RESEARCH ARTICLE

SYNTHESIS OF SUBSTITUTED PHOSPHOROTHIOATES AS ANTIMICROBIAL AND PESTICIDAL AGENTS

Deepak R. Nagargoje

Department of Chemistry,

Ramsheth Thakur Arts Commerce & Science College, Dist. Palghar - 401 604 (M. S.)

Corresponding author E-mail: ndeepak2112@yahoo.co.in

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Abstract:

In agrochemistry, organophosphorous compounds comprising phosphates, dithiophosphates and phosphorothioates are used as pesticidal agents. The biodegradable nature of these compounds makes them preferable and safer alternative in comparison with DDT, BHC etc. Phosphorothioates have a broad spectrum of applications in industrial, agricultural, and medicinal chemistry due to their biological and physical properties as well as their synthetic utility. These phosphorothioates have been prepared as pesticides, potential chemotherapeutic agents and as inhibitor of different enzymes.

Keywords: Organophosphorous Compounds, Phosphorothioates, Agrochemistry, Pesticidal Activity.

Introduction:

Pyrazole chemistry has been the focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives which are appearing as anti-microbial, antiviral, antitumor, anti-inflammatory, antihistaminic, anticobvulsant, antidepressant agents in medical sciences [1-7].

On the hand in agrochemistry, organophosphorous compounds comprising phosphates, dithiophosphates and phosphorothioates are used as pesticidal agents [8-13]. The biodegradable nature of these compounds makes them preferable and safer alternative in comparison with DDT, BHC etc. Synthetic pesticides and nematicides which are phosphorous derivatives are getting importance due to environmental concern and their biodegradable nature.

Phosphorothioates have a broad spectrum of applications such as industrial, agricultural and in medicinal chemistry due to their biological and physical properties as well as their synthetic utility [13]. These phosphorothioates have been prepared as pesticides and thio-analogues of biologically active phosphoric diesters [14]. Some of the derivatives of phosphorothioates have introduced as potential chemotherapeutic agents [15] and inhibitor of different enzymes [16].

In a study, one of major pest of crops *Helicoverpa armigera* in Indian subcontinent which accounts for loss of US $ 300-500 million per annum to cotton and pulses alone [17], was found to be active against the commercially available pesticides. Cypermethrin, Fenvalerate, Endosulfan, Quinalphos and some methomyl insecticides rapidly losing battle against the pest, however, the pest is still susceptible to Monocrotophos- a phosphorothioate derivative [18-19].

Apart from agricultural chemistry, in medicinal chemistry many phosphonic acids and derivatives thereof have been also shown to exhibit important biological properties including antibiotic, antileukemic depending on the nature of substituent on the phosphonic group [20-21].

Some of the commercially used phosphorothioates have been listed in Fig.1.

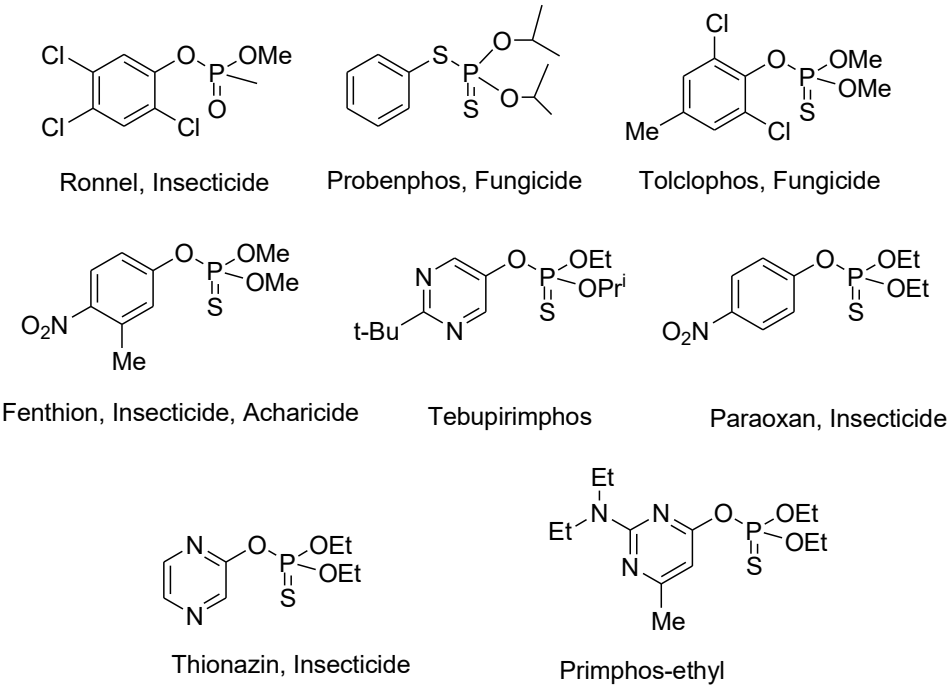
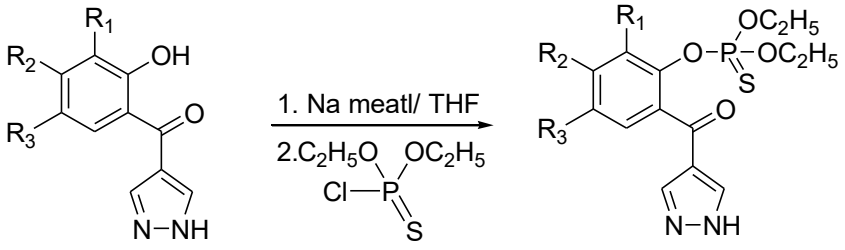


Figure 1: Commercially useful phosphorothioates.

In literature, phosphorothioates have been prepared by the reaction of dialkyl phosphates with sulfenyl chlorides [22], sulfenyl cyanides [23], thiosulphonates [24], disulfides [25] and sulfur [26]. Additionally, condensation of phosphorochlorithioates with thiols [27] is a method of choice.

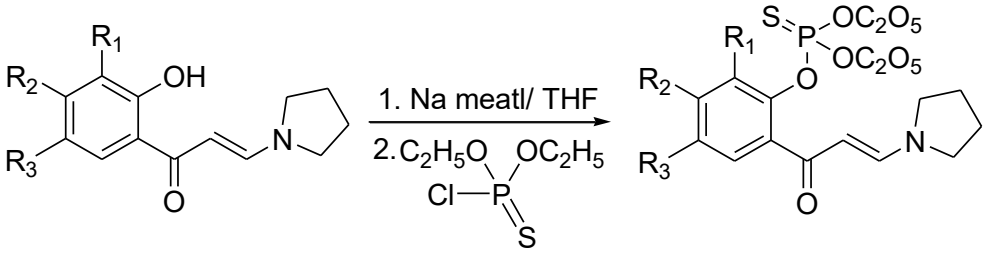
Literature survey revealed that attempts were made to couple piperidinyl, pyrazolyl and quinolyl compounds and phosphochlorothioates and evaluate their biological activities.

N. S. Joshi [28] synthesized various O, O- diethyl O-[2-(1*H*-pyrazole-4-carbonyl)-Phenyl] phosphorothioate from substituted 2-hydroxy phenyl-(1*H*-pyrazol-4-yl-methanone and phosphochlorothioate with sodium metal in dry THF. (Scheme 1)



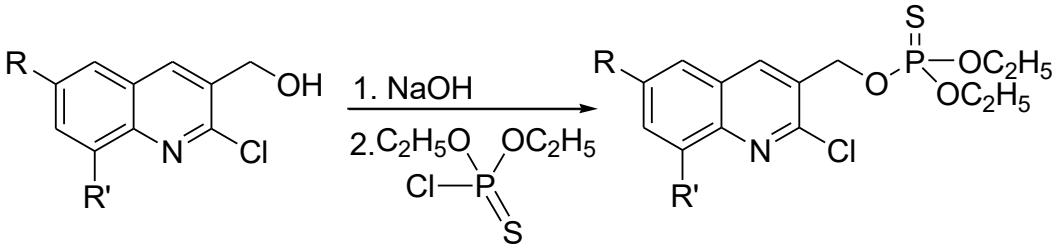
Scheme 1

In another report, same author reported [29] the condensation of 1-(6-hydroxyphenyl)-3-piperidino-2-propen-1-one with O, O-diethyl phosphochlorothioate to produce O,O-diethyl O-[1-(6-hydroxyphenyl)-3-piperidino-2-propen-1-one] phosphorothioate. (Scheme 2)



Scheme 2

Pokalwar *et al.* [30] have synthesized some of the phosphorothioate derivatives of (2-chloroquinolin-3-yl) methanol with phosphorochlorothioate in NaOH and acetone. (Scheme 3)



Scheme 3

Experimental Section:

1. Materials and methods

All the reagents and solvents were obtained from SD-Fine Chemicals ltd. and used without further purification. The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of all compounds was checked by TLC on silica gel plates. IR spectra were recorded on Jasco FT-IR-4100 in KBr disc. H^1 NMR spectra were recorded on a Varian 400 MHz spectrometer in DMSO-d_6 and $CDCl_3$; chemical shifts (δ) were in ppm relative to TMS and coupling constant (J) were expressed in hertz (Hz) using tetramethylsilane as an internal standard. Mass spectra were recorded on a Macro mass spectrometer (Waters) by electro spray method (ESI). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer.

2. Synthesis of O, O-diethyl O-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methyl phosphorothioate (24c)

In a round bottom flask, (3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl) methanol **22c** (0.5gm, 0.0017mol) in acetone was taken. To this solution, crushed pellets of NaOH (0.135gm, 0.0034mol) were added and stirred. After 15 min., O, O- diethyl thiochlorophosphate **23** (0.32gm, 0.0017mol) was added in it. On completion of reaction (checked by TLC), the solvent was evaporated under reduced pressure to get the solid which was poured into water. The separated product was filtered, dried, and crystallized from alcohol.

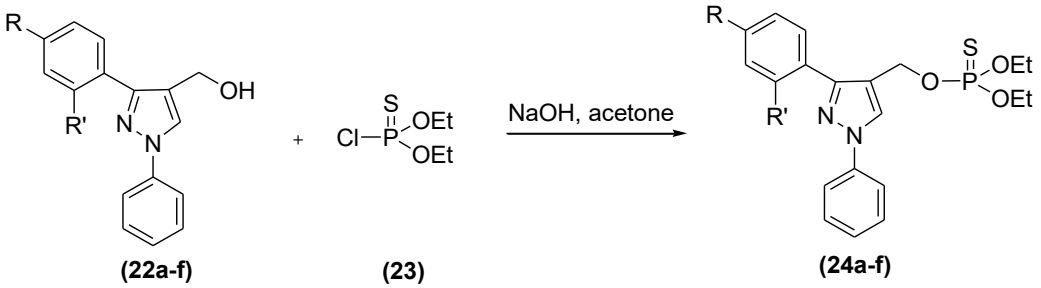


Table 1: Physical data of the compounds. (24a-f)

Comp. No.	R	R_1	Yield (%)	M. P. (°C)
24a	H	H	73	------ *
24b	CH_3	H	78	200-202
24c	NO_2	H	67	214-216
24d	F	H	70	194-196
24e	Br	H	82	------ *
24f	OCH_3	H	80	210-212

* Colourless oily liquids.

Spectral analysis:

H^1NMR: Comp. (24c): δppm 1.29 (t, 6H, methyl protons); 4.11 (q, 4H, methylene protons); 5.2 (s, 2H); 7.36 (t, *J= 7.2 Hz*, 1H); 7.5 (t, *J=7.2Hz*, 2H); 7.75 (d, *J= 8.0 Hz*, 2H); 8.06 (d, *J= 8.4 Hz*, 2H); 8.17 (s, 1H, pyrazole proton); 8.32 (d, *J= 8.4 Hz*, 2H)

I.R.:Comp. (24c) cm^{-1}: 1597 (C=N), 1528 (NO_2), 1273 (O-P=S).

Mass: Comp. (24c): Mass (m/z) 448.1 (M^+)

Results and Discussion:

In the present investigation the reaction of formyl pyrazole 22c with O, O- diethyl thiochlorophosphate 23 in presence of NaOH catalyst under room temp. afforded product 24c in quantitative yield of 73%. The structure of 24c was confirmed by its physical constant and IR spectral data. The formation of product 24c was a neat reaction which does not require any specific temperature to complete the reaction. The formation of compound 24c was established using analytical techniques viz. IR, NMR and Mass spectrometry. The IR spectrum of 24c exhibited characteristic absorption bands in the region 1597cm-1 due to C=N, another band at 1528 cm^{-1} due to NO_2 stretching. Further, the presence of absorption band at 1273cm^{-1} due to (O-P=S) group indicated the existence of oxygen-phosphorous-sulfur linkage in resulting compound.

The H^1NMR spectrum of 24c displayed characteristic signals. A signal at 1.29 due to 6 methyl, 4.11 due to 4 methylene protons, a set of multiplet for aromatic benzenoid protons of aromatic ring, another singlet at 8.17 due to one aromatic protoncorresponding to pyrazolyl proton. Mass spectrometry revealed the compound has molecular mass which agrees with the theoretical value.

Conclusion:

In the present investigation synthesis of O, O-diethyl O-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) methyl phosphorothioate have been achieved in good yield. The structures of these compounds were confirmed by their elemental analysis, IR, H^1NMR and mass spectral data.

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