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Iron(III) tosylate-catalyzed deprotection of aromatic acetals in water

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ABSTRACT

The deprotection of aromatic as well as conjugated acetals and ketals in water is catalyzed by iron(III) tosylate (1.0–5.0 mol %). Iron(III) tosylate is an inexpensive and readily available catalyst. The use of water, the most environmentally benign solvent, makes this procedure especially attractive for acetal deprotection.

The deprotection of acetals is an important step in organic synthesis due to the wide application of acetals, especially in the course of a total synthesis.[1] Hence, many reagents have been developed for this purpose.[2] Considerable efforts have also been directed toward developing mild and selective methods for acetal deprotection.[3] However, many of the reagents employed for this purpose are corrosive and often toxic. Our continued interest in developing environmentally friendly synthetic methodology prompted us to investigate a mild and catalytic method for the deprotection of acetals utilizing inexpensive, commercially available reagents. Herein we wish to report that iron(III) tosylate[4] is an efficient, inexpensive, and easy to handle catalyst for the deprotection of a wide range of aromatic acetals. Iron(III) tosylate is commercially available as the hexahydrate and was used as such. In spite of the lack of solubility of most organic compounds in water, the low cost, easy availability, and non-flammability of water as well as the observation of unexpected rate accelerations have led to an increasing number of organic reactions being carried out in water.[5]

The results of this study are summarized in Table 1. Preliminary studies were conducted in aqueous THF but gratifyingly, subsequent attempts in water proved successful. As can be seen from Table 1, a wide range of aromatic acetals and ketals underwent smooth deprotection to give the corresponding carbonyl compound in good to excellent yields. In most cases, the crude product was found to be >98% pure by ^{1}H and ^{13}C NMR spectroscopy, thus avoiding the need for expensive silica gel chromatographic purification. Although iron(III) tosylate is water soluble, the substrates shown in Table 1 are all insoluble in water, and hence the reactions were carried out by stirring a suspension of the substrate in water. Under the reaction conditions, it was possible to cleave an acetal (entry 9) in the presence of a *tert*-butyldimethylsilyl ether (TBDMS).[6] Such chemoselectivity is especially useful in the course of a total synthesis where selective deprotection of protecting groups is often necessary. The trityl group did not survive the reaction conditions (entry 10) although it was necessary to carry out the reaction in CH_3OH/H_2O (8:2, v/v).

Deprotection of aliphatic acetals was not as successful using these reaction conditions. For example, when the dimethyl acetal of dodecanal was subjected to the reaction conditions, less than 50% dodecanal formed after 22 h at reflux temperature. The deprotection of the dimethyl acetal of dodecanal was also attempted with 5.0 mol % *p*-TsOH in H_2O (pH ∼2) and in this case no dodecanal formed after 22 h at reflux.

Although detailed mechanistic studies were not carried out, a few points merit comment. The deprotection reactions were either not successful or were incomplete in the absence of the catalyst. The observation that a solution of iron tosylate in water is acidic (pH ∼2) suggests that the *p*-TsOH might be an active catalyst, though the role of Fe^{3+} as a Lewis acid cannot be ruled out. The use of $Fe(OTs)_3$ is still preferable to *p*-TsOH because the latter compound is highly toxic and its handling poses a health hazard.[7]

In summary, a mild method for the deprotection of aromatic as well as conjugated acetals and ketals catalyzed by iron(III) tosylate in H_2O has been developed.

Two representative procedures are given here (Table 1, entry 5): A mixture of the dimethylacetal of *p*-anisaldehyde (0.5049 g, 2.77 mmol) in H_2O (5.0 mL) was stirred at room temperature as $Fe(OTs)_3{\cdot}6H_2O$ (0.0188 g, 0.0277 mmol, 1.0 mol %) was added. The

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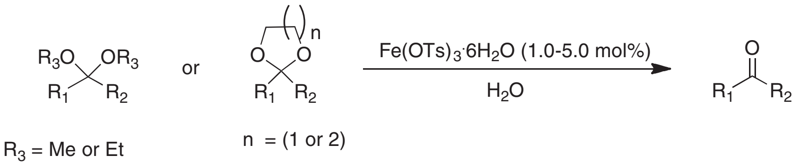
Table 1
Deprotection of aromatic and conjugated acetals in water catalyzed by $\mathrm{Fe(OTs)_3 \cdot 6H_2O}$



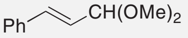
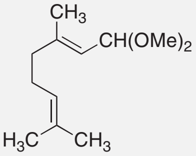
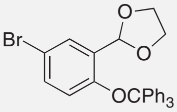
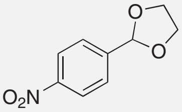
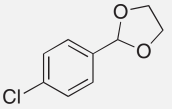
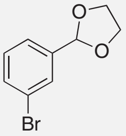
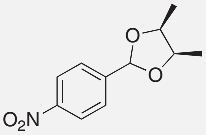
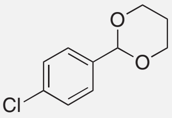
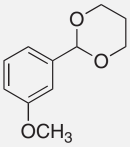
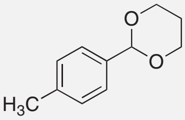
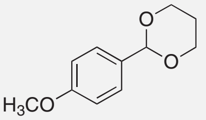
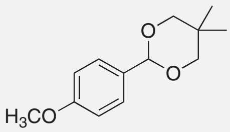
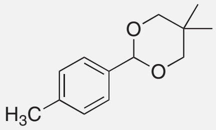
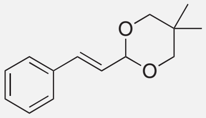
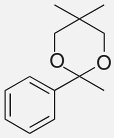
Entry	Acetal[a]	Catalyst (mol %)	Temp	Time[b]	Yield[c,d] (%)
1	*p*-$\mathrm{ClC_6H_4CH(OMe)_2}$	1.0	rt	19 h	84
2	*m*-$\mathrm{BrC_6H_4CH(OEt)_2}$	5.0	Reflux	1 h	95
3	*o*-$\mathrm{BrC_6H_4CH(OEt)_2}$	5.0	Reflux	2.5 h	86
4	*p*-$\mathrm{HOCC_6H_4CH(OEt)_2}$	2.5	rt	16 h	77[e]
5	*p*-$\mathrm{CH_3OC_6H_4CH(OMe)_2}$	1.0	rt	1 h	88[e]
6	*p*-$\mathrm{Me_2NC_6H_4CH(OMe)_2}$	1.0	rt	45 min	94
7		1.0	rt	4 h	96
8		1.0	rt	2 h	89[e]
9	*p*-$\mathrm{{}^tBuMe_2SiOC_6H_4CH(OMe)_2}$	2.0	rt	45 min	92[f]
10		5.0	Reflux	4 h	78[g]
12		5.0	Reflux	40 min	98
13		5.0	Reflux	1 h	73
14		5.0	Reflux	40 min	92
15		5.0	Reflux	1 h	94
16		5.0	Reflux	1 h	97
17		5.0	Reflux	1 h	81
18		5.0	Reflux	1 h	83
19		5.0	Reflux	1 h	92

Table 1 (*continued*)

Entry	Acetal[a]	Catalyst (mol %)	Temp	Time[b]	Yield[c,d] (%)
20		5.0	Reflux	1 h	98[e]
21		5.0	Reflux	1 h	86
22		5.0	Reflux	1 h	74
23		5.0	Reflux	1.25 h	92[e]

[a] Acetals were either purchased commercially or synthesized by a previously reported method.[8]

[b] The progress of the reaction was followed by GC, TLC or ^{1}H NMR.

[c] Refers to yield of the isolated product. The crude products from acyclic acetals were found to be $\geqslant$98% pure and hence further purification was deemed unnecessary. It was necessary to purify crude products from a few cyclic acetals (entries 14, 15, 17, 21 and 22) by flash chromatography.

[d] All products are commercially available and were characterized by ^{1}H and ^{13}C NMR spectroscopy, and by GC analysis.

[e] Product was 97% pure by GC analysis.

[f] The product was 4-(*tert*-butyldimethylsilyloxy)benzaldehyde.

[g] The reaction was carried out in CH_3OH/H_2O (8:2, v/v). The crude product was purified by dissolving in ether and extraction with aqueous 2 M NaOH, followed by acidification with aqueous 3 M H_2SO_4. The product was 5-bromo-2-hydroxybenzaldehyde.

progress of the reaction was monitored by GC. After 1 h, the reaction mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (15 mL), aqueous saturated NaCl (15 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 0.3327 g (88%) of *p*-anisaldehyde as a clear liquid. The product was determined by GC analysis, and ^{1}H and ^{13}C NMR spectroscopy to be 97% pure.

(Table 1, entry 9): A mixture of *tert*-butyl(4-(dimethoxymethyl)phenoxy)dimethylsilane (0.2109 g, 0.75 mmol) in H_2O (4.0 mL) was stirred at room temperature as $Fe(OTs)_3 \cdot 6H_2O$ (0.0101 g, 0.0149 mmol, 2.0 mol %) was added. The progress of the reaction was monitored by GC. After 45 min, the reaction mixture was extracted with EtOAc (2 × 20 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (10 mL), aqueous saturated NaCl (10 mL), dried (Na_2SO_4), and concentrated on a rotary evaporator to yield 0.1617 g (92%) of 4-(*tert*-butyldimethylsilyloxy)benzaldehyde as a clear liquid. The product was determined by GC analysis and ^{1}H NMR to be 99% pure.

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6. We have recently reported (see Ref. 4c) the iron(III) tosylate catalyzed deprotection of *tert*-butyldimethylsilyl ethers in CH_3OH as a solvent. However, in this case no deprotection was observed in water as a solvent.
7. According to the MSDS sheets, iron(III) tosylate is safer to use than *p*-toluenesulfonic acid. Iron(III) tosylate has a HMIS (hazardous material identification system) rating of 2 (moderate hazard) while *p*-toluenesulfonic acid has a HMIS rating of 3 (serious hazard).
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