

REGIOSELECTIVE INTRAMOLECULAR CYCLOADDITION OF C-(1-ACRYLOYL-2-PYRROLYL)-N-BENZYLNITRONE: ENTRY TO 6-HYDROXY-5-OXOINDOLIZIDINES

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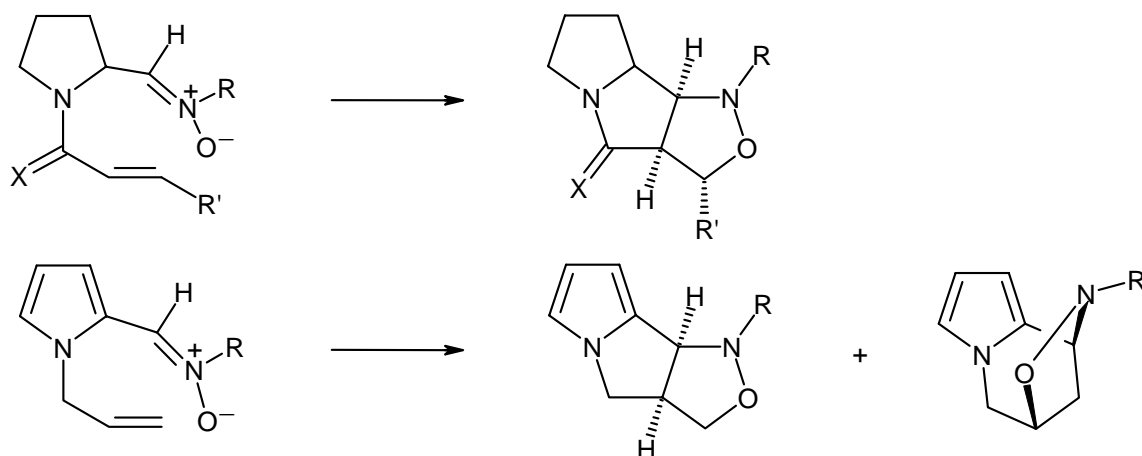
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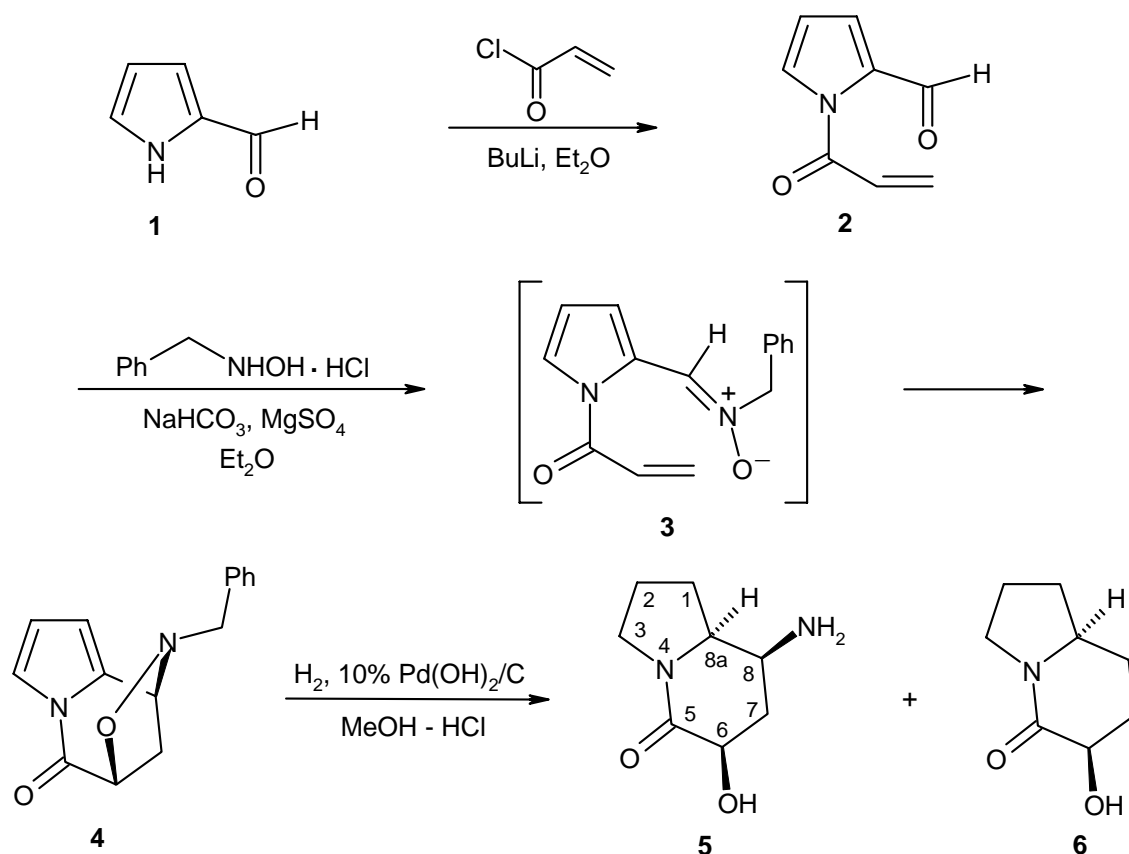
Abstract-The title nitronone underwent intramolecular cycloaddition in regioselective and stereoselective manner, giving one bridged-ring cycloadduct (**4**). Further elaboration of the latter led to 6-hydroxy-5-oxoindolizidine derivatives (**5**) and (**6**), which can be seen as useful intermediates in alkaloids synthesis.

Indolizidine alkaloids have been isolated from plants, fungi, and animal sources.^{1,2} Several of these natural products and related unnatural compounds have aroused an interest as potential antitumoral and antiviral agents due to their inhibitory effect toward glycosidases.^{3,4} This ensures their importance as targets of chemical synthesis and a variety of methods have been actually reported for the construction of the indolizidine skeleton.^{5,6} As recently reviewed,⁷ intramolecular 1,3-dipolar cycloadditions have been amply exploited to such a purpose.

Literature data^{8,9} show that the intramolecular cycloaddition of nitrones derived from both 1-allyl- and 1-cinnamoyl-2-pyrrolidinecarbaldehyde affords exclusively products containing the pyrrolizidine nucleus (Scheme 1). Conversely,^{10,11} nitrones derived from 1-allyl-2-pyrrolecarbaldehyde can originate two kinds of intramolecular cycloadducts, *i.e.* the pyrrolizidine-like one and its regioisomer containing the tetrahydroindolizidine nucleus. The extent of the latter cycloadduct spreads over a wide range, being strongly dependent on steric factors and geometric restraints. In this context, we reasoned that nitrones derived from 1-acryloyl-2-pyrrolecarbaldehyde should have a less flexible molecular geometry and perhaps more appropriate for the intramolecular approach leading to the indolizidine skeleton.

Scheme 1

On the basis of the above considerations, we synthesized the new compound (**2**) and submitted it to reaction with benzyloxyamine (Scheme 2). The first-formed nitrene (**3**) escaped isolation; nevertheless, the work-up of the reaction mixture after 5 days at room temperature furnished, apart from some uncharacterizable material, one intramolecular cycloadduct in 28% yield. NMR spectra taken under routine conditions were of little diagnostic significance as containing broadened signals, probably due to slow interconversion of invertomers at the pyramidal nitrogen.¹² However, more resolved signals were observed in the NMR spectra taken at 55 °C, which suggested the bridged-ring structure (**4**). The latter was established unequivocally by X-Ray diffractometric crystal analysis (Figure 1).

Scheme 2

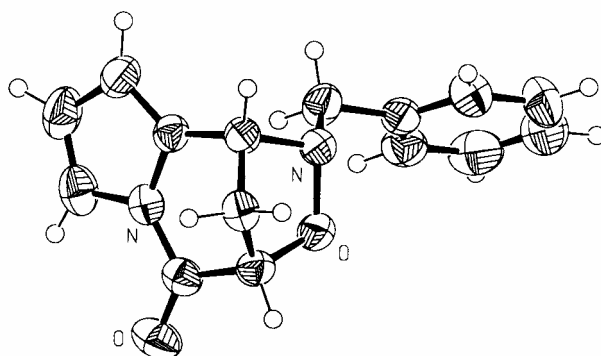
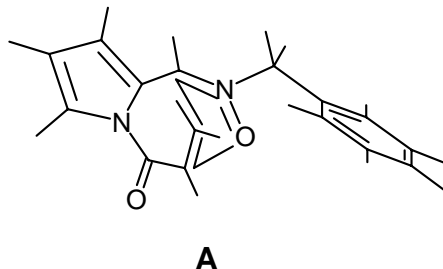


Figure 1. ORTEP plot of **4** determined by X-Ray analysis. Thermal ellipsoids at 50% probability level, hydrogen atoms not to scale.

The behavior of nitron (**3**) deserves a comment. According to molecular models, the *transoid* conformation of the acryloyl pendant seems more suitable to the intramolecular reaction than the *cisoid* one, but provided that the carbon of the dipole bonds to the external carbon of the dipolarophile. Hence, one may roughly represent the transition state of the cycloaddition as in formula (**A**), which justifies the observed regiochemical and stereochemical outcomes.



In the further stage of our work, we performed the cleavage of the isoxazolidine ring of **4** upon catalytic hydrogenation with the concomitant aim of saturating the pyrrole nucleus. Actually, the latter goal was achieved only in a strongly protic medium which, however, also promoted the detachment of the benzylic amino group. As a consequence, although the hydrogenation was fully stereoselective, a mixture of amino alcohol (**5**) and alcohol (**6**) was formed. The product structures were consistent with ¹H-NMR spectra, which show rather downfield signals for hydrogens in 8 and 8a positions, so indicating their *cis* relationship with respect to the lone electron pair of the bridgehead nitrogen.

In conclusion, we have described here a facile synthesis of two 6-hydroxy-5-oxoindolizidines which, in the light of previous literature reports,¹³⁻¹⁶ may serve as intermediates for total synthesis of indolizine alkaloids.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded on an FT-IR Perkin Elmer 1725 X spectrophotometer. MS spectra were taken with a VG-70EQ apparatus.

¹H-NMR spectra were measured at 300 MHz with a Bruker AMX 300 instrument in CDCl₃ solutions; chemical shifts are given as δ ppm from Me₄Si and *J* values are given in Hz. ¹³C-NMR spectra were obtained at 75 MHz using the same instrument.

1-Propenoyl-1*H*-pyrrole-2-carbaldehyde (2). A solution of 1.6 M butyllithium in hexane (9.2 mL, 14.7 mmol) and acryloyl chloride (1.75 mL, 21.5 mmol) was added, under nitrogen atmosphere, to a solution of 2-pyrrolecarbaldehyde (**1**) (2.03 g, 21.3 mmol) in dry ether (100 mL). After stirring at rt for 90 min, the mixture was poured into the water (100 mL), the layers were separated and the aqueous one was extracted with ether. The collected organic parts were dried on sodium sulfate and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column with light petroleum/ethyl acetate 2:1 as eluent to give **2** (1.32 g, 42%). Oil; IR (nujol): 1730, 1670 (cm⁻¹); ¹H-NMR: 6.12 (1H, dd, *J*=1.4, 10.2), 6.39 (1H, dd, *J*=3.2, 3.2), 6.70 (1H, dd, *J*=1.4, 16.8), 6.87 (1H, dd, *J*=10.2, 16.8), 7.25 (1H, dd, *J*=1.6, 3.2), 7.42 (1H, dd, *J*=1.6, 3.2), 10.19 (1H, s); MS: *m/z* 149 (M⁺). *Anal.* Calcd for C₈H₇NO₂: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.25; H, 4.86; N, 9.51.

Reaction of 1-propenoyl-1*H*-pyrrole-2-carbaldehyde (2) with *N*-benzylhydroxylamine. A suspension of *N*-benzylhydroxylamine hydrochloride (0.32 g, 2.0 mmol) and sodium hydrogencarbonate (0.23 g, 2.8 mmol) in dry ether (60 mL) was stirred for 15 min. Magnesium sulfate (4.8 g, 40.2 mmol) and **2** (0.30 g, 2.0 mmol) were added, then the resultant mixture was stirred at rt for 72 h. The undissolved material was filtered off through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with light petroleum/ethyl acetate 2:1 as eluent to give (1*R**,4*S**)-2-benzyl-1,2-dihydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepin-5(4*H*)-one (**4**) (0.14 g, 28%). mp 92-93 °C (from diisopropyl ether); IR (nujol): 1730 (cm⁻¹); ¹H-NMR (55 °C): 2.38 (1H, d, *J*=11.8), 2.80 (1H, ddd, *J*=4.3, 5.9, 11.8), 3.65 (2H, br s), 4.47 (1H, d, *J*=4.3), 4.75 (1H, d, *J*=5.9), 6.08 (1H, d, *J*=2.9), 6.27 (1H, d, *J*=2.9), 7.25-7.35 (5H, overlapping), 7.40 (1H, br s); ¹³C-NMR (55 °C): 40.42 (t), 57.55 (d), 59.26 (t), 77.32 (d), 112.46 (d), 113.47 (d), 117.31 (d), 128.02 (d), 128.68 (d), 128.97 (d), 129.33 (d), 129.54 (d), 130.24 (s), 136.98 (s), 167.10 (s); MS: *m/z* 254 (M⁺). *Anal.* Calcd for C₁₅H₁₄N₂O₂: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.01; H, 5.51; N, 10.88.

Hydrogenation of 4. A mixture of 10% Pd(OH)₂/C (130 mg) and **4** (100 mg, 0.40 mmol) in a 0.04 N solution of HCl in methanol (20 mL) was stirred under hydrogen for 18 h. After filtration through Celite, the solvent was removed under reduced pressure. The residue was treated with a 30% sodium hydroxide solution (1 mL) and extracted with dichloromethane. After evaporation of the solvent, the crude product was chromatographed on silica gel with chloroform/methanol/30% ammonium hydroxide (10:1:1) as eluent. The first fraction gave (6*R**,8*aS**)-6-hydroxy-2,3,6,7,8,8*a*-hexahydroindolizin-5(1*H*)-one (**6**) (15

mg, 24%). mp 82-83 °C (from diisopropyl ether); IR (nujol): 3375, 1630 (cm⁻¹); ¹H-NMR: 1.40-1.58 (2H, overlapping), 1.70-1.87 (2H, overlapping), 1.91-2.10 (2H, overlapping), 2.11-2.21 (2H, overlapping), 3.36-3.65 (4H, overlapping, 3H after deuteration), 4.06 (1H, dd, *J*=7.0, 7.4); ¹³C-NMR: 23.15 (t), 25.72 (t), 27.84 (t), 33.28 (t), 45.01 (t), 57.11 (d), 66.23 (d), 171.20 (s); MS: *m/z* 155 (M⁺). *Anal.* Calcd for C₈H₁₃NO₂: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.83; H, 8.63; N, 8.89. The second fraction gave (6*R**,8*S**,8*aS**)-8-amino-6-hydroxy-2,3,6,7,8,8*a*-hexahydroindolizin-5(1*H*)-one (**5**) (19 mg, 28%). mp 104-105 °C (from diisopropyl ether); IR (nujol): 3380, 3055, 2930, 1635 (cm⁻¹); ¹H-NMR: 0.82-0.91 (1H, m), 1.76-2.12 (7H, overlapping, 4H after deuteration), 2.41 (1H, ddd, *J*=5.5, 7.4, 14.3), 3.33 (1H, ddd, *J*=3.3, 3.3, 5.1), 3.47-3.61 (3H, overlapping), 4.08 (1H, dd, *J*=5.1, 7.4); ¹³C-NMR: 23.33 (t), 27.93 (t), 37.92 (t), 45.66 (d), 45.71 (t), 61.65 (d), 65.43 (d), 170.84 (s); MS: *m/z* 170 (M⁺). *Anal.* Calcd for C₈H₁₄N₂O₂: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.55; H, 8.46; N, 16.48.

Crystallographic analysis. Single-crystal X-Ray diffraction measurements were performed on a Nonius CAD4 diffractometer, graphite monochromator, Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). The crystal data are as follows: C₁₅H₁₄N₂O₂, *M_r* = 254.28, orthorhombic, space group *Pccn*, *a* = 32.782(5), *b* = 10.433(2), *c* = 7.5469(13) \AA , *V* = 2581.2(8) \AA^3 , *Z* = 8, *D_c* = 1.309 g.cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.088 \text{ mm}^{-1}$; 3580 collected data, 3331 unique [2342 with *I_o* > 2 σ (*I_o*)], *R_{ave}* = 0.0096. Structure solved by SIR-92¹⁷ and refined by SHELX-97;¹⁸ final disagreement factors for all(observed) reflections: *R_w*(*F*²) = 0.0896(0.0796) and *R* = 0.0642(0.0391). All crystallographic data (excluding structure factors) were deposited to the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 167597. Copies of the data can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK, e-mail deposit@ccdc.cam.ac.uk

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