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Reduction of 1,2-diketones with titanium tetraiodide: a simple approach to α-hydroxy ketones

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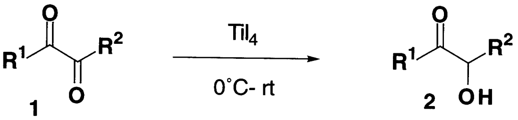
Abstract

1,2-Diketones are readily reduced with titanium tetraiodide to give α-hydroxy ketones in good to excellent yields. Regioselectivity on the reduction of unsymmetrical substrates is also discussed. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: 1,2-diketones; titanium tetraiodide; α-hydroxy ketones.

Although α-hydroxy ketones are useful synthones in organic synthesis,[1] their preparations are not always readily conducted.[2] While oxidation of enolates or their equivalents offers convenient methodologies,[3] another useful approach to this class of compounds involves the reduction of 1,2-diketones.[4] However, there appear to be difficult problems of over-reduction to diols and/or mono-ketones. In order to circumvent these problems, several methods have been developed. For example, the use of low valent $TiCl_3$ in MeOH effects the reduction of 1,2-diketones to 1,2-diols,[5a] and heating 1,2-diketones in aqueous HI at reflux gives mono-ketones.[5b,c] The use of low valent VCl_2 or Zn also gives α-hydroxy ketones selectively.[6] However, the search for a new reduction method with easier experimental operation under mild conditions is still a worthwhile goal. We have recently disclosed that TiI_4 is an excellent reagent for the reductive coupling of aldehyde, leading to the formation of pinacol coupling products in good to excellent yields.[7] We have now found that TiI_4 effects the reduction of 1,2-diketones to give α-hydroxy ketones in good yields and wish to report herein an efficient method for the preparation of α-hydroxy ketones (Scheme 1).



Scheme 1.

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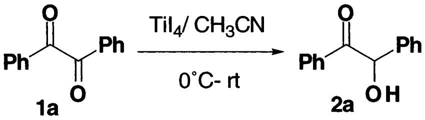
An initial examination into the reduction of benzil with 0.5 equivalents of TiI_4 met with the formation of the desired mono-reduction product **2a** in 20% yield.[8] Further examination into the amount of TiI_4 led to the formation of benzoin in good yield, and the results are summarized in Table 1.

Table 1
Reduction of benzil **1a** with TiI_4[a]



Entry	TiI_4/equiv.	Time/h	Yield/%[b]
1	0.5	21.0	20
2	0.75	15.0	51
3	1.0	5.4	85
4	1.5	5.3	92
5	2.0	2.0	90
6[c]	1.5	18.0	88

[a] The reaction was carried out according to the typical procedure.

[b] Isolated yields.

[c] CH_2Cl_2 was used as a solvent.

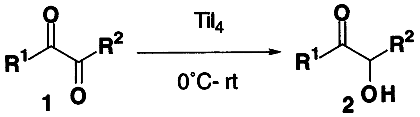
Benzoin **2a** was obtained in excellent yield, when more than 1.0 equivalent of titanium tetraiodide was used. The best result was obtained using 1.5 equivalents of TiI_4 in acetonitrile, and benzoin **2a** was obtained in 92% yield. Regarding the solvent, acetonitrile was proved to be the solvent of choice in terms of the product yield and the reduction rate.

A typical procedure under the optimum conditions follows: Acetonitrile (1.0 ml) was added to TiI_4 (263.3 mg, 0.512 mmol) at room temperature under an argon atmosphere. After stirring for 10 min, to it was added a solution of benzil **1a** (50.0 mg, 0.237 mmol) in acetonitrile (1.0 ml) at 0°C. After being stirred at 0°C to room temperature, the reaction was quenched with sat. aq. $NaHCO_3$ and then 10% aq. $NaHSO_3$. The mixture was filtered through a Celite pad, and extracted with ethyl acetate (10 ml×3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification on preparative silica gel TLC (*n*-hexane:ethyl acetate = 3:2 as an eluent) gave benzoin **2a** (46.2 mg, 92%) as a colorless oil.

Under the optimum conditions, the reduction of various 1,2-diketones **1** proceeded to give the mono-reduction products **2**, and the results are summarized in Table 2. α-Hydroxy ketone **2** was obtained in the reduction of 4,4′-dimethyl-, 4,4′-dimethoxy-, or 3,3′,5,5′-tetramethoxy benzil possessing electron donating groups in excellent yield (entries 1, 2, and 5), whereas reduction of the 1,2-diketone possessing 4,4′-dibromo or 2,2′-dimethoxy groups gave the product in slightly lowered yield (entries 3 and 4). The latter lowered yield may be due to the steric hindrance caused by the *ortho* substituent on the aromatic ring. Alicyclic diketone also underwent clean reduction to give cyclic α-hydroxy ketone in moderate yield (entry 6).

Furthermore, the present reaction was applied to unsymmetrical 1,2-dicarbonyl compounds bearing other functional groups such as ester and aldehyde. The results of the reduction of unsymmetrical 1,2-dicarbonyl compounds are summarized in Table 3.

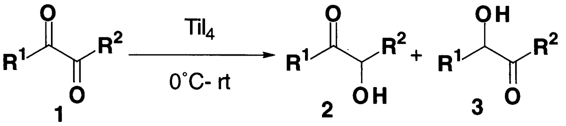
Table 2
Reduction of 1,2-diketones **1** with TiI_4[a]



Entry	R^1	R^2	Solvent	Yield/%[b]
1	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	CH_3CN	94
2	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	CH_3CN	88
3	$4\text{-}BrC_6H_4$	$4\text{-}BrC_6H_4$	$PhCH_3$	73
4	$2\text{-}MeOC_6H_4$	$2\text{-}MeOC_6H_4$	CH_3CN	69
5	$3,5\text{-}(MeO)_2C_6H_3$	$3,5\text{-}(MeO)_2C_6H_3$	CH_3CN	86
6		$-(CH_2)_6-$	CH_3CN	67

[a] The reaction was carried out according to the typical procedure.
[b] Isolated yields.

Table 3
Reduction of unsymmetrical 1,2-dicarbonyl compounds **1** with TiI_4[a]

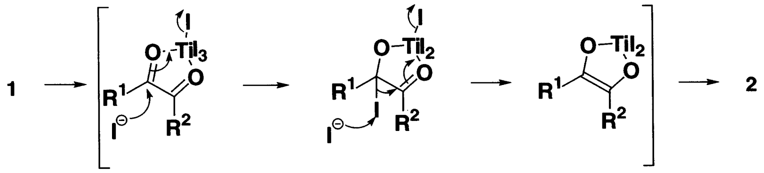


Entry	R^1	R^2	Solvent	Yield of **2**/%[b]	Yield of **3**/%[b]
1	Ph	Me	C_2H_5CN	54[c]	13[c]
2	*n*-Pr	Me	CH_3CN	25[c]	17[c]
3	Ph	H	CH_3CN	40	–
4	Ph	OMe	CH_3CN	–	33

[a] The reaction was carried out according to the typical procedure.
[b] Isolated yields.
[c] Determined by ^1H NMR.

Complete discriminations were observed in the reductions of phenylglyoxal and methyl phenylglyoxylate where one of the two carbonyls was selectively reduced, although the product yields were low (entries 3 and 4). In contrast, the discrimination between two identical ketones was not trivial (entry 2). However, the selective reduction was observed to some extent by carrying out the reduction with due care (entry 1). The low yields in the above cases were mainly due to the formation of by-products, which decomposed despite attempted purifications.

There are several arguments on the reaction mechanism, and one of them involves a single-electron transfer mechanism, which has many precedents in dissolving metal reduction.[9] Another concerns the iodination of the carbonyl group of 1,2-diketone **1**, followed by the attack with iodide anion from TiI_4 to form an enolate species, which in turn quenched with a proton source to give the reduction product **2** (Scheme 2). From the results in Table 3 where the formation of benzyl radicals was not favorable (Table 3, entries 1 and 3), the mechanism shown in Scheme 2 appears to be likely. We are currently investigating the true reactive species in detail, and the results will be reported shortly.



Scheme 2.

In conclusion, the reduction of 1,2-dicarbonyl compounds with TiI_4 gave α-hydroxy carbonyl compounds in good to excellent yields. Since titanium tetraiodide is commercially available and inexpensive, and that the experimental procedure is quite simple, the present procedure offers a convenient and practical method for α-hydroxy ketones. Furthermore, this is a useful example of the reduction of 1,2-dicarbonyl compounds without the use of low valent metal species.

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