The Application of *N*-Substituted Trichloroacetamides as *in situ* Isocyanate Generating Reagents for the Synthesis of Acylureas and Sulfonylureas

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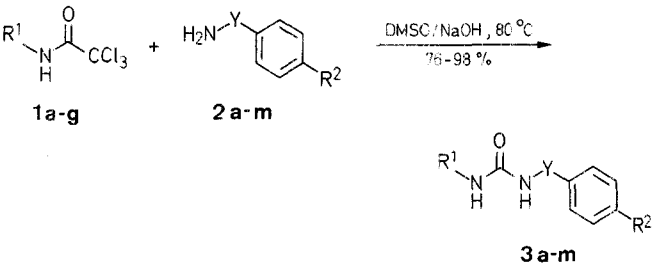
In dimethylsulfoxide solution in the presence of excess of powdered sodium hydroxide, *N*-subsituted trichloroacetamides **1** are used as *in situ* isocyanate generating reagents which can react with carboxamides or sulfonamides **2** to afford acylureas or sulfonylureas **3**.

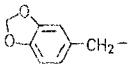
Trichloroacetic acid and its derivatives are used in organic synthesis for a variety of synthetic purposes. Sodium trichloroacetate in dimethoxyethane is a dichlorocarbene generating reagent, which can be used under neutral conditions.[1] Trichloroacetic acid is used for the introduction of a trichloromethyl group.[2] Trichloroacetyl chloride and anhydride are used for trichloroacetylation[3] and as mild dehydrating reagents, which can convert primary amides into nitriles.[4] Isoxazole-5-carboxylic acid has also been prepared from trichloroacetyl chloride, ethyl vinyl ether and hydroxylamine.[5]

Now we report that *N*-substituted trichloroacetamides can be used as *in situ* isocyanate generating reagents. They may be applied for the synthesis of acylureas and sulfonylureas. These very important biologically active compounds[6-9] are usually obtained by reaction of isocyanates with carboxamides or sulfonamides as well as by reaction of acyl isocyanates or sulfonyl isocyanates with amines.[10-12] The above mentioned methods have several disadvantages: a) the synthesis of isocyanates usually involves the use of highly toxic phosgene; b) most of the isocyanates are toxic, unstable, and their storage is inconvenient. Acyl isocyanates and sulfonyl isocyanates are also hazardeous compounds, and their synthesis likewise usually involves the use of phosgene. The new synthetic method described here avoids the above problems and is a valuable addition to the known methods for the production of isocyanates without the use of phosgene.[13]

The reaction of different *N*-substituted trichloroacetamides **1** with carboxamides or sulfonamides **2**, which affords acylureas or sulfonylureas **3**, takes place when a dimethylsulfoxide solution containing equimolar amounts of **1** and **2** is stirred at 80 °C for 30 min in the presence of excess powdered sodium hydroxide. The products **3** are separated after cooling, the addition of water, and adjusting the pH with sulfuric acid.

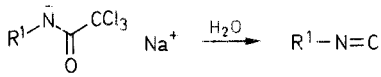


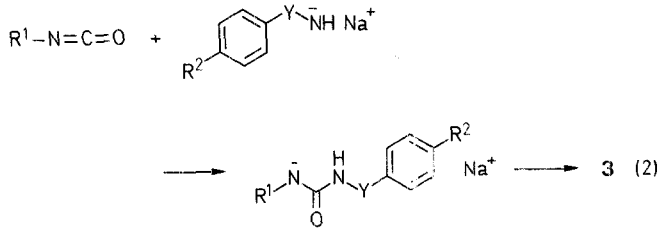
1a-g **2a-m** **3a-m**

1	2, 3	R^1	R^2	Y
a	a	2,6-$(C_2H_5)_2C_6H_3$	H	CO
	b	2,6-$(C_2H_5)_2C_6H_3$	Cl	CO
	c	2,6-$(C_2H_5)_2C_6H_3$	H	SO_2
b	d	2-CH_3-6-$C_2H_5C_6H_3$	H	CO
	e	2-CH_3-6-$C_2H_5C_6H_3$	H	SO_2
	f	2-CH_3-6-$C_2H_5C_6H_3$	CH_3	SO_2
c	g	2-$CH_3OC_6H_4$	H	CO
	h	2-$CH_3OC_6H_4$	H	SO_2
d	i	2-$CH_3C_6H_4$	H	CO
e	j	C_6H_5	H	CO
f	k		H	SO_2
g	l	*c*-C_5H_9	H	CO
	m	*c*-C_5H_9	H	SO_2

The yields, the spectral and physical data of **3** are given in Table 1.

The reaction possibly proceeds *via* isocyanate intermediates formed from *N*-substituted trichloroacetamides under strong alkaline conditions (eq. 1). The latter compounds react with the sodium salt of a carboxamide or sulfonamide to give **3** (eq. 2).


(1)


(2)

Treatment of trichloroacetamides **1** with sodium hydroxide under the above conditions yielded symmetric *N,N'*-disubstituted ureas **4** in good yield (Table 2). The reaction probably proceeds *via* isocyanates, but the obtained trichloroacetylureas are unstable under the reaction conditions.

Table 1. Acylureas or Sulfonylureas **3**

Product	Yield (%)	m.p.[a] (°C)	Molecular Formula[b] or Lit. m.p. (°C)	IR[c] (cm^{-1}) ν_{NH}	IR[c] (cm^{-1}) ν_{CO}	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, J(Hz)	MS (70 eV) *m/e* (M^+)
3a	96	217–218	$C_{18}H_{20}N_2O_2$ (296.4)	3250 3400	1660 1680	1.19 (t, 6H, J = 10); 2.67 (q, 4H, J = 10); 7.09 (s, 3H); 7.4–8.2 (m, 5H)[f]	296
3b	98	196–198	$C_{18}H_{19}ClN_2O_2$ (330.8)	3250 3400	1660 1680	1.16 (t, 6H, J = 10); 2.57 (q, 4H, J = 10); 7.03 (s, 3H); 7.39 (d, 2H, J = 10); 7.92 (d, 2H, J = 10)	330
3c	98	205–207	$C_{17}H_{20}N_2O_3S$ (332.4)	3160 3300	1660	0.96 (t, 6H, J = 10); 2.34 (q, 4H, J = 10); 6.93 (s, 3H); 7.4–8.2 (m, 4H)	332
3d	95	172–173	$C_{17}H_{18}N_2O_2$ (282.3)	3250 3400	1660 1680	1.16 (t, 3H, J = 10); 2.04 (s, 3H); 2.3–2.9 (m, 2H); 7.06 (s, 3H); 7.4–8.2 (m, 5H)[f]	282
3e	95	210–211	$C_{16}H_{18}N_2O_3S$ (318.4)	3180 3300	1660	0.92 (t, 3H, J = 10); 1.98 (s, 3H); 2.1–2.5 (m, 2H); 6.93 (s, 3H); 7.2–8.0 (m, 5H)	318
3f	90	183–184	$C_{17}H_{20}N_2O_3S$ (332.4)	3180 3300	1660	0.63 (t, 3H, J = 10); 1.98 (s, 3H); 2.38 (s, 3H); 2.08–2.61 (m, 2H); 6.93 (s, 3H); 7.29 (d, 2H, J = 8); 7.72 (d, 2H, J = 8)	332
3g	76	222–223	$C_{15}H_{14}N_2O_3$ (270.3)	3200 3400	1670 1690		270
3h	82	176–178	$C_{14}H_{14}N_2O_4S$ (306.4)	3180 3300	1660	3.79 (s, 3H); 6.5–8.5 (m, 9H)	306
3i	95	210–211	210[15]	3220 3350	1660 1700		254
3j	83	208–210	210[16]	3150 3320	1660 1690		240
3k	95	162–163	$C_{15}H_{14}N_2O_5S$ (334.4)	3100 3300	1650	3.8–4.5 (m, 2H); 5.87 (s, 2H); 6.67 (br. s, 3H); 7.2–8.0 (m, 5H)	334
3l	92	136–137	$C_{13}H_{16}N_2O_2$ (232.3)	3100 3300	1670	1.3–2.3 (m, 9H); 7.0–8.8 (m, 5H)	232
3m	78	167–168	$C_{12}H_{16}N_2O_3S$ (268.4)	3080 3320	1650	1.1–2.0 (m, 9H); 7.2–7.9 (m, 5H)	268

[a] Uncorrected, measured with a hot-stage „Boetius PHMK 05" apparatus.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.29, N ±0.45.
[c] Recorded in nujol on a C. Zeiss Specord 71 IR spectrophotometer.
[d] Obtained on a Perkin-Elmer R-24B spectrometer at 60 MHz.
[e] Recorded on a Jeol-JMS-D300 spectrometer.
[f] In pyridine-d_5 as a solvent.

Table 2. Symmetrical Ureas **4**.

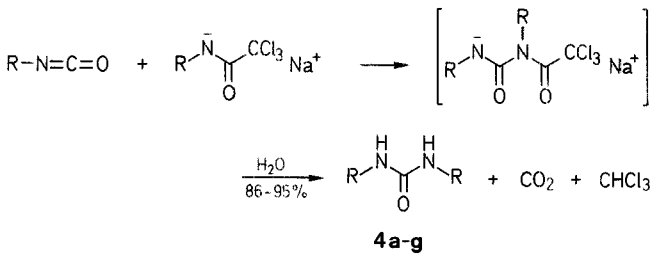
Product	Yield (%)	m.p.[a] (°C)	Molecular Formula[b] or Lit. m.p. (°C)	IR[c] (cm^{-1}) ν_{NH}	IR[c] (cm^{-1}) ν_{CO}	MS (70 eV)[d] *m/e* (M^+)
4a	92	286–288	$C_{21}H_{28}N_2O$ (324.5)	3260	1620	324
4b	91	249–250	$C_{15}H_{16}N_2O_3$ (272.3)	3300	1610	272
4c	91	236–237	235[19]	3300	1620	212
4d	95	206–208	$C_{19}H_{24}N_2O$ (296.4)	3300	1620	296
4e	92	219–220	$C_{17}H_{16}N_2O_5$ (328.3)	3300	1610	328
4f	86	104–106	$C_{11}H_{20}N_2O$ (196.3)	3220	1620	196

[a] Uncorrected, measured with a hot-stage "Boetius PHMK 05" apparatus.
[b] Satisfactory microanalysis obtained: N ±0.23.
[c] Recorded in nujol on a C. Zeiss Specord 71 IR spectrophotometer.
[d] Recorded on a Jeol-JMS-D300 spectrometer.

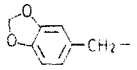
Table 3. Trichloroacetamides **1**.

Product	Yield (%)	m.p.[a] (°C)	Molecular Formula or Lit. m.p. (°C)	IR[b] (cm^{-1}) ν_{NH}	IR[b] (cm^{-1}) ν_{CO}	MS (70 eV)[c] *m/e* (M^+)
1a	92	157–159	$C_{12}H_{13}Cl_3NO$ (293.6)	3260	1695	294
1b	90	149–150	$C_{11}H_{12}Cl_3NO$ (280.6)	3260	1695	281
1c	85	150–151	$C_9H_8Cl_3NO_2$ (268.5)	3350	1700	269
1d	90	94–96	94–96[17]	3290	1690	239
1e	83	141–143	$C_{11}H_{12}Cl_3NO$ (280.6)	3250	1680	281
1f	91	83–85	$C_{10}H_8Cl_3NO_3$ (296.5)	3320	1690	297
1g	87	94–96	$C_7H_{10}Cl_3NO$ (230.5)	3300	1695	231

[a] Uncorrected, measured with a hot-stage "Boetius PHMK 05" apparatus.
[b] Recorded in nujol on a C. Zeiss Specord 71 IR spectrophotometer.
[c] Recorded on a Jeol - JMS-D300 spectrometer.



4a-g

4	R	4	R
a	2,6-$(C_2H_5)_2C_6H_3$	d	4-(i-C_3H_7)C_6H_4
b	2-$CH_3OC_6H_4$	e	
c	C_6H_5	f	c-C_5H_9

The resulting ureas **4** have wide application as intermediates in the synthesis of drugs, antioxidants and additives to oils and polymers.[7,18] The above described procedure has some advantages as a non-phosgene method for obtaining symmetrical ureas.[14]

The starting trichloroacetamides **1** are readily prepared. They have been obtained by reaction of trichloroacetic acid with the corresponding amines in the presence of phosphorus trichloride. The yields and spectral data of these compounds are given in Table 3.

Trichloroacetamides 1; General Procedure:
Phosphorus trichloride (0.76 g, 5.5 mmol) is added dropwise to a stirred suspension of amine (5.5 mmol) and trichloroacetic acid (0.9 g, 5.5 mmol). The mixture is heated at 110°C for 30 min. Ice water (50 mL) is added and the separated solid is filtered and washed with water. The crude **1** is recrystallized from methanol (Table 3).

Acylureas or sulfonylureas 3 a–m; General Procedure:
Trichloroacetamide **1** (5 mmol) is added to a stirred suspension of acetamide or sulfonamide **2** (5 mmol) and powdered NaOH (0.5 g, 12.5 mmol) in DMSO (5 mL). The mixture is stirred at 80°C for 30 min and, after cooling, poured into water (50 mL). The resultant mixture is acidified (pH ~ 2) with conc. sulfuric acid. The precipitated product is isolated by filtration or extraction with CH_2Cl_2. The crude product is recrystallized from benzene/hexane to give pure **3** (Table 1).

Symmetrical ureas 4 a–g; General Procedure:
Trichloroacetamide **1** (5 mmol) is added to a stirred suspension of powdered NaOH (0.5 g, 12.5 mmol) and DMSO (5 mL). The mixture is heated at 80°C for 30 min. and, after cooling, is poured into water (50 mL). The precipitated product is isolated by filtration or extraction with methylene chloride (Table 2).

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