Synthetic and antifungal studies of some novel alkylidenamidothiophosphoric esters

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Phosphorylation of N-alkylcycloiminium halides of two important N-heterocycles, namely thiazole and benzothiazole has been accomplished with phosphorus trichloride in presence of a base. The intermediate aminodichlorophosphines thus generated in situ undergo nucleophilic substitution and oxidation reaction to yield eleven new alkylidenamidothiophosphoric esters, which have been screened for their fungitoxic activity.

Organophosphoric esters and related compounds are well known for their broad spectrum biocidal activity and superiority to organochlorine pesticides. Halophosphines have been used widely as versatile starting materials for the synthesis of variety of organophosphorus derivatives. Aminohalophosphines incorporating N-heterocyclic ring have become accessible recently by a facile synthetic route. In the present communication, we report the synthesis of title compounds incorporating thiazole or benzothiazole ring through the intermediacy of the corresponding aminohalophosphines. Resulting thiophosphoric esters have been tested for their fungitoxic properties.

Results and discussion

N-Alkyl-2-aminothiazolium/benzothiazolium halides 1 on reaction with equimolar amount of phosphorus trichloride in the presence of two-fold amount of triethylamine in methylene chloride resulted in the formation of the corresponding aminohalophosphines 2, which were subsequently subjected to nucleophilic substitution with diethyamine or α/β-cresol accompanied with oxidation with sulfur. In this manner, eleven new representatives of two series of alkylidenamidothiophosphoric esters, namely (3-alkyl-2-thiazol/benzothiazolylidenamido)bis(diethylamido)thiophosphates 3 and (3-alkyl-2-thiazol/benzothiazolylidenamido)bis(0-2/4-methylphenyl)thiophosphates 4 were obtained (Scheme 1).

All the products (3,4) are new crystalline stable solids and have been characterized by the downfield 31P NMR signal at δ 59–78 in the expected range of tetra coordinated phosphorus. In the 1H NMR spectra of 3a, 3c, 4a
and 4b, H-4 and H-5 protons of the thiazole ring show long range coupling ($\delta J_{HH}$ 1.4–2.8 Hz) with phosphorus. It is interesting to note that in the case of 3a, the NCH$_2$ protons of diethylamino moiety are diastereotopic and give two sets of ddq at $\delta$ 3.12 and 3.22 due to the coupling with phosphorus in addition to the vicinal and geminal couplings. In the case of 1d, the product obtained from the reaction with p-cresol and sulfur was found to be a mixture of disubstituted 4d ($\delta$ $^{31}$P 77.7) and monosubstituted 4d' ($\delta$ $^{31}$P 80.6) compounds; however, from the reaction with o-cresol and sulfur only monosubstituted product 4g' ($\delta$ $^{31}$P 79.6) was obtained probably due to stearic reasons.

Bioactivity:

Compounds 3a,b,c and 4a,b were screened for fungitoxic activity against *Fusarium oxysporum* and *Alternaria cymopsidies* from cumin (*cuminum cyminum*) and clusterbean (*cymopsis tetragonal*), respectively by adopting food poisoning technique. The results in terms of radial growth in mm along with the statistical analysis of the data have been presented in Table 1. The test samples have been tested at 100 and 500 ppm concentrations and compared with the solvent control. The potato dextrose agar nutrient medium was poisoned with test compound and using three replica sets radial growth was measured to evaluate their fungitoxic activity. All the compounds except compound 3c were found to be significantly active against both the fungi. 3b was found to be most effective in reducing the radial growth of the mycelium at both concentrations and in the case of *Alternaria cymopsidies*, zero radial growth was observed. At higher concentration, 4b was found to be as effective as 3b in reducing the radial growth of *Fusarium oxysporum*. These observations reveal that a bulky N-alkyl substituent (N-CH$_2$C$_6$H$_4$CH$_3$) in 3b and 4b enhances the fungitoxic activity for each fungi, in conformity with the earlier results reported in the literature. Also, trisamidothiophosphates 3 have been found to show stronger fungicidal activity than amidodiarylthiophosphates 4.

### Experimental

All the commercial reagents and solvents were dried and distilled by common methods before use. M.ps. were determined by capillary method and are uncorrected. All operations involving phosphorus compounds were carried out in dry equipment under nitrogen atmosphere. NMR spectra were recorded on Jeol FX 90Q ($^{1}$H NMR at 89.55 MHz, $^{31}$P NMR at 36.23 MHz) or Bruker Spectrospin DPX 300 ($^{1}$H NMR at 300.13 MHz, $^{31}$P NMR at 121.49 MHz) spectrometer using TMS as internal or 85% H$_3$PO$_4$ as external standard.

### 3-Alkyl-2-aminothiazol/benzothiazolium halides (1):

**General procedure:** To a solution of 2-aminothiazole/benzothiazole (0.04 mol) in tetrahydrofuran (40 ml) was added an equimolar amount of substituted methyl bro­mide/iodide and stirring was continued for 10 to 12 days at RT. White to brown coloured solid thus separated was filtered and dried. In the case of 1b and 1e, solid was obtained by refluxing the reaction mixture in acetone (40 ml) for 45–50 h. 1a (57%); m.p. 110–112°; $\delta$ $^1$H (DMSO-$d_6$) 1.39 (3H, t, $^3$J$_{HH}$ 7.3 Hz, NCH$_2$CH$_3$), 4.15 (2H, q, $^3$J$_{HH}$ 7.3 Hz, NCH$_2$), 6.46 (1H, d, $^3$J$_{HH}$ 4.6 Hz, H-5), 7.31 (1H, d, $^3$J$_{HH}$ 4.6 Hz, H-4), 9.41 (2H, s, NH$_2$). 1b (87%); 220–221°; $\delta$ $^1$H (DMSO-$d_6$) 2.29 (3H, s, CH$_3$).
(3-Alkyl-2-thiazol/benzothiazolylidenamido)bis (diethyliamido)phosphatetes (3): General procedure: To a well stirred suspension of 3-alkyl-2-aminothiazol/benzothiazolium halide (0.01 mol) in methylene chloride (15 ml) at 0–5° was added phosphorus trichloride (0.01 mol) followed by dropwise addition of a solution of triethylamine (0.02 mol) in methylene chloride (20 ml). After 5–20 h of stirring at RT, a solution of diethylamine (0.04 mol) in methylene chloride was added to the reaction mixture followed by sulfur (0.01 mol). Stirring was continued for 20–24 h; the solvent was thereafter removed under reduced pressure and the residue extracted with diethyl ether (2 × 50 ml). The combined ethereal extracts were concentrated and left in refrigerator, whereupon colourless to pale yellow crystals deposited, which were filtered and dried. 3a syrupy mass; δ 31P 67.8; δ 1H (CDCl3) 1.08 (12H, t, 3JH,H 7.1, PNC3H2CH3), 1.30 (3H, t, 3JH,H 7.1, NCH2CH3), 3.12 (4H, dq, 2JH,H 14.2, 3JPH 12.2, 3JH,H 7.1, PNC3H2), 3.22 (4H, dq, 2JH,H 14.2, 3JPH 12.2, 3JH,H 7.1, PNC3H2), 3.87 (2H, q, 3JH,H 7.3, NCH2CH3), 6.24 (IH, dd, 3JH,H 4.9, 3JPH 1.4, H-5), 6.71 (1H, dd, 3JH,H 4.9, 3JPH 2.2, H-4), 3b (65%); m.p.: 78–80° (Found: C, 55.85; H, 7.76; N, 13.55. C16H18N2O2S2P requires: C, 55.66; H, 7.62; N, 13.67%; δ 31P 65.8; δ 1H (CDCl3) 1.02 (12H, t, 3JH,H 7.1, NCH2CH3), 2.29 (3H, s, C6H4CH3), 3.12 (8H, dq, 2JH,H 12.2, 3JH,H 7.1, NCH2CH3), 4.89 (2H, s, NCH2CH3), 6.14 (1H, d, 3JH,H 5.7, H-5), 6.51 (1H, d, 3JH,H 5.7, H-4), 7.03 (4H, s, C6H4). 3c (60%); δ 31P 65.7; δ 1H (CDCl3) 1.11 (12H, t, 3JH,H 8.5, NCH2CH3), 3.16 (8H, dq, 3JPH 12.8, 3JH,H 7.1, NCH2CH3), 3.40 (3H, s, NCH2CH3), 6.21 (IH, dd, 3JH,H 5.6, 5JPH 2.0, H-5), 6.69 (1H, dd, 3JH,H 5.6, 5JPH 2.8, H-4). 3d (63%); 60–61°; δ 31P 65.7; δ 1H (CDCl3) 1.08 (12H, t, 3JH,H 7.1, NCH2CH3), 3.13 (8H, dq, 3JPH 12.7, 3JH,H 7.1, NCH2CH3), 3.5 (3H, s, NCH3), 7.06–7.57 (4H, m, ArH).

(3-Alkyl-2-thiazol/benzothiazolylidenamidobis (O-2,4- methylnphenyl)thiophosphatetes (4): General procedure: A procedure similar to that for 3 was followed using triethylamine (0.02 mol) and a solution of o/p-cresol (0.02 mol) in methylene chloride (10 ml) in place of diethylamine when pale yellow crystals of 4 were obtained. 4a (73%); m.p. 82–84° (Found: C, 56.13; H, 5.09; N, 6.70. C19H21N3O2S2P requires: C, 56.42; H, 5.23; N, 6.92%; δ 31P 58.7; δ 1H (CDCl3) 1.20 (3H, t, 3JH,H 3.1, NCH2CH3), 2.31 (6H, s, OCH3), 3.89 (2H, q, 3JH,H 8.5, NCH2CH3), 6.46 (1H, dd, 3JH,H 5.7, 3JPH 2.1, H-5), 6.81 (1H, dd, 3JH,H 5.6, 5JPH 2.8, H-4), 7.26–7.32 (8H, m, OCH3). 4b (58%); 90–92° (Found: C, 61.92; H, 5.17; N, 5.6. C25H25N3O2S2P requires: C, 62.48; H, 5.24; N, 5.82%; δ 31P 59.6; δ 1H (CDCl3) 2.30 (3H, s, CH3CH2CH3), 2.32 (6H, s, OCH3), 4.89 (2H, s, NCH2CH3), 6.21 (1H, dd, 3JH,H 5.6, 5JPH 1.4, H-5), 6.52 (1H, dd, 3JH,H 5.6, 5JPH 2.8, H-4), 7.16 (12H, s, ArH). 4d + 4d' (4d 72%; δ 31P 77.7; δ 1H (CDCl3) 2.29 (6H, s, OCH3), 3.55 (3H, s, NCH3), 7.08–7.54 (12H, m, ArH) + (4d' 28%); δ 31P 80.6; δ 1H 2.32 (6H, s, OCH3), 3.61 (3H, s, NCH3), 7.08–7.54 (8H, m, ArH). 4e (69%); 80–83°; δ 31P 76.6; δ 1H (CDCl3) 1.14 (3H, t, 3JH,H 7.2, NCH2CH3), 2.17 (6H, s, OCH3), 4.36 (2H, q, 3JH,H 7.2, NCH2CH3), 7.21–7.51 (12H, m, ArH). 4f (59%); 110–112°; δ 31P 77.4; δ 1H (CDCl3) 2.27 (6H, s, OCH3), 5.29 (2H, s, NCH2CH3), 7.04 (4H, d, 3JH,H 8.3, m-H), 7.02–7.16 (6H, m, H-5, H-6, o-H), 7.19 (1H, d, 3JH,H 7.5, H-7), 7.25 (5H, s, CH2C6H5), 7.49 (1H, d, 3JH,H 7.5, H-4). 4g' (64%); 90–92°; δ 31P 79.6; δ 1H (CDCl3) 2.43 (3H, s, OCH3), 3.63 (3H, s, NCH3), 7.14 (IH, d, 3JH,H 7.2, H-7), 7.19 (1H, d, 3JH,H 7.2, H-4), 7.22–7.47 (5H, m, H-5, H-6, p-H, m-H), 7.60 (1H, d, 3JH,H 7.8, o-H). 4h (65%); 70–72°; δ 31P 76.6; δ 1H (CDCl3) 1.18 (3H, t, 3JH,H 7.2, NCH2CH3), 2.33 (6H, s, OCH3), 4.09 (2H, q, 3JH,H 7.2, NCH2CH3), 7.01–7.52 (12H, m, ArH).

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