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An Efficient Procedure for the Diastereoselective Dehydration of *β*-Hydroxy Carbonyl Compounds by $CeCl_3 \cdot 7H_2O$/NaI System

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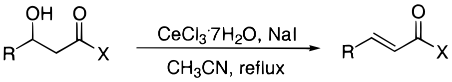
ABSTRACT



The dehydration of *β*-hydroxy ketones and *β*-hydroxy esters is a synthetically useful method for the conversion of these compounds to the corresponding α,*β*-unsaturated derivatives. Cerium(III) chloride heptahydrate in combination with sodium iodide in refluxing acetonitrile acts as an efficient reagent for this conversion. The present procedure, which utilizes cheap and "friendly" reagents, offers the corresponding (*E*)-enones in good yields as the only isolable products.

In the past decade we have been engaged in the chemistry of cerium(III) chloride[1] and, more recently, we have developed the combination of cerium(III) chloride heptahydrate and sodium iodide as a promoter that facilitates a variety of useful organic transformations. For example, the $CeCl_3 \cdot 7H_2O$/NaI system in acetonitrile is an efficient reagent for the cleavage of *p*-methoxybenzyl ethers in the presence of benzyl ethers[2] and for the deprotection of 1,3-dioxolanes[3] and trialkylsilyl ethers.[4] The nontoxic and water tolerant features,[5] the low cost and efficient activity in combination with sodium iodide, make $CeCl_3$ an attractive alternative to classical Lewis acids such as $TiCl_4$. Thus, recently, we have discovered that $CeCl_3$ is also an ideal Lewis acid for affecting one-pot conversion of a hydroxy group into an iodo group.[6]

The synthesis of conjugated unsaturated carbonyl compounds is of great importance since this functionality is one of the most alluring structural units for synthetic organic chemists.[7] This bifunctional moiety is present in a large number of molecules that are particularly important due to their widespread occurrence in biologically essential compounds.[8] Moreover, the α,*β*-enones are important as intermediates in many addition reactions of nucleophiles at the

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(1) (a) Bartoli, G.; Marcantoni, E.; Petrini, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1061−1062. (b) Bartoli, G.; Marcantoni, E.; Sambri, L.; Tamburini, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2046−2048. (c) Bartoli, G.; Marcantoni, E.; Petrini, M.; Sambri, L. *Chem. Eur. J.* **1996**, *2*, 913−918. (d) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem. Eur. J.* **1997**, *3*, 1941−1950. (e) Bartoli, G.; Bosco, M.; Cingolani, S.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1998**, *63*, 3624−3630. (f) Ballini, R.; Marcantoni, E.; Perrella, S. *J. Org. Chem.* **1999**, *64*, 2954−2956. (g) Alessandrini, S.; Bartoli, G.; Bellucci, M. C.; Dalpozzo, R.; Malavolta, M.; Marcantoni, E.; Sambri, L. *J. Org. Chem.* **1999**, *64*, 1986−1993.

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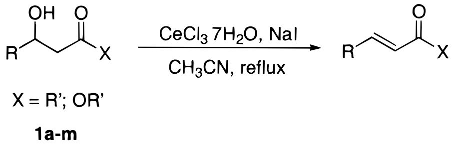
β-position due to the inductive polarization of a carbonyl group for organic synthesis.[9] Therefore, several methods for synthesis of these systems based on the formation of double carbon−carbon bonds have been reported, and among them the direct aldol condensation and related processes still occupy a prominent position.[10] However, many of these methods require harsh reaction conditions or expensive and toxic reagents or give poor yields and low selectivity. Thus, although several subsequent modifications and alternatives have alleviated many of these problems, there is still a need for the development of selective and better strategies for the dehydration of β-hydroxy carbonyl compounds.

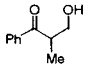
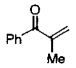
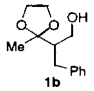
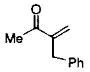
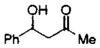
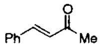
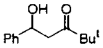
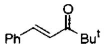
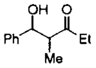
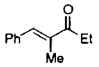
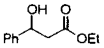
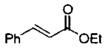
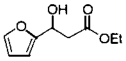
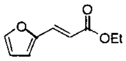
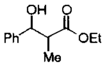
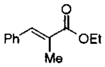
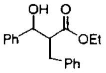
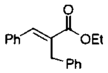
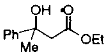
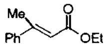
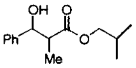
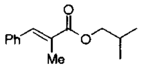
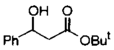
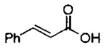
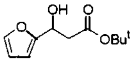
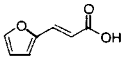
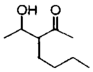
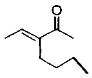
We report herein a new and efficient combination of reagents for the dehydration of β-hydroxy carbonyl compounds by the use of the $CeCl_3$·$7H_2O$/NaI system in acetonitrile (Scheme 1).

Scheme 1



The reaction proceeds with excellent yields at reflux to give α,β-enones of (*E*)-configuration as summarized in Table 1.[11] Recently, we observed that during the conversion of alcohols into the corresponding iodides by the $CeCl_3$·$7H_2O$/NaI system, a β-hydroxy carbonyl compound (**1a**) was transformed into the corresponding α,β-unsaturated derivative via dehydration.[12] Particularly interesting, this reaction of dehydration also occurred when the carbonyl moiety was protected as a 1,3-dioxolane (**1b**). Very probably the cleavage of acetal[3] is faster than hydroxyl substitution and the β-hydroxy ketone intermediate immediately gives the corresponding α,β-unsaturated ketone. Encouraged by these results, we prepared and investigated a number of other β-hydroxy carbonyl compounds to probe their behavior under the current dehydration conditions. As shown in Table 1, this simple methodology can be successfully applied to a variety of β-hydroxy ketones and β-hydroxy esters, and in particular, the relative increase in steric bulk of the carboalkoxy moiety does not hamper their conversions to the

Table 1. Dehydration of β-Hydroxy Carbonyl Compounds by $CeCl_3$·$7H_2O$/NaI System in Acetonitrile

Entry	Starting Material[a]	Time	Product[b]	Yield (%)[c]
1	 **1a**	9 h		89
2	 **1b**	4 h		86
3	 **1c**	10 h		89
4	 **1d**	10 h		96
5	 **1e**	10 h		88
6	 **1f**	16 h		86
7	 **1g**	16 h		89
8	 **1h**	16 h		91
9	 **1i**	16 h		90
10	 **1j**	48 h		83
11	 **1k**	16 h		91
12	 **1l**	10 h		90
13	 **1m**	10 h		86
14	 **1n**	14 h		81

[a] All starting materials were commercially available or were prepared by conventional methods. [b] All products were identified by their IR, NMR, and GC/MS spectra. [c] Yields of products isolated by column chromatography.

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(11) **Representative experimental procedure:** To a stirred suspension of 4-hydroxy-4-phenylbutan-2-one (**1c**; 82 mg, 0.5 mmol) and cerium(III) chloride heptahydrate (0.28 g, 0.75 mmol) in acetonitrile (5 mL) was added sodium iodide (0.11 g, 0.75 mmol), and the resulting mixture was stirred for 10 h at reflux. The reaction progress was monitored by withdrawing aliquots which were analyzed by GC, and the products were identified by GC-MS. The reaction mixture was diluted with ether and treated with 0.5 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic layers were washed twice with an aqueous saturated $NaHCO_3$ solution and a saturated NaCl solution and dried over anhydrous Na_2SO_4. The extracts were then concetrated under reduced pressure, and the residue was chromatographed on a silica gel column (eluent: hexanes−ethyl acetate, 8:2) to give 65 mg (89% yield) of the corresponding α,β-unsaturated enone as an oil.

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corresponding α,β-unsaturated esters (entry 11). On the other hand, we observed that if the carboalkoxy group is a *tert*-butyl ester, no selectivity is obtained and the *tert*-butyl ester is also removed (entries 12 and 13). It has been observed that in the case of a tertiary carbinol carbon (**1j**) a longer reaction time is necessary (entry 10). Table 1 indicates that a β-hydroxy carbonyl compound is also dehydrated in the presence of a furan ring (entries 7 and 13), and no ring opening reaction has been revealed. Moreover, in all cases examined, the recovered α,β-unsaturated carbonyl compounds are isolated with good yields, and the geometry of carbon−carbon double bond is obtained with high diastereoselection. In fact, our dehydration of the β-hydroxy compound affords the (*E*)-isomer as the unique form (determined by NMR analysis of the crude reaction mixture). It is well documented[13] that when the enone system is singly α- or β-substituted the *trans* coupling constant is larger than the *cis* coupling constant between the two olefinic hydrogens. In addition, the ranges of the *trans* and *cis* coupling constants are separate enough to allow unambiguous structural assignment even if only one isomer is available. When, instead, the olefin is trisubstituted, the configuration is assigned by NOE experiments. Consequently, the NMR chemical shifts provide a reliable guide for the assignment of the olefin configuration.

The mechanism of the reaction is not very clear. Undoubtely the presence of NaI is essential for the process; in fact the reaction carried out in its absence does not work. In addition, we have not detected traces of the β-iodo carbonyl compound by GC/MS analysis of the crude reaction mixture after acetonitrile reflux of the mixture of β-hydroxy ester **1f** and the $CeCl_3 \cdot 7H_2O$/NaI system.

In conclusion, we have developed an efficient procedure for the diastereoselective dehydration of β-hydroxy ketones and β-hydroxy esters to the corresponding α,β-unsaturated compounds. Our method shows that there are many advantages to the use of the cerium(III) chloride heptahydrate/sodium iodide system in acetonitrile: no strongly basic or acidic conditions are employed, no expensive reagents are required, and no precautions need to be taken to exclude moisture or oxygen from the reaction system. Additional studies to extend this methodology to other highly functionalized α,β-unsaturated systems are currently underway and will be reported in due course.

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