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LETTERS TO THE EDITOR

Reaction of 3-(Dimethylamino)-2,2-dimethylpropanal with Trialkylphosphites in the Presence of Acetic Anhydride

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Previously we have developed a new version of the Birum reaction using carboxylic acid anhydrides as the third electrophilic reagent [1] instead of P(III) chlorides [2].

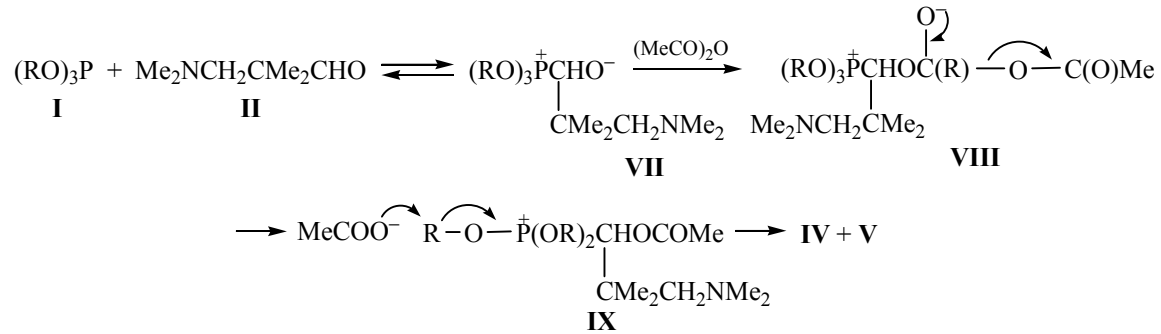
Hitherto the functionally substituted aldehydes were not introduced into the new version of the Birum reaction. We first used the readily accessible 3-(dimethylamino)-2,2-dimethylpropanal in this reaction. This choice was dictated by the fact that, firstly, the presence of pharmacophore amine group can lead to the synthesis of new types of multifunctional organophosphorus compounds possessing potential biological activity. Secondly, the new reaction routes can be realized under the influence of the three-coordinated nitrogen atom.

An equimolar mixture of trialkylphosphite **I**, 3-(dialkylamino)aldehyde **II**, and acetic anhydride **III** was kept at room temperature for 1 month. After every week we registered the ^{1}H NMR spectrum of the reaction mixture and observed a gradual decrease in the signal intensity of the aldehyde group proton (δ 10 ppm). The signal intensity of methine proton of the reaction products **IV** and **VI** increases at δ 6.5 and 5.2 ppm. After one month the intensity of these signals ceased to change, although the ^{31}P NMR spectrum of the reaction mixture indicates a substantial amount of the starting trialkylphosphite **I**. The main reason of this is the consumption of reagents **II** and **III** in the formation of the non-phosphorus product **VI**.

$$\underset{\mathbf{I}}{(RO)_3P} + \underset{\mathbf{II}}{Me_2NCH_2CMe_2CHO} + \underset{\mathbf{III}}{(MeCO)_2O} \xrightarrow[\mathbf{V}]{-MeCOOR} \underset{\mathbf{IV}}{(RO)_2P(O)CH(OCOMe)CMe_2CH_2NMe_2} + \underset{\mathbf{VI}}{Me_2NCH_2CMe_2CH(OCOMe)_2}$$

IV, R = Me (**a**), Et (**b**).

After the removal of volatile substances including trialkylphosphite **I**, the residue was distilled in vacuum to form two fractions, whose re-distillation gave compounds **IV** and **VI** in individual form.



We suggest the scheme above of the formation of products **IV** and **V**.

Compounds **I** and **II** form bipolar ion **VII**, reaction of which with anhydride **III** gives rise to a new bipolar ion **VIII**. The latter releases the acetate anion to form quasi-phosphonium intermediate **IX**, which is stabilized through the formation of the Arbuzov reaction products **IV** and **V**.

Diacetals of the amino-substituted aldehydes **VI** were not previously known in the literature. We synthesized them via a model three-component reaction of 3-(dialkylamino)-substituted aldehyde **II** with anhydride **III**.

$$\mathbf{II} + (RCO)_2O \xrightarrow[\mathbf{III}]{} Me_2NCH_2CMe_2CH(OCOR)_2$$

III, R = Me, Et.

Reaction of 3-(dimethylamino)-2,2-dimethylpropanal with triethylphosphite in the presence of acetic anhydride. A mixture of 6.44 g (0.039 mol) of triethylphosphite **Ib**, 5 g (0.039 mol) of 3-(dimethylamino)-2,2-dimethylpropanal **II**, and 3.95 g (0.039 mol) of acetic anhydride was kept in a closed flask for 1 month. The volatiles were removed. The residue was distilled in vacuum to form two fractions: bp 52–54ºC (0.06 mm Hg), 4.6 g, and bp 90–106ºC (0.06 mm Hg), 1.6 g. The repeated distillation of the second fraction gave 1.2 g (20%) of *O*,*O*-diethyl[3-(dimethylamino)-2,2-dimethyl-1-(ethanoyloxy)propyl]phosphonate **Vb**, bp 79–80°C (0.047 mm Hg), n_D^{20} 1.4442. ^{1}H NMR spectrum (acetone-*d*), δ, ppm: 0.90 s, 0.97 s (6H, CMe_2), 1.12 s (9H, CMe_3), 1.21 t, 1.25 t (6H, $POCH_2\underline{Me}$, $^3J_{HH}$ 7.5 Hz), 2.20 s (6H, NMe_2), 2.12 s, 2.30 s (2H, CH_2N), 3.75–4.20 m (4H, $POCH_2$), 5.21 d (1H, PCH, $^2J_{PH}$ 8.75 Hz). Found, %: N 3.87; P 8.70. $C_{16}H_{34}NO_5P$. Calculated, %: N 3.98; P 8.81.

From the first fraction 4.1 g (45%) of 3-(dimethylamino)-2,2-dimethylpropanal diacetate **VIa** was obtained, bp 50–52°C (0.06 mm Hg), n_D^{20} 1.4334. ^{1}H NMR spectrum (acetone-*d*), δ, ppm: 6.5 s (1H, CH), 2.17 s (6H, NMe_2), 2.07 s (2H, CH_2N), 0.8 s (6H, CMe_2), 1.93 s (6H, COMe). Found N, %: 6.17. $C_{11}H_{21}NO_4$. Calculated, %: N 6.06.

Reaction of 3-(dimethylamino)-2,2-dimethylpropanal with trimethylphosphite in the presence of acetic anhydride. Similarly, *O*,*O*-dimethyl-[3-(dimethylamino)-2,2-dimethyl-1-ethanoyloxypropyl]-phosphonate **IVa** (0.8 g, 23.8%) and compound **VIa** (2.8 g, 59%) were obtained from 5.11 g (0.041 mol) of trimethylphosphite, 5.32 g of aldehyde **II**, and 3.95 g (0.041 mol) of acetic anhydride. Compound **IVa**: bp 73–75°C (0.058 mm Hg), n_D^{20} 1.4448. ^{1}H NMR spectrum (acetone-*d*), δ, ppm: 0.85 s, 0.90 s (6H, CMe_2), 2.01 s (3H, MeCO), 2.1 s, 2.2 s (2H, CH_2N), 2.2 s (6H, NMe_2), 3.60 s, 3.63 s (6H, POMe, $^2J_{PH}$ 11.2 Hz), 5.25 d (1H, PCH, $^2J_{PH}$ 9.0 Hz). Found, %: N 4.81; P 10.87. $C_{11}H_{24}NO_5P$. Calculated, %: N 4.98; P 11.03. Compound **VIa**: bp 50–52°C (0.06 mm Hg), n_D^{20} 1.4337.

3-(Dimethylamino)-2,2-dimethylpropanal diacetate (VIa). A mixture of 5 g (0.038 mol) of 3-(dimethylamino)-2,2-dimethylpropanal **II** and 3.957 g (0.038 mol) of acetic anhydride was kept in a sealed ampule for 14 days and then distilled in vacuum. Yield 8 g (54%), bp 51–52°C (0.06 mm Hg), n_D^{20} 1.4336.

3-(Dimethylamino)-2,2-dimethylpropanal dipropanoate (VIб) was obtained similarly from 5 g (0.038 mol) of 3-(dimethylamino)-2,2-dimethylpropanal **II** and 5.04 g (0.038 mol) of propionic anhydride. Yield 6.3 g (62.7%), bp 73–74°C (0.082 mm Hg), n_D^{20} 1.4352. ^{1}H NMR spectrum (acetone-*d*), δ, ppm: 6.55 s (1H, CH), 2.15 s (2H, CH_2N), 2.70 s (6H, NMe_2), 2.10 q (4H, $COCH_2$, $^3J_{HH}$ 7 Hz), 0.90 t (6H, $COCH_2\underline{CH_3}$, $^3J_{HH}$ 7 Hz), 0.80 s (6H, CMe_2).

The ^{1}H NMR spectra were registered on a Tesla BS-567A spectrometer operating at 100 MHz, internal reference TMS. The ^{31}P NMR spectra were recorded on a RYa-2303 instrument (21 MHz) relative to 85% H_3PO_4.

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