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Esters of 2-Aryl-2-isocyanato-3,3,3-trifluoropropionic Acid in Cyclocondensation with Amines

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Abstract—The hitherto unknown representatives of fluorinated isocyanates, esters of 2-aryl-2-isocyanato-3,3,3-trifluoropropionic acid, were prepared. The synthetic potential of these compounds for preparation of trifluoromethylated hydantoins by the reactions of cyclocondensation with primary amines was demonstrated.

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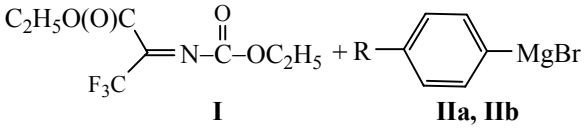
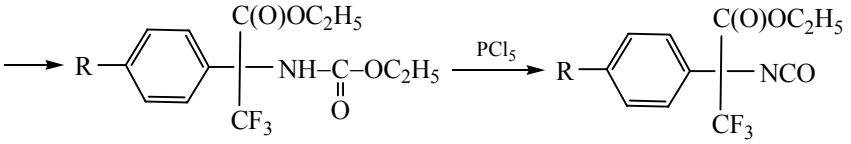
The derivatives of esters of trifluoropyruvic acid, like *N*-substituted imines of trifluoropyruvates, are successfully used in the synthesis of fluorinated heterocyclic compounds [1–5]. The most promising in this respect is the use of these reagents as 1,3-bielectrophiles in the reactions of cyclocondensation [6–10]. The goal of the present study is the synthesis of new bielectrophiles based on ethyl fluoropyruvate, that is, the esters of 2-aryl-2-isocyanato-3,3,3-trifluoropropionic acid, and investigation of their behavior in the reactions of cyclocondensation.

The procedure of preparation of ethyl esters of 2-aryl-2-isocyanato-3,3,3-trifluoropropionic acid (**IVa, IVb**) includes the arylation of ethoxycarbonylimine of ethyltrifluoropyruvate (**I**) with arylmagnesium bromides **IIa, IIb** to carbamates **IIIa, IIIb**, whose subsequent dealkoxylation with phosphorus pentachloride results in isocyanates **IVa, IVb**.

Ethoxycarbonylimine **I** reacts exothermally with arylmagnesium bromides with the formation of the corresponding carbamates **IIa, IIb** isolated in 74 and 68% yield, respectively. The composition and the structure of compounds **IIIa, IIIb** were proved by the data of elemental analysis and ^{1}H and ^{19}F NMR spectroscopy. The characteristic signal in the ^{19}F NMR spectra is the singlet at 6.4–6.7 ppm, and in the ^{1}H NMR spectra, the singlet of the NH proton at 6 ppm. The subsequent dealkoxylation of carbamates **IIIa, IIIb** upon reflux with PCl_5 in the $POCl_3$ solution for 2–3 h gives rise to isocyanates **IVa, IVb** in 68–71% yield.



I **IIa, IIb**

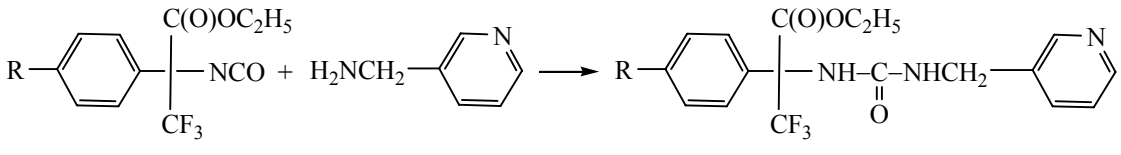


IIIa, IIIb **IVa, IVb**

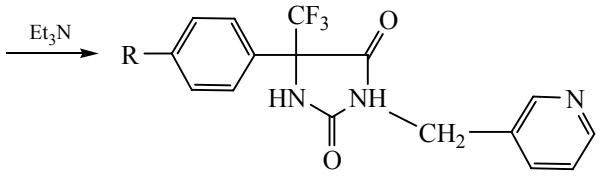
II, III, IV: R = H (**a**), F (**b**).

Isocyanates **IVa, IVb** are colorless mobile high-boiling liquids prepared in 58 and 62% yield, respectively, their composition and structure are proved by the data of elemental analysis and the ^{1}H and ^{19}F NMR spectroscopy. The characteristic signal in the ^{19}F NMR spectra is the singlet at 4 ppm.

The presence in the molecules of isocyanates **IVa, IVb** of two functional groups, isocyanate and alkoxycarbonyl, allows regarding these compounds as 1,4-bielectrophilic reagents in the reactions of cyclocondensation with binucleophiles proceeding via the mechanism of addition of the binucleophile followed by heterocyclization. Indeed, isocyanates **IVa, IVb** react exothermally with amines to form ureas; the subsequent heating of the latter in the presence of catalytic amounts of Et_3N results in the corresponding imidazolidine-2,4-diones **VIIa–VIIe**. In the case of the reaction of isocyanate **IVa** with 3-aminomethylpyridine, urea **VI** was isolated as an individual compound and characterized; after heating in DMF in the presence of catalytic amounts of Et_3N it was converted into imidazolidine-2,4-dione **VIIa**.

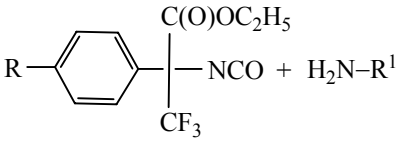


IVa **Va** **VI**

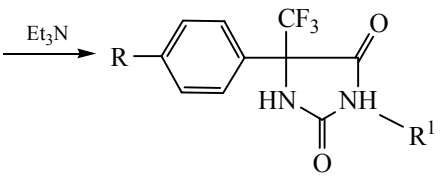


VIIa

Imidazolidine-2,4-diones **VIIa–VIIe** are prepared in 68–78% yield without isolation of the intermediate adducts (ureas) by heating the equimolar amounts of the reagents in DMF in the presence of catalytic amounts of Et_3N.



IVa, IVb **Va–Ve**



VIIa–VIIe

IV: R = H (**a**), F (**b**); **VII**: R^1 = (pyridin-3-yl)methyl (**a**), 5-methylpyridi-2-yl (**b**), pyridin-2-yl (**c**), 2-(4-methoxyphenyl)ethyl (**d**), (furan-2-yl)methyl (**e**).

Compounds **VIIa–VIIe** are crystalline substances, their composition and structure were proved by the data of elemental analysis and the ^{1}H and ^{19}F NMR spectroscopy. The characteristic signal in the ^{19}F NMR spectra is the singlet of the trifluoromethyl group at 2–3 ppm, and in the ^{1}H NMR spectra, the singlet of the NH proton at 10–11 ppm.

Therefore, we have synthesized the hitherto unknown representatives of fluorinated isocyanates: esters of 2-aryl-2-isocyanato-3,3,3-trifluoropropionic acid, which are promising synthons for preparation of various fluorinated hydantoins by the reaction of cyclocondensation.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13 and 188.29 MHz in $CDCl_3$ relative to tetramethylsilane (internal reference) and CF_3COOH (external reference) respectively. Melting points were determined in a glass capillary. The starting ethoxycarbonylimine of ethyltrifluoropyruvate **I** was synthesized by the procedure

[11], amines **VIIa–VIIe** (Aldrich) were used without additional purification.

Ethyl 3,3,3-trifluoromethyl-2-phenyl-2-ethoxycarbonylaminopropionate (IIIa). To the solution of 0.1 mol of compound **I** in 100 ml of tetrahydrofuran at 0°C while stirring 0.1 mol of compound **IIa** in 100 ml of tetrahydrofuran was added. The reaction mixture was stirred for 1 h, 200 ml of water was added, the organic layer was separated, dried over Na_2SO_4, and evaporated, the residue was crystallized from hexane. Yield 31.9 g (74%), mp 65–67°C. ^{1}H NMR spectrum, δ, ppm: 1.18–1.41 m (6H, Me); 4.17 q (2H, CH_2O, *J* 7.1 Hz); 4.39 q (2H, CH_2O, *J* 7.3 Hz); 5.96 s (1H, NH); 7.42–7.60 m (5H, Ph). ^{19}F NMR spectrum, δ, ppm: 6.74 s. Found, %: C 52.44; H 5.26; N 4.55. $C_{14}H_{16}F_3NO_4$. Calculated, %: C 52.67; H 5.05; N 4.39.

Ethyl 3,3,3-trifluoromethyl-2-(4-fluoro-phenyl)-2-ethoxycarbonylaminopropionate (IIIb) was prepared similarly to **IIIa**. Yield 68 %, mp 57–59°C. ^{1}H NMR spectrum, δ, ppm: 1.16 t (3H, Me, *J* 7.2 Hz); 1.45 t (3H, Me, *J* 7.3 Hz); 4.25 q (2H, CH_2O, *J* 7.1 Hz); 4.44 q (2H, CH_2O, *J* 7.3 Hz); 6.09 s (1H, NH); 7.46 d (2H, CH_{Ar}); 7.78 m (2H, CH_{Ar}). ^{19}F NMR spectrum, δ, ppm: 6.49 s (3F, CF_3); –42.70 m (1F, CF_{Ar}). Found, %: C 50.11; H 4.59; N 4.02. $C_{14}H_{15}F_4NO_4$. Calculated, %: C 49.86; H 4.48; N 4.15.

Ethyl 3,3,3-trifluoro-2-isocyanato-2-phenylpropionate (IVa). The mixture of 0.05 mol of compound **IIIa** and 0.05 mol of PCl_5 in 30 ml of $POCl_3$ was refluxed for 2 h, $POCl_3$ was removed, the residue was distilled. Yield 8.1 g (59 %), bp 106–108°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, Me, *J* 7.1 Hz); 4.13 q (2H, CH_2O, *J* 7.2 Hz); 7.32–7.53 m (5H, CH_{Ar}). ^{19}F NMR spectrum, δ, ppm: 4.21 s. Found, %: C 52.55; H 3.91; N 5.30. $C_{12}H_{10}F_3NO_3$. Calculated, %: C 52.75; H 3.69; N 5.13.

Ethyl 3,3,3-trifluoro-2-isocyanato-2-(4-fluoro-phenyl)propionate (IVb) was prepared similarly to **IVa**. Yield 62%, bp 100–102°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, Me, *J* 7.2 Hz); 4.23 q (2H, CH_2O, *J* 7.3 Hz); 7.52 d (2H, CH_{Ar}); 7.61 m (2H, CH_{Ar}). ^{19}F NMR spectrum, δ, ppm: 4.11 s (3F, CF_3); –42.12 m (1F, CF_{Ar}). Found, %: C 49.68; H 3.33; N 4.63. $C_{12}H_9F_4NO_3$. Calculated, %: C 49.50; H 3.12; N 4.81.

Ethyl 3,3,3-trifluoromethyl-2-phenyl-2-(3-pyridin-3-ylmethylureido)propionate (VI). To the solution of 0.01 mol of compound **IVa** in 20 ml of DMF at 20°C while stirring 0.01 mol of compound **Va** was added. The reaction mixture was stirred for 1 h, 50 ml of water was added, the precipitate formed was crystallized from hexane. Yield 3.1 g (81%), mp 148–150°C. ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, Me, *J* 7.4 Hz); 4.13 q (2H, CH_2O, *J* 7.4 Hz); 4.34 m (2H, CH_2N); 6.91 t (1H, NH, *J* 6.1 Hz); 7.29–7.56 m (7H, CH_{Ar} + NH); 7.75 d (1H, CH_{Ar}, *J* 9.1 Hz); 8.48 d (2H, CH_{Ar}, *J* 9.3 Hz). ^{19}F NMR spectrum, δ, ppm: 5.26 s. Found, %: C 56.50; H 4.94; N 11.21. $C_{18}H_{18}F_3N_3O_3$. Calculated, %: C 56.69; H 4.76; N 11.02.

5-Trifluoromethyl-3-(pyridin-3-yl)methyl-5-phenylimidazolidine-2,4-dione (VIIa). *a*. To the solution of 0.005 mol of compound **VI** in 10 ml of DMF 0.1 g of Et_3N was added. The reaction mixture was heated for 1 h at 80°C, 50 ml of water was added, the precipitate formed was crystallized from hexane. Yield 1.2 g (72%), mp 147-149°C. ^{1}H NMR spectrum, δ, ppm: 4.64 s (2H, CH_2N); 7.27 m (1H, CH_{Ar}); 7.42 m (3H, CH_{Ar}); 7.61 d (1H, CH_{Ar}, *J* 8.6 Hz); 7.80 m (2H, CH_{Ar}); 8.47 m (2H, CH_{Ar}); 10.28 s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 2.58 s. Found, %: C 57.11; H 3.83; N 12.34. $C_{16}H_{12}F_3N_3O_2$. Calculated, %: C 57.32; H 3.61; N 12.53.

b. To the solution of 0.005 mol of compound **IVa** in 10 ml of DMF 0.005 mol of compound **Va** was added at 20°C while stirring. The reaction mixture was stirred for 1 h, 50 ml of water was added, the precipitate formed was crystallized from hexane. Yield 1.3 g (78%).

3-(5-Methylpyridin-2-yl)-5-trifluoromethyl-5-phenylimidazolidine-2,4-dione (VIIb) was prepared similarly to **VIIa** (method *b*). Yield 73%, mp 150–152°C. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, Me); 7.20 d (1H, CH_{Ar}, *J* 8.5 Hz); 7.44 m (3H, CH_{Ar}); 7.59 d.d (1H, CH_{Ar}, J_1 1 8.5 Hz, J_2 2 2.8 Hz); 7.87 m (2H, CH_{Ar}); 8.36 d (1H, CH_{Ar}, *J* 2.7 Hz); 10.40 s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 2.44 c. Found, %: C 57.14; H 3.83; N 12.32. $C_{16}H_{12}F_3N_3O_2$. Calculated, %: C 57.32; H 3.61; N 12.53.

3-Pyridin-2-yl-5-trifluoromethyl-5-(4-fluoro-phenyl)imidazolidine-2,4-dione (VIIc) was prepared similarly to **VIIa** (method *b*). Yield 70%, mp 182–184°C. ^{1}H NMR spectrum, δ, ppm: 7.23 t (2H CH_{Ar}, *J* 8.2 Hz); 7.48 m (1H, CH_{Ar}); 7.82 m (1H, CH_{Ar}); 7.95 m (2H, CH_{Ar}); 8.58 d.d (1H, CH_{Ar}, J_1 5.3 Hz, J_2 2.0 Hz); 8.63 d (1H, CH_{Ar}, *J* 2.0 Hz); 10.66 s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 2.69 s (3F, CF_3); –42.12 m (1F, CF_{Ar}). Found, %: C 53.33; H 2.45; N 12.21. $C_{15}H_9F_4N_3O_2$. Calculated, %: C 53.11; H 2.67; N 12.39.

3-[2-(4-Methoxyphenyl)ethyl]-5-trifluoromethyl-5-(4-fluorophenyl)imidazolidine-2,4-dione (VIId) was prepared similarly to **VIIa** (method *b*). Yield 68%, mp 143–145°C. ^{1}H NMR spectrum, δ, ppm: 2.81 and 3.65 t (2H, CH_2, *J* 7.0 Hz); 3.78 s (3H, MeO); 6.62 and 6.97 d (2H, CH_{Ar}, *J* 8.4 Hz); 7.15 d (2H, CH_{Ar}, *J* 8.8 Hz); 7.77 m (2H, CH_{Ar}); 10.05 s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 2.78 s (3F, CF_3); –42.12 m (1F, CF_{Ar}). Found, %: C 57.76; H 4.22; N 6.83. $C_{19}H_{16}F_4N_2O_3$. Calculated, %: C 57.58; H 4.07; N 7.07.

5-Trifluoromethyl-5-(4-fluorophenyl)-3-(furan-2-ylmethyl)imidazolidine-2,4-dione (VIIe) was prepared similarly to **VIIa** (method *b*). Yield 76%, mp 111–113°C. ^{1}H NMR spectrum, δ, ppm: 4.63 s (2H, CH_2N); 6.27 d (2H, CH_{Ar}, *J* 8.4 Hz); 7.17 t (2H, CH_{Ar}, *J* 8.8 Hz); 7.38 m (1H, CH_{Ar}); 7.87 m (2H, CH_{Ar}); 10.24 s (1H, NH). ^{19}F NMR spectrum, δ, ppm: 2.51 s (3F, CF_3); –42.12 m (1F, CF_{Ar}). Found, %: C 52.47; H 2.78; N 8.33. $C_{15}H_{10}F_4N_2O_3$. Calculated, %: C 52.64; H 2.95; N 8.19.

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