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A NOVEL REAGENT FOR THE VILSMEIER-HAACK REACTION

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It has been known that the reaction of an active methylene compound with a Vilsmeier complex, the adduct of N,N-dimethylformamide (DMF) with phosphorus oxychloride or phosgene, affords an N,N-dimethylaminomethylene derivative (1). In the course of a study of formylation of several kinds of compounds, we have found that the reaction of an active methylene compound with ethyl chloroformate proceeded in a way similar to Vilsmeier-Haack reaction when DMF was used as a solvent. The present paper refers to this interesting results.

The treatment of malononitrile with ethyl chloroformate in DMF afforded ethoxymethylene malononitrile (I) in good yield (80%) along with the evolution of carbon dioxide. The reaction of ethyl cyanoacetate also gave an expected ethoxymethylene compound (II); however, the yield was lower than that of I.

When the reaction was carried out in the presence of triethylamine, an N,N-dimethylaminomethylene compound was obtained, that is, III from malononitrile (yield, 10%) and IV from ethyl cyanoacetate (yield, 31%). (See Chart 1). The relatively low yields of the products under basic conditions must be caused by the successive reaction of the primary products with respective starting materials. The isolation of V (2) and VI as potassium salts supported this assumption. The latter product was also obtained from the reaction of II and the potassium salt of ethyl cyanoacetate in good yield. The data of VI are reported as the following: VI, mp 271-273° (dec.). UV $^{\text{EtOH}}_{\text{m}\mu}$ (log ϵ) 222 (4.22), 355 (4.76). IR $^{\text{Nujol}}_{\text{cm}^{-1}}$ 2220 (C≡N), 1680 (C=O), 1535 (C=C). NMR (d$_6$-acetone) τ 8.82^{t} (6H, J = 7 cps, 2 X -C$\underline{H}_3$), 5.92^{q} (4H, J = 7 cps, 2 X -C$\underline{H}_2$-), 1.82^{s} (1H, >C=C$\underline{H}$-$\bar{C}$<).

Successful isolation of an imino ether (VII) as a tetrafluoroborate (VIII) (3) from a mixture of DMF and ethyl chloroformate (4, 5) pointed out that the reaction should be rationalized as a Vilsmeier-Haack reaction (6, 7). A possible mechanism of the reaction is proposed as shown in Chart 2. The electrophilic

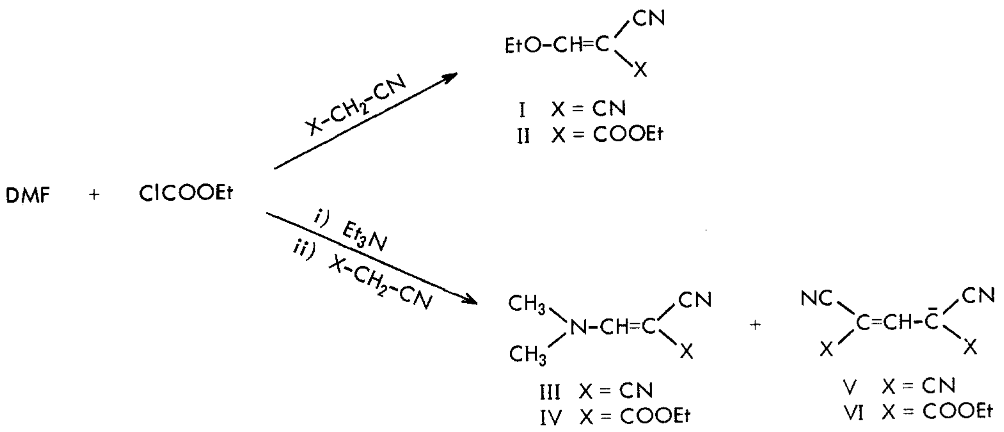

Chart 1

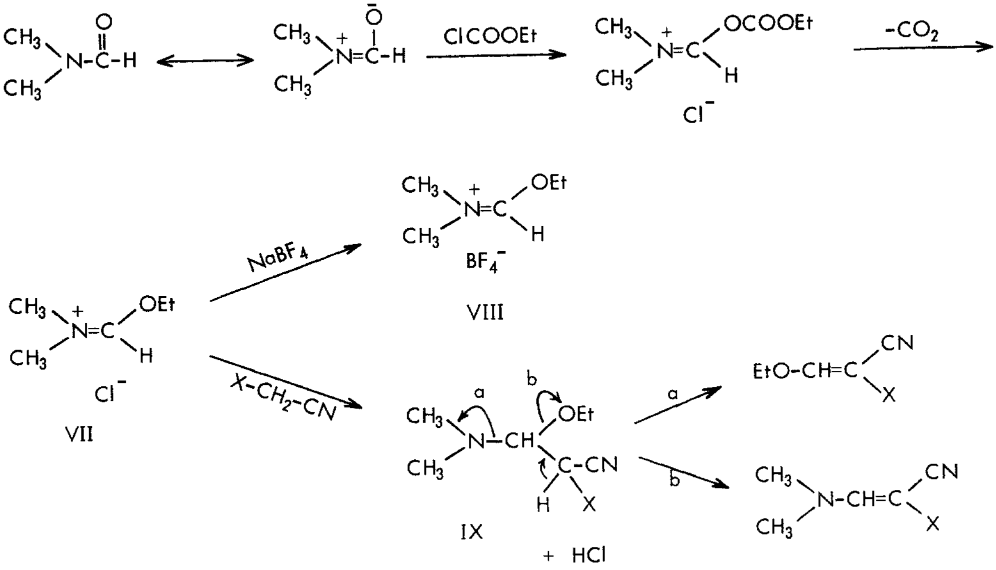

Chart 2

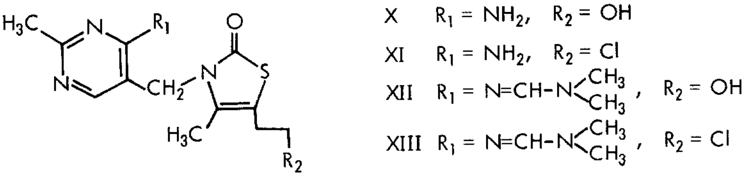

Chart 3

attack of VII to a malonic acid derivative forms an intermediate (IX). The elimination of dimethylamine converts IX into an ethoxymethylene compound. On the other hand, that of ethanol from IX gives an N,N-dimethylaminomethylene compound. The preferable deamination under acidic conditions must be caused by the quaternization of the basic nitrogen of IX. The fact that the reaction of malononitrile with VIII yielded I also supported this mechanism (8). The difference of the reactivity between malononitrile (pKa 11) and ethyl cyanoacetate (pKa 9) under these conditions must be attributable to that of their nucleophilicities.

Another reaction using the mixture of DMF and ethyl chloroformate was carried out. When X, having both amino and hydroxyl groups, was treated with the mixture, the formation of XI, XII and XIII were observed along with the evolution of carbon dioxide (see Chart 3). The structures of these products were determined by the spectral data and elemental analysis. The data are given below: XI, mp 166-168° (dec.). $\mathrm{UV}_{\mathrm{m\mu}}^{\mathrm{EtOH}}$ (log ϵ) 236 (4.17), 276 (sh). XII, mp 215-220° (dec.). $\mathrm{UV}_{\mathrm{m\mu}}^{\mathrm{EtOH}}$ (log ϵ) 222 (4.09), 265 (4.17), 314 (4.38). NMR (d_6-DMSO) τ 6.82^s (3H), 6.91^s (3H), $(-N{<}^{C\underline{H}_3}_{C\underline{H}_3})$, 1.33^s (1H, $-N{=}C\underline{H}{-}N{<}$). XIII, mp 169-170° (dec.). $\mathrm{UV}_{\mathrm{m\mu}}^{\mathrm{EtOH}}$ (log ϵ) 223 (4.05), 265 (4.15), 314 (4.35). NMR ($CDCl_3$) τ 6.87^s (3H), 6.83^s (3H) $(-N{<}^{C\underline{H}_3}_{C\underline{H}_3})$, 1.39^s (1H, $-N{=}C\underline{H}{-}N{<}$). Compounds XI and XIII were also obtainable from typical Vilsmeier-Haack reaction using a mixture of DMF and phosphorus oxychloride.

As mentioned above, the mixture of DMF and ethyl chloroformate is conveniently applicable for a modified Vilsmeier-Haack reaction, which is especially useful for the synthesis of I, an important intermediate for thiamine production (9), and that of amide acetals (3).

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