On the Formation of (Sulfonylamino)sulfonyl Isocyanates and (Aryloxy)sulfonyl Isocyanates

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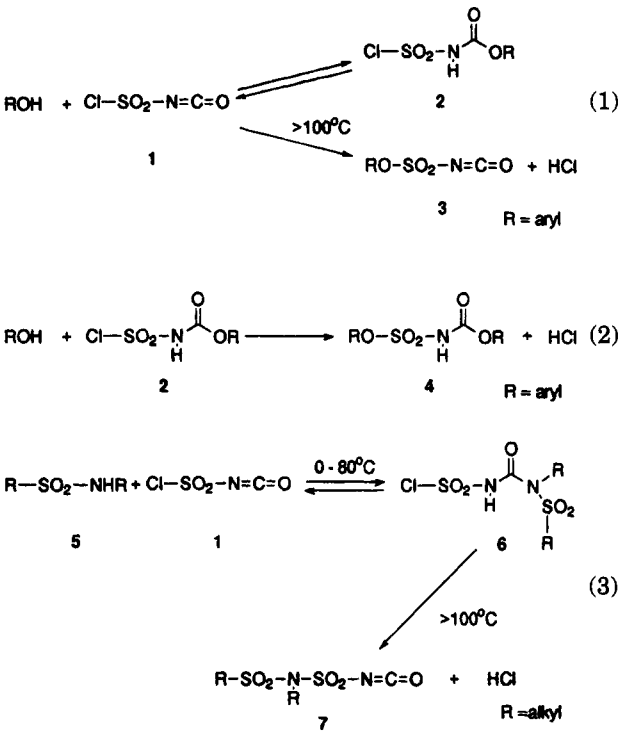
A revised mechanism for formation of (aryloxy)sulfonyl isocyanates and (sulfonylamino)sulfonyl isocyanates is proposed. New key intermediates, 4-methylphenyl ((4-methylphenoxy)sulfonyl)-carbamate (**8b**) and 1-(methanesulfonyl)-1-methyl-3-((*N*-(methanesulfonyl)-*N*-methylamino)sulfonyl)-urea (**8a**), have been identified and synthesized. The structure of **8a** has been confirmed by X-ray crystallography.

Phenols react with chlorosulfonyl isocyanate (**1**) at room temperature to yield the chlorosulfonyl carbamates **2**.[1] Above 100 °C this reaction becomes reversible, and another irreversible pathway to produce (aryloxy)sulfonyl isocyanates **3** and HCl dominates.[2] The chlorosulfonyl carbamates **2** are also known to undergo further reaction with phenols to produce (aryloxy)sulfonyl carbamates **4**.[1] The sulfonamides **5** show analogous reactivity toward **1**.[3] In this case, N-substituted sulfamoyl chlorides **6**, which are obtained at 0–80 °C, can be transformed to (*N*-sulfonylamino)sulfonyl isocyanates **7** upon heating over 100 °C. Up to a 2-fold excess of **1** enhances the reaction rate of the reaction with both phenols[4] and sulfonamides.[3] We undertook an NMR study of these unusual reactions with the aim of better understanding their mechanisms.



Results and Discussion

First, we studied the reaction between equimolar quantities of sulfonamide **5a** and isocyanate **1** in chlorobenzene at room temperature. After a few minutes a sponge-like precipitate of sulfamoyl chloride **6a** was observed. At this stage, moisture-sensitive **6a** can be isolated in 86% yield by filtration under an inert atmosphere. Careful heating of the reaction mixture to 40 °C causes dissolution of the solid and partial reappearance of the two methyl peaks of **5a** in the NMR spectrum (2.77 and 2.89 ppm, Figure 1a) due to equilibration between **5a**, **1**, and **6a** (3.12 and 3.30 ppm), respectively. Further reaction at 80 °C for 60 min is accompanied by evolution of about half the expected amount of hydrogen chloride gas (volumetric measurement). During this hour a gradual change occurs in the NMR spectra as four new methyl peaks begin to appear (3.14, 3.23, 3.25, and 3.49 ppm, Figure 1b), which correspond to a previously unknown intermediate of structure **8a**.

At the end of this period **8a** becomes the main component of the reaction mixture (Figure 1c) and the evolution of HCl almost ceases. Further transformation of this complex mixture to isocyanate **7a** demands prolonged heating (3 h) at over 100 °C, which is accompanied by slow evolution of the second half of the expected volume of HCl. This reaction period is characterized by a gradual loss of the four methyl peaks of **8a** and the corresponding growth of the two methyl peaks (3.31 and 3.33 ppm) of isocyanate **7a** (Figure 1d). Finally, the isocyanate **7a** can be isolated via distillation in 60–80% yield.

Some additional experiments, which are summarized in Scheme 1, were necessary to clarify the process. Thus, 2 equiv of sulfonamide **5a** heated at 80 °C during 2 h in chlorobenzene with 1 equiv of chlorosulfonyl isocyanate **1** furnished, upon cooling, the crystalline product whose NMR is identical to that of the observed intermediate **8a**. This product was isolated in 90% yield,[5] and its structure was confirmed by X-ray analysis.[6] Treatment of pure **8a** in chlorobenzene at reflux (132 °C) over several hours leads to complex decomposition with some formation of

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(3) Hoechst AG (Lohaus, G.; Mildenberger, H., Inv.) D.O.S. 2257240, 1972; *Chem. Abstr.* **1974**, *81*, 91049j.

(4) Graf, R. *Angew. Chem.* **1968**, *80*, 179.

(5) For application of **8a** in plant growth regulator synthesis see: Griffith, G.; Previdoli, F.; Ryan, G.; Warm, A. E.P. 92104612.4, 1992; *Chem. Abstr.* **1992**, *118*, 38937d.

0022-3263/94/1959-3540$04.50/0

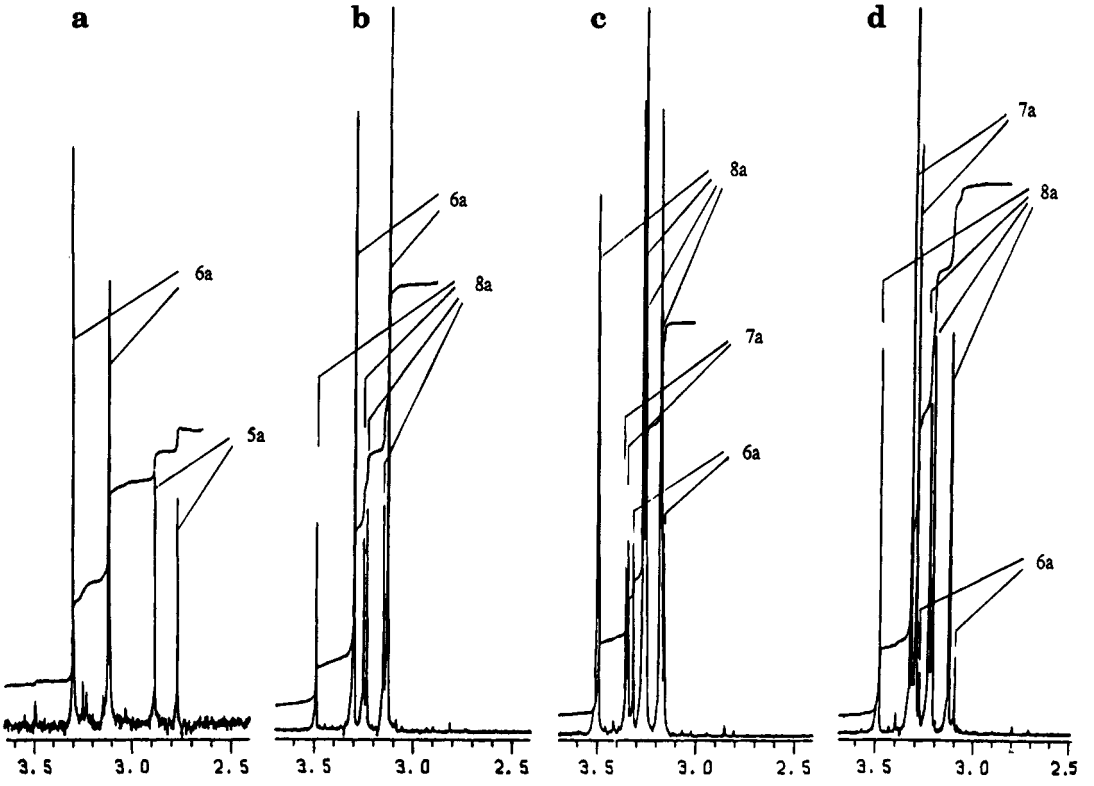
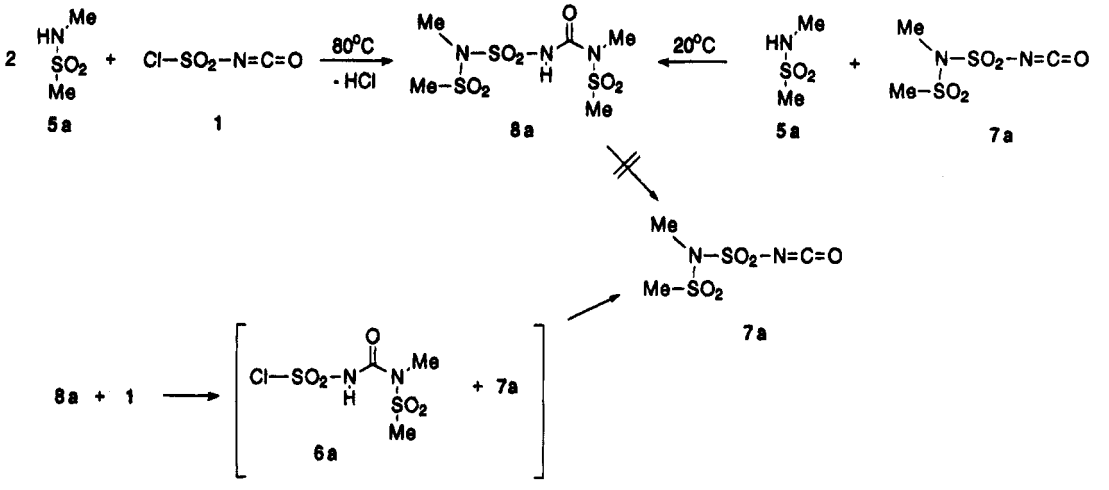
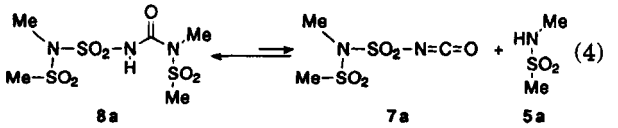


Figure 1. ^{1}H NMR spectra (300 MHz, $CDCl_3$/PhCl) taken during the formation of **7a** from **1** (see text).

Scheme 1



sulfonamide **5a** (NMR). Isocyanate **7a**, however, could not be detected in the impure mixture. On the other hand, **5a** reacted completely and rapidly with isocyanate **7a** over the whole range of temperatures between 20 °C and 132 °C to give **8a**. These two experiments show that the equilibrium between **5a** and **7a** on one side and **8a** on the other is almost completely shifted toward the latter.



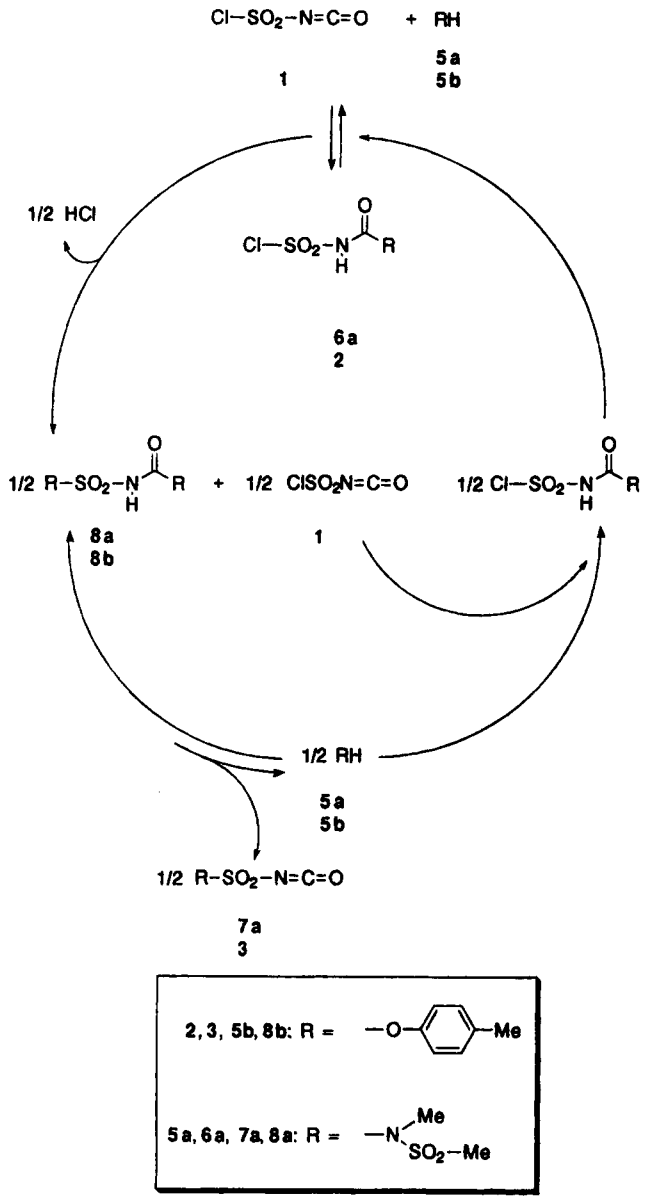
(4)

However, reaction between equimolar quantities of **8a** and **1** in chlorobenzene at 100 °C results in appearance of both **6a** and **7a** in the NMR spectrum; chlorosulfonyl isocyanate **1** is vitally important to trap the liberated sulfonamide **5a**, thus shifting the equilibrium toward isocyanate **7a**. This is in accordance with the aforementioned observation that an excess of **1** accelerates the reaction.[3] Further heating leads, as expected, to almost complete conversion to **7a**.

The facts described suggest a sequence of reactions leading to the the formation of isocyanate **7a**, which is shown in the cycle in Scheme 2. Although **5a** and **1** progress easily in the cycle to **8a**, further progression in the cycle to **7a** absolutely requires at least an additional 0.5 equiv of chlorosulfonyl isocyanate in order to react with the **5a** which is re-formed. An analogous set of experiments, including an NMR-monitored reaction between 4-methylphenol **5b** and isocyanate **1**, leading to isocyanate **3**, was performed in the phenol series (see Experimental Section), confirming the common character of both sulfonamide and phenol reactions.

(6) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 2



Experimental Section

All reactions were performed under a N_2 atmosphere. The *N*-methylmethanesulfonamide (**5a**) was prepared according to a literature procedure.[7]

***N*-(*N*-(Methanesulfonyl)-*N*-methylcarbamoyl)sulfamoyl Chloride (6a).** To a 20 °C solution of **1** (6.55 g, 46.3 mmol) in chlorobenzene (30 mL) was added compound **5a** (5.00 g, 45.8 mmol) over 10 min (mild exotherm). After 1 h, the sponge-like precipitate was filtered under N_2, washed with pentane (20 mL), and then dried at rt with a stream of N_2 to afford **6a** as white moisture-sensitive needles (9.93 g, 87%): mp 95–96 °C; IR (KBr) 3404 , 3251, 1688, 1422, 1376, 1328, 1286, 1198, 1178, 1159 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/PhCl) δ 3.30 (s, 3H), 3.12 (s,3H); (C_6D_6) δ 2.52, 1.62.

Anal. Calcd for $C_3H_7ClN_2O_5S_2$: C, 14.37; H, 2.81; N, 11.18. Found: C, 14.15; H, 3.15; N, 11.33.

1-(Methanesulfonyl)-1-methyl-3-((*N*-(methanesulfonyl)-*N*-methylamino)sulfonyl)urea (8a). To a solution of **5a** (20.0 g, 133 mmol) in chlorobenzene (60 mL) was added within 20 min chlorosulfonyl isocyanate (**1**, 13.0 g, 91.9 mmol) at 80 °C. After 2 h at 80 °C some precipitate formed. After the mixture was cooled to 20 °C over 10 h, the white crystals were filtered, washed with hexane (20 mL), and dried at 20 °C under vacuum (26.9 g, 91%): mp 126–128 °C; IR (KBr) 3257, 1714, 1464, 1383, 1351, 1183, 1165, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$/PhCl) δ 3.51(s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 3.18 (s, 3H); (C_6D_6) δ 3.26, 2.57, 2.35, 2.02; MS *m/z* (relative intensity) 245(3) [probably $M^{\bullet+} - CH_2{=}SO_2$], 215 (4), 172 (9), 136 (8), 122 (8), 108 (23), 94 (15), 79 (100), 73 (18).

Anal. Calcd for $C_5H_{13}N_3O_7S_3$: C, 18.57; H, 4.05; N, 12.99. Found: C, 18.40; H, 3.80; N, 13.10.

***N*-(Methanesulfonyl)-*N*-(methylamino)sulfonyl isocyanate (7a)** was obtained as described in the literature:[3] bp 95–100 °C/0.15 Torr (lit.[3] bp 94–98 °C/0.1 Torr); IR (CCl_4) 2248, 1584, 1478, 1446, 1403, 1370, 1189, 1168 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$/PhCl) δ 3.31 (s, 3H), 3.33 (s, 3H); (C_6D_6) δ 2.76, 2.37.

4-Methylphenyl (Chlorosulfonyl)carbamate (2). To a solution of *p*-cresol (**5b**, 13.0 g, 120 mmol) in chlorobenzene (40 mL) was added chlorosulfonyl isocyanate (**1**, 17.0 g, 120 mmol) over 45 min at 20 °C (mild exotherm). After 1 h the gel-like precipitate was filtered under N_2, washed with pentane (20 mL), and then dried under vacuum to yield white crystals (26.6 g, 89%): mp 110–112 °C; IR (KBr) 3109, 3082, 1769, 1741, 1508, 1464, 1402, 1245, 1173 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.78 (s, 4H), 1.97 (s, 3H).

Anal. Calcd for $C_8H_8ClNO_4S$: C, 38.49; H, 3.23; N, 5.61. Found: C, 38.20; H, 3.20; N, 5.90.

4-Methylphenyl ((4-Methylphenoxy)sulfonyl)carbamate (8b). To a solution of *p*-cresol (**5b**, 24.8 g, 229 mmol) in chlorobenzene (50 mL) was added chlorosulfonyl isocyanate (**1**, 16.2 g, 114 mmol) at rt. The mixture was heated at reflux for 12 h and cooled to 20 °C, and hexane (65 mL) was added. After a further 12 h, the white crystalline precipitate was filtered off, washed with hexane (50 mL), and then dried at 20 °C under vacuum to give white needles (32.2 g, 88%): mp 78–79 °C; IR (KBr) 3135, 1736, 1503, 1467, 1407, 1394, 1249, 1188, 1146 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.42 (bs, 1H, NH), 7.19 (d, J = 9 Hz, 2H), 6.88 and 6.71 (2d, J = 9 Hz, 4H, AB-system), 6.72 (d, J = 9 Hz, 2H), 1.98 (s, 3H), 1.91 (s, 3H); MS *m/z* (relative intensity) 321 (1) [$M^{\bullet+}$], 213 (12), 108 (100), 77 (55).

Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.07; H, 4.71; N, 4.36. Found: C, 56.20; H, 4.60; N, 4.50.

(4-Methylphenoxy)sulfonyl isocyanate (3) was obtained as described in the literature:[2] bp 80 °C/0.2 Torr (lit.[2] 80–83 °C/0.2 Torr); IR (film) 3305, 2250, 1502, 1409, 1204, 1176, 1144 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 6.87 (d, J = 9 Hz, 2H), 6.65 (d, J = 9 Hz, 2H), 1.87 (s, 3H); MS *m/z* (relative intensity) 213 (3) [$M^{\bullet+}$], 107 (100), 79 (45), 77 (51).

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Supplementary Material Available: X-ray ORTEP diagram and atomic coordinates of **8a** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) Helferich, B.; Grünert, H. *Chem. Ber.* **1940**, *73*, 1133.