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Jason D. Bonk [a], David T. Amos [a] & Sarah J. Olson [a]
[a] 3M Pharmaceuticals, Chemistry Department, St. Paul, Minnesota, USA
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Convenient One-Pot Synthesis of Sulfonamides from Thiols using Trichloroisocyanuric Acid

Jason D. Bonk, David T. Amos, and Sarah J. Olson
3M Pharmaceuticals, Chemistry Department, St. Paul, Minnesota, USA

Abstract: A convenient synthesis of sulfonamides from thiols is described. *In situ* preparation of sulfonyl chlorides from thiols is accomplished by oxidation with trichloroisocyanuric acid (TCCA), benzyltrimethylammonium chloride and water (2.5 equiv). The sulfonyl chlorides are then further allowed to react with excess amine in the same reaction vessel. Triethylamine can be optionally added as acid scavenger.

Keywords: oxidation, sulfonamides, thiol, trichloroisocyanuric acid

As a part of our medicinal chemistry program, we wished to synthesize various imidazoquinoline-based sulfonamides for which existing methods were largely unsatisfactory. We discovered that the chemistry described herein suited our needs nicely.[1,2] This communication details our exploration of the scope and optimization of the method.

Frequently, sulfonamides are formed from a sulfonyl chloride and a primary or secondary amine. In turn, sulfonyl chlorides can be prepared from the corresponding thiols using a number of methods, commonly by bubbling Cl_2 gas into aqueous acid or a biphasic mixture containing the thiol.[3–7] Although this methodology is relatively general, issues associated with the use of excess oxidant and/or aqueous acid have prompted the development of alternative methods.[8,9] We describe an oxidation/substitution

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Address correspondence to Jason D. Bonk, 3M Pharmaceuticals, Chemistry Department, 3M Center, Building 270 4S 02, St. Paul, MN 55144-1000, USA. E-mail: jbonk@mmm.com

sequence that is mild and minimizes both the amount of oxidant required and the aqueous component.

Initially, we surmised that it might be possible to generate controlled amounts of Cl_2 in nonprotic organic solvents by mixing a tetraalkylammonium chloride salt with trichloroisocyanuric acid (TCCA).[10] We were pleased to find that treatment of benzyltrimethyl ammonium chloride (3.4 equiv) with TCCA (1.1 equiv) in CH_2Cl_2 (30 min, rt) provided a light yellow solution; neither of the white solids (TCCA nor $BnMe_3NCl$) are substantially soluble in CH_2Cl_2, but within 30 min the suspension became a light yellow solution (in CH_3CN, a small amount of undissolved white solid remained). This solution, when added to an ice-cooled solution of a thiol containing H_2O (2.5 equiv), provided the corresponding sulfonyl chloride (observable by liquid chromatography-mass spectrometry (LC-MS)) within 30 min. Subsequent addition of a primary or secondary amine (6.5 equiv) afforded the desired sulfonamide (method A).

Ultimately, we found that the reaction could be rendered truly one-pot by using CH_3CN as solvent. Thus, an ice-cooled solution of thiol, H_2O, and $BnMe_3NCl$ was treated with TCCA (30 min), followed by the amine (method B). Optionally, 1.2 equiv of amine can be added, along with 5.5 equiv of Et_3N (method C). Standard workup followed by silica gel chromatography provided the sulfonamides in excellent overall yields.

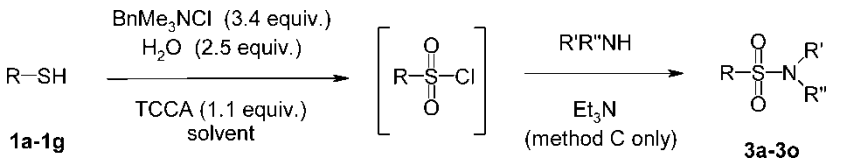
The stoichiometry of the sulfonyl chloride formation theoretically requires 3 equiv of oxidant (Cl_2) and 2 equiv of water, so the reaction proceeds cleanly with only a slight excess of each. Also, HCl is evolved, which necessitates the use of excess amine.

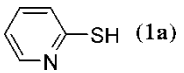
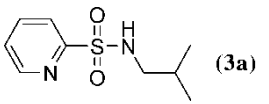
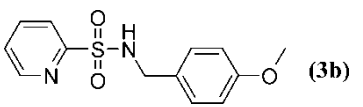
When CH_3CN is used as solvent, the scope of the reaction appears to be fairly general (Table 1). Aryl thiols appeared to be insensitive to substitution. Both electron withdrawing (entries 11, 12) and electron donating (entries 17, 18) are tolerated, as well as ortho substitution (entries 14–16). 1-Butanethiol (entry 13) also was oxidized efficiently. In general, there is no significant difference in yield among the three different procedures (entries 1–3).

We were unable to successfully oxidize heterocyclic thiols (entries 24–26) other than 2-mercaptopyridine, even when keeping the internal temperature colder than $-25^{\circ}C$. In fact, a 70% isolated yield of 2-chloropyrimidine was obtained from thiol **1f**. Analysis by LC-MS indicated that 2-chlorobenzothiazole was formed cleanly from thiol **1g**,[11] although we did observe the transient presence of a small amount of the sulfonyl chloride.

Yields using CH_2Cl_2 as solvent are unpredictable using method B (entries 5, 20, 22) but are good using method A. We attribute this variability at least in part to the poor solubility of TCCA in CH_2Cl_2. In some cases where yields were poor, we observed formation of the disulfide.[12] Curiously, using method B and an *aged* bottle of TCCA, we obtained consistently acceptable yields (>75%). We are currently investigating the nature of these results.

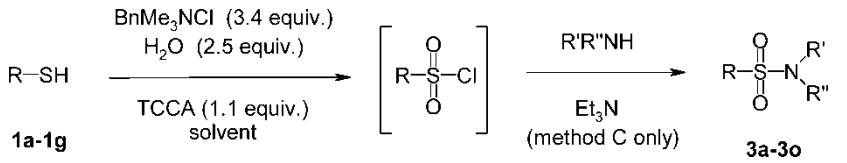
Table 1. Effect of method and solvent on yield

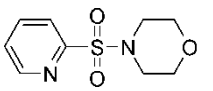
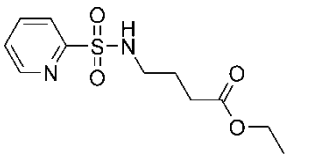
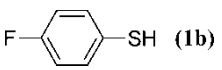
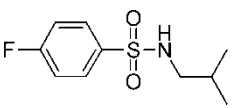


Entry	Thiol (**1**)	Product (**3**)	Method[a]	Solvent	Yield (%)
1	 **(1a)**	 **(3a)**	A	CH_3CN	85
2	**1a**	**3a**	B	CH_3CN	94
3	**1a**	**3a**	C	CH_3CN	91
4	**1a**	**3a**	A	CH_2Cl_2	90
5	**1a**	**3a**	B	CH_2Cl_2	69
6	**1a**	**3a**	B	THF	67
7	**1a**	**3a**	B	EtOAc	53
8	**1a**	 **(3b)**	B	CH_3CN	91

(*continued*)

Table 1. Continued

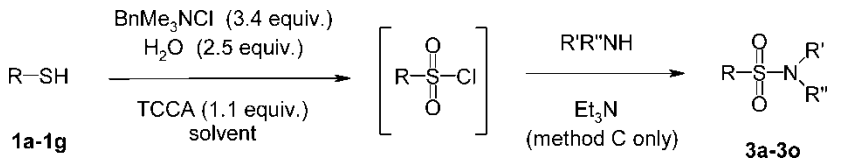


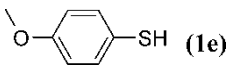
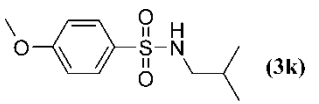
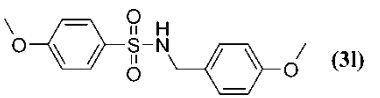
Entry	Thiol (**1**)	Product (**3**)	Method[a]	Solvent	Yield (%)
9	**1a**	 **(3c)**	B	CH_3CN	88
10	**1a**	 **(3d)**	C[b]	CH_3CN	74
11	 **(1b)**	 **(3e)**	B	CH_3CN	89

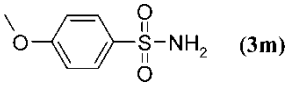
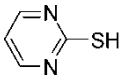
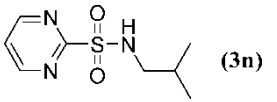
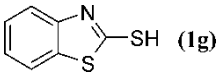
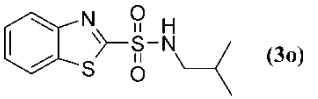
12	**1b**	**(3f)**	B	CH_3CN	93
13	**(1c)**	**(3g)**	B	CH_3CN	92
14	**(1d)**	**(3h)**	B	CH_3CN	92
15	**1d**	**(3i)**	B	CH_3CN	82
16	**1d**	**(3j)**	B	CH_3CN	75

(*continued*)

Table 1. Continued



Entry	Thiol (**1**)	Product (**3**)	Method[a]	Solvent	Yield (%)
17	 **(1e)**	 **(3k)**	B	CH_3CN	94
18	**1e**	 **(3l)**	B	CH_3CN	93
19	**1e**	**3l**	A	CH_2Cl_2	92
20	**1e**	**3l**	B	CH_2Cl_2	51
21	**1e**	**3l**	B	THF	83

22	**1e**	 **(3m)**	B	CH_2Cl_2	0
23	**1e**	**3m**	B	CH_3CN	76
24	 **(1f)**	 **(3n)**	A	CH_3CN	0
25	**1f**	**3n**	B	CH_3CN	0[c]
26	 **(1g)**	 **(3o)**	B	CH_3CN	0[d]

[a]A: $BnMe_3NCl$ and TCCA were premixed (30 min), then added to a solution of thiol and water; after 30 min the amine was added. B: TCCA was added to a mixture of $BnMe_3NCl$, thiol, and water; after 30 min the amine was added. C: TCCA was added to a mixture of $BnMe_3NCl$, thiol, and water; after 30 min the amine and Et_3N were added.

[b]Used 6.5 equiv of Et_3N with ethyl 4-aminobutyrate hydrochloride.

[c]Obtained 2-chloropyrimidine at $-25^{\circ}C$.

[d]Observed 2-chlorobenzothiazole at $-25^{\circ}C$.

We made a number of observations regarding the reaction parameters. The reaction between $BnMe_3NCl$ and TCCA itself (method A) is not exothermic generating very little pressure if conducted in a capped vial on a 2-mmol scale. For either procedure A or B, a transient 10–15°C temperature increase during the formation of the sulfonyl chloride was observed; this could be mitigated by portionwise addition of the TCCA over several min. This phenomenon was true of the amine addition as well.

EXPERIMENTAL

All reactions were conducted open to the atmosphere using commercially available reagents, which were used as received. NMR analyses were conducted on a Bruker 300-, 500-, or 700-MHz NMR; the chemical shifts are referenced to tetramethylsilane at δ0.00 ppm. Melting points were obtained on an OptiMelt automated instrument (Stanford Research Solutions, Sunnyvale, CA). MS analyses were conducted on a Hewlett Packard 1100 HPLC system using an electrospray ionization source in positive ion mode. Elemental analyses were performed by Robertson Microlit Laboratories (Madison, NJ) and were within 0.4% of the theoretical values. All final compounds **3a**–**3m** were purified by silica-gel chromatography using reagent-grade ethyl acetate/hexanes. Reactions performed in the attempts to synthesize **3n** and **3o** were conducted at −30 to −25°C by intermittent cooling in a dry ice/acetone bath, measured with internal temperature probe.

General Procedures for the Conversion of Thiols to Sulfonamides: N-Isobutylpyridine-2-sulfonamide (3a).

Method A

To a stirred suspension of $BnMe_3NCl$ (1.26 g, 3.4 equiv) in CH_3CN (9 mL) at ambient temperature, trichloroisocyanuric acid (0.51 g, 1.1 equiv) was added as a solid in one portion. After 30 min, the clear yellow solution was added dropwise to a stirred 0°C solution of 2-mercaptopyridine (0.22 g, 1.0 equiv, 2.0 mmol) and water (90 μL, 2.5 equiv) in CH_3CN (9 mL) over about 2 min. After 30 min isobutylamine (1.28 mL, 6.5 equiv) was added to the mixture over 1–2 min. After 5 min, the ice bath was removed and the mixture was allowed to stir for 1 h. The mixture was filtered and rinsed twice with CH_3CN (10 mL). The filtrate was evaporated. Column chromatography on silica gel eluting with ethyl acetate/hexanes provided the product (85%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (d, $J = 5.0$ Hz, 1H), 8.01 (d, $J = 7.5$ Hz, 1H), 7.91 (td, $J = 7.5$, 1.9 Hz, 1H), 7.52–7.47 (m, 1H), 5.04 (br t, $J = 5.9$ Hz, 1H), 2.85 (t, $J = 6.5$ Hz,

2H), 1.75 (septet, $J = 6.5$ Hz, 1H), 0.90 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 150.0, 138.1, 126.6, 122.3, 51.0, 28.7, 19.8; MS (ESI) m/z 215 $(M + H)^+$; anal. calcd. for $C_9H_{14}N_2O_2S$: C, 50.45; H, 6.59; N, 13.07. Found: C, 50.56; H, 6.30; N, 13.06.

Method B

To a stirred mixture of 2-mercaptopyridine (0.22 g, 1.0 equiv, 2.0 mmol), $BnMe_3NCl$ (1.26 g, 3.4 equiv), and water (90 μL, 2.5 equiv) in CH_3CN (18 mL) at 0°C trichloroisocyanuric acid (0.51 g, 1.1 equiv) was added as a solid in portions over 1–2 min. After 30 min, isobutylamine (1.28 mL, 6.5 equiv) was added to the mixture over 1–2 min. The reaction was stirred for 1 h, then processed as in method A to provide the desired product in 94% yield.

Method C

To a stirred mixture of 2-mercaptopyridine (0.22 g, 1.0 equiv, 2.0 mmol), $BnMe_3NCl$ (1.26 g, 3.4 equiv), and water (90 μL, 2.5 equiv) in CH_3CN (18 mL) at 0°C trichloroisocyanuric acid (0.51 , 1.1 equiv) was added as a solid in portions over 1–2 min. After 30 min, triethylamine (1.5 mL, 5.5 equiv) was added followed by isobutylamine (1.28 mL, 6.5 equiv). The reaction was stirred for 1 h, then processed as in method A to provide the desired product in 91% yield.

Note: when CH_2Cl_2 was used as solvent, the reaction was worked up as follows. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed twice with H_2O (75 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resultant residue is purified by column chromatography as before.

Data

N-(4-Methoxybenzyl)pyridine-2-sulfonamide (3b). Off-white solid, mp 96–97°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, $J = 3.7$ Hz, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 7.88 (td, $J = 7.8$, 1.9 Hz, 1H), 7.49–7.44 (m, 1H), 7.16 (d, $J = 8.7$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 5.38 (br t, $J = 5.9$ Hz, 1H), 4.19 (d, $J = 5.6$ Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 157.7, 150.0, 137.9, 129.4, 128.4, 126.5, 122.2, 114.0, 55.3, 47.3; MS (ESI) m/z 279 $(M + H)^+$; anal. calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 55.94; H, 4.95; N, 9.86.

4-(Pyridin-2-ylsulfonyl)morpholine (3c). White solid, mp 91–92°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75–8.72 (m, 1H), 7.96 (m, 2H), 7.55–7.49 (m, 1H), 3.75 (t, $J = 4.7$ Hz, 4H), 3.34 (t, $J = 5.0$ Hz, 4H); ^{13}C NMR

(176 MHz, $CDCl_3$) δ 156.0, 150.1, 138.0, 126.8, 123.2, 66.4, 46.5;MS (ESI) m/z 229 $(M+H)^+$; anal. calcd. for $C_9H_{12}N_2O_3S$: C, 47.36; H, 5.30; N, 12.27. Found: C, 47.59; H, 5.22; N, 12.32.

Ethyl 4-[(pyridin-2-ylsulfonyl)amino]butanoate (3d). Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, $J = 4.7$ Hz, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.91 (td, $J = 7.7$, 2.2 Hz, 1H), 7.51–7.47 (m, 1H), 5.21 (br t, $J = 5.8$ Hz, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.13 (q, $J = 6.6$ Hz, 2H), 2.38 (t, $J = 7.3$ Hz, 2H), 1.84 (pentet, $J = 6.9$ Hz, 2H), 1.24 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 157.6, 150.0, 138.1, 126.7, 122.2, 60.6, 43.0, 31.2, 25.1, 14.2; anal. calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.53; H, 6.24; N, 10.17.

4-Fluoro-N-isobutylbenzenesulfonamide (3e). White solid, mp 85–87°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (m, 2H), 7.18 (m, 2H), 4.70 (br t, $J = 6.0$ Hz, 1H), 2.77 (t, $J = 6.6$ Hz, 2H), 1.71 (nonet, $J = 6.7$ Hz, 1H), 0.88 (dd, $J = 0.5$, 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (d, $J = 255$ Hz), 136.3, 129.8, 129.7, 116.4, 116.2, 50.6, 28.5, 19.8; MS (ESI) m/z 232 $(M+H)^+$; anal. calcd. for $C_{10}H_{14}FNO_2S$: C, 51.93; H, 6.10; N, 6.06. Found: C, 52.07; H, 6.19; N, 6.01.

4-Fluoro-N-(4-methoxybenzyl)benzenesulfonamide (3f). White solid, mp 93–95°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (m, 2H), 7.18 (m, 2H), 7.09 (m, 2H), 6.81 (m, 2H), 4.55 (br t, $J = 5.5$ Hz, 1H), 4.09 (d, $J = 6.0$ Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (d, $J = 254$ Hz), 159.4, 136.1, 129.9, 129.8, 129.3, 128.0, 116.4, 116.2, 114.1, 55.3, 46.8; anal. calcd. for $C_{14}H_{14}FNO_3S$: C, 56.94; H, 4.78; N, 4.74. Found: C, 56.87; H, 4.62; N, 4.63.

N-(4-Methoxybenzyl)butane-1-sulfonamide (3g). White solid, mp 68–70°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (m, 2H), 6.88 (m, 2H), 4.49 (br t, $J = 5.9$ Hz, 1H), 4.22 (d, $J = 6.1$ Hz, 2H), 3.80 (s, 3H), 2.90 (m, 2H), 1.73 (m, 2H), 1.38 (sextet, $J = 7.4$ Hz, 2H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 129.3, 129.0, 114.3, 55.4, 53.1, 46.8, 25.6, 21.5, 13.5; anal. calcd. for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44. Found: C, 55.94; H, 7.38; N, 5.34.

N-Isobutyl-2-methylbenzenesulfonamide (3h). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 1H), 7.45 (ddd, $J = 1.4$, 7.5, 7.5 Hz, 1H), 7.31 (m, 2H), 4.56 (br, 1H), 2.75 (t, $J = 6.6$ Hz, 2H), 2.66 (s, 3H), 1.71 (nonet, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.7$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.0, 132.7, 132.5, 129.5, 126.2, 50.5, 28.5, 20.3, 19.9; MS (ESI) m/z 228 $(M+H)^+$; anal. calcd for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16. Found: C, 58.03; H, 7.82; N, 6.07.

N-(4-Methoxybenzyl)-2-methylbenzenesulfonamide (3i). Off-white solid, mp 76–77°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.0$ Hz, 1H), 7.46 (td, $J = 7.6$, 1.3 Hz, 1H), 7.34–7.27 (m, 2H), 7.07 (d, $J = 8.2$ Hz, 2H), 6.79 (d, $J = 8.5$ Hz, 2H), 4.56 (br t, $J = 6.3$ Hz, 1H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.77 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 137.1, 132.8, 132.5, 129.7, 129.3, 128.4, 126.2, 114.2, 55.3, 46.7, 20.3; anal. calcd. for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.56; H, 5.88; N, 4.79.

N-Benzyl-N,2-dimethylbenzenesulfonamide (3j). Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, $J = 8.8$ Hz, 1H), 7.46 (td, $J = 7.6$, 1.3 Hz, 1H), 7.36–7.24 (m, 7H), 4.31 (s, 2H), 2.69 (s, 3H), 2.267 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.2, 135.8, 132.8, 132.7, 129.8, 128.7, 128.4, 127.9, 126.1, 53.5, 33.6, 20.6; MS (ESI) m/z 276 $(M + H)^+$; anal. calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.47; H, 6.43; N, 5.13.

N-Isobutyl-4-methoxybenzenesulfonamide (3k). White solid, mp 55–56°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 4.79 (t, $J = 6.3$ Hz, 1H), 3.87 (s, 3H), 2.73 (t, $J = 6.6$ Hz, 2H), 1.71 (septet, $J = 6.6$ Hz, 1H), 0.86 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 131.8, 129.2, 114.2, 55.6, 50.6, 28.4, 19.9; MS (ESI) m/z 244 $(M + H)^+$; anal. calcd. for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76. Found: C, 54.27; H, 6.74; N, 5.66.

4-Methoxy-N-(4-methoxybenzyl)benzenesulfonamide (3l). White solid, mp 112–113°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 6.80 (d, $J = 8.5$ Hz, 2H), 4.55 (t, $J = 6.0$ Hz, 1H), 4.05 (d, $J = 6.0$ Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 159.4, 131.6, 129.3, 129.3, 128.4, 114.3, 114.1, 55.6, 55.3, 46.8; anal. calcd. for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56. Found: C, 58.64; H, 5.29; N, 4.56.

4-Methoxybenzenesulfonamide (3m). White solid, mp 110–112°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (m, 2H), 6.98 (m, 2H), 4.77 (br s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 163.1, 133.7, 128.7, 114.3, 55.7; anal. calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48. Found: C, 45.05; H, 4.89; N, 7.38.

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