# A Useful, Alternative Synthesis of Unsymmetrical and Symmetrical *N,N'*-Disubstituted Sulfamides by Transamidation Reactions of Sulfamides with Amines

Séan D. McDermott, William J. Spillane*

Department of Chemistry, University College, Galway, Ireland

The only general route to unsymmetrical sulfamides involves the reaction of the appropriate sulfamyl chlorides and amines[1]. Recently, some examples have been given of an alternative synthesis from the reaction of 2-hydroxyphenyl alkylsulfamate esters with amines[2]. There is also a report of the transamidation reaction of *N*-*n*-butylsulfamide and cyclohexylamine leading to the formation of *N*-*n*-butyl-*N'*-cyclohexylsulfamide[3]. The viability of the monosulfamide-amine transamidation reaction as a route to unsymmetrical sulfamides has not been explored. In this report, conditions have been found under which the reaction of monosulfamides and amines can provide a useful, high-yield synthesis of unsymmetrical *N,N'*-disubstituted sulfamides. In some cases, symmetrical disubstituted sulfamides are also formed and these reactions, while useful, represent limitations of this synthetic procedure.

In previous studies, the reactions of sulfamide with aliphatic[3,4], alicyclic[3,4], heterocyclic[3,4], and aromatic[5] amines has been used to prepare mono- ('half-exchanged') and di- ('fully-exchanged') substituted sulfamides. However, in all cases, the disubstituted sulfamides formed are the symmetrically substituted compounds. Amine (amide) exchange (interchange) also occurs with *N,N'*-disubstituted sulfamides when the amine is more basic than the parent amine of the sulfamide[6,7].

In the reaction of mono-substituted sulfamides **1** ($R^2 = H$) with amines **2**, several amine exchange products are possible as outlined below. The most interesting of these are the mixed or unsymmetrical sulfamides **3**. It was felt that the particular product which formed in these reactions would be dependent on the reaction variables: time, temperature, and the molar ratio of **2** to **1**. If the amine exchange process is a stepwise one (and some evidence in support of a stepwise process is given below) then *a priori* one would expect that shorter reaction

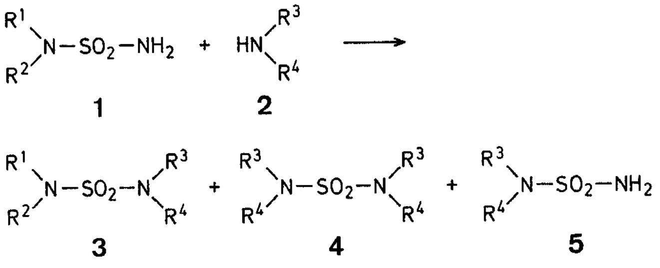

**Table 1.** Unsymmetrical *N,N'*-Disubstituted Sulfamides **3** ($R^2 = R^3 = H$) prepared

| Sulfamide **1** No. | $R^1$ ($R^2 = H$) | Amine **2** No. | $R^4$ ($R^3 = H$) | Product | Yield [%] Method A | Yield [%] Method B | m.p. [°C] | Molecular formula[a] or Lit. m.p. [°C] | $^{13}$C-N.M.R. (CDCl$_3$ or DMSO-$d_6$/TMS)[b] $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | *c*-$C_6H_{11}$ | **2a** | *n*-$C_4H_9$ | **3aa** | 69 | — | 99–101° | 100–101°[3] | 24.82, 25.34, 34.04, 52.63 (*c*-$C_6H_{11}$); 13.64, 19.88, 31.58, 42.88 (*n*-$C_4H_9$) |
| **1a** | *c*-$C_6H_{11}$ | **2b** | *n*-$C_5H_{11}$ | **3ab** | 22 | 54 | 87–90° | $C_{11}H_{24}N_2O_2S$ (248.4) | 24.80, 25.30, 34.18, 52.63 (*c*-$C_6H_{11}$); 14.03, 22.22, 29.11, 29.37, 43.27 (*n*-$C_5H_{11}$) |
| **1a** | *c*-$C_6H_{11}$ | **2c** | *n*-$C_6H_{13}$ | **3ac** | 63 | 85 | 72–76° | $C_{12}H_{26}N_2O_2S$ (262.4) | 24.88, 25.34, 34.11, 52.69 (*c*-$C_6H_{11}$); 14.03, 22.55, 26.44, 29.56, 31.45, 43.27 (*n*-$C_6H_{13}$) |
| **1a** | *c*-$C_6H_{11}$ | **2d** | *n*-$C_8H_{17}$ | **3ad** | — | 83 | 82–86° | $C_{14}H_{30}N_2O_2S$ (290.5) | 24.42, 24.81, 33.13, 51.45 (*c*-$C_6H_{11}$); 13.50, 21.70, 25.98, 28.32 (2C); 28.71, 30.92, 42.10 (*n*-$C_8H_{17}$) |
| **1a** | *c*-$C_6H_{11}$ | **2e** | *i*-$C_5H_{11}$ | **3ae** | — | 79 | 77–79° | $C_{11}H_{24}N_2O_2S$ (248.4) | 24.42, 24.81, 33.13, 51.45 (*c*-$C_6H_{11}$); 21.96, 24.81, 37.81, 40.28 (*i*-$C_5H_{11}$) |
| **1a** | *c*-$C_6H_{11}$ | **2f** | $C_6H_5CH_2$ | **3af** | — | 84 | 129–131° | 133–135°[2] | 24.38, 24.68, 33.13, 51.71 (*c*-$C_6H_{11}$); 46.13, 126.56, 127.21, 127.60, 138.39 ($C_6H_5CH_2$) |
| **1b** | *n*-$C_4H_9$ | **2b** | *n*-$C_5H_{11}$ | **3bb** | — | 72 | 125–127° | $C_9H_{22}N_2O_2S$ (222.4) | 13.64, 19.88, 31.57, 42.88 (*n*-$C_4H_9$); 13.90, 22.22, 28.84, 29.23, 43.14 (*n*-$C_5H_{11}$) |
| **1b** | *n*-$C_4H_9$ | **2c** | *n*-$C_6H_{13}$ | **3bc** | 20 | 73 | 112–114° | $C_{10}H_{24}N_2O_2S$ (236.4) | 13.64, 19.88, 31.38, 42.88 (*n*-$C_4H_9$); 13.97, 22.54, 26.37, 29.49, 31.38, 43.14 (*n*-$C_6H_{13}$) |
| **1b** | *n*-$C_4H_9$ | **2f** | $C_6H_5CH_2$ | **3bf** | — | 89 | 128–130° | $C_{11}H_{18}N_2O_2S$ (242.3) | 13.38; 19.36; 30.92, 41.84 (*n*-$C_4H_9$); 45.61, 126.82, 127.60, 128.00, 138.39 ($C_6H_5CH_2$) |
| **1b** | *n*-$C_4H_9$ | **2g** | *c*-$C_6H_{11}$ | **3bg** | — | 74 | 96–99° | (≡ **3aa**) | — |
| **1c** | $C_6H_5CH_2$ | **2b** | *n*-$C_5H_{11}$ | **3cb** | — | 66 | 138–140° | $C_{12}H_{20}N_2O_2S$ (256.4) | 13.77, 21.70, 28.45 (2C), 42.23 (*n*-$C_5H_{11}$); 45.61, 126.82, 127.47, 128.00, 138.39 ($C_6H_5CH_2$) |
| **1c** | $C_6H_5CH_2$ | **2c** | *n*-$C_6H_{13}$ | **3cc** | — | 78 | 119–120° | $C_{13}H_{22}N_2O_2S$ (270.4) | 45.74, 126.69, 127.47, 128.00, 138.39 ($C_6H_5CH_2$); 13.51, 21.70, 25.72, 28.71, 30.66, 42.23 (*n*-$C_6H_{13}$) |
| **1c** | $C_6H_5CH_2$ | **2d** | *n*-$C_8H_{17}$ | **3cd** | — | 95 | 114–116° | $C_{15}H_{26}N_2O_2S$ (298.4) | 45.74, 126.95, 127.60, 128.12, 138.52 ($C_6H_5CH_2$); 13.90, 22.09, 26.37, 28.71 (3C), 31.31, 42.23 (*n*-$C_8H_{17}$) |
| **1c** | $C_6H_5CH_2$ | **2g** | *c*-$C_6H_{11}$ | **3cg** | — | 88 | 130–131° | (≡ **3af**) | — |
| **1d** | *n*-$C_6H_{13}$ | **2a** | *n*-$C_4H_9$ | **3da** | — | 69 | 113–114° | (≡ **3bc**) | — |
| **1d** | *n*-$C_6H_{13}$ | **2b** | *n*-$C_5H_{11}$ | **3db** | — | 67 | 116–118° | $C_{11}H_{26}N_2O_2S$ (250.4) | 13.90, 21.83, 28.58 (2C), 42.10 (*n*-$C_5H_{11}$); 13.90, 22.09, 25.98, 28.84, 30.92, 42.10 (*n*-$C_6H_{13}$) |
| **1d** | *n*-$C_6H_{13}$ | **2e** | *i*-$C_5H_{11}$ | **3de** | — | 68 | 95–97° | $C_{11}H_{26}N_2O_2S$ (250.4) | 22.35, 25.07, 37.81, 40.93 (*i*-$C_5H_{11}$); 13.90, 22.35, 25.98, 28.84, 30.92, 42.23 (*n*-$C_6H_{13}$) |
| **1d** | *n*-$C_6H_{13}$ | **2f** | $C_6H_5CH_2$ | **3df** | — | 80 | 125–126° | (≡ **3cc**) | — |
| **1d** | *n*-$C_6H_{13}$ | **2g** | *c*-$C_6H_{11}$ | **3dg** | - | 89 | 76–78° | (≡ **3ac**) | — |
| **1d** | *n*-$C_6H_{13}$ | **2h** | *c*-$C_7H_{13}$ | **3dh** | — | 92 | 66–68° | $C_{13}H_{28}N_2O_2S$ (276.4) | 23.39, 27.41, 35.08, 53.66 (*c*-$C_7H_{13}$); 13.51, 21.70, 25.72, 28.71, 30.66, 42.10 (*n*-$C_6H_{13}$) |

[a] Satisfactory microanalyses obtained: C ±0.4, H ±0.39, N ±0.4; exceptions: **3cc**: H +0.53; **3db**: C −0.5.

[b] JEOL FX-60 spectrometer. The group *c*-$C_6H_{11}$ etc. after each set of $^{13}$C values indicates the end of the unsymmetrical sulfamide to which that the signals are assigned.

Table 2. Symmetrical $N,N'$-Disubstituted Sulfamides **4** ($R^4 = H$) prepared

| Sulfamide **1** No. | $R^1$ | $R^2$ | Amine **2** No. | $R^3$ | $R^4$ | Product | Reaction conditions: Ratio **2:1** | Temperature [°C] | Time | Yield [%] | m.p. [°C] found | reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $c$-$C_6H_{11}$ | H | **2f** | $C_6H_5CH_2$ | H | **4f** | 1:16 | 182–185° | 12 h | 84 | 181–183° | 180–182°[2,8,9] |
| **1a** | $c$-$C_6H_{11}$ | H | **2c** | $n$-$C_6H_{13}$ | H | **4c** | 1:13.5 | 131–132° | 12 h | 74 | 123–124° | 123–124°[10] |
| **1a** | $c$-$C_6H_{11}$ | H | **2c** | $n$-$C_6H_{13}$ | H | **5c** | 1:1[a] | 100° | 12 h | 40 | 65–68° | 65–68°[10] |
| **1a** | $c$-$C_6H_{11}$ | H | **2c** | $n$-$C_6H_{13}$ | H | **5c** | 1:1 | 80° | 12 h | 40 | 65–68° | 65–68°[10] |
| **1a** | $c$-$C_6H_{11}$ | H | **2i** | $C_2H_5$ | $C_2H_5$ | none[b] | 1:17 | 56° | 12 h | — | — | — |
| **1b** | $n$-$C_4H_9$ | H | **2g** | $c$-$C_6H_{11}$ | H | **4g** | 1:13.3 | 134° | 2 h | 80 | 151–153° | 153–154°[3] |
| **1b** | $n$-$C_4H_9$ | H | **2c** | $n$-$C_6H_{13}$ | H | **4c** | 1:11.5 | 131–132° | 2 h | 85 | 121–123° | 123–124°[10] |
| **1e** | $C_6H_5$ | H | **2a** | $n$-$C_4H_9$ | H | **4a** | 1:17.5 | 78° | 12 h | 79 | 125–127° | 126.5°[11] |
| **1e** | $C_6H_5$ | H | **2g** | $c$-$C_6H_{11}$ | H | **4g** | 1:15 | 134° | 14 h | 86 | 153–156° | 153–154°[3] |
| **1e** | $C_6H_5$ | H | **2j** | $-(CH_2)_5-$ | | **5j** | 1:17.8 | 106° | 12 h | 63 | 120–122° | 121–122°[4] |
| **1f** | $n$-$C_4H_9$ | $n$-$C_4H_9$ | **2f** | $C_6H_5CH_2$ | H | **4f** | 1:1 | 130° | 2 h | 53 | 176–178° | 180–182°[2,8,9] |
| **1f** | $n$-$C_4H_9$ | $n$-$C_4H_9$ | **2c** | $n$-$C_6H_{13}$ | H | **4c** | 1:15.8 | 131–132° | 2 h | 83 | 122–123° | 123–124°[10] |
| **1g** | $-(CH_2)_5-$ | | **2a** | $n$-$C_4H_9$ | H | **4a** | 1:16.6 | 78° | 12 h | 23[c,d] | 124–126° | 126.5°[11] |
| **1g** | $-(CH_2)_5-$ | | **2g** | $c$-$C_6H_{11}$ | H | **4g** | 1:14 | 134° | 12 h | 72 | 153–154° | 153–154°[3] |

[a] In $H_2O$ (~5 ml).

[b] 60% starting material recovered.

[c] After 4 h, 60% starting material recovered.

[d] 55–70% starting material recovered when allylamine (b.p. 53 °C), isobutylamine (b.p. 67–69 °C), and piperidine (b.p. 106 °C) were refluxed with **1g** for 12, 4, and 4 h, respectively, maintaining a 1:16 molar ratio of amine to **1g**.

times and moderate temperatures together with a 1:1 molar ratio of reactants should optimise the conditions for the formation of compounds **3**. Working on this basis and following a series of preliminary experiments (not reported here) two sets of conditions (Methods A and B) which led generally to high yields of the unsymmetrical sulfamides **3** were developed.

In Table 1, fifteen unsymmetrical $N,N'$-disubstituted sulfamides are listed which have been prepared thus. The reaction reported by Paquin[3] (**1b**+**2g**) has been repeated under the present conditions and the 'reverse' reaction (**1a**+**2a**) has also been carried out. Both routes gave approximately similar though slightly lower yields of **3aa** (≡**3bg**) than that reported by Paquin (77%). Compound **3af** (≡**3cg**) has also been prepared in approximately equal amounts in two ways (**1a**+**2f** and **1c**+**2g**). Method A is not as efficient as Method B (compare preparations of **3ab**, **3ac**, and **3bc**).

From the results in Table 2, the monosulfamide-amine reaction is seen to provide a route also to symmetrical disubstituted sulfamides **4**. In a few experiments an exchanged monosulfamide **5** was formed. The conditions under which these reactions were carried out (Method C) generally differed from those employed in Methods A and B. An excess of amine strongly favors the formation of compounds **4** (compare **1b**+**2g**, Table 2 and **1b**+**2g**, Table 1; **1b**+**2c**, Table 2 and **1a**+**2c**/**1d**+**2a**, Table 1). Raising the temperature but otherwise maintainence of Method A conditions results in the formation of compounds **4** (**1a**+**2f** and **1g**+**2g**, Table 2). This reaction affords an alternative route to symmetrically substituted sulfamides compared to the reactions of amines with sulfuryl chloride or sulfamide[12].

Some of the experiments in Table 2 illustrate some limitations of the monosulfamide-amine reaction as a route to compounds **3**. Thus, the conditions developed are unsuitable for the formation of mixed aryl/alkyl sulfamides. For **1e**+**2a** (Method A) the expected product, $N$-phenyl-$N'$-$n$-butylsulfamide is not formed. In the 'reverse' reaction using **1b** and aniline, trans-sulfonation and trans-sulfamylation occur when the reaction is carried out at reflux temperatures[13]. The extension of the reaction to the synthesis of trisubstituted sulfamides has been tried without success (**1a**+**2i**; **1f**+**2f**; **1f**+**2c**). Finally, the symmetrical sulfamide, **4a**, and not a 'mixed' alkyl/heterocyclic sulfamide, was obtained from **1g**+**2a** (Method A conditions).

Support for a stepwise amine exchange process comes from the fact that when the 'mixed' sulfamide, **3aa**, was reacted with excess cyclohexylamine for 2 h at 130 °C, a 90% yield of compound **4g** was formed. Compound **1b** in excess cyclohexylamine after 2 h at 130 °C gave an 80% yield of **4g** (Table 2).

In summary, the reactions of monosulfamides with amines provide an efficient, high-yield, alternative synthesis of both unsymmetrical and symmetrical $N,N'$-disubstituted sulfamides.

The identification of products listed in Tables 1 and 2 was based on C, H and N analysis, comparison where possible of m.p.'s with literature values, comparison of I.R. frequencies with those reported for disubstituted sulfamides[14], and measurement of $^{13}C$-N.M.R. spectra.

The aliphatic/alicyclic amines were distilled prior to use. The monosulfamides were synthesised by literature methods[4,5a].

### Reactions of Sulfamides 1 with Amines 2; General Procedures

Method A: The sulfamide **1** (200 mg) is added to the amine **2** (2 ml). The solution (the amide dissolves shortly after heating is commenced) in a tightly stoppered reaction flask is maintained at ~80 °C for 12 h. On cooling and addition of water (~10 ml), the crude product precipitates out. This material is recrystallised from aqueous ethanol and dried in vacuo over phosphorus pentoxide.

Method B: The sulfamide **1** (100 mg) and an equimolar amount of the amine **2** are heated in a tightly stoppered or sealed reaction flask in an oil bath at 130 °C for 2 h. Dilute hydrochloric acid (2 ml) is added, and the crude product is filtered off, recrystallised from aqueous ethanol and dried in vacuo over phosphorus pentoxide.

### Reaction of Phenylsulfamide (1e) with $n$-Butylamine (2a); Typical Procedure for Method C:

Phenylsulfamide (**1e**; 200 mg, 1.16 mmol) and $n$-butylamine (**2a**; 2 ml, 20.3 mmol) are refluxed for 12 h. After reaction, the solution is cooled and on addition of water (~10 ml), the crude product precipitates out.

Recrystallisation from aqueous ethanol and drying in vacuo over phosphorus pentoxide gives **4a**; yield: 190 mg (79%).

The other experiments in Table 2 are carried out at the reported temperatures (generally the reflux temperatures of the amines) and times and similarly worked up. In those experiments where starting material **1** or product **5** mono-substituted sulfamides are recovered, the work up procedure is as follows: after cooling the reaction solution, water is added and, on concentration of the aqueous amine solution almost to dryness, the crude sulfamide precipitates out. The recovered material is recrystallised from aqueous ethanol and dried in vacuo over phosphorus pentoxide.

**Reaction of *N*-*n*-Butyl-*N'*-cyclohexylsulfamide (3aa) with Cyclohexylamine (2g):**

Sulfamide **3aa** (100 mg, 0.43 mmol) and cyclohexylamine (**2g**, 1 ml, 8.7 mmol) are refluxed for 2 h. The solution is cooled and, on addition of water (~10 ml), a white material precipitates out. This is recrystallised from aqueous ethanol and dried in vacuo over phosphorus pentoxide to give *N,N'*-dicyclohexylsulfamide; yield: 100 mg (90%); m.p. 151-152 °C (Ref.[3], m.p. 153-154 °C).

*The authors wish to thank the Department of Education (Ireland) for a grant to S. D. McD.*

Received: August 24, 1982

---

* Author to whom correspondence should be addressed.

[1] (a) K. W. Wheeler, E. F. Degering, *J. Am. Chem. Soc.* **66**, 1242 (1944).
(b) A. Fuhrman, E. F. Degering, *J. Am. Chem. Soc.* **67**, 1245 (1945).
(c) A. Vandi, T. Moeller, L. F. Audrieth, *J. Org. Chem.* **26**, 1136 (1961).

[2] G. E. DuBois, *J. Org. Chem.* **45**, 5373 (1980).

[3] A. M. Paquin, *Angew. Chem.* **60**, 316 (1948).

[4] K. Hamann, *German Patent* 869065 (1953); *C. A.* **48**, 1412 (1954).

[5] (a) A. V. Kirsanov, *Zh. Obshch. Khim.* **23**, 223 (1953); engl. translation p. 233.
(b) A. V. Kirsanov, I. M. Zolotov, *Zh. Obshch. Khim.* **28**, 343 (1958); engl. translation p. 340.

[6] W. J. Spillane, J. A. Barry, F. L. Scott, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2666.

[7] W. J. Spillane, J. A. Barry, W. A. Heaphy, F. L. Scott, *Z. Naturforsch.* [b] **29**, 702 (1974).

[8] H. Burckhardt, W. J. Dieter, *J. Prakt. Chem.* **14**, 177 (1961).

[9] L. Denivelle, *Bull. Soc. Chim. Fr.* **1936**, 2143.

[10] H. Yamaguchi, K. Nakano, *Hiroshima Daigaku Kogakubu Kenkyu Hokoku* **21**, 23 (1972); *C. A.* **79**, 65420 (1973).

[11] R. Sowada, *J. Prakt. Chem.* **20**, 310 (1963).

[12] See Ref. [3] in Ref. [2].

[13] S. D. McDermott, W. J. Spillane, unpublished results.

[14] R. Sowada, *J. Prakt. Chem.* **311**, 228 (1969).