Photochemistry of Cyclopentanone Derivatives in the Synthesis of Prostaglandin and Thromboxane Analogues

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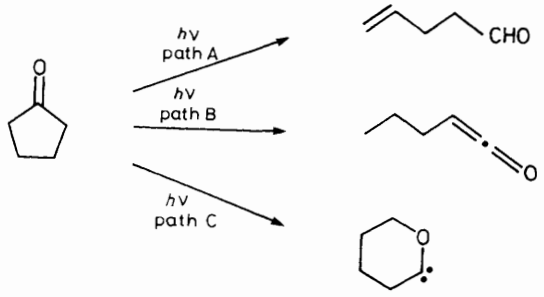
Photolysis of the ketone (**10**) gave the ester (**11**) (a potential precursor of prostaglandin-H analogues) while photolysis of the ketone (**14**) under the same conditions afforded the acetal (**15**).

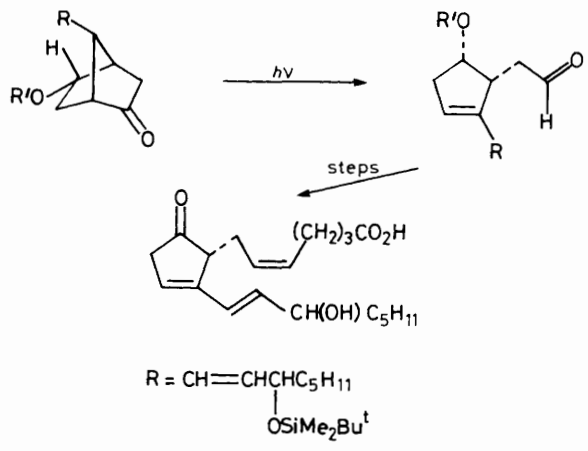
The photochemistry of cyclopentanone derivatives has been extensively investigated. The excited ketone usually suffers cleavage of the bond adjacent to the ketone moiety to give an acyl–alkyl diradical (Norrish type I cleavage). This diradical can rearrange by a number of pathways (A—C, Scheme 1). For simple cyclopentanones Norrish cleavage followed by hydrogen abstraction by the acyl radical leads to alk-4-enals[1] (path A, Scheme 1).

The same reaction takes place for 7-substituted norbornan-2-ones and we have used this method to prepare prostaglandin-C and analogues (Scheme 2).[2] Vanderwalle has also used this strategy in the synthesis of natural products such as the iridoid anti-feedant specionin.[3]

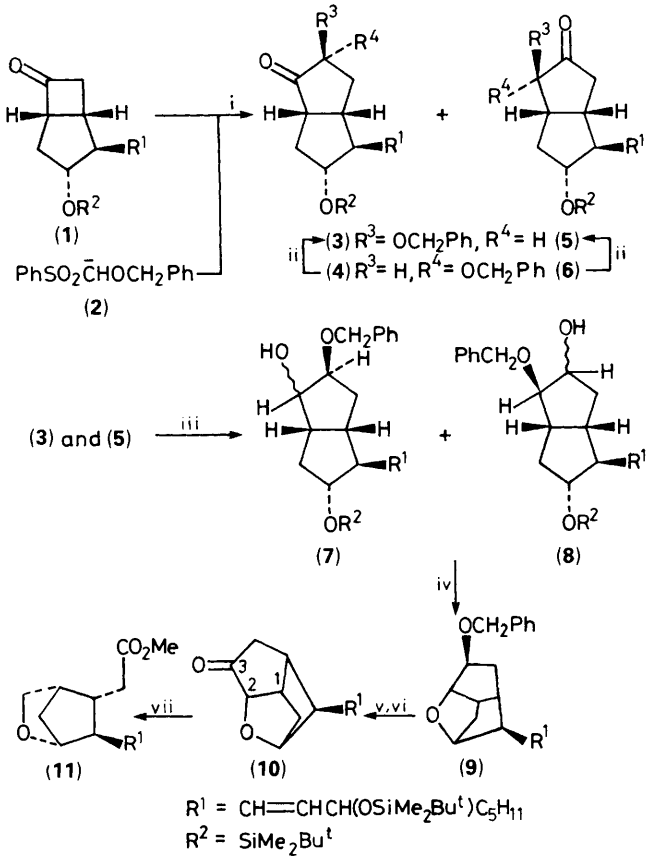


Scheme 1

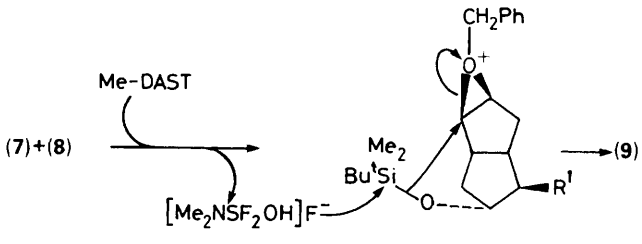
If, for some reason, the acyl radical is not able to abstract a hydrogen radical from the distal position, then the alkyl radical can take the opportunity to abstract a hydrogen atom from C-2 to give rise to a ketene (path B, Scheme 1). We report a potentially useful photochemical reaction of this type (Scheme 3).



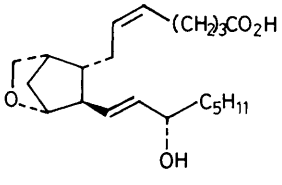
Scheme 2



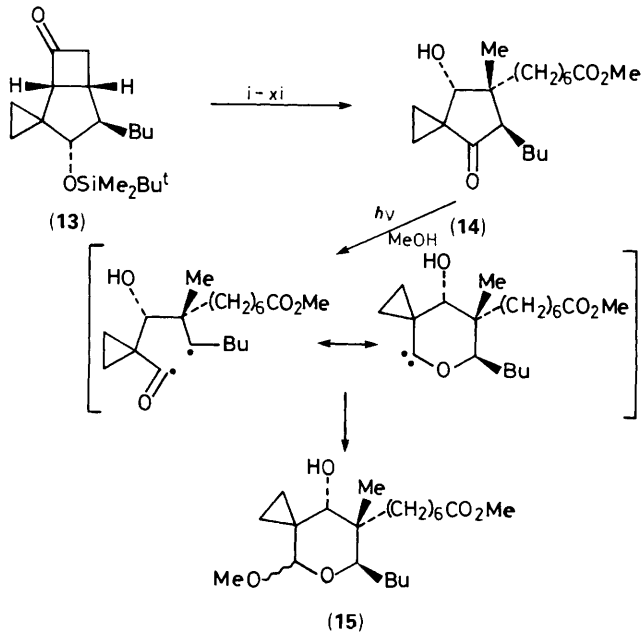
Scheme 3. *Reagents:* i, Bu$^i_2$AlCl; ii, DBU; iii, $NaBH_4$, EtOH, −78 °C; iv, Me-DAST, CH_2Cl_2, −60 °C → room temperature; v, Na, NH_3, Et_2O, −78 °C; vi, $(COCl)_2$, dimethylsulphoxide (DMSO), CH_2Cl_2, then NEt_3; viii, *hv*, MeOH, $NaHCO_3$.



Scheme 4



Treatment of the ketone (**1**)[3] with the anion (**2**) followed by addition of di-isobutylaluminium chloride in a reaction styled on work detailed in a recent report by Trost[4] gave four diastereoisomers (**3**)—(**6**) in the ratio 3:1.5:4.5:1 (50% yield). The *exo*-benzyloxy compounds (**3**) and (**5**) were separated from the *endo*-benzyloxy compounds (**4**) and (**6**) by chromatography over silica and the latter pair could be converted into the former pair by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Reduction of the mixture of ketones (**3**) and (**5**) gave four alcohols as two pairs of diastereoisomers (**7**) and (**8**) (83%).



Scheme 5. *Reagents:* i, $MeCO_3H$; ii, lithium di-isopropylamide (LDA) then PhSeCl; iii, H_2O_2; iv, Me_2CuLi; v, di-isobutylaluminium hydride (DIBAL); (vi) $Ph_3PCH(CH_2)_3CO_2^-$; vii, CH_2N_2; viii, chromatography; ix, pyridinium chlorochromate (PCC); x, HF, MeCN; xi, Pt/C, H_2.

This gross mixture gave the required tricyclic compound (**9**) as the only product in 72% yield on treatment with dimethylaminosulphur trifluoride (Me-DAST). A possible mechanism for this confluent reaction is described in Scheme 4. Debenzylation of compound (**9**) followed by Swern oxidation gave the ketone (**10**) (60%). Photolysis of compound (**10**) in methanol using a medium pressure mercury lamp and quartz apparatus led to a clean conversion into the 2-oxabicycloheptane (**11**) (50%), a compound directly related to the Upjohn thromboxane agonist (**12**).[5] The spectral data for compound (**11**) were as follows: $\nu_{max.}$ ($CHBr_3$) 1729 cm^{-1}; δ_H ($CDCl_3$) 5.41 (1H, ddd, =C–H), 5.38 (1H, ddd, H–C=), 4.01 (2H, m, 2 × H-3), 3.78 (1H, d, H-1), 3.67 (3H, s, OCH_3), 3.58 (1H, m, CHOSi), 2.50 (3H, m, H-4 and CH_2CO–), 2.32—2.00 (4H, m, 2 × H-7, H-5, and H-6), 1.76—1.50 (8H, m, 4 × CH_2), 1.56 [12H, s, $C(CH_3)_3$ and t, CH_3], 0.03 and 0.00 (6H, 2 × s, $SiMe_2$); δ_c ($CDCl_3$) *inter alia* 173.03 (CO_2Me) 134.39 and 129.74 (2 × =CH), 80.83 and 73.33 (2 × CH–O), 66.23 (CH_2O), 51.48 (CH_3O), 52.98 and 41.96 (C-4 and C-5).

Photolysis of the ketone (**10**) obviously leads to cleavage of the C-2–C-3 bond; the acyl radical does not abstract the hydrogen atom at C-1 since the resultant alkene would contravene the Bredt rule. Instead the molecule isomerizes to form a ketene which is trapped by methanol to afford the observed product.

If the hydrogen atom capture by the acyl radical *and* the alkyl radical is denied then a photoexcited cyclopentanone derivative can undergo a ring expansion reaction, proceeding through the intermediacy of an oxacarbene (path C, Scheme 1).

To illustrate the potential of this strategy in synthesis the bicycloalkanone (**13**)[6] was converted, by a series of standard reactions, into the ketone (**14**) (Scheme 5). Photolysis of this ketone in methanol using a medium pressure mercury lamp and quartz apparatus gave, after chromatography, the thromboxane analogue (**15**) (41%). It is noteworthy that photolysis of the ketone (**14**) in acetonitrile or hexadeuteriobenzene did not give rise to product(s) derived by intra-molecular trapping of the oxacarbene.[7]

By the judicious incorporation of substituents onto the five-membered ring, cyclopentanones can be converted into alkenals, esters, or 2-alkoxytetrahydropyrans (that may act as prostanoid/thromboxane precursors) by photolytic reactions set at a late stage in a synthetic scheme.

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