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A New Strategy for the Construction of Carbo- and Oxycycles by Intramolecular Reductive Coupling of α,β-Unsaturated Esters.

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Abstract: Intramolecular coupling of α, β-unsaturated esters by photosensitised one electron reductive activation is reported to provide carbo- and oxycycles.

Increasing attention is given currently to explore the synthetic potentials of one-electron reductive reactions, particularly, in the carbon-carbon bond formation reactions. Generally, low-valent metallic species[1,2] have emerged as useful reagents in this context, however, limited use of these reagents are reported[2d,e] in the coupling of α,β-unsaturated esters. Coupling of α,β-unsaturated esters employing cathodic[3] and Mg/MeOH[4] reductions are known, however, these methodologies are either too difficult to adopt in normal synthetic laboratories[3] or involve toxic reagents[2d] and/or dry reaction conditions.[4] In the present era of increased ecological concern and increasing demand for the development of simpler and efficient synthetic

Fig.-1 PS - A

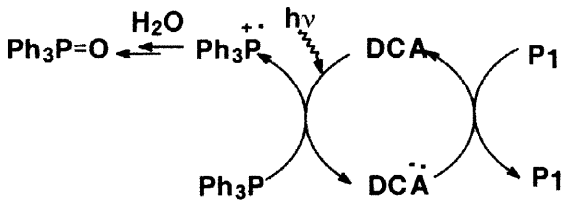
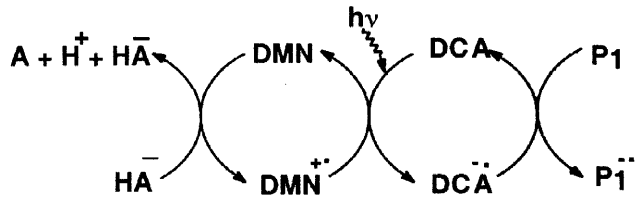


Fig.-2 PS - B



P1= Compounds, DCA= 9,10-Dicyanoanthracene, DMN=1,5-Dimethoxynaphthalene, HA-.= Ascorbate ion

methodology using aqueous solvent, an alternative strategy to effect one electron reductive chemistry is

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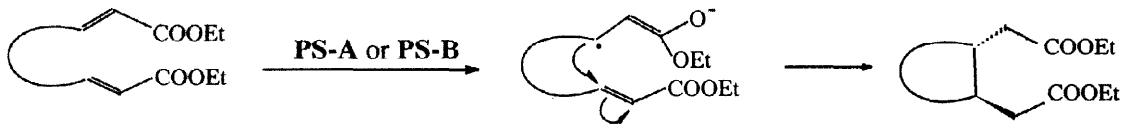
essential. As a part of our efforts in this direction, recently, we have developed two photosystems[5] [**PS-A**, (Fig. 1) and **PS-B**, (Fig. 2)] for initiating photosensitized one electron reductive β-activation of α, β-unsaturated ketones to carbon centered radicals[5] and aldehydes and ketones to ketyl radicals.[6] In order to explore the scope of these photosystems in the intramolecular coupling of α,β-unsaturated esters, as shown in **Scheme-I,** we are pleased to disclose our preliminary results in this communication.

SCHEME - I



1 2 3

To realize the transformation as depicted in **Scheme-I**, photosensitised electron transfer (PET) activation of **4** was at first initiated using **PS-A** reaction condition.[5, 6] It essentially involved the irradiation (405 nm) of a mixture of **4** (2.4 mmol), DCA (0.6 mmol) and Ph_3P (1.45 mmol) in DMF: i-PrOH: H_2O (88:10:2). The 405 nm light was obtained by allowing the light from a 450-W Hanovia medium pressure lamp to pass through a $CuSO_4.5H_2O$: NH_3 solution as filter.[7] Progress of the reaction was monitored by GC analysis. After ≈ 95% disappearance of **4**, reaction was worked up as usual to get **10** as a non-separable mixture of two diastereomers in 90 % overall yield. Ph_3PO was formed as side product and DCA was recovered back almost quantitatively (≈ 98 %). The diastereomeric ratio of **10** (*trans/cis*, 17 : 3) was established by GC (25 m, phenyl methyl silicone capillary column) analysis. The structure of the product was characterised by ^1H NMR, ^{13}C NMR and mass spectral data.

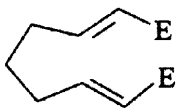
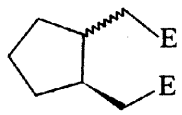
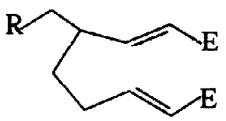
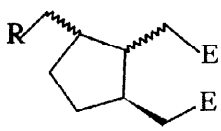
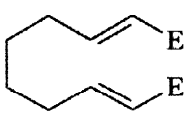
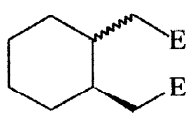
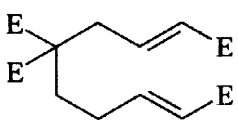
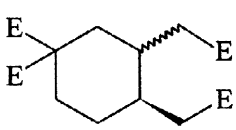
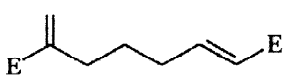
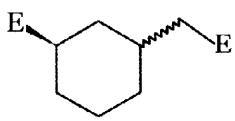
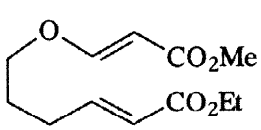
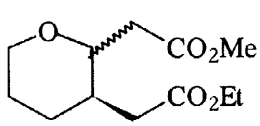
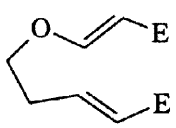
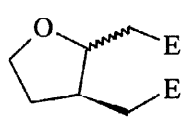
Analogous PET activation of **4** using **PS-B** reaction condition[5, 6] also gave **10** in 92 % yield. The **PS-B** reaction condition involved irradiation of a mixture of **4** (2.4 mmol), DMN (0.4 mmol) and ascorbic acid (6.2 mmol) in the presence of DCA (0.6 mmol) at 405 nm. At the end of the reaction, DCA and DMN were recovered back almost quantitatively as observed earlier.[5, 6]

To evaluate the generality of this cyclisation strategy, substrates **4 - 9** were studied and the results are depicted in **Table-I**.

Since the success of this coupling (**SCHEME - I**) is based on the redox potential difference between α,β-unsaturated esters and $DCA^{\cdot-}$, it was envisaged that this reaction could be made selective by altering the electronic behavior of one of the interacting ester moiety. In this context, we envisioned that the PET reduction of **16** would lead to the selective activation of α,β-unsaturated ester moiety over the β-alkoxy acrylate and subsequent cyclisation of the resultant ester enolate radical would provide an easy and attractive

strategy for the stereoselective synthesis of 2,3-disubstituted cyclic ethers[8] prevalent in numerous polyether and ionophore natural products.[9]

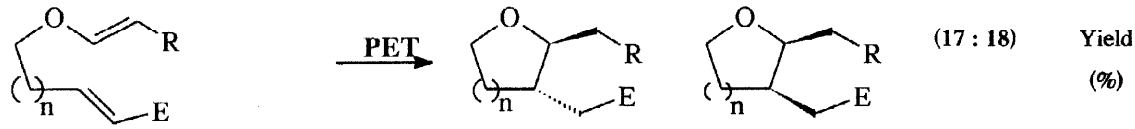
Table-I ***Intramolecular reductive coupling of α,β-unsaturated esters***

Substrate[a]	Products[b, c]	Yields[d](%)	Trans/Cis[e]
 4	 10	90	(85 :15)
 5 (R = OTBDMS)	 11	80	(80 :20)
 7	 13	85	(75 :25)
 8	 14	80	(70 :30)
 9	 15	60	(40 :60)
 10	 16	55	(75:25)
 11	 17	75	(80:20)

(a) E = COOEt (b) Characterised by ^{1}H NMR, ^{13}C NMR, Mass spectral data (c) Average time of irradiation for all the substrates is 20-25 h. (d) Isolated yields but not optimised, (e) Estimated by capillary GC (25 m, Phenyl methyl silicone)

Towards this end, when substrate **16** was subjected to PET activation, in an identical fashion as described for **4**, using either **PS - A** or **PS - B** reaction conditions, afforded cyclic ethers (**17** and **18**) in moderate to good yield (55-75 %) (**SCHEME - II**).These products were characterised by ^{1}H NMR, ^{13}C NMR and mass spectral data.

SCHEME - II



			(17 : 18)	Yield (%)
16a, n = 1, R= E = COOEt	**17**	**18**	80 : 20	75
16b, n = 2, R = COOMe, E = COOEt			75 : 25	55

In summary, we have developed a new strategy for the intramolecular coupling of α,β-unsaturated esters to construct the carbo- and oxycyclic ring systems by visible-light initiated one electron reductive activations.

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