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Tetrahedron Letters 44 (2003) 6691–6693

TETRAHEDRON
LETTERS

$CeCl_3/NaClO$: a safe and efficient reagent for the allylic chlorination of terminal olefins

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Received 13 June 2003; revised 16 June 2003; accepted 30 June 2003

Abstract—The preparation of allylic chlorides by reaction of terminal olefins with sodium hypochlorite in the presence of cerium trichloride heptahydrate is described. The scope, limitations and synthetic perspectives of the reaction are discussed.

Many natural products bear an isopropenyl group as a part of their structure.[1] Very often this isopropenyl group is the starting point to reach more complex atomic arrangements.[2]

A convenient way to functionalize an isopropenyl group is the allylic chlorination since further manipulation on the chloride may afford several functional groups.[3] Although this procedure can be performed directly by bubbling molecular chlorine through the reaction medium, this is always tedious due to the difficulty of handling chlorine gas. As an alternative, Li and co-workers, in the synthesis of eudesmane acids employed a combination of the Vilsmeier reagent and H_2O_2 but the presence of $POCl_3$ exclude the use of acid-sensitive substrates.[4]

In 1980, Wolinsky and co-workers, reported the preparation of allylic chlorides through a combination of solid CO_2 and calcium hypochlorite. This procedure was effective for the preparation of allylic chlorides in some highly hindered olefins.[5]

In the course of our research programme aimed at the synthesis of natural sesquiterpenoids, we have had to carry out this transformation. We have discovered a more straightforward way to accomplish this reaction by means of a combination of sodium hypochlorite and cerium trichloride heptahydrate. The generation of chlorine has been previously reported using sodium hypochlorite and acetic acid,[6] but the presence of the acetic acid limits the reaction to non-sensitive substrates.

The replacement of acetic acid (a Brønsted acid) by cerium trichloride (a Lewis acid) provides a milder environment in which reaction takes place smoothly in a two-phase system (dichloromethane/water) under vigorous stirring to ensure the homogeneus distribution of the in situ generated electrophilic chlorine.

We first checked the reaction on dihydrocarvone **1** in order to optimize the reaction conditions. The results are summarized in Table 1.

The optimum solvent was found to be a biphasic system of dichloromethane and water (entries 6–10). From entries 1 and 12 can be deduced that the presence of cerium trichloride is needed for the reaction to proceed. The stoichiometry of the reaction is also a key point. Loads of three equivalents of cerium trichloride and sodium hypochlorite provide quantitative yields in case of this particular substrate, although in simpler substrates, the reaction proceeds better with two equivalent of each reagent (vide infra).

In order to assess the scope and limitations of this reaction, different substrates were studied (Table 2).

Entries 1–4 show, respectively, the almost quantitative conversion of dihydrocarvone (entry 1), 7-*epi*-cyperone (entry 2), 6β-hydroxy-7-*epi*-cyperone (entry 3), and 6-oxo-7-*epi*-cyperone into their chlorinated derivatives. This reaction also works well with carvone and other related substrates. As a blank test, we ran the reactions

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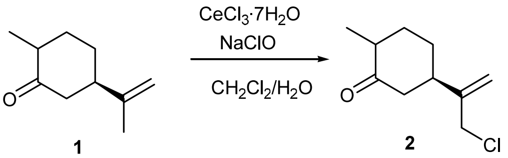
doi:10.1016/S0040-4039(03)01630-7

Table 1. Allylic chlorination of dihydrocarvone **1**

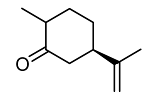
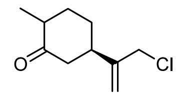
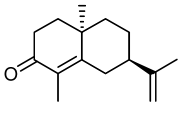
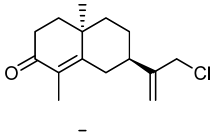
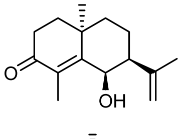
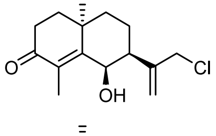
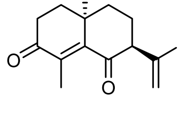
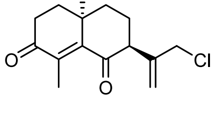
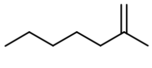
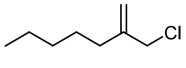
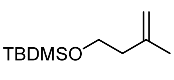
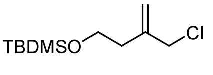
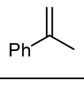
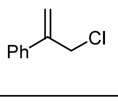
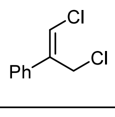


(1)

Entry	Equivalents of $CeCl_3$	Equivalents of NaClO	Solvent	**2** yield (%)	Recovered **1** (%)
1	0	3	$^{i}PrOH/H_2O$	0	100
2	1	1	$^{i}PrOH/H_2O$	9	54
3	3	3	$^{i}PrOH/H_2O$	27	33
4	5	5	$^{i}PrOH/H_2O$	Complex mixture	
5	2	2	CH_2Cl_2	46	47
6	1.1	1.1	CH_2Cl_2/H_2O	29	66
7	1.1	2	CH_2Cl_2/H_2O	44	53
8	1.1	3	CH_2Cl_2/H_2O	69	18
9	2	2	CH_2Cl_2/H_2O	60	31
10	3	3	CH_2Cl_2/H_2O	98	0
11	0.3	5	CH_2Cl_2/H_2O	25	55
12	0	3	CH_2Cl_2/H_2O	0	100

with these four substrates by bubbling chlorine gas through the solution. The reaction took place sluggishly.

Table 2. Allylic chlorination with $CeCl_3 \cdot 7H_2O$ and NaClO

Entry	Substrate	Products	Yield[a]
1			98
2			97
3			96
4			96
5			92
6			95
7		 	60:12

[a]Entries 1-4: 3 equiv. of $CeCl_3 \cdot 7H_2O$ and 3 equiv. of NaClO. Entries 5-7: 2 equiv. of $CeCl_3 \cdot 7H_2O$ and 2 equiv. of NaClO.

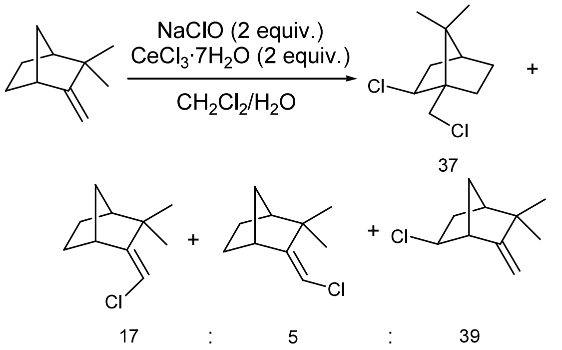
Simple alkenes show very high conversion, as in 2-methylprop-1-ene (entry 5), in which the reaction takes place very cleanly. The presence of hydroxyl groups is tolerated (entry 3) as long as the hydroxyl group is not allowed to interfere with the incipient carbocation. When this is the case, a simple protection with TBDMSCl is enough to avoid this problem (entry 6).[7]

Entry 7 shows the case in which the intermediate carbocation is stabilized by a phenyl group. In this case, along with the allylic chloride, a second addition of chlorine is observed. This fact is also detected in other substrates when more than three equivalents of $CeCl_3$/NaClO are added.

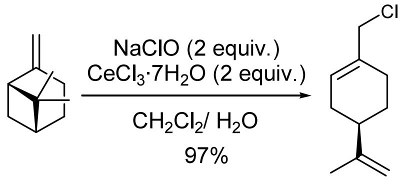
As previously pointed out, it is noteworthy to mention that no reaction takes place in the absence of cerium trichloride. The procedure is therefore based on the mild generation of electrophilic chlorine. Chlorination of the corresponding alkene and loss of a proton of the cationic intermediate leads to formation of the chlorinated products. In order to shed some light on the mechanism of this reaction, we ran an experiment using camphene. This substrate is very prone to undergo rearrangements and the same products described when the camphene is treated with molecular chlorine were obtained (Scheme 1).[8]

Camphene provides a complex mixture of products due to the different possibilities of rearrangement and carbocation trapping by the nucleophile. But when this possibility is constrained, the reaction can be synthetically useful as is the case of β-pinene in which a single product is obtained in high yield (Scheme 2).

Different sources of cerium were checked to evaluate the importance of the anion in this process, replacing in Eq. (1), the $CeCl_3$ by different cerium salts (Table 3).



Scheme 1.



Scheme 2.

Table 3. Role of the cerium counterion (2 equiv. of metal source)

Entry	Metal source	**2** yield (%)	Recovered **1** (%)
1	$Ce(NO_3)_3$	47	42
2	$Ce(SO_4)_2$	80	0
3	CeO_2	0	100

$Ce(NO_3)_3$ provides modest results, in part due to the absence of the Cl^- ions. Ce(IV) is observed to be also effective when $Ce(SO_4)_2$ is used. CeO_2 fails due to its low solubility.

We also wanted to know whether sodium hypochlorite was the only source of chlorine or $CeCl_3$ also contributed to its supply. We thus checked different oxidants instead of NaClO, some of them lacking chlorine atoms. The reaction of dihydrocarvone **1** with the organic peroxyacids MCPBA and MMPP (2 equiv. of $CeCl_3·7H_2O$, 2 equiv. of oxidant) as oxidant under similar conditions took place, although in low yields (20 and 11%, respectively). Consequently, the reaction is possible in the absence of sodium hypochlorite. The chlorine present in $CeCl_3$ may play some role in the process, although the major part seems to come from the sodium hypochlorite. $NaClO_2$ also provided the allylic chloride in low yield (22%).

In summary, the main advantages of this method lie in its technical simplicity, safety and high yields. The use of protic acids is avoided, being replaced by cerium trichloride, which effectively promotes the formation of electrophilic chlorine. Some other metallic salts have been checked and interesting results have been obtained with some transition metal chlorides. Investigation on these results is being conducted at present and will be reported in due course.

General procedure

1 mmol of the alkene is dissolved in CH_2Cl_2:H_2O (1:1, 10 mL) and $CeCl_3·7H_2O$ is added (2 equiv.). The mixture is vigorously stirred and diluted NaClO (10–13% available chlorine, 2 equiv.) is added dropwise for 5 min. After 30 min, saturated aqueous Na_2SO_3 is added and the mixture is extracted with CH_2Cl_2 (3×20 mL). The organic layer is dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded the corresponding chloride.

Acknowledgements

We wish to thank the Spanish Ministerio de Ciencia y Tecnología (grant BQU2001-3076) and Junta de Andalucía (PAI-2000) for the financial support. F.L.M is grateful to the Junta de Andalucía for a fellowship. We are also grateful to Professor M. J. Tenorio for his helpful comments.

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6. For a recent example, see: VanBrunt, M. P.; Ambenge, R. O.; Weinreb, S. M. *J. Org. Chem.* **2003**, *68*, 3323.
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