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Base-free monosulfonylation of amines using tosyl or mesyl chloride in water

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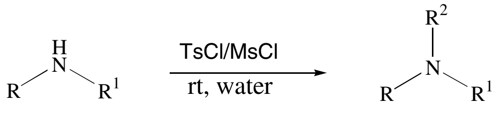
Abstract—A mild and efficient procedure has been developed for the monosulfonylation of various amines using mesyl or tosyl chlorides in water at room temperature to afford the corresponding sulfonamides in high yields.

Sulfonamides are a diverse group of pharmaceutically important compounds[1,2] widely used as antibacterial, anticancer, anticonvulsant, antiinflammatory and antiviral agents and HIV protease inhibitors. Examples of recently approved drugs possessing a sulfonamide include the antihypertensive agent bosentan,[3] the antiviral HIV protease inhibitor amprenavir[4] and the phosphodiesterase-5 inhibitor sildenafil.[5] In addition, numerous sulfonamide derivatives have been in preclinical development. Sulfonylation is a significant reaction in the synthesis of naturally occurring bioactive molecules and is an important method for the protection of amines.[6,7] Although many efforts have been made towards the development of novel sulfonamides,[8] the conventional synthesis involves the reaction of amino compounds with sulfonyl chlorides.[9] However, these procedures involve the use of organic solvents, base and elevated temperatures, especially for less reactive aniline substrates. For sterically hindered primary amines with electron withdrawing substituents, bissulfonylation is a common side reaction, which necessitates a further mono desulfonylation step.[10] Recently, Deng and Mani reported[11] the synthesis of sulfonamides in water. However, pH control with Na_2CO_3 was necessary and the isolation of the product involved acidification up to pH 2 with HCl.

In recent years, organic reactions in water have received considerable attention. The use of water as a solvent has several advantages, including preventing the generation of waste, avoiding the use of hazardous substances (e.g., halogenated and high-boiling solvents)[12] and minimization of energy requirements.[13] Thus, the use of water instead of organic solvents has gained much importance in the development of sustainable chemistry.[14] There are only limited examples of organic reactions that have been carried out in water, particularly in the absence of a catalyst.[15] In continuation of our efforts to develop environmentally friendly synthetic methodologies,[16,17] we have investigated the base-free monosulfonylation of amines in water. In these monosulfonylation reactions, comparable yields were obtained using tap as well as distilled water; here, the reactions were carried out in tap water.

In a typical procedure, a suspension of amine in water was treated with an addition of *p*-toluenesulfonyl chloride or methanesulfonyl chloride at room temperature to afford the corresponding sulfonamide in high yields ranging from 85% to 95% (Scheme 1). The reactions were rapid with most of the amines studied (20–60 min) and were compatible with a variety of primary



R = aryl, benzyl, furfuryl, cycloalkyl; R^1 = H ; R^2 = Ts, Ms

Scheme 1.

Keywords: Sulfonamides; Amines; *p*-Toluenesulfonyl chloride; Methanesulfonyl chloride; Water.

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Table 1. Sulfonamide synthesis in water

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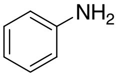
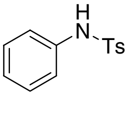
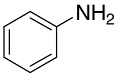
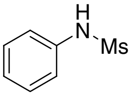
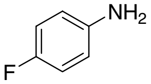
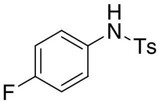
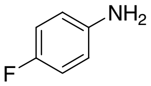
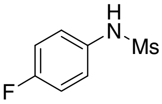
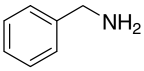
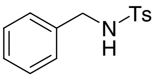
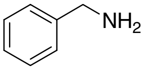
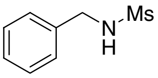
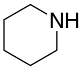
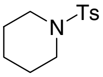
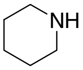
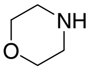
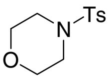
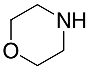
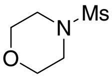
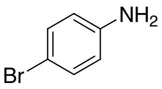
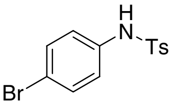
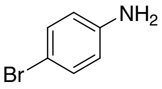
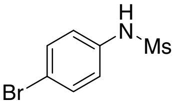
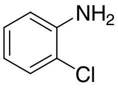
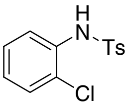
1			25	95
2			35	91
3			30	90
4			35	85
5			25	89
6			35	87
7			30	90
8			40	87
9			30	92
10			35	87
11			25	95
12			35	91
13			30	90

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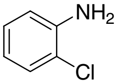
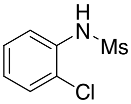
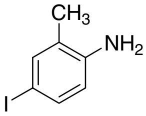
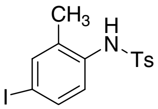
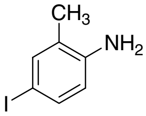
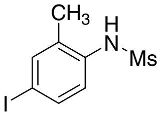
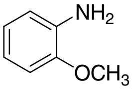
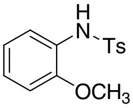
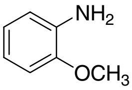
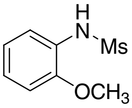
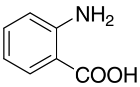
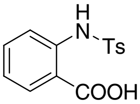
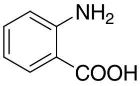
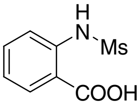
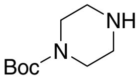
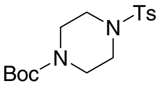
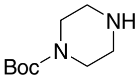
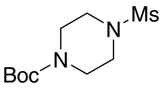
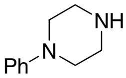
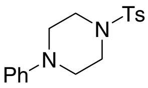
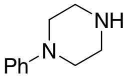
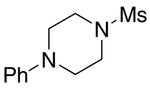
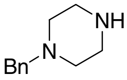
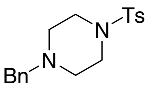
14			35	85
15			25	89
16			35	87
17			30	90
18			40	87
19			30	92
20			35	87
21			25	95
22			35	91
23			30	90
24			35	85
25			25	89

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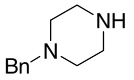
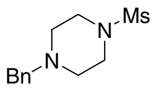
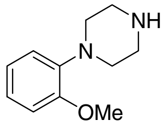
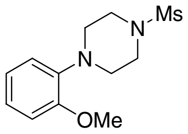
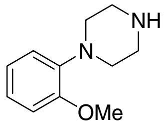
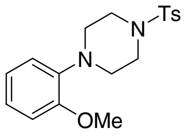
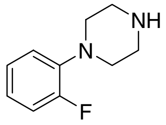
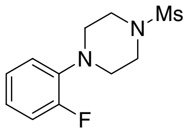
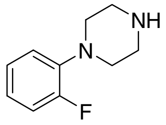
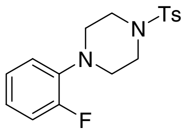
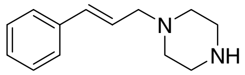
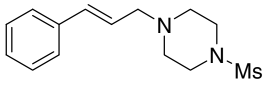
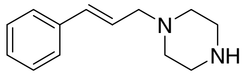
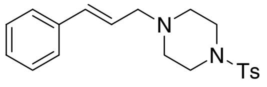
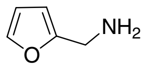
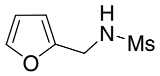
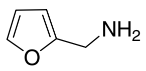
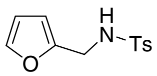
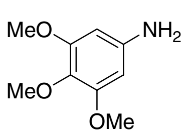
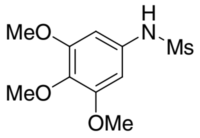
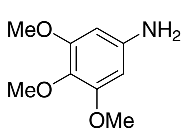
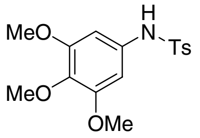
26			35	87
27			30	90
28			40	87
29			30	92
30			35	87
31			25	95
32			35	91
33			25	89
34			35	87
35			30	90
36			40	87

and secondary amines (Table 1). Bis-sulfonylated products were not observed using this procedure. All the products were characterized by ^{1}H NMR as well as mass spectral data, and by a comparison with known compounds. Further, the reaction rates with amines possessing different electronic and steric characteristics have been studied. The formation of sulfonamide product was more rapid with the aliphatic amines when compared to aromatic amines due to nucleophilicity. The involvement of hydrogen bonds in determining the rate of the reaction was clearly observed with furfurylamine. Intramolecular hydrogen bond formation between the N–H hydrogen atom and the oxygen of the furan ring increases the nucleophilicity at the nitrogen atom and should enhance the rate of the reaction. However, the opposite was observed, probably because intramolecular hydrogen bond formation in 2-furfuryl amine prevented the hydrogen bond formation between the N–H hydrogen and the oxygen of water, which in turn decreased the rate of the reaction.

In conclusion, we have developed a simple methodology for the monosulfonylation of various amines in water without the use of a base.[18,19] The products were obtained in high yields. This could find several applications in the syntheses of biologically important organic compounds.

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18. *General experimental procedure*: To a stirred solution of amine (1 mmol) in water (10 mL) was added TsCl or MsCl (1.2 mmol) at room temperature and stirring was continued until the reaction was complete (monitored by TLC). The reaction mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc–hexane) on silica gel (60–120 mesh) to yield the pure product.
19. *Spectral data for novel sulfonamides (Table 1)*: *1-(2-Methoxyphenyl)-4-(methylsulfonyl)piperazine (entry 27)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.14 (s, 4H), 3.40 (s, 4H), 3.80 (s, 3H), 6.85–7.12 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.9, 45.2, 49.8, 55.1, 113.5, 115.7, 118.2, 121.3, 143.1, 150.8 ppm; IR (KBr): 3262, 3000, 2948, 2834, 1597, 1326, 1129, 897, 751 cm^{-1}; MS(ESI): m/z 271 $(M+1)^+$; HRMS m/z: $(M+1)^+$ calcd for $C_{12}H_{19}N_2O_3S$, 271.1116; found, 271.1118; *1-(2-Methoxyphenyl)-4-tosylpiperazine (entry 28)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.18 (s, 4H), 3.26 (s, 4H), 3.78 (s, 3H), 6.77–6.99 (m, 4H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.3, 46.1, 50.0, 55.3, 111.1, 118.3, 120.7, 123.7, 125.5, 127.8, 129.6, 132.0, 143.6, 151.8 ppm; IR (KBr): 3449, 2953, 2914, 2830, 1593, 1344, 1136, 949, 759 cm^{-1}; MS(ESI): m/z 347 $(M+1)^+$; HRMS m/z: $(M+1)^+$ calcd for $C_{18}H_{23}N_2O_3S$, 347.1429; found, 347.1433; *1-(2-Fluorophenyl)-4-(methylsulfonyl)piperazine (entry 29)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75 (s, 3H), 3.15 (s, 4H), 3.40 (s, 4H), 6.88–7.13 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.1, 45.9, 50.1, 116.2, 119.3, 123.4, 124.5, 154.0, 157.3 ppm; IR (KBr): 3287, 2930, 1631, 1316, 984, 751 cm^{-1}; MS(ESI): m/z 259 $(M+1)^+$; HRMS m/z: $(M+1)^+$ calcd for $C_{11}H_{16}FN_2O_2S$, 259.0916; found, 259.0916; *1-(2-Fluorophenyl)-4-tosylpiperazine (entry 30)*: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.15 (s, 4H), 3.42 (s, 4H), 6.72–6.96 (m, 4H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.65 (d, $J = 8.2$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 46.1, 52.1, 115.8, 118.6, 122.7, 123.5, 126.8, 130.1, 132.8, 143.5, 153.2, 156.1 ppm; IR (KBr): 3426, 3043, 2983, 2830, 1595, 1345, 1124, 956, 727 cm^{-1}; MS(ESI): m/z 335 $(M+1)^+$; HRMS m/z: $(M+1)^+$ calcd for $C_{17}H_{20}FN_2O_2S$, 335.1229; found, 335.1234; *1-(Methylsulfonyl)-4-[(E)-3-phenyl-2-propenyl]piperazine (entry 31)*: ^{1}H NMR (300 MHz, DMSO): δ 2.72 (s, 3H), 3.14 (s, 4H), 3.36 (s, 4H), 3.88 (d, $J = 7.2$ Hz, 2H), 6.23–6.42 (m, 1H), 6.78(d, $J = 15.8$ Hz, 1H), 7.12 (d,

$J = 7.9$ Hz, 2H), 7.32–7.49 (m, 3H) ppm; ^{13}C NMR (75 MHz, DMSO): δ 34.2, 42.6, 49.8, 56.9, 116.3, 125.1, 126.0, 126.8, 129.4, 138.2 ppm; IR (KBr): 3442, 3017, 2923, 1620, 1332, 976, 746 cm^{-1}; MS(ESI): *m*/*z* 282 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_{14}H_{21}N_2O_2S$, 281.1323; found, 281.1347; *1-[(4-Methylphenyl)sulfonyl]-4-[(E)-3-phenyl-2-propenyl]piperazine (entry 32)*: ^{1}H NMR (300 MHz, DMSO): δ 2.4 (s, 3H), 3.04 (s, 4H), 3.24 (s, 4H), 3.88 (d, 2H, $J = 7.2$ Hz), 6.23–6.42 (m, 1H), 6.78 (d, $J = 15.8$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 2H), 7.24–7.43 (m, 3H), 7.51 (d, $J = 7.9$ Hz, 2H), 7.62 (d, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, DMSO): δ 20.8, 42.8, 49.5, 57.1, 116.9, 125.2, 126.5, 127.3, 128.4, 129.6, 131.4, 134.9, 139.0, 143.8 ppm; IR (KBr): 3455, 3026, 2921, 2859, 1648, 1349, 978, 816, 728 cm^{-1}; MS(ESI): *m*/*z* 357 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_{20}H_{25}N_2O_2S$, 357.1636; found, 357.1653; *N-(furan-2-ylmethyl)methanesulfonamide (entry 33)*: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.77 (s, 3H), 4.26 (d, $J = 5.2$ Hz, 2H), 6.31 (s, 2H), 7.36 (s, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 34.5, 42.6, 107.5, 109.8, 141.8, 149.2 ppm; IR (KBr): 3287, 2930, 1631, 1316, 984, 751 cm^{-1}; MS(ESI): *m*/*z* 176 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_6H_{10}NO_3S$, 176.0381; found, 176.0384; *N-(furan-2-ylmethyl)-4-methylbenzenesulfonamide (entry 34)*: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.45 (s, 3H), 4.15 (d, $J = 6.04$ Hz, 2H), 6.06 (s, 1H), 6.17 (s, 1H), 7.19 (s, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.71 (d, $J = 8.3$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.3, 40.0, 108.1, 110.2, 126.9, 129.5, 136.7, 142.3, 143.3, 149.5 ppm; IR (KBr): 3443, 3017, 2923, 1620, 1332, 976, 746 cm^{-1}; MS(ESI): *m*/*z* 252 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_{12}H_{14}NO_3S$, 252.0694; found, 252.0690; *N-(3,4,5-trimethoxyphenyl)methanesulfonamide (entry 35)*: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.98 (s, 3H), 3.78 (s, 3H), 3.84 (s, 6H), 6.47 (s, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 34.7, 55.1, 60.3, 97.8, 132.7,133.9, 151.4 ppm; IR (KBr): 3208, 2969, 2846, 1603, 1320, 1125, 885, 756 cm^{-1}; MS(ESI): *m*/*z* 262 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_{10}H_{16}NO_5S$, 262.3026; found, 262.3033; *4-Methyl-N-(3,4,5-trimethoxyphenyl)benzenesulfonamide (entry 36)*: ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.46 (s, 3H), 3.62 (s, 3H), 3.82 (s, 6H), 6.43 (s, 2H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.58 (d, $J = 7.9$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.8, 55.2, 60.2, 98.0, 126.4, 128.8, 133.1, 133.9, 136.2, 142.5, 152.5 ppm; IR (KBr): 3262, 2948, 2834, 1597, 1326, 1129, 897, 751 cm^{-1}; MS(ESI): *m*/*z* 262 (M+1)$^+$; HRMS *m*/*z*: (M+1)$^+$ calcd for $C_{16}H_{20}NO_5S$, 338.1062; found, 338.1072.