Reaction of 1-Diethylaminopropyne with Difunctionalized 4-Nitroisoxazoles: a Single Step Access to the Novel Isoxazolo[4,5-c]isoxazole System

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Abstract: The nitroderivatives **1a-c** were found to react with the title ynamine **2** under mild conditions to give the corresponding fused isoxazoles **3a-c**, as proved by an X-ray diffraction of **3a**; a plausible mechanistic pattern for these conversions is presented.

Recent results from our laboratory demonstrated that the suitably activated C(4)-C(5) double bond of the nitroisoxazoles **1b** and **1c** can be advantageously employed both as a dipolarophile^{1a,b} and a dienophile^{1c} in [2+4] cycloaddition processes for the synthesis of different polycyclic ring systems; on the other hand, some findings on the reactivity of **1a** and **1b** with 4-(1-cyclopenten-1-yl)morpholine clearly indicated that these products can behave as 1-azadiene components in [4+2] cycloadditions leading to polyfunctionalized pyridine derivatives². In this context and with the aim to expand the scope of these new reactions, we decided to explore the behaviour of the above compounds towards an ynamine counterpart.



Scheme 1

Unexpectedly, when the nitroester 1a was allowed to react with 1-diethylaminopropyne 2^3 (molar ratio 1:1, 48 h) at room temperature in dry acetonitrile and the reaction mixture was subjected to flash-column chromatography [silica gel 60 (Merck, 230-400 mesh); 40-70°C petroleum ether/ethyl acetate (3:2 v/v) as eluent], we isolated a previously unknown binuclear isoxazole system, namely methyl (*SR*,*SR*) -6,6a-dihydro-6-(*N*,*N*-diethylcarbamoyl)-6-methyl-3-phenylisoxazolo[4,5-c]isoxazole-6a-carboxylate (3a)⁴, as a pure product (22% yield, based on the recovered starting material)⁵.



Figure 1. ORTEP drawing of 3a derived from the X-ray coordinates.

Although the diagnostic IR stretching absorption of the CONEt2 group at 1636 cm⁻¹ and the ¹³C NMR resonances of the C-6 and C-6a quaternary carbons between δ 102.05 and 103.93 strongly supported the proposed structure⁶, the framework of **3a** as well as the relative stereochemistry of the substituents, showed in Figure 1, were unambiguously determined by a single crystal X-ray analysis⁷.



Treatment of 1b and 1c with the above reagent under the same conditions afforded compounds 3h and 3c (27% and 21% yields, respectively, based on the recovered nitroderivatives)⁵, whose structures were established by comparison of their spectral data with those of $3a^6$.

In the light of the peculiar reactivity of 4-nitroisoxazoles with nucleophiles¹⁰, the not straightforward conversion of **1a-c** into **3a-c** can be rationalized by a sequence involving in the primary step a Michael addition of **2** to the remarkably electrophilic C-5 carbon of the isoxazole ring, followed by a nucleophilic attack of the oxygen of the nitronate moiety at the α position of the ketene iminium derivatives **4a-c**; the resulting [4+2] oxazine cycloadducts **5a-c** can then undergo a retro-diene cleavage leading to the unsaturated nitrile oxides **6a-c** that, in turn, easily evolve into the final products by intramolecular 1,3-dipolar cycloadditions.

Although compounds 5a-c were so far elusive in our hands, they closely resemble the cyclic nitronic esters invoked by Reinhoudt as key intermediates for the formation of stable 2,3-dihydroazete 1-oxides from nitroalkenes and ynamines¹¹; these products now prefer to give rise to the open-chain derivatives 6a-c instead of the corresponding four-membered bicyclic nitrones, due to the remarkable additional strain introduced in the latters by the fused isoxazole ring. Finally, an alternative collapse of 5a-c into 3a-c via condensed nitrosocyclopropanecarboxamides does not appear more conceivable since it conflicts with the relative stability of other 1,5-difunctionalized 2-oxa-3-azabicyclo[3.1.0]hex-3-ene derivatives^{1a,b}.

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References and Notes

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- Satisfactory combustion or high resolution mass spectral analytical data were obtained for the new compounds.
- 5. A total conversion of the nitroisoxazoles 1a-c could be easily achieved with 2 or 3 equivalents of 2 but, unfortunately, no significant improvement was observed for the yields of 3a-c, owing to the concomitant increase of untractable polyaddition products already present under the original conditions (GC/MS and NMR spectra).
- Selected physical and spectral data for 3a: m.p. 138-139 °C; IR (KBr) ν 1763 (<u>CO</u>₂Me), 1636 cm⁻¹
 (<u>CO</u>NEt₂); ¹H NMR (200 MHz, CDCl₃) δ 1.15 (t, J = 7.0 Hz, 3H, C<u>H</u>₃CH₂N), 1.33 (t, J = 7.0 Hz, 3H, C<u>H</u>₃CH₂N), 1.71 (s, 3H, 6-CH₃), 3.20-3.84 (m, 4H, 2 CH₃C<u>H</u>₂N), 3.78 (s, 3H, CH₃O); ¹³C NMR (50 MHz, CDCl₃) δ 12.31 (q, <u>C</u>H₃CH₂N), 14.40 (q, <u>C</u>H₃CH₂N), 19.475 (q, 6-CH₃), 41.84 (t, CH₃<u>C</u>H₂N), 42.69 (t, CH₃<u>C</u>H₂N), 53.22 (q, CH₃O), 102.05 (s, C-6/C-6a), 103.93 (s, C-6a/C-6), 149.33 (s, C-3), 166.20 (s, <u>C</u>O₂CH₃), 167.08 (s, <u>C</u>ONEt₂), 168.62 (s, C-3a). 3b: colourless sticky oil;

IR (CHCl₃) ν 1765, 1731 (<u>CO</u>₂Et), 1633 cm⁻¹ (<u>CO</u>NEt₂); ¹H NMR (200 MHz, CDCl₃) δ 1.14 (t, J = 7.0 Hz, 3H, C<u>H</u>₃CH₂N), 1.70 (s, 3H, 6-CH₃), 3.10-3.85 (m, 4H, 2 CH₃CH₂O), 1.33 (t, J = 7.0 Hz, 3H, CH₃CH₂N), 1.70 (s, 3H, 6-CH₃), 3.10-3.85 (m, 4H, 2 CH₃C<u>H</u>₂N), 4.23 (q, J = 7.2 Hz, 2H, CH₃C<u>H</u>₂O); ¹³C NMR (50 MHz, CDCl₃) δ 12.33 (q, CH₃CH₂N), 13.80 (q, CH₃CH₂O), 14.61 (q, CH₃CH₂N), 19.70 (q, 6-CH₃), 41.66 (t, CH₃CH₂N), 42.56 (t, CH₃CH₂N), 62.70 (t, CH₃CH₂O), 101.97 (s, C-6/C-6a), 103.72 (s, C-6a/C-6), 149.01 (s, C-3), 165.17 (s, CO₂Et), 166.79 (s, CONEt₂), 168.43 (s, C-3a). 3c: m.p. 128 °C ; IR (KBr) ν 1680 (<u>CO</u>Ph), 1640 cm⁻¹ (<u>CO</u>NEt₂); ¹H NMR (200 MHz, CDCl₃) δ 1.01 (t, J = 7.0 Hz, 3H, CH₃CH₂N), 1.365 (t, J = 7.0 Hz, 3H, CH₃CH₂N), 1.845 (s, 3H, 6-CH₃), 3.10-3.85 (m, 4H, 2 CH₃CH₂N); ¹³C NMR (50 MHz, CDCl₃) δ 12.22 (q, CH₃CH₂N), 14.58 (q, CH₃CH₂N), 19.96 (q, 6-CH₃), 41.73 (t, CH₃CH₂N), 42.77 (t, CH₃CH₂N), 105.37 (s, C-6/C-6a), 107.77 (s, C-6a/C-6), 150.135 (s, C-3), 167.06 (s, CONEt₂), 169.11 (s, C-3a), 198.08 (s, COPh).

- 7. Crystallographic supplementary material has been deposited at the Cambridge Data Centre. Crystal data for 3a: C₁₈H₂₁N₃O₅, white needles from ether, M = 359.4, orthorhombic, space group $P2_{12121}$, a = 5.845(2), b = 16.557(5), c = 18.783(4) Å, V = 1817.7(9) Å³, Z = 4, F(000) = 760, $\mu = 0.91$ cm⁻¹, $D_c = 1.31$ g cm⁻³, graphite monochromated (Mo-K α) radiation ($\lambda = 0.7107$ Å). 1879 Reflections were collected on an Enraf-Nonius CAD4 automatic diffractometer in the range $5 \le 2\theta \le 50^{\circ}$. 1350 Unique reflections with $I \ge 3\sigma(I)$ were used in the structure determination and refinement. The structure was solved by using the direct methods of SIR88 program⁸ and successive Fourier syntheses; the refinement was carried out by using the full-matrix least squares SHELX76 program⁹ to R = 0.052 and $R_w = 0.044$, were $w = 1/\sigma^2(F_0)$. Anisotropic thermal parameters were used for all the non-hydrogen atoms.
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