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# Unique solvent effect on photochemistry of *ortho*-alkylphenacyl benzoates

Bong Ser Park *, Hyuk Jun Ryu

*Department of Chemistry, Dongguk University, Seoul 100-715, Republic of Korea*

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Dedicated to Professor Peter J. Wagner who died of a cancer on August 6th 2009

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ABSTRACT

Photolysis of 2,4,6-trialkylphenacyl benzoates gives not only the corresponding indanones and benzoic acid, but also the corresponding benzocyclobutenols (CBs), which are also detected in the photolysis of mono-alkylphenacyl benzoates for the first time. The product selectivity was heavily dependent upon solvents and *o*-alkyl group. H-bonding acceptor solvents strongly favor the formation of the CB. As the size of the *o*-alkyl group increases, the relative amount of the CB increases.



The photochemistry of *ortho*-alkylphenyl ketones has received much attention not only in mechanistic studies,[1] but also in synthetic application.[2] The mechanism is now well established: intramolecular hydrogen abstraction from the triplet excited state forms a short-lived triplet enol, which decays to ground state isomers with *Z* and *E* configurations at the enol carbon. The former reverts to the starting ketone via fast 1,5-sigmatropic internal return, while the latter cyclizes to form benzocyclobutenols or undergoes catalyzed reversion to the reactant ketone. The photocyclization to benzocyclobutenols occurs efficiently in benzene, but is inefficient or even not detected in methanol.[3] The reaction is known to be readily quenched by acids and bases.[4]

If the *ortho*-alkylphenyl ketones have a leaving group X such as chloride, carboxylates, sulfonates or phosphates at alpha position to carbonyl, indanone formation via HX elimination becomes the major reaction route upon photolysis, which is one of the recently developed photocages.[5] The reaction mechanism seems to vary depending on the leaving group and the reaction medium (Scheme 1). When the leaving group was Cl, Klan and Wirz showed that the indanone was formed from the ground state *E*-enol in benzene but from *Z*-enol in methanol.[6] If the relatively poor leaving group carboxylates are used, the reaction occurs through the *E*-enol regardless of the solvent.[7] In the case of the sulphonates, Wessig proposed the intermediacy of 1,5-triplet biradical formed by fast HX elimination from the initially formed 1,4-triplet biradical.[8]

It is interesting to note that the formation of benzocyclobutenols has not been reported in all of their studies on the photochemistry of α-substituted *o*-alkylphenyl ketones, even though the initial stage of the reaction seems to share a common intermediate with photoreactions of the unsubstituted *o*-alkylphenyl ketones. In our continuing efforts to find structure–reactivity relationship in ketone photochemistry,[9] we recently had a chance to investigate photochemical behaviors of several *ortho*-alkylphenyl ketones having a benzoate leaving group at the alpha position and found that such system do indeed form benzocyclobutenols and shows an interesting solvent effect. Here we would like to report our preliminary findings.

At the beginning of this research, we were interested in steric effects on photoinduced indanone formation from *o*-alkylphenacyl benzoates. Accordingly, the trialkyl-substituted ketones, **1**–**3**, (in Table 1) were prepared using routine synthetic procedures: Friedel–Crafts acylation of the corresponding benzene, alpha bromination, followed by substitution by benzoyloxy group.[10] The purified ketones were irradiated in benzene or methanol (typically 0.02 M) using the Pyrex filtered UV light of 450 W Hanovia medium pressure mercury arc lamp until all the starting material had disappeared. The resulting photoproducts were isolated by routine purification methods using silica gel column chromatography. Each of the isolated products was identified by analyzing its spectroscopic data. The photolysis was also done in various solvents on an NMR sample scale by attaching the degassed sample solution by an immersion well equipped with the Hanovia medium pressure mercury arc lamp in order to monitor the reaction more closely.

* Corresponding author. Tel.: +82 2 2260 3223.
*E-mail address:* parkbs@dongguk.edu (B.S. Park).

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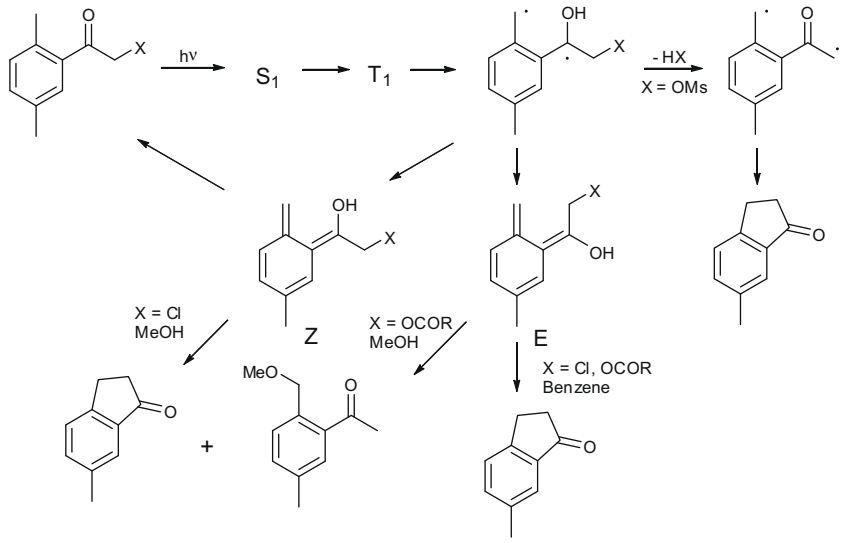
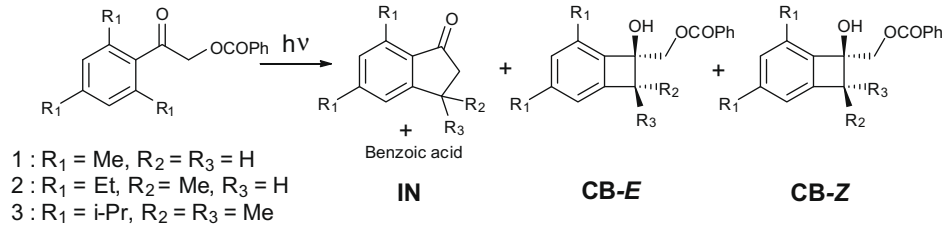



**Scheme 1.**

**Table 1**
Product ratios (IN–CB) of photolysis of **1**–**3** in various solvents



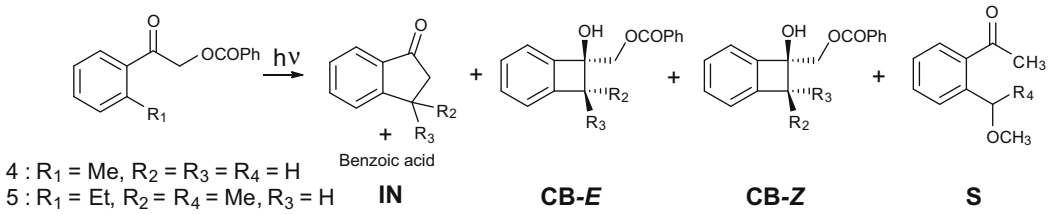

| Compound | Solvent | Ratio (IN:CB) |
|---|---|---|
| **1** | Benzene | 3.7:1[a] (78.5%:21.5%) |
| | MeOH | 1:14.3 (6.5%:93.5%) |
| | $CH_3CN$ | 1:2.9 (25.7%:74.3%) |
| | Acetone | 1:2.4 (29.1%:70.9%) |
| | DMSO | CB only |
| **2** | Benzene | 1:1 (50%:50%[b]) |
| | MeOH | CB only (*E*:*Z* = 3.4:1) |
| | $CH_3CN$ | CB only (*E*:*Z* = 2.2:1)– |
| | Acetone | CB only (*E*:*Z* = 3.7:1)– |
| | DMSO | CB only (*E*:*Z* = 3.0:1) |
| **3** | Benzene | 1:2.8 (26.4%:73.6%) |
| | MeOH | CB only |
| | $CH_3CN$ | CB only |
| | Acetone | CB only |
| | DMSO | CB only |

[a] Normalized to 100%. Material balances of photoproducts including benzoic acid which is omitted in the table were in the range of 90–95% based on starting materials.
[b] *E*-isomer only.

Photolysis of **1**–**3** gave not only the corresponding indanones (IN) and benzoic acid, but also the benzocyclobutenols (CBs).[11] The ratios of IN to CB were strongly dependent upon solvents and *ortho*-alkyl groups as shown in Table 1.[12] As the size of the *ortho*-alkyl groups increases, the formation of CB becomes more favored over IN. Solvent effects were more dramatic; for **1**, in polar solvents CB was strongly favored over IN, while in benzene the opposite preference was shown. For the ethyl derivative, **2**, *E*- and *Z*-benzocyclobutenols were formed in various ratios depending on the solvents. The stereochemical assignment was made by NOE experiments of $^1$H NMR.

The results are very interesting considering the fact that the benzocyclobutenol products have not been observed in the photolysis of *o*-alkylphenyl ketones containing a leaving group at alpha position to the carbonyl, even though they are very common in photochemistry of the unsubstituted system. Moreover, the dramatic shift of product selectivity depending upon solvents is quite intriguing, assuming that the reaction occurs through the ground state enol intermediate as discussed in earlier reports. Wagner observed that the photoinduced formation of benzocyclobutenol from *o*-alkylphenyl ketones could be inhibited in methanol[3] and Scaiano later demonstrated that the reaction could efficiently be quenched by the addition of acids and bases.[4] Our results show that methanol does not seem to give such a negative effect on the formation of benzocyclobutenols from **1 to 3** at least in chemical yields, which rather makes it predominate over indanone formation.

**Table 2**
Product distribution in percentage of photolysis of **4** and **5** in various solvents




| Compound | Solvent | Product[a] (%) | | |
|---|---|---|---|---|
| | | IN | CB | S |
| **4** | Benzene | 100 | — | — |
| | Benzene (with 2.0 equiv of NMI) | 90.9 | 9.1 | — |
| | Benzene (with 4.0 equiv of NMI) | 89.7 | 10.3 | — |
| | MeOH | 61.0 | 18.3 | 20.7 |
| | $CH_3CN$ | 100 | — | — |
| | Acetone | 100 | — | — |
| **5** | Benzene | 92.8 | 7.2[c] | — |
| | Benzene[b] (with 2.0 equiv of NMI) | 89.9 | 10.1[c] | — |
| | Benzene (with 4.0 equiv of NMI) | 81.6 | 18.4[c] | — |
| | MeOH | 27.2 | 71.8[c] | 0 |
| | $CH_3CN$ | 70.6 | 29.4[c] | — |
| | Acetone | 63.4– | 36.6[c] | — |

[a] Normalized to 100%. Material balances of isolated products including benzoic acid which is omitted in the table were in the range of 89–95% based on starting materials.
[b] NMI: *N*-methyl imidazole.
[c] *E*-isomer only.

Sterically demanding 2,4,6-trialkylphenyl ketones are known to be more tolerable to such inhibiting effects of methanol, and benzocyclobutenols have been observed in photolysis of trialkylacetophenones in alcoholic solvents.[13] Thus, photochemistry of mono-substituted analogues, **4** and **5**, was also investigated in several different solvents under the same reaction condition as described above. Table 2 summarizes the results.

Again, the benzocyclobutenols were observed in photolysis of **4** and **5** in methanol, even though the relative amount was less than those from trialkyl analogues. To our best knowledge, this is the first time to observe the benzocyclobutenol products from photolysis of *ortho*-alkylphenyl ketones containing a leaving group at alpha position to carbonyls. The CB product was not observed in photolysis of **4** in benzene but started to appear upon addition of a base (*N*-methylimidazole, NMI), and the relative amount of the CB increased as more NMI was added. The result is very unusual if dienol intermediates are involved in the cyclobutenol formation since bases are known to quench dienol intermediates even more efficiently than acids do.[4] The fact that NMI alters the ratio of IN to CB would suggest the base do more than just quench the dienols, assuming that both products come from the *E*-enols. It may be questioned if the CB really comes from the dienol intermediates. In fact, there has been a famous argument over the intermediacy of the dienols in photochemistry of 2,4,6-trialkylbenzophenone.[14] However, in the acetophenone cases, there seems to be an agreement over the involvement of dienols in the cyclobutenol formation. Forming only *E*-isomer of two possible CB products from **2** and **5** in benzene supports the picture of thermal conrotatory closure from the *E*-dienol intermediate with stereospecific manner. If CB is formed at the diradical stage, it would have given mixtures of two isomers for both cases.

Increasing trend of CB formation in going from **1** to **3** in benzene was not unexpected. A sterically demanding alkyl group makes the planar dienol intermediate unstable and forces to twist the bond connecting the hydroxyl carbon to benzene, which makes the CB form relatively easier and stable. The steric effect will be more enhanced in methanol than in benzene because solvation of the dienol OH by hydrogen bonding will make the planar dienols sterically congested further. The idea is consistent with the fact that the relative amount of CB increases in methanol and **2** and **3** give only CB in methanol.

Solvolysis product by nucleophilic solvents such as **S** in Table 2 was observed only in photolysis of **4** in methanol. The reaction is known to occur by a nucleophilic attack at benzylic position of dienol intermediates. Absence of the solvolysis product from the trialkyl ketones **1**–**3** and from the monoethyl ketone **5** indicates that the reaction is very sensitive to steric crowding.

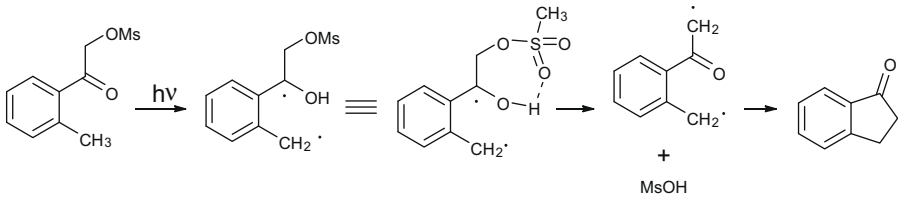
Lower quantum yield in methanol (0.09) than in benzene (0.23) in photolysis of 2,5-dimethylphenacyl benzoate has been used as a clue to the *E*-dienol being the precursor of indanone formation.[7] The *E*-dienol can revert to the starting ketone catalytically in methanol, while the *Z*-dienol can stay longer without returning to the starting ketone because methanol can hinder the intramolecular 1,5-H shift of the *Z*-dienol. If the benzoate is replaced by the better leaving group such as Cl in photolysis of 2,5-dimethylphenacyl benzoate, the indanone product comes from *Z-dienol* via heterolytic cleavage of C–Cl bond in methanol, which gives the higher quantum yield (0.76) than that in benzene (0.11).[7] We, therefore, measured the quantum yield from **1**–**5** using valerophenone actinometer and obtained the results summarized in Table 3.

For all the ketones that we tested, the quantum yield in methanol was lower than those in benzene. The result implies that the photoreaction occurs from an intermediate to be quenched by methanol, whose strong candidate would be the *E*-dienol. Then,

**Table 3**
Quantum yields[a] in photolysis of **1**–**5** in benzene and methanol

| Compound | $\Phi_{benzene}$ | $\Phi_{methanol}$ |
|---|---|---|
| **1** | 0.39 ± 0.04 | 0.07 ± 0.01 |
| **2** | 0.12 ± 0.01 | 0.06 ± 0.01 |
| **3** | 0.09 ± 0.01 | —[b] |
| **4** | 0.29 ± 0.03 | 0.05 ± 0.01 |
| **5** | 0.26 ± 0.03 | |

[a] Quantum yields of disappearance of starting ketones.
[b] Difficult to measure due to solubility problem.




**Scheme 2.**

a question remains why the ratio of IN and CB varies markedly in changing the solvent from benzene to methanol. For the trialkyl ketones **1**–**3**, it may be explained that solvation of OH by methanol induces more steric demand at the *E*-dienol intermediate and favors formation of CB over IN just like the *ortho*-alkyl size effect. However, the mono-alkyl analogues, **4** and **5**, lacking the buttressing effect by an extra ortho substituent requires additional factors to be considered to explain the observed solvent effects.

Wessig has addressed the importance of intramolecularly hydrogen-bonded structure shown in Scheme 2 in his studies on photoinduced indanone formation from *o*-alkylphenacyl sulfonates.[8]

In his proposed reaction mechanism, the intramolecularly H-bonded triplet biradical releases the sulfonic acid rapidly to give the 1,5-biradical intermediate, which then forms indanone product. It is possible that the indanone formation from **1** follows the similar reaction pathway, even though the timing of the elimination is still an open question, vide infra. If the H-bonding facilitates the departure of the leaving group, addition of H-bonding acceptor molecules would inhibit such a departure. Methanol and acetonitrile can disrupt the intramolecular H-bond and slow down the elimination step to make the indanone formation inefficient. It is worthwhile to note that only CB is formed from **1** in DMSO, a strong H-bonding acceptor.[15] The fact that adding NMI to the benzene solution of **4** increases the ratio of CB to IN can also be explained by the same mechanistic scenario. Interestingly, Wessig has used the same base to optimize the yield of indanone by neutralizing the sulfonic acids released in photolysis of *o*-alkylphenacyl mesylates. For comparison, we have also prepared *o*-methylphenacyl mesylate, 2,4,6-trimethylphenacyl mesylate, *o*-methylphenacyl chloride, and 2,4,6-trimethylphenacyl chloride, and irradiated them using the same reaction condition as described above. These ketones, however, did not give benzocyclobutenols under any reaction conditions that we have tried, including H-bond acceptor solvents and the addition of NMI.

Klan has studied the mechanism of photochemistry of *o*-methylphenacyl sulfonates[16] and reported that the reaction in methanol proceeds from *Z*-dienol via heterolytic cleavage, while in benzene the elimination occurs from the *E*-dienol. The reaction mechanism parallels with those of *o*-alkylphenacyl chlorides and phosphates, but is different from that of the carboxylate whose elimination occurs from the *E*-dienol regardless of solvents. For the system having relatively poor leaving group such as carboxylates, the elimination step is too slow to compete with the other reaction path such as reketonization to starting material via 1,5-H shift from the *Z*-dienol. In such a system, the decay process from triplet dienol (or biradical) to the ground state dienol would occur before the elimination, so the retardation of the elimination step by methanol or bases such as NMI would also be made at the ground state dienol rather than at the biradical state.

Our mechanistic reasoning for the predominant formation of cyclobutenol over indanone in methanol can be summarized as follows. We believe that both CB and IN come from *E*-dienol as described above. Methanol would then decrease the efficiency of forming both products by catalyzing reketonization of the *E*-dienol to the starting material, which would result in reduced quantum yield. However, the methanol's quenching effect would be larger for formation of indanone than for that of cyclobutenol by disrupting the proper geometry for releasing the benzoates with the intramolecular H-bonding. Moreover, the solvation of the dienol OH by methanol increases the steric strain to force to twist the enol C=C bond, which makes the cyclobutenol form easier and the indanone form more difficult.

In summary, photolysis of 2,4,6-trialkylphenacyl benzoates in benzene resulted in an efficient formation of the corresponding indanones and benzoic acid, but in methanol it gave predominantly the corresponding benzocyclobutenols, which were also detected in the photolysis of mono-alkylphenacyl benzoates for the first time. The dramatic shift of product selectivity depending upon the solvents can be explained by assuming that solvation of OH group in *E*-dienols by methanol disrupt the intramolecular hydrogen bonding between the OH and carbonyl oxygen of benzoyl group, which is a strong driving force for the release of the carboxylate leaving group. Adding bases such as NMI or using other H-bonding acceptor solvents such as acetonitrile and DMSO also enhances the product selectivity favoring the cyclobutenol.

## Acknowledgment

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10. *As a representative example, spectroscopic data of* **1***:* $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.13 (distorted d, 2H, $J$ = 7.4 Hz), 7.63 (distorted t, 1H, $J$ = 7.4 Hz), 7.49 (distorted t, 2H, $J$ = 7.4 Hz), 6.90 (s, 2H), 5.18 (s, 2H), 2.35 (s, 6H), 2.32 (s, 3H), $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 203.0, 166.1, 139.6, 135.2, 134.1, 133.5, 130.0,

129.4, 128.7, 128.6, 69.7, 21.2, 19.2 ppm, IR (KBr) 1725, 1716 (C=O str.) $cm^{-1}$, EIMS 282 ($M^+$).

11. *As a representative example, spectroscopic data of IN-***1***:* $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.10 (s, 1H), 6.94 (s, 1H), 3.06 (AA′BB′, 2H), 2.68 (AA′BB′, 2H), 2.61 (s, 3H), 2.40 (s, 3H), $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 207.5, 156.6, 145.1, 138.6, 132.4, 130.4, 124.5, 37.0, 25.3, 21.9, 18.3 ppm, IR (KBr) 1698 (C=O str.) $cm^{-1}$, EIMS 160 ($M^+$). *Spectroscopic data of CB-***1***:* $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 8.11 (distorted d, 2H, $J$ = 7.4 Hz), 7.62 (distorted t, 1H, $J$ = 7.4 Hz), 7,48 (distorted t, 2H, $J$ = 7.4 Hz), 6.86 (s, 1H), 6.85 (s, 1H), 4.73, 4.66 (AB quartet, 2H, $J$ = 11.6 Hz), 3.47, 3.21 (AB quartet, 2H, $J$ = 14.0 Hz), 2.34 (s, 3H), 2.30 (s, 3H), 2.07 (s, 1H, –OH), $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 167.0, 142.3, 141.1, 140.1, 133.3, 132.7, 130.0, 129.9, 129.6, 128.5, 121.6, 78.8, 69.9, 43.8, 22.1, 17.3 ppm, IR (KBr) 3463 (O–H str.), 1726 (C=O str.) $cm^{-1}$, EIMS 282 ($M^+$).
12. The ratios in the table were unchanged within experimental errors after irradiating for time periods twice as long as those taken to complete consumption of starting ketones, which showed that any contribution from the secondary photoreactions of initially formed products is negligible under our experimental conditions.
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15. A referee pointed out that our experimental results were in good agreement with the β scale (solvent hydrogen bond acceptor basicity proposed by Taft and co-workers: Kamlet, M. J.; Abboud, J.-L. M.; Abraham, M. H.; Taft, R. W. *J. Org. Chem.* **1983**, *48*, 2877–2887.). We appreciate for the useful comment.
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