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Cerium(III) chloride mediated regioselective synthesis of cyclic α-chloro-α,β-enones and α-chloro-β-hydroxy ketones

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Abstract

Reaction of cyclic α,β-epoxy ketones with Ce(III) chloride under hydrous or anhydrous conditions yields the corresponding cyclic α-chloro-α,β-enones or cyclic α-chloro-β-hydroxy ketones, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

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α-Halo-α,β-unsaturated ketones are valuable and versatile synthetic building blocks, in particular for the generation of α-carbon substituted enones.[1] Traditionally, these compounds have been prepared via halogenation–dehydrohalogenation procedures[2] and addition–elimination sequences of selenium-based reagents to conjugated enones[3] or α-diazoketones.[4] In addition, cyclic α-chloro-α,β-unsaturated ketones can be synthesized via oxidative chlorination of the corresponding α,β-unsaturated derivatives,[5] addition of dichlorocarbene to cyclic enamines,[6] or replacing hydroxyl for chloride.[7] More recent methods involve the catalytic cleavage of α,β-epoxy ketones using yttrium salts[8] or silica gel supports.[9] Herein, we report a new and efficient regioselective synthesis of cyclic α-chloro-α,β-enones and α-chloro-β-hydroxy ketones from reaction of the corresponding α,β-epoxy ketones with cerium(III) chloride.

Commercially available α,β-unsaturated ketones were readily converted into their α,β-epoxy derivatives **1a–g** following the method reported by Yamazaki et al.[10] Treatment of compounds **1a–g** with one equivalent of cerium(III) chloride heptahydrate in a refluxing 3:1 mixture of MeOH:H_2O gave the corresponding α-chloro enones **2a–g** in moderate to good yields as the only isolable products (Table 1). While the reactions were inefficient at room temperature, complete conversions were achieved after 3–4 h at reflux temperature. Pure products were obtained after filtration (Celite) of the inorganic salts which precipitated during the reaction, followed by column chromatography on silica (CH_2Cl_2). The multiplicity (t) of the vinylic H-3 in the proton NMR spectra of compounds **2a**, **2c** and **2g** and the fact that the 3-methyl substituted chloroenones **2b**, **2d** and **2e** were obtained, proves the α-regioselectivity of

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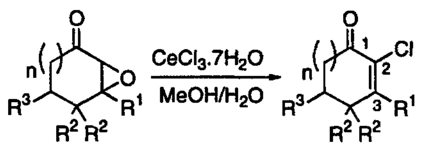
Table 1
Formation of cyclic α,β-chloro enones **2** from reaction of α,β-epoxy ketones **1** with cerium(III) chloride heptahydrate



1 **2**

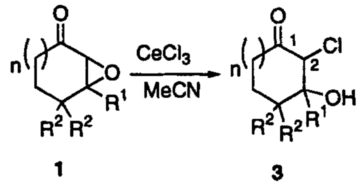
Entry	Epoxide	n	R^1	R^2	R^3	Product	Yield (%)[a]
1	**1a**	0	H	H	H	**2a**	73
2	**1b**	0	Me	H	H	**2b**	74
3	**1c**	1	H	H	H	**2c**	55
4	**1d**	1	Me	H	H	**2d**	88
5	**1e**	1	Me	H	Me	**2e**	50
6	**1f**	1	H	Me	H	**2f**	60
7	**1g**	2	H	H	H	**2g**	40

[a] Yields are based upon isolated products purified by column chromatography.

the reaction. All other spectroscopic data (MS, IR, ^{13}C) for compounds **2a–g** are in full agreement with the proposed structures.[3–9]

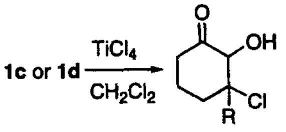
Analysis of the ^{1}H NMR spectra of the crude products obtained after 30 min showed a mixture of the corresponding α-chloro enones and halohydrins. We reasoned that the corresponding chlorohydrins should be accessible by changing from a polar protic to a polar aprotic solvent system (switch from E_1 to E_2 mechanism). Indeed, treatment of the epoxycyclohexanones **1c**, **1d** and **1f** with one equivalent of anhydrous cerium(III) chloride in dry acetonitrile gave the corresponding chlorohydrins **3c**, **3d** and **3f** as the only products (Table 2, entries 3–5). The expected *trans*-stereochemistry[11] of the epoxide cleavage was confirmed by the observed coupling constants of 9.6 and 10.6 Hz for the H-2 in the proton NMR spectra of halohydrins **3c**[12] and **3f**, respectively. In addition, the α-regioselectivity of the epoxide ring-opening was again confirmed through conversion of the chlorohydrins into their corresponding α-chloro enones and by comparison with the chlorohydrins obtained from reaction with $TiCl_4$[13] (clearly distinguishable by ^{1}H and ^{13}C NMR spectroscopy). When the epoxyketone **1c** was treated with titanium(IV) chloride in dichloromethane at −78°C, for example, the β-halohydrin **4c** was obtained exclusively in 55% yield, whereas compound **1d** gave a non-regioselective 1.5:1 mixture of the β-halohydrin **4d** and the α-chloro enone **2d** (Scheme 1). Conversion of compounds **3c**, **3d** and **3f** into their corresponding α-chloro derivatives **2c**, **2d** and **2f** was accomplished in essentially quantitative yields by refluxing in a mixture of aqueous hydrochloric acid (2 M) and methanol or cerium(III) chloride heptahydrate in $MeOH/H_2O$. Interestingly, epoxycyclopentanones **1a** and **1b**, when reacted under the same conditions ($CeCl_3/MeCN$), gave in the first case only the α-chloro enone **2a** and in the latter case a 3:1 mixture of the corresponding chlorohydrin **3b** and α-chloro enone **2b** (Table 2, entries 1 and 2). These results can be rationalized by the fact that the α-hydrogen and the β-hydroxy group can more easily adopt a *syn*-periplanar conformation (considering the *anti*-geometry of the epoxide ring opening)

Table 2
Formation of cyclic α-chloro-β-hydroxyketones 3 from reaction of α,β-epoxy ketones 1 with cerium(III) chloride



Entry	Epoxide	n	R^1	R^2	Product	Yield (%)
1	**1a**	0	H	H	**2a**	70
2	**1b**	0	Me	H	**3b** + **2b**	80
3	**1c**	1	H	H	**3c**	75
4	**1d**	1	Me	H	**3d**	84
5	**1f**	1	H	Me	**3f**	88

in the five-membered ring, thus facilitating the elimination-step. It is interesting to note that although epoxides with electron withdrawing groups react preferentially at the β-position[11a] (as observed in the Ti-catalyzed reaction), this new procedure yields exclusively α-substituted products despite Lewis acid activation.



4c: R = H
4d: R = Me

Scheme 1.

Further mechanistic and synthetic studies will be the subject of future reports.

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