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REACTIONS OF ACID HALIDES AND CHLOROFORMATES INVOLVING AN INTERMEDIATE WITH DIMETHYLFORMAMIDE

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Various authors have studied the Lewis acid adducts of N,N-dimethylformamide (DMF) illustrating the reactivity of the carbonyl oxygen[1-4]. Hall[5] isolated 1:1 crystalline salts following the treatment of DMF with acyl bromides which were formulated as $(CH_3)_2\overset{+}{N}=CHOCOR\ X^-$ on the basis of elemental analysis data, conductivity experiments and formation of anilides on further treatment with aniline. Pattison et al.[6] have previously reported that substituted aryl chloroformates (1a and 1b) react in the presence of excess DMF to produce carbon dioxide and aryloxy-substituted immonium salts (3a and 3b) (eq. 1). These in turn were found to react with methanol to generate DMF, the corresponding phenol and methyl chloride (eq. 2).

$$X\text{-}C_6H_4OCOCl + HCON(CH_3)_2 \longrightarrow (CH_3)_2\overset{+}{N}=CHO\text{-}C_6H_4\text{-}X + Cl^- + CO_2 \qquad \text{(eq. 1)}$$

1a, X = p - CH_3 3a, X = p - CH_3
1b, X = p - CH_2Cl 3b, X = p - CH_2Cl
1c, X = H 3c, X = H

$$(CH_3)_2\overset{+}{N}=CHO\text{-}C_6H_4\text{-}X + Cl^- + CH_3OH \longrightarrow CH_3Cl + HCON(CH_3)_2 + X\text{-}C_6H_4\text{-}OH \qquad \text{(eq. 2)}$$

We wish to report here, the previously unreported finding, that when DMF is allowed to react with an equimolar quantity of phenyl chloroformate at 0° an isolable adduct 2 is formed. Upon standing at room temperature 2 loses carbon dioxide to produce 3c (eq. 3).

$$C_6H_5OCOCl + HCON(CH_3)_2 \longrightarrow (CH_3)_2\overset{+}{N}=CHOCOOC_6H_5\ Cl^- \longrightarrow \underline{3c} + CO_2 \qquad \text{(eq. 3)}$$

Furthermore, the present work illustrates that adduct 2 leads to an efficient production of ethers and esters when reacted under mild conditions (0°C) with alcohols and carboxylic acids, respectively (eqs. 4 and 5).

$$\underset{\underline{2}}{(CH_3)_2\overset{+}{N} = CHOCOOC_6H_5\ Cl^-} + ROH \longrightarrow C_6H_5OR + CO_2 + DMF \cdot HCl \qquad \text{(eq. 4)}$$

$$(CH_3)_2\overset{+}{N} = CHOCOOC_6H_5\ Cl^- + RCO_2H \longrightarrow C_6H_5OCOR + CO_2 + DMF \cdot HCl \qquad \text{(eq. 5)}$$

On refrigeration of an equimolar mixture of phenyl chloroformate and DMF in petroleum ether, the formation of a yellowish brown solid mass was observed. The product was filtered and immediately washed with ether. Structure 2 was assigned to this product on the basis of its nmr spectrum in $CDCl_3$: $\delta\ C\underline{H}_3 = 3.52$ and 3.82 (for DMF $\delta\ C\underline{H}_3 = 2.83$ and 2.94), $\delta\ C\text{-}\underline{H} = 7.1$ (for DMF, $\delta\ C\text{-}\underline{H} = 8.05$), $\delta\ C_6\underline{H}_5 = 7.6$ (m).

The products obtained by the treatment of adduct 2 with various nucleophiles at 0° are shown in table 1. Similar results were obtained by reacting the nucleophiles at 0° without prior isolation of intermediate 2. When 2 was reacted with aniline the corresponding carbamate was formed in good yields, a fact which further substantiates structure 2. However, on treatment of 2 with various alcohols (such as methyl, *i*-propyl, and *n*-butyl alcohol) the formation of the corresponding phenyl ethers, with concomitant loss of carbon dioxide at 0°, was observed (eq. 4). Addition of acetic acid also caused fast evolution of carbon dioxide resulting in the formation of phenyl acetate (eq. 5). On standing at room temperature adduct 2 loses carbon dioxide giving rise to a reddish brown crystalline solid. Structure 3c was assigned to this product on the basis of its spectral data (pmr) which closely resemble those of structures 3a and 3b reported by Pattison, *et al.*[6] The reactions of this product were identical to those of 3a and 3b described by these authors forming the alkyl halides with various alcohols.

In order to obtain more information on the chemical reactivity of DMF-acyl halide adducts, 4a and 4b were prepared from acetyl and benzoyl bromide with DMF, respectively[5]. The products obtained by the reactions of compound 4b[8] with alcohols are presented in table 2. It is interesting that although with aniline amides are formed[5], we have found the previously unreported fact that alkyl halides are obtained with alcohols instead of the corresponding esters.

$$(CH_3)_2\overset{+}{N} = CHOCOR\ X^-$$

4a, $R = CH_3$
4b, $R = C_6H_5$

Formation of carbamates and amides from DMF-chloroformate and DMF-acyl halide adducts can be readily explained as a nucleophilic displacement by the amine nitrogen at the carbonyl of these adducts. The formation of ethers by the reactions of 2 with alcohols is a novel observation. Since the addition of alcohols initiates the evolution of carbon dioxide, it is evident that the alcohols react with 2 and not with other species such as 3c[7].

The DMF adducts described above provide new synthetic routes to esters, ethers and alkyl halides under mild conditions. The simplicity of operation and high yields are of added significance in the preparation of chemically sensitive compounds such as those of medicinal value.

Table 1 -- Reactions of 2 with Nucleophiles

Nucleophile	Products	Yield (by isolation)
aniline	$C_6H_5NHCOOC_6H_5$[9]	70%
i-propyl alcohol (*i*-PrOH)	*i*-$PrOC_6H_5$[10]	75%
acetic acid	$CH_3COC_6H_5$[10]	75%

Table 2 -- Reactions of 4b[8] with Nucleophiles

Nucleophile	Products[11]	Yield (by isolation)
methyl alcohol	CH_3Br	95%
i-propyl alcohol (*i*-PrOH)	*i*-PrBr	95%
n-butyl alcohol	*n*-BuBr	80%

NOTES AND REFERENCES

1. S. J. Kuhn and J. S. McIntyre, Can. J. Chem., 43, 375 (1965).
2. S. J. Kuhn and J. S. McIntyre, Can. J. Chem., 43, 995 (1965).
3. W. Garrard, M. F. Lappert, H. Pyrzora and J. W. Wallis, J. Chem. Soc., 2144 (1960).
4. R. A. Y. Jones and A. R. Katritzky, Chem. Ind., London, 722 (1961).
5. H. K. Hall, J. Amer. Chem. Soc., 78, 2717 (1956).
6. V. A. Pattison, J. G. Colson, and R. L. K. Carr, J. Org. Chem., 33, 1084 (1968).
7. The reaction of alcohols with 3c results in the formation of halides and not ethers.
8. Similar products and yields were obtained by using 4a instead of 4b.
9. One mole of 2 was generated by mixing equimolar amounts of phenylchloroformate and DMF at 0°. Addition of one mole of aniline to this precipitated the carbamate (PhNHCOOPh) which was filtered, washed with H_2O and recrystallized from ethanol.
10. One mole of alcohol was added to one mole of 2[9] at 0°, and the contents were extracted with petroleum ether. The product was obtained by distillation after removing the solvent.
11. One mole of corresponding alcohol was added to one mole of 4b with cooling and the product collected by distillation.