An Unexpected Product From the Reaction of Imidazole with Ethyl 3-Ethoxy-2-nitropropenoate

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Treatment of ethyl 3-ethoxy-2-nitropropenoate with imidazole afforded ethyl 1-imidazoyl(hydroximino)-acetate rather than the expected addition-elimination product.

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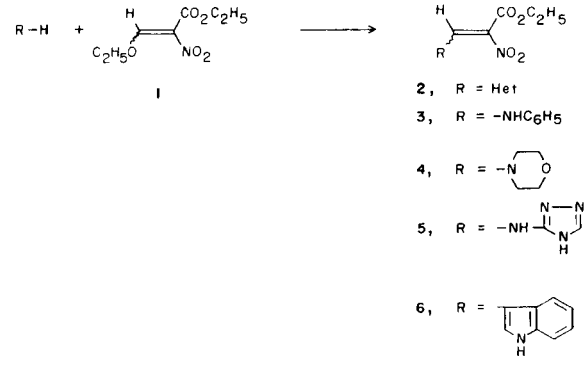
As part of a synthetic progran to prepare novel nitroheterocycles [1,3] for study as hypoxic cell radiosensitizers [4], we have attempted to prepare vinylogous nitro heterocycles, as characterized by **2** (Scheme I). We anticipated a

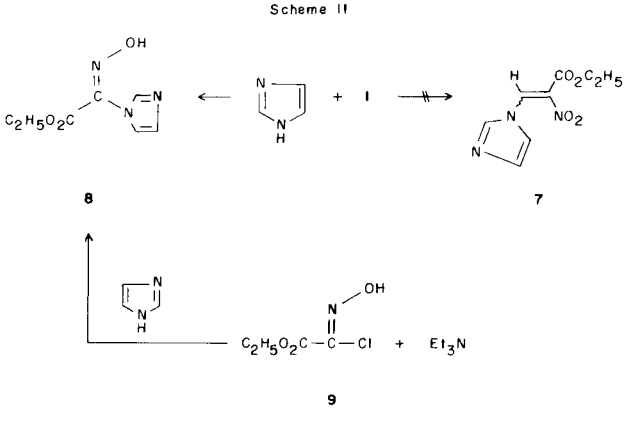
Scheme I

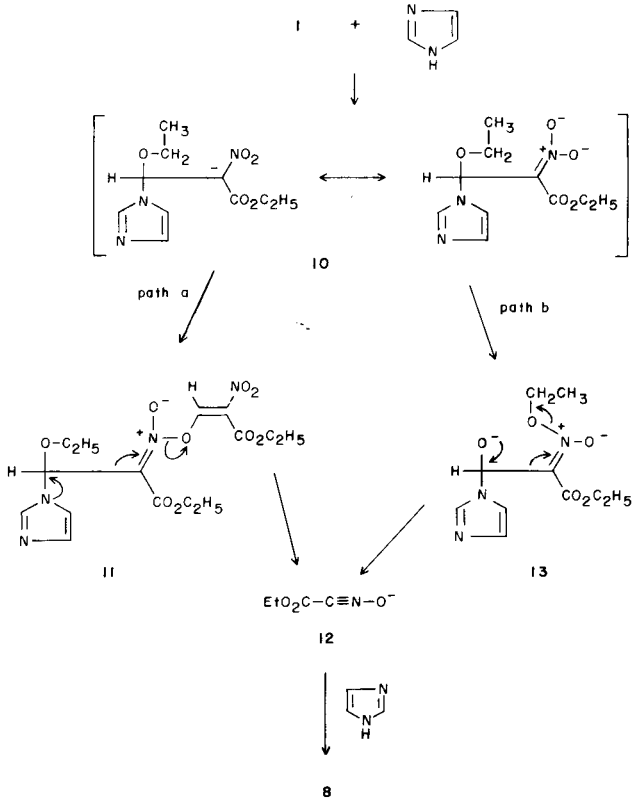


direct synthesis of compounds such as **2** from treatment of a Michael-retro-Michael olefin, such as ethyl 3-ethoxy-2-nitropropenoate (**1**) with a nucleophilic heterocycle. The literature indicates that **1** readily undergoes addition-elimination reactions [5-7] with amines such as aniline, morpholine, 2-amino-1,3,4-triazene, and indole [8,9] to afford **3**, **4**, **5**, and **6**, respectively.

Based on the above and the observation that imidazole is efficiently cyanoethylated on nitrogen with acrylonitrile [10], we expected that reaction of **1** with imidazole would provide **7** (Scheme II). Treatment of **1** in acetonitrile solution at room temperature with a slight excess of imidazole gave a yellowish reaction mixture, in which **1** was consumed in three hours at room temperature. The major product (57%) of this reaction was a white solid which surprisingly lacked in the nmr, the olefinic proton characteristic of **7** [11]. Single crystal X-ray analysis [12] of this material showed it to be oxime **8**, in which the hydroxy group was *syn* to the imidazole. This assignment was confirmed by nmr, elemental and mass spectral analyses, and a sample of **8** was independently synthesized from the chloro oxime **9** [13,14] by treatment with triethylamine and imidazole [15,16].

Scheme II





There appears to be no clear precedent for the formation of oxime **8** from imidazole and **1**. A possible mechan-

ism for this transformation involves attack of imidazole on **1** to give anion **10**, which following *O*-alkylation (path a) by **1** to give **11**, decomposes to nitrile oxide **12**. Attack of imidazole on **12** then gives **8**. Alternatively, intramolecular alkylation of the nitro group (path b), followed by the indicated decomposition would also afford **12**. However such a process is highly unlikely, being disfavored on stereoelectronic grounds [17].

We are continuing to study the mechanism and synthetic utility of reactions between heterocycles and Michael-retro-Michael olefins.

EXPERIMENTAL

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. The nmr spectra were recorded on a Varian T-60 spectrometer with TMS as an internal standard. Mass spectra were obtained by Dr. H. Ramjit on a LKB-9000S mass spectrometer at 70 eV. Microanalyses were performed by the Merck analytical department.

Ethyl 3-Ethoxy-2-nitropropenoate (**1**).

This compound was prepared by the method of Prystas and Gut [18].

Ethyl 1-Imidazoyl(hydroximino)acetate (**8**).

To 2.0 g (0.01 mole) **1** dissolved in 35 ml of acetonitrile at room temperature was added 0.74 g (0.011 mole) of imidazole with stirring. The reaction mixture was stirred at room temperature for 3 hours at which time the analysis showed that no **1** remained. The solvent was removed on the rotary evaporator and the residue subjected to flash chromatography in silica gel (230-400 mesh) eluted with 10% methanol/chloroform to give **8** as a white solid (R_f 0.5), 1.04 g (57%); mp 156-157° dec; ms: m/e 183 (100), 151, 143, 126, 113, 110, 100, 94, 81; nmr (DMSO-d_6): δ 1.28 (3 H, t), 4.30 (2 H, q), 6.98 (1 H, d), 7.35 (1 H, dd), 7.92 (1 H, d).

Anal. Calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 46.09; H, 5.06; N, 22.98.

Preparation of **8** from Ethyl Chloro(hydroxyimino)acetate (**9**).

To 1.5 g (0.01 mole) **9** [13,14] in 35 ml of acetonitrile at room temperature was added a solution of 0.7 g (0.01 mole) of imidazole and 2.0 g (0.02 mole) of triethylamine in 10 ml of acetonitrile with stirring. After 3 hours at room temperature the solvent was removed on the rotary evaporator and the residue was purified by flash chromatography on silica gel (230-400 mesh) eluted with 10% methanol/chloroform to give 1.55 g (85%) of **8**.

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