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Reaction of Dihydroazinylidene Cyanoacetic Esters with Nitric Acid: A New Method for the Synthesis of Dihydroazinylidene Nitroacetonitriles

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An approach to the synthesis of previously unknown dihydroazinylidene nitroacetonitriles (derivatives of pyridine, pyrimidine, pyrazine and pyridazine) has been developed involving nitration of the corresponding dihydroazinylidene cyanoacetic esters at the side chain α-C-atom and dealkoxycarbonylation of the resulting products.

Derivatives of α-nitronitriles are known to be biologically-active compounds, initiators of chain polymerization, inhibitors of the thermooxidation ageing of polymers, components of energy-intensive compositions and synthons of use in synthesis.[1] However, only a few azinylnitroacetonitriles are known,[2] and the method reported is not of general applicability.

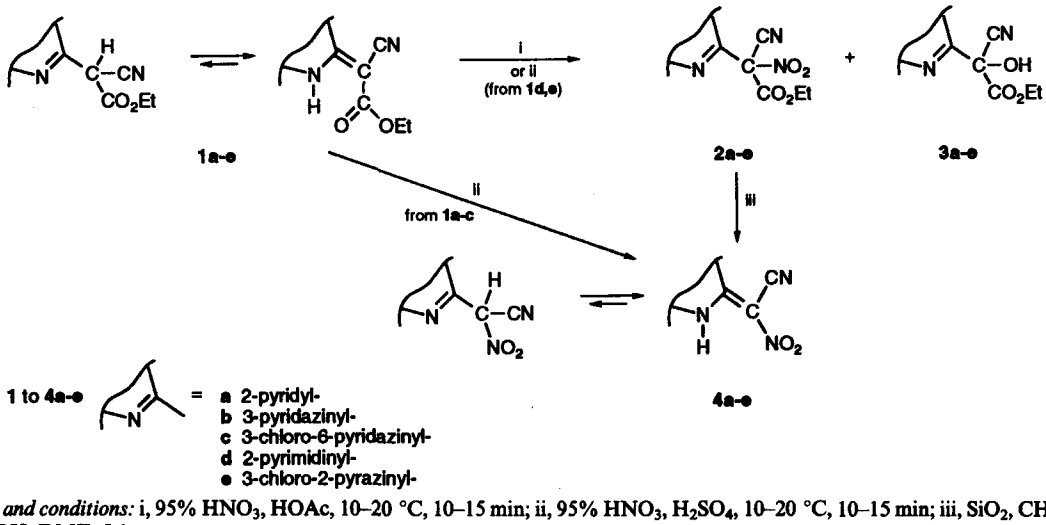
Recently we have found[3] that alkyl(aryl)-substituted 2- and 6-dihydropyrimidinylidene cyanoacetic esters in acetic acid are nitrated by fuming nitric acid at the side chain α-C-atom in high yields. We have also shown[3] that the resulting α-nitro-α-pyrimidinylcyanoacetic esters are transformed quantitatively into the corresponding dihydropyrimidinylidene nitroaceto-nitriles by keeping its chloroform solutions on silica gel.

In this communication we report the application of the same principle to the synthesis of pyridine **4a**, pyridazine **4b,c**, pyrimidine **4d** and pyrazine **4e** derivatives of nitroacetonitrile from the accessible and synthetically useful dihydroazinylidene cyanoacetic esters **1a–e**.[4]

Dihydroazinylidene derivatives of nitroacetonitrile **4a–c** are isolated immediately in 90–95% yields by the action of fuming nitric acid on cyanoacetic esters of pyridine **1a** and pyridazines **1b,c** in sulfuric acid at 10–20 °C. Using acetic acid as the medium for nitration of compounds **1a–c** at the same temperature results in the formation of nitrocyanoacetic esters **2a–c** (90–95% yields).

These compounds as well as small amounts of by-products (hydroxy derivatives **3a–c**) are identified in the product mixtures by IR and ^{1}H NMR spectroscopy. Separation of products **2a–c** and **3a–c** by column chromatography on silica gel in chloroform solution leads to the quantitative transformation of the former (in 0.5 h) into nitroacetonitriles **4a–c**.

Derivatives of pyrimidine **1d** and pyrazine **1e** are converted into nitrocyanoacetic esters **2d,e** and minor hydroxy derivatives **3d,e** in high yields, using nitric acid in both sulfuric and acetic acid. Preparative transformations of products **2d,e** into the corresponding nitroacetonitriles **4d,e** are achieved by keeping its chloroform solutions on silica gel (100–160 μ) at 20 °C. Apparently silica gel acts as an acid catalyst in the hydrolysis



Scheme 1 *Reagents and conditions:* i, 95% HNO_3, HOAc, 10–20 °C, 10–15 min; ii, 95% HNO_3, H_2SO_4, 10–20 °C, 10–15 min; iii, SiO_2, $CHCl_3$, 20 °C, 0.5–720 h, then EtOH–DMF, 5:1.

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of the ethoxycarbonyl (see *e.g.*, ref. 5) and the resulting azinylnitrocyanoacetic acids from compounds **2a–e**, since such aliphatic derivatives [6] are easily decarboxylated.

It should be noted that complete transformation of pyrimidinyl nitrocyanoacetic ester **2d** on silica gel into the corresponding nitroacetonitrile takes place in 240 h but that of pyrazine derivative **2e** in 720 h. In this way the readiness of dealkoxycarbonylation of azinylnitrocyanoacetic esters falls in the order **2a–c**, **2d**, **2e**; this is possibly connected with a decrease in basicity (see, *e.g.*, change in basicity of the methoxy derivatives of the corresponding heterocycles.[7]

UV and IR spectroscopy† indicate that the azinylnitroacetonitriles **4a–e**, like the cyanoacetic esters **1a–e**, exist predominantly in the ylidene form when solid and in ethanol solution. The IR spectra of compounds **4a–e** when recorded in KBr pellets show a conjugated nitrile at 2220–2230 cm^{-1}. All compounds show absorbtion maxima in the region > 350 mμ, indicating that extended conjugation is likely to the ylidene tautomers of substituted methylazines.[8]

† All new compounds isolated **2d,e**, **3a–e** to **4a–e** gave satisfactory elemental analyses and were characterized by IR, UV and ^{1}H NMR spectroscopy. Selected data for compounds **4a–e**: **4a**: m.p. 213–215 °C (decomp.), UV (EtOH), λ_{max}/nm (lg ε) 257(3.57), 352 (4.00), 385 (3.76); IR ν_{max}/cm^{-1} 2220 (C≡N). ^{1}H NMR ([$^2H_6$]DMSO) δ 7.39 (dd, 1H, H–5), 7.42 (dd,1H,H–3), 8.21 (dd,1H,H–4), 8.38 (dd,1H,H–6), 14.51 (s, 1H,NH); J_{34} = 7.5, J_{45} = J_{56} = 6, J_{35} = J_{46} = 1.5 Hz. **4b**: m.p. 182–184 °C (decomp.), UV (EtOH), λ_{max}/nm (lg ε) 255(3.94), 328(4.03), 360(4.15); IR ν_{max}/cm^{-1} 2220 (C≡N). ^{1}H NMR ([$^2H_6$]DMSO) δ 7.78 (dd, 1H, H–5), 8.22 (dd,1H,H–4), 8.81 (dd,1H,H–3), J_{34} = J_{45} = 8, J_{35} = 1Hz. **4c**: m.p. 157–160 °C (decomp.), UV (EtOH), λ_{max}/nm (lg ε) 265(3.90), 358(4.29), IR ν_{max}/cm^{-1} 2230 (C≡N). 1H NMR ([$^2H_6$]DMSO) δ 7.93 (d, 2H, H–4,5), J_{45} = 2Hz. **4d**: m.p. 184–186 °C (decomp.), UV (EtOH), λ_{max}/nm (lg ε) 355(4.07); IR ν_{max}/cm^{-1} 2230 (C≡N). ^{1}H NMR ([$^2H_6$]DMSO) δ 7.36 (t,1H,H–5), 8.85 (d,2H,H–4,6), J_{45} = J_{56} = 5 Hz. **4e**: m.p. 170–172 °C (decomp.), UV (EtOH), λ_{max}/nm (lg ε) 270(3.85), 362(4.07); IR ν_{max}/cm^{-1} 2220 (C≡N). ^{1}H NMR ([$^2H_6$]DMSO) δ 8.27 (d,1H,H–5), 8.53 (d, 1H,H–6); J_{56} = 5,5 Hz.

^{1}H NMR spectroscopy indicates that dihydroazinylidene nitroacetonitriles **4b–e** are ionised in more basic solvent ([$^2H_6$]DMSO), *e.g.* dihydropyrimidinylidene cyanoacetic esters[8] whereas pyridine **4a** remains in a non-ionised ylidene form in this solvent.

We hope that the approach described may eventually lead to the development of a general method for the synthesis of heteroarylnitroacetonitriles.

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