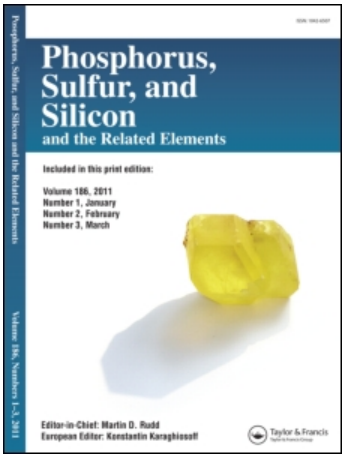

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Synthesis and Characterization of O,O-Dimethyl-N-(2,2,2-trichloro-1-arylaminoethyl) Phosphoramidothioates

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Several novel trichloromethyl-containing O,O-dimethyl phosphoramidothioate derivatives have been synthesized by the reaction of O,O-dimethyl phosphoramidothioate with chloral imines. The latter were prepared in good yields by refluxing the dichloroethane solution of chloral and substituted anilines using 3 Å molecular sieves as dehydrating agent. Structures of title compounds were confirmed by IR, ^{1}H NMR, ^{31}P NMR, and FT-MS studies.

Keywords Phosphoramidothioate; synthesis; trichloromethyl

INTRODUCTION

Organophosphorus compounds, being ubiquitous in nature, have found many applications. Phosphoramidothioates, bioisosteres of natural amino acids—α-aminophosphorothioates,[1] have been found to exhibit a wide range of biological activities, such as herbicides, insecticides, and fungicides.[2–5] As a consequence, the interest of organic chemists in the synthesis of new phosphoramidothioate derivatives remains high. Also various trichloromethyl-containing compounds are associated with fungicidal, insecticidal, and plant growth regulatory activities.[6–8]

There are many reports on the synthesis and biological activities of organophosphorus compounds during the last 20 years,[9,10] but very

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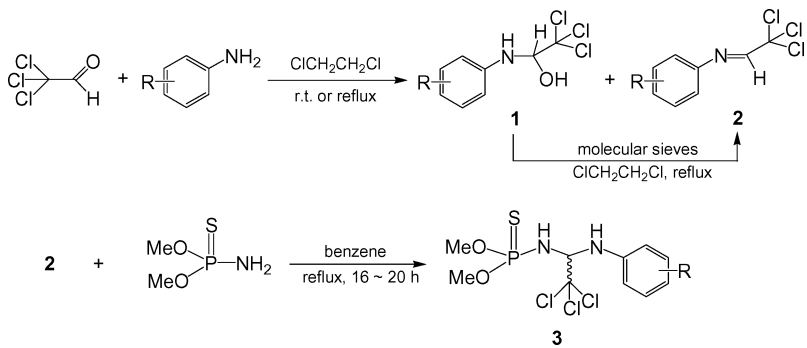
few reports about the synthesis of phosphoramidothioates. In continuation of our efforts towards the synthesis of various biologically important compounds, we were interested in the preparation of phosphoramidothioates with a trichloromethyl substituent, as it can serve as a masked carboxylic acid equivalent,[11] it can be replaced by other groups,[12,13] and it can also be transformed into a chlorovinyl group.[14] To our surprise, there was no general method available for the synthesis of such phosphoramidothioates bearing a trichloromethyl group at the α-C position, though Drach et al.[15] reported the addition of N-dialkoxyphosphonyltrichloroethylidenimines and amines in 1969. We herein report a simple and efficient preparation of various chloral imines and their application in the synthesis novel trichloromethyl-containing O,O-dimethyl phosphoramidothioate derivatives. The synthetic route of compounds is shown in Scheme 1.



SCHEME 1

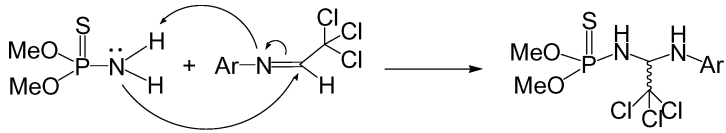
RESULTS AND DISCUSSION

Synthesis

We utilized a molecular-sieves–catalyzed method reported by Michiko et al.[16] and Garcia et al.[17] for the condensation of arylamine and ketone, and thus chloral imines were prepared successfully. Initially, a solution of anhydrous chloral in dichloroethane was treated with aniline at 0–5°C and then stirred at room temperature for 10 h or refluxed for 4 h. The TLC analysis indicated plenty of undehydrated aminol **1** and a small amount of imine **2** produced, which was further confirmed by GC-MS. However, we were able to prepare the required chloral imines **2** by continuing to reflux the reaction mixture in the presence of 3 Å molecular sieves as a dehydrating agent with the removal of the water

formed in the reaction. Moreover, the chloral imine **2** was also prepared directly by refluxing a mixture of anhydrous chloral and aniline in dichloroethane with the removal of water using 3 Å molecular sieves. Chloral imines **2a–2g** were prepared by this method in good yields. Most of these imines were highly moisture sensitive and reverted to the aminols. Imines **2a–2g** were further reacted with O,O-dimethyl phosphoramidothioate via nucleophilic addition in dry benzene under refluxing conditions to give the phosphoramidothioate derivatives **3a–3g**.

There are methods available for the construction of the various substituted phosphoramidothioates. However, a widely used method is via a nucleophilic substitution reaction between phosphonothionic chloride and amine.[18,19] Moreover, there are numerous reports on the phosphonylation of Schiff's base with dialkyl phosphate, which provides a useful method for access to various substituted phosphoramidates, in particular, α -aminophosphonate.[20,21] In our experiments, referring to this method, the nucleophilic addition for preparation of the title phosphoramidothioates occurred smoothly. It can be inferred that a trichloromethyl group of the imines will increase the susceptibility of the CH=N group of the Schiff's base chloral imine towards nucleophilic attack and make the reaction take place more easily. The mechanism of the reaction is suggested to be as is shown Scheme 2, according to the literature.[15,22]



2 **3**

SCHEME 2

Infrared Spectra

The infrared spectrum of phosphoramidothioate derivatives **3** showed absorption bands at 3419–3296 cm^{-1} for N-H stretching. The characteristic stretching vibrations ν (P-N-C) and ν (P=S) appears at 1031–1025 cm^{-1}, 827–787 cm^{-1}, and 753–681 cm^{-1}, respectively.

^{1}H NMR Spectra

In the ^{1}H NMR spectra of **3**, the -NH proton signals were observed at δ 3.79–3.84 ppm as a multiplet (S=P-N**H**-CH) and δ 4.16–4.36 ppm as a

doublet (CH-N**H**-Ar), respectively. The CH proton appeared at δ 5.47–5.61 ppm as a quartet due to the influences of both NH protons and "P" splitting, which indicated the conversion of -CH=N- group (CH proton signal of intermediates **2** was observed at δ 7.86–7.96 ppm as a singlet) to >CH-NH- group. The methoxyl protons [$(CH_3O)_2P$=S] appeared at δ 3.60–3.66 ppm as two doublets due to "P" splitting. The other peaks observed were the aromatic protons at δ 6.74–7.31 ppm and an additional singlet at δ 2.26 ppm and δ 2.21 ppm in compounds **3g** and **3f**, respectively, due to -CH_3 group attached to phenyl ring.

^{31}P NMR Spectra

All the synthesized phosphoramidothioate compounds **3a–3g** were characterized by the downfield ^{31}P NMR signal at δ 74.34–76.83 ppm due to the induction effect of the trichloromethyl group.[23]

EXPERIMENTAL

Melting points were determined using a Taike X-4 apparatus and were uncorrected. Refractive indexes were determined using a WZS-1 Abbe refractometer. Infrared spectra were recorded on a Nicolet 570 spectrophotometer as KBr discs. ^{1}H NMR spectra were measured on a Bruker AV-300 instrument (300 MHz) using TMS as an internal standard and $CDCl_3$ as solvent. ^{31}P NMR spectra were measured on a Varian Mercury Plus 400 instrument (400 MHz) using TMS as an internal standard and $CDCl_3$ as solvent. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0T).

Synthesis of Substituted-N-(2,2,2-trichloroethylidene) Aniline (2)

To a stirred solution of chloral (30 mmol) in anhydrous ethylene dichloride (1 5 mL), substituted aniline (30 mmol) in dry EDC (5 mL) was added slowly at 0–5°C, and the reaction mixture was then allowed to warm to room temperature and stirred for 30 min. It was then refluxed for 5–8 h with the removal of water using molecular sieves (3 Å). The reaction mixture was then cooled and concentrated under vacuum to give the crude product, which was purified by column chromatography using petroleum ether and ethyl acetate as solvents (volume ratio 30:1) to yield the chloral imine **2**.

2a: Pale yellow oil, yield 73%, n_D^{28} 1.5596; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.93(s, 1H, CH), 7.21–7.45(m, 5H, Ph-H).

2b: Yellow oil, yield 96%, n_D^{28} 1.5537; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.93 (s, 1H, CH), 7.10–7.26 (m, 4H, Ph-H).

2c: Yellow oil, yield 75%, n_D^{28} 1.5879; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.92 (s, 1H, CH), 7.39 (d, $J = 8.4$ Hz, 2H, Ph-H), 7.18 (d, $J = 8.4$ Hz, 2H, Ph-H).

2d: Yellow oil, yield 84%, n_D^{28} 1.5805; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.92 (s, 1H, CH), 7.10–7.38 (m, 4H, Ph-H).

2e: Colorless crystals, yield 83%, mp 84–86°C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.94 (s, 1H, CH), 7.23 (d, $J = 8.0$ Hz, 2H, Ph-H), 7.16 (d, $J = 8.0$ Hz, 2H, Ph-H), 2.39 (s, 3H, CH_3).

2f: Yellow oil, yield 88%, n_D^{28} 1.5645; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (s, 1H, CH), 6.94–7.26 (m, 4H, Ph-H), 2.35(s, 1H, CH_3).

2g: Yellow oil, yield 95%, n_D^{28} 1.6083; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.96 (s, 1H, CH), 7.03–7.39 (m, 9H, Ph-H).

Synthesis of O,O-Dimethyl-N-(2,2,2-trichloro-1-arylaminoethyl) Phosphoramidothioates (3)

To a stirred solution of chloral imine (**2**, 2 mmol) in dry benzene, a solution of O,O-dimethyl phosphoramidothioate (93% purity, 1.5 mmol) in dry benzene was added dropwise. The reaction mixture was then refluxed under nitrogen atmosphere for 16–20 h. Then it was cooled and concentrated to give a red sticky oil, which was purified by column chromatography using petroleum ether and ethyl acetate as solvents (volume ratio 20:1) to yield the title compound **3**.

O,O-Dimethyl-N-(2,2,2-trichloro-1-phenylaminoethyl) Phosphoramidothioate (3a)

Red oil, yield 46%, n_D^{28} 1.6108; IR: 3367(NH), 1603, 1510, 1499, 1456 (benzene ring), 1028 (P-N-C), 827, 751 (P=S); ^{1}H NMR (300 MHz): 6.82–7.24 (m, 5H, Ph-H), 5.57 (q, $J = 9.9$ Hz, 1H, CH), 4.27 (d, $J = 10.2$ Hz, 1H, Ph-NH), 3.81 (m, 1H, NHP=S), 3.64 (d, $J_{P-H} = 13.8$ Hz, 3H, OCH_3), 3.60 (d, $J_{P-H} = 13.8$ Hz, 3H, OCH_3); ^{31}P NMR (400 MHz): 74.45(P=S); ESI-FTMS for $C_{10}H_{14}Cl_3N_2O_2PS$ $[M-H]^-$: Calcd. 360.9506, Found 360.9502.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(4-flurophenylamino)ethyl] Phosphoramidothioate (3b)

Red oil, yield 39%, n_D^{28} 1.6160; IR: 3355, 3330(NH), 1611, 1511, 1456 (benzene ring), 1025 (P-N-C), 820, 752 (P=S); ^{1}H NMR (400 MHz): 6.85–6.97 (m, 4H, Ph-H), 5.47 (q, $J = 9.6$Hz, 1H, CH), 4.18 (d, $J = 9.6$ Hz, 1H, Ph-NH), 3.80 (m, 1H, NHP=S), 3.65 (d, $J_{P-H} = 14.0$ Hz, 3H, OCH_3),

3.60 (d, $J_{P-H} = 14.0$ Hz, 3H, OCH_3); ^{31}P NMR (400 MHz): 74.55 (P=S); ESI-FTMS for $C_{10}H_{13}Cl_3FN_2O_2PS$ $[M-H]^-$: Calcd. 378.9412, Found 378.9410.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(4-chlorophenylamino)ethyl] Phosphoramidothioate (3c)

Red oil, yield 58%, n_D^{28} 1.6522; IR: 3361(NH), 1599, 1504, 1456 (benzene ring), 1029 (P-N-C), 819, 683 (P=S); ^1H NMR(300 MHz): 7.20 (d, $J = 8.7$ Hz, 2H, Ph-H), 6.83 (d, $J = 8.7$ Hz, 2H, Ph-H), 5.52 (q, $J = 9.9$ Hz, 1H, CH), 4.29 (d, $J = 9.6$ Hz, 1H, Ph-NH), 3.82 (m, 1H, NHP=S), 3.66(d, $J_{P-H} = 14.1$ Hz, 3H, OCH_3), 3.62(d, $J_{P-H} = 14.1$ Hz, 3H, OCH_3); ^{31}P NMR (400 MHz): 74.50 (P=S); ESI-FTMS for $C_{10}H_{13}Cl_4N_2O_2PS$ $[M-H]^-$: Calcd. 394.9117, Found 394.9123.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(3-chlorophenylamino)ethyl] Phosphoramidothioate (3d)

Red oil, yield 54%, n_D^{28} 1.6461; IR: 3360(NH), 1599, 1510, 1483 (benzene ring), 1029 (P-N-C), 825, 681 (P=S); ^1H NMR (300 MHz): 6.74–7.18 (m, 4H, Ph-H), 5.53 (q, $J = 9.9$ Hz, 1H, CH), 4.36 (d, $J = 9.9$ Hz, 1H, Ph-NH), 3.82 (m, 1H, NHP=S), 3.66 (d, $J_{P-H} = 14.1$ Hz, 3H, OCH_3), 3.64 (d, $J_{P-H} = 14.1$ Hz, 3H, OCH_3); ^{31}P NMR (400 MHz): 74.34(P=S); ESI-FTMS for $C_{10}H_{13}Cl_4N_2O_2PS$ $[M-H]^-$: Calcd. 394.9117, Found 394.9109.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(4-methylphenylamino) ethyl] Phosphoramidothioate (3e)

Yellow solid, yield 49%, mp 70–72°C; IR: 3359, 3319(NH), 1617, 1591, 1521, 1495 (benzene ring), 1026 (P-N-C), 797, 744 (P=S); ^1H NMR (300 MHz): 7.04 (d, $J = 8.4$ Hz, 2H, Ph-H), 6.79 (d, $J = 8.4$ Hz, 2H, Ph-H), 5.52 (m, 1H, CH), 4.16 (br, 1H, Ph-NH), 3.79 (m, 1H, NHP=S), 3.64 (d, $J_{P-H} = 13.8$ Hz, 3H, OCH_3), 3.61 (d, $J_{P-H} = 13.8$ Hz, 3H, OCH_3), 2.26 (s, 3H, CH_3); ^{31}P NMR (400 MHz): 74.50 (P=S); ESI-FTMS for $C_{11}H_{16}Cl_3N_2O_2PS$ $[M-H]^-$: Calcd. 374.9663, Found 374.9667.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(2-methylphenylamino) ethyl] Phosphoramidothioate (3f)

Red oil, yield 46%, n_D^{28} 1.6251; IR: 3419, 3296(NH), 1607, 1588, 1548, 1456 (benzene ring), 1029 (P-N-C), 787 (P=S); ^1H NMR (400 MHz): 6.77–7.20 (m, 4H, Ph-H), 5.61 (q, $J = 9.6$ Hz, 1H, CH), 4.29 (d, $J = 9.6$ Hz, 1H, Ph-NH), 3.84 (m, 1H, NHP=S), 3.65 (d, $J_{P-H} = 14.0$ Hz, 3H, OCH_3), 3.63 (d, $J_{P-H} = 14.0$ Hz, 3H, OCH_3), 2.21 (s, 3H, CH_3); ^{31}P NMR (400 MHz): 76.83 (P=S); ESI-FTMS for $C_{11}H_{16}Cl_3N_2O_2PS$ $[M-H]^-$: Calcd. 374.9663, Found 374.9666.

O,O-Dimethyl-N-[2,2,2-trichloro-1-(4-phenoxyphenylamino) ethyl] Phosphoramidothioate (3g)

Red oil, yield 41%, n_D^{28} 1.6514; IR: 3334(NH), 1598, 1508, 1488, 1456 (benzene ring), 1031 (P-N-C), 827, 753 (P=S); ^{1}H NMR (400 MHz): 6.88–7.31 (m, 9H, Ph-H), 5.51 (q, $J = 9.2$ Hz, 1H, CH), 4.21 (d, $J = 7.6$Hz, 1H, Ph-NH), 3.81 (m, 1H, NHP=S), 3.66 (d, $J_{P-H} = 14.8$ Hz, 3H, OCH_3), 3.62 (d, $J_{P-H} = 14.8$ Hz, 3H, OCH_3); ^{31}P NMR (400 MHz): 74.50 (P=S); ESI-FTMS for $C_{16}H_{18}Cl_3N_2O_3PS$ $[M-H]^-$: Calcd. 452.9769, Found 452.9764.

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