Substituent Effect on Diastereoselectivity in Photochemistry of Valerophenone

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Valerophenone shows a dramatic shift of photoreactivity by a cyclopropyl group at alpha position to the carbonyl group. By the minor change of structure, the diastereoselectivity of the Yang photocyclization is reversed and the ratio of cyclization to elimination products increases significantly.

Key Words : Substituent effect, Photochemistry, Valerophenone, Diastereoselectivity

Introduction

Asymmetric synthesis has been a hot topic in the history of organic chemistry for a long time. In recent years diastereoselective synthesis in the excited state has become a main focus in organic chemistry due to the attractive fact that light can be an environmentally friendly substitute for thermal energy.[1] The difficulty of inducing diastereoselectivity in photochemistry arises mainly from the much faster reaction rates than those in the ground states. It is a general concept that stereoselection in photochemistry can be controlled by conformational bias in the starting compound or reactive intermediates such as biradicals.[2] Thus, many examples of diastereoselective synthesis are known in photochemical reactions in the solid states.[3] Photochemical reactions in homogeneous solutions, however, require a certain amount of barriers of the bond rotations near the reaction centers which differentiate conformational population of many possible diastereomers in order to obtain the stereoselectivity.[4]

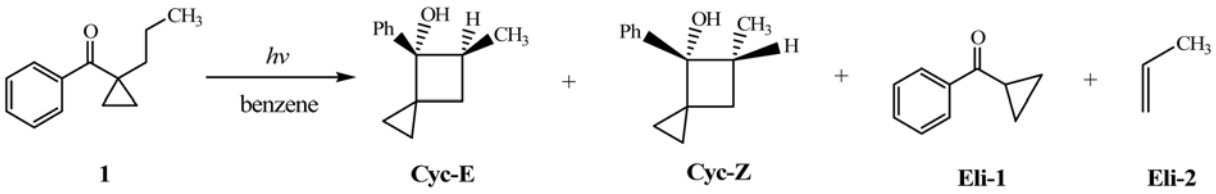
The Yang photocyclization of carbonyl compounds has recently received much attention concerning the diastereoselectivity in photochemistry.[5] In the course of our research on photochemistry of α-(ortho-alkylphenyl)acetophenones containing small rings,[6] we have recently found that diastereoselectivity in the Yang photocyclization is reversed upon introducing a cyclopropyl group at the alpha position to carbonyls. In order to see how general the substituent effects are, we decided to investigate photochemistry of a substituted valerophenone, which had long been considered as a representative compound for the Yang photocyclization. Herein we report on photochemical reactions of 1-benzoyl-1-propylcyclopropane, **1**, which has a cyclopropyl group at the alpha position to the carbonyl group of valerophenone, in detail.

Results and Discussion

The compound **1** was prepared straightforward by methylenation of valerophenone followed by cyclopropanation using methylsulphoxonium ylid.[7] The purified ketone **1** in benzene was irradiated with Pyrex filtered light until all the starting matereial had disappeared. After evaporating all the volatiles and chromatographing over silica gel, three products were isolated, whose structures were identified by their spectroscopic properties and/or comparing them with those of authentic compounds. Among them, two isomeric products were spiro[3,2]hexanols, Cyc-*E* and Cyc-*Z*, and the remaining product was cyclopropyl phenyl ketone, Eli-1, as shown in Scheme 1. Another product, Eli-2, was later identified in a separate experiment, *vide infra*.

For stereochemical assignment, methyl doublets at higher field were particularly useful because it has been generally accepted that a methyl *cis* to a phenyl is significantly shielded relative to the one trans to phenyl.[8] The assignment was confirmed further by NOE experiments. When a methyl doublet of ^{1}H NMR spectrum of Cyc-*E* was irradiated in the NOE experiment, a doublet corresponding to the two ortho protons of the phenyl ring was enhanced. The enhancement was not observed from the NOE of Cyc-*Z*.

In order to obtain the more detailed information about the reaction, the photolysis was repeated using the sample made by dissolving the ketone **1** in benzene-d_6 in an NMR tube. The degassed NMR sample was irradiated under the same condition as the above and the reaction was monitored by ^{1}H NMR spectra taken at regular intervals. The NMR spectra revealed presence of the fourth product, which was identified as propene, Eli-2. Since the product was gas, it escaped our detection in preparative scale photolysis experiment. The NMR peaks of Eli-2 gradually disappeared even in the NMR scale photolysis for obvious reasons. The product



Scheme 1. Photochemical Reaction of 1-Benzoyl-1-propylcyclopropane.

Table 1. Product Ratios of Photochemical Reaction of **1** at Various Temperature

Temperature (K)	Cyc-*E* (%)	Cyc-*Z* (%)	Eli-1 (%)	Eli-2 (%)
273	40.4	11.6	24.0	24.0
295	35.8	12.0	26.1	26.1
335	32.5	12.6	27.45	27.45
368	29.2	13.0	28.9	28.9

Table 2. Product Ratios of Photochemical Reactions of Various Valerophenones

	Cyc-*E*/Cyc-*Z*	Cyc/Eli
Compound **1**	3.0	0.92
VP	0.32	0.28
DMVP	0.70	2.5

ratios were taken from NMR integration of two ortho protons of each product, which were nicely separated, and the amount of Eli-2 was made equal to that of Eli-1 for mechanistic reason, *vide infra*.

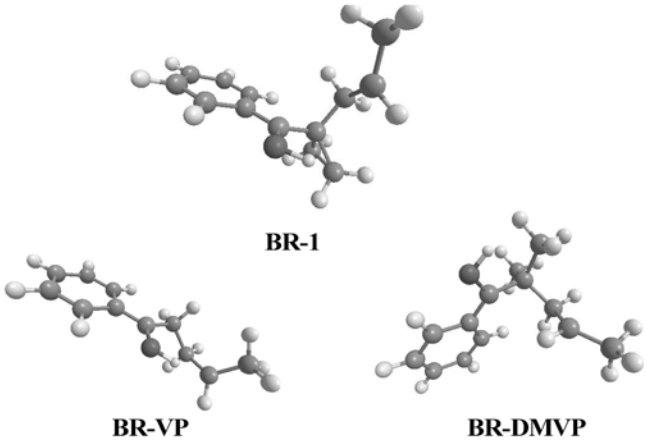
The *E/Z* ratios increase with decreasing temperature and there is a linear relationship of ln(*E/Z*) *vs.* 1/T at the observed temperature range. The Arrhenius plot of the above data gives the activation energy difference ΔEa, Ea_z-Ea_e, of 0.89 kcal/mol and the pre-exponetial factor ratio A_E/A_Z of 0.66.

The Yang cyclization normally favors *Z* isomers as represented by photolysis of valerophenone (VP), which gives ca. 1 to 3 ratio of *E*- and *Z*-cyclobutanol in benzene. Our experiment showed that the stereoselectivity was reversed by introducing a cyclopropyl group at the alpha position to the carbonyl group of VP. It is interesting to note that 2,2-dimethylvalerophenone (DMVP), which is very similar to the compound **1** structurally, gives *E*- to *Z*-product ratio of 0.70 in benzene still favoring *Z*-isomer (Table 2).[9]

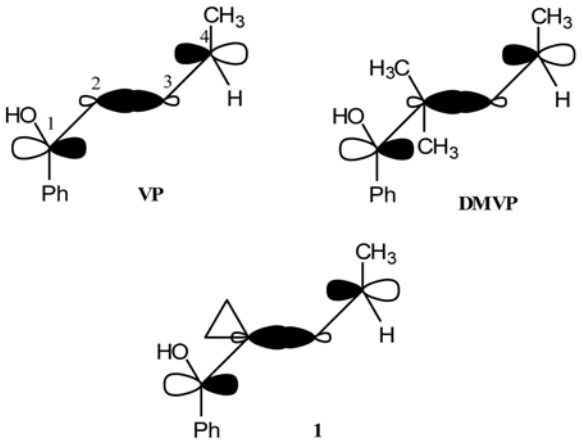
For the purpose of finding an explanation for the reversal of diastereoselectivity in the Yang reaction of **1**, a theoretical calculation was performed using the Gaussian Package (B3LYP 6-31G*).[10] Scheme 2 shows the energy minimized structures of 1,4-biradical intermediates from **1**, VP, and DMVP.

BR-**1** in Scheme 2 clearly shows that it can cyclize to form the *E*-cyclobutanol preferentially over the *Z*-cyclobutanol with minimal motions, which agrees well with our experimental results.[11] However, it is not clear to see the structural bias in BR-VP or BR-DMVP. In these cases, steric repulsions occurring when the two ends of the biradical begin to bond may be the more important factor determining the stereochemical outcome than the preexisting conformational preferences in the biradicals. Accordingly, VP and DMVP give the *Z*-isomers, in which the methyl and OH are cis to each other to reduce steric hindrance, slightly more than the *E*-isomers.

It is well known that VP gives not only cyclization products but also elimibation products, which originate from



Scheme 2. Energy Minimized Structures of Biradical Intermediates from **1**, VP, and DMVP.



Scheme 3. Transoid Conformers of Biradical Intermediates from VP, DMVP and **1**.

the same 1,4-biradical intermediate. Thus, it would be also interesting to compare the cyclization to elimination product ratio of **1** with those of VP and DMVP, which is shown in Table 2.

The cyclization is normally a minor reaction pathway for γ-hydrogen containing ketones as indicated by the cyclization to elimination product ratio of 0.28 for VP. But, the relative portion of cyclization increases significantly when ketones have α-alkyl substituents as in the case of **1** and DMVP. The magnitude of the increment is larger for DMVP than the compound **1**.

It is generally accepted that the elimination occurs preferentially from a transoid conformation of the biradical intermediate shown in Scheme 3.[9] The 1,2-eclipsing interaction between substituents at carbon 1 and 2 can destabilize the transoid conformation, which can reduce the yield of the elimination product. The eclipsing interaction is the largest in DMVP and **1** is intermediary, which agrees well with the results shown in Table 2.

In summary, Valerophenone shows a dramatic shift of photoreactivity by a cyclopropyl group at alpha position to the carbonyl group. By the minor change of structure, the diastereoselectivity of the Yang photocyclization is reversed

and the ratio of cyclization to elimination products increases significantly. Other ketones are currently being tested in our laboratory to see how general the phenomena can be.

Experimental Section

Synthesis of 1. The compound 1 was prepared by alpha-methylenation of valerophenone, followed by cyclopropanation using the same procedure in ref. 7.

Spectroscopic properties of 1: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85 (distorted doublet, 2H), 7.50 (distorted triplet, 1H), 7.43 (distorted triplet, 2H), 1.71 (m, 2H), 1.29-1.19 (m, 4H), 0.80-0.76 (m, 5H) ppm, ^{13}C NMR ($CDCl_3$, 56 MHz) δ 203.5, 137.5, 131.8, 128.4, 128.2, 38.5, 30.5, 21.1, 13.9, 12.8 ppm. IR (KBr): 1675 (C=O str.) cm^{-1}. EIMS 188 (M^+).

Photolysis of 1 The starting ketone in benzene (typically 0.01-0.02 M) was irradiated in an immersion well with argon bubbling using Pyrex (or Uranium) filtered light of a 450 W Hanovia medium pressure mercury arc lamp. The reaction mixture was concentrated at reduced pressure and the resulting crude product mixture was separated by column chromatography using n-hexane and ethyl acetate in 7 to 1.

For NMR scale photolysis, an NMR tube containing ketones in benzene-d_6 was degassed and irradiated by attaching it to the side of an immersion well using Pyrex (or Uranium) filtered light of a 450 W Hanovia medium pressure mercury arc lamp. To control reaction temperature the sample was immersed in an temperature control bath during the irradiation.

Spectroscopic properties of Cyc-*E*: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (distorted doublet, 2H), 7.37 (distorted triplet, 2H), 7.27 (distorted triplet, 1H), 2.70 (ddq, 1H, J = 10.5, 7.0, 6.5 Hz), 2.01 (dd, 1H, J = 9.5, 6.5 Hz), 1.84 (broad s, 1H, -OH), 1.75 (dd, 1H, J = 10.5, 9.5 Hz), 0.95 (m, 1H), 0.82 (m, 1H), 0.63 (d, 3H, J = 7.0 Hz), 0.62-0.53 (m, 2H) ppm, IR (neat): 3400 (O-H) cm^{-1} EI mass: 188 (M^+).

Spectroscopic properties of Cyc-*Z*: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (distorted doublet, 2H), 7.34 (distorted triplet, 2H), 7.23 (distorted triplet, 1H), 2.88 (ddq, 1H, J = 9.0, 7.0, 6.5 Hz), 2.23 (dd, 1H, J = 10.5, 9.0 Hz), 1.87 (dd, 1H, J = 10.5, 6.5 Hz), 1.59 (broad s, 1H, -OH), 1.21 (d, 3H, J = 7.0 Hz), 0.76 (m, 1H), 0.60-0.44 (m, 2H), 0.34 (m, 1H) ppm, IR (neat): 3380 (O-H) cm^{-1} EI mass: 188 (M^+).

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11. Another conformer having a local minimum, which can lead to the Z-isomer, is calculated to be 1.34 kcal higher in energy than BR-1.