A new preparative method for the synthesis of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate *via* an imino phosphonate

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A preparative method for the synthesis of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate from trifluoroacetic anhydride and benzyl carbamate *via* diethyl 1-benzyloxycarbonylimino-2,2,2-trifluoroethylphosphonate is developed. Optimum conditions for the chlorination of benzyl *N*-trifluoroacetylcarbamate with $SOCl_2$—Py to afford the imidoyl chloride, phosphorylation of the latter under the conditions of the Arbuzov reaction, as well as diazotization of amino phosphonate with isopropyl nitrite are found.

Key words: trifluoromethylated imidoyl chloride, imino phosphonate, amino phosphonate and diazophosphonate, Arbuzov reaction.

Phosphorus-containing analogs of carboxylic acids are undoubtedly of interest for the medicinal chemistry.[1,2] At the same time, introduction of fluorine atoms or fluoroalkyl residues into the molecules of physiologically active compounds can significantly influence their biological properties.[3—5] Therefore, the development of universal building blocks for the synthesis of new fluorine-containing phosphonates is a topical task.

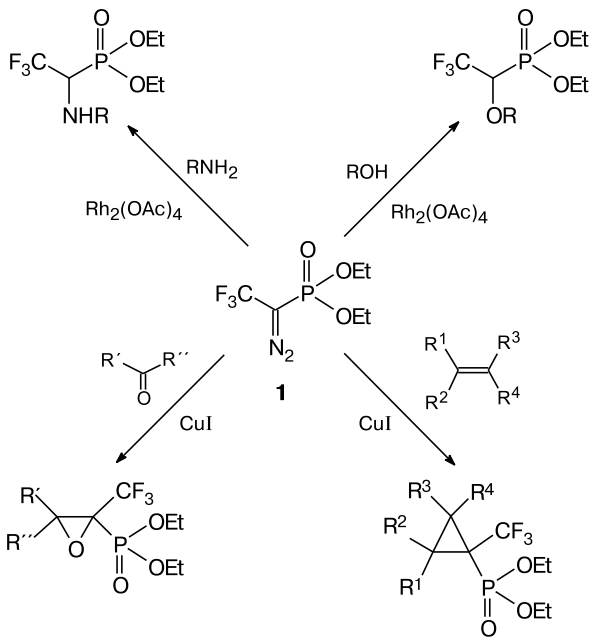
Earlier we have shown[6,7] that copper and rhodium salts catalyse the insertion of the carbene generated from diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (**1**) into NH and OH bonds and also cyclopropanation and epoxidation reactions giving the corresponding trifluoromethyl-containing phosphonates (Scheme 1).

The method of synthesis of diazocompound **1**, which we have preliminary published, is based on the use of trifluoroacetaldehyde diethyl acetal as the starting compound; it includes several steps requiring purification of products by column chromatography, that is why this method is difficult to scale up.[8,9]

The present work is devoted to the development of a more convenient alternative approach to the synthesis of diazophosphonate **1** from commercially available trifluoroacetic anhydride and benzyl carbamate (Scheme 2). It is worth noting that the method envisages the formation of an intermediate trifluoromethyl-containing imino phosphonate **4**, having independent interest as the fundamental synthon for the synthesis of phosphorus analogs of α-amino-α-trifluoromethyl acids.[10—12]

Though imino phosphonates of the similar type have been described earlier,[13,14] their synthetic potential as the universal precursors of the corresponding α-amino phosphonic acids has not been fully disclosed, probably, because of the low yields (less than 40%) and also because of the difficulty of the subsequent removal of protecting groups from the amino function. For the first time, we have obtained imino phosphonate with orthogonal benzyloxycarbonyl (Cbz) and ester protecting groups, which are the most often used in the chemistry of amino acids and peptides. Using the standard method,[15] we initially employed PCl_5 as the chlorinating agent for the synthesis

Scheme 1



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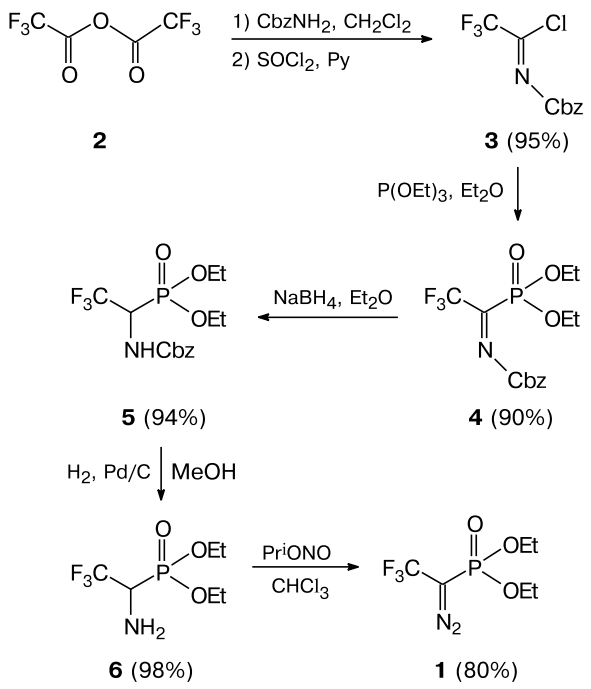
Scheme 2



of imidoyl chloride **3**. In this case, a number of admixtures is formed as the result of the Cbz-group destruction (benzyl chloride is identified in the reaction mixture), and this decreases the yield of **3** to 30—40%. Milder chlorinating agent (thionyl chloride in pyridine), which totally eliminates the destruction mentioned, has been found as the result of optimization. For example, chlorination carried out at room temperature with a molar ratio of reagents $CbzNHC(O)CF_3 : SOCl_2 : Py = 1 : 3 : 1.5$ occurs without formation of by-products and yields 95% of imidoyl chloride **3** after 24 h .

Reactions of N-acylated α-trifluoromethyl-imidoyl chlorides with trivalent phosphorus derivatives have been investigated earlier,[14] but their regularities are not well-studied, and this often leads to unpredictable results. The Arbuzov reaction leading to imino phosphonate is the main direction in the case of trialkyl phosphites.

It has been established that imidoyl chloride **3** reacts with triethyl phosphite even at room temperature leading along with the Arbuzov reaction product **4** to several by-products (^{19}F and ^{31}P NMR data), which could not be identified. We successed in minimizing the formation of by-products and preparing *N*-Cbz-imino phosphonate **4** in a yield of up to 90%. The best result was obtained when triethyl phosphite was slowly added to a concentrated ethereal solution of imidoyl chloride **3** at −10 °C with vigorous stirring of the reaction mixture: the reaction is fully completed in 2 h. It is interesting to note that because of the high electrophilicity of imidoyl chloride **3**, the Arbuzov reaction occurs even at lower temperatures though the reaction rate noticeably decreases.

The reduction of a double bond with sodium borohydride with the subsequent removal of the Cbz-protection by catalytic hydrogenolysis leads to α-amino phosphonate **6** in almost quantitative yield. During preparation of the present work, an article[16] devoted to the alternative two-step method for the synthesis of amino phosphonate **6** based on the reaction of trifluoroacetonitrile with diethyl phosphite in the presence of pyridine followed by reduction of a nonsubstituted intermediate imine with a $BH_3 \cdot SMe_2$ complex has been published. From our point of view, the necessity of a special equipment (autoclave) when working with gaseous trifluoroacetonitrile is an essential disadvantage of this method.

Diazotization of α-amino phosphonate **6** was carried out using the method which has previously been developed,[6] *viz.*, the addition of an equimolar amount of isopropyl nitrite to a solution of **6** in ether at room temperature. After addition of approximately half of isopropyl nitrite, the exothermic reaction started; the remaning nitrite was added at a rate providing mild boiling of the reaction mixture. As the result, the target diazo compound **1** was obtained after vacuum distillation in 80% yield.

In conclusion, it is worth noting that we have developed a new convenient approach to the synthesis of diethyl 1-diazo-2,2,2-trifluoroethylphosphonate — the universal synthon for the simultaneuos introduction of trifluoromethyl and phosphoryl groups into bioactive molecules. High yields of the intermediate products in the developed synthetic sequence excluding the use of chromatographic purification allow large-scale preparation of the final diazo compound.

Experimental

NMR spectra were recorded using a Bruker AV-300 spectrometer at 300 MHz for ^1H, 282 MHz for ^{19}F (CF_3CO_2H) and 121.5 MHz for ^{31}H (H_3PO_4), respectively. All solvents used for the reaction were dried by standard methods. Monitoring of the reactions was carried out using TLC on plates with silica gel Merck 60 F_{254}

1-Benzyloxycarbonylimino-2,2,2-trifluoroacetimidoyl chloride (3). $SOCl_2$ (35.7 g, 0.3 mol) was added dropwise to a mixture of benzyl *N*-trifluoroacetylcarbamate (24.7 g, 0.1 mol) and anhydrous pyridine (11.8 g, 0.15 mol) with intensive stirring at 0 °C. After 24 h at 20 °C, the reaction mixture was concentrated *in vacuo*, the product was extracted with anhydrous ether (5×50 mL), ether was evaporated, the residue was distilled. Imidoyl chloride **3** (25.2 g, 95%) was obtained, b.p. 73—74 °C (0.8 Torr). ^1H NMR spectrum ($CDCl_3$): δ 5.43 (s, 2 H, OCH_2); 7.49 (br.s, 5 H, Ph). ^{19}F NMR spectrum ($CDCl_3$): δ 5.21 (s, CF_3).

Diethyl 1-benzyloxycarbonylimino-2,2,2-trifluoroethylphosphonate (4). A solution of triethyl phosphite (9.9 g, 60 mmol) in anhydrous ether (30 mL) was added dropwise for 2 h to a solution of imidoyl chloride **3** (15.9 g, 60 mmol) in anhydrous ether

(30 mL) with vigorous stirring at −10°C . The reaction mixture was stirred at −10 °C for 1 h, and kept at +5 °C for 24 h. Ether was evaporated, the residue was fractionated. Imino phosphonate **4** (19.8 g, 90%) was obtained, b.p. 141 °C (1 Torr). ^{1}H NMR spectrum ($CDCl_3$, δ): 1.37 (t, 6 H, 2 CH_3, $^3J_{H,H}$ = 7.0 Hz); 4.19—4.30 (m, 4 H, 2 OCH_2); 5.37 (s, 2 H, OCH_2); 7.40—7.46 (m, 5 H, Ph). ^{19}F NMR spectrum ($CDCl_3$): δ 8.15 (s, CF_3). ^{31}P NMR spectrum ($CDCl_3$): δ −4.56.

Diethyl 1-benzyloxycarbonylamino-2,2,2-trifluoroethylphosphonate (5). A mixture of imino phosphonate **4** (18.3 g, 50 mmol) and sodium borohydride (2.8 g, 75 mmol) in anhydrous ether was refluxed with stirring in an argon atmosphere for 1.5 h, then cooled to 0°C and 1 *M* HCl (50 mL) was added portionwise. The layers were separated, the aqueous phase was extracted with ether (3 × 30 mL), the combined ethereal extracts were dried with magnesium sulphate. Amino phosphonate **5** (17.3 g, 94%) was obtained after filtration and concentration in the form of low-melting crystals, m.p. 53—55 °C. ^{1}H NMR spectrum ($CDCl_3$, δ): 1.27—1.37 (m, 6 H, 2 CH_3); 4.11—4.20 (m, 4 H, 2 OCH_2); 4.69—4.82 (m, 1 H, CH); 5.19 (d, 1 H, OCH_2, $^2J_{AB}$ = 12.3 Hz); 5.21 (d, 1 H, OCH_2, $^2J_{AB}$ = 12.3 Hz); 6.39 (br.s, 1 H, NH); 7.36 (br.s, 5 H, Ph). ^{19}F NMR spectrum ($CDCl_3$, δ): 8.21 (d, CF_3, $^3J_{F,P}$ = 6.9 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ): 13.03 (q, $^3J_{P,F}$ = 6.9 Hz).

Diethyl 1-amino-2,2,2-trifluoroethylphosphonate (6) was obtained from compound **5** in quantitative yield by catalytic hydrogenolysis with hydrogen in the presence of 10% Pd/C (5 mol%) at atmosphere pressure at 20°C in methanol for 2 h. Physicochemical characteristics of compound **6** corresponded to those described in literature.[17] ^{1}H NMR spectrum ($CDCl_3$, δ, *J*/Hz): 1.35 (t, 6 H, 2 CH_3, $^3J_{H,H}$ = 7.0 Hz); 2.75 (br.s, 2 H, NH_2), 3.57—3.67 (m, 1 H, CH); 4.23—4.28 (m, 4 H, 2 OCH_2). ^{19}F NMR spectrum ($CDCl_3$, δ, *J*/Hz): 6.19 (d, CF_3, $^3J_{F,P}$ = 7.1 Hz). ^{31}P NMR spectrum ($CDCl_3$, δ, *J*/Hz): 16.43 (q, $^3J_{P,F}$ = 7.1 Hz).

Diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (1) was synthesized from compound **6** using the known procedure.[6] Freshly obtained isopropyl nitrite (9.5 g, 0.106 mol) was added to a solution of amino phosphonate **6** (19.6 g, 0.083 mol) in chloroform (300 mL) with vigorous stirring. As the reaction is exothermic, the addition was carried out so that uniform boiling of the reaction mixture was provided. The reaction mixture was stirred for 40 min, after this time the temperature of the reaction mixture decreased to room temperature. The solvent was removed *in vacuo*, the residue was distilled. Diazo compound **1** (16.4 g, 80%) was obtained as light-yellow liquid, b.p. 47—50 °C (1 Torr). IR-spectrum (KBr), ν/cm^{-1}: 2160 (C=N_2); 1150 (P=O). ^{1}H NMR spectrum ($CDCl_3$, δ): 1.40 (t, 6 H, CH_3, $^3J_{H,H}$ = 7.1 Hz), 4.21—4.27 (m, 4 H, OCH_2). ^{19}F NMR spectrum ($CDCl_3$): δ 23.00 (s, CF_3). ^{31}P NMR spectrum ($CDCl_3$): δ 9.23 (s, 1 P). ^{13}C NMR spectrum ($CDCl_3$, δ, *J*/Hz): 15.90 ($\underline{C}H_3$—CH_2), 63.6 ($\underline{C}H_2$—CH_3), 118.60 (m, C—$\underline{C}$—CF_3), 124.10 (d.q, $^1J_{C,F}$ = = 271.0 Hz, $^1J_{C,P}$ = 12.1 Hz).

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