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Heterocyclization of Functionalized Heterocumulenes with C,N-, C,O, and C,S-Binucleophiles: IX.* Reaction of 1-Aryl-1-chloro-2,2,2-trifluoroethyl Isocyanates with Sulfanylacetic Acid Esters as a Convenient Synthetic Route to 2-Aryl-2-trifluoromethyl-4-oxo-1,3-thiazolidine-5-carboxylates

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Abstract—1-Aryl-1-chloro-2,2,2-trifluoroethyl isocyanates reacted with methyl and ethyl sulfanylacetates to give the corresponding alkyl 2-aryl-2-trifluoromethyl-4-oxo-1,3-thiazolidine-5-carboxylates.

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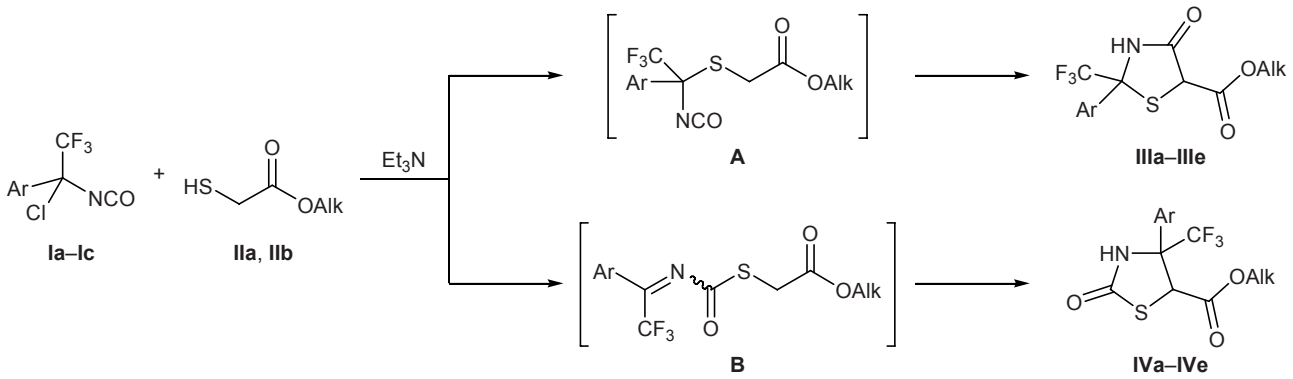
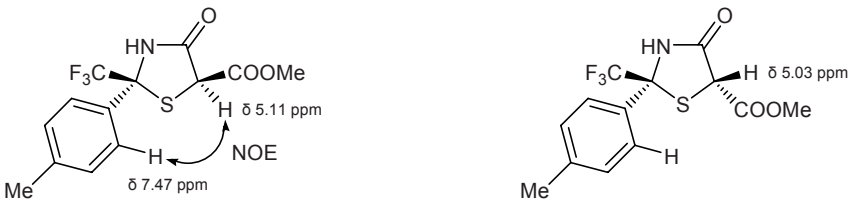
Thiazolidin-4-ones constitute an important group of compounds exhibiting a broad spectrum of biological activity [2]. Insofar as the presence of a trifluoromethyl group in organic molecules often favors their sorption and transport in biological systems [3, 4], development of effective methods for the synthesis of new trifluoromethyl-substituted heterocyclic compounds, especially of nitrogen-containing heterocycles with a CF_3 group in the α-position with respect to the nitrogen atom [5–8], is an actual problem. First representatives of 2-trifluoromethyl-1,3-thiazolidin-4-ones were synthesized in 1974 by condensation of hexafluoroacetone imine with sulfanylacetic acid and its analogs [9]. Such compounds were later prepared by reactions of tetrakis(trifluoromethyl)-1,3-dithietane with potassium cyanate [10] and of 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates with sulfanylacetic acid [11], as well as by recyclization of alkylation products of 2-trifluoromethyl-2,3-dihydro-1*H*-pyrido-[1,2-*c*]pyrimidine-3-thiones [12]. Sulfanylacetic acid

Scheme 1.



I, Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-MeC_6H_4 (**c**); **II**, Alk = Me (**a**), Et (**b**); **III**, Ar = Ph, Alk = Me (**a**), Et (**b**); Ar = 4-FC_6H_4, Alk = Me (**c**); Ar = 4-MeC_6H_4, Alk = Me (**d**), Et (**e**).

* For communication VIII, see [1].



Diastereoisomers of compound **IIId**. Main coupling in the 2D NOESY ^{1}H NMR spectrum of diastereoisomer (2*R*,5*R*)-**IIId** is shown.

acted as 1,4-S,O-difunctional nucleophile in the cyclocondensation with 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates.

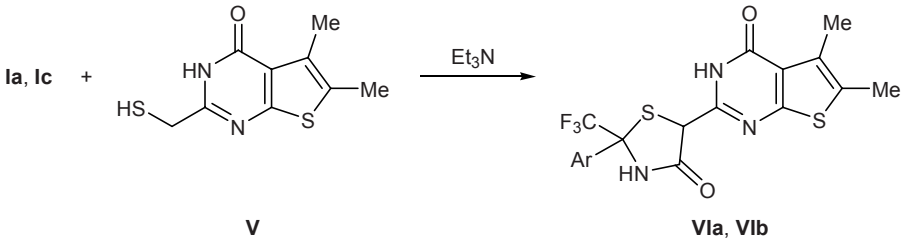
The present article reports on the synthesis of 2-trifluoromethyl-1,3-thiazolidin-4-ones having an ester moiety on the heteroring, which extends their potential for subsequent chemical modifications. The proposed procedure is based on the reaction of 1,3-bielectrophilic 1-aryl-1-chloro-2,2,2-trifluoroethyl isocyanates **Ia**–**Ic** [13] with 1,2-C,S-binucleophilic alkyl sulfanylacetates **IIa** and **IIb**. The reactions were carried out in toluene at room temperature in the presence of triethylamine, and the products were the corresponding alkyl 2-aryl-2-trifluoromethyl-4-oxo-1,3-thiazolidine-5-carboxylates **IIIa**–**IIIe** (Scheme 1).

Taking into account that 1-chloroalkyl isocyanates **Ia**–**Ic** are capable of reacting with alkane- and benzenethiols at both isocyanato group and α-carbon atom [14], sulfanylacetates **IIa** and **IIb** could be expected to produce both thiazolidin-4-ones **III** and isomeric thiazolidin-2-ones through intermediate *N*-alkylidenethiocarbamates **B**. However, despite the yield of compounds **IIIa**–**IIIe** was not high (31–58%), no signals assignable to alternative products **IV** were observed in the ^{19}F NMR spectra of the reaction mixtures. Presumably, compounds **III** are formed as a result of intramolecular cyclization of the primary intermediates, 1-[(alkoxycarbonyl)methylsulfanyl]alkyl isocyanates **A** via attack on the strongly electrophilic isocyanate fragment by carbanion generated from the alkoxycarbonylmethylene group by the action of a base (Scheme 1).

The structure of compounds **IIIa**–**IIIe** was proved by IR and ^{1}H, ^{19}F, and ^{13}C NMR spectra. The ^{19}F NMR spectra of **IIIa**–**IIIe** contained two signals in the region δ_F −75 to −78 ppm [11, 15], indicating that they are mixtures of two diastereoisomers at a ratio of 1 : 1.7 (according to the signal intensity ratio). The same follows from the presence of double sets of signals from protons and carbon nuclei in the ^{1}H and ^{13}C NMR spectra. The two-dimensional ^{1}H–^{13}C heteronuclear correlation spectrum (HMBC) of **IIId** lacked cross peak between the 5-H proton (δ 5.03, 5.11 ppm) and *ipso*-carbon atom in the 4-tolyl substituent (δ_C 131.95, 132.59 ppm), providing support to structure **III** rather than **IV**. The 2D NOESY ^{1}H NMR spectrum of **IIId** displayed coupling between the NH proton (δ 10.79 ppm) and 5-H (δ 5.03, 5.11 ppm), which is possible only in structure **III**. Furthermore, the 2D NOESY spectrum showed nuclear Overhauser effect between 5-H (δ 5.11 ppm) and proton in the *ortho* position of the tolyl substituent (δ 7.47 ppm) of one stereoisomer, (2*R*,5*R*)-**IIId**; this means that the 5-H and *o*-H protons therein are spatially close (see figure).

The scope of the described reaction may be extended so as to obtain 2-trifluoromethylthiazolidin-4-ones having other functional substituents in the 5-position. For example, sulfanylmethyl-substituted azines were found to behave similarly to sulfanylacetic acid esters. The reactions of 1-chloroalkyl isocyanates **Ia**

Scheme 2.



Ar = Ph (**a**), 4-MeC_6H_4 (**b**).

and **Ib** with 2-sulfanylmethyl-5,6-dimethylthieno-[2,3-*d*]pyrimidin-4(3*H*)-one (**V**) gave heterocyclic ensembles **VIa** and **VIb** as mixtures of diastereoisomers at a ratio of 1:4 (Scheme 2).

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-20 spectrometer. The ^{1}H and ^{19}F NMR spectra were measured on a Varian Gemini instrument at 299.94 and 188.14 MHz, respectively, relative to tetramethylsilane (^{1}H) and CCl_3F (^{19}F) as internal standards. The ^{13}C NMR spectra were obtained on a Bruker Avance DRX-500 spectrometer at 125.75 MHz using tetramethylsilane as internal reference. Compound **IIIb** was purified by preparative liquid chromatography using a Combiflash Companion chromatograph equipped with a diode matrix detector and a column packed with 12 g of silica gel (Merck 40–63 μm); eluent chloroform–ethyl acetate (90:10), flow rate 30 ml/min; R_t 13 min; the peak was separated into three fractions which were subjected to repeated chromatographic separation using chloroform–ethyl acetate (97:3) as eluent; R_t 34 min; detection at λ 254 nm.

1-Aryl-1-chloro-2,2,2-trifluoroethyl isocyanates **Ia**–**Ic** were synthesized according to the procedure described in [14].

Alkyl 2-aryl-4-oxo-2-trifluoromethyl-1,3-thiazolidine-5-carboxylates IIIa–IIIe and 5,6-dimethyl-2-(2-aryl-4-oxo-2-trifluoromethyl-1,3-thiazolidin-5-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones VIa and VIb (*general procedure*). Isocyanate **Ia**–**Ic**, 1.5 mmol, was dissolved in 10 ml of anhydrous toluene, 1.5 mmol of alkyl sulfanylacetate **IIa** or **IIb** or 0.339 g (1.5 mmol) of 2-sulfanylmethylthieno[2,3-*d*]pyrimidine (**V**) was added, and a solution of 0.182 g (1.8 mmol) of triethylamine in 5 ml of anhydrous toluene was added under stirring over a period of 0.5 h. The mixture was stirred for 6 h and left to stand for 12 h, the precipitate was filtered off, washed with water, and dried, the filtrate was evaporated, 4 ml of hexane and 0.7 ml of propan-2-ol (in the synthesis of compounds **IIIa** and **IIIc**–**IIIe**) or 4 ml of ethanol (in the synthesis of **VIa** and **VIb**) were added, and the mixture was heated to the boiling point. After cooling, the precipitate was filtered off, combined with the first portion of the product, and purified by recrystallization. Compound **IIIb** was isolated by evaporation of the reaction mixture and subsequent separation of the residue by preparative liquid chromatography (see above).

Methyl 4-oxo-2-phenyl-2-trifluoromethyl-1,3-thiazolidine-5-carboxylate (IIIa). Yield 58%, mp 141–143°C. IR spectrum, ν, cm^{-1}: 1705 (C=O), 1750 (C=O, ester), 3190 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.65 s and 3.74 s (3H, $COOCH_3$), 5.06 s and 5.13 s (1H, 5-H), 7.43–7.61 m (5H, H_{arom}), 10.75 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 48.78, 49.78 (C^5); 53.06, 53.18 (OCH_3); 68.88 q, 68.91 q (C^2, J = 28 Hz); 124.97 q, 125.50 q (CF_3, J = 285 Hz); 126.25, 126.31, 128.65, 128.69, 129.50, 129.57 (CH_{arom}); 134.92, 135.57 (C_{arom}); 167.19, 167.22 (C=O); 169.21, 169.62 (C^4). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –76.04, –76.44. Found, %: C 47.19; H 3.40; N 4.57. $C_{12}H_{10}F_3NO_3S$. Calculated, %: C 47.21; H 3.30; N 4.59.

Ethyl 4-oxo-2-phenyl-2-trifluoromethyl-1,3-thiazolidine-5-carboxylate (IIIb). Yield 31%, mp 112–116°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 1750 (C=O, ester), 3190 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 t and 1.33 t (3H, CH_3, J = 7.2 Hz), 4.18 d.q and 4.29 d.q (2H, CH_2, J = 7.2, 2.0 Hz), 4.67 s and 4.77 s (1H, 5-H), 7.40–7.52 m (5H, H_{arom}), 8.85 s and 9.13 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.77, 13.87 (CH_3); 49.71, 50.36 (C^5); 62.85 (CH_2); 70.06 q, 70.09 q (C^2, J = 28 Hz); 124.30 q, 124.84 q (CF_3, J = 283 Hz); 126.16, 126.44, 128.79, 128.85, 129.71, 129.73 (CH_{arom}); 134.39, 135.00 (C_{arom}); 166.30, 166.38 (C=O); 171.10, 171.32 (C^4). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: –77.87, –77.92. Found, %: C 48.79; H 3.68; N 4.37. $C_{13}H_{12}F_3NO_3S$. Calculated, %: C 48.90; H 3.79; N 4.39.

Methyl 2-(4-fluorophenyl)-4-oxo-2-trifluoromethyl-1,3-thiazolidine-5-carboxylate (IIIc). Yield 51%, mp 162–165°C. IR spectrum, ν, cm^{-1}: 1710 (C=O), 1750 (C=O, ester), 3200 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.65 s and 3.74 s (3H, OCH_3), 5.06 s and 5.14 s (1H, 5-H), 7.30–7.38 m (2H, H_{arom}), 7.62–7.66 m (2H, H_{arom}), 10.80 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 48.92, 49.85 (C^5); 53.10, 53.21 (OCH_3); 68.58 q, 68.61 q (C^2, J = 29 Hz); 115.56, 115.61, 115.74, 115.78 d (CH_{arom}, J = 21 Hz); 124.43 q, 124.80 q (CF_3, J = 284 Hz); 128.84 m (CH_{arom}); 131.36, 131.38, 131.90, 131.93 d (C_{arom}, J = 2.5 Hz); 161.43, 161.47, 163.40, 163.44 d (C_{arom}, J = 5 Hz); 167.11, 167.23 (C=O); 169.18, 169.58 (C^4). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –76.19, –76.52. Found, %: C 44.39; H 2.80; N 4.27. $C_{12}H_9F_4NO_3S$. Calculated, %: C 44.59; H 2.81; N 4.33.

Methyl 2-(4-methylphenyl)-4-oxo-2-trifluoromethyl-1,3-thiazolidine-5-carboxylate (IIId). Yield 51%, mp 142–144°C. IR spectrum, ν, cm^{-1}: 1700

(C=O), 1752 (C=O, ester), 3190 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.32 s and 2.33 s (3H, CH_3), 3.65 s and 3.73 s (3H, OCH_3), 5.03 s and 5.11 s (1H, 5-H), 7.26–7.31 m (2H, H_{arom}), 7.42–7.47 m (2H, H_{arom}), 10.70 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.57 (CH_3); 48.76, 49.78 (C^5); 53.04, 53.17 (OCH_3); 68.88 q, 68.92 q (C^2, J = 28 Hz); 125.01 q, 125.50 q (CF_3, J = 285 Hz); 126.16, 126.22, 129.12, 129.17 (CH_{arom}); 131.95, 132.59, 139.15, 139.23 (C_{arom}); 167.22, 167.25 (C=O); 169.17, 169.60 (C^4). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –76.12, –76.55. Found, %: C 49.06; H 3.82; N 4.45. $C_{13}H_{12}F_3NO_3S$. Calculated, %: C 48.90; H 3.79; N 4.39.

Ethyl 2-(4-methylphenyl)-4-oxo-2-trifluoromethyl-1,3-thiazolidine-5-carboxylate (IIIe). Yield 44%, mp 99–102°C. IR spectrum, ν, cm^{-1}: 1692 (C=O), 1750 (C=O, ester), 3190 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.10 s and 1.22 s (3H, CH_3), 4.08–4.20 m (2H, CH_2), 4.99 s and 5.08 s (1H, 5-H), 7.28–7.51 m (4H, H_{arom}), 10.67 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.80, 13.86 (CH_3); 21.11 (CH_3); 49.65, 50.35 (C^5); 62.83 (CH_2); 69.77 q, 69.81 q (C^2, J = 27 Hz); 124.36 q, 124.91 q (CF_3, J = 285 Hz); 126.00, 126.28, 129.48, 129.53 (CH_{arom}); 131.28, 131.97, 139.89, 139.92 (C_{arom}); 166.29, 166.37 (C=O); 170.86, 171.07 (C^4). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –75.94, –76.25. Found, %: C 50.46; H 4.22; N 4.11. $C_{14}H_{14}F_3NO_3S$. Calculated, %: C 50.45; H 4.23; N 4.20.

5,6-Dimethyl-2-(4-oxo-2-phenyl-2-trifluoromethyl-1,3-thiazolidin-5-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (VIa). Yield 49%, mp >250°C (decomp.). IR spectrum, ν, cm^{-1}: 1680 (C=O), 3230 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.33 s, 2.39 s, and 2.51 s (6H, CH_3); 5.22 s and 5.31 s (1H, 5-H); 7.45–7.63 m (5H, H_{arom}); 10.74 s and 10.82 s (1H, NH); 12.48 s and 12.55 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.59, 12.63, 12.71, 12.76 (CH_3); 48.66, 49.79 ($C^{5'}$); 68.80 q, 68.81 q ($C^{2'}$, J = 28 Hz); 122.11, 122.20 (C_{arom}); 125.25 q, 125.34 q (CF_3, J = 285 Hz); 126.38, 126.46, 128.68, 129.46, 129.63, 130.08, 130.12, 134.57, 136.25 (CH_{arom}, C_{arom}); 151.55, 152.05 (C^2); 158.12, 158.26 (C^4); 161.33, 161.45 (C^{7a}); 169.97, 170.95 ($C^{4'}$). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –75.21, –76.62. Found, %: C 51.01; H 3.34; N 9.85. $C_{18}H_{14}F_3N_3O_2S_2$. Calculated, %: C 50.82; H 3.32; N 9.88.

5,6-Dimethyl-2-[2-(4-methylphenyl)-4-oxo-2-trifluoromethyl-1,3-thiazolidin-5-yl]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (VIb). Yield 46%, mp 214–218°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 3225 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.31 s, 2.34 s, and 2.35 s (6H, CH_3); 5.18 s and 5.27 s (1H, 5-H); 7.28 d (2H, H_{arom}, J = 8.0 Hz); 7.46–7.51 m (2H, H_{arom}); 10.65 s and 10.73 s (1H, NH); 12.42 s and 12.51 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.55, 12.58, 12.66, 12.70, 20.59 (CH_3); 48.61, 49.76 ($C^{5'}$); 68.49 q, 68.51 q ($C^{2'}$, J = 28 Hz); 122.07, 122.16 (C_{arom}); 125.24 q, 125.31 q (CF_3, J = 285 Hz); 126.30, 128.64, 128.67, 129.09, 129.12, 130.01, 130.06, 131.57, 133.28, 139.01, 139.20 (CH_{arom}, C_{arom}); 151.52, 152.02 (C^2); 158.07, 158.20 (C^4); 161.33, 161.41 (C^{7a}); 169.85, 170.82 ($C^{4'}$). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –75.35, –76.77. Found, %: C 51.91; H 3.65; N 9.56. $C_{19}H_{16}F_3N_3O_2S_2$. Calculated, %: C 51.93; H 3.67; N 9.56.

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