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# Low-valent titanium induced reductive deprotection of oximes

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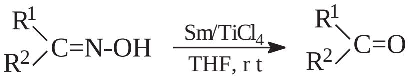
An efficient regeneration of carbonyl compounds through low-valent titanium induced reductive deprotection of oximes is described in this paper.

**Keywords:** low-valent titanium, carbonyl compounds, oximes

Oximes are extensively used as derivatives for the protection, purification and characterisation of aldehydes and ketones. In addition, their availability from non-carbonyl compounds, such as by nitrosation of an active methylene group,[1] nitrosation of $\alpha$-halocarbonyl compounds[2] and condensation of nitroalkenes with aldehydes,[3] provides an alternate pathway to carbonyl compounds. Thus, the development of procedures for the effective cleavage of oximes to regenerate the carbonyl compounds has received much attention over recent years.[4] The classical method for the conversion of oximes to the corresponding aldehydes or ketones is acid hydrolysis, which limits the scope of the reaction as it excludes substrates which are acid-sensitive. Basic hydrolysis is less efficient and also excludes base-sensitive compounds. Therefore, numerous new methods for oxidative[5] or reductive[6] cleavage of oximes have been reported. While some of these methods have some degree of success compared with the classical hydrolysis methods, many require long reaction times and the use of expensive reagents or appear to be unsuitable for the regeneration of aldehydes from aldoximes.

The application of low-valent titanium as an efficient reductive or reductive coupling reagent in organic synthesis has received increasing attention over the last two decades.[7] Several methods have been introduced, such as $TiCl_3$–$LiAlH_4$, $TiCl_4$–Mg (Hg), $TiCl_4$–Zn and the $CpTiCl_3$–$LiAlH_4$ system to prepare low-valent titanium reagents.[8] Our group has found that low-valent titanium reagents could be derived from $Cp_2TiCl_2$–Sm[9] or $TiCl_4$–Sm[10] systems. While these low-valent titanium reagents prepared from different systems have many properties in common, differences do exist in their reactivity towards some substrates. It has been recently reported that aromatic oximes can undergo reductive coupling to give 1, 2-diamines with Zn–$TiCl_4$.[11] However, with our $TiCl_4$-Sm system, no reductive coupling products from oximes could be obtained; instead, the corresponding parent carbonyl compounds were formed in excellent yields. Considering that it might be developed as an alternative method for the reductive deprotection of oximes, we investigated the system and herein report our results concerning the efficient cleavage of oximes with the use of the low-valent titanium reagent prepared from metallic samarium and $TiCl_4$. The reaction is shown in Scheme 1 and the results are listed in Table 1.



**Scheme 1**

The reaction is very rapid and proceeds within 10–20 min upon addition of oxime to a suspension of the low-valent titanium reagent prepared *in situ* from metallic samarium and $TiCl_4$ in THF at room temperature. Table 1 shows that oximes from aromatic and aliphatic aldehydes and ketones can be transformed into their corresponding carbonyl counterparts in good to excellent yields. In addition, the selectivity of the method is illustrated by several examples (entries 4–6), in that such reducible groups as halogens (F, Cl, Br) remain unchanged under the reaction conditions. However, substrates bearing other reducible groups, such as nitro or the carbonyl group of a ketone gave inseparable mixtures rather than the desired carbonyl compounds. It may be due to the rather strong reducing ability of the system, because the Sm/$TiCl_4$ system not only can promote the cleavage of oxime, but also the reduction of nitro groups and the reduction and/or reductive coupling of carbonyl groups presented on the substrates simultaneously.[12] These results may seem to be incompatible

**Table 1** Reductive cleavage of oximes to carbonyl compounds with Sm/$TiCl_4$

| Entry | Carbonyl product[a] | Yield/% | Time/min | M.p. or B.p. /torr (°C) | Lit.[13] M.p. or B.p. /torr (°C) |
|---|---|---|---|---|---|
| 1 | Benzaldehyde | 91 | 10 | 177–178/760 | 179/751 |
| 2 | *p*-Methylbenzaldehyde | 92 | 10 | 110–111/11 | 106/10 |
| 3 | *p*-Methoxybenzaldehyde | 90 | 10 | 132–133/12 | 134–5/12 |
| 4 | *p*-Chlorobenzaldehyde | 90 | 10 | 45–46 | 47 |
| 5 | *p*-Florobenzaldehyde | 92 | 10 | 180–181/760 | 181/758 |
| 6 | *m*-Bromobenzaldehyde | 88 | 10 | 120–122/12 | 66–8/2 |
| 7 | Cinnamaldehyde | 78 | 20 | 112–114/10 | 252/760 |
| 8 | Heptaldehyde | 68 | 20 | 150–151/760 | 152/760 |
| 9 | Acetophenone | 89 | 20 | 200–201/760 | 202/760 |
| 10 | *p*-Methylacephenone | 90 | 20 | 117–118/12 | 112.5/11 |
| 11 | *p*-Bromoacephenone | 91 | 20 | 49–50 | 51 |
| 12 | Benzophenone | 72 | 30 | 46–47 | 48.5–49 |
| 13 | Cyclohexanone | 72 | 30 | 153–154/760 | 155/760 |
| 14 | 3-Pentanone | 73 | 30 | 100–101/760 | 101.5/760 |

[a]All the products were fully characterised by their physical data ( mp./bp.), spectral characteristics (IR, $^1$H-NMR), and comparison with those of authentic samples.

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with the fact that Sm/$TiCl_4$ system can effectively promote the regeneration of carbonyl group from the corresponding oxime without any further reduction or reductive coupling. However, it can be well understood by taking the possible mechanism of this reductive process into account. According to the literature,[6] the oxime may first be deoxygenated to an imine intermediately upon treatment with the Sm/$TiCl_4$ system. The corresponding aldehyde or ketone can only be obtained through subsequent hydrolysis of the so-formed imine. Therefore, it is the imine intermediate rather than the aldehyde or ketone that competes with the oxime to consume the low-valent titanium reagent. It must be the much lower reactivity or even the inertness of the imine intermediate toward the low-valent titanium reagent compared with that of the oxime that enables the chemoselective reductive cleavage of the oximes.

In order to determine if this reductive cleavage process could proceed smoothly in the presence of acid-sensitive or base-sensitive groups, an equimolar mixture of benzaldoxime and benzaldehyde ethylene acetal was exposed to 2 mol equivalents of the reagent for 30 min; this led to the nearly quantitative recovery of the unreacted acetal along with benzaldehyde in 86% yield based on the benzaldoxime used. These results suggest that our method may be suitable for the chemoselective cleavage of oximes bearing other acid-sensitive groups, which could not be obtained with the classical hydrolysis methods.

In summary, with its mildness, convenience, rapidity and selectivity, the method presented here may be used as an attractive alternative to the previously reported methods for deprotection of oximes.

## Experimental

*General experimental details*: Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. Metallic samarium and $TiCl_4$ solution are commercially available. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer. $^1$H NMR spectra were determined on a Bruker AC 80 spectrometer as $CDCl_3$ solutions, chemical shifts being expressed in ppm downfield from internal tetramethylsilane.

*General procedure for the reductive deprotection of oximes*: Titanium tetrachloride (0.22 ml, 2 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.3 g, 2 mmol) in THF (20 ml) at room temperature under a nitrogen atmosphere. After the completion of addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent thus formed was cooled to room temperature and a solution of the oxime (2 mmol) in anhydrous THF (2 ml) was added *via* a syringe. The black colour of the solution changed into a brownish red within several minutes. After completion of the reaction (monitored by TLC), it was quenched with 2 N HCl and extracted with ether (3 × 20 ml). The combined extract was washed with saturated brine (15 ml) and dried over anhydrous $Na_2SO_4$. After filtration and evaporating the solvent under reduced pressure, the resulting crude product was purified by preparative TLC using ethyl acetate and cyclohexane (1 : 6) as eluant. All the products have physical (b.p. or m.p.) and spectral (IR and $^1$H NMR) data in agreement with those of the authentic specimens.

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