Catalytic Effect of Ammonium Chloride on the Synthesis of Imidate Esters

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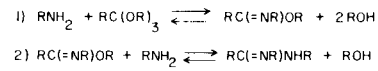
Preparation of imidate esters by reaction arylamines containing electron withdrawing groups with ethyl 3-ethoxy-3-imino-propionate in methanol is described. Evidence is presented for an orthoester intermediate. The unusual catalytic effect of ammonium chloride is discussed.

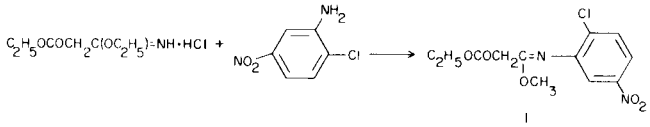
J. Heterocyclic Chem., **16**, 1287 (1979).

Imidates are important intermediates in the synthesis of heterocycles especially imidazoles (1), oxazoles (1), thiazoles (1) and pyrazolones (2). Imidates are commonly prepared by reaction of amines with orthoesters (1,3). The reaction is complicated by the formation of amidines arising from the reaction of the imidate with a second mole of amine. Use of acid catalysts such as *p*-toluenesulfonic acid,



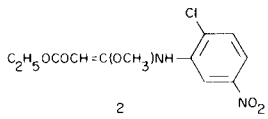
acetic acid and hydrogen chloride generally favor imidate formation.

In the course of our studies on the synthesis of pyrazolones it was found that reaction of 2-chloro-5-nitroaniline with excess (15 to 66 mole percent) ethyl 3-ethoxy-3-iminopropionate hydrochloride in anhydrous methanol produced the imidate ester **1**. The imidate ester was

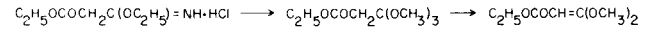


formed without the use of an acid catalyst.

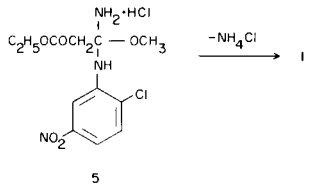
The isomeric structure **2** was ruled out because of the absence of Olefin absorption in the nmr and the absence of N-H absorption in the ir spectrum (4).



The reaction is driven to the right by removal of methanol. The yield of imidate ester **1** is raised to 65-70% by using toluene as a high boiling solvent allowing the reaction temperature to reach 110° during the distillation. The most likely path involves the intermediacy of an orthoester **3** or the corresponding ketene acetal **4**.



No reaction occurred to produce the imidate ester when *tert*-butyl alcohol, which is too hindered to form an orthoester, is subtituted for methanol. An intermediate such as **5** formed by addition of the anilino derivative followed by elimination of ammonium chloride would not require use of alcohol.



All attempts to carry out the reaction using acetonitrile, nitrobenzene or *N*-methylpyrrolidone in place of methanol failed to produce the imidate **1**. The orthoester **3** (5) and the ketene acetal **4** (6) failed to react with nitrochloroaniline in the absence of ammonium chloride. This unusual catalytic effect of ammonium chloride is quite unexpected. Use of a strong acid (gaseous hydrogen chloride) protonates the aniline causing it to precipitate, rendering it inert to reaction.

All attempts to catalyze the reaction with toluenesulfonic or acetic acid failed. The ammonium chloride probably reacts as a proton source facilitating the elimination of methanol from the orthoester.

EXPERIMENTAL

Nuclear magnetic resonance spectra (nmr) were recorded on a Varian A-60 spectrometer and tetramethylsilane was used as an internal standard. Infrared spectra were recorded using a Bechman 1R-10 spectrometer. Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Reagents.

Ethyl 3-ethoxy-3-iminopropionate hydrochloride was made by the method of S. A. Glickman and A. C. Cope (6). The 4-nitroaniline was purchased from Eastman Kokak and the 2-chloro-5-nitroaniline from Gallard Schlesinger.

Ethyl 3-methoxy-3-(2-chloro-5-nitrophenylimino)propionate (**1**).

Ethyl 3-ethoxy-3-iminopropionate hydrochloride (156.0 g., 0.8 mole), 2-chloro-5-nitroaniline (103.0 g., 0.6 mole) and anhydrous methanol (500 ml.) were allowed to react for 16 hours at room temperature. The reaction mixture was refluxed 1 hour and methanol distilled off to a reaction temperature of 100°. After cooling to 25° the ammonium chloride was filtered and the salt washed with ice cold methanol (200 ml.). The filtrate cooled to 5-10° to precipitate the imidate. The filtered product was recrystallized from isopropanol-heptane (50/50 by volume), 84.6 g. (47%), m.p. 60-62°; ir (chloroform): no NH absorption, 1735 cm^{-1} (ester), 1515 and 1340 cm^{-1} (NO_2), 1670 cm^{-1} (C = N); nmr (deuteriochloroform): δ

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8.0-7.4 (m, 3, aromatic H), 4.1 (q, 2, J = 6Hz, OCH_2-CH_3), 3.9 (s, 3, OCH_3), 3.2 (s, 2, C-CH_2C=O), 1.2 (t, 3, J = 6 Hz, CH_2-CH_3).

Anal. Calcd. $C_{12}H_{13}ClN_2O_5$: C, 47.92; H, 4.35, Cl, 11.79; N, 9.32. Found: C, 47.81; H, 4.32; Cl, 11.95; N, 9.29.

In a similar experiment where 100 ml. of toluene was added with the methanol, a 68% yield of 3-methxoy-3-(2-chloro-5-nitrophenylamino)propionate (**1**) was obtained.

Ethyl 3-Methoxy-3-(4-nitrophenylimino)propionate.

Ethyl 3-ethoxy-3-iminopropionate hydrochloride (156.0 g., 0.8 mole), 4-nitroaniline (82.8 g., 0.6 mole) and anhydrous methanol (500 ml.) were allowed to react at room temperature for 16 hours. The reaction mixture was refluxed 1 hour and the methanol distilled off to a miximum reaction temperature of 100°. After cooling to room temperature, the ammonium chloride was filtered and washed with ice cold methanol (200 ml.). The filtrate cooled and the imidate filtered. Recrystallization from isopropanol-water yielded 109.0 g. (69% of Theory), m.p. 104-8°; ir (chloroform): no NH absorption, 1735 cm^{-1} (ester), 1670 cm^{-1} (C=N); nmr (deuterochloroform): δ 8.4-6.9 (m, 4, aromatic H), 4.2 (q, 2, J = 6 Hz, OCH_2CH_3), 3.9 (s, 3, OCH_3), 3.2 (s, 2, C-CH_2C=O), 1.3 (t, 3, J = 6Hz CH_2-CH_3).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13;H, 5.30; N, 10.52. Found: C, 54.26; H, 5.26; N, 10.49.

REFERENCES AND NOTES

(1) R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961) and references cites therein.

(2) D. J. Tracy, *J. Heterocyclic Chem.*, accepted for publication; see also D. J. Tracy and W. Hoffstadt U. S. Patent 4,113,954; 4,129,739 and 4,139,571.

(3) R. H. DeWolfe, *Synthesis*, 153 (1974).

(4) Attempts to slow the nitrogen inversion in compound **1** by cooling the nmr spectrum to -60° failed.

(5) E. Meier and K. Kuffner, U. S. Patent 3,798,234 (1974).

(6) S. A. Glickamn and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).