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Original article

Pharmacophoric 2-hydroxyalkyl benzenesulfonamide: A single-step synthesis from benzenesulfonamide via hemiaminal☆

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Abstract

ortho-Acylation attempt of benzenesulfonamide afforded the corresponding hemiaminal as major product. The in situ reduction of the reaction mixture, reported herein, directly provided 2-hydroxyalkyl benzenesulfonamide, an important pharmacophoric element for designing drug-like scaffolds. Its application is demonstrated through designing a novel series of 1,5-diarylpyrazoles for cyclooxygenase-2 (COX-2) inhibition.

Keywords: Benzenesulfonamides; Benzisothiazoles; Hemiaminal–carbonyl mixture; 2-Hydroxyalkyl benzenesulfonamide

1. Introduction

Benzenesulfonamide moiety is an integral part of many drugs and drug-like scaffolds [1–3]. We needed 2-hydroxyalkyl benzenesulfonamides **4** and **12**, the important starting materials, in large quantities, for the structure–activity relationship (SAR) study during the search of cyclooxygenase-2 (COX-2) inhibitors as anti-inflammatory agents [4–6]. Synthetically, these materials could be obtained from corresponding 2-methyl benzenesulfonamides [7], by the ring opening of saccharin derivatives [8] or, by Lombardino's *ortho*-metalation of corresponding sulfonamides [9,10]. Though the first two methods appeared simple, much chemistry was required for generating the starting materials with desired substitution. Therefore, we conceived the *n*-BuLi induced *ortho*-metalation of compounds **1** and **7** to introduce an acyl group adjacent to sulfonamide which on further reduction would afford the desired functionality. Though many 2-hydroxyalkyl benzenesulfonamides have been synthesized by reacting the *ortho*-metalated intermediates with aldehyde and ketone [11,12], it was practically too difficult for us to get the desired quantity of 2-hydroxymethyl or hydroxyethyl derivatives using this method because of extremely poor yield (5–10%). Thus, we attempted the *ortho*-formylation of 4-halo N^1-*tert*-butyl benzenesulfonamides **1a–b**. But, the reaction failed to give the desired products. The major products isolated in these experiments were identified to be 2-*tert*-butyl-3-hydroxy-5-halo-2,3-dihydro-1,2-benzisothiazole-1,1-dioxides **2a–b** (Scheme 1). Literature also supported the formation of cyclic products during *ortho*-formylation/acylation reactions [13,14]. Pasteris had extensively used similar cyclic hemiaminals obtained after trapping the dianion with HCO_2Et or DMF during herbicidal research [15,16]. Even with our trials to negotiate with reaction conditions, we could increase the quantity of the *ortho*-formylated product to a maximum of ~13%. The literature also revealed the isomerization of these *ortho*-formylated products to corresponding hemiaminals [17,18]. However,

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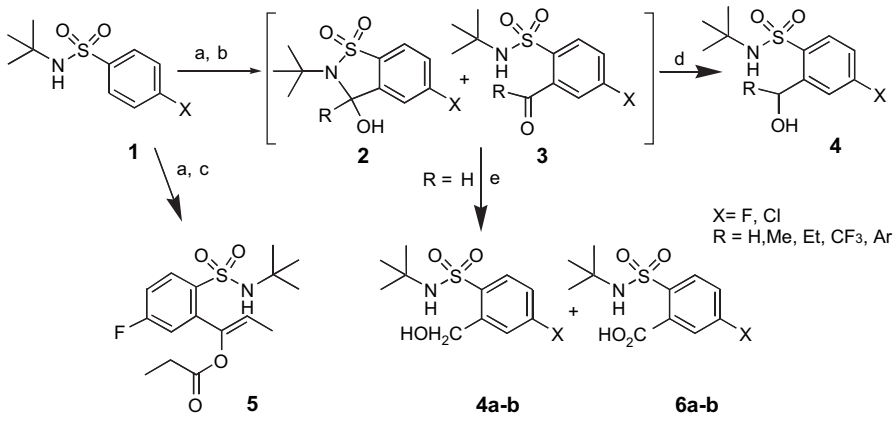


Scheme 1. Reagents and conditions: (a) *n*-BuLi (2.10 equiv.), THF, −78 °C, 0.5 h. (b) R = H (DMF or $HCO_2C_2H_5$), R = CH_3 [$(CH_3CO)_2O$ or CH_3CO_2Et), R = C_2H_5 ($C_2H_5CO_2C_2H_5$], R = CF_3 ($(CF_3CO)_2O$ or CF_3CO_2Et), R = Ar ($ArCO_2Me$) (1.50 equiv.). (c) $(C_2H_5CO)_2O$ (1.50 equiv.), −78 °C for 3–4 h followed by ambient temperature, 12 h. (d) $NaBH_4$ or $LiBH_4$ (0.5 equiv.), 0–30 °C, 0.5 h. (e) For the mixture of **2** and **3** (R = H), NaOH or NaH (1.0 equiv.), 0–30 °C, 0.5 h.

the cyclic hemiaminal being in equilibrium with the carbonyl isomer has been reported to undergo condensation reactions [17]. But, to the best of our knowledge, the reductive opening of this hemiaminal to 2-hydroxyalkyl benzenesulfonamides **4** and **12** (R = H, Me, Et, CF_3) has not been disclosed so far. Therefore, we report herein a highly efficient scalable single-step synthesis of 2-hydroxyalkyl benzenesulfonamides **4** and **12**, the useful components of drug research, from benzenesulfonamide via in situ reduction of hemiaminal–carbonyl mixture, and its application in designing COX-2 inhibitors.

2. Results and discussion

The *ortho*-lithiation of N^1-(*tert*-butyl)-4-fluoro benzenesulfonamide **1a** using 2.1 equiv. of *n*-BuLi in dry THF at −78 °C followed by an electrophilic quenching with 1.5 equiv. of dry DMF or HCO_2Et afforded a non-separable mixture (~87:13) of 2-*tert*-butyl-3-hydroxy-5-fluoro-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide **2a** and N^1-(*tert*-butyl)-4-fluoro-2-formyl benzenesulfonamide **3a** (Scheme 1). However, this mixture left behind crystals of pure product **2a** when dissolved in ethyl acetate and kept at room temperature for slow evaporation. The structure of compound **2a** was confirmed by X-ray diffraction studies (Fig. 1). The reported event of thermal isomerization [17,18] was checked by recording the ^1H NMR (DMSO-d_6) of this non-separable mixture of **2a** and **3a** (~87:13) at 30, 60 and 90 °C. The content of product **3a** in the mixture was found to increase with rise in temperature, but went up to only ~33% at 90 °C.

The ratio of these two products was found to depend on the nature of the electrophiles. It was neither affected by the quantity of the reagents nor by the reaction temperature (Table 1). An electrophilic quenching of the *ortho*-lithiated intermediate with Ac_2O exclusively afforded the 2-acetylated product **3c** whereas quenching with EtOAc afforded a mixture of **2c** and **3c** (~30:70). While the quenching of *ortho*-lithiated intermediate with $EtCO_2Et$ afforded a mixture (~44:56) of benzisothiazole **2d** and 2-propanoyl derivative **3d**, treatment with $(EtCO)_2O$ exclusively afforded a different product, (*Z*)-propionic acid 1-(2-*tert*-butylsulfamoyl-5-fluorophenyl)-propenyl ester **5**. Apart from the spectroscopic evidences, the structure of compound **5** was assigned by the X-ray diffraction studies (Fig. 1). Possibly, this product was formed via 2-propanoyl derivative **3d** when the carbanion generated on its α-carbon was stabilized by *N*-Li co-ordination and the resulting *cis*-enolate got further *O*-acylated. An electrophilic quenching with $(CF_3CO)_2O$ exclusively afforded *ortho*-trifluoroacetyl product **3e** while CF_3CO_2Et gave a 40:60 mixture of **2e** and **3e**. But, the *ortho*-acylation with the esters of aromatic acids exclusively afforded the corresponding 2-benzoyl benzenesulfonamides **3f–g** [13].

We also studied the effect of same electrophiles on *N*-ethyl benzenesulfonamide **7** (Scheme 2 and Table 1). While the ratio of the hemiaminal–carbonyl products in *ortho*-formylation and trifluoroacylation reaction remained almost same during DMF or HCO_2Et and $(CF_3CO)_2O$ or CF_3CO_2Et quenching, the *ortho*-acetylation attempt exclusively afforded an elimination product **10** with Ac_2O, and a mixture of **10** (50%) and **11** (30%) with EtOAc. However, the *ortho*-acylation with esters of aromatic acids exclusively afforded the corresponding 2-benzoyl benzenesulfonamides **9c–d**. In none of these cases we could isolate the product accounting *ortho*-directing effect of 4-fluoro/chloro groups.

Isothiazoles and their benzo derivatives are known to undergo ring cleavage [8]. The mode of cleavage is either via S–N or C–N bond fission, and depends on the reaction condition [19]. The stable benzisothiazoles **2** and **8** which could not completely isomerize even after heating, were reacted with a range of reagents, such as $NaBH_4$, $LiAlH_4$, $LiBH_4$, NaH and NaOH under different reaction conditions. To our delight, $NaBH_4$ and $LiBH_4$ exclusively afforded the corresponding 2-hydroxyalkyl benzenesulfonamides **4a–b** and **12a–b** from the respective mixture of **2a–b** and **3a–b**, and **8a–b** and **9a–b** in very high yield (~84%) at room temperature (Table 2). While the ring cleavage of **2a–b** and **8a** also occurred with the use of NaOH and NaH at slightly higher temperature, there was no effect of $LiAlH_4$ even after heating for several hours.

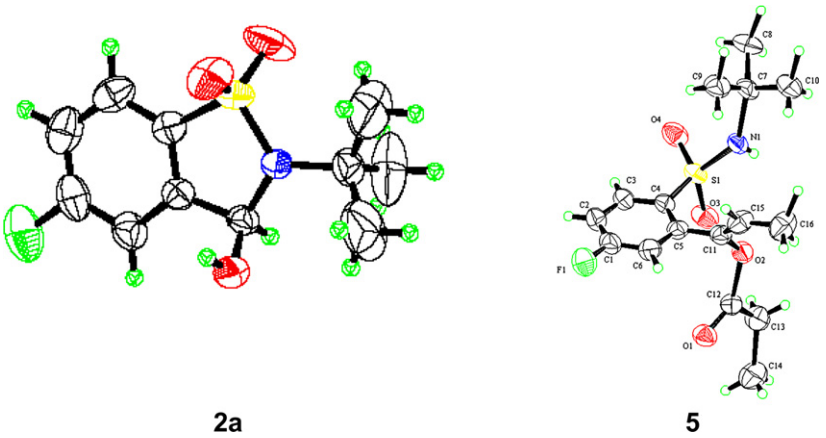


Fig. 1. Crystal structure of compounds **2a** and **5**.

The effect of groups (R = H, Me, Et, CF_3) at position-3 of benzisothiazole **2** and **8** was found to be very significant during reduction. While the reduction of **2a–b**, **e** and **8a–b** (R = H, CF_3) was observed to be very facile, the methyl derivative **2c** required longer reaction time, more quantity of reducing agent and high temperature for completion. The ethyl derivative **2d** was found to be quite inert even under drastic conditions. Therefore, on optimization, 2-hydroxymethyl, 2-(1-hydroxyethyl) and 2-(2,2,2-trifluoro-1-hydroxyethyl) benzenesulfonamides were prepared in very high yield by in situ reduction of the corresponding mixture of hemiaminal–carbonyl products whereas 2-(1-hydroxypropyl) and 2-(hydroxyphenylmethyl) benzenesulfonamides were prepared by reducing the corresponding 2-acyl or 2-benzoyl derivatives. Though not important at this stage, the asymmetric reduction has also been recently taken up to obtain optically pure 2-hydroxyalkyl benzenesulfonamides.

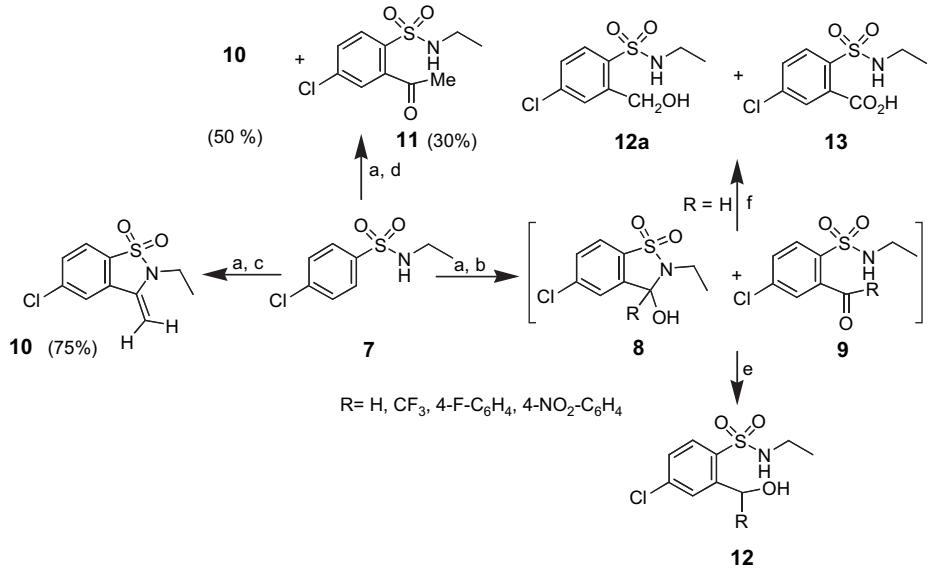
The ineffectiveness of $LiAlH_4$ indicated that the reducing agents generating alkaline solution during aqueous work-up, e.g. $NaBH_4$ and $LiBH_4$ were necessary for this conversion. Conversion of benzisothiazoles **2a–b** and **8a** to corresponding 2-hydroxymethyl benzenesulfonamides **4a–b** and **12a** with NaH and NaOH under heating condition occurred due to Cannizzaro disproportionation [20]. This fact became more clear when oxidation products, sulfamoyl benzoic acids **6a–b** and **13** (~32%) [9] were isolated in these cases apart from alcohols **4a–b** and **12a** (~40%) in contrast to an exclusive formation of **4a–b** (~82%) during $NaBH_4$ and $LiBH_4$ reaction.

To demonstrate the utility of this single-step transformation in drug discovery, the *tert*-butyl group of 2-hydroxyalkyl benzenesulfonamide **4a** was removed by an azeotropic distillation using catalytic amount of *p*-toluenesulfonic acid in refluxing toluene and the resulting benzenesulfonamide **14** was transformed to the desired phenylhydrazine **15** by refluxing with

Table 1
Ratio of benzisothiazole and *O*-acylated product during *ortho*-metalation reaction of **1** and **7**[a]

Substrate	X	R	Reagent	Overall yield (%)	Products (relative %)[b]	
1a	F	H	DMF	78	**2a** (87)	**3a** (13)
1a	F	H	HCO_2Et	75	**2a** (86)	**3a** (14)
1b	Cl	H	DMF	80	**2b** (85)	**3b** (15)
1b	Cl	H	HCO_2Et	82	**2b** (87)	**3b** (13)
1c	F	CH_3	$(CH_3CO)_2O$	74	**2c** (2)	**3c** (98)
1c	F	CH_3	CH_3CO_2Et	76	**2c** (30)	**3c** (70)
1d	F	C_2H_5	$(C_2H_5CO)_2O$	68[c]	[c]	[c]
1d	F	C_2H_5	$C_2H_5CO_2C_2H_5$	65	**2d** (44)	**3d** (56)
1e	F	CF_3	$(CF_3CO)_2O$	71	**2e** (3)	**3e** (97)
1e	F	CF_3	CF_3CO_2Et	70	**2e** (40)	**3e** (60)
1f	F	4-F–C_6H_4–	4-F–C_6H_4–CO_2Me	75	**2f** (2)	**3f** (98)
1g	F	4-NO_2–C_6H_4–	4-NO_2–C_6H_4–CO_2Me	78	**2g** (4)	**3g** (96)
7a	Cl	H	DMF	76	**8a** (86)	**9a** (14)
7a	Cl	H	HCO_2Et	75	**8a** (88)	**9a** (12)
7b	Cl	CF_3	$(CF_3CO)_2O$	80	**8b** (2)	**9b** (98)
7b	Cl	CF_3	CF_3CO_2Et	76	**8b** (45)	**9b** (55)
7c	Cl	4-F–C_6H_4–	4-F–C_6H_4–CO_2Me	78	**8c** (3)	**9c** (97)
7d	Cl	4-NO_2–C_6H_4–	4-NO_2–C_6H_4–CO_2Me	77	**8d** (2)	**9d** (98)

[a] Schemes 1 and 2.
[b] Not separable on TLC/column chromatography, estimated only by ^1H NMR, ^{13}C NMR and HPLC.
[c] A different product **5** was isolated (Fig. 1).



Scheme 2. Reagents and conditions: (a) *n*-BuLi (2.10 equiv.), THF, −78 °C, 0.5 h. (b) R = H (DMF or $HCO_2C_2H_5$), R = CF_3 [$(CF_3CO)_2O$ or CF_3CO_2Et)], R = Ar ($ArCO_2Me$) (1.50 equiv.). (c) $(CH_3CO)_2O$ (1.50 equiv.). (d) CH_3CO_2Et (1.50 equiv.), −78 °C for 3–4 h followed by ambient temperature, 12 h. (e) $NaBH_4$ or $LiBH_4$ (0.5 equiv.), 0–30 °C, 0.5 h. (f) For the mixture of **8a** and **9a** (R = H), NaOH or NaH (1.0 equiv.), 0–30 °C, 0.5 h.

anhydrous hydrazine. This phenylhydrazine **15** on coupling with suitable 1,3-diketones provided novel series of 1,5-diarylpyrazoles **16** with modified benzenesulfonamide core suitable for effective COX-2 inhibition (Scheme 3) [4,6]. A few of these compounds were found to be highly potent in different animal models of inflammation [5].

3. Conclusion

In conclusion, we described here the practical variation in the product formation during *ortho*-acylation of benzenesulfonamides and demonstrated a single-step high yielding reductive conversion of the hemiaminal–carbonyl mixture to corresponding 2-hydroxyalkyl benzenesulfonamide. Though this conversion is limited to smaller groups at position-3 of benzisothiazole, it still can be used as a simple tool to introduce a highly amenable hydroxylalkyl group adjacent to sulfonamide for designing many drug-like scaffolds.

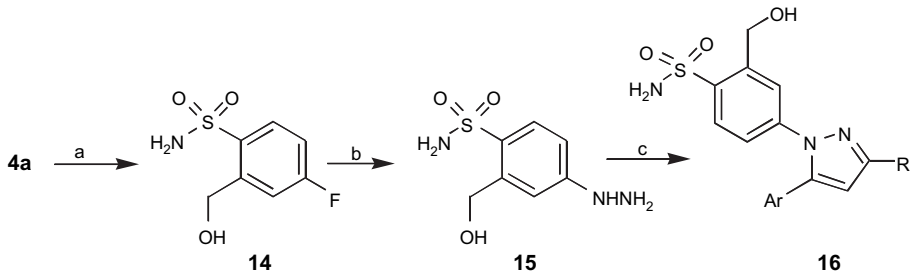
4. Experimental protocols

The reactions involving *n*-BuLi were performed under argon atmosphere using dry THF. Melting points are uncorrected. IR spectra were recorded on Perkin–Elmer FT-IR

Table 2
In situ conversion of mixture of benzisothiazoles and *O*-acylated products to 2-hydroxyalkyl benzenesulfonamides[a]

Mixture	X	R	Reagent	Solvent	Temp (°C)	Time (h)	Product (% yield)
2a + **3a**	F	H	$NaBH_4$	THF–H_2O	0–35	0.25	**4a** (82)
2a + **3a**	F	H	NaOH	THF–H_2O	60–65	0.50	**4a** (40)[b]
2a + **3a**	F	H	NaH	THF	40–50	0.50	**4a** (38)[b]
2a + **3a**	F	H	$LiBH_4$	THF	0–35	0.25	**4a** (84)
2a + **3a**	F	H	$LiAlH_4$	THF	50–60	1.50	**4a** (7)[c]
2b + **3b**	Cl	H	$NaBH_4$	THF–H_2O	0–35	0.25	**4b** (84)
2b + **3b**	Cl	H	$LiBH_4$	THF	0–35	0.25	**4b** (80)
2c + **3c**	F	CH_3	$NaBH_4$	THF–H_2O	40–50	0.50	**4c** (80)
2c + **3c**	F	CH_3	$LiBH_4$	THF	40–50	0.50	**4c** (79)
2d + **3d**	F	C_2H_5	$NaBH_4$	THF–H_2O	Reflux	3.00	**4d** (42)[d]
2d + **3d**	F	C_2H_5	$LiBH_4$	THF	Reflux	3.00	**4d** (45)[d]
2e + **3e**	F	CF_3	$NaBH_4$	THF–H_2O	0–35	0.25	**4e** (80)
2e + **3e**	F	CF_3	$LiBH_4$	THF	0–35	0.25	**4e** (76)
8a + **9a**	Cl	H	$NaBH_4$	THF–H_2O	0–35	0.25	**12a** (85)
8a + **9a**	Cl	H	$LiBH_4$	THF	0–35	0.25	**12a** (82)
8b + **9b**	Cl	CF_3	$NaBH_4$	THF–H_2O	0–35	0.25	**12b** (81)
8b + **9b**	Cl	CF_3	$LiBH_4$	THF	0–35	0.25	**12b** (79)

[a] Schemes 1and 2.
[b] Yield loss was due to the formation of compound **6**.
[c] Starting material recovered.
[d] No change was observed in the cyclic product **2d**. The product **4d** was obtained only from the reduction of **3d**.



Scheme 3. Reagents and conditions: (a) PTSA (0.2 equiv.), toluene, reflux, 1.0 h, 87–92%. (b) Anhydrous N_2H_4 (5.0 equiv.), CH_3CN, reflux, 72 h, 69–73%. (c) Refs. [4–6].

1650 spectrometer. ^{1}H NMR and ^{13}C NMR experiments were performed at 200, 400 or 500 MHz Varian Gemini spectrometer using TMS as internal standard. The chemical shifts (δ) are reported in parts per million. Mass spectra were recorded on HP-5989A spectrometer and the elemental analyses were carried out for C, H, N using Perkin–Elmer 2400 series II CHN/O analyzer. The purity of the compounds was determined by HPLC using "System 1" consisting column Hichrom RPB (250 mm) and mobile phase 0.01 M KH_2PO_4/CH_3CN (50:50), and "System 2" comprising column Intersil ODS 3V (250 mm) and mobile phase H_2O/CH_3CN (50:50) running at 1.0 mL/min with UV detection at respective λ_{max}.

*4.1. Mixture of 2-tert-butyl-5-fluoro-1,1-dioxo-2,3-dihydro-1H-benzo[d]isothiazol-3-ol **2a** and N-tert-butyl-4-fluoro-2-formyl benzenesulfonamide **3a** (representative ortho-acylation)*

N^1-(*tert*-Butyl)-4-fluoro benzenesulfonamide **1a** (2.0 g, 8.65 mmol) dissolved in dry THF (20 mL) under argon atmosphere, was cooled to −78 °C and 1.6 M *n*-BuLi (12.08 mL, 18.12 mmol) was injected. The reaction mixture after agitating at this temperature for 30 min was brought to −20 °C for 15 min. It was again cooled to −78 °C and dry DMF (0.94 g, 12.98 mmol) was introduced slowly. The reaction mixture was stirred at this temperature for 4 h and then allowed to stir overnight at ambient temperature. The reaction mass was poured over ice-cold ammonium chloride solution and stirred for 5 min. The whole mass was extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to get a brownish gummy mass which was purified by column chromatography using 230–400 mesh silica-gel and a mixture of ethyl acetate and petroleum ether (10:90). The colorless viscous mass was triturated with ethyl acetate–petroleum ether to get a 87:13 mixture of the title compounds (1.7 g, 75%). Mp 102–104 °C. IR (KBr) 3440, 2922, 1600 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.05 (d, $J = 6.0$ Hz, 1H), 7.95 (dd, $J = 6.4$ and 2.8 Hz, 1H), 7.65–7.58 (m, 3H), 7.45 (dd, $J = 6.4$ and 2.8 Hz, 1H), 6.95 (d, $J = 9.4$ Hz, 1H), 6.05 (d, $J = 9.4$ Hz, 1H), 1.53 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 189.9, 164.7 (d, $J = 249.6$ Hz), 163.8 (d, $J = 251.8$ Hz), 141.2, 140.3 (d, $J = 9.4$ Hz), 135.5 (d, $J = 6.8$ Hz), 131.9 (d, $J = 2.6$ Hz), 131.7, 122.8 (d, $J = 9.4$ Hz), 120.4 (d, $J = 22.3$ Hz), 118.3 (d, $J = 24.3$ Hz), 115.3 (d, $J = 23.9$ Hz), 112.3 (d, $J = 23.9$ Hz), 79.3 (d, $J = 1.9$ Hz), 56.9, 54.2, 29.2, 28.9. MS (CI Method) 260 $(M + H)^+$, 244, 204. HPLC (System 1) 86.9% **2a** and 13.5% **3a**; (System 2) 87.2% **2a** and 12.6% **3a**.

*4.2. (Z)-Propionic acid 1-(2-tert-butylsulfamoyl-5-fluorophenyl)-propenyl ester **5***

A white solid was obtained in 75% yield when propionic anhydride was used in the reaction. Mp 146–148 °C. IR (KBr) 3392, 2982, 1759, 1576 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, $J = 6.6$ and 2.4 Hz, 1H), 7.22 (dd, $J = 6.6$ and 2.4 Hz, 1H), 7.15–7.10 (m, 1H), 5.75 (q, $J = 6.6$ Hz, 1H), 5.20 (bs, 1H), 2.50 (q, $J = 6.0$ Hz, 2H), 1.77 (d, $J = 6.6$ Hz, 3H), 1.10 (s, 9H), 1.01 (t, $J = 6.0$ Hz, 3H). ^{13}C NMR (DMSO-d_6) 171.9, 162.8 (d, $J = 249.2$ Hz), 144.1, 137.7 (d, $J = 3.2$ Hz), 137.2 (d, $J = 9.0$ Hz), 131.0 (d, $J = 9.1$ Hz), 118.4 (d, $J = 23.7$ Hz), 117.7, 115.4 (d, $J = 21.5$ Hz), 53.6, 29.3, 26.6, 11.4, 8.6. MS (CI Method) 344 $(M + H)^+$, 288, 270, 252, 232, 214, 196, 176. HPLC (System 1) 98.4%; (System 2) 97.9%. Anal. ($C_{16}H_{22}FNO_4S$) C: calcd, 55.96; found, 56.12; H: calcd, 6.46; found, 6.78; N: calcd, 4.08; found, 4.25.

*4.3. 5-Chloro-2-ethyl-3-methylene-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide **10***

A colorless solid was obtained in 82% yield when acetic anhydride was used in the reaction of **7**. Mp 65–67 °C. IR (KBr) 3087, 1739, 1688, 1622, 1574 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, $J = 10.8$ Hz, 1H), 7.69 (s, 1H), 7.54 (d, $J = 10.8$ Hz, 1H), 4.99 (d, $J = 3.2$ Hz, 1H), 4.53 (d, $J = 3.2$ Hz, 1H), 3.72 (q, $J = 7.2$ Hz, 2H), 1.41 (t, $J = 7.2$ Hz, 3H). MS (CI Method) 244 $(M + H)^+$, 215. Anal. ($C_{10}H_{10}ClNO_2S$) C: calcd, 49.28; found, 49.55; H: calcd, 4.14; found, 3.96; N: calcd, 5.75; found, 5.68.

*4.4. N-tert-Butyl-4-fluoro-2-hydroxymethyl benzenesulfonamide **4a** (representative hemiaminal–carbonyl reduction)*

After stirring the reaction mixture overnight [*ortho*-acylation of N^1-(*tert*-butyl)-4-fluoro benzenesulfonamide **1a** leading to a mixture of **2a** and **3a**], the whole mass was poured over

ice-cold ammonium chloride solution and stirred for 5 min. $NaBH_4$ (0.16 g, 4.32 mmol) was added in three lots and stirring was continued for another 30 min. The whole mass was extracted with ethyl acetate, dried (Na_2SO_4) and evaporated to get a gummy mass which was purified by column chromatography over 230–400 mesh silica-gel using a mixture of ethyl acetate and petroleum ether (15:85). The colorless viscous mass was triturated with ethyl acetate–petroleum ether to get a colorless solid of the desired product **4a** (1.9 g, 82%). Mp 118–120 °C. IR (neat) 3408, 1582, 1449 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.07–8.02 (m, 1H), 7.27 (dd, $J = 6.8$ and 2.4 Hz, 1H), 7.08–7.01 (m, 1H), 5.01 (bs, 1H), 4.98 (s, 2H), 3.05 (bs, 1H), 1.22 (s, 9H). ^{13}C NMR (DMSO-d_6) δ 163.7 (d, $J = 248.3$ Hz), 145.2 (d, $J = 7.9$ Hz), 136.1, 131.1 (d, $J = 9.2$ Hz), 113.8 (d, $J = 23.8$ Hz), 113.2 (d, $J = 21.8$ Hz), 59.1, 53.5, 29.6. MS (CI Method) 261 $(M)^+$, 246, 228, 206, 188. HPLC (System 1) 98.4%. Anal. ($C_{11}H_{16}FNO_3S$) C: calcd, 50.56; found, 50.42; H: calcd, 6.17; found, 6.34; N: calcd, 5.36; found, 5.29.

4.5. N^1-(tert-Butyl)-4-chloro-2-hydroxymethyl benzenesulfonamide **4b**

A colorless solid was obtained in 84% yield when a mixture of products **2b** and **3b** was treated in situ with $NaBH_4$ at room temperature. Mp 124–126 °C. IR (KBr) 3402, 1585, 1452 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, $J = 6.0$ Hz, 1H), 7.32 (d, $J = 6.0$ Hz, 1H), 7.02 (s, 1H), 5.05 (bs, 1H), 5.00 (d, $J = 3.8$ Hz, 2H), 2.95 (bs, 1H), 1.20 (s, 9H). MS (CI Method) 278 $(M + H)^+$, 260, 208. HPLC (System 1) 98.3%. Anal. ($C_{11}H_{16}ClNO_3S$) C: calcd, 47.56; found, 47.32; H: calcd, 5.81; found, 6.10; N: calcd, 5.04; found, 5.74.

4.6. N-tert-Butyl-4-fluoro-2-[(1RS)-1-hydroxyethyl)] benzenesulfonamide **4c**

A colorless foam was obtained in ~80% yield when a mixture of products **2c** and **3c** was treated in situ with $NaBH_4$ or $LiBH_4$ at 40–50 °C. IR (neat) 3451, 3281, 2976, 1582 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, $J = 6.8$ Hz, 1H), 7.39–7.20 (m, 2H), 5.69 (q, $J = 6.2$ Hz, 1H), 4.93 (bs, 1H), 2.80 (bs, 1H), 1.57 (d, $J = 6.2$ Hz, 3H), 1.25 (s, 9H). MS (CI Method) 260 $(M - CH_3)^+$, 242, 216, 201, 185, 168, 159, 123, 109, 101, 95. HPLC (System 1) 97.8%. Anal. ($C_{12}H_{18}FNO_3S$) C: calcd, 52.35; found, 52.77; H: calcd, 6.59; found, 6.25; N: calcd, 5.09; found, 5.23.

4.7. N-tert-Butyl-4-fluoro-2-[(1RS)-1-hydroxypropyl)] benzenesulfonamide **4d**

A colorless solid was obtained as one of the components in 42% yield when the mixture of products **2d** and **3d** was in situ reduced with $NaBH_4$ under reflux. Mp 121–122 °C. IR (neat) 3485, 3294, 2982, 1532 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.95 (d, $J = 6.2$ Hz, 1H), 7.45–7.20 (m, 2H), 5.35–5.30 (m, 1H), 5.28 (bs, 1H), 3.35 (bs, 1H), 2.30–1.30 (m, 2H), 1.15 (s, 9H), 0.95 (t, $J = 6.4$ Hz, 3H). MS (CI Method) 290 $(M + H)^+$, 272, 256, 234, 216, 187, 157, 123. HPLC (System 1) 97.5%. Anal. ($C_{13}H_{20}FNO_3S$) C: calcd, 53.96; found, 54.28; H: calcd, 6.97; found, 7.21; N: calcd, 4.84; found, 5.12.

4.8. 2-tert-Butyl-(3RS)-3-ethyl-5-fluoro-1,1-dioxo-2,3-dihydro-1H-benzo[d]isothiazol-3-ol **2d**

A colorless solid was obtained as one of column fraction (35%) in the above reaction. Mp 105–107 °C. IR (KBr) 3424, 2928, 1581 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 8.20 (d, $J = 6.6$ Hz, 1H), 7.35–7.25 (m, 2H), 6.80 (bs, 1H), 2.58 (q, $J = 7.0$ Hz, 2H), 1.14 (s, 9H), 0.88 (t, $J = 7.0$ Hz, 3H). MS (CI Method) 290 $(M + H)^+$, 272, 232, 216, 176, 123, 109. HPLC (System 2) 98.7%. Anal. ($C_{13}H_{18}FNO_3S$) C: calcd, 54.34; found, 54.22; H: calcd, 6.31; found, 6.01; N: calcd, 4.87; found, 4.72.

4.9. N-tert-Butyl-4-fluoro-2-(2,2,2-trifluoro-1-hydroxyethyl) benzenesulfonamide **4e**

A colorless gummy mass was obtained in ~80% yield by the in situ reduction of a mixture of components **2e** and **3e** with $NaBH_4$ or $LiBH_4$ at room temperature. IR (neat) 3288, 2978, 1588, 1478 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.10 (m, 1H), 8.00–7.88 (m, 1H), 7.57 (dd, $J = 6.0$ and 1.6 Hz, 1H), 6.18 (m, 1H), 4.62 (bs, 1H), 3.50 (bs, 1H), 1.25 (s, 9H). MS (CI Method) 330 $(M + H)^+$, 294, 277, 156. HPLC (System 1) 97.3%. Anal. ($C_{12}H_{15}F_4NO_3S$) C: calcd, 43.77; found, 44.02; H: calcd, 4.59; found, 4.80; N: calcd, 4.25; found, 4.61.

4.10. 4-Chloro-N-ethyl-2-hydroxymethyl benzenesulfonamide **12a**

An off-white viscous mass was obtained in ~85% yield by the in situ reduction of a mixture of components **8a** and **9a** with $NaBH_4$ or $LiBH_4$ at room temperature. IR (neat) 3375, 3324, 1512 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.88 (d, $J = 6.8$ Hz, 1H), 7.42 (d, $J = 6.8$ Hz, 1H), 7.08 (s, 1H), 5.10 (d, $J = 3.0$ Hz, 2H), 4.20 (bt, 1H), 3.76 (q, $J = 7.0$ Hz, 2H), 2.82 (bs, 1H), 1.15 (t, $J = 7.0$ Hz, 3H). MS (Electrospray) 250 $(M + H)^+$, 232, 197. HPLC (System 1) 98.2%; (System 2) 97.8%. Anal. ($C_9H_{12}ClNO_3S$) C: calcd, 43.29; found, 43.35; H: calcd, 4.84; found, 5.02; N: calcd, 5.61; found, 5.27.

4.11. 4-Chloro-N-ethyl-2-(2,2,2-trifluoro-1-hydroxyethyl) benzenesulfonamide **12b**

An off-white viscous mass was obtained in ~80% yield by the in situ reduction of a mixture of components **8b** and **9b** with $NaBH_4$ or $LiBH_4$ at room temperature. IR (neat) 3372, 3318, 1505 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, $J = 7.0$ Hz, 1H), 7.35 (d, $J = 7.0$ Hz, 1H), 6.98 (s, 1H), 6.05 (m, 1H), 4.90 (bs, 1H), 3.68 (q, $J = 6.8$ Hz, 2H), 2.96 (bs, 1H), 1.10 (t, $J = 6.8$ Hz, 3H). MS (Electrospray) 318 $(M + H)^+$, 291, 226, 191. HPLC (System 1) 99.0%. Anal.

($C_{10}H_{11}ClF_3NO_3S$) C: calcd, 37.80; found, 37.43; H: calcd, 3.49; found, 3.28; N: calcd, 4.41; found, 4.61.

4.12. Representative preparation of 4-fluoro-2-hydroxymethyl-1-benzenesulfonamide **14**

A mixture of *p*-toluenesulfonic acid (2.92 g, 15.2 mmol) and *N-tert*-butyl-4-fluoro-2-hydroxymethyl benzenesulfonamide **4a** (20.0 g, 76.5 mmol) was refluxed with toluene (200 mL) using Dean–Stark water separator for 1 h. The reaction mixture was brought to room temperature, poured over ice-water and extracted with ethyl acetate. The combined organic layer was sequentially washed with 5% aqueous $NaHCO_3$ and water. The solvent was dried (Na_2SO_4) and evaporated to get a viscous mass which on trituration with ethyl acetate–petroleum ether afforded a colorless solid (12.0 g, 76%) of the desired compound. Mp 122–124 °C. IR (KBr) 3607, 3363, 3251, 3106, 1605, 1583, 1448, 1324 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.90 (dd, $J = 5.8$ and 3.0 Hz, 1H), 7.50 (dd, $J = 7.0$ and 2.6 Hz, 1H), 7.48 (bs, 2H, D_2O exchangeable), 7.27 (dd, $J = 5.8$ and 2.6 Hz, 1H), 5.61 (bt, $J = 5.0$ Hz, 1H, D_2O exchangeable), 4.92 (d, $J = 4.0$ Hz, 2H). ^{13}C NMR (50 MHz, DMSO-d_6) 164.3 (d, $J = 248.5$ Hz, C_4), 144.8 (d, $J = 7.8$ Hz, C_2), 136.4 (C_1), 130.2 (d, $J = 8.9$ Hz, C_6), 114.2 (d, $J = 24.0$ Hz, C_3), 113.3 (d, $J = 23.8$ Hz, C_5), 59.5 (CH_2O). MS (CI Method) 206 $(M + H)^+$, 188, 170, 159, 152, 143, 123, 115, 95. HPLC (System 1) 97.3%; (System 2) 97.5%. Anal. ($C_7H_8FNO_3S$) C: calcd, 40.97; found, 41.21; H: calcd, 3.93; found, 3.77; N: calcd, 6.83; found, 7.01.

4.13. Representative preparation of 4-hydrazino-2-hydroxymethyl-1-benzenesulfonamide **15**

4-Fluoro-2-hydroxymethyl benzenesulfonamide **13** (12.0 g, 58.5 mmol), dissolved in dry acetonitrile (200 mL) was added with anhydrous hydrazine (9.36 g, 292.6 mmol) under argon atmosphere and refluxed for 72 h. The solvent was completely evaporated and water (40 mL) was added. After a gentle shake, the solution was kept in fridge overnight. The off-white solid separated, was filtered and washed with chilled water (minimum) to get the desired title compound (8.5 g, 67%). Mp 152–154 °C. IR (Nujol) 3340, 2924, 2853, 1599, 1462, 1376, 1316 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.58 (d, $J = 8.7$ Hz, 1H), 7.45 (s, 1H, D_2O exchangeable), 7.08 (s, 1H), 6.95 (s, 2H, D_2O exchangeable), 6.69 (dd, $J = 6.4$ and 1.4 Hz, 1H), 5.31 (t, $J = 5.0$ Hz, 1H, D_2O exchangeable), 4.82 (d, $J = 5.0$ Hz, 2H), 4.17 (s, 2H, D_2O exchangeable). MS (CI Method) 217 $(M)^+$, 202, 201, 183, 182, 169, 152, 138, 136, 120, 107, 105, 92. HPLC (System 1) 98.2%; (System 2) 97.8%. Anal. ($C_7H_{11}N_3O_3S$) C: calcd, 38.70; found, 39.05; H: calcd, 5.10; found, 5.04; N: calcd, 19.34; found, 19.60.

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