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EXPLORATION IN SYNTHESIS AND FUNGICIDAL ACTIVITIES OF SOME NOVEL O-ETHYL O-HETEROARYL 2-CHLOROETHYL PHOSPHONATES

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Abstract

Novel O-ethyl O-heteroaryl 2-chloroethyl phosphonates have been prepared by condensing 2-chloroethyl phosphonyl dichloride by the sequential addition of ethanol and –OH and –SH carrying heteroaryls. Attempts of the above reaction with –NH carrying heteroaryl (benzimidazole) furnished a different product than the expected one by different reaction path.

Keywords

1-Methyl benzimidazole, 3-Hydroxy 5-phenyl isoxazole, O-Methyl O-(5-phenyl isoxazol-3-yl) 2-chloroethyl phosphonate, O-Ethyl O-(5-phenyl isoxazol-3-yl) 2-chloroethyl phosphonate, O-Ethyl O-(quinolin-8-yl) 2-chloroethyl phosphonate, O-Ethyl S-(benzimidazol-2-yl) 2-chloroethyl phosphonate, O-Ethyl S-(benzothiazol-2-yl) 2-chloroethyl phosphonate

Introduction

Organophosphonate pesticides are well known for their various activities like insecticidal, bactericidal, fungicidal and others. Several series of phosphonate fungicides were developed from our laboratories[1a, 1b] to obtain most active and safer fungicide as compared to Ediphenfos. One such series is O-methyl O-aryl 2-chloroethyl phosphonates[2] **(1)** which possessed very good fungicidal activities.
Replacement of the aryl moiety by a heterocyclic moiety is known to increase the insecticidal activities of phosphonates. This led us to synthesize O-methyl O-(5- isoxazolyl) 2-chloroethyl phosphonate **(2)** by reacting 2-chloroethyl phosphonyl dichloride first with methanol and then with 3-hydroxy isoxazole in the presence of triethylamine (Scheme-I).Then we tried to hook –NH carrying heteroaryl moiety (benzimidazole) in place of 3-hydroxy isoxazole by using various bases and different reaction conditions, but all our efforts resulted in the formation of 1-methyl benzimidazole **(4)** only (Scheme-I).

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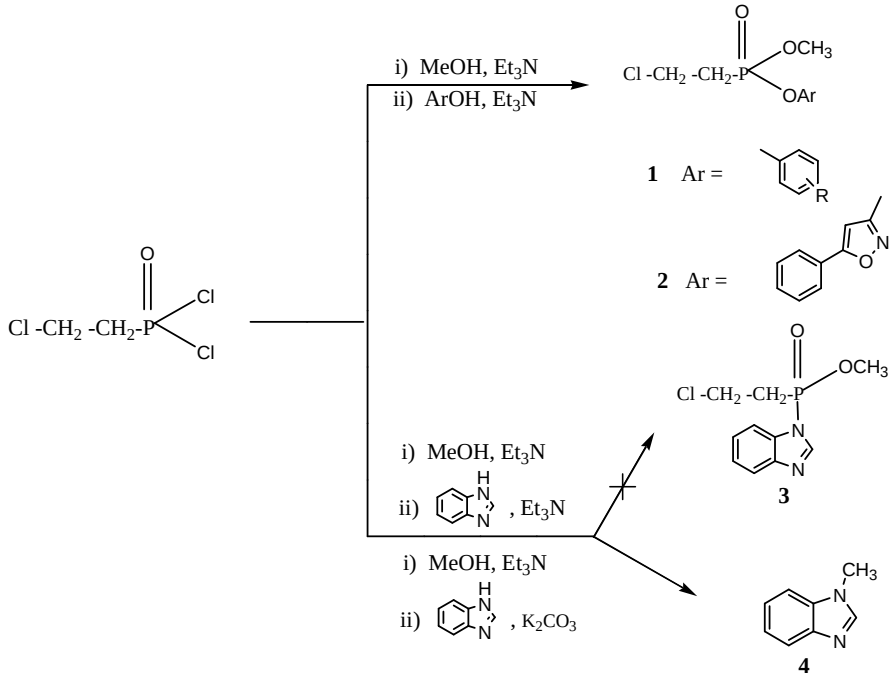
Scheme-I



We extended our research for novel fungicides by increasing the alkyl chain and a series of O-aryl O-ethyl 2-chloroethyl phosphonates were synthesized with the evaluation of their fungicidal and nematicidal activities [3, 4].In the present series we replaced the aryl moiety with some –OH and –SH carrying heteroaryls and four novel compounds **(5 – 8)** obtained which were assayed for their fungitoxicity (Scheme-II).

Scheme-II:

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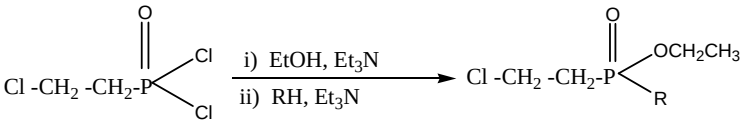
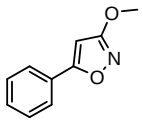
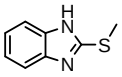


5 R =

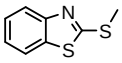


6 R =

7 R =



8 R =



Materials and methods

Melting points are uncorrected.[1]H NMR spectra were recorded on a Varian EM-300 (60 MHz) spectrometer in $CCl_4/CDCl_3$ solvent using TMS as internal standard. IR spectra were recorded in a Nicolet FT-IR spectrometer (Model Impact 400) as liquid film (LF) for liquid samples and in KBr pellets for solid samples.GC/MS was carried out on a Fisons instruments TRIO-1000.

3-Hydroxy 5-phenyl isoxazole:

In a 250 mol RB flask, KOH (132.4g), $NH_2OH.HCl$ (2.8g) were stirred at RT with H_2O (100mL) and EtOH (100mL) to get a clear solution. Ethyl cinnamate dibromide (prepared from ethyl cinnamate and Br_2 in CCl_4) (13.44g) was added, stirred at RT overnight and then refluxed for 6 h. After acidification with conc.HCl at RT, the reaction mass was concentrated at 70^0C U/V completely to get a brownish solid which was then recrystallised from hexanes to give white needles,m.p.164 ^{0}C,lit [5]m.p.163-165^{0}C.Yield 4.3g(78 %).

UV ($\lambda_{max,}$ MeOH, mμ): 260-261.

IR (KBr):1448, 1639, 3019-3200 (b, H-bonded OH) cm^{-1}.

^{1}H NMR ($CDCl_3$, δ):6.25 (s, 1H, H-4), 7.60 (m, 5H, -Ph), 9.40 (br, 1H, D_2O exchangeable, 3-O**H**).

O-Heteroaryl O-alkyl 2-chloroethyl phosphonates: General procedure:

β-Chloroethyl phosphonyl dichloride[3](0.012 moles) in 50 ml dry benzene was stirred at 0-5 ^{0}C in a 250 mL dry RB flask under nitrogen and a mixture of absolute ethanol (0.006 moles) and dry triethylamine (0.006 moles) in 10 mL dry benzene was added in 15 min.After the addition was complete, the reaction mixture was stirred for 1 hr at RT and then for

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another 1hr at 50-60^{0}C.Then the reaction mass was cooled to 15^{0}C and a mixture of heteroaryl phenols or thiols (0.006 moles) and dry triethylamine (0.006) in 15 ml dry benzene was added in 15 min after which it was stirred at RT for 3-5 hrs(monitored by TLC,benzene:EtOAc,1:1,V/V).The triethylamine hydrochloride salt was filtered and the filtrate was washed with chilled 1% NaOH aqueous solution (2×10 mL) and then with H_2O (3×10 mL).The organic layer was dried over anhyd Na_2SO_4 and concentrated *in vacuo* and the resultant crude material was purified by column chromatography over silica gel using benzene:EtOAc(1:1,V/V) as eluant. The purity of the product was checked by TLC and the structures were confirmed by IR, ^{1}H NMR and MS spectra.

O-Ethyl O-(5-phenyl isoxazol-3-yl) 2-chloroethyl phosphonate (5): Viscous colorless liquid, Yield 47 %.

IR (LF): 763, 815, 933, 1044 (PO-alkyl), 1201 (PO-aryl), 1254 (P=O), 1404, 1452 (P-CH_2), 2780 cm^{-1}.

^{1}H NMR (CCl_4,δ): 1.42(t, 3H, J=8Hz, -OCH_2-C**H_3**), 2.60(d, t, 2H, J=19Hz, 8Hz, -PO-C**H_2**-CH_2), 3.88(q, 2H, J=8Hz, -OC**H_2**-CH_3), 4.18(d, t, 2H, 26Hz, 8Hz,ClC**H_2**CH_2-P=O), 6.22(s,1H,H-4),7.72 (m,5H,hetero Ph).

EI MS (m/z, %):315/317 (M^+, 43/14), 280 (M^+-Cl, 4), 252 (M^+-CH_2CH_2Cl, 18), 195 (47), 173 (39), 161(82, ArOH), 118 (26), 115 (12), 91 (65), 77 (58), 65 (44).

O-Ethyl O-(quinolin-8-yl) 2-chloroethyl phosphonate (6): Viscous yellow liquid, Yield 47 %.

IR (LF): 762, 815, 972, 1025 (PO-alkyl), 1200 (PO-aryl), 1269(P=O), 1350, 1433 (P-CH_2), 1495, 2960 cm^{-1}.

^{1}H NMR (CCl_4,δ): 1.38(t, 3H, J=8Hz,-OCH_2-C**H_3**), 2.40(d, t, 2H, J=18Hz,8Hz, -PO-C**H_2**-CH_2), 3.22(q, 2H, J=8Hz,-OC**H_2**-CH_3), 3.30(d, t, 2H, 19Hz, 8Hz, ClC**H_2**CH_2-P=O), 7.76(m, 4H, H-3, H-5, H-6, H-7), 8.60 (m,1H, H-4), 9.12 (m,1H, H-2).

EI MS(m/z,%):297 (M^+-2, 72), 207 (M^+-CH_2CH_2Cl-CH_2, 58), 173 (14), 146 (32), 145 (ArOH, 38), 119 (18), 118 (34), 117 (31), 115 (41), 114 (21), 109 (15), 107 (22), 105 (19), 99 (28), 91 (65), 90(2), 89 (5), 77 (12), 65 (79), 63 (32), 38 (1), 51 (9).

O-Ethyl S-(benzimidazol-2-yl) 2-chloroethyl phosphonate (7): Yellowish viscous liquid, Yield 48 %.

IR (LF): 764, 815, 923, 1047 (PO-alkyl), 1204 (PO-aryl), 1258 (P=O), 1456 (P-CH_2), 2980 cm^{-1}.

^{1}H NMR (CCl_4,δ): 1.46(t, 3H, J=8Hz, -OCH_2-C**H_3**), 2.78(d, t, 2H, J=19Hz, 8Hz, -PO-C**H_2**-CH_2), 3.98(q, 2H, J=8Hz,-OC**H_2**-CH_3), 4.40(d, t, 2H, 26Hz, 8Hz, ClC**H_2**CH_2-P=O), 6.82(s, 4H, hetero Ar).

EI MS(m/z,%):304/306 (M^+, 42/14), 289/291 (M^+-CH_3, 100/33), 277 (1), 269 (M^+-Cl, 1.0), 150 (ArOH, 1), 149 (2), 127/129 (49/16), 99/101 (35/12), 91(98),77 (70), 65 (55), 51 (19).

O-Ethyl S-(benzothiazol-2-yl) 2-chloroethyl phosphonate (8): Yellow viscous liquid, Yield 48 %.

IR (LF): 762, 815, 970, 1045 (PO-alkyl), 1202 (PO-aryl), 1249 (P=O), 1405, 1450 (P-CH_2), 2987 cm^{-1}.

^{1}H NMR (CCl_4,δ): 1.40(t, 3H, J=8Hz, -OCH_2-C**H_3**), 2.42(d, t, 2H, J=18Hz, 8Hz, -PO-C**H_2**-CH_2), 3.38(q, 2H, J=8Hz, -OC**H_2**-CH_3), 3.68(d, t, 2H, 20Hz, 8Hz, ClC**H_2**CH_2-P=O), 7.36(m, 3H, H-4,H-5,H-6), 7.84 (m,1H, H-7).

EI MS(m/z,%):321 (M^+, NA), 211 (M^+-CH_2Cl-O-O-Et, 36), 195 (73), 181 (79), 167 (100), 166 (16), 140/142 (4/1), 139/141 (10/3), 136 (27), 135 (21), 123 (18), 121 (14), 109 (28), 108 (30), 104 (14).

O-Methyl O-(5-phenyl isoxazol-3-yl) 2-chloroethyl phosphonate (2):

Methanol was used instead of ethanol in this reaction. Yellowish viscous liquid,
Yield 49 %.

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IR (LF): 765, 820, 930, 1045 (PO-alkyl), 1200 (PO-aryl), 1255 (P=O), 1404, 1454 (P-CH_2), 2980 cm^{-1}.

^{1}H NMR (CCl_4, δ): 2.61(d, t, 2H, J=19Hz, 8Hz, -POC**H_2**CH_2), 3.76(d, 3H, J=12Hz,-OC**H_3**), 4.19(d, t, 2H, 26Hz, 8Hz, ClC**H_2**CH_2-P=O), 6.22(s, 1H, H-4), 7.72 (m, 5H, hetero Ph).

1-Methyl benzimidazole (4):

We failed to obtain any product except recovered benzimidazole, following the procedure as described above for **(2)** using benzimidazole in place of –OH/ -SH carrying heteroaryls. Treating the reaction product obtained after methanol addition with benzimidazole and NaH in the presence of dry DMF furnished no other product than starting benzimidazole. As observed in TLC. However, the only product 1-Methyl benzimidazole was obtained when attempted the following process.

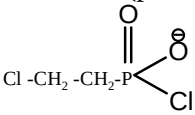
In a 250 mL RB flask. β-Chloroethyl phosphonyl dichloride (0.012 mol) was stirred with 50 mL dry benzene and at 0-5 ^{0}C, a mixture of methanol (0.006 mol) and dry triethylamine (0.006 mol) was added in 15 min.The reaction mixture was then stirred at rt for 1 h and then at 50-60 ^{0}C for another 1 h after which the solvent was evaporated *in vacuo*.The resultant liquid mass was taken in dry acetone (50 mL) and to that benzimidazole (0.006 mol) and anhyd. K_2CO_3 (0.03 mol) were added. The reaction mixture was refluxed for 48 h and the progress of the reaction was monitored by TLC (benzene:acetone,90:10,v/v).When the reaction was homogeneous (TLC showed only two spots, one is benzimidazole Rf =0.4, another spot above it Rf = 0.6), filtration followed by evaporation of acetone to dryness yielded the crude mass which was chromatographed in silica gel using a mixture of benzene: acetone, 95:5,v/v as eluant.Initial fractions yielded a solid compound (0.61 g, 39 %) which was characterized to be 1-Methyl benzimidazole **(4)**. m.p.60 ^{0}C (lit [6] 60-61^{0}C)

IR (LF): 701, 739, 1328, 1465, 1502, 1615, 2965, 3298 cm^{-1}.

^{1}H NMR ($CDCl_3$, δ): 3.50(s, 3H, N-C**H_3**), 6.74(m, 2H, H-5, H-6), 7.25(m, 2H, H-4, H-7).

EI MS (m/z, %):132 (M^+, 76), 117 (M^+-CH_3, 100), 103 (29), 76 (37).

Results and Discussions

The experimental results reveal that in case of –OH and –SH carrying heteroaryls, the expected products formed, but incase of –NH carrying heteroaryls, a different product obtained. The explanation for this unusual behavior can be explained through the reaction mechanism. The product formation depends upon the nucleophilicity of –OH, -SH and –NH groups towards phosphorus and carbon and also upon the nature of leaving group. If the nucleophile attacks on phosphorus atom (path A) the normal product **3** would obtain where Cl^- is the leaving group and if it attacks on carbon atom (path B), the unusual product **4** formed and  is the leaving group (Scheme III).

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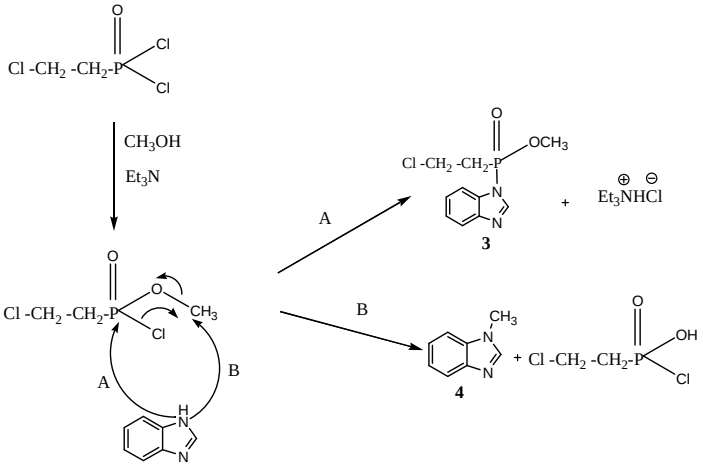
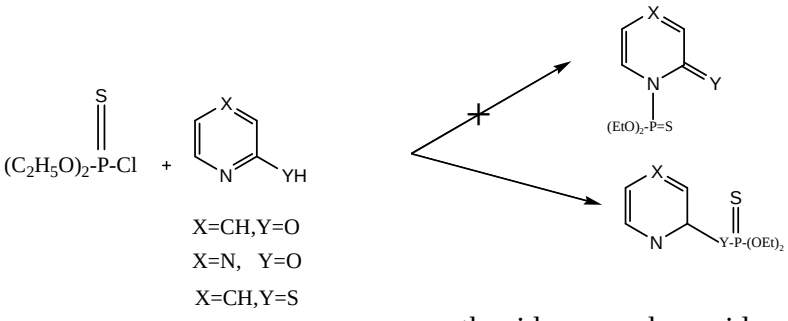
Scheme-III:



According to the literature[7], O-thiophosphorylated and S-thiophosphorylated products rather than N-thiophosphorylated products were obtained in the reaction of potassium 2-pyridinolate, 2-pyrrazinolate and 2-pyridine thiophenolate with O, O-diethyl phosphorochloridothioate (Scheme-IV).

Scheme-IV:



It is also reported[8] that, thiophenolate ion is less effective in displacing a chloride ion from O, O-diisopropyl phosphorochloridate [$(iPrO)_2$-P(=O)-Cl] than ethoxide or phenoxide ion and it has high nucleophilicity towards carbon than phosphorus. Contrary to above reports, the present investigation revealed that –OH and -SH carrying heteroaryls

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follow path A because their nucleophilicity is more towards phosphorus and
-NH carrying heteroaryls follow path B because their nucleophilicity is more towards carbon.
The fungicidal activity of the synthesized compounds **(5-8)** was evaluated against two phytopathogenic fungi viz. *Sclerotium rolfsi* and *Rhizoctonia solani* by the poisoned food technique[9].The fungitoxicity was evaluated in terms of their ED_{50} values expressed in $mgmL^{-1}$ (Table-I).The reaction stirring period after –OH or –SH carrying heteroaryls added and the yield of the corresponding products are also listed in Table-1.

Table-1

Physical data and fungitoxicity of O-ethyl O-heteroaryl 2-chloroethyl P phosphonates (5-8).

Compound	Time (hr)	Yield (%)	*S. rolfsi*	*R. solani*
5	4.0	47	138.5	19.8
6	3.5	47	53.1	35.0
7	4.5	48	49.1	30.5
8	5.0	48	19.9	9.8
Ediphenphos	-	-	60.0	2.8

In case of *S. rolfsi* although **5** did not show significant activity, other three compounds showed noticeable activity and the order is **8** > **7** > **6** > **5**.The compound **8** i.e. O-ethyl S-(2-benzimidazolyl)-2-chloroethyl phosphonate was found to be most active one having
ED_{50} value 19.9 ppm. In case of our previous series[3] the chloride substituents in the phenyl ring showed better activities and the 2,4,5-trichloro derivative showed maximum activity (ED_{50} = 28 ppm).In the present series even better active compound (ED_{50} = 19.9 ppm) obtained.
In case of *R.solani* the compounds showed some fungitoxicities but not more than the standard Ediphenphos.The activity follows the order 8 > 5 >7 > 6.In the previous series[3] also only one compound having pentachloro substituted phenyl ring had the ED_{50} as 2.9 ppm which is comparable to Ediphenphos.

Conclusion

The synthetic approach of introducing heterocyclic moieties to the phosphonates led to obtain very good active compounds against *Sclerotium rolfsi* and one unusual product. Although remarkable activities were not observed for *Rhizoctonia solani*, efforts and new strategies are underway to achieve those.

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Acknowledgement

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