The Reaction of Oxalyl Chloride with Amides. IV. Synthesis of Acyl Isocyanates

A. J. Speziale, Lowell R. Smith, and Joan E. Fedder

Research Department, Agricultural Division, Monsanto Company, St. Louis 66, Missouri

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The facile preparation of acyl isocyanates from amides and oxalyl chloride[1] prompted us to extend the reaction to a variety of amides to determine its scope and utility as a synthetic method. The reaction is quite general and of considerable synthetic value. Aromatic amides give excellent results regardless of substitution but yields with aliphatic amides are not very satisfactory unless an electron-withdrawing group is present on the α-carbon atom or there are no α-hydrogen atoms. Carbamates undergo the reaction quite readily to give isocyanato formates (Table I).

Reaction of cyclopropanecarboxamide (I) and oxalyl chloride did not give the expected cyclopropanecarbonyl isocyanate (II), but rather γ-chlorobutyroyl isocyanate (III). III was evidently formed from I or II and the liberated hydrogen chloride. The proof of the structure of γ-chlorobutyroyl isocyanate (III) was obtained by an examination of the n.m.r. spectrum of the derivative IV formed with 2-chloroallyl alcohol. IV showed absorption assigned to the NH proton at τ 1.75 (one proton), the vinyl protons at 4.5 (multiplet, two protons), the methylene group adjacent to the oxygen atom at 5.23 (two protons), and the three methylene groups at 6.38 (triplet, two protons), 7.02 (triplet, two protons), and 7.8 (multiplet, two protons). The spectrum shows clearly that the product is the γ-chloro rather than the α-chloro derivative. Since the acyl isocyanates were too reactive toward atmospheric

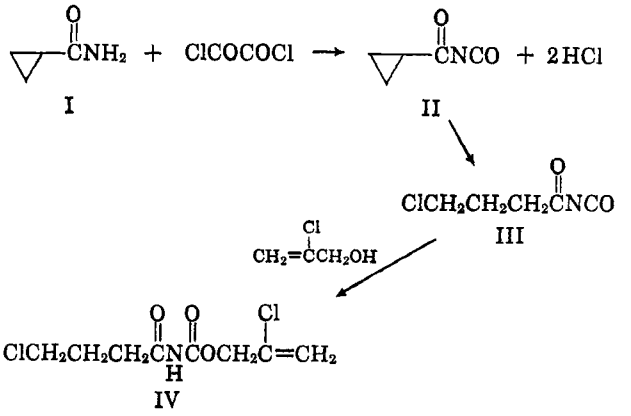

Table I

Acyl isocyanates, $RCN{=}C{=}O$			2-Chloroallyl N-acylcarbamates, $RCNCOCOCH_2C{=}CH_2$								
					Anal., %							
					Calcd.				Found			
R	B.p., °C. (mm.)	Yield, %	M.p., °C.	Yield, %	C	H	N	Cl	C	H	N	Cl
CH_3CH_2	35 (95)	0.8	96–98	32	43.87	5.26			44.07	5.55		
$(CH_3)_3C$	110	63	101–102	60	49.21	6.42			49.17	6.37		
Cyclo-C_6H_{11}	70–75 (10–15)	31	109–112	38	53.77	6.56			53.40	6.60		
CH_3CCl_2	63 (50)	33	64–67	66	32.27	3.09	5.38	40.83	32.32	3.18	5.60	40.88
$ClCH_2CH_2CH_2$[a]	72–76 (12)	59	82–87	76	40.02	4.62	5.84	29.53	40.06	4.65	6.09	29.45
CH_3O	26–29 (35–45)	59	70–72	59	37.22	4.16	7.24	18.32	37.34	4.23	7.04	18.58
C_6H_5O	70–75 (0.25)	67	103–106	78			5.48	13.87				
							5.73	13.60				
$C_6H_5OCH_2$	105–110 (0.75)	61	72–75	63	53.44	4.49	13.15		53.56	4.61	12.77	
2,4-$Cl_2C_6H_3OCH_2$	146 (0.75)	56	110–113	66	42.57	2.98			42.54	3.16		
$2CH_3C_6H_4$	50–55 (0.75)	96	132–134	66	56.81	4.77			56.79	4.89		
$3CH_3C_6H_4$	65–70 (0.7)	69	92–93	67	56.81	4.77	5.52	13.98	56.87	4.89	14.10	
$4CH_3C_6H_4$	61–67 (0.75)	79	93–95	63	56.81	4.77			57.24	4.90		
$2ClC_6H_4$	80–85 (0.4)	60	116–117.5	66	48.20	3.31			47.80	3.30		
4-ClC_6H_4	80–90 (0.75–2.0)	87	105–107	56	48.20	3.31	5.11	25.87	48.36	3.31	4.98	25.98
2,4-$Cl_2C_6H_3$	100–105 (1.7)	56	171–173[b]	64	48.37	3.69			48.35	3.71		
2-$NO_2C_6H_4$	120–122 (0.5)	62	99–101	77	46.41	3.19	9.84	12.46	46.67	3.29	10.05	12.25
3-$NO_2C_6H_4$	120–125 (0.7)	64	166–168[c]	79	53.01	4.45	16.86		53.03	4.41	17.01	
4-$NO_2C_6H_4$	122 (1.5)	65	136–138	66	46.41	3.19			46.71	3.24		
$C_6H_5CH{=}CH$	82–90 (0.8)	37	118–120	42	58.76	4.55	5.27	13.35	58.97	4.67	5.11	13.42

[a] From cyclopropanecarboxamide. [b] N-(2,4-dichlorobenzoyl)-N′-allylurea. [c] N-(3-nitrobenzoyl)-N′-allylurea

Other methods for the synthesis of acyl isocyanates, acid chlorides with silver cyanate,[2] amides with phosgene[3] (this reaction has also been reported to give nitriles[4]), and acid chlorides with isocyanica cid,[5] suffer the disadvantages of either low yields of complex procedures.

(1) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 3742 (1962); **28**, 1805 (1963).
(2) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1095 (1940).
(3) E. Waltmann and E. Wolf, U. S. Patent 2,346,202 (April 11, 1944).
(4) R. Greenhalgh, British Patent 488,036 (June 29, 1938).
(5) P. R. Steyermark, *J. Org. Chem.*, **28**, 586 (1963).

moisture to be analyzed, they were characterized as their derivatives.

Experimental Section

p-**Toluoyl Isocyanate.**—Oxalyl chloride (31.7 g., 0.25 mole) in ethylene dichloride was added to *p*-toluamide (24.3 g., 0.18 mole) in ethylene dichloride at 0°. The solution was allowed to warm to room temperature, then refluxed with stirring for *ca.* 24 hr. The solvent was evaporated *in vacuo*, and the residue was distilled under reduced pressure to give *p*-toluoyl isocyanate (23.0 g., 0.14 mole, 79%), b.p. 61–67° (0.75 mm.).

The other acyl isocyanates were prepared similarly, except methylene chloride was used as the solvent for the preparation of the low-boiling isocyanates (propionyl and carbomethoxy).

2-Chloroallyl-N-(*p*-toluoyl) Carbamate.—2-Chloro-2-propen-1-ol (2.3 g., 0.025 mole) in methylene chloride was added to *p*-toluoyl isocyanate (4.06 g., 0.025 mole) in methylene chloride, and the resulting solution was heated and concentrated. The addition of hexane and cooling gave 2-chloroallyl-N-(*p*-toluoyl) carbamate which was recrystallized from methylene chloride–hexane (4.0 g., 0.016 mole, 63%), m.p. 93–95°. The derivatives of other acyl isocyanates were prepared similarly.

Reaction of Cyclopropanecarboxamide and Oxalyl Chloride.—Oxalyl chloride (20.3 g., 0.16 mole) in methylene chloride was added to cyclopropanecarboxamide (11.9 g., 0.14 mole) in methylene chloride at 0°. The solution was allowed to warm to room temperature and stirred for 2.5 hr., and the solvent was removed *in vacuo*. The residue was distilled to give γ-chlorobutyroyl isocyanate (18.0 g., 0.08 mole, 0.12 *M*, 87%), b.p. 78–80° (15 mm.).

The Preparation of the Inner Salts of Two Aminophosphonates

ROBERT D. BURPITT AND V. WILSON GOODLETT

Research Laboratories, Tennessee Eastman Company, Division of Eastman Kodak Company, Kingsport, Tennessee

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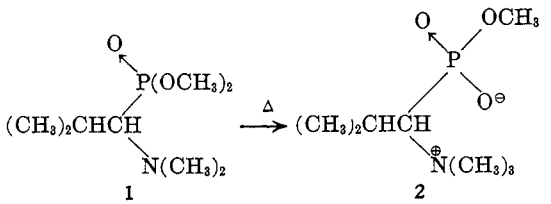
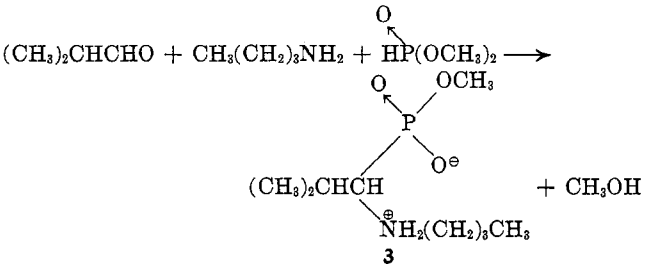
Aminophosphonates are well-known and readily available compounds.[1,2] The conversion of two aminophosphonates to the corresponding inner salts has been encountered in these laboratories. Their structural assignments were based on elemental analyses and n.m.r. spectra. When dimethyl 1-(dimethylamino)-2-methylpropylphosphonate (**1**), prepared[2] by the addition of dimethyl hydrogen phosphite to N,N-dimethylisobutenylamine, was heated, a crystalline hygroscopic solid resulted. This solid was insoluble in common organic solvents but quite soluble in water. It was assigned the structure of the inner salt of trimethyl-[2-methyl-1-(methylphosphono)propyl]ammonium hydroxide (**2**).



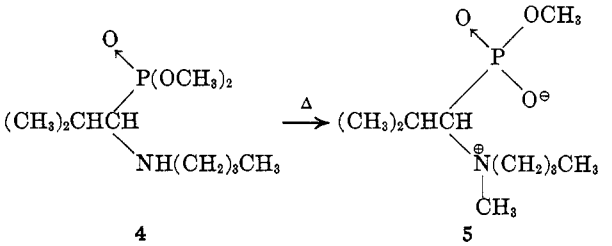
1 **2**

In an attempt to prepare dimethyl 1-(butylamino)-2-methylpropylphosphonate (**4**) by allowing isobutyraldehyde to react with a mixture of dimethyl hydrogen phosphite and butylamine,[1] we obtained, instead, the inner salt of butyl-[2-methyl-1-(methylphosphono)-propyl]ammonium hydroxide (**3**). This compound may have arisen from partial hydrolysis of the intermediate aminophosphonate **4** under the conditions of its formation.



3

Compound **4** was obtained by addition of dimethyl hydrogen phosphite to N-(2-methylpropylidene)butylamine. A small amount of solid from the distillation residue proved to be the inner salt **3**. When **4** was heated, the inner salt of butylmethyl-[2-methyl-1-(methylphosphono)propyl]ammonium hydroxide (**5**) was formed as an impure oil.



4 **5**

Diethyl 1-(dimethylamino)-2-methylpropylphosphonate, dimethyl 1-(dibutylamino)-2-methylpropylphosphonate, and dimethyl 1-(dimethylamino)butylphosphonate gave yields of intractable unidentified oily mixtures when heated. Dibutyl 1-(dimethylamino)-2-methylpropylphosphonate and dimethyl 1-(dimethylamino)cyclohexylphosphonate decomposed to starting materials when heated.

Experimental Section[3]

Dimethyl 1-(Dimethylamino)-2-methylpropylphosphonate (**1**).—The method described by Opitz[2] was utilized in the preparation of this compound. It was obtained in 78% yield: b.p. 64–66° (*ca.* 0.3–0.4 mm.); $n^{20}D$ 1.4452; infrared absorptions (neat) 8.06, 8.45, and 9.7 μ; n.m.r. spectrum (neat) pair of doublets with chemical shifts of 3.65 and 3.67 p.p.m. and J = 10.4 c.p.s. with a combined area equivalent to 6 protons [$(-OCH_3)_2$], doublet with spacing of 2.7 c.p.s. centered at 2.42 [$-N(CH_3)_2$], pair of doublets with splittings of 9.0 and 14.5 c.p.s. centered at 2.45 (>N–CH–P<, one of the peaks is obscured by the >N–CH_3 peak), multiplet at 2.02, and pair of doublets at 1.00 [$-CH(CH_3)_2$] p.p.m.

Anal. Calcd. for $C_8H_{20}NO_3P$: N, 6.7. Found: N, 6.6.

Inner Salt of Trimethyl-[2-methyl-1-(methylphosphono)propyl]ammonium Hydroxide (**2**).—The crude reaction mixture from the reaction of N,N-dimethylisobutenylamine (99 g., 1 mole) and dimethyl hydrogen phosphite (110 g., 1 mole) was refluxed at atmospheric pressure. The temperature of this mixture rose from 160 to 170° during the 1-hr. reflux period. No loss of weight occurred. The resulting viscous syrup crystallized on standing. The mixture, on trituration with acetone, gave an 85-g. (50%) yield of **2**. The filtrate was distilled to give a 40-g. yield of the aminophosphonate **1**. A sample of **2** was recrystallized from acetonitrile, m.p. 233–235° dec. This material proved

(1) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).

(2) G. Opitz, A. Griesinger, and H. Schubert, *Ann. Chem.*, **665**, 91 (1963).

(3) The boiling and melting points are uncorrected. The melting points were determined on a Fischer-Johns melting point block. N.m.r. spectra were measured at 60 Mc. on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were determined on Baird AB-2 and MK-1A spectrophotometers.