4370 *J. Org. Chem.* **2002,** *67,* 4370−4371

Hammett ρ of Reactions of MeLi with Benzophenones

Keith M. Maclin and Herman G. Richey, Jr.*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania l6802

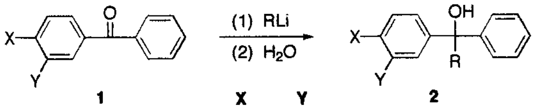
hgr@chem.psu.edu

Received December 22, 2001

Abstract: Relative rates of reactions of MeLi with benzophenones in diethyl ether at 0 °C that furnish methyldiarylmethanols were determined using slow addition of a MeLi solution to solutions containing an excess of two benzophenones. The additions exhibit a Hammett ρ of 0.94.

After toluene solutions of Et_3ZnLi were found to rapidly form products of addition to the carbonyl groups of several aldehydes and ketones,[1,2] we tried to determine rates of such reactions with a series of substituted acetophenones to obtain substituent effects. The rates, however, proved to be too fast to determine by the conventional procedure of taking and analyzing aliquots. A competition procedure, adding Et_3ZnLi to an excess of a pair of acetophenones, was used instead. After a reaction is quenched, an analysis of the mixture of two addition products should provide the *relative* reactivities of the acetophenones. Initial results suggested that substituent effects were small, but these results were not reproducible. Results that were reproducible and indicated substituent effects to be significant finally were obtained by using a lower temperature and *slow* addition of Et_3ZnLi to the solution of acetophenones. Apparently, the rates are so fast that addition competed with mixing of the reagents in the initial studies: the less reactive acetophenone seemed more reactive than it really was because its reaction with Et_3ZnLi was faster than the mixing that ideally would lead to Et_3ZnLi always encountering a constant ratio of the two acetophenones.

The large Hammett ρ of 2.78 for Et_3ZnLi reactions with acetophenones is similar in magnitude to the ρ of 3.0 observed[3] for additions of *t*-BuMgCl to benzophenones, reactions in which electron transfer from the organometallic reactant to the ketone generally is considered to be rate determining.[4] Except for a ρ of 1.96 for addition[5] of "Me_2CuLi" to benzophenones, additions of other polar organometallic reagents to aryl carbonyl compounds have much smaller ρ values: for example, 0.4−1.4 for seven additions[3,6−8] of methyl, butyl, and phenyl Grignard reagents to acetophenones or benzophenones and only 0.2−0.3 for four additions[5,8,9] of methyllithium, butyllithium, and phenyllithium to benzaldehydes or benzophenones.



1 → **2** (1)

	X	Y
a	H	H
b	H	Me
c	H	CF_3
d	F	H
e	Cl	H
f	H	Cl
g	OMe	H

We wondered if mixing problems similar to those we encountered might have influenced other results obtained by competition reactions, a possibility more likely for additions of organolithium reagents than of the less reactive Grignard reagents.[10] A brief study[11] (data in Table 1) of ethyllithium and benzophenones (eq 1, R = Et) in hexane at 5 °C, a system not previously studied, found a ρ of 1.16, prompting an examination of a previously studied system.

We chose to investigate reactions of methyllithium and benzophenones (eq 1, R = Me), for which a ρ of 0.27 was reported.[5] The solvent (diethyl ether) and temperature (0 °C) were those used previously. Rather than the 1:1:1 portions of methyllithium, benzophenone, and substituted benzophenone (initial concentrations of ca. 0.10 M) used before, however, 1:5:5 portions (initial ketone concentrations of ca. 0.15 M) were used. In the previous work, methyllithium had been added with a hypodermic syringe at an unspecified rate; in this work, methyllithium was added slowly with a syringe pump and through a needle that reached below the surface of the rapidly stirred solution of ketones so that addition was continuous rather than in drops. The only product found from each benzophenone had the same GC retention time as an authentic sample of the corresponding **2**. The observed rates relative to that of unsubstituted benzophenone are listed in Table 1. A Hammett plot[12] (Figure 1) gives a ρ of 0.94 ($r^2 = 0.983$), a value in the range observed with Grignard reagents.

Factors that might influence the relative reactivities must change as the ratio of ketone to organolithium reagent is increased; both the extent to which the organolithium compound is coordinated by the ketone and the amount of uncoordinated ketone, for example, must be greater when the ketone is in considerable excess. In fact, reactions with 1:1:1 methyllithium, **2a**, and **2f** (initial concentrations of 0.03 M, where a correction for depletion of the ketones was made) gave a

---

* To whom correspondence should be addressed. Fax: 814 865-3314.

[1] Musser, C. A.; Richey, H. G., Jr. *J. Org. Chem.* **2000**, *65*, 7750.

[2] Also see: Maclin K. M.; Richey, H. G., Jr. *J. Org. Chem.*, in press.

[3] Holm, T.; Crossland, I. *Acta Chem. Scand.* **l971**, *25*, 59.

[4] A review of mechanisms of Grignard reagent reactions: Holm, T., Crossland, I. In *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000; Chapter 1.

[5] Yamataka, H.; Fujimura, N.; Kawafuji, Y.; Hanafusa, T. *J. Am. Chem. Soc.* **l987**, *109*, 4305.

[6] Lewis, R. N.; Wright, J. R. *J. Am. Chem. Soc.* **l952**, *74*, 1257. Anteunis, M.; Van Schoote, J. *Bull. Soc. Chim. Belg.* **l963**, *72*, 776.

[7] Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **l989**, *111*, 4912.

[8] Yamataka, H.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **l991**, *56*, 2573.

[9] Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **l989**, *54*, 4706.

[10] In fact, *actual rates* were determined for two of the Grignard reagent addition series using a thermochemical method;[4] therefore, the relative rates of the reactions of these series are not susceptible to the problems associated with using a competition procedure.

[11] Experiments were performed by Curtis A. Musser.

[12] Hammett σ values taken from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **l991**, *91*, 165.

10.1021/jo0111762 CCC: $22.00

Table 1. Relative Rates of Addition of Alkyllithium Compounds to Substituted Benzophenones and σ Values of Substituents

substituent	σ [a]	relative rate
3-CF_3	0.43	2.82[b]
3-Cl	0.37	2.47[b]
4-Cl	0.23	1.72[b]
4-Cl	0.23	1.81[c]
4-F	0.06	1.19[b]
none	0	(1.00)[b,c]
3-Me	−0.06	0.84[b]
4-OMe	−0.27	0.67[b]
4-OMe	−0.27	0.48[c]

[a] Values from ref 12. [b] Methyllithium in diethyl ether at 0 °C. [c] Ethyllithium in hexane at 5 °C.

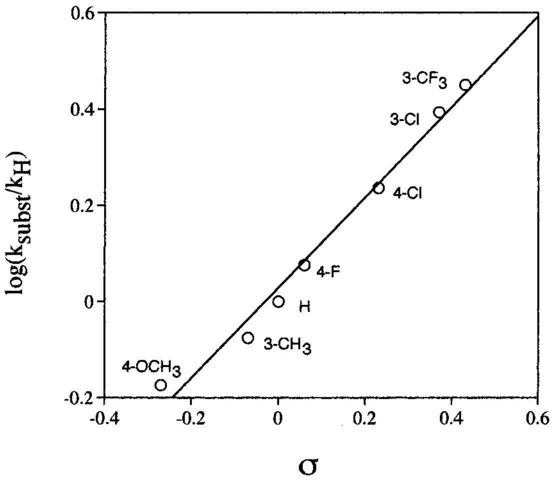


Figure 1. Plot against Hammett σ values of the logarithm of relative rates of addition of methyllithium to substituted benzophenones. Reactions are in diethyl ether at 0 °C.

relative rate that was 20% greater than that observed when the ketones were in larger excess.

Under at least some circumstances, therefore, ρ for addition of an organolithium reactant to an aryl ketone is greater than previously reported. A kinetic isotope effect was reported to be absent ($^{12}k/^{14}k = 1.000 \pm 0.002$) in addition of MeLi to benzophenone isotopically substituted at the carbonyl carbon but significant ($^{12}k/^{14}k = 1.023 \pm 0.004$) in a similar experiment with 2,4,6-trimethylbenzophenone.[5,13,14] The very different isotope effects were attributed to different rate-determining steps for the additions to benzophenone and 2,4,6-trimethylbenzophenone. Since these isotope effects were determined by a competition between the two isotopomers, however, an alternate explanation considers both ketones to react by the same rate-determining step; mixing is slower than addition to benzophenone, masking inherent rate differences between the isotopomers, but faster than addition to very hindered 2,4,6-trimethylbenzophenone.

Experimental Section

Procedures involving organometallic compounds were performed under a nitrogen atmosphere in a glovebox. Glassware was dried in an oven at 180 °C. Diethyl ether and THF were distilled over sodium benzophenone ketyl immediately prior to use. Hexane was washed with a 50/50 solution of concentrated sulfuric and nitric acids, concentrated sulfuric acid, water, 10% aqueous sodium carbonate, and water; it then was dried ($MgSO_4$) and distilled from Na. Methyllithium (1.4 M in diethyl ether), the benzophenones, and 1,3-diphenyl-2-propanone *p*-tosylhydrazone were commercial samples. Ethyllithium was prepared following a literature procedure except that the solvent was hexane instead of toluene.[1] Samples of the addition products (**2**) were synthesized by routine reactions of the benzophenones (**1**) with methyllithium or ethyllithium.

Reactions of Organolithium Compounds and Benzophenones. Methyllithium solutions were prepared by diluting the purchased solution with diethyl ether. Concentration was determined by adding a portion to a standard solution of 1,3-diphenyl-2-propanone tosylhydrazone in THF until an orange color persisted;[15] the concentration used was the average of three determinations. Benzophenone solutions were prepared by weighing benzophenone and the substituted benzophenone into a volumetric flask and diluting with diethyl ether. In a glovebox, samples of benzophenone solution (1.5 mL, 0.15 M in each ketone) were measured into three small reaction vials, each containing a magnetic stirring bar, which then were sealed with septa. A 1 mL gastight syringe with a 12 in., 20 gauge needle was filled with methyllithium solution (usually ca. 0.15 M). The end of the needle was sealed temporarily by pressing it into a septum. A vial and the syringe were removed from the glovebox. A nitrogen line with a needle on the end was inserted into the septum of the vial to maintain a positive pressure of nitrogen, and the vial was placed in a stirred ice bath. The syringe was mounted on the syringe pump in a horizontal orientation. The syringe needle, which had a 90° bend, was inserted into the septum of the vial until the tip of the needle was below the liquid surface. The methyllithium solution (0.3 mL) was pumped slowly (usually 1.04×10^{-5} mol/min) into the vial whose contents were rapidly stirred. This pumping rate was chosen, as described previously,[1] after finding that somewhat higher rates led to the same results with the more reactive ketones. The nitrogen and syringe needles were then transferred to the next vial, and the addition was repeated. A reaction was quenched by addition of water (2 mL) and xylene (2 mL). The water was removed, and the organic layer was dried (Na_2SO_4) and filtered in preparation for GC analysis. Similar procedures were used for the reactions with ethyllithium in hexane (the bath temperature was 5 °C).

Acknowledgment. We thank the National Science Foundation for supporting this work and Curtis A. Musser for preliminary experiments.

Supporting Information Available: Description of the GC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0111762

---

[13] Negligible $^{12}k/^{14}k$ kinetic isotope effects also were reported for additions of phenyllithium to benzophenone and benzaldehyde isotopically substituted at the carbonyl carbon.[9]

[14] Significant $^{12}k/^{14}k$ isotope effects were observed in reactions of MeMgBr and MeMgI with benzophenones isotopically substituted at the carbonyl group.[7] A negligible isotope effect was noted with *t*-BuMgCl,[7] but a more recent investigation suggests that finding to be erroneous [Holm, T. *J. Am. Chem. Soc.* **1993**, *115*, 916]. Reactions of benzophenone with *t*-BuMgCl are faster than with MeMgBr;[4] perhaps the rate of mixing was slow compared to rates of addition of methyl Grignard reagents but not of *t*-BuMgCl.

[15] Lipton, M. F.; Sorenson, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.