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IMIDATES IN ORGANIC SYNTHESIS: METHYL *N*-CYANOMETHYLMETHANIMIDATE

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Synthesis, preliminary properties and reactions of the reagent Methyl N-cyanomethyl-methanimidate are reported.

Imidate esters are versatile reagents for organic synthesis,[1-4] and have recently been employed in the synthesis of heptaazaphenalene[1] and other cyclazines.[5] In this context, esters of *N*-cyanomethylmethanimidic acid (1) should serve as useful reagents for incorporating the synthetic fragment C-N-C-C-N onto nucleophiles. On the other hand, while the ethyl ester

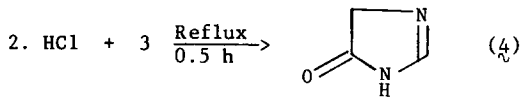
$$N\equiv C\text{-}CH_2\text{-}N{=}CH\text{-}OR \quad (1)$$

(1a, R=Et) can be prepared[6] by the reaction of aminoacetonitrile bisulfate with ethyl formimidate hydrochloride, the yield is poor[6] and variable[7] presumably due to the partial decomposition of the moisture-sensitive imidate hydrochloride in the aqueous reaction medium. In addition, the products of the reaction of 1a and primary amines are produced only in poor yields.[6] I report here a simple, efficient procedure for preparing the corresponding methyl ester (1b, R=Me)[8] as well as a method which routinely gives high yields of the products generated from the addition of nucleophiles to 1b.

The reagent 1b can be efficiently prepared by the slow (30 min) addition of aminoacetonitrile (2, free base) to an excess of refluxing trimethyl orthoformate (3, R=Me) over anhydrous sodium sulfate, in the presence of a catalytic amount of sulfuric acid, while simultaneously removing the methanol which formed. After the solvent was removed on a rotary evaporator, the residual oil was distilled in a Kügelrohr apparatus [25-35°C (oven temp)/ 0.2-0.25 mm]. The product, methyl *N*-cyanomethylmethanimidate (1b) was obtained in 94-95% yield as a colorless oil; ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 3, CH_3), 4.35 (s, 2, CH_2), 7.9 (s, 1, CH); IR (neat) 3000 (=CH), 2300 (C≡N), 1680-1660 (C=N) cm^{-1}; mass spectrum (70 *eV*) *m/e* 98 (M^+), 67 (M^+-OCH_3), 58 (M^+-CH_2CN); *Anal.*[9] C, H, N.

$$\underset{2}{N\equiv C\text{-}CH_2\text{-}NH_2} + \underset{3}{H\text{-}C(OR)_3} \xrightarrow[\text{Anhy. } Na_2SO_4]{\text{conc. } H_2SO_4} \underset{}{1b}$$

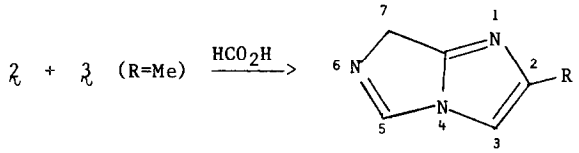
A presumably straightforward synthesis of 1a or 1b by the reaction of aminoacetonitrile hydrochloride with the ortho ester 3 (R=Me or Et) only led to an unexpected product, 4(5)-imidazolone (4), as evidenced by the elemental microanalyses,[9] spectral data[10] and the



(4)

molecular weight determination by vapor pressure osmometry (VPO).[11] A mechanism which involved the initial formation of the intermediate 1, followed by alcoholysis of the nitrile of 1 and ring-closure to form 5-alkoxy-4*H*-imidazole (or its 1*H* tautomer), and the subsequent nucleophilic displacement by the halide ion on the alkoxy function of the latter to form alkyl halide and 4 was supported by the reaction of 1 with methanolic hydrogen chloride, which gave 4. The imidazolone 4 has long been postulated to be the intermediate in the biological degradation of xanthine to formiminoglycine[12,13] but its synthesis in isolable quantities is not reported,[12] therefore, only the UV spectral data of 4 *in situ* are published.[12,13] Compound 4, which is obtained by the above procedure in ≥90% yield, is a colorless, high boiling (150-152°C/0.35 mm), dense liquid which, if protected from moisture and light, can be stored in a freezer for several months.

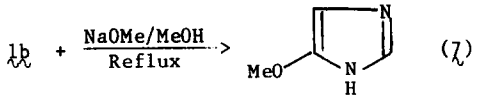
The reaction of 2 with an excess 3 (R=Me) in the presence of catalytic amounts of formic acid as in the reported preparation of methyl *N*-cyanomethanimidate (NC-N=CH-OMe)[3] gave a solid, mp 101-102°C, whose spectral[14] and analytical[9] data are in agreement with the



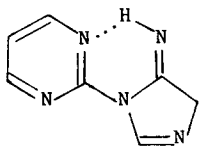
proposed structure 5 (methyl *N*-7*H*-imidazo[1,5-*a*]imidazol-2-ylmethanimidate). Compound 5 (yield, 24%) is apparently formed through the initial partial formation of the reagent 1b which further reacts with 2 to yield 6 which eventually transpires to 5.

The electrophilic reactivity of 1b was studied with H_2O/D_2O as a nucleophile. By monitoring the ^1H NMR spectrum with time of the mixture of 1b and D_2O at room temperature, and by separate external addition of the products of the reaction, it was proved that the methanol, and not the aminoacetonitrile, was the leaving group from the intermediate adduct of 1b with nucleophiles, as desired.

The reagent 1b reacted only slowly with NaOMe/MeOH at room temperature, but at reflux rapidly provided 4(5)-methyoxyimidazole (7) (mp 115-116°C),[15,16] thus pointing to the susceptibility of the nitrile function of 1b to strong base/nucleophile under strenuous reaction conditions.



The reactions of 1b with heterocyclic amines either in the absence or presence of Brönsted acids or bases led to the recovery of the starting materials or resulted in intractable products. However, the use of trimethylsilyl triflate[17] as a Lewis acid catalyst facilitated the reactions of 1b in acetonitrile with 2-aminopyrimidine and 2-aminothiazole to afford at room temperature in 82% and 91% yields, respectively 2-(5-imino-2-imidazolin-1-yl)pyrimidine (8) [mp 158°C (dec); ^{1}H NMR (DMSO-d_6) δ 4.42, 4.49 (2 pseudo s, 2, CH_2), 7.05 (dd, J= 4.8 & 4.7 Hz, 1, pyrimidine H-5), 8.55 (2 overlapping d, J = 4.8 & 4.7 Hz, 2, pyrimidine H-4 & H-6), 8.79 (s, 1, imidazoline H-2), 10.45 (br, 1, NH); mass spectrum (70 e*V*) *m/e* 161 (M^+), 134 (M^+-HCN), 121 (M^+-CH_2CN); *Anal.*[9] C, H, N], and 2-(5-imino-2-imidazolin-1-yl)thiazole (9) [mp 126°C (dec); ^{1}H NMR (DMSO-d_6) δ 4.33, 4.39 (2 pseudo s, 2, CH_2), 7.13 (d, J= 3.7 Hz, 1, thiazole H-4), 7.35 (d, J= 3.7 Hz, 1, thiazole H-5), 8.34 (br s, 2, imidazoline H-2 and NH); mass spectrum (70 e*V*) *m/e* 166 (M^+), 139 (M^+-HCN), 126 (M^+-CH_2CN); *Anal.*[9] C, H, N].



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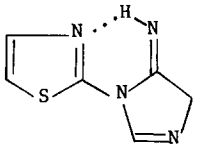

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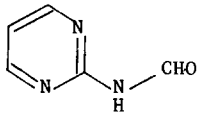

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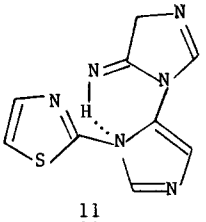

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Compound 8 underwent facile acid hydrolysis to yield N^2-formylaminopyrimidine (10, 94%) (mp 200-202°C).[18,19] The proposed reaction pathway for 10 involves the hydrolysis of the imine of 8 to the corresponding imidazolone, followed by ring-opening and a second hydrolysis to provide 10 and glycine.

The reaction of 2-aminothiazole with two equivalents of 1b yielded 2-[5-(5-imino-2-imidazolin-1-yl)imidazol-1-yl]thiazole (11, 52%) [mp 206°C (dec); ^{1}H NMR (DMSO-d_6) δ 5.27 (s, 2, CH_2), 6.93 (s, 1, imidazole H-4), 7.3 (d, J= 3.5 Hz, 1, thiazole H-4), 7.53 (d, J= 3.5 Hz, 1, thiazole H-5), 7.66 (s, 1, imidazoline H-2), 8.3 (s, 1, imidazole H-2), 11.7 (br s, 1, NH); mass spectrum (70 e*V*) *m/e* 232 (M^+). The IR spectra of all three compounds, 8, 9 & 11, exhibited a strong hydrogen-bonded NH stretching frequency in the region 3100-2700 cm^{-1}.

The study of the reactions of heterocyclic amines with several equivalents of the reagent 1b to form heterocyclic polymers in a single step is currently in progress.

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7. In my hands, the reproducibility of this reaction was inconsistent. When successful, my yields ranged 10-14%.
8. The preference for 1b over 1a lies in the convenience of preparation of the former: trimethyl orthoformate with its lower boiling point (than its ethyl analog) can be conveniently removed on a rotary evaporator after the reaction is complete.
9. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and were within ±0.3% of the calculated values.
10. Spectral Data for 4: ^{1}H NMR (DMSO-d_6) δ 4.14, 4.21 (CH_2), 8.15 (CH), 8.64 (NH); IR (neat) 3370 (NH), 1690 (C=O) cm^{-1}; mass spectrum (70 e*V*) *m/e* 84 (M^+); UV (H_2O) λ max 259 nm (Lit.[12] 259 nm).
11. The VPO experiment was carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee on a Model 302 instrument: MW = 84 (CH_3CN).
12. Freter, K.; Rabinowitz, J.C.; Witkop, B. *Ann. Chem.* 1957, *607*, 174.
13. Oien, H.G.; Wright, L.D. *J. Bacteriol.* 1971, *105*, 1229.
14. Spectral Data for 5: ^{1}H NMR (DMSO-d_6) δ 3.86 (OMe), 5.2 (CH_2), 6.78 (H-3), 7.6 (H-5), 8.37 (side-chain CH); IR (KBr) 2900 (CH), 1640 (C=C) cm^{-1}; mass spectrum (70 e*V*) *m/e* 164 (M^+), 133 (M^+-OMe).
15. An examination of the literature revealed that this simple imidazole derivative is still unknown.
16. Spectral Data for 7: ^{1}H NMR (DMSO-d_6) δ 3.65 (s, 3, OMe), 6.37 (d, *J* = 1.5 Hz, 1, H-4(5)), 7.23 (d, *J* = 1.5 Hz, 1, H-2); mass spectrum (70 e*V*) *m/e* 98 (M^+), 67, (M^+-OMe).
17. Stang, P.J.; White, M.R. *Aldrichimica Acta* 1983, *16*, 15.
18. The ^{1}H NMR (DMSO-d_6) data of this compound were in agreement to the reported values;[19] however, no melting point has been reported for this compound to enable mp comparison.
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