SHORT PAPER

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Acid catalysed reactions of ω-mercaptoalkylphosphinic anilides: reluctance of the thiol group to participate in displacement of the aniline moiety†

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Acid catalysed cyclisation occurs readily with $HO(CH_2)_{n+3}P(O)(NHPh)Ph$ (n = 0 or 1) in MeOH but only acyclic $HS(CH_2)_{n+3}P(O)(OMe)Ph$ is obtained when $HS(CH_2)_{n+3}P(O)(NHPh)Ph$ (n = 0 or 1) is treated with HCl in $CDCl_3$ containing 1% MeOH; cyclisation can occur if MeOH is excluded completely but even the five-membered cyclic thiophosphinate **5** (n = 0) is not formed readily.

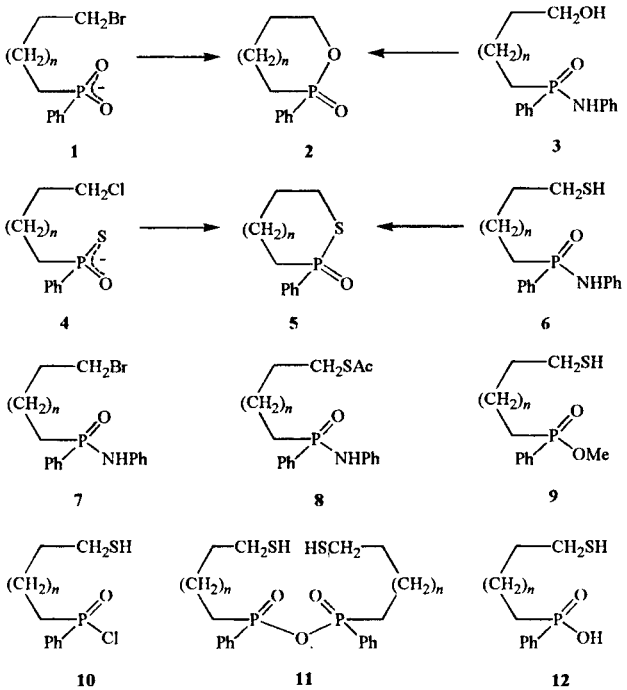
Five-membered rings are generally formed much more readily than six in cyclisations (k^5/k^6 ~10^2)[1] but that may not be the case when the products are cyclic P=O compounds,[2] *e.g.* the ω-bromo-phosphinate **1** (n = 0 or 1) undergoes intramolecular nucleophilic substitution only 4.3 times faster when n = 0 than when n = 1.[3] Unusually severe ring strain in the product **2** (n = 0) could be to blame and the behaviour of the thiophosphinate **4** (n = 0 or 1) may be significant: reduced strain is likely when the ring contains a S atom[4] and now there is a 30-fold difference in the rates of formation of **5** (n = 0) and **5** (n = 1).[3] On the other hand, a large rate difference (k^5/k^6 = 70 in $CHCl_3$, 50 in MeOH) has also been observed in the acid catalysed cyclisation of the hydroxy phosphinic anilide **3** (n = 0 or 1), even though the product is again the phosphinate **2** with oxygen in the ring.[5] By examining the mercapto anilide **6** we hoped to learn more about k^5/k^6 rate ratios and the factors that determine them.

The ω-bromo anilides **7** (n = 0, 1)[5] were converted into the thiol acetates **8** ($\nu_{C=O}$ ~ 1680 cm^{-1}) using CH_3COSH–Et_3N. Deacetylation with NaOMe afforded the ω-mercapto anilides **6** (n = 0, 1) as reasonably stable crystalline solids. Triplets δ_H 1.2–1.3 (J_{HH} 8), exchangeable with D_2O, confirmed the presence of CH_2SH groups.

In MeOH containing 0.1 mol dm^{-3} HBF_4 the mercapto anilides **6** gave only the acyclic phosphinates **9** (n = 0 or 1) (≥ 95 %) resulting from methanolysis of the P–N bond; no trace of the cyclic thiophosphinates **5** (n = 0 or 1) (≤ 1%) was found by NMR or GLC (comparison with authentic samples[3]). Monitoring by ^{31}P NMR (δ_P 34 → 50) indicated half lives of 64 and 55 min at 20 °C [$k = 1.8 \times 10^{-4}$ (n = 0) and 2.1×10^{-4} s^{-1}]. The mercapto compounds are therefore similar in reactivity to the bromo anilide **7** (n = 1) ($t_{1/2}$ 51 min),[5] which cannot cyclise, and much less reactive than the hydroxy compounds **3** (n = 0, 1) ($t_{1/2}$ 0.02 and 0.95 min), which give almost entirely the cyclic phosphinates **2** (≥ 98 %).[5] The difference in reactivity when n = 0 is 3200 and ≤ 1 % of the reaction of the mercapto compound involves cyclisation; the SH group is therefore at least 3×10^5 less effective than the OH group in intramolecular nucleophilic attack. We had expected a substantial difference (P=O is a hard centre) but not one as great as this.

So that intramolecular attack might compete more effectively the reaction medium was changed to $CDCl_3$ containing just 1% MeOH. Also, because $CDCl_3$–insoluble complexes (salts) were formed with HBF_4, the acid was changed to HCl (~ 0.1 mol dm^{-3}). For each of the mercapto compounds **6** (n = 0, 1) the reaction mixture after 10 min at 25 °C was a mixture (~ 1:1:2) of starting material (δ_P 46), the phosphinic chloride **10** (δ_P 58) (identity not proven), and the methanolysis product **9** (δ_P 53.5). Only the last of these remained after 50 min, together with a little of the phosphinic acid **12** (~ 5 %) resulting from unavoidable traces of moisture. Closer examination (NMR, GLC) revealed a very small amount of the five-membered cyclic thiophosphinate **5** (n = 0) (2 %) but not a trace of the six-membered analogue. Even with a very low concentration of MeOH attack by the SH group can hardly compete.

With MeOH excluded completely, the mercapto anilides **6** (n = 0, 1) were unchanged after 48 h in $CDCl_3$ containing 0.02 mol dm^{-3} CF_3CO_2H whereas the hydroxy compounds **3** (n = 0, 1) cyclised rapidly ($t_{1/2}$ 0.1 and 7.5 min at 20 °C).[5] The dramatic difference in reactivity between SH and OH groups is again in evidence here. Using HCl (~ 0.1 mol dm^{-3}) in $CDCl_3$ the mercapto compounds formed the phosphinic chlorides **10** (n = 0, 1) ($t_{1/2}$ ~0.5 h at 25 °C) and these then reacted further. With n = 0 reaction was complete in 21 h at 37 °C giving a 4:1 mixture of the cyclic thiophosphinate **5** (n = 0) (δ_P 75.5) and the hydrolysis product **12**. At 60 % completion (t = 2.1 h) there was evidence of some of the phosphinic anhydride **11** [meso and (±)] corresponding to partial hydrolysis [δ_P ~ 42; 2 peaks each 7–8 % of the total phosphorus] but



† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

intramolecular attack by the SH group would convert this into **5** and **12**. With $n = 1$ the phosphinic chloride was more persistent and still accounted for 70 % of the total phosphorus after 21 h. The products were the acid **12** and anhydride **11** although later on (70% completion) a small amount of the cyclic thiophosphinate **5** ($n = 1$) (2 %) (δ_P 45.6) could be detected (^{1}H NMR, GLC). In the time taken for **10** ($n = 0$) to be 80 % converted into the cyclic product **5** ($n = 0$) not more than 1% of **10** ($n = 1$) reacts by cyclisation. The k^5/k^6 ratio thus seems to be ~10^2, in line with cyclisations generally, but because of the very low nucleophilicity of the SH group towards the hard P=O centre, and the high nucleophilicity of H_2O, we cannot be precise.

This result, together with that for the hydroxy anilides **3** suggests that small k^5/k^6 ratios are confined to cyclisations in which the P=O group is part of the nucleophile and the phosphorus atom retains its tetrahedral geometry in the transition state. When it is the P=O group that is being attacked, and the phosphorus atom becomes trigonal-bipyramidal in the cyclic intermediate or transition state, normal k^5/k^6 ratios (~10^2) are seen. We have previously considered why this might be,[5] but our ideas are still no more than speculation.

Experimental

^{1}H NMR spectra were recorded at 250 MHz (Me_4Si internal standard; J in Hz) and ^{31}P NMR spectra at 101 or 121 MHz (positive δ_P downfield from 85 % H_3PO_4). Mass spectra were obtained with Kratos Concept or Micromass Quattro LC spectrometers. GLC analyses employed a 15 m × 0.53 mm column coated with OV 1701 (1 μm film) (He carrier, 16 ml min^{-1}). Methanol was distilled from the Mg salt and $CHCl_3$ was dried over molecular sieve.

Acetylthioalkyl(phenyl)phosphinic anilides **8**: The bromo anilide **7** ($n = 0$ or 1)[5] (1.0 mmol) was stirred with AcSH (152 mg, 2.0 mmol) and Et_3N (212 mg, 2.1 mmol) in $CHCl_3$ (3.6 ml) (N_2 atmosphere) at 30 °C for 3 h (δ_H 3.5–3.2 replaced by 3.0–2.75). The mixture was diluted ($CHCl_3$, 25 ml) and washed with water (5 × 25 ml). Crystallisation from $CHCl_3$–light petroleum (bp 60–80 °C) gave the thiol acetate **8** ($n = 0$) (85 %), m.p. 138.5–140.5 °C; *m*/*z* 333 (M^+, 6 %), 290 (M^+–Ac, 20), 93 (95) and 77 (100); δ_P ($CDCl_3$) 28.0; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.85 (5 H), 5.65 (1 H, d, J_{PH} 10, NH), 2.91 (2 H, m, C*H*$_2$SAc), 2.31 (3 H, s, SAc) and 2.25–1.7 (4 H); ν_{max} (Nujol)/ cm^{-1} 3200 (NH) and 1685 (C=O) (Found: C, 61.0; H, 6.1; N, 4.2. $C_{17}H_{20}NO_2PS$ requires C, 61.2; H, 6.05; N, 4.2 %) or **8** ($n = 1$) (85%), m.p. 97–98 °C; *m*/*z* 347 (M^+, 8 %), 304 (M^+–Ac, 25), 93 (100) and 77 (55); δ_P ($CDCl_3$) 28.3; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.8 (5 H), 5.66 (1 H, d, J_{PH} 10, NH), 2.81 (2 H, m, C*H*$_2$SAc), 2.32 (3 H, s, SAc), 2.2–1.9 (2 H) and 1.75–1.55 (4 H); ν_{max} (Nujol)/cm^{-1} 3240 (NH) and 1680 (C=O) (Found: M^+ 347.11085. $C_{18}H_{22}NO_2PS$ requires *M*, 347.1109).

Mercaptoalkyl(phenyl)phosphinic anilides **6**: The thiol acetate **8** ($n = 0$ or 1) (0.35 mmol) was dissolved in MeOH (N_2-flushed) (2.8 ml) containing NaOMe (0.7 mmol). After 10 min reaction was quenched (NH_4Cl; 1.2 mmol), most of the solvent was removed, and water was added to precipitate the product. Recrystallisation from $CHCl_3$–light petroleum afforded the mercapto anilide **6** ($n = 0$) (96 %), m.p. 128–130 °C; *m*/*z* 291 (M^+, 80 %), 258 (M^+–SH, 15), 244 (M^+–CH_2SH, 90) and 230 (M^+–C_2H_4SH, 100); δ_P ($CDCl_3$) 28.2; δ_H ($CDCl_3$) 7.9–7.4 (5 H), 7.2–6.9 (5 H), 5.55 (1 H, d, J_{PH} 10, NH), 2.54 (2 H, dt, J_{HH} ~8, 8; collapses to t with D_2O; C*H*$_2$SH), 2.3–1.7 (4 H) and 1.27 (1 H, t, J_{HH} 8; exchanges with D_2O; SH); ν_{max} (Nujol)/ cm^{-1} 3210 (NH) (Found: C, 61.2; H, 6.1; N, 4.8; M^+ 291.08465. $C_{15}H_{18}NOPS$ requires C, 61.8; H, 6.2; N, 4.8 %; *M* 291.0847) or **6** ($n = 1$) (85 %), mp 144–146 °C; *m*/*z* 305 (M^+, 20 %), 272 (M^+–SH, 35), 217 (M^+–C_4H_8S, 80), 216 (M^+–C_4H_8SH, 20) and 93 (100); δ_P ($CDCl_3$) 28.2; δ_H ($CDCl_3$) 7.9–7.35 (5 H), 7.2–6.85 (5 H), 5.54 (1 H, d, J_{PH} 10, NH), 2.43 (2 H, dt, J_{HH} ~7, 8; collapses to t with D_2O; C*H*$_2$SH), 2.2–1.9 (2 H), 1.8–1.5 (4 H) and 1.25 (1 H, t, J_{HH} 8; exchanges with D_2O; SH); ν_{max} (Nujol)/cm^{-1} 3190 (NH) (Found: C, 62.3; H, 6.5; N, 4.5; M^+ 305.1003. $C_{16}H_{20}NOPS$ requires C, 62.9; H, 6.6; N, 4.6 %; *M* 305.1003).

Reactions of mercaptoalkyl(phenyl)phosphinic anilides **6**: (a) A solution of **6** ($n = 0$ or 1) (3 mg) in MeOH (0.5 ml) containing HBF_4·Et_2O (0.10 mol dm^{-3}) was maintained at 20 ± 1 °C and the ^{31}P NMR spectrum was recorded at intervals [δ_P 33.5 → 50 ($n = 0$) or 34 → 50.5 ($n = 1$]; 9 spectra were obtained during 2.5–3 h (> 90 % completion) and the fraction of unchanged substrate in each was deduced from the integral. First order plots were reasonably linear and from them the values of k (± 10 %) were deduced. On completion $NaHCO_3$ (small excess) was added, the solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and very dilute aqueous HCl. The organic portion afforded the methyl phosphonate **9** ($n = 0$), t_R 3.4 min at 180 °C; *m*/*z* 230 (M^+, 40 %), 197 (M^+–SH, 15), 183 (M^+–CH_2SH, 100), 170 (M^+–C_2H_4S, 60) and 169 (M^+–C_2H_4SH, 80); δ_P ($CDCl_3$) 45.6; δ_H ($CDCl_3$) 7.85–7.45 (5 H), 3.63 (3 H, d, J_{PH} 10, OMe), 2.58 (2 H, dt, J_{HH} 7, 8), 2.15–1.75 (4 H) and 1.30 (1 H, t, J_{HH} 8, SH) (Found: M^+, 230.0530. $C_{10}H_{15}O_2PS$ requires *M*, 230.0530) or **9** ($n = 1$), t_R 5.0 min at 180 °C; *m*/*z* 244 (M^+, 30 %), 211 (M^+–SH, 35), 197 (M^+–CH_2SH, 15), 156 (M^+–C_4H_8S, 100) and 155 (M^+–C_4H_8SH, 80); δ_P ($CDCl_3$) 45.8; δ_H ($CDCl_3$) 7.85–7.45 (5 H), 3.62 (3 H, d, J_{PH} 10, OMe), 2.49 (2 H, dt, J_{HH} ~7, 8), 2.05–1.8 (2 H), 1.8–1.6 (4 H) and 1.30 (1 H, t, J_{HH} 8, SH) (Found: M^+, 244.0688. $C_{11}H_{17}O_2PS$ requires *M*, 244.0687). GLC showed no trace (≤ 1 %) of the cyclic thiophosphinates **5** (n = 0, 1) (authentic samples[3] both t_R 7.1 min at 180 °C).

(b) A gentle stream of HCl was passed through $CDCl_3$ containing MeOH (0.25 mol dm^{-3}) for 5 min and the anilide **6** ($n = 0$ or 1) (4 mg) was dissolved in the resulting solution (*ca* 0.1 mol dm^{-3} HCl) (0.5 ml). Conversion into the methyl phosphinate **9** ($n = 0$ or 1) (δ_P 46.1 or 46.6 → 53.3 or 53.8) was complete in 50 min (T ~ 20 °C). An intermediate (δ_P 57.9 or 58.1) was deemed to be the phosphinic chloride **10** ($n = 0$ or 1). A highfield shoulder (~ 5 %) on the phosphinate signal shifted 25 ppm upfield when Et_3N was added, suggesting the phosphinic acid **12** ($n = 0$ or 1) [*m*/*z* (ES) 215 or 229 $(M–H)^-$]. In one case ($n = 0$) a small amount of the cyclic thiophosphinate **5** (2 %) was observed [δ_P 73.3; GLC; *m*/*z* (ES) 199 $(M+H)^+$].

(c) The anilide **6** ($n = 0$ or 1) (8 mg) in $CDCl_3$ (0.5 ml) containing HCl (*ca* 0.1 mol dm^{-3}) was maintained at 25–30 °C until much had been converted into the phosphinic chloride **10** (~ 2 h). The temperature was increased to 37 °C and ^{31}P NMR spectroscopy was used to follow changes in the relative amounts of **10** ($n = 0$ or 1) (δ_P 55.5 or 56.2) and the phosphinic anhydride **11** (diastereoisomers; δ_P 42.4, 41.9 or 43.1, 42.7), the phosphinic acid **12** (δ_P 48.5 or 51.5), and the cyclic thiophosphinate **5** (δ_P 75.5 or 45.6). The identity of the phosphinic acid was confirmed by conversion (CH_2N_2) into the methyl phosphinate **9** ($n = 0$ or 1), spectra as in (a). The cyclic thiophosphinate **5** ($n = 0$) was isolated and characterised by comparison (GLC, MS, ^{1}H NMR) with an authentic sample.[3] A very small amount of **5** ($n = 1$) was evident in the ^{1}H NMR spectrum of the reaction mixture [characteristic multiplets δ_H 3.5 and 3.0 (C*H*$_2$SP)] and was confirmed by GLC and by enhancement of the signal δ_P 45.6 on addition of authentic material.[3]

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References

1 C.J.M. Stirling, *Tetrahedron*, 1985, **41**, 1631; M.A. Casadei, C. Galli and L. Mandolini, *J. Am. Chem. Soc.*, 1984, **106**, 1051; D.F. DeTar and N.P. Luthra, *J. Am. Chem. Soc.*, 1980, **102**, 4504, and references cited therein.
2 Y.-K. Li and L.D. Byers, *J. Chem. Res. (S)*, 1993, 26.
3 A. Chaudhry, M.J.P. Harger, P. Shuff and A. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1347.
4 A.S. Pell and G. Pilcher, *Trans. Faraday Soc.*, 1965, **61**, 71.
5 S. Collison and M.J.P. Harger, *J. Chem. Res. (S)*, 2000, 28.