Ain Shams University
Faculty of Education
Department of Chemistry

Utility of Phosphonic Dihydrazide in Synthesis of Biologically Active Heterocyclic Systems

Thesis Submitted
by

Somaia Mohamed Abdel-Kariem Mostafa

Demonstrator
Department of Chemistry, Faculty of Education, Ain shams University
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Supervisors

Dr. Salah Abdel-Ghaffar Abdel-Aziz

Dr. Tarik El-Sayed Ali Ismail

Dr. Kamelia Mohamed El-Mahdy

Department of Chemistry
Faculty of Education
Ain shams University
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Abstract

Utility of phosphonic dihydrazide in synthesis of biologically active heterocyclic systems

Somaia Mohamed Abdel-kariem Mostafa
Department of Chemistry, Faculty of Education, Ain-Shams University.

Vilsmeier-Haack reaction conditions were applied on phosphonic dihydrazones **3a-d** to yield *bis*(4-formylpyrazolyl)phosphine oxides **4a,b**, *bis*-(4-hydroxy-2,4-dihydrochromeno[4,3-*c*]pyrazole)phosphine oxide **6** and *bis*-(chromeno[2,3-*g*]indazole)phosphine oxide **8**, respectively. Compounds **4a**,**b** were condensed with aniline, phenacyltriphenylphosphonium bromide and 4-phenylthioemicarbazide to give the corresponding products **9**, **12** and **18**, respectively. The products **9**, **12** and **18** were treated with thioglycolic acid, diethyl phosphite and/or acetic anhydride to yield a novel class of *bis*-pyrazoles containing sulfur and phosphorus derivatives. Also, a synthetic method has been reported for the preparation of novel classes of phosphorus macrocycles in which the pyrazole rings are appended to phosphorus atom. The methodology is based on the cyclocondensation reaction of *bis*(4-formylpyrazolyl)phosphine oxides **4a**,**b** with nitrogen nucleophiles containing terminal amino groups to give the [1+1] macrocycles **23a**,**b** and **24a**,**b**, and [2+2] macrocycles **25a**,**b** and **26a**,**b**. Structures of all novel products were established on the basis of elemental and spectral data. Most of the newly synthesized compounds were evaluated for their *in vitro* antibacterial and antifungal activities. Preliminary results indicated that most of the compounds demonstrated lower to moderate antimicrobial activity, comparable to the standard drugs.

Keywords: Phosphonic dihydrazones, hydrophosphoryl, Vilsmeier-Haack reaction, *bis*-pyrazoles, sulfur-phosphorus heterocycles, phosphorus macrocycles, nitrogen nucleophiles, antimicrobial activity.

Supervisors
Dr. Salah Abdel-Ghaffar Abdel-Aziz
Ass. Prof. of Organic Chemistry, Faculty of Education, Ain Shams University.
Dr. Tarik El-Sayed Ali
Lecturer of Organic Chemistry, Faculty of Education, Ain Shams University.
Dr. Kamelia Mohamed El-Mahdy
Lecturer of Organic Chemistry, Faculty of Education, Ain Shams University.

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Approval Sheet

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Supervisors	*Signature*

Dr. Salah Abdel-Ghaffar Abdel-Aziz ……

Ass. Prof. of Organic Chemistry, Faculty of Education, Ain Shams University.

Dr.Tarik El-Sayed Ali Ismail ……...

Lecturer of Organic Chemistry, Faculty of Education, Ain Shams University**.**

Dr. Kamelia Mohamed El-Mahdy ….……

Lecturer of Organic Chemistry, Faculty of Education, Ain Shams University.

Head of Chemistry Department

Prof. Dr. Said M. Khalil

…….

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Aim of the work

1] Study the effect of Vilsmeier-Haack reagent on different phosphonic dihydrazones.

2] Study the chemical reactivity of *bis*(4-formylpyrazolyl) phosphine oxides towards nitrogen and carbon nucleophilic reagents.

3] Synthesis of novel sulfur heterocycles linked to pyrazole moieties at position 4 in *bis*(4-pyrazolyl)phosphine oxide derivatives.

4] Synthesis of novel acyclic and cyclic a-aminophosphonates incorporation at position 4 of pyrazole moieties in *bis*(4-pyrazolyl)phosphine oxide derivatives.

5] Synthesis of some novel phosphorus macrocycles with nitrogen, oxygen, sulfur and phosphorus as donor atoms.

6] Characterization of the spectroscopic properties of the newly synthesized compounds.

7] Evaluation of antimicrobial activity for the synthesized compounds and study the relationship between the structure and activity.

Synthetic Methods for Phosphorus Compounds Containing Pyrazole Moieties

1. Introduction

Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials [1]. Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. Pyrazole and its derivatives, a class of well known nitrogen containing heterocyclic compounds, occupy an important position in medicinal and pesticide chemistry with having a wide range of bioactivities such as antimicrobial [2], anticancer [3], antiinflammatory [4], antidepressant [5], anticonvulsant [6,7], antihyperglycemic [8], antipyretic [9], antibacterial [10], antifungal activities [11], CNS regulants [12] and selective enzyme inhibitory activities [13]. It has been found that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases [14]. It has been shown *in vivo* that some of the pyrazole derivatives have appreciable antihypertensive activity [15]. These compounds also exhibited properties such as cannabinoid hCB1 and hCB2 receptor, inhibitors of p38 Kinase and CB1 receptor antagonists [16,17].

On the other hand, it is known that phosphorus substituents regulate important biological functions such as pesticides, antichloine esterase, antiviral, antimicrobial activity, war gases [18-21], and that molecular modifications involving the introduction of organophosphorus functionalities in simple synthons could be very interesting for the preparation of biologically active compounds.

Pyrazole derivatives containing a phosphorus atom have been showed good biological activities, for example, pyraclofos and

flupyrazofos have been developed as good insecticides [22,23]. For many years, the synthesis of phosphorus derivatives of pyrazoles has been a subject of interest in several laboratories. The present survey considers all the literature data on methods developed for the synthesis of phosphorus compounds containing pyrazole moieties starting from their appearance up to the 2010. The described methods for the synthesis of phosphorus compounds containing pyrazole moieties can be divided into three routes: a) Phosphorylation of pyrazole moieties and/or their side functional groups, b) Ring closure of acyclic phosphorus compounds into phosphonopyrazoles and c) Cyclization of side functional groups at pyrazole moieties or phosphorus rings to give phosphorus heterocyclic systems fused with pyrazole rings. It is hoped that this survey will demonstrate the synthetic potential of the synthesis of phosphorus containing pyrazole moieties and generate some new ideas in this area.

2. Synthetic Approaches

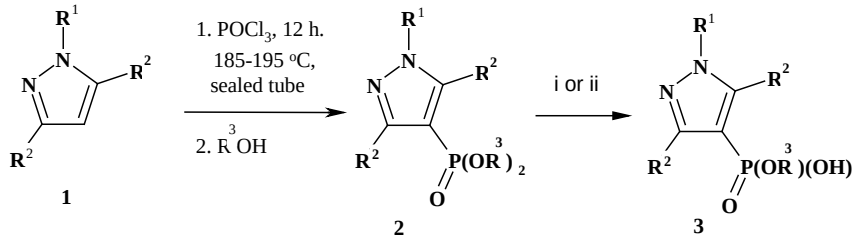
There are three routes for the synthesis of phosphorus compounds containing pyrazole moieties.

2.1. Phosphorylation of pyrazole moieties and/or their side functional groups.

2.1.1. C-Phosphorylation of pyrazole moieties

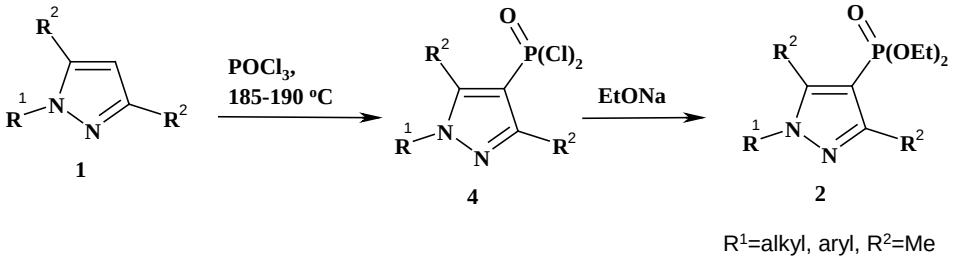
It is known that pyrazoles with unsubstituted 4-position and lacking electron-acceptor groups in the ring react with $POCl_3$ to form 4-pyrazolylphosphonyl dichlorides [24]. This property was used in the synthesis of a series of phosphonylated pyrazoles [24]. Thus, heating of alkyl substituted pyrazoles **1** and $POCl_3$ in an ampule for 12 hours, followed by treatment with absolute alcohol, concentration and addition of NaOH, and further workup. In this way, three dialkyl 1,3,5-trialkylpyrazol-4-ylphosphonates **2** could be

prepared in 31-44% yield (Scheme 1). Also, other substitution patterns were successful with R^1=Ph and R^2=Me or H. The dibutyl 1-phenylpyrazol-4-ylphosphonate could be converted into the monobutyl ester by heating with KOH in propanol, followed by acidification. Hydrolysis of the dialkyl esters with acids gave syrupy phosphonic acids that could not be purified.



Scheme 1

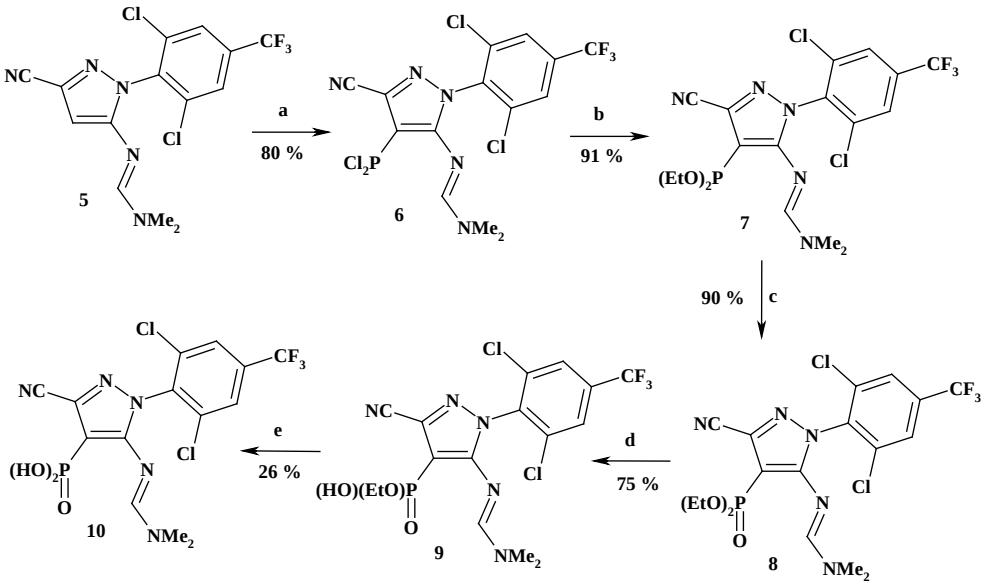
A similar type of substitution reaction resulted from the treatment of pyrazole **1** with phosphoryl chloride in which the product after esterification was the ester **2** [25] (Scheme 2)**.**



Scheme 2

The synthesis of diethyl 3-cyanopyrazol-4-ylphosphonate **8** and the corresponding phosphonic acid **10** was patented in 2005 [26,27]. The synthetic route is depicted in Scheme 3 and consists of a phosphonylation step, followed by an oxidation to prepare the phosphonate **8**. Conversion to the phosphonic acid **10** occurred in two steps, *via* the monoalkyl ester (Scheme 3). The envisaged end

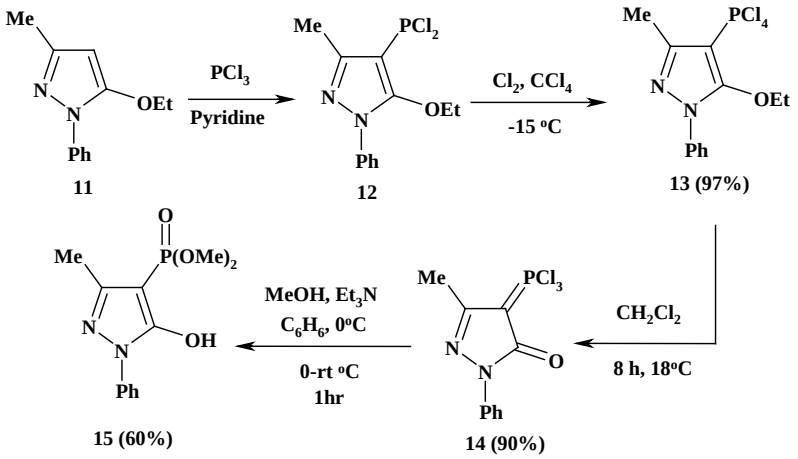
products were used for pest control and preparation of veterinary drugs, since they are useful for the control of arthropods and helminthes.



(a) 1. PCl_3, Py, -30°C, (15 min.); 15°C (2h); 2. Et_3N, 1h.; (b) Et_3N, EtOH, Et_2O, 0°C (20min.); 20°C (14h.); (c) H_2O_2 in EtOH at -30°C, 47 in EtOH at -50 °C (15min.): heating to 20°C and workup; (d) LiN_3, DMF, 1h. 95-100°C; (e) TMSI, MeCN, 24h., 20°C.

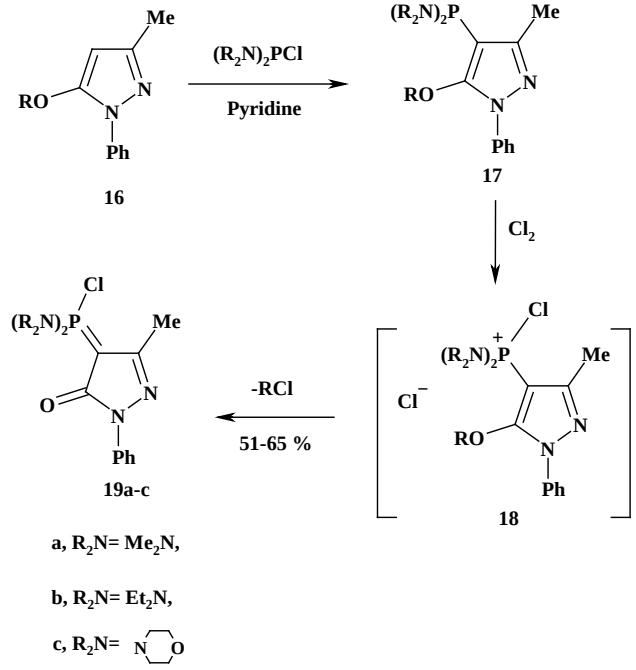
Scheme 3

Treatment of **11** with PCl_3 in pyridine provided 5-ethoxy-3-methyl-1-phenylpyrazol-4-yl dichlorophosphine (**12**). Chlorination of **12** was described by the researchers earlier [28], and afforded phosphorane **13**. This phosphorane underwent selective rearrangement into the P-ylide **14** under strictly controlled conditions. The latter compound reacted with methanol to yield dimethyl pyrazol-4-ylphosphonate **15** (Scheme 4).



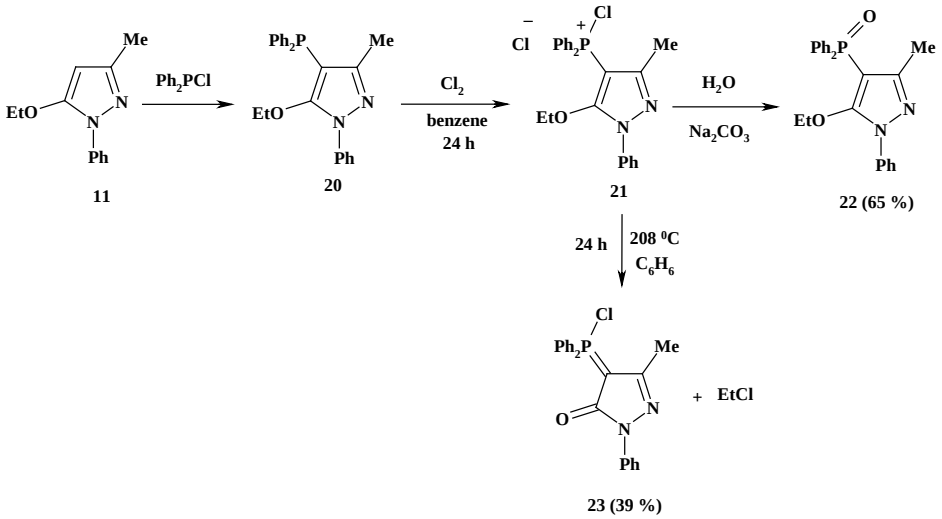
Scheme 4

Reaction of dialkylaminophosphonyl chloride with 5-alkoxy-3-methyl-1-phenyl-1*H*-pyrazole **16** in pyridine afforded 5-alkoxy-pyrazoles **17**. Further, it was found that the chlorination of **17** with chlorine led to stable chloro ylides **19a-c** rather than to the expected chlorophosphonium chloride **18** [29] (Scheme 5).



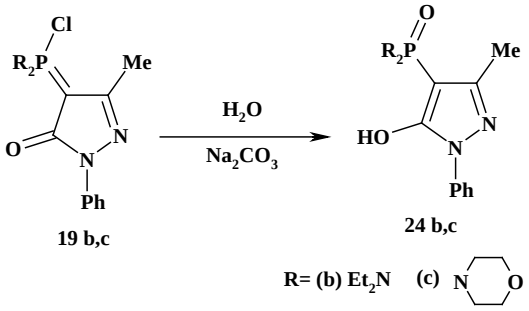
Scheme 5

5-Ethoxy-3-methyl-1-phenylpyrazole (**11**) reacted with Ph_2PCl giving phosphine **20**. Contrary to the behavior of compounds **17**, phosphine **20** was chlorinated to provide a rather stable chlorophosphonium salt **21** that could not be isolated in a pure state, although its structure was supported by ^{31}P NMR spectral data as well as by hydrolyzing it to diphenyl (3-methyl-1-phenyl-5-ethoxy-pyrazol-4-yl)phosphine oxide (**22**). When the chlorophosphonium salt **21** was maintained at 208 ^0C in benzene for 24 hours, it decomposed to give 4-(diphenylphosphino)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one-chloromethane (**23**), and ethyl chloride [29] (Scheme 6).



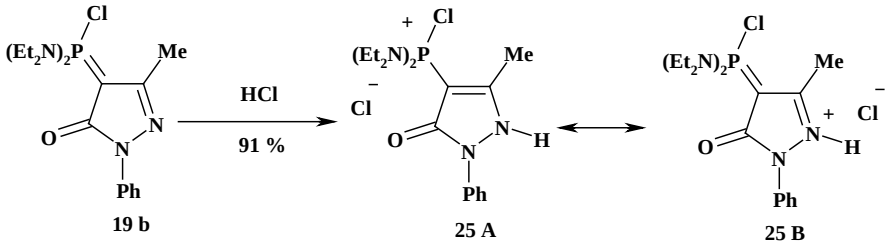
Scheme 6

P-chloro ylides **19b,c** were readily hydrolyzed by atmospheric moisture or by reaction with aqueous sodium carbonate to give the corresponding phosphonates **24** [29] (Scheme 7).



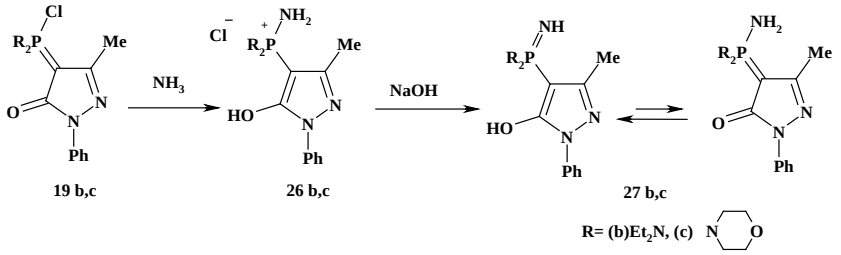
Scheme 7

Also, chloro ylide **19b** reacted with hydrogen chloride to furnish tetraethyldiamino (3-methyl-5-oxo-1-phenyl-2,5-dihydro-pyrazol-4-yl) chlorophosphonium chlorides (**25A,B**) as stable compounds in air [29] (Scheme 8).



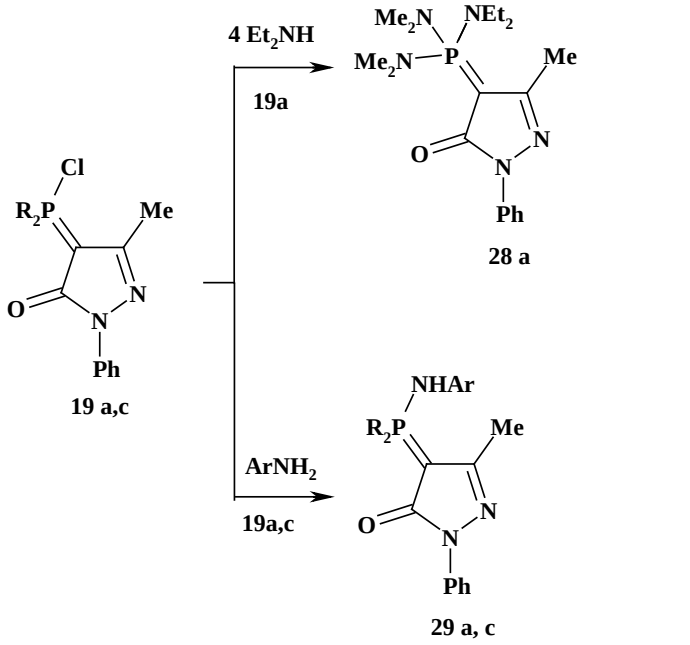
Scheme 8

Under the action of gaseous ammonia, chlorine atoms in the chloro ylides **19b,c** were readily displaced by amino groups to produce iminophosphonates **27b,c** [29] (Scheme 9).



Scheme 9

The ease of substitution of the chlorine atom in chloro ylides **19a-c** by a dialkylamino or an arylamino group was mainly governed by steric effects of substituents at the phosphorus atom. For example, in the case of dimethylamino groups bonded to the phosphorus atom, the reaction with diethylamine and aniline (arylamine) were carried out at 208 ^{o}C for 24 hours to reach completion [29] (Scheme 10).



Scheme 10

Treatment of dichlorophosphine **12** with diisopropylamine gave 5-ethoxy-3-chloro-4-[chloro(diisopropylamino)phosphino] pyrazole (**30**). Chlorination of **30** led to the dichlorophosphoniumchloride **31**, which underwent transformation into the dichloro(diisopropylamino) phosphonio[5-(4*H*)-pyrazol-4-ylide] (**32**), as a result of dealkylation through loss of ethyl chloride [30] (Scheme 11).