SHORT PAPER

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Structural studies on bioactive compounds. Part 31. Interaction of 9-azidoacridine and 1-morpholinocyclohexene: formation, decomposition and rearrangement of the intermediate 1,2,3-triazoline†

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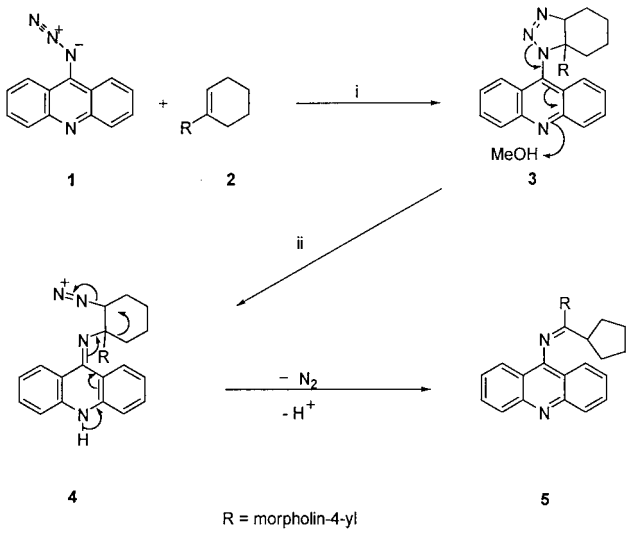
9-Azidoacridine **1** and the cyclic enamine **2** undergo a selective 1,3-dipolar cycloaddition reaction to give the 1,2,3-triazoline **3** with the expected regiochemistry. Exposure of the triazoline **3** to methanol induces the extrusion of nitrogen accompanied by a ring contraction to furnish the amidino-acridine **5** in high yield.

Recently we have reported the synthesis of 9-(1,2,3-triazol-1-yl) acridines through cycloaddition of 9-azidoacridine with either alkynes *via* the classical concerted route, or *via* the base-catalysed addition of activated methylene compounds.[1,2] As a part of a programme aiming to develop general syntheses of polycyclic acridines from triazolylacridines we investigated the usage of enamines as reaction partners of 9-azidoacridine. 1,2,3-Triazolines derived from organic azides and enamines or enol ethers have been used widely as precursors in the synthesis of the corresponding 1,2,3-triazoles.[3,4] In addition to the characteristic aromatisation of the 1,2,3-triazolines by thermal or acid catalysed 1,2-elimination of either the amine or the alcohol, nitrogen expulsion can be regarded as a possible side reaction and very often this pathway dominates the chemical behaviour of the unsaturated heterocycle.[5,6]

The 1,2,3-triazoline **3** was prepared by the 1,3-dipolar cycloaddition of 9-azidoacridine **1** to the electron rich double bond of 1-morpholino-1-cyclohexene **2** in dichloromethane (Scheme 1). Excess of the cyclic enamine improved the yield and reduced the reaction time. The product **3** was characterised by spectroscopic methods and analytical data (elemental analysis) as the mass spectrum did not reveal the molecular ion. Hindered rotation around the *meso* CN single bond of **3** at room temperature was evident by both ^{1}H and ^{13}C NMR spectroscopy. The typical ABCD pattern of the acridine hydrogens was observed at elevated temperatures although slow decomposition occurred upon heating the sample in chloroform. Investigation of the reaction of 9-azidoacridine **1** with other enamines, the morpholino derivatives of cyclopentene and cycloheptene demonstrates that the exclusive products of the 1,3-dipolar additions were the result of electronic control leading to the sterically less-favoured adducts. The terminal nitrogen of the azide dipole is directed to the carbon of the C=C bond bearing the negative charge. The reaction of 9-azidoacridine with enol ethers led to an almost quantitative recovery of starting materials.



Scheme 1 Reaction conditions: (i) CH_2Cl_2, 24 h, 25°C; (ii) MeOH, 25°C

The 1,2,3-triazoline **3** readily underwent selective fragmentation in methanol yielding the corresponding amidine **5** (Scheme 1). The extrusion of nitrogen was complete within several minutes and formation of the amidine **5** was confirmed by analytical as well spectral (MS and ^{1}HNMR) data. The geometrical assignment of the amidine **5**, where the bulkier morpholino group is in a *trans* arrangement to the acridine moiety was predicted by semiempirical MO calculations[7], where the calculated enthalpy of formation of the *trans* form is about 5.1 kcal mol^{-1} lower compared to the corresponding value of the *cis* isomer. These predictions were corroborated by an X-ray crystal structure analysis of the amidine **5** (Fig 1).

The mechanism of the methanol-induced conversion **3** → **5** probably involves an initial heterolytic ring opening of the triazoline ring facilitated by the electron-withdrawing character of the acridine ring. The cyclohexyldiazonium species **4** then undergoes an expected 1,2-shift with elimination of dinitrogen. Overall there is a ring-contraction of the cyclohexane ring.

Crystal data for **5**: $C_{23}H_{25}N_3O$, M = 359.46, monoclinic, space group $P2_1/n$, a = 10.131 (1), b = 14.299 (3), c = 13.379 (1) Å, α = 90.00 (1)°, β = 90.77 (1)°, γ = 90.00 (1)°, U = 1937.9 (5) Å^3, Z = 4, Dc = 1.232 g cm^{-3}, F(000) = 768. A lath 0.35 × 0.30 × 0.25 mm grown from hexane–dichloromethane was mounted on an Enraf-Nonius CAD 4 diffractometer. 3677 unique reflections were collected and phased by direct methods.[8] Full-matrix least-squares refinement [9] on F^2 with anisotropic thermal parameters for non hydrogen atoms and all hydrogen atom positions determined from difference Fourier synthesis. At convergence, R = 0.046, R_w = 0.167 and GOF = 1.083 for 2816 observed reflections [I > 2σ(I)].

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† This is a Short Crystallographic Paper, there is therefore no corresponding material in *J Chem. Research (M).*

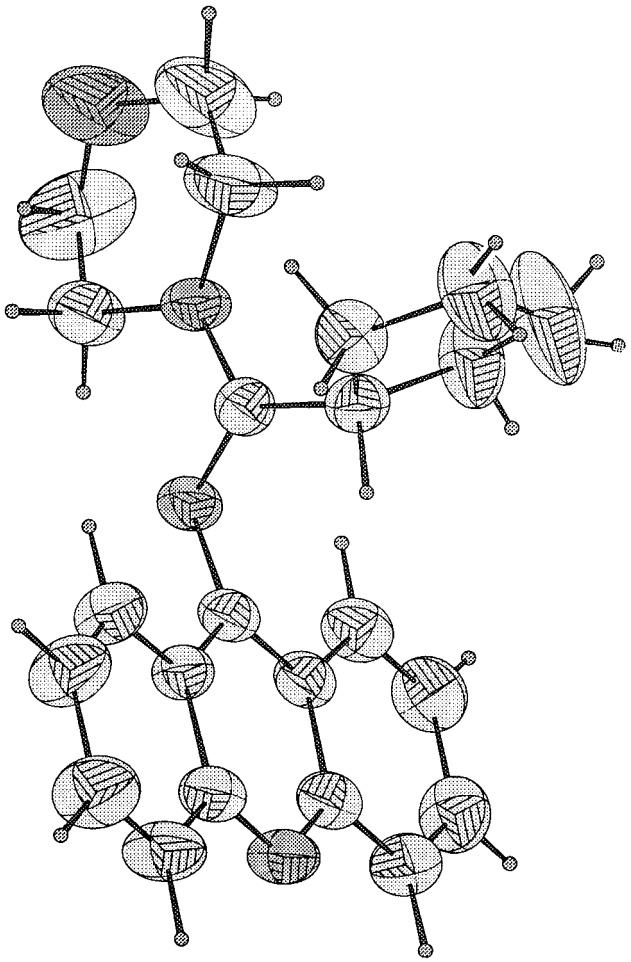

Fig. 1 CAMERON[10] view of the structure of compound **5**. Displacement ellipsoids are shown at 50% probability level

Experimental

All NMR spectra were acquired on a Bruker ARX 250 instrument. Chemical shifts are reported in δ units and referenced to the solvent as internal standard. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 2020 Galaxy Series FT-IR spectrometer. Mass spectra were recorded on a Micromass Platform spectrometer.

General procedure for the reaction of 9-azidoacridine with enamines: To a solution of 9-azidoacridine **1** (220 mg, 1.00 mmol) in dry dichloromethane (10 ml) was added the enamine (10.00 mmol). The reaction mixture was stirred for 24 h in the darkness under nitrogen, solvent was evaporated and the remaining reddish oil was treated with diethyl ether to precipitate a yellow powder. After filtration the powder was washed with a little diethyl ether and recrystallised from diethyl ether-dichloromethane to give the air sensitive triazoline.

9-[3a,4,5,6,7,7a-hexahydro-7a-(morpholin-4-yl)-benzo-1,2,3-triazol-1-yl]acridine **3** was formed as bright yellow crystals (71%), mp 126–128°C (decomp.); ν_{max} (KBr)/cm^{-1} 2959, 2857, 1626, 1553, 1516, 1491, 1476, 1451, 1439, 1410, 1362, 1275, 1146, 1121, 1094, 1034, 1009, 959, 926, 770 and 754; δ_H (250.13 MHz; $CDCl_3$) 0.96 (1 H, m), 1.17-1.53 (3 H, m), 1.71 (1 H, m), 1.81-1.95 (2 H, m), 2.38-2.53 (3 H, m), 2.68 (2 H, br s), 3.52-3.80 (4 H, m), 4.79 (1 H, dd, *J* 10.0 and 7.2), 7.51 (2 H, ddd, *J* 8.8, 6.5 and 1.3), 7.75 (2H, ddd, *J* 8.8, 6.5 and 1.3), 8.22 (2 H, d, *J* 8.8) and 8.63 (2 H, br s); δ_C (62.90 MHz; $CDCl_3$) 20.2 (CH_2), 20.9 (CH_2), 24.9 (CH_2), 26.2 (CH_2), 46.1 (CH_2), 67.0 (CH_2), 73.3 (CH), 82.0 (C), 124.0 (C), 125.8 (CH), 129.8 (CH), 129.9 (CH), 141.5 (C) and 150.0 (C); *m/z* (APCI) 360 ($MH^+ - N_2$, 100%); (Found: C, 71.16; H, 6.56; N, 17.90. $C_{23}H_{25}N_5O$ requires C, 71.29; H, 6.50; N, 18.07%).

Also prepared were the following: from 9-azidoacridine and 1-morpholinocyclopentene,

9-[4,5,6,6a-tetrahydro-6a-(morpholin-4-yl)-3aH-cyclopenta-1,2,3-triazol-1-yl]acridine as bright yellow crystals (79%), mp 131–133°C (decomp.); (Found: C, 70.38; H, 6.23; N, 18.82. $C_{22}H_{23}N_5O$ requires C, 70.76; H, 6.21; N, 18.75%); from 9-azidoacridine and 1-morpholinocycloheptene, *9-[4,5,6,7,8,8a-hexahydro-8a-(morpholin-4-yl)-3aH-cyclohepta-1,2,3-triazol-1-yl]acridine* as bright yellow crystals (65%), mp 134-135 °C (decomp.); *m/z* (APCI) 374 ($MH^+ - N_2$, 100%).

(E)-9-(1-Cyclopentyl-1-morpholinomethylenimino)acridine **5**: To a solution of **3** (193 mg, 0.50 mmol) in chloroform (3 ml) was added methanol (5 ml). The mixture was refluxed for 2 min and the solvents were removed upon evaporation. The residue was recrystallised from hexane-dichloromethane to give orange prisms (169 mg, 94%), mp 193-195 °C; ν_{max} (KBr)/cm^{-1} 2961, 2915, 2872, 2849, 1605, 1557, 1514, 1460, 1445, 1398, 1354, 1244, 1121, 972 and 764; δ_H (250.13 MHz; $CDCl_3$) 1.32 (2 H, m), 1.51-1.75 (6 H, m), 2.68 (1 H, quintet, *J* 9.4), 3.66 (4 H, dd *J* 5.1 and 4.4), 3.81 (4 H, dd *J* 5.1 and 4.4), 7.36 (2 H, ddd, *J* 8.3, 6.6 and 1.1), 7.69 (2H, ddd, *J* 8.4, 6.6 and 1.5), 7.87 (2H, ddd, *J* 8.3, 1.5 and 1.4), 8.10 (2 H, ddd, *J* 8.4, 1.4 and 1.1); δ_c (62.90 MHz; $CDCl_3$) 25.9 (CH_2), 30.5(CH_2), 42.4 (CH), 46.8 (CH_2), 66.8(CH_2), 118.6 (C), 123.5(CH), 124.5 (CH), 129.2(CH), 130.1 (CH), 149.6 (C), 154.4 (C) and 161.2 (C); *m/z* (APCI) 360 (MH^+, 100%), 180 (45%); (Found: C, 76.67; H, 7.01; N, 11.69. $C_{23}H_{25}N_3O$ requires C, 76.85, H, 7.01; N, 11.68%).

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