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$CeCl_3 \cdot 7H_2O$–NaI Catalyzed Hydrooxacyclization of Unsaturated 3-Hydroxy Esters

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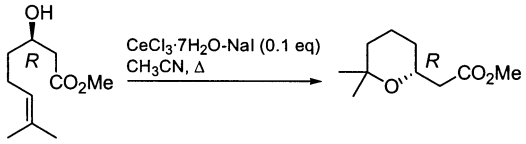
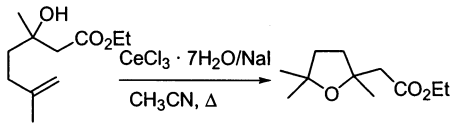
ABSTRACT



Cerium(III) chloride heptahydrate and sodium iodide in boiling acetonitrile promote cyclization of 3-hydroxyalkenoic acids esters giving 5-substituted tetrahydrofuranacetic acid esters and 6-substituted tetrahydropyranacetic acid esters in fair to good yield and with complete retention of the absolute configuration of the starting 3-hydroxy ester.

Cerium(III) chloride heptahydrate[1] has emerged as a very cheap, water-tolerant, and "friendly" reagent, able to promote a variety of selective functional group transformations.[2,3] It was found that the presence of sodium iodide reinforces its activity.[4] Our attention was drawn to the dehydration of β-hydroxy ketones and esters that selectively give the corresponding (*E*)-α,β-unsaturated derivatives.[5]

Herein, we report the results that originated from the attempts to apply this method to the dehydration of 3-hydroxyalkenoic acid esters.[6] When 3-hydroxy-3,6-dimethyl-6-heptenoic acid ethyl ester was subjected to the reported protocol—1.5 equiv of $CeCl_3 \cdot 7H_2O$ and 1.5 equiv of NaI in boiling acetonitrile—no doubly unsaturated ester was formed, instead (2,5,5-trimethyltetrahydrofuran-2-yl)acetic acid ethyl ester was isolated in 91% yield (eq 1).



(1)

Several different substrates and conditions were then studied. From the results reported in Table 1, it is rather interesting to note the following: (i) the use of only 10% equiv of $CeCl_3 \cdot 7H_2O$—NaI gave better results in terms of both yields and practicality; (ii) it is the more substituted

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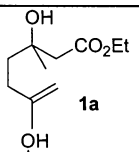
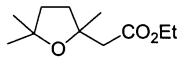
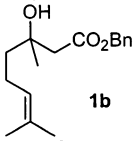
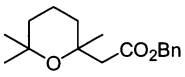
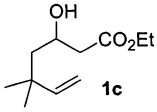
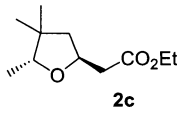
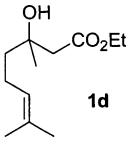
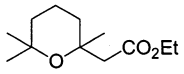
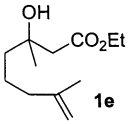
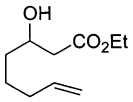
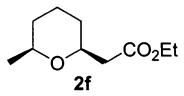
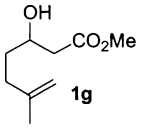
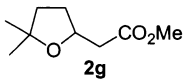
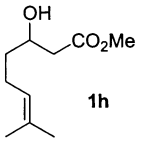
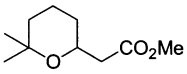
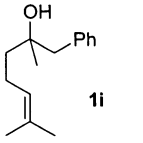
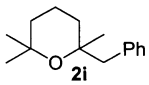
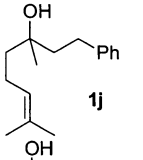
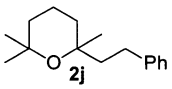
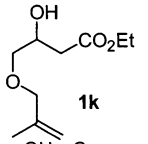
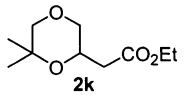
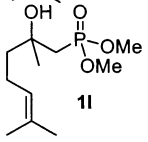
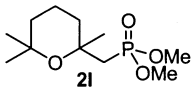
Table 1. Hydrooxacyclization of Unsaturated β-Hydroxy Derivatives by $CeCl_3 \cdot 7H_2O$−NaI in Boilng Acetonitrile

entry	3-hydroxy ester	product	equiv	time (h)	yield (%)
1	 **1a**	 **2a**	1.5 0.1	5 5	91 91
2	 **1b**	 **2b**	0.1	24	57
3	 **1c**	 **2c**	1.5 0.1	40 23	52 71
4	 **1d**	 **2d**	1.5 0.1	23 21	56 74
5	 **1e**	**2d**	0.1	24	68
6	 **1f**	 **2f**	1.5 0.1	26 48	-- 16
7	 **1g**	 **2g**	0.1	22	98
8	 **1h**	 **2h**	0.1	7	79
9	 **1i**	 **2i**	1.5 0.1	2.5 2.5	51 43
10	 **1j**	 **2j**	1.5	5.5	28
11	 **1k**	 **2k**	1.5 0.1	21 24	-- --
12	 **1l**	 **2l**	1.5 0.1	3.5 18.5	-- --

olefinic carbon atom to undergo cyclization; (iii) all the cyclization processes gave *favored* ring closures (5-*exo*-trig, 6-*exo*-trig, and 6-*endo*-trig) according to the Baldwin's rules;[7] (iv) **1c** and **1f** undergo a stereospecific cyclization and afford the corresponding products **2c** and **2f** as only one stereoisomer; and (v) the ester group seems to play an important role (entries 9 and 10). However, substrates such as **1k** and **1l** were recovered unchanged after treatment with $CeCl_3 \cdot 7H_2O$−NaI in boiling acetonitrile (entries 11 and 12).

Tetrahydrofurans and tetrahydropyrans[8] are found in many natural products of biological interest and the preparation of such important subunits is still a challenge for synthetic chemists in order to find safer and milder conditions utilizing more "friendly" reagents as well as to have good selectivity and efficiency. Therefore, several experiments with Ce(III) halides have been performed to gain more insights on the cyclization of these three-functionalized substrates. The main results are summarized in Table 2.

Table 2. Results Observed with a Variety of CeX_3 in Different Reaction Conditions


1d **2d**

entry	Ce(III) halide (0.1 equiv)	CH_3CN,[a] Δ	yield (%)
1	$CeCl_3 \cdot 7H_2O$−NaI		74
2	$CeCl_3$ + NaI	dried-dist.	24
3	$CeCl_3 \cdot 7H_2O$		trace[b]
4	$CeBr_3$		44
5	CeI_3	dried-dist.	22
6	CeI_3		62
7	CeI_3	dried-dist. + H_2O (0.7 equiv)	60

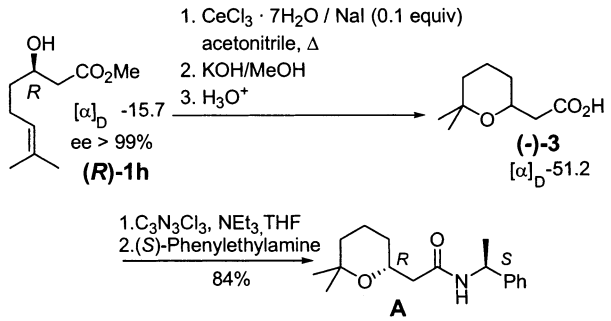
[a] Freshly opened bottle of ACS reagent-grade acetonitrile for 21 h used in N_2 atmosphere when not otherwise specified. [b] With recovery of **1d**.

They indicate the following: (i) both $CeCl_3 \cdot 7H_2O$ and NaI are necessary (entries 1 and 3); (ii) $CeCl_3 \cdot 7H_2O$ alone gave only a trace amount of the oxacyclic product with almost complete recovery of the starting material (entry 3); (iii) a dramatic drop in yield has been observed when anhydrous $CeCl_3$ and NaI were used in anhydrous boiling acetonitrile (entry 2); (iv) anhydrous CeI_3 is able to promote cyclization in the absence of NaI and is more efficient when used in boiling wet acetonitrile (entries 5, 6, and 7); and (iv) similarly, $CeBr_3$ induces cyclization in the same reaction conditions but is less effective when compared with CeI_3 (entry 4).

The $CeCl_3 \cdot 7H_2O$−NaI (10% equiv) cyclization of (*R*)-3-hydroxy-6-octenoate **1h**[9] in boiling acetonitrile gave, after ester hydrolysis, the carboxylic acid (−)-**3** (Scheme 1).

(7) Baldwin, J. E.; Kruse, L. I. *Chem. Commun.* **1977**, 233.
(8) For recent reviews, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1. (b) Koert, U. *Synthesis* **1995**, 115. (c) Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (d) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

Scheme 1. Asymmetric Synthesis of (*R*)-**1h** and (−)-**3**



This latter was converted into the corresponding enantiopure acetamide by reaction with (*S*)-phenylethylamine, in the presence of cyanuric chloride[10] and triethylamine. The absolute configuration of compound **A** was assigned by X-ray diffraction analysis[11] (Figure 1). Therefore, the $CeCl_3 \cdot 7H_2O$−NaI catalyzed cyclization occurs with *retention* of the absolute configuration of the starting 3-hydroxy esters.

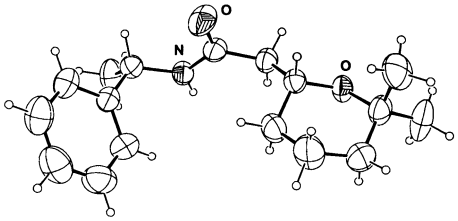


Figure 1. X-ray crystal structure of **A**.

Further studies are necessary to understand better the possible mechanism of this $CeCl_3 \cdot 7H_2O$−NaI catalyzed cyclization, and especially if the cerium plays an active role in this process. However, a simple Broensted acid (HI) catalyzed mechanism cannot explain all the observations we have made. In particular it is not clear why an acid-catalyzed mechanism should prevent substrates **1f** and **1j**−**l** from cyclizing; and the crucial role of water is not understood (Table 2, entries 5−7). The mechanism might involve an *oxyceriation* of the double bond.[12]

In conclusion, the results reported here show that this $CeCl_3 \cdot 7H_2O$−NaI catalyzed cyclization is of general applicability for 3-hydroxyalkenoic acid esters. This procedure makes use of an inexpensive catalyst under mild reaction conditions. Moreover, the ability to maintain the absolute configuration of the starting 3-hydroxyalkenoate and the easy availability of these substrates in enantiomerically pure form are two important aspects. Additionally, this cyclization can generate stereogenic centers with a high degree of control (Table 1, entries 2, 3, and 6).

It is also worth noting that the starting 3-hydroxy alkenoic acid esters could have undergone at least three different known reactions promoted by $CeCl_3 \cdot 7H_2O$−NaI and claimed as general the following: the conversion of the hydroxy group into the corresponding iodine derivative,[2e] the ester hydrolysis to a free carboxylic acid,[4] and more important, the 1,2-dehydratation of the 3-hydroxy ester to the α,β-unsaturated ester.[5] Instead, a new hydrooxacyclization took place affording tetrahydrofurans and pyrans, without the formation of any byproduct arising from the alternative known transformations.

These remarks call to mind the words of Professor R. B. Woodward "...One finds, for example, that there are no general reactions. And each case has to be studied, carefully, experimentally. That's the glory of chemistry—that it is an experimental science. And it will remain that for a long time to come."[13]

Acknowledgment. This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Programma di Ricerca "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni"), Italy, the Consiglio Nazionale delle Ricerche (CNR), Italy, and the Università di Bologna, Italy (Progetto d'Ateneo: Metodologie sintetiche a basso impatto ambientale).

Supporting Information Available: Descriptions of experimental procedures and selected characterization data, and X-ray crystal structures and data for compounds **A** and **B**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Hirama, M.; Shimizu, M.; Iwashita, M. *Chem. Commun*. **1983**, 599. (b) Hirama, M.; Shimizu, M.; Iwashita, M. J. 2.1.12; Bakers' yeast reduction of β-keto carboxylic acids salt. In *Preparative Biotransformations*; Roberts, S. M., Ed; University of Exeter: Exeter, UK; Wiley ISBN 0 471 929867.

(10) Baccolini, G.; Caglioti, L.; Poloni, M.; Rosini, G. La *Chim., l'Ind. (Milano)* **1969**, *51*, 287 (*Chem. Abstr*. **1970**, *72*, 3441s). For recent utilizations of this method, see: (a) Rayle, H. L.; Fellmeth, L. *Org. Proc. Res. Dev*. **1999**, *3*, 172. (b) Kaminski, Z. J.; Paneth, P.; Rudzinki, J. *J. Org. Chem*. **1998**, *63*, 4248.

(11) Crystal data for **A**: orthorombic system, space group P_{212121}, a = 9.4582(7) Å, b = 11.2046(9) Å, c = 15.389(1) Å, V = 1630.8(2) Å^3, Z = 4, ρ_{calc} = 1.122 Mg/m^3, R = 0.0559 (R_w = 0.1142) for 1813 observed reflections (170 parameters) with $I > 2\sigma I$. Goodness of fit = 0.975.

(12) A similar process of "oxyindiation" and referred to "an additive incorporation of an oxygen and indium across a double bond" has been proposed recently: Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc*. **2001**, *123*, 2450.

(13) Woodward, R. B. In *Proceedings of the Robert A. Welch Foundation Conference on Chemical Research, XII. Organic Synthesis*; Milligan, W. O., Ed.; Huston, TX, 1969; pp 3−6.