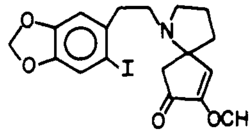
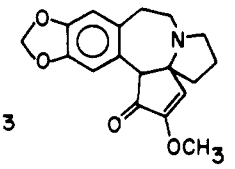
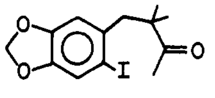
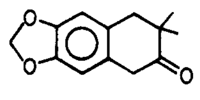
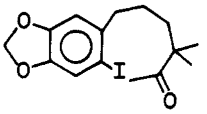
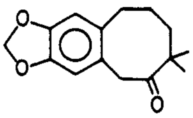
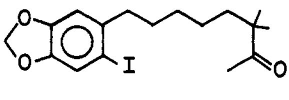
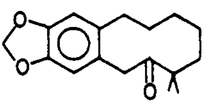
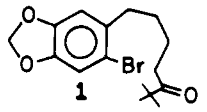
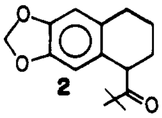
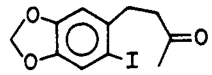
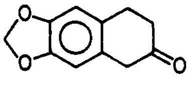
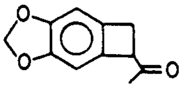
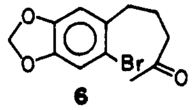
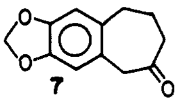
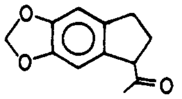
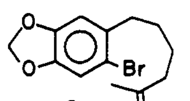
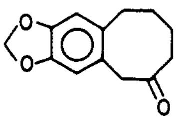
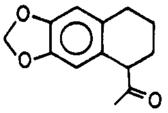
Communications

Cyclizations of Enolates onto Aromatic Rings via the Photo-$S_{RN}1$ Reaction. Preparative and Mechanistic Aspects

Summary: Six-, seven-, eight-, and ten-membered rings are obtained by photostimulated aromatic nucleophilic substitution by enolate anions, but only when internal H-atom transfer from the γ position of the ketone is blocked, as shown by deuterium labeling.

Sir: The photoinitiated substitution of carbanions for halide in aromatic rings, discovered by Bunnett and Rossi,[1] promises to be an important new method of nucleophilic aromatic substitution. Following the initial reports of simple intermolecular examples,[2] we found an efficient application of the reaction in the synthesis of cephalotaxine,[3] and thus became interested in the factors which govern the generality of the reaction for organic synthesis, particularly in cyclizations. Here we report preliminary results which begin to delineate the conditions under which the intramolecular photo-$S_{RN}1$ reaction is likely to be successful, and demonstrate that hydrogen atom migration can provide a serious side reaction in both intra- and intermolecular examples.

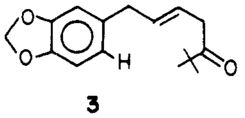
Table I. Photocyclization of Keto Halo Aryls

Entry	Halo ketone	Cyclzn products (yield[a] %)	
1.			(94)
2.			(99)
3.			(71,[b] 28)[c]
4.			(35)
5.	 1	 2	(11)
6.			(0)[d]
			(0)[d]
7.	 6	 7	(42)[d]
			(4)[d]
8.	 8		(19)[d]
			(3)[d]

[a] The yields are based on isolated material unless otherwise noted. [b] This yield was obtained at low concentration, ~0.00125 M. [c] This yield was obtained at the usual concentration, ~0.05 M. [d] The product ratios are based on uncalibrated GLC analyses; the combined yield is based on the weight of the mixture obtained after purification.

The studies have involved methylenedioxophenyl derivatives (Table I) which were chosen to test questions of ring size preferences in the cyclizations, including regioselectivity with ketones that can give two enolate anions. The reactions were carried out by dissolving the aryl halo ketone (1 mmol) and potassium *tert*-butoxide (6 mmol) in liquid ammonia (75–80 mL, reflux) in a Pyrex flask and irradiating with an external medium-pressure mercury arc (Hanovia 450 W) until the aryl halo ketone was consumed. Conventional isolation procedures provided the crude organic products from which the cyclized product was isolated by short-path distillation and chromatography. The yields are based on isolated material, unless otherwise indicated.[4]

Entries 1–3 of Table I demonstrate the cyclizations can be achieved efficiently; the ten-membered ring (entry 4) was obtained in reasonable yield assuming no special preference for medium-sized rings in this method. However, in cases where the more substituted (internal) enolate can appear (entries 5–9), the cyclizations are much less efficient. For example, compound **1** leads to the tetralin derivative **2** in only 11% yield (entry 5). The major monomeric product (67%) was the β,γ-unsaturated ketone **3** (presumably from isomerization of the α,β isomer, **4a**),[5] while a trace of the reduction product, **5a**, was detected by GC–MS. Where a four- and a six-membered ring could reasonably be expected, neither was obtained (entry 6) and the reduction product (**5b**) could be isolated in 21% yield as the only monomeric product. Compound **6** produced mainly the seven-membered ring (**7** entry 7) along with approximately equal amounts of five-membered ring, the



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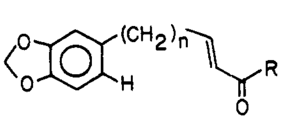
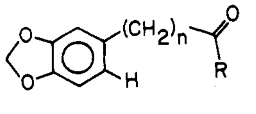


4a: R = C(CH$_3$)$_3$, n = 2
b: R = CH$_3$, n = 1
c: R = CH$_3$, n = 2



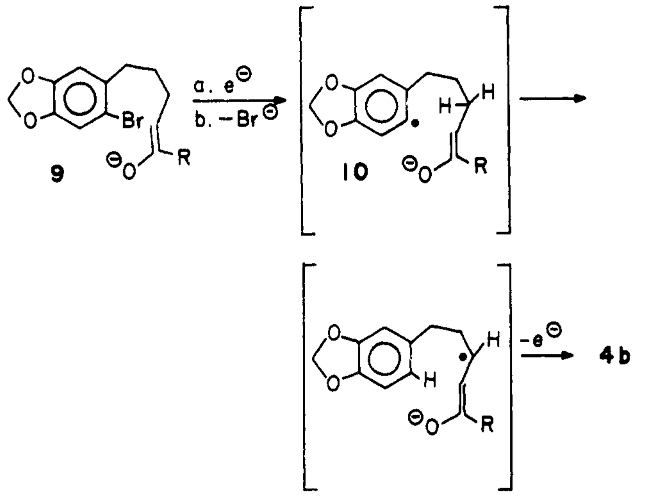
5a: R = C(CH$_3$)$_3$, n = 4
b: R = CH$_3$, n = 2
c: R = CH$_3$, n = 3
d: R = CH$_3$, n = 4

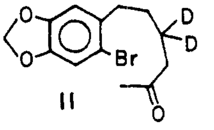
α,β-unsaturated ketone (**4b**) and the reduction product (**5c**). From **8**, the yield of monomeric material was 31%, trace amounts of reduction product (**5d**, 3%) and the six-membered ring (entry 8, 3%), and larger amounts of the α,β-unsaturated ketone (**4c**, 7%) and the eight-membered ring (entry 8, 19%).

In related experiments, the enolate anions were generated quantitatively using potassium amide. Irradiation produced a larger proportion of product resulting from cyclization through the unsubstituted (presumably, kinetic) enolate. From **6** (entry 7) under these conditions, only reduction product **5c** (23% yield) and the seven-membered ring (21% yield) were obtained. From 8 (entry 8), the reduction product **5d** (3%) and the eight-membered ring (11%) were obtained. There was only a trace of the six-membered ring.

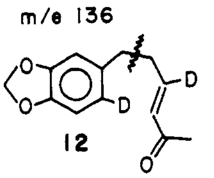
The formation of unsaturated ketones with concomitant replacement of halogen by hydrogen suggested the possibility of intramolecular hydrogen atom transfer from the β position of the enolate (e.g., **9** in Scheme I) to the transient phenyl radical (i.e., in **10**);[6] then hydrogen-atom abstraction through a six-atom transition state would produce the enone–radical anion (Scheme I), the usual species formed in electron transfer to α,β-unsaturated ketones. This reaction would serve as a propagation step in the radical-chain mechanism,[7] and intermolecular reactions of the intermediates might explain the low yields of monomeric products sometimes observed. Consistent with this hypothesis, the dideuterated analogue **11** under the usual reaction conditions produced the unsaturated ketone (i.e., **12**) with 2.0 ± 0.1 deuterium atoms/molecule and 1.0 ± 0.1 deuteriums/unit in the mass spectral fragment at m/e 136, the piperonyl ring unit.

Scheme I





11



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There has been no direct evidence reported which implicates hydrogen-atom transfer from the enolate anion as a significant side reaction in intermolecular examples of the photo-$\mathrm{S_{RN}}1$ reaction.[8] However, alkyl-substituted enolate anions, where the β hydrogen is available, are known[9] to undergo the photo-$\mathrm{S_{RN}}1$ reaction much less efficiently than unsubstituted analogues. For example, the lithium enolate of *tert*-butyl 2-methylpropionate reacted with p-bromoanisole upon irradiation to give *tert*-butyl 2-(p-methoxyphenyl)-2-methylpropionate in 5% yield; the major product was anisole (35–50%). Lithio *tert*-butyl acetate reacted under the same conditions, affording *tert*-butyl (p-methoxyphenyl)acetate (67%) and *tert*-butyl di(p-methoxyphenyl)acetate (29%). Irradiation of the enolate from *tert*-butyl 2-(trideuteriomethyl)-3,3,3-trideuteriopropionate with p-bromoanisole under the usual conditions produced anisole in 54% yield, with 35% of it labeled with one deuterium, confirming the major role of H-atom abstraction from the enolate.

These studies suggest that the photo-$\mathrm{S_{RN}}1$ reaction of enolate anions with aryl halides can be efficient for intramolecular cases as well as in the well-established intermolecular examples, but, when a hydrogen atom is present at the β carbon in the enolate anion, hydrogen-atom transfer to the transient phenyl radical is generally the dominant process.[10]

References and Notes

(1) J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976), and references therein.
(2) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).
(3) (a) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975); (b) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973).
(4) All new compounds showed satisfactory spectral data (^{1}H NMR, IR, low resolution mass spectra). The starting compounds in entries 1, 2, 3, 5, 6, 7, and 8 and the products in entries 1, 2, and 3 of Table I have given satisfactory combustion analysis.
(5) The α,β ketone **4b** was prepared by aldol condensation between pinacolone and 3-(3,4-methylenedioxophenyl)propionaldehyde and fully characterized. Upon treatment with potassium *tert*-butoxide in liquid ammonia (approximately the conditions for the photo-$\mathrm{S_{RN}}1$ reaction except in darkness), the α,β isomer was converted essentially quantitatively to the β,γ isomer **3**. Therefore we believe the α,β-unsaturated ketone **4b** to be the first-formed product from the photo-$\mathrm{S_{RN}}1$ reaction of **1**.
(6) The intermediacy of phenyl radicals in the photo-$\mathrm{S_{RN}}1$ reaction has been suggested and supported by Bunnett and his coworker.[2]
(7) The radical-chain mechanism has been proposed by R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 683 (1972).
(8) Bunnett and Sundberg have obtained hexamethyloctanedione as a rate-depressing side product in the reaction of diisopropyl ketone enolate with iodobenzene.[1]
(9) (a) T. Bargar, unpublished work at Cornell; (b) ref 1.
(10) We wish to acknowledge generous financial support from the Public Health Service through NIH Grant AI-08687. In addition we are grateful to Mr. Jeffery Hayes who carried out the experimental tests for one of the entries in the table (entry 4).
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(12) National Institutes of Health predoctoral trainee, 1973–1976.

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Nucleophilic Hydroboration of Substituted Styrenes with Lithium Triethylborohydride. A Simple Convenient Procedure for the Markownikoff Hydroboration of Aromatically Conjugated Olefins and the Synthesis of Mixed Organoboranes with the Benzylic (α-Arylalkyl) Moiety

Summary: Lithium triethylborohydride ($\mathrm{LiEt_3BH}$) adds to substituted styrenes under relatively mild conditions to give the corresponding tetraalkylborates, readily hydrolyzed to the corresponding saturated hydrocarbons or protonolyzed with strong acids to the mixed trialkylboranes containing a benzylic group.

Sir: We wish to report a simple regiospecific addition of lithium triethylborohydride to aromatically conjugated olefins under remarkably mild conditions to give the addition product 1 (eq 1). Furthermore, by the treatment of 1 with water, the