3,3,3-Trifluoro-2,2-dihydroxypropanesulfonamides as Building Blocks for Trifluoromethyl-containing Pyrazoles and Benzimidazoles

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1-Alkyl-3-trifluoromethylpyrazole-4-sulfonamides **10**, (2-trifluoromethyl-2,3-dihydrobenzimidazol-2-yl)methanesulfonamides **12**, and (2-benzimidazolyl)methanesulfonamides **13** were prepared starting from 3,3,3-trifluoro-2,2-dihydroxypropanesulfonamides **1**.

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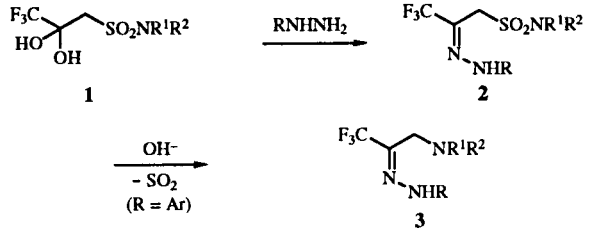
We have been interested in using sulfonamides as building blocks for heterocycles, and reported that 5-arylamino-3-arylimino-1,2-dithiole-3-sulfonamides were obtained in one pot by the reaction of carbanions of methanesulfonamides with aryl isothiocyanates followed by oxidation with hydrogen peroxide [1]. We also reported that trifluoroacetylation of methyl sulfones by ethyl trifluoroacetate in the presence of base afforded a monohydrate of the trifluoroacetylated derivatives, 3,3,3-trifluoro-2,2-dihydroxypropyl sulfones, which were useful for the synthesis of trifluoromethyl-containing pyrazoles [2] and 1,4-thiazine 1,1-dioxides [3]. Similar treatment of methanesulfonamides with ethyl trifluoroacetate gave the corresponding 3,3,3-trifluoro-2,2-dihydroxypropanesulfonamides **1**, which seem also to serve as building blocks for trifluoromethyl-containing heterocycles [4]. However, the previous attempt to prepare trifluoromethyl-containing pyrazoles from their arylhydrazones **2** resulted in an unexpected formation of the corresponding amines **3** accompanied by an interesting extrusion of sulfur dioxide [5] (Scheme 1).

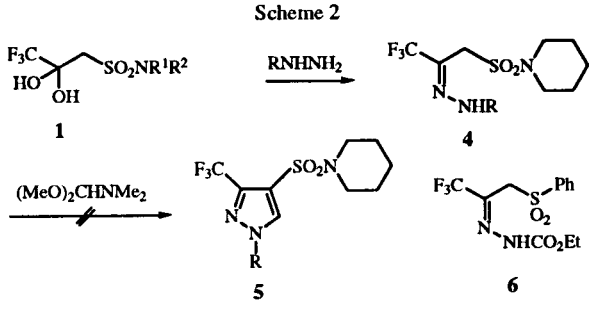
Scheme 1



In the course of our further studies on the synthesis of trfluoromethyl-containing heterocycles using **1**, it was found that 1-alkyl-3-trifluoromethylpyrazole-4-sulfonamides **10** could be prepared from **1** and that the trifluoromethyl group at the 2 position of dihydrobenzimidazoles **12** obtained from **1** and *o*-phenylenediamines was extruded as trifluoromethane to give (2-benzimidazolyl)-methanesulfonamides **13**. These results will be described in this paper.

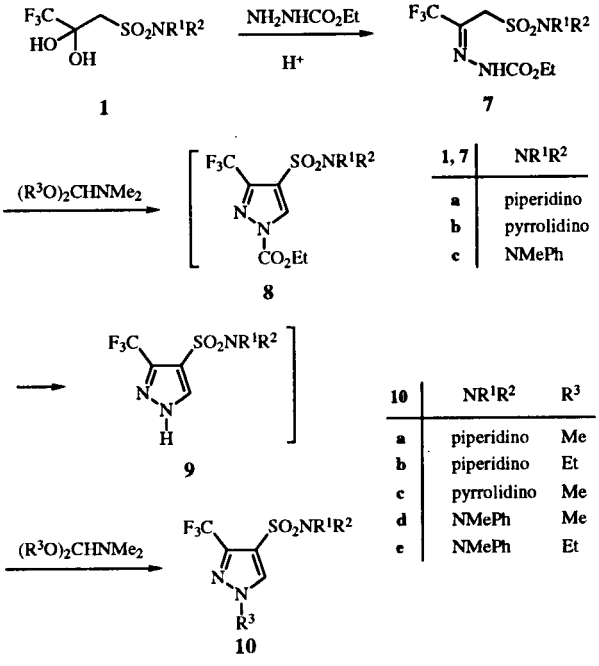
The reaction of hydrazones **4** with dimethylformamide dimethylacetal [6] would form 3-trifluoromethylpyrazole-4-sulfonamides **5** (Scheme 2). However, all attempts to

Scheme 2



cyclize hydrazone **4** (R = H), phenylhydrazone **4** (R = Ph), and benzoylhydrazone **4** (R = PhCO) to **5** were unsuccessful. Previously we reported that 1-alkyl-3-trifluoromethyl-4-phenylsulfonylpyrazoles were prepared from ethoxycarbonylhydrazone **6** of 1,1,1-trifluoro-3-phenylsulfonyl-2-propanone [2]. Similar results are expected in the case of ethoxycarbonylhydrazones **7** of sulfonamides **1** (Scheme 3). Thus, ethoxycarbonylhydrazones **7a-c** were

Scheme 3



1, 7	NR^1R^2
a	piperidino
b	pyrrolidino
c	NMePh

10	NR^1R^2	R^3
a	piperidino	Me
b	piperidino	Et
c	pyrrolidino	Me
d	NMePh	Me
e	NMePh	Et

Table 1
Physical Properties of Compounds **7**, **10**, **12**, and **13**

	Yield (%)	Mp (°C)	Molecular Formula	Found C	Found H	Found N	(Calcd.) C	(Calcd.) H	(Calcd.) N
7a	77	125-127	$C_{11}H_{18}N_3O_4SF_3$	38.23	5.14	12.26	(38.25	5.25	12.17)
7b	80	138-139	$C_{10}H_{16}N_3O_4SF_3$	36.11	4.77	12.55	(36.25	4.87	12.69)
7c	75	149-151	$C_{13}H_{16}N_3O_4SF_3$	42.37	4.41	11.71	(42.50	4.39	11.44)
10a	35	127-129	$C_{10}H_{14}N_3O_2SF_3$	40.19	4.64	14.42	(40.40	4.75	14.14)
10b	51	105-106	$C_{11}H_{16}N_3O_2SF_3$	42.43	5.11	13.33	(42.43	5.18	13.50)
10c	30	129-131	$C_9H_{12}N_3O_2SF_3$	37.89	4.22	15.03	(38.16	4.25	14.84)
10d	27	126-127	$C_{12}H_{12}N_3O_2SF_3$	44.92	3.71	12.86	(45.13	3.79	13.16)
10e	53	92-93	$C_{13}H_{14}N_3O_2SF_3$	46.57	4.29	12.66	(46.84	4.23	12.61)
12a	65	131-132	$C_{14}H_{18}N_3O_2SF_3$	47.92	5.11	11.92	(48.13	5.19	12.03)
12b	64	153-154	$C_{16}H_{22}N_3O_2SF_3$	50.87	5.77	11.05	(50.92	5.88	11.13)
12c	63	140-141	$C_{15}H_{20}N_3O_2SF_3$	49.57	5.50	11.56	(49.58	5.55	11.56)
12d	44	142-143	$C_{14}H_{17}N_3O_2SClF_3$	43.79	4.49	10.93	(43.81	4.46	10.95)
13a	77	208-209	$C_{13}H_{17}N_3O_2S \cdot 1/2H_2O$	54.12	5.93	14.29	(54.14	6.24	14.58)
13b	75	162-164 dec	$C_{15}H_{21}N_3O_2S$	58.23	6.83	13.82	(58.61	6.89	13.67)

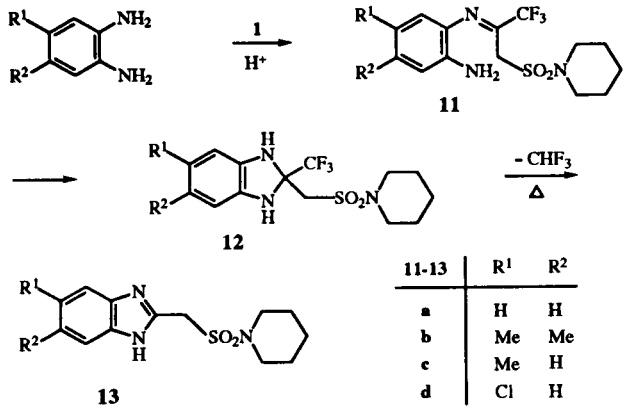
prepared in 75-80% yields by refluxing a mixture of **1** and ethyl carbazate in ethanol in the presence of *p*-toluenesulfonic acid. A mixture of ethoxycarbonylhydrazone **7a** and dimethylformamide dimethylacetal was refluxed without solvent for 2 hours under a nitrogen atmosphere to afford 1-methyl-3-trifluoromethylpyrazole-4-sulfonamide **10a** (35%). Other 1-alkyl-3-trifluoromethylpyrazole-4-sulfonamides **10b-e** were similarly obtained using the corresponding dimethylformamide dialkylacetals in 27-53% yields (Tables 1 and 2). The structure of the product was confirmed on the basis of the elemental analyses and the spectral data. The C-5 hydrogen of the pyrazole ring was observed at around δ 7.4-7.9 as a singlet in the nmr spectra, and its stretching vibration absorption in the ir spectra was shown as a sharp peak at around 3110-3140 cm^{-1}. It is noteworthy that alkylation occurred at the N-1 position of **10** by dimethylformamide acetals. The ethoxycarbonyl-nitrogen bond of the initial cyclized products **8** would be weakened by the two strongly electron-withdrawing trifluoromethyl and sulfonamide substituents and therefore broken by the attack of alcohols or dimethylamine formed during cyclization to give **9**. Excess dimethylformamide dialkylacetal would alkylate [6] the N-1 position of **9** to yield the final products **10**. A unique synthesis of trifluoromethyl-containing pyrazoles has been thus established in the case of sulfonamides as well as sulfones [7].

Table 2
Spectral Date of Compounds **7**, **10**, **12**, and **13**

	MS, m/z (%)	IR (Potassium bromide), cm^{-1}	^{1}H-NMR (deuteriochloroform), δ
7a	345 (M^+, 0.5), 198 (19), 125 (14), 84 (100)	3220, 2950, 1710 1545, 1370, 1250	1.34 (t, J = 6.7 Hz, 3H), 1.60-1.70 (m, 6H), 3.32 (t, J = 5.1 Hz, 4H), 4.04 (s, 2H), 4.33 (q, J = 6.7 Hz, 2H), 9.87 (br s, 1H)
7b	286 (M^+-OEt, 3), 198 (22), 125 (20), 70 (100)	3310, 2990, 1755 1535, 1360, 1325	1.35 (t, J = 6.8 Hz, 3H), 1.87-2.01 (m, 4H), 3.42 (t, 4H, J = 6.8 Hz), 4.13 (s, 2H), 4.33 (q, J = 6.8 Hz, 2H), 9.90 (br s, 1H)
7c	367 (M^+, 5), 215 (4) 125 (27), 107 (100)	3235, 1725, 1545 1500, 1365, 1260	1.31 (t, J = 7.4 Hz, 3H), 3.39 (s, 3H), 4.11 (s, 2H) 4.29 (q, J = 7.4 Hz, 2H), 7.35-7.46 (m, 5H), 9.59 (br s, 1H)
10a	297 (M^+, 31), 296 (40) 213 (58), 83 (100)	3140, 2950, 1520 1495, 1345, 1240	1.54 (m, 2H), 1.64-1.69 (m, 4H), 3.11 (t, J = 4.9 Hz, 4H), 3.99 (s, 3H), 7.85 (s, 1H)
10b	311 (M^+, 32), 310 (41) 227 (47), 83 (100)	3125, 2935, 1490 1345, 1225, 1165	1.48-1.69 (m, 6H), 1.56 (t, J = 7.7 Hz, 3H), 3.12 (t, J = 5.1 Hz, 4H), 4.25 (q, J = 7.7 Hz, 2H), 7.88 (s, 1H)
10c	283 (M^+, 26), 284 (27) 213 (31), 70 (100)	3135, 1490, 1355 1235, 1170, 1150	1.86-1.90 (m, 4H), 3.31 (t, J = 6.9 Hz, 4H), 3.99 (s, 3H), 7.90 (s, 1H)
10d	319 (M^+, 24), 255 (6) 214 (6), 106 (100)	3110, 1495, 1360 1235, 1165, 1145	3.29 (s, 3H), 3.90 (s, 3H), 7.19-7.36 (m, 5H), 7.46 (s, 1H)
10e	333 (M^+, 77), 269 (24) 228 (29), 106 (100)	3100, 1495, 1360 1170, 1160, 1140	1.45 (t, J = 7.9 Hz, 3H), 3.29 (s, 3H), 4.15 (q, J = 7.9 Hz, 2H) 7.19-7.35 (m, 5H), 7.42 (s, 1H)
12a	349 (M^+, 16), 280 (50) 187 (44), 131 (100)	3300, 2950, 1495 1440, 1340, 1270	1.53-1.63 (m, 6H), 3.20 (t, J = 7.1 Hz, 4H), 3.36 (s, 2H), 4.73 (br s, 2H), 6.70-6.78 (m, 4H)
12b	377 (M^+, 15), 308 (23) 215 (42), 159 (100)	3350, 2820, 1500 1430, 1320, 1250	1.54-1.65 (m, 6H), 2.14 (s, 6H), 3.22 (t, J = 5.0 Hz, 4H), 3.34 (s, 2H), 4.61 (br s, 2H), 6.54 (s, 2H)
12c	363 (M^+, 13), 294 (34) 201 (38), 145 (100)	3360, 2930, 1510 1460, 1325, 1260	1.53-1.63 (m, 6H), 2.23 (s, 3H), 3.21 (t, J = 4.9 Hz, 4H), 3.35 (s, 2H), 4.65 (s, 1H), 4.70 (s, 1H), 6.56-6.63 (m, 3H)
12d	383 (M^+, 18), 314 (43) 221 (52), 165 (100)	3370, 2950, 1495 1325, 1270, 1245	1.57-1.65 (m, 6H), 3.22 (t, J = 5.8 Hz, 4H), 3.34 (s, 2H), 4.72 (s, 1H), 4.80 (s, 1H), 6.59-6.73 (m, 3H)
13a	279 (M^+, 0.2), 132 (100), 84 (27)	3350, 2940, 1430 1330, 1160, 1140	1.45-1.55 (m, 6H), 3.13 (t, J = 5.2 Hz, 4H), 4.67 (s, 2H), 7.27-7.32 (m, 4H), 10.35 (br s)
13b	307 (M^+, 6), 160 (100) 144 (4), 84 (11)	3570, 2940, 1450 1315, 1160, 1135	1.45-1.52 (m, 6H), 2.35 (s, 6H), 3.11 (t, J = 4.8 Hz, 4H), 4.60 (s, 2H), 7.36 (br s, 2H)

Fluorine-containing benzimidazoles are important in the field of agrochemicals and medicines [8]. Compounds **1** also appear to be a good building block for the preparation of benzimidazoles [9] having a trifluoromethyl group. Treatment of **1a** with *o*-phenylenediamine in refluxing benzene gave a Schiff's base **11a** (86%), which was further transformed into 2,3-dihydrobenzimidazole **12a** on refluxing in ethanol in the presence of *p*-toluenesulfonic acid (Scheme 4). Benzimidazole **12a** was obtained directly in 65% yield by refluxing a mixture of **1a** and *o*-phenylenediamine in ethanol in the presence of *p*-toluenesulfonic acid. Other 2,3-dihydrobenzimidazoles **12b-d** were prepared in 44-64% yields in the same manner, and their physical and spectral data are shown in Tables 1 and 2. 2,2-Dialkyl substituted 2,3-dihydrobenzimidazloes are known to give 2-monoalkyl substituted benzimidazoles on heating with elimination of alkane [9]. It seems interesting which substituent, trifluoromethyl or sulfamoylmethyl, in **12** would be eliminated on heating. Thus, heating a solution of **12** in dimethyl sulfoxide at 140° gave (2-benzimidazolyl)methanesulfonamides **13a-c** selectively in 48-77% yields, losing the trifluoromethyl group. Benzimidazole **12d** yielded an inseparable reaction mixture. Similar elimination of trifluoromethane has been observed in the heteroaromatization of 3,3-bis(trifluoromethyl)-1,2,4-triazolines into 3-trifluoromethyl-1,2,4-triazoles on heating in the presence of azobisisobutyronitrile [10].

Scheme 4



11-13	R1	R2
a	H	H
b	Me	Me
c	Me	H
d	Cl	H

EXPERIMENTAL

Melting points were determined with a MRK MEL-TEMP II and are uncorrected. The ir spectra were measured on a JASCO A-102 spectrophotometer. Mass and ^{1}H-nmr spectra were taken with a JEOL JMS DX-300 spectrometer and a JEOL GSX-400 spectrophotometer, respectively. Microanalyses were performed with a YANAKO CHN-CODER MT-5. The starting materials **1a** and **b** were prepared as described in the previous paper [5] and **1c** was used in the next step without isolation because of difficulty in purification.

2-(Ethoxycarbonyl)hydrazono-3,3,3-trifluoropropanesulfonamides **7.**

General Procedure.

A mixture of **1** (7.0 mmoles), ethyl carbazate (10.5 mmoles), and *p*-toluenesulfonic acid monohydrate (1.0 mmole) in ethanol (7 ml) was refluxed for 10 hours. After cooling, the precipitate was collected by filtration and the filtrate was concentrated *in vacuo* to give additional precipitate. The combined precipitate was recrystallized from methanol to give **7**.

1-Alkyl-3-trifluoromethyl-4-pyrazolesulfonamides (**10**)

General Procedure.

A mixture of **1** (1.0 mmole) and *N,N*-dimethylformamide dialkylacetal (2 ml) was refluxed for 2-5 hours under a nitrogen atmosphere. The excess acetal was removed *in vacuo* to give a brown oily residue, which solidified gradually. The solid product was collected by filtration and recrystallized from chloroform-hexane or dichloromethane-hexane to give **10**.

N-[3,3,3-Trifluoro-2-(2-aminoanilidene)propanesulfonyl]piperidine (**11a**).

A mixture of **1a** (280 mg, 1.0 mmole) and *o*-phenylenediamine (160 mg, 1.5 mmoles) in benzene (2 ml) was refluxed for 6 hours. The residue obtained after evaporation of the solvent was column-chromatographed on silica gel with an eluent of hexane-ethyl acetate (3:2) to give yellow **11a** (300 mg, 86% yield), mp 114-115° (methanol); ir (potassium bromide): 3450, 3350, 2920, 1610, 1490, 1420, 1320 cm^{-1}; ms: (%) m/z 349 (M^+, 27), 280 (55), 187 (42), 131 (100); ^{1}H-nmr (deuteriochloroform): δ 1.51-1.72 (m, 6H), 3.07-3.34 (m, 4H), 3.86 (br s, 2H), 4.19 (s, 2H), 6.75-7.12 (m, 4H).

Anal. Calcd. for $C_{14}H_{18}N_3O_2SF_3$: C, 48.13; H, 5.19; N, 12.03. Found: C, 48.07; H, 5.30; N, 11.76.

N-[(2-Trifluoromethyl-2,3-dihydrobenzimidazol-2-yl)methanesulfonyl]piperidines **12a-d.**

General Procedure.

A mixture of **1a** (2.0 mmoles), *o*-phenylenediamine (4.0 mmoles), and *p*-toluenesulfonic acid monohydrate (2.0 mmoles) in ethanol (4 ml) was refluxed for 6 hours. After cooling, the mixture was poured into water (50 ml). The precipitate formed was collected by filtration and recrystallized from methanol to give **12.**

N-[(2-Benzimidazolyl)methanesulfonyl]piperidines **13a-c.**

General Procedure.

A mixture of **12** (1.0 mmole) in dimethyl sulfoxide (5 ml) was heated at 140° with stirring for 1 hour. After cooling, the mixture was poured into water (50 ml), and the resulting precipitate was collected by filtration and recrystallized from chloroform-hexane to give **13**. Product **13c** (48% yield) was difficult to prepare an analytically pure sample, mp 59-83°; ir (potassium bromide): 3300, 2920, 1440, 1320, 1140, 1045 cm^{-1}; ms: (%) m/z 293 (M^+, 2), 214 (1), 146 (100), 84 (17); ^{1}H-nmr (deuteriochloroform): δ 1.43-1.54 (m, 6H), 3.46 (s, 3H), 3.12 (t, J = 5.4 Hz, 4H), 4.65 (s, 2H), 7.11-7.36 (m, 3H), 10.27 (br s, 1H).

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