Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5783-5786, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01225-7

Photocycloaddition on 2-Methyloxazolo[5,4-b]pyridine: a route to the oxazolo[5,4-b]azocine system.

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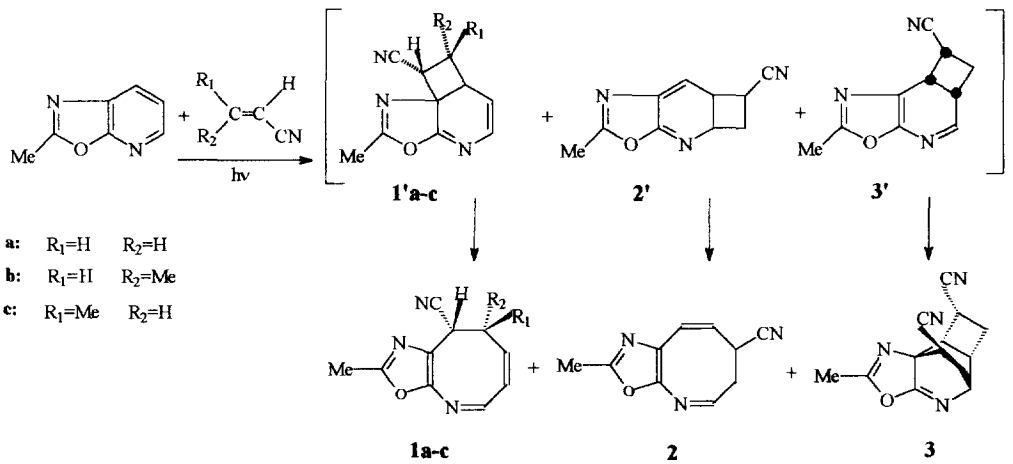
Abstract : Regio- and stereospecific cycloaddition of acrylonitrile and 2-butenenitrile on 2-Methyloxazolo[5,4-b]pyridine, followed by ring-opening, lead to 2-Methyloxazolo[5,4-b] dihydroazocines as main products. Copyright © 1996 Elsevier Science Ltd

Following our researches on the synthetic usefulness of photochemically produced intermediates, we recently focused our attention on the photorearrangment of isoxazolopyridines to oxazolopyridines.[1,2] During an attempt to trap the intermediates in the photochemical transformation from 3-Methylisoxazolo[5,4-b] pyridines to 2-Methyloxazolo[5,4-b]pyridines we isolated some dihydrooxazolo[5,4-b]azocine derivatives. Because these products were recognised as being derived from the 2-Methyloxazolo[5,4-b]pyridine photochemically produced, we were prompted to investigate the photochemical behaviour of the 2-Methyloxazolo[5,4-b]pyridine[3] and of the corresponding [4,5-b], [4,5-c], [5,4-c] systems with the aim to prepare different oxazoloazocines, a new heterocyclic system.

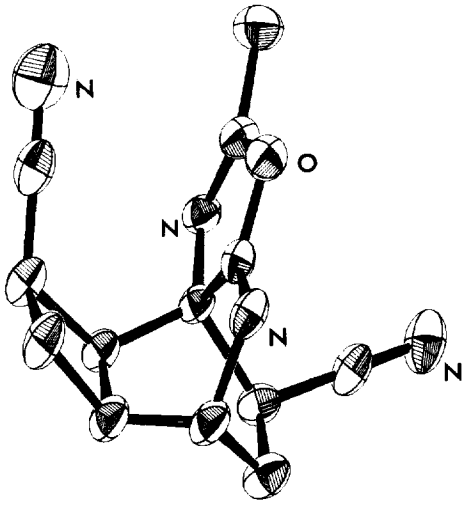
All the compounds examined were photochemically stable under irradiation at 254 nm in CH_3CN solution, but in presence of an excess (10:1) of acrylonitrile, only the 2-Methyloxazolo[5,4-b]pyridine reacted, giving the products **1a**, **2** and **3** in the ratio **1a:2:3**=45:42:13.



a: R_1=H R_2=H
b: R_1=H R_2=Me
c: R_1=Me R_2=H

The dihydrooxazoloazocines **1a** and **2** were identified by ^{1}H and ^{13}C - NMR spectroscopy,[4] whereas the complete stereochemical assignment of compound **3** was performed *via* X-Ray crystallographic analysis (see note 5 and Figure). No other significant products were detected in the ^{1}H-NMR spectrum of the crude reaction mixture obtained after the solvent evaporation.

These products are explainable supposing an initial 2+2 photocycloaddition of acrylonitrile on 3a-4, 5-6, or 4-5 bonds respectively, yielding the corresponding cyclobutane intermediates. Thermal or photochemical ring opening on the intermediates **1'a** and **2'** lead to azocines **1a** and **2**, whereas Diels-Alder addition of acrylonitrile on the azadiene system in the intermediate **3'** gave the adduct **3.** It is to be noted that *endo*-addition is involved in both the photoaddition and in the Diels-Alder reaction



X-Ray Structure of **3**

The structures of the compounds obtained show the reaction as highly regiospecific, but not site specific. In order to acquire information on the stereospecificity, we irradiated the 2-Methyloxazolo[5,4-b]pyridine in presence of *cis-* or *trans*-2-butenenitrile obtaining the azocine **1b** or **1c** respectively as the only product: the site specificity in this case was strongly increased and the reaction appears stereospecific: in fact we observed only the azocine with retained stereochemistry.

These results show this reaction of valuable interest as clean and easy entry in the functionalized oxazolo[5,4-b] azocine system and taking into account the easy opening of the oxazole moiety, also as a route to azocine derivatives itself. Photochemical cyclo-addition on 2-piridones, followed by ring expansion leading to tetrahydroazocine-2-one derivatives is reported.[6] However only few formal analogies may be found between the two reactions.

The lack of reactivity of the other oxazolopyridines, i.e. [4,5-b], [4,5-c], [5,4-c], prevent the extension of this reaction for the preparation of other oxazoloazocines. An explanation for the different behaviour probably lies in the different nature of the lowest electronic level, i.e. π–π^* for the [5,4-b], n-π^* (or mixed) for the other oxazolopyridines. The hypothesis was suggested by some fluorescence data: in n-hexane solution only the oxazolo[5,4-b]pyridine strongly fluoresces with a maximum at 305 nm, whereas in acetonitrile solution the corresponding [4,5-b] also shows a similar, although less intense, fluorescence spectrum. Assuming that the

corresponding [4,5-b] also shows a similar, although less intense, fluorescence spectrum. Assuming that the fluorescence arise from $\pi-\pi^*$ excited state, the behaviour of the [4,5-b] is interpreted as a "state switching" due to the hypsochromic shift of the $n-\pi^*$ transitions in polar solvents. If, as usual, the stereospecific 2+2 cycloadditions arise from lowest singlet $\pi-\pi^*$, only the 2-Methyloxazolo[5,4-b]pyridine owns the requisite electronic structure. This picture is substantially confirmed by semiempirical CS-INDO-CI calculations[7] of the singlet levels for the four oxazolopyridines.[8]

N-quaternarized or differently substituted oxazolopyridines are expected to have the lowest excited level of $\pi-\pi^*$ type and consequently to give photocycloadditions, opening the route to the other oxazoloazocines. These possibilities are actually under investigation.

Acknowledgements. We would like to thank Prof. I. Baraldi for the calculations of the electronic spectra and helpful discussions.The availability of the Mass Spectrometer and of the X-Ray Diffractometer in the "Centro di Analisi e Determinazioni Strutturali" of the University of Siena is gratefully acknowledged. Work supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST).

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3. Improved synthesis of 3-Methyloxazolo[5,4-b]pyridine (60% yield) was achieved following the procedure reported for the oxazolo[4,5-b]pyridines by M. Doise et. al.: *Tetrahedron Lett.* **1990**, *31*, 1155.
4. Selected physical and spectral data :
   Compond **1a.** pf: 89-92 °C; IR(KBr): 2240(CN), 1650, 1625,1585, cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ:7.96 (d, $J_{8,7}$=2.1 Hz, H_8), 6.38(ABX2, J_{AB}=11.08 Hz, $J_{6,5'}$=7.75 Hz, H_6), 6.27(ABX, J_{AB}=11.08 Hz, $J_{7,8}$=2.1 Hz, H_7), 2.72 (ABX2, J_{AB}=14.98 Hz, $J_{5,6}$=$J_{5,4}$=7.75 Hz, H_5), 2.65 (ABXY, J_{AB}=14.98 Hz, $H_{5'}$), 4.16(dd, $J_{4,5}$=7.75 Hz, $J_{4,5'}$ =3.93 Hz, H_4), 2.44 (s, Me) ppm; ^{13}C-NMR ($CDCl_3$) δ: 13.7(Me), 28.3(C_5), 30.6(C_4), 118.9(CN), 120.7(C_{3a}), 129.9(C_7), 137.6(C_6), 149.3(C_{9a}), 158.6(C_2), 159.2(C_8) ppm; MS, m/z(%):187(M^+, 19.4), 136(10.3), 118(21.7), 94(14.5), 70(66.6), 67(11.5), 43(100); HRMS found 187.0744; $C_{10}H_9N_3O$ requires 187.0745.
   Compound **2a.** IR(KBr): 2240 (CN) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ: 7.91(t, $J_{8,7}$=$J_{8,7'}$=6.2 Hz, H_8), 6.56 (dd, $J_{4,5}$=12.64 Hz $J_{4,6}$=2.28 Hz, H_4) 5.95(dd, $J_{5,4}$=12.68, $J_{5,6}$ =4.75 Hz, H_5), 3.89 (tdd, $J_{6,4}$=2.28 Hz, $J_{6,5}$=4.75 Hz, $J_{6,7}$=$J_{6,7'}$=3.6 Hz, H_6) , 2.99 (A_2XY, $J_{7,8}$=$J_{7',8}$=6.2, $J_{7,6}$=$J_{7',6}$=3.6 Hz, H_7, $H_{7'}$), 2.43 (s, Me) ppm; ^{13}C-NMR($CDCl_3$) δ: 13.8(Me), 30.7(C_6), 33.4(C_7), 118.7(CN), 120.2(C_{3a}), 123.9(C_5), 125.6(C_4), 159.3 (C_{9a}), 160.1(C_2), 164.2(C_8) ppm.

Compound **3.** pf: 182-184 °C; ^{1}H-NMR($CDCl_3$) δ: 4.42(ddd, $J_{7,11}$=3Hz, $J_{7,8'}$=3.4 Hz, $J_{7,8}$=1.9 Hz, H_7), 3.28 ddd, $J_{13,10}$=9 Hz, $J_{13,12}$= 10.8 Hz, $J_{13,12'}$=8.4 Hz, H_{13}) , 3.00(dd, $J_{9,8'}$=5.1 Hz, $J_{9,8}$=9.9 Hz, H_9), 3.05(br t, $J_{10,11}$=$J_{10,13}$=9 Hz, $J_{10,12}$=$J_{10,12'}$= 1 Hz, H_{10}), 2.77(tdd, $J_{11,12}$=9 Hz, $J_{11,12'}$=5.3 , $J_{11,10}$= 9 Hz, $J_{11,7}$=3 Hz, H_{11}), 2.43(ABXY, J_{AB}=11.7 Hz, $J_{12,13}$= 10.8 Hz, $J_{12,10}$ = 1Hz, $J_{12,11}$=9 Hz, H_{12}), 2.44 (s, Me). 2.18(ABXYZ, J_{AB}=11.7 Hz, $J_{12',13}$=8.4 Hz, $J_{12',10}$= 1 Hz, $J_{12,11}$= 5.3 Hz, H_{12}), 2.03(ABXY, J_{AB}=13.8 Hz, $J_{8,7}$=1.9 Hz, $J_{8,9}$=9.9 Hz, H_8), 1.79 (ABXY, J_{AB}=13.8 Hz, $J_{8',7}$=3.4 Hz, $J_{8'9}$=5.1 Hz, $H_{8'}$)ppm; ^{13}C-NMR($CDCl_3$) δ: 15.2(Me), 21.2(C_2), 25.4(C_{12}), 28.5(C_8), 31.2(C_9), 32.9(C_{11}), 37.9(C_{10}), 67.4(C_1), 117.3(CN), 117.4(CN), 170.9 (C_3 or C_5), 174.2 (C_5 or C_3) ppm; MS m/z (%) : 240 (M^+,7.4), 187(72.1), 146(12.9), 145(100), 134(23.5), 104(13.7); HRMS found 240.1013; $C_{13}H_{12}N_4O$ requires 240.1011.

Compound **1b.** ^{1}H-NMR ($CDCl_3$) δ:7.90(d, $J_{8,7}$=2.1 Hz, H_8), 6.13-6.20(ABX, J_{AB}=11.2 Hz, $J_{6,5}$ =6.7 Hz, H_6), 4.02(d, $J_{4,5}$=2.8 Hz, H_4), 2.75 (m, $J_{5,4}$=2.8 Hz, $J_{5,6}$=$J_{5\text{-Me}}$=6.7 Hz, H_5), 2.42 (s, 2-Me); 1.38(t, $J_{\text{Me-}H_5}$=6.7, 5-Me) ppm; ^{13}C-NMR($CDCl_3$) δ: 13.7(3-Me), 18.4(5-Me), 32.9(C_4), 39.5(C_5), 118.3(CN), 120.5(C_{3a}), 127.1(C_7), 143.9(C_6), 149.1(C_{9a}), 158.7(C_2), 159.8(C_8) ppm.

Compound **1c.** ^{1}H-NMR ($CDCl_3$) δ:7.99(d, $J_{8,7}$=2.1 Hz, H_8), 6.13-6.20(ABX, J_{AB}=11.0 Hz, $J_{6,5}$=8.6 Hz, H_6), 3.82(d,$J_{4,5}$=11.6 Hz, H_4), 2.70 (m, H_5), 2.43 (s, 2-Me); 1.44(t, $J_{\text{Me-}H_5}$=6.6, 5-Me) ppm; ^{13}C-NMR ($CDCl_3$) δ: 13.7(3-Me), 19.2(5-Me), 34.1(C_4), 36.3(C_5), 117.8(CN), 120.5 (C_{3a}), 127.0(C_7), 144.2(C_6), 149.1(C_{9a}), 158.5(C_2), 160.4(C_8) ppm.

5. Crystal data for Compound **3:** $C_{13}H_{12}N_4O$, M_w=240.3, monoclinic, space group $P2_1/n$, Z=4, a= 7.801(2), b= 16.252.3, c=9.526(2) Å, β=91.81(3)°, V=1207.1(5) Å^3, D_c=1.322 gcm^{-3}, F(000)=504, Mo-K_α radiation, λ=0.71073 Å ,. Intensity data were collected with Siemens R3m/V. 2121 independent reflections measured, 1216 observed with I>3 σ(I). The structure was solved by direct method using SHELXTL PLUS . Anisotropic temperature factors were used for non-hydrogen atoms. The position of hydrogen atoms were found by Difference Fourier map, and refined isotropically. Final R= 0.0487 and R_w= 0.0585 (w^{-1}= $\sigma^2(F)$+0.0005F^2).
List of the fractional atomic coordinates, bond lenghts and angles, thermal parameters have been deposited at the Cambridge Crystallographic Data Center, U.K. as supplementary material.

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8. Lowest singlet levels (e.V.) obtained by CS-INDO-CI methods, including selected double and triple excitations: [4,5-b] 4.319(π–π*), 4.368(n-π*) ; [4,5-c] 4.699(n-π*), 4.732(π–π*) ; [5,4-c] 4.305 (n-π*), 4.514(π–π*) ; [5,4-b] 4.354(π–π*), 4.483(n-π*) .

(*Received in UK* 11 *April* 1996; *revised* 19 *June* 1996; *accepted* 21 *June* 1996)