SYNTHESIS OF 3-TRIFLUOROMETHYLPYRAZOLES AND 3-TRIFLUOROMETHYLPYRIDAZINES FROM 2-AMINO-1,1,1-TRIFLUORO-3-PHENYLSULFONYL-2-PROPANOL

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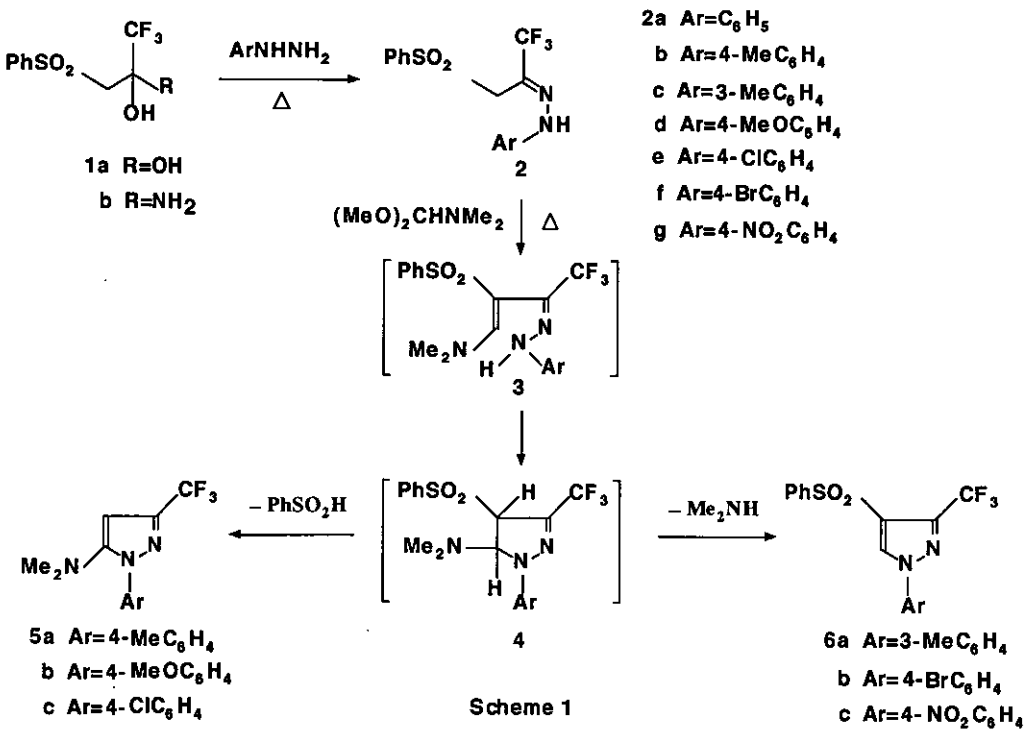
Abstract-----3-Trifluoromethylpyrazoles and 3-trifluoromethylpyridazines were prepared from 2-amino-1,1,1-trifluoro-3-phenylsulfonyl-2-propanol. In some cases elimination or substitution of the phenylsulfonyl group was observed.

Heterocycles substituted by fluorine or fluoroalkyl groups have attracted much attention because of their potential biological activities[1] as well as interesting chemical behaviors.[2] In the course of developement of sulfone derivatives as building blocks for heterocycles,[3] we took an interest in trifluoromethylated sulfone derivatives and their cyclization to heterocycles having trifluoromethyl substituents. In the previous paper we reported a simple preparation of 1,1,1-trifluoro-3-phenylsulfonylpropane-2,2-diol (**1a**) and its cyclization to 1-alkyl-3-trifluoromethyl-4-phenylsulfonylpyrazoles.[4] We describe here the synthesis of some 3-trifluoromethylpyrazoles (**5** and **6**) and 3-trifluoromethylpyridazines (**9** and **10**) starting from the hydrazones of **1.**

Ammonia adduct (**1b**) of 1,1,1-trifluoro-3-phenylsulfonyl-2-propanone is now readily available on treatment of the carbanion of methyl phenyl sulfone with ethyl trifluoroacetate followed by quenching with aqueous ammonium chloride.[4] It was unsuccessful to prepare 3-trifluoromethyl-4-phenylsulfonylpyrazoles on treatment of hydrazone (**7**) with *N, N*-dimethylformamide dimethyl acetal, while similar treatment of arylhydrazones (**2**) gave two types of pyrazole derivatives. Heating **2** in *N, N*-dimethylformide dimethyl acetal without solvent followed by purification by column chromatography afforded 1-aryl-3-trifluoromethyl-5-dimethylaminopyrazoles (**5a-c**) in the moderate yields or 1-aryl-3-trifluoromethyl-4-phenylpyrazoles (**6a-c**) in the low yields (Scheme 1). The spectral and analytical data of the products are shown in Table 1 and 2, respectively. Formation of **5** and **6** would be explained as follows; the intermediary dihydropyrazoles (**4**) which were produced through dimethylaminomethylene derivative (**3**) would give **5** on extrusion of sulfinic acid, while **6** would be derived from

4 on extrusion of dimethylamine. The effect of the substituents on the products is obscure because of difficulties in complete separation of the products from the reaction mixture. Only isolable products are shown in Table 1. Recently pyrazoles which have trifluoromethyl groups have been prepared from a variety of synthetic blocks bearing trifluoromethyl groups.[5]

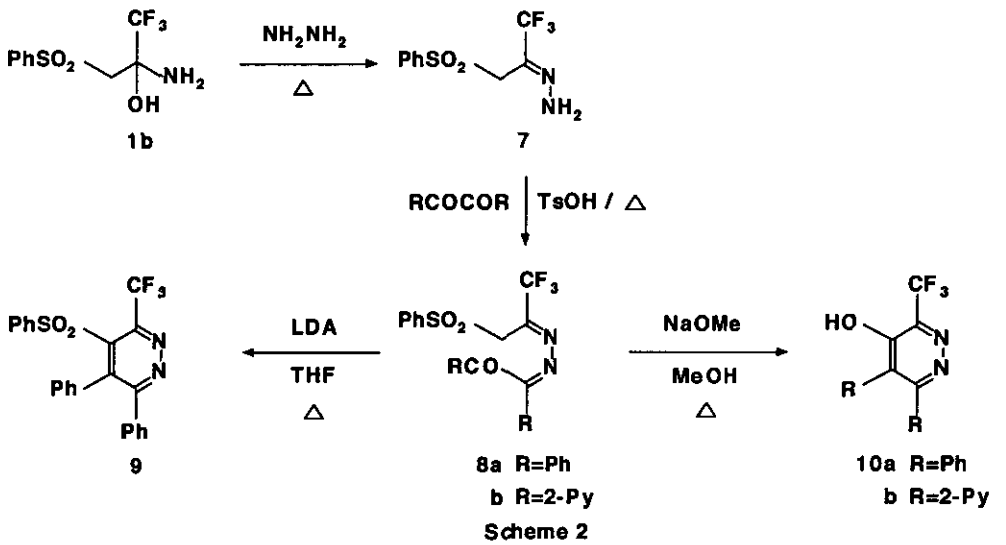
In contrast to trifluoromethylated pyrazoles, pyridazines which have trifluoromethyl groups seem to be less known in the literature,[2] although some trifluorinated pyridazines were developed as agrochemicals.[1b] We tried to prepare pyridazines starting from **1b**, and some 3-trifluoromethylated pyridazines were obtained. Treatment of **7** with 1,2-dicarbonyl compounds in the presence of *p*-toluenesulfonic acid in refluxing ethanol gave azines (**8**) (Scheme 2). 3-Trifluoromethyl-5,6-diphenyl-4-phenylsulfonylpyridazine (**9**) was an isolable product (15% yield) when **8a** was treated with lithium diisopropylamide in refluxing tetrahydrofuran. However, treatment of **8a** and **b** with sodium methoxide in refluxing methanol followed by neutralization by hydrochloric acid yielded 5,6-diaryl-3-trifluoromethylpyridazin-4-ols (**10a** and **b**) in 58% and 14% yields, respectively.



Scheme 1

It seems that the phenylsulfonyl group was substituted by hydroxide ion which was produced during the condensation. The structures of **8**, **9**, and **10** were unambiguously assigned on the basis of the spectral and analytical data (Tables 1 and 2).

In conclusion we have shown the usefulness of **1** for the synthesis of 3-trifluoromethylpyrazoles and 3-trifluoromethylpyridazines and observed elimination or substitution of the sulfonyl group during the reaction.



Scheme 2

EXPERIMENTAL

1,1,1-Trifluoro-3-phenylsulfonyl-2-propanone arylhydrazones (2) and hydrazone (7)

A general procedure: A mixture of **1b**[4] (540 mg, 2.0 mmol) and arylhydrazine or its hydrochloride (2.0 mmol) in aqueous EtOH (3 ml of water and 3 ml of EtOH) was refluxed for 2 to 16 h. After cooling, the precipitates were collected by filtration and recrystallized from benzene, iso-PrOH, or EtOH to give **2**. Hydrazone (**7**) was similarly prepared from **1b** and hydrazine hydrate.

Cyclization of 2 to 1-aryl-3-trifluoromethyl-5-dimethylaminopyrazoles (5) or 1-aryl-3-trifluoromethyl-4-phenylsulfonylpyrazoles (6)

A general procedure: A mixture of **2** (1.0 mmol) and *N*, *N*-dimethylformamide dimethyl acetal (2.0 ml, 15 mmol) was refluxed for 2 to 6 h under nitrogen atomosphere. After cooling, the reaction mixture was diluted with water (20 ml) and was extracted with $CHCl_3$. After removal of the solvent and excess *N*, *N*-dimethylformamide dimethyl acetal under reduced pressure, the residue was purified by column chromatography on silica gel using $CHCl_3$ to give **5** or **6**, which were recrystallized from benzene or iso-PrOH.

Table 1. Preparation of Compounds **2** and **5-10**

	Yield %	mp °C	Ms (M^+) m/z	Ir (KBr) cm^{-1}	^{1}H-Nmr d, ppm (solvent)
2a	42	147-148	342	3320 1600 1580 1495	4.69 (s, 2H), 6.92-8.06 (m, 10H), 9.93 (br s, 1H) (acetone-d_6)
2b	78	142-143	356	3300 1600 1570 1505	2.25 (s, 3H), 4.65 (s, 2H), 7.06 (s, 4H), 7.55-8.04 (m, 5H), 9.83 (br s, 1H) (acetone-d_6)
2c	84	146-148	356	3300 1615 1585 1500	2.35 (s, 3H), 4.28 (s, 2H), 6.77-7.90 (m, 9H), 9.77 (br s, 1H) ($CDCl_3$)
2d	61	159-161	372	3350 1580 1510 1450	3.77 (s, 3H), 4.28 (s, 2H), 6.83 (d, J=9 Hz, 2H), 7.13 (d, J=9 Hz, 2H), 7.49-7.95 (m, 5H), 9.74 (br s, 1H) ($CDCl_3$)
2e	83	161-163	376	3300 1590 1490 1445	4.31 (s, 2H), 7.15-7.89 (m, 9H), 9.86 (br s, 1H) ($CDCl_3$)
2f	90	163-165	420	3340 1605 1585 1490	4.19 (s, 2H), 6.81-7.86 (m, 9H), 9.81 (br s, 1H), ($CDCl_3$)
2g	24	196-198	387	3330 1590 1505 1490	4.83 (s, 2H), 7.26-8.27 (m, 9H), 10.41 (br s, 1H) ($CDCl_3$)
5a	62	68-69	269	2870 2800 1560 1520	2.38 (s, 3H), 2.62 (s, 6H), 6.17 (s, 1H), 7.22 (d, J=8 Hz, 2H), 7.59 (d, J=8 Hz, 2H) (acetone-d_6)
5b	58	oil	285	2960 2840 1555 1515	2.57 (s, 6H), 3.82 (s, 3H), 6.00 (s, 1H), 6.91 (d, J=9 Hz, 2H), 7.54 (d, J=9 Hz, 2H) ($CDCl_3$)
5c	61	oil	289	2960 2840 2800 1585	2.60 (s, 6H), 6.00 (s, 1H), 7.36 (d, J=9 Hz, 2H), 7.64 (d, J=9 Hz, 2H) ($CDCl_3$)
6a	10	167-169	366	3140 1615 1595 1520	2.42 (s, 3H), 7.30-7.97 (m, 5H), 8.47 (s, 1H) ($CDCl_3$)
6b	13	168-170	430	3150 1520 1490 1445	7.47-8.02 (m, 9H), 8.50 (s, 1H) ($CDCl_3$)
6c	19	170-172	397	3140 1600 1530 1485	7.49-8.40 (m, 9H), 8.66 (s, 1H) ($CDCl_3$)
7	85	137-138	266	3450 3330 1600 1450	4.57 (s, 2H), 7.58-7.98 (m, 5H), 8.06 (s, 2H) (DMSO-d_6)
8a	75	149-150	458	3025 2950 1685 1630	4.72 (s, 2H), 7.17-7.92 (m, 15H) ($CDCl_3$)
8b	51	126-127	460	3010 2940 1705 1630	4.92 (s, 2H), 7.25-8.48 (m, 13H) (acetone-d_6)

9	15	158-159	440	1480 1445 1360 1330	6.64-7.48 (m, 15H) (acetone-d_6)
10a	58	>300	316	3210 3050 2940 1610	7.12-7.30 (m, 10H) (DMSO-d_6)
10b	14	229-231	318	2850 1615 1590 1500	6.97-8.62 (m, 8H) (DMSO-d_6)

Table 2. Elemental Analyses of Compounds(**2**)and(**5-10**)

Compound	Molecular Formula	Calcd %			Found %		
		C	H	N	C	H	N
2a	$C_{15}H_{13}F_3N_2O_2S$ (342.34)	52.63	3.83	8.18	52.81	4.00	8.16
2b	$C_{16}H_{15}F_3N_2O_2S$ (356.36)	53.93	4.24	7.86	54.05	4.28	7.63
2c	$C_{16}H_{15}F_3N_2O_2S$ (356.36)	53.93	4.24	7.86	53.92	4.19	7.72
2d	$C_{16}H_{15}F_3N_2O_3S$ (372.36)	51.61	4.06	7.52	51.56	4.21	7.38
2e	$C_{15}H_{12}ClF_3N_2O_2S$ (376.78)	47.82	3.21	7.43	47.88	3.25	7.25
2f	$C_{15}H_{12}BrF_3N_2O_2S$ (421.23)	42.77	2.87	6.65	42.71	3.03	6.49
2g	$C_{15}H_{12}F_3N_3O_4S$ (387.33)	46.51	3.12	10.85	46.54	3.29	10.66
5a	$C_{13}H_{14}F_3N_3$ (269.27)	57.99	5.24	15.61	57.97	4.96	15.79
5b	$C_{13}H_{14}F_3N_3O$ (285.27)	54.74	4.97	14.73	54.96	4.86	14.57
5c	$C_{12}H_{11}ClF_3N_3$ (289.69)	49.75	3.83	14.51	49.78	3.88	14.28
6a	$C_{17}H_{13}F_3N_2O_2S$ (366.36)	55.73	3.58	7.65	55.89	3.57	7.57
6b	$C_{16}H_{10}BrF_3N_2O_2S$ (431.22)	44.56	2.34	6.50	44.76	2.51	6.32
6c	$C_{16}H_{10}F_3N_3O_4S$ (397.33)	48.37	2.54	10.58	48.50	2.43	10.49
7	$C_9H_9F_3N_2O_2S$ (266.24)	40.60	3.41	10.52	40.77	3.52	10.58
8a	$C_{23}H_{17}F_3N_2O_3S$ (458.45)	60.26	3.74	6.11	60.54	3.84	5.92
8b	$C_{21}H_{15}F_3N_4O_3S$ (460.43)	54.78	3.28	12.17	54.91	3.34	11.91
9	$C_{23}H_{15}F_3N_2O_2S$ (440.44)	62.72	3.43	6.36	62.33	3.40	6.05
10a	$C_{17}H_{11}F_3N_2O$ (316.28)	64.56	3.51	8.86	64.77	3.46	8.58
10b	$C_{15}H_9F_3N_4O$ (318.26)	56.61	2.85	17.60	56.52	2.80	17.66

5-Trifluoromethyl-1,2-diphenyl-6-phenylsulfonyl-3,4-diazahexa-2,4-dien-1-one (8a)

A mixture of **7** (270 mg, 1.0 mmol), benzil (210 mg, 1.0 mmol), and a catalytic amount of *p*-toluenesulfonic acid in EtOH (5 ml) was refluxed for 5 h. The precipitates were collected by filtration and recrystallized from EtOH to give **8a** (340 mg, 75%).

5-Trifluoromethyl-6-phenylsulfonyl-1,2-di(2-pyridyl)-3,4-diazahexa-2,4-dien-1-one (8b)

A mixture of **7** (270 mg, 1.0 mmol), 2,2'-bipyridyl (210 mg, 1.0 mmol), and a catalytic amount of *p*-toluenesulfonic acid in dimethoxyethane (3 ml) was refluxed for 15 h. After removal of the solvent, the residue was purified by column chromatography on silica gel using $CHCl_3$ to give **8b** (230 mg, 51%), which was recrystallized from iso-PrOH.

3-Trifluoromethyl-5,6-diphenyl-4-phenylsulfonylpyridazine (9)

To a solution of **8** (460 mg, 1.0 mmol) in THF (3 ml) was added a solution of lithium diisopropylamide in hexane (1.0 ml) prepared from diisopropylamine and butyllithium (1.6 mol/*l* in hexane) under nitrogen atomosphere, and the reaction mixture was refluxed for 10 h. After addition of saturated aqueous solution of NH_4Cl the mixture was extracted with $CHCl_3$. The residue after removal of the solvent was purified by column chromatography on silica gel using $CHCl_3$ to give **9** (65 mg, 15%), which was recrystallized from iso-PrOH.

3-Trifluoromethyl-5,6-pyridazin-4-ol (10a)

A mixture of **8a** (460 mg, 1.0 mmol) and NaOMe (270 mg, 5.0 mmol) in MeOH (3 ml) was refluxed for 5 h. Addition of water followed by neutralization with diluted hydrochloric acid gave precipitates, which were collected by filtration and recrystallized from iso-PrOH to give **10a** (180 mg, 58%). In the case of **8b** (460 mg, 1.0 mmol) the neutralized mixture was extracted with $CHCl_3$ and the residue after removal of the solvent was recrystallized from iso-PrOH to give **10b** (44 mg, 14%).

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