Cyclocondensation of trifluorolactates with isocyanates*

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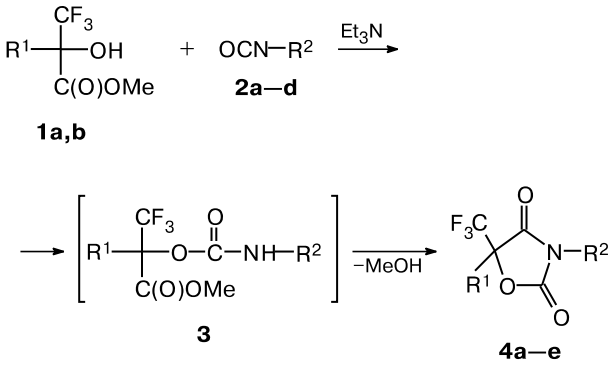
Cyclocondensation of trifluorolactates with isocyanates gives 3-substituted 5-trifluoromethyloxazolidine-2,4-diones.

Key words: trifluorolactates, isocyanates, cyclocondensation, organofluorine compounds.

Oxazolidine-2,4-diones are a promising class of biologically active compounds. Thus, *N*-acetyl- and *N*-sulfonyloxazolidine-2,4-diones are efficient inhibitors of serine proteases,[1] 5-aryl substituted oxazolidine-2,4-diones are selective EP_3-receptor antagonists.[2] These compounds are usually synthesized by constracting oxazolidine ring from lactic ester derivatives and isocyanates, followed by heterocyclization of the thus formed carbamates at 175—180 °C in the presence of pyridine[3] or upon reflux in toluene in the presence of Et_3N.[4] Various substituted lactates were thus transformed, however, the problem of preparation of fluorine-containing oxazolidine-2,4-diones remained unsolved.

The purpose of the present work was to study reactions of methyl 3,3,3-trifluoro-2-hydroxypropionates (**1a**) and methyl 2-hydroxy-2-trifluoromethylbutanoates (**1b**) in the reaction with alkyl and aryl isocyanates.

Scheme 1



1: R^1 = H (**a**), Et (**b**);
2: R^2 = Pr (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), $PhCH_2$ (**d**);
4: R^1 = H, R^2 = Pr (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), $PhCH_2$ (**d**);
R^1 = Et, R^2 = Ph (**e**)

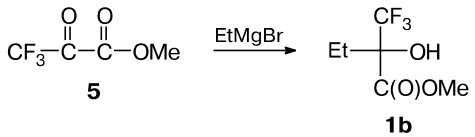
Results and Discussion

Trifluorolactates **1a**,**b** were shown to exothermically react with isocyanates **2a**—**d** exclusively in the presence of catalytic amounts of Et_3N (Scheme 1). The products of addition of lactates **1a**,**b** to isocyanates **2a**—**d**, urethanes **3**, were not isolated in the individual state, since at room temperature they considerably underwent heterocyclization to oxazolidine-2,4-diones **4a—e**. For the reaction of compounds **1a** and **2a**, the ^1H NMR spectra of the reaction mixture exhibited signals confirming the formation of urethane **3** (the singlet signals for the protons of the methoxy group at δ 3.29 and the NH fragment at δ 5.09). To complete the cyclocondensation, a short-time (10 min) reflux of the reaction mixture in acetonitrile was required.

The composition and the structure of compounds **4a**—**e** were confirmed by elemental analysis and ^1H and ^{19}F NMR spectroscopy. The ^1H NMR spectra of compounds **4a**—**d** exhibit characteristic quartets in the region of δ 5.0—5.2 with the spin-spin coupling constants of 6.5—6.6 Hz. The ^{19}F NMR spectra exhibit doublets in the region of δ 2.9—5.2 with the spin-spin coupling constant of 6.2—6.8 Hz.

Note that methyl 2-hydroxy-2-trifluoromethylbutanoate (**1b**) was obtained by the reaction of methyl trifluoropyruvate (**5**) with ethylmagnesium bromide in 73% yield (Scheme 2).

Scheme 2



In conclusion, cyclocondensation of trifluorolactates with isocyanates afforded earlier unknown trifluoromethyl-containing oxazolidine-2,4-diones.

* Dedicated to academician of the Russian Academy of Sciences I. P. Beletskaya on the occasion of her anniversary.

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Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer (200.13 and 188.29 MHz), using Me_4Si as an internal standard and CF_3COOH as an internal reference. Melting point was determined in a capillary tube. Methyl 3,3,3-trifluoro-2-hydroxypropionate (**1a**) was synthesized according to the known procedure.[5] Isocyanates **2a**—**d** (Aldrich) were used as purchased.

Methyl 2-hydroxy-2-trifluoromethylbutanoate (1b). Ethylmagnesium bromide (13.3 g) in THF (100 mL) was added to a solution of methyl trifluoropyruvate (**5**) (15.6 g, 0.1 mol) in THF (100 mL) at −30 °C with stirring. The reaction mixture was stirred for 1 h at 20 °C, then poured into saturated aqueous NaCl (300 mL), the organic layer was separated, the solvent was evaporated, the residue fractionally distilled. The yield was 13.6 g (73%), b.p. 40—43 °C (10 Torr). Found (%): C, 38.53; H, 4.66. $C_6H_9F_3O_3$. Calculated (%): C, 38.72; H, 4.87. ^{1}H NMR ($CDCl_3$), δ: 0.87 (t, 3 H, Me, J = 7.1 Hz); 1.87 (m, 2 H, CH_2); 3.72 (s, 3 H, MeO); 3.78 (s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: −1.05 s.

3-Propyl-5-trifluoromethyloxazolidine-2,4-dione (4a). Triethylamine (0.1 g) was added to a solution of methyl 3,3,3-trifluoro-2-hydroxypropionate (**1a**) (1.58 g, 0.01 mol) and propyl isocyanate (**2a**) (0.85 g, 0.01 mol) in MeCN (10 mL) at 20 °C with stirring. After the exothermic reaction was over, the reaction mixture was refluxed for 10 min, the solvent was evaporated, the residue was subjected to chromatography on silica gel (eluent methanol—chloroform, 1 : 20). The yield was 1.77 g (81%), oil. Found (%): C, 39.63; H, 4.06; N, 6.47. $C_7H_8F_3NO_3$. Calculated (%): C, 39.82; H, 3.82; N, 6.63. ^{1}H NMR ($CDCl_3$), δ: 0.95 (t, 3 H, Me, J = 7.3 Hz); 1.72 (sextet, 2 H, CH_2, J = 7.4 Hz); 3.60 (td, 2 H, CH_2, J_t = 7.3 Hz, J_d = 1.5 Hz); 5.12 (quartet, 1 H, CH, J = 6.6 Hz). ^{19}F NMR ($CDCl_3$), δ: 5.19 (d, J = 6.8 Hz).

3-Phenyl-5-trifluoromethyloxazolidine-2,4-dione (4b) was obtained similarly to **4a** from **1a** (1.58 g, 0.01 mol) and phenyl isocyanate (**2b**) (1.19 g, 0.01 mol). The yield was 1.9 g (78%), m.p. 70—72 °C. Found (%): C, 49.21; H, 2.28; N, 5.53. $C_{10}H_6NO_3$. Calculated (%): C, 48.99; H, 2.47; N, 5.71. ^{1}H NMR ($CDCl_3$), δ: 5.20 (quartet, 1 H, CH, J = 6.5 Hz); 7.35—7.46 (m, 2 H, CH_{Ar}); 7.48—7.57 (m, 2 H, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 2.94 s (d, J = 6.3 Hz).

3-(4-Chlorophenyl)-5-trifluoromethyloxazolidine-2,4-dione (4c) was obtained similarly to **4a** from **1a** (1.58 g, 0.01 mol) and 4-chlorophenyl isocyanate (**2c**) (1.54 g, 0.01 mol). The yield was 2.2 g (79%). M.p. 91—93 °C. Found (%)): C, 42.72; H, 2.28; N, 5.22. $C_{10}H_5ClF_3NO_3$. Calculated (%): C, 42.96; H, 2.47; N, 5.01. ^{1}H NMR ($CDCl_3$), δ: 5.21 (quartet, 1 H, CH, J = 6.4 Hz); 7.38 (d, 2 H, CH_{Ar}, J = 8.9 Hz); 7.50 (d, 2 H, CH_{Ar}, J = 8.9 Hz). ^{19}F NMR ($CDCl_3$), δ: 3.05 (d, J = 6.2 Hz).

3-Benzyl-5-trifluoromethyloxazolidine-2,4-dione (4d) was obtained similarly to **4a** from **1a** (1.58 g, 0.01 mol) and benzyl isocyanate (**2c**) (1.33 g, 0.01 mol). The yield was 2.2 g (85%), m.p. 59—61 °C. Found (%): C, 50.77; H, 3.29; N, 5.19. $C_{11}H_8F_3NO_3$. Calculated (%): C, 50.98; H, 3.11; N, 5.40. ^{1}H NMR ($CDCl_3$), δ: 4.73 (s, 2 H, CH_2); 5.03 (quartet, 1 H, CH, J = 6.6 Hz); 7.37 (m, 5 H, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 2.88 (d, J = 6.5 Hz).

5-Ethyl-3-phenyl-5-trifluoromethyloxazolidine-2,4-dione (4e) was obtained similarly to **4a** from **1b** (1.86 g, 0.01 mol) and phenyl isocyanate (**2b**) (1.19 g, 0.01 mol). The yield was 2.1 g (77%), m.p. 70—72 °C. Found (%): C, 52.53; H, 3.51; N, 5.34. $C_{11}H_8F_3NO_3$. Calculated (%): C, 52.75; H, 3.69; N, 5.13. ^{1}H NMR ($CDCl_3$), δ: 1.12 (t, 3 H, Me, J = 7.7 Hz); 2.32 (septet, 2 H, CH_2, J = 7.7 Hz); 7.36—7.46 (m, 2 H, CH_{Ar}); 7.48—7.58 (m, 3 H, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 0.29 s.

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