Three component reactions of enamines, *O,O*-dialkyldithiophosphoric acids, and electrophiles

M. B. Gazizov, R. A. Khairullin, Yu. S. Kirillina, S. Yu. Ivanova, K. S. Gazizova, and Kh. R. Khayarov*

Kazan National Research Technological University,
68 ul. K. Marksa, 420015 Kazan, Russian Federation.
Fax: +7 (843) 231 9505. E-mail: mukattisg@mail.ru

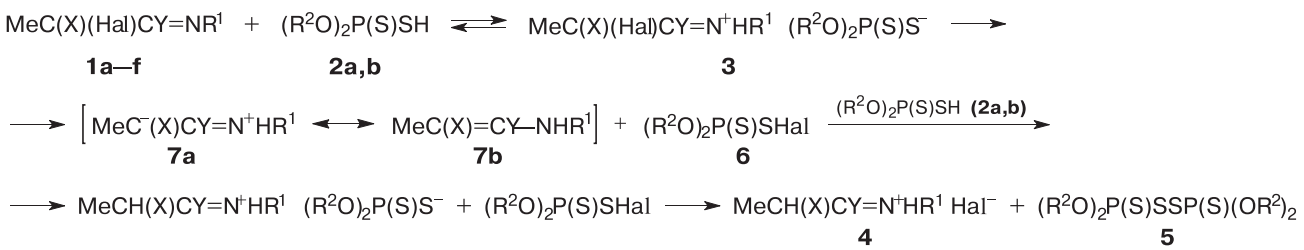
The product of addition of *O,O*-dialkyldithiophosphoric acid to enamine reacted with the third reaction component of electrophilic nature, for instance, acetyl chloride, α-bromo ether, or sulfenyl bromide. The reaction involving sulfenyl bromide gave the product of reduction of the C—Hal bond of iminium salt and bis(dialkoxythiophosphorylthio) disulfide. This experimentally confirmed the occurrence of the reaction between 2-halo-substituted ald- or ketimines with thio acids *via* enamine intermediates.

Key words: enamines, *O,O*-dialkyldithiophosphoric acids, sulfenyl bromides, bis(dialkoxythiophosphoryl) disulfide, iminium salts.

Phosphorus(IV) dithio acids occupy a prominent place in the chemistry of organophosphorus compounds.[1—4] Pronounced electrophilic and nucleophilic properties of phosphorus(IV) dithio acids are caused by their relatively strong acidity and the high nucleophilicity of the P(S)S triad. These acids readily add to multiple bonds, for instance, to the C=N iminium double bonds.[4—8] The reaction carried out in ethanol gives adducts $R^2C_6H_4$-$CH(NHC_6H_4R^3)SP(S)(OR^1)_2$,[7] while in hexane the reaction stops at the protonation step to produce iminium salts $[PhCH{=}N^+HR^2][^-SP(S)(OR^1)_2]$, which were isolated pure.[9] In the solutions, these salts reversibly transform into the adducts, but upon long-term storage they gave the complex product mixtures. Of halo-substituted imines, only chloral imine was involved in the reactions with phosphorus(IV) dithio acids. These transformations gave a stable adduct $CCl_3CH(NHPh)$-$SP(S)(OR)_2$.[10]

Earlier, we preformed the first studies of the reactions of 2-monohalo- and 2,2-dihalo-substituted *N*-alkyl-substituted ald- and ketimines **1** with *O,O*-dialkyldithiophosphoric acids **2**. The possibilities to find new reactions leading to novel multifunctional derivatives were also anticipated. We have found that *O,O*-dialkyldithiophosphoric acids **2** reacted with *N*-alkyl-2-bromo-2-methyl (**1a,b**)[11—13], -2-chloro-2-phenyl (**1c**)[14], -2,2-dichloro (**1d**), and -dibromo (**1e**) aldimines[15,16] and 2-methyl-1-phenyl-2-chloro ketimine (**1f**)[14] to give initially iminium salts **3**. The excess of acid **2** caused the reduction of the C—Hal bond of the cation of salts **3** to produce iminium salts **4** and bis(dialkoxythiophosphoryl) disulfides **5** as the main products.[11—16] We suggested that the reduction of salt **3** is a halophilic elimination initiated by *O,O*-dialkyldithiophosphoric anion $(RO)_2P(S)S^-$ that proceeds *via* intermediate (dialkoxythiophosphoryl)sulfenyl halide $(RO)_2P(S)SHal$ **6** and bipolar ion **7a**. Structure **7a** can be regarded as a resonance structure of enamine **7b** with the separated charges.[14—16] Protonation of species **7** and abstraction of dithiophosphoric anion with sulfenyl halide **6** provides the final products **4** and **5** (Scheme 1).

Scheme 1



1: X = Me, Hal = Br, Y = H, R^1 = Pr^i (**a**), Bu (**b**); X = Ph, Hal = Cl, Y = H, R^1 = Bu^t (**c**); X = Hal = Cl, Y = H, R^1 = Bu^t (**d**); X = Hal = Br, Y = H, R^1 = Pr^i (**e**); X = Me, Hal = Cl, Y = Ph, R^1 = Pr^i (**f**); **2:** R^2 = Pr^i (**a**), Et (**b**)

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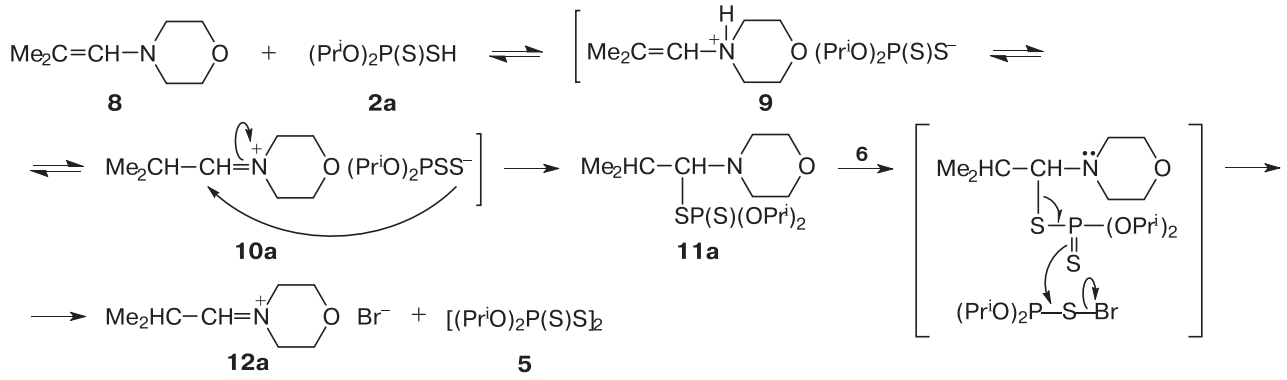
Scheme 2



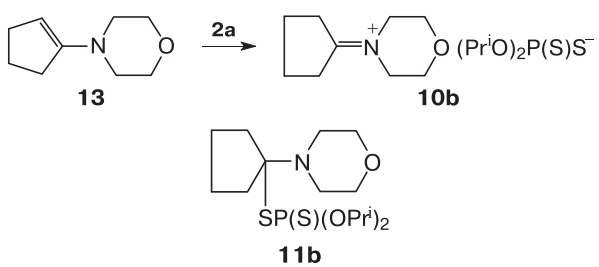
To the best of our knowledge, the reactions of *O,O*-dialkyldithiophosphoric acids **2** with enamines have not been described. In order to confirm the occurrence of the reduction of salt **3** *via* enamine intermediate we studied herein the reactions of readily available and stable enamine **8** with a series of phosphoric acids **2**.

Since sulfenyl halide **6** is involved in the formation of disulfide **5** (see Scheme 1), we started our studies from the successive reactions of enamine **8** with acid **2a** and compound **6** (Scheme 2).

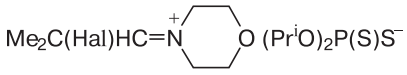
These reactions give the product of addition to the double bond **11a**. We believe that the reaction is initiated by protonation of the nitrogen atom of enamine **8** with acid **2a** to give an ammonium salt, *O*,*O*-diisopropyl *S*-4-(2-methyl-1-propenyl)morpholinium dithiophosphate (**9**). Next, due to a prototropic exchange, salt **9** is interconverted into an iminium salt, 4-(2-methylpropylidene)-morpholinium dithiophosphate (**10a**). Finally, salt **10a** is transformed into the isolated product of the reaction, *O*,*O*-diisopropyl *S*-1-(morpholin-4-yl)-2-methylpropyl dithiophosphate (**11a**).

We were unable to experimentally confirm the formation of salts **9** and **10a**. Besides, the structurally related 4-cyclopentylidenemorpholinium *O*,*O*-diisopropyl dithiophosphate **10b** was prepared pure from enamine **13** (Scheme 3). It should be noted that in this case product **11b** was not detected.

Scheme 3



Addition of sulfenyl bromide **6** to the reaction mixture initiated the exothermic process leading to disulfide **5** and the product of reduction **12a** (see Scheme 2). Compound **12a** can be considered as the analog of the hypothetical structure **14**, which, in turn, is the analog of the iminium salt **3** initially formed from compounds **1** and **2**. This result of the three-component reaction of enamine, dithio acid, and sulfenyl bromide proves the occurrence of the reaction between compounds **1** and **2** *via* enamine intermediates of type **7** (see Scheme 1).



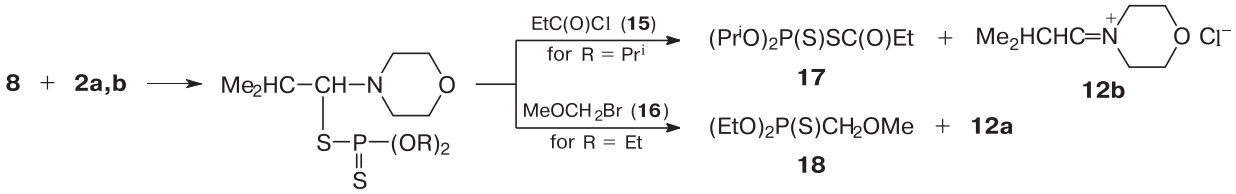
With the aim to synthesize new multifunctional derivatives, we expanded the scope of the electrophiles. For instance, we examined the behavior of propionyl chloride (**15**) and α-bromo ether **16** (Scheme 4).

Propionyl thio derivative **17** has not been previously described. However, closely related *S*-acetyl *O*,*O*-dialkyl dithiophosphates $(RO)_2P(S)SCOMe$, including $(Pr^iO)_2P(S)SCOMe$, are known. For the synthesis of these compounds several following methods were suggested: the reaction of potassium ($(RO)_2P(S)SK$) or lead ($[(RO)_2P(S)S]_2Pb$) salts of dialkyldithiophosphoric acid with acetyl chloride;[17] the addition of sulfur to *S*-acetyl dialkyl thiophosphites $(RO)_2PSC(O)Me$;[18] and the reaction of MeCN with acid **2** in the presence of acetic acid.[19] Thus, we developed a new synthetic procedure to *O,O*-dialkyl *S*-alkanoyl dithiophosphates.

We also suggested a new method for synthesizing *O,O*-diethyl *S*-methoxymethyl dithiophosphate (**18**) (see Scheme 4). Earlier, compound **18** was synthesized by methylation of *O,O*-diethyl *S*-hydroxymethyl dithiophosphate $(EtO)_2P(S)SCH_2OH$ with diazomethane.[20]

In summary, three component reactions of enamines, *O*,*O*-diisopropyldithiophosphoric acid, and (diisopropoxythiophosphoryl)sulfenyl bromide as the electrophilic

Scheme 4



1: R = Pt^{i} (**a**), Et (**c**)

species give bis(diisopropoxythiophosphoryl) disulfide and the product of the reduction of the C—Br bond of iminium salt. This result experimentally confirms the formation of enamine intermediate in the reactions of 2-halo-substituted ald- and ketimines with dithio acids. New methods towards *P,S*-containing organic compounds were elaborated.

Experimental

^{1}H and ^{13}C NMR spectra were recorded with Tesla BS-567A (working frequency of 100 MHz) and Bruker AVANCE 400WB (working frequencies of 400.13 and 100.61 MHz, respectively) spectrometers in $CDCl_3$. The ^{1}H and ^{13}C chemical shifts are given in the δ scale relative to the residual proton signal (^{1}H) and the central signal of the carbon atom (^{13}C) of the solvent and recalculated to Me_4Si. ^{31}P NMR spectra were run on a Bruker AVANCE 400WB (working frequency of 161.98 MHz) instrument. The ^{31}P chemical shifts are given relative to 85% H_3PO_4 (an external standard).

***O,O*-Diisopropyl *S*-1-(morpholin-4-yl)-2-methylpropyl dithiophosphate (11a)**. To a solution of enamine **8** (1.41 g, 10 mmol) in CCl_4 (5 mL), a solution of acid **2a** (2.14 g, 10 mmol) in CCl_4 (10 mL) was added dropwise maintaining the reaction temperature at 0—5 °C. Cooling was removed and the reaction mixture was kept at room temperature for 24 h. Removal of the volatiles *in vacuo* afforded 3.27 g (92%) of crystalline product **11a** with purity of 96%, m.p. 78—79 °C. ^{1}H NMR ($CDCl_3$), δ_H: 1.12 (d, 6 H, CH$\underline{Me}_2$, $^{3}J_{H,H}$ = 6.6 Hz); 1.32 (d, 12 H, $\underline{Me}_2$CHO, $^{3}J_{H,H}$ = 6.3 Hz); 2.16 (m, 1 H, $\underline{C}$HMe$_2$); 2.72 (t, 4 H, NCH_2, $^{3}J_{H,H}$ = 4.7 Hz); 3.70 (t, 4 H, OCH_2, $^{3}J_{H,H}$ = 4.7 Hz); 4.73 (sept, 2 H, CHOP, $^{3}J_{H,H}$ = 6.3 Hz); 4.97 (d, 1 H, CHN, $^{3}J_{H,H}$ = 10.2 Hz). ^{13}C NMR ($CDCl_3$), δ_C: 20.98 (CH$\underline{Me}_2$), 23.73 (d, $\underline{Me}_2$CHO, $^{3}J_{P,C}$ = 5.0 Hz); 32.81 ($\underline{C}$HMe$_2$), 49.84 (NCH_2), 63.72 (SCH), 66.33 (OCH_2), 72.47 (d, POCH, $^{2}J_{P,C}$ = 7.5 Hz). ^{31}P NMR ($CDCl_3$), δ_P: 98.9. Found (%): C, 47.16; H, 8.23; N, 3.61; P, 8.51. $C_{14}H_{30}NO_3PS_2$. Calculated (%): C, 47.30; H, 8.51; N, 3.94; P, 8.73.

4-(3-Methylpropylidene)morpholinium bromide (12a). To a solution of enamine **8** (2.79 g, 13 mmol) in CCl_4 (10 mL), a solution of acid **2a** (1.84 g, 13 mmol) in CCl_4 (10 mL) was added dropwise maintaining the reaction temperature at 0—5 °C. Cooling was removed and the mixture was stirred at room temperature for 5 h. ^{31}P NMR spectrum showed intense resonance at δ_P 98.9 attributable to the phosphorus atom of compound **11a**. The mixture was cooled to −15 °C and treated dropwise with a solution of (diisopropoxythiophosphoryl)sulfenyl bromide (**6**) in CCl_4, prepared from disulfide **5** (2.77 g, 6.5 mmol) and bromine (1.04 g, 6.5 mmol). Cooling was removed and the reaction mixture was kept at room temperature for 16 h. The precipitate formed was collected by filtration and dried to afford 2.45 g (85%) of iminium salt **12a**. ^{1}H NMR ($CDCl_3$), δ_H: 1.39 (d, 6 H, CH$\underline{Me}_2$, $^{3}J_{H,H}$ = 6.7 Hz); 3.24 (m, 1 H, $\underline{C}$HMe$_2$); 3.96 (m, 4 H, OCH_2); 4.03 (m, 4 H, N^+CH_2); 9.39 (d, 1 H, HCN^+, $^{3}J_{H,H}$ = 8.5 Hz). ^{13}C NMR ($CDCl_3$), δ_C: 19.50 (CH$\underline{Me}_2$), 30.62 ($\underline{C}$HMe$_2$), 51.89, 59.14 ($N^+(CH_2)_2$), 66.35 ($O(CH_2)_2$), 180.1 (HCN^+). Found (%): C, 42.63; H, 6.98; N, 6.01. $C_8H_{16}BrNO$. Calculated (%): C, 43.26; H, 7.26; N, 6.31. Concentration of the mother liquor *in vacuo* afforded 4.30 g (78%) of disulfide **5**, m.p. 92 °C (*cf.* Ref. 21: m.p. 91.5—93.0 °C). ^{1}H NMR ($CDCl_3$), δ_H: 1.40, 1.42 (both d, 24 H, $\underline{Me}_2$CH, $^{3}J_{H,H}$ = 6.4 Hz); 4.90 (d.hept, 4 H, CHOP, $^{3}J_{H,H}$ = 6.4 Hz, $^{3}J_{P,H}$ = 12.0 Hz). ^{13}C NMR ($CDCl_3$), δ_C: 23.75 (d, Me, $^{3}J_{P,C}$ = 4.5 Hz); 23.57 (d, Me, $^{3}J_{P,C}$ = 5.5 Hz); 74.76 (d, CH, $^{2}J_{P,C}$ = 6.7 Hz). ^{31}P NMR ($CDCl_3$), δ_P: 81.70.

***O,O*-Diisopropyl *S*-propionyl dithiophosphate (17).** A reaction mixture prepared from enamine **8** (1.41 g, 10 mmol), acid **2a** (2.14 g, 10 mmol), and dioxane (20 mL) was treated dropwise with a solution of propionyl chloride **15** (0.92 g, 10 mmol) in dioxane (10 mL) at −5 °C. Cooling was removed and the reaction mixture was kept at room temperature for 16 h. The precipitate formed was collected by filtration and dried to afford 1.70 g (96%) of 4-(3-methylpropylidenemorpholinium) chloride (**12b**). ^{1}H NMR ($CDCl_3$), δ_H: 1.40 (d, 6 H, CH$\underline{Me}_2$, $^{3}J_{H,H}$ = 6.6 Hz); 3.03 (m, 1 H, $\underline{C}$HMe$_2$); 4.04 (m, 4 H, OCH_2); 4.27 (m, 4 H, N^+CH_2); 9.90 (d, 1 H, HCN^+, $^{3}J_{H,H}$ = 8.3 Hz). Found (%): C, 53.79; H, 8.87; N, 7.53. $C_8H_{16}ClNO$. Calculated (%): C, 54.08; H, 9.08; N, 7.88. Concentration of the mother liquor *in vacuo* and vacuum distillation of the residue afforded 2.13 g (77%) of product **17**, b.p. 101—102 °C (0.09 Torr). ^{1}H NMR ($CDCl_3$), δ_H: 1.18 (t, 3 H, $\underline{Me}CH_2$, $^{3}J_{H,H}$ = 7.5 Hz); 1.34, 1.39 (both d, 12 H, CH$\underline{Me}_2$, $^{3}J_{H,H}$ = 6.2 Hz); 2.65 (q, 2 H, Me$\underline{C}H_2$, $^{3}J_{H,H}$ = 7.5 Hz); 4.96 (sept, 2 H, CHOP, $^{3}J_{H,H}$ = 6.2). ^{31}P NMR ($CDCl_3$), δ_P: 76.86. Found (%): C, 39.73; H, 7.26; P, 11.32. $C_9H_{19}O_3PS_2$. Calculated (%): C, 39.98; H, 7.08; P, 11.46.

***O,O*-Diethyl *S*-methoxymethyl dithiophosphate (18).** A reaction mixture prepared from enamine **8** (4.10 g, 29 mmol), acid **2b** (5.39 g, 29 mmol), and CCl_4 (40 mL) was treated dropwise with a solution of bromo(methoxy)methane **16** (3.60 g, 30 mmol) in CCl_4 (40 mL) at −5 °C. Cooling was removed and the mixture was kept at room temperature for 16 h. The precipitate formed was collected by filtration and dried to afford 5.50 g (86%) of iminium salt **12a**. Concentration of the mother liquor *in vacuo* and vacuum distillation of the residue afforded 5.20 g (79%) of product **18**, b.p. 75—76 °C (0.05 Toff) (*cf.* Ref. 20: b.p. 103 °C (0.1 Torr)). ^{1}H NMR ($CDCl_3$), δ_H: 1.35 (t, 6 H, $\underline{Me}CH_2$, $^{3}J_{H,H}$ = 7.1 Hz); 3.38 (s, 3 H, OMe); 4.10, 4.18 (both q, 4 H, CH_2OP, $^{3}J_{H,H}$ = 7.1 Hz); 5.06 (d, 2 H, SCH_2, $^{3}J_{P,H}$ = 20.4 Hz).

^{13}C NMR ($CDCl_3$), δ_C: 15.90 (Me), 56.95 (OMe), 63.75 (d, $POCH_2$, $^2J_{P,C}$ = 5.6 Hz), 78.48 (d, SCH_2, $^2J_{P,C}$ = 3.8 Hz). ^{31}P NMR ($CDCl_3$), δ_P: 94.77. Found (%): C, 31.12; H, 6.78; P, 13.45. $C_6H_{15}O_3PS_2$. Calculated (%): C, 31.29; H, 6.57; P, 13.28.

4-Cyclopentylidenemorpholinium *O*,*O*-diisopropyl dithiophosphate (10b). To a solution of 4-(cyclopent-1-en-1-yl)morpholine (**13**) (1.53 g, 10 mmol) in anhydrous CCl_4 (10 mL), a solution of acid **2a** (2.14 g, 10 mmol) was added dropwise under argon maintaining the reaction temperature at 0—5 °C. Cooling was removed and the reaction mixture was stirred at room temperature for 5 h. The precipitate formed was collected by filtration and dried to afford 3.50 g (95%) of salt **10b** contaminated with 5% morpholinium dithiophosphate. ^1H NMR ($CDCl_3$), δ_H: 1.25 (d, 12 H, MeCHOP, $^3J_{H,H}$ = 6.6 Hz); 2.13 (m, 4 H, 2 CH_2); 3.22 (m, 4 H, $=C(CH_2)_2$); 4.09 (m, 4 H, $O(CH_2)_2$); 4.14 (m, 4 H, $N^+(CH_2)_2$); 4.69 (sept, 2 H, CHOP). Found (%): C, 48.79; H, 7.95; N, 4.03; P, 8.21. $C_{15}H_{30}NO_3PS_2$. Calculated (%): C, 49.02; H, 8.23; N, 3.81; P, 8.45.

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