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Photoinduced C−Br Homolysis of 2-Bromobenzophenones and Pschorr Ring Closure of 2-Aroylaryl Radicals to Fluorenones

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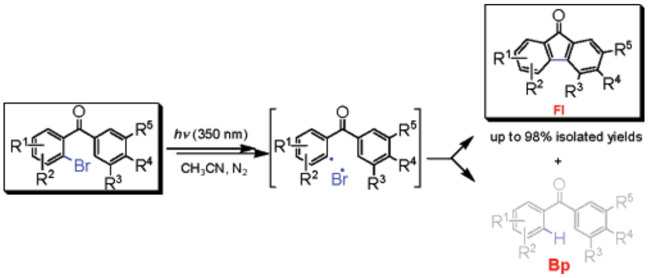
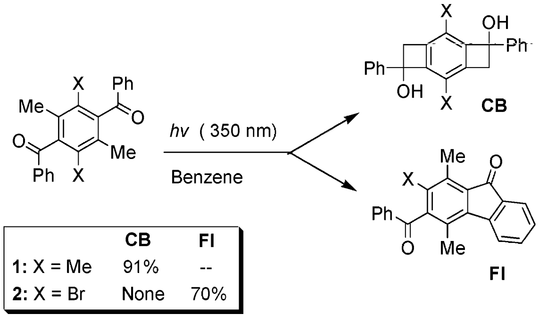


A variety of diversely substituted 2-aroylaryl radicals, generated by photoinduced homolysis of 2-bromoarylketones, is shown to undergo Pschorr cyclization to yield fluorenones in moderate to excellent yields. The photochemical results illustrate that the substituents in the two phenyl rings of the 2-bromobenzophenone skeleton exert a dramatic influence on the reactivity of the derived 2-aroylaryl radicals. The disubstitution by methoxy groups in the radical ring renders the aryl σ-radical highly electrophilic and unreactive for hydrogen abstraction and cyclization. On the other hand, the substituents in the non-radical ring that strongly stabilize the hydrofluorenyl π-radical, formed subsequent to the attack of the 2-aroylaryl radical on the non-radical ring, promote cyclization to furnish fluorenones in excellent isolated yields.

The intramolecular cyclization of aryl radicals generated via decomposition of aryl diazonium salts by either alkali or copper salts is known as the Pschorr reaction.[1] When performed on 2-aroylbenzene diazonium salts, the Pschorr reaction leads to fluorenones,[2] which are excellent building blocks of several natural products and organic materials; this protocol indeed constitutes a traditional approach for the synthesis of fluorenones in general. However, it is disadvantageous from the point of view of strongly alkaline conditions employed to conduct the reaction, poor yields of fluorenones, etc. Karady et al. have shown that the 4-methyl-2-benzoylphenyl radical, generated by the photolysis of its precursor iodo derivative or the corresponding diazoniun salt, undergoes (i) a 1,5-hydrogen shift to rearranged radicals, (ii) cyclization to the fluorenone, and (iii) trapping in the presence of added radical scavengers to yield dehalogenated ketones.[3] Their extensive investigations have been limited to mechanistic details of 1,5-hydrogen shifts in the photogenerated 2-aroylaryl radicals. In principle, photoinduced dehydrohalo cyclization of 2-halobenzophenones can be a convenient protocol for the synthesis of fluorenones. Surprisingly, the synthetic potential of the Pschorr cyclization of 2-aroylaryl radicals generated by photoinduced homolysis of 2-haloketones has not been explored.

SCHEME 1



	CB	Fl
1: X = Me	91%	--
2: X = Br	None	70%

In continuation of our recent studies on diphotocyclization of dicarbonyl-substituted benzenes such as **1** (Scheme 1),[4] we serendipitously discovered that the analogous dibromodiketone **2** yielded the corresponding 9-fluorenone (**Fl**) in 70% isolated yield, while the formation of bis-benzocyclobutenol (**CB**) was not observed at all (Scheme 1). This result spurred us to explore the extent to which the photoinduced cyclization of 2-bromobenzophenones can be modulated. In the present investigation, we examined the photobehavior of a broad set of 2-bromobenzophenones (cf. Table 1). Herein, we report that the photochemical approach is facile for the synthesis of fluorenones. The results demonstrate that the reactivity of the 2-aroylphenyl σ-radical[5,6a] to undergo Pschorr ring closure depends crucially on the substituents in the two phenyl rings.

All 2-bromoketones **3**−**8** (Table 1) were conveniently prepared by the reaction of appropriately substituted 2-bromobenzaldehyde with aryl magnesium bromide followed by PCC oxidation of the resultant alcohol (see Supporting Information). The preliminary results for the photolysis of 2-bromo-4′-methoxybenzophenone **3b**, a representative case, in nonpolar benzene and polar acetonitrile solvents revealed that the

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[1] (a) Abramovitch, R. A. *Advances in Free Radical Chemistry*; Heyden and Sons: London, 1967; Vol. 2, p 87. (b) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

[2] (a) DeTar, D. F.; Whiteley, T. E. *J. Am. Chem. Soc.* **1957**, *79*, 2498. (b) Kyba, E. P.; Lue, S.-T.; Chockalingam, K.; Reddy, B. R. *J. Org. Chem.* **1988**, *53*, 3513.

[3] (a) Cummins, J. M.; Dolling, U.-H.; Douglas, A. W.; Karady, S.; Leonard, W. R.; Marcune, B. F. *Tetrahedron Lett.* **1999**, *40*, 6153. (b) Karady, S.; Abramson, N. L.; Dolling, U.-H.; Douglas, A. W.; McManemin, G. J.; Marcune, B. *J. Am. Chem. Soc.* **1995**, *117*, 5425. (c) Karady, S.; Cummins, J. M.; Dannenberg, J. J.; Rio, E.; Dormer, P. G.; Marcune, B. F.; Reamer, R. A.; Sordo, T. L. *Org. Lett.* **2003**, *5*, 1175.

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[5] Madhavan, V.; Schuler, R. H.; Fessenden, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 888.

[6] (a) Chandler, S. A.; Hanson, P.; Taylor, A. B.; Walton, P. H.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **2001**, 214. (b) Hanson, P.; Hammond, R. C.; Goodacre, P. R.; Purcell, J.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **1994**, 691. (c) Hanson, P.; Hammond, R. C.; Gilbert, B. C.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2195. (d) Hason, P.; Lövenich, P. W.; Rowell, S. C.; Walton, P. H.; Timms, A. W. *J. Chem. Soc., Perkin Trans. 2* **1999**, 49.

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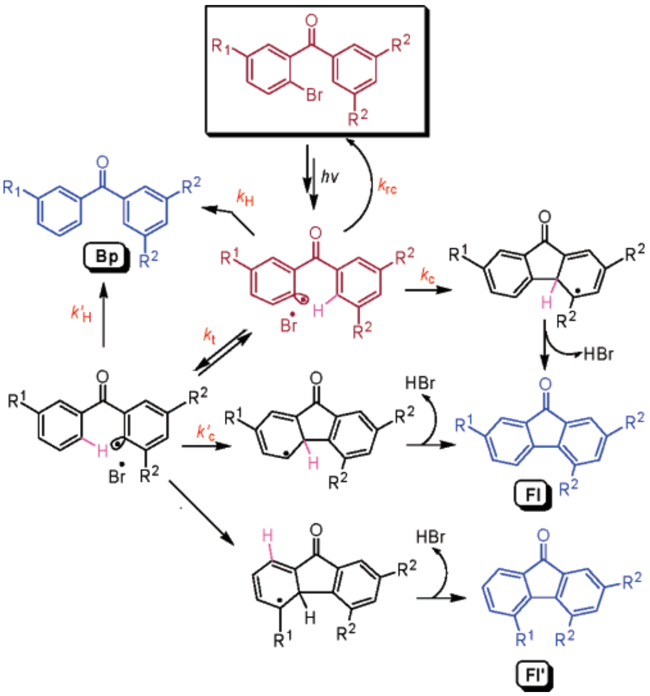
cyclization occurs in at least 6-fold higher yield in acetonitrile as a solvent as compared to that in benzene, as monitored by GC and ^{1}H NMR analyses. Thus, the photolyses of all ketones **3**−**8** were conducted in N_2-purged CH_3CN solutions in a photoreactor fitted with λ ca. 350 nm lamps (cf. Supporting Information). The photolysate in each case was monitored by TLC and GC analyses. After photolysis, the solvent was removed in vacuo, and the residue was subjected to silica-gel column chromatography to isolate the photoproducts, viz., fluorenone (**Fl**) and the dehalogenated benzophenone (**Bp**). For some ketones, the reactions were run for longer durations to ensure high conversions, as the colored fluorenone products severely interfered with the absorption of UV radiation by their precursor 2-bromobenzophenone reactants.

A perusal of the results in Table 1 suggests that the photochemical route does indeed lead to respectable yields of cyclization products depending on the nature of substituents and their pattern of substitution; the conversion and mass balance are reasonable for most cases. While the photolysis of parent 2-bromobenzophenone **3a** and the corresponding 4′-trifluoromethyl analogue **3c** yielded fluorenones in only ca. 32−34% yield (Table 1, entries 1 and 3), that of the methoxy analogues **3b**, **4a**, and **4b** led to relatively higher yields of fluorenones, ca. 48% (Table 1, entries 2, 7, and 8); of course, the other major product in all these cases is the dehalogenated benzophenone. All other ketones with the exception of **6a**, **7a**, and **8c** afforded the corresponding fluorenones in 67−98% isolated yields (Table 1, entries 4−6, 9−11, 13, and 15−17); **6a** and **7a** (Table 1, entries 12 and 14) were found to be unreactive, while **8c** yielded the corresponding fluorenone in 53% yield (Table 1, entry 18).

The photoinduced C−Br/I bond homolysis of Br/I-phenylketones has been sufficiently investigated. In particular, Wagner and co-workers have elucidated the mechanistic details of photoinduced C−Br/I bond homolysis of bromo- and iodoacetophenones and benzophenones.[7] Accordingly, the C−Br cleavage is endothermic by 6−12 kcal/mol for triplet-excited benzophenones, while it is exothermic for the corresponding iodo analogues, due to the difference in Ph−Br (78−80 kcal/mol) and Ph−I (64 kcal/mol) bond dissociation energies; the triplet-excited energies of various benzophenones are 68−70 kcal/mol.[8] It is assumed that for bromobenzophenones, the lowest triplet-excited n,π^* states convert into π,π^* states before cleavage. Further, Wagner et al. have shown that the triplets of *o*-bromophenylketones undergo cleavage 600-fold faster than those of *meta*- and *para*- analogues. Thus, photoinduced homolytic C−Br/I bond cleavage is a facile pathway to generate aroylphenyl radicals.

Mechanistically, various pathways that determine the fate of the initially formed 2-aroylaryl radical, viz., radical translocation (k_t), hydrogen abstraction (k_H), recombination (k_{rc}), and cyclization (k_c), are shown in Scheme 2. The cyclization of translocated radical may, in principle, lead to two regioisomeric fluorenones. Indeed, Karady et al. showed that the photolysis of deuterated methyl-substituted iodobenzophenone does lead to the isomeric fluorenones.[3a] From their studies on 2-benzoylbenzene diazonium salts, Hanson and co-workers have determined rate constants for various pathways of the parent 2-benzoylphenyl radical.[6] They have shown that a simple substitutent such as a methyl group may modify the cyclization rates (k_c and k'_c) of the 2-benzoylphenyl radical, and it is rearranged one by 1−2 orders of magnitude.[6a] Thus, the photochemical outcome of ketones **3**−**8**,[8] which depends on the partitioning of derived 2-aroylphenyl radicals among various pathways, should be subject to the influence of substituents present in both phenyl rings of benzophenone.[9] From the analysis of preparative photochemical results consolidated in Table 1, some generalizations emerge with regard to the reactivity of the 2-aroylaryl radical in general.

SCHEME 2



For the sake of discussion of the influence of substituents on the photoinduced cyclization of 2-bromobenzophenones **3**−**8**, we shall term the halogen-containing ring that leads to the aryl radical as a radical ring and the other as a non-radical ring. First, the results in Table 1 reveal that all ketones in which the non-radical ring contains substituents that stabilize the incipient hydrofluorenyl radical afford good to excellent yields of fluorenones. That is, for ketones **3d**,**e**, **4c**,**d**, **5**, **6b**, **7b**, and **8b** (Table 1, entries 4, 5, 9−11, 13, 15, and 17), the initially formed 2-aroylphenyl σ-radical may stabilize via cyclization to the corresponding cyclohexadienyl π-radical. This is in line with the observation by Karady et al.[3b] that the substituents that stabilize the cyclohexadienyl radical accelerate ring closure (k_c, Scheme 2), thereby minimizing hydrogen migrations (k_t). Accordingly, the formation of the regioisomeric fluorenone product (**Fl′**, Scheme 2) was not observed from ketones **5** and **6b** upon photolysis. Thus, it may be concluded that the ketones for which the hydrofluorenyl radical, formed subsequent to the attack of the 2-aroylaryl radical on the non-radical ring, is stabilized strongly by the substituents due to their nature as well

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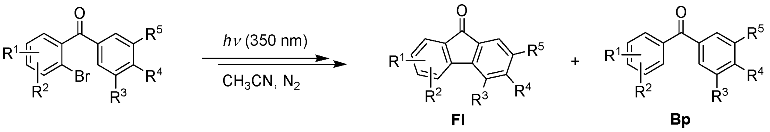
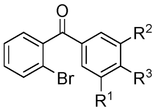
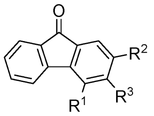
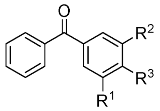
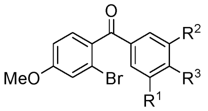
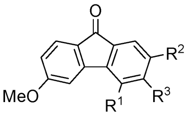
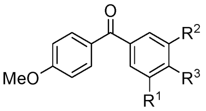
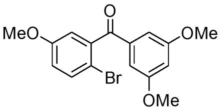
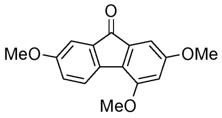
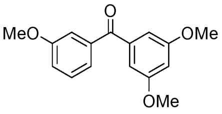
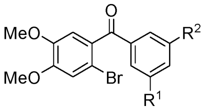
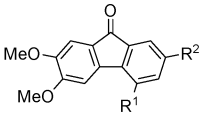
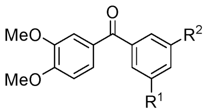
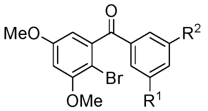
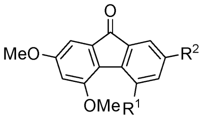
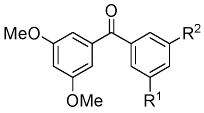
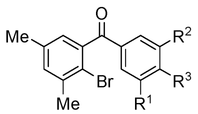
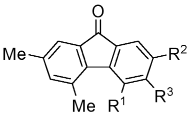
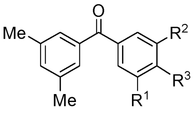
[7] (a) Wagner, P. J.; Sedon, J.; Waite, C.; Gudmundsdottir, A. *J. Am. Chem. Soc.* **1994**, *116*, 10284. (b) Wagner, P. J.; Waite, C. I. *J. Phys. Chem.* **1995**, *99*, 7388. (c) Wagner, P. J.; Sedon, J. H.; Gudmundsdottir, A. *J. Am. Chem. Soc.* **1996**, *118*, 746.

[8] Triplet energies are less likely to vary considerably for all ketones **3**−**8**, see: Leigh, W. J.; Arnold, D. R. *J. Chem. Soc., Chem. Commun.* **1980**, 406.

[9] State-switching for substituted benzophenones does not occur except for dialkylamino substituents, see: Wagner, P. J.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. II, Ch. 4.

TABLE 1. Results of Photocyclization of 2-Bromobenzophenones 3−8 to the Corresponding Fluorenones[a]



entry	substrate	conv[b] (%)	time (h)	fluorenone[c] (%)	benzophenone[c] (%)
					
1	**3a**: R^1 = R^2 = R^3 = H	100	14	34[d]	62
2	**3b**: R^1 = R^2 = H; R^3 = OMe	100	14	48	39
3	**3c**: R^1 = R^2 = H; R^3 = CF$_3$	100	14	32[d]	57
4	**3d**: R^1 = OMe; R^2 = R^3 = H	91	36	75 (1:1.8)[e]	20[d]
5	**3e**: R^1 = R^2 = OMe; R^3 = H	90	72	80	3
6	**3f**: R^1 = R^2 = Me; R^3 = H	100	16	67	21
					
7	**4a**: R^1 = R^2 = R^3 = H	100	14	48	39
8	**4b**: R^1 = R^2 = H; R^3 = OMe	100	24	48	34
9	**4c**: R^1 = OMe; R^2 = R^3 = H	100	48	77 (1:1.5)[e]	18[d]
10	**4d**: R^1 = R^2 = OMe; R^3 = H	100	36	92	-
					
11	**5**	100	48	95	-
					
12	**6a**: R^1 = R^2 = H	<8	36	-[f]	-
13	**6b**: R^1 = R^2 = OMe	76	72	75	-
					
14	**7a**: R^1 = R^2 = H	-[g]	48	-	-
15	**7b**: R^1 = R^2 = OMe	58	72	94	-
					
16	**8a**: R1 = R^2 = R^3 = H	100	36	80	-
17	**8b**: R^1 = R^2 = OMe; R^3 = H	100	48	98	-
18	**8c**: R^1 = R^2 = H; R^3 = CF$_3$	95	36	53	8

[a] All photolyses were carried out in dry acetonitrile as a solvent under N$_2$ in a photoreactor (λ ca. 350 nm). [b] Based on the recovered starting material. [c] Unless otherwise mentioned, the isolated yields (%) are based on starting material reacted; the deficit corresponds to an intractable polar material that did not elute on silica gel. [d] Fluorenone and dehalogenated benzophenone were isolated as an inseparable mixture, and their relative yields were determined from ^{1}H NMR analyses. [e] Relative ratio of the two regioisomers as calculated from ^{1}H NMR and GC analyses is given in parentheses. [f] GC analysis showed <5% of the fluorenone. [g] No ketone decomposition was observed.

as location in the ring undergo efficient cyclization. The radical rearrangement does not appear to compete with cyclization in such ketones.

Second, the lack of formation of any product from dimethoxy-substituted bromoketones **6a** and **7a** even after several hours of irradiation attests to the fact that both cyclization (k_c) and translocation (k_t) simply do not occur for these ketones; if translocation of the initially formed radical occurred, the resultant radical would cyclize readily since the hydrofluorenyl radical formed subsequent to cyclization would be more stable for both of these ketones. In other words, the dimethoxy substitution appears to render the aryl σ-radicals highly electrophilic and unreactive to both translocation and cyclization; of course, such radicals undergo cyclization readily when there is incentive through location of substituents in the non-radical ring that stabilize the hydrofluorenyl radicals as in **6b** and **7b**. It should be noted that the methoxy substituents exert inductive electron withdrawing influence on the σ-aryl radical,[10] while they stabilize the cyclohexadienyl π-radical through resonance when present in the non-radical ring.

Third, for ketones that yield 2-aroylaryl radicals containing substituents that exert only a moderate electron donating or electron withdrawing effect, we believe that the translocation is competitive to cyclization. Indeed, Karady et al. have shown that such translocations do occur for radicals derived from methyl-substituted 2-iodoketones. Thus, the ketones **3a**−**c**, **3f**, **4a**, **8a**, and **8c** may be grouped under this category for which the hydrogen rearrangements occur. For these cases, the fluorenones may be formed via preferential formation of that hydrofluorenyl radical that is stabilized by the substituents. The surprisingly similar yields of fluorenones from ketones **3b**, **4a**, and **4b** are clearly suggestive of the occurrence of radical translocations in these cases.[11] Further, the comparable yields of fluorenones from **3f** and **8a** can similarly be reconciled based on radical translocations before cyclization.

The reactivity of 2-aroylaryl radicals has been rationalized by Hanson and co-workers based on the interaction of the SOMO of the aryl radical with the upper two bonding π-orbitals of the attacked/non-radical ring.[6a] The theoretical AM1 UHF calculations on the parent 2-benzoylphenyl radical appear to indicate that the SOMO lies at a lower energy than the upper two bonding π-orbitals of the attacked ring. They reported that the enhanced reactivity observed for the 5-methyl-2-benzoylphenyl radical as compared to the parent 2-benzoylphenyl radical could be rationalized based on the consideration that the methyl group raises the energy of the SOMO slightly such that the interaction between the SOMO and the upper bonding orbitals of the attacked ring is enhanced. The photochemical results for all ketones **3**−**8** in Table 1 can be nicely rationalized based on energetic considerations of the orbitals described previously. For example, the lack of reactivity of **6a** and **7a** is possibly due to the fact that the electron withdrawing methoxy substituents (for σ-aryl radicals) increase the energy difference between the SOMO and the highest bonding molecular orbitals of the non-radical ring. In contrast, higher yields of fluorenones from dimethyl-substituted ketones **3f** and **8a** should be explicable from a marginal energy difference; of course, the radical translocation must occur in the case of **3f** before cyclization, such that the energetic ordering of the orbitals is appropriate for efficient cyclization.

In summary, we have shown that a variety of diversely substituted 2-aroylaryl radicals, generated by photoinduced homolysis of 2-bromoarylketones, undergo Pschorr cyclization to yield fluorenones in moderate to excellent yields; incidentally, the photoinduced Pschorr cyclization has not been systematically investigated except for 1,5-hydrogen shifts in the 2-aroylaryl radicals. The photochemical results suggest that the substituents in the two phenyl rings of the 2-bromobenzophenone skeleton exert a dramatic influence on the reactivity of the initially derived 2-aroylaryl radicals. It is found that (i) cyclization occurs efficiently for ketones in which the hydrofluorenyl radical formed subsequent to attack of the 2-aroylaryl radical is strongly stabilized, (ii) 1,5-hydrogen shifts compete with cyclization in ketones that contain substituents that stabilize the hydrofluorenyl radical only moderately, and (iii) the 2-aroylaryl radicals are virtually unreactive to both hydrogen rearrangements as well as cyclization when rendered to be highly electrophilic by methoxy substituents, which are electron withdrawing for aryl σ-radicals.

Experimental Section

General Procedure for Photolysis of Ketones. A 2.5−4.5 mM solution of the 2-bromobenzophenone derivative in dry acetonitrile contained in a Pyrex tube was purged with N_2 gas for 30 min and irradiated in a photoreactor fitted with $\lambda \approx 350$ nm lamps. Depending upon the substrate, the colorless solutions of ketones turned to yellow to orange to red/reddish-brown within a few hours of photoirradiation. The progress of the reaction was monitored by GC and TLC analysis. After photolysis, the solvent was removed in vacuo, and the residue was subjected to a careful silica-gel column chromatography to isolate the photoproducts, viz., the fluorenone derivative and dehalogenated benzophenone. All the fluorenone derivatives were characterized by spectroscopic data. The dehalogenated ketones were characterized by comparison of their ^{1}H NMR spectral data with the literature reported data.

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Supporting Information Available: Details of synthesis of bromoketones, photolysis, and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Augood, D. R.; Williams, G. *Chem. Rev.* **1957**, *57*, 123.

[11] Preparative photolyses were run for an extended duration to maximize conversion of 2-bromoketones to products, as the products also absorb. Therefore, relative durations of irradiation should not be correlated with the reactivities of ketones.