Highly Selective Formation and Ring Fission of some Cyclobutaquinolizidinones and Cyclobutaindolizidinones†

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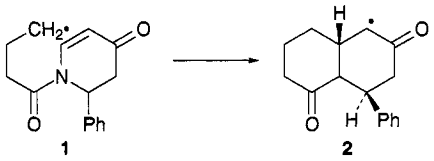
Intramolecular photochemical cycloaddition in *N*-alkenoyldihydropydinones or 3-acetyl-*N*-alkenoyltetrahydropydines is highly diastereoselective and affords substituted cyclobutaquinolizidinones and cyclobutaindolizidinones, suitable derivatives of which undergo highly regioselective radical ring opening of the cyclobutane ring.

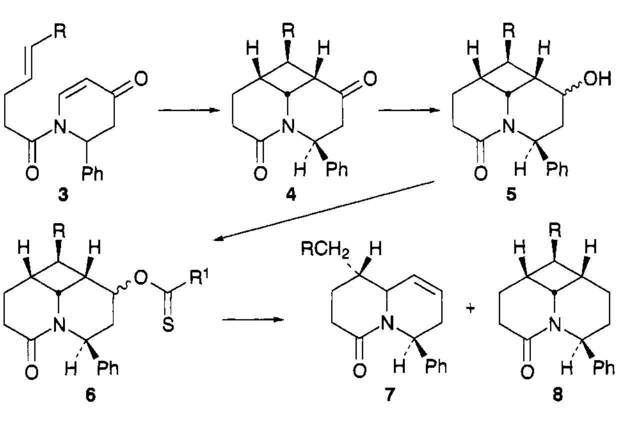
Intramolecular addition in radicals (*e.g.* **1**) generated from 6-substituted *N*-ω-haloacyldihydropyridine-4-ones proceeds with very high diastereoselectivity to give cyclised radicals (*e.g.* **2**) in which the newly formed bond is *trans* to the substituent.[1] The reaction constitutes the key step in a convenient diastereoselective synthesis of various indolizine, quinolizidine and dihydroquinoline alkaloids.[1] Molecular mechanics calculations[1] and X-ray studies[2] of the starting materials and products indicate that the diastereoselectivity reflects the preferred conformation of **1** in which the amide carbonyl oxygen is *syn* to the substituent, while the substituent is in a pseudo-axial conformation, thus directing radial attack onto the opposite face of the dihydropyridinone ring. We have now found that photochemical [2 + 2] cycloaddition[3] in related systems proceeds with similar diastereoselectivity to afford fused cyclobutanes, suitable derivatives of which undergo highly regioselective radical ring opening of the cyclobutane ring. Previous related work in this area includes intermolecular and intramolecular [2 + 2] cycloadditions to pyridones,[4,5] dihydropyridones[6,7] and quinolones.[8]

Addition of pent-4-enoyl chloride to 4-methoxypyridine afforded a slurry of the 1-acylpyridinium salt which was converted into **3a** in 77% yield by treatment with phenylmagnesium bromide at −30 °C. Irradiation of **3a** through Pyrex with a 250 W medium pressure Hanovia Hg lamp at *ca.* 30 °C in various solvents (aqueous MeOH, toluene, dioxane and acetonitrile) gave the cycloaddition product **4a** (Scheme 1). The yield varied with the solvent; the best was found to be dioxane which gave ⩾80%. The cycloaddition was highly selective; the only diastereoisomer detected was **4a**, the relative stereochemistry of which was determined by X-ray analysis (Fig. 1).‡ Reduction of **4a** with sodium borohydride in EtOH gave a mixture (3 : 2) of the diastereoisomeric alcohols **5a** (84%) which was treated with phenyl thionochloroformate to afford a mixture of the diastereoisomers of the thionocarbonate **6a** (R^1 = OPh).

Slow addition (syringe pump, 3.5 h) of tributylstananne and di-*tert*-butylperoxide (20 mol%) in toluene to a solution of **6a** (R^1 = OPh) in toluene under reflux gave a mixture of ring-opened and directly reduced products, **7a** and **8a** (Scheme 1), in yields of 70 and 19% respectively, which were separated by chromatography. No other isomer of **7a** was detected. The highly regioselective formation of **7a** is attributable to stereoelectronic control[9] of the ring opening of the radical **9a** generated from **6a**. The structure obtained by molecular mechanics calculations for **9b** (Fig. 2), the radical analogous to **9a** but lacking the phenyl substituent, shows that the SOMO is almost coplanar with the bond observed to undergo fission. The other β-bond potentially capable of undergoing fission is almost orthogonal to the SOMO.

Cycloaddition and ring fission occurred with equally high selectivity when the starting material **3b** was prepared from *trans*-hex-4-enoyl chloride. Irradiation of **3b** in dioxane gave a single product **4b** in which the stereochemistry of the methyl substituent has been tentatively assigned by analogy with products obtained from similar reactions with 2-pyridones.[4]





Scheme 1 a, R = H; b, R = Me

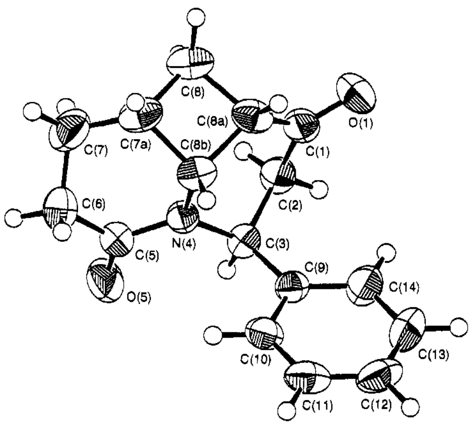


Fig. 1 Crystal structure of **4a**

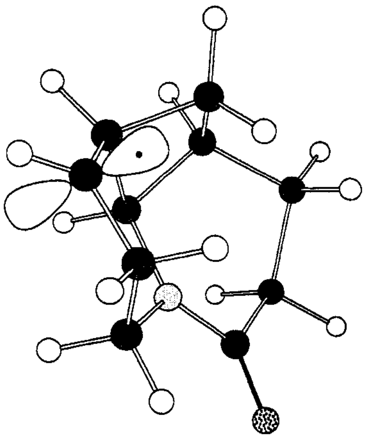
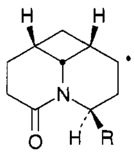


Fig. 2 Molecular mechanics (MM2) simulation of the radical **9b**

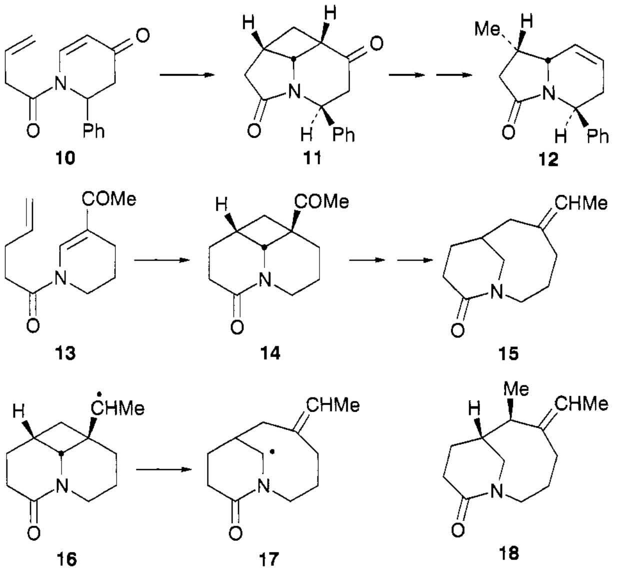
Compound **4b** was converted consecutively into **5b** (85%), **6b** (R^1 = SMe) (89%) and **7b** (72%) as described above. No diastereoisomer of **7b** could be detected in the crude product.

Photolysis of the *N*-but-3-enoyl compound **10** in dioxane was less efficient and less diastereoselective than for the higher homologue **3a** and afforded the cyclobutaindolizidine derivative **11** in 55% yield. The ^{13}C NMR spectrum of the crude reaction mixture also indicated the presence of a small amount (*ca.* 6%) of a compound tentatively identified as the other possible diastereoisomer. The same series of reactions as described above, when applied to **11** gave successively the corresponding alcohol (97%), its methyl xanthate (82%), and a single diastereoisomer of the ring-opened compound **12** (67%).

Finally, we examined the behaviour of the cyclobutaquinozilidine derivative **14** formed in lower yield (44%) by UV photolysis through silica of **13** in acetone. As described above, **14** was then converted into the methyl xanthate which was treated with tributylstannane to afford the ethylidene azabicyclodecanone **15** as a 1 : 1 mixture of *Z* and *E* isomers. In this case there is no stereoelectronic preference for β-fission of either of the cyclobutane bonds in the intermediate radical **16** because of free rotation about the exocyclic bond. The reaction therefore proceeds along the thermochemically favoured pathway to afford the more stable possible intermediate radical **17**. A similar series of reactions on the *N*-*trans*-hex-4-enoyl analogue of **13** gave, albeit in low yield, the compound **18** as a mixture of geometric isomers (*E* : *Z* = 6.7 : 1).



9a R = Ph
b R = H



In summary, the above reactions illustrate the importance of stereoelectronic control in the fission of cyclobutylcarbinyl radicals,[9] and provide novel routes for the stereoselective formation of substituted quinolizidine, indolizidines and azabicyclodecanes.

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Footnotes

† Some aspects of the work were presented at the Annual Meeting of the Japanese Pharmaceutical Society, Tokyo, March 1993.

‡ Crystals of **4a**, mp 81–82 °C suitable for diffraction were grown from diethyl ether.

Crystal data: $C_{16}H_{17}NO_2$, M = 255.32, crystal size 0.28 × 0.12 × 0.03 mm, orthorhombic, space group *Pbca*, a = 8.817(1), b = 16.770(1), c = 18.314(1) Å, U = 2708.1(4) Å^3, Z = 8, D_c = 1.252 g cm^{-3}, λ(Cu-Kα) = 1.54178 Å, $F(000)$ = 1088, Rigaku AFC6R diffractometer, ω/2θ scans, ω scan speed 8° min^{-1} with up to 3 rescans for weak reflections, $4 \leq 2\theta \leq 120°$, $0 \leq h \leq 9$, $0 \leq k \leq 18$, $0 \leq l \leq 20$, 2325 unique reflections with 1193 observed [$I \geq 3\sigma(I)$], μ = 6.23 cm^{-1}, R = 0.038, R_w = 0.028, S = 1.91, max shift/σ = 0.01, 173 variables, ρ(max, min) 0.12, −0.14 e Å^{-3}.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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