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The intermolecular β-coupling of cyclic enones with activated alkenes and alkynes: Unexpected β-alkoxy elimination from a 4-alkoxy-2-alkyl-1-hydroxy-cyclopentenyl radical

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Abstract: *Intermolecular β-coupling of cyclic enones with activated alkenes or alkynes and an unexpected β-alkoxide elimination from 17 during the extension of this strategy towards the synthesis of optically pure prostaglandin analogues by the coupling of* **16** and **11** *is reported.*

Recently, we have developed two novel photosystems (**PS-A** & **PS-B**) for harvesting visible light photons into electrons and have shown their utility for the activation of α,β-unsaturated ketones (enones) at their β-positions[1,2] as carbon centered radical precursors. Intramolecular additions of these radicals to tethered activated olefins provided unique opportunities for the stereoselective construction of *trans*-1,2-disubstituted cycloalkanes[2]. We have explored the scope of these photosystems[1,2] for the development of a carbon-carbon bond formation strategy at the β-position of enones, generally achieved only by the conjugate addition of carbon nucleophiles[3] or alkane radicals[4]. We report herein the intermolecular coupling of enones at their β-positions with activated alkenes and alkynes (**Scheme-I**).

Scheme-1

1 **2** **3**

This communication also includes an unexpected β-alkoxide elimination from **17** which was observed during the extension of this strategy towards the syntheses of optically pure prostaglandin analogues (**15**). To the best of our knowledge, this is the first report of this chemistry.

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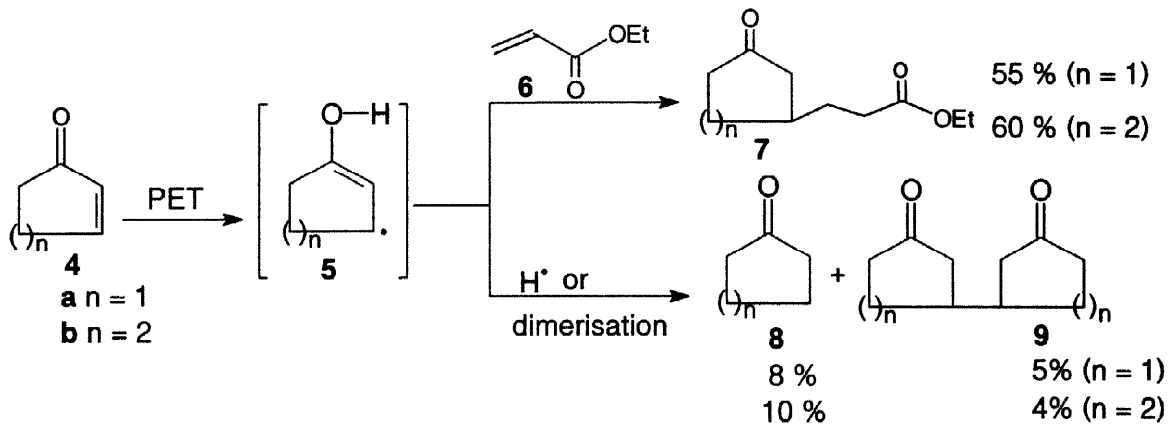
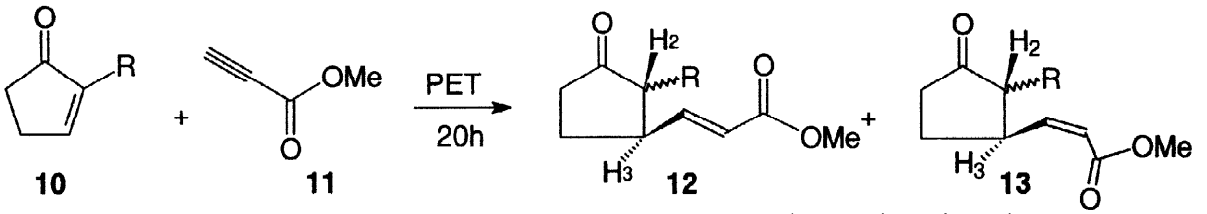
In order to evaluate the intermolecular coupling as shown in **Scheme-1**, PET activation of a mixture of cyclopentenone (**4a**) with ethyl acrylate (**6**) was studied. The coupling between **4** and **6** involved the irradiation (**PS-A** conditions) of a mixture containing 9,10-dicyanoanthracene (DCA) (0.2 equiv.), **4** (1 equiv.), Ph_3P (0.8 equiv.) and **6** (2.5 equiv.) in DMF:iPrOH:H_2O (88:10:2) using 405 nm light[5]. Evaporation of the solvent under reduced pressure followed by purification gave **7** (55 %) along with the reduced enone (**8**, 10 %), the dimer (**9**, 5 %) and some polymeric material (**Scheme-2**). DCA was recovered almost quantitatively (>98 %). Identical results with cyclohexenone (**4b**, n = 2) suggested the generality of the reaction.

Scheme-2



There are several naturally occurring, biologically active compounds possessing 3-*E*-alkenylcyclopentanones (e. g. prostaglandins[6]). PET activation of the cyclopentenone (**10a**) with methyl propiolate (**11**) was considered as a route to these compounds. Usual PET activation (**PS-B** conditions)[7] of a mixture of **10a** and **11** gave **12a** (major) and **13a** (minor) in a ratio of 5:1 with a combined yield of 65 %. The geometry of the olefin in **12a** as well as in **13a** was established by ^1H NMR spectral data. Furthermore, to extend the scope of this coupling strategy for the synthesis of 2,3-dialkylated cyclopentanones and also to establish the relative stereochemistry between H_2 and H_3, as there are several important biologically active 2,3-dialkylated cyclopentanones e. g. jasmone[8] and prostaglandins[6], the coupling between **10b** with **11** was studied. PET reductive activation of a mixture of **10b** and **11**, in manner analogous to that described above, led to the formation of **12b** and **13b** which were easily analysed in 62 % yield (**Scheme-3**). The product **12b** was characterised as a mixture of two diastereomers, the ratio of which was measured by comparing the integrations of the 2-methyl protons in the ^1H NMR spectrum. The structural assignment of **12b** was confirmed by ^1H COSY, NOE and detailed decoupling experiments. The relative stereochemistry between H_2 and H_3 was assigned as *trans* from decoupling and measuring the coupling constant between these two protons (J = 10.8 Hz). The *trans* relationship between H_2 and H_3 in **12b** is likely due to control of the enol-ketone isomerisation subsequent to the C-C bond formation[9]. The generality of the reaction and its stereochemistry were further illustrated by the reaction of **10c** with **11**, see **Scheme-3**.

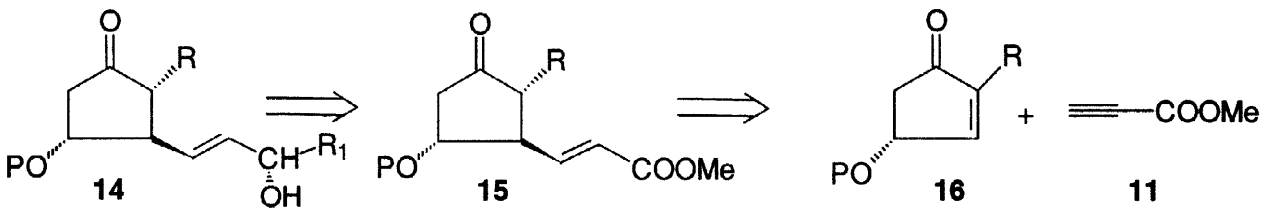
Scheme-3



	Trans / Cis (H_2 / H_3)	(*E* / *Z*)
a) R = H		5 : 1
b) R = Me	10 : 1	5 : 1
c) R = *n*-pentyl	10 : 1	5 : 1

The successful coupling between **10b** or **10c** and **11**, and the observed 2,3-*trans* stereoselectivity and *E*-geometry in **12b-c** encouraged us to attempt a synthesis of the optically pure PG analogue **15** as shown in **Scheme-4**. The transformation of **15** to **14** would be achieved by procedure of Otera et al[10].

Scheme-4



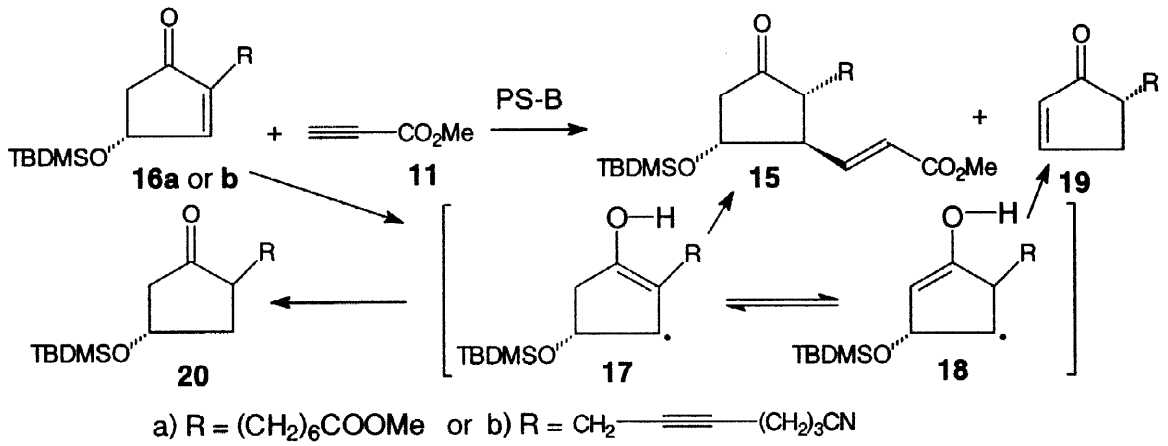
R = CH_2—≡—$(CH_2)_3CN$, or, $(CH_2)_6COOMe$; P = TBDMS, R_1 = amyl

Despite the attractiveness of the three component coupling approach[11a] for the assembly of **14**, serious limitations *viz.*, enol isomerisation[11b] (e.g. **17** → **18**) and β-alkoxide elimination (e.g. **18** → **19**) from **17** has made the two component coupling approach a highly studied[12] route. This led us to attempt an extension of the above strategy as an alternative to the classical two-component coupling approach (**Scheme-5**). Since our photolysis reaction is performed in aqueous solvent, it was envisaged that it might help in restricting the enol equilibrium step (e.g. **17** → **18**) due to quenching of the initially formed intermediate **17** by a proton from water. It was also envisioned that our approach might become attractive as it avoids the use of sensitive organometallic reagents and dry reaction conditions.

Towards this end, a mixture of chiral enone **16** (1 equiv.), synthesised by a slight modification of the literature procedure[13,14], and **11** (4 equiv.) was activated using **PS-B** irradiation conditions. To our surprise, the coupling product **15** was only obtained in poor yield (15 %). The formation of the β-alkoxide elimination product **19** (yield 40 %) and the enone reduced product **20** (yield 20%) dominated the reaction. The formation of **19** suggests that the competing enol isomerisation (**17** → **18**) and elimination reaction from the intermediate **18** remain predominant even in aqueous media (**Scheme-5**).

Further studies of the enolate isomerisation are under progress.

Scheme-5



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[7] The coupling of **10** with **11** was carried out using **PS-B** reaction conditions as under **PS-A** reaction conditions yield to some extent competing thermal reaction product between PPh_3 and **11**.

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