An Improved Method for the Synthesis of Sulfonylureas

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Treatment of isocyanates with sulfonamides in dimethylformamide in the presence of copper(I) chloride affords sulfonylureas in high yields under mild conditions.

Sulfonylureas are products of outstanding pharmacological significance.[1,2] Various methods for their synthesis have been described,[3-6] one of the most widely used consisting of the addition of the alkali metal or alkaline-earth metal salt of a sulfonamide to an isocyanate in an inert solvent.[7] The highly alkaline medium may cause unwanted secondary reactions; a new method by which the reactions can be conducted in a neutral medium and under mild conditions would therefore be of interest.

A recently described method performs the known reaction of sulfonamides with isocyanates in the presence of diethyl ether boron trifluoride complex.[8] On the other hand, copper(I) chloride has been described as an efficient catalyst for the additions of alcohols to isocyanates,[9] amines to isocyanates,[10] and alcohols to carbodiimides.[11] We therefore explored the effect of copper(I) chloride on the reaction of sulfonamides **1** with isocyanates **2**, and we observed a remarkable catalytic effect of Cu^+ ion which rendered possible the preparation of several sulfonylureas **3** under improved experimental conditions; i.e., by adding an isocyanate **2** to a solution of a sulfonamide **1** in dimethylformamide containing copper(I) chloride (5 mol %). After a reaction time of 3–24 hours at ambient temperature, sulfonylureas **3** can be isolated in high yields by pouring the reaction mixture into ice/water, and filtration or decantation. Without the addition of the catalyst, the reaction (e.g., *p*-toluensulfonamide + cyclohexyl isocyanate, 48 hours) does not proceed.

Products **3f**, **3h**, **3i**, and **3j** are new compounds and product **3g** has previously been obtained by methylation of **3b**,[12] but not by the direct addition of *N*-methyl-*p*-toluenesulfonamide to butyl isocyanate.

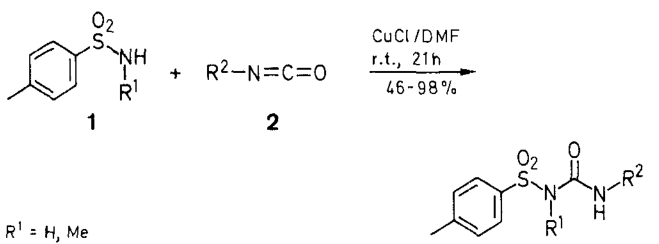

Table 2. Spectral Data of Compounds 3

3	IR (KBr) ν(cm^{-1})	^{1}H-NMR (80 MHz, $CDCl_3$/TMS) δ, J(Hz)
a	3320, 3220, 1690	
b	3330, 3100, 1660	
c	3340, 3215, 1675	
d	3340, 3210, 1690	
e	3340, 3190, 1650	
f	3390, 1690[a]	1.18 (t, 3H, $J = 7$), 2.47 (s, 3H), 3.11 (s, 3H), 3.31 (dq, 2H, $J_1 = 7$, $J_2 = 1.8$), 7.34 (two overlapping d, 3H), 7.73 (d, 2H, $J = 9$)
g	3400, 1700	
h	3390, 1710[a]	1.35 (s, 9H), 2.45 (s, 3H), 3.08 (s, 3H), 7.35 (d + NH, 3H, $J = 9$), 7.73 (d, 2H, $J = 9$)
i	3360, 1700	2.44 (s, 3H), 3.17 (s, 3H), 7.0–7.58 (m, 7H), 7.73 (d, 2H, $J = 9$), 9.34 (s, NH, 1H)
j	3380, 1690	1.0–2.0 (m, 11H), 2.44 (s, 3H), 3.11 (s, 3H), 7.31 (d + NH, 3H, $J = 9$), 7.70 (d, 2H, $J = 9$)

[a] Measured as film.

Table 1. Compounds 3 Prepared

3	R^1	R^2	Reaction Time (h)	Yield (%)	mp (°C)/ bp (°C)/(Torr)[a]	Molecular Formula[b] or Lit. mp (°C)	MS (70 eV) *m/z*
a	H	Et	19	70	138–140	140–141[13]	
b	H	Bu	21	85	126.5–130	126–127[13]	
c	H	*t*-Bu	23.5	68	162–164.5	165–166[13]	
d	H	Ph	19.5	76	159–160.5	172[14]	
e	H	*c*-C_6H_{11}	24	98	170–172	171–172[3]	
f	Me	Et	3	88	115–119/(0.01)	$C_{11}H_{16}N_2O_3S$ (256.3)	241 ($M - CH_3$, < 1), 192 (14), 155 (34), 121 (44), 91 (100), 85 (85), 65 (40)
g	Me	Bu	7	89	43–47	49–50[12]	
h	Me	*t*-Bu	16.5	46	128–132/(0.03)	$C_{13}H_{20}N_2O_3S$ (284.3)	269 ($M - CH_3$, 14), 212 (12), 185 (18), 155 (61), 121 (36), 91 (100), 65 (41), 57 (94)
i	Me	Ph	3	93	97–79 (MeOH)	$C_{15}H_{16}N_2O_3S$ (304.3)	304 (M^+, 17), 155 (48), 132 (23), 92 (36), 91 (100), 65 (46)
j	Me	*c*-C_6H_{11}	3.5	79	109–110 (H_2O)	$C_{15}H_{22}N_2O_3S$ (310.35)	310 (M^+, < 1), 185 (17), 155 (60), 139 (38), 121 (43), 98 (32), 91 (100), 55 (29)

[a] Oven temperature.

[b] Satisfactory microanalyses: C ±0.3, H ±0.25, N ±0.15.

N'-Butyl-N-tosylurea (3b); Typical Procedure:

To a stirred solution of *p*-toluenesulfonamide (5.0 g, 29.2 mmol) and CuCl (0.150 g, 1.52 mmol) in DMF (20 mL), butyl isocyanate (3.38 mL, 30 mmol) is added and stirring is continued for 21 h at ambient temperature. The mixture is then poured, slowly and with vigorous agitation, into ice/water (200 mL) and the resultant mixture is acidified with conc. aqueous HCl (1 mL). The solid product is isolated by suction and washed with H_2O to give colorless **3b**; yield: 7.4 g (85%); mp 126.5–128 °C (MeOH/H_2O (Lit.[13,14] mp 126–127 °C).

We thank Prof. Dr. M. Moreno-Mañas for assistance and M. Teixidó and E. Cayón for recording the ^{1}H-NMR spectra.

Received: 5 June 1989; revised: 15 September 1989

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