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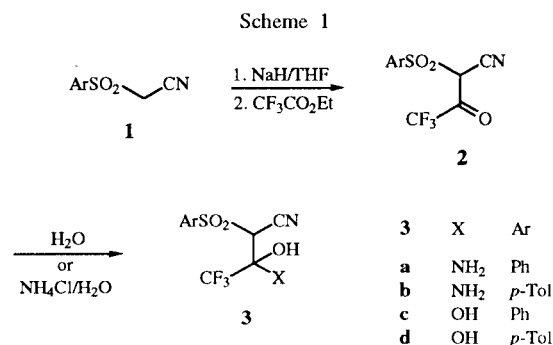
Trifluoromethylated sulfones, 3-amino-2-arylsulfonyl-4,4,4-trifluoro-3-hydroxybutanenitrile (**3**) and 3-(aroylmethyl)sulfonyl-1,1,1-trifluoropropane-2,2,-diols **12**, were prepared and cyclized to 4-arylsulfonyl-5-trifluoromethyl-3-hydrazinopyrazoles **9** and 5-arylsulfonyl-3-trifluoromethyl-3-hydroxy-2,3-dihydro-4*H*-1,4-thiazine 1,1-dioxides **13**, respectively.

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Heterocycles bearing fluorine groups have been drawing considerable interest because of their biological activities and specific chemical behaviors [1]. Since usefulness of sulfone functionality in organic synthesis has been recognized in recent years [2], it seems interesting to use sulfone derivatives as synthetic blocks for introduction of fluorine atoms or fluoroalkyl groups into heterocycles. However, only a few studies have been reported for such purposes. For instance, 1,3-dipolar cycloaddition of 1-methyl-3-oxidopyridinium with 1-phenylsulfonyl-1-fluoroethene gave monofluorinated 2-tropanol [3]. 1-Fluoro-1-alkenyl sulfones and sulfoxides were used for the synthesis of 3-fluoropyrroles [4]. 5-Amino-1,1-bis(trifluoromethyl)-2-sulfonyl-1-pentanol and its homologue provided the corresponding pyrrolidine or piperidine through intramolecular substitution of the arylsulfonyl group [5]. A 32-membered fluorinated multifunctional heterocycle was obtained from 2-(1,1,2,2,-tetrafluoro-2-iodoethoxy)-1,1,2,2-tetrafluoroethanesulfonyl fluoride [6]. We have been interested in this area and reported that 1,1,1-trifluoro-3-phenylsulfonylpropane-2,2-diol was useful building blocks for synthesis of both trifluoromethyl and sulfonyl groups-containing heterocycles such as 3-trifluoromethylpyrazoles [7] and 3-trifluoromethyl-4-phenylsulfonylpyridazines [8]. As an extension of above work we have prepared some new trifluoromethylated sulfones and tried to cyclize them to heterocycles.

The readily available sulfones having an active methylene group such as chloromethyl phenyl sulfone [9], benzoylmethyl phenyl sulfone [10], and (phenylsulfonyl)acetonitrile (**1**) [11] were allowed to react with ethyl trifluoroacetate in the presence of bases. Although in the case of the former two sulfones it was difficult to isolate their trifluoroacetylated products **1** was easily trifluoroacetylated to give **3** in moderate yields. Thus, the anion of **1** was generated by sodium hydride in tetrahydrofuran, and was then treated with ethyl trifluoroacetate. When the reaction mixture was quenched with aqueous ammonium chloride, the product was not the expected trifluoroacetylated compound **2** but its ammonia adducts **3a** (69%) and **b** (73%) as observed previously [7]. On the

other hand, when quenched with water, hygroscopic hydrated products **3c** and **d** were obtained. All the mass spectra of **3a-d** showed no molecular ion peaks, but the fragment ion peaks corresponding to loss of water or ammonia from the parent ion molecules.

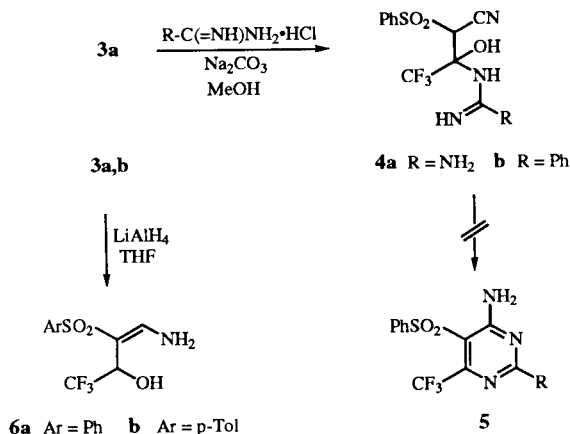


We first studied the cyclization of **3** by use of bifunctional nucleophiles. Reaction of guanidine and benzamidine hydrochloride seemed to give 3-amino-6-trifluoromethyl-4-phenylsulfonylpyrimidines (**5**). However, the reaction of **3a** with those reagents carried out in methanol in the presence of sodium carbonate gave only the corresponding substituted products **4a** (73%) and **b** (70%), respectively. All attempts to cyclize **4** to pyrimidine **5** under acidic or basic conditions were unsuccessful or sometimes decomposition to the starting **3a** was observed.

(Arylsulfonyl)acetonitrile is reported to be reduced by lithium aluminium hydride to give (arylsulfonyl)vinylamines, which were cyclized to dihydropyridines [12]. Application of this reduction to **3a** and **b** yielded trifluoromethylated enaminoalcohols **6a** and **b**, respectively. However, their cyclization to heterocycles was abandoned because of the low yields.

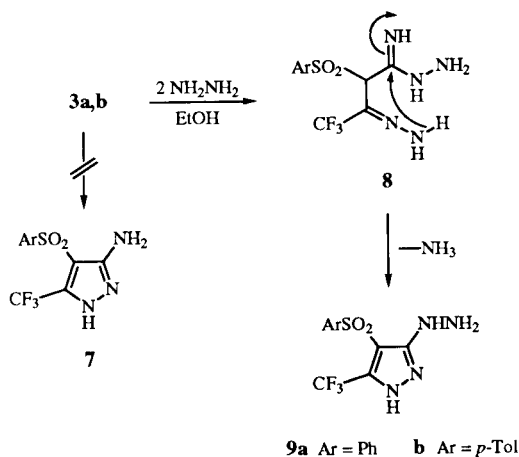
Treatment of **3** with hydrazine hydrate appeared to be a promising approach to 3-amino-4-arylsulfonyl-5-trifluoromethylpyrazoles **7**. The reaction was carried out in refluxing ethanol, leading to a mixture of a cyclized product and the decomposed product **1**. The structures of the cyclized product products were readily proved to be 4-arylsulfonyl-5-trifluoromethyl-3-hydrazinopyrazoles **9a**

Scheme 2



(36%) and **b** (10%) on the basis of the spectral and analytical data. This unexpected reaction could be explained by assuming the initial formation of hydrazono amidrazone **8** followed by cyclization to **9** with loss of ammonia. The sulfone **3a** did not react with phenylhydrazine, while on treatment with hydroxylamine hydrochloride it gave (phenylsulfonyl)acetoamidoxime, eliminating the trifluoromethyl group.

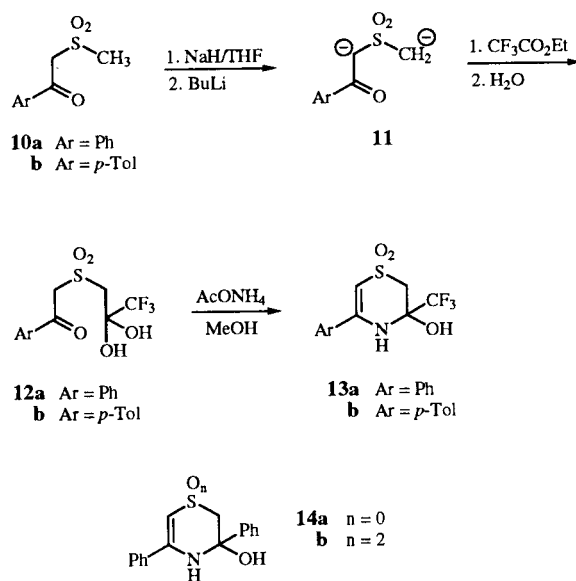
Scheme 3



We next focused our effort on trifluoroacetylation of aroylmethyl methyl sulfones **10** [13]. The dianions [**14**] **11** were generated by successive addition of sodium hydride and butyllithium according to the literature method [15]. Addition of ethyl trifluoroacetate to **11** yielded the hydrates **12a** (74%) and **b** (30%) of the trifluoroacetylated compounds. Unfortunately, all attempts to cyclize **12** to 1,4-thiazine 1,1-dioxide on dehydration, 1,4,5-thiadiazepines on cyclization by hydrazine hydrate, or 1,4-dithiin 1,1-dioxides on treatment with phosphorus pentasulfide were unsuccessful. Finally, synthesis of 5-aryl-3-trifluoromethyl-3-hydroxy-2,3-dihydro-4*H*-1,4-thi-

azine 1,1-dioxides **13a** (26%) and **b** (65%) was achieved by refluxing a mixture of **12** and ammonium acetate in methanol. The structures of these products were confirmed on the basis of analytical and spectral data. It was reported that bis(phenacyl)sulfide reacted with ammonia to yield 2*H*-1,4-thiazines, while 4*H*-1,4-thiazine 1,1-dioxides were obtained from bis(phenacyl) sulfones on the same treatment [16]. In both cases, 3-hydroxy-2,3-dihydro-1,4-thiazines **14** are postulated as the intermediates, which would dehydrate spontaneously to fully saturated 1,4-thiazines [17]. It is noteworthy that the present trifluoromethylated products **13** correspond to the intermediates **14**. The stability of **13** is apparently attributable to the strong electron withdrawing nature of the trifluoromethyl group.

Scheme 4



EXPERIMENTAL

Melting points were determined on Yanagimoto micromelting point apparatus and are uncorrected. The ¹H-nmr, ir, and mass spectra were measured with JEOL JNM-PMX 60, JASCO A-102, and JEOL JMS DX-300, respectively. Microanalysis was performed with Yanako CHN Coder MT-5.

3-Amino-4,4,4-trifluoro-3-hydroxy-2-(phenylsulfonyl)butanenitrile (**3a**).

A solution of **1** [**11**] (34.2 mmoles, 6.20 g) in dry tetrahydrofuran (40 ml) was added to a mixture of 60% sodium hydride in oil (55.3 mmoles, 2.21 g) in dry tetrahydrofuran (5 ml) cooled at 0° under nitrogen atmosphere. The mixture was stirred for 15 minutes, added to trifluoroacetate (60.0 mmoles, 8.56 g) and it was stirred at room temperature overnight. After quenching the mixture with water (20 ml) it was concentrated to the 1/3 volume

in vacuo, neutralized with hydrochloric acid, and was then washed with chloroform (20 ml x 3). Ammonium chloride was added to the aqueous layer to give a precipitate, which was collected by filtration. The insoluble material in the precipitate in hot ethyl acetate was removed by filtration. Evaporation of the filtrate left a solid, which was recrystallized from chloroform-ethyl acetate to give **3a** (6.94 g, 69%), mp 230-232°; ir (potassium bromide): 3120, 2180, 1610, 1395, 1270, 1190, 1140 cm⁻¹; ¹H nmr (deuterioacetone): δ 7.69-8.00 (m); ms: m/z 277 (M⁺-NH₃).

Anal. Calcd. for C₁₀H₉F₃N₂O₃S: C, 40.81; H, 3.08; N, 9.52. Found: C, 40.70; H, 3.09; N, 9.51.

3-Amino-4,4,4-trifluoro-3-hydroxy-2-(4-methylphenylsulfonyl)-butanenitrile (**3b**).

This compound was obtained in the same manner as described above in 73% yield, mp 190-200°; ir (potassium bromide): 3170, 2190, 1580, 1440, 1280, 1135 cm⁻¹; ¹H nmr (deuterioacetone): δ 2.35 (s, 3H), 7.20 (d, J = 8 Hz, 2H), 7.27 (br s, 3H), 7.77 (d, J = 8 Hz, 2H); ms: m/z 291 (M⁺-NH₃).

Anal. Calcd. for C₁₁H₁₁F₃N₂O₃S: C, 42.85; H, 3.59; N, 9.08. Found: C, 42.76; H, 3.58; N, 9.34.

4,4,4-Trifluoro-3-guanidino-3-hydroxy-2-(phenylsulfonyl)-butanenitrile (**4a**).

A solution of **1** (5.2 mmoles, 910 mg) in dry tetrahydrofuran (15 ml) was added dropwise to a stirred mixture of sodium hydride (60% in oil) (7.0 mmoles, 280 mg) in dry tetrahydrofuran (2 ml) at 0° under nitrogen atmosphere. The mixture was stirred for additional 15 minutes, added with trifluoroacetic anhydride (6.0 mmoles, 1.26 g), and was then stirred at room temperature for 6 hours. Guanidine hydrochloride (6.0 mmoles, 570 mg) was added to the mixture, which was stirred at room temperature overnight. After addition of water (10 ml) the mixture was concentrated to a 1/3 volume *in vacuo* and was neutralized by dilute hydrochloric acid. The mixture was extracted with ethyl acetate (20 ml x 3) and the combined organic layer was dried over magnesium sulfate. Evaporation of the solvent left a solid, which was recrystallized from chloroform to give **4a** (1.24 g, 73%), mp 187-189°; ir (potassium bromide): 3420, 2180, 1655, 1595, 1555, 1275, 1195, 1150 cm⁻¹; ms: m/z 277 (M⁺-guanidine).

Anal. Calcd. for C₁₁H₁₁F₃N₄O₃S: C, 39.28; H, 3.29; N, 16.66. Found: C, 38.99; H, 3.35; N, 16.20.

3-Benzamidino-4,4,4-trifluoro-3-hydroxy-2-(phenylsulfonyl)-butanenitrile (**4b**).

A mixture of **3a** (1.5 mmoles, 440 mg) and benzamidino hydrochloride monohydrate (2.0 mmoles, 350 mg) in ethanol (5 ml) was refluxed for 2 hours. After removal of the solvent water (10 ml) was added to the residue and the mixture was extracted with ethyl acetate (20 ml x 3). Drying over magnesium sulfate followed by removal of the solvent left a solid, which was recrystallized from ethyl acetate-chloroform to give **4b** (420 mg, 70%), mp 115-116°; ir (potassium bromide): 3400, 3150, 2160, 1670, 1600, 1275, 1180, 1120 cm⁻¹; ¹H nmr (deuterioacetone): δ 7.40-8.00 (m, 11H), 8.77 (br s, 2H); ms: m/z 277 (M⁺-benzamidino).

Anal. Calcd. for C₁₇H₁₄F₃N₃O₃S: C, 51.38; H, 3.55; N, 10.57. Found: C, 51.41; H, 3.67; N, 10.66.

4-Amino-1,1,1-trifluoro-3-phenylsulfonyl-3-buten-2-ol (**6a**).

To a stirred mixture of **3a** (3.0 mmoles, 890 mg) in dry tetrahydrofuran (3 ml) was added dropwise a mixture of lithium

aluminum hydride (7.0 mmoles, 270 mg) in tetrahydrofuran (17 ml) at 0° under nitrogen atmosphere. The temperature of the reaction mixture was gradually risen to room temperature and the mixture was stirred overnight. An aqueous solution (15 ml) saturated with ammonium chloride was added to the reaction mixture, the insoluble materials were filtered off, and the filtrate was neutralized with dilute hydrochloric acid. The filtrate was extracted with ether (20 ml x 3), and the combined ethereal solution was dried over magnesium sulfate. Removal of the solvent left a solid, which was recrystallized from chloroform to give **6a** (260 mg, 30%), mp 162-163°; ir (potassium bromide): 3350, 1650, 1590, 1260, 1170, 1120, 1070 cm⁻¹; ¹H nmr (deuterioacetone): δ 4.70-5.17 (m, simplified to q with J = 8 Hz on addition of deuterium oxide, 1H), 5.87 (d, J = 5 Hz, 1H, deuterium oxide-exchangeable), 6.40 (broad s, 2H, deuterium oxide-exchangeable), 7.40-7.93 (m, 6H); ms: m/z 281 (M⁺).

Anal. Calcd. for C₁₀H₁₀F₃NO₃S: C, 42.70; H, 3.58; N, 4.98. Found: C, 42.54; H, 3.65; N, 4.89.

4-Amino-1,1,1-trifluoro-3-(4-methylphenyl)sulfonyl-3-buten-2-ol (**6b**).

This compound was obtained in the similar manner as described above in 15% yield, mp 166-169° (chloroform); ir (potassium bromide): 3350, 1640, 1590, 1255, 1170, 1115, 1070 cm⁻¹; ms: m/z 295 (M⁺).

Anal. Calcd. for C₁₁H₁₂F₃NO₃S: C, 44.74; H, 4.09; N, 4.74. Found: C, 44.68; H, 4.10; N, 4.80.

5-Trifluoromethyl-3-hydrazino-4-(phenylsulfonyl)pyrazole (**9a**).

A mixture of **3a** (1.0 mmole, 300 mg) and hydrazine hydrate (2.0 mmoles, 100 mg) in ethanol (5 ml) was heated with stirring at 60° for 4 hours. Evaporation of the solvent left a solid, which was column-chromatographed on silica gel with an eluent of chloroform to give **1** (110 mg, 60%) and **9a** (110 mg, 36%), mp 186-187° (ethyl acetate-chloroform); ir (potassium bromide): 3350, 2950, 1530, 1490, 1450, 1305, 1200, 1150 cm⁻¹; ms: m/z 306 (M⁺).

Anal. Calcd. for C₁₀H₉F₃N₄O₂S: C, 39.21; H, 2.96; N, 18.29. Found: C, 39.22; H, 3.00; N, 18.03.

5-Trifluoromethyl-3-hydrazino-4-(4-methylphenylsulfonyl)pyrazole (**9b**).

This compound was obtained in the similar manner as described above in 10% yield, mp 177-178° (ethyl acetate-chloroform); ir (potassium bromide): 3340, 3270, 1595, 1485, 1300, 1200, 1140 cm⁻¹; ¹H nmr (deuterioacetone): δ 2.43 (s, 3H), 6.01 (br s, deuterium oxide-exchangeable, 2H), 7.38 (d, J = 9 Hz, 2H), 7.66 (d, J = 9 Hz, 2H); ms: m/z 320 (M⁺).

Anal. Calcd. for C₁₁H₁₁F₃N₄O₂S: C, 41.24; H, 3.46; N, 17.49. Found: C, 41.17; H, 3.46; N, 17.43.

3-(Benzoylmethylsulfonyl)-1,1,1-trifluoropropane-2,2-diol (**12a**).

To a stirred mixture of sodium hydride (60% in oil) (4.4 mmoles, 180 mg) in dry tetrahydrofuran (10 ml) cooled at 0° under nitrogen atmosphere was added dropwise a solution of **10a** [13] (4.0 mmoles, 790 mg) in tetrahydrofuran (15 ml). After the mixture was stirred for an additional hour, it was cooled to -78° and was then added with a hexane solution of *n*-butyllithium (1.68 M) (4.0 mmoles, 2.4 ml). The mixture was stirred for 30 minutes, added with ethyl trifluoroacetate (8.0 mmoles, 1.14 g), and was stirred for 6 hours at room temperature. It was

neutralized with dilute hydrochloric acid and extracted with ethyl acetate (30 ml x 3). The combined organic layer was dried over magnesium sulfate and evaporation of the solvent left a solid, which was recrystallized from methanol-hexane to give **12a** (930 mg, 74%), mp 88-92°; ir (potassium bromide): 3420, 2980, 1670, 1590, 1440, 1315, 1250, 1200, 1170 cm⁻¹; ¹H nmr (dimethyl sulfoxide-d₆): δ 3.75 (s, 2H), 5.14 (s, 2H), 7.50-8.08 (m, 5H); ms: m/z 294 (M⁺-H₂O).

Anal. Calcd. for C₁₁H₁₁F₃O₅S: C, 42.31; H, 3.55. Found: C, 42.24; H, 3.51.

1,1,1-Trifluoro-3-[(4-methylbenzoyl)methylsulfonyl]propane-2,2-diol (**12b**).

This compound was prepared in the similar manner as described above in 30% yield, mp 134-136° (chloroform); ir (potassium bromide): 3450, 2960, 1675, 1585, 1280, 1240, 1180, 1105 cm⁻¹; ms: m/z 308 (M⁺-H₂O).

Anal. Calcd. for C₁₂H₁₃F₃O₅S: C, 44.17; H, 4.01. Found: C, 44.06; H, 3.60.

3-Trifluoromethyl-5-phenyl-2,3-dihydro-4H-1,4-thiazin-3-ol 1,1-Dioxide (**13a**).

A mixture of **12a** (4.0 mmoles, 1.25 g) and ammonium acetate (8.0 mmoles, 620 mg) in methanol (6 ml) was refluxed for 4 hours. After evaporation of the solvent *in vacuo*, the residue was added with water (30 ml) and extracted with chloroform. Drying and evaporation of the solvent left a residue, which was recrystallized from methanol to afford **13a** (310 mg, 26%), mp 150-170° dec; ir (potassium bromide): 3300, 1605, 1530, 1270, 1250, 1175, 1105 cm⁻¹; ¹H nmr (deuterioacetone): δ 3.63 (s, 2H), 5.65 (s, deuterium oxide-exchangeable, 1H), 6.38 (s, deuterium oxide-exchangeable, 1H), 7.22 (br s, 1H), 7.45-7.65 (m, 5H); ms: m/z 293 (M⁺).

Anal. Calcd. for C₁₁H₁₀F₃NO₃S: C, 45.05; H, 3.44; N, 4.78. Found: C, 45.20; H, 3.48; N, 4.60.

3-Trifluoromethyl-5-(4-methylphenyl)-2,3-dihydro-4H-1,4-thiazin-3-ol 1,1-Dioxide (**13b**).

This compound was prepared in the similar manner as

described above in 65% yield, mp 177-180° (chloroform); ir (potassium bromide): 3560, 3320, 1595, 1510, 1275, 1245, 1185, 1110 cm⁻¹; ¹H nmr (deuterioacetone): δ 2.36 (s, 3H), 3.65 (s, 2H), 5.60 (s, 1H), 6.44 (br s, 1H), 7.20 (d, J = 8 Hz, 2H), 7.44 (d, J = 8 Hz, 2H); ms: m/z 307 (M⁺).

Anal. Calcd. for C₁₂H₁₂F₃NO₃S•1/3H₂O: C, 46.00; H, 4.04; N, 4.47. Found: C, 46.16; H, 4.44; N, 4.42.

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