Improved Synthesis of Fluoromethanesulfonyl Chloride

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Introduction of fluorine into 4-chlorobenzyl chloromethyl sulfide (7) by crown-ether-assisted nucleophilic substitution furnishes 4-chlorobenzyl fluoromethyl sulfide (5), a key intermediate for the preparation of fluoromethanesulfonyl chloride (1).

Fluoromethanesulfonyl chloride (1), which is of considerable interest as an intermediate for studies of sulfene^{1,2)} and sulfine chemistry³⁾ and of potentially cytostatic sulfonic acid esters of the busulfan type⁴⁾, became first available in high purity in 1985 when Rheude and Sundermeyer published a straightforward, but somewhat cumbersome synthesis of 1 consisting of the steps $(1)-(3)^{2)}$. This synthesis was an inprovement of a procedure published in 1979 by Moore⁵⁾ consisting of the steps (2)-(3).

$$\begin{array}{c} \text{CH}_2\text{BrCl} & \xrightarrow{\text{KF}} & \text{CH}_2\text{ClF} \\ \mathbf{2} & \mathbf{3} \end{array} \tag{1}$$

$$3 + 4 - \text{ClC}_6\text{H}_4\text{CH}_2\text{SH} \xrightarrow[-\text{HCl}]{} 4 - \text{ClC}_6\text{H}_4\text{CH}_2\text{SCH}_2\text{F}$$
(2)

$$5 \xrightarrow{\operatorname{Cl}_2/\operatorname{H}_2O} \operatorname{CH}_2\operatorname{FSO}_2\operatorname{Cl} + 4\operatorname{-ClC}_6\operatorname{H}_4\operatorname{CH}_2\operatorname{Cl}$$
(3)
$$1 \qquad 6$$

With its modest total yield of 19% the sequence (1)-(3) suffers from the additional drawback of involving the handling and distillation of chlorofluoromethane (3) with a boiling point below room temperature.

It occurred to us that the requirement of handling 3 could be eliminated by preparation of 4-chlorobenzyl fluoromethyl sulfide (5) from 4-chlorophenylmethanethiol (4) via the known 4-chlorobenzyl chloromethyl sulfide (7)⁶⁾ according to the steps (4)–(5).

$$4 \xrightarrow{\text{HCHO/HCI}} 4\text{-ClC}_{6}\text{H}_{4}\text{CH}_{2}\text{SCH}_{2}\text{Cl}$$

$$7$$
(4)

We were able to show that the sequence $(4) \rightarrow (5) \rightarrow (3)$ is indeed feasible with an improved total yield of 29%. In step (5) with KF/ 18-crown-6 the reaction time of 72 h can be reduced to 24 h when the more expensive systems CsF/18-crown-6 or CsF/cis-dicyclohexano-18-crown-6 are employed as the fluorinating agent⁷; the yield is approximately the same in all three cases.

In step $(3)^{2}$ we sometimes identified chloromethanesulfonyl chloride (8) as an additional byproduct; however, the formation of 8 can be avoided by performing the chlorination at exactly -5 °C. Also, in step (3) we found that it is unnecessary to use a spinningband column for distillation. A Claisen column suffices because of the great difference between the boiling points of 1 and 6.

CH₂ClSO₂Cl

8

The most recent methodological improvement concerning the introduction of fluorine into aliphatic substrates involves the use of $Et_3N \cdot 2$ HF as fluorinating agent⁸⁾ and might possibly allow a further streamlining of the synthesis of 1.

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Experimental

¹³C NMR: Gemini (50 MHz); TMS/CDCl₃ as internal standards.

4-Chlorophenylmethanethiol (4) is commercially available. If required it can be conveniently prepared from 4-chlorobenzyl chloride (6)⁹⁾. 4-Chlorobenzyl chloromethyl sulfide (7) was prepared in 61% yield according to the literature procedure⁶⁾ [¹³C NMR (CDCl₃, 50 MHz): $\delta = 34.3$ (s), 48.1 (s), 129.4 (s), 131.1 (s), 133.9 (s), 135.3 (s)]. Potassium and cesium fluoride were predried for 24 h at 120°C/20 Torr⁷⁾. The progress of the reaction $7 \rightarrow 5$ was monitored by ¹H and ¹³C NMR.

4-Chlorobenzyl Fluoromethyl Sulfide (5)⁷: A mixture of 4.50 g (0.017 mol) of 18-crown-6, 250 ml of anhydrous acetonitrile, and 25.6 g (0.44 mol) of anhydrous potassium fluoride was stirred under nitrogen for 1 h. 4-Chlorobenzyl chloromethyl sulfide (7) (45.0 g, 0.22 mol) was added and the reaction mixture heated to reflux with rapid stirring for 72 h. After cooling, the reaction mixture was diluted with 250 ml of ice-cold water, extracted with 400 ml of dichloromethane, the organic phase was separated, dried with anhydrous sodium sulfate, and subsequently distilled in vacuo; yield 28.2 g (68%) of 5. – B.p. 88°C/0.45 Torr (ref.²⁾ 55–58°C/0.005 Torr, this b.p. appears to be in error, the true pressure was probably 0.05 Torr). – $n_D^{21} = 1.5612$. – ¹³C NMR (CDCl₃, 50 MHz): $\delta = 34.8$ (s), 85.7 (d, J = 213 Hz), 129.4 (s), 131.0 (s), 133.8 (s), 135.8 (s).

Fluoromethanesulfonyl Chloride (1)²⁾: A mixture of 70.5 g (0.37 mol) of 5, 80 ml of dichloromethane, and 150 ml of water was stirred at -5° C and saturated with chlorine (1/2-1 h). The organic layer was separated, the aqueous phase extracted with 50 ml of dichloromethane, the combined organic phases were dried with anhydrous sodium sulfate and distilled in vacuo; yield 34.0 g (69%) of 1. - B.p. 40°C/14 Torr (ref.²⁾ 40°C/14 Torr). $-n_{D1}^{21} = 1.4312.$ - ¹³C NMR (CDCl₃, 50 MHz): $\delta = 97.0$ (d, J = 234 Hz). - Furthermore, 43.9 g (74%) of 6 was isolated. - B.p. 98°C/14 Torr (ref.¹⁰⁾ 100.5-101°C/15 Torr).

CAS Registry Numbers

- 1: 42497-69-8 / 5: 98181-84-1 / 7: 15894-25-4
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