A New Ketyl Radical Probe. Dehalogenation of *o*-Halobenzophenone[1)]

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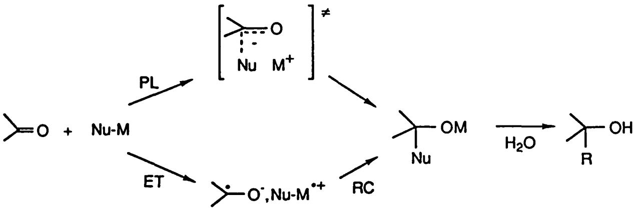
(Received December 6, 1991)

Synopsis. The reactions of *o*-, *m*-, or *p*-bromobenzophenone and *o*-iodobenzophenone with various Grignard reagents were carried out in diethyl ether at 0 °C. The product analysis showed that these halobenzophenones can be a good chemical probe to evaluate the electron-transfer ability of nucleophiles to the aromatic ketones.

Nucleophilic additions to carbonyl compounds have two possible reaction routes, polar (PL) and electron transfer-radical coupling (ET-RC) pathways (Eq. 1). Involvement of an ET process has been suggested in some reactions by a variety of techniques including spectroscopic and chemical probe experiments.[2)] We have recently shown that ^{14}C kinetic isotope effect is useful in distinguishing the ET rate-determining reaction from the RC rate-determining one in the ET-RC sequence.[3)] However, the PL pathway and the ET pathway with rate-determining RC are difficult to discriminate by the isotope effect technique.



(1)

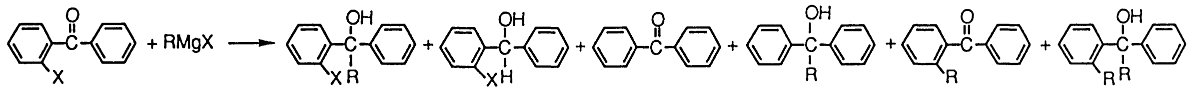
Although the possibility of ET can be evaluated in principle in terms of the redox potentials of a substrate and a nucleophile, it is often hampered by the experimental difficulty in measuring the oxidation potential of a nucleophile.[4)] Under such circumstances, enone-isomerization experiment has been used to assess the ET ability of a nucleophile;[5)] isomerization of a *cis* enone to a *trans* enone when mixed with a nucleophile can be taken as the occurrence of ET from the nucleophile to the particular enone. Here we wish to report a new probe that can be used to show the possible ET from a nucleophile to aromatic ketones and suggest the presence of the ketyl radical anion of sufficient lifetime under the reaction conditions.

The idea is based on the report that electrochemically generated bromobenzophenone radical anion undergoes a dehalogenation reaction.[6,7)] It can then be expected that when bromo- or iodobenzophenone accepts an electron from any nucleophile the ketyl thus formed undergoes the dehalogenation reaction if the lifetime of the ketyl is long enough, and therefore the detection of a dehalogenated product can be evidence for the nucleophile to have enough ability to transfer an electron to the aromatic ketone. The practical difficulty for the dehalogenation to occur may arise from the rapid reaction of the ketyl with the counter radical cation to give the normal product, which can not be happened in the electrochemical reaction. However, this difficulty may be avoided by using *o*-halobenzophenone, for which the reaction with the counter radical cation should be slowed down by the steric reason.

The applicability of the ketyl radical probe was tested by running the Grignard reactions of bromo- or iodo-substituted benzophenone with MeMgI, PhMgBr, and $CH_2=CHCH_2MgBr$. This reaction system was chosen because the ET character of the reactions has been well-documented.[2d,8)] Furthermore, since the former two reagents were previously concluded to proceed via fast ET followed by slow subsequent steps while the latter reagent via rate-determining ET,[3b,9)] it is possible to compare the results for a series of reactions of the different rate-determining step and thus of the different lifetime of the ketyl intermediate.

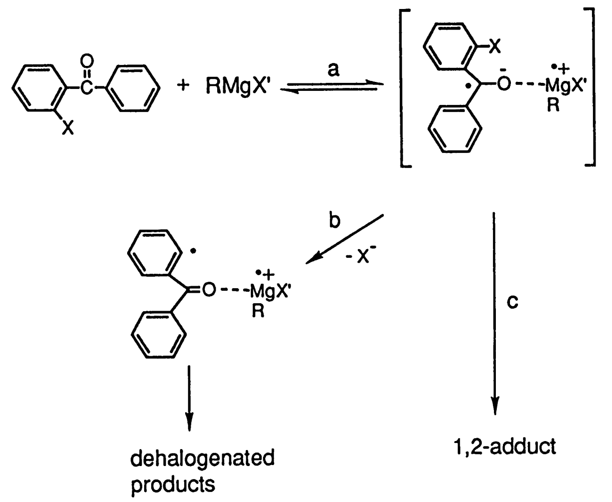
Table 1 lists the product distribution for the reactions of *o*-halobenzophenones with MeMgI and PhMgBr; it is noticeable here that all these reactions afforded dehalogenated products in detectable yields. It can also be seen in Table 1 that (1) the reactions with PhMgBr gave larger amounts of dehalogenated products than MeMgI; (2) the major dehalogenated products arose from displacement of halogen by the R group; (3) iodobenzophenone gave larger amounts of dehalogenated products

Table 1. Product Distributions in the Reactions of *o*-Halobenzophenones with MeMgl and PhMgBr[a)]



I	MeMgl[b)]	80.5±5.3%	d)	d)	d)	11.7±2.0%	4.2±0.7%
Br	MeMgl[b)]	88.0±1.3%	d)	d)	d)	6.2±0.5%	2.4±0.2%
I	PhMgBr[c)]	d)	4.9±0.1%	~1%	15.1±0.1%	54.1±0.2%	d)
Br	PhMgBr[c)]	21.7±0.4%	8.1±0.8%	~3%	16.6±0.6%	16.8±0.8%	d)

a) In Et_2O, at 0 °C. Yields are based on the ketone consumed. Figures are average GC yields (%) from 2—3 runs. Errors are standard deviations. b) 0.5 h. c) 1.5 h. d) Not detected.



Scheme 1.

than bromobenzophenone. On the other hand, the normal 1,2-adducts were obtained exclusively in the reactions of *m*- and *p*-bromobenzophenones with MeMgI and PhMgBr. The reactions of $CH_2=CHCH_2MgBr$ also gave the normal adducts as a sole product even with *o*-halobenzophenones.

The results can be explained in terms of Scheme 1, the simplest revised version of the ET scheme presented previously.[3b,10] Here, the radical ion pair is formed through the initial electron transfer. For MeMgI and PhMgBr, steric hindrance of the ortho halogen substituent in the normal 1,2-addition (path c in scheme 1)[3b] together with the liability to the C–X bond rupture probably makes the dehalogenation (path b) competitive with the radical coupling process (path c) in the radical ion-pair intermediate. This is reasonable since the ortho steric effect is very large in the C–C bond forming process; e.g., $k_{o\text{-Cl}}/k_{p\text{-Cl}}=0.01$ for PhMgBr.[3b] The benzophenone radical thus formed either reacts with $RMgX'^{\cdot+}$ to give ortho R-substituted benzophenone or abstracts hydrogen from solvent to yield benzophenone. These newly formed ketones may further react with RMgX' to give secondary products. The absence of dehalogenated products in the reaction of *o*-halobenzophenone with $CH_2=CHCH_2MgBr$ (rate-determining ET) reflects an insufficient lifetime of the ketyl intermediate (rapid formation of the 1,2-adduct from the radical ion-pair intermediate).

In summary, the present study indicated that *o*-bromo- or *o*-iodobenzophenone can be a good chemical probe for occurrence of ET from a nucleophile to the aromatic ketone and for the involvement of radical ion of sufficient lifetime. The probe experiment is consistent with the ET character of the Grignard reactions of aromatic ketones with MeMgI and PhMgBr.

Experimental

Materials. Diethyl ether was dried over $LiAlH_4$ and distilled before use. *o*-Bromo- and *o*-iodo-substituted benzophenones were prepared by the Friedel–Crafts acylation with the corresponding substituted benzoic acids and purified by distillation (*o*-Br derivative) or column chromatography (*o*-I derivative). $CH_2=CHCH_2MgBr$, MeMgI, and PhMgBr were prepared from the appropriate halides and doubly sublimed Mg (Ventron). The Grignard reagents were standardized by using 2,2′-biquinoline as described in the literature.[11]

Reactions. Reactions were carried out at 0.0±0.1 °C under dry nitrogen[12] as reported previously.[3] All products listed in Table 1 except benzhydrols were isolated from the reaction mixture and were purified by using column chromatography (silica gel), gel permeation chromatography, and normal-phase (Unisil Q30, silica gel) as well as reversed-phase (ODS) HPLC, and their structures were characterized by ^1H NMR (Bruker 360). Halobenzhydrols that could not be isolated from the reaction mixture were prepared by the reactions of corresponding halobenzophenones with $NaBH_4$. The product distribution was determined by means of gas chromatography (PEG-HT, 2 m) by calibrating the detector response factor of each product against the internal reference compound, 1,2-diphenoxyethane.

We are indebted to the Material Analysis Center of ISIR for the NMR measurement. This research was supported in part by Grant-in-Aid for Scientific Research No. 03640451 from the Ministry of Education, Science and Culture.

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