Reaction of Methylhydrazine with Dimethyl Chlorothiophosphate

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The reaction of 2 equivalents of methylhydrazine with 1 equivalent of $(MeO)_2P(S)Cl$ at 0 °C produced the phosphorus hydrazide $(MeO)_2P(S)NMeNH_2$ **1** in good yield. However, at 25 °C a mixture of three products was obtained according to ^1H and ^{31}P NMR spectra. The pure individual components were separated by column chromatography. Proton and ^{31}P NMR analysis revealed them to be **1**, $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2** and $(MeO)_2P(S)NHNHMe$ **3**. During the chromatographic separation of **1**–**3** another component was also eluted in 5–8% yield, ^1H, ^{31}P NMR and FAB mass spectrometric analysis of which indicated it to be $(MeO)_2P(S)(NMeNH)(O)P(OMe)Me$ **4**. New synthetic strategies to produce **2** in good yields are also described.

Nucleophilic substitution reactions of phosphorus-(III) and -(V) halides with amino functionalities have been the subject of extensive investigations in the last three decades.[1-15] In sharp contrast, the corresponding reactions of phosphorus halides with hydrazine-based nitrogen functionalities have received limited attention.[16,17] Hydrazine and its derivatives can be mono- (*e.g.* $RHN-NR_2$) or bi-functional (*e.g.* RHN–NHR or H_2N-NH_2), therefore, their reactions with the phosphorus halides may generate new compounds with P–N–N and P–N–N–P linkages. We are currently interested in the main-group and transition-metal chemistry of hydrazines because our recent investigations, especially with the phosphorus hydrazides, have demonstrated that main-group hydrazides can be used as versatile ligands in the co-ordination chemistry of various transition metals.[18-23] In this paper we report a systematic investigation into the reactions of methylhydrazine with $(MeO)_2P(S)Cl$ and describe synthetic strategies to produce (*a*) $(MeO)_2P(S)NMeNH_2$ **1** and (*b*) $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2**. We also report the spectroscopic identification of $(MeO)_2P(S)NHNHMe$ **3** and $(MeO)_2P(S)(NMeNH)(O)P(OMe)Me$ **4**. This study represents the first example of the isolation and identification of all the possible nucleophilic substitution reaction products from the interaction of $(MeO)_2P(S)Cl$ with methylhydrazine.

Experimental

Physical Measurements and Instrumentation.—Nuclear magnetic resonance spectra (^1H and ^{31}P) were recorded on a Bruker AMX 500 spectrometer. The ^1H NMR chemical shifts are reported in ppm downfield from external standard $SiMe_4$. The ^{31}P NMR spectra were recorded with 85% H_3PO_4 as an external standard and positive shifts lie downfield of the standard. Elemental analyses of the new compounds were performed by Oneida Research Services, New York. Mass spectra were obtained on a Kratos MS-25 spectrometer. Thin-layer chromatography was performed on 0.2 mm (layer thickness) silica gel plates (Fluka). A typical mobile phase used was hexane–ethyl acetate–methanol (9:3:1).

Reagents and Materials.—Reagents such as dimethyl chlorothiophosphate, methylhydrazine and triethylamine were obtained from Aldrich and used without further purification. All experimental manipulations were performed under an atmosphere of dry argon. Solvents were dried and distilled prior to use.

Synthesis of $(MeO)_2P(S)NMeNH_2$ **1**.—A solution of methylhydrazine (3.45 g, 75 mmol) in chloroform (100 cm^3) was added dropwise to a solution of dimethyl chlorothiophosphate (4.8 g, 30 mmol) also in $CHCl_3$ (100 cm^3) maintained at −20 °C. The reaction mixture was stirred at room temperature for 6 h before the methylhydrazine hydrochloride adduct was filtered off and the filtrate evaporated to dryness *in vacuo*. The ^{31}P NMR spectrum of the crude product showed an intense peak at δ 81.5. A peak of relatively low intensity at δ 85.5 due to the unreacted $(MeO)_2P(S)Cl$ was also seen. The final purification of compound **1** was achieved by column chromatography on silica gel 60 with hexane–ethyl acetate–methanol (9:3:1) as the mobile phase: yield as an oil (R_f = 0.35) 85% (Found: C, 21.10; H, 6.60; N, 16.40. Calc. for $C_3H_{11}N_2O_2PS$: C, 21.10; H, 6.50; N, 16.45%).

Reaction of Dimethyl Chlorothiophosphate with Methylhydrazine at 25 °C.—A solution of methylhydrazine (2.4 g, 50 mmol) in $CHCl_3$ (75 cm^3) was added dropwise to a solution of dimethyl chlorothiophosphate (3.2 g, 20 mmol) also in chloroform (75 cm^3) at 25 °C. The reaction mixture was stirred for 6 h before the solvent was removed *in vacuo*. The TLC of the crude product indicated the presence of three components with R_f values of 0.23, 0.35 and 0.62. Separation and final purification of the three products was achieved by column chromatography as described above. They were characterized by ^1H and ^{31}P NMR and mass spectrometry and elemental analysis: **1** (R_f = 0.35), yield 30% (Found: C, 21.10; H, 6.50; N, 16.45%); $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2** (R_f = 0.62), oil, yield 20%, (Found: C, 19.85; H, 5.00; N, 9.45. Calc. for $C_5H_{16}N_2O_4P_2S_2$: C, 20.40; H, 5.50; N, 9.55%); and $(MeO)_2P(S)NHNHMe$ **3** (R_f = 0.23), oil, yield 5% (Found: C, 20.95; H, 5.45; N, 16.05. Calc. for $C_3H_{10}N_2O_2PS$: C, 21.30; H, 5.95; N, 16.25%).

During the chromatographic separations of compounds **1**–**3** a new compound **4**, characterized as $(MeO)_2P(S)(NMeNH)(O)P(OMe)Me$, was also eluted in 5–8% yields: R_f = 0.15, oil, yield 5% (Found: C, 22.15; H, 5.95; N, 10.45. Calc. for $C_5H_{16}N_2O_4P_2S$: C, 22.90; H, 6.15; N, 10.70%). We believe that its formation was a result of the interaction of **2** with silica gel during the chromatographic separations. This was confirmed upon repeated elution of pure **2** through a column loaded with silica gel: in all the experiments **2** was transformed into **4** in 5–8% yield.

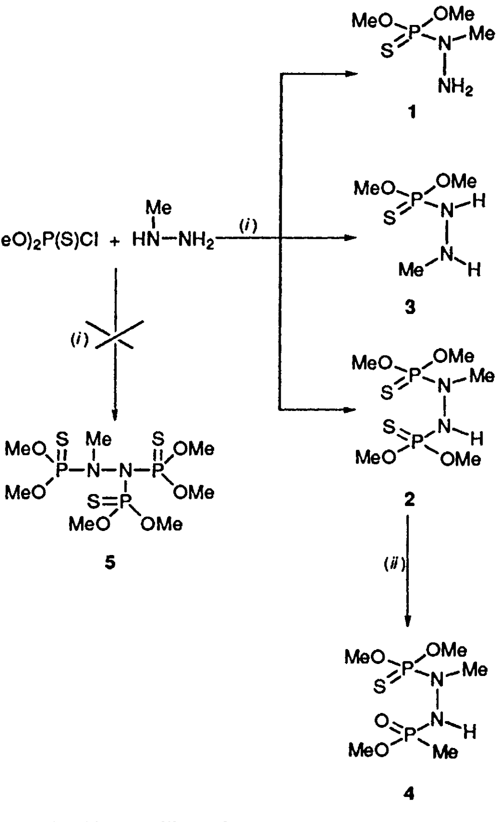
Synthesis of $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2**.—Compound **2** was also synthesised independently by the following two routes. (*a*) To a solution of dimethyl chlorothiophosphate (4 g, 25 mmol) in $CHCl_3$ (75 cm^3) was added dropwise (15 min) at 25 °C with stirring a solution of methylhydrazine (0.58 g, 12.5 mmol) in $CHCl_3$ (50 cm^3). The mixture was stirred for 2 h at room temperature (r.t.) before it was filtered and the solvent removed *in vacuo* to yield a viscous oil. Upon TLC the reaction mixture showed three spots at R_f 0.62, 0.35 and 0.07. These were attributed to compounds **2**, **1** and the starting material (dimethyl chlorothiophosphate) in that order. Separation by column chromatography yielded **2** in 75% yield (Found: C, 19.90; H, 5.35; N, 9.40%). (*b*) A solution of dry NEt_3 (4.3 g, 43 mmol) was added to a prestirring solution of methylhydrazine (1 g, 21.5 mmol) in $CHCl_3$ (75 cm^3) at −20 °C. To this mixture was added dropwise (15 min) a solution of dimethyl chlorothiophosphate (6.9 g, 43 mmol) in $CHCl_3$ (75 cm^3). The reaction mixture was stirred at r.t. for 2 h, before the solvent was removed *in vacuo* to yield the product as a thick viscous oil. Purification and separation by column chromatography afforded compound **2** in 82% yield: R_f 0.62 (Found: C, 19.80; H, 5.40; N, 9.50%).

Results and Discussion

The reaction of $(MeO)_2P(S)Cl$ with 2 equivalents of methylhydrazine at −20 °C gave the new phosphorus hydrazide $(MeO)_2P(S)NMeNH_2$ **1** in 85% yield (Scheme 1). This compound has been characterized by MS, ^1H and ^{31}P NMR spectroscopy (Table 1) and by an X-ray crystallographic analysis of its palladium(II) complex.[21] However, when this reaction was attempted at 25 °C a mixture of products was observed in the ^{31}P NMR spectrum a detailed analysis of which revealed three products. The spectrum consisted of a singlet at δ 81.5, doublets centred at δ 81.0 and 74.3 [J(P–P) = 18.14 Hz] and an additional singlet at δ 75.7. The relative proportions of these three compounds as estimated from the ^{31}P NMR peak integrations were 40:18:10 respectively. Our efforts to separate these compounds through fractional distillation were unsuccessful because the mixture decomposed at 120 °C (0.2 Torr, *ca.* 266 Pa).

Thin-layer chromatographic analysis (silica gel) of the mixture confirmed the presence of three species with R_f values of 0.23, 0.35 and 0.62, respectively. Their separation was achieved by column chromatography. The ^{31}P NMR spectral data for each compound are listed in Table 1 and the spectra are shown in Fig. 1. Spectrum (*a*) was easily attributed to $(MeO)_2P(S)NMeNH_2$ **1**. The AX spin pattern shown in Fig. 1(*b*) was attributed to $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2** and the singlet at δ 75.7 [Fig. 1(*c*)] to $(MeO)_2P(S)NHNHMe$ **3**.

The proton NMR spectra of compounds **1**–**3** (Table 1) were consistent with the structures proposed. Those of **1** and **3** consisted of doublets centred at δ 3.72 [^3J(P–H) = 13.5] and 3.78 [^3J(P–H) = 13.4 Hz] respectively and were readily assigned to the OMe protons. The NMe protons in **1** resonated as a doublet [δ 2.92; ^3J(P–H) = 10.9 Hz]. The spectrum of **3** did not show a doublet signal due to coupling of the NMe protons, consistent with its formation through reaction at the NH_2 nitrogen rather than the NHMe site. The latter route would have given a doublet for the NMe group due to coupling with the phosphorus across three bonds.[16–22] The OMe protons in **2** resonated as two distinct doublets centred at δ 3.75 [^3J(P–H) = 13.6] and 3.77 [^3J(P–H) = 13.4 Hz], suggesting the presence of two OMe groups bonded to each of the P(S) and P(O) centres.



Scheme 1 (*i*) $CHCl_3$; (*ii*) silica gel

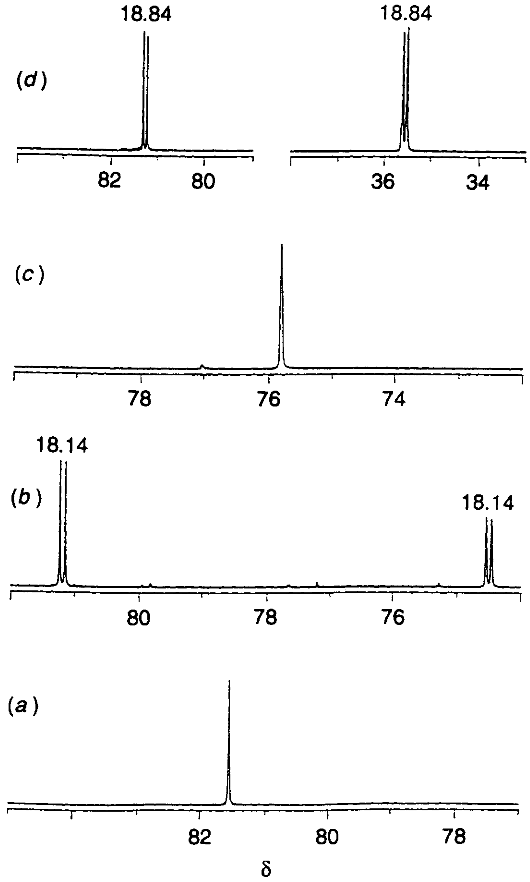


Fig. 1 The ^{31}P NMR spectra of (*a*) $(MeO)_2P(S)NMeNH_2$ **1**, (*b*) $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$ **2**, (*c*) $(MeO)_2P(S)NHNHMe$ **3** and (*d*) $(MeO)_2P(S)(NMeNH)(O)P(OMe)Me$ **4**. The numbers above the peaks are ^3J(P–P)/Hz values

Table 1 Phosphorus-31, ^{1}H NMR and mass spectrometric data for phosphorus hydrazides **1**–**4**

Compound	^{31}P NMR[a] δ[P(S)]	^{1}H NMR[b] δ(OMe)		Mass spectrum (M^+), m/z[c]
		δ(OMe)	δ(NMe)	
1 $(MeO)_2P(S)NMeNH_2$	81.5 (s)	3.72 (d, 13.5)	2.92 (d, 10.9)	171 (92)
2 $(MeO)_2P(S)(NMeNH)(S)P(OMe)_2$	81.0 (d, 18.14)	3.75 (d, 13.6)	2.98 (d, 11.1)	295 (85)
	74.3 (d, 18.14)	3.77 (d, 13.4)		
3 $(MeO)_2P(S)NHNHMe$	75.7 (s)	3.78 (d, 13.4)	2.63 (s)	171 (87)
4 $(MeO)_2P(S)(NMeNH)(O)P(OMe)Me$[d]	81.1 (d, 18.84)	3.72 (d, 13.3)	3.03 (d, 15.0)	263 (82)
		3.79 (d, 13.4)		

[a] Spectra in $CDCl_3$; ppm *vs.* 85% H_3PO_4, ^3J(P–P)/Hz in parentheses. [b] Spectra in $CDCl_3$; ppm *vs.* $SiMe_4$, ^3J(P–H)/Hz in parentheses. [c] Intensity (%) in parentheses. [d] The PMe protons resonated at δ 2.35 [^2J(P–H) = 15.12 Hz] in the ^{1}H NMR spectrum. In the ^{31}P NMR spectrum, δ[P(O)] 35.4 [d, ^3J(P–P) = 18.84 Hz].

The signal due to the NMe group appeared as a doublet centred at δ 2.98 [^3J(P–H) = 11.1 Hz].

During the chromatographic separations of compounds **1**–**3** a new component **4** was also repeatedly eluted in 5–8% yields. Its ^{31}P NMR spectrum [Fig. 1(*d*)] contained a doublet centred at δ 35.4 [^3J(P–P) = 18.84 Hz] indicating the presence of a P(O) functionality. The two doublets centred at δ 81.1 and 35.4 indicate the presence of a combination of P(S) and P(O) functionalities. The formation of this unexpected compound may be rationalized in terms of a Wittig-type transformation of one of the P(S) in **2** into a P(O) functionality. This conversion is presumably catalysed by the silica gel during the chromatographic separations of **1** and **2**. A distinctive feature in the ^{1}H NMR spectrum of **4** was the presence of a doublet centred at δ 2.35 with a coupling constant of 15.12 Hz. This chemical shift is characteristic of methyl groups directly bonded to phosphorus (*i.e.* PMe) and the magnitude of the coupling constant is within the range expected for ^2J(P–H). In addition to this doublet signal, there were two sets of doublets centred at δ 3.72 [^3J(P–H) = 13.3] and 3.79 [^3J(P–H) = 13.4 Hz] in the ratio 1 : 2, readily assigned to the two different types of OMe groups present. Based on the ^{1}H and ^{31}P NMR spectroscopic results, the structure in Scheme 1 has been assigned for **4**. The C, H and N analytical data and the observation of a peak corresponding to the molecular ion (M^+) at m/z 263 confirmed this assignment.

A directed synthetic strategy to produce compound **2** starting from $(MeO)_2P(S)Cl$ and methylhydrazine has also been developed. The interaction of 2 equivalents of $(MeO)_2P(S)Cl$ with 1 equivalent of methylhydrazine in the presence of 2 equivalents of triethylamine at −20 °C resulted in the formation of **2** in 82% yield. This reaction also produced **3** in 10% yield. The reaction of methylhydrazine with 2 equivalents of $(MeO)_2P(S)Cl$ in the absence of any tertiary base also produced **2** in 75% yield.

The Wittig type of desulfurization of one of the P(S) functionalities in compound **2** to give **4** is noteworthy (Scheme 1). The source of oxygen and a methyl group to produce a P(O)Me group in **4** is evidently one of the OMe groups of the $NP(S)(OMe)_2$ part of **2**. This type of Arbuzov rearrangement of methoxy groups on phosphorus to produce (O)PMe is well known in phosphorus chemistry.[1–6] Comparison of ^{31}P NMR data for **1**, **2** and **4** indicates that the OMe group bound to the NHP(S) phosphorus centre in **2** has undergone the rearrangement. The ^{31}P NMR chemical shifts of δ 81.5, 81.0 and 81.1 attributed to the $(MeO)_2P(S)NMe$ phosphorus centres in **1**, **2** and **4**, respectively, remain virtually unchanged.

The doublet signal centred at δ 74.3 observed for compound **2** was not seen in the ^{31}P NMR spectrum of **4**. This observation may be rationalized in terms of the transformation of the $HNP(S)(OMe)_2$ functionality of **2** into the HNP(O)(OMe)Me unit in **4**. The concurrent appearance of the doublet at δ 35.4 in **4** and additional features of the ^{1}H NMR spectrum (discussed above) lend conclusive support to the double Wittig–Arbuzov transformation.

Conclusion

The reaction of methylhydrazine with $(MeO)_2P(S)Cl$ should produce, theoretically, five products (Scheme 1). In the present investigation we have demonstrated that the products **1**–**4** can be identified spectroscopically (^{1}H and ^{31}P NMR) and separated by column chromatography. The hexamethoxy derivative $(MeO)_2P(S)(NMeN)[(S)P(OMe)_2]_2$ **5** could not be identified in the ^{1}H and ^{31}P NMR spectra of the reaction mixture. The elusive nature of **5** may be rationalized in terms of the considerable steric constraints of having two P(S)(OMe) groups on the terminal hydrazidic nitrogen. Phosphorus hydrazides have been shown to be good chelating frameworks to transition metals.[18–23] The application of the new functionalized phosphorus hydrazides **1**–**4** in the co-ordination chemistry of transition metals is underway.

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