Ferric Chloride Hexahydrate: A Mild Hydrolytic Agent for the Deprotection of Acetals

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Introduction

Acetals are widely used as protecting groups in organic synthesis and, as a consequence, many methods have been examined for both their formation and removal.[1] Typically, deprotection of acetals requires the use of protic or Lewis acids,[1,2] although more recently alternative methods that use DDQ, aqueous DMSO, lithium halides, silanes, or insoluble acidic matrices have been developed.[3] Previously, we reported the utility of ferric chloride hexahydrate ($FeCl_3·6H_2O$) as a promoter in the cyclization of an *N*-acyl enamide polyene having a dioxolane initiator, where this less commonly used Lewis acid served as both a deprotecting and cyclization agent.[4] Because of the reaction's mild conditions and apparent compatibility with acid sensitive functionalities, a more thorough examination of $FeCl_3·6H_2O$ as a deacetalization agent was undertaken.

The known acetals (entries 1−12, Table 1) were prepared and reacted with 3.5 equiv $FeCl_3·6H_2O$ in CH_2Cl_2. In most cases, the reaction was complete within 15 min at rt and provided aldehyde or ketone in excellent yield. For materials less susceptible to acetal deprotection (e.g., entries 6 and 7), using reflux temperature or adding acetone (to better dissolve the Lewis acid and to participate in transacetalization) resulted in both increased yields and deacetalization rates. The dioxane functionality, which is typically difficult to remove under mild conditions,[5] was effectively hydrolyzed with $FeCl_3·6H_2O$ as demonstrated by the near quantitative deprotection of the 1,3-dioxane of cinnamaldehyde (entry 8).

The ability of $FeCl_3·6H_2O$ to cleave related alcohol protecting groups such as THP and MOM ethers was also investigated (entries 10 and 11, respectively, Table 1). The THP ether of octanol was efficiently removed by reaction with $FeCl_3·6H_2O$ at rt; however, the corresponding MOM ether was significantly less reactive. Deprotection of this latter material at rt or in refluxing CH_2Cl_2 provided a variable mixture of octanol and formaldehyde dioctyl acetal which could be eliminated by the addition of acetone.

To better understand the role and nature of the iron species in solution, the effect of several factors, including Lewis acid equivalents, reaction time, water content, and reaction reversibility, was investigated. Removal of the 1,3-dioxolane moiety of octanal using 1−6 equiv of $FeCl_3·6H_2O$ showed hyperbolic behavior, with deacetalization reaching nearly maximal yield within 20 min (Figure 1). The addition of increasing equivalents of Lewis acid resulted in a proportionate increase in octanal formation up to a maximum of 3.5 equiv; thereafter, the presence of more $FeCl_3·6H_2O$ had an inhibitory effect. For the more reactive 1,3-dioxolane of benzophenone, the use of less than 1 equiv of $FeCl_3·6H_2O$ resulted in efficient deprotection; reaction yields using fewer equivalents (0.15, 0.3, and 0.5 equiv of $FeCl_3·6H_2O$, entry 5, Table 1) suggest that deprotection involves stoichiometric displacement of each of the chloride ligands from the metal center. The reversibility of the $FeCl_3·6H_2O$-mediated deacetalization was demonstrated by the formation of the 1,3-dioxolane of dihydrocinnamaldehyde, by the reaction of aldehyde with 10 equiv of ethylene glycol in the presence of 3.5 equiv of $FeCl_3·6H_2O$ in CH_2Cl_2 at rt (data not shown).

Although ferric chloride has been previously demonstrated by others to promote deprotection chemistry,[6] we found that treatment of several acetals with either anhydrous $FeCl_3$ or $FeCl_3·6H_2O$ absorbed onto silica gel provided varied results. For the 1,3-dioxolanes of *tert*-butylcyclohexanone and dihydrocinnamaldehyde, anhydrous $FeCl_3$ deprotection was as efficient as the corresponding $FeCl_3·6H_2O$-mediated reactions (entries 2 and 6, Table 1), while treatment of the dimethyl acetal of phenylacetaldehyde (entry 9) with anhydrous $FeCl_3$ caused complete decomposition to several unidentified materials. In our hands, we found that the absorption of $FeCl_3·6H_2O$ onto silica gel provided a generally weaker deprotecting agent, having similar reaction selectivity to the corresponding nonabsorbed material. Thus, deacetalization of the 1,3-dioxolane of dihydrocinnamaldehyde and of 3-*O*-(*tert*-butyldimethylsilyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (entry 12) was considerably faster when $FeCl_3·6H_2O$ was used.[7] For the latter compound, neither hydrated iron reagent caused loss of the TBDMS group; however, the increased reactivity of $FeCl_3·6H_2O$ allowed for selective deprotection of either one or both acetals by varying the reaction time and the number of equivalents used.

All of these results are difficult to explain in terms of a traditional Lewis acid-promoted hydrolysis mechanism since the solubility of $FeCl_3·6H_2O$ in CH_2Cl_2 is low,

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[1] Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1991.

[2] (a) Barbot, F.; Miginiac, P. *Synthesis* **1983**, 651−654. (b) Sterzycki, R. *Synthesis* **1979**, 724−725. (c) Kantam, M. L.; Swapna, V.; Santhi, P. L. *Synth. Commun.* **1995**, *25*, 2529−2532. (d) Ma, S.; Venanzi, L. M. *Tetrahedron Lett.* **1993**, *34*, 8071−8074. (e) Ford, K. L.; Roskamp, E. J. *J. Org. Chem.* **1993**, *58*, 4142−4143. (f) Chang, C.; Chu, K. C.; Yue, S. *Synth. Commun.* **1992**, *22*, 1217−1220. (g) Sarmah, P.; Barua, N. C. *Tetrahedron Lett.* **1989**, *30*, 4703−4704. (h) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708. (i) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267−277.

[3] (a) Tanemura, K.; Suzuki, T.; Horaguchi, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 290−292. (b) Kametani, T.; Kondoh, H.; Honda, T.; Ishizone, H.; Suzuki, Y.; Mori, W. *Chem. Lett.* **1989**, 901−904. (c) Maiti, G.; Roy, S. C. *J. Org. Chem.* **1996**, *61*, 6038−6039. (d) Chen Y.-H.; Tseng, Y.-T.; Luh, T.-Y. *J. Chem. Soc., Chem. Commun.* **1996**, 327−328. (e) Elmorsy, S. S.; Bhatt, M. V.; Pelter, A. *Tetrahedron Lett.* **1992**, *33*, 1657−1660. (f) Rao, M. N.; Kumar, P.; Singh, A. P.; Reddy, R. S. *Synth. Commun.* **1992**, *22*, 1299−1305. (g) Hoyer, S.; Laszlo, P. *Synthesis* **1986**, 655−657. (h) Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 5743−5746. (i) Coppola, G. M. *Synthesis* **1984**, 1021−1023.

[4] Sen, S. E.; Roach, S. *J. Org. Chem.* **1996**, *61*, 6646−6650.

[5] Stowell, J. C.; Keith, D. R. *Synthesis* **1979**, 132−133.

[6] (a) Ikemoto, N.; Kim, O. K.; Lo, L.-C.; Satyanarayana, V.; Chang, M.; Nakanishi, K. *Tetrahedron Lett.* **1992**, *33*, 4295−4298. (b) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823−3824. (c) Fadel, A.; Yefsah, R.; Salaün, J. *Synthesis*, **1987**, 37−40. (d) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404−407. (e) Singh, P. P.; Gharia, M. M.; Dasgupta, F.; Srivastava, H. C. *Tetrahedron Lett.* **1977**, 439−440.

[7] It should be noted that increased reaction rate is, in part, a function of the amount of $FeCl_3·6H_2O$ present. For deprotections involving $FeCl_3·6H_2O$ absorbed onto silica gel, only 1 mol% metal promoter is used.

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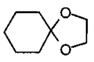
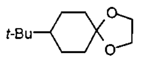
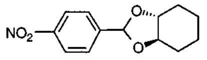
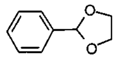
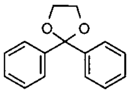
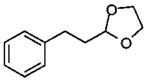
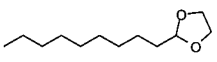
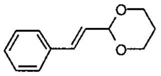
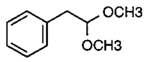
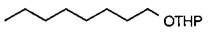
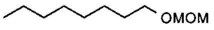
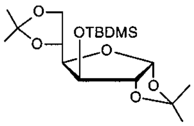
Table 1

ENTRY	COMPOUND	EQUIV[a]	TEMP	% GLC YIELD (time, min)	ISOLATED YIELD
1		3.5	RT	100 (15)	96
2		3.5 3.5[b]	RT RT	94 (15) 97 (120)	95
3		3.5	RT	97 (15)	91
4		3.5	RT	100 (30)	97
5		3.5 1 0.5 0.3 0.15	RT RT RT RT RT	100 (15) 100 (15) 93 (60) 87 (90) 48 (90)	94
6		3.5 3.5[d] 3.5[b] 0.01[e]	RT RT RT RT	75[c] (120) 100 (15) 71 (120) 12 (30)	98
7		3.5 3.5[d] 3.5	RT RT reflux	82 (90) 100 (60) 100 (30)	95
8		3.5	RT	96 (15)	94
9		3.5 3.5[b]	RT RT	95 (15) 0[f] (90)	93
10		3.5	RT	93 (30)	90
11		3.5 3.5 3.5[d]	RT reflux RT	15[g] (120), 37[h] (120) 58[g] (120), 21[h] (120) 14[g,i] (120)	
12		3.5 0.1 0.01[e]	RT RT RT	80[j] (10) 70[k] (10) <1[k,l] (10)	77

[a] Reaction conditions: $FeCl_3 \cdot 6H_2O$ added to 0.06 M solution of protected compound in CH_2Cl_2. [b] Using anhydrous $FeCl_3$. [c] GLC yield after 16 h: 80%. [d] 4:1 CH_2Cl_2:acetone (v/v). [e] Using $FeCl_3 \cdot 6H_2O$ absorbed onto silica gel. [f] No starting material remaining; decomposition. [g] Percent octanol formed. [h] Percent formaldehyde dioctyl acetal formed. [i] GLC yield after 16 h: 72%. [j] Removal of both isopropylidene groups occurred. [k] Monodeprotection to the corresponding 5,6-diol. [l] GLC yield after 24 h: 40%.

making the amount of metal in solution nearly catalytic. Therefore, it seems likely that deprotection is mediated by protonation in addition to metal complexation, through the intermediacy of an as yet uncharacterized hydrated iron species (eqs 1 and 2, respectively, Scheme 1). The fact that the crystal structure of $FeCl_3 \cdot 6H_2O$ is best represented as *trans*-$[FeCl_2(H_2O)_4]Cl \cdot 2H_2O$[8] and that aqueous solutions of $FeCl_3$ contain a mixture of the weakly acidic hydrates $[Fe(H_2O)_6]^{3+}$ and $[Fe(H_2O)_5(OH)]^{2+}$ [9] supports this premise; whether these or other related acidic species are reactive forms in $FeCl_3 \cdot 6H_2O$-mediated deprotection chemistry has yet to be determined and awaits further study.

The above deprotection methodology was successfully incorporated into a short synthesis of the unnatural juvenile hormone precursor **5** (Scheme 2).[10] Conjugate addition of the alkyl cuprate[11] of **1** to ethyl 2-pentynoate gave dioxolane **2**, which was subsequently treated with 2.8 equiv of $FeCl_3 \cdot 6H_2O$ in refluxing CH_2Cl_2 for 20 min to give isomerically pure aldehyde **3** in an 87% isolated yield. Deprotection of dioxolane **3**, which bears an acid-

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(8) Lind, M. D. *J. Chem. Phys.* **1967**, *47*, 990–993.

(9) Nicholls, D. In *Comprehensive Inorganic Chemistry*; Bailar, J. C., Jr. Emeléus, H. J., Nyholm, R., Trotman-Dickenson, A. F., Eds.; Pergamon Press: Oxford, 1973, Vol. 3, pp 1038–1049.

(10) Sen, S. E.; Ewing, G. J. *J. Org. Chem.* **1997**, *62*, 3529–3536.

(11) (a) Lipshutz, B. H.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E.; Barton, J. C.; Whitney, S. E.; Kotsuki, H. *Tetrahedron* **1986**, *42*, 2873–2879. (b) Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409–435. (c) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045–5050.

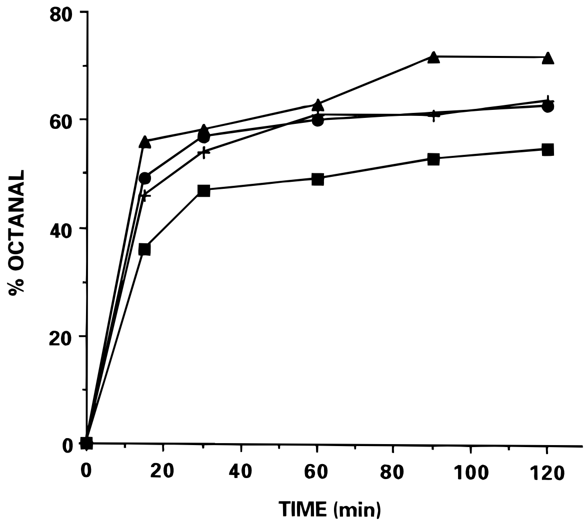
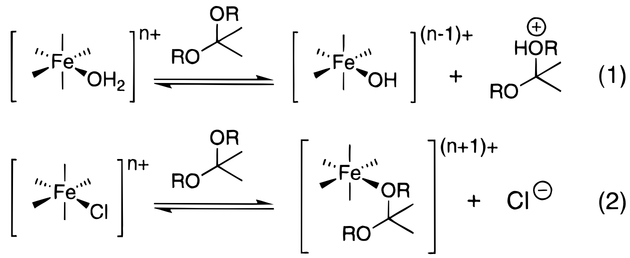


Figure 1. Deprotection study using increasing equivalents of $FeCl_3 \cdot 6H_2O$. Reaction conditions: 0.5 M solution of octanal 1,3-dioxolane in CH_2Cl_2 at rt using (■) 1 equiv, (●) 2 equiv, (▲) 3.5 equiv, or (+) 6 equiv of $FeCl_3 \cdot 6H_2O$.

Scheme 1. Proposed Mechanism for $FeCl_3 \cdot 6H_2O$-Promoted Deacetalization



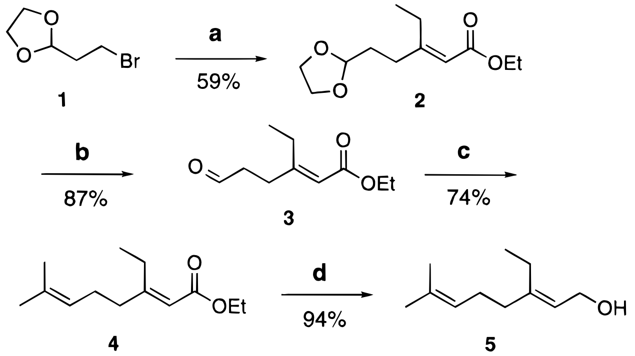
sensitive α,β-unsaturated system, was inert to olefin isomerization when treated with $FeCl_3 \cdot 6H_2O$, even after long (>4 h at rt) reaction times. Subsequent Wittig homologation and DIBALH reduction gave allylic alcohol **5** in a 36% overall yield.

Experimental Section

Anhydrous $FeCl_3$ and $FeCl_3 \cdot 6H_2O$ were obtained from Aldrich Chemical Co. Acetals were prepared using previously described methods.[12] CH_2Cl_2 was distilled from CaH_2 prior to use in anhydrous $FeCl_3$ and $FeCl_3 \cdot 6H_2O$ reactions.[13] $FeCl_3 \cdot 6H_2O$ absorbed onto silica gel was prepared by the method of Kim and co-workers.[6d] Gas–liquid chromatography was performed using a DB5-HT 30 m capillary column (J & W Scientific).

General Deprotection Methods. A. Standard $FeCl_3 \cdot 6H_2O$ Deprotection of Acetals. To a solution of cinnamaldehyde 1,4-dioxane (65 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) at rt was added $FeCl_3 \cdot 6H_2O$ (322 mg, 3.5 equiv). The resulting yellow to amber colored suspension was stirred for 15 min and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was redissolved in a minimum amount of CH_2Cl_2 and passed through a short silica gel plug to remove any remaining iron species. Concentration of the resulting eluent under reduced pressure provided cinnamaldehyde (42 mg, 94%).

Scheme 2. Synthesis of (2*E*)-3-Ethyl-7-methyl-2,6-octadien-1-ol[a]



[a] (a) (1) Mg, THF; (2) 2-ThCu(CN)Li, −78 °C; (3) ethyl 2-pentynoate, THF, −78 °C; (b) 2.8 equiv $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, reflux, 20 min; (c) isopropyltriphenylphosphorane, THF, 0 °C; (d) DIBALH, THF, −40 to 0 °C.

B. $FeCl_3 \cdot 6H_2O$ Deprotection of Acetals in Refluxing CH_2Cl_2. To a solution of ethyl (*E*)-3-ethyl-6,6-(ethylenedioxy)-2-hexen-1-oate (**2**, 1.9 g, 8.3 mmol) in 400 mL of CH_2Cl_2 at reflux was added $FeCl_3 \cdot 6H_2O$ (6.3 g, 2.8 equiv). After refluxing for 20 min (reaction times greater than 30 min cause decomposition of $FeCl_3 \cdot 6H_2O$), the reaction was poured into 100 mL of saturated aqueous $NaHCO_3$. The mixture was extracted three times with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the resulting oil using 7% EtOAc/hexane yielded ethyl (*E*)-3-ethyl-6-oxo-2-hexen-1-oate (**3**, 1.34 g, 87%).

C. $FeCl_3 \cdot 6H_2O$ Deprotection of Acetals Using Acetone as Cosolvent. To a solution of dihydrocinnamaldehyde 1,3-dioxolane (18 mg, 0.1 mmol) in a 4:1 mixture of CH_2Cl_2:acetone (1.5 mL) at rt was added $FeCl_3 \cdot 6H_2O$ (95 mg, 3.5 equiv). The resulting yellow solution was stirred for 1 h and quenched by the addition of saturated aq $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was redissolved in a minimum amount of CH_2Cl_2 and passed through a short silica gel plug to remove any remaining iron impurities. Concentration of the resulting eluent under reduced pressure provided dihydrocinnamaldehyde (13 mg, 98%).

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[12] (a) Daignault, R. A.; Eliel, E. L. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, pp 303–306. (b) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772–3774. (c) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276.

[13] Anhydrous $FeCl_3$ reactions were performed according to the procedure described in ref 6b.