" Reactions of Organophosphorus Reagents with Active Centers in Some Organic Compounds"

A Thesis Submitted for M.Sc. Degree in Organic Chemistry

Presented by

Shaimaa Tarek Ahmed Mansour
(B.Sc. 2003)

To

Department of Chemistry

Faculty of Science- Ain Shams University

Supervised By

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Professor of Organic Chemistry,
Faculty of Science,
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2017

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APPROVAL SHEET

" Reactions of Organophosphorus Reagents with Active Centers in Some Organic Compounds"

By

"Shaimaa Tarek Ahmed Mansour"

B.Sc. (Chemistry)

This Thesis for Master Degree, Presented to Chemistry Department
Faculty of Science Ain Shams University.
Has been approved by:

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/ / 2017

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POST GRADUATE STUDIES FOR M.Sc. STUDENTS IN ORGANIC CHEMISTRY (2014/2015)

This is to certify that Shaimaa Tarek Ahmed Mansour had attended and passed successfully the following post graduate courses as partial fulfillment for the Degree of Master of Science.

1- Advanced studies in physical organic chemistry:

* Reaction mechanisms and pericyclic reactions.

2- Advanced studies in heterocyclic chemistry.

3- Advanced studies in applied spectroscopic analysis

Electronic spectra infrared, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy of organic compounds.

4- Advanced studies in natural products.

5- Advanced studies in microanalysis.

6- Advanced studies in organometallic compounds.

7- Advanced studies in photochemistry.

8- Advanced studies in polymer chemistry.

Prof. Dr. Ibrahim H. A. Badr

Head of Chemistry Department

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Shaimaa Tarek Ahmed Mansour

CONTENTS

ABSTRACT

Abstract

The original work presented in this thesis aims at studying the reactions of different nucleophilic active phosphacumulenes and stabilized phosphonium ylides with active centers in certain isothiocyanate and isocyanate derivatives. The reaction products depend on the nature of the reagent, substrate and the conditions of the reaction used. New heterocyclic 4-membered or 6-membered sulphur and nitrogen compounds such as phosphoranylidene, thietane, thiazinane, azetidine were obtained. On the other hand, the stable phosphonium ylides with the iso(thio)cyanate afforded phosphoranylidene thiocarbamoyl derivatives. Possible reaction mechanisms are considered and the structural assignments are based on compatible analytical and spectroscopic data.

The in vitro cytotoxic activity results of the synthesized compounds against human cancer cell lines (HepG2 and breast MCF-7) indicated that all compounds showed growth inhibitor activity against liver HepG2, and breast MCF-7 cancer cell.

Key Words:

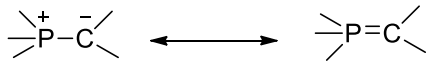
isothiocyanate, isocyanate, phosphonium ylides, phosphoran-ylidene, thietane, thiazinane, azetidine, thiocarbamoyls, cytotoxic activity.

SUMMARY

Summary

Part (1) : Reactions of Active and Stabilized Phosphonium Ylides with Isothiocyanate and Isocyanate Derivatives. Synthesis of Phosphoranylidene, Thietane, Thiazinane, Azetidine, Acid ester and Amide Compounds as Potent Chemo Preventative Agents.

Phosphonium ylides have proved to be extremely useful reagents in the field of organophosphorus chemistry. They are nucleophilic reagents and their electronic structure is generally described as a resonance hybrid (a→b). Their reactivity varies according to the



a b

substituent attached to the carbon end of the dipole. They have been classified as either active or stable. Active ylides must be prepared and handled under an inert gas. So the aim of this work can be presented according to the following sequences:

1- Synthesis of the active phosphacumulenes, namely, (2-oxovinylidene)- **(2a)** and (N-phenyliminovinylidene)- triphenyl-phosphorane (**2b**). Which are represented by the resonance structures **2A** and **2B**.

2- Preparation of the stable ylides, namely, methoxycarbonyl- (**11a**), ethoxycarbonyl-(**11b**) and acetyl- methylenetriphenyl-phosphorane (**11c**).

3- A Comparative study between the reactivity of the active (**2a**, **2b**) and stable phosphonium ylides (**11a-c**) towards isothiocyanate and isocyanate

derivatives such as, 4-methoxyphenylisothiocyanate (**1**), methylisothiocyanate (**5**) and 1,2-dichloro-4-isocyanatobenzene (**8**) have been performed.

4- Characterization of the isolated new compounds and explanation of the reaction mechanisms.

Thus, the reaction of 4- methoxyphenylisothiocyanate (**1**) with (2-oxovinylidene) -(**2a**) and/or (N-phenyliminovinylidene)triphenyl-phosphorane (**2b**), afforded firstly the dipolar intermediate **3**. Cyclization in the intermediate occurs via the sulphur, which is more nucleophilic than the nitrogen to give the four-membered heterocyclic thiocarbomyl compounds, 4-((4-methoxyphenyl)imi-no)-3-(triphenylphosphoranylidene)thietan-2-one (**4a**). and 4-methoxy-N-4-(phenylimino)-3-(triphenylphosphoranylidene)thie-tan-2-ylidene)aniline (**4b**) respectively (Scheme 1). The structure of the new compounds **4a,** and **b** was assigned according to compatible analytical and spectroscopic (IR, ^{1}H, ^{13}C, and ^{31}P NMR, and MS) measurments. The ^{31}P NMR of **4a,b** support phosphorus moiety on the 4-membered ring. Moreover, the proposed structure of **4a** was further unequivocally confirmed by X-ray crystallography (Fig 1).

Next, the reactions of methyl isothiocyanate (**5**) with the active phosphacumulenes **2a,b** were performed to give the dipolar intermediates **6**, which under the experimental conditions reacted with another molecule of methyl isothiocyanate **5** to give the six membered, 3-methyl-6-(methylimino)-2-thioxo-5-(triphenylphos-phoranylidene)-1,3-thiazinan-4-one (**7a**) or 3-methyl-6-(methyl-imino)-4-(phenylimino)-5-(triphenylphosphoranylidene)-1,3-thia-zinane-2-thione (**7b**) respectively. The structure of the six membered compounds **7a,b** was confirmed from their spectroscopic data, specially the ^{31}P

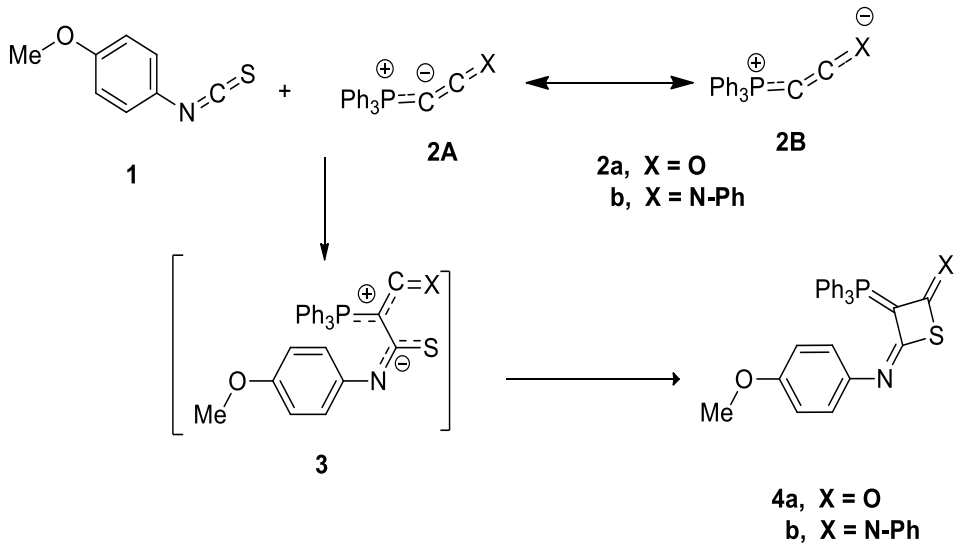
NMR spectrum which support phosphorus group in the six membered ring (Scheme 2).

Moreover, the reaction of 1,2-dichloro-4-isocyanatobenzene (**8**) with the phosphacumulenes **2a,b**, afforded firstly the dipolar intermediates **9a,b**. [2+2]-Cycloaddition through the carbon-nitrogen, leads to the four-membered heteroiminocarbonyl compounds, 1-(3,4-dichlorophenyl)-3-(triphenyl-λ^5-phosphanyl-idene)azetidine-2,4-dione (**10a**), and 1-(3,4-dichlorophenyl)-4-phenylimino-3-(triphenyl-λ^5-phosphanylidene)azetidin-2-one (**10b**) (Scheme 3).

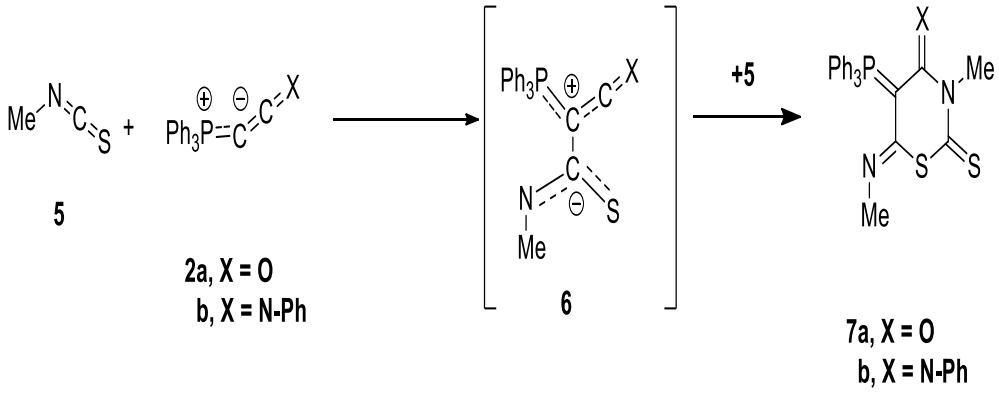
On the other hand, the stabilized phosphonium ylides namely, methoxycarbonyl- (**11a**), ethoxycarbonyl-(**11b**) and acetyl-methylenetriphenylphosphorane (**11c**) reacted with the isothio-cyanate **1** to give the intermediate betains **12a-c**, which produce the new phosphonium ylides **13a-c**. But in case of using the stabilized phosphonium ylide **11c**, adduct **13c** was isolated together with 1,3-bis(4-methoxyphenyl)thiourea (**14**). Formation of the thiourea **14** is catalysed by the phosphorane **11c** (Scheme 4).

Moreover, methyl isothiocyanate (**5**) and 3,4-dichlorophenyl isocyanate (**8**) react with the stabilized phosphonium ylides **11a-c** to give the corresponding thiocarbamoylphosphanylidenes **15a-c** (Scheme 5) and the phosphanylidenes **16a-c** (Scheme 6) respectively. In case of using the phosphorane **11c**, the urea derivative **17** was also isolated with the reagent **16c**.

The structures of the resulting new products has been confirmed through elemental analyses and spectroscopic results. Besides the X-ray crystallography of compound **15a** is reported in (Fig 2).



Scheme 1



Scheme 2