

0040-4020(94)E0104-2

Efficient Cleavage of Cyclopropyl Bond by Adjacent Ketyl Radical Generated Under PET Conditions

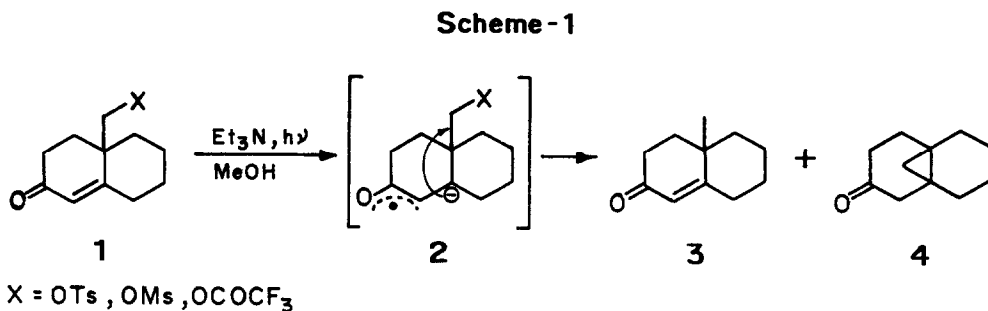
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Abstract: Photolysis of various conjugated cyclopropyl and epoxy ketones in 20% triethyl amine (TEA) and ethanol leads to cleavage of cyclopropyl bond. Significant wavelength dependence phenomenon is observed during photolysis for the cleanliness and efficient photo transformation. Steroidal cyclopropyl ketones cleave efficiently at 300nm photolysis, whereas exo-cyclopropyl ketones cleave at 254nm. The regiochemistry of cyclopropyl bond cleavage is governed by the principle of maximum overlap. The nature of chemistry generated by ketyl radical is shown to be a function of methodology of their generation.

In the preceding publication, the generality and limitations of cyclobutyl bond cleavage adjacent to PET (Photoinduced Electron Transfer) generated ketyl radicals has been examined.¹ Additionally, the cleavage of even cyclopentane ring in the bicyclic ring systems, during efficient isomerization of Diels-Alder endo to exo isomers has been indicated.²⁻⁵ Although the cleavage of strained ring systems of cyclobutane and cyclopropane conjugated to ketone has been of considerable interest, from the photochemical⁶ and from electron transfer studies via electrochemical,⁷ samarium iodide⁸ and alkali metal induced transformation,⁹ no detailed studies under PET conditions are available.¹ Givens et al¹⁰ have postulated the cleavage of cyclopropane ring during photolysis of **1** under PET conditions and an interesting mechanism involving cyclopropyl radical formed by nucleophilic displacement of tosylate, mesylate, triflate etc. from distonic radical anion **2** has been proposed (Scheme-1). During an earlier study involving the photochemistry of a cyclopropyl ketone **5** with electron rich diene i.e., 2-silyloxy-1,3-butadiene,¹¹ it was tempting to presume that the initial step was an electron transfer from the diene to excited ketone **5**, which led to cleavage of cyclopropane, followed by coupling of two species. Thus, we were curious whether the cleavage of cyclopropyl ketones will be feasible under our new PET conditions i.e., photolysis in a polar and protic solvent ethanol with TEA. Here we report that unlike cyclobutyl ketones,¹ the cleavage of cyclopropyl ketone and epoxy ketone under our new PET conditions is a facile process. The regiochemistry of bond cleavage is governed by the principle of maximum overlap of σ and π^* orbitals. Thus, exocyclic cyclopropanes could be utilized as ethyl equivalent synthon. Our studies reveal an interesting wavelength dependence (254nm vs 300nm) phenomenon for efficient PET cleavage.

Dedicated to Dr.B.A. Nagasampagi on the occasion of his 60th birthday.

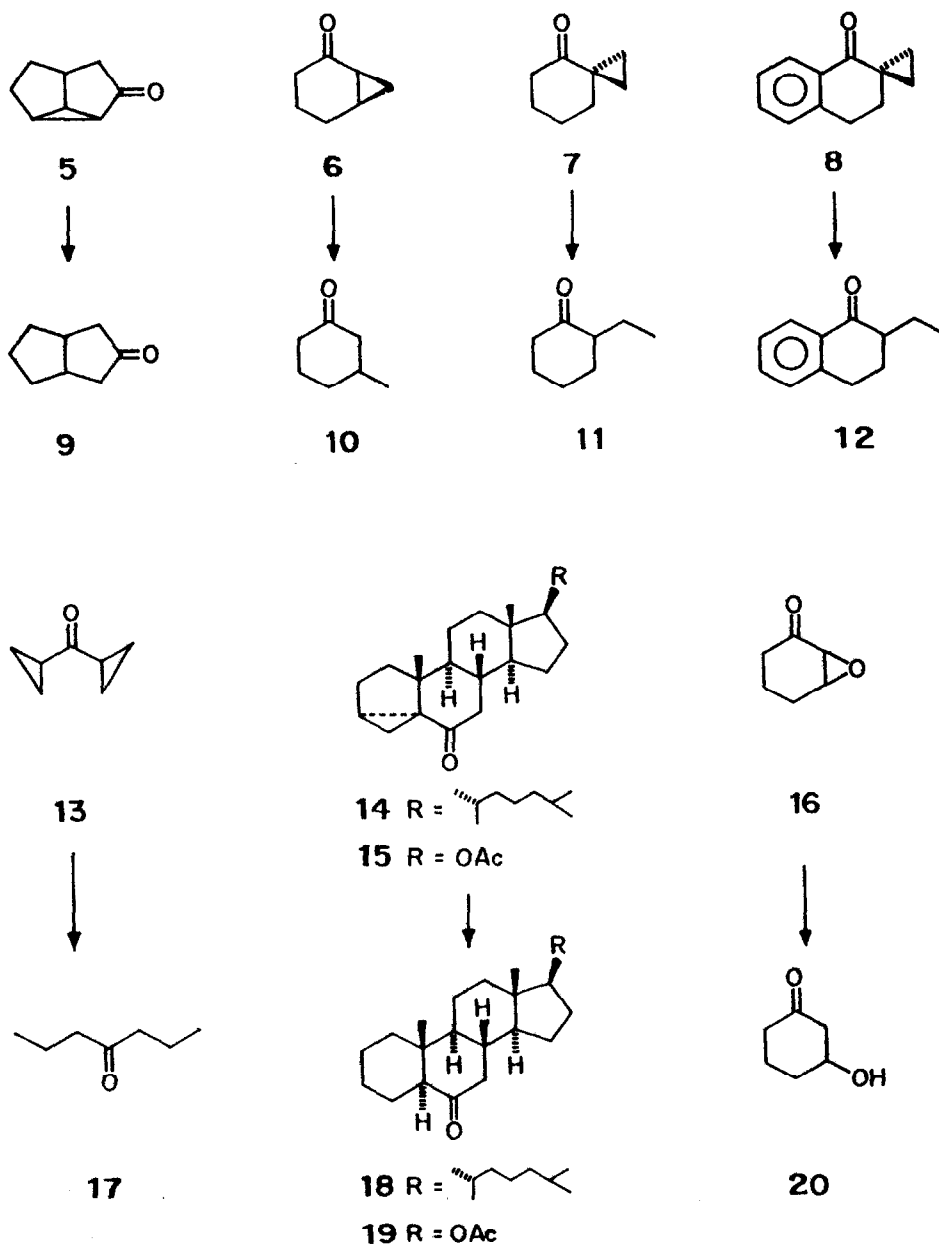
**Table-1:**

Entry No.	Starting Ketone	Reaction condition ^a	Irradiation ^b (nm)	Duration (h)	Product (Yield %)
1	5	A	300	6	9 (79)
2	6	A	300	4	10 (55) ^c
3	6	B	254	2	10 (48) ^c
4	6	C	254	10	10 (40) ^c
5	7	A	300	4	11 (40) ^c
6	8	A	254	8	12 (79)
7	8	A	300	8	8 (90)
8	8	A	350	8	8 (92)
9	13	A	300	4	17 (36) ^c
10	14	A	254	6	14 (96)
11	14	A	300	6	18 (80)
12	15	A	254	6	15 (92)
13	15	A	300	6	19 (87)
14	16	A	254	3	20 (49) ^c
15	16	A	300	3	20 (15) ^d

- a: A: Reaction condition means that substrate (0.02M) was dissolved in 20% TEA/EtOH by volume, degassed and irradiated as indicated
 B: Cossy procedure-0.05M substrate in CH₃CN and 5 eq. of TEA in quartz vessel irradiated at 254nm.¹²
 C: Mattay's procedure-0.05M substrate in CH₃CN and TEA (254nm) irradiated in sealed glass tube.¹²
- b: Rayonet reactors with either 350nm/300nm or 254nm lamps were used.
- c: The mass balance was >90%.
- d: Side products and tar are obtained.

The various cyclopropyl and epoxy ketones examined in our studies eg. 5¹³, 6⁶, 7¹⁴, 8¹⁴, 13¹⁵, 14¹⁶, 15¹⁶ and 16¹⁷ were prepared as per literature procedures (Table-1). The products eg 9¹⁸, 10¹⁹, 11²⁰, 12²¹, 17²², 18⁹, 19²³ and 20²⁴ were characterized by comparison with the IR, ¹H-NMR, MS and physical characteristics of authentic sample. The experimental conditions were utilized as developed in the preceding and earlier publications.^{1,2,3,5} Thus, a 0.02M solution of the substrate in 20% TEA in ethanol (by volume) was irradiated at suitable wavelength (at 254nm in

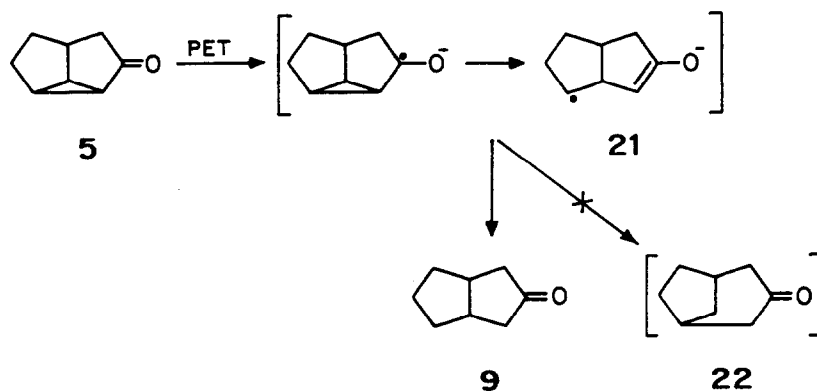
Scheme-2



Quartz or 300nm/350nm in Pyrex vessel and successful cleavage of cyclopropyl group was achieved.²⁵ It is well established that an efficient electron transfer can occur from the amine to the excited ketones.²⁶ The PET conditions are possible either by exciting the ketones at 300/350nm or by exciting the donor molecule TEA at 254nm.²⁷

One of the important observation is the fact that the wavelength of excitation eg., Rayonet 254nm vs 300nm, matters in governing reactivity and selectivity, in cleavage related to cyclopropyl and epoxy ketones. Thus, the irradiation of **8** at 300 or 350nm does not lead to any change in starting material (entry 7 & 8), whereas irradiation at 254nm leads to complete conversion to cleaved product **12** (79%, entry 6). Similarly, the irradiation of PET-reaction mixture of epoxy ketone **16** gives a better and cleaner yield of cleaved product **20** at 254nm, than at 300nm (entry 14 & 15). On the contrary, in steroidal cyclopropyl ketones eg., **14** and **15**, no cleavage could be effected at 254nm, whereas 300nm irradiation led to efficient conversion to cleaved products **18** and **19** (entry 10-13). Interestingly, the cleavage of chromophorewise highly identical cyclopropyl ketones **7** and **8** was influenced by wavelength of irradiation. Thus, **7** gave efficient transformation at 300nm, whereas **8** gave efficient cleavage at 254nm (entry 5-8). Comparably, for the efficient transformation of **6** to **10** without any side product eg., reduced alcohol, under our experimental condition at 300nm irradiation, has been found to be more suitable than 254nm irradiation reported by Mattay and Cossy¹² (entry 2-4). Thus, cleavage of cyclopropyl ketones seems to be quite wavelength specific. This specificity leads to yet another dimension in the complexity of understanding and generalizing the PET-related chemistry. Thus, the method of generating radical anions, either by exciting the donor molecule TEA or by exciting the ketone, matters in effecting chemical transformations.

Scheme - 3



During the transformation from **5** to **9** under PET-conditions, complete regioselectivity of cyclopropyl bond cleavage was observed (Scheme-3). Interestingly, similar regioselectivity of bond cleavage was observed earlier during its photochemical studies and the biradical was trapped by a reactive diene.¹¹ Additionally, the efficient transformation of exo-cyclic cyclopropyl ketones eg., **7** to **11**, **8** to **12** and **13** to **17** clearly indicates that cyclopropyl

group can as well be thought of as synthetic equivalent of ethyl group. Normally, it is utilized as dimethyl equivalent only *via* catalytic hydrogenation. The mechanism of PET induced cleavage of cyclopropyl ketones can be visualized as shown in Scheme-3. The transfer of electron from TEA to enones and ketone is well established.^{1-3, 26-30} Thus, the radical anion of **5** cleaves to give **21**, which is trapped by EtOH to give **9**. Interestingly, under our PET conditions, no reduction of ketones occurs either to alcohols or to deoxygenated analogues, which are a common side products under ground state electron transfer reactions. Compared to Givens,¹⁰ where pinacol type products dominated, no such products were observed under our PET conditions. The regioselectivity of bond cleavage is governed by the maximum overlap principle between σ of cyclopropyl bonds and π^* of carbonyl or vice-versa.^{6,9} Thus, no products similar to **22** were observed from **5**. Whether our PET is governed by single electron transfer (SET) principle, it is difficult to decide. It is possible to get products by double electron transfer as well.

In conclusion, an efficient PET methodology has been developed for regioselective cleavage of cyclopropyl and epoxy ketones. These reactions show significant wavelength dependence. The nature of chemistry generated by ketyl radical anions has been shown to be a function of methodology of their generation.

Experimental:¹

For general information regarding instrumentation, analytical techniques employed, see the experimental section of preceding publication.

The various substrates used for β -cleavage studies eg. cyclopropyl ketones **5**¹³, **6**⁶, **7**¹⁴, **8**¹⁴, **13**¹⁵, **14**¹⁶, **15**¹⁶, and epoxyketone **16**¹⁷ were prepared as per literature procedures. The substrates (0.02M) were dissolved in 20% TEA:EtOH (by volume). The solution was purged with slow stream of nitrogen gas for 10 min and then irradiated in Srinivasan-Rayonet photochemical reactor at 254nm in a quartz vessel or 300nm in pyrex tube for 2 to 10h (Table-1). The progress of the reaction was monitored by GC/TLC. The solvent and TEA were evaporated under reduced pressure and the crude product obtained was purified on silica gel column using pet.ether:acetone as eluent. The products eg. **9**¹⁸, **10**¹⁹, **11**²⁰, **12**²¹, **17**²², **18**⁹, **19**²³, and **20**²⁴ were fully characterized by comparison with the IR, ¹H-NMR, MS and physical characteristics of authentic sample.

Acknowledgements¹ : This is NCL communication No.5903.

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(Received in UK 24 November 1993; accepted 21 January 1994)