

Oxa-di- π -methane Photochemical Rearrangement of Quinuclidinones. Synthesis of Pyrrolizidinones

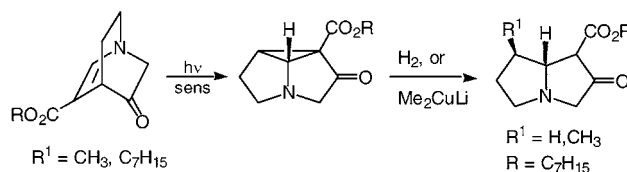
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ABSTRACT



The oxa-di- π -methane (ODPM) photochemical rearrangement, a triplet-sensitized sigmatropic 1,2-acyl shift of β,γ -enones, was successful utilizing methyl and heptyl 1-aza-3-carboalkoxybicyclo[2.2.2]oct-2-en-5-ones (quinuclidinones) as the photoprecursors. The cyclopropane of the heptyl ester tricyclic photoproduct could be opened with lithium dimethylcuprate or via hydrogenolysis to produce the corresponding pyrrolizidinone skeletons.

The ongoing discoveries of new biologically active nitrogen heterocycles such as pyrrolizidine, indolizidine, and tropane alkaloids continue to attract interest in the development of new methods for their syntheses.¹ We are currently exploring the use of the photochemical oxa-di- π -methane (ODPM) rearrangement,^{2,3} a triplet-sensitized sigmatropic 1,2-acyl

shift, to ultimately produce these various alkaloids. In this communication, we present the first successful ODPM rearrangement of the quinuclidinones, 1-azabicyclo[2.2.2]octenones **1a,b** ($R = \text{CO}_2R'$) to the tricyclic compounds **2a,b** (Scheme 1), and the subsequent ring-opening to the pyrrolizidine skeleton.

The synthetic potential of the photochemical ODPM rearrangement of various all-carbon bicyclo[2.2.2]octenones to produce bi- and tricyclopentanoid compounds has been illustrated by several groups.^{2,3} When we first designed our original photoprecursor, **1**, we wondered if the lone pair of electrons on the nitrogen would interfere with the photochemistry, as it is known that amines can undergo photo-activated single-electron transfer (SET) reactions.^{4e} To our knowledge, the majority of nitrogen-containing photoprecursors have been studied in either the di- π -methane rearrangement where the nitrogen did not participate in the

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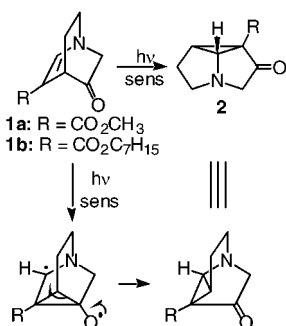
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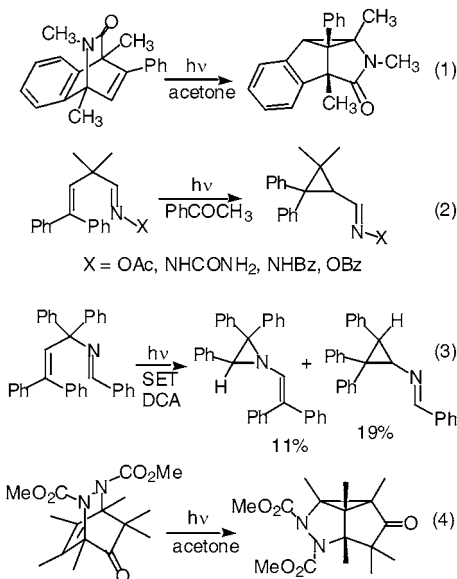
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Scheme 1



rearrangement (as shown in Scheme 2, eq 1)^{2a,e,4a,b} or the aza-di- π -methane rearrangement (Scheme 2, eqs 2 and

Scheme 2



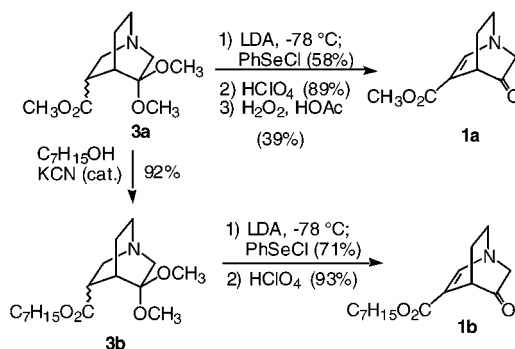
3).^{2a,4d,e} The oxa-di- π -methane rearrangement of the bicyclohydrazide (Scheme 2, eq 4) is a rare example of a nitrogen-containing bicyclic system being rearranged via the ODPM reaction.^{4f}

To test the viability of the ODPM rearrangement on the quinuclidinone skeleton, **1a** and **1b** were prepared via a classical route, as the synthesis of **3a** was a literature preparation from commercially available 3,4-pyridinedicarboxylic acid.⁵ Installations of the double bonds in **3a** and **3b** were successful via the standard procedures outlined in

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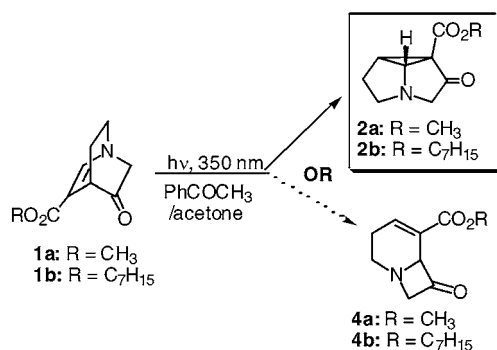
Scheme 3



Scheme 3.⁶ The methyl ester derivative **3a** required two steps to effect the installation of the double bond, followed by deprotection of the ketal with perchloric acid.⁵ However, in the preparation of the less volatile heptyl ester derivative **1b**, the perchloric acid served not only to deprotect the dimethyl ketal but also to oxidize the phenylselenenyl group, which subsequently eliminated under the reaction conditions.

The photochemical irradiation of bicyclic compound **1a** was run under triplet-sensitized conditions (acetophenone, quartz, 450 W Hanovia medium-pressure lamp).⁷ Two possible products, the 1,2-acyl shift (ODPM) product **2a** and the 1,3-acyl shift product **4**, are theoretically possible (Scheme 4).² The 1,3-acyl shift product normally arises from

Scheme 4



photolysis under nonsensitized conditions but can be formed from certain compounds under sensitized photolysis conditions. The 1,2-acyl shift product **2a** was the expected product under our reaction conditions.

From one-dimensional proton and carbon NMR spectra, the only product isolated from the photochemical rearrangement did not exhibit an olefin, as would be seen in the α,β -unsaturated ester **4a**. The carbonyl carbon peaks were at 207.6 and 165.9 ppm, consistent with the ketone and ester groups, respectively, in **2a**. A standard COSY spectrum

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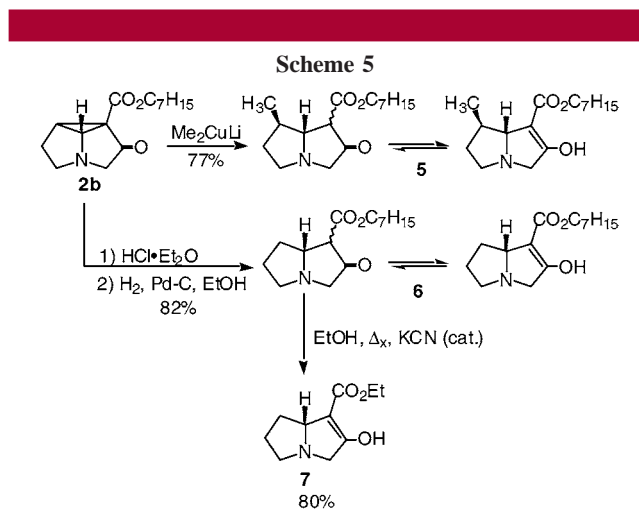
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established all of the proton–proton coupling networks.^{7,8} To assist in the assignments, the tricyclic structure **2a** was submitted to molecular mechanics calculations to estimate the dihedral angles between the protons and thus approximate the coupling constants using the Karplus equation.^{7a,8} The ¹³C and HETCOR spectra, as well as NOE experiments, further verified the proposed structure **2a**. Thus, the rearrangement occurred via an oxa-di- π -methane rearrangement and not by a 1,3-acyl shift mechanism.

In our initial photolyses, we utilized acetophenone as the solvent and the sensitizer. However, problems existed in the isolation of the photoproduct due to the volatility of **2a** and the amount of acetophenone sensitizer used. Therefore, we transesterified the methyl ester in **3a** to the heptyl ester **3b** in order to decrease the volatility of the photoproduct. Installation of the alkene in **3b** and hydrolysis of the ketal as described above yielded the photoprecursor **1b**. Subsequent photolysis under sensitized conditions using either 100% acetophenone or 5% acetophenone/95% acetone yielded the corresponding ODPM product **2b** as the only product isolated in 70% yield (material balance was starting material **1b**). Note that when 100% acetone was used as the solvent and the sensitizer, very poor conversion to the ODPM product was seen (2%). Optimization of the conversion was achieved by increasing the amount of acetophenone in small increments.

Thus, we have the first experimental evidence that the ODPM photochemical rearrangements of 1-aza-3-carboalkoxybicyclo[2.2.2]oct-2-en-5-ones did indeed produce the expected tricyclic photoproducts **2a** and **2b**.

To form the pyrrolizidine substructure, ring-opening reactions of the cyclopropane have been performed on the photoproduct **2b**.^{7b} Utilization of “soft” nucleophiles that were successful in the all-carbon systems, such as Nafion–TMS and CF₃CO₂TMS,^{3a,9} led to no reaction with the nitrogen-containing photoproduct **2b**. However, the harder nucleophile, lithium dimethylcuprate, worked well to open the three-membered ring to afford **5** in 77% yield as a single stereoisomer at the methyl group, but as a mixture of keto–



enol forms (Scheme 5). NOE experiments indicated that the relative stereochemistry of the methyl group was as shown.

Reductive cleavage of the cyclopropane in **2b** was also readily accomplished using H₂/Pd–C (after protonation of the nitrogen) to produce **6** in 82% yield as a mixture of the keto–enol forms. We have also successfully prepared the corresponding ethyl ester (**7**) in 80% yield via transesterification of the heptyl ester in **6**.^{7b} Benn and Rüeger have reported the hydrochloride salt of **7**.¹⁰ Further transformations of **2b** to other pyrrolizidine alkaloids are currently underway.

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Supporting Information Available: Experimental procedures and characterization data for **1a,b**, **2a,b**, **3a,b**, and **5–7**; two-dimensional NMR spectra of **2a,b**; selected one-dimensional NMR spectra; and a table of calculated proton dihedral angles with estimated and observed *J* couplings for **2a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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