4602 *J. Org. Chem.* **2002,** *67,* 4602−4604

# A Kinetic Study of Reactions of $Et_3ZnLi$ and Di-*tert*-Butyl Ketone

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

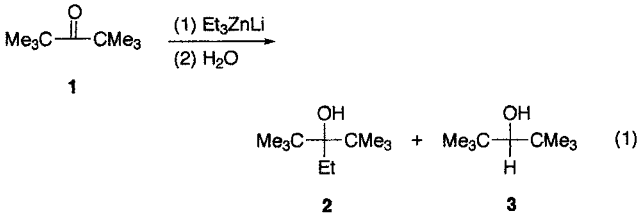
*Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania l6802*

*hgr@chem.psu.edu*

*Received December 20, 2001*

**Abstract:** An organozincate of composition $Et_3ZnLi$ and di-*tert*-butyl ketone react in toluene to form (after hydrolysis) ethyl-di-*tert*-butylmethanol. The rate is proportional to approximately $[Et_3ZnLi]^{-0.5}[\mathrm{ketone}]^1$ when the initial concentration of $Et_3ZnLi$ is greater than that of the ketone but proportional to $[Et_3ZnLi]^1[\mathrm{ketone}]^{-1}$ when the initial concentration of ketone is greater than that of $Et_3ZnLi$. The rate of addition of $Et_3ZnK$ to di-*tert*-butyl ketone is $<10^{-4}$ that of $Et_3ZnLi$.

Toluene solutions of $Et_3ZnLi$, $Et_3ZnNa$, $Et_3ZnK$, and some other organozincates[1] were reported[2] recently to form addition products with several aldehydes and ketones (the organozincate formulas are compositions and *imply neither molecular weights nor structures* of the dominant species in solution). The reactions were too fast to study kinetically by a routine procedure of quenching aliquots followed by their analysis. Relative rates of a group of substituted acetophenones were obtained by competition studies, however, and revealed large electronic and steric effects of substituents.[2] This note describes (1) a study of rates of an addition reaction of $Et_3ZnLi$ and a ketone that provide information about transition state composition and (2) an observation of the relative reactivities of $Et_3ZnLi$ and $Et_3ZnK$ in addition to a ketone.



Our goal was to determine the dependence of the rate of reaction of $Et_3ZnLi$ and a ketone on reactant concentrations. The necessary ingredient for this study was provided when we found that reactions (eq 1) of $Et_3ZnLi$ and di-*tert*-butyl ketone (**1**) at ambient temperature were sufficiently slow to be studied by taking aliquots followed by quenching and analysis. The solvent was benzene, a noncoordinating solvent that has been useful for studies of organometalate compounds since (1) many are stable in it, (2) some organometalate compounds with large ions are more soluble in it than in coordinating solvents (e.g., diethyl ether, THF) frequently used for polar organometallic compounds, and (3) the deuterated solvent needed for $^1H$ NMR studies is relatively inexpensive.[3] Preliminary studies showed **1** to be essentially completely consumed in reactions with an equimolar amount of $Et_3ZnLi$. The only significant product was **2**, resulting from addition, although traces (<3%) of **3**, resulting from reduction, sometimes were present. Metalation of the ketone was precluded by its lack of α-hydrogens.

A kinetic experiment was initiated by adding a solution of **1** (and a GC standard) to a much larger volume of a stirred $Et_3ZnLi$ solution in a flask in a constant-temperature bath (24.75 °C). Aliquots were removed, quenched with water, and analyzed by GC. The initial concentration of one reactant was always sufficiently greater than that of the other that it did not decrease significantly during a reaction and can be treated as constant. Four concentration regimes were studied: (1) zincate in excess and varied, (2) zincate in excess and ketone varied, (3) ketone in excess and varied, and (4) ketone in excess and zincate varied.

One set of experiments in regime 1 exemplifies the procedure. The initial concentration of **1** was 0.020 M and that of $Et_3ZnLi$ was varied from 0.23 to 1.18 M. The half times for appearance of **2** were ca. 3−10 min. Aliquots were removed from 0.5 to 14 min, and for "infinity" values at 60, 90, and 120 min. For each aliquot, a value of **2**/standard was determined by GC analysis and then converted to a concentration of **2**. The $[\mathbf{2}]_\infty$ value for each run was obtained by averaging the values obtained from the infinity aliquots (variation $<\pm1\%$). In all cases >95% of **1** was consumed. Values of $\ln([\mathbf{2}]_\infty/([\mathbf{2}]_\infty - [\mathbf{2}]_t))$ were plotted against time, and slopes ($S$) of the resultant least-squares lines were determined (the plots are reasonably linear, $R^2 \geq 0.990$). The slope of a plot of log $S$ against $\log[Et_3ZnLi]_0$ provides the kinetic order in $Et_3ZnLi$. The slope is $-0.44$ ($r^2 = 0.998$) for the experiments described and $-0.38 \pm 0.06$ for all experiments.

Adherence to first-order kinetics of the reactions with a high- and varied-zincate concentration and a low- and constant-ketone concentration indicated a first-order dependence on ketone. This dependence was confirmed by experiments (regime 2) with a high-, constant-zincate concentration (0.50 M) and a low-, varied-ketone concentration (0.01−0.10 M). Plots of $\ln([\mathbf{2}]_\infty/([\mathbf{2}]_\infty - [\mathbf{2}]_t))$ against time were linear, and the slopes were nearly identical (e.g., $0.094 \pm 0.007$ in a typical reaction series); both features indicate a ca. first-order dependence on ketone.

Similar experiments (regime 3) with a high-, varied-initial ketone concentration and a low-, constant-zincate concentration gave an average value of −0.94 for the reaction order in ketone; adherence to first-order kinetics indicated a ca. first-order dependence on zincate. Experiments (regime 4) with a high-, constant-ketone concentration and a low-, varied-zincate concentration confirmed a first-order dependence on zincate: plots of $\ln([\mathbf{2}]_\infty/([\mathbf{2}]_\infty - [\mathbf{2}]_t))$ against time were linear, and the slopes were essentially identical.

Rates ordinarily were reproducible to ±5% when the same $Et_3ZnLi$ stock solution was used but were less reproducible (ca. ±10%) when different $Et_3ZnLi$ solutions

---

(1) A comprehensive review of organozincate structures and reactions: Linton, D. J.; Schooler, P.; Wheatley, A. E. H. *Coord. Chem. Rev.* **2001**, *223*, 53.

(2) Musser, C. A.; Richey, H. G., Jr. *J. Org. Chem.* **2000**, *65*, 7750.

(3) Toluene, a similar solvent, also has been useful.[2]

10.1021/jo0111659 CCC: $22.00

were used. Consequently, kinetic orders obtained from independent experiments varied >0.1 in some instances. Errors in defining concentrations are the most severe limit to precision. The concentration is particularly significant since rates varied with the composition of the "$Et_3ZnLi$" solution; in one set of experiments (organozincate in excess), for example, preparations with $Et_2Zn/EtLi$ ratios of 1.10 and 0.90 gave rates 0.83 and 1.5 times that of a preparation with a ratio of 1.00, respectively.

The following discussion assumes idealized rate laws: rate $= k[\text{zincate}]^{-0.5}[\mathbf{1}]^1$ when $[\text{zincate}]_0$ is high and rate $= k'[\text{zincate}]^1[\mathbf{1}]^{-1}$ when $[\mathbf{1}]_0$ is high. Free diethylzinc is not the reactant responsible for the additions since most $R_2Zn$ compounds react only sluggishly with aldehydes and not at all with ketones.[4] Neither is free ethyllithium the reactant since solutions of $Et_3ZnLi$ give[2] predominately 1,4-addition to 2-cyclohexenone instead of the mainly 1,2-addition characteristic of organolithium compounds and exhibit[2] a very much larger Hammett $\rho$ (2.74) for additions to substituted acetophenones than do similar additions[5] of organolithium compounds. While it is conceivable that dissociation of an organozincate species forms EtLi, which then reacts with **1** while in a form different than $(EtLi)_6$, the dominant species[6,7] in benzene solutions of ethyllithium, the kinetic observations make this possibility unlikely. Consider a reaction in which $[\text{zincate}]_0$ is greater than $[\mathbf{1}]_0$. If reaction of a nonequilibrium form of EtLi with **1** is more rapid than reincorporation into the zincate, then the rate of formation of this special EtLi probably would be proportional to [zincate] (or to $[\text{zincate}]^2$, etc.); if, instead, its reaction with **1** was slower than its reincorporation into zincate, then the equilibrium concentration of this special EtLi should be drastically lower and the rate correspondingly slower[8] when more $Et_2Zn$ than EtLi is used to prepare the organozincate solution. We conclude therefore that organozincate species are responsible for the additions.

$$(Et_3ZnLi)_2 \rightleftharpoons 2\,Et_3ZnLi \qquad (2)$$

NMR studies[9] indicate that a species having a 1:1 reactant ratio dominates in benzene solutions of EtLi and $Et_2Zn$, and molecular weight determinations[6] of 1:1 solutions indicate that "$Et_3ZnLi$" is dimeric. In considering steps for addition, therefore, we assume that when $[\text{zincate}]_0$ is much larger than $[\mathbf{1}]_0$, the principal zincate species is $(Et_3ZnLi)_2$ and the concentration of monomeric $Et_3ZnLi$ is small (i.e., the equilibrium in eq 2 lies significantly to the left).

$$(Et_3ZnLi)_2(\mathbf{1}) \rightleftharpoons (Et_3ZnLi)_2 + \mathbf{1} \qquad (3)$$

The observation that rate is proportional to $[\text{zincate}]^{-0.5}[\mathbf{1}]^1$ when $[Et_3ZnLi]_0$ is larger than $[\mathbf{1}]_0$ and the reasonable assumption that when zincate is in excess, most molecules of **1** are coordinated to the dominant $(Et_3ZnLi)_2$ (eq 3), imply the transition state composition $Et_3ZnLi(\mathbf{1})$. If the rate-determining step, for example, is a unimolecular reaction of $Et_3ZnLi(\mathbf{1})$, present in small amounts in equilibrium with $(Et_3ZnLi)_2(\mathbf{1})$ (eq 4), then $[Et_3ZnLi(\mathbf{1})]\ \alpha\ [(Et_3ZnLi)_2(\mathbf{1})][(Et_3ZnLi)_2]^{-1/2}$, in accord with the experimental results since $[(Et_3ZnLi)_2(\mathbf{1})] \cong [\mathbf{1}]_{tot}$ ("tot" refers to all of a component not incorporated into the addition product). This step might be an internal addition; an alternative requires dissociation to $Et_3ZnLi$ and **1** and involvement of one or both of these species in a step much faster than reassociation to $Et_3ZnLi(\mathbf{1})$. Since the transition state composition also would be $Et_3ZnLi(\mathbf{1})$, a bimolecular reaction of monomeric $Et_3ZnLi$ and uncoordinated **1** is another possibility.[10] Of course, if the equilibria involved (e.g., those in eqs 3 and 4) do not lie almost completely to one side, then the true reaction orders will deviate from −0.5 and 1; the results are not sufficiently precise to rule out this possibility.[11]

$$2\,(Et_3ZnLi)_2(\mathbf{1}) \rightleftharpoons 2\,Et_3ZnLi(\mathbf{1}) + (Et_3ZnLi)_2 \qquad (4)$$

When $[\mathbf{1}]_0$ is larger than $[\text{zincate}]_0$, the kinetic observations indicate that the transition state of the rate-determining step has one molecule of **1** less than a species whose concentration is proportional to $[\text{zincate}]_{tot}$. If the dominant zincate species is $(Et_3ZnLi)_2(\mathbf{1})_2$, for example, then the transition state composition is $(Et_3ZnLi)_2(\mathbf{1})$. The rate-determining step could be a unimolecular reaction of a small amount of $(Et_3ZnLi)_2(\mathbf{1})$ in equilibrium with the dominant $(Et_3ZnLi)_2(\mathbf{1})_2$ or, less probably, a bimolecular reaction of $(Et_3ZnLi)_2$ with **1**. If $Et_3ZnLi(\mathbf{1})_2$ is the dominant zincate species, the transition state composition is $Et_3ZnLi(\mathbf{1})$.

No addition product was noted after several days from solutions containing $Et_3ZnK$ and **1**; the rate of addition of $Et_3ZnK$, therefore, is $<10^{-4}$ that of $Et_3ZnLi$. Other experiments used equal initial concentrations of $Et_3ZnLi$, **1**, and a third component, which was added to the solution of **1** before adding $Et_3ZnLi$. TMEDA or THF as the third component increased the addition rate; half-times were seconds instead of the several minutes observed in its absence. HMPA or N3 (2,5,8-trimethyl-2,5,8-triazanonane) decreased the rate; half-times were several hours.

As does[2] $Et_3ZnLi$ (but not ordinarily $R_2Zn$ or RZnX), $Et_3ZnK$ forms addition products rapidly (reactions[2] were

---

[4] Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, l991; Vol. 4 (Semmelhack, M. F., Ed.), Section 1.2.2.1.4. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, l992; Chapters 1−3.

[5] Values of Hammett $\rho$ in the range 0.2−0.3 are reported for four additions of methyllithium, butyllithium, and phenyllithium to substituted benzaldehydes or benzophenones: Yamataka, H.; Fujimura, N.; Kawafuji, Y.; Hanafusa, T. *J. Am. Chem. Soc.* **1987**, *109*, 4305. Yamataka, H.; Kawafuji, Y.; Nagareda, K.; Miyano, N.; Hanafusa, T. *J. Org. Chem.* **1989**, *54*, 4706. Yamataka, H.; Miyano, N.; Hanfusa, T. *J. Org. Chem.* **1991**, *56*, 2573. Somewhat larger values (ca. 1) have been reported for reactions of benzophenones with methyllithium and ethyllithium: Maclin, K. M.; Richey, H. G., Jr. *J. Org. Chem.*, in press.

[6] Hein, F.; Schramm, H. *Z. Phys. Chem.* **1930**, *151*, 234.

[7] Brown, T. L.; Gerteis, R. L.; Bafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2135. Brown, T. L. *Acc. Chem. Res.* **1968**, *1*, 23.

[8] The effect should be very much larger than the small rate decrease noted when the organozincate solution was prepared with a small excess of $Et_2Zn$.

[9] Toppet, S.; Slinckx, G.; Smets, G. *J. Organomet. Chem.* **1967**, *9*, 205. Also, see: Rijnberg, E.; Jastrzebski, T. B. H.; Boersma, J.; Kooijman, H.; Veldman, N.; Spek, A. L.; van Koten, G. *Organometallics* **1997**, *16*, 2239. NMR observations indicate that mixed species form even in coordinating solvents: 2:1 and 3:1 $MeLi/Et_2Zn$ compositions in diethyl ether [Seitz, L. M.; Brown, T. L. *J. Am. Chem. Soc.* **1966**, *88*, 4140] and 1:1 and 2:1 compositions in THF [Seitz, L. M.; Little, B. F. *J. Organomet. Chem.* **1969**, *18*, 227].

[10] Loss of $Et_3ZnLi$ from $(Et_3ZnLi)_2(\mathbf{1})$ to form $Et_3ZnLi(\mathbf{1})$ cannot be rate determining: if reaction of $Et_3ZnLi(\mathbf{1})$ to form product was much more rapid than its reversion to $(Et_3ZnLi)_2(\mathbf{1})$, then the rate would be proportional to $[(Et_3ZnLi)_2(\mathbf{1})] \cong [\mathbf{1}]_{tot}$.

[11] The more rapid rate observed when an organozincate solution was prepared with somewhat more EtLi than $Et_2Zn$ possibly is due to formation of some $Et_4ZnLi_2$.[1] The somewhat slower rate observed when an organozincate solution was prepared with an excess of $Et_2Zn$ might be due to coordination of some **1** by $Et_2Zn$ rather than by the organozincate.

substantially complete when quenched after 10 min) with relatively unhindered aldehydes and ketones. The failure to observe any reaction with very hindered **1**, however, reveals that $Et_3ZnK$ is very much less reactive than $Et_3ZnLi$. As is $Et_3ZnLi$, $Et_3ZnK$ is dimeric in benzene.[6] X-ray studies show that $R_3ZnK$ solids have essentially independent $R_3Zn^-$ and $K^+$ ions.[12] $Et_3ZnK$ must tend more than $Et_3ZnLi$ to be ionic in solution, yet it reacts less rapidly. Addition to $Et_3ZnLi$ solutions of HMPA or N3 that, by coordinating to $Li^+$, might create freer organozincate anions, also slows the reactions. Addition of TMEDA or THF, however, speeds the reactions; perhaps these feebler coordinating agents reduce dimerization of $Et_3ZnLi$ or coordination of zincate species to **1**, without leading significantly to organozincate anions (i.e., $Et_3Zn^-$) and coordinated $Li^+$ cations.[13]

The kinetic observations eliminate many possible reaction pathways but, as so often is the case, still leave several. The possibilities could be reduced further by more information about the compositions of the dominant species in $Et_3ZnLi$−ketone solutions.

## Experimental Section

Procedures involving organometallic compounds were performed under a nitrogen atmosphere using a vacuum line or glovebox. Prior to use, benzene was distilled from calcium hydride, THF from sodium benzophenone ketyl, and pentane from ethyllithium. Di-*tert*-butyl ketone was stirred over molecular sieves. TMEDA and 2,5,8-trimethyl-2,5,8-triazanonane were distilled from sodium. HMPA was distilled at reduced pressure over molecular sieves. Ethyl bromide was washed with concentrated sulfuric acid, water, a dilute aqueous sodium carbonate solution, and water; it then was dried ($MgSO_4$) and distilled from $P_2O_5$. The lithium contained 0.5−1.0% sodium. Samples of di-*tert*-butylmethanol and ethyl-di-*tert*-butylmethanol for GC calibration were prepared by routine reactions of di-*tert*-butyl ketone with lithium aluminum hydride and ethyllithium, respectively.

**Preparation of $Et_3ZnLi$, $Et_3ZnK$, and Di-*tert*-butyl Ketone Solutions.** Ethyllithium was synthesized conventionally from ethyl bromide and lithium in pentane. The solvent was evaporated under reduced pressure. Benzene was added to the residue, which then was filtered. The solvent was evaporated under reduced pressure, and the residue was sublimed by heating gradually to 95 °C at reduced pressure. Diethylzinc and ethyllithium were weighed into a volumetric flask, and benzene was added gradually (ethyllithium dissolves slowly). $Et_3ZnK$ solutions were prepared and standardized as already described.[2] Di-*tert*-butyl ketone solutions were prepared by weighing the ketone and pentacosane (the GC standard) into a volumetric flask and adding benzene.

**Reactions of Organozincates and Di-*tert*-butyl Ketone.** Volumes varied, but the following is typical. Organozincate solution (2 mL), measured with a gastight syringe, was placed in a small reaction vial containing a magnetic stirring bar; the vial was stoppered with a septum, and a piece of Parafilm M was placed over the septum and held in place with a wire. The vial was removed from the glovebox, and a needle connected to a nitrogen line was inserted into the septum to maintain a positive pressure of nitrogen. The vial was placed in a constant-temperature bath (24.75 ± 0.05 °C) and allowed to reach the bath temperature. Ketone solution (0.2 mL) was withdrawn into a gastight syringe and injected into the reaction vial to initiate a reaction. Aliquots (0.2 mL) were withdrawn with a syringe, quenched with a saturated aqueous ammonium chloride solution (1.5 mL), and stirred for a few minutes. Water (1 mL) and benzene (0.5 mL) were added; the mixture was stirred, and the aqueous layer was removed with a pipet. The organic layer was dried ($Na_2SO_4$), filtered, and analyzed by GC using a carbowax capillary column (0.53 mm id × 15 m). The injector temperature was 300 °C, and the (hydrogen flame ionization) detector temperature was 250 °C. Direct injection used a direct injection liner sleeve. Getting the entire sample rapidly onto the column required small, dilute samples ($\sim$0.2 $\mu$L, $\leq$10 mM) and a high carrier gas flow rate (ca. 10 mL/min). Some air was drawn into the syringe, followed by 0.1−0.2 $\mu$L of sample, followed again by air. The "hot-needle" injection technique[14] was used; after it was inserted into the injection port, the needle was allowed to heat for about 5 s before injection. The GC column was maintained at 90 °C; the following were typical retention times: **1**, $\sim$0.5 min; **2**, 1.1 min; **3**, 2.3 min; pentacosane, 3.0 min. Peak areas were determined with an electronic integrator. Repeated analysis of the same sample gave area ratios with $\leq\pm1\%$ variation. Product yields were calculated using response factors[15] to convert peak areas into relative weights.

**Acknowledgment.** We thank the National Science Foundation for supporting this research.

JO0111659

---

[12] Purdy, A. P.; George, C. F. *Organometallics* **1992**, *11*, 1955. Also see Putzer, M. A.; Neumüller, B.; Dehnicke, K. *Z. Anorg. Allg. Chem.* **1997**, *623*, 539.

[13] NMR observations[2] indicate that TMEDA in a benzene solution of $Et_3ZnLi$ is coordinated to a metal. $R_3Zn^-$ ions (at least one R is bulky) are found in some solids in which $Li^+$ is coordinated with TMEDA or 1,3,5-trimethylhexahydro-1,3,5-triazine. Westerhausen, M.; Rademacher, B.; Schwarz, W. *Z. Anorg. Allg. Chem.* **1993**, *619*, 675. Westerhausen, M.; Rademacher, B.; Schwarz, W.; Henkel, S. *Z. Naturforsch. B* **1994**, *49*, 199. Westerhausen, M.; Wieneke, M.; Ponikwar, W.; Nöth, H.; Schwarz, W. *Organometallics* **1998**, *17*, 1438. Thiele, K.; Görls, H.; Seidel, W. *Z. Anorg. Allg. Chem.* **1998**, *624*, 555.

[14] Grob, K. *Classical Split and Splitless Injection in Capillary Gas Chromatography*, 2nd ed.; Dr. Alfred Huethig: Heidelberg, 1988.

[15] David, D. J. *Gas Chromatographic Detectors*; Wiley: New York, 1974; Chapter 3.