## The dimethyl formamide – acyl halide complex and its application to the synthesis of acyl azides

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A description of the conditions which favor the formation of the acid chloride – dimethyl formamide complex is given. The utility of the complex is illustrated by its application to the synthesis of acyl azides and, in particular, by the selective formation of 3-bromopropionyl azide from the corresponding acid chloride. The complex also results from a carboxylic acid salt and N,N-dimethyl chloroformiminium chloride, and thus provides an alternative method of effecting the direct conversion of a carboxylic acid into the corresponding acid azide.

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In connection with a study involving the incorporation of physiologically active aminoalkyl substituents into the 2-position of the oxazoline ring system, we required large quantities of 2-bromoethylisocyanate and several of its derivatives.

# $\begin{array}{ll} [1] & \operatorname{BrCH}_2\operatorname{COX} + \operatorname{NaN}_3 \to \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & &$

Bloom *et al.* (1) reported that prolonged heating of a benzene solution of 3-bromopropionyl chloride in the presence of activated sodium azide gave the parent compound, but the yield was not specified (eq. [1], X = Cl). Repetition of this work has shown that it is difficult to obtain reproducibly good yields of the bromoisocyanate free of contaminants containing the C-azido moiety. The Weinstock procedure (2), when applied to 3-bromopropionic acid, was equally nonselective, as evidenced by the infrared spectrum of the crude product (before rearrangement), which showed an intense C-azido absorption (3) at 2 120 cm<sup>-1</sup>, in addition to strong bands for the isocyanate (3) and the acyl azide (4) at 2 280 and 2 155 cm<sup>-1</sup>, respectively. As a consequence, a method was sought whereby preferential formation of the acyl azide could be induced, and the dimethyl formamide – acyl halide complex (see below) was chosen as a reasonable species in which such selectivity might be expected.

The formation of a complex was first proposed (5) to account for the observation that conducting solutions resulted on admixture of various acyl halides and dimethyl formamide (DMF). Whereas conductivity data suggested that, for acyl chlorides, less than 3% of the complex was present at equilibrium at room temperature, the corresponding acid bromides yielded hygroscopic crystalline solids. Acetonitrile solutions of these solids gave, with primary amines or water, products derived solely from attack at the acyl carbon, and it was on this basis that Hall (5) assigned structure I (eq. [2]) to the complexes. Bredereck

[2]  $RCOX + (CH_3)_2NCHO \rightleftharpoons$ 

## [(CH<sub>3</sub>)<sub>2</sub>N==-CH==OCOR]+X-

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et al. (6) pointed out, however, that these reactions should be interpreted as proceeding via the free acid bromide, inasmuch as, under the above conditions, dissociation of the complex into its components could be expected. Utilizing aniline as a nucleophile, and the benzoyl bromide derived complex, these authors demonstrated that both acyl and formyl carbon attack occurred (eq. [3]),

 $\begin{array}{ll} [3] & [(CH_3)_2N & = CH & = OCOC_6H_5]^+Br^- + C_6H_5NH_2 \\ & \rightarrow & (CH_3)_2NCH & = NC_6H_5 + C_6H_5CONHC_6H_5 \end{array}$ 

and that the relative amount of N,N-dimethyl-N'-phenylformamidine increased with increasing DMF concentration.

The site of nucleophilic attack on an ambident cation is profoundly influenced

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by the nature of the nucleophile as well as by such factors as solvent and temperature (7). It was anticipated that azide ion would display an overall selective acyl attack (eq. [4]); some support for this supposition was obtained when it was shown that the addition of sodium azide to an anhydrous DMF solution of 3-bromopropionyl chloride (at 20°) gave, after rearrangement, a modest yield of 2-bromoethylisocyanate, whose infrared spectrum

## [4] $[(CH_3)_2NCHOCOR]^+ + N_3^- \rightarrow$

## $RCON_3 + (CH_3)_2NCHO$

was devoid of azide absorption. With the assumption that this selectivity was a manifestation of an acid chloride – DMF complex, experiments were then devised to determine the conditions favoring its formation.

Acetyl and benzoyl chloride were chosen as representative acid chlorides, and aniline was used as a measure of the complex formation. The amounts of acid chloride (20 mmoles) and aniline (40 mmoles) were held constant, and the effect of other changes was gauged from the formamidineanilide\_ratio (Table I). The results confirmed the expectation that this ratio would depend on the nature of the leaving group (experiments 3 and 5), as well as on the characteristics of the acyl residue (experiments 4 and 6). An increase in the DME acetyl chloride ratio favored formamidine formation, as did a decrease in the temperature. This latter important observation was unexpected, and has not been noted by previous investigators.

The conditions employed in experiments 4 and 6 were then applied to the preparation of acyl azides. The addition of sodium azide in one lot to an equimolar amount of 3-bromopropionyl chloride in DMF (0°) produced a small (ca. 5°), easily controlled exotherm.<sup>2</sup> Processing the reaction mixture

	TABLE I		
Reaction of the	DMF – acyl halide aniline	complexes	with

Experi- ment	Acid halide	DMF (ml)	Tem- perature (°C)	Formam- idine- anilide ratio*
$\begin{array}{c}1\\2\\3\end{array}$	Acetyl chloride Acetyl chloride Acetyl chloride	$10 \\ 10 \\ 10 \\ 10$	$25 \\ 15 \\ 0$	$0.47 \\ 0.59 \\ 0.73$
4 5 6 7	Acetyl chloride Acetyl bromide Benzoyl chloride Phosgene§	$20 \\ 10 \\ 20 \\ 20 \\ 20$	0 0 0 0	$0.88 \\ 1.30 \\ 1.29 \\ 0.75$

\*These values are reproducible to  $\pm 0.05$  (average of three determinations). †Accurate to within  $\pm 1$  °C. ‡Determined by isolation. §A 12.5% solution of phosgene in benzene (15.8 ml) was used. After 1 h, 20 mmoles of sodium acetate was added, and after an additional hour, 40 mmoles of aniline was added.

after 1.5 h, followed by rearrangement of the intermediate acyl azide, gave a satisfactory yield (66.5% as the phenylurea, 46% by isolation) of pure 2-bromoethylisocyanate. The same procedure, when applied to a variety of aliphatic and aromatic acid chlorides (Table II), gave uniformly good yields of the corresponding isocyanates (determined as the known phenylureas). This synthesis has considerable utility for the preparation of the lower aliphatic isocyanates, where the yields are equivalent to, or better than, those obtained via existing methods (8). The yield (74%) of t-butylisocyanate obtained from the pivaloyl chloride complex is striking, especially when compared with the result observed (15%) for inverse addition.

Experiment 7 (Table I) was particularly interesting because it showed that the chloroiminium chloride II (eq. [5]) could serve as a source of the DMF - acyl halide complex, and it implied that the direct conversion of a carboxylic acid into the corresponding carboxylic acid azide should be feasible. The results shown in Table III confirmed this expectation. In general, it  $[5] \quad [(CH_3)_2N = CHCl]^+Cl^- + RCO_2^- \rightarrow$ 

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## $[(CH_3)_2N = CHOCOR]^+Cl^- + Cl^-$

was more convenient to utilize the triethylammonium salt of the carboxylic acid rather than the sodium salt. To minimize the elimination of hydrogen bromide from 3-bromopropionic acid, it was necessary to

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<sup>&</sup>lt;sup>2</sup>A very exothermic reaction occurred when the addition was performed in the inverse manner. For 3-bromopropionyl chloride, azide attack was no longer confined to the acyl carbon, and a  $5{-}10\%$ decrease in the isocyanate yield was usually observed for the other acid chlorides. Under these conditions, it can be inferred that the complex does not play a significant role in acyl azide formation, e.g. when acetyl chloride was added to excess aniline in DMF, the formamidine-anilide ratio was less than 0.1.

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			Melting point of urea (°C)	
Acid chloride	Isocyanate	%	Observed	Reported
Acetyl	Methyl	60.5	147-149	151†
Propionyl	Ethyl	74	97 - 97.5	100†
Valeryl	n-Butyl	81	127 - 128	130†
Pivaloyl	t-Butyl	<b>74</b>	165 - 166	$160^{+}$
B-Bromopropionyl	2-Bromoethyl	66.5	99 - 105	109-1118
Phenylacetyl	Benzyl	77.5	169 - 169.5	169 - 170
Diphenylacetyl	Benzhydryl	88	218 - 220	220-222
Benzoyl	Phenyl	92	240 - 242	236 - 237
l-Chlorobenzoyl	4-Chlorophenyl	89	245 - 247	237 - 238
-Methoxybenzoyl	4-Methoxyphenyl	100	192 - 194	186-190**
8-Nitrobenzoyl	3-Nitrophenyl	86	203 - 205	195-196††

TABLE II Isocyanate yields determined as the 1-phenyl-3-alkylureas\*

ting points refer to crude products.

Taken from ref. 10. Taken from ref. 11.

See Experimental. Taken from ref. 12. Taken from ref. 13.

\*\*Taken from ref. 14. †Taken from ref. 15.

add the base to the chloroiminium chloride carboxylic acid mixture. The product yield was thus considerably diminished, but the positional selectivity observed previously was nevertheless maintained. In these experiments, no special emphasis was placed on the best conditions for acyl azide formation, but the yields do compare favorably (with the above exception) with those obtained via the acid chloride. This procedure therefore constitutes a useful alternative to the mixed anhydride method (2) of obtaining acyl azides.

### EXPERIMENTAL

The melting points were determined in a Gallenkamp melting point apparatus and are not corrected. The infrared spectra were measured on a Perkin-Elmer 237B grating spectrophotometer. The gas-liquid partition chromatographic analyses were performed on a Wilkens Aerograph Autoprep A-700 with a 14 ft  $\times \frac{1}{4}$  in. column of 0.25% SE-30 on 80–100 mesh glass beads at a temperature of 125° and a helium flow rate of 30 ml/min. Thermal conductivity factors, relative to N,N-dimethylaniline, were determined for the products, and the peak areas were measured with a planimeter.

DMF was rendered anhydrous by distilling a solution containing 20 volume % of benzene until the boiling point of DMF was reached. The fraction with b.p. 153–154° was collected and stored over Linde molecular sieve (type 4A) for at least 24 h before use. The acid halides were of reagent-grade quality purchased from commercial sources, or were prepared by standard methods. A 12.5% solution of phosgene in benzene, available commercially, was used for all of the experiments. Triethylamine was

TABLE III

Direct conversion of carboxylic acids into acyl azides

Experi- ment*	Carboxylic acid	Salt of acid	Isocyanate	%†
$egin{array}{c} 1 \\ 2 \\ 3 \end{array}$	Acetic‡ Acetic 3-Bromopropionic∥	A§ B B	Methyl Methyl 2-Bromo-	50.3 55.8
$\begin{array}{c} 4\\5\\6\end{array}$	Phenylacetic Diphenylacetic Benzoyl	B B B	Benzyl Benzhydryl Phenyl	$   \begin{array}{r}     28.0 \\     70.4 \\     78.1 \\     83.4   \end{array} $

\*Standard conditions: carboxylic acid salt (20 mmoles), chloroiminium chloride (21 mmoles), DMF (30 ml), and so-dium azide (21 mmoles); temperature 0°. TThe isocyanate yields were determined as the known 1-phenyl-3-alkylureas and refer to crude products. DDMF (20 ml) was used. SA = sodium salt. B = triethylammonium salt. The acid was added to the chloroiminium chloride, followed by the dropwise addition of triethylamine.

distilled, and the fraction with b.p. 71-72° was stored over potassium hydroxide pellets before use.

All liquid transfers were performed with hypodermic syringes. In all experiments when solid reagents were added or solvents removed, a strong flow of dry nitrogen was maintained through the apparatus.

#### Reaction of the DMF-Acid Halide Complex with Aniline (See Table I)

A 50 ml three-necked flask containing a magnetic stirring bar and fitted with a thermometer, a calcium chloride drying tube, and a rubber septum was flame dried. The required amount of DMF (10 or 20 ml) was introduced, and the apparatus was placed in a water bath maintained at the desired temperature. The acid halide (20 mmoles) was added through the rubber septum all at once, and the solution was stirred for 1 h at the above temperature. Aniline (3.64 ml, 3.725 g, 40 mmoles) was added at a rate such that the reaction temperature was maintained within  $\pm 1^{\circ}$  of that originally specified. When the addition was completed, stirring was continued for 1 h, and then the solution was poured into 100 ml of ice-cold water. The resultant mixture was made alkaline with 15 ml of 20% sodium hydroxide solution and the products were extracted with dichloromethane (3  $\times$  12 ml). The extract was shaken with 10 ml of water and then dried over anhydrous sodium sulfate. The filtered solution was made up to 50 ml with dichloromethane and then subjected to gas-liquid partition chromatographic analysis.

If the formamidine was to be isolated, the aqueous solution from above was acidified with 25 ml of 1 Nhydrochloric acid. The anilide was removed by filtration and (or) extraction with dichloromethane. The aqueous phase was basified with 30 ml of 20%sodium hydroxide solution, and the liberated bases were extracted with benzene  $(3 \times 25 \text{ ml})$ . The benzene phase was shaken with water  $(2 \times 25 \text{ ml})$ , dried over sodium sulfate, and then evaporated in vacuo (ca. 20 mm) at 40°. The residual liquid was evaporatively distilled at 90-100° and 20 mm to remove aniline. Evaporative distillation of the liquid residue from the above operation at 90° and 0.02 mm gave pure N, N-dimethyl-N'-phenylformamidine. Benzoyl chloride (20 mmoles) and aniline (40 mmoles), under the conditions of experiment 6 (Table I), gave 1.233 g (41.7%) of N,N-dimethyl-N'-phenylformamidine. The picrate was prepared in ethanol and recrystallized from the same solvent to give a material with m.p. 159–161° (reported (6)m.p. 162-164°).

## Reaction of the DMF – Acid Chloride Complex with Sodium Azide

General Procedure (See Table II)

A dry, 50 ml three-necked flask containing a magnetic stirring bar and fitted with a gas inlet, a calcium chloride drying tube, and a thermometer was charged with 20 ml of DMF. The apparatus was cooled to 0° in an ice bath and the acid chloride (20 mmoles) was added all at once, with stirring. After 1 h at 0°, 1.366 g (21 mmoles) of sodium azide was added all at once, and then stirring was continued for 1.5 to 2 h. The reaction mixture was poured into 100 ml of ice-cold water, and the acyl azide was extracted with three or four 25 ml portions of toluene. The toluene phase was shaken with ice water  $(2 \times 25 \text{ ml})$  and then with a small amount of anhydrous sodium sulfate. The solution was dried further at  $0^{\circ}$  for 0.5 to 1 h over sodium sulfate. The filtered solution was heated on a steam bath for 1 h for the low molecular weight acyl azides, or for 1 h at reflux when relatively nonvolatile isocyanates were to be produced. Aniline (1.82 ml, 1.862 g, 20 mmoles) was added to the cooled solution, and the resultant mixture was maintained at gentle reflux for 15 min. The crystalline 1-phenyl-3-alkylureas were isolated by filtration (after the mixtures were cooled to 0°). Evaporation of the filtrate in vacuo gave an additional small crop of the urea.

The ureas were characterized by comparison of

their physical properties with those of authentic specimens synthesized by standard methods.

2-Bromoethylisocyanate

The reaction conditions were similar to those described above, except that sodium azide was not used in excess, and it was added during 10 min at a rate such that the reaction temperature did not exceed 5°. After rearrangement of the acyl azide, the toluene was removed on a spinning-band column at a reflux ratio of 3:1. The residual liquid was distilled *in vacuo* and the fraction with b.p. 57–59° at 20 mm was collected. From a 400 mmole scale reaction was obtained 34.55 g (46.2%) of the isocyanate. It was difficult to remove the last traces of toluene from this material. For example, a redistilled portion (b.p. 59–61° at 21 mm) still contained 3.5% toluene, as shown by the analytical figures and by gas-liquid partition chromatography.

Anal. Calcd. for  $C_3H_4BrNO + 3.5\%$   $C_7H_8$ : Ć, 26.37; H, 2.90; Br, 51.40; N, 9.01. Found: C, 26.01; H, 3.33; Br, 51.03; N, 8.99.

The infrared spectrum (liquid film) had an intense band centered at 2 280 cm<sup>-1</sup>.

To a solution of the isocyanate (150 mg) in 5 ml of anhydrous benzene was added 93.1 mg of aniline. After several hours at room temperature, the urea (204 mg, 84%), m.p. 109–111°, was collected by filtration.

Anal. Calcd. for C<sub>9</sub>H<sub>11</sub>BrN<sub>2</sub>O: Br, 32.88. Found: Br, 32.71.

This urea has been prepared by Winstein *et al.* (9), but no physical properties were reported.

### Direct Conversion of Carboxylic Acids into Carboxylic Acid Azides via N,N-Dimethyl Chloroformiminium Chloride (See Table III)

A 100 ml, flame-dried apparatus similar to that described above, except that one neck bore a twoway inlet tube to allow the introduction of dry nitrogen, was used. The flask was charged with 25 ml of anhydrous toluene and 16.6 ml of a 12.5% solution of phosgene (21 mmoles) in benzene. The stirred solution was cooled to  $-5^{\circ}$  or less in an ice-salt bath, and 1.7 ml (1.61 g, 22 mmoles) of anhydrous DMF was introduced at a rate such that the reaction temperature did not exceed 5° (ca. 10 min). The mixture was stirred until gas evolution ceased (about  $\frac{1}{2}$  h), and then the solvent was sucked off through a sintered-glass disk which had been sealed into the extended right leg of an "h"-shaped tube. The solid residue was slurried with 20 ml of DMF and cooled to 0°. The solid sodium salt (experiment 1), or a solution of the triethylammonium salt (prepared from 20 mmoles of the carboxylic acid and 2.8 ml (2.02 g, 20 mmoles) of triethylamine) in 10 ml of DMF, was added to the iminium salt (except for experiment 3) while the temperature was maintained at 5° or less (5-10 min). After 1 h at 0°, sodium azide (1.366 g, 21 mmoles) was added, and the mixture was stirred for an additional 1.5-2 h. The reaction mixture was then processed in the manner already described.

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