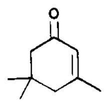
J. Org. Chem. 1984, 49, 3669-3670

Preparation of a New, Highly Reactive Form of Iron(0) and Its Use in Deprotonation of Carbonyl Compounds

Summary: A new, highly reactive form of zerovalent iron, prepared from the reaction of methylmagnesium bromide and ferric chloride, has been found to deprotonate cyclic unsymmetrical ketones in the presence of trimethylsilyl chloride to give thermodynamic (more substituted) silyl enol ethers regiospecifically.

Sir: Nucleophilic metal complexes have been found to be of considerable utility in synthesis.[1] Several of these complexes, particularly highly reduced carbonylmetallates, are also capable of acting as bases toward weakly acidic organic compounds.[2] However, the use of zerovalent metal species in deprotonation reactions is, to our knowledge, unprecedented. We report herein the preparation of a unique and reactive form of zerovalent iron and its use as a base for the deprotonation of aldehydes and ketones.

In 1941, Kharasch reported the reaction of isophorone (**1**) with ethereal methylmagnesium bromide in the presence of a catalytic amount of ferric chloride to produce β,γ-unsaturated ketone **2**.[3,4] This unusual reaction has received virtually no attention since this time, although it has been used as part of a synthetic sequence on several occasions.[5] We postulated that **2** had been formed by kinetic protonation of the corresponding endocyclic dienolate. Confirmation of this postulate was provided by the finding that treatment of isophorone with methylmagnesium bromide in the presence of catalytic ferric chloride, followed by enolate trapping with trimethylsilyl chloride (Me_3SiCl),[6] led to the formation of dienol ether **3**, virtually uncontaminated by isomeric silyl dienol ethers.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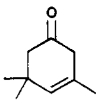
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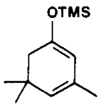

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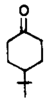
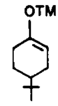
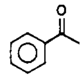
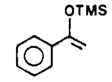
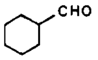
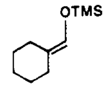
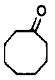
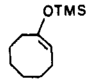
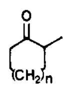
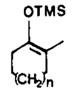
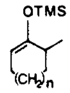
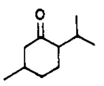
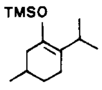
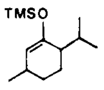
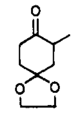
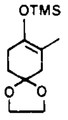
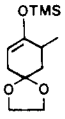
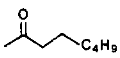
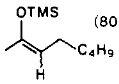
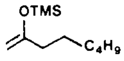
Further exploration showed this reaction to be of disappointingly little generality. Despite modifications of catalyst (ferric acetonylacetate was found to be most effective), temperature (optimum results were obtained at 0 °C), and solvent, a variety of cyclohexenones reacted under these conditions to produce dienol ether contaminated by substantial amounts (25–75%) of tertiary alcohol formed via 1,2-addition of Grignard reagent to the enone. Saturated ketones also reacted to produce substantial amounts of 1,2-addition products.

Table I. Formation of Trimethylsilyl Enol Ethers from Ketones[14]

ketone	enol ethers[15] (ratio)[16]			yield[17]
				98%
				92%
				86%
				93%
 n = 1 n = 2		(97:3) (93:7)		99% 90%
		(98:2)		97%
		(98:2)		98%
		(80:20)		95%

With the hope of finding an efficacious stoichiometric reagent for these purposes, we have studied the reaction of Grignard reagents with ferric chloride. Upon addition of 1 molar equiv of ethereal methylmagnesium bromide to 1 molar equiv of ethereal ferric chloride at 0 °C,[7] a tan precipitate, presumably iron(II), was formed, and 0.6 molar equiv of gas (2:1 ethane:methane)[8] was instantaneously evolved. Upon subsequent addition of two additional molar equiv of methylmagnesium bromide, the tan precipitate was converted to a finely divided black powder suspended in a colorless ether solution. The composition of this material, possibly $(CH_3)_2FeL_x$, is currently unknown and will be the subject of future investigation. Over the course of 1 h at 25 °C this suspension evolved an additional 1.2 molar equiv of gas (2:1 ethane:methane),[8] although the appearance of the black precipitate remained unchanged.

The air-sensitive black powder could be separated and washed repeatedly (under a nitrogen atmosphere) with anhydrous degassed ether. The residue obtained upon evaporation of the ethereal washings was composed of magnesium halide etherate; the black powder was formulated on the basis of elemental analysis as a mixture of elemental iron and magnesium halide etherate. Definitive evidence for the stoichiometric generation of iron(0)[9,10] was

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[1] See, for example: (a) Ellis, J. E.; Fjare, K. L.; Hayes, T. G. *J. Am. Chem. Soc.* **1981**, *103*, 6100. (b) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342 and references contained therein.

[2] (a) Chen, Y.; Ellis, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 1141. (b) Reference 1b.

[3] Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308; **1945**, *67*, 128.

[4] Mixtures of ferric chloride with Grignard reagents have found use as catalysts for other reactions: (a) Felkin, H.; Swierczewski, G. *Tetrahedron* **1975**, 2735. (b) Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1971**, *31*, 289. (c) Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 303. (d) Kharasch, M. S.; Lambert, F. L.; Urry, W. H. *J. Org. Chem.* **1945**, *10*, 292, 298. (e) Neumann, S. M.; Kochi, J. K. *Ibid.* **1975**, *40*, 599. (f) Smith, R. S.; Kochi, J. K. *Ibid.* **1976**, *41*, 502. (g) Corey, E. J.; Yamamoto, H.; Herron, D. K.; Achiwa, K. *J. Am. Chem. Soc.* **1970**, *92*, 6635. (h) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, 315. (i) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (j) Ashby, E. C.; Wiesmann, T. L. *Ibid.* **1978**, *100*, 189. (k) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545. (l) Ashby, E. C.; Wiesmann, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 7117. (m) Ashby, E. C.; Buhler, J. D.; Wiesmann, T. L.; Laemmle, J. T. *Ibid.* **1976**, *98*, 6561.

[5] (a) Meinwald, J.; Hendry, L. *Tetrahedron Lett.* **1969**, 1657. (b) Heymes, A.; Teisseire, P. *Recherches* **1971**, *18*, 104. (c) Haubenstock, H.; Quezada, P. *J. Org. Chem.* **1972**, *37*, 4067.

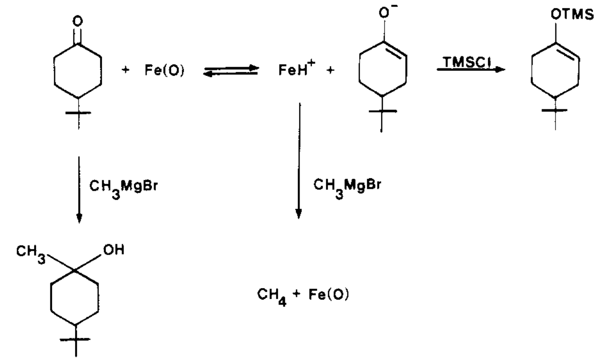
[6] Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

[7] Anhydrous ferric chloride was used as received from Aldrich Chemical Co.; ethereal methylmagnesium bromide solution was prepared by standard methodology and was used within 6 months of preparation.

[8] Evolved gases were identified by GC analysis using 5-Å molecular sieves, 80/100 mesh, 6 ft × 1/8 in. column. We thank Professor H. M. McNair for providing this column and authentic gas samples.

0022-3263/84/1949-3669$01.50/0

Scheme I



provided by titration of the washed black residue with potassium chromate solution.[11]

This iron(0) powder was found to be surprisingly basic. For example, addition of an ethereal solution of a ketone or aldehyde to the black residue followed by the addition of Me_3SiCl, triethylamine (Et_3N), and hexamethylphosphoramide (HMPA) afforded, after a period of 8–10 h at 25 °C, the corresponding trimethylsilyl enol ether in excellent yield. Results obtained for a variety of saturated carbonyl compounds are listed in Table I. Alhough ketones and aldehydes were converted to silyl enol ethers in high yield, esters did not react under these conditions.[12] Unsymmetrical cyclic ketones gave rise to an extremely high ratio of thermodynamic (more substituted) to kinetic (less substituted) trimethylsilyl enol ethers.[13]

During the course of these reactions, the iron powder was converted to a black, insoluble, tarry substance. We postulate this substance to be a cationic iron(II) "hydride" produced by transfer of a proton from the ketone or aldehyde to iron(0). Indeed, upon completion of the reaction, the ethereal solution of Me_3Si enol ether may be withdrawn, and the remaining black, tarry residue may be washed repeatedly with anhydrous ether. Subsequent addition of 1.0 molar equiv of either methyllithium or methylmagnesium bromide to the tarry residue resulted in the immediate evolution of 1.0 molar equiv of methane[8] and regeneration of the active iron(0) precipitate. The iron(0) precipitate regenerated in this way was found to deprotonate subsequently added ketone with no loss of efficacy.

Our rationalization of these observations is shown in Scheme I. The reversibility of the deprotonation reaction is supported by the following experiment. An ethereal solution of ketone was added to an ethereal suspension of activated iron; the mixture was stirred at 25 °C for 8 h before addition of 1.0 molar equiv of ethereal methylmagnesium bromide. Approximately 0.3 molar equiv of methane[8] (from reaction of Grignard with FeH^+) was instantly evolved and, upon aqueous extraction of the mixture, tertiary alcohol was isolated in ca. 70% yield. We postulate that methylmagnesium bromide reacts rapidly and irreversibly with each of the species in equilibrium: (a) reaction with ketone provides tertiary alcohol; (b) reaction with FeH^+ provides Fe(0) and methane. Of course, under the usual reaction conditions, the equilibrium is driven by reaction of enolate with Me_3SiCl.

Stoichiometric reaction of activated $Fe(0)/Me_3SiCl/Et_3N$ with enones as well as the precise nature of the Kharasch reagent will be described in a future communication.

Acknowledgment. We thank Professor John G. Mason for helpful discussions. We appreciate the generous financial support of the National Cancer Institute.

Registry No. $PhC(O)CH_3$, 98-86-2; $CH_3C(O)(CH_2)_5CH_3$, 111-13-7; Fe, 7439-89-6; $FeCl_3$, 7705-08-0; MeMgBr, 75-16-1; 4-*tert*-butylcyclohexanone, 98-53-3; cyclohexanecarboxaldehyde, 2043-61-0; cyclooctanone, 502-49-8; 2-methylcyclohexanone, 583-60-8; 2-methylcycloheptanone, 932-56-9; 2-isopropyl-5-methylcyclohexanone, 10458-14-7; 2′-methylspiro[1,3-dioxolane-2,4′-cyclohexanone], 702-69-2; 1-[(trimethylsilyl)oxy]-4-*tert*-butylcyclohexene, 19980-19-9; [1-[(trimethylsilyl)oxy]ethenyl]benzene, 13735-81-4; [[(trimethylsilyl)oxy]methylene]cyclohexane, 53282-55-6; 1-[(trimethylsilyl)oxy]cyclooctene, 50338-42-6; 1-[(trimethylsilyl)oxy]-2-methylcyclohexene, 19980-35-9; 1-[(trimethylsilyl)oxy]-6-methylcyclohexene, 19980-33-7; 1-[(trimethylsilyl)oxy]-2-methylcycloheptene, 64639-26-5; 1-[(trimethylsilyl)oxy]-7-methylcycloheptene, 91759-98-7; 5-methyl-1-[(trimethylsilyl)oxy]-2-isopropylcyclohexene, 86565-31-3; 3-methyl-1-[(trimethylsilyl)oxy]-6-isopropylcyclohexene, 72311-09-2; 1′-[(trimethylsilyl)oxy]-2′-methylspiro[1,3-dioxolane-2,4′-cyclohexene], 91759-99-8; 1′-[(trimethylsilyl)oxy]-6′-methylspiro[1,3-dioxolane-2,4′-cyclohexene], 91760-00-8; 2-[(trimethylsilyl)oxy]-2-octene, 69843-64-7; 2-[(trimethylsilyl)oxy]-1-octene, 55314-45-9.

Marie E. Krafft, Robert A. Holton*

Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061

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(9) This appears to be the first conclusive evidence for the stoichiometric generation of Fe(0) in this reaction, see: (a) Champetier, G. *Bull. Soc. Chim. Fr.* **1930**, *47*, 1131. (b) Oddo, B. *Gazz. Chim. Ital.* **1914**, *44*, 268. (c) References 4b,c,e,f,i-m.

(10) Rieke has prepared a highly reactive iron powder by a different route: Kavaliunas, A. V.; Taylor, A.; Rieke, R. D. *Organometallics* **1983**, *2*, 377 and references contained therein. A direct comparison of the reactivity of the iron powder we have prepared with that of "Rieke iron" has not been carried out.

(11) Titration was performed by an adaptation of the method describe in Kolthoff, I. M.; Sandell, E. B.; Meehan, E. J.; Bruckenstein, S. "Quantitative Chemical Analysis", 4th ed.; MacMillan: New York, 1969; pp 839–840.

(12) Ethyl octanoate was recovered unchanged upon treatment with Fe(0) under these[14] conditions. In contrast to this result, treatment of ethyl octanoate with BMDA[13] gave the product of Claisen condensation in 80% isolated yield.

(13) We have previously found $BMDA/Me_3SiCl/Et_3N$ to be an effective reagent for the formation of the more highly substituted Me_3Si enol ether from an unsymmetrical ketone: Krafft, M. E.: Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345. Although BMDA and Fe(0) provide similar ratios of regioisomers in several cases, the two reagents are complimentary in nature. BMDA is a much stronger base than is Fe(0) and promotes condensation reactions of unhindered substrates but appears to be effective in applications to very hindered substrates. The use of Fe(0) is usually not complicated by the formation of unwanted condensation products, but preliminary evidence indicates that its application to hindered substrates may be of limited utility.

(14) Typical experimental procedure: To an orange ethereal solution of 162 mg (1.0 mmol) of anhydrous ferric chloride in 8 mL of anhydrous ether at 0 °C was slowly added 0.91 mL (3.0 mmol) of an ethereal solution of methylmagnesium bromide. The resulting slurry was stirred for 1 h at 25 °C before addition of 0.9 mmol of ketone dissolved in 2 mL of anhydrous ether. After 15–30 min at 25 °C, 0.33 mL (3 mmol) of Me_3Si, 0.36 mL (3.1 mmol) of Et_3N, and 0.17 mL (1 mmol) of HMPA were added in that order. After stirring for ca. 8 h at 25 °C, the solution was diluted with ether, washed twice with cold saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated. The resulting colorless oil was filtered through a plug of silica gel (10% EtOAc/hexane) to remove HMPA and Et_3N. The eluant was concentrated to yield a colorless oil which usually needed no further purification.

(15) All products have been characterized by IR and ^1H NMR. Elemental composition has been verified by combustion analysis or high-resolution mass spectroscopy.

(16) Isomer ratios were determined by both ^1H NMR analysis and GC analysis (8% OV-101 on Chromosorb W, 8 ft × $^1/_8$ in., or 10% Carbowax on Chromosorb W, 8 ft × $^1/_8$ in.).

(17) All yields refer to isolated, chromatographically and spectrally (NMR) homogeneous (except for regioisomers) products.