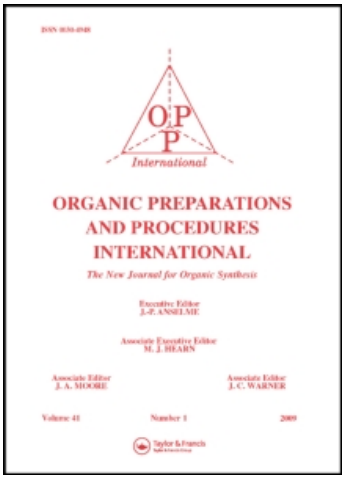

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AN IMPROVED PROCEDURE FOR THE DICHLOROACETYLATION OF PRIMARY AND SECONDARY AMINES

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EXPERIMENTAL SECTION

Reaction of Sodium Salt of Benzophenonetosylhydrazone (2a) with Trimethylsilyl Cyanide. Representative Procedure.- To a solution of 2a (7.36 g, 20 mmol) in anhydrous diglyme (50 ml) was added sodium hydride (50% in oil, 0.72 g, 30 mmol). After evolution of hydrogen gas had ceased, trimethylsilyl cyanide (9.90 g, 100 mmol) was added and the mixture was heated at 125° for 5 min. to evolve a quantitative amount of nitrogen gas. After filtration the filtrate was diluted with ether (200 ml), washed with water (200 ml x 5), dried over anhydrous sodium sulfate, and finally the solvent was evaporated on a rotary evaporator. The oily residue was chromatographed on silica gel (hexane-benzene 6:4) to give 3a (1.87 g, 49%).

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AN IMPROVED PROCEDURE FOR THE DICHLOROACETYLATION OF PRIMARY AND SECONDARY AMINES†

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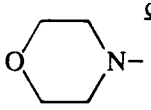
The dichloroacetamido moiety (-NHCOCHCl$_2$) is prevalent in number of biologically

active molecules.[1-3] Chloramphenical, a broad spectrum antibiotic and diloxanide, an antiamebic

TABLE 1. Dichloroacetamides

Product No.	R^1	R^2	Yield(%) Isolated	Yield(%) lit.	mp(°C) Obs	mp(°C) lit.
1	i-C_3H_7-	H	99	45[2]	127	127[2]
2	c-C_6H_{11}-	H	98	82[7]	138	140[7]
3	$CH_3CH_2CHCH_2OCOCHCl_2$	H	98	a	50	-
4	m-$CH_3C_6H_4$-	H	94	-	98	99[10]
5	i-C_3H_7-	i-C_3H_7-	85	62[2]	81	81[2]
6	c-C_6H_{11}-	c-C_6H_{11}-	78	b	85	-
7			78	38[7]	65	64[7]

a) new compound: Anal. Calcd for $C_8H_{11}Cl_4NO_3$: C, 30.89; H, 3.57; N, 4.50
Found : C, 31.00; H, 3.75; N, 4.77

b) new compound: Anal.Calcd for $C_{14}H_{23}Cl_2NO$: C, 57.54; H, 7.93; N, 4.79
Found : C, 57.77; H, 7.95; N, 4.89

TABLE 2. Physical Data of Dichloroacetamides

Product	IR (cm^{-1})	^{1}H-NMR δ[ppm]	MS m/e
1	3275, 1670	1.22(d, 6H, J = 6.3); 1.62 (s,1H); 4.04 (m, 1H); 5.8 (s, 1H)	169 (M+); 154; 86 (100%)
2	3250, 1660	1.03-2.13 (m, 10H); 3.75 (m,1H); 5.91 (s, 1H); 6.42 (broad s, 1H)	209 (M+); 174; 166; 128; 83 (100%)
3	3300, 1770, 1680	1.03 (t, 3H, J = 7.0); 1.64 (m, 2H); 3.93-4.48 (m, 3H); 5.93 (s, 1H); 6.03 (s, 1H); 7.17 (m, 1H)	309 (M+); 226; 182; 168; (100%); 152; 116; 83
4	3250, 1680	1.59 (s, 1H); 2.36 (s, 3H); 6.0 (s, 1H); 6.89-7.42 (m, 4H)	217 (M+); 182; 146; 134 (100%); 106; 91; 83; 77
5	1665	1.29 (d, 6H, J = 6.5); 1.42 (d, 6H, J = 6.5); 3.51 (m, 1H); 4.35 (m, 1H); 6.15 (s, 1H)	211 (M+); 196; 176; 154; (100%); 128; 86
6	1660	1.11-2.09 (m, 18H); 2.33 (m, 2H); 2. 98 (m, 1H); 3.85 (m, 1H); 6.11 (s, 1H)	291 (M+); 256 (100%); 210; 83
7	1665	3.70 (broad s, 8H); 6.15 (s, 1H)	197 (M+); 182; 162; 153; 132; 114 (100%); 86; 83; 70

agent with this moiety are of commercial importance. α, α-Dichloroacetamides have been prepared by reaction of amine or its hydrochloride with dichloroacetyl chloride.[2,4] The disadvantage of this reaction is that the substrate amine reacts with the liberated hydrogen chloride. Although pyridine has been used as a base in solvents such as benzene and acetone[4,5] the competion between pyridine and the usually more basic limits the yield of the dichloroacetamide. The use of methyl dichloroacetate results in low to moderate yields and requires prolonged time.[6] A patent described the preparation of dichloroacetylation of primary and secondary amines using chloral hydrate, sodium cyanide and precipitated calcium carbonate.[7]

To our knowledge a systematic study of the use of dichloroketene[8] for dichloroacetylation of amines has not been reported. We now describe here a simple and efficient procedure for dichloroacetylation of number of primary and secondary amines. Dichloroketene was generated in chloroform following the procedure of Corey et al.[9] Thus simultaneous addition of chloroform solution of triethylamine and dichloroacetyl chloride to the amine in chloroform is essential to obtain the high yield of the dichloroacetamides reported. The advantages of this method are that the reaction is fast and clean and involves a simple workup procedure and the products require no further purification. All the primary and secondary amines used gave much increased yields of the corresponding dichloroacetamides than reported earlier (Table 1). No selectivity was observed in the reaction of 2-aminobutanol with one molar equivalent of dichloroketene, yielding a 33% yield of O- and N-diacylated product. Use of two molar equivalents of dichloroketene afforded a 98% yield of O- and N-diacylated product.

EXPERIMENTAL SECTION

Mps. were determined with a Buchi melting point apparatus in capillary tubes and are uncorrected. The IR spectra were recorded in nujol mull on a Perkin-Elmer model 599B spectrophotometer. ^1H NMR spectra were taken on Jeol PMX 60, Varian FT-80A or Bruker WH-90 spectrometer in $CDCl_3$ solution using TMS as an internal standard. Mass spectra were recorded on a Finigan Mat 1020C mass spectrometer at 70 eV.

Dichloroacetylation of Primary and Secondary Amines. A General Procedure.- In a three-necked round bottom flask fitted with a thermometer and two pressure equalized dropping funnels a solution of an amine (50 mmol) in chloroform (40 ml) was cooled to 0°. To this, solutions of dichloroacetyl chloride (56 mmol) in chloroform (10 ml) and triethylamine (56 mmol) in chloroform (10 ml) were added simultaneously during 20 minutes with stirring keeping the temperature below 10°. The reaction mixture was stirred for a further period of 30 minutes at 10°. It was then poured in separatory funnel and was diluted with chloroform (50 ml). The chloroform solution was washed successively with water (25 ml), 2% cold hydrochloric acid (2 x 25 ml), water (2 x 25 ml), saturated sodium bicarbonate solution (2 x 25 ml) and finally with water (2 x 25 ml). The chloroform extract was dried over anhydrous sodium sulfate and product was obtained on evaporation of chloroform. Analytical samples were prepared by recrystallization.

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