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Practical Sulfonylation of Amines with 4-Hydroxybenzenesulfonyl Chloride: In Situ Silylation–Desilylation

Jeremy I. Levin,* Mila T. Du, and Kaapjoo Park

Wyeth Research, Pearl River, New York, USA

ABSTRACT

A one-pot procedure for the efficient sulfonylation of amines with 4-hydroxybenzenesulfonyl chloride involving in situ protection and deprotection of the phenol with *N*,*O*-bis(trimethylsilyl)acetamide (BTSA) is presented.

Key Words: Sulfonylation; 4-Hydroxybenzenesulfonyl chloride; Silylation–desilylation; Sulfonamides.

INTRODUCTION

The sulfonylation of amines with 4-hydroxybenzenesulfonyl chloride is potentially an extremely valuable procedure. For example, 4-hydroxybenzene-

*Correspondence: Jeremy I. Levin, Wyeth Research, 401 N. Middletown Rd., Pearl River, NY 10965, USA; E-mail: levinji@wyeth.com.

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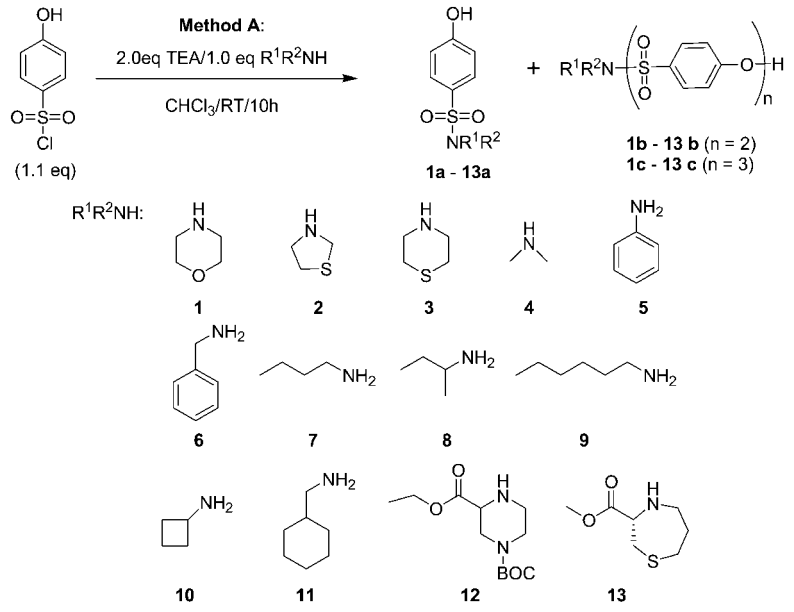
sulfonamides are intermediates in the construction of sulfonamide hydroxamate matrix metalloproteinase inhibitors.[1] However, although 4-hydroxybenzenesulfonyl chloride is readily available in large quantities,[2] we have found that poor yields are generally obtained on the direct reaction of primary or secondary amines with this reagent. Thus, the reaction of 4-hydroxybenzenesulfonyl chloride with a variety of primary and secondary amines, **1**–**13**, at room temperature in the presence of triethylamine (method A) provides the corresponding sulfonamides, **1a**–**13a** (Sch. 1), in 6–66% yield along with significant amounts of by-products formed from the mono-sulfonylation (**1b**–**13b**), and di-sulfonylation (**1c**–**13c**) of the initial 4-hydroxybenzenesulfonamide (Table 1). Thus, temporary protection of this hydroxy group should eliminate these side-products and provide more useful yields of the desired sulfonamides.

Among the literature methods that circumvent this problem are the use of 4-benzyloxyphenylsulfonyl chloride followed by hydrogenolysis to remove the benzyl protecting group,[1] sulfonylation with 4-fluorophenylsulfonyl chloride and subsequent S_NAr displacement of fluoride with alkoxides,[3] or the use of 4-methoxybenzenesulfonyl chloride followed by ether cleavage with ethanethiol and aluminum chloride.[4] The extra synthetic step involved



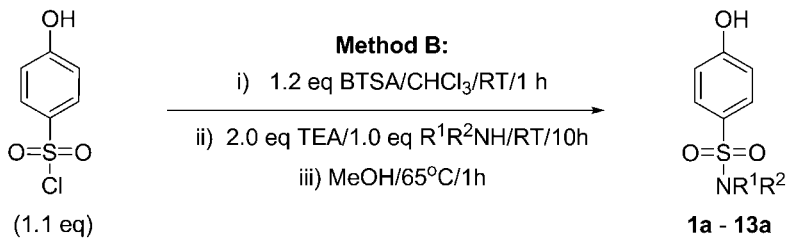
Scheme 1.

Table 1. Reactions of 4-hydroxybenzenesulfonyl chloride with amines **1–13** in chloroform with 2.0 equiv. of triethylamine (method A).

R^1R^2NH	Product (**a**)/dimer (**b**)/trimer (**c**) (% yield)
1	**1a**/**1b**/**1c** (56/12/5)
2	**2a**/**2b**/**2c** (49/12/8)
3	**3a**/**3b**/**3c** (66/9/3)
4	**4a**/**4b**/**4c** (39/15/9)
5	**5a**/**5b**/**5c** (17/9/11)
6	**6a**/**6b**/**6c** (34/15/12)
7	**7a**/**7b**/**7c** (10/22/14)
8	**8a**/**8b**/**8c** (6/10/11/2)
9	**9a**/**9b**/**9c** (30/16/12)
10	**10a**/**10b**/**10c** (27/13/9)
11	**11a**/**11b**/**11c** (30/16/11)
12	**12a**/**12b**/**12c** (31/8/8)
13	**13a**/**13b**/**13c** (28/10/9)

in these alternate routes is inconvenient and may be incompatible with other functionality in the target molecules, making a more direct method desirable.

We have found that by adding *N*,*O*-bis(trimethylsilyl)acetamide (BTSA) to a chloroform solution of 4-hydroxyphenylsulfonyl chloride to silylate the free phenol prior to the addition of the desired amine, and then briefly refluxing the reaction mixture with added methanol prior to work-up (Sch. 2, method B), excellent yields of 4-hydroxybenzenesulfonamides **1a–13a** can be obtained (Table 2). Primary and secondary alkyl amines and aromatic amines react under these conditions to provide greater than 85% yields of the desired sulfonamides. Even *n*-butyl and *sec*-butyl amine, which give yields of less than 10% in the absence of BTSA, react efficiently when the



Scheme 2.

Table 2. Reactions of 4-hydroxybenzenesulfonyl chloride with amines in the presence of 1.2 equiv. of BTSA (method B).

R^1R^2NH	Product (% yield)
1	**1a** (88)
2	**2a** (90)
3	**3a** (91)
4	**4a** (90)
5	**5a** (92)
6	**6a** (91)
7	**7a** (89)
8	**8a** (87)
9	**9a** (93)
10	**10a** (94)
11	**11a** (94)
12	**12a** (88)
13	**13a** (86)

sulfonyl chloride is protected in situ. Furthermore, none of the products of di- or tri-sulfonylation, **1b,c–13b,c**, are observed under the conditions of method B.

In summary, we have developed an efficient method for the sulfonylation of amines with 4-hydroxybenzenesulfonyl chloride utilizing an in situ protection/deprotection protocol with BTSA. This methodology affords rapid and efficient access to intermediates for the synthesis of compounds of chemical and pharmacological interest.

GENERAL EXPERIMENTAL PROCEDURE

All reactions were performed under nitrogen atmosphere. Purification of the products was carried out by preparative HPLC (Gilson) using a $250 \times 21.25\,mm^2$ 5 μm C18 column and acetonitrile/water (containing 0.02% TFA) as eluent. Melting points are uncorrected. ^1H NMR spectra were recorded at 400 MHz on a Bruker DRX-400 spectrometer. Tetramethylsilane ($\delta = 0$ ppm) was used as an internal standard and DMSO-d_6 was used as the solvent. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker DRX-400 spectrometer. Mass spectra were obtained using a Micromass Platform Electrospray Ionization Quadrapole mass spectrometer.

Method A

General procedure for the 4-hydroxybenzenesulfonylation of amines in the absence of BTSA. To a solution of 4-hydroxybenzenesulfonyl chloride (120 mg, 0.623 mmol) in chloroform (1 mL) were added TEA (158 μL, 1.133 mmol) and the amine (0.566 mmol) at room temperature. After stirring overnight at room temperature, the reaction mixture was concentrated and the residue was purified by preparative HPLC to give the desired product.

Method B

General procedure for the 4-hydroxybenzenesulfonylation of amines in the presence of BTSA. To a solution of 4-hydroxybenzenesulfonyl chloride (120 mg, 0.623 mmol) in chloroform (1 mL) was added BTSA (168 μL, 0.680 mmol). The reaction mixture was stirred for 1 hr at room temperature. To the mixture were added TEA (158 μL, 1.133 mmol) and the amine (0.566 mmol) and the reaction mixture was stirred overnight at room temperature. To the reaction mixture was added MeOH (2 mL), and the solution was heated to 65°C for 1 hr. The reaction mixture was cooled to room temperature and concentrated, and the residue was purified by preparative HPLC to give the desired product.

4-(Morpholino-4-sulfonyl)phenol (1a). Pale yellow solid, m.p. 149–151°C (lit. 151–152°C[5]); IR (KBr): 3299, 2908, 2855, 1604, 1584, 1504 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.57 (s, 1H), 7.56 (d, $J = 8.81$ Hz, 2H), 6.96 (d, $J = 8.81$ Hz, 2H), 3.62 (t, $J = 4.80$ Hz, 2H), 2.80 (t, $J = 4.80$ Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 161.7, 130.0 (2C), 123.9, 115.7 (2C), 65.2 (2C), 45.8 (2C); HRMS (EI): calcd for $C_{10}H_{14}NO_4S$ $[M + H]^+$ 244.0638, found 244.0642; Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.19; H, 5.10; N, 5.69.

4-(Thiazolidino-3-sulfonyl)phenol (2a). Yellow solid; IR (KBr). 3431, 3064, 1586, 1500 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.57 (s, 1H), 7.68 (d, $J = 8.81$ Hz, 2H), 6.92 (d, $J = 8.81$ Hz, 2H), 4.39 (s, 2H), 3.52 (t, $J = 6.41$ Hz, 2H), 2.65 (t, $J = 6.41$ Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 161.9, 129.9 (2C), 126.4, 115.7 (2C), 51.1, 50.2, 29.9; HRMS (EI): calcd for $C_9H_{12}NO_3S_2$ $[M + H]^+$ 246.0253, found 246.0258; Anal. Calcd for $C_9H_{11}NO_3S_2$: C, 44.06; H, 4.52; N, 5.71. Found: C, 43.79; H, 4.25; N, 5.68.

4-(Thiomorpholine-4-sulfonyl)phenol (3a). Yellow solid; m.p. 124–126°C; IR (KBr): 3406, 2850, 1656, 1603, 1583, 1501 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.55 (s, 1H), 7.56 (d, $J = 8.81$ Hz, 2H), 6.96 (d, $J = 8.81$ Hz, 2H), 3.13 (m, 2H), 2.65 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 161.5, 129.6 (2C), 125.6, 115.7 (2C), 47.7 (2C), 26.3 (2C); HRMS (EI): calcd for $C_{10}H_{14}NO_3S_2$

$[M + H]^+$ 260.0410, found 260.0414; Anal. Calcd for $C_{10}H_{13}NO_3S_2$: C, 46.31; H, 5.05; N, 5.40. Found: C, 46.31; H, 4.96; N, 5.71.

4-Hydroxy-*N*,*N*-dimethylbenzenesulfonamide (4a). Pale yellow solid; m.p. 93–95°C (lit. 94°C[6]); IR (neat): 3139, 2965, 1658, 1601, 1584, 1502 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.50 (s, 1H), 7.58 (d, $J = 8.81$ Hz, 2H), 2.54 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 161.8, 130.3 (2C), 124.7, 116.0 (2C), 38.0 (2C); HRMS (EI): calcd for $C_8H_{12}NO_3S$ $[M + H]^+$ 202.0532, found 202.0537.

4-Hydroxy-*N*-phenylbenzenesulfonamide (5a). Pale yellow solid; m.p. 135–137°C (lit. 137–138°C[7]); IR (KBr): 3388, 3269, 2925, 1657, 1600, 1584, 1499 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.41 (s, 1H), 10.03 (s, 1H), 7.57 (d, $J = 8.80$ Hz, 2H), 7.22 (t, $J = 8.01$ Hz, 2H), 7.06 (d, $J = 8.80$ Hz, 2H), 6.99 (t, $J = 8.80$ Hz, 1H), 6.83 (d, $J = 8.81$ Hz, 2H), 3.13 (m, 2H), 2.65 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 161.6, 138.4, 129.8, 129.4 (4C), 124.0, 120.1 (2C), 115.9 (2C); HRMS (EI): calcd for $C_{12}H_{12}NO_3S$ $[M + H]^+$ 250.0532, found 250.0537.

***N*-Benzyl-4-hydroxybenzenesulfonamide (6a).** Pale yellow solid; m.p. 66–68°C; IR (KBr): 3426, 3304, 1661, 1601, 1584, 1499 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.35 (s, 1H), 7.87 (d, $J = 6.41$ Hz, 1H), 7.62 (d, $J = 8.81$ Hz, 2H), 7.26 (m, 5H), 6.89 (d, $J = 8.81$ Hz, 2H), 3.91 (d, $J = 6.41$ Hz, 2H); ^{13}C NMR (DMSO-d_6): δ 160.7, 137.7, 130.5, 128.7 (2C), 128.1 (2C), 127.4 (2C), 126.9, 115.4 (2C), 46.0; HRMS (EI): calcd for $C_{13}H_{14}NO_3S$ $[M + H]^+$ 264.0689, found 264.0693.

***N*-Butyl-4-hydroxybenzenesulfonamide (7a).** Pale yellow solid; m.p. 77–79°C (lit. 79–81°C[5]); IR (KBr): 3275, 2960, 2930, 2870, 1651, 1578 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.33 (s, 1H), 7.60 (d, $J = 8.79$ Hz, 2H), 7.26 (t, $J = 8.01$ Hz, 1H), 6.89 (d, $J = 8.79$ Hz, 2H), 2.66 (q, $J = 6.81$ Hz, 2H), 1.32 (m, 2H), 1.23 (m, 2H), 0.79 (t, $J = 7.21$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 160.6, 130.4, 128.6 (2C), 115.3 (2C), 42.0, 30.9, 19.1, 13.4; HRMS (EI): calcd for $C_{10}H_{14}NO_3S$ $[M - H]^-$ 228.0700, found 228.0699.

7b. Yellow solid; IR (neat): 3290, 3105, 2955, 2931, 2883, 1654, 1585 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.95 (s, 1H), 7.78 (d, $J = 8.81$ Hz, 2H), 7.67 (d, $J = 8.81$ Hz, 2H), 7.63 (t, $J = 5.85$ Hz, 1H), 7.24 (d, $J = 8.81$ Hz, 2H), 6.95 (d, $J = 8.81$ Hz, 2H), 2.71 (q, $J = 6.81$ Hz, 2H), 1.29 (m, 2H), 1.21 (m, 2H), 0.77 (t, $J = 7.21$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 163.3, 151.4, 139.4, 130.8 (2C), 128.5 (2C), 123.0, 122.9 (2C), 116.1 (2C), 42.0, 30.9, 19.0, 13.3; HRMS (EI): calcd for $C_{16}H_{18}NO_6S_2$ $[M - H]^-$ 384.0581, found 384.0582.

7c. Yellow solid; IR (neat): 3201, 3101, 2956, 2935, 2880, 1650, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.01 (s, 1H), 7.94 (d, $J = 8.81$ Hz, 2H), 7.81 (d, $J = 8.81$ Hz, 2H), 7.68 (m, 3H), 7.32 (d, $J = 8.81$ Hz, 2H),

7.25 (d, $J = 8.81$ Hz, 2H), 6.97 (d, $J = 8.81$ Hz, 2H), 2.73 (q, $J = 6.81$ Hz, 2H), 1.29 (m, 2H), 1.21 (m, 2H), 0.77 (t, $J = 7.21$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 163.5, 153.5, 150.9, 139.8, 132.3, 130.9 (2C), 130.6 (2C), 128.6 (2C), 123.6 (2C), 122.9 (2C), 122.7, 116.2 (2C), 42.0, 30.9, 19.0, 13.3; HRMS (EI): calcd for $C_{22}H_{24}NO_9S_3$ $[M + H]^+$ 542.0607, found 542.0613.

***N-sec*-Butyl-4-hydroxybenzenesulfonamide (8a).** Yellow oil; IR (neat): 3282, 2979, 2932, 2880, 1651, 1583, 1501 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.29 (s, 1H), 7.60 (d, $J = 8.79$ Hz, 2H), 7.22 (t, $J = 8.01$ Hz, 1H), 6.89 (d, $J = 8.79$ Hz, 2H), 2.97 (sep, $J = 6.41$ Hz, 1H), 1.28 (qn, $J = 7.21$ Hz, 2H), 0.85 (d, $J = 6.81$ Hz, 3H), 0.70 (t, $J = 7.21$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 160.5, 131.9, 128.5 (2C), 115.2 (2C), 50.4, 29.4, 20.4, 9.9; HRMS (EI): calcd for $C_{10}H_{14}NO_3S$ $[M - H]^-$ 228.0700, found 228.0698.

***N*-Hexyl-4-hydroxybenzenesulfonamide (9a).** Yellow oil; IR (neat): 3286, 2955, 2926, 2861, 1655, 1587, 1501 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.33 (s, 1H), 7.60 (d, $J = 8.81$ Hz, 2H), 7.26 (t, $J = 8.01$ Hz, 1H), 6.90 (d, $J = 8.81$ Hz, 2H), 2.67 (q, $J = 7.20$ Hz, 2H), 1.32 (m, 2H), 1.18 (m, 3H), 0.82 (t, $J = 6.81$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 161.1, 130.9, 129.1 (2C), 115.8 (2C), 42.8, 31.1, 29.2, 26.1, 22.3, 14.2; HRMS (EI): calcd for $C_{12}H_{20}NO_3S$ $[M + H]^+$ 258.1158, found 258.1168.

***N*-Cyclobutyl-4-hydroxybenzenesulfonamide (10a).** White solid; m.p. 91–93°C; IR (neat): 3281, 2978, 1644, 1587, 1501 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.32 (s, 1H), 7.66 (d, $J = 8.01$ Hz, 1H), 7.58 (d, $J = 8.81$ Hz, 2H), 6.89 (d, $J = 8.81$ Hz, 2H), 2.97 (six, $J = 8.41$ Hz, 1H), 1.88 (m, 2H), 1.70 (m, 2H), 1.47 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 160.7, 131.4, 128.6 (2C), 115.3 (2C), 47.4, 30.4 (2C), 14.4; HRMS (EI): calcd for $C_{10}H_{12}NO_3S$ $[M - H]^-$ 226.0543, found 226.0542.

10b. Pale yellow solid; IR (neat): 3281, 3102, 2971, 2935, 1651, 1580 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.94 (bs, 1H), 8.00 (d, $J = 8.01$ Hz, 1H), 7.78 (d, $J = 8.81$ Hz, 2H), 7.64 (d, $J = 8.81$ Hz, 2H), 7.23 (d, $J = 8.81$ Hz, 2H), 6.93 (d, $J = 8.81$ Hz, 2H), 3.59 (six, $J = 8.01$ Hz, 1H), 1.81 (m, 2H), 1.63 (m, 2H), 1.47 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 163.3, 151.5, 140.2, 130.9 (2C), 128.5 (2C), 122.9 (2C), 122.8, 116.2 (2C), 47.4, 30.3 (2C), 14.4; HRMS (EI): calcd for $C_{16}H_{16}NO_6S_2$ $[M - H]^-$ 382.0425, found 382.0425.

10c. Pale yellow solid; IR (neat): 3285, 3101, 2987, 2941, 1648, 1586 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.02 (s, 1H), 8.03 (d, $J = 8.01$ Hz, 1H), 7.90 (d, $J = 8.81$ Hz, 2H), 7.79 (d, $J = 8.81$ Hz, 2H), 7.68 (d, $J = 8.81$ Hz, 2H), 7.30 (d, $J = 8.81$ Hz, 2H), 7.22 (d, $J = 8.81$ Hz, 2H), 6.98 (d, $J = 8.81$ Hz, 2H), 3.62 (six, $J = 8.41$ Hz, 1H), 1.81 (m, 2H), 1.63 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 163.5, 153.5, 151.0, 140.7, 132.1, 130.9 (2C), 130.7 (2C), 128.6 (2C), 123.6 (2C), 122.8 (2C), 122.6,

116.2 (2C), 47.4, 30.3 (2C), 14.3; HRMS (EI): calcd for $C_{22}H_{20}NO_9S_3$ $[M - H]^-$ 538.0305, found 538.0301.

***N*-Cyclohexylmethyl-4-hydroxybenzenesulfonamide (11a).** Yellow oil; IR (neat): 3287, 2920, 2851, 1653, 1581, 1502 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.32 (s, 1H), 7.60 (d, $J = 8.81$ Hz, 2H), 7.28 (t, $J = 8.01$ Hz, 1H), 6.88 (d, $J = 8.81$ Hz, 2H), 2.51 (m, 2H), 1.28 (m, 1H), 1.11 (m, 3H), 0.79 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 160.6, 130.6, 128.6 (2C), 115.3 (2C), 48.6, 37.1, 30.1 (2C), 25.8, 25.2 (2C); HRMS (EI): calcd for $C_{13}H_{20}NO_3S$ $[M + H]^+$ 270.1158, found 270.1154.

4-(4-Hydroxy-benzenesulfonyl)piperazine-1-boc-3-carboxylic acid ethyl ester (12a). White solid; m.p. 58–60°C; IR (neat): 3280, 2981, 2922, 1733, 1698, 1662, 1598 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.49 (s, 1H), 7.56 (d, $J = 8.81$ Hz, 2H), 6.91 (d, $J = 8.81$ Hz, 2H), 4.47 (d, $J = 2.80$ Hz, 1H), 4.20 (d, $J = 13.6$ Hz, 1H), 3.92 (m, 1H), 3.85 (q, $J = 6.81$ Hz, 2H), 3.51 (d, $J = 12.1$ Hz, 1H), 3.25 (m, 1H), 3.10 (m, 1H), 2.74 (m, 1H), 1.32 (s, 9H), 1.10 (t, $J = 6.81$ Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 168.8, 161.4 (2C), 129.2 (2C), 128.5, 115.5 (2C), 79.3, 60.8 (2C), 53.9, 41.1 (2C), 27.7 (3C), 13.6; HRMS (EI): calcd for $C_{18}H_{27}N_2O_7S$ $[M + H]^+$ 415.1533, found 415.1527.

D-4-(4-Hydroxy-benzenesulfonyl)[1,4]thiazepane-3-carboxylic acid methyl ester (13a). Pale yellow solid; IR (neat): 3390, 2953, 1736, 1720, 1586 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.42 (s, 1H), 7.59 (d, $J = 8.81$ Hz, 2H), 6.88 (d, $J = 8.81$ Hz, 2H), 4.60 (dd, $J = 10.0$, 6.00 Hz, 1H), 3.70 (dt, $J = 16.0$, 3.20 Hz, 1H), 3.46 (s, 3H), 3.18 (m, 2H), 2.88 (dd, $J = 15.2$, 10.0 Hz, 1H), 2.59 (m, 2H), 1.88 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (DMSO-d_6): δ 170.6, 161.1, 129.8, 129.2 (2C), 115.5 (2C), 60.3, 51.9, 43.9, 35.5, 32.3, 32.1; HRMS (EI): calcd for $C_{13}H_{18}NO_5S_2$ $[M + H]^+$ 332.0621, found 332.0617.

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