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LETTERS

Intramolecular Aromatic 1,5-Hydrogen Transfer in Free Radical Reactions. II. Rearrangement of Iodobenzophenones.

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Abstract: Products derived from the homolysis of the aromatic C–I bond of *ortho*–iodobenzophenones by photolysis or tributyltin radicals indicate 1,5-hydrogen migration. The reactions include iodine migration, hydrogen abstraction and arylation. © 1999 Elsevier Science Ltd. All rights reserved.

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While radical induced hydrogen migration is very common in aliphatic compounds [1] it has not been generally recognized to occur when the departing hydrogen is on an aromatic carbon [2, 3]. In an earlier paper we showed that hydrogen migration dominates the chemistry of benzophenone radicals generated from diazonium salts [4]. Thus, hydrogen transfer takes place in such commonly used synthetic transformations as Pschorr cyclizations, Sandmeyer reactions, and hydro-, hydroxy-, and iododediazoniation reactions. Recently published theoretical calculations predict a low energy barrier for this type of hydrogen shift [5]. In this paper we show that 1,5-hydrogen transfer is significant when the radicals are generated by homolysis of an aromatic C–I bond.

The chemistry of iodobenzophenones (e.g., **1a**) was investigated by varying both the method of radical initiation and the trapping agents. The radicals were generated by photolysis or by reaction with tributyltin radicals. The radicals were trapped by cyclization, iodine, deuteriomethanol and aromatic solvents. Hydrogen shift took place in every reaction tested. We postulate (Scheme 1) that the originally formed radical **A** rearranges to radicals **B** and **C** by sequential 1,5-hydrogen migrations and that all the products are derived from these three radicals. A cyclization reaction (analogous to the Pschorr cyclization) leads to the two isomeric fluorenones **4** and **5**. Competing with the cyclization is the trapping of the radicals leading to compounds **1**, **2**, and **3**. The extent of the rearrangement and the ratio of the products formed depends on the length of the reaction and on the nature of the trapping agents.

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[1] The ninth place in the Westinghouse Science Talent Search of 1995 was awarded to J. M. Cummins, then student in Livingston High School, Livingston, N. J., for part of the work described in this paper.

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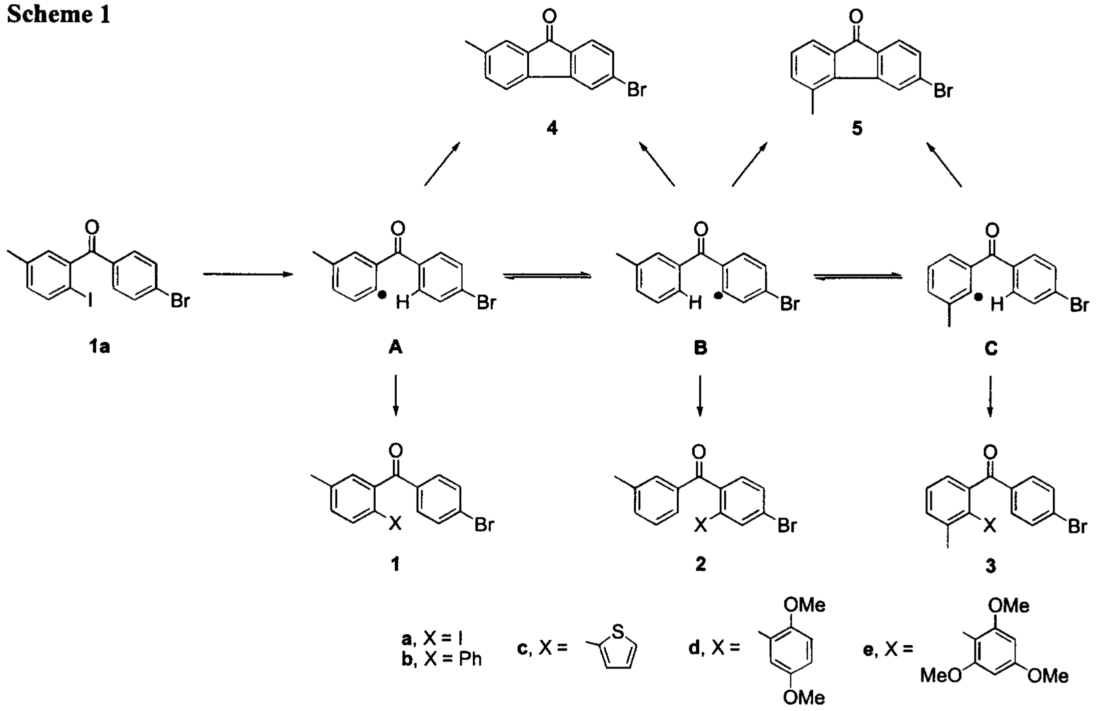
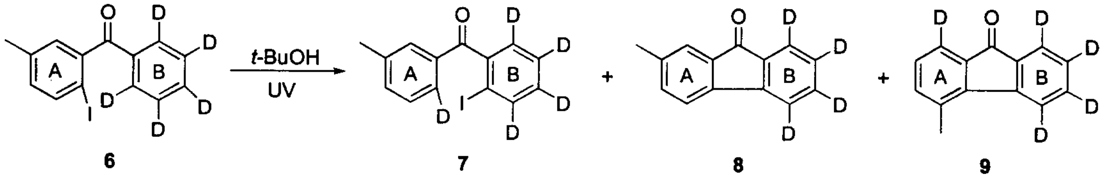
Scheme 1



Irradiation[2] of iodobenzophenone **1a** in *t*-butanol (an unreactive solvent) for 2.5 h, generated a 3:1 mixture[3] of **1a** and **2a**, accompanied by a small amount of **3a**, indicating that 1,5-hydrogen migration, consequently, a formal 1,5-iodine transfer, took place. On prolonged irradiation, the iodo compounds were gradually converted to fluorenones. Thus after 18 h, a 3:2 mixture of fluorenones **4** and **5** (31% yield) was produced in addition to the mixture of isomeric iodo compounds (51% yield).[3,4] It is remarkable that the isomer ratio of iodo compounds **1a**, **2a** and **3a** was now 10:8:7, indicating that an equilibration took place between the isomers

The origin of the migrating hydrogen was shown by the photolysis of pentadeuterio analog **6** in *t*-butanol. The rearrangement in this case was reduced (ratio of **8**:**9** = 10:1) due to the deuterium isotope effect. The formation of **7** and **9** however, clearly established that deuterium migration took place from ring **B** to ring **A**.



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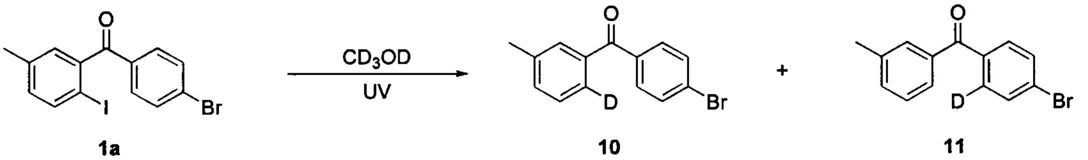
[2] A nitrogen purged solution of iodobezophenone **1a** (300 mg) in *t*-butanol (17 mL) was irradiated for 18 h in a borosilicate test tube attached to the cooled quartz well of a Hanovia high pressure mercury lamp. The progress of the reaction was followed by HPLC. The products were separated by chromatography on silica gel followed by preparative TLC on silica gel. Iodo compounds **2a** and **3a** were identified by comparison with authentic samples [4].

[3] Ratios determined by GC/MS, compounds characterized by ^{1}H and ^{13}C NMR and by comparison with samples described in [4].

[4] Yields determined by HPLC wt% assay vs standards.

Reaction with the solvent can be expected when the radicals are generated in reactive solvents. If these solvent reactions are not significantly faster than the hydrogen shift, we can expect isomeric products. The most common free radical reaction, hydrogen or deuterium abstraction, was tested by photolyzing **1a** in deuteriomethanol. The 1,5-hydrogen transfer effectively competed with deuterium abstraction resulting in a 4:1 mixture[3] of deuterio benzophenones **10** and **11** [4].



When the radicals were generated in aromatic solvents, aromatic substitution products were created. The ratio of fluorenones to substitution products **1**, **2**, and **3** was indicative of the effectiveness of the trap. Thus when photolysis was carried out in benzene, thiophene, dimethoxy- or trimethoxybenzene, the predominant formation of isomeric substituted benzophenones **1b**, **1c**, **1d**, **1e**, and **2b**, **2c**, **2d**, **2e** was observed (Table 1).[5] In some cases the double rearrangement product **3** was also detected. Similar results were obtained when the radicals were generated with $(Bu_3Sn)_2$ + AIBN [6].[6] The yields of these substitution reactions were moderate and depended on the length of the reaction. For example, the combined yield of **1b** and **2b** in a $(Bu_3Sn)_2$ initiated reaction in benzene was 68%, while photolysis in thiophene generated **1c** and **2c** in 58% combined yield.

Interestingly, the ratio[3] of products **1** and **2** was dependent on the aromatic substituents, as shown in Table 1.

Table 1: The Ratio of Aromatic Substitution Reaction Products 1 and 2 (Scheme 1)

Solvent	X =	Products	Ratio 1:2
Benzene	Phenyl	**1b, 2b**	1.8:1
Thiophene	Thiopheneyl	**1c, 2c**	3:1
1,4-dimethoxybenzene	1,4-dimethoxyphenyl	**1d, 2d**	0.5:1
2,4,6-trimethoxybenzene	2,4,6-trimethoxyphenyl	**1e, 2e**	0.9:1

It is remarkable that with the electron rich dimethoxy- and trimethoxybenzene, rearrangement became the dominant pathway. This could be the result of the polar effect [7], which would require that the electron rich aromatic systems react preferentially with the more electron deficient radical **B**. With electron poor aromatics, dichloro- and difluorobenzene, only a few percent substitution was observed and ring closure was the dominant reaction.

An experiment with deuterio benzophenone **6** showed that radical trapping by benzene was also preceded by deuterium migration to give product **13**.[3]

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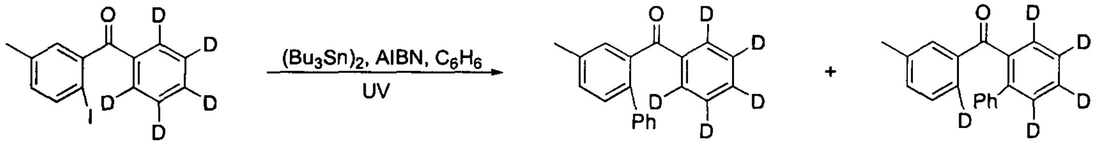
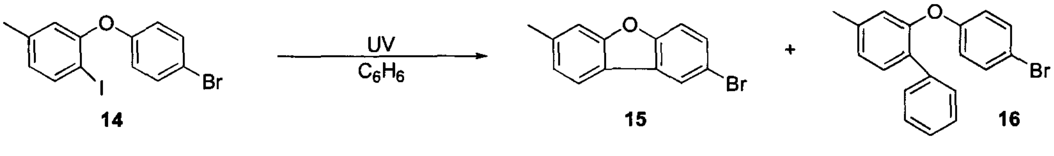
[5] Photolysis was carried out with the equipment described in footnote 2, except, when needed, the aromatic solvent was melted by partial immersion of the quartz tube in a heated oil bath and the mixture was agitated with a magnetic stirrer. Periodically the mixture was extracted with Na_2SO_3 solution to remove the iodine color. Alternatively, the photolysis was carried out in a stirred two-phase system with saturated Na_2SO_3 solution. The time required for the consumption of **1a** was 8–16 h. The products were isolated by column chromatography or preparative TLC on silica gel.

[6] In our case, 24 h irradiation in the presence of 20 wt % of hexabutylditin with AIBN was required to complete the reaction.

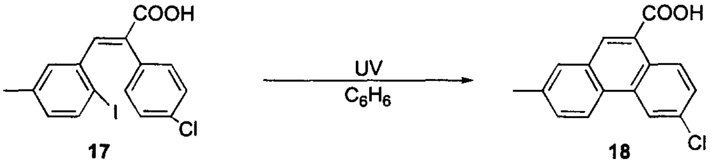


6 **12** **13**

In order to test the generality of the aromatic hydrogen shift, two other systems were investigated. Irradiation of **14** in benzene produced a 1:3 mixture of **15** and **16**. Ring closure was the predominant reaction of the photolysis of **17**. No isomeric products indicating hydrogen transfer were detected in these reactions.



14 **15** **16**



17 **18**

A recent molecular orbital calculation by T. L. Sordo and J. J. Dannenberg [8] showed that the hydrogen bond between the carbonyl and the aromatic *ortho* hydrogens plays an important role in bringing the benzophenone system to coplanarity, thus making the 1-5 hydrogen shift possible and energetically favorable. Earlier theoretical calculations [5] indicated that hydrogen shift is favorable in rigid aromatic systems. Experimentally, hydrogen migration was only observed with *ortho*–benzophenone radicals. Therefore, the generality of this phenomenon in other aromatic systems remains to be established.

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