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A novel approach for the synthesis of alkyl and aryl sulfonamides

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Abstract—A novel approach for the synthesis of alkyl and aryl sulfonamides by the reaction of sulfonic acids, isocyanides and water in dichloromethane is reported at ambient temperature in excellent yields within 20 min. To the best of our knowledge this is the first report on the synthesis of this biologically important family using easily available sulfonic acids and isocyanides.

1. Introduction

Sulfonamides, an important class of pharmaceutical compounds exhibit a wide spectrum of biological activities.[1] Over 30 drugs containing this functionality are in clinical use, including, antibacterials, diuretics, anticonvulsants, hypoglycemics and HIV protease inhibitors.[2] More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as Alzheimer's disease, arthritis and cancer.[3]

The vast majority of sulfonamides are prepared from the reaction of a sulfonyl chloride with ammonia or primary or secondary amines or via related transformations.[4,5] In turn, arenesulfonyl chlorides are prepared from arenes by electrophilic aromatic substitution using an excess of chlorosulfonic acid or from arenesulfonic acids by reaction with phosphorus pentachloride.[6] Given the harshness of these reaction conditions, sulfonyl chlorides are rarely introduced into an advanced intermediate via C–S bond formation. As a consequence, the diversity of sulfonamide functionality is actually limited and cannot be readily varied at both nitrogen and sulfur in the final step of the generation of a large ensemble of compounds. Furthermore, as previously reported, sulfonyl chlorides have disadvantages and can be difficult to handle and are not amenable to long-term storage.[7] Only a very small number of these compounds are commercially available due to their instability.

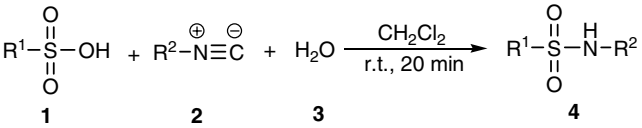
In continuation of our interest in isocyanide-based multi-component reactions,[8] herein we report on a hitherto unknown reaction, which starting from simple and readily available precursors, affords alkyl and aryl sulfonamide derivatives (Scheme 1).

As indicated in Table 1, alkyl or aryl sulfonic acid **1** and isocyanide **2**, in the presence of water, undergo a smooth 1:1:1 addition reaction in dichloromethane at room temperature to produce sulfonamide derivatives **4**.

The structures of the products were deduced from their IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate m/z values.

To illustrate the need for H_2O, the reaction of camphorsulfonic acid and cyclohexyl isocyanide was studied in the absence of H_2O in dry dichloromethane. Under these conditions no product was obtained even after 24 h at room temperature.

Although the mechanism of the reaction between the isocyanide and alkyl or aryl sulfonic acid has not yet been recognized experimentally, a possible explanation is proposed in Scheme 2. On the basis of the well established reaction chemistry of isocyanides with acids,[9] it is



Scheme 1.

Keywords: Isocyanide; Sulfonamides; Sulfonic acid.
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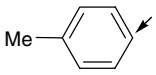
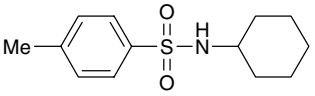
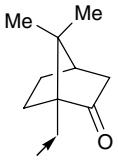
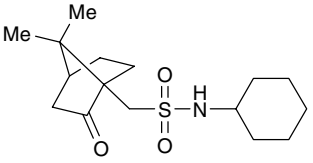
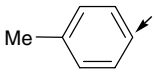
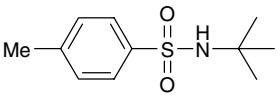
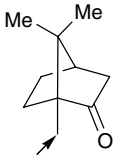
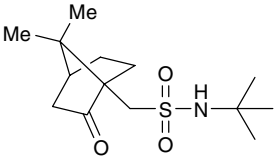
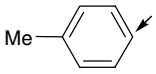
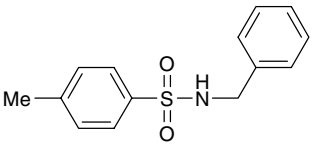
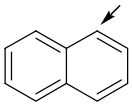
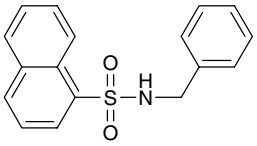
Table 1. Synthesis of sulfonamides

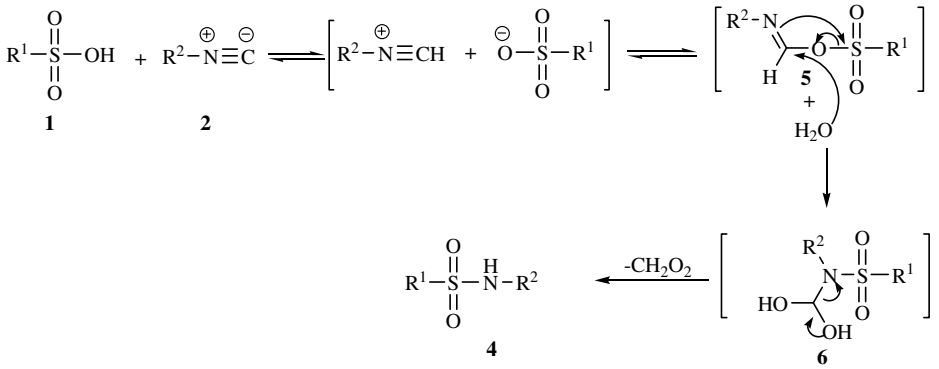
Entry	R^1	R^2	Product	Yield (%)
1		Cyclohexyl	 **4a**	90
2	 (-)	Cyclohexyl	 **4b**	93
3		*tert*-Butyl	 **4c**	89
4	 (-)	*tert*-Butyl	 **4d**	92
5		Benzyl	 **4e**	91
6		Benzyl	 **4f**	86

reasonable to assume that protonation of the isocyanide by the alkyl or aryl sulfonic acid produces intermediate **5**, which followed by quenching with water generates intermediate **6**. Elimination of formic acid from intermediate **6** produces product **4**.

In conclusion, we have developed a new and general method for the preparation of alkyl and aryl sulfonamides from the readily available alkyl and aryl sulfonic acids and isocyanides under neutral conditions without using any catalyst. The reaction has been shown to display good functional group tolerance and is high yielding and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

2. Typical procedure for the preparation of *N*-tosylcyclohexanamine (4a)

To a magnetically stirred mixture of *p*-toluenesulfonic acid (0.19 g, 1.0 mmol) and H_2O (1 mL) in CH_2Cl_2 (10 mL) was added cyclohexyl isocyanide (0.11 g, 1 mmol) and the resulting mixture was stirred for 20 min at room temperature. After completion of the reaction, the solvent was removed under vacuum and the residue was crystallized from ethyl acetate and the product **4a** was obtained in the form of colourless crystals (0.23 g, yield 90%); mp 181–182 °C. IR (KBr) (ν_{max}/cm^{-1}): 3045, 2940, 2861, 1600, 1535, 1452. MS, *m*/*z* (%): 253 (M^+, 1), 238 (M^+-Me, 5), 172 (55), 155 ($M^+-C_6H_{12}N$, 25), 107 (55), 100 (50), 91 ($M^+-C_6H_{12}NO_2S$, 100), 65 (95), 57 (95), 39 (95). ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.97–1.89 (10H, m, $5CH_2$ of cyclo-



Scheme 2.

hexyl), 2.38 (3H, s, CH_3), 2.82 (1H, m, CH–N of cyclohexyl), 7.23 (2H, d, $^3J_{HH} = 7.9$ Hz, H–Ar), 7.65 (1H, br s, NH), 7.78 (2H, d, $^3J_{HH} = 7.9$ Hz, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 21.32 (CH_3), 24.56, 24.57, 30.61 ($5CH_2$ of cyclohexyl), 50.69 (CH–N of cyclohexyl), 125.97, 129.02, 140.72, 141.36 (C–Ar).

3. *N*-Cyclohexyl-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (4b)

Colourless crystals (0.29 g, yield 93%); mp 225–226 °C. IR (KBr) (ν_{max}/cm^{-1}): 2931, 2858, 1742, 1635, 1548, 1492. MS, *m*/*z* (%): 313 (M^+, 1), 233 (4), 215 ($M^+-C_6H_{12}N$, 3), 151 ($M^+-C_6H_{12}NO_2S$, 25), 109 (70), 81 (70), 56 (100), 42 (80). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.84, 1.08 (6H, 2s, $2CH_3$ of camphor), 1.20–2.65 (17H, m, $8CH_2$ and CH of cyclohexyl and camphor), 2.78 (1H, d, $^3J_{HH} = 14.7$ Hz, CH_2–SO_2), 3.11 (1H, m, CH–N of cyclohexyl), 3.30 (1H, d, $^3J_{HH} = 14.7$ Hz, CH_2–SO_2), 7.51 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 19.78, 19.97 ($2CH_3$), 24.42, 24.53, 30.75 ($5CH_2$ of cyclohexyl), 24.82, 26.98, 42.61, 42.85, 47.44, 47.93, 58.43 (C-camphor), 50.66 (CH–N of cyclohexyl), 216.65 (C=O).

4. 2-Methyl-*N*-tosylpropan-2-amine (4c)

Colourless crystals (0.20 g, yield 89%); mp 221–222 °C. IR (KBr) (ν_{max}/cm^{-1}): 3041, 2922, 1630, 1526, 1494, 1403. MS, *m*/*z* (%): 227 (M^+, 1), 185 (3), 172 (75), 155 ($M^+-C_4H_{10}N$, 5), 107 (55), 91 ($M^+-C_4H_{10}NO_2S$, 95), 77 (35), 65 (55), 58 (100), 39 (60). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.28 (9H, s, $C(CH_3)_3$), 2.38 (3H, s, CH_3), 7.21 (2H, d, $^3J_{HH} = 7.9$ Hz, H–Ar), 7.71 (1H, br s, NH), 7.80 (2H, d, $^3J_{HH} = 7.9$ Hz, H–Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 21.35 (CH_3), 27.46 ($C(CH_3)_3$), 52.33 ($C(CH_3)_3$), 126.03, 128.98, 140.58, 141.53 (C–Ar).

5. *N-tert*-Butyl-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (4d)

Colourless crystals (0.26 g, yield 92%); mp 287–290 °C. IR (KBr) (ν_{max}/cm^{-1}): 3032, 2955, 1743, 1634, 1538, 1514. MS, *m*/*z* (%): 287 (M^+, 2), 233 (90), 215, ($M^+-C_4H_{10}N$, 25), 151 ($M^+-C_4H_{10}NO_2S$, 75), 113 (90), 109 (100), 81 (95), 58 (100), 39 (45). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 0.84, 1.10 (6H, 2s, $2CH_3$), 1.43 (9H, s, $C(CH_3)_3$), 1.65–2.69 (6H, m, $3CH_2$ of camphor), 2.80 (1H, d, $^3J_{HH} = 14.7$ Hz CH_2–SO_2), 2.86 (1H, m, CH of camphor), 3.32 (1H, d, $^3J_{HH} = 14.7$ Hz, CH_2–SO_2), 7.53 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 19.78, 20.04 ($2CH_3$), 24.53, 26.96 (C-camphor), 27.61 ($C(CH_3)_3$), 42.60, 42.82, 47.54, 47.89, 58.45 (C-camphor), 52.33 ($C(CH_3)_3$), 216.79 (C=O).

6. Phenyl-*N*-tosylmethanamine (4e)

Colourless crystals (0.24 g, yield 91%); mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 2950, 1637, 1630, 1488, 1448. MS, *m*/*z* (%): 261 (M^+, 2), 172 (75), 155 ($M^+-C_7H_8N$, 10), 106 ($M^+-C_7H_7O_2S$, 100), 91 ($M^+-C_7H_8NO_2S$, 98), 79 (95), 77 (90), 65 (75), 42 (70), 34 (75). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.28 (3H, s, CH_3), 4.00 (2H, s, CH_2), 7.11–7.42 (9H, m, H–Ar), 8.16 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 21.18 (CH_3), 42.96 (CH_2), 126.00, 128.51, 128.92, 129.04, 129.26, 134.32, 138.24, 146.04 (C–Ar).

7. Naphthalene-1-sulfonic acid benzylamide (4f)

Colourless crystals (0.26 g, yield 86%); mp 166–168 °C. IR (KBr) (ν_{max}/cm^{-1}): 3052, 1624, 1517, 1382, 1216. MS, *m*/*z* (%): 297 (M^+, 2), 208 (95), 191 ($M^+-C_7H_8N$, 2), 144 (25), 127 ($M^+-C_7H_8NO_2S$, 65), 115 (100), 106 (90), 91 ($M^+-C_{10}H_8NO_2S$, 45), 79 (80), 53 (60), 34 (75). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 4.05 (2H, s, CH_2), 7.39–8.85 (12H, m, H–Ar), 8.16 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 47.58 (CH_2), 129.09, 129.41, 129.71, 130.87, 130.95, 131.66, 131.85, 132.73, 133.07, 133.74, 133.87, 134.11, 134.85, 139.82 (C–Ar).

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