Chemistry of Heterocyclic Compounds, Vol. 42, No. 2, 2006

CONVENIENT METHOD FOR SYNTHESIS OF 2-TRIFLUOROMETHYL-1,3-OXATHIOLAN-5-ONES

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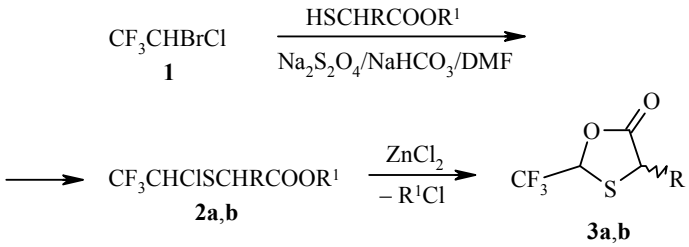
Keywords: 2-bromo-2-chloro-1,1,1-trifluoroethane, sodium dithionite, thiol, 2-trifluoromethyl-1,3-oxathiolan-5-one.

Derivatives of 1,3-oxathiolan-5-one exhibit a broad spectrum of biological activity [1, 2]. Up to now, there has been no convenient method for synthesis of 2-trifluoromethyl-1,3-oxathiolan-5-ones **3**, which are potential synthons for obtaining fluorinated analogs of biologically active compounds. The only representative of this series, 2-trifluoromethyl-1,3-oxathiolan-5-one (**3a**), was obtained in [2] in low yield from trifluoroacetaldehyde.

We have developed a simple and effective method for obtaining compounds **3** from commercially available starting compounds.

2-Bromo-2-chloro-1,1,1-trifluoroethane (**1**), under conditions where CF_3CHCl radicals are generated [3], react with esters of thioglycolic and thiolactic acids to form the previously unknown sulfides **2**.



2 a R = H, R^1 = Et, **b** R = R^1 = Me; **3 a** R = H, **b** R = Me

The sulfides **2** obtained in the first step, when heated in the presence of catalytic amounts of anhydrous zinc chloride, form the target compounds **3** in high yields. We should point out the stereoselective nature of this reaction. Heterocyclization of a mixture (1:1) of diastereoisomers **2b** leads to predominance (2:1) of one of the stereoisomers, probably the less sterically hindered *E*-isomer **3b**.

The ^1H and ^{19}F NMR spectra were recorded on a Varian VXR-300 (300 MHz and 282 MHz respectively) in $CDCl_3$, internal standard TMS and $FCCl_3$ respectively.

[(1-Chloro-2,2,2-trifluoroethyl)thio]acetic Acid Ethyl Ester (2a). Compound **1** (40 ml, 0.380 mol) was added dropwise over a 30 min period at a temperature of 35-40°C with stirring to a mixture of sodium dithionite (54.6 g, 85%, 0.267 mol), sodium bicarbonate (22.5 g, 0.267 mol), and thioglycolic acid ethyl ester

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 0009-3122/06/4202-0278

(28 ml, 0.255 mol) in DMF (200 ml). The reaction mixture was held for 3 h 30 min at 40-45°C, poured into water, and extracted with ether; the extract was washed with water, dried with anhydrous sodium sulfate and filtered, and the filtrate was distilled. Compound **2a** (48 g, 80%) was obtained; bp 78-80°C (12 torr). ^{1}H NMR spectrum, δ, ppm (*J*, Hz); 1.31 (3H, t, $^3J_{HH}$ = 7.2, $OCH_2C\underline{H}_3$); 3.52 (1H, d, $^2J_{HH}$ = 15.9, AB, $SC\underline{H}_2$); 3.61 (1H, d, $^2J_{HH}$ = 15.9, AB, $SC\underline{H}_2$); 4.24 (2H, q, $^3J_{HH}$ = 7.2, $OCH\underline{H}_2CH_3$); 5.51 (1H, q, $^3J_{HF}$ = 6.6, $CF_3C\underline{H}$). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): -72.80 (3F, d, $^3J_{HF}$ = 6.6, $C\underline{F}_3CH$). Found, %: Cl 15.33; S 13.39. $C_6H_8ClF_3O_2S$. Calculated, %: Cl 14.98; S 13.55.

[2-(1-Chloro-2,2,2-trifluoroethyl)thio]thio]propionic Acid Methyl Ester (2b) was obtained as for compound **2a**, as a mixture of diastereoisomers (1:1). Yield 72%; bp 80-82°C (12 torr). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (3H, d, $^3J_{HH}$ = 7.3, $C\underline{H}_3CH$) and 1.57 (3H, d, $^3J_{HH}$ = 7.3, $C\underline{H}_3CH$): 3.75 (1H, q, $^3J_{HH}$ = 7.3, $C\underline{H}CH_3$) and 3.78 (1H, q, $^3J_{HH}$ =7.3, $C\underline{H}CH_3$); 3.79 (3H, s, $OC\underline{H}_3$) and 3.793 (3H, s, $OC\underline{H}_3$); 5.47 (1H, q, $^3J_{HF}$ = 6.7, $C\underline{H}CF_3$) and 5.58 (1H, q, $^3J_{HF}$ = 6.7, $C\underline{H}CF_3$). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): -72.86 (3F, two d, $^3J_{HF}$ = 6.7, $C\underline{F}_3CH$) and -73.63 (3F, d, $^3J_{HF}$ = 6.7, $C\underline{F}_3CH$). Found, %: Cl 15.24; S 13.41. $C_6H_8ClF_3O_2S$. Calculated, %: Cl 14.98; S 13.55.

2-Trifluoromethyl-1,3-oxathiolan-5-one (3a). A mixture of sulfide **2a** (25 g, 0.106 mol) and anhydrous zinc chloride (3 g, 22 mmol) was heated for 45 min at a temperature of 160-170°C. The reaction mixture was extracted with boiling hexane (4 × 20 ml) and the crystals that precipitated after cooling were filtered out. Compound **3a** (15.6 g, 86%) was obtained; mp 61-62°C (mp 62-63°C [2]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.63 (1H, dq, $^2J_{HH}$ = 16.2, AB, $^5J_{HF}$ = 1.2, $SC\underline{H}_2$); 3.81 (1H, d, $^2J_{HH}$ = 16.2, AB, $SC\underline{H}_2$); 5.60 (1H, q, $^3J_{HF}$= 5.7, $CF_3C\underline{H}$). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): -78.96 (3F, dq, $^3J_{HF}$ = 5.7, $^5J_{HF}$ = 1.2, $C\underline{F}_3CH$).

4-Methyl-2-trifluoromethyl-1,3-oxathiolan-5-one (3b) was obtained as for compound **3a**, as a mixture of *E*- and *Z*-stereoisomers in a 2:1 ratio. Yield 81%; bp 68-70°C (15 torr). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *E*-isomer: 1.69 (3H, d, $^3J_{HH}$ = 7.2, $CHC\underline{H}_3$); 4.05 (1H, q, $^3J_{HH}$ = 7.2, $C\underline{H}CH_3$); 5.59 (1H, q, $^3J_{HF}$ = 5.2, $C\underline{H}CF_3$); *Z*-isomer: 1.62 (3H, d, $^3J_{HH}$ = 6.8, $CHC\underline{H}_3$); 4.06 (1H, q, $^3J_{HH}$ = 6.8, $C\underline{H}CH_3$); 5.51 (1H, q, $^3J_{HF}$ = 5.7, $C\underline{H}CF_3$). ^{19}F NMR spectrum, δ, ppm (*J*, Hz): *E*-isomer: -79.74 (3F, d, $^3J_{HF}$ = 5.2, $C\underline{F}_3CH$); *Z*-isomer: -79.68 (3F, d, $^3J_{HF}$ = 5.7, $C\underline{F}_3CH$). Found, %: F 30.44; S 17.13. $C_5H_5F_3O_2S$. Calculated, %: F 30.62; S 17.22.

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