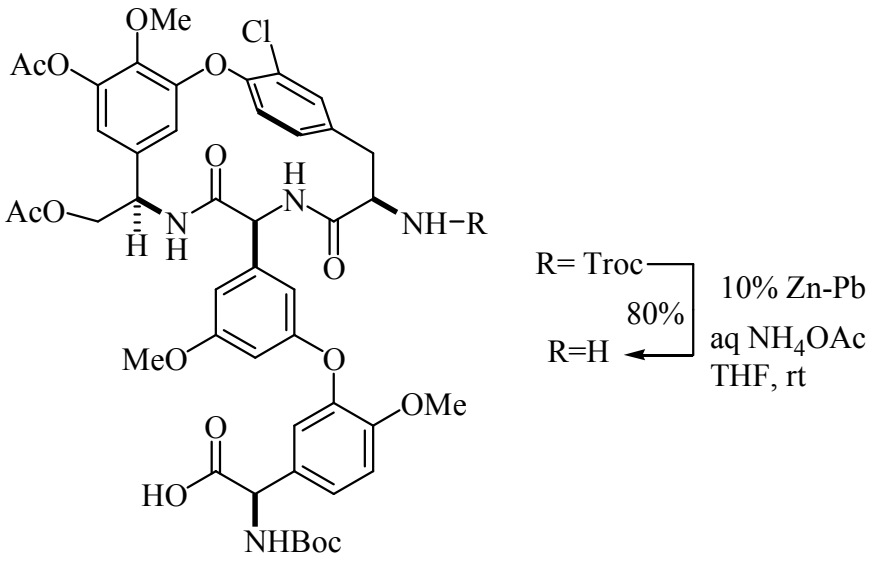
Scheme II.39

II.2.3.6. The 2,2,2-trichloroethoxycarbonyl (Troc)

2,2,2-trichloroethoxycarbonyl (Troc) group belongs to groups cleaved by reductive β-elimination. The Troc group can be removed in the presence of trifluoroacetamides, Cbz, Boc, Aloc, and Fmoc groups. It easily survives the conditions for removing Boc and Fmoc groups, but it is unstable towards hydrogenolysis as used for removal of Cbz groups.

Cleavage

Various metals were used as reductants such as zinc, cadmium and cadmium-lead couple, but the best results (80% yield) were obtained using Zinc-lead couple in M aqueous ammonium acetate in THF at room temperature (Scheme II.40).



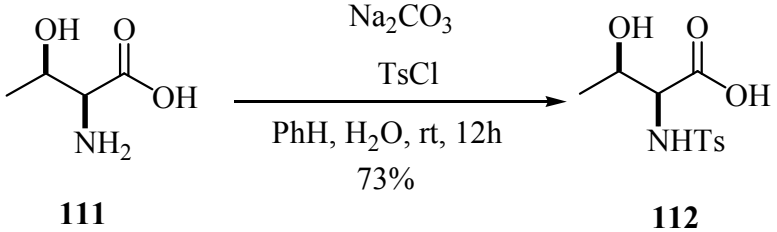
Scheme II.40

II.2.3.7. Arylsulfonyl derivatives

Arylsulfonyl groups are highly effective protecting groups for a wide range of amine derivatives including the amino functions of α-amino acids. They were first used in 1915 by Fischer, used for the protection of the amine function.[64] They are a very important class of compounds used in the pharmaceutical industry, being very used as anticancer, antitumor and antiviral.[65]They are stable to most reaction conditions, provide a strong chromophore, and have been especially useful when a carboxyl group is destined to undergo reactions with an organometallic reagent. The use of sulfonyl chlorides is the method of choice for the sulfonylation of functions containing acidic protons, because of reactivity and ease of handling.[66]

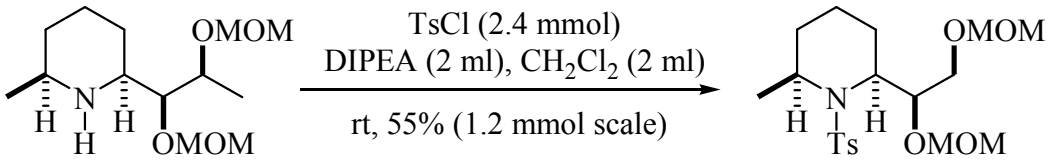
Formation

N-Arylsulfonylation of primary and secondary amines is usually accomplished with the appropriate sulfonyl chloride in the presence of suitable base in both anhydrous (Scheme II.41) and aqueous conditions (Scheme II.42).



111 **112**

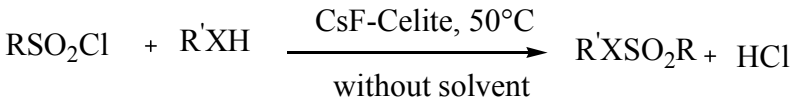
Scheme II.41



113 **114**

Scheme II.42

The mono-sulfonylation of the primary and secondary amines using TsCl and $PhSO_2Cl$ was conducted in the presence of CsF-Celite as a heterogeneous catalyst (Scheme II.43).[67]



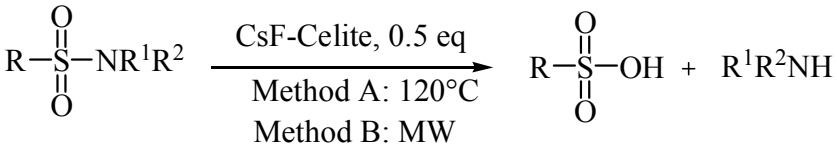
R= Ar, R'= Ar, Alkyl

X= N

Scheme II.43

Cleavage

Tamaddon *et al.*[67] have employees CsF-Celite under MW or 120 ° C for the deprotection *N*-Ts and *N*- Ms, the yields are excellent (Scheme II.44).



Scheme II.44

II.2.3.8. Amide

Among the different methods of protection of the amide function, acylation has aroused great attention, she finds industrial applications. Amides are stable *via* the acidic and basic hydrolysis and are hydrolyzed by heating in highly acidic or basic conditions.

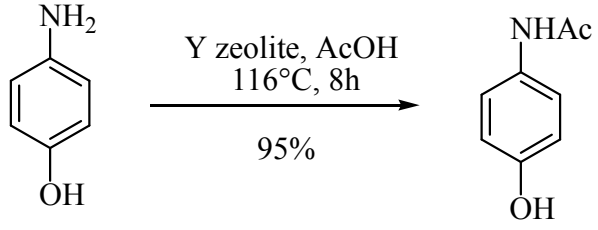
- ***Acetamide***

Amides are often prepared from the corresponding acid chloride or anhydrides. Other reagents and methods for coupling of amine have been developed for the amide formation.[68]

Formation

The use of acetic acid instead of conventional reagents is advantageous from the point of view of economy atoms. Kulkarni *et al.*[69] have developed a new approach of chemoselective acylation of aliphatic, aromatic and cyclical amines.

This is performed with acetic acid in the presence of Y zeolite (SAR 5.2 silica / alumina ratio) (Scheme II.45).

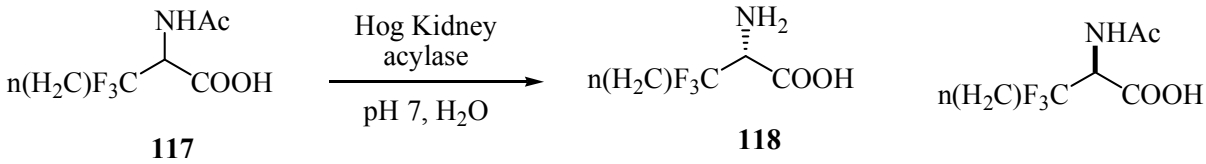


115 **116**

Scheme II.45

Cleavage

The enzymatic hydrolysis of the acetamide with Hog kidney acylase was performed with a significant enantioselective resolution (Scheme II.46).[70]



117 **118**

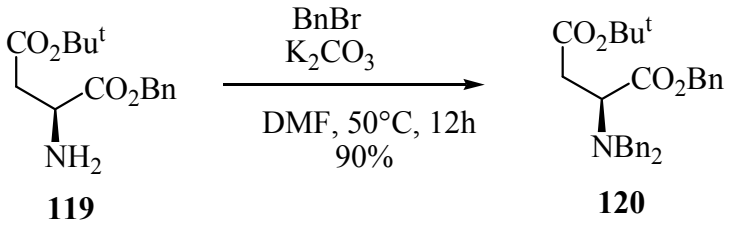
Scheme II.46

II.2.3.9. Benzyl (Bn) and Diphenylmethyl (Dpm)

Benzyl groups are the second fiddles of the amine protection repertoire, and they are especially useful when a substrate is to be subjected to powerful organometallic reagents or metal hydrides which might attack a carbamate. Benzylamines are not generally cleaved by lewis acids under preparatively useful conditions. The following discussion embraces benzylamines, diphenylmethylamines and their methoxy-substituted derivatives.

Formation

Alkylation of amines and amides with benzylic halides is an early and useful method for the protection of amines and amides. Primary amines can alkylate twice to give the *N,N*-dibenzyl derivative, but severe steric congestion prevents quaternisation (Scheme II.47).



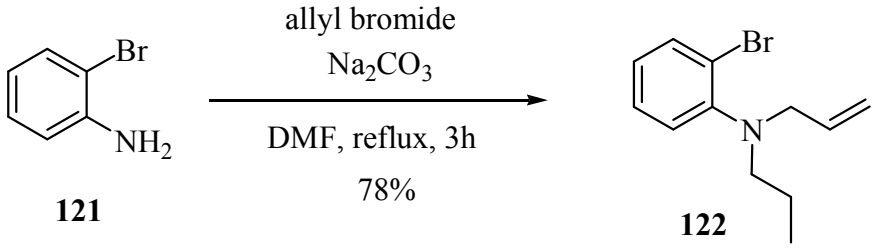
119 **120**

Scheme II.47

II.2.3.10. Allyl

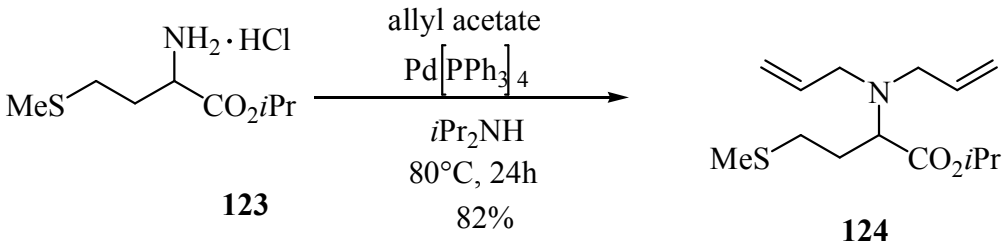
Formation

Two methods are used to introduce an allyl group into an amine. The first method is a simple alkylation reaction using allyl bromide in DMF in the presence of solid sodium carbonate (Scheme II.48). The second method is a Pd(0)-catalysed allylation of an amine with allyl acetate (Scheme II.49).



121 **122**

Scheme II.48



123 **124**

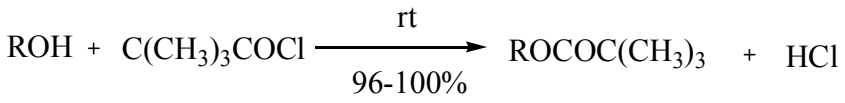
Scheme II.49

II.3. Methods of Protection using pivaloyl chloride

II.3.1. Protection for Alcohol Under Solvent- and Catalyst-Free Conditions

A simple and highly efficient protocol for pivaloylation of alcohols without using a catalyst under solvent-free conditions has been developed. The key advantages of the reaction are short reaction time, high yields, simple workup, and no need for further purification.

Selectivity was observed between primary alcohols vs. secondary alcohols and aliphatic alcohols vs. aromatic alcohols (Scheme II.50).[71]

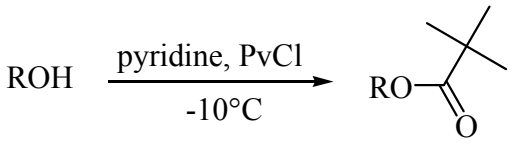


R = aliphatic, aryl

Scheme II.50

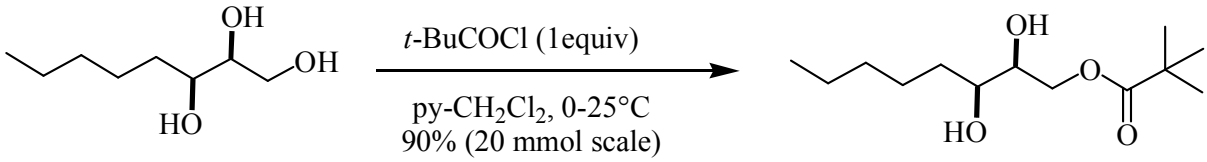
II.3.2. Protection of alcohols with pivaloyl chloride using pyridine

A solution of the corresponding primary and secondary alcohol was added to solution of pivaloyl chloride in dry pyridine at -10°C gave after the purification by column chromatography to the expected protected alcohols (Scheme II.51).



Scheme II.51

Selective acylation of a primary alcohol in the presence of one or more second-ary alcohols is easily achieved with hindered acylating agents such as pivaloyl chloride[72] (Scheme II.52).



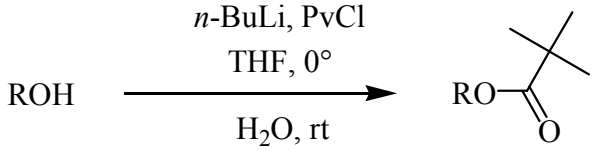
125 **126**

Scheme II.52

II.3.3. Protection of alcohols with pivaloyl chloride using *n*-butyl lithium

To a stirred solution of the alcohol (10.0 mmol) in anhyd THF (10 mL) under argon at 0 °C was added dropwise 2.5 M of n-BuLi in hexane (4 mL, 10.0 mmol); the mixture was stirred at this temperature for 10 min. Pivaloyl chloride (1.23 mL, 10.0 mmol) was added to the mixture over ca. 5 min and it was stirred at r.t. overnight. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were

washed with brine (5 mL), dried (Na_2SO_4), filtered, the solvent evaporated to give a residue that was purified by column chromatography (hexane–EtOAc) to afford pure product (Scheme II.53).[73]



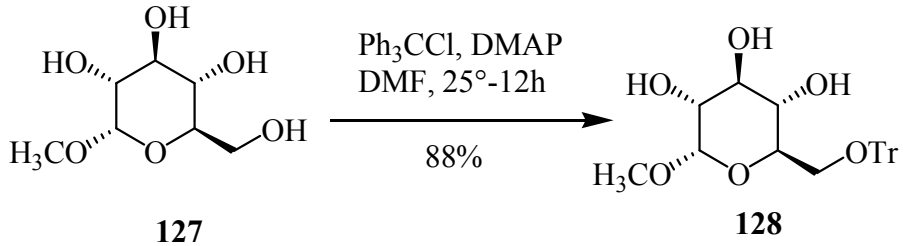
Scheme II.53

II.4. Methods of Protection using triphenylmethyl (trityl)

Hydroxyl groups are present in a number of compounds of biological and synthetic interest, including nucleosides, carbohydrates, steroids, macrolides, polyethers, and the side chain of some amino acids. During oxidation, acylation, halogenation with phosphorus or hydrogen halides, or dehydration reactions of these compounds, a hydroxyl group must be protected. In polyfunctional molecules, selective protection becomes an issue that has been addressed by the development of a number of new methods. Ethers are among the most used protective groups in organic synthesis and vary from the simplest, most stable methyl ether to the more elaborate, substituted trityl ethers developed for use in nucleotide synthesis. Ethers are formed and removed under a wide variety of conditions.

II.4.1. Tritylation of alcohols in dimethylformamid

The reaction of compound **127** with triphenylmetyl and dimethylaminopyridine in dimetylformamid at room temperature gave a selective protection of primary hydroxyl group. A secondary alcohol reacts more slowly (40-45°, 18-24 h, 68-70% yield). In general, excellent selectivity can be achieved for primary alcohols in the presence of secondary alcohols (Scheme II.54).

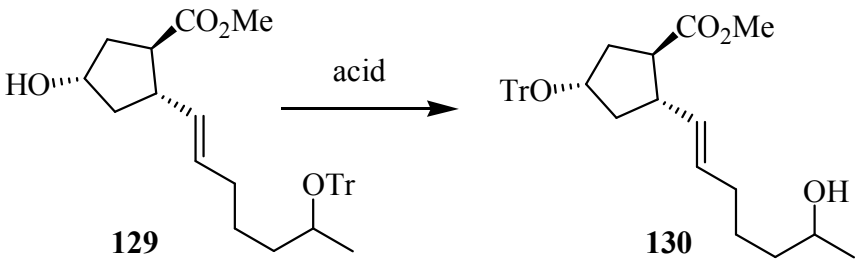


127 **128**

DMAP = 4-N,N-dimethylaminopyridine

Scheme II.54

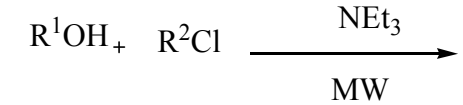
The trityl group can migrate from one secondary center to another under acid catalysis (Scheme II.55).



Scheme II.55

II.4.2. Tritylation of alcohols and nucleosides using microwave irridation

A very simple and efficient method is described for protection of alcohols with trityl (triphenylmethyl), mono and dimethoxytrityl chlorides in the presence of triethylamine under microwave irradiation. The mixture of alcohol and triethylamine was reacted with trityl chloride (or its derivatives) in molar ratio of (1:2.5:1.2), respectively (Scheme II.56). Aliphatic and benzylic alcohols are protected very easily by this method with excellent yields.[1]



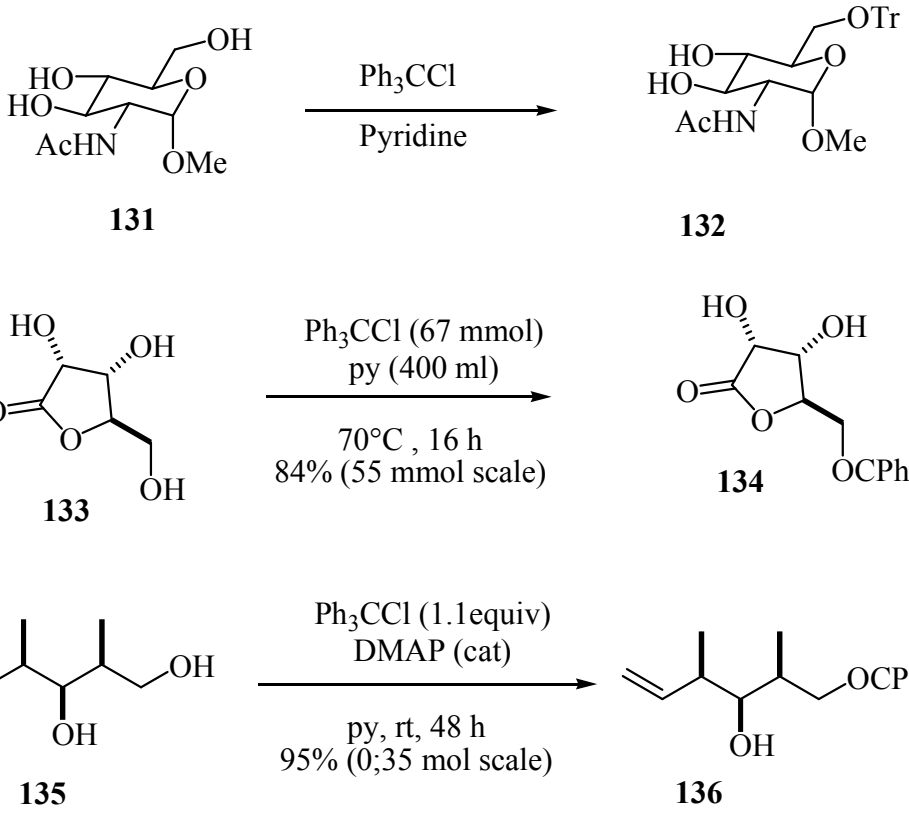
R^1 = cyclohexyl	R^2 = DMT	T= 50s	90%
R^1 = $PhCH_2$-	R^2 = Tr	T= 120s	65%
R^1 = $PhCH_2CH_2CH_2$-	R^2 = MMT	T= 120s	75%

Scheme II.56

II.4.3. Tritylation of alcohols in pyridine

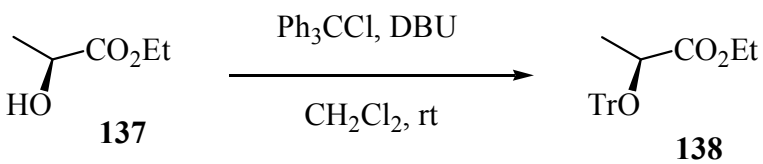
Concerning the strategy of increasing the steric hindrance for alcohol protection, the trityl group (Tr), historically developed for carbohydrate chemistry and later aiding the construction of oligonucleotides, is the most important. Therefore, selective protection of these hydroxyls is possible (Scheme II.57). The classical method for the introduction of the trityl group involved the reaction of primary alcohol (secondary alcohols react very slowly –if at all) with triphenylmethyl chloride (mp 110-112 C°) in pyridine .the reaction can be slow

and more convenient procedure using DMAP or DBU to accelerate the reaction and it is applicable to large scale as shown in the synthesis of a fragment of the macrolide antibiotic Erythronolide B (Scheme II.57).[74] The reaction of (2S, 3R, 4S)-2,4-Dimethyl-5-hexene-1,3-diol in pyridine with trityl chloride and DMAP was stirred at 22 °C for 2 days. Then, crushed ice was added to the mixture and concentrated *in vacuo* to remove the pyridine. Flash chromatography gave 1-trityl derivative as clear colorless oil (Scheme II.57). In the presence of the more powerful base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), even secondary alcohols can be tritylated (Scheme II.58).[75]



131 **132** **133** **134** **135** **136**

Scheme II.57



137 **138**

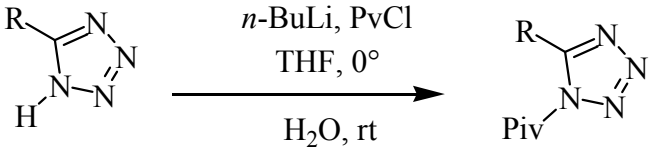
Scheme II.58

II.5. Results and discussion

II.5.1. Protection of tetrazoles with pivaloyl chloride

The synthesis of tetrazoles allows us to protect them using pivaloyl chloride. The pivaloyl group is widely used in organic synthesis to protect alcohols, amines, and thiols, due to its easy introduction, stability under a variety of reaction conditions, and relatively easy removal to give the corresponding depivalated compounds. The tetrazole moiety is present in several biologically active compounds, such as sartans, which are pharmaceuticals that are efficient for the treatment of hypertension, kidney damage caused by diabetes, and heart failure. The synthesis of sartans generally requires protection and deprotection steps to the tetrazole ring.[76] The effective protection caused by the high steric demand of the pivaloyl group, together with the ease of its introduction into and its removal from the nitrogen atom, are features that potentially make the pivaloyl group useful in the preparation of interesting family of drugs like sartans.

To a stirred solution of the tetrazole in anhyd THF under argon at 0 °C was added dropwise *n*-BuLi in hexane; the mixture was stirred at this temperature for 10 min. Pivaloyl chloride was added to the mixture over ca. 5 min and it was stirred at r.t. overnight. The reaction was quenched with H_2O and extracted with EtOAc. The combined organic phases were dried, filtered, and the solvent evaporated to give a residue that was purified by recrystallization (hexane–EtOAc) to afford pure product.The Table II.1 summarize the physical properties of protected tetrazoles with good yields (Scheme II.59).



Scheme II.59

Table II.1: Protection of tetrazoles with pivaloyl chloride.

Entry	Product	R	Time (h)	Mp (°C)	Yield (%)
1	**1a**	Ph	Overnight	218-220	65
2	**1b**	2-(4-MeC_6H_4)C_6H_4	Overnight		62
3	**1c**	*t*-Bu	Overnight	104-106	70
4	**1d**	CH_2CO*t*-Bu	Overnight		80
5	**1e**	Me	Overnight	152-157	85
6	**1f**	$CHPh_2$	Overnight	154-158	90

All protected tetrazoles were identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR.

IR Spectroscopy

Analysis of IR spectroscopic of all compounds showed disappearance of NH peak at 2987-3336 cm^{-1}. Absorption between 1701-1732 cm^{-1} shows the presence of a carbonyl group for all the compounds. Protected tetrazoles are also verified by the presence of band at [685-754] cm^{-1} who corresponds to the methylene groups.

^{1}H NMR Spectroscopy

We have made the protection of NH of tetrazoles with pivaloyl chloride. These protected tetrazoles devise on two parts the first is tetrazole rings, the second is pivaloyl group so we have a common three methylene groups which resonne in the strong field between [0.92-2.74] ppm with integration 9H.

Compound (1a)

The spectrum showed the appearance of singlet signal at 1.06 ppm corresponding to three methylene group. A multiplet appears in the range [7.45-7.90] ppm with integration 5H corresponding to aromatic protons.

Compound (1b)

The spectrum of this compound showed a singlet (s) absorption band for group CH_3 with integration 3H at 2.27 ppm. The aromatic protons resonne at [6.93-7.63] ppm as multiplet (m) with integration 8H.

Compound (1c)

We note another three methylene group in this compound as a singlet peak at 1.42 ppm.

Compound (1d)

We note also another three methylene group in this compound as a singlet peak at 2.74 ppm. Another singlet peak at 2.80 ppm for group CH_2.

Compound (1e)

This spectrum showed the presence of two singlet signals, the first at 0.92 ppm with integration 9H, the second at 2.31 ppm with integration 3H.

Compound (1f)

We observe in the spectrum of this compound a singlet signal at 5.80 ppm corresponding to CH. Also the ten aromatic protons appear at [7.23-7.38] ppm as multiplet (m).

Table II.2: ^{1}H NMR for compounds **1a-1f**.

Compounds	CH	CH_2	CH_3	H_{arom}
1a	---	---	1.06, s, 9H	7.45-7.90, m, 5H
			0.92, s, 9H	6.93-7.08, m, 4H
1b	---	---	2.27, s, 3H	7.45-7.63, m, 4H
1c	---	---	1.42, s, 18H	---
1d	---	2.80, s, 2H	2.74, s, 18H	---
1e	---	---	0.92, s, 9H	---
			2.31, s, 3H	
	5.80, s, 1H			7.23-7.38, m, 10H
1f		---	1.07, s, 9H	

^{13}C NMR Spectroscopy

The signals located in high fields are those of methyl group; which located between [21.1-27.6] ppm. Spectral analysis of the prepared compound shows the existence of a weak magnetic field signal between [182.5-214.1] ppm corresponding to the carbonyl group.

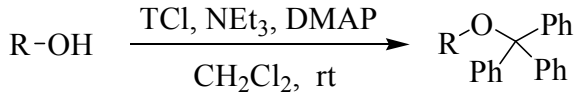
We note also the presence of aromatic protons which resonne between [128.2-130.5] ppm, [128.7-132.5] ppm, [128.6-129.9] ppm for compound **1a, 1b,** and **1f** respectively. We have the presence of another carbonyl at 210.1 ppm, and CH_2 peak at 31.7 ppm for compound **1d**.We observe CH peak at 47.8.7 ppm for compound **1f**.

Table II.3: ^{13}C NMR for compounds **1a-1f**.

Compounds	CH	CH_2	CH_3	CO	C_{arom}
1a	---	---	27.6	---	128.2-132.5
1b	---	---	21.1	---	128.7-132.5
			27.6		
1c	---	---	29.5	214.1	---
			31.8		
1d	---	31.7	26.4	182.5	---
			27.9	210.1	
1e	---	---	26.8	182.5	---
			27.6		
1f	47.8	---	26.8	182.5	128.6-129.9

II.5.2. Protection of alcohols with trityl

The trityl (triphenylmethyl) group is often employed for the selective protection of primary alcohols and amines in carbohydrate, peptide and nucleotide chemistry, due to its high steric demand. This protecting group can easily be removed by acid hydrolysis, but some acid-sensitive functional groups cannot survive under the rather harsh reaction conditions. A solution of the corresponding alcohol in CH_2Cl_2 was added to solution of tritylchloride, NEt_3 and DMAP in CH_2Cl_2 at r.t. and the mixture was stirred overnight. The reaction was then quenched with water and extracted with EtOAc and the combined organic phases were washed and dried. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc) affording the expected trityl ethers (Scheme II.60).



Scheme II.60

Note

The same procedure was applied for the compounds **1f'**, **1i'** but with double quantity of reactifs because we have two functions OH to protect them.

Table II.4: Protection of alcohols 1a'-1m'.

Entry	Product	Time (h)	Mp (°C)	Yield (%)
1	**1a'**	Overnight	---	88
2	**1b'**	Overnight	85	92
3	**1c'**	Overnight	70	95
4	**1d'**	Overnight	95	90
5	**1e'**	Overnight	---	75
6	**1f'**	Overnight	160	53
7	**1g'**	Overnight	---	69
8	**1h'**	Overnight	84	62
9	**1i'**	Overnight	122	55
10	**1j'**	Overnight	---	33
11	**1k'**	Overnight	---	40
12	**1l'**	Overnight	---	78
13	**1m'**	Overnight	---	76

All tritylated alcohols were identified by spectroscopic methods IR, ^{1}H NMR, ^{13}C NMR and also by comparison with authentic samples.

IR Spectroscopy

Analysis of IR spectroscopic of all compounds showed disappearance of OH peak at 2987-3336 cm^{-1} except in the product **1j'** which has two functions OH and we have made the protection only for one OH so we still have one hydroxyl group. The IR spectrums of the all products showed strong absorption band characteristic of the CO function in 1000; 1054, and a second strip of frequency toward 1450; 1500 cm^{-1} due to stretching of HC=C for aromatic rings. Absorption in 650 cm^{-1} shows the presence of aliphatic chains.

^{1}H NMR Spectroscopy

Nuclear magnetic resonance spectra of the proton ^{1}H NMR of all the products present a common signals, corresponding to The protons of the aromatic ring of triphenyl, the first

resonne between [7.13-7.37] ppm with integration 9H, while the second resonne between [7.33-7.58] ppm with integration 6H, another signal corresponding to CH_2-O between [2.20-3.50] ppm.

Compound (1a')

The spectrum showed the appearance of three singlet signals at 1.45, 1.62, 1.70 ppm respectively corresponding to three methylene groups. A multiplet (m) with integration 1H in the range [5.13-5.15] ppm corresponding to the *H*C=CMe_2, another multiplet (m) with integration 1H in the range [5.39-5.42] ppm corresponding to the CHCO. Without forget the aromatic protons between [7.23-7.47] ppm.

Compound (1b')

The analysis of this spectrum showed two multiplets of cyclohexylic ring , the first at [1.01-1.35] ppm with integration 6H, the second at [1.52-1.61] ppm with integration 4H. Another multiplet (m) with integration 1H at 3.46 ppm corresponding to the CHO. the aromatic protons resonne between [7.23-7.47] ppm as multiplet (m) with integration 15H.

Compound (1c')

The protons of this compound appear with different multiplicity as follows:

- Multiplet (m) belongs to aromatic protons resonne between [7.13-7.25] ppm.
- Multiplet (m) with integration 2H at 2.51 ppm corresponding to CH_2CO.
- Multiplet (m) with integration 24H in the range [1.18-1.56] ppm corresponding to [Me(CH_2)$_{12}$].
- Triplet at 0.81 ppm corresponding to CH_3 with coupling constant J = 4 Hz.

Compound (1d')

We note in this spectrum the appearance of singlet peak at 3.51 ppm with integration 2H corresponding to CH_2O. We not also two multiplets, the first in the range [7.22-7.34] ppm with integration 14H, The second in the range [7.54-7.58] ppm with integration 6H.

Compound (1e')

We note different multiplicity for the protons of this compound:

- Multiplet (m) belongs to aromatic protons resonne between [7. 25-7.51] ppm.
- Triplet at 3.06 ppm corresponding to CH_2O with coupling constant J = 8 Hz.
- Multiplet (m) with integration 1H between [1.72-1.79] corresponding to $CH(Me)_2$).
- Multiplet (m) with integration 2H between [1.47-1.53] corresponding to CH_2CH_2O.
- Two doublets corresponding to two CH_3; the first at 0.80 ppm with coupling constant J = 8 Hz, the second at 0.92 ppm with coupling constant J = 4Hz.

Compound (1f')

In this case we have a double protection of hydroxyl group. In the region of the strong field, we observe two multiplets, the first in the range [1.30-1.33] ppm with integration 4H corresponding to 2 × CH_2CH_2 , The second in the range [1.53-1.62] ppm with integration 4H corresponding to 2 × CH_2CO. we oberve also a triplet at 3 ppm with integration 4H corresponding to 2 × CH_2O with coupling constant J = 6.6 Hz. in the region of the weak field, we observe two multiplets, the first in the range [7.19-7.29] ppm with integration 18H, The second in the range [7.41-7.44] ppm with integration 12H.

Compound (1g')

In this spectrum the protons of this compound appear with different multiplicity as follows:

- Multiplet (m) belongs to aromatic protons resonne between [7.23-7.50] ppm.
- Multiplet (m) with integration 2H between [3.76-3.88] ppm, corresponding to CH_2CO.
- Multiplet (m) with integration 6H in the range [1.53-1.81] ppm corresponding to [Me $(CH_2)_3$].
- Doublet at 1.22 ppm corresponding to CH_3 with coupling constant J = 6.1 Hz.

Compound (1h')

In the region of the weak field, we observe two multiplets, the first in the range [7.25–7.37] ppm with integration 9H , The second in the range [7.55–7.58] ppm with integration 6H corresponding to aromatic protons. We observe also another multiplet with integration 1H between [4.06–4.10] corresponding to CHO. In the region of the strong field, we observe two multiplets the first in the range [1.33–1.65] ppm with integration 2H, The second in the range [0.93–1.18] ppm with integration 6H.

Compound (1i')

In this case we have also a double protection of hydroxy group like compound **1f'**.

The protons in this spectrum appear with different multiplicity as follows:

- Two multiplets (m) belong to aromatic protons, the first resonne between [7.29-7.35] ppm with integration 18H, the second resonne between [7.41-7.45] ppm with integration 12H
- Multiplet (m) with integration 1H between [3.57-3.60] ppm, corresponding to CHO.
- Multiplet (m) with integration 2H between [2.80-2.97] ppm, corresponding to CH_2CO.
- Multiplet (m) with integration 4H in the range [1.13-1.70] ppm.
- Doublet at 0.93 ppm corresponding to CH_3 with coupling constant J = 6 Hz.

Compound (1j')

In this spectrum the protons of this compound appear with different multiplicity as follows:

- Multiplet (m) belongs to aromatic protons resonne between [7.23-7.44] ppm.
- Multiplet at 3.93 ppm corresponding to CHOH with with integration 1H.
- Multiplet (m) with integration 2H at 2.51 ppm corresponding to CH_2OTr.
- Multiplet (m) with integration 8H between [0.87–1.52] ppm corresponding to OH, $2\times CH_2$ and methyl.

Compound (1k')

The aromatic protons of triphenyl resonne between [7.22-7.44] ppm as multiplet (m) with integration 15H. The aromatic protons of phenyl appear with two multiplicities:

- Doublet of doublet (dd) between [6.63-6.79] ppm with integration 3H.
- Triplet with integration 2H at 7.00 ppm and with coupling constant J = 8.4 Hz.

Compound (1l')

This spectrum shows three multiplets, the first in the range [7.19-7.52] ppm corresponding to aromatic protons, the second in the range [3.51–3.58] ppm corresponding to CHO, the third in the range [1.05–1.23] ppm with integration 10H corresponding to protons of aliphatic chains. We observe a doublet at 0.86 ppm corresponding to CH_3CO with coupling constant J = 4 Hz, we have also a triplet at 0.83 ppm corresponding to CH_3CH_2 with coupling constant J = 8 Hz.

Compound (1m')

- Multiplet with integration 15H corresponding to aromatic protons resonne between [7. 19-7.46] ppm.
- Triplet at 3.03 ppm corresponding to CH_2O with coupling constant J =6.7 Hz.
- Multiplet (m) with integration 2H between [1.51–1.65] corresponding to CH_2CO.
- Multiplet (m) with integration 14H between [1.24–1.36] corresponding to Me $(CH_2)_7$.
- Triplet at 0.87 ppm corresponding to CH_3 with coupling constant J =8 Hz.

Table II.5: ^{1}H NMR for tritylated compounds.

Compounds	CH	CH_2	CH_3	H_{arom}
1a'	5.13-5.15, m, 1H 5.39-5.42, m, 1H	2.03-2.18, m, 4H 3.57, d, 2H	1.45, s, 3H 1.62, s, 3H 1.70, s, 3H	7.23-7.33, m, 9H 7.43-7.47, m, 6H
1b'	3.46, m, 1H	1.01-1.35, m, 6H 1.52-1.61, m, 4H	---	7.19-7.29, m, 9H 7.53-7.55, m, 6H
1c'	---	1.18-1.56, m, 24H 2.20-2.22, m, 6H 2.51, m, 2H 2.96, t, 2H	0.81, t, 3H	7.13-7.25, m, 9H 7.36-7.38, m, 6H
1d'	---	3.51, s, 2H	---	7.22-7.34, m, 14H 7.54-7.58, m, 6H
1e'	1.72-1.79 m, 1H	1.47-1.53, m, 2H 3.06, t, 2H	0.80, d, 3 H 0.92, d, 3 H	7.25–7.36, m, 9H 7.49–7.51, m, 6H
1f'	---	1.30-1.33, m, 4H 1.53-1.62, m, 4H 3.00, m, 4H	---	7.19-7.29, m, 18H 7.41-7.44, m, 12H
1g'	---	1.53-1.81, m, 6H 3.08-3.17, m, 2H 3.76-3.88, m, 2H	1.22, d, 3H	7.23-7.37, m, 9H 7.42-7.50, m, 6H
1h'	4.06–4.10, m, 1H 3.57-3.60	1.33–1.65, m, 2H 1.13-1.30, m, 2H	0.93–1.18, m, 6H	7.25–7.37, m, 9H 7.55–7.58, m, 6H

1i'	m, 1H	1.46-1.70, m, 2H 2.80-2.97, m, 2H	0.93, d, 3H	7.19-7.35, m, 18H 7.41-7.45, m, 12H
1j'	3. 93, m, 1H	2.51, m, 2H		7.23–7.37, m, 9H 7.37–7.44, m, 6H
1k'	---	---	---	6.63-6.79, dd, 3H 7.00, t, 2H 7.22-7.31, m, 9H 7.33-7.44, m, 6H
1l'	3.51–3.58 , m, 1H	1.05–1.23, m, 10 H	0.86, d, 3H 0.83, t, 3H	7.19–7.30, m, 9H 7.49–7.52, m, 6 H
1m'		1.24–1.36, m, 14 H 1.51–1.65, m, 2H 3.03, t, 2H	0.87, t, 3H	7.19–7.31, m, 9H 7.43 –7.46, m, 6H

^{13}C NMR Spectroscopy

Spectral analysis of all compounds shows the existence of common signals which are:

- CH Aromatic of triphenyl appears in the interval [120.0-129.8] ppm.
- Aromatic carbone appears in the interval [144.3-146.9] ppm.
- Peak of CH_2O appears in the interval [62.2-68.0] ppm.
- Peak of CO appears in the interval [86.2-87.9] ppm.

Compound (1a')

We note in this spectrum the appearance of three peaks of methylene groups at 16.5, 17.8, 25.9 ppm respectively. We have also a peak of CHCO at 122.5 ppm; another peak at 125.1 ppm belongs to $CH{=}CMe_2$, two peaks at 132.4, 139.7 ppm correspond at CMe_2, $CH_2C{=}C$ respectively.

Compound (1b')

We observe in this spectrum the presence of CH of cyclohexyl which appear in the range between [24.4-33.9] ppm, a peak of CHO at 72.1 ppm.

Compound (1c')

The aliphatic carbons appear in the range between [4.2-40.3] ppm correspond to $[Me(CH_2)_{17}]$.

Compound (1d')

In this spectrum we have the CH of benzylic groups between [126.8-129.1] ppm, the peak of CH_2O at 72.1 ppm and another aromatic carbone of benzylic groups at 146.7 ppm.

Compound (1e')

The spectrum of this compound shows the appearance of peak at 22.8 ppm refers to two methyl groups, we note also two signals at 25.2 and 39.1 ppm corresponding to $CH(Me)_2$ and CH_2 respectively.

Compound (1f')

We have a double protection of hydroxy group by triphenyl chloride, two peaks are observed at 26.2 and 30.1 ppm corresponding to $2\times CH_2CH_2$ and $2\times CH_2CO$. we have also a peak at 63.6 ppm corresponding to $2\times CH_2O$. Two carbonyls are observed at 86.3 ppm.

Compound (1g')

This spectrum showed the appearance of peak at 23.6 refers to methyl group, we note also three signals at 26.5, 36.4, 63.8 ppm corresponding to CH_2Me, $2\times CH_2$, CH_2CH_2O respectively.

Compound (1h')

We observe in this spectrum the presence of CH of cyclopentyl which appear at 23.8 and 33.6 ppm, we note another peak of CHO at 72.8 ppm.

Compound (1i')

We have a double protection of hydroxy group by triphenyl chloride, In this spectrum we have the presence of:

- Signal at 21.2 belongs to CH_3.
- The carbons of CH_2CH_2 resonate at 25.4 ppm.
- The carbon of CH_2CHO resonates at 34.0 ppm.
- The carbon of CHO shows at 69.8 ppm.
- Two carbonyls appear at 69.8 and 86.3 respectively.

Compound (1j')

We have in this spectrum the presence of peak of methylene group at 23.1 ppm. The two aliphatic carbons appear at 33.0 ppm. We have also a peak of CH_2O at 66.2 ppm; another peak at 75.8 ppm belongs to CHOH.

Compound (1k')

The aromatic carbons of triphenyl and phenyl groups resonate between [126.8-129.1] ppm. Two peaks at 72.1 and 86.5 ppm refer to two CO.

Compound (1l')

We note in this spectrum the appearance of two peaks of methylene groups at 14.2 and 21.3 ppm respectively. The aliphatic carbons appear in the range [22.7-37.6] ppm corresponding to [Me $(CH_2)_5$]. We note also a peak of CHO at 70.2 ppm.

Compound (1m')

We observe in this spectrum the appearance of peak of methylene group at 14.2 ppm. We note the presence of aliphatic carbons in the range [22.8-32.0] ppm corresponding to [Me $(CH_2)_8$]. We note also a peak of CH_2O at 63.8 ppm.

Table II.6: ^{13}C NMR for compounds **1a'-1m'**.

Compounds	C	CH	CH_2	CH_3	CO	C_{arom}
1a'			27.4			
		122.5	40.6	16.5		
	145.7	125.1	62.2	17.8	87.9	128.0-129.8
			139.7	25.9		
			24.4	---		
1b'	145.8	72.1	25.9		86.5	126.9-129.1
			33.9			
1c'	144.5	---	63.6	4.2-40.3	86.2	126.7-128.6
1d'	146.7	---	72.1	---	86.5	126.8-129.1
	146.9					
1e'	144.6	25.2	39.1	22.8	86.4	126.9-128.8
			68.2			
1f'	144.6	---	26.2	---	86.3	126.9-128.8
			30.1			
			63.6			
1g'	144.3	---	26.5	23.6	86.7	127.0-128.7
			36.4			
			63.8			

			68.0			
1h'	145.5	72.8	23.8	---	86.9	126.8-129.0
			33.6			
1i'	144.6	69.8	25.4	21.2	86.3	120.0-129.0
	145.6		34.0		86.5	
			64.0			
1j'	145.0	75.8	33.0	23.1	86.3	126.9-128.4
			66.2			
1k'	146.7	---	---	---	72.1	126.8-129.1
	146.9				86.5	
1l'	145.7	70.2	22.7	14.2	86.5	126.8-129.1
			25.0	21.3		
			29.5			
			31.9			
			37.6			
	144.6	---	22.8	14.2	86.3	126.9-128.8
			26.4			
1m'			29.4			
			29.6			
			29.7			
			30.2			
			32.0			

II.6. Conclusion

In this chapter, some protective groups were studied in detail by highlighting each of its chemical characteristics that affect the well protection / deprotection in different environments. We also introduced the necessity of using various protective groups in total synthesis for the design of the orthogonality. The presence of the hydroxyl and amine function in various active biologically compounds makes the protection necessary for their synthesis.

The need for protection requires the use of environmental and economic processes to develop new methods that aim to minimize the possible environmental and toxicological impacts. In this context, the research focuses to the investigation of the possibility of using useful protective groups for blocking the amine function with pivaloyl chloride, and hydroxyl function with trityl.

The protected products were obtained with greater yield and were identified by spectroscopic methods IR, ^{1}H NMR, ^{13}C NMR.

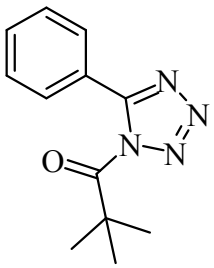
II.7. Experimental part

II.7.1. Protection of tetrazoles with pivaloyl chloride

General procedure

To a stirred solution of the tetrazole (10.0 mmol) in anhyd THF (10 mL) under argon at 0 °C was added dropwise 2.5 M of *n*-BuLi in hexane (4 mL, 10.0 mmol); the mixture was stirred at this temperature for 10 min. Pivaloyl chloride (1.23 mL, 10.0 mmol) was added to the mixture over ca. 5 min and it was stirred at r.t. overnight. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered and the solvent evaporated to give a residue that was purified by recrystallization (hexane–EtOAc) to afford pure product.

2,2-dimethyl-1-(5-phenyl-1-*H*-tetrazol-1-yl)propan-1-one (1a)

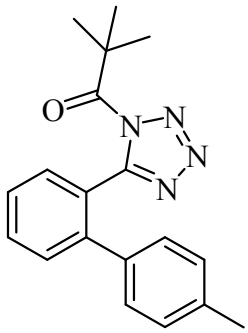


1a

Following the general procedure, the reaction of 5-phenyl-1*H*-tetrazole (1.46 g, 10mmol), pivaloyl chloride (1.23 ml), *n*-BuLi (4ml) in THF (10 mL) at 0° gave **1a** as a white solid.

- **Yield**= 65% (1.49 g).
- **Mp**= 218-220°C.
- **IR (KBr):** 1701, 1608, 1562, 1484, 1409, 1256, 685 cm^{-1}.
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 1.06 (s, 9 H), 7.45–7.90 (m, 5 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 27.6 (3× CH_3), 39.3 (C), 125.6 (C), 128.2 (2× CH), 130.5 (2× CH), 132.5 (CH), 157.7 (C).
- **Anal. Calcd** for $C_{12}H_{14}N_4O$: C, 62.69; H, 6.13; N, 24.33. Found: C, 62.66; H, 6.15; N, 24.37.

2,2-dimethyl-1-[5-(4'-methylbiphenyl-2-yl)-1*H*-tetrazole-1-yl]propan-1-one (1b)

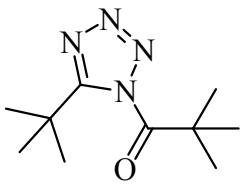


1b

Following the general procedure, the reaction of 5-(4'-methyl-[1,1'-biphenyl]-2-yl)-1*H*-tetrazole (0.086 g), pivaloyl chloride (0.041 ml), *n*-BuLi (0.13 ml) in THF (0.33 mL) at 0° gave **1b** as a yellow solid.

- **Yield**= 62% (1.98 g).
- **IR (KBr):** 1712, 1482, 1244, 1078, 823, 754 cm^{-1}.
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 0.92 (s, 9 H), 2.27 (s, 3 H), 6.93–7.08 (m, 4 H), 7.45–7.63 (m, 4 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 21.1 (CH_3), 27.6 (3 ×CH_3), 124.2 (C), 128.7, 129.9, 130.2, 131.6, 131.8, 132.5 (8 ×CH), 137.6 (C), 138.8 (2 C), 143.6 (2 C), 156.8 (C).
- **Anal. Calcd** for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.23; H, 6.32; N, 17.53.

1-(5-(*tert*-butyl)-1*H*-tetrazole-1-yl)-2,2-dimethylpropan-1-one (1c)

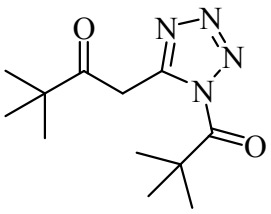


1c

Following the general procedure, the reaction of 5-(tert-butyl)-1*H*-tetrazole (0.028 g), pivaloyl chloride (0.027 ml), *n*-BuLi (0.088 ml) in THF (0.22 mL) at 0° gave **1c** as a white solid.

- **Yield**= 70% (1.47 g).
- **Mp**= 104-106°C.
- **IR (KBr):** 1732, 1264, 1218, 1045, 703 cm^{-1}.
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 1.42 (s, 18 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 29.5 (3× CH_3), 31.8 (3× CH_3), 165.7 (C), 214.1 (CO).
- **Anal. Calcd** for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.12; H, 8.62; N, 26.66.

3,3-dimethyl-1-(1-pivaloyl-1*H*-tetrazole-5-yl)butan-2-one (1d)

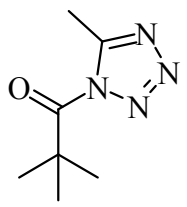


1d

Following the general procedure, the reaction of 3,3-dimethyl-1-(1H-tetrazol-5-yl)butan-2-one (1 g), pivaloyl chloride (0.73 ml), *n*-BuLi (2.38 ml) in THF (5.25 mL) at 0° gave **1d** as a brown solid.

- **Yield**= 80% (2.01 g).
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 2.74 (s, 18 H), 2.80 (s, 2 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 26.4, 26.8, 27.5 (3× CH_3), 27.6, 27.7, 27.9 (3× CH_3), 31.7 (CH_2), 39.3 (C), 45.5 (C), 152.5 (C), 182.5 (C=O), 210.1 (C=O).
- **Anal. Calcd** for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.10; H, 8.01; N, 22.24.

2, 2-dimethyl-1-(5-methyl-1*H*-tetrazol-1-yl) propan-1-one (1e)

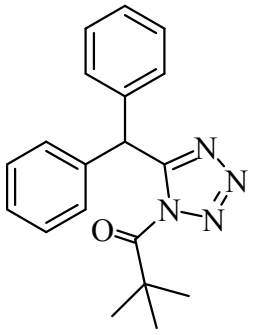


1e

Following the general procedure, the reaction of 5-methyl-1*H*-tetrazole (0.84, 10 mmol), pivaloyl chloride (1.23ml, 10 mmol), *n*-BuLi (4 ml, 2.5M) in THF (10 mL) at 0° gave **1e** as a white solid.

- **Yield**= 85% (1.43 g).
- **Mp**= 152-157°C.
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 0.92 (s, 9 H), 2.31 (s, 3 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 8.4 (CH_3), 26.8 (CH_3), 27.6 (2× CH_3), 39.3 (C), 154.1 (C), 182.5 (CO).
- **Anal. Calcd** for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.96; H, 7.14; N, 33.33.

1-[5-(diphenylmethyl)-1*H*-tetrazol-1-yl]-2,2-dimethylpropan-1-one (1f)



1f

Following the general procedure, the reaction of 5-benzhydryl-1*H*-tetrazole (1.30 g), pivaloyl chloride (0.67 ml), *n*-BuLi (2.20 ml) in THF (5 mL) at 0° gave **1f** as a white solid.

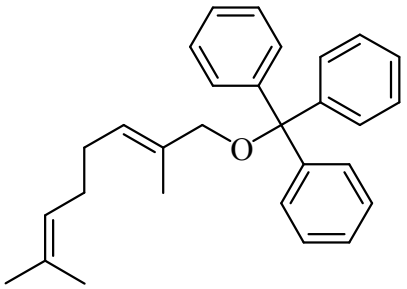
- **Yield**= 90% (2.88 g).
- **Mp**= 154-158°C.
- **^{1}HNMR: (400 MHz, CD_3OD):** δ = 1.07 (s, 9 H), 5.80 (s, 1 H), 7.23–7.38 (m, 10 H).
- **^{13}CNMR: (100 MHz, CD_3OD):** δ = 26.8, 27.5, 27.6 (3× CH_3), 39.3 (C), 47.8 (CH), 128.6 (2× CH), 129.6 (4× CH), 129.9 (4× CH), 140.8 (2 C), 159.9 (C), 182.5 (C=O).
- **Anal. Calcd** for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.24; H, 6.26; N, 17.45.

II.7.2. Protection of alcohols

General procedure

A solution of the corresponding alcohol (5 mmol) in CH_2Cl_2 (2,5mL) was added to solution of trityl chloride (1.55g, 5,5 mmol), NEt_3 (1.25 ml, 8,8 mmol) and DMAP (0.046g, 0.2 mmol) in CH_2Cl_2 (5 mL) at r.t. and the mixture was stirred overnight. The reaction was then quenched with water (2,5 mL) and extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (2,5 mL) and dried over sodium sulfate. After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane–EtOAc) affording the expected trityl ethers.

Geranyl Trityl Ether (1a')

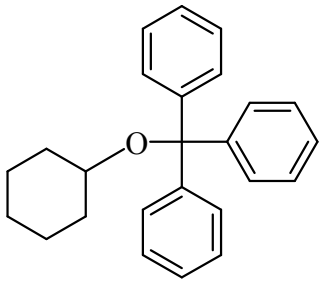


1a'

Following the general procedure, the reaction of geraniol (0.87 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1a'** as a Colourless oil.

- **Yield**= 88% (1.75 g).
- **IR (KBr):** 3085, 3058, 3022, 1688, 1597, 1490 (HC=C), 1054 (CO). cm^{-1} .
- **^{1}HNMR: (250 MHz, MeOD-d_4):** δ = 1.45 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.03–2.18 (m, 4 H, CH_2CH_2), 3.57 (d, 2 H, *J* = 6.4 Hz, CH_2O), 5.13–5.15 (m, 1 H, *H*C=CMe_2), 5.39–5.42 (m, 1 H, CHCO), 7.23–7.33 (m, 9 H, ArH), 7.43–7.47 (m, 6 H, ArH).
- **^{13}CNMR: (62.5 MHz, MeOD-d_4):** δ = 16.5 (Me), 17.8 (Me), 25.9 (Me), 27.4 (CH_2CH_2), 40.6 (CH_2CH_2), 62.2 (CH_2O), 87.9 (CO), 122. 5 (CHCO), 125.1 (CH=CMe_2), 132.4 (CMe_2), 139.7 (CH_2C=C), 128.0 (3 C), 128.7(6 C), 129.8 (6 C), 145.7 (3 C, ArC).

Cyclohexyl Trityl Ether (1b')

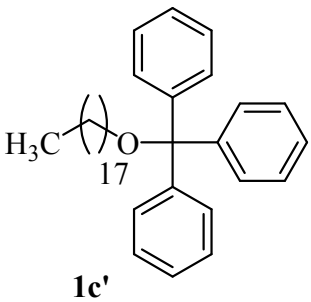


1b'

Following the general procedure, the reaction of cyclohexanol (0.52 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1b'** as a White solid.

- **Yield**= 92% (1.58 g).
- **Mp**= 85°C.
- **IR (KBr):** 3010, 3000, 1600, 1450 (HC=C), 1000 cm^{-1} (CO).
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 1.01–1.35 (m, 6 H, 3 × CH_2), 1.52–1.61 (m, 4 H, 2 × CH_2), 3.46 (m, 1 H, CHO), 7.19–7.29 (m, 9 H, ArH), 7.55–7.53 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 24.4 (2 C), 25.9, 33.9 (3 C) (5 × CH_2), 72.1 (CHO), 86.5 (CO), 126.9 (3 C), 127.7 (6 C), 129.1 (6 C), 145.8 (3 C, ArC).

Stearyl Trityl Ether (1c')



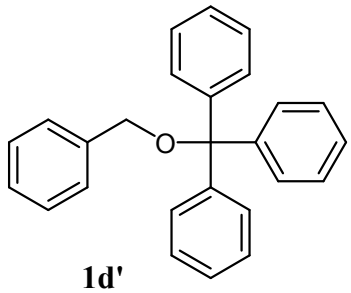
1c'

Following the general procedure, the reaction of stearic alcohol (1.35 g, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino)pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1c'** as a White solid.

- **Yield**= 95% (2.45 g).
- **Mp**= 70°C.

- **IR (KBr):** 3000, 2950, 2400, 1500, 1450 (HC=C), 1500, 1300, 1050, 1010 (CO), 650 cm^{-1}.
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 0.81 (t, 3 H, *J* = 4 Hz, Me), 1.18–1.56 [m, 24 H, Me (CH_2)$_{12}$], 2.20–2.22 (m, 6H),2.51 (m, 2 H, CH_2CO), 2.96 (t, 2 H, *J* = 6.7 Hz, CH_2O), 7.13–7.25 (m, 9 H, ArH), 7.36 –7.38 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 4.2, 10.2, 14.1, 22.6, 26.2, 29.3, 29.6, 30.0, 31.9, 39.9, 40.1, 40.3 [Me (CH_2)$_{17}$], 63.6 (CH_2O), 86.25 (CO), 126.7 (3 C), 127.6 (6 C), 128.6 (6 C), 144.5 (3 C, ArC).

Benzyl Trityl Ether (1d')

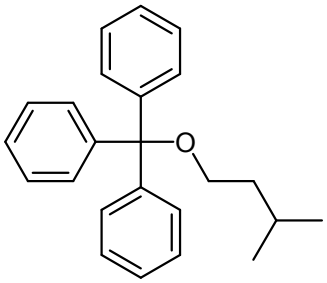


1d'

Following the general procedure, the reaction of benzylic alcohol (0.51ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1d'** as a White solid.

- **Yield**= 92% (1.58 g).
- **Mp**= 95°C.
- **IR (KBr):** 3059, 3053, 3031, 3023, 1594, 1489 (HC=C), 1085, 1060 cm^{-1} (CO).
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 3.51 (s, 2 H, CH_2), 7.22–7.34 (m, 14 H, ArH), 7.54–7.58 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 72.1 (CH_2), 86. 5 (CO), 126.8 (2 C), 127.3 (3 C), 127.6, 127.8 (6 C), 128.0 (2 C), 129.0, 129.1 (6 C), 146.7, 146.9 (3 C, ArC).

Isoamyl Trityl Ether (1e')

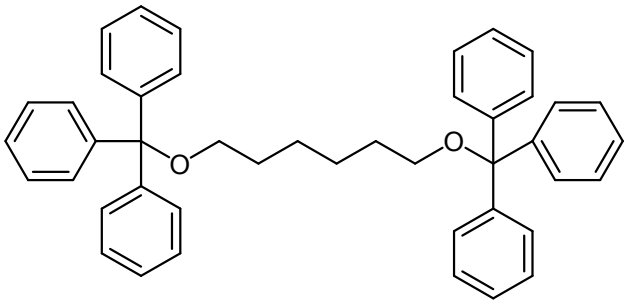


1e'

Following the general procedure, the reaction of isoamylic alcohol (0.54 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25mL, 8.8 mmol) and 4(dimethylamino)pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1e'** as a Colourless oil.

- **Yield**= 75% (1.24 g).
- **IR (KBr):** 3070, 3024, 2912, 1485 (HC=C), 1446, 1083 cm^{-1} (CO).
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 0.80 (d, 3 H, *J* = 8 Hz, Me), 0.92 (d, 3 H, *J* = 4Hz, Me),1.47-1.53 (m, 2 H, CH_2CH_2O),1.72-1.79 (m, 1 H, $CH(Me)_2$), 3.06 (t, 2 H, *J* = 8 Hz, CH_2O), 7.25–7.36 (m, 9 H, ArH), 7.49–7.51 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 22.8 (2 ×Me), 25.2 ($CH(Me)_2$), 39.1 (CH_2), 68.2 (CH_2O), 86.4 (CO), 126.9 (3C), 127.8 (6C), 128.8 (6C), 144.6 (3 C, ArC).

1,6-Di(trityloxy)hexane (1f')

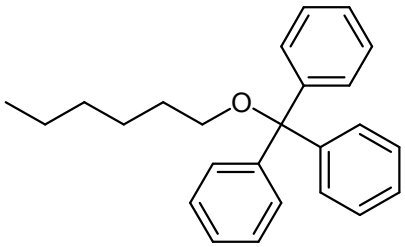


1f'

Following the general procedure, the reaction of hexadiol (0.59 g, 5 mmol), trityl chloride (3 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 **1f'** as a White solid.

- **Yield**= 53% (1.60 g).
- **Mp**= 160°C.
- **IR (KBr):** 3000, 2950, 3010, 1450 (HC=C), 1010 (CO), 1000 cm^{-1}.
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 1.30–1.33 (m, 4 H, 2 × CH_2CH_2), 1.53–1.62 (m, 4 H, 2 × CH_2CO), 3.00 (t, 4 H, *J* = 6.6 Hz, 2 × CH_2O), 7.19–7.29 (m, 18 H, ArH), 7.41–7.44 (m, 12 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 26.2 (2 C, 2 × CH_2CH_2), 30.1 (2 C, 2 × CH_2CO), 63.6 (2 C, 2 × CH_2O), 86.3 (2 C, 2 × CO), 126.9 (6 C), 127.8 (12 C), 128.8 (12 C), 144.6 (6 C, ArC).

Hexyl Trityl Ether (1g')

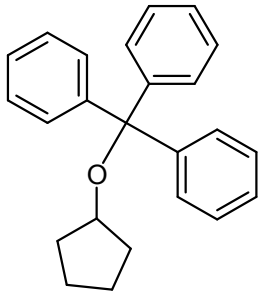


1g'

Following the general procedure, the reaction of hexanol (0.62 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (15 mL) at r.t. gave **1g'** as a Colourless oil.

- **Yield**= 62% (1.18 g).
- **IR (KBr):** 3166, 3058, 3028, 1593, 1488 (HC=C), 1080, 1068 cm^{-1} (CO).
- **^{1}HNMR: (250 MHz, $CDCl_3$):** δ = 1.22 (d, 3 H, *J* = 6.1 Hz, Me), 1.53–1.81 [m, 6 H, Me (CH_2)$_3$], 3.08–3.17 (m, 2 H, CH_2 CH_2O), 3.76–3.88 (m, 2 H, CH_2O), 7.23–7.37 (m, 9 H, ArH), 7.42–7.50 (m, 6 H, ArH).
- **^{13}CNMR: (62.5 MHz, $CDCl_3$):** δ = 23.6 (Me), 26.5 (CH_2Me), 36.4 (2×CH_2), 63.8 (CH_2CH_2O), 68.0 (CH_2O), 86.7 (CO), 127.0 (3C), 127.8 (6 C), 128.7 (6 C), 144.3 (ArC).

Cyclopentyl Trityl Ether (1h')

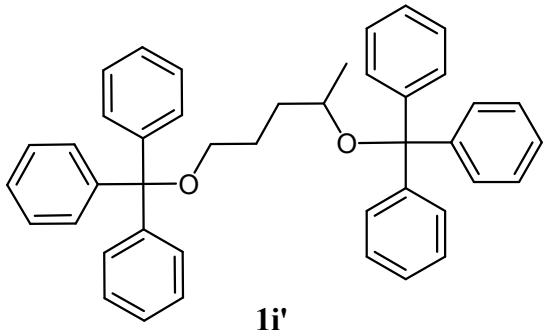


1h'

Following the general procedure, the reaction of cyclopentanol (0.45 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino)pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1h'** as a transparent crystal.

- **Yield**= 62% (0.82g).
- **Mp**= 84°C.
- **IR (KBr):** 3055, 3028, 1596, 1485 (HC=C), 1045 cm^{-1} (CO).
- **^{1}HNMR: (250 MHz, $CDCl_3$):** δ = 0.93–1.18 (m, 6 H, 3 × CH_2), 1.33–1.65 (m, 2 H, CH_2), 4.06–4.10 (m, 1 H, CHO), 7.25–7.37 (m, 9 H, ArH), 7.55–7.58 (m, 6 H, ArH).
- **^{13}CNMR: (62.5 MHz, $CDCl_3$):** δ = 23.8 (3 C), 33.6 (1 C) (4 × CH_2), 72.8 (CHO), 86.9 (CO), 126.8 (3 C), 127.3 (6 C), 129.0 (6 C), 145.5 (3 C, ArC).

1,4-Di(trityloxy)pentane(1i')

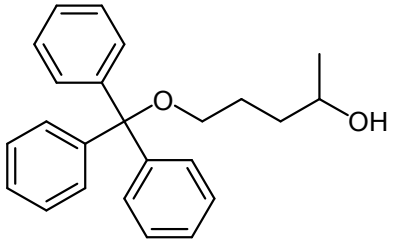


1i'

Following the general procedure, the reaction of 1, 4 pentadiol (0.53 ml, 5 mmol), trityl chloride (3 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**= 55% (1.62g).
- **Mp**= 122°C.
- **IR (KBr):** 3083, 3052, 3022, 1598, 1500 (HC=C), 1081, 1075 cm^{-1} (CO).
- **^{1}HNMR: (250 MHz, $CDCl_3$):** δ = 0.93 (d, 3 H, *J* = 6.07 Hz, Me), 1.13–1.30 (m, 2 H, CH_2CH_2), 1.46–1.70 (m, 2 H, CH_2CHO), 2.80–2.97 (m, 2 H, CH_2O), 3.57–3.60 (m, 1 H, CHO), 7.19–7.35 (m, 18 H, ArH), 7.41–7.45 (m, 12 H, ArH).
- **^{13}CNMR: (62.5 MHz, $CDCl_3$):** δ = 21.2 (Me), 25.4 (CH_2CH_2), 34.0 (CH_2CHO), 64.0 (CH_2O), 69.8 (CHO), 86.3 (CO), 86.5 (CO), 120.0 (3 C), 126.9 (3 C), 127.7 (6 C), 127.8 (6 C), 128.8 (6 C), 129.0 (6 C), 144.6 (3 C), 145.6 (3 C, ArC).

5-Trityloxy-2-pentanol (1j')

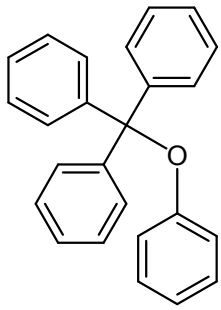


1j'

Following the general procedure, the reaction of 1, 4 pentadiol l (0.45 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1j'** as Colourless oil.

- **Yield**= 62% (0.82g).
- **Mp**= 84°C.
- **IR (KBr):** 3024, 2950, 2862, 1593, 1488 (HC=C), 1045 cm^{-1} (CO).
- **^{1}HNMR: (250 MHz, DMSO-d_6):** δ =.0.87–1.52 [m, 8 H, Me, 2×CH_2, and OH], 2.51 (m, 2 H, CH_2OTr), 3. 93 (m, 1 H, CHOH), 7.23–7.37 (m, 9 H, ArH), 7.37–7.44 (m, 6 H, ArH).
- **^{13}CNMR: (62.5 MHz, DMSO-d_6):** δ = .1 (Me), 33.0 (2 C, 2 × CH_2), 66.2 (CH_2O), 75.8 (CHOH), 86.3 (CO), 126.9 (3 C), 127.8 (6 C), 128.4 (6 C), 145.0 (3 C, ArC).

Phenyl trityl ether (1k')

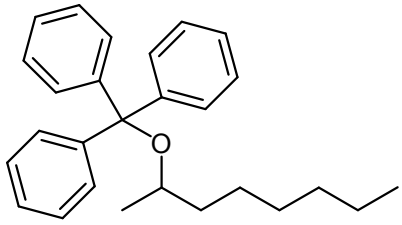


1k'

Following the general procedure, the reaction of phenol (0.47 g, 5 mmol),hydroxyl de potassium (0.49, 8.8ml) in mixture of MeOH (5 ml) and THF (5ml) trityl chloride (1.55 g, 5.5 mmol), and 4-(dimethylamino)pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5mL) at r.t. gave **1k'** as a Colourless oil.

- **Yield**= 38% (1.62g).
- **IR (KBr):** 3166, 3055, 2947, 1593, 1485 (HC=C), 1076 cm^{-1} (CO).
- **^{1}HNMR: (250 MHz, $CDCl_3$):** δ = 6.63-6.79 (dd, 3 H), 7.00 (t, 2H, *J* = 8.4 Hz), 7.22–7.31 (m, 9 H, ArH), 7.33– 7.44 (m, 6 H, ArH).
- **^{13}CNMR: (62.5 MHz, $CDCl_3$):** δ = 86.5 (CO), 122.1 (2 C), 122.4 (2 C), 128.2 (3 C), 128.6 (6 C), 129.3 (6 C), 129.8 (1 C), 145.3 (3 C, ArC), 146.6 (1 C, ArC).

2-Trityloxyoctane (1l')



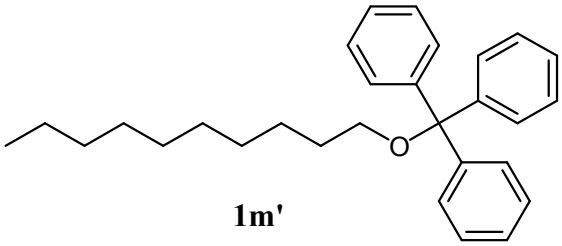
1l'

Following the general procedure, the reaction of 2-octanol (0.45 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1l'** as a Colourless oil.

- **Yield**= 78% (1.60g).
- **IR (KBr):** 3055, 2925, 1598, 1489 (HC=C), 1075, 1026 cm^{-1} (CO).

- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ =. 0.83 (t, 3 H, *J* = 8 Hz, C*H*$_3$CH$_2$), 0.86 (d, 3 H, *J* = 4 Hz, CH_3CO), 1.05–1.23 [m, 10 H, $(CH_2)_5$], 3.51–3.58 (m, 1H, CHO), 7.19–7.30 (m, 9 H, ArH), 7.49–7.52 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ = 14.2 (*C*H$_3$CH$_2$), 21.3 (*C*H$_3$CO), 22.7 (CH_2), 25.0 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 37.6 (CH_2), 70.2 (CHO), 86.5 (CO), 126.8 (3 C), 127.7 (6 C), 129.1 (6 C), 145.7 (3 C, ArC).

***n*-Decyl Trityl Ether (1m')**



1m'

Following the general procedure, the reaction of decanol (0.45 ml, 5 mmol), trityl chloride (1.55 g, 5.5 mmol), Et_3N (1.25 mL, 8.8 mmol) and 4-(dimethylamino) pyridine (46 mg, 0.2 mmol) in CH_2Cl_2 (7.5 mL) at r.t. gave **1m'** as a Colourless oil.

- **Yield**= 76% (1.85g).
- **IR (KBr):** 3085, 3057, 3031, 1596, 1489 (HC=C), 1086, 1068 cm^{-1} (CO).
- **^{1}HNMR: (400 MHz, $CDCl_3$):** δ = 0.87 (t, 3 H, *J* = 8 Hz, Me), 1.24–1.36 [m, 14 H, Me (C*H*$_2$)$_7$], 1.51–1.65 (m, 2 H, CH_2CO), 3.03 (t, 2 H, *J* = 6.7 Hz, CH_2O), 7.19–7.31 (m, 9 H, ArH), 7.43 –7.46 (m, 6 H, ArH).
- **^{13}CNMR: (100 MHz, $CDCl_3$):** δ =14.2 (Me), 22.8, 26.4, 29.4, 29.6, 29.7 (2 C), 30.2, 32.0 [Me (*C*H$_2$)$_8$], 63.8 (CH_2O), 86.3 (CO), 126.9 (3 C), 127.8 (6 C), 128.8 (6 C), 144.6 (3 C, ArC).

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[5] Peptide and nucleotide chemistry are, however, same exceptions. The most advantageous combination of protecting groups and strategies for the synthesis of oligopeptides and oligonucleotides have often been commented on in the relevant publications and textbooks because the types of functions requiring protection in these classes of compounds is limited and the number of reaction to be carried out is restricted the problem is more easily defined in this area of synthesis than in the stereoselective synthesis of a complex natural product. For discussions about protecting group strategy in peptide synthesis, see for example: a) Rudinger, J. *Pure Appl. Chem* **1963**, 355. b) Reetz, M. T.; Drewes, M. W.; Chmitz, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.

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CHAPTER III

Removal of pivaloyl tetrazoles with arene catalyzed lithiation and trityl ethers via indium and lithium chloride

III.1. Introduction

The protection and deprotection in organic functions play an important role in organic synthesis multi-steps. The great significance of selective introduction and removal of protecting groups in organic synthesis is well established. The success of the methodology largely depends on the stability of the protecting groups towards different acidic or non-acidic reagents and how easily they can be installed and removed. Protection of hydroxyl groups into trityl ethers and tetrazoles groups into pivaloyltetrazoles as well as their cleavage to the corresponding alcohols and amines compounds is well recognized as a useful method especially during the last few years.

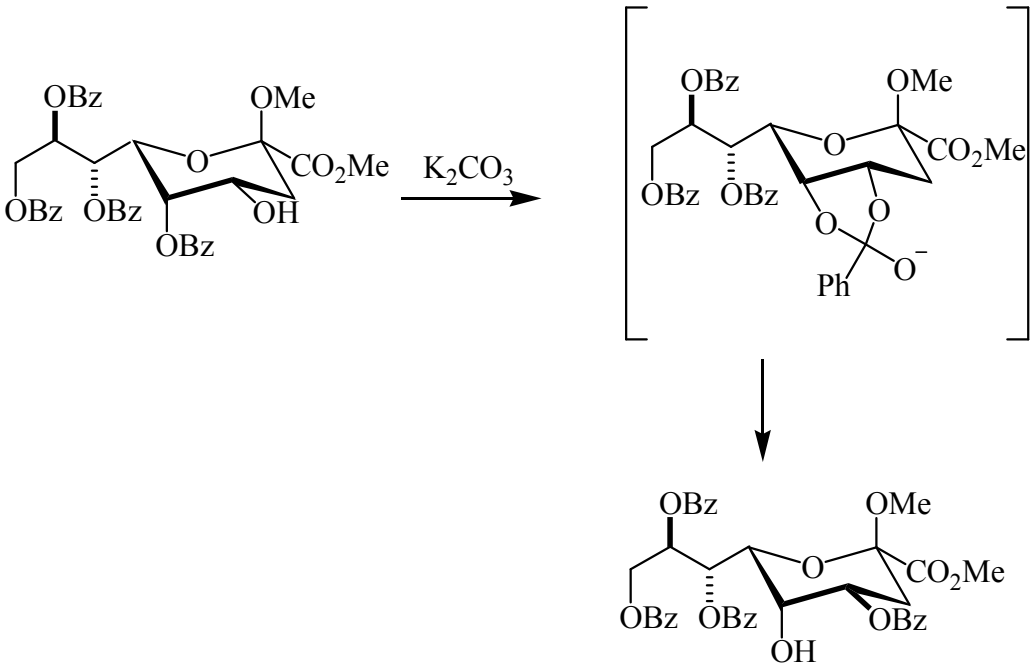
However, the various conventional methods of introduction and cleavage of these groups reported in the literature have disadvantages such as manipulation under stringent conditions and generation of byproducts and that the selectivity is unfulfilled.

There are many methods for the conversion of trityl ethers and pivaloyltetrazoles into the corresponding alcohols and amines compounds, but a mild and neutral method that would effect the selective cleavage in the presence of other sensitive functional groups is still desirable. Moreover, to our knowledge, selective deprotection using metals is extremely reported in the literature as very mild, efficient and highly selective method for the removal of C-N and C-O bonds.

III.2. Deprotection methods

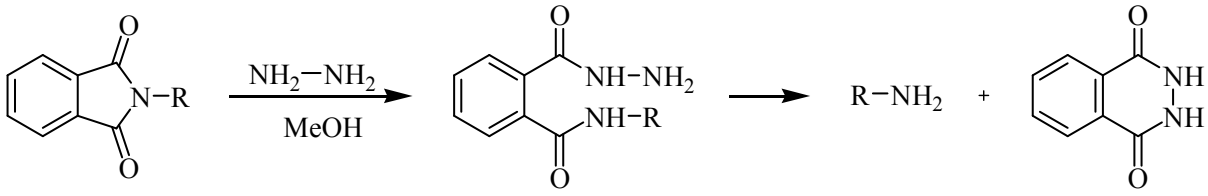
III.2.1. Protecting groups cleaved by basic solvolysis

The acyl derivatives of thiols, hydroxyls, (alcohols and carboxyls), and amino groups are amongst the oldest protecting groups still in standard use today. They are all easily prepared by standard methods from activated carboxylic acids but the relative ease hydrolysis with base varies widely. Thiol esters are too susceptible to nucleophilic attack to offer sustained protection for the thiol group[1] but acetate, benzoate, and pivalate esters offer protection over a wide enough range of conditions to be synthetically useful. Acetates and benzoates especially are prized because they can be removed with potassium carbonate or ammonia in methanol. Furthermore, the ease of cleavage can be tuned by taking advantage of steric effects and electronic effects (Scheme III.1).



Scheme III.1

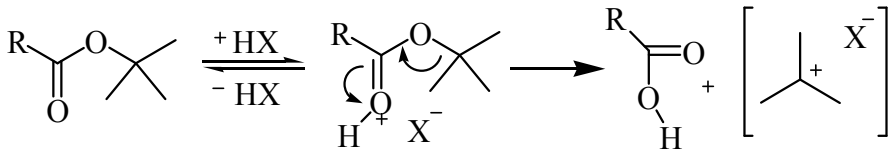
Phthalimides are a special case because their cleavage by hydrazine in methanol or ethanol is not strictly a solvolysis reaction. The reason for using hydrazine is apparent in the mechanism Outlined in (Scheme III.2).



Scheme III.2

III.2.2. Protecting groups cleaved by acid

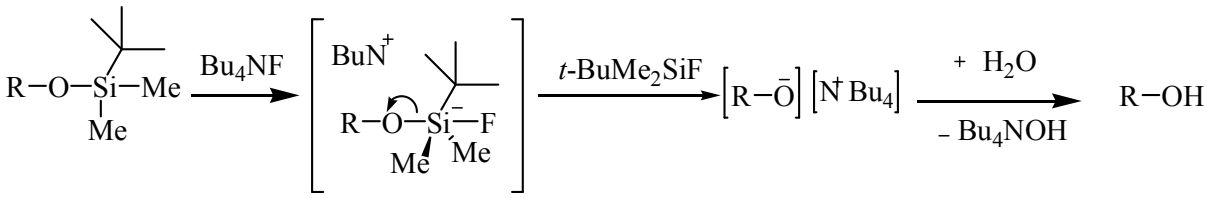
The acid-labile protecting groups are the most difficult to classify because virtually all protecting groups can be cleaved by acid albeit under conditions that may be brutal. Nevertheless, in the synthesis of polyfunctional molecules, certain protecting groups have come to be valued custom and practice for their lability under acidic conditions and these groups are sufficiently tolerant of protecting groups to be useful (Scheme III.3).



Scheme III.3

III.2.3. Protecting groups cleaved by fluoride ions

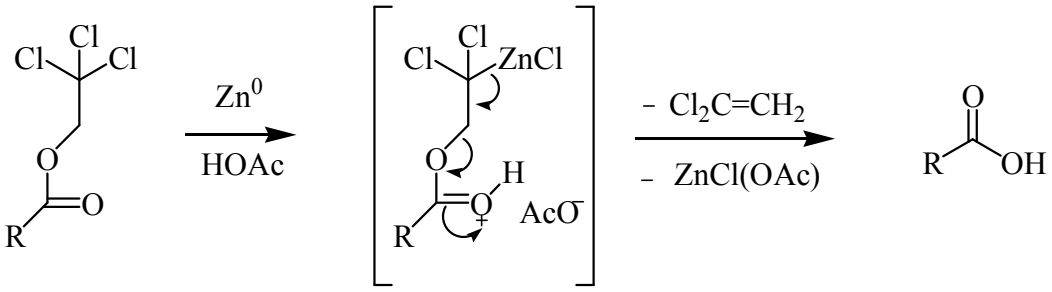
All of the common trialkylsilyl ether protecting groups are labile to acid or base hydrolysis to widely varying degrees and their stability and ease of deprotection can be finely tuned by adjusting the substitution on silicon. However, it is the high thermodynamic of silicone for fluorine (Si-F bond strength =810 KJ mol^{-1} vs 530 810 KJ mol^{-1} for Si-O bond) which is especially advantageous in the deprotection since the usual reagents tetrabutylammonium-fluoride (TBAF) in THF or HF in acetonitrile. Deprotection with fluoride proceeds via formation a pentavalent fluorosiliconate intermediate (Scheme III.4).



Scheme III.4

III.2.4. Protecting groups cleaved by reductive elimination

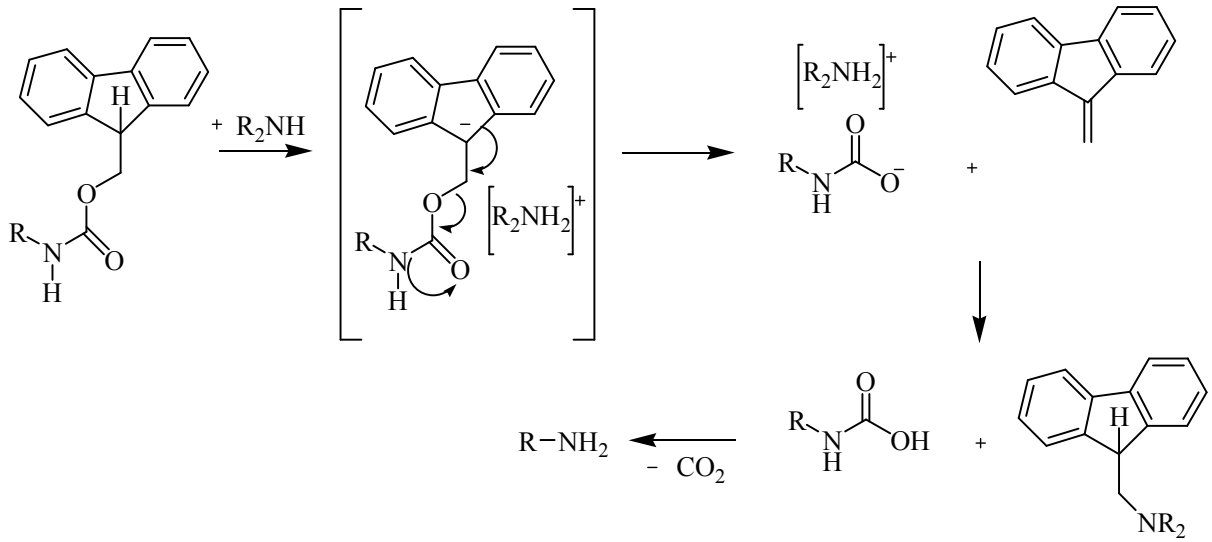
The second reaction which is akin to a β-elimination involves reductive elimination of 2,2,2-trichloroethyl ester on treatment with zinc in acetic acid or zinc copper couple in DMF to give 1,1-dichloroethylene (Scheme III.5).[2]



Scheme III.5

III.2.5. Protecting groups cleaved by β-elimination reactions

An important example involves the mild base-catalysed deprotection of 9-fluoroenylmetho-xycarbonyl (FMOC) groups[3] resulting in the liberation of amino groups. The rapid deprotonetion of the fluorine group (pKa=23), which is greatly facitilated by the aromatic nature of the resultant dibenzocyclopentadienide anion, is accomplished with piperidine or morpholine in DMF. In a subsequent slower step, elimination generates dibenzofulvene and carbamate residue which then decomposes with loss of carbone dioxide to release free amine (Scheme III.6).

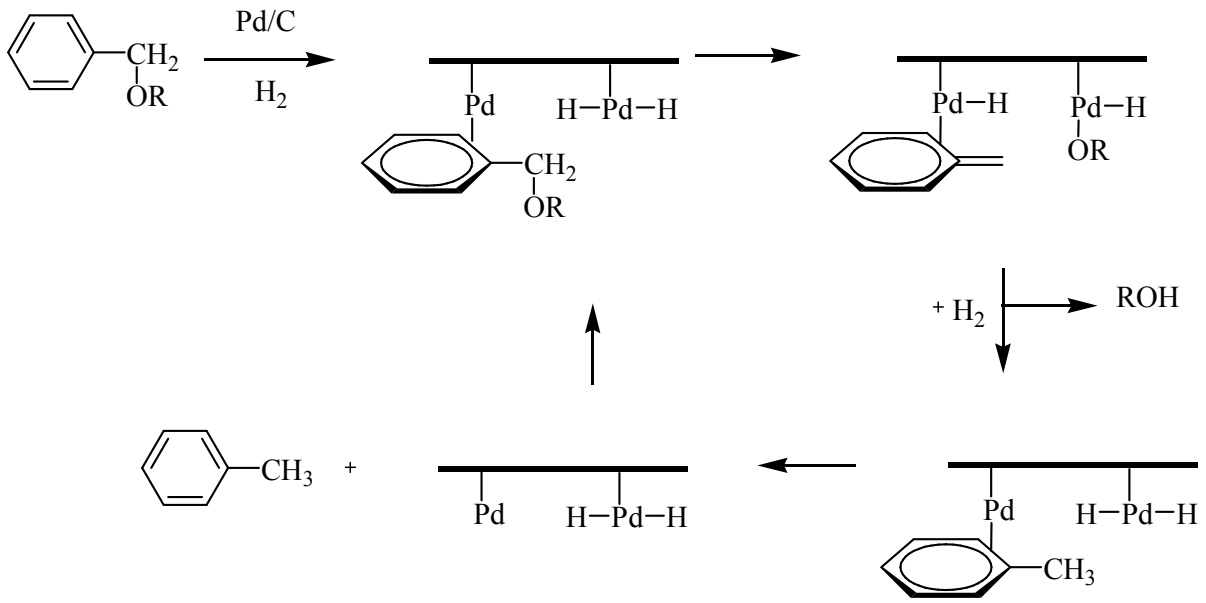


Scheme III.6

III.2.6. Protecting groups cleaved by hydrogenolysis

An excellent method for cleaving benzylic ethers, esters, carbamates, and amines uses hydrogen in the presence of transition metal catalyst such as Pd. Alternatively a process known as catalytic transefert hydrogenation can be employed which uses 1,4-cyclohexadiene, cyclohexene, formic acid or ammonium formate as source of hydrogen.[4] The method is exceptionally mild and compatible with most functional groups devoid of unsaturation. A

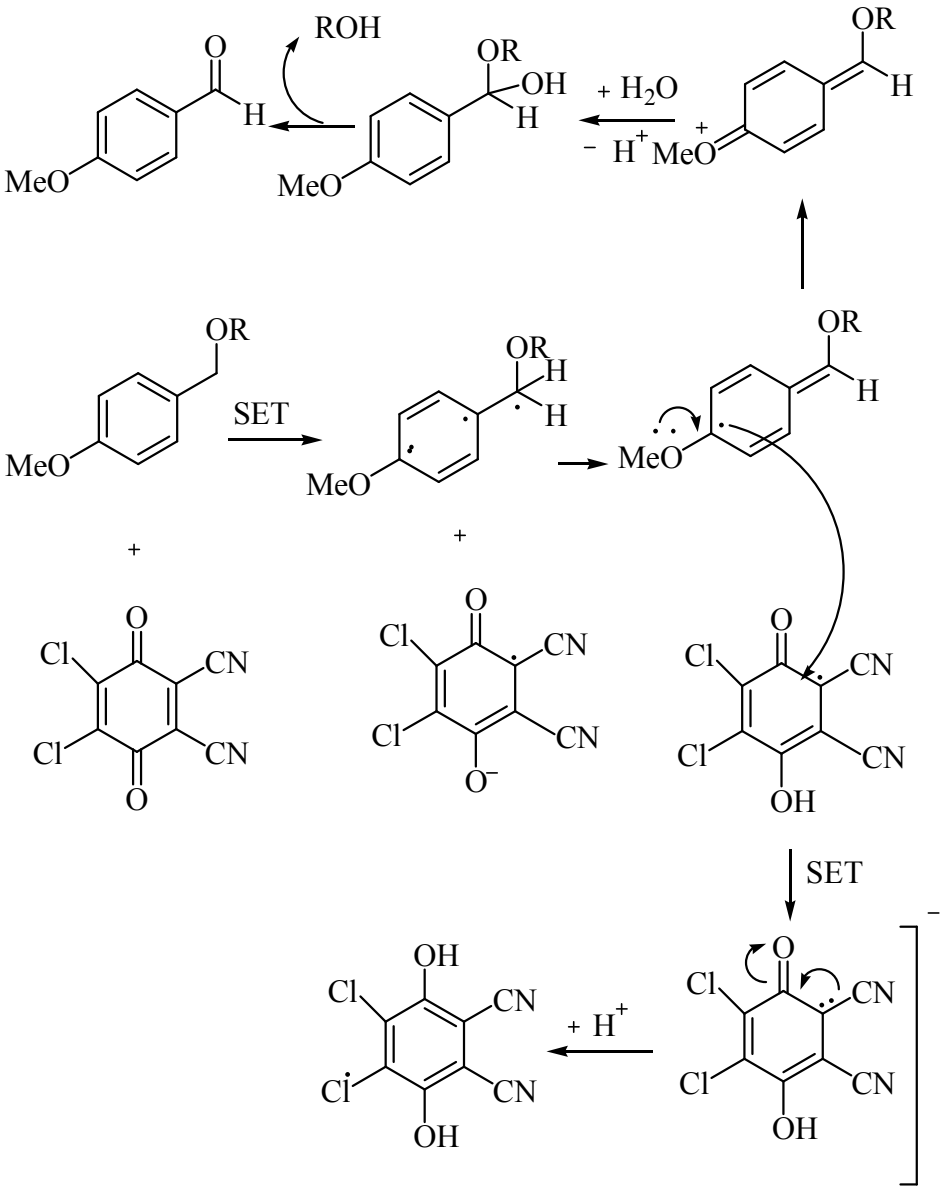
notional mechanism for the hydrogenolysis of benzyl derivatives on a solid-supported palladium catalyst is given in (Scheme III.7).



Scheme III.7

III.2.7. Protecting groups cleaved by oxidation

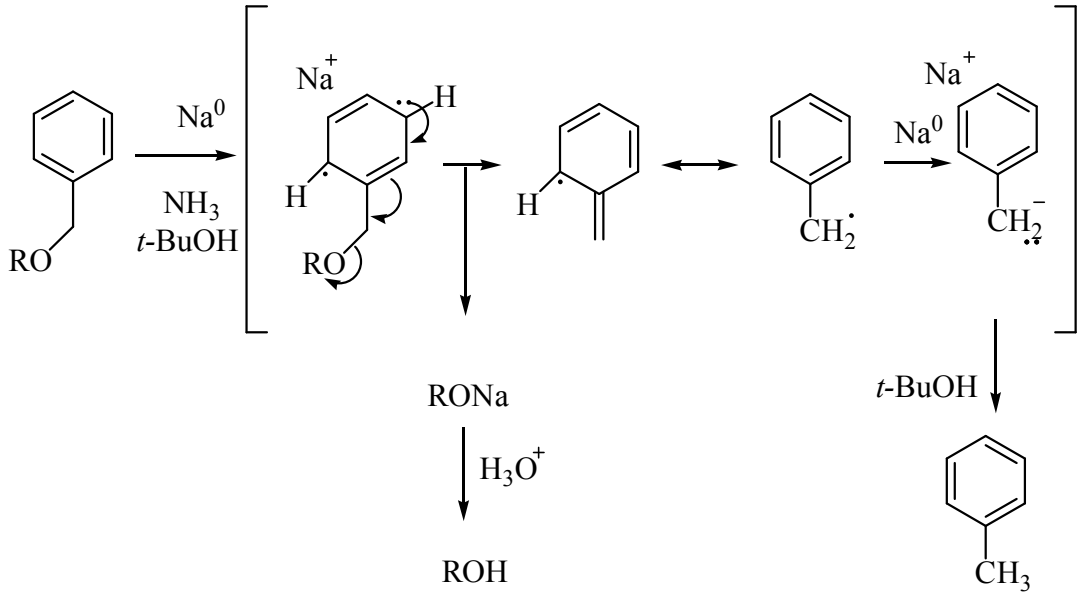
Oxidative methods for removing protecting groups are few in number but significant in impact. *P*-Methoxy and 3,4-dimethoxybenzyl ethers are conspicuous members of the repertoire of standard protecting groups because they undergo easy single electron transfer (SET) to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to generate an oxonium ion which can be captured by water (Scheme III.8).



Scheme III.8

III.2.8. Protecting groups cleaved by disssloving metal reduction

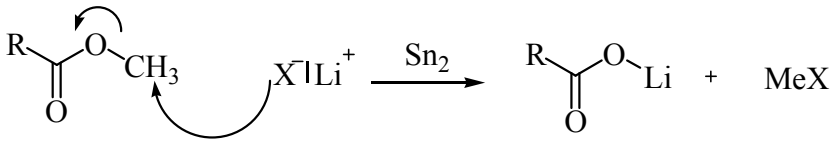
Sodium or lithium in liquid ammonia cleaves benzylic ethers or esters in the presence of proton source to provide pentadienyl anion which expels an alkoxide or carboxylate leaving group. An aqueous acidic workup returns the carboxylic acid or alcohol and toluene. Many functional groups are unable to survive such powerful reducing conditions (Scheme III.9).



Scheme III.9

III.2.9. Protecting groups cleaved by nucleophilic substitution

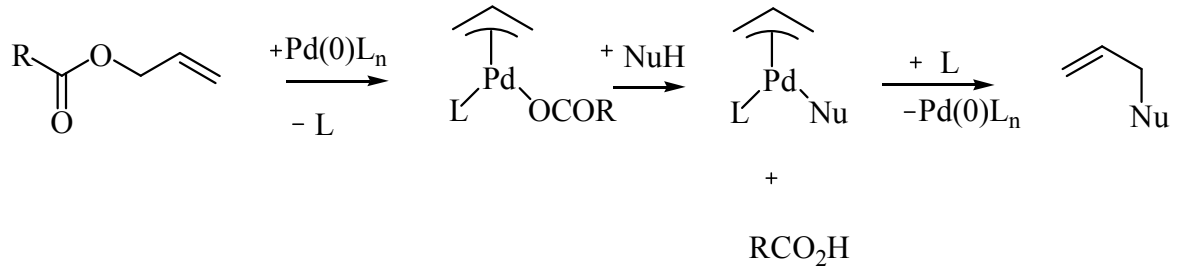
The resonance stabilisation of phenolate and carboxylate anions is just sufficient for them to serve as leaving groups in a classical bimolecular nucleophilic substitution (Scheme III.10) as deprotection tactic; the reaction has comparatively narrow scope being limited to the scission of O-Me and O-Et bonds. Typical nucluophiles include chloride, iodide, cyanide, and phenylthiolate in dipolar aprotic solvents at elevated temperature.



Scheme III.10

III.2.10. Protecting groups cleaved by transition metal catalysis

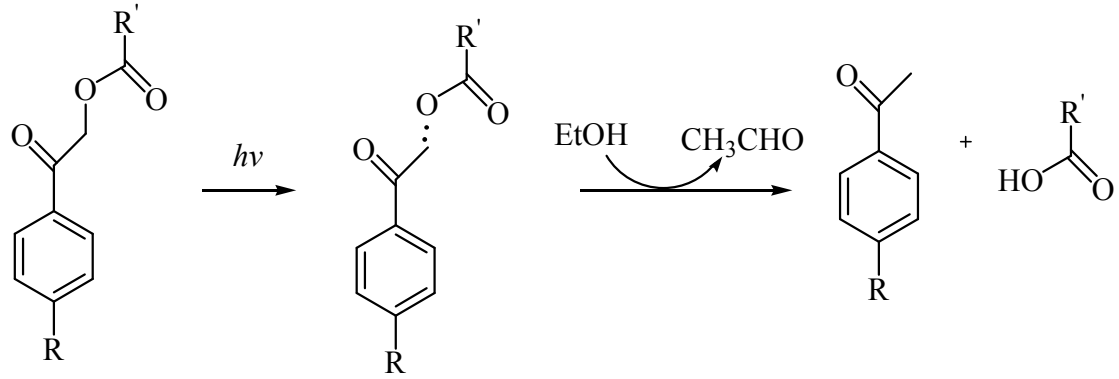
The resonance stabilisation of carboxylate and carbamates anions activates allyl esters, carbonates, carbamates to nucleophilic attack by palladium (O) catalysts to afford π-allylpalladium complexes which can be then trapped by mild nucleophiles such as morpholine, dimedone or barbituric acid as depicted in (Scheme III.11).



Scheme III.11

III.2.11. Protecting groups cleaved by light

Photocleavage of phenacyl derivatives was first reported by Shechan and Umezawa in 1973. In the contrast to the 2-nitrobenzyl protecting groups, choice of solvent is important because the solvent acts as hydrogen donor. Typical solvents include ethanol, dioxane, and benzene containing cumene as hydrogene donor (Scheme III.12).[5]



Scheme III.12

III.2.12. Protecting groups cleaved by enzymes

The multifunctionality of the peptide-nucleotide conjugates requires the application of a variety of orthogonally stable amino, carboxyl, phosphate, and hydroxyl groups.Fully protected serine/threonine nucleopeptides are both acid and base labile. The conditions of the enzyme--mediated selective deprotections are so mild that neither depurination (an acid-catalysed process) nor β-elemination (a base-catalysed process) are observed.

III.3. Organometallic compounds: historic summary

Organometallic compound are compounds that have a carbon-metal bond. They lie at the place where Organic and Inorganic Chemistry meet. As an example, sodium acetylide ($NaC{\equiv}CH$) has an ionic bond between carbon and sodium. But just because a compound contains both a metal and carbon isn't enough to classify it as organometallic. Like sodium acetylide, sodium methoxide ($NaOCH_3$) is an ionic compound. Unlike sodium acetylide, however, the negative charge in sodium methoxide resides on oxygen, not on carbon.

The properties of organometallic compounds are different from those of the other classes of organic compounds. The most important is the fact that many organometallic compounds are powerful sources of nucleophilic carbon, something that make them especially valuable to the synthetic organic chemistry.

Some important dates during the development of organometallic compounds are the following.

- 1760 Paris, Cadet works on inks based on Co salts. Prepared from cobalt minerals. .
- 1827 Zeise prepared the first olefin complex: $Na[PtCl_3C_2H_4]$ (Zeise's salt)
- 1849 Frankland prepared diethylzinc.
- 1863 Fridel and Crafts prepared organochlorosilanes
- 1899 Grignard reagents were prepared for the first time
- 1917 Schlenk prepared Li alkyls via transmetallation from R_2Hg
- 1930 Ziegler and Gilman simplified organolithium preparation, using ether cleavage and alkyl halide metallation, respectively.
- 1953 Wittig discovered the reaction bearing his name
- 1955 Ziegler and Natta developed olefin polymerisation at low temperature at low pressure using a mixed metal catalyst (transition metal halide / AlR_3)
- 1956 Brown developed hydroboration
- 1965 Wilkinson and Coffey presented $(PPh_3)_3RhCl$ as a homogeneous catalyst for the hydrogenation of alkenes
- 1981 R. West: $(1,3,5\text{-}Me_3C_6H_2)_4Si_2$, first stable compound with a Si=Si double bond.

- 1981 R. Hoffmann and K. Fukui: semiempirical MO-concepts in a unified discussion of structure and reactivity of inorganic and organometallic molecules.

The decade from 1982 to 1992 was an eventful and exciting period in the history of alkali metal organometallic compounds. That was a period in which new structural principles and theoretical interpretations gave fresh insights into the factors affecting both the modes of aggregation and solvation of such alkali metal complexes and the nature of bonding occurring within them. These advances have constituted a genuine maturing of an area which owes its roots to the early pioneering work of Schlenk in 1914. The First International Conference on the Chemistry of Alkali and the Alkaline Earth Metals in 1994 (Cambridge, UK) illustrated the sheer diversity and enormous quantity of work being carried out in the area of alkali metal organometallic throughout the world.[6]

III.4. Arene catalysed lithiation

Carbon-carbon bond formation is one of the most important reactions in synthetic organic chemistry, as it is the mechanism by which the backbone of any organic molecule is formed. To that end, organolithium compounds, as a source of carbanionic components, play a pivotal role by reacting with carbon electrophiles.[7,8] Different methods are used to generate an organolithium intermediate, including: (i) deprotonation of compounds bearing activated hydrogen atoms, using a lithium base (a lithium amide or an organolithium reagent); (ii) halogen/lithium exchange, mainly starting from brominated or iodinated materials and using either lithium metal or an organolithium compound. Other procedures, such as carbon-heteroatom (heteroatom: oxygen, nitrogen, or sulfur) bond reductive cleavage, the addition of lithium or an organolithium compound to carbon carbon multiple bonds, tin- or mercury-lithium transmetalations, or the Shapiro reaction, are far less commonly employed . However, the use of chlorinated starting materials and lithium metal may offer the best combination for preparing an organolithium considering the stability and price of the substrates and the source of the metal. However, chlorine/lithium exchange is problematic, especially at low temperatures, due to the low reactivity of the carbon-chlorine bond; therefore, it is usually necessary to activate the metal in order to obtain the corresponding lithiation. Among the different procedures to activate lithium, arene-promoted lithiation[7] is probably the most effective from a preparative point of view, as it can be performed either stoichiometrically[9] or catalytically.[10] In the first case, an arene [naphthalene and 4,4'-di-*tert*-butylbiphenyl (DTBB)

being the most commonly used] and lithium metal are dissolved in equimolecular amounts in tetrahydrofuran and used in solution.[11] In the catalytic version, a substoichiometric amount (<10%) of the arene is used in the presence of an excess of lithium in the same solvent.[12,13] The catalytic reaction has been shown to be more effective than the stoichiometric one, the probable reason being the participation in the first case of an arene dianion instead of the corresponding arene radical-anion, widely accepted as the electron-transfer agent for the stoichiometric reaction. The arene dianion is a much more potent electron-transfer agent than the corresponding radical anion, transfer ring electrons to the substrate in a single-electron transfer (SET) process.[14,15]

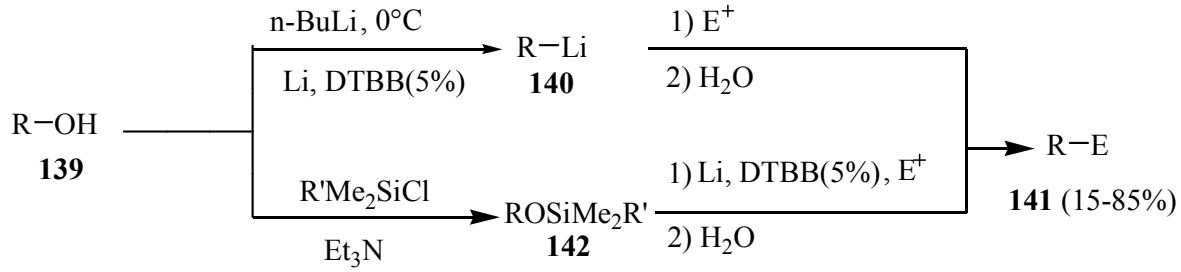
Arene-catalyzed lithiation has been successfully used in the following reactions: (i) the preparation of simple organolithium compounds starting from non-halogenated precursors (alcohols, ethers, silyl ethers, thioethers, sulfoxides and sulfones, sulfonates, sulfonamides, carbonates, carbamates, and ureas);[16] (ii) preparation of very sensitive functionalized organolithium compounds by chlorine/lithium exchange, sulfur/lithium exchange[17] or reductive ring opening of heterocycles;[18,19] (iii) generation of dilithiated synthons[20] ; and (iv)activation of transition metals.[21,22]

III.4.1. Organolithium compounds from Non-Halogenated Materials

III-4-1-1-Reductive carbon-oxygene cleavage

Allylic or benzylique alcohols **139** are transformed into the corresponding organolithium compounds **140** by successive deprotonation with *n*-butyllithium and DTBB-catalysed lithiation: final reaction with different electrophile gives, after hydrolysis, the expected products **141**.

Alternatively, the same reaction products are available starting from the corresponding *O*-silyl derivatives **142**, in this case the catalysed lithiation being performed in the presence of the electrophile (Barbier- type process) **(**Scheme III.13).[23] Recently, this methodology has been applied to the synthesis of olivetol and related compounds.[24]

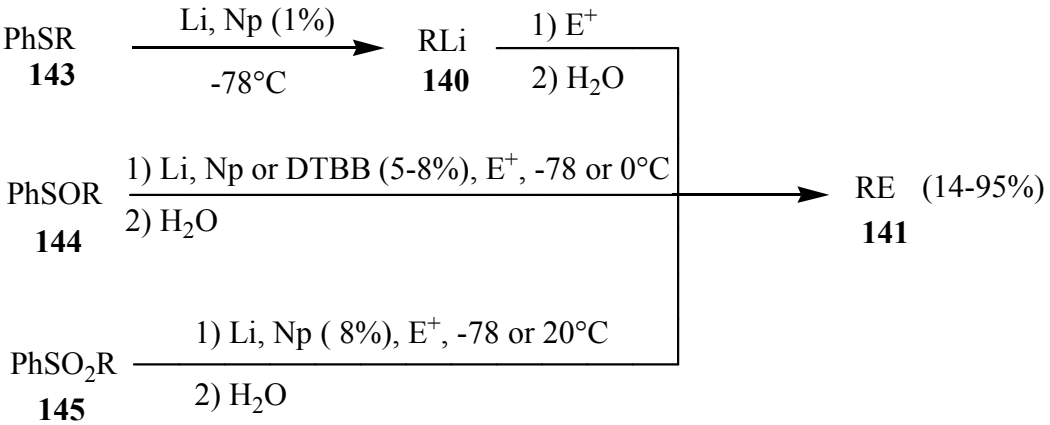


R= CH_2=$CHCH_2$, $CMeCH_2$,CHCHMe, $PhCH_2$, geranyl, PhCHMe
R'= Me, Ph
E^+= Me_3SiCl, *i*PrCHO, PhCHO, Et_2CO

Scheme III.13

III.4.1.2. Reductive Carbon-sulfur cleavage

Phenyl sulfides **143** react with lithium powder at low temperature in the presence of a catalytic amount of naphthalene to give the expected alkyllithium compounds **140**, which behave as usual towards electrophiles giving products **141**.[25] This reaction has been recently applied to the synthesis of alfa –silylated organolithium intermediates. When the same procedure is used with phenyl sulfoxides **144**[26] or phenyl sulphone **145**[27] it is necessary to work under Barbier-type reaction conditions in order to avoid decomposition of the *in situ* generated organolithi-ium compound even at low temperatures (Scheme III.14).

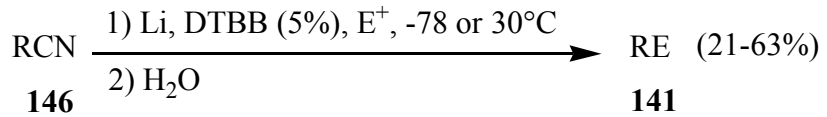


R= Me, Et, CH_2=$CHCH_2$, Pr, $PhCH_2$
E^+= H_2O, Me_3SiCl, PrCHO, PhCHO, Et_2CO, $CH_2(CH_2)_4CO$, Ph_2CO

Scheme III.14

III.4.1.3. Reductive carbon-carbon cleavage

Nitriles **146** have been decynated reductively using a DTTBB-catalysed lithiation and working under Barbier-type reaction conditions at low temperatures, 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 cyno group) (Scheme III.15).[28]

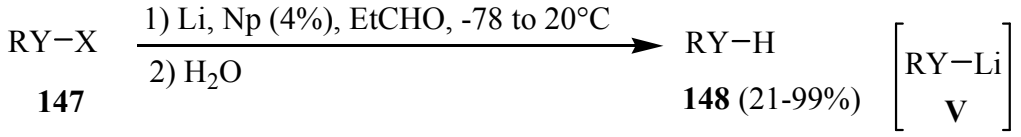


R= Me, Et, c-C_3H_5, Ph, $PhCH_2$
E^+= Me_3SiCl, PrCHO, PhCHO, *n*-$C_7H_{15}CHO$, Et_2CO, $CH_2(CH_2)_4CO$, Ph_2CO

Scheme III.15

III.4.1.4. Reductive Deprotections

A naphthalene-catalyzed lithiation process has been employed for the reductive deprotection of allyl-, benzyl-, and sulfonyl-substituted alcohols, amines and amides **147** at temperatures ranging from -78 to 25°C (Scheme III.16). 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.

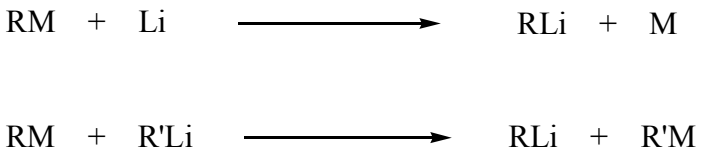


Y= O, NH, NR, NBzl, NCOR, NCOR, NCO_2t-Bu, $NCONiPr_2$
R= Alkyl, CH_2=$CHCH_2$
X= CH_2=$CHCH_2$, Bzl, Ms, Ts

Scheme III.16

III.4.1.5. Transmetallation

This methodology consists on metal exchange between two organometallic compounds. It is especially useful when the previous methods are not easily applicable, as it is the case of the obtention of allyllithium and benzyllithium reagents. The reaction will be developed according to any of the possibilities indicated in (Scheme III.17).[29]



M = Hg, Si, Sn, Pb, Sb, Bi, Cd, Zn, B, Se, Te

Scheme III.17

Among the metals that are indicated in (Scheme III.17), the ones that are used more often are tin and mercury.

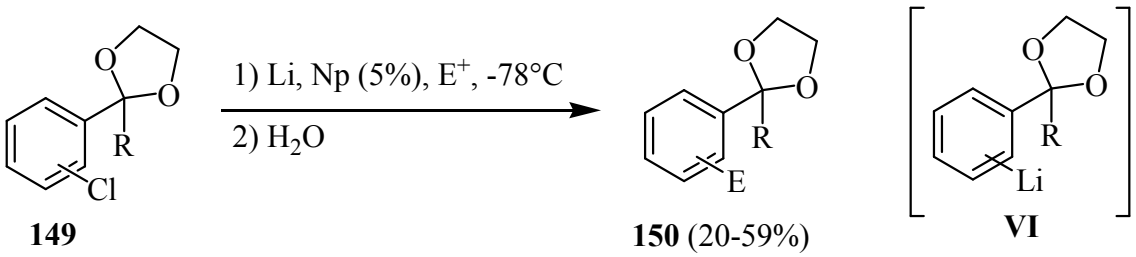
III.4.2. Lithiation of Functionalized Halogenated Materials

Functionalized non stabilized organolithium derivatives 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.4.2.1. Lithiation of Functionalized chlorinated Materials

1-(Benzyldimethylsilyl) naphthalene has been used as an electron shuttle in the lithiation of chlorobenzene and 9- chloroanthracene yielding the expected aryllithium derivatives. 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.

Functionalized halogenated arenes have been submitted to naphthalene-catalyzed lithiations. Thus, lithiation of 2-(chlorophenyl)-1,3-dioxolanes **149** in the presence of carbonyl compounds gives, after hydrolysis, the expected benzylic derivatives **150** with masked carbonyl functionalities, formally *via* the intermediate **VI** (Scheme III.18). 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.



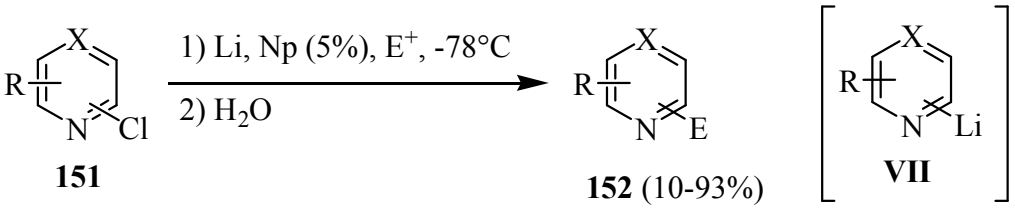
149 **150** (20-59%) **VI**

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

Scheme III.18

Naphthalene-catalyzed lithiation of 2-(4-bromophenyl)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. In this process, the lithiation and subsequent reaction with water proceed without any racemization. Chlorinated azines **151** have been successfully lithiated by means of a naphthalene-catalyzed process. 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-triazines, even those bearing methyl or methoxy substituents (Scheme III.19). When the reaction is carried out in the absence of an arene, a mixture of di-, tri-, and oligoazines is formed

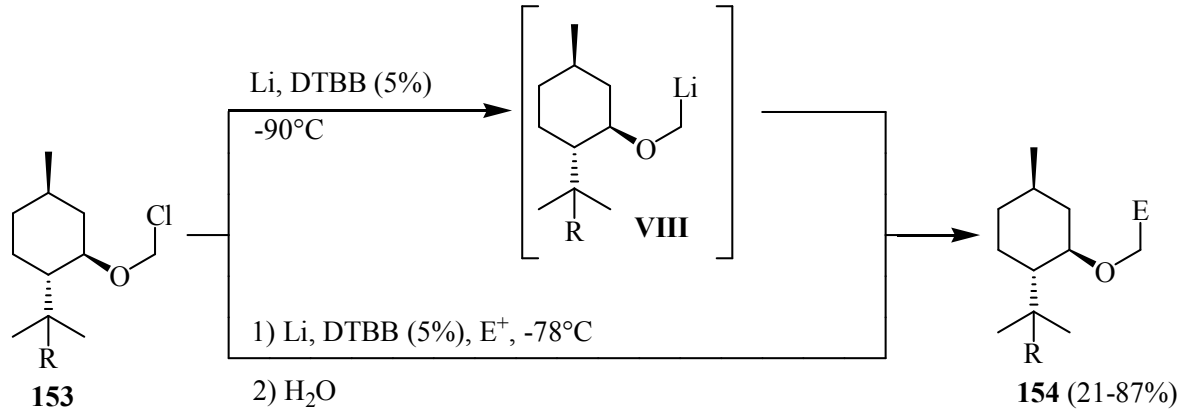
initially, which can play the role of the catalyst for the lithiation reaction, therefore giving a lower yield than with the naphthalene-catalyzed process.



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

Scheme III.19

α-Functionalized organolithium compounds, the socalled ”carbenoids”, have been prepared from several chlorinated materials. Thus, the DTBB-catalyzed lithiation of chiral chloromethyl menthyl ethers **153** at 290°C gives the expected chiral carbenoids **VIII**, which can be trapped by reaction with various electrophiles (Scheme III.20). The same reaction can be performed at 278°C, although the electrophile must be present in order to avoid the corresponding α-elimination. In the case of prostereogenic carbonyl compounds, the diastereomeric ratio never exceeds 65:35.

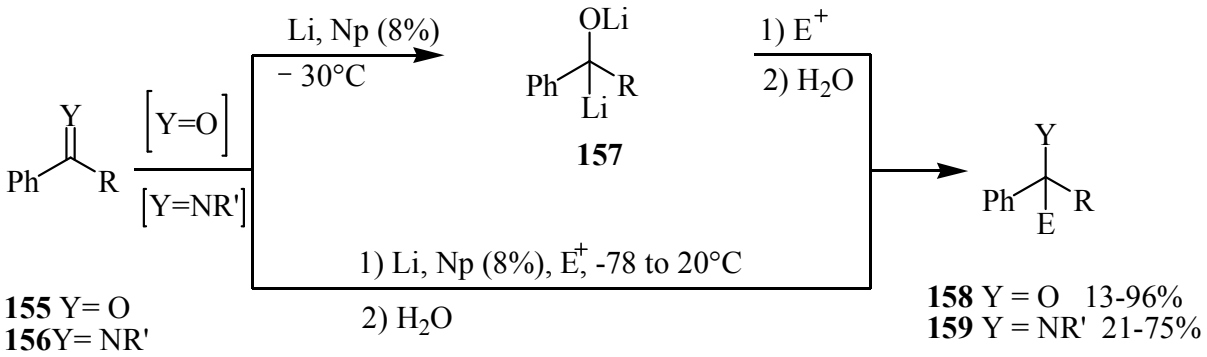


R= H, Ph
E^+= H_2O, D_2O, Me_3SiCl, *t*-BuCHO, PhCHO, Et_2CO, $(CH_2)_4CO$, PhCOMe, Ph_2CO, PhCH=NPh, DMF

Scheme III.20

III.4.2.2. Lithiation of phenones and phenones imines

Treatment of different phenones **155** with lithium and a catalytic amount of naphthalene yields the dianion **157**, which by reaction with several electrophiles gives, after hydrolysis, the corresponding reaction products **158** (SchemeIII.21).[30] When the corresponding imines **156** are used as starting materials the reaction has to be performed at lower temperature and under Barbier-type reaction conditions in order to avoid destruction of the corresponding intermediate of type **157**; after hydrolysis, functionalised amines **159** are prepared.

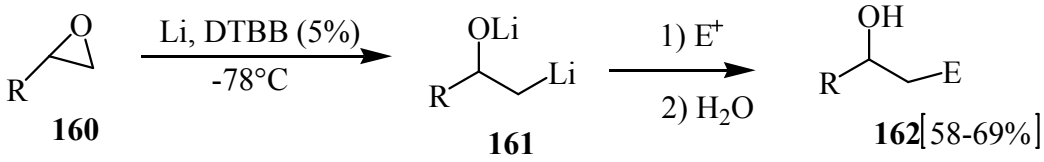


R = H, Me, Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,4-$Me_2C_6H_3$
R' = Me, Ph, c-C_6H_{11}
E^+=MeI, EtBr, *i*-PrCHO, PhCHO, Me_2CO, Et_2CO, $CH_2[CH_2]_3CO$, $CH_2[CH_2]_4CO$, MeCN

Scheme III.21

III.4.2.3. Reductive opening of saturated heterocycles

The reductive opening of epoxides, which may be carried out with a stoichiometric amount of an arene,[31a,b]can also be performed in a catalytic fashion starting from chiral epoxides **160** and using DTBB as the electron-carrier agent. Thus, *via chiral* intermediates **161**, β-functionalised organolithium compounds, enantiomercially pure products **162** may be prepared (Scheme III.22). Nevertheless, when products **162** are mixture of diastereoisomers, they can be easily separated by flash chromatography, so giving both diastereoisomers enantiomerically pure. This is a typical example of enantiomerically pure compouds (EPC) synthesis.[31c] this methodology has been applied to the synthesis of chiral polyols using a protected hydroxy epoxide (**160** with R= $MOMOCH_2$) as starting material.



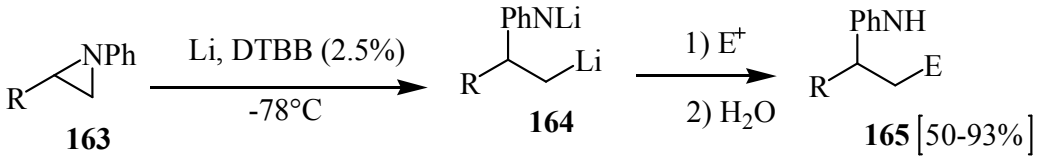
160 **161** **162**[58-69%]

R = Me, $MOMOCH_2$

E^+ = CO_2, *t*-BuCHO, PhCHO, PhCOMe, $CH_2[CH_2]_4CO$

Scheme III.22

In the contrast to the behaviour illustrated in Scheme III.22 for epoxides, aziridines **163** can not be opened by lithium-arene reagent. However, they suffer reductive opening using a catalytic amount of naphtalene, so β-nitrogenated organolithium intermediates **164** may be prepared, which by reaction with different electrophiles give the expected functionalised amines **165**, after the final hydrolysis. A limitation of this reaction is that it works only if a phenyl group is attached somewhere on the aziridine ring. Scheme III.23 shows the reaction with substitued *N*-phenylaziridines **163**. The process has been applied to chiral aziridine [easily prepared from enantiomerically pure (-)-ephedrine], so chiral products of the type **165** are accessible by this methodology.[32]



163 **164** **165** [50-93%]

R = H, Me

E^+ = H_2O, D_2O, Me_2S_2, MeI,

CH_2=$CHCH_2Br$, *t*-BuCHO, PhCHO, Me_2CO, $CH_2[CH_2]_4CO$, $(EtO)_2CO$, CH_2=$CHCO_2Me$

$PhCON[CH_2]_3CH_2$, PhCH=NPh

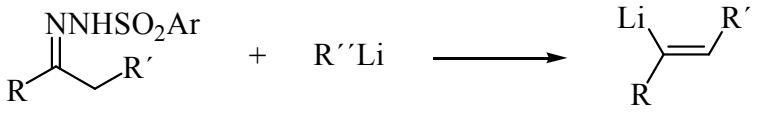
Scheme III.23

III.4.3. Other methods

There are some other methods which are less frequently used.

III.4.3.1. The Shapiro reaction

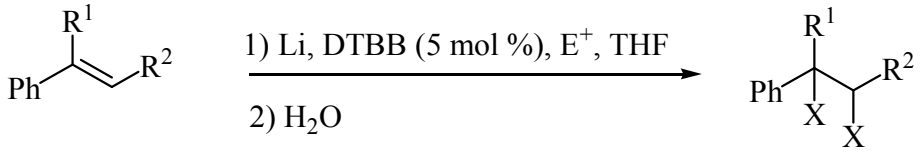
This reaction allows the preparation of sp^2 organolithium compounds. An arylsulfonylhydrazone is treated with an excess of an alkyllithium and provides the corresponding alkenyllithium reagent (Scheme III.24).[33]



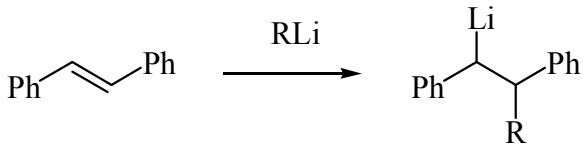
Scheme III.24

III.4.3.2. Addition reactions to a C=C bond

The generation of an organolithium compound has also been achieved by addition of lithium or an organolithium derivative to a carbon-carbon double bond, which must present a group able to stabilize the negative charge that will be developed on carbon (Scheme III.25 and III.26).[34,35]



Scheme III.25



Scheme III.26

III.4.4. Methods of activation of lithium

Several methods of preparation of organolithium compounds use lithium metal. In many occasions, the lithium metal is not active enough and the reaction does not take place or is carried out in an unsatisfactory way (too slow, with a lot of by-products, with little

reproducibility...). These problems can be attributed to the passivation of the metals.[36] Lithium metal reacts with the oxygen and the water present in the atmosphere giving rise to an oxide layer and/or hydroxide layer that covers the surface of the metal and prevents it to react.

It also happens that lithium metal is not active enough when a lithiation must be performed under very mild reaction condition (at low temperature, for example). For all of these reasons, several methods to activate lithium metal have been developed. Some of them are:

1. Activation by reagents and solvents.
2. Rieke's Method.
3. Activation by mechanical methods.
4. Reduction of metallic salts.
5. Techniques of deposition of the steam of the metal.
6. Ultrasound activation.
7. Use of the metal inserted in graphite.
8. Decomposition of organometallic compounds.

III.4.5. Activation of lithium by use of electron carriers

Among all the previously mentioned methods for the activation of lithium, chemists will pay a special attention to the method of activation by means of an arene in substoichiometric amounts. 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 dianionic 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 figure III.1.

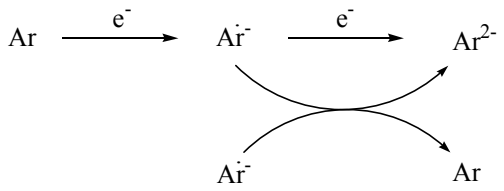


Figure III.1. Activation of lithium by use of electron carriers.

One way to get very active lithium is to dissolve the metal in a stoichiometric amount of an arene,[37] 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. The mechanism of this catalytic lithiation process is shown in figure III.2.

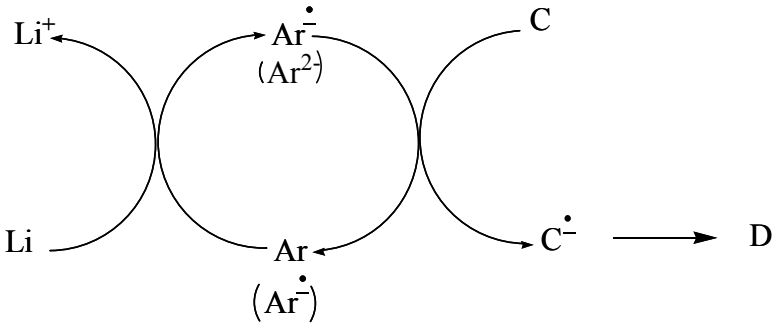


Figure III.2. Mechanism of catalytic lithiation.

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.5. Indium

III.5.1 Introduction

The element indium, named for the luminous indigo line in its spectrum, was discovered in 1863 by German chemist Ferdinand Reich, together with his assistant Theodor Richter. Although indium was discovered very early, and even though the discovery of the Grignard reaction in 1900 prompted scientific investigation into the use of metals in synthetic organic chemistry, organic chemists took little interest in indium or its salts until the early 1990's.

Recently, however, roles of indium in organic synthesis have widened to include a variety of applications. As a result of these efforts, indium and its salts have found use in various functional group transformations and other organic, reactions such as ring-openings of epoxides and aziridines, Mukaiyama-type reactions, intramolecular Prins type cyclizations, Diels–Alder cycloadditions, reductive Friedel–Crafts alkylations and acylations, thioacetali-

zations of aldehydes and ketones, etc. As well as indium halides, organoindium reagents and chiral indium complexes have also been explored, highlighting the synthetic potential of indium and its derivatives in the field of organic chemistry.

The wide application of indium metal is attributable to its diverse physical properties. Unlike most of the other metals, indium is stable to air and moisture, which offers the potential for recovery and recycling of the catalyst.

Whereas the fact that it is non-toxic enables its reactions to be handled very easily. The low first ionization potential of this metal makes it an ideal reagent to participate in SET reactions and its lower heterophilicity makes it an effective catalyst or reagent for C–C bond-formation reactions, due to the fact that it can readily tolerate other functional groups containing N, O, S, etc.[38]

III.5.2. Oxidation state of indium

Development of innovative metal catalysis for selective bond formation is an important task in organic chemistry. General, the oxidation state III is the most stable among elements; however, going down the group, the low-oxidation state I becomes increasingly relevant. The metal indium is appealing for catalysis because indium-based compounds have low toxicity, are selective, and are tolerant toward various functional groups. Indeed, indium (III) reagents are well-established Lewis acids in synthesis, including asymmetric catalysis. In contrast, the chemistry of indium in its low-oxidation state I is underexplored; only sporadic examples of its use as a stoichiometric reagent have been reported.[39]

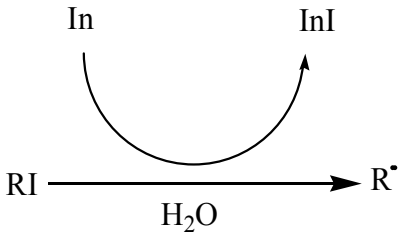
What makes indium metal so attractive is its low first ionization potential, along with its inertness towards water and its lack of toxicity. Table III.1 gives the ionization potential values of some common metals. It turns out that indium has a first ionization potential almost as low as that of the alkali metals, much lower than that of magnesium, tin, or zinc. Moreover, the advantage of indium, compared to aluminium, lies in its low propensity to form oxides in air. Indium powder, when placed in a Schlenk tube for half an hour under gentle stirring and vacuum, gives satisfactory results in terms of reactivity, so that further activation is often unnecessary.[40]

Table III.1: First Ionization Potential of Some Metals.

Metal	Potential (eV)
Lithium	5.39
Sodium	5.12
Magnesium	7.65
Aliminium	5.98
Indium	5.79
Tin	7.43

III.5.3. Indium-mediated Radical Reactions in Aqueous Medium

The utility of indium as a free radical initiator in aqueous media can be directly linked with the first ionisation potential (5.8 eV) and is as low as that of lithium and sodium. Therefore, it is well accepted that indium has the potential to induce radical reactions as a radical initiator via a single electron transfer process. In 1991, Li and Chan reported the use of indium to mediate Barbier-Grignard type reactions in water. The work was designed on the basis of the first ionisation potentials of different elements, in which indium has the lowest first ionisation potential relative to the other metallic elements near it in the periodic table. On the other hand, indium metal is not sensitive to boiling water or alkali and does not form oxides readily in air. Such special properties of indium indicate that it is perhaps a promising metal for aqueous Barbier–Grignard-type reactions. Indeed, it appears that indium is the most reactive (Scheme III.27).



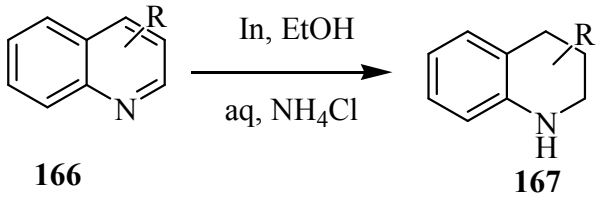
Scheme III.27

III.5.4. The applications of indium in organic synthesis

III.5.4.1. Reduction of benzo-fused nitrogen heterocycles

The selective reduction of the heterocyclic ring in benzo-fused heterocyclic compounds such as quinolines and isoquinolines is an important transformation since the resulting tetrahydro derivatives serve as useful synthetic intermediates. A number of methods have been used for the selective reduction of the heterocyclic ring in benzo-fused heterocyclic compounds such as quinolines and isoquinolines including catalytic hydrogenation or transfer hydrogenation, alkali metals such as sodium or lithium, diborane,[41] Given that indium can replace alkali metals in the reductive coupling of imines.

The reduction of a series of quinolines was carried out bysimply heating the substrate with indium powder in aqueous ethanol containing ammonium chloride, and gave, after chromatography, the corresponding 1,2,3,4-tetrahydroquinolines in modest to good yield (Scheme III.28).

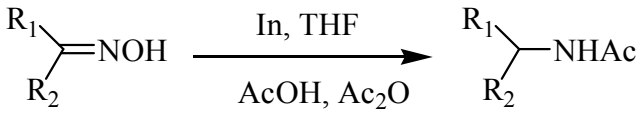


166 **167**

Scheme III.28

III.5.4.2. Reduction of oximes

Oximes were also thought to be potential substrates for reduction by indium despite the fact that they are generally regarded as more resistant than imines to reduction.[42] The reduction was carried out by simply heating the α-oximino carbonyl compound in THF containing 4 equivalents of acetic acid and 2.5 equivalents of acetic anhydride, and a suspension of 4 equivalents of indium powder, and gave the *N*-acetyl amines in good to excellent yield (Scheme III.29).

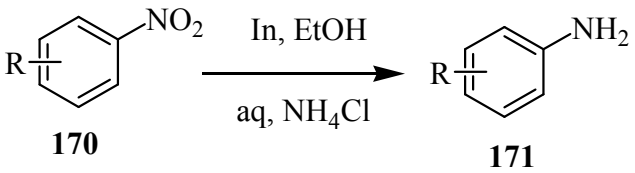


168 **169**

Scheme III.29

III.5.4.3. Reduction of nitro compounds

Although a large range of methods for the reduction of aromatic nitro compounds have been developed,[43,44,45] many of these are incompatible with other functional groups in the molecule. For example, the selective reduction of nitro groups in the presence of carbonyl groups, nitriles, halides and alkenes is often difficult, and in such cases catalytic hydrogenation, which is often the method of choice for nitro reduction, is inappropriate. Reduction of aromatic nitro compounds proceeded readily on heating the substrate with indium powder in aqueous ethanolic ammonium chloride. The reactions are extremely easy to carry out, are usually complete within 1–3 hours, and give the corresponding aniline in good to excellent yield (Scheme III.30).

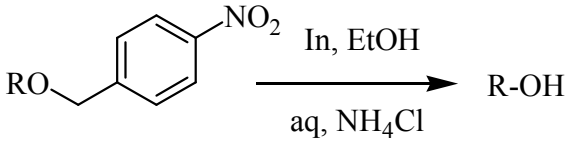


170 **171**

Scheme III.30

III.5.4.4. Deprotection of 4-nitrobenzyl ethers and esters

A series of alcohols, phenols and acids was protected as their corresponding 4-nitrobenzyl ethers and esters. The deprotection reactions were carried out using indium metal under the usual aqueous conditions. Simple extractive work-up involving acid–base wash to remove the 4-toluidine by-product gave the deprotected material in good yield (Scheme III.31).[46]

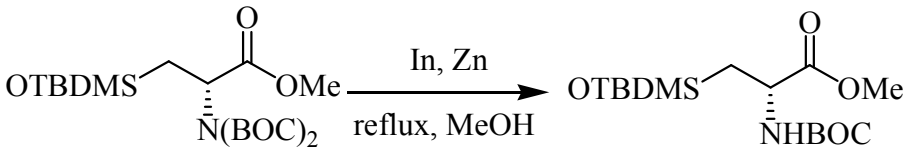


172

Scheme III.31

III.5.4.5. Cleavage of the t-butoxycarbonyl group from di-t-butylimidodicarbonate

The cleavage of di-BOC protected amides was effected by indium metal in methanol at reflux temperature. This method is highly selective for cleavage of the *t*-BOC group from *N*-BOC protected cabamates and leaves simple BOC protected amines unaffected. The deprotection of *t*-butylimidodicarbonates proceeded smoothly to give exclusively mono-BOC protected amines in excellent yields. Such selectivity can be applied in synthetic sequences in which two BOC groups must be unmasked at different stages of the synthesis (Scheme III.32).[47]

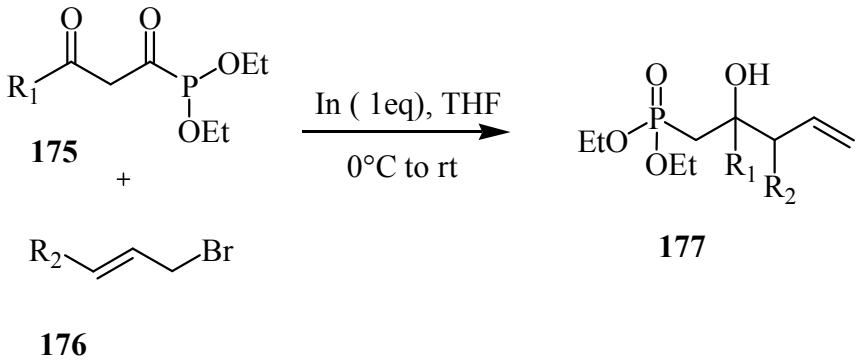


173 **174**

Scheme III.32

III.5.4.6. 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[48] (Scheme III.33). Here, allylindium generated in situ reacts with the β-keto phosphonate without any catalyst. β-Keto phosphonates with alkyl groups or cycloalkyl or aromatic rings at their β-positions and cyclic β-keto phosphonates also react smoothly under these conditions.



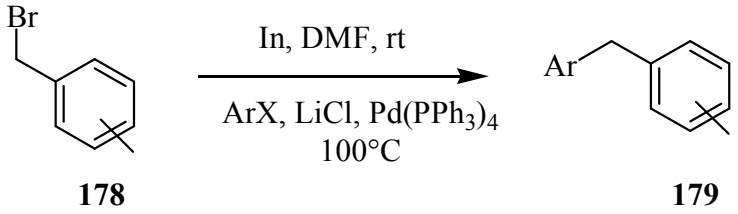
175 + **176** **177**

Scheme III.33

III.5.4.7. Cross-Coupling Reactions of Benzylindium Reagents and Aryl Iodides

Palladium-catalyzed cross-coupling reactions between benzylindium reagents and aryl iodides have also been reported recently [49] (Scheme III.34). Here, benzylindium, generated *in*

situ, is coupled with aryl iodides. This method provides a simpler method for the synthesis of diarylmethanes.

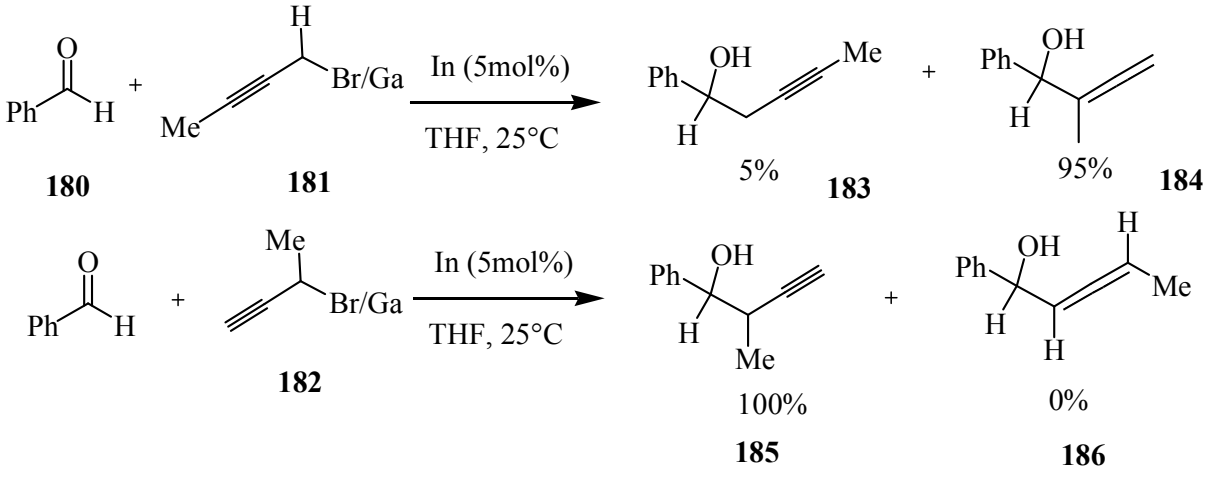


Scheme III.34

III.5.4.8. Addition of Carbonyl Compounds

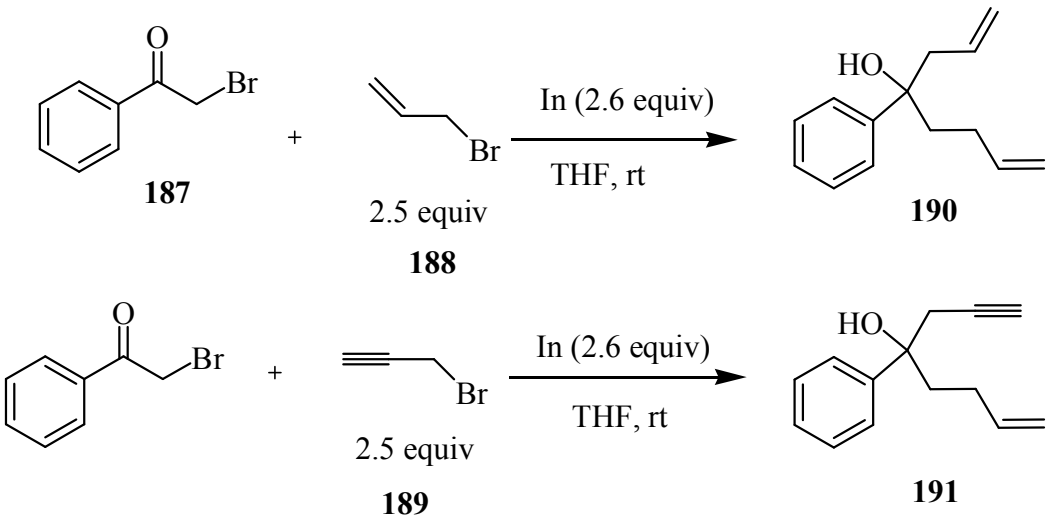
Regioselective additions of propargylgallium reagents to carbonyl compounds are a relatively unexplored area in relation to the use of propargylindium.[50]These reactions, which result in the formation of homopropargyl alcohols, has their own importance in the field of organic synthesis.[51] Although many methods have already been developed,[52] 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/InX_3-mediated (X = F or Br) reactions between 3-bromo-1-(trialkylsilyl)prop-1-ynes and various aldehydes have been reported.[53]

This selectivity can also be achieved with propargylgallium in the presence of indium metal.[54] 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 III.35).



Scheme III.35

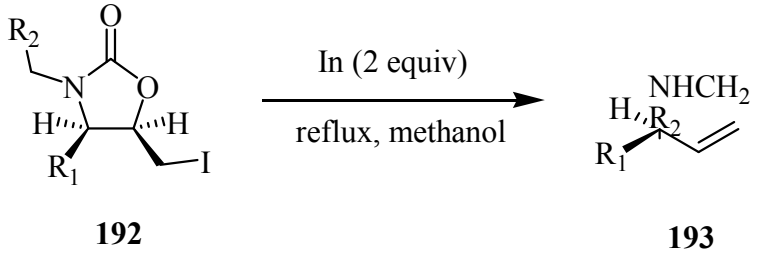
This method tolerates aromatic or aliphatic carbonyl compounds and the order of their reactivity is found to be in the order: aromatic aldehyde>aliphatic ketone > aromatic ketone. *vic*-Dipropargylated or *vic*-diallylated compounds have recently been prepared from phenacyl bromide through the use of propargylindium or allylindium reagents[55] (Scheme III.36).



Scheme III.36

III.5.4.9. Synthesis of Chiral Allylic Amines

Chiral allylic amines are reliable as peptide mimetics, β-turn promoters,[56] and intermediates for aza-Claisen rearrangements.[57] There are several reported methods for their synthesis, such as asymmetric allylic amination,[58] asymmetric additions to alkynes[59], etc. Indium-mediated conversion of 5-iodomethyl-2-oxazolidones into chiral allenic amines has also been reported[60] (Scheme III.37). The advantage over the other existing methods is that under these reaction conditions there is no decomposition or racemization of the product.[61]



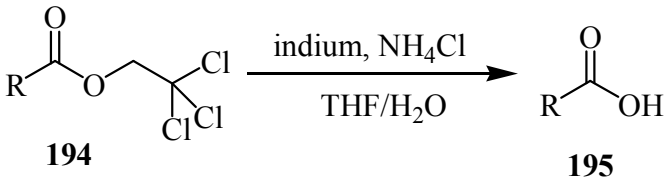
Scheme III.37

III.5.4.10. Deprotection and demonochlorination of 2,2,2-trichloroethyl esters

Among the protecting groups explored, the 2,2,2-trichloroethyl moiety serves as a convenient masking unit for alcohols, amines, and carboxylic acids, as well as phosphorus

compounds. The trichloroethyl moiety can be routinely cleaved with Zn/AcOH, electrolysis, SmI_2, $Se/NaBH_4$, and Cd/AcOH. The alternative indium-mediated methods for its removal under mild conditions have been developed.[62,63]

T. Mineno *et al*. in their continuous efforts to explore indium-based methodologies, indium metal has been found to be sufficiently effective to deprotect trichloroethyl benzoates. Thus, a mixture of trichloroethyl esters and indium powder, with THF/H_2O as the solvent, was heated in the presence of NH_4Cl to achieve an exclusive cleavage to benzoic acids. A variety of aromatic and aliphatic carboxylates were subjected to an indium-mediated reaction to furnish the carboxylic acids in good to excellent yields (Scheme III.38).[64]



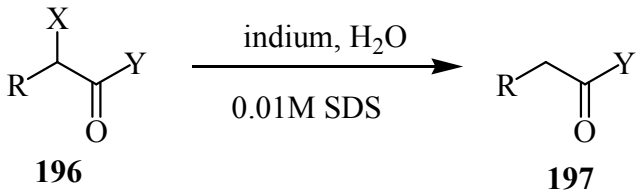
194 **195**

Scheme III.38

III.5.4.11. Reductive dehalogenation of α -halocarbonyl compounds in water

While the reductive dehalogenation reactions of α- halocarbonyl compounds **196** using various reagents such as active metals, low-valent metals, metal hydrides, or halide salts in organic solvents have been studied extensively,[65] only a quite limited number of procedures have been reported to be conducted in aqueous media. These known methods are effective with limited carbonyl functional groups,[66] using sonication,[67] or suffer from low yields[68]of products. L. Park *et al*. in their continuous efforts[69] to explore the utility of indium metal for organic synthesis in mild conditions led them to find that α-halocarbonyl compounds **196** can be effectively reduced to the parent carbonyl compounds **197** in a reaction mediated by indium in the presence of sodium dodecyl sulfate (SDS) in water. This is the first case in which indium-mediated reductive dehalogenation of α-halocarbonyls is carried out in micellar systems. We wish to report herein the versatile and efficient dehalogenation method of various α-halocarbonyl compounds **196** using indium in water.

Treatment of the α-halocarbonyl compounds **196** with 130–170 M% of indium powder (~100 mesh) in the presence of 1 M% of sodium dodecyl sulfate (SDS) in water from room temperature to 80 °C for the time required to complete the reaction yielded the corresponding carbonyl compounds **197** in excellent yields (Scheme III.39).[70]



196 **197**

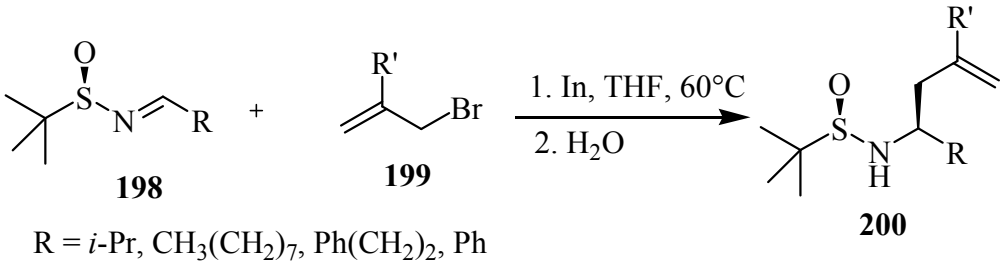
X = Br, Cl

Y = alkyl, aryl, OH, OR, NHR, NR_2

Scheme III.39

III.5.4.12. Addition of allyl bromides to enantiomerically pure N-tert-butylsulfinyl aldimines

The reaction of different *N-tert*-butylsulfinyl aldimines **198** with allyl bromides **199** and indium powder in THF at 60°C affords, after hydrolysis with water, the corresponding N-*tert*-butylsulfinylamines **200** with high chemical yields and diastereoselectivities.



198 **199** **200**

R = *i*-Pr, $CH_3(CH_2)_7$, $Ph(CH_2)_2$, Ph

R' = H, Me

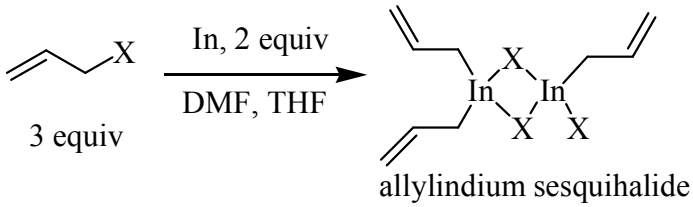
Scheme III.40

F.Foubelo and M.Yus investigated first the reaction conditions for the allylation of the benzaldehyde derivative (R = Ph) by treatment with allyl bromide (R'= H) in the presence of indium metal. Based on their previous experience with indium-mediated allylation of aldimines, they used 1.3 equiv of indium metal and 1.3 equiv of allyl bromide, THF being the solvent of choice. It was supposed that in these processes the formation of an allylindium intermediate was facilitated in aqueous media, although in the cases of using water or a water/THF mixture, hydrolysis of the starting (R)-*N-tert*-butylsulfinyl aldimine occurred, yielding benzaldehyde and other reaction products derived from it. In contrast, the allylation of *N*-sulfonyl imines performed in aqueous media has already been reported. Regarding the temperature, although the reaction does not progress significantly at room temperature while at 40°C it takes 12h to drive it to completion, complete conversion was achieved at 60°C after 4h without loss of stereoselectivity (Scheme III.40).[71]

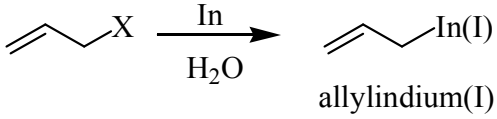
III.5.5. The preparation and application of organoindium reagents

III.5.5.1. Allylindium reagents

Allylindium reagent was first introduced in1988 by Araki, Ito, and Butsugan for the allylation of carbonyl compounds in DMF. Three years later, the importance of allylindium reagent was further demonstrated by Li and Chan when they observed that the indium-mediated allylation reaction also can be performed in water, in most cases showing even better performance than the same reaction carried out in organic solvents. The direct insertion of indium (0) into allyl halide serves as an important method for the preparation of allylindium reagent. Both organic and aqueous solvents can be used as reaction media, and allylindium sesquihalide (Scheme III.41) and allylindium (Scheme III.42) are generally considered to be the allylindium species formed in these two different solvent media, respectively. Usually, allyl iodide and bromide are employed as the substrates.[72]



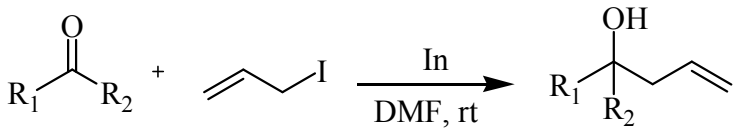
Scheme III.41



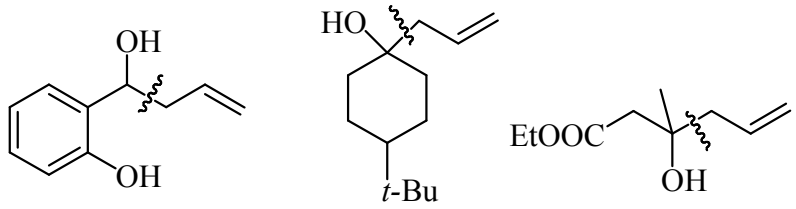
Scheme III.42

- ***Addition to Carbonyl Compound***

As demonstrated by Araki, Ito, and Butsugan in 1988, the insertion of powdered indium(0) into allyl bromide or iodide occurs efficiently in DMF at room temperature and the *in situ* generated allylindium reagent spontaneously reacts with various carbonyl compounds to give homoallylic alcohols in moderate to good yields (Scheme III.43).[73]



201 **202**



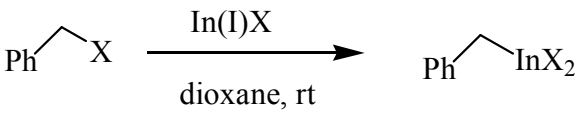
98% 89% 57%

axial OH:equatorial OH =83:17

Scheme III.43

III.5.5.2. Benzylindium reagent

The first benzylindium compound was synthesized back in1973 through the direct insertion of indium (I) halide into benzyl halide, carried out in dioxane at room temperature (Scheme III.44). However, only the preparation was reported and no further utility of the compound in organic synthesis was disclosed.[74]

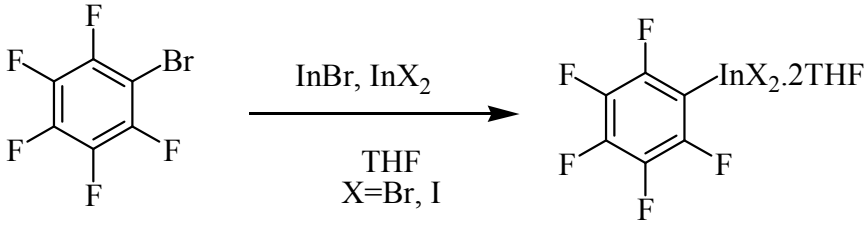


Scheme III.44

III.5.5.3. Arylindium reagent

Compared to the easy insertion of indium into reactive organohalides like allyl halide, propargyl halide, α-halo ester, and benzyl halide, the preparation of organoindium reagents from the insertion of indium into less reactive organohalides such as aryl and alkyl halides proved to be difficult. The difficulties may arise from the low reactivities of both the aryl halide and the indium metal. In 2001, further studies made by Tyrra revealed that an arylindium compound that was assumed to have a formulation of $[C_6F_5In(II)X]_2$ was afforded when an equimolar mixture of indium and pentafluorophenyl iodide was stirred at room temperature in THF. In addition, an pentafluorophenyl indium compound can be easily synthesized by means of the reaction of pentafluorophenyl halide with In(I)X (or generated in

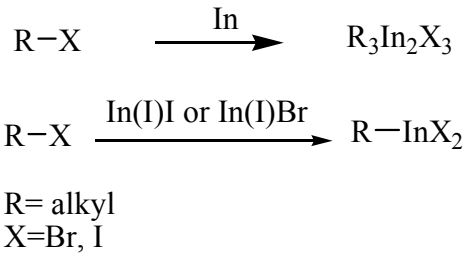
situ by mixing 1 equiv of indium with 0.5 equiv of X_2; X = Br, I) in THF (Scheme III.45).[75] X-ray analysis showed that the arylindium species coordinated with THF and has a general formulation of $C_6F_5InX_2 \cdot 2THF$.



Scheme III.45

III.5.5.4. Alkylindium reagent

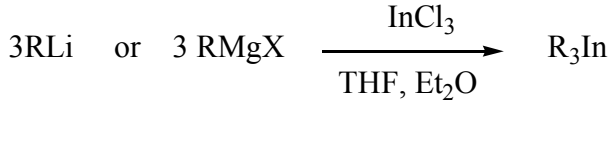
Similarly, alkylindium reagents can be prepared by the direct insertion of indium(0) and indium(I) halide into alkyl halides (Scheme III.46).



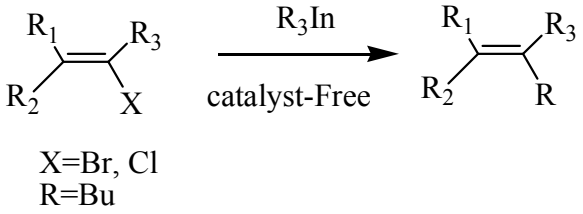
Scheme III.46

III.5.5.5. Triorganoindium reagent

The transmetalation of highly reactive and easily accessible organometallic reagents such as organolithium (RLi) or organomagnesium reagent (RMgX) with indium(III) halides serves as an important method for the preparation of triorganoindium reagent (Scheme III.47). The example of synthetically useful procedures using R_3In as coupling reagent was reported by Nomura *et al*. The cross-coupling of R_3In with haloalkene occurs under catalyst free conditions (Scheme III.48).[76]



Scheme III.47



X=Br, Cl
R=Bu

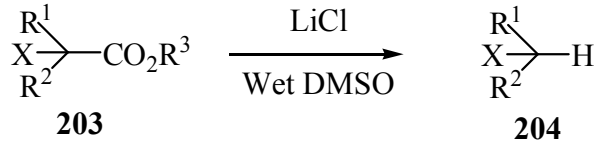
Scheme III.48

III.6. Lithium chloride

III.6.1. Source of Chloride Nucleophile

The solubility of LiCl in many organic dipolar solvents renders it an effective source of nucleophilic chloride anion. Lithium chloride converts alcohols to alkyl chlorides[77] under Mitsunobu conditions,[78] or by way of the corresponding sulfonates[79] or other leaving groups.[80] This salt cleanly and regioselectively opens epoxides to chlorohydrins in the presence of acids and Lewis acids such as Acetic Acid,[81] Amberlyst 15 resin,[82] and Titanium(IV) Chloride.[83] In the presence of acetic acid, LiCl regio- and stereoselectively hydrochlorinates 2-propynoic acid and its derivatives to form the corresponding derivatives of (*Z*)-3- chloropropenoic acid.[84] Oxidative decarboxylation of carboxylic acids by Lead(IV) Acetate in the presence of 1 equiv of LiCl generates the corresponding chlorides.[85]

In wet DMSO, LiCl dealkoxycarbonylates various activated esters (Scheme III.49).[86,87] If the reaction is performed in anhyd solvent the reaction generates a carbanion intermediate, which can undergo inter- or intramolecular alkylation or elimination. Other inorganic salts (NaCN, NaCl, Lithium Iodide) and other dipolar aprotic solvents (HMPA, DMF) can also be employed. Under similar conditions, lithium chloride cleaves alkyl aryl ethers having electron-with drawing substituents at the ortho or para positions.[88]



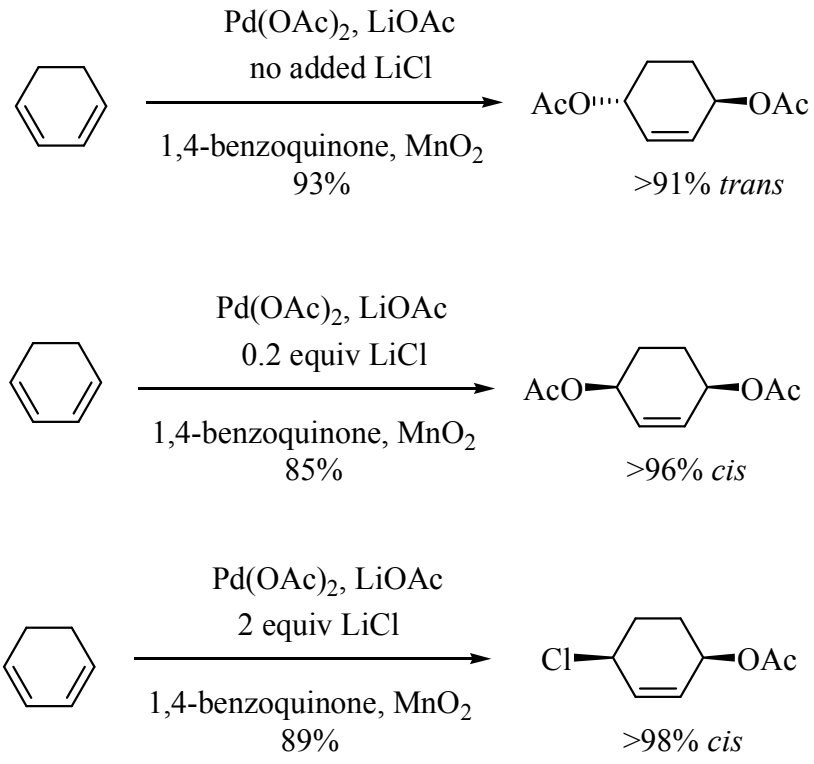
203 **204**

X= CO_2R, COR, CN, SO_2R; R^3= Me, Et

Scheme III.49

III.6.2. Source of Chloride Ligand.

In palladium-catalyzed reactions, LiCl is often the reagent of choice as a source of chloride ligand. Lithium chloride is a necessary component in palladium-catalyzed coupling and carbonylative coupling reactions of organostannanes and vinyl triflates.[89,90] Lithium chloride has a dramatic effect on the stereochemical course of palladium-catalyzed 1,4-additions to 1,3-dienes.[91] Treatment of 1,3-cyclohexadiene with Palladium(II) Acetate and LiOAc and the oxidizing agents 1,4-Benzoquinone and Manganese Dioxide affords 1,4-*trans*-diacetoxy-2-cyclohexene. In the presence of a catalytic quantity of LiCl, the *cis* isomer is formed. If 2 equiv LiCl are added, the *cis*-acetoxychloro compound forms. These methods are general for both cyclic and acyclic dienes, and have recently been extended to the stereospecific formation of fused heterocycles.[92]Lithium chloride is also used in the preparation of Dilithium Tetrachloropalladate(II)[93] and zinc organocuprate reagents (Scheme III.50).[94]



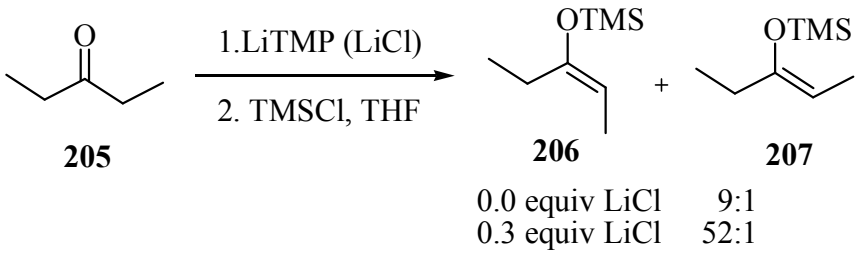
Scheme III.50

III.6.3. Weak Lewis Acid.

Lithium chloride is a weak Lewis acid that forms mixed aggregates with lithium dialkylamides, enolates, alkoxides, peptides, and related "hard" Lewis bases.[95] Thus LiCl often has a dramatic effect on reactions involving these species. In the deprotonation of 3-

pentanone by Lithium 2,2,6,6-Tetramethylpiperidide (LTMP), addition of 0.3 equiv LiCl increases the (*E*)/(*Z*) selectivity from 9:1 to 52:1.[96]

Enhancement in the enantioselectivity of deprotonation of prochiral ketones by a chiral lithium amide has also been reported .[97]Lithium chloride stabilizes anions derived from a-phosphonoacetates, permitting amine and amidine bases to be used to perform Horner-Wadsworth-Emmons reactions on base-sensitive aldehydes under exceptionally mild conditions .[98]Lithium chloride and other lithium salts disrupt peptide aggregation and increase the solubilities of peptides in THF and other ethereal solvents, often by 100-fold or greater. [99]These effects render LiCl a useful additive in the chemical modification of peptides (e.g. by the formation and alkylation of peptide enolates).[96,100] Lithium chloride has also shown promise as an additive in solid-phase peptide synthesis, increasing resin swelling and improving the efficiencies of difficult coupling steps (Scheme III.51).[101]

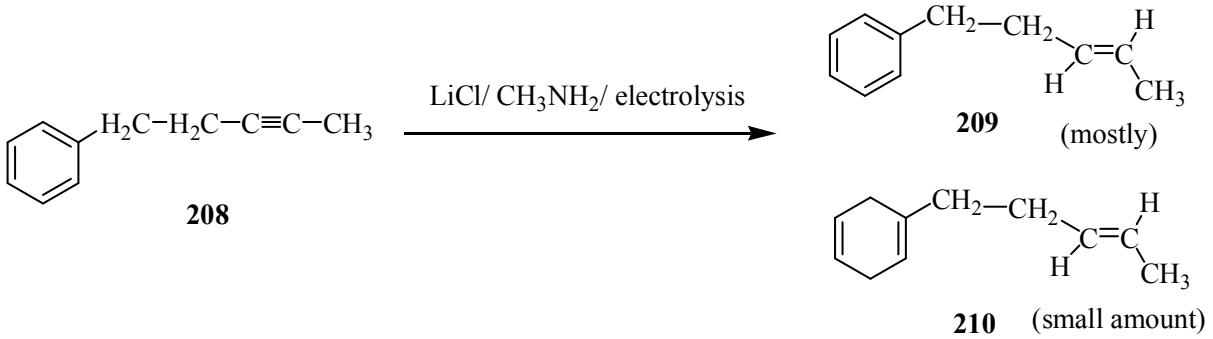


Scheme III.51

III.6.4. The applications of lithium chloride in organic synthesis

III.6.4.1. Reduction of alkynes

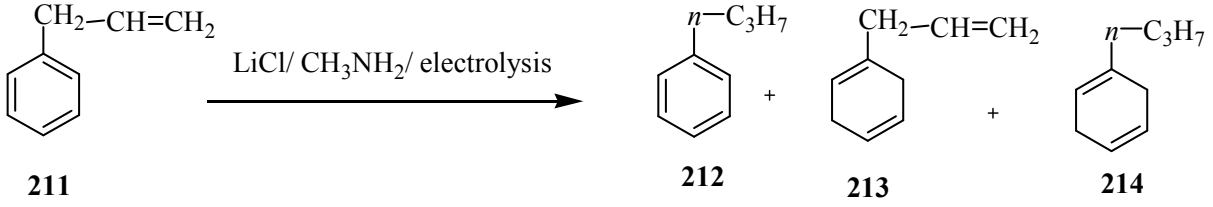
Certain alkyl-and arylalkyl have been subjected to electrolytic reduction in methylamine using lithium chloride as the electrolyte.[102] Thus, undiveded cell electrolyses of 2-octyne, 3-octyne and 5-decyne give good to excelent yields of the corresponding *trans*-olefins. Phenylacetylene and 1-phenyl-1-butyne, upon electrocatalytic reduction, afford 1-phenylethane and 1-phenylbutane, respectivly, acompanied by nearly equal amounts of the starting alkyne. Thus, alkynes conjucated with aromatic systems can not be selectively reduced to aromatic olefins by this method. On the other hand, application of these electrocatalytic reductions to unconjucatezd arylalkynes like 4-phenyl-1-butyne and 5-phenyl-2-pentyne 2**08**, give mostly the the corresponding *Trans*-olefins (Scheme III.52) in good yield. While the latter two reductions also afford a small amount of the 2,5-dihydro derivatives **210**, the conjucated arylalkynes described above give none of these products.



Scheme III.52

III.6.4.2. Reduction of phenyl-substitued alkenes

Electrolyses of styrene in methylamine with lithium chloride do, However, give ethylbenzene in 69% yield.[103] The related electrocatalytic reduction of allylbenzene **211** using enough current to reduce only the allylic double bond gives *n*-propylbenzene **212** in good yield accompanied by small amounts of triene **213** and diene **214**. Interestingly, when the reduction is carried out in the presence of ethanol, **213** is formed as the major product and hydrocarbons **212** and **214** are generated only in low yield. When the electrolysis with ethanol is realised with enough current to reduce two double bonds, though, diene **214** becomes the major products. Since the unconjucated dienes do not undergo isomerization in undivided cell electrolyses, it is not surprising that such an electrolysis of **213** in the presence of ethanol leads to **214** in good yield (Scheme III.53).

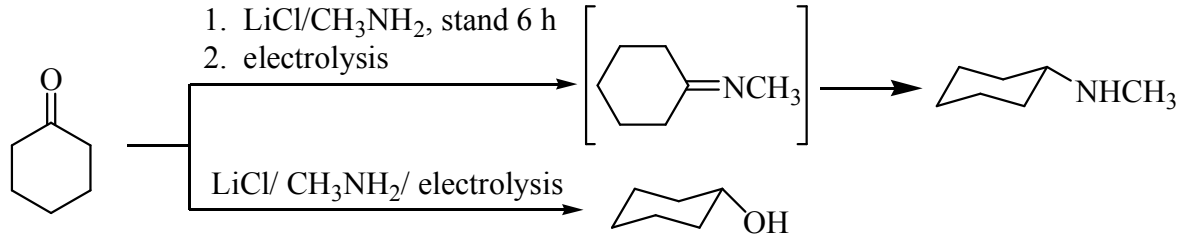


Scheme III.53

III.6.4.3. Reduction of aliphatic ketones and imines

From a synthetic standpoint, a more recent report dealing with electrocatalytic reductions of aliphatic ketones in methylamine in an undivided cell is more useful. Thus, 2-heptanone, cyclohexanone, cyclopentanone, and others are converted to the corresponding alcohols in good to excelent yield by adding the ketone to lithium chloride/methylamine and

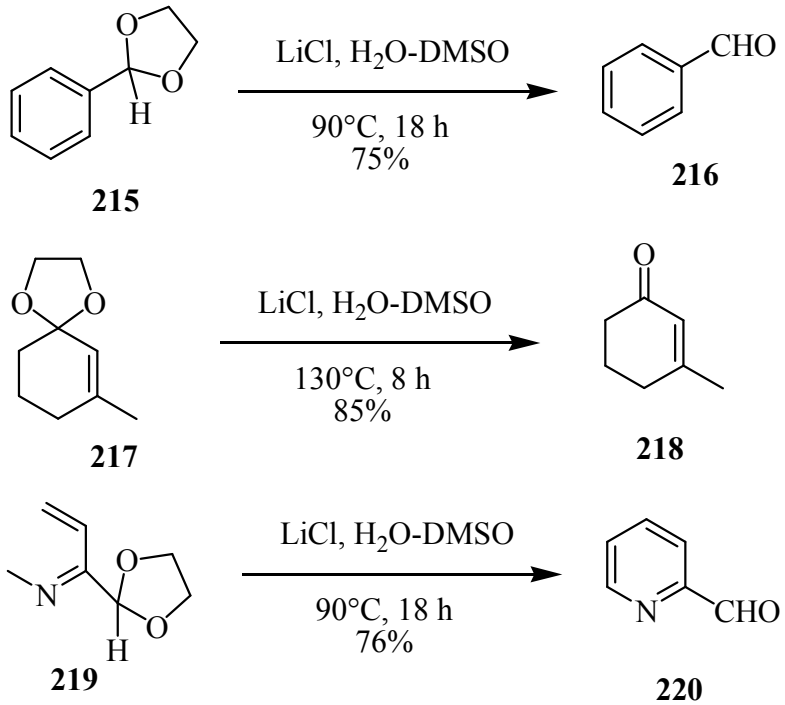
electrolyzing immediately (Scheme III.54).[104] On the other hand, if the reagents are mixed and allowed to stand for six hours prior to electrolysis, the ketones are converted to N-methyl alkylamines in good yield. The results are rationalized simply since during the six hour waiting period, the ketones are converted to their N-methylamine which then undergo reduction to the amines.



Scheme III.54

III.6.4.4. Selective cleavage of ketals and acetals using lithium chloride in water-dimethylsulfoxide

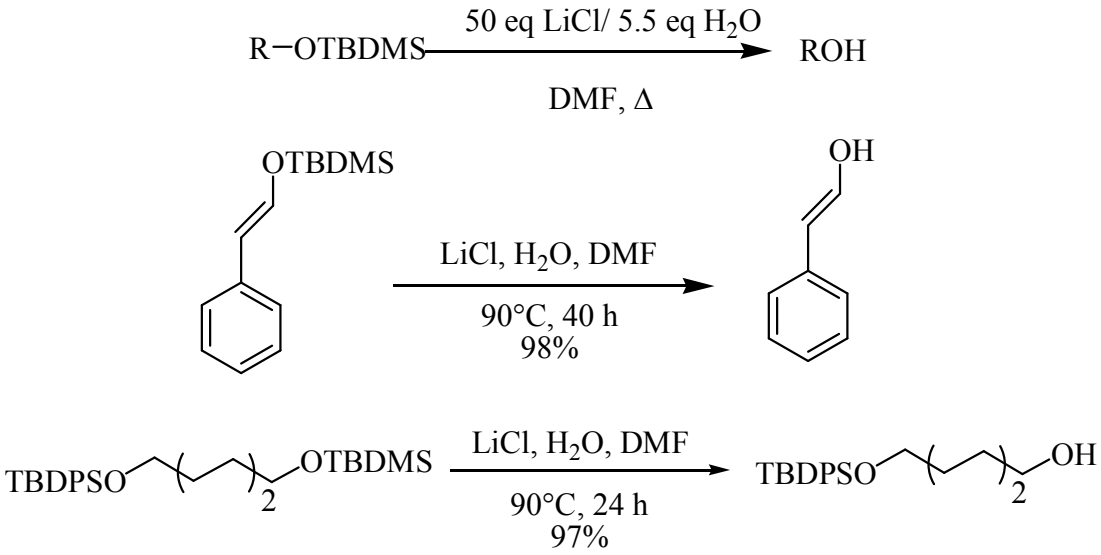
P.k.Mandal *et al*.reported a mild and efficient neutral aqueous method for selective cleavage of ketals and acetals to the corresponding carbonyl compounds has been established by LiCl in H_2O-DMSO at elevated temperature in good yield (Scheme III.55) which will provide an attractive addition to the range of procedures already nown for this general transformation.[105]



Scheme III.55

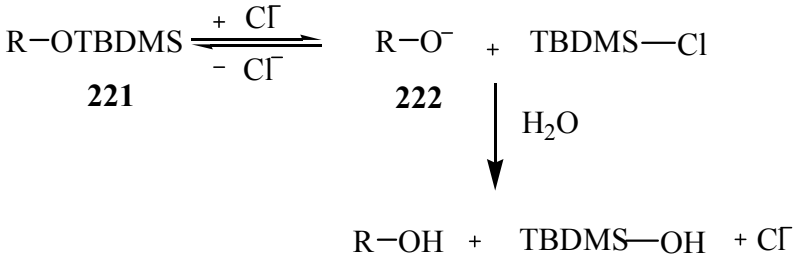
III.6.4.5. Cleavage of tert-butyldimethylsilyl ethers by chloride ion

J.Farras *et al*. reported a general method for the selective cleavage of *tert*-butyldimethylsilyl in the presence of *tert*-butyldiphenylsilyl ones has been established using combination of water and concentrated solution of lithium chloride in DMF at 90°C (Scheme III.56). Since no acids, bases, reducing or oxidizing agents are used; the method seems to be very appropriate for the deprotection of TBDMS ethers in the presence of others sensitive functions groups.[106]



Scheme III.56

The strength of the Si-F bond has been claimed as the "driving force" of the reaction between the TBDMS ethers and fluoride anions but this does not hold for the Si-Cl bond.Thus, from a mechanistic point of view, they assumed equilibrium between TBDMS ethers **221** and the alkoxides **222**, which almost completely displaced towards the starting materials. The subsequent reaction of the alkoxides and TBDMS-Cl with water to furnish the desired alcohols probably is the "driving force" of the overall process.



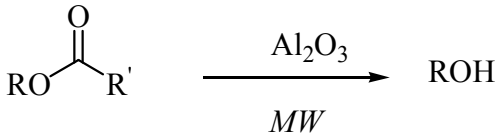
Scheme III.57

Such a hypothesis is supported by the fact that both Cl^- and H_2O are required for the reaction to work. It must be pointed out that the amount of water is crucial. Without water the reaction doesn't work, but an excess of water stop the reaction. They assume that only unsolvated chloride ions are nucleophilic enough to catalyse the Si-O bond cleavage in effective way. A 9-10:1 Cl^-/H_2O molar ratio work nicely but the need to maintain an excess of chloride ions over the amount of H_2O present in the reaction mixture preclude the use a catalytic amount of Cl^- (Scheme III.57).

III.7. Deprotection methods of Pivaloyl

III.7.1. Deprotection of pivaloyl using microwave promoted hydrolysis absorbed on alumina

It is rapid and efficient deprotection of pivaloyl and other ester by absorption onto alumina and microwave irridations, the results shows that this rapid and selective deprotection (1.5-30 min) is observed to regerenating the corresponding alcohol cleanly and in high yield (Scheme III.58).[107]



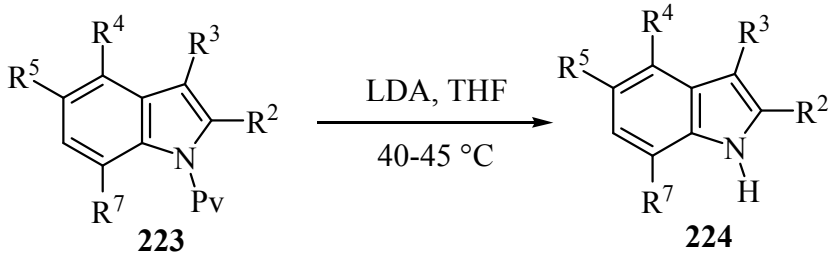
R = Ph	R' = $(Me)_3$	T= 1.5 min	80%
R = $PhCH_2$	R' = *t*-Bu	T= 22 min	97%
R = cyclohexyl	R' = Me	T= 4 min	74%
R = C_8H_{17}	R' = *t*-Bu	T= 14 min	84%

Scheme III.58

III.7.2. Deprotection of N-Pivaloylindoles, Carbazoles and b-Carbolines with LDA

Treatment of pivaloylindole itself with two equivalents of LDA in THF at 40–45 °C for two hours led to its quantitative deprotection. In order to verify the generality of the method, several variously substituted pivaloylindole derivatives were prepared by generation of the anion of the suitable indole derivative by treatment with sodium hydride, followed by addition of pivaloyl chloride. This method was also extended to *N*-pivaloylcarbazoles and b-

carbolines. The results obtained in the reaction of these compounds with LDA under the same conditions developed for the model are summarized in (Scheme III.59).[108]



223 **224**

R^2 = H, C_6H_5, CH_3 T = 2, 40, 90h 33-100%

R^3 = H, CH_3, CHO, $CH_2CH_2CO_2H$

R^4 = H, $CO_2C_2H_5$

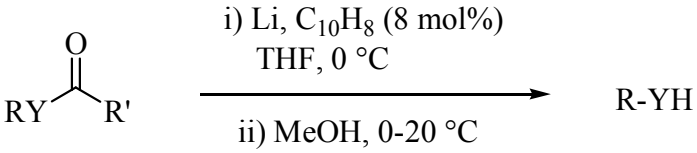
R^5 = H, $CO_2C_2H_5$, OCH_3

R^7 = H, CH_3

Scheme III.59

III.7.3. Deprotection of pivaloyl by a Naphthalene-Catalysed Lithiation

The reaction of different esters, thioesters and amides derived from pivalic, benzoic and 4-*tert*-butylbenzoic acids with an excess of lithium and a catalytic amount of naphthalene (8 mol %) led, after methanolysis, to the corresponding alcohols, thiols and amines, respectively, through a reductive non-hydrolytic procedure. This methodology represents a reasonable alternative to other non reductive protocols (Scheme III.60).[109]



Y = O, S, N

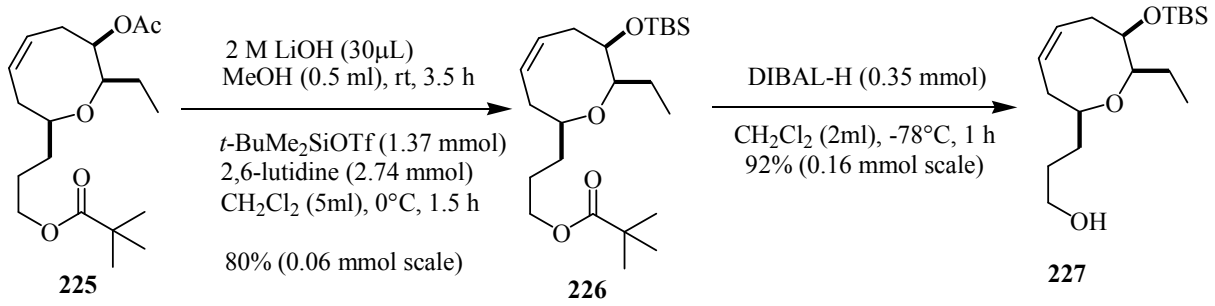
R' = $C(CH_3)_3$, Ph

R = cyclohexyl, Ph, 2-Octyl, $C_{10}H_{20}$

Scheme III.60

III.7.4. Deprotection of pivaloyl by diisobutylalane

Increased hydrolytic stability of the ester function is readily attained by shielding the carbonyl group from nucleophilic attack. Thus, pivalates are slow to deprotect compared with acetates and the protracted reaction times requires for cleavage of the pivalate may be incompatible with other protecting groups such as the TBS ethers. In such instance, the pivalate may be cleaved in good yield by reduction with diisobutylalane.[110] In a synthesis of Laurencin, a secondary acetate was selectively cleaved in the presence of primary pivalate with lithium hydroxide in aqueous methanol[111] (Scheme II.61). Subsequent deprotection of the pivalate in the presence of the TBS ether was then effected with diisobutylalane.



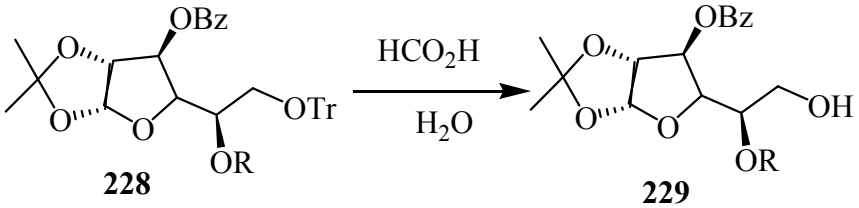
225 **226** **227**

Scheme II.61

III.8. Deprotection methods of trityl

III.8.1. Deprotection of trityl ethers with formic acid

In addition to providing selective protection of primary hydroxyl groups, the trityl group offers good resistance to bases but is easily removed by acid treatment, TFA, HCO_2H, and AcOH offering progressively milder cleavage conditions. Formic acid in ether is sufficiently selective to cleave trityl ether in the presence of other acid-sensitive groups including acetals and *t*-butyldimethylsilyl (TBDMS) ethers. This methodology represents an efficient detritylation procedure under acidic reaction conditions. This detritylation of carbon-oxygen bond with formic acid in water affording to the corresponding alcohols in good to excellent yields (Scheme III.62).[112]

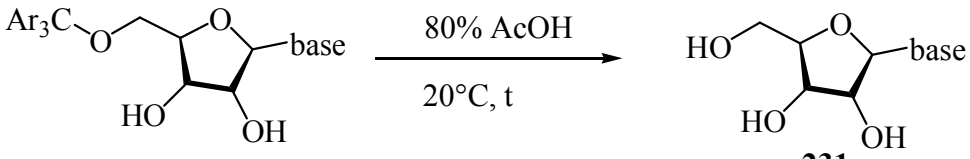


228 **229**

R = Ac	92%
R = TBDMS	88%
R = THP	60%/40% cleavage

Scheme III.62

The rate of trityl group cleavage can be fine-tuned by substituents on one or more of the phenyl rings. Electron-donating groups favour cation formation, which speeds the cleavage process, and vice versa. This is particularly useful in the protection of the 5'-OH in nucleosides where more acid-labile variants of the trityl PG can be removed without competing loss of the base (which can be a problem with the trityl group itself). Below there is a comparison of the times required to effect complete hydrolysis of trityl (Tr), *p*-methoxyphenyldiphenylmethyl (MMTr), di(*p*-methoxyphenyl)phenylmethyl (DMTr), and tri(*p*-methoxyphenyl)methyl (TMTr)[113] ethers (Scheme II.63).



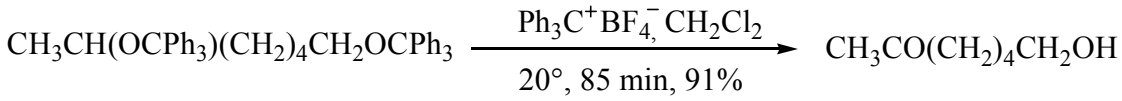
230 **231**

Ar_3c=Tr	*t* = 48 h
MMTr	2 h
DMTr	15 min
TMTr	1 min

Scheme II.63

III.8.2. Deprotection of trityl ethers with $Ph_3C^+BF_4^-$

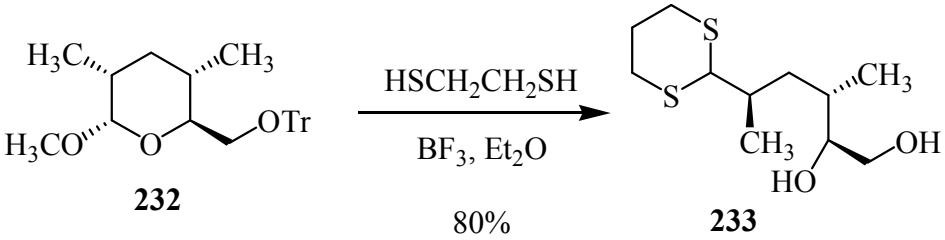
Since a secondary alcohol is oxidized in preference to a primary alcohol by $Ph_3C^+BF_4^-$, this reaction could result in selective protection of a primary alcohol (Scheme III.64).



Scheme III.64

III.8.3. Deprotection of trityl ethers with BF_3

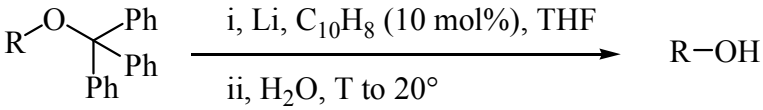
The detritylation of carbon-oxygen bond with BF_3 in ethoxyethane affording to the corresponding alcohols in good to excellent yields 80% (Scheme III.65).



Scheme III.65

III.8.4. Deprotection of trityl ethers with lithium naphtalened

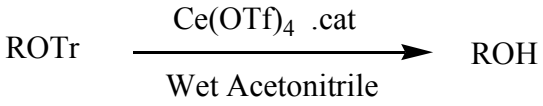
The reaction of primary, secondary, allylic and benzylic trityl ethers with lithium powder and a catalytic amount of naphthalene led to reductive cleavage of the trityl-oxygen bond, affording the corresponding alcohols in good to excellent yields under very mild reaction conditions. This methodology represents a new and efficient detritylation procedure under non-acidic reaction conditions (Scheme III.66).[114]



Scheme III.66

III.8.5. Deprotection of trityl ethers with ceric triflate

A very simple and efficient method is described for deprotection of trityl using catalytic amount of ceric triflate in acetonitrile under mild reaction conditions high reactivity was observed for detritylation for satureted and benzylic ethers and also for strucyurally different nucleosides (Scheme III.67).[115]

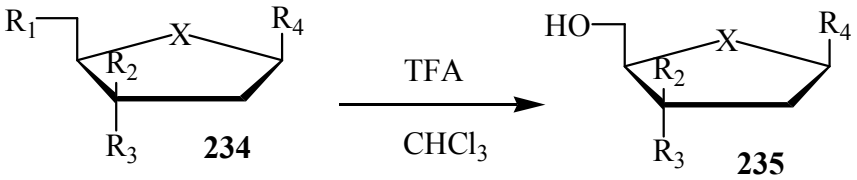


R = alkyl, benzyl, or nucleosides

Scheme III.67

III.8.6. Deprotection of trityl ethers using column chromatography

A mild, efficient and inexpensive detritylation method is reported that uses trifluoroacetic acid on a silica gel column to obtain pure, detritylated compounds in one-step. This method is applicable to acid stable as well as acid sensitive compounds with only slight alterations in the procedure (Scheme III.68).[116]



R_1 = Tr

R_2 = H, OH, OMs

R_3 = OH, NH_2, H, N_3

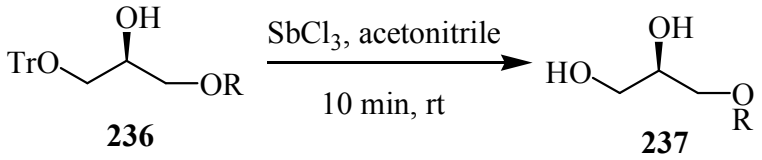
R_4 = Uracil, Thymine, Adenine.

X = CH_2, O, S.

Scheme III.68

III.8.7. Deprotection of trityl ethers with Antimony Trichloride

Selective detritylation is quite crucial in synthetic chemistry. A mild and efficient procedure for selective hydrolysis of trityl ethers in the presence of other frequently used hydroxy protecting groups: TBDPS, Bz, Bn, Ac and Ts with antimony trichloride was described and 50-trityl uridine was detritylated smoothly too (Scheme III.69).[117]



236 **237**

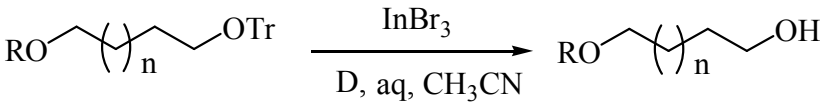
R = Bn, Bz, Ts, TBDPS.

Scheme III.69

III.8.8. Deprotection of trityl ethers by indium tribromide

It is a novel and catalytic method for detritylation using indium tribromide in aqueous acetonitrile. The cleavage was affected by a catalytic amount of indium tribromide in refluxing aqueous acetonitrile with high chemoselectivity.

The procedure is highly selective to deprotect trityl ethers leaving other functional groups intact. Trityl ethers are deprotected in high yields (80–95%) within 0.5–2.5 h of reaction time. The deprotection was clean, high yielding and completed in a short reaction time (Scheme III.70).[118]

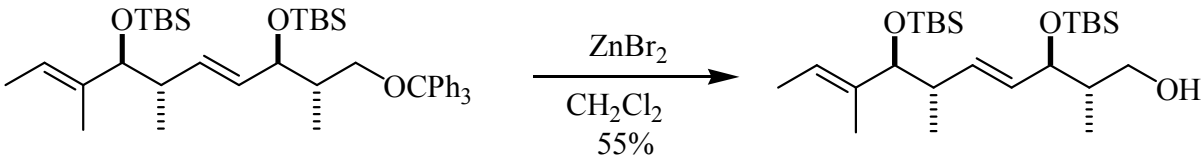


238 **239**

Scheme III.70

III.8.9. Deprotection of trityl ethers by zinc bromide

Most lewis acids such as zinc bromide in methanol, dichloroethylalane in dichloromethane, trifluoroboraneetherate and ethane-1,2-dithiol in methanol, or iron III chloride will also cleave trityl ethers the (Scheme III.71) illustrates the use of zinc bromide in dichloromethane to remove a trityl ether in the presence of two allylic TBS ethers during a synthesis of ACRL toxin IIIb.



240 **241**

Scheme II.71

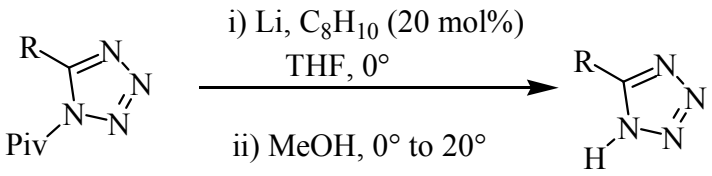
III.9. Results and discussion

III.9.1. Reductive Removal of the Pivaloyl Protecting Group from Tetrazoles by a Naphthalene-Catalyzed Lithiation Process

The arene-catalyzed lithiation method for generating organolithium compounds has been a topic of many research activities for several years. 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, nonhalogenated materials, or heterocycles, leading to the corresponding organolithium compounds, including some functionalized examples. This lithiation methodology permits reductive cleavage of C–N bonds in various organic compounds.

In the last few years our research group has been using arene-catalyzed lithiation to perform lithiations under very mild reaction conditions. This lithiation methodology has been applied to the reductive cleavage of trityl ethers and amines, the desilylation of silylated alcohols, amines, and thiols, the cleavage of carbonates, carbamates, and thiocarbonates, and the deacylation of esters, thioesters, and amides.

The reaction of various 5-substituted 1-pivaloyltetrazoles with excess lithium powder (1:20 molar ratio) and a catalytic amount of naphthalene (1:0.4 molar ratio) in tetrahydrofuran at 0 °C for three hours led, after quenching with methanol, to the corresponding free tetrazoles through reductive C–N bond cleavage. This methodology represents a reasonable alternative to other non reductive protocols (Scheme III.72).



Scheme III.72

The mechanism

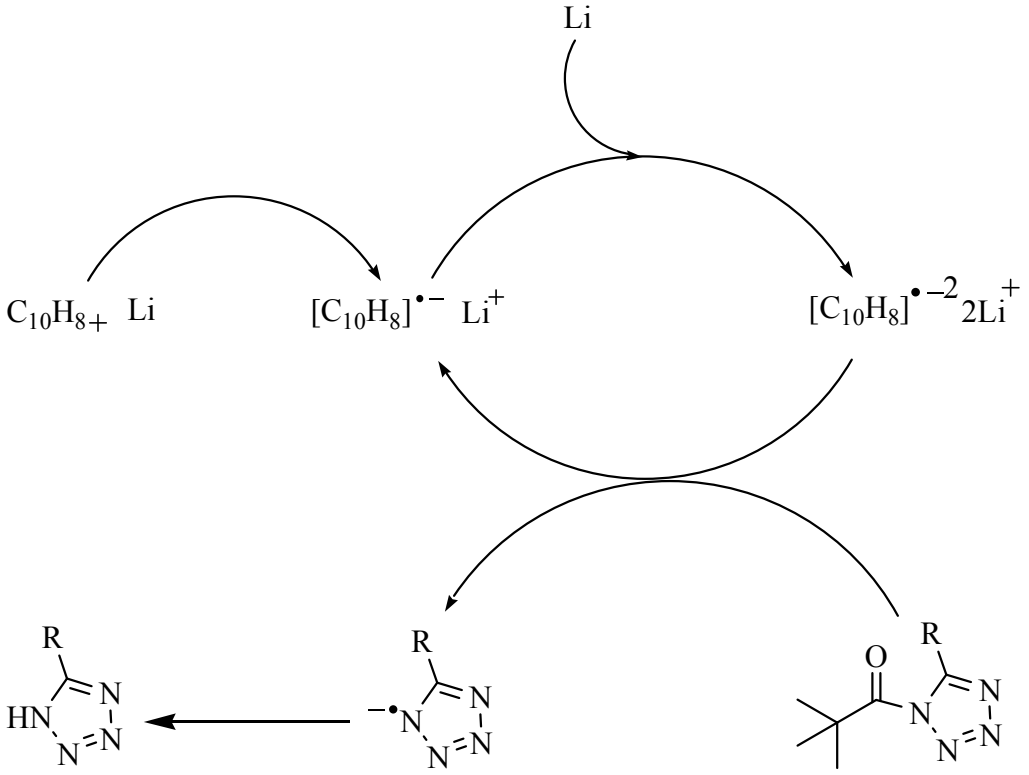


Figure III.3. Mechanism of arene catalysed lithiation.

Table III.2: Deprotection of tetrazoles by a naphthalene-catalysed lithiation.

Entry	Product	R	Time (h)	Mp (°C)	Yield (%)
1	**2a**	Ph	3	215-216	63
2	**2b**	2-(4-MeC_6H_4)C_6H_4	3	149-151	56
3	**2c**	*t*-Bu	3	208-210	55
4	**2d**	CH_2CO*t*-Bu	3	152-154	62
5	**2e**	Me	3	138-140	61
6	**2f**	$CHPh_2$	3	165-166	61

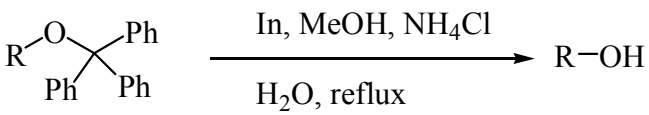
The deprotected tetrazoles **2a**–**f** were isolated generally in good yields (Table III.2). In general, moderate to good yields were obtained in the deprotection of 5- aryl-1- pivaloyltetrazoles **2a**, **2b** (entries 1 and 2), 5-alkyl-1- pivaloyltetrazoles **2c**, **2e** (entries 3 and 5), or 5-benzhydryl-1- pivaloyltetrazole **2f** (entry 6). Interestingly, 5-(3,3-dimethyl- 2-

oxobutyl-1-pivaloyl)-1*H*-tetrazole (**1d**), containing a carbonyl group in the 5-substituent that could undergo reduction under these reaction conditions, underwent solely depivalation to give **2d** in 62% yield (entry 4). All the lithiation processes were complete in a reaction time of three hours.

III.9.2. Reductive removal of trityl ethers by indium

Several alternative procedures for the removal of a trityl group have been developed involving, for instance, Lewis acids, electrolytic reduction, catalytic hydrogenation, or reduction with sodium in liquid ammonia, but some of these methods are not applicableto a wide range of unsaturated substrates or other reducible groups. In the search for better methods for selective removal of the trityl group, some reductive cleavages of the trityl-oxygen bond have recently been published, which use triethylsilane or low-valent titanium reagents. Catalytic amounts of cerium (IV) ammonium nitrate adsorbed on silica gel are able to oxidatively cleave trityl oxygen bonds in nucleosides and nucleotides very efficiently. The reaction of primary, secondary, allylic and benzylic trityl ethers with indium powder and saturated ammonium chloride solution led to reductive cleavage of the trityl-oxygen bond, affording the corresponding alcohols in good to excellent yields. The detritylation process could successfully be extended to several hydroxy, alkoxy and amino functionalized trityl ethers. This methodology represents a new and efficient detritylation procedure under non-acidic reaction conditions.

Indium powder was added to a solution of trityl ethers in methanol and saturated ammonium chloride solution and the mixture heated at reflux. The cooled reaction mixture was then quenched with water and extracted with EtOAc and the combined organic phases were washed and dried. The resulting residue was purified by column chromatography (silica gel, hexane–EtOAc) affording the expected alcohols (Scheme III.73).



Scheme III.73

The trityl group could chemoselectively be removed in the presence of a geranyl or a benzyl group, which are also prone to undergo reductive cleavage by reaction with indium. The reaction of indium with NH_4Cl of geranyl trityl ether **1a'** and benzyl trityl ether **1d'** afforded

the corresponding alcohols **2a'**and **2d'**, respectively, in good yield (Table III.3, entries 1 and 4). The detritylation of cyclohexyl trityl ether **1b'** and cyclopentyl trityl ether **1h'** was performed in 31 hours and gave 70% and 75% yields of cyclohexanol and cyclopentanol respectively (Table III.3, entries 2 and 8). The solution of stearyl trityl ether **1c'** (Table III.3, entry 3) in methanol was added to indium and saturated ammonium chloride solution at reflux in 35 hours, After complete disappearance of the starting material, hydrolysis with water at the same temperature gave a mixture of stearic alcohol and triphenylmethane in a 1:1 ratio (Table III.3, entry 3). Therefore, the expected removal of the trityl- oxygen bond had taken place. The formation of triphenylmethane could be explained by further reduction of the trityl radical by indium to give the corresponding anion, followed by proton abstraction from water in the hydrolysis step.

Some other simple trityl ethers were also tested as substrates for this detritylation process (Table III.3, entries 5, 7, 10 and 13). The reaction time, temperature and yield obtained in the reductive cleavage of each starting material are indicated in Table III.3.

When ditritylated hexadiol **1f'** was used as starting material, it was possible to remove one or both trityl groups depending on the reaction conditions. Reaction of **1f'** at reflux gave in 34 hours a 60% yield of the hexadiol **2f'** as starting material (Table III.3, entry 6).

The cleavage of both oxygen-trityl bonds in compound **1i'** was performed in 30 h and gave only a 58% yield of the expected diol **2i'** (Table III.3, entry 9).

The reaction of **1k'** and indium with NH_4Cl gave with successfully **2k'** in 25 hours with 68% yield (Table III.3, entry 11).

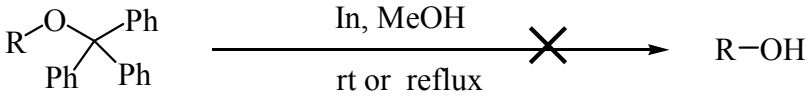
When compound **1l'** (which possesses a secondary alkyl group) was used as substrate, the reaction gave the starting material in 32 hours and gave a 68% yield of 2-octanol (Table III.3, entry 13).

In all cases, triphenylmethane was obtained as a by-product, resulting from hydrolysis of the triphenylmethyllindium generated during the process, but it could easily be separated from the desired detritylation products by column chromatography.

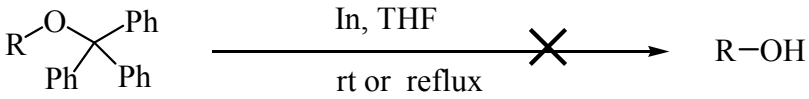
Reactions didn't work with indium

The reaction of alcohols with indium didn't work in the first time we have made many experiences to realize the reductive cleavage of trityl-oxygene bond.

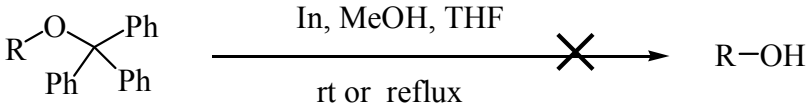
The first one we try to dissolve our compound in solution of methanol at room temperature with indium but the reaction didn't work the same solution but this time at reflux, but the same result.



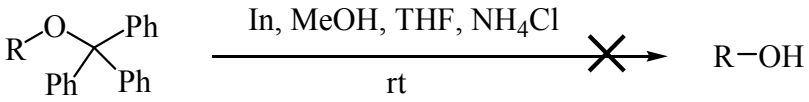
We changed the solvent, we dissolve our trityl ether in THF with indium at room temperature but the reaction hadn't take place so we tried the same solution but at reflux also the same result.

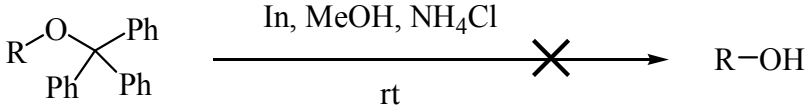


We thought about a mixture between methanol and THF at room temperature and at reflux but the reaction didn't work in both conditions.



This time we added a solution of NH_4Cl to a solution of our product and indium in mixture of MeOH and THF at room temperature but the reaction hadn't take place, we changed the solvent we used only a methanol and also the same result.





when we used a solution of NH_4Cl with trityl ether and indium in methanol at reflux the reaction had taken place and the reductive of C-O bond happened.

General procedure

Indium powder (0.02 g) was added to a solution of the substrate (0.1 mmol) in methanol (3ml) and saturated ammonium chloride solution (1ml) and the mixture heated at reflux. After the time indicated in table the cooled reaction mixture was then quenched with water (2,5 mL) and extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (2,5 mL) and dried over sodium sulfate. After evaporation of the solvents; the resulting residue was purified by column chromatography (silica gel, hexane–EtOAc) affording the expected alcohols. The table III.3 summarises the time and yields of tritylated compounds.

Table III.3: Detritylation of trityl ethers **1a'-1m'** by indium.

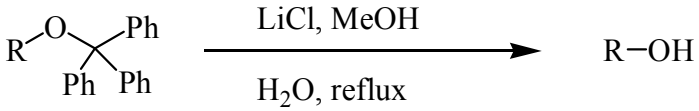
Entry	Product	Time (h)	Yield (%)
1	**1a'**	30	62
2	**1b'**	31	70
3	**1c'**	35	80
4	**1d'**	27	81
5	**1e'**	30	62
6	**1f'**	34	60
7	**1g'**	30	70
8	**1h'**	31	75
9	**1i'**	30	58
10	**1j'**	28	56
11	**1k'**	25	68
12	**1l'**	32	68
13	**1m'**	28	71

III.9.3. Removal of trityl ethers by lithium chloride

General procedure

Lithium chloride (0.1 g) was added to a solution of the substrate (1 mmol) in methanol (3ml) and the mixture heated at reflux over night the cooled reaction mixture was then quenched with water (2,5 mL) and extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with brine (2,5 mL) and dried over sodium sulfate. After evaporation of the solvents; the resulting residue was purified by recrystallization affording the expected

alcohols. The table III.4 summarises the time and yields of tritylated compounds (Scheme III.74).



Scheme III.74

Table III.4: Detritylation of alcohols by lithium chloride.

Entry	Product	Time (h)	Yield (%)
1	**1a'**	overnight	63
2	**1b'**	overnight	84
3	**1c'**	overnight	88
4	**1d'**	overnight	87
5	**1f'**	overnight	71
6	**1g'**	overnight	72
7	**1h'**	overnight	93
8	**1i'**	overnight	60
9	**1j'**	overnight	71
10	**1k'**	overnight	80

A tritylated alcohol bearing an unsaturation (geraniol) was deprotected with good results (entry 1). Detritylation of cyclohexyl and cyclopentyl ethers (**1b'** and **1h'**) under the optimized reaction conditions gave the expected free alcohols **2b'** and **2h'** in 84 and 93% yield, respectively (Table III.4, entries 2 and 7). The detritylation procedure was also effectively applied to trityl ethers 1c', **1g'**, and **1j'**, which contains aliphatic chains (entries 3, 6, and 9). The benzyl and phenyl trityl ether **1d'** and **1k'** were affected by these reaction conditions, leading to the expected deprotected alcohols **2d'** and **2k'** in 87 and 80% yield, respectively (entries 2 and10).

Interestingly, the two compounds **1f'** and **1i'**, which contains a double trityl, could be detritylated under our mild reaction conditions to give in the result **2f'** and **2i'** in 71% and 60% yields (Table III.4, entry 5 and 8).

Note

The use of three methods (the first: arene catalysed lithiation and catalytic amount of naphtalene, the second: indium and a saturated ammonium chloride solution, the third: lithium chloride in methanol) is very efficient for the removal of pivalated tetrazoles and detritylation of trityl ethers yielding to starting materials tetrazoles and alcohols which are commercially available and we needn't to the identification spectroscopic.

III.10. Conclusion

The literature review showed that there was little work for the introduction and cleavage of the protecting groups for the amine and hydroxy functions under mild conditions.

This is what motivated us to develop methods of deprotection using metals as agents (lithium, indium) and lithium chlorie .These methodologies permit removal of C–N and C-O bonds in various organic compounds. Deprotection of N-pivaloylated tetrazoles bearing aliphatic, aromatic, or heteroaromatic substituents was performed by a naphthalene-catalyzed lithiation process in the presence of excess of lithium and a catalytic amount of naphthalene led to the corresponding free tetrazoles without decomposition of the tetrazole ring.

Deprotection of O-tritylated alcohols was performed also in the presence of indium and aqueous solution of ammoniac, the same tritylated alcohols was deprotected with lithium chloride soluble in methanol, led to the corresponding free alcohols.

This procedure is an alternative to other methodologies, especially those involving hydrolysis, which usually require harsh reaction conditions. The results seem very interesting compared to the results of conventional methods of speed perspective, efficiency and selectivity.

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GENERAL CONCLUSION

General Conclusion

The objectives of this work were the search for the use of metals like lithium, indium and lithium chloride in the removal of carbon-oxygen and carbon-nitrogen bond of trityl and pivaloyl protecting groups. This problem led us to register our work partly under methodology of deprotection/ protection.

Our practice is based on the role of metals as agent in the mild reaction conditions, which has proven effective in many reactions. At the time of assessment, taking into account the results presented in this thesis, we can consider that the objective that we have assigned is reached.

We have presented general information on methods of introduction and cleavage of various protecting groups on functional groups (NH, OH, diol ... etc) in the bibliographic status of the subject.

Our work allows us the synthesis of starting materials tetrazoles bearing various aliphatic, aromatic, or benzylic substituents in the 5-position by reaction of sodium azide with the corresponding nitriles in the presence of an amine and then pivalytated on N1 by reaction with pivaloyl chloride, giving protected tetrazoles in good yields.

We report the use of a naphthalene-catalyzed lithiation to perform the removal of the pivaloyl protecting group from tetrazoles under very mild conditions by lithium and a catalytic amount of naphthalene with remarkable selectivity.

A simple protection reaction is made to protect a wide range of alcohols with trityl chloride giving trityl ethers in good yields.

In this work we have presented a very efficient method for the detritylation of trityl ethers using indium and lithium chloride under very mild reaction conditions.

This methodology has proved to be useful for the removal of the trityl group from tritylated primary, secondary, allylic or benzylic alcohols, and this method represents also a good alternative to the commonly used detritylation procedures, which use acidic reaction conditions.

The results have shown that the use of metals(Li, In) and without forgetting the use of lithium chloride in the removal of carbon-oxygen and carbon-nitrogen bond is very effective with high yields and reduced reaction time affording to the corresponding starting materials.

The obtained products are identified by spectroscopic methods (IR, RMN^{1}H, ^{13C}) with good yield.

Résumé en Français

Introduction

L'utilisation des groupements protecteurs en synthèse organique a pris un essor important ces dernières années, en témoignant les nombreuses méthodes décrites dans la littérature consacrées à ce sujet. Les considérations environnementales et économiques ont été mises en évidence pour les recherches académiques et industrielles en concevant des procédés de synthèse propres, sélectives, rentables et faciles à mettre en œuvre.

De nombreuses méthodes d'introduction et de clivage des groupements pivaloyl et trityl ont été décrites dans la littérature, nous avons suivis les méthodes les plus employées et qui font appel à des conditions opératoires faciles, ceci nous a permis d'éviter des problèmes de chimiosélectivité et de régénération des produits secondaires.

Les besoins récents en chimie organique de synthèse appliquée focalisent les efforts des chercheurs au développement de nouvelles voies efficaces et versatiles pour la préparation de molécules bioactives, en prenant en comptes en particulier les critères économiques et environnementaux. Nous avons suivi une méthode novatrice et écologique pour la préparation de tétrazoles. Ce groupe fonctionnel trouve des applications dans des domaines varies allant des matériaux aux explosifs, et est d'un intérêt tout particulier en chimie médicinale. Cette importance nous a conduit à synthétisé des tétrazoles. La méthode utilisée permet la formation de tétrazoles à partir de nitriles de façon très efficace, adaptable à l'échelle industrielle.

Dans le cadre de présent travail, nous nous intéresserons au développement des méthodes d'introduction et de clivage des groupements protecteurs dans des conditions réactionnelles très douces. Nous nous intéressons à la protection/déprotection dans des conditions neutres de la fonction amine par le pivaloyl et la fonction hydroxyle par le trityl tout en utilisant les (Li, In and LiCl) comme des agents réducteurs. Avec cette méthodologie, nous avons été en mesure d'atteindre l'élimination réductrice de la liaison carbone-azote, de liaisons carbone-oxygène dans les différents substrats. Dans le cadre de ce processus; nous avons effectué la déprotection réductrice des tétrazoles pivaloylés avec lithium et des alcools tritylés avec indium et lithium chloride.

Ce travail est subdivisé en trois chapitres :

- Le premier chapitre sera concerneré sur la synthèse des tétrazoles.
- Le deuxième chapitre représente la discussion des résultats obtenus de la protection des tetrazoles avec le pivaloyl chloride el les alcools avec le trityl chloride.

- Le troisième chapitre sera consacré à la création et à la mise en oeuvre d'une méthode originale de la déprotection des tétrazoles pivaloylés avec lithium et des alcools tritylés avec indium et lithium chloride.

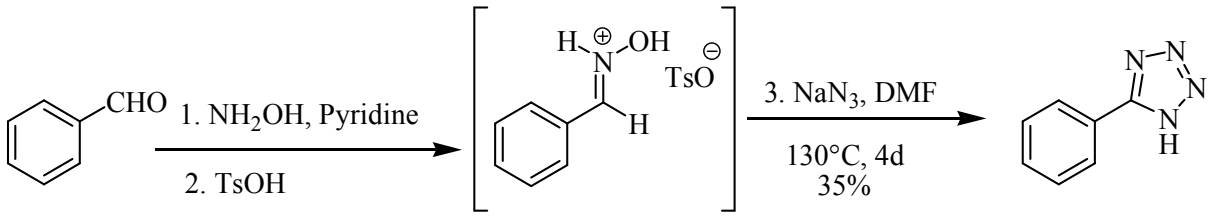
I.Tétrazoles

Les besoins récents en chimie organique encouragent les efforts des chercheurs au développement de nouvelles voies avantageuses pour la synthèse de molécules bioactives, en prenant en comptes en particulier les critères économiques et environnementaux. Nous avons utilisée une méthode novatrice et simple pour la préparation de tétrazoles. Ce groupe fonctionnel trouve des applications dans des différent domaines varies tout particulier en chimie médicinale et en biologie.

I.1.Les méthodes de synthèse

- ***À partir du sel d'oxime***

L'utilisation du sel d'oxime **22** avec le sodium azide est une méthode efficace pour la préparation des 5-tétrazoles dévelopée par Antonowa et Hauptmann.Dans ce procedure, le benzaldehyde **21** est transformé directement au aryl tétrazole **23** (Schéma I.10).



21 **22** **23**

Schéma I.10

- ***À partir du b-amino alcools***

F. Couty *et al*.ont rapporté que la chlorination ($SOCl_2$) de N-cyanomethyl b-amino alcools dérivé de b-amino alcools était régio-stéreoselective et donne les amines chlorinés en bons rendements. Ces produits sont de même convertis aux 2-cyano azetidines. Ils ont trouvé que Le traitement de ces chlorides avec le sodium azide en DMSO à 150°C donne des tetrazole–piperazines[27]en bons rendements (Schéma I.13).

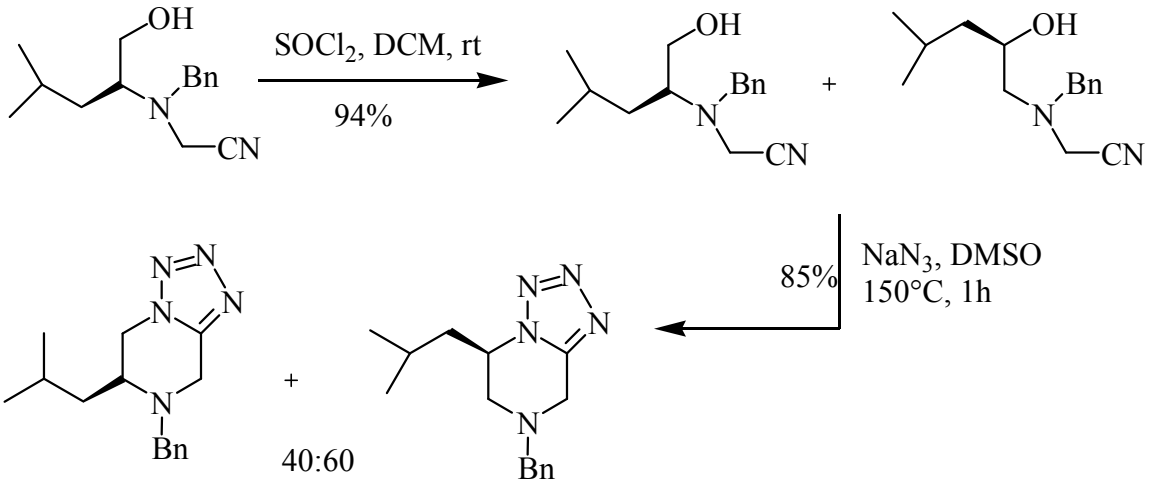


Schéma I.13

II. La protection des tétrazoles et des alcools

II.1. Les groupements protecteurs en synthèse organique

Quand une réaction chimique doit être effectuée, sélectivement, à un site réactif dans un composé multifonctionnel, d'autres sites réactifs doivent être temporairement bloqués. Beaucoup de groupes de protection (PG) ont été, et sont développés à cet effet. Un groupe protecteur doit remplir un certain nombre d'exigences:

- Il doit réagir sélectivement avec un bon rendement pour donner un substrat protégé qui est stable à la réaction projetée.
- le groupe protecteur doit être éliminé sélectivement avec un bon rendement par des réactifs aisément disponibles, de préférence non toxiques qui n'attaquent pas le groupe fonctionnel régénéré.
- le groupe protecteur doit former un dérivé (sans la génération de nouveaux centres stéréo gènes) qui peut être facilement séparé des produits secondaires liés à sa formation ou son clivage.
- le groupe protecteur doit avoir un minimum de fonctionnalités supplémentaires pour éviter d'autres réactions secondaires.

Tout bien considéré, aucun groupe protecteur n'est le meilleur. Actuellement, la science et l'art de la synthèse organique ont un long chemin à parcourir avant que nous puissions l'appeler une discipline finie et bien définie, comme il est amplement illustré par l'utilisation étendue de la protection des groupes lors de la synthèse de molécules multifonctionnelles. Un

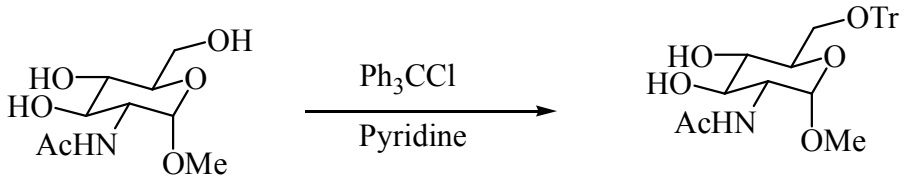
plus grand contrôle sur la chimie utilisée dans la construction de cadres d'origine naturelle moléculaires architecturalement belles et variées, ainsi que des structures artificielles, est nécessaire si l'on considère le nombre de protection et de déprotection, étapes souvent utilisées pour synthétiser une molécule.

II.2. Les groupements protecteurs des alcools (R-OH)

II.2.1. Trityl d'ethers

Formation

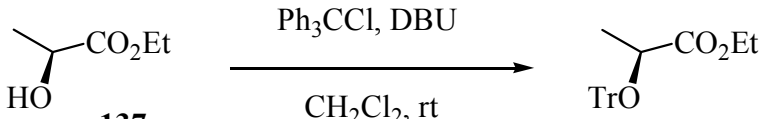
En ce qui concerne cette stratégie d'augmentation de l'encombrement stérique de la protection de l'alcool, le groupe trityle (Tr), historiquement développé pour aider la chimie des glucides et plus tard la construction d'oligonucléotides, est le plus important. Seuls les alcools primaires réagissent à un taux utile avec le chlorure de trityle dans la pyridine. Par conséquent, une protection sélective de ces groupes hydroxyles est possible (Schéma II.57).



131 **132**

Schéma II.57

Cette caractéristique est une raison majeure pour utiliser cette PG. En présence de la base plus puissante 1,8-diazabicyclo [5.4.0] undéc-7-ène (DBU), même les alcools secondaires peuvent être tritylés (Schéma II.58).



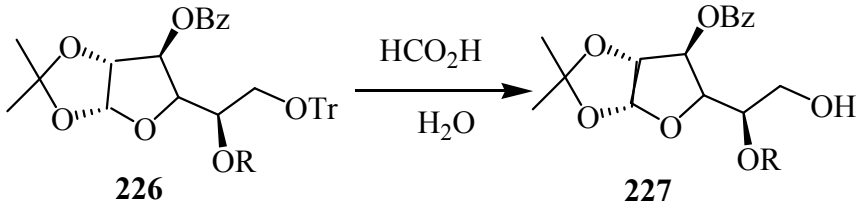
137 **138**

Schéma II.58

Clivage

En plus de fournir une protection sélective des groupes hydroxyles primaires, le groupe trityle offre une bonne résistance aux bases, mais il est facilement éliminé par traitement acide, TFA, HCO_2H, et AcOH offrant des conditions de clivage progressivement plus douces. L'acide

formique dans de l'éther est suffisamment sélectif pour cliver l'éther de trityle en présence d'autres groupes sensibles aux acides, y compris les acétals et t-butyldiméthylsilyle (TBDMS) éthers (Schéma III. 62).

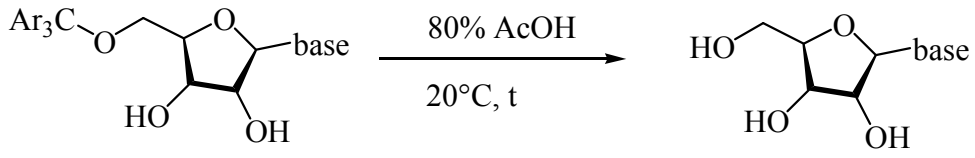


226 **227**

R = Ac	92%
R = TBDMS	88%
R = THP	60%/40% cleavage

Schéma III.62

Le taux de groupe trityle clivage peut être affiné par des substituants sur l'un ou plusieurs des noyaux phényle. Donneur d'électrons, les groupes favorisent la formation de cations, ce qui accélère le processus de clivage, et vice versa. Ceci est particulièrement utile dans la protection de la 5'-OH dans les nucléosides dans le cas où plusieurs variantes d'acide-labiles du GEP trityle peut être retiré sans perte concurrentielle de la base (qui peut être un problème avec le groupe trityle lui-même). Ci-dessous, il existe une comparaison des temps nécessaires pour effectuer l'hydrolyse complète des groupes trityle (Tr), p-méthoxyphényle diphénylméthyle (MTR), di (p-méthoxyphényl) phénylméthyle (DMTr), et le tri (pméthoxyphényl) méthyle (MTR) éthers (Schéma III.63).



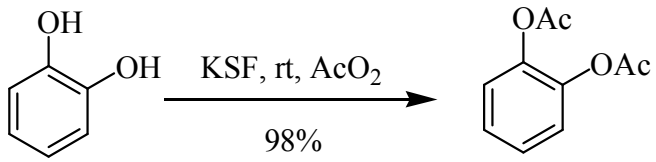
228 **229**

Ar_3c=Tr	*t* = 48 h
MMTr	2 h
DMTr	15 min
TMTr	1 min

Schéma III.63

II.2.1. Acetate d'ester

L'acétylation est une réaction importante dans la synthèse organique. Cette dernière s'effectue à température ambiantes pour les alcools el les phénols utilisant anhydride acide comme agent d'acylation à la présence de montmorillonites KSF ou K10. Les alcools primaires réagissent préférentiellement que les secondaires (mais une quantité du produit diacétylé se produit à 6% dans le cas du **31** (Schéma II.1).[10]



31 **32**

Schéma II.1

II.3. La protection des amines

II.3.1. Amide

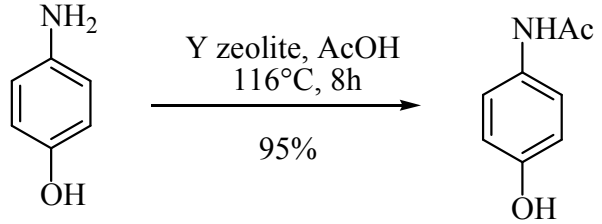
Parmi les différentes méthodes de protection de la fonction amine, l'acylation a pris une grande importance, elle a des applications industrielles. Les amides sont stables dans l'hydrolyse acide et basique et peut être hydrolysées par un chauffage dans des conditions acides ou basiques.

Acétamides

Les amides sont généralement protégés à partir de chlorure d'acide ou d'anhydrides correspondant. D'autres réactifs et de procédures de couplage des amines ont été développés pour la préparation des amides.[68]

Formation

L'utilisation de l'acide acétique plutôt que les réactifs conventionnels est efficace de point de vue économie d'atomes. Kulkarni et *al.*[69] ont développés une nouvelle méthode d'acylation chimiosélective d'amines aliphatiques, aromatiques et cycliques. La réaction se produit par l'acide acétique en présence de zéolite Y (SAR 5.2 silica/alumina ratio) (Schéma II.45).

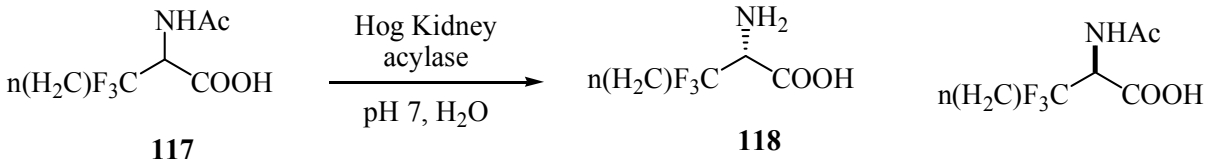


115 **116**

Schéma II.45

Clivage

L'hydrolyse enzymatique de l'acétamide avec l'acylase de Hog kidney a été réalisée avec une résolution énantiosélective intéressante (Schéma II.46).[70]



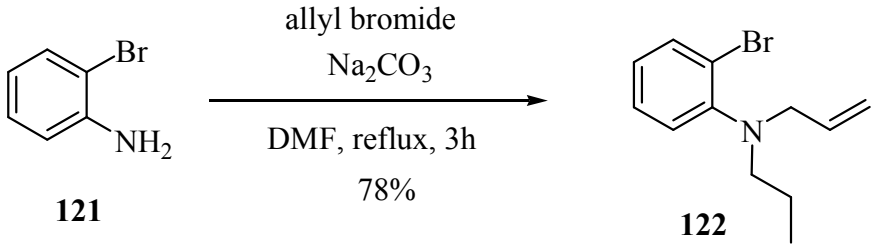
117 **118**

Schéma II.46

II.3.2. Allyl

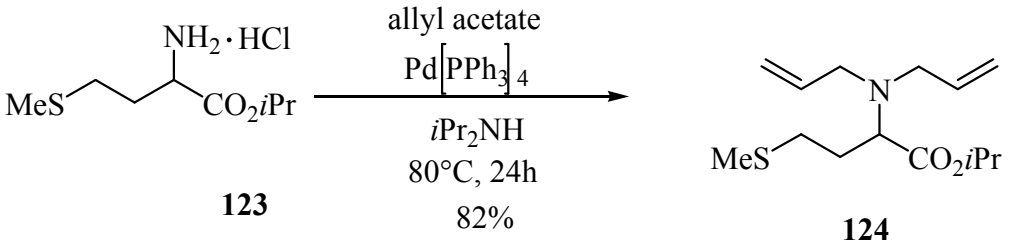
Formation

Deux méthodes ont été utilisées pour la protection de la fonction amine par le groupement d'allyle. La première c'est une simple alkylation utilisant le bromide d'allyle en THF en présence des carbonates du sodium (Schéma II.48). La deuxième méthode est l'allylation du Pd(0) catalysé avec l'acétate d'allyle (Schéma II.49).



121 **122**

Schéma II.48



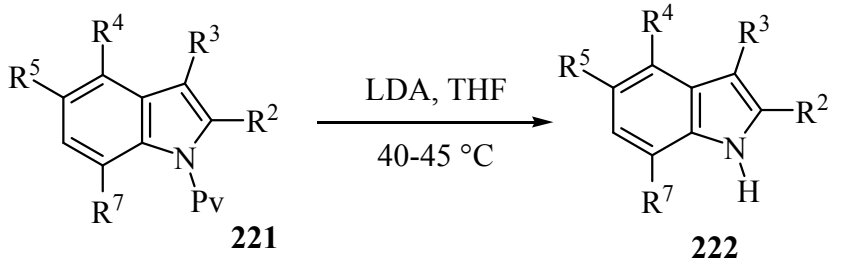
123 **124**

Schéma II.49

III. La déprotection des tétrazoles et des alcools protégés

III.1. Déprotection des N-pivaloylindoles avec LDA

Le traitement des pivaloylindoles avec deux équivalents de LDA en THF à 40-45°C pendant deux heures conduit à la déprotection quantitatives. Les résultats obtenus sont présentés dans le schéma III.59 suivant.[108]



221 **222**

R^2 = H, C_6H_5, CH_3 T = 2, 40, 90h 33-100%

R^3 = H, CH_3, CHO, $CH_2CH_2CO_2H$

R^4 = H, $CO_2C_2H_5$

R^5 = H, $CO_2C_2H_5$, OCH_3

R^7 = H, CH_3

Schéma III.59

III.2. Déprotection des éthers tritylés avec lithium

La réaction des éthers tritylés primaires, secondaires, allylique et benzylique avec le lihtium et une quantité catalytique du naphtalène conduit au clivage the la liaison trityl-oxygène, donnant les alcools correspondants en bons rendements dans des conditions réactionnelles très douces (Shéma III.66).[114]

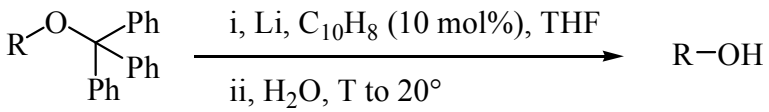


Schéma III.66

III.3. Élimination réductrice de pivaloyl tétrazoles par lithiation catalytique

La réaction de divers tétrazoles pivalilés avec un excès de lithium (01:20 rapport molaire) et une quantité catalytique du naphtalène (1: 0,4 rapport molaire) dans le tétrahydrofurane à 0 ° C pendant trois heures conduit, après l'ajout du methanol, aux tétrazoles correspondants par élimination réductrice de la liaison C-N. Cette méthodologie représente une alternative raisonnable à d'autres protocoles non réducteurs (Schéma III.72).

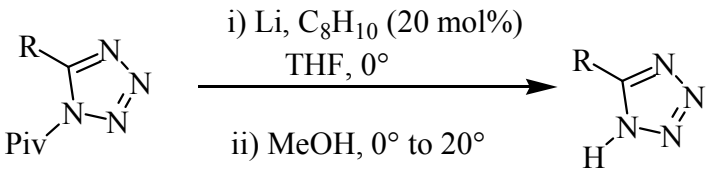


Schéma III.72

III.4. Elimination réductrice des éthers tritylés par l'indium

L'indium a été ajouté à une solution des éthers tritylés dans le methanol et une solution saturée de chlorure d'ammonium, le mélange a été chauffé à reflux. Le mélange réactionnel a été ensuite arrêté avec l'eau et on l'extrait avec l'EtOAc et on a lavé et sèché les phases organiques combinées. Le résidu résultant a été purifié par colonne Chromatographique (gel de silice, hexane-EtOAc) pour donner les alcools (Schéma attendus III.73).

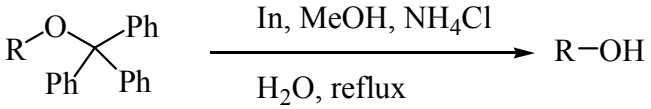


Schéma III.73

III.5. Elimination des éthers tritylés par le chlorure de lithium

Lithium chloride a été ajouté à une solution des éthers tritylés dans le methanol, le mélange a été chauffé à reflux. Le mélange réactionnel a été ensuite arrêté avec l'eau et on l'extrait avec l'EtOAc et on a lavé et sèché les phases organiques combinées. Le résidu résultant a été purifié par colonne Chromatographique (gel de silice, hexane-EtOAc) pour donner les alcools (Schéma attendus III.74).

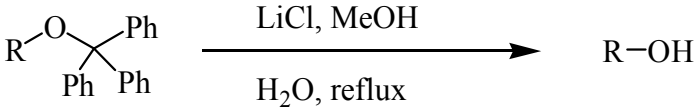


Schéma III.74

Conclusion

Les objectifs de ce travail étaient la recherche de l'utilisation des métaux comme le lithium, l'indium dans le clivage réducteur de la liaison carbone-oxygène et de la liaison carbone-azote. Ce problème nous a amené à inscrire notre travail en partie sous la méthodologie de déprotection / protection. Notre pratique est basée sur le rôle des métaux comme des agents réducteurs dans des conditions douces, ce qui a démontré son efficacité dans de nombreuses réactions. Au moment de l'évaluation, en tenant compte des résultats présentés dans cette thèse, nous pouvons considérer que l'objectif que nous avons attribué est atteint.

Nous avons présenté des généralités sur les méthodes d'introduction et de clivage de divers groupements protecteurs sur les groupements fonctionnels (NH, OH, diol…etc) dans la situation bibliographique du sujet.

Notre travail nous a permis au départ la synthèse des tétrazoles qui portent différents substituants aliphatiques, aromatiques, ou benzyliques en position 5 par réaction de sodium azide avec les nitriles correspondants en présence d'un sel d'amine, puis la protégée par réaction avec le chlorure de pivaloyle, donnant des tétrazoles protégées avec de bons rendements.

Nous rapportons l'utilisation de la méthodologie de la lithiation catalysée pour effectuer la déprotection du groupement pivaloyle pour donner des tétrazoles dans des conditions très douces utilisant lithium comme agent réducteur et une quantité catalytique du naphtalène avec une sélectivité remarquable.

Une simple réaction de la protection est faite pour protéger une large gamme d'alcools avec du chlorure de trityle donnant des éthers de trityle avec de bons rendements.

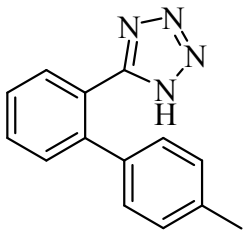
Dans ce travail, nous avons présenté un procédé très efficace pour la détritylation des éthers de trityle à l'aide de l'indium et du chlorure de lithium dans des conditions réactionnelles très douces.

Partie expérimentale

1 .Synthèse des tétrazoles 5 -substitués à partir de nitriles

Le mélange d'un nitrile (50 mmol), de NaN_3 (65 mmol) et du sel d'aminé (150 mmol) dans un solvant aromatique (100 ml) a été chauffé à 110 ° C pendant 17-30 h sous agitation. Après refroidissement, le produit a été extrait avec l'eau (100 ml). HCl 36 % a été ajouté goutte à goutte a la phase aqueuse, le sel de tétrazole se produit. Après filtration, le solide a été séché sous pression réduite, ce qui donne le tétrazole.

- **Synthèse de la 5- (4'- méthylbiphényl -2-yl)-1*H*- tétrazole (2b)**

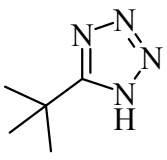


2b

En suivant le mode opératoire général, la réaction de 4'-méthyl- [1,1'-biphényl]-2-carbonitrile (3,94 g, 50 mmol), de NaN_3 (3,9 g, 65 mmol) et du sel d'aminé (8,22 g, 150 mmol) dans le toluène à 110 ° C a donné **2b** comme 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).

- **Synthèse de la 5-(*ter*t-butyl)-1*H*-tétrazole (2c)**

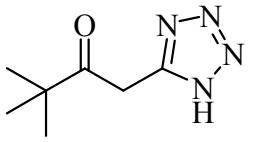


2c

En suivant le mode opératoire général, la réaction de pivalonitrile (2,25 ml, 50 mmol), de NaN_3 (3,9 g, 65 mmol) et du sel d'aminé (8,22 g, 150 mmol) dans le toluène à 110 ° C a donné **2c** 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).

- **Synthèse de 3,3-diméthyl-1-(1-*H*-tétrazole-5-yl)butan-2-one (2d)**

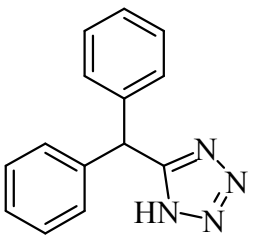


2d

En suivant le mode opératoire général, la réaction de 4,4-diméthyl-3- oxopentanenitrile (6,25 g, 50 mmol), de NaN_3 (3,9 g, 65 mmol) et du sel d'aminé (8,22 g, 150 mmol) dans le toluène à 110 ° C a donné **2d** comme un solide orange.

- **Rdt** = 85% (7.11 g).
- **$T._{fus}$** = 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).
- **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).

- **Synthèse de la 5 -benzhydryl -1 H- tétrazole (2f)**



2f

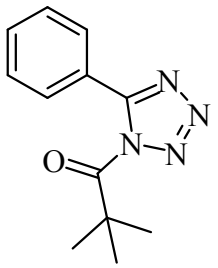
En suivant le mode opératoire général, la réaction de 2,2- diphénylacétonitrile (9,55 g, 50 mmol), de NaN_3 (3,9 g, 65 mmol) et du sel d'aminé (8,22 g, 150 mmol) dans le toluène à 110 ° C a donné **2f** comme un solide blanc.

- **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).

2. Protection des tétrazoles avec le chlorure de pivaloyle

Dans une solution du tétrazole (10,0 mmol) dans le THF anhydre (10 ml) sous argon à 0 ° C, on a ajouté goutte à goutte 2,5 M de *n*-BuLi dans l'hexane (4 mL, 10,0 mmol); le mélange a été agité à cette température pendant 10 min. Chlorure de pivaloyle (1,23 mL, 10,0 mmol) a été ajouté au mélange en ca. 5 min et il a été agité à température ambiante toute la nuit. La réaction est arrêtée avec H_2O (5 ml) et extraite avec de l'EtOAc (3 x 15 ml). Les phases organiques combinées ont été lavées avec du NaCl (5 ml), séchée avec le Na_2SO_4, filtré, et le solvant a été évaporé pour donner un résidu qui a été purifié par recristallisation (hexane -EtOAc) pour donner un produit pur.

- **2,2-diméthyl-1-(5-phényl-1*H*-tétrazole-1-yl)propan-1-one (1a)**

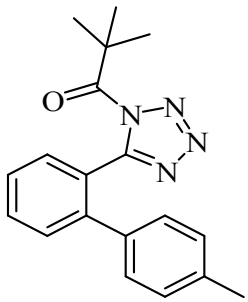


1a

En suivant le mode opératoire général, la réaction de 5-phényl-1H-tétrazole (1,46 g, 10 mmole), du chlorure de pivaloyle (1,23 ml), *n*-BuLi (4 ml) dans le THF (10 mL) à 0 ° a donné **1a** sous forme d'un solide blanc.

- **Rdt** = 65% (1.49 g).
- **$T._{fus}$** = 218-220°C.
- **IR (KBr):** 1701, 1608, 1562, 1484, 1409, 1256, 685 cm^{-1}.
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 1.06 (s, 9 H), 7.45–7.90 (m, 5 H).
- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 27.6 (3x CH_3), 39.3 (C), 125.6 (C), 128.2 (2 CH), 130.5 (2 CH), 132.5 (CH), 157.7 (C).

- **2,2-diméthyl-1-[5-(4'-méthylbiphényl-2-yl)-1*H*-tétrazole-1-yl]propan-1-one (1b)**

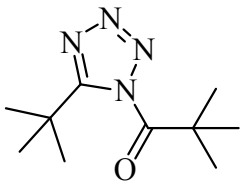


1b

En suivant le mode opératoire général, la réaction de la 5- (4'-méthyl- [1,1'-biphényl] -2-yl) -1*H*-tétrazole (0,086 g), du chlorure de pivaloyle (0,041 ml), *n*-BuLi (0,13 ml) dans le THF (0,33 ml) à 0 ° a donné **1b** sous forme d'un solide jaune.

- **Rdt** = 62% (1.98 g).
- **IR (KBr):** 1712, 1482, 1244, 1078, 823, 754 cm^{-1}.
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 0.92 (s, 9 H), 2.27 (s, 3 H), 6.93–7.08 (m, 4 H), 7.45–7.63 (m, 4 H).
- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 21.1 (CH_3), 27.6 (3x CH_3), 124.2 (C), 128.7, 129.9, 130.2, 131.6, 131.8, 132.5 (8 CH), 137.6 (C), 138.8 (2 C), 143.6 (2 C), 156.8 (C).

- **1- (5-(*tert*-butyl)-1*H*-tétrazole-1-yl)-2,2-diméthylpropan-1-one (1c)**

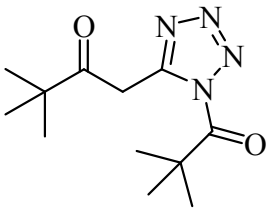


1c

En suivant le mode opératoire général, la réaction de la 5- (tert-butyl) -1*H*-tétrazole (0,028 g), du chlorure de pivaloyle (0,027 ml), *n*-BuLi (0,088 ml) dans le THF (0,22 ml) à 0 ° donnant lieu **1c** comme un solide blanc.

- **Rdt** = 70% (1.47 g).
- **T.$_{fus}$** = 104-106°C.
- **IR (KBr):** 1732, 1264, 1218, 1045, 703 cm^{-1}.
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 1.42 (s, 18 H).
- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 29.5 (3x CH_3), 31.8 (3x CH_3), 165.7 (C), 214.1 (CO).

- **3,3-diméthyl-1-(1-pivaloyl-1H-tétrazol-5-yl)butan-2-one (1d)**

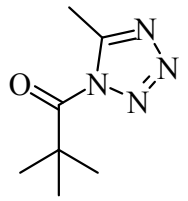


1d

En suivant le mode opératoire général, la réaction de 3,3-diméthyl-1-(1*H*-tétrazole-5-yl) butan-2-one (1 g), du chlorure de pivaloyle (0,73 ml), *n*-BuLi (2,38 ml) dans le THF (5,25 mL) à 0 ° C a donné **1d** sous forme d'un solide marron.

- **Rdt** = 80% (2.01 g).
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 2.74 (s, 18 H), 2.80 (s, 2 H).
- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 26.4, 26.8, 27.5 (3x CH_3), 27.6, 27.7, 27.9 (3x CH_3), 31.7 (CH_2), 39.3 (C), 45.5 (C), 152.5 (C), 182.5 (C=O), 210.1 (C=O).

- **2, 2dimethyl-1-(5-méthyl-1H-tétrazole-1-yl)propan-1-one (1e)**

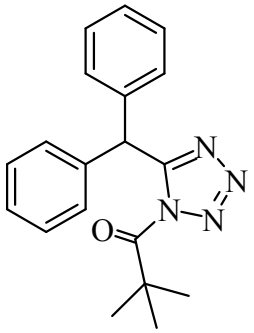


1e

Suivant le mode opératoire général, la réaction de 5-méthyl-1*H*-tétrazole (0,84, 10 mmol), du chlorure de pivaloyle (1.23ml, 10 mmol), de *n*-BuLi (2,5 M, 4 ml) dans le THF (10 mL) à 0 ° a donné **1e** sous forme d'un solide blanc.

- **Rdt** = 85% (1.43 g).
- **T.$_{fus}$** = 152-157°C.
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 0.92 (s, 9 H), 2.31 (s, 3 H).
- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 8.4 (CH_3), 26.8 (CH_3), 27.6 (2x CH_3), 39.3 (C), 154.1 (C), 182.5 (CO).

- **1-(5-diphenymethyl-1*H*-tétrazol-1-yl)-2,2-diméthylpropan-1-one (1f)**



1f

En suivant le mode opératoire général, la réaction de 5-benzhydryl-1*H*-tétrazole (1,30 g), du chlorure de pivaloyle (0,67 ml), *n*-BuLi (2,20 ml) dans du THF (5 ml) à 0 ° a donné **1f** sous forme d'un solide blanc.

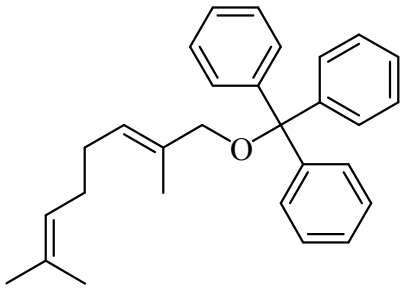
- **Rdt** = 90% (2.88 g).
- **T.$_{fus}$** = 154-158°C.
- **RMN^{1}H: (400 MHz, CD_3OD):** δ = 1.07 (s, 9 H), 5.80 (s, 1 H), 7.23–7.38 (m, 10 H).

- **RMN^{13}C: (100 MHz, CD_3OD):** δ = 26.8, 27.5, 27.6 (3x CH_3), 39.3 (C), 47.8 (CH), 128.6 (2 CH), 129.6 (4 CH), 129.9 (4 CH), 140.8 (2 C), 159.9 (C), 182.5 (C=O).

3. Protection des alcools

Une solution d 'alcool (5 mmoles) dans le CH_2CI_2 correspondant (2,5ml) a été ajouté à une solution de chlorure de trityle (1,55 g, 5,5 mmol), de NEt_3 (1,25 ml, 8,8 mmol) et du DMAP (0,046 g, 0,2 mmol) dans CH_2CI_2 (5 ml) à température ambiante et le mélange a été agité pendant une nuit. La réaction a été ensuite arrêtée avec l'eau (2,5 ml) et extraite avec l'EtOAc (3 x 10 ml) et les phases organiques combinées ont été lavées avec le NaCl (2,5 ml) et séchées avec le sulfate de sodium. Après évaporation des solvants (15 Torr), le résidu résultant a été purifié par colonne Chromatographique (gel de silice, hexane-EtOAc) pour donner les éthers tritylés attendus.

- **Geranyl Trityl Ether (1a')**



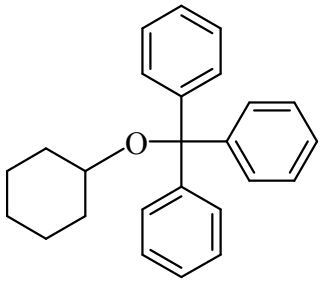
1a'

En suivant le mode opératoire général, la réaction de géraniol (0.87 ml, 5 mmol), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4-(diméthylaminopyridine) (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1a'** sous forme d'une huile incolore.

- **Rdt**= 88% (1.75 g).
- **IR (KBr):** 3085, 3058, 3022, 1688, 1597, 1490 (HC=C), 1054 (CO). $cm^{-1.}$
- **RMN^{1}H: (250 MHz, MeOD-d_4):** δ = 1.45 (s, 3 H, CH_3), 1.62(s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 2.03–2.18 (m, 4 H, CH_2CH_2), 3.57 (d, 2 H, *J* = 6.4 Hz, CH_2O), 5.13–5.15 (m, 1 H, *H*C=CMe_2), 5.39–5.42 (m, 1 H, CHCO), 7.23–7.33 (m, 9 H, ArH), 7.43–7.47 (m, 6 H, ArH).

- **RMN^{13}C: (62.5 MHz, MeOD-d$_4$):** δ = 16.5 (Me), 17.8 (Me), 25.9 (Me), 27.4 (CH_2CH_2), 40.6 (CH_2CH_2), 62.2 (CH_2O), 87.9 (CO), 122. 5 (CHCO), 125.1 ($CH=CMe_2$), 132.4 (CMe_2), 139.7 ($CH_2C=C$), 128.0 (3 C), 128.7(6 C), 129.8 (6 C), 145.7 (3 C, ArC).

- **Cyclohexyl Trityl Ether (1b')**

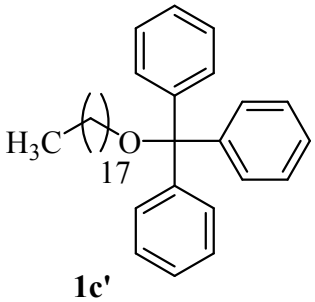


1b'

En suivant le mode opératoire général, la réaction du cyclohexanol (0,52 ml, 5 mmoles), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1b'** sous forme d'un solide blanc.

- **Rdt** = 92% (1.58 g).
- **T.$_{fus}$** = 85°C.
- **IR (KBr):** 3000, 3010, 1600, 1450 (HC=C), 1000 cm $^{-1}$ (CO).
- **RMN^{1}H: (400 MHz, CDCl$_3$):** δ = 1.01–1.35 (m, 6 H, 3 × CH_2), 1.52–1.61 (m, 4 H, 2 × CH_2), 3.46 (m, 1 H, CHO), 7.19–7.29 (m, 9 H, ArH), 7.55–7.53 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, CDCl$_3$):** δ = 24.4 (2 C), 25.9, 33.9 (3 C) (5 × CH_2), 72.1 (CHO), 86.5 (CO), 126.9 (3 C), 127.7 (6 C), 129.1 (6 C), 145.8 (3 C, ArC).

- **Stearyl Trityl Ether (1c')**

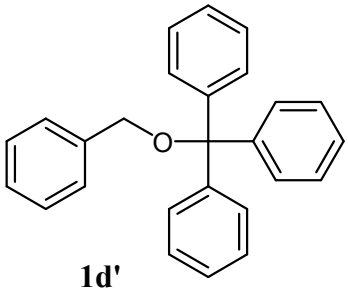


1c'

En suivant le mode opératoire général, la réaction de l'alcool stéarique (1,35 g, 5 mmol), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1c'** sous forme d'un solide blanc.

- **Rdt** = 95% (2.45 g).
- **T.$_{fus}$** = 70°C.
- **IR (KBr):** 3000, 2950, 2400, 1500, 1450 (HC=C), 1500, 1300, 1050, 1010 (CO), 650 cm^{-1}.
- **RMN^{1}H: (400 MHz, $CDCl_3$):** δ = 0.81 (t, 3 H, *J* = 4 Hz, Me), 1.18–1.56 [m, 24 H, Me (CH_2)$_{12}$], 2.20–2.22 (m, 6H),2.51 (m, 2 H, CH_2CO), 2.96 (t, 2 H, *J* = 6.7 Hz, CH_2O), 7.13–7.25 (m, 9 H, ArH), 7.36 –7.38 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ = 4.2, 10.2, 14.1, 22.6, 26.2, 29.3, 29.6, 30.0, 31.9, 39.9, 40.1, 40.3 [Me (CH_2)$_{17}$], 63.6 (CH_2O), 86.25 (CO), 126.7 (3 C), 127.6 (6 C), 128.6 (6 C), 144.5 (3 C, ArC).

- **Benzyl Trityl Ether (1d')**

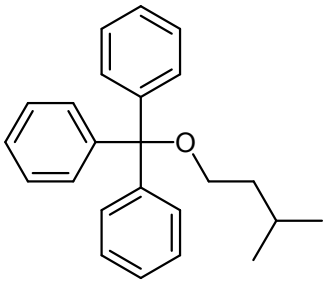


1d'

En suivant le mode opératoire général, la réaction de l'alcool benzylique (0.51ml, 5 mmol), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4-(diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1d'** comme un solide blanc.

- **Rdt** = 92% (1.58 g).
- **T.$_{fus}$** = 95°C.
- **IR (KBr):** 3059, 3053, 3031, 3023, 1594, 1489 (HC=C), 1085, 1060 cm^{-1} (CO).
- **RMN^{1}H: (400 MHz, $CDCl_3$):** δ = 3.51 (s, 2 H, CH_2), 7.22–7.34 (m, 14 H, ArH), 7.54– 7.58 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ = 72.1 (CH_2), 86. 5 (CO), 126.8 (2 C), 127.3 (3 C), 127.6, 127.8 (6 C), 128.0 (2 C), 129.0, 129.1 (6 C), 146.7, 146.9 (3 C, ArC).

- **Isoamyl Trityl Ether (1e')**

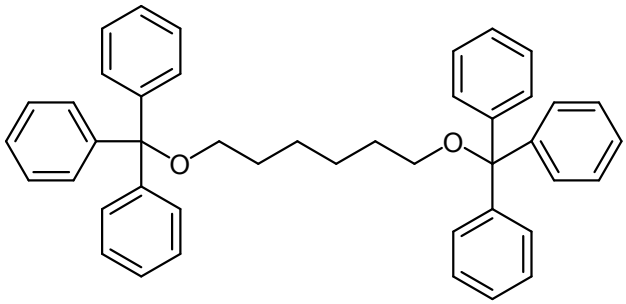


1e'

En suivant le mode opératoire général, la réaction de l'alcool isoamylique (0,54 ml, 5 mmoles), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4 (diméthylamino) pyridine (46 mg, 0,2 mmol) dans du le CH_2CI_2 (7,5 mL) à température ambiante a donné **1e'** comme une huile incolore.

- **Rdt** = 75% (1.24 g).
- **IR (KBr):** 3070, 3024, 2912, 1485 (HC=C), 1446, 1083 cm^{-1} (CO).
- **RMN^{1}H: (400 MHz, $CDCl_3$):** δ = 0.80 (d, 3 H, *J* = 8 Hz, Me), 0.92 (d, 3 H, *J* = 4Hz, Me),1.47-1.53 (m, 2 H, CH_2CH_2O),1.72-1.79 (m, 1 H, $CH(Me)_2$), 3.06 (t, 2 H, *J* = 8 Hz, CH_2O), 7.25–7.36 (m, 9 H, ArH), 7.49–7.51 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ = 22.8 (2 ×Me), 25.2 (CH $(Me)_2$), 39.1(CH_2), 68.2 (CH_2O), 86.4 (CO), 126.9 (3C), 127.8 (6C), 128.8 (6C), 144.6 (3 C, ArC).

- **1,6-Di(trityloxy)hexane (1f')**

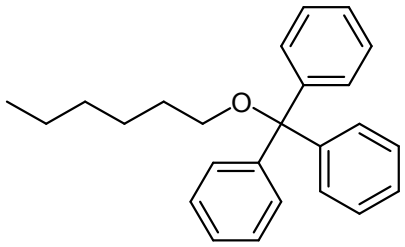


1f'

En suivant le mode opératoire général, la réaction de hexadiol (0,59 g, 5 mmol), de chlorure de trityle (3 g, 11 mmol), Et_3N (2,5 ml, 17,6 mmol) et de 4- (diméthylamino) pyridine (92 mg, 0,4 mmol) dans le CH_2CI_2 (15 mL) à température ambiante a donné **1f'** sous forme d'un solide blanc

- **Rdt** = 53% (1.60 g).
- **$T._{fus}$** = 160°C.
- **IR (KBr):** 2950, 3000, 3010, 1450 (HC=C), 1000, 1010 cm^{-1} (CO).
- **RMN^{1}H: (400 MHz, $CDCl_3$):** δ = 1.30–1.33 (m, 4 H, 2 × CH_2CH_2), 1.53–1.62 (m, 4 H, 2 × CH_2CO), 3.00 (t, 4 H, *J* = 6.6 Hz, 2 × CH_2O), 7.19–7.29 (m, 18 H, ArH), 7.41–7.44 (m, 12 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ = 26.2 (2 C, 2 × CH_2CH_2), 30.1 (2 C, 2 × CH_2CO), 63.6 (2 C, 2 × CH_2O), 86.3 (2 C, 2 × CO), 126.9 (6 C), 127.8 (12 C), 128.8 (12 C), 144.6 (6 C, ArC).

- **Hexyl Trityl Ether (1g')**

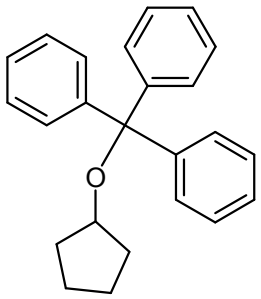


1g'

En suivant le mode opératoire général, la réaction de l'hexanol (0.62ml, 5 mmol), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (15 mL) à température ambiante a donné **1g'** sous forme d'une huile incolore.

- **Rdt** = 62% (1.18 g).
- **IR (KBr):** 3166, 3058, 3028, 1593, 1488 (HC=C), 1080, 1068 cm^{-1} (CO).
- **RMN^{1}H: (250 MHz, $CDCl_3$):** δ = 1.22 (d, 3 H, *J* = 6.1 Hz, Me), 1.53–1.81 [m, 6 H, Me (CH_2)$_3$], 3.08–3.17 (m, 2 H, CH_2 CH_2O), 3.76–3.88 (m, 2 H, CH_2O), 7.23–7.37 (m, 9 H, ArH), 7.42–7.50 (m, 6 H, ArH).
- **RMN^{13}C: (62.5 MHz, $CDCl_3$):** δ = 23.6 (Me), 26.5 (CH_2Me), 36.4 (2×CH_2), 63.8 (CH_2CH_2O), 68.0 (CH_2O), 86.7(CO), 127.0 (3C), 127.8 (6 C), 128.7 (6 C), 144.3 (ArC).

- **Cyclopentyl Trityl Ether (1h')**

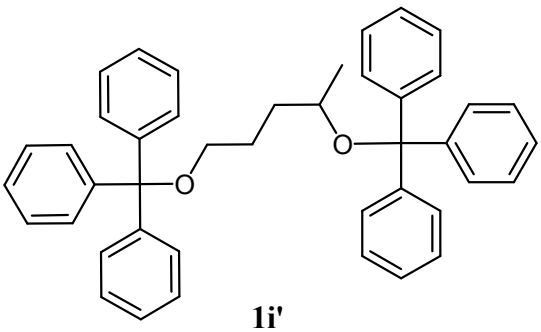


1h'

En suivant le mode opératoire général, la réaction de cyclopentanol (0,45 ml, 5 mmole), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1h'** comme un cristal transparent.

- **Rdt** = 62% (0.82g).
- **$T._{fus}$** = 84°C.
- **IR (KBr):** 3055, 3028, 1596, 1485 (HC=C), 1045 cm^{-1} (CO).
- **RMN^{1}H: (250 MHz, $CDCl_3$):** δ = 0.93–1.18 (m, 6 H, 3 × CH_2), 1.33–1.65 (m, 2 H, CH_2), 4.06–4.10 (m, 1 H, CHO), 7.25–7.37 (m, 9 H, ArH), 7.55–7.58 (m, 6 H, ArH).
- **RMN^{13}C: (62.5 MHz, $CDCl_3$):** δ = 23.8 (3 C), 33.6 (1 C) (4 × CH_2), 72.8 (CHO), 86.9 (CO), 126.8 (3 C), 127.3 (6 C), 129.0(6 C), 145.5 (3 C, ArC).

- **1,4-Di(trityloxy)pentane(1i')**



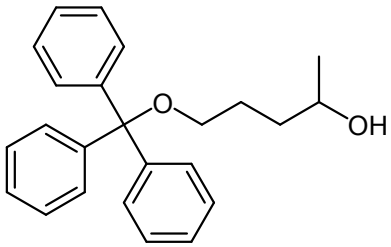
1i'

Suivant le mode opératoire général, la réaction de 1,4 pentadiol (0.53 ml, 5 mmol), de chlorure de trityle (3 g, 11 mmol), Et_3N (2,5 ml, 17,6 mmol) et de 4- (diméthylamino)

pyridine (92 mg, 0,4 mmol) dans le CH_2CI_2 (15 mL) à température ambiante a donné **1i'** sous forme d'un solide blanc.

- **Rdt** = 55% (1.62g).
- **T.$_{fus}$** = 122°C.
- **IR (KBr):** 3083, 3052, 3022, 1598, 1500 (HC=C), 1081, 1075 cm^{-1} (CO).
- **RMN^{1}H: (250 MHz, $CDCl_3$):** δ = 0.93 (d, 3 H, *J* = 6.07 Hz, Me), 1.13–1.30 (m, 2 H, CH_2CH_2), 1.46–1.70 (m, 2 H, CH_2CHO), 2.80–2.97 (m, 2 H, CH_2O), 3.57–3.60 (m, 1 H, CHO), 7.19–7.35 (m, 18 H, ArH), 7.41–7.45 (m, 12 H, ArH).
- **RMN^{13}C: (62.5 MHz, $CDCl_3$):** δ = 21.2 (Me), 25.4 (CH_2CH_2), 34.0 (CH_2CHO), 64.0 (CH_2O), 69.8 (CHO), 86.3 (CO), 86.5 (CO), 120.0 (3 C), 126.9 (3 C), 127.7 (6 C), 127.8 (6 C), 128.8 (6 C), 129.0 (6 C), 144.6 (3 C), 145.6 (3 C, ArC).

- **5-Trityloxy-2-pentanol (1j')**

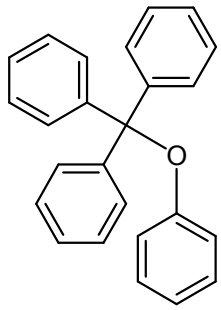


1j'

En suivant le mode opératoire général, la réaction de 1, 4 pentadiol l (0,45 ml, 5 mmoles), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4-(diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 mL) à température ambiante a donné **1j'** sous forme d'une huile incolore.

- **Rdt** = 62% (0.82g).
- **T.$_{fus}$** = 84°C.
- **IR (KBr):** 3024, 2950, 2862, 1593, 1488 (HC=C), 1045 cm^{-1} (CO).
- **RMN^{1}H: (250 MHz, DMSO-d_6):** δ =.0.87–1.52 [m, 8 H, Me, 2×CH_2, and OH], 2.51 (m, 2 H, CH_2OTr), 3. 93 (m, 1 H, CHOH), 7.23–7.37 (m, 9 H, ArH), 7.37–7.44 (m, 6 H, ArH).
- **RMN^{13}C: (62.5 MHz, DMSO-d_6):** δ = .1 (Me), 33.0 (2 C, 2 × CH_2), 66.2 (CH_2O), 75.8 (CHOH), 86.3 (CO), 126.9 (3 C), 127.8 (6 C), 128.4(6 C), 145.0 (3 C, ArC).

- **Phenyl trityl ether (1k')**

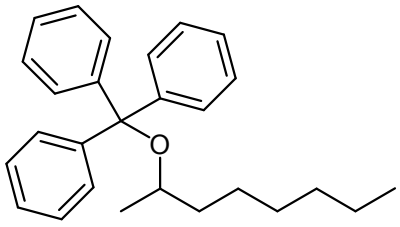


1k'

En suivant le mode opératoire général, la réaction du phénol (0,47 g, 5 mmol), l'hydroxyle de potassium (0,49, 8.8ml) dans le MeOH (5 ml) et le THF (5 ml) avec le chlorure de trityle (1,55 g, 5,5 mmol), et 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans le CH_2CI_2 (7,5 ml) à température ambiante' a donné **1k'** comme une huile incolore.

- **Rdt** = 38% (1.62 g).
- **IR (KBr):** 3166, 3055, 2947, 1593, 1485 (HC=C), 1076 cm^{-1} (CO).
- **RMN ^{1}H: (250 MHz, $CDCl_3$):** δ = 6.63-6.79 (dd, 3 H), 7 (t, 2H, *J* = 8.4 Hz), 7.22–7.31 (m, 9 H, ArH), 7.33– 7.44 (m, 6 H, ArH).
- **RMN^{13}C: (62.5 MHz, $CDCl_3$):** δ = 86.5 (CO), 122.1 (2 C), 122.4 (2 C), 128.2 (3 C), 128.6 (6 C), 129.3 (6 C), 129.8 (1 C), 145.3(3 C, ArC), 146.6 (1 C, ArC).

- **2-Trityloxyoctane (1l')**

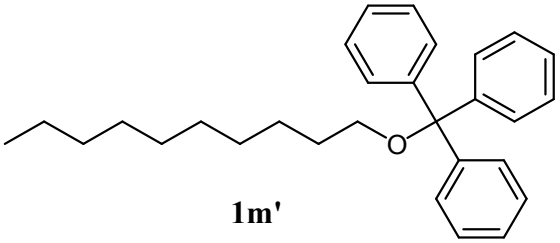


1l'

Suivant le mode opératoire général, la réaction du 2-octanol (0,45 ml, 5 mmoles), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans du CH_2CI_2 (7,5 mL) à température ambiante a donné **1l'** comme une huile incolore.

- **Rdt** = 78% (1.60g).
- **IR (KBr):** 3055, 2925, 1598, 1489 (HC=C), 1075, 1026 cm^{-1} (CO).
- **RMN ^{1}H: (400 MHz, $CDCl_3$):** δ =. 0.83 (t, 3 H, *J* = 8 Hz, CH_3CH_2), 0.86 (d, 3 H, *J* = 4 Hz, CH_3CO), 1.05–1.23 [m, 10 H, $(CH_2)_5$], 3.51–3.58 (m, 1H, CHO), 7.19–7.30 (m, 9 H, ArH), 7.49–7.52 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ = 14.2 (CH_3CH_2), 21.3 (CH_3CO), 22.7 (CH_2), 25.0 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 37.6 (CH_2), 70.2 (CHO), 86.5 (CO), 126.8 (3 C), 127.7 (6 C), 129.1 (6 C), 145.7 (3 C, ArC).

- ***n*-Decyl Trityl Ether (1m')**



1m'

En suivant le mode opératoire général, la réaction de décanol (0,45 ml, 5 mmole), de chlorure de trityle (1,55 g, 5,5 mmol), Et_3N (1,25 ml, 8,8 mmol) et de 4- (diméthylamino) pyridine (46 mg, 0,2 mmol) dans du du CH_2CI_2 (7,5 mL) à température ambiante a donné **1m'**comme une huile incolore.

- **Rdt** = 76% (1.85g).
- **IR (KBr):** 3085, 3057, 3031, 1596, 1489 (HC=C), 1086, 1068 cm^{-1} (CO).
- **RMN ^{1}H: (400 MHz, $CDCl_3$):** δ = 0.87 (t, 3 H, *J* = 8 Hz, Me), 1.24–1.36 [m, 14 H, Me $(CH_2)_7$], 1.51–1.65 (m, 2 H, CH_2CO), 3.03 (t, 2 H, *J* = 6.7 Hz, CH_2O), 7.19–7.31 (m, 9 H, ArH), 7.43 –7.46 (m, 6 H, ArH).
- **RMN^{13}C: (100 MHz, $CDCl_3$):** δ =14.2 (Me), 22.8, 26.4, 29.4, 29.6, 29.7 (2 C), 30.2, 32.0 [Me $(CH_2)_8$], 63.8 (CH_2O), 86.3 (CO), 126.9 (3 C), 127.8 (6 C), 128.8 (6 C), 144.6 (3 C, ArC).

ANNEX

Synthesis

Reviews and Full Papers in Chemical Synthesis

Thieme

Reductive Removal of the Pivaloyl Protecting Group from Tetrazoles by a Naphthalene-Catalyzed Lithiation Process

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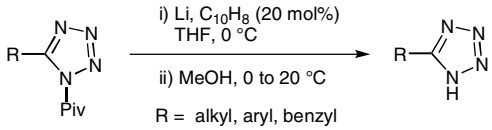

Dedicated to the memory of Professor Alan R. Katritzky

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Abstract The reaction of various 1-pivaloyl-1*H*-tetrazoles with excess lithium and a catalytic amount of naphthalene (20 mol%) led, after treatment with methanol, to the corresponding free tetrazoles through reductive C–N bond cleavage. This methodology represents a reasonable alternative to other nonreductive protocols.

Keywords tetrazoles, pivaloyl, lithium, deprotection

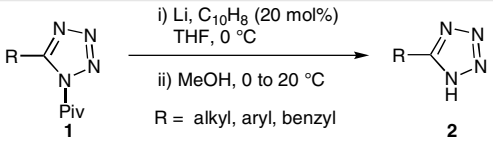
The pivaloyl group is widely used in organic synthesis to protect alcohols, amines, and thiols, due to its easy introduction, stability under a variety of reaction conditions, and relatively easy removal to give the corresponding depivalated compounds.[1] Among the different methodologies reported for the deacylation of protected alcohols and amines, we can find hydrolysis under basic or acidic conditions,[2] reduction with alkali metals in liquid ammonia,[3] reductive cleavage using an arene-catalyzed lithiation,[4] reaction with hydride sources,[5] electrolysis,[6] and enzymatic methods.[7]

The tetrazole moiety is present in several biologically active compounds, such as sartans, which are pharmaceuticals that are efficient for the treatment of hypertension, kidney damage caused by diabetes, and heart failure. The synthesis of sartans generally requires protection and deprotection steps to the tetrazole ring.[8] The effective protection caused by the high steric demand of the pivaloyl group, together with the ease of its introduction into and its removal from the nitrogen atom, are features that potentially make the pivaloyl group useful in the preparation of this interesting family of drugs. Thus, the development of procedures that remove the pivaloyl protecting group without affecting the tetrazole ring would be very interesting.[8]

In the last few years our research group has been using arene-catalyzed lithiation to perform metalations under very mild reaction conditions.[9–12] This lithiation methodology has been applied to the reductive cleavage of trityl ethers[13] and amines,[14] the desilylation of silylated alcohols, amines, and thiols,[15] the cleavage of carbonates, carbamates, and thiocarbonates,[16] and the deacylation of esters, thioesters, and amides.[17] Very recently, we have reported a reductive cleavage of tritylated tetrazoles using this lithiation methodology, which leads to the deprotected tetrazoles without affecting the heterocyclic ring.[18]

In this paper we wish to report the use of a naphthalene-catalyzed lithiation to perform the removal of the pivaloyl protecting group from tetrazoles under very mild conditions.

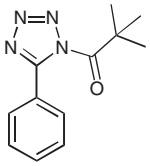
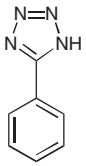
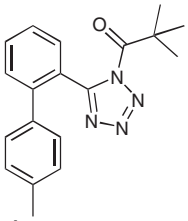
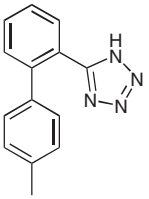
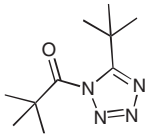
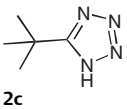
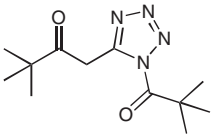
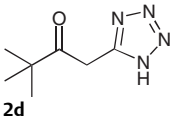
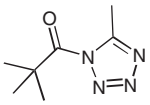
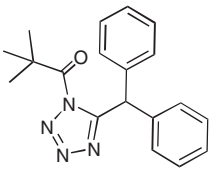
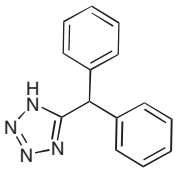
The reaction of various 5-substituted 1-pivaloyltetrazoles **1a**–**f** with excess lithium powder (1:20 molar ratio) and a catalytic amount of naphthalene (1:0.4 molar ratio) in tetrahydrofuran at 0 °C for three hours led, after quenching with methanol, to the corresponding free tetrazoles **2a**–**f** (Equation 1, Table 1).



Equation 1

The deprotected tetrazoles **2a**–**f** were isolated generally in good yields (Equation 1 and Table 1). In general, moderate to good yields were obtained in the deprotection of 5-aryl-1-pivaloyltetrazoles **2a**,**b** (entries 1 and 2), 5-alkyl-1-pivaloyltetrazoles **2c**,**e** (entries 3 and 5), or 5-benzhydryl-1-pivaloyltetrazole **2f** (entry 6). Interestingly, 5-(3,3-dimethyl-2-oxobutyl-1-pivaloyl)-1*H*-tetrazole (**1d**), containing a carbonyl group in the 5-substituent that could undergo re-

Table 1 Reductive Removal of the Pivaloyl Group from Protected Tetrazoles **1**

Entry	Substrate	Time (h)	Product	Yield[a] (%)
1	 **1a**	3	 **2a**	63
2	 **1b**	3	 **2b**	56
3	 **1c**	3	 **2c**	55
4	 **1d**	3	 **2d**	62
5	 **1e**	3	 **2e**	61
6	 **1f**	3	 **2f**	61

[a] Yield of isolated product after extraction and recrystallization, based on the starting material **1**.

duction under these reaction conditions, underwent solely depivalation to give **2d** in 62% yield (entry 4). All the lithiation processes were complete in a reaction time of three hours.

The starting tetrazoles were prepared by reaction of sodium azide with the corresponding nitriles in the presence of an amine. The isolated tetrazoles were then pivalated on N1 by reaction with pivaloyl chloride, giving the expected protected tetrazoles **1** in good yields.

In conclusion, we report an efficient method to remove the pivaloyl protecting group from various 1-pivaloyl-1*H*-tetrazoles bearing various aliphatic, aromatic, or benzylic substituents in the 5-position under very mild reaction conditions. This procedure is an alternative to other methodologies, especially those involving hydrolysis, which usually require harsh reaction conditions.

FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer using KBr plates (for solid compounds). NMR spectra were recorded on a Bruker spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using $CDCl_3$, DMSO-d_6, CD_3OD as solvents and TMS (δ = 0.00, ^{1}H) and $CDCl_3$ (δ = 77.0, ^{13}C), DMSO-d_6 (δ = 2.50, ^{1}H and δ = 39.75, ^{13}C), CD_3OD (δ = 4.87, ^{1}H and δ = 49.0, ^{13}C) as internal standards. Elemental analysis were measured by the Technical Services at the University of Alicante. Column chromatography was performed using silica gel 60 (35–70 mesh) or basic alumina (50–160 µm particle size). Li powder was prepared according to the procedure described.[19] Commercially available BuLi was titrated with a 1 M solution of *s*-BuOH in xylene using 1,10-phenanthroline as indicator.[20] Commercially available anhyd THF (99.9%, water content ≤ 0.006%, Acros) was used as solvent in all the lithiation reactions.

All reagents used for the synthesis of substrates **1** and naphthalene were commercially available (Acros, Aldrich) and were used without further purification. All glassware was dried in an oven at 100 °C and cooled to r.t. under argon before use.

Tetrazoles **2a**–**f** were prepared following the procedure recently described by us.[18] Physical and spectroscopic data of the obtained compounds **2a**–**f** were identical with those previously reported.[18]

CAUTION! Several tetrazole derivatives or their salts have been shown to have explosive properties, especially tetrazoles with electron-withdrawing substituents in position 5 of the ring.[21] Although we had no problems during the synthesis of any of the tetrazoles included in this paper, proper protective measures should be taken.

Protected Tetrazoles 1a–f; General Procedure

To a stirred solution of the tetrazole (10.0 mmol) in anhyd THF (10 mL) under argon at 0 °C was added dropwise 2.5 M BuLi in hexane (4 mL, 10.0 mmol); the mixture was stirred at this temperature for 10 min. Pivaloyl chloride (1.23 mL, 10.0 mmol) was added to the mixture over ca. 5 min and it was stirred at r.t. overnight. The reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4), filtered, and the solvent evaporated to give a residue that was purified by recrystallization (hexane–EtOAc) to afford pure product.

2,2-Dimethyl-1-(5-phenyl-1*H*-tetrazol-1-yl)propan-1-one (1a)

White solid; yield: 1.497 g (65%); mp 218–220 °C.

IR (KBr): 1701, 1608, 1562, 1484, 1409, 1256, 685 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 1.06 (s, 9 H), 7.45–7.90 (m, 5 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 27.6 (3 CH_3), 39.3 (C), 125.6 (C), 128.2 (2 CH), 130.5 (2 CH), 132.5 (CH), 157.7 (C).

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.69; H, 6.13; N, 24.33. Found: C, 62.66; H, 6.15; N, 24.37.

2,2-Dimethyl-1-[5-(4′-methylbiphenyl-2-yl)-1*H*-tetrazol-1-yl]propan-1-one (1b)

Yellow solid; yield: 1.986 g (62%).

IR (KBr): 1712, 1482, 1244, 1078, 823, 754 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.92 (s, 9 H), 2.27 (s, 3 H), 6.93–7.08 (m, 4 H), 7.45–7.63 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 21.1 (CH_3), 27.6 (3 CH_3), 124.2 (C), 128.7, 129.9, 130.2, 131.6, 131.8, 132.5 (8 CH), 137.6 (C), 138.8 (2 C), 143.6 (2 C), 156.8 (C).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.23; H, 6.32; N, 17.53.

1-(5-*tert*-Butyl-1*H*-tetrazol-1-yl)-2,2-dimethylpropan-1-one (1c)

White solid; yield: 1.472 g (70%); mp 104–106 °C.

IR (KBr): 1732, 1264, 1218, 1045, 703 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 1.42 (s, 18 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 29.5 (3 CH_3), 31.8 (3 CH_3), 165.7 (C), 214.1 (CO).

Anal. Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.12; H, 8.62; N, 26.66.

3,3-Dimethyl-1-(1-pivaloyl-1*H*-tetrazol-5-yl)butan-2-one (1d)

Brown solid; yield: 2.018 g (80%).

^1H NMR (400 MHz, CD_3OD): δ = 2.74 (s, 18 H), 2.80 (s, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 26.4, 26.8, 27.5 (3 CH_3), 27.6, 27.7, 27.9 (3 CH_3), 31.7 (CH_2), 39.3 (C), 45.5 (C), 152.5 (C), 182.5 (C=O), 210.1 (C=O).

Anal. Calcd for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21. Found: C, 57.10; H, 8.01; N, 22.24.

2,2-Dimethyl-1-(5-methyl-1*H*-tetrazol-1-yl)propan-1-one (1e)

White solid; yield: 1.430 g (85%); mp 152–157 °C.

^1H NMR (400 MHz, CD_3OD): δ = 0.92 (s, 9 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 8.4 (CH_3), 26.8 (CH_3), 27.6 (2 CH_3), 39.3 (C), 154.1 (C), 182.5 (CO).

Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.96; H, 7.14; N, 33.33.

1-[5-(Diphenylmethyl)-1*H*-tetrazol-1-yl]-2,2-dimethylpropan-1-one (1f)

White solid; yield: 2.884 g (90%); mp 154–158 °C.

^1H NMR (400 MHz, CD_3OD): δ = 1.07 (s, 9 H), 5.80 (s, 1 H), 7.23–7.38 (m, 10 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 26.8, 27.5, 27.6 (3 CH_3), 39.3 (C), 47.8 (CH), 128.6 (2 CH), 129.6 (4 CH), 129.9 (4 CH), 140.8 (2 C), 159.9 (C), 182.5 (C=O).

Anal. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.24; H, 6.26; N, 17.45.

Naphthalene-Catalyzed Lithiation of Compounds 1: Preparation of Products 2; General Procedure

To a green suspension of Li powder (70 mg, 10 mmol) and naphthalene (26 mg, 0.2 mmol) in THF (5 mL) under argon at 0 °C was added dropwise a solution of the protected tetrazole **1** (0.5 mmol) in THF (2 mL) and the mixture was stirred at this temperature for 3 h. MeOH (5 mL) was carefully added to the mixture, the cooling bath was removed, and the mixture was stirred until it reached r.t. The mixture was extracted with EtOAc (3 × 15 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 recrystallization (hexane–EtOAc), giving the corresponding free tetrazoles **2** in the following yields: **2a** (46 mg, 63%), **2b** (66 mg, 56%), **2c** (35 mg, 55%), **2d** (52 mg, 62%), **2e** (26 mg, 61%), and **2f** (72 mg, 61%) (see also Table 1). The obtained tetrazoles **2** were characterized by comparison of their physical and spectroscopic data with those previously synthesized.

Acknowledgement

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379457.

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Abstract

This manuscript encloses three principal parts: the first part, we have described the synthesis of tetrazoles which are a class of heterocycles with a wide range of applications in medicinal chemistry and in material sciences. We report herein a novel efficient process for transforming a wide variety of nitriles into the corresponding tetrazoles in high yield, using a simple and safe protocol.

We have reported in the second part, the protection of tetrazoles using pivaloyl chloride, the same reaction is made to protect a wide range of alcohols with trityl chloride giving trityl ethers and pivaloyl tetrazoles in good yields.

Finally, we have reported the use of lithium and a catalytic amount of naphthalene to remove the pivaloyl protecting group from tetrazoles under very mild condition we have reported successfully the use of a new catalyst for the detritylation of trityl ethers using indium and lithium chloride generally with very good yields.

Keywords: tetrazoles, alcohols, lithium, indium, lithium chloride, pivaloyl chloride, trityl ether.

Résumé

Ce manuscrit renferme trois parties principales: la première partie, nous avons décrit la synthèse de tétrazoles qui sont une classe d'hétérocycles avec une large gamme d'applications dans la chimie médicinale et en sciences des matériaux.

Nous rapportons ici un processus efficace pour transformer une grande variété de nitriles aux tétrazoles correspondants avec un rendement élevé, en utilisant un protocole simple et facile.

Nous avons rapporté dans la deuxième partie, la protection des tétrazoles à l'aide de chlorure de pivaloyle, la même réaction est réalisée pour protéger une large gamme d'alcools avec du chlorure de trityle donnant des éthers tritylés et tétrazoles pivaloylées avec un bon rendement.

Enfin, nous avons rapporté l'utilisation de lithium avec une quantité catalytique du naphtalène pour faire la déprotection des tétrazoles dans des conditions très douces, nous avons signalé aussi avec succès l'utilisation d'un nouveau catalyseur pour la détritylation des éthers utilisant l'indium et du chlorure de lithium avec un bon rendement.

Mots clés : tétrazoles, alcools, lithium, indium, chlorure de lithium, chlorure de pivaloyle, éther tritylé.

الـــمـــلخـــــص

هذا العمل يضم ثلاث أجزاء رئيسية :الجزء الأول، لقد وصفنا اصطناع التيترزول وهي فئة جد مهمة و لها عدة تطبيقات في الكيمياء الطبية والعلوم المادية. و لقد قمنا هنا بعملية فعالة تتمثل في تحويل مجموعة واسعة من النيتريلات الى تيترزولات المقابلة وذلك باستخدام طريقة بسيطة وآمنة.

لقد ذكرنا في الجزء الثاني، حماية التيترزولات باستخدام كلوريد البيفالويل و نفس الإجراء قمنا به لحماية مجموعة واسعة من الكحولات باستخدام كلوريد التريتيل لإعطاءالتيترزولات والكحولات المحمية مع مردود جيد.

أخيرا، لقد ذكرنا استخدام الليثيوم وكمية محفزة من النفتالين لإزالة البيفالويل من التيترزول تحت ظروف مناسبة ولقد استخدمنا بنجاح محفزات جديد لإزالة تريتيل الاثير باستعمال الإنديوم وكلوريد الليثيوم عموما مع مردود جيد.

مفاتيح اللفظ: التيترزول، الكحولات، الليثيوم، الإنديوم، كلوريد الليثيوم، كلوريد البيفالويل، تريتيل الاثير .