Alkyl 2-chloro-3,3,3-trifluoro-2-isocyanatopropionates

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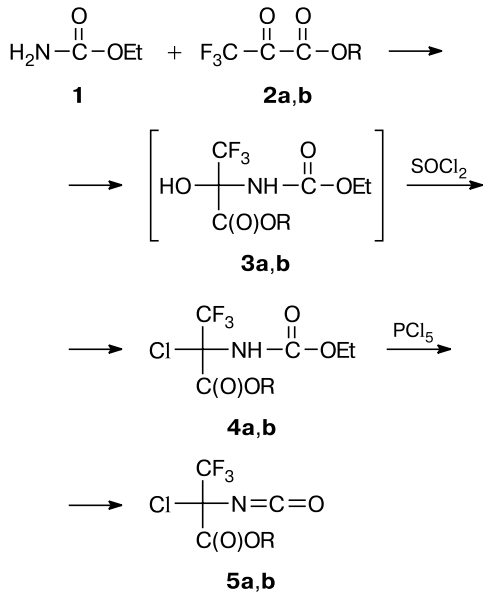
Earlier unknown representatives of fluorine-containing α-chloroalkylisocyanates, *viz.*, esters of 2-chloro-3,3,3-trifluoro-2-isocyanatopropionic acid, were obtained. Synthetic potentialities of these compounds in the preparation of 2-substituted derivatives of 3,3,3-trifluoroalanine were demonstrated.

Key words: trifluoropyruvates, carbamates, isocyanates, amino acids, aminals, alcohols, anilines, phosphorus pentachloride, organofluorine compounds.

Fluorine-containing α-chloroalkylisocyanates are important subjects of organic chemistry.[1] These compounds can be considered as the synthetic blocks for the introduction of fluorine-containing carbamine groups into the molecules of acyclic and heterocyclic substances,[2,3] in addition, they are of interest as the precursors of various fluorine-containing azomethines.[4] The present work is aimed at the synthesis of new representatives of fluorine-containing α-chloroalkylisocyanates, *viz.*, esters of 2-chloro-3,3,3-trifluoro-2-isocyanatopropionic acid (Scheme 1). These compounds have a specific feature consisting in the simultaneous presence in their molecules at the quaternary carbon atom of three fragments, interesting from the synthetic point of view: the labile chlorine atom, isocyanate and alkoxycarbonyl groups, the potential electrophilic reaction centers. The presence in the molecules **5a**,**b** of pharmacophoric trifluoroalanine fragment, which in a number of cases defines the high bacteriostatic activity of related compounds,[5] is appreciated from the quest for new potentially biologically active substances.

Scheme 1



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

A synthetic protocol for the preparation of compounds **5a**,**b** (see Scheme 1) consists in the chlorination of hemiaminals **3a**,**b**, which are obtained by the reaction of urethane **1** with esters of trifluoropyruvic acid **2a**,**b** upon treatment with $SOCl_2$. The subsequent dealkoxylation of the intermediate compounds **4a**,**b** upon reflux with PCl_5 in $POCl_3$ gives isocyanates **5a**,**b** in 62 and 69% yield, respectively.

Isocyanates **5a**,**b** are colorless mobile liquids with high boiling points, their composition and structures were confirmed by elemental analysis and ^1H and ^{19}F NMR spectroscopy data, as well as by chemical transformations in the reactions with nucleophilic reagents. Such reactions enable one to realize synthetic potentialities of these new bielectrophilic reagents, in particular, in the synthesis of various 2-substituted derivatives of 3,3,3-trifluoroalanine.

Isocyanates **5a**,**b** exothermically react with isopropanol (Scheme 2), leading to the corresponding carbamates **6a**,**b** in 81 and 78% yield. Their subsequent treatment with two equivalents of primary amines results in the substitution of the chlorine atom by the amino function to form aminals **7a**—**d** in 76—86% yield.

Compounds **7a**—**d** are solid crystalline substances. Their composition and structures were confirmed by elemental analysis and ^1H and ^{19}F NMR spectroscopy data. ^{19}F NMR spectra contain a characteristic singlet in the region δ 1—2.

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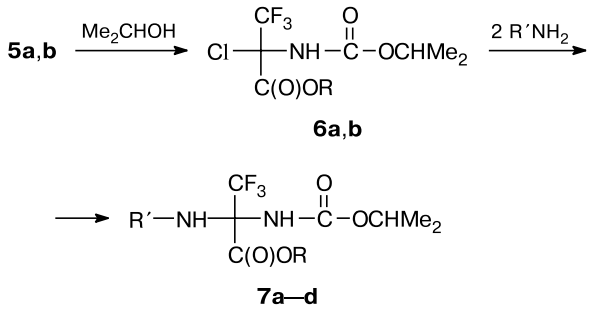
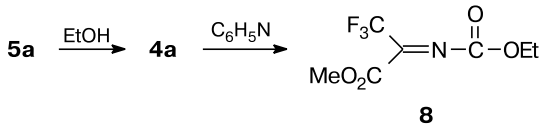
Scheme 2



6: R = Me (**a**), Et (**b**)
7: R = Me, R′ = 5-chloropyridin-2-yl (**a**); R = Et, R′ = 3-MeC_6H_4 (**b**); R = Et, R′ = 4-MeC_6H_4 (**c**); R = Et, R′ = 3-$F_3CC_6H_4$ (**d**)

Isocyanates **5** can be successfully used for the synthesis of *N*-alkoxycarbonylimines of trifluoropyruvic acid esters. The sequential treatment of compound **5a** with ethanol and pyridine in benzene affords *N*-ethoxycarbonylimine **8** in 81% yield (Scheme 3).

Scheme 3



In conclusion, polyfunctional α-chloro-substituted isocyanates, *viz.*, 2-chloro-3,3,3-trifluoro-2-isocyanatopropionic acid esters, synthesized by us for the first time, are prospective synthons for the synthesis of 2-substituted 3,3,3-trifluoroalanine derivatives, as well as *N*-alkoxycarbonylimines of trifluoropyruvic acid esters, potential 1,2-bielectrophiles in the cyclocondensation reaction.[6]

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in a glass capillary tube. The starting compounds, urethane **1**, trifluoropyruvates **2a**,**b**, anilines, and 2-amino-5-chloropyridine (Aldrich) were used as purchased.

Methyl 2-chloro-2-(*N*-ethoxycarbonylamino)-3,3,3-trifluoropropionate (4a). Methyl trifluoropyruvate **2a** (15.6 g, 0.1 mol) was added to urethane **1** (8.9 g, 0.1 mol). After the exothermic reaction was over, $SOCl_2$ (11.9 g, 0.1 mol) was added to this. The reaction mixture was heated for 2 h at 80 °C, after which it was subjected to the fractional distillation to obtain 22.8 g (84%) of compound **4a**, b.p. 80—82 °C (2 Torr). Found (%): C, 31.75; H, 3.29; N, 5.48. $C_7H_9ClF_3NO_4$. Calculated (%): C, 31.90; H, 3.44; N, 5.31. ^1H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.2 Hz); 3.94 (s, 3 H, MeO); 4.12 (m, 2 H, $CH_3C\underline{H}_2O$); 6.44 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 1.48 (s, CF_3).

Ethyl 2-chloro-2-(*N*-ethoxycarbonylamino)-3,3,3-trifluoropropionate (4b) was obtained similarly to ester **4a**. The yield was 87%, b.p. 83—85 °C (2 Torr). Found (%): C, 34.45; H, 3.82; N, 5.18. $C_8H_{11}ClF_3NO_4$. Calculated (%): C, 34.61; H, 3.99; N, 5.05. ^1H NMR ($CDCl_3$), δ: 1.20 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.2 Hz); 1.26 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.4 Hz); 4.10, 4.30 (both m, 2 H each, $CH_3C\underline{H}_2O$); 6.38 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 1.43 (s, CF_3).

Methyl 2-chloro-3,3,3-trifluoro-2-isocyanatopropionate (5a). A mixture of compound **4a** (13.2 g, 0.05 mol) and PCl_5 (10.4 g, 0.05 mol) in $POCl_3$ (30 mL) was refluxed for 2 h. Then, $POCl_3$ was evaporated and the residue was fractionally distilled *in vacuo* to obtain 7.5 g (69%) of isocyanate **5a**, b.p. 30—32 °C (18 Torr). Found (%): C, 27.49; H, 1.22; N, 6.27. $C_5H_3ClF_3NO_3$. Calculated (%): C, 27.61; H, 1.39; N, 6.44. ^1H NMR ($CDCl_3$), δ: 3.94 (s, MeO). ^{19}F NMR ($CDCl_3$), δ: 0.07 (s, CF_3).

Ethyl 2-chloro-3,3,3-trifluoro-2-isocyanatopropionate (5b) was obtained similarly to ester **5a**. The yield was 62%, b.p. 35—36 °C (15 Torr). Found (%): C, 31.28; H, 2.33; N, 6.23. $C_6H_5ClF_3NO_3$. Calculated (%): C, 31.12; H, 2.18; N, 6.05. ^1H NMR ($CDCl_3$), δ: 1.20 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.4 Hz); 4.28 (m, 2 H, $CH_3C\underline{H}_2O$). ^{19}F NMR ($CDCl_3$), δ: 0.03 (s, CF_3).

Methyl 2-chloro-3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)propionate (6a). Isopropanol (1.2 g, 0.02 mol) was added to a solution of isocyanate **5a** (4.4 g, 0.02 mol) in benzene (20 mL). The reaction mixture was stirred for 2 h, benzene was evaporated, and the residue was fractionally distilled *in vacuo* to obtain 4.5 g (81%) of product **6a**, b.p. 74—75 °C (1 Torr). Found (%): C, 34.45; H, 3.82; N, 5.18. $C_8H_{11}ClF_3NO_4$. Calculated (%): C, 34.61; H, 3.99; N, 5.05. ^1H NMR ($CDCl_3$), δ: 1.28 (d, 6 H, Me, J = 7.1 Hz); 3.93 (s, 3 H, MeO); 4.97 (m, 1 H, CHO); 6.05 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 0.86 (s, CF_3).

Ethyl 2-chloro-3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)propionate (6b) was obtained similarly to ester **6a**. The yield was 78%, b.p. 78—80 °C (1 Torr). Found (%): C, 37.21; H, 4.62; N, 4.65. $C_9H_{13}ClF_3NO_4$. Calculated (%): C, 37.06; H, 4.49; N, 4.80. ^1H NMR ($CDCl_3$), δ: 1.28 (d, 6 H, Me, J = 7.1 Hz); 1.38 (t, 3 H, $C\underline{H}_3CH_2O$, J = 8.6 Hz); 4.41 (m, 2 H, $CH_3C\underline{H}_2O$); 4.97 (m, 1 H, CHO); 6.05 (s, 1 H, NH). ^{19}F NMR ($CDCl_3$), δ: 0.92 (s, CF_3).

Methyl 2-(5-chloropyridin-2-yl)amino-3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)propionate (7a). 2-Amino-5-chloropyridine (1.28 g, 0.01 mol) was added to a stirred solution of compound **6a** (1.40 g, 0.005 mol) in THF (20 mL). The reaction mixture was stirred for 1 h, 2-amino-5-chloropyridine hydrochloride was filtered off, the filtrate was concentrated, and the residue was recrystallized from hexane to obtain 1.4 g (81%) of compound **7a**, m.p. 111—113 °C. Found (%): C, 42.38; H, 4.25; N, 11.12. $C_{13}H_{15}ClF_3N_3O_4$. Calculated (%): C, 42.23; H, 4.09; N, 11.37. ^1H NMR (DMSO-d_6), δ: 1.09, 1.18 (both d, 3 H each, Me, J = 6.3 Hz); 3.79 (s, 3 H, OMe); 4.71 (m, 1 H, CH); 6.94 (m, 2 H, CH_{Ar} + NH); 7.43 (dd, 1 H, CH_{Ar}, J = 9.3 Hz, J = 3.0 Hz); 7.92 (m, 2 H, CH_{Ar} + NH). ^{19}F NMR (DMSO-d_6), δ: 1.98 (s, CF_3).

Ethyl 3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)-2-(3-methylphenylamino)propionate (7b) was obtained similarly to compound **7a**. The yield was 79%, m.p. 98—99 °C. Found (%): C, 52.21; H, 5.68; N, 7.92. $C_{16}H_{21}F_3N_2O_4$. Calculated (%): C, 52.04; H, 5.84; N, 7.73. ^1H NMR (DMSO-d_6), δ: 0.92, 1.09

(both d, 3 H each, Me, J = 7.1 Hz); 1.31 (t, 3 H, $C\underline{H}_3CH_2O$, J = 8.6 Hz); 2.22 (s, 3 H, Me_{Ar}); 4.38 (m, 2 H, $CH_3C\underline{H}_2O$); 4.72 (m, 1 H, CHO); 7.07 (t, 1 H, CH_{Ar}, J = 6.3 Hz); 6.62—6.82 (m, 5 H, CH_{Ar} + 2 NH). ^{19}F NMR (DMSO-d_6), δ: 1.97 (s, CF_3).

Ethyl 3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)-2-(4-methylphenylamino)propionate (7c) was obtained similarly to compound **7a**. The yield was 82%, m.p. 79—80 °C. Found (%): C, 52.17; H, 5.69; N, 7.61. $C_{16}H_{21}F_3N_2O_4$. Calculated (%): C, 52.04; H, 5.84; N, 7.73. ^{1}H NMR (DMSO-d_6), δ: 0.91, 1.06 (both d, 3 H each, Me, J = 6.4 Hz); 1.31 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.1 Hz); 2.18 (s, 3 H, Me_{Ar}); 4.32 (m, 2 H, $CH_3C\underline{H}_2O$); 4.61 (m, 1 H, CHO); 6.86, 6.98 (both d, 2 H, CH_{Ar}, J = 8.3 Hz); 7.22, 7.92 (both s, 1 H each, NH). ^{19}F NMR (DMSO-d_6), δ: 1.91 (s, CF_3).

Ethyl 3,3,3-trifluoro-2-(*N*-isopropoxycarbonylamino)-2-(3-trifluoromethylphenylamino)propionate (7d) was obtained similarly to compound **7a**. The yield was 86%, m.p. 75—77 °C. Found (%): C, 46.32; H, 4.11; N, 6.88. $C_{16}H_{18}F_6N_2O_4$. Calculated (%): C, 46.16; H, 4.36; N, 6.73. ^{1}H NMR (DMSO-d_6), δ: 0.93, 1.08 (both d, 3 H each, Me, J = 6.5 Hz); 1.26 (t, 3 H, $C\underline{H}_3CH_2O$, J = 8.8 Hz); 4.37 (m, 2 H, $CH_3C\underline{H}_2O$); 4.64 (m, 1 H, CHO); 5.99 (s, 1 H, CH_{Ar}); 7.18 (m, 3 H, CH_{Ar} + NH); 7.34 (m, 2 H, CH_{Ar} + NH). ^{19}F NMR (DMSO-d_6), δ: 1.95, 15.6 (both s, 3 F each, CF_3).

Methyl 2-(*N*-ethoxycarbonylimino)-3,3,3-trifluoropropionate (8). Ethanol (3.0 g, 0.05 mol) was added to a stirred solution of isocyanate **5a** (10.9 g, 0.05 mol) in benzene (20 mL) at 20 °C, after 30 min, pyridine (3.6 g, 0.05 mol) was added, too. The reaction mixture was stirred for 2 h and filtered, the filtrate was concentrated, and the residue was distilled to obtain 9.2 g (81%) of imine **8**, b.p. 52—53 °C (3 Torr). Found (%): C, 37.21; H, 3.72; N, 6.33. $C_7H_8F_3NO_4$. Calculated (%): C, 37.02; H, 3.55; N, 6.17. ^{1}H NMR ($CDCl_3$), δ: 1.31 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.4 Hz); 4.05 (s, 3 H, MeO); 4.18 (m, 2 H, $CH_3C\underline{H}_2O$). ^{19}F NMR ($CDCl_3$), δ: 7.28 (s, CF_3).

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