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LETTERS TO THE EDITOR

To the 80th Anniversary of B.I. Ionin

Formation of Phosphorus–Carbon Bond in the Course of Amidoalkylation of Hydrophosphorylic Compounds

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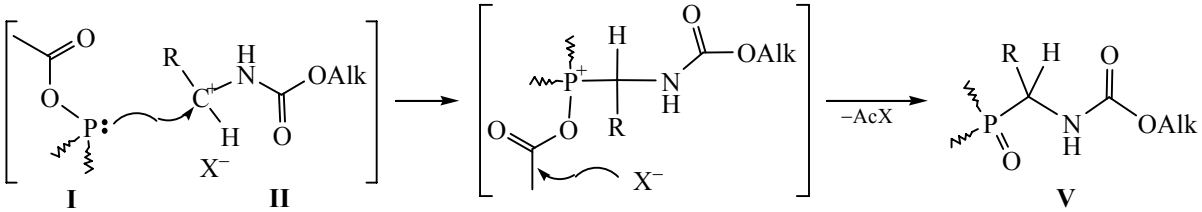
Amidoalkylation of hydrophosphorylic compounds, a very promising general method for incorporation of aminophosphoryl function retaining a protecting group at the nitrogen atom of the target molecule, has been undeservedly forgotten. We have earlier developed an efficient procedure to perform reaction of hydrophosphoryl compounds with aldehydes and alkyl carbamates in acetic anhydride upon cooling, and have proposed the mechanism of this multi-stage reaction [1–4]. According to the proposed mechanism, the formation of phosphorus–carbon bond is as a result of the Arbuzov reaction via nucleophilic attack of the trivalent phosphorus atom of acetyloxy derivative **I** at positively charged carbon atom of iminium cation **II** [1, 2], the reactants being generated *in situ* under the reaction conditions from hydrophosphorylic compound **III** and *N*,*N*'-alkylidenebis(carbamate) **IV**, respectively [1, 2]. Biscarbamates have been identified as stable (isolated from the reaction medium) intermediates formed from the reacting aldehydes and alkyl carbamates [1–4] (Scheme 1).

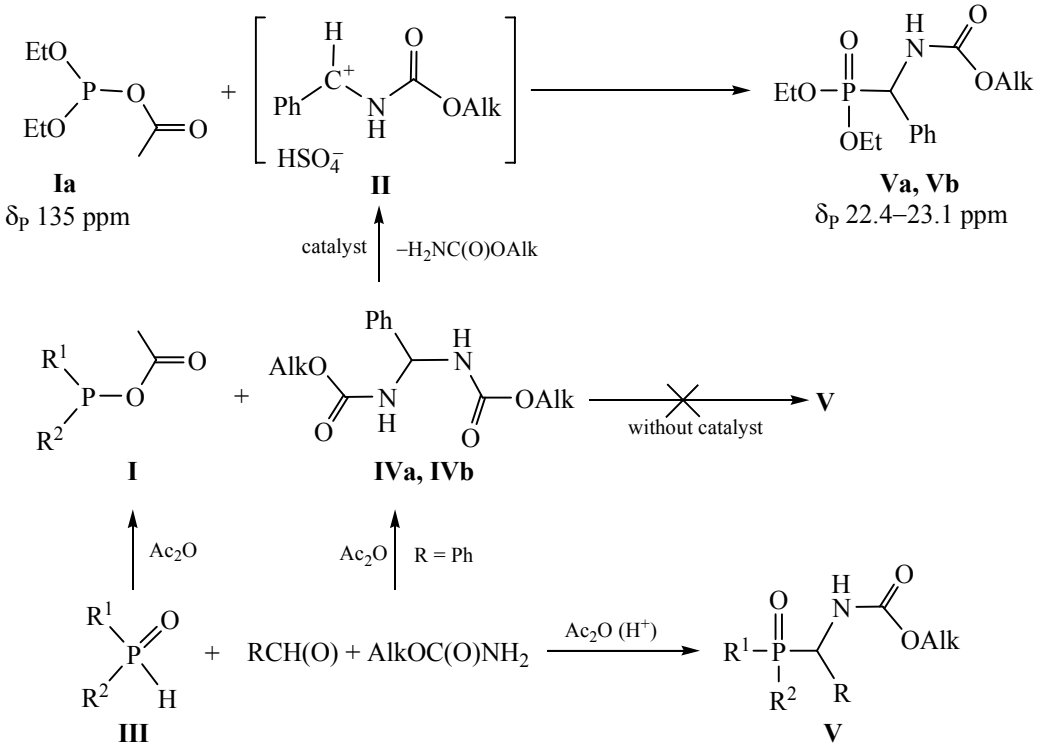
This work aimed to study of one of the proposed stages, formation of phosphorus–carbon bond during generation of the iminium cation from a presynthesized alkylidenebiscarbamate **III** in an aprotic solvent in the presence of solid superacid catalyst [5, 6]. *N*,*N*'-Benzylidenebis(carbamates) **IVa** and **IVb** synthesized from carbamate and benzaldehyde in acetic anhydride medium were used as iminium ion sources; diethyl acetylphosphite **Ia** [7] was used as the $AcOP^{III}$-phosphorus component.

It was found that biscarbamates **IVa** and **IVb** did not react with acetylphosphite **Ia** in an aprotic solvent in the absence of acid catalyst, as conditions of the iminium ion **II** generation were not met. We suggested that transformation of biscarbamate **IV** into the iminium cation **II** might occur in the presence of a solid superacid via protonation of nitrogen or oxygen atom (C=O) of amide fragment of biscarbamate with Brønsted sites of the catalyst in an inert solvent followed by evolution of the carbamate [1–4]. The so

Scheme 1.



Scheme 2.



Alk = Et (**a**), *tert*-Bu (**b**).

generated iminium cation **II** was probably sufficiently reactive, and a relatively weak nucleophile such as acetylphosphite **I** could attack the positively charged carbon atom of the iminium ion to form the target phosphorus–carbon bond (Scheme 2).

Indeed, a relatively rapid formation of the desired reaction product was observed when using sulfated solid superacid TiO_2/SO_4 or Al_2O_3/SO_4. The reaction was monitored by ^{31}P NMR: in the course of the reaction, the signal of acetylphosphite **Ia** at ~135 ppm disappeared and the signal of the corresponding α-aminophosphonate **V** appeared at ~22–23 ppm in the ^{31}P NMR spectrum of the reaction mixture. Pure phosphonates **Va** and **Vb** were isolated and characterized.

In summary, the results have confirmed the previously proposed mechanism of the phosphorus–carbon bond formation during amidoalkylation of hydrophosphoryl compounds. Use of superacid catalyst allowed for the first time to introduce aminophosphoryl fragment into the compound structure retaining the *tert*-butyloxycarbonyl protecting group at the nitrogen atom; the process is promising for peptide synthesis.

Alkylidenebiscarbamates were synthesized by reacting 2 eq. of benzaldehyde with ethyl or *tert*-butyl carbamate in acetic anhydride medium in the presence of trifluoroacetic acid (**IVa**) or without any catalyst (**IVb**) [1].

***N*,*N*'-Benzylidenebis(ethylcarbamate) (IVa).** Yield 72%, mp 172–173°C, R_f [$CHCl_3$–$(CH_3)_2CO$, 4 : 1] 0.8. ^1H NMR spectrum (DMSO-d_6–CCl_4, 1 : 4), δ, ppm: 1.25 t (6H, CH_3, $^3J_{HH}$ 7.0 Hz), 4.05 q (4H, CH_2, $^3J_{HH}$ 7.0 Hz), 6.15 d.d (1H, CH, J_{HH} 9.3 Hz), 7.2–7.5 m (5H, Ph, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.6 ($\underline{C}H_3CH_2$), 60.0 (CH_2O), 61.5 ($\underline{C}HN$); 126.3, 127.7, 128.3, 140.3 (Ph), 155.3 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 267 (<1) $[M + H]^+$, 104 (100) $[CH_3NH_2^+C(O)OCH_2CH_3]$, 77 (80) $[C_6H_5^+]$, 178 (21) $[PhCH^+NHC(O)OCH_2CH_3]$. Found, %: C 58.51, 58.49; H 7.01, 6.93; N 10.21, 10.43. $C_{13}H_{18}N_2O_4$. Calculated, %: C 58.64; H 6.81; N 10.52.

***N*,*N*'-Benzylidenebis(*tert*-butylcarbamate) (IVb).** Yield 56%, mp143–145°C, R_f [$CHCl_3$–$(CH_3)_2CO$, 4 : 1] 0.8. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 s (18H, $6CH_3$), 6.05 t (1H, CHN, $^3J_{HH}$ 7.3 Hz), 7.23–7.47 m (7H, Ph, 2NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 28.2 ($6CH_3$), 60.8 (CHN), 78.3 ($\underline{C}Me_3$); 126.1, 127.5, 128.2 (Ph), 140.9 and 154.3 (C=O). Found, %: C 63.17, 63.07; H 8.33, 8.45; N 8.41, 8.54. $C_{17}H_{26}N_2O_4$. Calculated, %: C 63.33; H 8.13; N 8.69.

Diethyl acetylphosphite (Ia). A mixture of anhydrous sodium acetate (0.1 mol) and diethylchlorophosphite (0.1 mol) in 30 mL of absolute diethyl ether was stirred during 12 h under argon atmosphere. The precipitate was separated; the filtrate was evaporated in vacuum. The residue was distilled in vacuum [7]. Yield 67%, oil, bp 75°C (10 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (6H, $2CH_3$, *J* 7.3 Hz), 2.13 s (3H, CH_3), 4.03 m (4H, $2CH_2$). ^{31}P NMR spectrum ($CDCl_3$): δ_P 134.8 ppm.

Solid superacid TiO_2/SO_4. Tetraisopropoxytitanium (28.4 g, 0.1 mol) was added dropwise to 400 mL of an aqueous ammonia solution (pH 9). The precipitate was filtered off and dried at 120°C during 3 h. The resulting hydrated titanium dioxide (4 g) was thoroughly powdered and mixed with 100 mL of 1 mol/L solution of $(NH_4)_2SO_4$, and the mixture was stirred during 1 h at room temperature. The resulting precipitate TiO_2/SO_4 was dried during 3 h at 120°C and calcined at 600°C during 2 h immediately before use.

Solid superacid Al_2O_3/SO_4. A mixture of 50 mL of an aqueous 2 mol/L solution of H_2SO_4 and 4 g of Al_2O_3 was stirred during 1 h; then the catalyst was filtered off and dried at 100°C during 2 h. The catalyst was calcined at 600°C during 2 h before use.

Synthesis of α-(alkyloxycarbonylamino)benzylphosphonates (V). A mixture of 1.0 g of superacid (TiO_2/SO_4 or Al_2O_3/SO_4) and 0.8 mmol of *N*,*N*'-benzylidenebis(carbamate) **IV** in 7.5 mL of methylene chloride was stirred under dry argon during 10–15 min. Then, 0.8 mmol of diethyl acetylphosphite **I** was added to the reaction mixture under argon. The stirring was continued during further 1 h. The catalyst was filtered off, and the filtrate was evaporated in vacuum. The residue was treated with petroleum ether, and alkyl carbamate was filtered off. The mother liquor was washed with water; then the organic layer was separated, dried over sodium sulfate, and evaporated in vacuum. The residue was crystallized from a mixture of diethyl ether–hexane or from diethyl ether.

Diethyl α-(ethyloxycarbonylamino)benzylphosphonate (Va). Yield 63%, mp 82–85°C, R_f [$CHCl_3$–$(CH_3)_2CO$, 4 : 1] 0.6. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 t (3H, CH_3, $^3J_{HH}$ 7.1 Hz), 1.21 t (3H, CH_3, $^3J_{HH}$ 7.1 Hz), 1.33 t (3H, CH_3, $^3J_{HH}$ 7.1 Hz), 3.59 m (1H, CH_2OP), 3.83 m (1H, CH_2OP), 4.09 m (4H, CH_2OP, CH_2OC), 5.03 d.d (1H, PCHN, $^3J_{HH}$ 9.3, $^2J_{PH}$ 21.5 Hz), 6.70 br.s (1H, NH), 7.15–7.35 m (3H, Ph), 7.35–7.55 m (2H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.5, 16.1 d ($^3J_{PC}$ 5.5 Hz), 16.4 d ($^3J_{PC}$ 5.8 Hz), 52.3 d ($^1J_{PC}$ 154.1 Hz), 61.5, 63.0 d ($^2J_{PC}$ 7.3 Hz), 63.3 d ($^2J_{PC}$ 6.6 Hz), 127.7, 127.8, 128.1, 128.6, 135.4, 155.8 d ($^3J_{PC}$ 11.3 Hz). ^{31}P NMR spectrum ($CDCl_3$): δ_P 22.4 ppm. Found, %: C 53.11, 53.05; H 7.11, 7.18. $C_{14}H_{22}NO_5P$. Calculated, %: C 53.33; H 7.03.

Diethyl α-(*tert*-butyloxycarbonylamino)benzylphosphonate (Vb). Yield 37%, mp 102–104°C, R_f [$CHCl_3$–$(CH_3)_2CO$, 4 : 1] 0.7. ^{1}H NMR spectrum (CCl_4), δ, ppm: 1.10 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 1.28 t (3H, CH_3, $^3J_{HH}$ 7.0 Hz), 1.41 s (9H, $3CH_3$), 3.71 m (1H, CH_2OP), 3.91 m (1H, CH_2OP), 4.09 m (2H, CH_2OP), 5.10 d.d (1H, PCHN, $^3J_{HH}$ 9.3, $^2J_{PH}$ 22.5 Hz), 6.10 br.s (1H, NH), 7.20–7.50 m (5H, Ph). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 16.1 d ($^3J_{PC}$ 5.1 Hz), 16.3 d ($^3J_{PC}$ 5.1 Hz), 28.2, 51.7 d ($^1J_{PC}$ 153.3 Hz), 62.9 d ($^2J_{PC}$ 7.3 Hz), 63.1 d ($^2J_{PC}$ 6.6 Hz), 80.2, 127.8, 128.4, 128.9, 129.6, 135.4, 155.8 d ($^3J_{PC}$ 9.5 Hz). ^{31}P NMR spectrum (CCl_4): δ_P 23.1 ppm. Found, %: C 55.83, 55.68; H 7.90, 7.77. $C_{16}H_{26}NO_5P$. Calculated, %: C 55.97; H 7.63.

^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded using a Bruker DPX-200 Fourier spectrometer. Melting points were determined with a Boetius PHMK instrument or via open capillary method.

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