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A dissertation submitted to obtain the Master degree

in Organic Chemistry

Synthesis of some Stilbene derivatives and the removal of Triphenylphosphineoxide (TPPO) by precipitation, Complexation with $ZnCl_2$ and dry Column Vacum Chromatography (DCVC)

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Finally, our thanks go to the staff of the Chemistry laboratory and to everyone who helped and has supported us to complete the research work.

Dedication

Dedication

Every challenging work needs self-efforts as well as guidance of elders especially those who were very close to my heart.

My humble effort is dedicated to the memory of my sweet and beloved

Mother

For all the love she gave us

I hope paradise will be her dwell by Allah's mercy, and ask Allah to make Her grave a garden from the gardens of Paradise.

Father

Thank you for being a great mentor, for being the strength that push me when I'm weak and for all your support.

My brothers

For the giving and generosity, wish you all the best.

Houssam

Dedication

This thesis is proudly dedicated to:

My father ***Djamal &*** *My mother* ***Salima*** *the reason of what I become today, Thank you for everything*

My sister ***Roumaissa****, My brothers for their encouragement and help*

*My little angels "****Adem****" "****Anes****" "****Mouatez****"*

I also dedicate this work and give special thanks to my best friend ***Kawter*** *who has never left my side*

Finally, I dedicate this thesis to everyone who has supported me to complete this work.

Rihem

Liste of Abbreviation

°C	Degree Celsius
C	Concentrated
CC	Column Chromatography
DBU	Diazabicycloundecane
DCVC	Dry Column Vacuum Chromatography
DCE	Dichloroethane
DEAD	Diethylazadicarboxylate
Eq	Equivalent
g	gram(s)
h	hour(s)
IsoPrOH	Isopropanol
Mg	Milligrams
Ml	Milliliters
Min	Minute(s)
Mp	Melting point
Mol	Molar
NaHMDS	Sodiumhexamethyldisilylamid
Rf	Retardation factor
RT(rt)	Room temperature
T-BuOK	Tertiobutoxide
THF	Tetrahydrofurane
TPPO	Triphenylphosphonium oxide
TLC	Thin-layer chromatography

Table of contents

Chapter II: Results and Discussion

ChapterIII: Experimental Section

Table of contents

LIST OF SCHEME

List of Table

General Introduction

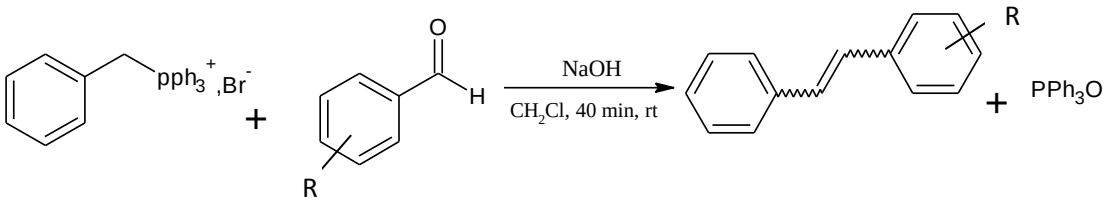
Introduction

Cascade reactions constitute a fascinating branch of organic chemistry, and one which has been the subject of intense research in recent years [1], this type of reaction involves some particular precursors such as polyene, en-ones, yne-one…Among the reactions that allow the synthesis of these precursors the Wittig reaction.

Despite the structurally various alkene obtained, Wittig reaction, as many other reactions using PPh_3, such as Corey-Fuch, aza-Wittig, Mitsunobu, has a major inconvenient is that triphenylphosphine oxide TPPO is a usual undesirable product which is difficult to get rid of.

In the present work, we focus on the synthesis of some simple alkenes by Wittig reaction and the application of some methods of separation of TPPO from the obtained alkene.

Thus, the first purpose is to synthesis alkenes from 5 different aldehydes to give stilbene and derivatives.



R = H, **1**
R = 4-Br, **2**
R = 4-NO_2, **3**

Bistyryl: **4**
R = 3-Br,5-OMe, **5**

The second purpose is to separate TPPO from the final product using 3 different techniques which are:

- ✓ Precipitation of TPPO in non-polar solvent.
- ✓ Complexation of TPPO with $ZnCl_2$ in different experimental conditions, during 18 h at room Temperature or during 2h in refluxing.
- ✓ Separation by dry column vacuum chromatography (DCVC).

The present manuscript is divided into three chapters, Chapter 1 contains an overview on Wittig and Corey-Fuchs reactions, which allow synthesis of cascade reaction precursors. In Chapter 2 are reported the obtained results and the corresponding discussions, and Chapter 3 contains the experimental part.

Chapter I

Wittig reaction

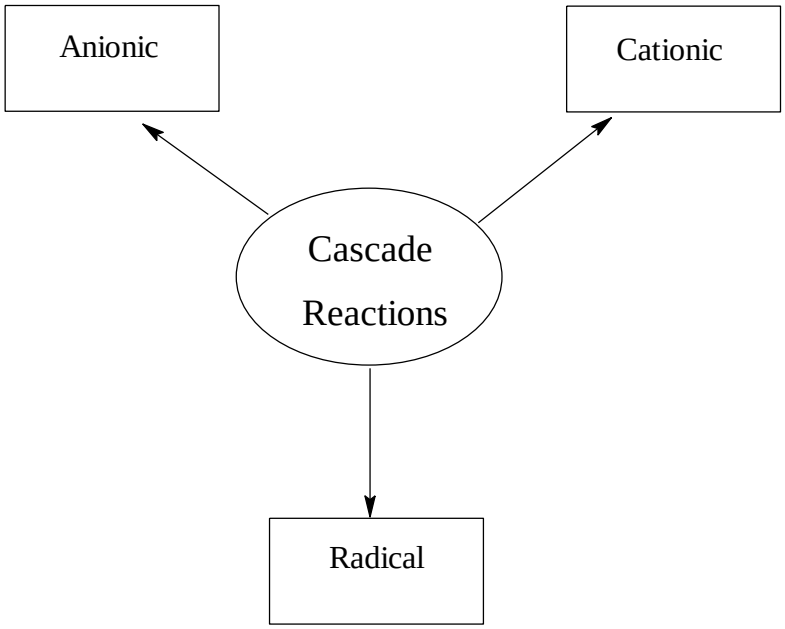
&

Corey-Fuchs reaction

I. Introduction

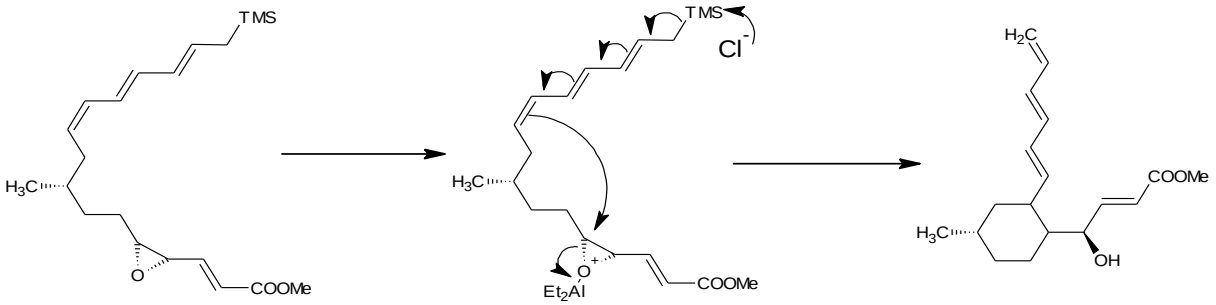
Cascade reactions [1] are one of the most important classes of reactions in organic synthesis. They allow access to bioactive compounds and structurally complex molecules (bicyclic, tricyclic and polycyclic). These reactions have been classified into three types: cationic, anionic, and radical **(Scheme I.1)**, depending on the nature of the first step of the process

- In anionic type, the first step is the formation of a nucleophile.
- In cationic type, the first step is the formation a carbocation intermediate.
- Radical type of cascade reactions starts with a radical entity and can be defined as a series of rapid intermolecular and intramolecular reaction.



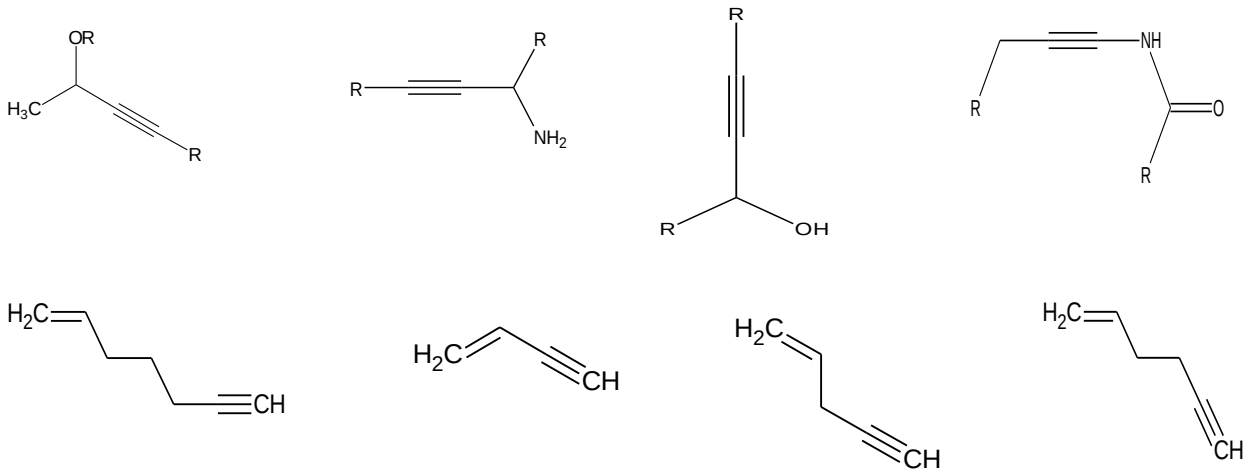
Scheme I.1: Types of cascade reactions

The efficiency of a cascade reaction relies in one hand, on the presence of unsaturated bonds; double bonds, triple bonds and other reactive sites in the precursors, and in the other hand, on the relative position of these unsaturated sites to each other's, thus when a bond is created in a first step, it generates a cascade of reactions and bonds forming leading in most cases to cycles formation. An example of cascade reaction [1] is given in **scheme I.2**.



Scheme I.2: Example of cascade reactions

Precursor requested for cascade reactions are generally unsaturated compounds; as represented in scheme **SchemeI.3.**



Scheme I.3: Some precursors of cascade reactions

Various reactions are available to synthesis polyunsaturated compounds used as precursors in cascade reactions.

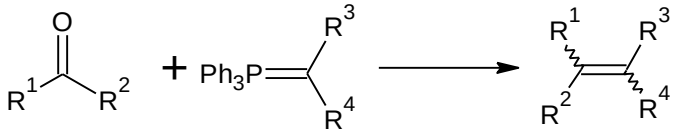
Among these reactions, we focus in this chapter on Wittig reaction and Corey-Fuchs reaction that allow to prepare, respectively alkene from aldehyde or ketone and alkyne from aldehyde. Both of these reactions have TPPO as a by-product. The strategies of elimination of TPPO are among our point of interest in the present work.

II. Wittig reaction

II.1 Description of Wittig reaction

The Wittig reaction and its variants are one of the most important classes of reactions because of its versatile utility in synthetic applications [2].

The reaction occurs between a carbonyl compound (aldehyde or ketone), and a phosphonium ylide. The latter species is a carbanion stabilized by an adjacent phosphorus bearing three alkyl or aryl groups (generally, phenyl groups) [3].

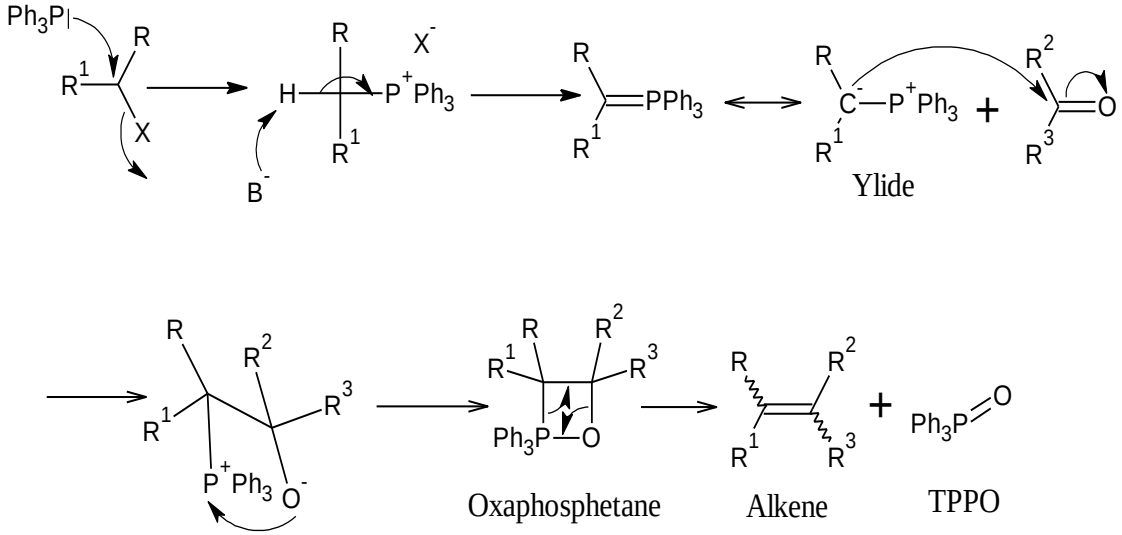


Scheme I.4: General scheme of Wittig reaction

The reaction between triphenylphosphine and alkyl halide gives triphenylphosphonium salt followed by attack of strong base to form ylide, then the nucleophilic attack on the carbonyl generates the intermediate named betaine which leads to the formation of a 4 membered ring (oxaphosphetane). The rapid opening of oxaphosphetane affords the alkene and TPPO as by-product.

The alkene formed has two possible stereoisomers,because the double bond formed is positioned unambiguously. It is possible to create alkenes of configuration Z or E depending on the starting reagents :

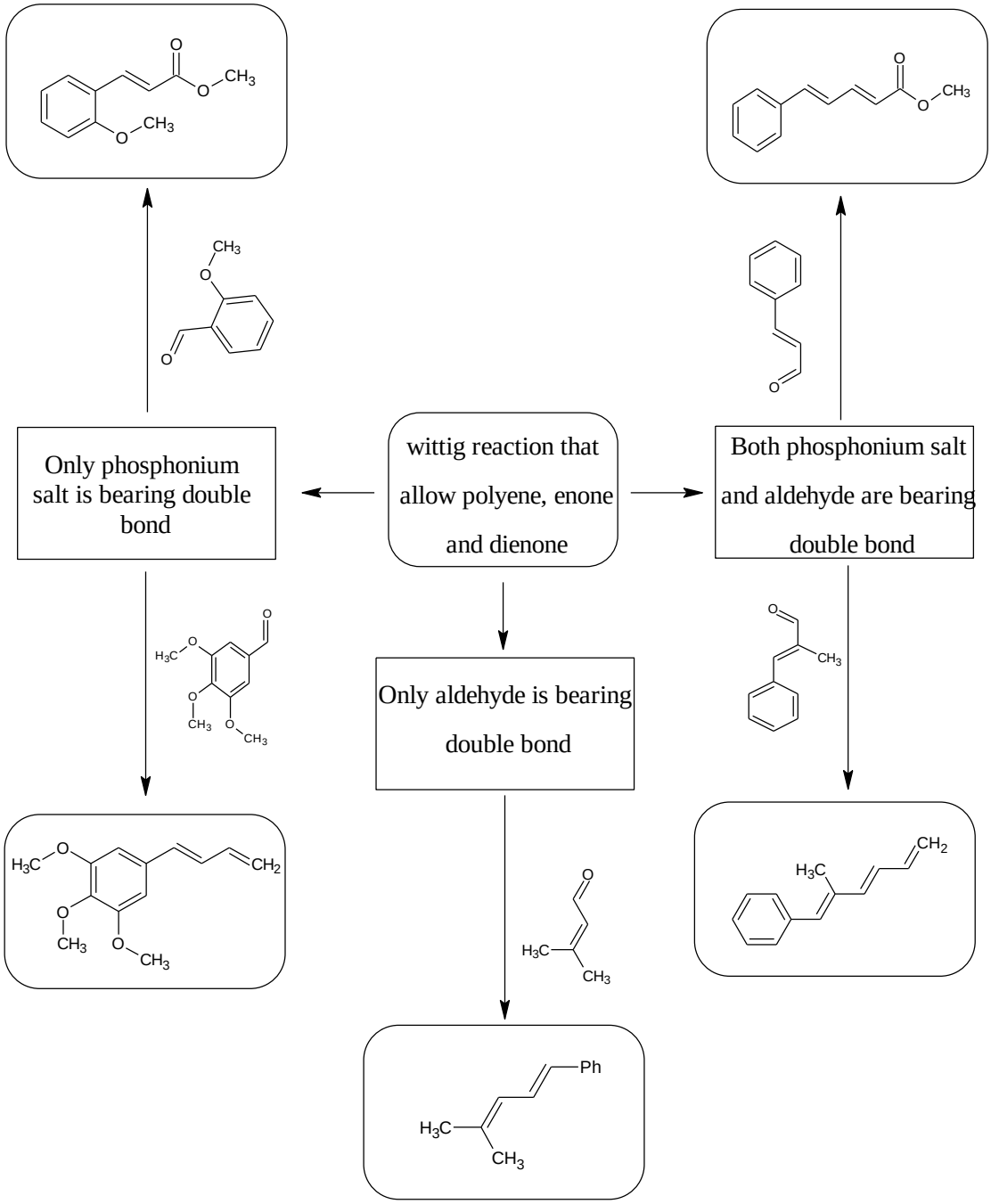
- Starting from an unstabilized ylide, the compound obtained is that of absolute configuration Z.
- Starting from a stabilized ylide, the predominant alkene is that of absolute configuration E.



Scheme I.5: Mechanism of Wittig reaction

II.2 Synthesis of unsaturated compounds by Wittig reaction

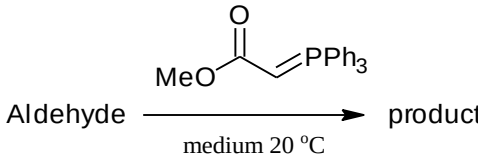
In its simple form, Wittig reaction give an alkene. Depending on the presence of additional double bonds, triple bonds or other unsaturated functional groups on the carbonyl derivative or on the phosphonium salt or both of them, Wittig reaction could be an efficient source of diene, polyene, dienone, en-yne and en-yne-one derivatives. These compounds are requested reagents for cascade reaction **Scheme I.6.**



Scheme I.6: Some unsaturated compounds by Wittig reaction

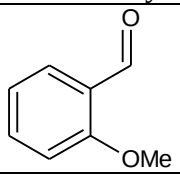
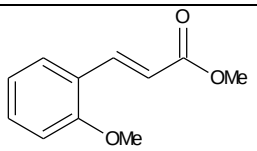
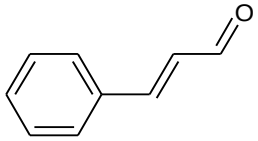
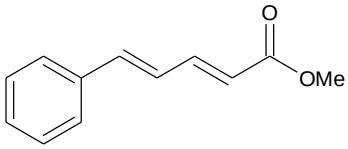
II.2.1- Synthesis of Unsaturated Esters

Water is demonstrated to be an effective medium for the Wittig reaction over a wide range of stabilized ylides and aldehydes. In this reaction **El Batta** and all synthesized unsaturated Esters from mixing Aldehydes, Bromoesters, PPh_3 and water as solvent, in good yields [4]



Scheme I.7: Some Wittig adducts obtained in water as solvent

Table I.1: Some Wittig adducts obtained in water as solvent

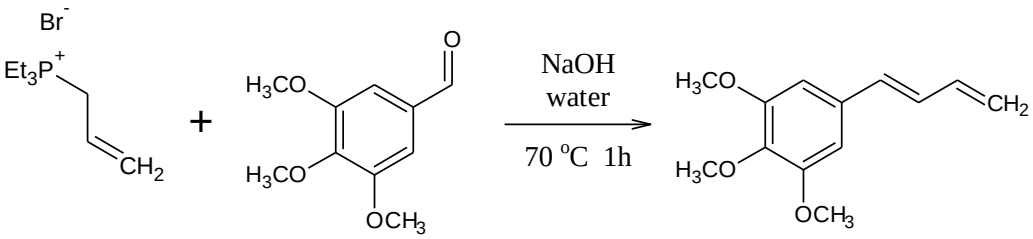
Aldehyde	Solvent	Time	Yield	Product
	Water	1h	81%	
	methanol	1h	92%	
	Water	2h	88%	
	methanol	2h	94%	

II.2.2- Synthesis of conjugated polyene

The synthesis of functionalized 1,3-dienes and polyenes is a central concern in synthetic organic chemistry. 1,3-diene sub-unit is itself found in a wide range of bioactive materials[5].

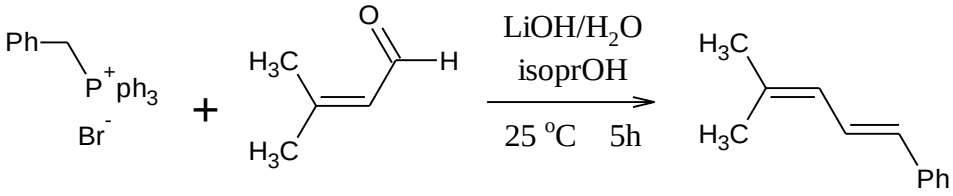
2.2.1- Synthesis of 1,3-diene

Synthesis of 1,3-dienes from the reaction of semi-stabilized ylides and unsaturated aldehydes is reported in water as solvent, employing sodium hydroxide as base. The dieneis obtained in a good yield (85%) [5].



Scheme I.8: 1,3-diene obtained by Wittig reaction in water

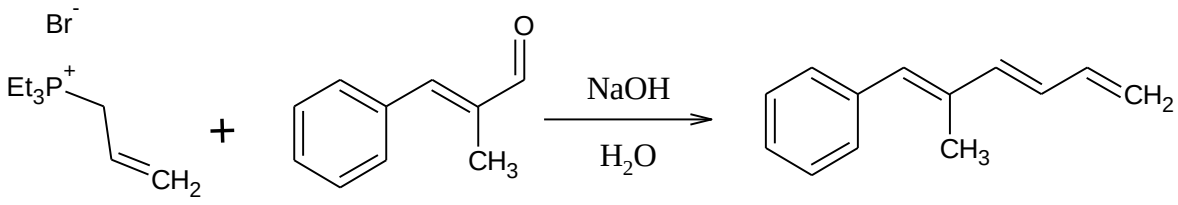
In another example, synthesis of 1,3-dienes from reaction of benzyl triphenylphosphonium bromide and 3-methylbut-2-enal by lithium hydroxide as base gives good yields as well [6].



Scheme I.9: Synthesis of 1,3-diene with LiOH as base

2.2.2- Synthesis of trienes

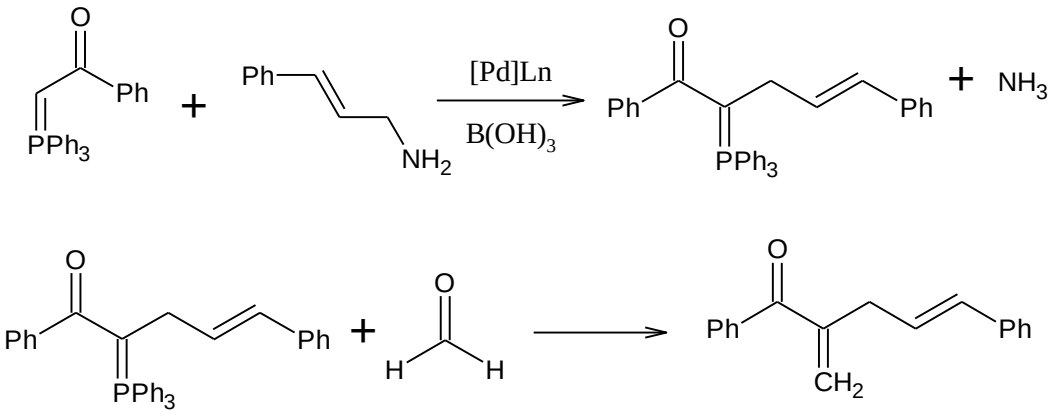
1,3,5-trienes from triethylphosphine ylides with unsaturated aliphatic aldehydes are obtained in good yields 79% [5].



Scheme I.10: Synthesis of 1,3,5-triene by Wittig reaction

2.2.3-Synthesis of 2,4dienone

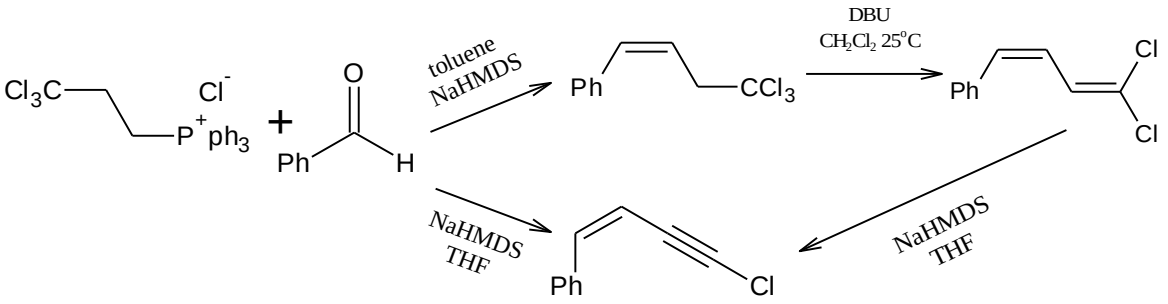
This reaction is a one-pot olefination of stabilized phosphonium ylides with Primary allylic amines [7].



Scheme I.11: Synthesis of dienone by Wittig reaction

2.2.4- Synthesis of 1,3enyne

The 1,3-enyne derivatives are quite common, as shown in the following example, they could be synthesized by Wittig adduct, obtained by metalizing3-Trichloropropyl-1-triphenylphosphorane in toluene followed by the addition of aldehyde. The final product is treated with DBU in dichloromethane to give (Z)-dichlorodiene. This reaction followed by treatment with NaHMDS in THF gives the desired product [8].

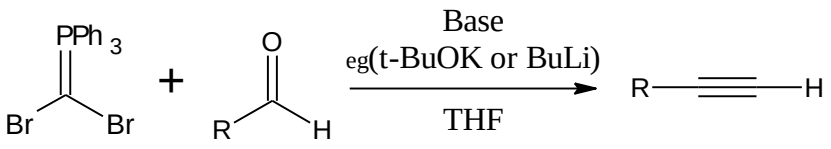


Scheme I.12: Synthesis of enyne

III- Corey-Fuchs reaction

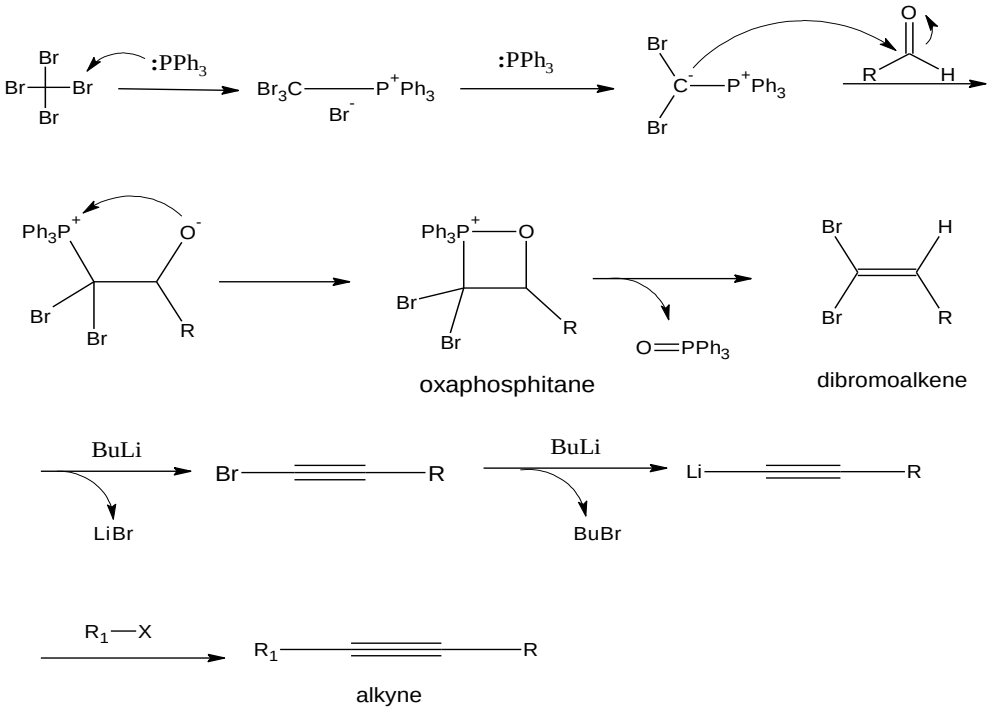
III.1- Description of the Corey-Fuchs reaction

The reaction is a two-step process used to prepare single-carbon homologous terminal alkynes from aldehydes **Scheme I.13** or to prepare alkyne derivatives by treating an acetylide intermediate with an electrophile. Sometimes it is also referred to as Corey-Fuchs dibromoolefination and Corey-Fuchs homologation [9].



Scheme I.13: General Scheme of Corey-Fuch reaction

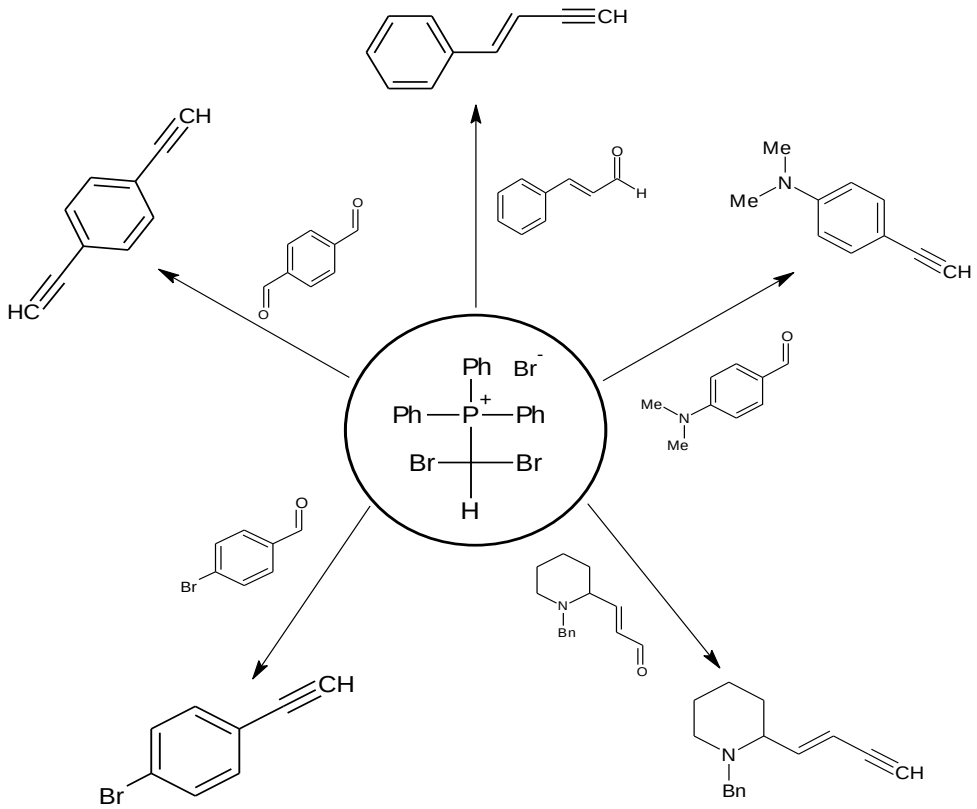
Triphenylphosphine react with tetrabromure to give tribromomethyltriphenyl-phosphoniumbromide which reacts with triphenylphosphine to produce dibromomethylene-triphenylphosphine, these last react with the aldehyde in the presence of the base to give an oxaphosphitan which leads to dibromoalkenes, the treatment with base and hydrolyzed with brine gives the alkyne[9].



Scheme I.14: Mechanism of Corey-Fuch reaction

III.2- Synthesis of some precursors by Corey-Fuch reaction

Corey-Fuchs reaction [5] was first designated to prepare simple alkynes but later, it has been developed to prepare more functionalized alkynes and other en-yne and yn-yne derivatives some examples are given in **scheme I.15.**

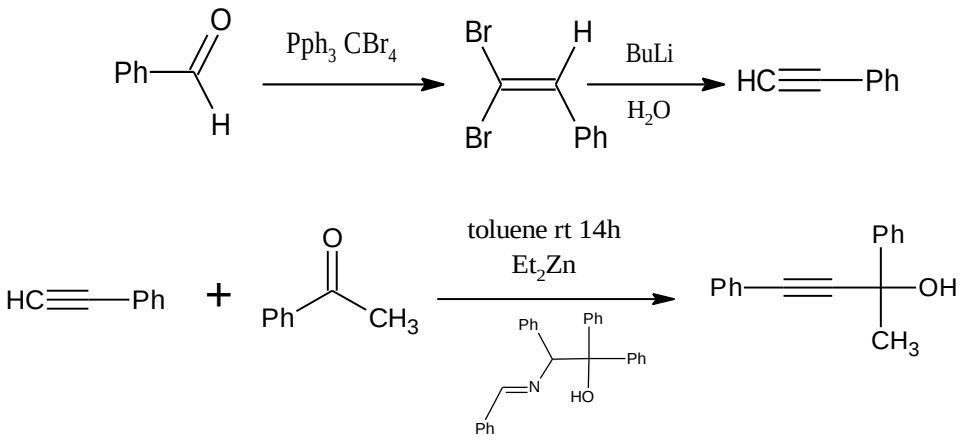


Scheme I.15: Some compounds obtained by Corey-Fuch reaction

2.1- Synthesis of propargylic alcohols

The following scheme shows an addition of terminal alkyne (phenylacetylene) to carbonyl compounds to form chiral propargylic alcohols **Scheme I.16**.

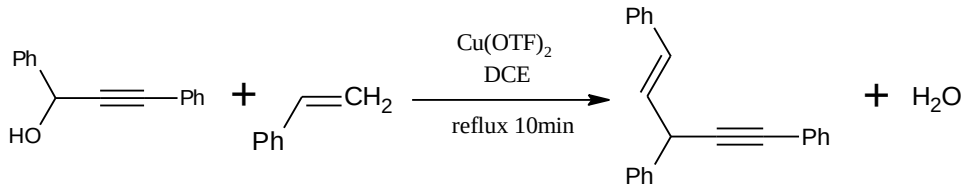
The terminal alkynes (phenylacetylene) are first formed by Corey-Fuchs reaction, followed by addition of acetophenone catalyzed by Schiff-Base Amino Alcohols at room temperature [10].



Scheme I.16: Propargyl alcohol from a Corey-Fuchs adduct

2.2- Synthesis of 1,4-enyne

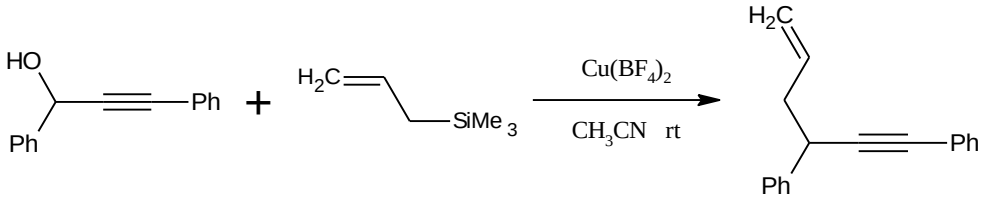
Huang and al propose another reaction to synthesize 1,4-enyne from terminal alkenes and propargylic alcohols using catalyst[11].



Scheme I.17: 1,4-enyne from a Corey-Fuchs adduct

2.3- Synthesis of 1,5enyne

Lewis acid catalyzes the coupling of propargyl alcohol with allylsilane. This is an important transformation because it provides a direct method to synthetically valuable 1,5-enynesin high yields [12].



Scheme I.18: 1,5-enyne from a Corey-Fuchs adduct

IV. TPPO as side product

Beside of Wittig reaction and its variants which yield to TPPO as by-product, there are Corey-Fuch reaction, Mitsunobu and aza-Wittig reactions.

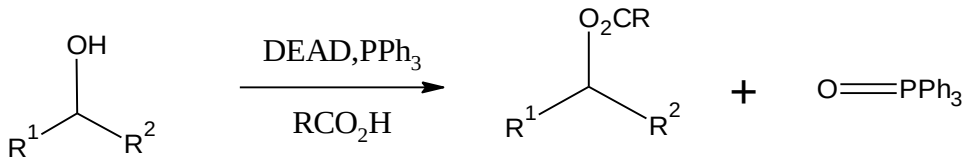
The resulting TPPO by-product can be difficult to separate from the reaction product. A number of strategies to separate TPPO from the final product are available [13].

Before examining these strategies, it is worth to remember Mitsunobu and aza-wittig reactions.

IV.1.Mitsunobu reaction

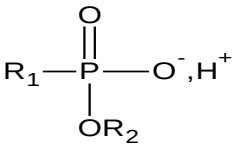
This reaction is about the synthesis of esters or lactons, ethers and phosphonate esters respectively from carboxylic acids, alcohols and phosphonic acids in the presence of diethyl azodicarboxylate(DEAD) and triphenylphoshine this reaction undergoes with inversion of the

configuration for asymmetric alcohols. TPPO and hydrazine dicarboxylate as by-products of this reaction [14].



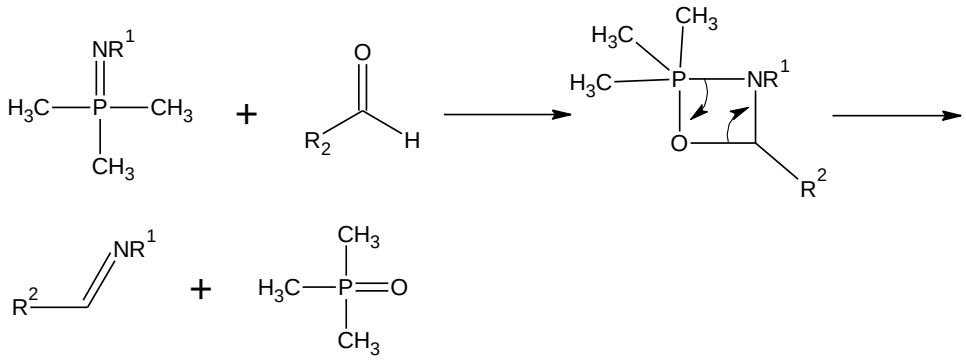
Scheme I.19: General scheme of Mitsunobu reaction

Table I.2: Some commun Mitsunobu adducts

NuH	$RCOO^-,H^+$	RO^-,H^+	
Mitsunobu aduct	Ester or Lacton	Ether	Phosphonate ester

IV.2- Aza-wittig reaction

Aza-Wittig reactions are similar to Wittig reactions in the way that they also involve the reaction of a phosphonium ylide, in this case an iminophosphorane (or phosphinimide), with a carbonyl group containing compound to form the carbon–nitrogen double bond of an imine along with phosphine oxide as byproduct [15].



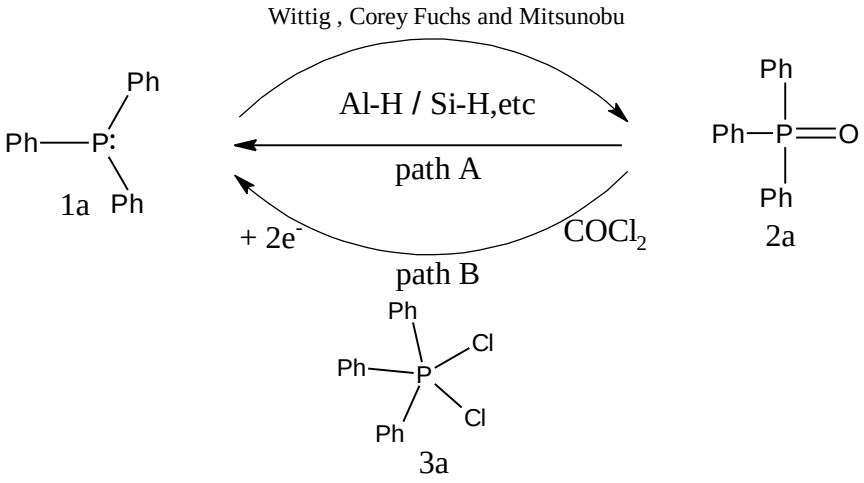
Scheme I.20: General scheme of aza-Wittig reaction

V.Strategies to remove TPPO

V.1. Reduction of TPPO

Reduction of TPPO **2a**to triphenylphosphine **1a**(path A) has been widely studied, and performed successfully with various reductants, such as metal hydrides (hydrosilanes, aluminum hydrides), low-valent metals (SmI_2/HMPA, $TiCp_2Cl_2$/Mg).

An alternative access to triphenylphosphine**1a,** Chlorination of TPPO**2a**, using chlorinating reagents such as phosgene oroxalyl chloride leads to triphenyl-phosphorus dichloride **3a**(path B). It is reasonable to assume that reduction of the P–Cl bond of **3a** proceeds more smoothly than that of the P=O bond of **2a**, since the P–Cl bond (310 kJ/mol) is far weaker than the P=O bond. Indeed, reduction of **3a** to **1a**was performed by hydrogenation catalyzed by transition-metal catalysts (Pt, Rh, and Pd) and reduction with several metals such as sodium, aluminum, silicon, and iron[16].



Scheme I.21: Strategies to eliminate TPPO by reduction

V.2- Separation by chromatography

2.1- Column chromatography

Chromatography is an important technique that enables the separation, identification, and purification of the components of a mixture for qualitative and quantitative analysis. It is based on the principle where molecules in mixture applied onto the surface of a stationary phase (solid phase) are separating from each other while moving with the aid of a mobile phase.

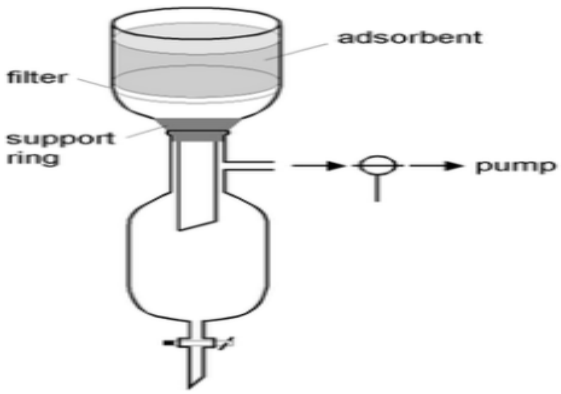
This separation process depends on molecular characteristics related to adsorption (liquid-solid), partition (liquid-solid), and affinity or differences in molecular weights. Because of these differences, some components of the mixture stay longer in the stationary phase, and they move slowly in the chromatography system, while others pass rapidly into mobile phase, and leave the system faster [17].

2.2- Dry column vacuum chromatography (DCVC)

The first step of this technique is to fill uniformly the column with dry silica gel; as usually done in flash chromatography. The column is then placed on the separatory funnel and the vacuum is applied.

The mixture is dissolved in a volatile solvent, and a suitable quantity of celite is added. The solvent is evaporated to dryness on a rotary evaporator, after that the mixture is added to the surface of the column.

The eluent solvent is added one fraction at the time (making very precise gradient elution very easy) and hence the column is sucked almost completely dry between fractions.



Scheme I.22: Representation of DCVC device

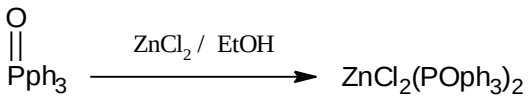
Dry column vacuum chromatography (DCVC) is an excellent alternative to the commonly used Flash Column Chromatography because, this technique has many advantages, it is economic and environmental-friendly, it has shown its efficiency in separation and purification of the reaction mixtures [18-19].

V.3- Complexation of TPPO

This technique is based on the reaction between TPPO and metal halides to form a stable complex and then the precipitation of TPPO in the form of TPPO-M (M= Mg ,Zn, Cu…).

3.1- Complexation with $ZnCl_2$

When direct precipitation of TPPO shows to be non-efficient, addition of $ZnCl_2$has been effective to precipitate easily as $ZnCl_2(TPPO)_2$ in polar solvents, which leads to separate TPPO from the final product of many reaction to obtain it in pure form.

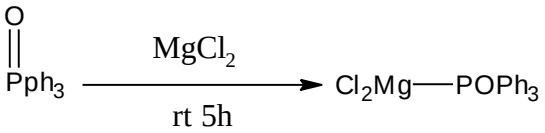


Scheme I.23: Complexation reaction using $ZnCl_2$

The crystal of $ZnCl_2(TPPO)_2$ have been known for over 100 years, and to use it for the purpose of separate TPPO from reaction product should be added 4eq of $ZnCl_2$ to the mixture and agitate it for 18h [13].

3.2- Complexation with $MgCl_2$

As a solution to the problem separation of TPPO from reaction products, some authors evaluated the possibility of TPPO precipitation from the reaction mixture via a complex formation by addition of 2eq of $MgCl_2$ to the mixture. The solvent play a significant role in this process, insofar as non-polar solvents give better separation than polar solvent ones[20].



Scheme I.24: Complexation reaction using $MgCl_2$

VI- Conclusion

In this chapter, a bibliographic overview on Wittig reaction and Corey-Fuchs reaction used to prepare unsaturated compounds is given. These compounds are suitable precursors for cascade reactions, a source of polycyclic bioactive compounds. Another point which we also focused on is the strategies to remove the TPPO, a by-product of Wittig reaction and Corey-Fuchs reaction.

Chapter II

Results and Discussions

I. Objectives of the work

The objective of the present work is to explore methods of removing TPPO from alkenes (stilbene derivatives) synthesized using Wittig reaction.

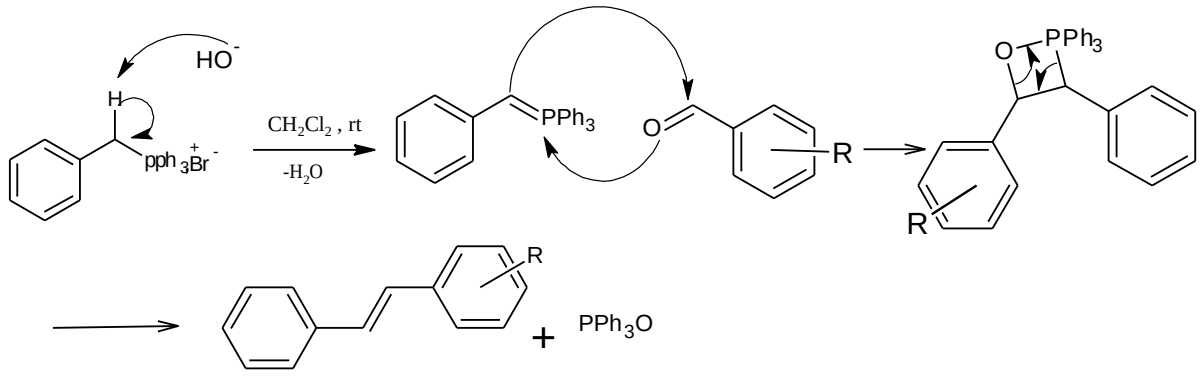
Using Wittig reaction, we prepared 5 stilbene derivatives by reacting various aldehydes with benzyl triphenylphosphonium bromide salt. As TPPO is a byproduct, we undergo to explore 3 methods (complexation with $ZnCl_2$, Precipitation in non-polar solvent and separation by Dry Column Vacuum Chromatography DCVC).

Our choice of Wittig reaction is motivated by the availability of the reagents and the fact that it will be used along with Corey-Fuchs reaction in further work. Hence, the aim of this work is to find out the best method to separating TPPO from the final product of these reactions.

II. Results and Discussion

The stilbene derivatives **1**-**5** obtained by Wittig reaction of benzaldehyde derivatives with benzyl triphenylphosphonium bromide salt are reported in **Table II.1.**

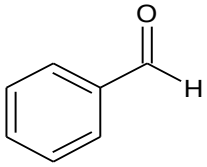
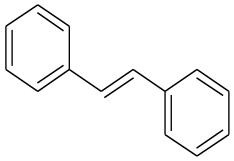
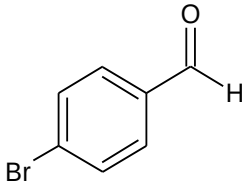
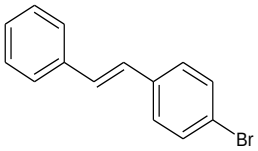
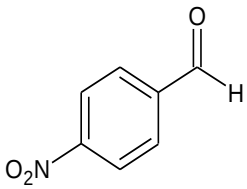
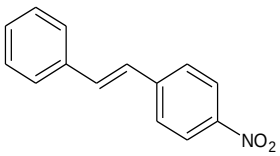
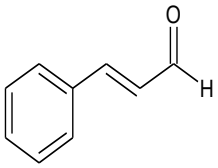
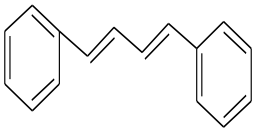
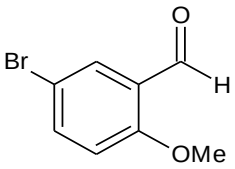
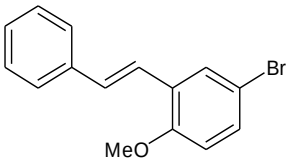
II.1. General mechanism of stilbenes's synthesis



R = H, **1** Bistyryl: **4**
R = 4-Br, **2** R = 3-Br,5-OMe, **5**
R = 4-NO_2, **3**

Scheme II.1: Mechanism of Stilbene derivatives synthesis

Table II.1: Stilbene derivatives obtained by Wittig reaction

Entry	Aldehydederivative	Stilbene	Number	Lit. Mp (°C)
Entry1			**1**	**123-125**
Entry2			**2**	**140**
Entry3			**3**	**157**
Entry4			**4**	**150-152**
Entry5			**5**	**Not found**

II.2- Removal of TPPO by complexation with $ZnCl_2$(RT, 18 h)

In this method we carry out the complexation reaction of TPPO with $ZnCl_2$at room temperature for 18h. The results obtained are summarized in **Table II.1**.

At the end of the reaction, a white precipitate is isolated. The measure of the melting point for the five entries 1-5, gives 232 °C, which is in agreement with the $ZnCl_2$-TTPO complex melting point found in literature [23].

The separation of TPPO from the final product is indicated by the complex's yields. It is worthy to note that, while the separation seems to be good for the entries 1, 2,4 and 5(62 % to 72%), it turns out to be less effective (45 %) for entry 3 corresponding to 4-nitrobenzaldehyde.

On the other hand, a white powder which is supposed to be the remaining TPPO was obtained by precipitation in a non-polar solvent (cyclohexane). The measured melting point of this powder (210-226 °C) shows it is different from the literature Melting point of TPPO (154-158 °C), thus it is reasonable to conclude that it is not TPPO.

Concerning stilbene derivatives, they are isolated after evaporation of the filtrate. Except for entry 5 where the alkene is liquid, the melting points measured for entry 3 and entry4 are in accordance with the literature. However, for entry 1 and entry 2, there a quite important deviation from literature. This is probably due to impurities.

Table II.1: Products characteristics

Entry	Product	**Stilbene derivatives**		**Complex $ZnCl_2(TPPO)_2$**		**White powder**
		Yield(%)	Mp(°C)	Yield(%)	Mp(°C)	Mp (°C)
1	**1**	39	115- 116	64	232.5-233.3	210.4- 214
2	**2**	39	117-126	62	232.5-233.3	217.0- 223.8
3	**3**	44	156- 156	45	231.9-232.2	213.1- 225.1
4	**4**	36	151-152	71	234.3- 234.8	226.8-227.8
5	**5**	61	Liquid	72	233,1-234,8	216.2-227.1

II.3 Removal of TPPO by complexation with $ZnCl_2$(Refluxing, 2h)

Inspired by the complexation with $ZnCl_2$ and with the aim to improve the published process, we carry out the same method in refluxing for 2 h instead of 18h. The results are summarized in **Table II.2.**

As for the previous method, the complex is formed as a white precipitate and isolated only for in this case, we focus only on the separation of the complex keeping TPPO and stilbene
derivatives mixed together as a crude product.

Although the measured melting point are in agreement with the literature. This method shows low efficiency, as it was successful only for entry 1, 2 and 5.

Table II. 2: Products characteristics

Entry	Product	**Complex $ZnCl_2(TPPO)_2$**		**TPPO/Stilbene derivatives**
		Yield(%)	Mp(°C)	Mass (mg)
1	**1**	36	234.3-234.5	268
2	**2**	55	227.5-231.5	477
3	**3**	Mixture (complexe/stilbene)		408
4	**4**	no complexation		
5	**5**	36	234.1-234.2	455

II.4- Removal of TPPO by precipitation in non-polar solvent

This method is quite simple and consists to make TPPO precipitate by using a non-polar solvent (cyclohexane), the TPPO is restored in good yields (**Table II.3**), and the measured melting point is in agreement with the literature (152-154°C) even if there is a slight deviation for entry 5. In addition to the issue encountered with entry 3 where the TPPO is obtained as a mixture with the stilbene derivative, they were not restored in pure form for all the other entries (traces of TPPO).

Table II.3: Products characteristics

Entry	Product	**TPPO**		**Stilbene derivatives**
		Yield(%)	Mp(°C)	Mass (mg)
1	**1**	92	152-153.7	102
2	**2**	64	152.4-153.7	142
3	**3**	Mixture (complexe/stilbene)		182
4	**4**	87	154.9-155.4	162
5	**5**	91	155.7-156.9	254

II.5- Removal of TPPO by dry column vacuum chromatography (DCVC) [20-21]

This technique, called dry column vacuum chromatography **(Table II.4)**, is fast, consumes less solvent and seems to be very effective.

Stilbene derivatives are restored with average to good yields and melting point are in good match with literature for most of them.

TPPO is obtained in good yields (73 %-82%) with measured melting point in accordance with literature (155-156 °C).

Table II.4: Products characteristics

Entry	Product	**Stilben derivatives**		**TPPO**	
		Yield(%)	Mp(°C)	Yield(%)	Mp(°C)
1	**1**	25	122	73	155-156
2	**2**	71	138-139	82	155-156
3	**3**	67	150-151	74	155-156
4	**4**	53	145-146	73	156
5	**5**	87	Liquid	82	155-156

III- Conclusion

In summary, in this chapter, we tried to remove TPPO from alkenes synthesized via Wittig reaction, by exploring three methods:

- The first one is the complexation of TPPO with $ZnCl_2$ following different conditions (at RT during 18 h and in refluxing for 2 h).
- The second one is precipitation of TPPO in non-polar solvent.
- The third one is separation of TPPO using dry column vacuum chromatography (DCVC)

From the results obtained, it appears that:

Precipitation in cyclohexane, is not very effective even if the TPPO was restored in good yields, the stilbene derivatives were not obtained in a pure form (according to TLC).

Complexation at RT during 18 h (according to Literature) takes too much time; needs further precipitation to remove all the TPPO; the other procedure (complexation; in refluxing for 2 h, which is our contribution to improve the process), turns out to be less effective (giving average to low yields).

Finally, Dry column vacuum chromatography (DCVC) has shown to be the most effective technique, with maximum separation, each product was restored in pure form and in good yield. This method will be adapted for our future work with Wittig and Corey-Fuchs reactions.

Chapter III

Experimental Section

I. Analytical methods and materials used

a-Thin-layer chromatography

The Thin-layer chromatography TLC is a technique for separation, it is used to control the completion of the reaction, to control the purity of the synthesized compounds and to determine retardation factor R_f. TLC was performed on aluminum plates coated with silica gel and revealed by a lamp UV adjusted to 254 nm.

b. Measurement of melting points

The melting points were measured using melting point apparatus (**BÜCHI** Melting Point **B-540**)

II. General procedure for the reaction of Wittig

II. 1-Synthesis of benzyl triphenylphosphonium bromide salt

A mixture of triphenylphosphine PPh_3 (1eq) and benzyl bromide (2eq) in toluene were kept under stirring for an appropriate time until a white precipitate had formed. The mixture was heated for 2h30min at 80°C. Completion of the reaction was indicated by TLC monitoring. the precipitate was filtrated.

Aspect: White solid

Yield = 87%

Mp= 294.5-294.6°C

Rf= 0 **(** salt) / eluent**:**Cyclohexane

II-2-General Synthesis of alkenes

To a mixture of benzyl triphenylphosphonium bromide (1.5eq) and benzaldehyde derivatives (1eq) in dichloromethane was added NaOH 50 % dropwise, the mixture was stirred for an appropriate time. The organic phase and aqueous phase were separated. The aqueous phase was extracted with dichloromethane (the operation was performed twice). The organic phase was dried with anhydrous magnesium sulfate and dichloromethane evaporated.

III. General procedure for method of removing TPPO

III.1-General procedure for precipitation of TPPO in non-polar solvent

After evaporation of dichloromethane, cyclohexane is added to precipitate TPPO then the precipitate is filtrated

III.2. General procedure for complexation of TPPO with $ZnCl_2$ 18h

After evaporation of dichloromethane, Ethanol and $ZnCl_2$ (4eq) is added to the crude product, the mixture is shaken for 18 h at RT to precipitate TPPO−Zn complex, after filtration the complex is dried.

In order to precipitate the remaining TPPO, the dichloromethane is evaporated and cyclohexane is added, TPPO is recovered. The filtrate obtained is evaporated to recover alkenes.

III.3 General procedure for complexation with $ZnCl_2$in refluxing 2 h

After evaporation of dichloromethane, Ethanol and $ZnCl_2$ (2eq) is added to the crude product, the mixture is shaken for 2h at 70°C to precipitate TPPO−Zn complex, after filtration the complex is dried.

III.4- General procedure for dry Column Vacuum Chromatography (DCVC)

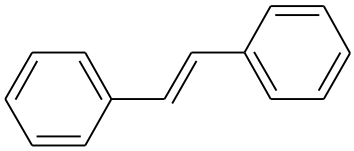
10 g of silica gel is added to a fritted funnel (which replace the classical column), the side of the funnel is gently pressed with a cork, a filter paper is added to not disturb the surface of the silica gel. The eluent (cyclohexane/ethyl acetate) is poured gently on to the surface (protected by the filter paper) while applying vacuum. On the other hand, the crud product is dissolved in dichloromethane; a small amount of silica gel is added, and the solvent is removed from the slurry under reduced pressure on a rotary evaporator. The powder formed is added in a thin uniform layer on the top of the fritted funnel. Vacuum is applied and the surface is pressed firmly as in the column packing step. The compounds mixture is eluted with (cyclohexane/ EtOAc 60/40) then the solvent polarity is increased (purEtOAc) and elution is continued. Elution of compounds is monitored by TLC. The resulting solution are combined and concentrated on a rotary evaporator.

III.5- General procedure for Column Chromatography

30 g of silica gel is added to a column, two pieces of cotton are added to the top and the bottom, a filter paper is added to not disturb the surface of the silica gel, filling the column with the eluant (cyclohexane /ethylacetate) putting the compounds mixture, opening the tap and keeping the eluant trickling, gently adding the eluant to get not the column dry, every 10 ml or 20 ml elution of compounds is monitored by TLC, with the same spot gathered together, The resulting solution is filtered and concentrated on a rotary evaporator.

IV. Synthesis of alkenes

IV.1 Synthesis of 1,2-diphenylethylene (stilben)



1

The product **1** was synthesized according to the general procedure for the reaction of Wittig using (0,5g) of salt, (0.078 ml) of benzaldehyde , (1 ml) of NaOH in 20 ml of dichloromethane

- **According to general procedure for precipitation of TPPO**

Aspect: White solid

Yield =92%

Mp= 152-153.7°C

Mp_{Lit}=154 to 158 °C

R_f=0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for complexation with $ZnCl_2$ 18h**
  - ✓ **Stilben**

Aspect: White solid

Yield= 39%

Mp= 115.1- 116.1°C

Mp_{Lit}= 123 to 125°C

R_f=0.75 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield = 64%

Mp= 233.9- 235.2°C

Mp_{Lit}= 232°C

R_f=0.18 /eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

Aspect: White solid

Yield = Not determined

Mp= 210.4- 214.0°C

R_f= 0.10 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for complexation with $ZnCl_2$ in refluxing 2h**
  - ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield = 36%

Mp= 234.3-234.5°C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for DCVC**
  - ✓ **Stilben**

Aspect: White solid

Yield = 25%

Mp= 121.5-122.4 °C

R_f= 0.89 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

Aspect: White solid

Yield = 73%

Mp= 155.2-156 °C

R_f= 0.16 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for column chromathography**
  - ✓ **Stilben**

Aspect: White solid

Yield = 39 %

Mp = 117.2-117.8 °C

R_f = 0.75 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

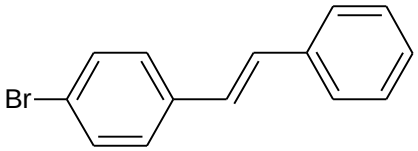
Aspect: White solid

Yield = 92 %

Mp= 154.7-155.9 °C

R_f= 0,13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

IV.2 Synthesis of 1-bromo-4-styrylbenzene (4-bromostilben)



2

The product **2**was synthesized according to the general procedure for the reaction of Wittig using, (0,5g) of salt, (0.141 g) of 4-bromobenzaldehyde, (1 ml) of NaOH in 20 ml of dichloromethane .

- **According to general procedure of precipitation of TPPO**

Aspect: White solid

Yield = 64%

Mp= 252.4-153.7°C

R_f= 0,10 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for complexation with $ZnCl_2$ 18h**
  - ✓ **4-bromostilben**

Aspect: White solid

Yield = 39%

Mp= 116.7-126.2°C

Mp_{Lit}= 140°C

R_f= 0.82 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield = 62%

Mp= 232.5-233.3°C

R_f= 0.17 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

Aspect: White solid

Yield = Not determined

Mp= 217- 223.8°C

R_f= 0.10 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for complexation with $ZnCl_2$in refluxing, 2h**.
  - ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield = 55%

Mp= 227.5-231.5°C

R_f= 0.11 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for DCVC**
  - ✓ **4-bromostilben**

Aspect: White solid

Yield = 71%

Mp= 138-139.1 °C

R_f= 0.89 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

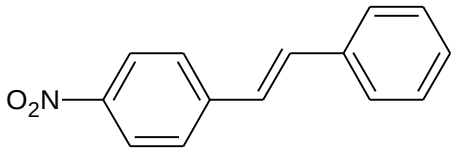
Aspect: White solid

Yield = 82%

Mp= 155.1-156.3 °C

R_f= 0.16 / eluent**:** Cyclohexane / Ethylacetate (3/2)

IV.3-Synthesis of 1-nitro-4-styrylbenzene (4-nitrostilben)



3

The product **3**was synthesized according to the general procedure for the reaction of Wittig using, (0,5g) of salt, (0.115g) of 4-nitrobenzaldehyde, (1 ml) of NaOH in 20 ml of dichloromethane

- **according to general procedure for the reaction of complexation with $ZnCl_2$ 18h**
  - ✓ **4-nitrostilben**

Aspect: Yellow solid

Yield = 44%

Mp= 155.6- 156.3 °C

Mp_{Lit}= 157°C

R_f= 0.83 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield= 45%

Mp= 231.9-232.2°C

R_f= 0.18 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **TPPO**

Aspect: White solid

Yield = Not determined

Mp= 213.1-225.1 °C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for DCVC**
  - ✓ **4-nitrostilben**

Aspect: yellow solid

Yield = 67%

Mp= 150.6-151 °C

R_f= 0.78 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **TPPO**

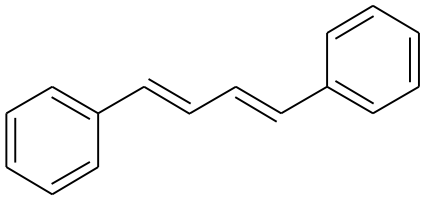
Aspect: White solid

Yield = 74%

Mp= 155-156.2 °C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

IV.4 Synthesis of 1,4-diphenylbuta-1,3-diene (bistyryle)



4

The product 4was synthesized according to the general procedure for the reaction of Wittig using, (0,5g) of salt, (0,093 ml) of cinnamaldehyde, (1 ml) of NaOH in 20 ml of dichloromethane

- **According to general procedure of precipitation of TPPO**

Aspect: White solid

Yield = 87%

Mp= 154.9-155.4°C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for the reaction of complexation with $ZnCl_2$ 18h**
  - ✓ **Bistyryle**

Aspect: White solid

Yield = 36%

Mp= 151.2-152.1°C

Mp_{Lit}= 151-154°C

R_f= 0.8 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: White solid

Yield= 71 %

Mp= 234.3- 234.8 °C

R_f= 0.11 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **TPPO**

Aspect: White solid.

Yield = Not determined

Mp= 226.8-227.8°C

R_f= 0.14 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for DCVC**
  - ✓ **Bistyryle**

Aspect: White solid

Yield = 53%

Mp= 145.3-145.9°C

R_f = 0.89 / eluent**:** Cyclohexane / Ethylacetate (3/2)

  - ✓ **TPPO**

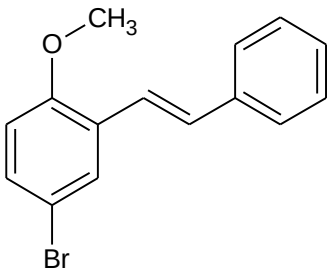
Aspect: White solid

Yield = 73%

Mp= 155.7-156.4 °C

R_f = 0.16 / eluent**:** Cyclohexane / Ethylacetate (3/2)

IV.5 synthesis of 4-bromo-1-methoxy-2-styrylbenzene



The product **5**was synthesized according to the general procedure for the reaction of Wittig using, (0,5g) of salt, (0,164g) of 5-bromo-2-metoxybenzaldehyde, (1 ml) of NaOH in 20 ml of dichloromethane

- **According to general procedure of precipitation of TPPO**

Aspect: White solid

Yield = 91%

Mp=155.7-156.9 °C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for the reaction of complexation with $ZnCl_2$ 18h**
  - ✓ **4-bromo-1-methoxy-2-styrylbenzene**

Aspect: Orange liquid

Yield = 61%

Mp(Liquid)

R_f= 0.82 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **Complex $ZnCl_2(TPPO)_2$**

Aspect: white solid

Yield= 72%

Mp= 233.1-234.8°C

R_f= 0.18 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

Aspect: White solid

Yield = Not determined

Mp= 216.2-227.1°C

R_f= 0.11 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for complexation with $ZnCl_2$reflux 2h**

Aspect: White solid

Yield =36%

Mp= 234.1-234.2°C

R_f= 0.13 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- **According to general procedure for DCVC**
  - ✓ **4-bromo-1-methoxy-2-styrylbenzene**

Aspect: Orange liquid

Yield = 87%

Mp (Liquid)

R_f= 0.75 / eluent**:** Cyclohexane / Ethylacetate (3/2)

- ✓ **TPPO**

Aspect: White solid

Yield = 82%

Mp= 155.2-156 °C

R_f= 0.10 / eluent**:** Cyclohexane / Ethylacetate (3/2)

General Conclusion

Conclusion

In the present work we proposed to explore Wittig reaction and Corey-Fuchs reaction which allow access to unsaturated compounds (dienes, enyne, enynone…), which are used as precursors of cascade reactions. Both of these reactions use PPh_3 and produce TPPO as by product. TPPO is a white precipitate generated along with the final product and is hard to remove.

We synthesized 5 Wittig adducts and applied3 methods to separate TPPO from the final alkene, in the aim to find the best method to get rid of the maximum of TPPO: precipitation in cyclohexane, Complexation with $ZnCl_2$ (18h, at RT) or in refluxing during 2 h and the last method is separation using dry column vacuum chromatography (DCVC). Yields of the different products were calculated; melting point were measured and a discussion was given.

From the results we conclude that, although complexation with $ZnCl_2$, at RT for 18 h is effective, it takes a long time and this method needs to be supplemented by precipitation to completely remove the remaining TPPO. On the other side, complexation with $ZnCl_2$, in refluxing during 2 h and precipitation in non-polar solvent are not very effective because the final alkene is still containing some traces of TPPO. The last method which is dry column vacuum chromatography (DCVC) turns out to be very effective leading to a good separation, and a pure final product .

The objective of our work is achieved and dry column vacuum chromatography (DCVC) could be adapted as the best way to separate TPPO from the final product in a future work using Wittig and Corey-Fuchs reactions.

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ملخص

في هذه الاطروحة قمنا بتصنيع خمس الكينات باتباع تفاعل فيتيغ و حاولنا حل مشكل تواجد أكسيد ثلاثي فنيل الفوسفين مع المركبات النهائية و ذلك بتطبيق ثلاث طرق مختلفة و المقارنة بين فعاليتها و هذا بهدف إيجاد الطريقة الانفع لاتباعها في اعمال بحث مستقبلا تقوم على تفاعل فيتيغ و تفاعل كوري فوكس و كلاهما ينتج أكسيد ثلاثي فنيل الفوسفين.

و هده الطرق هي ترسيب أكسيد ثلاثي فنيل الفوسفين في الهكسان الحلقي و التعقيد مع كلوريد الزنك لمدة 18 ساعة عند درجة الحرارة العادية او لمدة ساعتين مع التسخين و اخيرا الفصل باستعمال الكروماطوغرافيا (باستعمال جهاز ترشيح فراغي) و قد تين ان هذه الطريقة هي الأكثر فعالية في إزالة أكسيد ثلاثي فنيل الفوسفين و بالتالي يمكننا اعتمادها في اعمال بحث في المستقبل.

كلمات مفتاحية تفاعل فيتيغ, تفاعل كوري فوكس, أكسيد ثلاثي فنيل الفوسفين,.الترسيب, التعقيد, الكروماطوغرافيا.

Abstract

In this thesis, we synthesized five alkenes according to the Wittig reaction, and we tried to develop the best method to remove TPPO by applying three different processes and comparing their efficiency, with the aim to apply it in future research work based on Wittig reaction and Corey-Fuchs reaction which both generate TPPO as a side product.

These methods are precipitation of TPPO in cyclohexane, or complexation with zinc chloride for 18 hours at room temperature or for two hours. at reflux and finally separation by chromatography (DCVC). It has been found that DCVC is the most effective in removing TPPO, so we can adopt it in future research.

Keywords Wittig reaction, Corey-Fuchs reaction, triphenylphosphine oxide, precipitation, complexation, chromatography.

Resumé

Dans ce mémoire, nous avons synthétisé cinq alcènes selon la réaction de Wittig, et nous avons essayé de mettre au point la meilleure méthode pour éliminer OTPP en appliquant trois procédés différents et en comparant leur efficacité, dans le but de l'appliquer dans des travaux futurs utilisant la réaction de Wittig et la réaction de Corey-Fuchs qui génèrent toutes les deux OTPP comme produit secondaire.

Ces methodes sont: la précipitation dans le cyclohexane, ou la complexation avec du chlorure de zinc pendant 18 heures à température ambiante ou pendant deux heures au reflux et enfin la séparation par chromatographie (DCVC). Il a été constaté que la DCVC est la plus efficace pour éliminer OTPP, et nous pouvons donc l'adopter dans de futurs travaux de recherche.

Mots clés Réaction de Wittig, réaction de Corey-Fuchs, oxyde de triphénylphosphine, précipitation, complexation, chromatographie.