



## An expedient reductive method for conversion of ketoximes to the corresponding carbonyl compounds

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### ABSTRACT

A wide array of readily prepared pivalates of ketoximes can be converted to the corresponding ketones in good yields by treatment with iron powder in THF containing catalytic amounts of both trimethylsilyl chloride and glacial acetic acid at room temperature for 30 min, followed by a brief aqueous workup.

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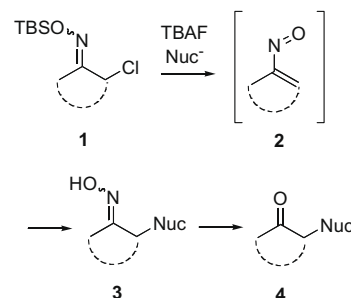
We have recently been actively involved in developing a methodology for effecting both inter- and intramolecular Michael-type conjugate additions of carbon nucleophiles to in situ-produced vinylnitroso compounds.<sup>1,2</sup> Thus, we have found that nitrosoalkene species **2** can easily be generated from  $\alpha$ -chloro-*O*-TBS-oximes **1** using a fluoride source in the presence of a carbon nucleophile to form  $\alpha$ -alkylated oximes **3** (Scheme 1). For many of our intended purposes, however, it was necessary to regenerate the carbonyl compounds **4** from the resulting oximes **3**.

Numerous methods have previously been described for converting oximes and their *O*-acyl derivatives to carbonyl compounds.<sup>3</sup> These procedures generally involve either hydrolytic, oxidative or reductive conditions. After some disappointing results using a few of the more common literature cleavage procedures (e.g.,  $\text{TiCl}_3$ ,<sup>4</sup> Dess–Martin periodinane,<sup>5</sup> etc.), we decided to explore a new methodology for this transformation. In particular, we were interested in developing a mild general procedure which would utilize inexpensive, commercially available reagents having long shelf lives. Moreover, since hydrolytic methods usually involve stringent reaction conditions, and oxidative procedures are often incompatible with the functionality in some of our systems (e.g., amines, indoles, etc.), we primarily focussed on devising a reductive protocol.

In 1998, Burk and coworkers discovered that *N*-acetyl enamides can be prepared in moderate to good yields directly from ketoximes by heating at 70 °C in toluene/acetic anhydride in the presence of iron powder.<sup>6a</sup> In an improvement of this methodology, Zhang et al. found that these reactions can be effected at room temperature

if DMF is used as a solvent, and also that the reaction is initiated by the addition of a catalytic amount of trimethylchlorosilane.<sup>6b</sup> More recently, we reported that other acylating reagents can be used in this process.<sup>6c</sup> We considered the possibility of using a variation of this methodology for converting oximes to carbonyl compounds by omitting the acylating reagent in order to form the NH imine, which would be susceptible to rapid hydrolysis. It should also be noted that an iron(0)-promoted cleavage of oximes has been reported, but which requires forcing conditions (Fe powder/concd HCl/MeOH, reflux).<sup>7,8</sup>

In initial exploratory experiments, the oxime **5** (12:1 *E/Z* mixture) was used as a test system (Eq. 1). However, exposure of this compound to iron powder and a catalytic amount of trimethylsilyl chloride in THF, MeOH, or toluene at either room temperature or at reflux led to no observable cleavage reaction but rather only oxime *E/Z* isomerization occurred. On the other hand, we were pleased to find that the corresponding oxime acetate **6**, when treated with



Scheme 1.

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**Table 1**  
Conversion of oxime pivalates to the corresponding carbonyl compounds

Entry	Oxime pivalate	Ketone product	Isolated yield (%)
A			81
B			54
C			71
D			95
E			91
F			75
G			79
H			84 <sup>a,b,c</sup>

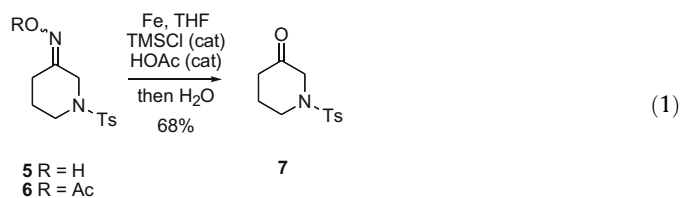
<sup>a</sup> This reaction was run at 0.03 M concentration.

<sup>b</sup> Under the same conditions the corresponding oxime acetate gave 57% of the ketone.

<sup>c</sup> These compounds are mixtures of diastereomers. Full spectral data will be reported in a subsequent publication.

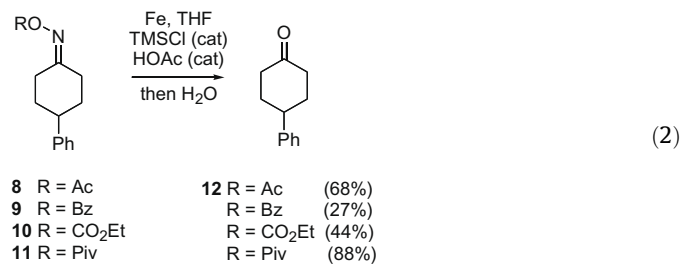
iron powder in THF containing a catalytic amount of TMSCl at room temperature for about 1 h, followed by stirring with water for an additional hour, afforded the desired ketone **7** in reasonable yield (>60%). Although this transformation worked as planned, we observed that the reaction was highly irreproducible. Surprisingly, in some runs ketone **7** was formed cleanly and in others no reaction occurred. After some detective work, it was discovered that the successful reactions had been run in round-bottomed flasks that were previously cleaned in a concentrated nitric acid bath, followed by washing with water several times before drying. Reactions run in flasks which had not been treated in this manner only led to recovery of starting material. Thus, it became evident that the oxime acetate reduction by iron(0) is apparently catalyzed by a trace of the acid remaining in the flask. In fact, addition of a catalytic amount of either nitric acid, *p*-toluenesulfonic acid, or trifluoroacetic acid led to successful reactions, but the best yields of ketone **7** (68%) were obtained by addition of a small amount of glacial acetic acid to the mixture. It should also be noted that omission of the TMSCl shuts down the cleavage. However, during the course of these studies it was also observed that some deacetylation of **6** was occurring under these conditions, leading to unreactive oxime

**5**. Therefore, in an attempt to avoid this problem, we decided to explore the cleavage of other *O*-acyl oxime derivatives.

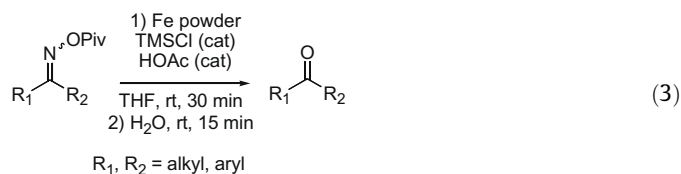


These studies were conducted on acyl derivatives **8–11** prepared from the oxime of 4-phenylcyclohexanone, and the results are outlined in Eq. 2. Thus, it was found that the pivalate ester<sup>9</sup> of this oxime gave the best yield of ketone **12**. The acetate **8**, benzoate **9**, and ethyl carbonate **10** all produced **12** in significantly lower yields. Using pivalate **11**, further optimization studies showed that the cleavage works best if the reduction step is carried out at room temperature for 30 min, followed by addition of water, and stirring for 15 min to effect imine hydrolysis. Longer reaction times for the reduction step generally led to lower yields of the ke-

tone and to the formation of significantly larger amounts of by-products. Also, using DMF as the solvent gave lower isolated yields of product **12** than the reactions run in THF.



Using what was learned above, a general procedure has been developed for the cleavage of a broad range of ketoxime pivalates<sup>9</sup> to their corresponding ketones under the reaction conditions shown in Eq. 3. This methodology has been applied to the representative examples listed in Table 1. It should be noted, however, that aldehyde oxime pivalates gave mixtures of the aldehyde and the corresponding nitrile under these reaction conditions. Thus, the work described here provides a very mild, general method for converting readily prepared pivalates of ketoximes to their corresponding ketones.



**General procedure for cleavage of oxime pivalates:** To a solution of the oxime pivalate<sup>9</sup> (0.10 mmol) in THF (1 mL) was added iron powder (55.8 mg, 1.0 mmol) followed by glacial AcOH (one drop)

and TMSCl (one drop). After stirring for 30 min at room temperature, the reaction mixture was diluted with H<sub>2</sub>O (1 mL) and stirred for an additional 15 min. The liquid phase was separated from the remaining Fe powder using a pipette and transferred to a separatory funnel. The Fe powder was then washed with EtOAc (3 × 2 mL) which was added to the separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate and hexanes. Isolated yields of carbonyl products formed from a series of oxime pivalates are shown in Table 1.

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