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α- or β-Trifluoromethyl epoxysulfones: new C_3 reagents for heterocyclisation ☆

Frédéric Laduron, Zdenek Janousek, Heinz G. Viehe *

Laboratoire de Chimie Organique, Université Catholique de Louvain, Place L. Pasteur, 1, B-1348 Louvain-La-Neuve, Belgium

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Abstract

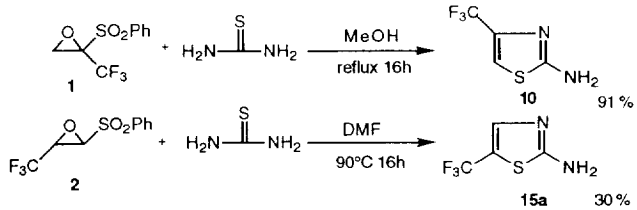
The syntheses of α- and β-trifluoromethyl epoxysulfones **1** and **2** are described. Compound **1** reacts with nucleophiles and bis-nucleophiles to furnish trifluoromethyl ketones and trifluoromethyl heterocycles in good yield, while its isomer **2** leads to the opposite thiazole regioisomers with thioamides.

Keywords: Trifluoromethyl epoxysulfones; Heterocyclisation; Regioisomers; NMR spectroscopy; IR spectroscopy

1. Introduction

The efficient synthesis of heterocycles bearing trifluoromethyl substituents remains a challenge, particularly since these compounds have biological potential [1]. In practice, C_1 reagents may be applied – via CF_3 radical or CF_3 metallorganic species [2]. More frequently, C_2 reagents [3] are used, often derived from trifluoroacetic acid, its aldehyde or alcohol, while typical C_3 reagents are derivatives of trifluroacetone or of trifluoropyruvic acid [4].

We have studied the new α-trifluoromethyl epoxysulfone **1**, obtained from trifluoropropene, and have found it more reactive than its β-isomer **2** in heterocyclisations with bis-nucleophiles, as illustrated with thiourea (Scheme 1).



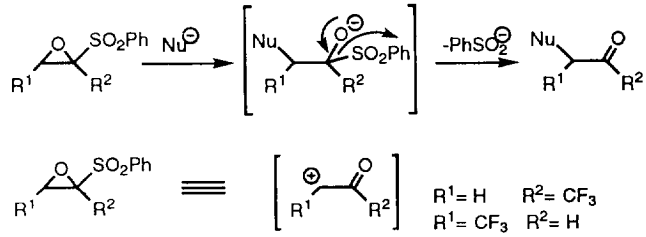
Scheme 1.

2. Results and discussion

Epoxysulfones may undergo β-attack by nucleophiles. Subsequent sulfinate elimination generates carbonyl groups and, hence, these reagents can be regarded as the synthetic equivalent of the α-acyl carbocation, with particular use in heterocyclisations involving bis-nucleophiles (Scheme 2).

Trifluoromethyl epoxides can be prepared either by the cyclisation of halohydrins or of alcoholate adducts of α-bromo-trifluoromethyl ketones [5], by the methylation of trifluoromethyl carbonyl groups with diazomethane [6] or by the oxidation of olefins [7]. We describe here the epoxidation of trifluoromethyl vinylsulfones under either acidic or basic conditions.

In practice, α-trifluoromethyl epoxysulfone (**1**) was obtained from the readily available α-phenylthiotrifluoropropene (**3**) [8], which was prepared from the commercial trifluoropropene. Oxidation of **3** was performed using *m*-chloroperbenzoic acid (*m*-CPBA 50%–60%) in a one-pot reaction via the sulfoxide and



Scheme 2.

☆ Dedicated to Professor W. Schroth on the occasion of his 65th birthday.

* Corresponding author.

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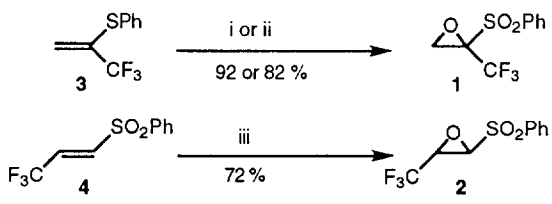
the sulfone [9a]. When *m*-CPBA was used in higher concentration (70%–75%) the epoxidation of the known intermediate vinylsulfone [9b] became unreliable unless traces of $NaHCO_3$ (10%) were added; under these conditions, a rapid and exothermic reaction occurs. Comparison of **3** with the known β-vinylsulfone **4** [10] is interesting, the latter being stable towards *m*-CPBA under the same conditions and requiring basic conditions for its successful epoxidation. Clearly, the polar α-vinylsulfone also reacts by peracid anion addition, even under acidic conditions (Scheme 3).

The isomeric epoxysulfones **1** and **2** are crystalline substances and are stable at room temperature. Compound **1** reacts cleanly with soft nucleophiles such as thiolate or triphenylphosphine, producing the known β-substituted trifluoromethyl ketones **5** and **6** in high yield [11,12] (Scheme 4).

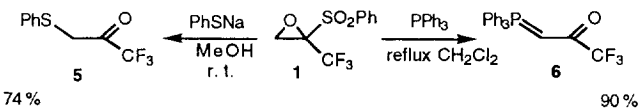
Thus, **1** may serve as a more convenient and more efficient reagent than the alternative bromotrifluoroacetone, a lachrymatory liquid [13]. This advantage is particularly apparent in heterocyclisations of **1** with bis-nucleophiles. The known trifluoromethyl derivatives, formerly produced in lower yield from α-bromotrifluoroacetone [14], are listed in Table 1. Careful control of the reaction conditions has allowed optimization of the yields. We have found that these heterocyclisations permit the use of an aprotic and apolar solvent such as 1,2-dichloroethane, but methanol or ethanol were also found to have practical application in some cases.

In some cases, hydroxysulfinate salts precipitated and could be isolated. Such intermediates confirm the reaction pathway and make heating necessary for dehydration (Scheme 5).

Of synthetic importance is the fact that the isomeric β-trifluoromethyl epoxysulfone (**2**) produces the expected different regioisomers with dissymmetric bis-nucleophiles. Nevertheless, 5-trifluoromethyl thiazoles remain the sole products obtained (Scheme 6).



Scheme 3.



Scheme 4.

In summary, α-trifluoromethyl epoxysulfone **1** and its isomer **2** are useful reagents for heterocyclisations with complementary regiochemistry.

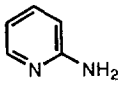
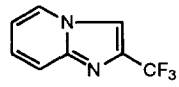
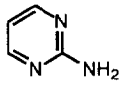
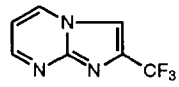
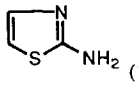
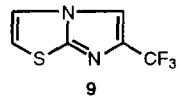
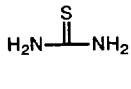
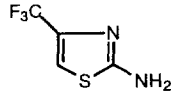
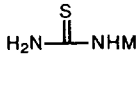
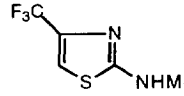
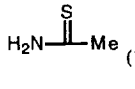
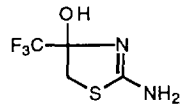
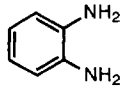
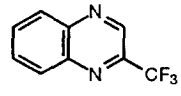
3. Experimental details

Melting points were determined with a Buchi apparatus using capillaries and are uncorrected. The ^1H NMR spectra were recorded on Gemini-200 (200 MHz) and Gemini-300 (300 MHz) spectrometers using tetramethylsilane (TMS) as internal standard. The ^{13}C NMR spectra were recorded on Gemini-200 (50 MHz) and Gemini-300 (75 MHz) spectrometers using $CDCl_3$ or DMSO-d_6 as reference. The ^{19}F NMR spectra were recorded on a Gemini 300 using $CFCl_3$ as the external standard (δ are given in ppm and J in Hz). IR were recorded on a Nicolet-205 apparatus. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM). (*E*)-1-Phenylsulfonyl-3,3,3-trifluoropropene (**4**) was prepared as described for 1-phenylsulfenyl-3,3,3-trifluoropropene, starting from phenylmethyl sulfone [15].

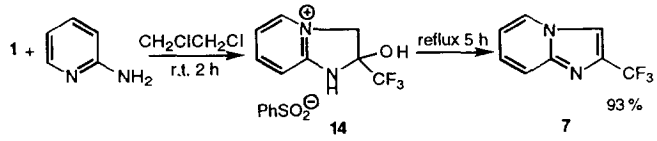
2-Trifluoromethyl-2-phenylsulfonyloxirane (**1**): *m*-CPBA (3.5 equiv.) (70%–75%) was added to a solution consisting of 4.37 g (21.4 mmol) of vinylthioether **3** in 80 ml of CH_2Cl_2. After stirring the mixture for 1 h at room temperature, 0.15 g (0.1 equiv.) of $NaHCO_3$ was added. The *m*-CBA was filtered off after 30 min and the filtrate washed with a solution of saturated $NaHCO_3$. Usual work-up and chromatography on silica gel (CH_2Cl_2) afforded 3.8 g (82%) of **1** as a colorless solid; m.p. 58 °C. IR (cm^{-1}, KBr): 1343; 1297; 1203; 1185; 1171; 852. ^{19}F NMR ($CDCl_3$) δ: −68.3 ppm. ^1H NMR ($CDCl_3$) δ: 3.39 (d, J=5.3 Hz, 1H); 3.81 (dq, J_{H-F}=1.4 Hz, 1H); 7.70 (m, 3H); 7.98 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 49.13, 67.99 (J_{C-F}=38.2 Hz); 120.70 (J_{C-F}=280.4 Hz); 129.30; 129.73; 135.28; 135.86 ppm. Analysis: Calc. for $C_9H_7F_3O_3S$: C, 42.86; H, 2.80%. Found: C, 42.46; H, 2.94%.

trans-2-Trifluoromethyl-3-phenylsulfonyloxirane (**2**): To a cooled solution (−78 °C) consisting of 12 mmol of BuLi in anhydrous THF was added 12 mmol of ^{t}BuOOH in anhydrous octane. After stirring for 1 h at −78 °C, 2.35 g (10 mmol) of vinylsulfone **4** was added dropwise. The mixture was stirred at −78 °C for 1 h and then quenched with 10% HCl. After the usual work-up and chromatography on silica gel (CH_2Cl_2), 1.8 g (72%) of **2** were obtained; m.p. 66 °C. IR (cm^{-1}, KBr): 1344; 1291; 1278; 1162. ^{19}F NMR ($CDCl_3$) δ: −73.4 (d, J=5.7 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 4.15 (qd, J_{H-F}=4.43 Hz, J=1.42 Hz, 1H); 4.34 (d, J=1.42 Hz, 1H); 7.25 (m, 3H); 7.8 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ: 52.37 (J_{C-F}=42.8 Hz); 64.09, 120.84 (q, J_{C-F}=276.2 Hz); 128.95; 129.70; 135.24; 135.76 ppm.

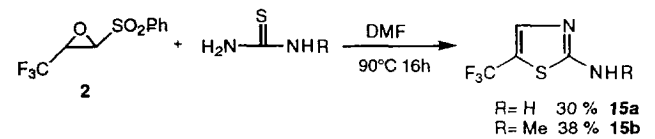
Table 1
Reaction of **1** with bis-nucleophiles

Nucleophile (equiv.)	Conditions	Product	Yield [a] (%) (lit. [14] yield)	^{19}F NMR [b]
 (1.1)	CH_2ClCH_2Cl 1) r.t. 2 h 2) reflux 5 h	 **7**	93(8)	−63.2
 (1.1)	CH_2ClCH_2Cl 1) r.t. 16 h 2) reflux 3 h	 **8**	46(5)	−63.8
 (1.1)	CH_2ClCH_2Cl 1) r.t. 16 h 2) reflux 4 h	 **9**	88(9)	−63.2
 (1.1)	MeOH reflux 16 h	 **10**	91(75)	−65.6
 (1.1)	CH_2ClCH_2Cl 1) r.t. 16 h 2) reflux 30 min	 **11**	99(56)	−65.4
 (1.1)	CH_2ClCH_2Cl r.t. 16 h	 **12**	86(46)	−82.1
 (2)	EtOH 1) r.t. 2 h 2) reflux 16 h	 **13**	45	−67.5

[a] Yields reported are for isolated, purified products.
[b] In ppm, $CDCl_3$ ($CFCl_3$).



Scheme 5.



Scheme 6.

Analysis: Calc. for $C_9H_7F_3O_3S$: C, 42.86; H, 2.80%. Found: C, 42.82; H, 2.87%.

3-Phenylthio-1,1,1-trifluoropropanone (**5**) [11]: To a solution consisting of 0.52 g (4 mmol) of PhSNa in methanol (10 ml) was added 1.0 g (4 mmol) of **1** dissolved in a minimum of methanol at room temperature. The mixture was stirred for 4 h. After the usual work-up, the crude product was distilled at reduced pressure to give 0.65 g (74%) of **5**; b.p. 40 °C/0.06 mmHg (lit. value [11]: 84–85 °C/5 mmHg). IR (cm^{-1}, neat): 1749; 1207; 1156. ^{19}F NMR ($CDCl_3$) δ: −76.7 ppm. ^{1}H NMR ($CDCl_3$) δ: 3.91 (s, 2H); 7.37 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$) δ: 39.19, 115.45 (q, J_{C-F} = 292.8 Hz); 128.39, 129.37, 131.91, 132.32, 185.00 (J_{C-F} = 34.3 Hz) ppm.

Trifluoroacetylmethylenetriphenyl phosphorane (**6**) [12]: Compound **1** (1.0 g, 4 mmol) and 1.25 g (4.77 mmol) of triphenylphosphine were heated at reflux in 15 ml of dry CH_2Cl_2 for 2 h. The solvent was evaporated and the residue washed with diethyl ether. Recrystallisation from diethyl ether/CH_2Cl_2 afforded 1.33 g (90%) of colorless crystals; m.p. 230 °C (lit. value [12]: 230–231 °C). IR (cm^{-1}, KBr): 1595; 1237; 1130; 1107. ^{19}F NMR ($CDCl_3$) δ: −75.6 ppm. ^{1}H NMR ($CDCl_3$) δ: 4.27 (d, J_{H-P} = 20 Hz, 1H); 7.58 (m, 15H) ppm. ^{13}C NMR ($CDCl_3$)

δ: 52.20 (J_{C-P} = 40.5 Hz); 118.81 (J_{C-F} = 290.7 Hz, J_{C-P} = 22.5 Hz); 124.88, 129.19, 132.83, 133.08, 173.62 (J_{C-F} = 31.7 Hz, J_{C-P} = 4.7 Hz) ppm.

As an example of the reaction of **1** with a bis-nucleophile, the preparation of 2-trifluoromethylimidazo[1,2-*a*]pyridine (**7**) is described. A solution consisting of 1.0 g (4 mmol) of **1** and 0.44 (4.77 mmol) of 2-aminopyridine in 30 ml of CH_2ClCH_2Cl was stirred at room temperature for 2 h, during which time a voluminous pink precipitate appeared. The mixture was then heated at reflux for 5 h. The solvent was evaporated at reduced pressure and the product purified by chromatography on silica gel (eluent: diethyl ether) to furnish 0.64 g (93%) of **7**; m.p. 95–96 °C (lit. value [14]: 93–95 °C). IR (cm^{-1}, KBr): 1225; 1145; 1116; 1108. ^{19}F NMR ($CDCl_3$) δ: −63.3 ppm. ^1H NMR ($CDCl_3$) δ: 6.91 (dd, J = 6.8 Hz, J = 6.9 Hz, 1H); 7.30 (ddd, J = 9.2 Hz, J = 6.8 Hz, J = 1.3 Hz, 1H); 7.68 (d, J = 9.2 Hz, 1H); 7.89 (s, 1H); 8.15 (dd, J = 6.9 Hz, J = 1.3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 111.48, 113.84, 118.43, 121.59 (J_{C-F} = 268.2 Hz); 126.25; 126.46, 135.70 (J_{C-F} = 38.2 Hz); 145.34 ppm.

Hydrated phenylsulfinate of **7**: The pink precipitate obtained before heating as described in the above procedure was collected by filtration, washed with CH_2Cl_2, then diethyl ether and recrystallized from ethanol/diethyl ether to give colorless crystals of **14**; m.p. 135 °C. IR (cm^{-1}, KBr): 2708; 1656; 1186; 1151; 1040; 996; 954. ^{19}F NMR (DMSO-d_6) δ: −81.8 ppm. ^1H NMR (DMSO-d_6) δ: 4.87 (dd, J = 14.4 Hz, 2H); 6.97 (split t, 1H); 7.07 (d, J = 8.9 Hz, 1H); 7.39 (m, 5H); 7.96 (split t, 1H); 8.18 (d, J = 6.5 Hz, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ: 57.65, 88.12 (J_{C-F} = 32.5 Hz); 109.36, 114.14, 122.68 (J_{C-F} = 283.2 Hz); 124.10; 127.94; 128.59; 137.35; 144.97; 154.31; 156.56 ppm. Analysis: Calc. for $C_{14}H_{13}F_3N_2O_3S$: C, 48.55; H, 3.78; N, 8.09%. Found: C, 48.33; H, 3.70; N, 7.84%.

3.1. General procedure for the synthesis of thiazoles ***15a, b***

A solution consisting of 1.0 g of **1** and 2 equiv. of thiourea or thioamide in 4 ml of dimethylformamide was heated overnight at 90 °C. After cooling, 40 ml of CH_2Cl_2 were added and the dark solution washed successively with water and brine. Charcoal was then added and after filtration and evaporation of the solvent, the residue was chromatographed on silica gel.

2-Amino-5-trifluoromethylthiazole (**15a**): viscous oil. IR (cm^{-1}, neat): 3163; 3314; 1149; 1117. ^{19}F NMR ($CDCl_3$) δ: −55.3 ppm. ^1H NMR ($CDCl_3$) δ: 5.88 (s br., 2H); 7.40 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 114.54 (J_{C-F} = 37.5 Hz); 122.14 (J_{C-F} = 267.3 Hz); 140.51 (J_{C-F} = 4.8 Hz); 171.17 ppm. Analysis: Calc. for $C_4H_3F_3N_2S$: C, 28.57; H, 1.80; N, 16.66%. Found: C, 28.62; H, 1.68; N, 16.57%.

2-Methylamino-5-trifluoromethylthiazole (**15b**): m.p. 114–116 °C. IR (cm^{-1}, KBr): 3219; 1123; 1104. ^{19}F NMR ($CDCl_3$) δ: −55.0 ppm. ^1H NMR ($CDCl_3$) δ: 2.97 (s, 3H); 7.17 (s br., 1H); 7.44 (q, J_{H-F} = 1.28 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ: 32.15, 112.60 (J_{C-F} = 38.3 Hz); 122.37 (J_{C-F} = 266.5 Hz); 141.09 (J_{C-F} = 4.8 Hz); 173.86 ppm. Analysis: Calc. for $C_5H_5F_3N_2S$: C, 32.97; H, 2.77; N, 15.38%. Found: C, 33.20; H, 2.78; N, 15.35%.

Acknowledgements

The authors are grateful to the Services de la Programmation de la Politique Scientifique (Belgium) and the Fonds National de la Recherche Scientifique (Belgium) for financial support. We thank Martine Redon for valuable experimental information.

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