Faculty of Science
Chemistry Department

Rational Synthesis of Novel Pharmacological Heterocyclic Phosphor Derivatives for Therapeutical Uses (Models for Pharmaceutical Intermediates)

A DISSERTATION

Presented By

Mohamed Sayed. M . Bekheit
B.Sc.; M. Sc. (Cairo University)

National Research Center

For

The Degree of Doctor of Philosophy
(In Organic Chemistry)

Under Supervision

Prof. Dr. Galal H. Sayed
Prof. Dr. Wafaa M. Abdou (D.Sc.)
Dr. Reham F. Barghash

Cairo, Egypt
(2013)

Faculty of Science
Chemistry Department

Rational Synthesis of Novel Pharmacological Heterocyclic Phosphor Derivatives for Therapeutical Uses (Models for Pharmaceutical Intermediates)

A DISSERTATION

Presented By

Mohamed Sayed M. Bekheit
B.Sc.; M. Sc. (Cairo University)

National Research Center

For

The Degree of Doctor of Philosophy
(In Organic Chemistry)

Cairo, Egypt
(2013)

APPROVAL SHEET OF THE THESIS

ENTITLED

Rational Synthesis of Novel Pharmacological Heterocyclic Phosphor Derivatives for Therapeutical Uses (Models for Pharmaceutical Intermediates)

THESIS ADVISORS	THESIS APPROVED
Prof. Dr. Galal H. Sayed	…….....….
Prof. Dr. Wafaa M. Abdou	…….....….
Dr. Reham F. Barghash	…….....….

Prof. Dr. Maged Shafeek Antonius

Head of Chemistry Department
Faculty of Science
Ain-Shams University
Cairo, Egypt

ACKNOWLEDGEMENTS

The candidate is deeply thankful to ***Professor Galal Hosni Sayed,*** Professor of Organic Chemistry, Faculty of Science, Ain-Shams University, for his sponsorship, encouragement, and continuous support.

The candidate is sincerely indebted and greatly appreciated to ***Professor Wafaa Mahmoud Abdou (D.Sc.)***, Professor of Organic Chemistry, Chemical Industries Division; National Research Centre *(NRC)*, for suggesting the topic of this work, valuable criticism, supervision and constructive assistance that make this works a reality.

Great thanks are owed to ***Dr. Reham F. Barghash,*** Researcher of Organic Chemistry, Chemical Industries Division, *(NRC)*, for the continuous assistance and guidance.

Thanks are also extended to the staff and fellow colleagues of Department of Pesticide Chemistry, National Research Centre.

The candidate is highly indebted to the National Research Centre, Cairo, Egypt for the facilities provided throughout this work.

Mohamed Sayed M. Bekheit

The Candidate dedicates this thesis

to

his late father,

his mother. and to :

his sisters

Abbreviations

THF	Tetrahydrofuran
Py	Pyridine
TEA	Triethylamine
R.T.	Room temperature
TPP	Triphenylphosphine
SAR	Structure-activity Relationships
NMR	Nuclear Magnetic Resonance
DMF	N, N-Dimethylformamide
NOE	Nuclear Overhauser effect
DAP	Dialkyl phosphite
TAP	Trialkyl phosphite
DMP	Dimethyl phosphite
DEP	Diethyl phosphite
TCE	Tetrachloroethylene
Acace	Acetylacetone
Bn	Benzyl
Ts	4-Toluenesulfonyl (Tosyl)
Tf	Trifluoroethane sulfonyl

Contents Page

ABSTRACT

Name: Mohamed Sayed M. Bekheit

Title: Rational Synthesis of Novel Pharmacological Heterocyclic Phosphor Derivatives for Therapeutically uses (Models for Pharmaceutical Intermediates)

Degree: Philosophy of Doctor (Ph.D.)

The thesis has been focused on phosphorus chemistry. The general work reflected the importance of the phosphorus reagents, in particular trivalent ones in organic and pharmaceutical chemistry. The original work, which included three parts, relied on applying a variety of phosphorus reagents on different substrates, which characterized by the presence of pyrazole core structure for pharmacological evaluation. The new synthesized phosphorus compounds were reported and evaluated as anti-inflammatory, analgesic and anticancer agents.

In the first part, a one-pot three-components reaction for the synthesis of a series of α-aminophosphonates *via* Kabachnik-field reaction was reported, from pyrazolo-carbaldehyde and amine in the presence of phosphorus reagents (dialkyl- or trialkyl phosphites). Substituted α-hydroxyphosphonates and phosphine diamides were also synthesized and pharmaceutically evaluated.

In the second part, carbodiimide, which was generated *in situ via* the aza-Wittig reaction of iminophosphorane with phenyliso-cyanate was used as intermediate, and was allowed to react with dialkyl- and trialkyl phosphites as well as saturated and unsaturated

Horner-Emmon reagents. The investigation offered a facile and efficient regioselective method for the preparation of a new series of α-amino-/enaminophosphonates in moderate to high yields.

In the third part, the same previous protocol was applied on a different substituted carbodiimide. The similarities and differences in the behavior of the two carbodiimides toward the phosphorus reagents, under the same reaction conditions, were studied. It was demonstrated that the hetero-ketene center (-N=C=N) is the point of the first attack by the phosphorus nucleophiles, nevertheless, the final products were influenced by the surrounding function groups of the starting materials.

Keywords:

α-Aminophosphonates; α-Enaminophosphonates; α-Hydroxy-phosphonates; Azaphosphones; Schiff base; Pyrazole; Kabachnik-Fields reaction; Horner-Emmons reagents; analgesic/anti-inflammatory agents; antitumor bioassay

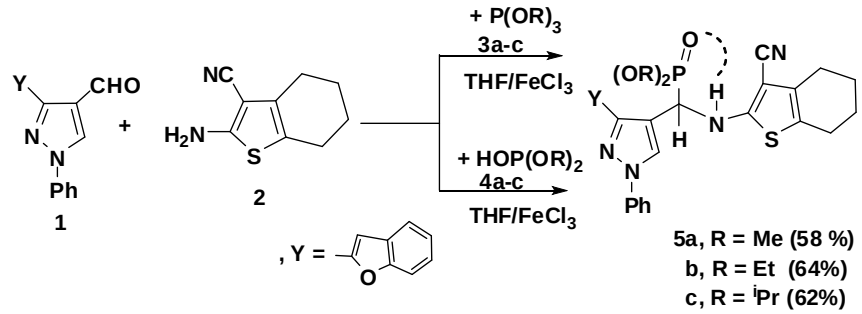
****

SUMMARY OF THE ORIGINAL WORK

Part I: Multicomponent Reactions in a one-pot Synthesis of *α*-Aminophosphonates and α-Aminophosphonic Diamides with Anti-inflammatory Properties*

α-Aminophosphonates have attracted medicinal chemists because of their wide uses in drug development; for example, *α*-aminophosphonates can serve as both hyperglycemic and hypoglycemic agents in different concentrations, antitumor agents, pharmacogenic agents, and as inhibitors of serine hydrolases. In the continuation of our interest in the development of new synthesis routes to heterocycle-based mono- and bisphosphonates, it is reported the multicomponent reactions (MCRs) that included three or more reactants combined in a one-pot procedure to give a single product.

The reaction of the substituted pyrazole 4-carbaldehyde **1** and 2-aminothiophene (**2**) with trialkyl phosphites **3a-c** or dialkyl phosphites **4a-c** in THF containing 10% $FeCl_3$ gave the *α*-aminophosphonates **5a-c** (Scheme 1)

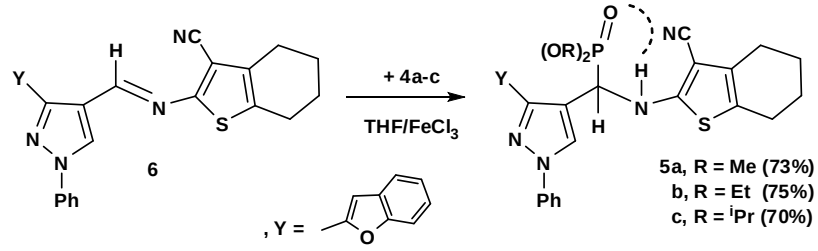


Scheme 1

The Schiff base **6**, which previously prepared from the condensation of the aldehyde **1** with the amine **2** was allowed to react with DAP **4a-c,** under the same pervious experimental conditions, to

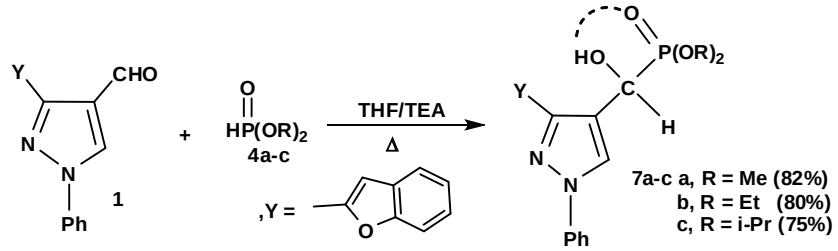
* This work has been published in: *Monatsh chem*, **2011**, *142*, 649-656

give the same α-aminophosphonates **5a-c** in higher yield (75%) (Scheme 2).



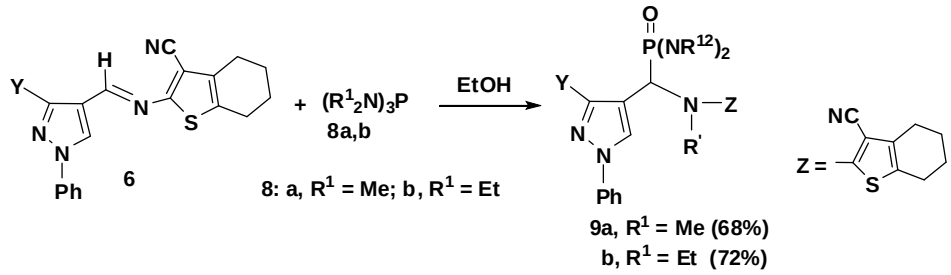
Scheme 2

Dialkylphosphites **4a-c** was also allowed to react with the parent aldehyde **1** to yield the α-hydroxyphosphotates **7a-c** (Scheme 3).



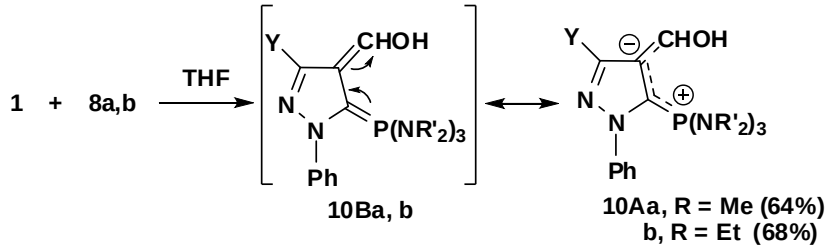
Scheme 3

Furthermore, the Schiff base **6** was treated with tris(dialkylamino) phosphines **8a** and **8b** in boiling ethanol to give the respective phosphinic diamides **9a,b** (Scheme 4).



Scheme 4

Nevertheless, the trisaminophosphonium dipolar ion **10** were formed when the trisaminophosphine **8a,b** reacted with the pyrazole 4-carbaldehyde **1**.



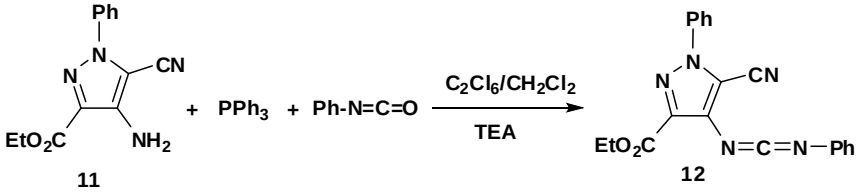
Scheme 5

The new products were established upon compatible elemental analysis and molecular weight measurements as well as spectroscopic interpretation (IR, MS, ^{1}H-, ^{13}C- and ^{31}P NMR).

****

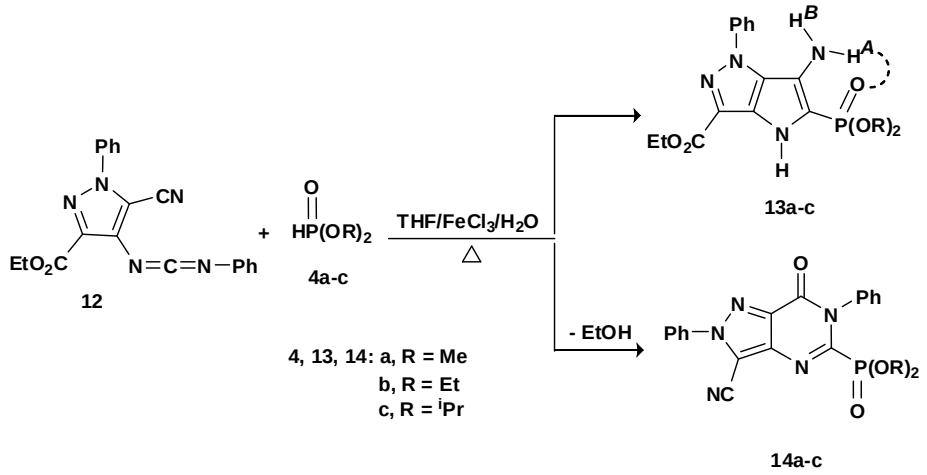
Part II: Carbodiimides in the Synthesis of Enamino- and *α* –Amino phosphonates as Peptidomimetics of Analgesic /Antiinflammatory and Anticancer Agents*

In continuation of the preparation of *α*-aminophosphonates of potency pharmacological, carbodiimide **12** reacted with dialkyl phosphites in presence of $FeCl_3$/THF/H_2O to give the pyrrolo-phosphonate (**13a-c**, 14%) and the pyrimidino-phosphonate (**14-c**, 57%) (Scheme 6). The carbodiimide **12** was prepared by the reaction of the aminopyrazole **11** with triphenylphosphine and phenyl isothiocyanate. (Eq. 1)



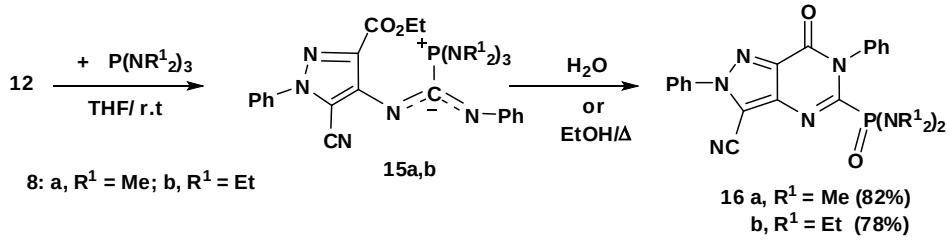
Eq. 1

* This work has been published in: *Arch. Pharm. Chem. Life. Sci.*, **2012**, *345*, 884-895



Scheme 6

The carbodiimide **12** also reacted with tris(dialkylamino)-phosphines **8a,b** in THF at room temperature to afford the Zwitter ion **15a,b,** which is highly water sensitive. When a protonating agent (e.g., 1 mL H_2O) presents in the reaction medium, the reaction was markedly accelerated leading to the formation of the phosphonic diamides **16a,b** (≈ 80%) (Scheme 7).



Scheme 7

The behavior of carbodiimide **12** toward some phosphonyl carbanions was next investigated in the presence of suitable base to obtain more phosphorylated heterocycle. First, saturated Horner-Emmon reagents **17a-d** were applied to afford the pyridine phosphonate derivatives **18a-d**, while the unsaturated Horner-Emmon reagents such as diethylvinyl- or diethyl(2-methylallyl)-phosphonate