An Expedient Synthesis of Alkynyl Trifluoromethyl Sulfones

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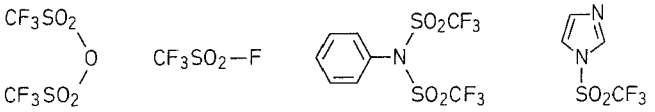
The hitherto difficultly attainable alkynyl trifluoromethyl sulfones **7** were prepared by the reaction of alkynyl sodium salts **6** with trifluoromethanesulfonic anhydride **(1)** in modest to good yields. The reactivity of **7** with different nucleophiles was studied.

Alkynyl sulfones are known to be reactive compounds, especially as dienophiles in [4 + 2] cycloaddition reactions.[1] Due to its negative inductive effect, the sulfonyl group is a strong electron-withdrawing group, resulting in an electron deficiency at the triple bond. This effect is even more pronounced in the alkynyl trifluoromethyl sulfones **7**. While the trifluoromethanesulfonyl group is the strongest electron-withdrawing substituent known,[2] synthesis and reactions of trifluoromethanesulfonyl substituted alkynes are of great interest.

The reactivity of such electron-poor systems as dienophiles in [4 + 2] and 1,3-dipolar cycloaddition reactions has not been extensively studied until now,[3] mainly due to the difficulty to obtain the alkynyl trifluoromethyl sulfones **7**.

Two general methods can be visualized for the preparation of alkynes **7**:[1]

- oxidation of trifluoromethyl sulfides; and
- reaction of metal alkynides with electrophilic reagents such as trifluoromethanesulfonic anhydride **(1)**, trifluoromethanesulfonyl fluoride **(2)**, *N,N*-bis(trifluoromethanesulfonyl)aniline **(3)** and 1-trifluoromethanesulfonylimidazole **(4)**.



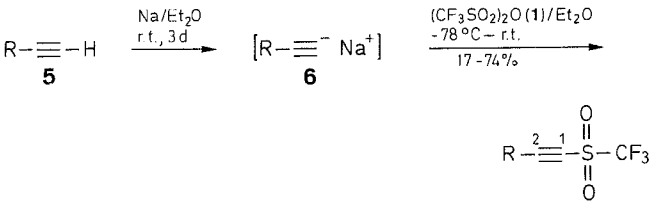
1 **2** **3** **4**

The first method requires the synthesis of alkynyl trifluoromethyl sulfides, which are available[4] from trifluoromethanesulfenyl chloride and alkynyl Grignard reagents. The yield by this method is poor, further disadvantages of this route are the high toxicity and the difficulty to obtain the trifluoromethanesulfenyl chloride.

The second method is more or less restricted to the anhydride **1** as an electrophile. Trifluoromethanesulfonyl fluoride **(2)** would have been the proper choice, however, **2** is not commercially available and the laboratory preparation by electrochemical fluorination of methanesulfonyl chloride[5] in anhydrous hydrofluoric acid needs special apparatus and cannot be realized in all laboratories.

The only synthesis of alkynyl trifluoromethyl sulfones of the type **7** reported[3,6] was the reaction of trifluoromethanesulfonic anhydride **(1)** with alkynyl lithium compounds in low yields. An undesirable side reaction, which was observed in case of phenylethynyl lithium, is the oxidative coupling of the organometallic nucleophile in presence of the anhydride **1**.[3,7] The anhydride **1** could not be successfully replaced by *N,N*-bis(trifluoromethanesulfonyl)aniline **(3)**,[8] or 1-trifluoromethanesulfonylimidazole **(4)**,[8] because the reactivity of **3** and **4** towards organometallic nucleophiles was not strong enough. Our attempts[9] to substitute alkynyl lithium reagents with alkynyl silanes[10] and alkynyl aluminum compounds[11] also failed.

We have now succeeded in synthesizing the required sulfones **7**, in modest to good yields by using the sodium salt of the alkynes[12] instead of the lithium salt. Unlike the more covalent lithium salts, the sodium alkynides are more basic and polar.Hence, the sodium salts **6** do not tend to undergo radical side reactions in the same way as the lithium compounds. The reaction was carried out by adding trifluoromethanesulfonic anhydride **(1)** to sodium alkynides **6** in ether at −78 °C. The sulfones **7** were obtained in 17–74% yield.



5 **6** **7**

5–7	R	5–7	R	5–7	R
a	Ph	**d**	*n*-C_5H_{11}	**f**	*c*-C_6H_{11}
b	4-FC_6H_4	**e**	*n*-C_6H_{13}	**g**	4-$CH_3OC_6H_4$
c	*n*-C_4H_9				

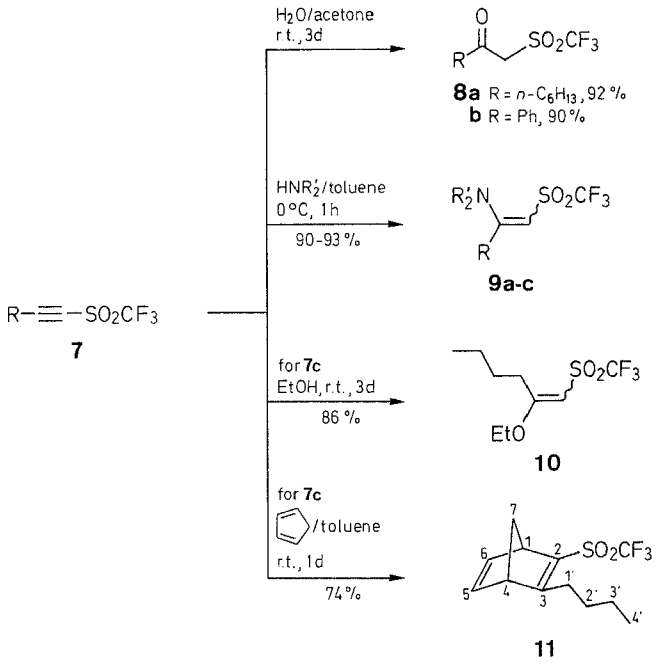
The synthesis described here is applicable in general to alkynes **5**, except where R is an aryl group carrying a heteroatom substituent, e.g. 4-methoxyphenylacetylene (**5g**). Presumably the anhydride **1** coordinates at the free electron pair of the methoxy group and render it inactive.

The alkynyl trifluoromethyl sulfones **7** are thermally labile, colorless to pale yellow oils with characteristic odor, which partially crystallize at 0 °C (Table 1).

The triple bond in sulfones **7** shows a pronounced reactivity towards nucleophiles. Thus, water can be added already at room temperature to form e.g. ketones **8a, b**; with secondary amines, the corresponding enamines **9a–c** were obtained in an exothermic reaction from **7a** and **7c**. Addition of ethanol to **7c**, gives the enol ether **10**.

The preferential formation of only one isomer of **9a–c** was noted in the case of addition of amines to alkynyl sulfones **7a** and **7c**. Although the configuration of **9a–c** cannot be assigned now, we suggest that the thermodynamically stable *E*-isomer is formed preferentially to the *Z*-isomer.[13,14] In the case of addition of ethanol to **7c**, the product was found to be a mixture of *E*/*Z*-isomers in the ratio of 10 : 1. The major isomer is assigned the *E*-configuration for the same reason as-given above.

The alkynyl sulfones **7** are, in general, very reactive towards cyclopentadiene. For example with **7c**, the Diels–Alder adduct **11** was obtained already at room temperature. The addition reactions were carried out on only a few selected examples of alkynyl sulfones, in order to illustrate their generality (Table 2).



9	R	R′	R′
a	*n*-C_4H_9	$-(CH_2)_4-$	
b	*n*-C_4H_9	Et	Et
c	Ph	$-(CH_2)_4-$	

Table 1. Alkynyl Trifluoromethyl Sulfones **7** Prepared

Product	Yield[a] (%)	bp (°C/mbar)[b]	Molecular[c] Formula	IR (film)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$)[f] δ, J(Hz)	MS (70 eV)[g] m/z (M^+)
7a	74	90/2	$C_9H_5F_3O_2S$ (234.2)	2195, 1385, 1240–1210, 1125	7.35–7.76 (m, 5 H_{arom})	77.4 (C-1); 102.6 (C-2); 116.0 (C-1′); 119.9 (q, $^1J_{C-F}$ = 322, CF_3); 129.6 (C-3′, C-5′); 133.2 (C-4′); 134.9 (C-2′, C-6′)[h]	234
7b	17	80/2	$C_9H_4F_4O_2S$ (252.2)	2193, 1385, 1223, 1122	7.04–7.29 (m, $H_{arom,ortho}$); 7.60–7.81 (m, 2 $H_{arom,meta}$)	77.4 (C-1); 101.7 (C-2); 112.5 (d, $^4J_{C-F}$ = 3, C-1′); 117.9 (d, $^2J_{C-F}$ = 23, C-3′, C-5′); 119.9 (q, $^1J_{C-F}$ = 322, CF_3); 138.1 (d, $^3J_{C-F}$ = 10, C-2′, C-6′); 166.7 (d, $^1J_{C-F}$ = 257, C-4′)[h]	252
7c	60	80/6	$C_7H_9F_3O_2S$ (214.2)	2220, 1380, 1240–1210, 1135	0.92 (t, 3H, J = 6.2, H-6); 1.23–1.79 (m, 4H, H-4, H-5); 2.53 (t, 2H, J = 6.7, H-3)	12.8 (C-6); 18.7 (C-3); 21.7 (C-5); 28.5 (C-4); 70.1 (C-1); 106.0 (C-2); 118.6 (q, $^1J_{C-F}$ = 322, CF_3)	–
7d	50	80/6	$C_8H_{11}F_3O_2S$ (228.2)	2210, 1380, 1250–1200, 1130	0.90 (t, 3H, J = 7.4, H-7); 1.26–1.74 (m, 6H, H-4, H-5, H-6); 2.53 (t, 2H, J = 6.8, H-3)	13.5 (C-7); 19.1 (C-3); 21.8 (C-6); 26.2 (C-4); 30.7 (C-5); 70.3 (C-1); 106.1 (C-2); 119.0 (q, $^1J_{C-F}$ = 323, CF_3)	–
7e	50	70/4	$C_9H_{13}F_3O_2S$ (242.3)	2217, 1382, 1230–1200, 1132	0.88 (t, 3H, J = 6.0, H-8); 1.20–1.74 (m, 8H, H-4, H-5, H-6, H-7); 2.53 (t, 2H, J = 6.8, H-3)	13.8 (C-8, [q]); 19.3 (C-3, [t]); 22.4 (C-7, [t]); 26.6 (C-4, [t]); 28.4 (C-5, [t]); 31.0 (C-6, [t]); 70.4 (C-1, [s]); 106.0 (C-2, [s]); 119.0 (q, $^1J_{C-F}$ = 322, CF_3, [q])	242
7f	72	70/4	$C_9H_{11}F_3O_2S$ (240.2)	2198, 1382, 1230–1200, 1132	1.23–1.93 (m, 10H, H-2′, H-3′, H-4′, H-5′, H-6′); 2.60–2.90 (m, 1H, H-1′)	24.2 (C-4′, [t]); 25.2 (C-3′, C-5′, [t]); 29.2 (C-1′, [d]); 30.3 (C-2′, C-6′, [t]); 70.3 (C-1, [s]); 108.9 (C-2, [s]); 118.9 (q, $^1J_{C-F}$ = 323, CF_3, [q])	240

[a] Yield of pure isolated product.
[b] Refers to bath temperature of Kugelrohr distillation.
[c] Satisfactory microanalyses obtained: C ±0.28, H ±0.28, S ±0.28; except for **7a** (C +0.44, S +0.55) and **7b** (C +0.51).
[d] Recorded on a Perkin Elmer 398 infrared spectrophotometer.
[e] Recorded on Varian EM 360 (60 MHz), Bruker WH 90 (90 MHz), Bruker HFX 90 (90 MHz), and Bruker WM 400 (400 MHz) spectrometers.
[f] Recorded on Bruker WP 80 (20.1 MHz), Bruker WH 90 (22.6 MHz), and Bruker WM 400 (100 MHz) spectrometers; [ ] refers to the multiplicity of the signal in the off-resonance spectrum.
[g] Recorded on a Varian MAT 711 (70 eV).
[h] Solvent: acetone-d_6.

Table 2. Compounds **8–11** Prepared

Product	Reactants	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr, film)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)	^{13}C-NMR ($CDCl_3$)[f] δ, J(Hz)	MS (70 eV)[g] m/z (M^+)
8a	**7e** + H_2O	92	68	$C_9H_{15}F_3O_3S$ (260.3)	1720, 1362, 1225–1195, 1120	0.85 (t, 3H, J = 5.6, H-8); 1.25–1.67 (m, 8H, H-4, H-5, H-6, H-7); 2.69 (t, 2H, J = 7.0, H-3); 4.24 (s, 2H, H-1)	13.8 (C-8, [q]); 22.3, 23.0, 28.3, 31.3 (C-4, C-5, C-6, C-7, [t]); 44.5 (C-3, [t]); 59.7 (C-1, [t]); 126.3 (q, $^1J_{C-F}$ = 327, CF_3, [q]); 194.6 (C-2, [s])	260
8b	**7a** + H_2O	90	35	$C_9H_7F_3O_3S$ (252.1)	1689, 1375, 1200–1225, 1120	4.84 (s, 2H, H-1); 7.41–8.03 (m, 5H_{arom})	–	252
9a	**7c** + pyrrolidine	93	59	$C_{11}H_{18}F_3NO_2S$ (285.3)	1532, 1349, 1200–1170, 1110	0.91 (t, J = 6.8, 3H, H-6); 1.29–1.64 (m, 4H, H-4, H-5); 1.91–2.08 (m, 4H, $NCH_2\underline{CH_2}$); 2.65 (t, 2H, J = 7.9, H-3); 3.21, 3.51 (2 × t, 2 × 2H, J = 6.7, 6.8, NCH_2CH_2); 4.34 (s, 1H, H-1)	13.5 (C-6, [q]); 22.1, 30.0, 30.7 (C-3, C-4, C-5, [t]); 24.6, 25.3 ($NCH_2\underline{C}H_2$, [t]); 48.3, 49.3 ($N\underline{C}H_2CH_2$, [t]); 77.9 (C-1, [d]); 120.8 (q, $^1J_{C-F}$ = 326, CF_3, [q]); 167.0 (C-2, [s])	285
9b	**7c** + Et_2NH	90	36	$C_{11}H_{20}F_3NO_2S$ (287.3)	1545, 1380, 1210–1170, 1123	0.89 (t, 3H, J = 6.5, H-6); 1.18 (t, 6H, J = 7.2, $NCH_2\underline{CH_3}$); 1.33–1.60 (m, 4H, H-4, H-5); 2.61 (t, 2H, J = 7.8, H-3); 3.29 (q, 4H, J = 7.0, $NCH_2\underline{CH_3}$); 4.43 (s, 1H, H-1)	11.0, 14.4 ($NCH_2\underline{C}H_3$, [q]); 13.8, 28.7, 32.7 (C-3, C-4, C-5, [t]); 45.3, 45.6 ($N\underline{C}H_2CH_3$, [d]); 77.6 (C-1, [d]); 121.8 (q, $^1J_{C-F}$ = 326, CF_3, [q]); 168.7 (C-2, [s])[h]	287
9c	**7a** + pyrrolidine	90	110	$C_{13}H_{14}F_3NO_2S$ (305.2)	1523, 1350, 1207, 1179, 1119	1.74–2.22 (m, 4H, $NCH_2\underline{CH_2}$); 2.99, 3.36 (2 × t, 2 × 2H, J = 6.8, 6.5, NCH_2CH_2); 4.72 (s, 1H, H-1); 7.14–7.48 (m, 5H_{arom})	24.9, 25.1 ($NCH_2\underline{C}H_2$, [t]); 49.0, 50.7 ($N\underline{C}H_2CH_2$, [t]); 80.3 (C-1, [d]); 120.5 (q, $^1J_{C-F}$ = 326, CF_3, [q]); 127.6, 128.0, 129.4 (C-2′, C-3′, C-4′, C-5′, C-6′, [d]); 133.0 (C-1′, [s]); 164.4 (C-2, [s])	305
10	**7c** + EtOH	86	oil	$C_9H_{15}F_3O_3S$ (260.3)	1575, 1370, 1200, 1129	0.89 (t, 3H, J = 6.8, H-6); 1.14–1.65 (m, 7H, H-4, H-5, $OCH_2\underline{CH_3}$); 2.68 (t, 2H, J = 7.4, H-3); 3.92 (q, 2H, J = 7.0, $OCH_2\underline{CH_3}$); 5.17 (s, 1H, H-1)	13.6, 13.8 (C-6, $OCH_2\underline{C}H_3$, [q]); 22.3, 29.7, 31.8 (C-3, C-4, C-5, [t]); 66.0 ($O\underline{C}H_2CH_3$, [t]); 91.1 (C-1, [d]); 120.1 (q, $^1J_{C-F}$ = 325, CF_3, [q]); 182.5 (C-2, [s])	260
11	**7c** + cyclopentadiene	74	oil	$C_{12}H_{15}F_3O_2S$ (280.3)	1598, 1360, 1225–1180, 1130	0.79–1.00 (t, 3H, J = 7.2, H-4′); 1.18–1.65 (m, 4H, H-2′, H-3′); 2.04–2.21 (2 × dt, 2H, $^2J_{H-H}$ = 7.0, $^3J_{H-H}$ = 1.6, H-7); 2.74 (t, 2H, J = 7.5, H-1′); 3.75, 3.98 (2 × s, 2H, H-1, H-4); 6.65–6.99 (m, 2H, H-5, H-6)	13.6 (C-4′, [q]); 22.5, 28.7, 29.7 (C-1′, C-2′, C-3′, [t]); 52.9, 57.9 (C-1, C-4, [d]); 72.2 (C-7, [t]); 119.9 (q, $^1J_{C-F}$ = 326, CF_3, [q]); 136.6 (C-2, [s]); 139.8, 143.5 (C-5, C-6, [d]); 187.3 (C-3, [s])	280

[a] Yield of pure isolated product.
[b] Compounds **8a, b** were recrystallized from *n*-hexane, compounds **9–11** were purified by flash chromatography. Melting points, measured with a Büchi-SMP 20 apparatus, are uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.25, H ±0.18, N ±0.17, S ±0.27.
[d–g] See Table 1.
[h] Solvent: acetone-d_6.

All reactions were conducted under anhydrous conditions in an atmosphere of nitrogen. Trifluoromethanesulfonic anhydride (**1**) was prepared as described[8] and redistilled from diphosphorus pentoxide immediately before use. GC analyses were done on Hewlett-Packard, HP-5890 A and Carlo Erba FTV 2150 gas chromatographs using glass and fused silica capillar columns coated with SE 52.

Alkinyl Trifluoromethyl Sulfones 7; General Procedure:
To a suspension of small pieces of sodium (0.92 g, 40 mmol), in ether (100 mL), is added the corresponding alkyne **5** (40 mmol) with a syringe. The mixture is stirred at room temperature until all sodium has reacted completely (ca. 3 d). The sodium salt precipitates as a voluminous white-yellow powder. After cooling the suspension to −78 °C, a solution of trifluoromethanesulfonic anhydride (10.82 g, 40 mmol) in ether (50 mL) is added dropwise under continued stirring. The mixture is allowed to come to room temperature slowly. It is washed with sat. $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated. The residual brown oil is purified by Kugelrohr distillation (Table 2).

To remove traces of acid eventually present, the product is dissolved in petroleum ether (30/50, 10 mL) and shaken with powdered anhydrous $NaHCO_3$ (0.5 g) and anhydrous $MgSO_4$ for 1–2 min and filtered.

Addition of Water to Alkynyl Sulfones 7; 2-Oxooctyl Trifluoromethyl Sulfone (8a); Typical Procedure:
To 1-octynyl trifluoromethyl sulfone (**7e**; 0.73 g, 3 mmol) and water (2.7 g, 150 mmol) is added acetone till the mixture is homogeneous.

After stirring at room temperature for 3 d, the solvent is evaporated and the residue recrystallized from *n*-hexane; yield: 0.72 g (92%).

Addition of Amines to Alkynyl Sulfones 7; 2-(1-Pyrrolidinyl)-1-hexenyl Trifluoromethylsulfone (9a); Typical Procedure:

1-Hexynyl trifluoromethyl sulfone (**7c**; 0.96 g, 4.5 mmol) is dissolved in absolute toluene (10 mL). The mixture is cooled in an ice-bath and a solution of freshly distilled pyrrolidine (0.32 g; 4.5 mmol) in toluene (10 mL) is slowly added. After stirring for another 1 h, the solvent is evaporated. The crystalline residue is purified by flash chromatography on silica gel (eluent: *n*-hexane/EtOAc, 1:1) to give colorless crystals; yield: 1.2 g (93%).

Addition of Ethanol to Alkynyl Sulfones 7; 2-Ethoxy-1-hexenyl Trifluoromethyl Sulfone (10):

1-Hexynyl trifluoromethyl sulfone (**7c**, 1.28 g, 6 mmol) is dissolved in absolute EtOH (10 mL) and the solution is stirred at room temperature for 3 d. The EtOH is evaporated, and the oily residue is purified by flash chromatography on silica gel (eluent: EtOAc). A colorless oil is obtained, which crystallizes on storage in a refrigerator; yield: 1.3 g (86%).

Addition of Cyclopentadiene to Alkynyl Sulfones 7; 3-Butyl-2-trifluoromethanesulfonylbicyclo[2.2.1]heptadiene (11):

A solution of 1-hexynyl trifluoromethyl sulfone (**7c**; 0.75 g, 3.5 mmol) and cyclopentadiene (0.23 g; 3.5 mmol) dissolved in absolute toluene (15 mL) is stirred at room temperature for 1 d. The solvent is evaporated, and the oily residue is purified by flash chromatography on silica gel (eluent: *n*-hexane/EtOAc, 1:1); colorless oil; yield: 0.73 g (74%).

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