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Interaction of P_2S_5–pyridine with enamines. Synthesis and reactions of 1,6-trimethylene-5-cyano-2-mercapto-1,3,2-diazaphosphorine-2-thione

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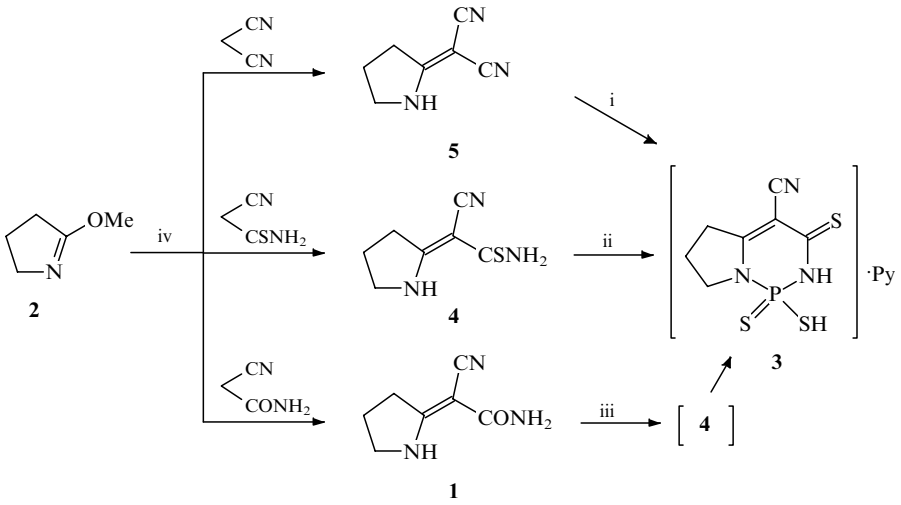
A new synthesis of 1,6-trimethylene-5-cyano-2-mercapto-1,3,2-diazaphosphorine-2,4-dithione (by treatment of enamines with phosphorus pentasulfide in the presence of pyridine) has been developed and some of its reactions are discussed.

It is known that aromatic and heteroaromatic compounds containing amino and carbamoyl (or thiocarbamoyl) groups in the *ortho*-position can be transformed into condensed 1,3,2-diazaphosphorines.[1–5] A similar disposition of 'active' substituents is typical of some non-aromatic systems, *e.g.*, for some enaminoamides. Based on these compounds, it seemed to be of interest to investigate the possibility of synthesising



Scheme 1 *Reagents and conditions:* i–iii, P_2S_5, pyridine, bp, 5 min; iv, DMF, bp, 3 h.

diazaphosphorine derivatives which do not contain condensed aromatic (heteroaromatic) rings.

2-(2′-Cyano-2′-carbamoyl)pyrrolidine **1**, obtained by reaction of *O*-methylbutyrolactime **2** with cyanoacetamide is chosen as the starting material.[6] The reaction of **1** with phosphorus pentasulfide in the presence of pyridine leads smoothly to 1,6-trimethylene-5-cyano-2-mercapto-1,3,2-diazaphosphorine-2,4-dithione **3** in the form of a pyridine solvate of variable composition, yield 91%,† mp 190–195 °C (decomp.) (DMF–water, 1:1); mass *m*/*z* 261 (33) $[M]^+$, 228 (27) $[M-SH]^+$, 196 (8) $[M-SH-S]^+$, 169 (27) $[M-SH-S-CN]^+$, 151 (10) $[M-SH-S-PN]^+$, 79 (100) $[Py]^+$.

The first stage of the interaction of enaminoamides with P_2S_5 probably involves formation of the intermediate thiocarbamoyl derivative **4**. This compound is specially synthesized by treatment of **2** with thiocyanoacetamide, yield 25%, mp 179–182 °C (DMF–water, 1:1), IR (KBr) ν/cm^{-1} 3340, 3280 and 3160 (NH, NH_2); 2180 (CN), mass *m*/*z* 167 (100) $[M]^+$, 139 (32) $[M-CH_2CH_2]^+$, 134 (70) $[M-SH]^+$, 60 (10) $[CSNH_2]^+$. Compound **4** readily reacts with P_2S_5–pyridine under the above conditions to yield diazaphosphorine **3**, yield 22%.

Further investigation found that it was possible to synthesize **3** from a compound without a carbamoyl group in the position *ortho* to the amino-group. It was established that the reaction of 2,2-dicyanomethylenepyrrolidine **5** with P_2S_5 and pyridine proceeds with formation of **3**, yield 42%. In this case the first stage of the process is undoubtedly acylation of the pyrrolidine NH-group by P_2S_5 (confirming our previous supposition[5]), with formation of H_2S which transforms the cyano group to thiocarbamoyl group. Closure of the phosphorus-containing ring proceeds according to Scheme 1.

Compound **3** is an attractive object for the synthesis of different diazaphosphorines with an amino group in the phosphorus containing heterocycle. Since such a transformation implies alkylation of mercapto groups under basic conditions, the stability of **3** under action of MeONa was studied. It was established that refluxing of **3** in a MeONa–MeOH solution leads to diazaphosphorine ring opening with formation of thiocarbamoyl derivative **4**. Under milder conditions **3** gave the Na derivative (with MeONa or NaOH) which was transformed by alkylation with haloalkyls or dialkylsulfates into 2,4-dialkylmercapto-1,3,2-diazaphosphorine-2-thiones **6a**,**b** and **7a**–**c**, characterized by spectral data (similar to compound **3**) and elemental analyses. For **6a**, yield 90%, mp 179–190 °C (DMF–water 3:1) **6b** yield 60%, mp 143–145 °C (DMF–water 2:1); ^1H NMR ($[^2H_6]$DMSO) δ, ppm 1.18 (3H, t, P–S–CH_2CH_3), 1.27 (3H, t, 4-S-CH_2CH_3), 2.08 (2H, m, β-CH_2), 2.56‡ (1H, m, P–S–CH_a), 2.68‡ (1H, m, P–S–CH_b, $^3J_{P,SCH_a} = {}^3J_{P,SCH_b} = 16.1$ Hz, $^2J_{SCH_a,SCH_b} = 13.2$ Hz), 3.07 (2H, q, 4-SCH_2CH_3), 3.17 (2H, m, α-CH_2), 3.91‡ (1H, m, γ-CH_a), 4.00‡ (1H, m, γ-CH_b), $^2J_{\gamma-CH_a,\gamma-CH_b} = 10.9$ Hz; ^{13}C NMR ($[^2H_6]$DMSO): δ, ppm 14.5 (C_4–SCH_2–CH_3), 15.3 (P–SCH_2–CH_3, $J_{P,CH_3} = 6.1$ Hz), 19.7 (C_β, $J_{P,C_\beta} = 6.1$ Hz), 24.8 (C_4–SCH_2CH_3, $J_{P,CH_2} = 2.3$ Hz), 28.4 (C_α, $J_{P,C_\alpha} = 4.6$ Hz), 34.9 (P–S–CH_2–CH_3, $J_{P,CH_2} = 3.1$ Hz), 52.3 (C_γ), 81.7 (C_5, $J_{P,C_5} = 22.2$ Hz), 115.7 (CN), 172.2 (C_6), 174.0 (C_4, $J_{P,C_4} = 16.8$ Hz); mass *m*/*z* M^+ 317; **7a**, yield 58%, mp 182–184 °C (DMF); mass *m*/*z* M^+·441; **7b**, yield 64%, mp 100–103 °C (DMF–water, 2:1), IR (KBr) ν/cm^{-1} 2240 and 2220 (CN), 1760 and 1740 (CO) and **7c**, yield 62%, mp 96–99 °C (DMF–water, 1:1).

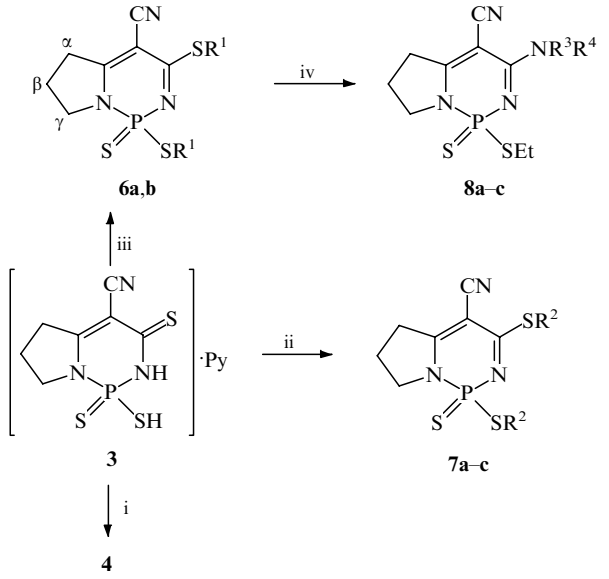
It is known that similar compounds are able to react with different amines with formation of amino derivatives of diazaphosphorines.[1,8] The interaction of **6b** with some amines gives compounds **8**. For compound **8a**, yield 48%, mp 129–132 °C (ethanol), ^1H NMR ($[^2H_6]$DMSO) δ, ppm 0.99 (3H, t, CH_3), 2.04 (2H, m, β-CH_2), 2.20‡ (1H, m, SCH_a), 2.38 (1H, m, SCH_b), ($^3J_{P,CH_a} = 12.3$ Hz, $^3J_{P,CH_b} = 12.9$ Hz), $^2J_{CH_a,CH_b} = 12.9$ Hz), 3.11 (2H, m, α-CH_2), 3.78‡ (1H, m, γ-CH_a), 3.90‡ (1H, m, γ-CH_b), ($^2J_{\gamma-CH_a,\gamma-CH_b} = 10.6$ Hz), 4.42‡ (1H, q, NCH_a), 4.54‡ (1H, q, NCH_b), ($^2J_{NCH_a,NCH_b} = 14.9$ Hz, $\Sigma^3J_{rmNH,CH_a} + {}^3J_{NH,CH_b} = 11.9$ Hz), 7.25 (5H, m, Ph), 8.54 (1H, q, NH); ^{13}C NMR ($[^2H_6]$DMSO): δ, ppm 15.0 (S–CH_2CH_3, $J_{P,CH_3} = 6.8$ Hz), 20.0 (C_β, $J_{P,C_\beta} = 6.1$ Hz), 27.6 (C_α, $J_{P,C_\alpha} = 4.6$ Hz), 34.6 (SCH_2CH_3, $J_{P,CH_2} = 3.05$ Hz), 51.5 (C_γ), 72.6 (C_5, $J_{P,C_5} = 17.6$ Hz), 116.3 (CN), 127.2 (1C), 127.9 (2C), 128.5 (2C), 139.1 (1C) (Ph), 158.1 (C_4, $J_{P,C_4} = 2.3$ Hz), 171.9 (C_6); IR (KBr) ν/cm^{-1} 3390 (NH), 2200 (CN); mass *m*/*z* 362 (67) $[M]^+$, 334 (27) $[M-CH_2CH_2]^+$, 301 (100) $[M-SEt]^+$, 269 (64) $[M-SEt-S]^+$, 91 (81) $[CH_2Ph]^+$; **8b**, yield 60%, mp 151–154 °C (DMF–water, 1:1); **8c**, yield 30%, mp 190–194 °C (ethanol).

It is necessary to note that the amidation reaction proceeds regioselectively and only the SR-group at position 4 exchanges amino groups. Evidence for this is provided by ^1H and ^{13}C NMR spectral data. Thus, upon transformation of **6b** to **8a** the fragments P–S–CH_2CH_3 in the ^{13}C NMR spectra are the same, but the C_4 atom shifts to higher field ($\Delta\delta$ C_4 = 15.9 ppm). This is connected with the presence of an aminobenzyl group near this atom (C_4). A similar conclusion

† To calculate the yields of products obtained from **3** we used the average content of pyridine in this solvate as 2/3 M on 1 M of diazaphosphorine. In all other cases the compounds synthesised show satisfactory elemental analysis and spectral data.

‡ Asymmetric phosphorus atoms in the molecule lead to non-equivalent methylene protons.

is applicable to a comparison of the ^{1}H NMR spectra of **6b** and **8a**.



6a R^1 = Me, **6b** R^1 = Et
7a R^2 = CH_2Ph, **7b** R^2 = CH_2COOMe, **7c** R^2 = CH_2COOEt
8a R^3 = CH_2Ph, R^4 = H, **8b** R^3R^4 = morpholine,
8c R^3 = *p*-MeC_6H_4, R^4 = H

Scheme 2 *Reagents and conditions:* i, MeOH/MeONa, bp, 2 h; ii MeOH/MeONa, Hal–R^1, 20 °C, 12 h; iii, NaOH/H_2O, $(R^2)_2SO_4$, 20 °C, 2 h; iv, HNR^3R^4, bp, 20 min.

Thus, the present work has established that P_2S_5–pyridine shows thionating and cyclizating action relative to nonaromatic enaminoamides, enaminothioamides and enaminonitrile derivatives, leading to the formation of trimethylendiazaphosphorine derivatives.

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