N-Acylation of sulfonamides using N-acylbenzotriazoles

Alan R. Katritzky,* Sebastian Hoffmann, and Kazuyuki Suzuki

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, FL 32611-7200
E-mail: katritzky@chem.ufl.edu

Dedicated to Professor Alexander Konovalov on the occasion of his 70th birthday
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Abstract
Reactions of sulfonamides with readily available N-acylbenzotriazoles (RCOBt, where R is an aryl, heteroaryl, or N-Cbz-protected-α-amino(alkyl) group), in the presence of NaH, produced N-acylsulfonamides in 76−100% yields. The ability to utilize N-acylbenzotriazoles for which the corresponding acid chlorides are not easily prepared, may be especially advantageous.

Keywords: N-Acylbenzotriazole, N-acylsulfonamide, sulfonamides, N-acylation

Introduction

N-Acylsulfonamides have received considerable attention due to their diverse biological activities as precursors of therapeutic agents for Alzheimer’s disease,1a as antibacterial inhibitors of tRNA synthetases,1b as prostaglandin F1a sulfonamides for the potential treatments of osteoporosis,1c as antagonists for Angiotensin II,1d and as Leukotriene D4-receptors.1e

Most N-acylations of sulfonamides have utilized acid chlorides or anhydrides in the presence of triethylamine, pyridine,2a-b or alkali hydroxide.2c-e Direct coupling of sulfonamides with carboxylic acids has utilized reagents such as carbodiimide (DCC, EDC),1b,3a and N,N'-carbonyldiimidazole.1c,1f Oxidative de-ethoxycarbonylation of N-benzenesulfonyl phenylglycinate prepared from phenylglycinate and benzenesulfonyl chloride gives N-benzoylsulfonamide.3b Reactions of sulfonamides with 1.5 equiv. of carboxylic acid anhydrides in the presence of 96% H2SO4 (3 mol%) at 60 °C was recently reported to give N-acylsulfonamides in 44−98% yields.4

We recently demonstrated that N-acylbenzotriazoles are efficient neutral coupling reagents for: (i) N-acylation to give primary, secondary, and tertiary amides,5a Weinreb amides,5b trifluoroacetoamides,5c chiral amino-acylation,5d peptide coupling in organic/aqueous media,5e and cinnamoyl hydrazides;5f (ii) regioselective C-acylation of a) ketone enolates to give β-diketones;6a-b) of primary and secondary alkyl cyanides to give α-cyano ketones,6b c) of sulfones
to give β-ketosulfones,6c and d) in Friedel-Crafts reaction of pyrroles, indoles,6d 2-methylfuran, and thiophene;6e (iii) O-acylation of aldehydes.7a,b We now present a new and convenient method for the preparation of N-acylsulfonamides including those containing N-acyl groups for which the corresponding acid chlorides are difficult to make or use.

**Results and Discussion**

The present work with N-acylbenzotriazoles 1a–j includes common arylcarbonyl derivatives such as 4-tolyl (1a), 4-methoxyphenyl (1b), and 4-nitrophenyl (1j), together with some less studied compounds, including cases, where the corresponding acyl halides are not stable or are inconvenient to prepare, for instance, 4-diethylaminophenyl (1c), 4-pyridyl (1e), and 2-pyrrolyl (1f). The starting N-acylbenzotriazoles 1ae, j (R1 = 4-tolyl, 4-methoxyphenyl, 4-pyridyl, 2-furyl, N-Boc-phe, 4-nitrophenyl) were prepared from the corresponding carboxylic acids by treatment with 1-(methylsulfonyl)benzotriazole (MeSO₂Bt) following the reported general procedure.5a-b Other N-acylbenzotriazoles (1f, 1g, 1h, and 1i) derived from 2-pyrrolylcarboxylic acid, 2-indolylcarboxylic acid, and N-Cbz-protected amino acids were obtained by reaction with the intermediate prepared from BtH and SOCl₂ following a recently reported procedure,5e,8 in order to prevent side-reactions such as dimerization of pyrrole and indole derivatives or epimerization of amino acid derivatives.

Preparation of N-acylsulfonamides has previously been performed by direct coupling of sulfonamides with carboxylic acids using carbodiimides.1b,4a Although the direct coupling reactions give good yields (53–66%), significant excesses (3 equiv.) of carboxylic acid, DCC, DMAP, and pyridine are required.1b N,N'-Carbonyldiimidazole (CDI) is another common agent for the coupling reactions, but this protocol gave poor yields for the preparation of sulfonylcarboxamide derivatives of quinoline.1f

Preparation of N-acylsulfonamides utilizing N-acylbenzotriazoles was carried out by reaction with sulfonamides (methylsulfonamide, p-tolylsulfonamide, and acetazolamide) in THF in the presence of NaH for 1.5 h. Removing THF gave the sodium salt of the corresponding N-acylsulfonamides which on acidification with 2N HCl solution gave N-acylsulfonamides 2a–n in 76–98% yields (Table 1). Reactions of the N-acylbenzotriazoles with acetazolamide gave 3a–d in 81–100% yields [3a, 3c, 3d as the acid forms and 3b as the sodium salt (Table 2)]. We also investigated different bases such as Et₃N and DBU, and different conditions (time and temperature 24–60 °C) for the reaction of 1a with p-tolylsulfonamide, but NMR of the crude product failed to detect any of the desired product 2b under these conditions.
Table 1. Synthesis of N-acylsulfonamides utilizing N-acylbenzotriazoles and sulfonamides

\[
\begin{align*}
\text{O} & \quad \text{Bt} \quad + \quad \text{R}^2 \quad \text{SO}_2 \quad \text{NH}_2 \\
\text{1a-i} & \quad \xrightarrow{\text{NaH, THF}} \quad \text{O} & \quad \text{N} & \quad \text{S} \quad \text{R}^2 \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>% Yield\textsuperscript{a}</th>
<th>m.p. (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-tolyl (1a)</td>
<td>Me</td>
<td>85 (2a)</td>
<td>160–161</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>4-tolyl (1a)</td>
<td>4-tolyl</td>
<td>95 (2b)</td>
<td>135–136</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>4-methoxyphenyl (1b)</td>
<td>Me</td>
<td>85 (2c)</td>
<td>132–133</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>4-methoxyphenyl (1b)</td>
<td>4-tolyl</td>
<td>98 (2d)\textsuperscript{b}</td>
<td>150–151</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>4-diethylaminophenyl (1c)</td>
<td>4-tolyl</td>
<td>98 (2e)\textsuperscript{c}</td>
<td>&gt;250</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>2-furyl (1d)</td>
<td>4-tolyl</td>
<td>95 (2f)</td>
<td>126–127</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>4-pyridyl (1e)</td>
<td>Me</td>
<td>98 (2g)\textsuperscript{c}</td>
<td>&gt;250</td>
<td>--</td>
</tr>
<tr>
<td>8</td>
<td>4-pyridyl (1e)</td>
<td>4-tolyl</td>
<td>97 (2h)\textsuperscript{c}</td>
<td>&gt;250</td>
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</tr>
<tr>
<td>9</td>
<td>2-pyrrolyl (1f)</td>
<td>Me</td>
<td>80 (2i)</td>
<td>167–168</td>
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<tr>
<td>10</td>
<td>2-pyrrolyl (1f)</td>
<td>4-tolyl</td>
<td>76 (2j)</td>
<td>216–217</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>2-indolyl (1g)</td>
<td>4-tolyl</td>
<td>83 (2k)</td>
<td>242–243</td>
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</tr>
<tr>
<td>12</td>
<td>Cbz-Ala (1h)</td>
<td>Me</td>
<td>78 (2l)</td>
<td>129–130</td>
<td>12</td>
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<tr>
<td>13</td>
<td>Cbz-Ala (1h)</td>
<td>4-tolyl</td>
<td>87 (2m)</td>
<td>131–132</td>
<td>13</td>
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<tr>
<td>14</td>
<td>Cbz-Phe (1i)</td>
<td>4-tolyl</td>
<td>90 (2n)\textsuperscript{c}</td>
<td>210–212</td>
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</table>

\textsuperscript{a} Isolated yield. \textsuperscript{b} The corresponding sodium salt was also obtained in 98% yield. \textsuperscript{c} Isolated as the corresponding sodium salts.

Table 2. Synthesis of N-acylsulfonamides derived from acetazolamide

\[
\begin{align*}
\text{O} & \quad \text{Bt} \quad + \quad \text{H}_2\text{N-SO}_2\text{N}-\text{N} \quad \text{NH}_2 \quad \text{O} \\
\text{3a-d} & \quad \xrightarrow{\text{NaH, THF}} \quad \text{O} & \quad \text{N} & \quad \text{S} \quad \text{N} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>% Yield\textsuperscript{a}</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-tolyl (1a)</td>
<td>88 (3a)</td>
<td>&gt;300</td>
</tr>
<tr>
<td>2</td>
<td>4-pyridyl (1e)</td>
<td>100 (3b)\textsuperscript{b}</td>
<td>&gt;300</td>
</tr>
<tr>
<td>3</td>
<td>Cbz-Ala (1h)</td>
<td>96 (3c)</td>
<td>188–189</td>
</tr>
<tr>
<td>4</td>
<td>4-nitrophenyl (1j)</td>
<td>81 (3d)</td>
<td>238–239</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield. \textsuperscript{b} Isolated as the corresponding sodium salt.
Compounds 2d, 2e, 2g, 2h, 2n, and 3b were isolated as the corresponding sodium salts and characterized by $^1$H, $^{13}$C NMR (in DMSO-$d_6$) and elemental analysis. The corresponding acid forms for 2e, 2g, 2h, and 3b were difficult to isolate in high yields from the aqueous HCl solution due to their water-solubilities, presumably because 4-diethylaminophenyl and pyridyl groups are protonated under strongly acidic conditions.

Reaction of N-methyl p-tolylsulfonamide with N-acylbenzotriazole 1a was also achieved under similar reaction conditions to those used for the preparation of 2 and 3 (Scheme 1). N-Methyl p-tolylsulfonamide, after treatment with NaH, reacted with 1a in a shorter time (15 min) and a lower temperature (24 °C) than the conditions (1.5 h, 60 °C) used for p-tolylsulfonamide to give the desired product 4 in 82% isolated yield.

![Scheme 1. Reaction with N-methyl p-tolylsulfonamide.](image)

We have also looked into an alternative way to prepare N-acylsulfonamides. Reactions of 1-methylsulfonylbenzotriazole $^5a$ (5a) and 1-(p-tolylsulfonyl)benzotriazole (5b) with amides (the reverse reaction) were carried out in the presence of NaH in THF refluxing for 24 h. Although the reaction took a longer time, yields of 2b, 2g, and 2h were comparable to the yields for the reactions with N-acylbenzotriazoles (Table 3).

### Table 3. Synthesis of N-acylsulfonamides utilizing sulfonylbenzotriazoles and amides (the reverse reaction)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^3$ ($R^3$SO$_2$Bt)</th>
<th>$R^4$</th>
<th>% yield$^a$</th>
<th>m.p. (°C)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (5a)</td>
<td>4-tolyl</td>
<td>34 (2a)</td>
<td>160–161</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>4-tolyl (5b)</td>
<td>4-tolyl</td>
<td>83 (2b)</td>
<td>135–136</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>Me (5a)</td>
<td>4-pyridyl</td>
<td>77 (2g)$^b$</td>
<td>&gt;250</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>4-tolyl (5b)</td>
<td>4-pyridyl</td>
<td>91 (2h)$^b$</td>
<td>&gt;250</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield. $^b$ Isolated as the corresponding sodium salts.
Conclusions

We have demonstrated a general procedure for the preparation of \( N \)-acylsulfonamides from sulfonamides (methylsulfonamide, \( p \)-tolylsulfonamide, and acetazolamide, and \( N \)-methyl \( p \)-tolylsulfonamide) utilizing \( N \)-acylbenzotriazoles, and the reverse reaction using sulfonylbenzotriazoles and amides. These methods commonly provide high yields after easy work-up.

Experimental Section

General Procedures. Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra were recorded in CDCl\(_3\) or DMSO-\( d_6 \) with TMS for \( ^1H \) (300 MHz) and \( ^{13}C \) (75 MHz) as the internal reference unless specified otherwise. THF was distilled from sodium metal in the presence of benzophenone under nitrogen atmosphere immediately prior to use.

Procedure for the preparation of 1a–j. \( N \)-Acylbenzotriazoles 1a–e, j can be prepared by following the previously reported procedure with MeSO\(_2\)Bt (1 equiv.) in the presence of Et\(_3\)N (1.2 equiv.) in refluxing THF for 5 h.\(^{5a-b}\) Compounds 1f–i were obtained by reactions with the intermediate from BtH (4 equiv.) and SOCl\(_2\) (1 equiv.) at 25 °C for 2 h.\(^{8a-b}\)

General procedure for the preparation of \( N \)-acylsulfonamides 2 and 3
To the solution of sulfonamide (1.0 mmol) dissolved in dry THF (10 mL) at 24 °C, NaH (1.2 mmol, 60% suspended with mineral oil) was added and stirred for 10 min. Then, \( N \)-acylbenzotriazole (1.0 mmol) was added, and the reaction mixture was refluxed for 1.5 h. After cooling down, the solvent was removed under vacuum. The residue was treated with CH\(_3\)CN (3 mL) and 2N HCl (2 mL), and kept at 5–10 °C to give \( N \)-acylsulfonamide as precipitate. Further purification was performed by recrystallization from ethyl acetate/hexanes unless specified. Alternatively, the residue was washed with THF (5 mL) to obtain the sodium salt of \( N \)-acylsulfonamide for products 2e, 2g, 2h, 2n, and 3b.

General procedure for the reverse reactions
To a solution of amide (1.0 mmol) dissolved in dry THF (10 mL) at 24 °C, NaH (1.2 mmol, 60% suspended with mineral oil) was added and stirred for 10 min. Then, \( N \)-sulfonamide (1.0 mmol) was added, and the reaction mixture was heated under reflux for up to 24 h until TLC showed disappearance of 1-sulfonylbenzotriazole. After cooling, the solvent was removed under vacuum. The residue was treated with CH\(_3\)CN (3 mL) and 2N HCl (2 mL), and kept at 5–10 °C to give \( N \)-acylsulfonamide as a precipitate. The purification process is the same as the procedure described above.
N-(4-Methylbenzoylmethanesulfonamide (2a). White needles (ethyl acetate/hexanes), mp 160–161 °C; 85% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.38 (s, 3H), 3.37 (s, 3H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.86 (d, $J = 8.2$ Hz, 2H), 12.05 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.1, 41.4, 128.5, 128.9, 129.2, 143.7, 166.3. Anal. Calcd for C$_9$H$_{11}$NO$_3$S: C, 50.69; H, 5.20; N, 6.57. Found: C, 50.80; H, 5.25; N, 6.48.

N-(4-Methylbenzoyl)-4-methylbenzenesulfonamide (2b). White microcrystals, mp 135–136 °C (lit.$^9$ mp 136 °C); 95% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.35 (s, 3H), 2.39 (s, 3H), 7.29 (d, $J = 7.9$ Hz, 2H), 7.44 (d, $J = 7.9$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 12.39 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.1, 127.7, 128.4, 128.7, 129.1, 129.5, 136.7, 143.7, 144.2, 165.2. Anal. Calcd for C$_{15}$H$_{15}$NO$_3$S: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.02; H, 5.19; N, 4.79.

N-(4-Methoxybenzoyl)-4-methylsulfonamide (2c). White microcrystals, mp 132–133 °C; 85% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 3.36 (s, 3H), 3.84 (s, 3H), 7.05 (d, $J = 8.9$ Hz, 2H), 7.95 (d, $J = 8.9$ Hz, 2H), 11.94 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 41.4, 55.6, 113.9, 123.7, 130.7, 163.2, 165.6. Anal. Calcd for C$_9$H$_{11}$NO$_4$S: C, 47.15; H, 4.84; N, 6.11. Found: C, 47.24; H, 4.81; N, 5.98.

N-(4-Methoxybenzoyl)-4-methylbenzenesulfonamide (2d). White powder (ethyl acetate/hexanes), mp 150–151 °C (lit.$^9$ m.p 174 °C); 98% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.40 (s, 3H), 3.82 (s, 3H), 7.01 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 2H), 12.27 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 21.1, 55.5, 113.9, 123.5, 127.7, 129.5, 130.6, 136.8, 144.1, 164.6. Anal. Calcd for C$_{15}$H$_{15}$NO$_4$S: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.91; H, 5.19; N, 4.25.

It was also characterized in the sodium salt. White powder (ethyl acetate/hexanes), mp >250 °C; 98% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.31 (s, 3H), 3.75 (s, 3H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 7.71–7.76 (m, 4H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 20.7, 55.0, 112.4, 126.6, 127.9, 129.9, 131.8, 139.1, 143.6, 160.6, 169.6.

N-[4-(Diethylamino)benzoyl]-4-methylbenzenesulfonamide (2e). Characterized as the sodium salt. White powder (ethyl acetate/hexanes), mp >250 °C; 98% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 1.07 (t, $J = 6.9$ Hz, 6H), 2.31 (s, 3H), 3.34 (q, $J = 7.1$ Hz, 4H), 6.55 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 7.7$ Hz, 2H), 7.71–7.76 (m, 4H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 12.4(2), 20.9, 43.7(2), 109.6(2), 125.8, 126.6(2), 128.0(2), 130.1(2), 139.1, 144.1 148.8, 170.7. Anal. Calcd for C$_{18}$H$_{21}$N$_2$NaO$_3$S: C, 58.68; H, 6.02; N, 7.60. Found: C, 58.34; H, 6.00; N, 7.90.

N-(2-Furylcarbonyl)-4-methylbenzenesulfonamide (2f). White needles (ethyl acetate/hexanes), mp 126–127 °C (lit.$^{10}$ mp 127±1 °C); 94% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 1.07 (t, $J = 6.9$ Hz, 6H), 2.31 (s, 3H), 3.34 (q, $J = 7.1$ Hz, 4H), 6.55 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 7.7$ Hz, 2H), 7.71–7.76 (m, 4H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 12.4(2), 20.9, 43.7(2), 109.6(2), 125.8, 126.6(2), 128.0(2), 130.1(2), 139.1, 144.1 148.8, 170.7. Anal. Calcd for C$_{12}$H$_{11}$NO$_4$S: C, 58.68; H, 6.02; N, 7.60. Found: C, 58.34; H, 6.00; N, 7.90.

N-Isonicotinoylmethanesulfonamide (sodium salt) (2g). White powder (methanol/hexanes), mp >250 °C; 99% yield. $^1$H NMR (DMSO-$d_6$) $\delta$ 2.87 (s, 3H), 7.78 (d, $J = 5.9$ Hz, 2H), 8.59 (d, $J = 5.9$ Hz, 2H). $^{13}$C NMR (DMSO-$d_6$) $\delta$ 40.2, 122.3, 146.7, 149.5, 168.7. Anal. Calcd for C$_7$H$_7$N$_2$NaO$_3$S: C, 37.84; H, 3.18; N, 12.61. Found: C, 37.85; H, 3.03; N, 12.34.
N-isonicotinoyl-4-methylbenzenesulfonamide (sodium salt) (2h). White powder (methanol/hexanes), mp >250 °C; 97% yield. $^1$H NMR (DMSO-$d_6$) δ 2.32 (s, 3H), 7.20 (d, $J$ = 8.0 Hz, 2H), 7.70–7.74 (m, 4H), 8.54–8.58 (m, 2H). $^{13}$C NMR (DMSO-$d_6$) δ 20.9, 122.3, 126.9, 128.1, 139.7, 142.9, 146.5, 149.5, 167.9. Anal. Calcd for C$_{13}$H$_{11}$N$_2$NaO$_3$S: C, 52.34; H, 3.72; N, 9.39. Found: C, 52.07; H, 3.71; N, 9.18.

N-(1H-Pyrrol-2-ylcarbonyl)methanesulfonamide (2i). White powder (ethyl acetate/hexanes), mp 167–168 °C; 80% yield. $^1$H NMR (DMSO-$d_6$) δ 3.35 (s, 3H), 6.18 (d, $J$ = 2.2 Hz, 1H), 7.08 (s, 1H), 7.18 (d, $J$ = 1.2 Hz, 1H), 11.64 (s, 1H), 11.88 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 41.8, 109.7, 115.0, 123.5, 125.2, 159.0. Anal. Calcd for C$_6$H$_8$N$_2$O$_3$S: C, 38.29; H, 4.28; N, 14.88. Found: C, 38.77; H, 4.28; N, 14.63.

N-(1H-Pyrrol-2-ylcarbonyl)-4-methylbenzenesulfonamide (2j). Pale brown needles (ethyl acetate/hexanes), mp 216–217 °C (lit. mp 224–225 °C); 76% yield. $^1$H NMR (DMSO-$d_6$) δ 2.39 (s, 3H), 6.14 (d, $J$ = 2.2 Hz, 1H), 7.02 (s, 1H), 7.14 (s, 1H), 7.42 (d, $J$ = 8.0 Hz, 2H), 7.87 (d, $J$ = 7.8 Hz, 1H), 11.74 (s, 1H), 11.98 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 21.1, 109.6, 114.9, 123.3, 125.1, 127.7, 129.4, 137.1, 144.0, 157.9. Anal. Calcd for C$_{12}$H$_{12}$N$_2$O$_3$S: C, 54.53; H, 4.58; N, 10.60. Found: C, 54.24; H, 4.49; N, 10.41.

N-(3a,7a-Dihydro-1H-indol-2-ylcarbonyl)-4-methylbenzenesulfonamide (2k). Pale brown microcrystals (ethyl acetate/hexanes), mp 242–243 °C; 83% yield. $^1$H NMR (DMSO-$d_6$) δ 2.42 (s, 3H), 7.10 (t, $J$ = 7.6 Hz, 1H), 7.28 (t, $J$ = 7.6 Hz, 1H), 7.42–7.53 (m, 4H), 7.69 (d, $J$ = 8.0 Hz, 1H), 7.91 (d, $J$ = 8.2 Hz, 2H), 11.78 (br s, 1H), 12.54 (br s, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 21.1, 107.4, 112.5, 120.3, 122.4, 125.0, 126.6, 127.8, 128.4, 129.5, 136.7, 137.5, 144.3, 159.3. Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_3$S: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.02; H, 4.36; N, 9.15.

Benzyl N-{1-methyl-2-[(methylsulfonyl)amino]-2-oxoethyl}carbamate (2l). White microcrystals (ethyl acetate/hexanes), mp 129–130 °C (lit. mp 125.5–127.0 °C); 87% yield. $^1$H NMR (DMSO-$d_6$) δ 1.24 (d, $J$ = 7.3 Hz, 3H), 3.23 (s, 3H), 4.08 (quint, $J$ = 7.1 Hz, 1H), 5.01 (d, $J$ = 12.6 Hz, 1H, B part of AB system), 5.04 (d, $J$ = 12.6 Hz, 1H, A part of AB system), 7.36 (s, 5H), 7.72 (d, $J$ = 7.0 Hz, 1H), 11.88 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 17.1, 40.9, 50.3, 65.6, 127.8, 127.9, 128.4, 136.9, 155.8, 173.0. Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_5$S: C, 47.99; H, 5.37; N, 9.33. Found: C, 47.98; H, 5.30; N, 9.28.

Benzyl N-{1-methyl-2-[((4-methylphenyl)sulfonyl]amino]-2-oxoethyl}carbamate (2m). White needles (ethylacetate/hexanes), mp 131–132 °C (lit. mp 125.5–127.0 °C); 87% yield. $^1$H NMR (DMSO-$d_6$) δ 1.13 (d, $J$ = 7.3 Hz, 3H), 2.39 (s, 3H), 4.03 (quint, $J$ = 7.2 Hz, 1H), 4.97 (d, $J$ = 12.9 Hz, 1H, B part of AB system), 4.99 (d, $J$ = 12.9 Hz, 1H, A part of AB system), 7.32–7.36 (m, 5H), 7.42 (d, $J$ = 8.2 Hz, 2H), 7.60 (d, $J$ = 7.3 Hz, 1H), 7.79 (d, $J$ = 8.2 Hz, 2H), 12.19 (s, 1H). $^{13}$C NMR (DMSO-$d_6$) δ 16.9, 21.1, 50.2, 65.5, 127.4, 127.8, 128.4, 128.3, 136.5, 136.6, 142.2, 155.6, 171.8. Anal. Calcd for C$_{18}$H$_{20}$N$_2$O$_5$S: C, 57.43; H, 5.36; N, 7.44. Found: C, 57.39; H, 5.43; N, 7.33.

Benzyl N-{1-benzyl-2-[[4-methylphenyl)sulfonyl]amino]-2-oxoethyl}carbamate (sodium salt) (2n). White microcrystals, mp 210–212 °C; 90% yield. $^1$H NMR (DMSO-$d_6$) δ 2.33 (s, 3H), 2.71–2.78 (m, 1H), 3.00–3.06 (m, 1H), 3.91–3.97 (m, 1H), 4.91 (d, $J$ = 12.9 Hz, 1H, B part of
AB system), 4.96 (d, J = 12.9 Hz, 1H, A part of AB system), 6.53 (d, J = 8.0 Hz, 1H), 7.00–7.03 (m, 2H), 7.10–7.33 (m, 10H), 7.65 (d, J = 12.9 Hz, 1H, A part of AB system), 6.53 (d, J = 8.0 Hz, 2H). 13C NMR (DMSO-d6) δ 20.8, 37.8, 57.8, 64.7, 125.6, 126.7, 127.2(2), 127.4(2), 127.6(2), 127.9(2), 128.2(2), 129.2(2), 137.2, 138.6, 139.4, 143.0, 155.2, 175.0. Anal. Calcd for C24H23N2NaO5S: C, 60.75; H, 5.10; N, 5.90. Found: C, 60.73; H, 4.86; N, 5.75.

N-(5-{{(4-Methylbenzoyl)amino}[sulfonyl]-1,3,4-thiadiazol-2-yl}acetamide (3a). White crystals (ethyl acetate/hexanes), mp >300 °C; 88% yield. 1H NMR (DMSO-d6) δ 2.26 (s, 3H), 2.37 (s, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H). 13.15 (s, 1H), NH (in exchange, missing). 13C NMR (DMSO-d6) δ 21.1, 22.4, 128.6, 128.8, 129.2, 144.1, 161.4, 162.4, 166.4, 169.7. Anal. Calcd for C12H12N4O4S2: C, 42.34; H, 3.55; N, 16.46. Found: C, 42.26; H, 3.46; N, 16.28.

N-{5-{{(Isonicotinoylamino)sulfonyl}]-1,3,4-thiadiazol-2-yl}acetamide (sodium salt) (3b). White powder (ethanol/hexanes), mp >250 °C; 100% yield. 1H NMR (DMSO-d6) δ 2.20 (s, 3H), 7.76 (d, J = 5.9 Hz, 2H), 8.62 (d, J = 5.9 Hz, 2H), 12.67 (br s. 1H). 13C NMR (DMSO-d6) δ 22.5, 122.2, 145.2, 150.0, 160.9, 166.5, 169.0, 169.1. Anal. Calcd for C10H8N5NaO4S2: C, 34.38; H, 2.31; N, 20.05. Found: C, 34.68; H, 2.22; N, 19.50.

Benzyl N-{2-{{[5-(acetylamino)-1,3,4-thiadiazol-2-yl]sulfonyl}amino]-1-methyl-2-oxoethyl} carbamate (3c). White powder (ethyl acetate/hexanes), mp 188–189 °C; 96% yield. 1H NMR (DMSO-d6) δ 1.21 (d, J = 7.3, 3H), 2.26 (s, 3H), 4.09 (quint, J = 7.0 Hz, 1H), 4.99 (s, 2H), 7.28–7.38 (m, 5H), 7.71 (d, J = 7.0 Hz, 1H), 13.18 (s, 1H), NH (in exchange, missing). 13C NMR (DMSO-d6) δ 16.9, 22.5, 50.7, 65.7, 128.0, 127.9, 128.5, 136.9, 155.8, 160.5, 162.6, 169.8, 173.1. Anal. Calcd for C15H17N5O6S2: C, 42.15; H, 4.01; N, 16.38. Found: C, 42.20; H, 3.95; N, 15.99.

N-(5-{{(4-Nitrobenzoyl)amino}[sulfonyl]-1,3,4-thiadiazol-2-yl}acetamide (3d). White microcrystals (ethyl acetate/hexanes), mp 238–239 °C (decomposed); 81% yield. 1H NMR (DMSO-d6) δ 2.25 (s, 3H), 8.15 (d, J = 7.8 Hz, 2H), 8.29 (d, J = 7.8 Hz, 2H), 8.56 (br s, 1H), 12.90 (s, 1H). 13C NMR (DMSO-d6) δ 16.9, 22.5, 50.7, 65.7, 128.0, 127.9, 128.5, 136.9, 155.8, 160.5, 162.6, 169.8, 173.1. Anal. Calcd for C11H9N5O6S2: C, 35.58; H, 2.44; N, 18.86. Found: C, 35.70; H, 2.43; N, 18.31.

N-4-Dimethyl-N-(4-methylbenzoyl)benzenesulfonamide (4). To a solution of N-methylsulfonamide (1.0 mmol) dissolved in dry THF (10 ml) at 24 °C, NaH (1.2 mmol, 60% suspended with mineral oil) was added and stirred for 10 min. Then, 1a (1.0 mmol) was added, and the reaction mixture was refluxed for 1.5 h. After cooling down, the solvent was removed under vacuum. The residue was extracted with ethyl acetate, and the organic solution was washed with 5% Na2CO3, water, and dried with MgSO4. Evaporation of solvent gave 4, which was further recrystallized from ethyl acetate/hexanes. White microcrystals (ethyl acetate/hexanes), mp 78–79 °C; 82% yield. 1H NMR (CDCl3) δ 2.36 (s, 3H), 2.42 (s, 3H), 3.23 (s, 3H), 7.29 (d, J = 7.8 Hz, 2H), 7.45–7.50 (m, 4H), 7.87 (d, J = 8.2 Hz, 2H). 13C NMR (CDCl3) δ 21.1, 36.0, 128.0, 128.5, 129.0, 129.7, 131.1, 135.2, 142.4, 144.7, 170.7. Anal. Calcd for C16H17NO3S: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.33; H, 5.75; N, 4.68.
References


