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Norrish Type II photoreactivity of β-anisylalkanophenones and solvent effects on stereoselective Yang cyclization

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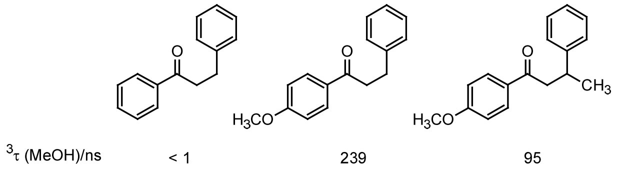
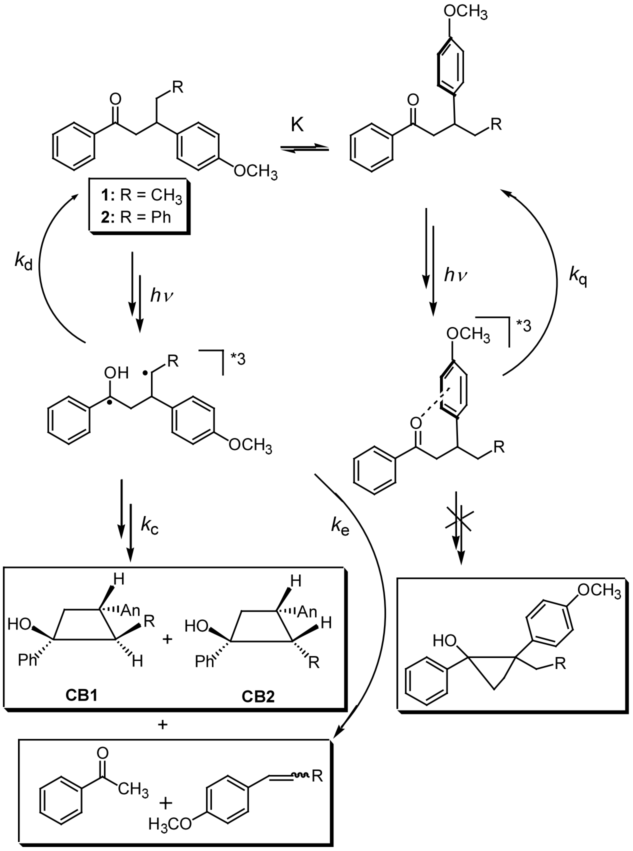
Abstract—In contary to the general notion that β-arylpropiophenones are photostable, photolysis of β-anisylketones **1** and **2** is found to result in Norrish Type II reactions; Yang cyclization affords two cyclobutanols in moderate yields (31–43%) in a highly stereoselective manner. The solvents are found to exert a dramatic influence on the relative ratios of the cyclobutanols in that the major product in a nonpolar solvent such as benzene becomes the minor one in a polar solvent such as acetonitrile or methanol.

β-Arylpropiophenones have been known to be photostable for well over three decades.[1,2] Their photostability has been attributed to quenching of the triplet-excited carbonyl by the β-aryl ring in a *gauche* conformation.[3–7] Extensive investigations utilizing laser flash photolysis have revealed the following: (1) the triplet lifetime for the n,π*-excited carbonyl of the parent β-phenylpropiophenone is less than 1 ns and the quantum yield for its decomposition is insignificant,[4,5] (2) triplet quenching by the β-aryl ring is insensitive to changes in the substituents of the β-aryl ring for ketones with pure n,π* lowest triplet-excited state character, while it is opposite for the ketones with π,π* lowest excited state character,[5–8] and (3) a methyl substituent at the β position leads to shortening of triplet lifetimes of *p*-methoxy-β-phenylpropiophenone, a ketone with π,π* lowest excited state character, via modification of conformational preferences.[8] In contrast to the photostability that is generally associated with β-arylpropiophenones, Wagner and co-workers recently demonstrated the possibility of productive photochemistry in ketones for which the β-aryl rings are substituted with highly electron-rich groups.[9] They showed that cyclopropanols are indeed formed in respectable yields via a mechanism that involves β-hydrogen transfer initiated by an intramolecular charge transfer between the triplet-excited carbonyl and the β-aryl ring (cf. Scheme 1).





Scheme 1.

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In the backdrop of this knowledge on the reactivity of β-arylalkanophenones, we were intrigued by the Norrish Type II reactivity reported for β,γ-diphenylbutyrophenone long ago;[10] elimination products were reported to be formed together with a 20% yield of the presumed cyclobutanols.[11] Given that the triplet quenching is very rapid in carbonyl compounds such as this with lowest n,π* character and that the β-substituents decrease the triplet lifetimes by modifying the conformational preferences[8] and reduce the cyclization yields,[12,13] the presumed formation of cyclobutanols is surprising. This prompted us to look at the photochemistry of substituted β-anisylpropiophenones **1** and **2** in more detail in solution as well as in the solid state; the latter constitutes the focus of our research program.[14] Herein, we report on highly stereoselective Yang cyclizations of **1** and **2** to cyclobutanols in respectable yields (ca. 35–40%) and on the influence of the solvent on the relative ratios of the diastereomeric cyclobutanols.

The ketones **1** and **2** were synthesized by 1,4-addition to 4-methoxychalcone of EtMgI and BnMgCl, respectively. Photolysis of benzene and acetonitrile solutions of **1** and **2** for 12–24 h under a nitrogen gas atmosphere in a Luzchem photoreactor fitted with 350 nm lamps did not lead to the formation of cyclopropanols as monitored by ^{1}H NMR (400 MHz) spectroscopy (Scheme 1). Interestingly, complete photodecomposition of the ketones was observed with concomitant formation of readily identified photoproducts arising from Norrish Type II reactions (Scheme 1). From preparative photolysis employing ca. 250 mg (1 mmol) of the ketones, the cyclobutanols were isolated in 30–40% yields by silica-gel column chromatography; the remainder corresponded to the elimination products, namely acetophenone, anethole (from **1**) and *p*-methoxystilbene (from **2**). The latter were isolated and characterized by direct comparison of their spectral data (^{1}H and ^{13}C NMR) with those of the authentic samples. The Yang cyclization of ketones **1** and **2** may in principle lead to four possible diastereomers. The ^{1}H NMR (400 MHz) analysis of the irradiated mixture based on the diagnostic α-methyl and methoxy (OMe) signals revealed the formation of only two diastereomers exclusively. The stereochemistry of both cyclobutanols, **CB1** and **CB2**, was established by comparison of the ^{1}H NMR chemical shifts of the diagnostic methyl signals with those reported for analogous cyclobutanols in the literature[13] and is also based on NOE experiments on the two cyclobutanols derived from ketone **1**.[15] It has been shown that the methyl signal in cyclobutanols appears at ca. δ 1.2 when it is *anti* to a phenyl group and that it gets shifted upfield by ca. δ 0.5 when it is *syn*.[13] Accordingly, the signal due to the methyl group in **CB1** formed from the ketone **1** appears at δ 1.23, while it is shifted upfield to δ 0.68 in the case of **CB2**. An analogous trend is observed for the pertinent protons of **CB1** and **CB2** formed from ketone **2**.[16]

Remarkably, the relative ratios of cyclobutanols were found to be dramatically influenced by variation of the solvent, although the elimination to cyclization ratio was almost invariant in a variety of solvents (Table 1). Thus, irradiation of ketones **1** and **2** in nonpolar solvents leads to the preponderant formation of **CB1**, while polar aprotic as well as protic solvents lead to increasing yields of **CB2** (Table 1). For both ketones **1** and **2**, the relative yield of **CB1** in nonpolar benzene as the solvent is as high as 80–85% (entries 1 and 9), while it falls down to 43–52% (entries 8, 10 and 11) in polar solvents. It is noteworthy that the solvent effects are more pronounced in the case of ketone **2** as compared to ketone **1**; the cyclobutanol **CB1**, the major product in benzene (85%), becomes the minor product (43%) upon changing the solvent to methanol or acetonitrile.

The photochemical results observed with the ketones **1** and **2** are significant in several respects: First of all, the β-anisyl ketones are not photostable any longer and the Norrish Type II process competes in these systems with unproductive triplet quenching. Secondly, the isolated yield of cyclobutanols from both the ketones is 31–43%, despite the fact that β-substitution has been shown to decrease the cyclization yields.[12,13] For comparison, the yields of cyclobutanols from valerophenone and γ-phenylbutyrophenone that lack a substituent at the β-position, is only 15–16%.[16] Third, a single diastereomer out of four possible isomers is selectively formed in 80–85% yields in a nonpolar solvent.[17,18] Last, the observed magnitude of solvent effects on the diastereomer distribution is unprecedented, although the ability of solvents to affect the composition of the mixture of diastereomers has been documented in earlier literature.[19] These observations thus point to the fact that the effects delineated for α and β substituents on the Type II process[12,13] do not apply to β,γ-disubstituted alkanophenones such as the ketones **1** and **2** in consideration. Incidentally, the ketones with sub-

Table 1. Results of photolysis of ketones **1** and **2** in various solvents[a]

Entry	Ketone	Solvent	Isolated yield (%)	Ratio **CB1**:**CB2**
1	**1**	Cyclohexane	40	80:20 (4.0:1.0)
2	**1**	Benzene	31	82:18 (4.6:1.0)
3	**1**	Ethyl acetate	40	56:46 (1.2:1.0)
4	**1**	Pyridine	32	60:40 (1.5:1.0)
5[b]	**1**	*t*-Butanol		60:40 (1.5:1.0)
6[c]	**1**	Methanol	40	57:43 (1.3:1.0)
7[d]	**1**	Acetonitrile	32	60:40 (1.5:1.0)
8	**1**	DMSO-d_6	35	52:48 (1.1:1.0)
9	**2**	Benzene	38	85:15 (5.7:1.0)
10	**2**	Acetonitrile	35	44:56 (0.8:1.0)
11	**2**	Methanol	43	43:57 (0.8:1.0)

[a] Unless otherwise mentioned, all photolyses were carried out in an NMR tube in a Luzchem photoreactor ($\lambda = 350$ nm) under a nitrogen gas atmosphere. The conversion in all cases was >90%.

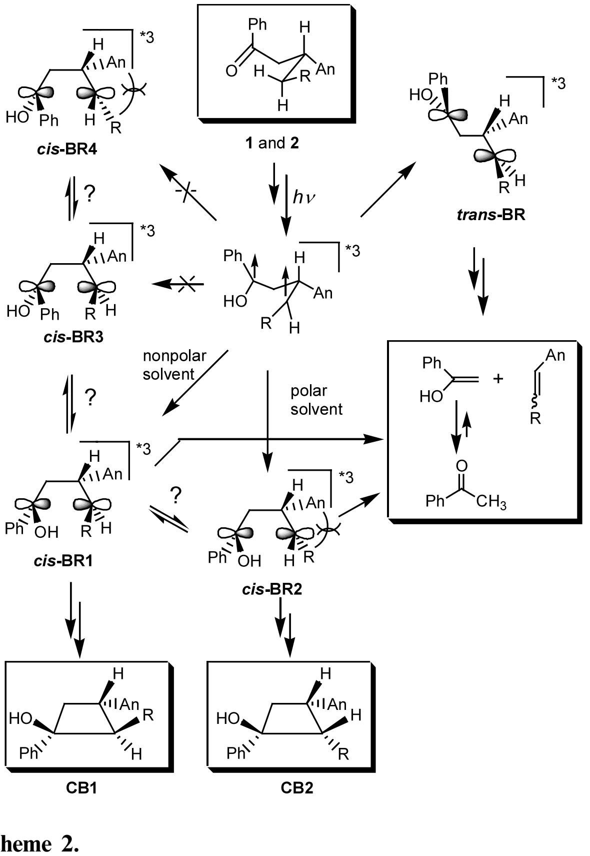
[b] The yield was not determined.

[c] From preparative photolysis. The yield of cyclobutanols was ca. 40%.

[d] Similar ratio from photolysis in CD_3CN.

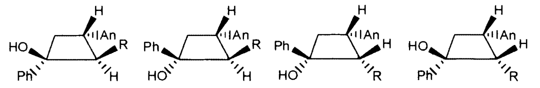
stituents at both β and γ positions have not been subjected to thorough investigation.

We shall now consider the origin of diastereoselectivity and rationalization of solvent effects. Scheme 1 is illustrative of events that occur subsequent to photoexcitation. As the triplet lifetime for these systems is typically less than 1 ns, we believe that conformational equilibration of the ketones **1** and **2** is unlikely to be established in the triplet manifold. Thus, the ground state equilibrium concentrations of the two different conformations are relevant for discussion. The photoexcitation of the population of **1** and **2** with a conformation in which the β-aryl ring is *gauche* can only lead to quenching (no cyclopropanol is formed as monitored by ^{1}H NMR spectroscopy). The ketones with the conformation in which the carbonyl is destined for γ-hydrogen abstraction yield triplet biradicals upon photoexcitation (Scheme 1). The biradicals may undergo disproportionation back to the starting materials (k_d), cyclization to cyclobutanols **CB1** and **CB2** (k_c) and elimination to acetophenone and olefins (k_e). The reason as to why only two cyclobutanols are observed can be reconciled based on the geometry in which the triplet biradical is generated (Scheme 2). That the γ-hydrogen abstraction occurs from a six-membered chair-like conformation has been well established.[20] Thus, the transition state for H-abstraction necessitates the β and γ substituents to assume a diequatorial *anti* relationship. The triplet biradical thus generated may adopt any of the five possible conformations (four *cisoid* and one *transoid* geometries) depending on their relative energies. The biradicals ***cis*-BR1** and ***cis*-BR2** are responsible for the observed cyclobutanols (**CB1** and **CB2**) as well as elimination products; the latter are formed exclusively from ***trans*-BR**. The biradicals ***cis*-BR3** and ***cis*-BR4** may lead to the cyclobutanols in which Ph and R are *syn* and An and R are *syn*, respectively. With the assumption that the energy differences calculated for the four diastereomeric cyclobutanols apply to their precursor biradicals (AM1 calculations, QCMP 137, MOPAC6/PC),[21] one calculates that the biradical ***cis*-BR1** is the most stable of all. It is unlikely that ***cis*-BR1** establishes equilibrium with other conformers (***cis*-BR2**, ***cis*-BR3** and ***cis*-BR4**) due to the short triplet lifetime.[22,23]



Scheme 2.

AM1 Calculated Relative Energies of all the Cyclobutanols



1: R = CH_3	0	+1.27	+2.87	+3.56
2: R = Ph	0	+0.60	+2.33	+4.37

The preferential formation of **CB1** in nonpolar solvents should be reconciled from the transition state structure for its formation, which should have less steric repulsion owing to the *anti* relationship between the sterically bulky Ph and CH_3 (Ph in **2**) groups at the 1,4 positions; since singlet biradicals are known to retain conformational memory of their precursor triplet biradicals before collapsing to the products,[24] the low-energy biradical ***cis*-BR1** is pertinent for the observed trend. It has been shown that polar solvents such as *t*-BuOH and pyridine increase the quantum yield of Type II processes by solvating 1,4-biradicals and that such a solvation leads to reduction in cyclization yields.[19] Interestingly, the elimination:cyclization ratio for ketones **1** and **2** is virtually invariant to changes in the solvent polarity. The increasing yield of **CB2** with increasing polarity can be understood based on the steric bulk of the hydroxy group. In the case of valerophenone, an analogous but less pronounced solvent effect has been explained based on the solvation increasing the steric bulk of the hydroxy group, thereby impeding the cyclization to *syn* cyclobutanols.[19,25] Similar consideration must apply to the ketones **1** and **2** here as well, implying that the steric bulk of the solvated hydroxy group predominates to such an extent as to invert the energetic ordering of the biradicals (i.e. solvated ***cis*-BR2** becomes more stable than that of ***cis*-BR1**) leading to loss of stereoselectivity; otherwise, the cyclobutanol **CB2** would not be observed. It is noteworthy that the effects are more pronounced in ketone **2**, which is understandable based on the steric effects in going from CH_3 to Ph.

In summary, we have shown that the Norrish Type II process operates competitively with aryl quenching in β-anisylalkanophenones. The Yang cyclization leads to modest yields of cyclobutanols in a highly stereoselective manner; only one out of four possible diastereomers is selectively formed in 80–85% yields. It has also been shown that the solvent polarity dramatically influences diastereomer composition.

Acknowledgements

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15. Typically, 1 mmol of the ketone in 100 mL of C_6H_6 or CH_3CN was irradiated under nitrogen gas in a Luzchem photoreactor for 12–24 h. The photolysate was stripped off the solvent in vacuo and the residue was subjected to silica-gel chromatography (25% EtOAc–pet. ether). The **CB1** eluted first followed by **CB2**.
    CB-1: Colorless oil; IR (neat): 3438, 2960, 1512 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 1.23 (d, 3H, J=6.8 Hz), 2.45–2.63 (m, 2H), 2.67–2.73 (m, 1H), 3.35 (q, 1H, J=9.0 Hz), 3.79 (s, 3H), 6.86 (d, 2H, J=8.0 Hz), 7.17 (d, 2H, J=8.0 Hz), 7.27 (t, 1H, J=7.2 Hz), 7.37 (t, 2H, J=7.2 Hz), 7.44 (d, 2H, J=7.2 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 12.6, 41.3, 41.7, 48.3, 55.3, 76.2, 113.8, 124.9, 127.2, 127.6, 128.5, 136.2, 146.6, 158.0.
    1CB-2: Colorless oil; IR (neat): 3438, 2933, 1513 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 0.68 (d, 3H, J=6.4 Hz), 2.34–2.41 (m, 1H), 2.60–2.66 (m, 2H), 3.12–3.18 (m, 1H), 3.80 (s, 3H), 6.88 (d, 2H, J=8.0 Hz), 7.22 (d, 2H, J=8.5 Hz), 7.30–7.34 (m, 1H), 7.43 (t, 2H, J=8.0 Hz), 7.55 (d, 2H, J=8.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 15.3, 38.3, 42.1, 52.3, 55.3, 75.8, 113.8, 126.2, 127.3, 127.8, 128.3, 135.9, 142.4, 158.1.
    2CB-1: Colorless oil; IR (neat): 3458, 2959, 1514 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.53–2.57 (m, 1H), 2.72–2.77 (m, 1H), 3.77 (s, 3H), 4.0 (d, 1H, J=10.0 Hz), 4.19 (q, 1H, J=8.8 Hz), 6.83 (d, 2H, J=8.8 Hz), 7.21 (d, 2H, J=8.8 Hz), 7.26–7.40 (m, 8H), 7.49 (d, 2H, J=8.0 Hz); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 38.1, 41.2, 55.3, 57.9, 77.1, 113.8, 125.0, 127.1, 127.2, 127.6, 128.41, 128.44, 128.6, 136.0, 137.2, 146.1, 158.1.
    2CB-2: Colorless oil; IR (neat): 3442, 2931, 1514 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.48 (t, 1H, J=10.8 Hz), 3.24–3.29 (m, 1H), 3.40–3.47 (m, 1H), 3.75 (s, 3H), 3.89 (d, 1H, J=10.8 Hz), 6.81 (d, 2H, J=8.8 Hz), 6.86–6.89 (m, 2H), 7.06 (d, 2H, J=8.8 Hz), 7.13–7.27 (m, 8H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 34.2, 41.0, 55.2, 62.5, 77.8, 113.8, 126.4, 126.5, 127.3, 127.72, 127.74, 127.87, 127.94, 135.4, 138.3, 141.2, 158.1.
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