Cyclocondensation of 2-alkoxy-2-isocyanato-3,3,3-trifluoropropionates with primary amines

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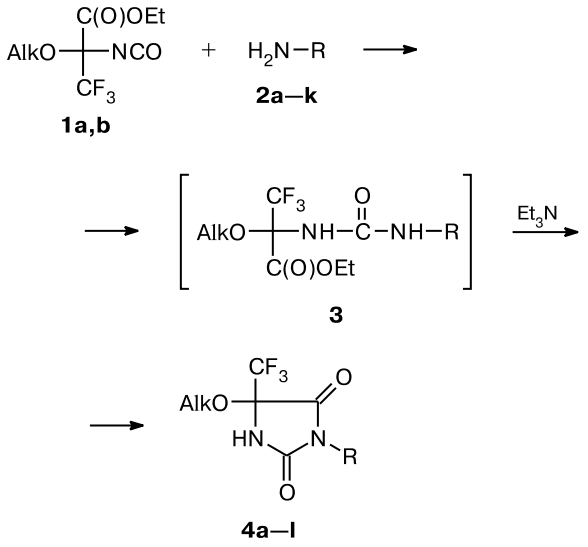
Cyclocondensation of ethyl 2-alkoxy-2-isocyanato-3,3,3-trifluoropropianates (novel 1,4-bielectrophiles) with primary amines resulted in 5-trifluoromethylimidazolidine-2,4-diones.

Key words: isocyanates, amines, imidazolidine-2,4-diones, organofluorine compounds, 1,4-bielectrophiles, cyclocondensation, heterocyclization.

Earlier,[1] we reported on the synthesis of novel polyfunctional α-substituted isocyanates, esters of 2-alkoxy-2-isocyanato-3,3,3-trifluoropropionic acids. They are promising intermediates for the synthesis of various acyclic 3,3,3-trifluoroalanine derivatives substituted at the position 2. The latter, taking into account the high bacteriostatic activity of 3,3,3-fluoroalanine, are potent biologically active substances.[2,3] These compounds can be regarded as derivatives of trifluoropyruvates; some of them, *e.g.*, *N*-substituted imines of trifluoropyruvates, are successfully used for the synthesis of fluorinated heterocyclic compounds,[4—8] also as 1,3-bielectrophiles in the cyclocondensation reactions.[9—13] In the present work, we studied chemical behavior of these novel 1,4-bielectrophiles, ethyl 2-alkoxy-2-isocyanato-3,3,3-trifluoropropionates **1a**,**b**, in the cyclocondensation with primary amines **2a**—**k** (Scheme 1).

Scheme 1



1: Alk = Et (**a**), Pr (**b**)
2: R = Ph (**a**), 3-ClC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**), 4-$Me_2CHC_6H_4$ (**d**), 3-$CF_3C_6H_4$ (**e**), 4-$CF_3C_6H_4$ (**f**), 3-Cl-4-FC_6H_3 (**g**), 5-F-2-MeC_6H_3 (**h**), 5-Cl-2-$MeOC_6H_3$ (**i**), CH_2CH_2Ph (**j**), 2-$PyCH_2$ (**k**)
4: Alk = Et, R = 3-ClC_6H_4 (**a**), 4-$MeOC_6H_4$ (**b**), 3-$CF_3C_6H_4$ (**c**), 3-Cl-4-FC_6H_3 (**d**), 2-Me-5-FC_6H_3 (**e**)
Alk = Pr, R = Ph (**f**), CH_2CH_2Ph (**g**), 2-$PyCH_2$ (**h**), 4-$CF_3C_6H_4$ (**i**), 4-$Me_2CHC_6H_4$ (**j**), 3-ClC_6H_4 (**k**), 5-Cl-2-$MeOC_6H_3$ (**l**)

Reaction of isocyanates **1a**,**b** with amines **2a**—**k** acting in these transformations as 1,1-binucleophiles proceeded as cyclocondensation involving (1) addition of amine to the C=N bond to give the corresponding urea **3** and (2) subsequent heterocyclization with removal of EtOH to yield imidazolidine-2,4-diones **4a**—**l**. Reactions were performed by mixing equimolar amounts of isocyanate **1** and amine **2** in DMF at 20 °C with further heating of the reaction mixture at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N.

In the case of isocyanate **1a** and 3-chloroaniline **2b**, we succeeded to isolate and characterize the individual intermediate adducts, urea **3a**. The latter was converted into imidazolidine-2,4-dione **4a** by heating in DMF at 90—100 °C for 2 h in the presence of catalytic amounts of Et_3N (Scheme 2).

Imidazolidine-2,4-diones **4a**—**l** synthesized in 65—79% yields are crystalline compounds. Composition and structure of **4a**—**l** were established by elemental analysis and ^1H and ^{19}F NMR spectroscopy. ^{19}F and NMR spectra exhibited singlets in the range of δ −(2—3) characteristic of the trifluoromethyl group; ^1H NMR spectra contained singlets in the range of δ 10—11 attributed to the protons of the NH group.

In summary, in the present work we introduced novel 1,4-bielectrophiles promising for cyclocondensation re-

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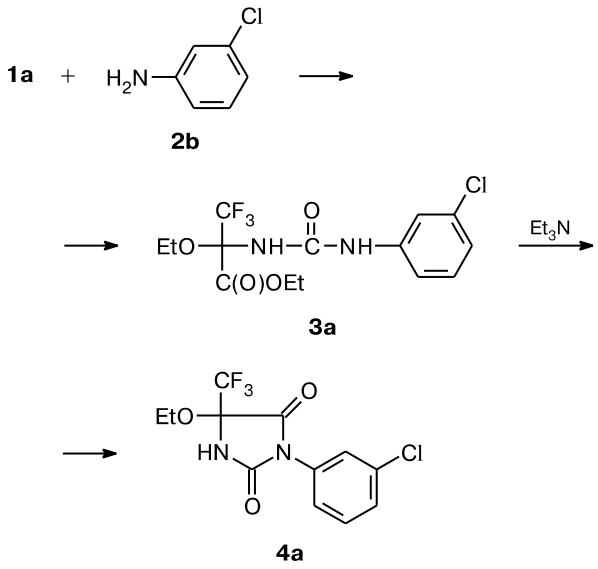
Scheme 2



actions, esters of 2-alkoxy-2-isocyanato-3,3,3-trifluoropropionic acids. These compounds could be used for the synthesis of various fluorinated hydantoins. It is of note that hydantoins are widely used in medical (anticonvulsants,[14] anticancer[15] agents) and agrochemical (herbicides[16]) practice.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (200.13 and 188.29 MHz, respectively) relative to Me_4Si (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in the glass capillary and uncorrected. The starting isocyanates **1a**,**b** were synthesized according to the known procedure,[1] amines **2a**—**k** (Aldrich) were used as purchased.

Ethyl 2-[3-(3-chlorophenyl)ureido]-2-ethoxy-3,3,3-trifluoropropionate (3a). To a solution of isocyanate **1a** (0.01 mol) in benzene (20 mL), aniline **2b** (0.01 mol) was added. After completion of the exothermic reaction, the mixture was stirred for 2 h, the solvent was removed *in vacuo*, the residue was recrystallized from hexane. Yield, melting points, elemental analysis data, and spectral data for compound **3a** are given in Tables 1 and 2.

3-(3-Chlorophenyl)-5-ethoxy-5-trifluoromethylimidazolidine-2,4-dione (4a). ***A.*** To a solution of urea **3a** (0.01 mol) in DMF (10 mL), Et_3N (0.1 g) was added. The reaction mixture was heated at 80 °C for 1 h, then water (50 mL) was added, the precipitate formed was recrystallized from hexane.

Tables 1. Yields, melting points, and elemental analysis data for compounds **3a** and **4a**—**l**

Compound	Yield (%)	M.p./°C	Molecular formula	Found / Calculated (%)		
				C	H	N
3a	88	142—143	$C_{14}H_{16}ClF_3N_2O_4$	46.74	4.51	7.82
				45.60	4.37	7.60
4a	81(*A*), 73 (*B*)	107—108	$C_{12}H_{10}ClF_3N_2O_3$	44.67	3.12	8.68
				44.78	3.34	8.51
4b	65	161—162	$C_{13}H_{13}F_3N_2O_4$	46.06	4.12	8.80
				46.21	4.35	8.59
4c	72	75—76	$C_{13}H_{10}F_6N_2O_3$	43.83	2.83	7.86
				43.64	2.98	7.58
4d	74	126—127	$C_{12}H_9ClF_4N_2O_3$	42.31	2.66	8.22
				42.12	2.45	8.44
4e	69	127—128	$C_{13}H_{12}F_4N_2O_3$	48.76	3.78	8.75
				78.57	3.95	8.56
4f	68	84—85	$C_{13}H_{13}F_3N_2O_3$	51.66	4.34	9.27
				51.47	4.15	9.05
4g	79	97—98	$C_{15}H_{17}F_3N_2O_3$	54.54	5.19	8.48
				54.36	5.36	8.29
4h	75	107—108	$C_{13}H_{14}F_3N_3O_3$	49.22	4.45	13.24
				49.03	4.27	13.45
4i	71	91—92	$C_{14}H_{12}F_6N_2O_3$	45.42	3.27	7.57
				45.26	3.12	7.35
4j	66	110—111	$C_{16}H_{19}F_3N_2O_3$	55.81	5.56	8.14
				55.63	5.38	8.32
4k	79	74—75	$C_{13}H_{12}ClF_3N_2O_3$	46.38	3.59	8.32
				46.17	3.75	8.14
4l	73	116—118	$C_{14}H_{14}ClF_3N_2O_4$	45.85	3.85	7.64
				45.59	3.62	7.46

Table 2. ^{1}H and ^{19}F NMR spectra (DMSO-d_6) of compounds **3a** and **4a—l**

Compound	^{1}H NMR, δ (*J*/Hz)	^{19}F NMR, δ
3a	1.26 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.5); 1.32 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.5); 3.72—3.94 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 4.31 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 6.64 (s, 1 H, CH$_{Ar}$); 7.12 (m, 1 H, CH$_{Ar}$); 7.28 (m, 2 H, CH$_{Ar}$); 7.56 (s, 1 H, NH); 7.68 (s, 1 H, NH)	–0.24 (s, CF$_3$)
4a	1.31 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.4); 3.72—3.94 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 6.64 (s, 1 H, CH$_{Ar}$); 7.12 (m, 1 H, CH$_{Ar}$); 7.28 (m, 2 H, CH$_{Ar}$); 9.56 (s, 1 H, NH)	–2.12 (s, CF$_3$)
4b	1.42 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.6); 3.69 (s, 3 H, MeO); 3.92—4.21 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 6.81, 7.32 (both d, 2 H, CH$_{Ar}$, *J* = 8.6); 10.05 (s, 1 H, NH)	—2.16 (s, CF$_3$)
4c	1.35 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.4); 3.78—4.01 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 7.15—7.26 (m, 2 H, CH$_{Ar}$); 7.36 (m, 2 H, CH$_{Ar}$); 9.88 (s, 1 H, NH)	–2.8 (s, CF$_3$); 15.71 (s, CF$_3$)
4d	1.22 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.5); 3.98 (m, 1 H, CH$_3$C<u>H</u>$_2$O); 4.28 (m, 1 H, CH$_3$C<u>H</u>$_2$O); 7.23 (m, 2 H, CH$_{Ar}$); 7.41 (m, 1 H, CH$_{Ar}$); 10.12 (s, 1 H, NH)	–37.02 (m, 1 F, CF$_{Ar}$); –2.11 (s, 3 F, CF$_3$)
4e	1.22 (t, 3 H, C<u>H</u>$_3$CH$_2$O, *J* = 7.5); 2.12 (s, 3 H, Me); 3.84 (m, 2 H, CH$_3$C<u>H</u>$_2$O); 7.12 (m, 1 H, CH$_{Ar}$); 7.28 (m, 2 H, CH$_{Ar}$); 9.98 (s, 1 H, NH)	–37.93 (m, 1 F, CF$_{Ar}$); –2.24 (s, 3 F, CF$_3$)
4f	1.10 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.82 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 3.99 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 6.98—7.29 (m, 5 H, CH$_{Ar}$); 9.81 (s, 1 H, NH)	–2.35 (s, CF$_3$)
4g	1.10 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.82 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 2.80 (t, 2 H, PhC<u>H</u>$_2$CH$_2$, *J* = 8.3); 3.82 (t, 2 H, PhCH$_2$C<u>H</u>$_2$, *J* = 8.3); 3.99 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 6.98—7.29 (m, 5 H, CH$_{Ar}$); 9.81 (s, 1 H, NH)	–2.43 (s, CF$_3$)
4h	0.99 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.88 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 4.02 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 5.06 (s, 2 H, CH$_2$); 7.32 (t, 1 H, CH$_{Ar}$, *J* = 7.3); 7.65 (d, 1 H, CH$_{Ar}$, *J* = 7.3); 8.35—8.62 (m, 2 H, CH$_{Ar}$); 10.23 (s, 1 H, NH)	–2.14 (s, CF$_3$)
4i	1.12 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.87 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 3.91 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 7.12, 7.26 (both m, 2 H, CH$_{Ar}$); 10.08 (s, 1 H, NH)	–2.71 (s, CF$_3$); –15.96 (s, CF$_3$)
4j	0.96 (d, 6 H, Me, *J* = 7.1); 1.08 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.92 (m, 1 H, Me$_2$CH); 1.79 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 3.89 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 6.81, 7.13 (both d, 2 H, CH$_{Ar}$, *J* = 8.1); 10.15 (s, 1 H, NH)	–2.20 (s, CF$_3$)
4k	1.08 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.79 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 3.89 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 6.88 (s, 1 H, CH$_{Ar}$); 7.19 (m, 1 H, CH$_{Ar}$); 7.36 (m, 2 H, CH$_{Ar}$); 9.86 (s, 1 H, NH)	–2.18 (s, CF$_3$)
4l	1.02 (t, 3 H, C<u>H</u>$_3$CH$_2$CH$_2$O, *J* = 7.5); 1.79 (m, 2 H, CH$_3$C<u>H</u>$_2$CH$_2$O); 3.71 (s, 3 H, MeO); 3.89 (m, 2 H, CH$_3$CH$_2$C<u>H</u>$_2$O); 7.02 (s, 1 H, CH$_{Ar}$); 7.28 (d, 1 H, CH$_{Ar}$, *J* = 7.9); 7.46 (d, 1 H, CH$_{Ar}$, *J* = 7.9); 10.16 (s, 1 H, NH)	–2.21 (s, CF$_3$)

B. To a stirred solution of aniline **2a** (0.01 mol) in DMF (10 mL), isocyanate **1a** (0.01 mol) was added at 20 °C. The reaction mixture was stirred for 1 h, then Et_3N (0.1 g) was added and the mixture was heated at 80 °C for 1 h. Water (50 mL) was added, the precipitate formed was recrystallized from hexane. Yield, melting point, elemental analysis data, and spectral data for compound **4a** are given in Tables 1 and 2.

5-Ethoxy-3-(4-methoxyphenyl)-5-trifluoromethylimidazolidine-2,4-dione (4b), **5-ethoxy-5-trifluoromethyl-3-(3-trifluoromethylphenyl)imidazolidine-2,4-dione (4c)**, **3-(3-chloro-4-fluorophenyl)-5-ethoxy-5-trifluoromethylimidazolidine-2,4-dione (4d)**, **5-ethoxy-3-(5-fluoro-2-methylphenyl)-5-trifluoromethylimidazolidine-2,4-dione (4e)**, **3-phenyl-5-propoxy-5-trifluoromethylimidazolidine-2,4-dione (4f)**, **3-(2-phenylethyl)-5-propoxy-5-trifluoromethylimidazolidine-2,4-dione (4g)**, **5-propoxy-3-(pyridin-2-ylmethyl)-5-trifluoromethylimidazolidine-2,4-dione (4h)**, **5-propoxy-5-trifluoromethyl-3-(4-trifluoromethylphenyl)imidazolidine-2,4-dione (4i)**, **3-(4-isopropylphenyl)-5-propoxy-5-trifluoromethylimidazolidine-2,4-dione (4j)**, **3-(3-chlorophenyl)-5-propoxy-5-trifluoromethylimidazolidine-2,4-dione (4k)**, and **3-(5-chloro-2-metoxyphenyl)-5-propoxy-5-trifluoromethylimidazolidine-2,4-dione (4l)** were synthesized similarly to the method ***B***. Yields, melting points, elemental analysis data, and spectral data for compounds **4b—l** are given in Tables 1 and 2.

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