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PHOTOREDUCTIVE CYCLIZATION OF UNSATURATED ALDEHYDES : AN EASY ACCESS TO SPIRANIC MOLECULES

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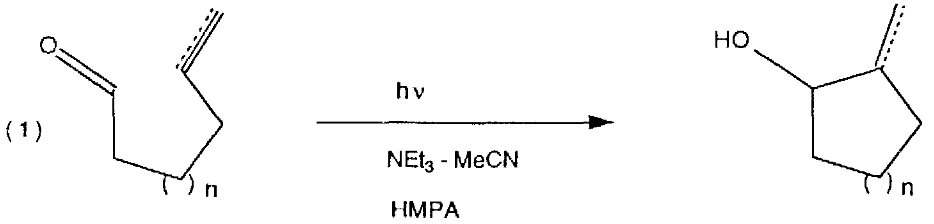
Summary : *The photoreductive cyclization of ω-unsaturated aldehydes is an efficient process which leads to substituted cycloalkanols. This process is used as a convenient approach to spiranic molecules.*

We previously reported that δ,ε-unsaturated ketones can undergo photoreductive cyclization in the presence of tertiary amines or hexamethylphosphoric triamide (HMPA)[1]. Polycyclic skeletons have been produced by this photochemically induced radical cyclization, and used in natural products synthesis[2,3]. Furthermore, this reaction proved to be an excellent approach towards furofuran skeleton[2].

The replacement of a ketone by an aldehyde group should not only favour the reduction process but also allow the formation of cyclized products substituted by a secondary alcohol [equation 1].

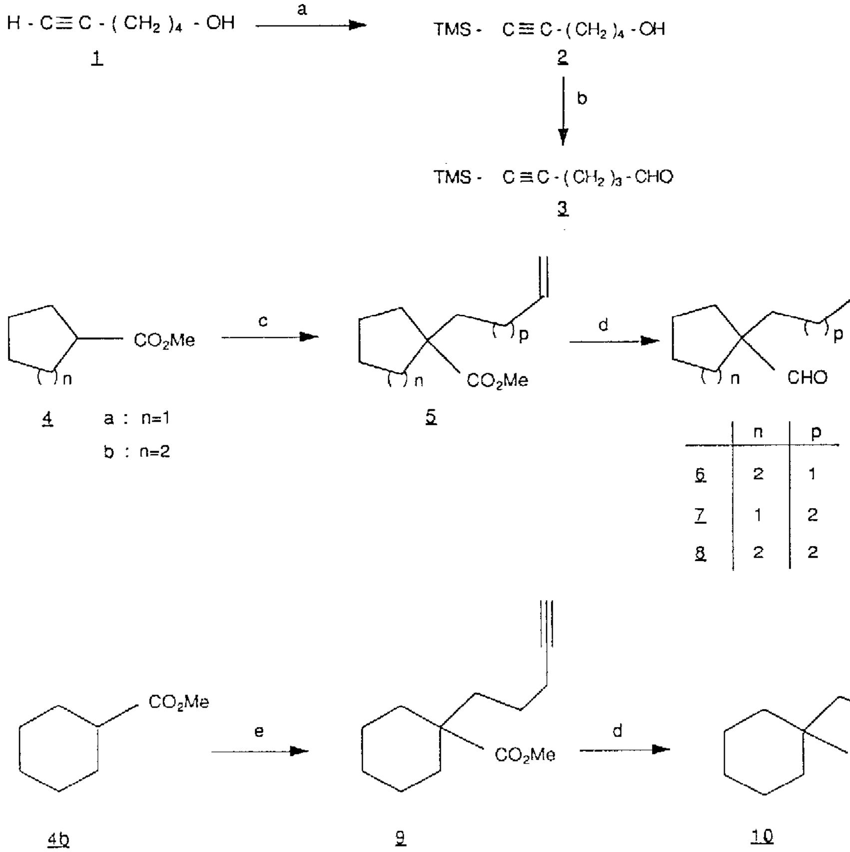
(1)



We report now that the photoreductive cyclization of unsaturated aldehydes is indeed an efficient process.

The unsaturated aldehydes were prepared according to scheme I.

Scheme I

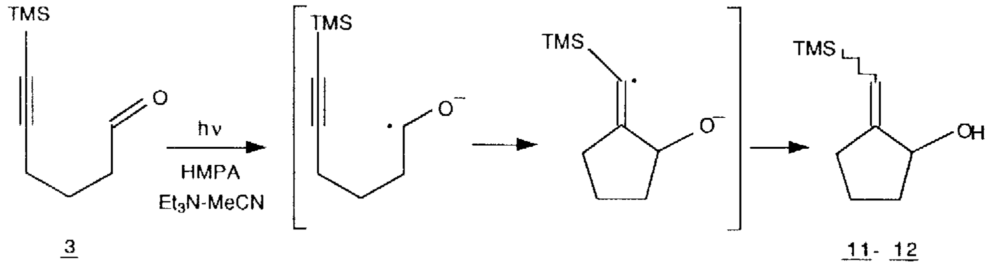


	n	p
6	2	1
7	1	2
8	2	2

(a) i: n BuLi (2.2 eq), TMSCl (2.2 eq), THF, -20°C ; ii: CH_3CO_2H, 3N (86%); (b) PCC (1.5 eq), CH_2Cl_2, molecular sieves 4 Å, 0°C (85%); (c) i: LDA, THF/-45°C; ii: HMPA (3 eq), $Br\text{-}CH_2\text{-}(CH_2)p\text{-}CH{=}CH_2$, -78°C (70%); (d) i: $LiAlH_4$ (1.5 eq), THF, 0°C; ii: PCC (1.5 eq), CH_2Cl_2, molecular sieves 4 Å, RT (75%); (e) i: LDA, THF, -78°C; ii: $Br\text{-}(CH_2)_3\text{-}C{\equiv}CH$, -78°C (70%).

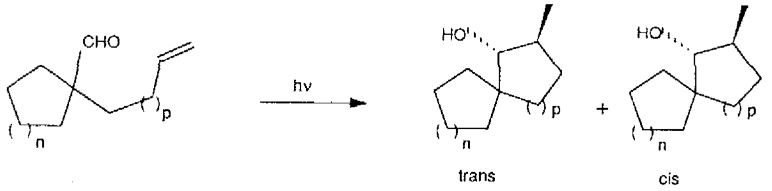
When 3 is irradiated in acetonitrile in the presence of triethylamine (5 eq), a mixture (1:1) of two alcohols 11 and 12 is obtained (equation 2). This unexpected absence of stereoselectivity implies that the hydrogen abstraction by the vinyl radical intermediate is not sensitive to steric hindrance[4] appearing in the final product.

(2)



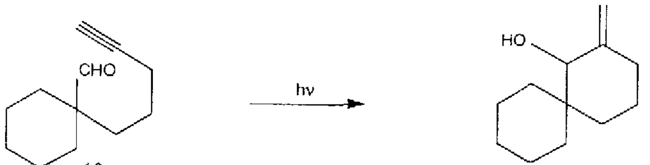
Very little attention has been paid to the access to spiranic molecules by radical cyclizations[5]. It appears that photoreductive cyclization of ω-unsaturated aldehydes should be very useful for this purpose according to scheme II.

Scheme II



	n	p	conditions	product	yield	trans/cis
6	2	1	HMPA	13	65%	90/10
			Et$_3$N-MeCN		74%	77/23
7	1	2	HMPA	14	40%	a*
			Et$_3$N-MeCN		38%	a*
8	2	2	HMPA	15	24%	58/42
			Et$_3$N-MeCN		30%	33/67

a* = not determined, low stereoselectivity



10

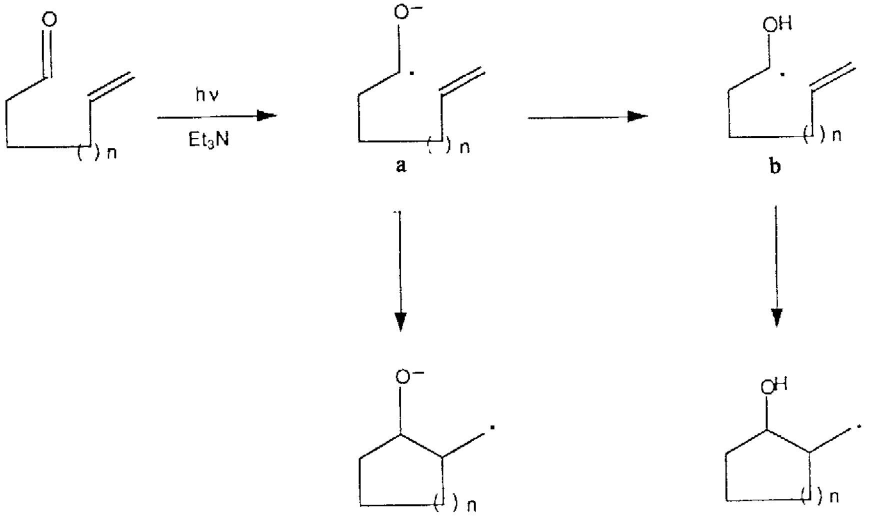
16

HMPA	55%
Et$_3$N-MeCN	68%

Spiro [4.5] decane or spiro [5.5] undecane skeletons are obtained by reductive photocyclization of unsaturated aldehydes 6-8 and 10. The efficiency of the reaction depends on the size of the newly formed cycle. The lower chemical yields observed for 14 and 15 than for 13 are explained by the greater difficulty to form 6- rather than 5-membered rings in radical cyclization. The ring size also affects the stereoselectivity. A decrease of the stereoselectivity is observed in 14 and 15 compared to 13. Furthermore, as previously noticed[1b], this stereoselectivity depends on the nature of the reducing medium HMPA or Et$_3$N-MeCN. The effect of the reducing agent is particularly remarkable on 15, where a reversal of the proportion of the two diastereoisomers is observed when HMPA is replaced by triethylamine.

The high selectivity obtained in the formation of 13 in HMPA seems to reflect the repulsive electronic interactions between the oxygen of the ketyl radical anion and the ethylenic double bond involved in the transition state leading to 5-membered ring. When 6-membered rings are formed, steric factors might be more important. The replacement of HMPA by triethylamine-acetonitrile induces a modification of the stereoselectivity as it has already been observed for the reductive cyclization of unsaturated ketones[1].

The protonation of a radical anion such as A by $Et_2\overset{\bullet+}{N}-CH_2-CH_3$ is known to be a very fast process[8] which can compete with the cyclization step. When the reductive cyclization is carried out in Et_3N-MeCN, the decrease of the selectivity can be explained by a protonation of A into B prior to the cyclization. Due to the protonation of the oxygen in B, the electronic repulsion between the oxygen and the ethylenic bond is then reduced and the stereoselectivity minimized.



This mild radical cyclization represents one of the few methods for obtaining functionalized spiranic molecules.

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6. The starting aldehydes dissolved in HMPA ($5x10^{-2}M$) or in a mixture of triethylamine (5 to 10 eq) and acetonitrile ($3.5x10^{-2}M$) are irradiated at 254 nm. The irradiation is stopped when all the starting material has disappeared as shown by TLC.
7. The stereochemistry of the cyclization products 13-15 is deduced from the coupling constants for the CHOH protons.
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