ONE-POT SYNTHESIS OF 2-SUBSTITUTED 3-TRIFLUOROMETHYL-3-HYDROXY-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES FROM *N*-SUBSTITUTED BENZENESULFONAMIDES

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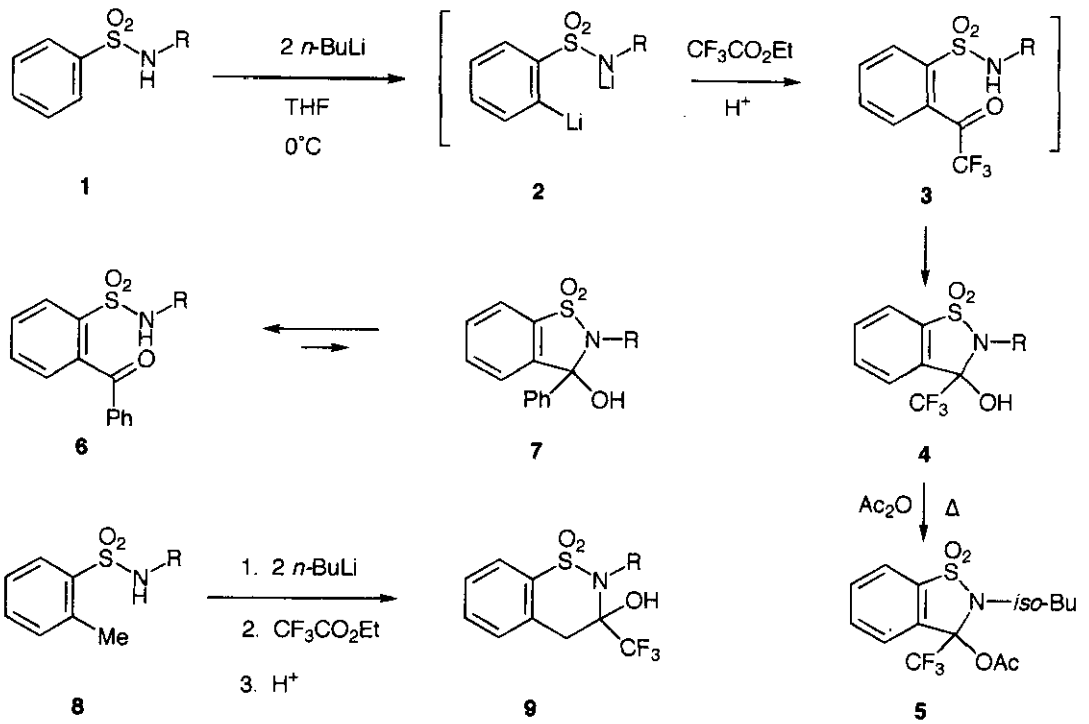
Abstract- *N*,*o*-Dilithiation of *N*-substituted benzenesulfonamides followed by the addition of ethyl trifluoroacetate gave 2-substituted 3-trifluoromethyl-3-hydroxy-1,2-benzisothiazole 1,1-dioxides in one-pot.

Benzenesulfonamides undergo directed ortho lithiation[1] upon treatment with *n*-butyllithium or lithium diisopropylamide (LDA), and their *o*-functionalized derivatives and heterocycles have been prepared using this method; *o*-lithiated benzenesulfonamides were treated with ketones,[2] nitriles,[3] carbon dioxide,[4] or isocyanate[5] to give *o*-functionalized benzenesulfonamides, which were then cyclized to afford 1,2-benzisothiazole 1,1-dioxide derivatives. Direct cyclization of benzenesulfonamides to 1,2-benzisothiazole 1,1-dioxides was accomplished when lithiated *N*,*N*-diphenylbenzenesulfonamides were treated with nitriles.[6] Saccharin (3-oxo-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide) was also obtained in one step using *N*,*N*-dimethylcarbamoyl chloride as the electrophile.[7] Another approach to the synthesis of 1,2-benzisothiazole 1,1-dioxides is the ortho lithiation of *N*-benzenesulfonylcarboxamides followed by the intramolecular nucleophilic attack at the carbonyl group.[8] Recently, 4*H*-1,2-benzothiazin-4-one 1,1-dioxides were synthesized by treatment of *N*-arylsulfonylated α-amino-carboxamides with LDA.[9] The lithiation of *N*-arylarenesulfonamides resulted in the rearrangement to 2-aminodiaryl sulfones where *o*-sulfonylium arenide was proposed as the intermediate.[10] In connection with our interest in the synthetic chemistry of sulfonamides,[11] we found that *N*-substituted benzenesulfonamides were cyclized to trifluoromethyl-containing 1,2-benzisothiazole 1,1-dioxides in one-pot.

A solution of readily available *N*-substituted benzenesulfonamides (**1**) in THF was treated with 2.1 equivalents of *n*-butyllithium in hexane at 0°C and then ethyl trifluoroacetate was added. After stirring for an additional hour at 0°C, the usual workup afforded 2-substituted 3-trifluoromethyl-3-hydroxy-3,4-dihydro-1,2-benzisothiazole 1,1-dioxides (**4a-f**) in 27-70% yields (Scheme 1 and Table 1). The

structures were confirmed on the basis of the analytical and spectral data (Tables 1 and 2) and further derivation of **4e** to the acetyl derivative **5** (81% yield); the characteristic absorption band of the hydroxyl group at 3420 cm^{-1} in the IR spectrum of **4e** disappeared in that of **5**, while the carbonyl group absorption of the acetate (**5**) was newly observed at 1780 cm^{-1}. The reaction proceeded through *N*,*o*-dilithiated benzenesulfonamides (**2**) and 2-trifluoroacetylbenzenesulfonamides (**3**). In fact, the trifluoroacetylated compound (**3g**) (R=*tert*-butyl) was isolated in 76% yield when the *N*-substituent was the bulky *tert*-butyl group. In the IR spectrum of **3g**, the carbonyl absorption appeared at 1725 cm^{-1} which was not observed in those of **4a-f**. In the ring-chain tautomerism between 2-benzoylbenzenesulfonamides (**6**) and 1,2-benzisothiazole 1,1-dioxides (**7**), the equilibrium is reported to lie so far to the ketones (**6**).[3] However, in our reaction, the ring tautomer is predominant because of the strong electron withdrawing ability of the trifluoromethyl group, forming **4**. It is emphasized that in spite of the increasing number of the fluorine-containing heterocycles,[12] the trifluoromethyl-containing benzisothiazoles are a rare class of compounds. The lithiation of the methyl group of *o*-methylbenzenesulfonamides (**8**) is also known, and was used for the synthesis of 1,2-benzothiazines.[3] We applied the above synthetic method of **4** to the preparation of the trifluoromethylated 1,2-benzothiazines (**9**). However, in this case, we obtained only 2-phenyl-1,2-benzothiazine 1,1-dioxide derivative (**9**, R=Ph) in low yield (22%). Other derivatives of **8** gave inseparable mixtures.



Scheme 1

Table 1. Preparation of Compounds (4a-f)

4	R	Yield %	Mp (°C) (Solvent)	Molecular Formula	Found % (Calcd %) C	H	N
a	Ph	29	194-195 (C_6H_6)	$C_{14}H_{10}NO_3F_3S$	50.68 (51.06	3.22 3.06	4.47 4.25)
b	4-MeC_6H_4	27	228-229 (hexane-AcOEt)	$C_{15}H_{12}NO_3F_3S$	52.58 (52.49	3.58 3.52	4.00 4.08)
c	Me	38	170-171 ($CHCl_3$)	$C_9H_8NO_3F_3S$	40.45 (40.46	3.05 2.99	5.28 5.24)
d	*n*-Bu	48	151-152 (hexane-$CHCl_3$)	$C_{12}H_{14}NO_3F_3S$	46.53 (46.61	4.48 4.53	4.57 4.53)
e	*iso*-Bu	61	150-151 (hexane-$CHCl_3$)	$C_{12}H_{14}NO_3F_3S$	46.67 (46.61	4.67 4.53	4.80 4.53)
f	$PhCH_2CH_2$	70	153-154 (hexane-$CHCl_3$)	$C_{16}H_{14}NO_3F_3S$	53.72 (53.79	4.04 3.92	3.97 3.92)

EXPERIMENTAL

Melting points were determined with a MRK MEL-TEMP II and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrophotometer. MS and ^{1}H-NMR spectra were taken with a JEOL JMS DX-300 spectrometer and a JEOL GSX-400 spectrometer, respectively. Microanalyses were performed with a YANAKO CHN-Coder MT-5. The starting materials (**1c**, R=Me and **1d**, R=*n*-Bu) are commercially available, and others were prepared according to the method described in *Beilsteins Handbuch der Organischen Chemie*.

***N-tert*-Butyl-2-trifluoroacetylbenzenesulfonamide (3g)**

This compound was prepared according to the method for **4** described below; yield 76%, mp 74-76°C (benzene-hexane). IR (KBr): 3250, 2950, 1725, 1305, 1160, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.27 (s, 9H), 4.90 (s, 1H), 7.66-8.15 (m, 4H). MS: *m/z* (%) 294 (M^+-CH_3, 100), 237 (77), 187 (47), 123 (73). Anal. Calcd for $C_{12}H_{14}NO_3F_3S$: C, 46.59; H, 4.56; N, 4.52. Found: C, 46.39; H, 4.58; N, 4.33.

2-Substituted 3-trifluoromethyl-3-hydroxy-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides (4a-f)

Table 2. Spectral Data of Compounds (4a-f)

4	MS, *m/z* (%)	IR (KBr), cm^{-1}	^{1}H-NMR, δ
a	329 (M^+, 46), 260 (68), 123 (19), 92 (100)	3280, 1490, 1300, 1170, 1225, 1045	7.48-8.19 (m, 9H), 9.17 (s, 1H) (DMSO-d_6)
b	343 (M^+, 34), 274 (21), 210 (4), 106 (100)	3420, 1510, 1305, 1190, 1150, 1060	2.37 (s, 3H), 7.32-8.16 (m, 8H), 9.08 (s, 1H) (DMSO-d_6)
c	267 (M^+, 0.5), 198 (100), 122 (4), 105 (4)	3400, 1495, 1340, 1295, 1220, 1200	2.87 (s, 3H), 7.84-8.10 (m, 4H), 8.84 (s, 1H) (DMSO-d_6)
d	309 (M^+, 1), 266 (39), 237 (100), 123 (44)	3350, 1300, 1255, 1180, 1160, 1140	0.95 (t, J=7.1 Hz, 3H), 1.32-1.42 (m, 2H), 1.67-1.82 (m, 2H), 3.10-3.17 (m, 1H), 3.37-3.45 (m, 1H), 4.37 (s, 1H), 7.68-7.85 (m, 4H) ($CDCl_3$)
e	309 (M^+, 1), 266 (66), 237 (100), 123 (40)	3420, 2970, 1475, 1320, 1295, 1190	0.94 (d, J=6.5 Hz, 3H), 1.00 (d, J=6.5 Hz, 3H), 2.11-2.22 (m, 1H), 2.91 (dd, J=13.7, 5.5 Hz, 1H), 3.11 (dd, J=13.7, 9.1 Hz, 1H), 4.71 (s, 1H), 7.70-7.84 (m, 4H) ($CDCl_3$)
f	357 (M^+, 7), 266 (79), 237 (100), 104 (39)	3370, 1300, 1255, 1220, 1175, 1130	2.93-3.00 (m, 1H), 3.07-3.15 (m, 1H), 3.25-3.31 (m, 1H), 3.58-3.66 (m, 1H), 4.58 (s, 1H), 7.21-7.80 (m, 9H) ($CDCl_3$)

A general procedure: To a stirred solution of **1** (2.0 mmol) in dry THF (8 mL) at 0°C under nitrogen was added dropwise 1.6M *n*-butyllithium in hexane (2.5 mL, 4.2 mmol). After the mixture was stirred for 1 h at 0°C, ethyl trifluoroacetate (0.30 mL, 2.4 mmol) was added, and the stirring was continued for an additional hour. The mixture was then neutralized with 5% hydrochloric acid and extracted with ether. The organic layer was dried over $MgSO_4$, evaporated to dryness, and the solid residue was recrystallized to give white crystals (**4**).

3-Acetoxy-3-trifluoromethyl-2-isobutyl-2,3-dihydro-1,2-benzisothiazole 1,1-dioxide (5)

A mixture of **4e** (620 mg, 2.0 mmol) in acetic andhydride (10 mL) was refluxed for 15 h. The mixture was poured into water (100 mL), and the aqueous solution was stirred overnight. The mixture which

contained precipitates was extracted with $CHCl_3$, the organic layer was dried over $MgSO_4$, and the solvent was evaporated to give a solid. Recrystallization from hexane-$CHCl_3$ gave white crystals (**5**) (570 mg, 81%), mp 128-129°C. IR (KBr): 1780, 1315, 1200, 1175, 1040 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 1.01 (d, J=6.8 Hz, 3H), 1.09 (d, J=6.8 Hz, 3H), 2.14 (s, 3H), 2.29-2.43 (m, 1H), 7.61-7.69 (m, 4H). MS : m/z (%) 308 (M^+-$COCH_3$), 291 (17), 278 (100), 236 (59), 185 (39). Anal. Calcd for $C_{14}H_{16}NO_4F_3S$: C, 47.87; H, 4.56; N, 3.99. Found: C, 47.79; H, 4.63; N, 4.14.

3-Trifluoromethyl-3-hydroxy-2-phenyl-3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (9)

To a stirred solution of *N*-phenyl-*o*-toluenesulfonamide (740 mg, 3.0 mmol) in dry THF (10 mL) at 0°C under nitrogen was added dropwise 1.6 M *n*-butyllithium in hexane (4.0 mL, 6.4 mmol). After the stirring was continued for 1 h, ethyl trifluoroacetate (0.33 mL, 3.0 mmol) was added. The mixture was stirred for 15 h at rt and neutralized with 5% hydrochloric acid. The mixture was extracted with $CHCl_3$, the organic layer was dried over $MgSO_4$, and the solvent was evaporated to give an oily product, which solidified after one day. Recrystallization from benzene gave white crystals (**9**) (230 mg, 22%), mp 119-121°C. IR (KBr): 3340, 1330, 1180, 1160, 1140 cm^{-1}. ^1H-NMR ($CDCl_3$): δ 3.58 (d, J=16 Hz, 1H), 3.98 (d, J=16 Hz, 1H), 4.52 (s, 1H), 6.92-7.84 (m, 4H). MS: m/z (%): 343 (M^+, 37), 276 (6), 109 (29), 93 (100). Anal. Calcd for $C_{15}H_{12}NO_3F_3S$: C, 52.47; H, 3.52; N, 4.08. Found; C, 52.59; H, 3.49; N, 4.32.

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