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Tetrahedron 62 (2006) 7466–7470
Tetrahedron

# $CeCl_3 \cdot 7H_2O$–NaI catalyzed intramolecular addition reactions of 7-hydroxy-1,3-dienes: a facile approach to hexahydrobenzofurans and tetrahydrofurans

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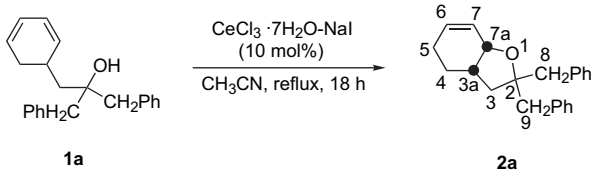
Received 29 March 2006; accepted 8 May 2006
Available online 5 June 2006

**Abstract**—$CeCl_3 \cdot 7H_2O$–NaI effectively catalyzed intramolecular cyclization of cyclic 7-hydroxy-1,3-dienes, yielding hexahydrobenzofurans in diastereoselective fashion. This cyclization has been applied to synthesize tetrahydrofurans from acyclic 7-hydroxy-1,3-dienes.


## 1. Introduction

Condensed heterocycles are widespread in nature, and many of these compounds show interesting biological activities.[1] The benzo[*b*]furan[2] and tetrahydrofuran rings[3,4] are often incorporated in pharmaceutical agents as a core structural motif.[5] Due to the high stereo- and regiochemical control, transition metals such as palladium,[6] molybdenum,[7] and indium[8] have been used to promote the furan-ring formation across unsaturated carbon–carbon bonds and a tethered hydroxyl group. However, many of these catalysts suffer from some drawbacks, which include use of expensive reagents under dry conditions. Therefore, the preparation of benzo[*b*]furan and tetrahydrofuran skeletons is still a challenge for synthetic chemists in order to find safer and milder conditions utilizing more 'friendly' reagents. Recently, cerium(III) chloride has emerged as a very cheap, water-tolerant, and safe reagent and is able to catalyze various selective chemical transformations and cyclizations.[9] In most cases, the activity of $CeCl_3$ can be increased in combination with NaI.[10] The cyclization of unsaturated 3-hydroxy esters to tetrahydrofuranacetic acid esters and tetrahydropyranacetic acid esters catalyzed by $CeCl_3 \cdot 7H_2O$–NaI has been previously reported.[9a] We now report that $CeCl_3 \cdot 7H_2O$–NaI (10 mol %) catalyzes (Scheme 1) intramolecular cyclization of 7-hydroxy-1,3-dienes under mild reaction conditions to afford hexahydrobenzofurans and tetrahydrofurans.




**1a** **2a**

**Scheme 1**.

## 2. Results and discussion

The starting material of 7-hydroxy-1,3-dienes **1a–i** (entries 1–9, Table 1) was prepared by addition of 2.5 equiv of Grignard reagents to the corresponding ester-functionalized 1,3-dienes according to the literature procedures.[11] The primary alcohol **1j** (entry 10, Table 1) was synthesized by addition of $LiAlH_4$ to the corresponding ester at 0 °C in diethyl ether. Secondary alcohol **1k** (entry 11, Table 1) was obtained from addition of $BrZnCH_2CO_2Et$/CuCN to the corresponding aldehyde at −78 °C in THF.[11c]

Our $CeCl_3 \cdot 7H_2O$–NaI catalyzed cyclization study was first carried out by using alcohol **1a**. Treatment of **1a** with 10 mol % equiv of $CeCl_3 \cdot 7H_2O$–NaI in boiling acetonitrile under nitrogen for 18 h afforded, after flash column chromatography, a 58% yield of 2,2-dibenzylhexabenzofuran derivative **2a** as the major product (Scheme 1). The structure for **2a** was established by comparing its $^1H$ and $^{13}C$ NMR spectral data with those of related compounds known in the literature.[12] Moreover, the relative stereochemistry of the ring juncture of **2a** was determined as cis on the basis of comparing the coupling constant (4.4 Hz) for hydrogen atoms at C(**3a**) and C(**7a**) to those of related compounds.[12] In order to gain more insights on the intramolecular cyclization of alcohol **1a**, anhydrous $CeCl_3$ (0.1 equiv) and NaI (0.1 equiv) were used. Thus, reaction of **1a** with $CeCl_3$ and NaI in boiling acetonitrile for 18 h produced **2a** in 51% yield. Therefore, water is not needed for the cyclization. However,

*Keywords*: Cerium chloride; 7-Hydroxy-1,3-diene; Hydroalkoxylation.
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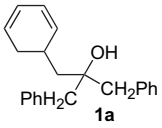
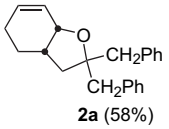
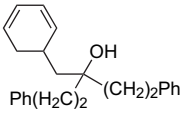
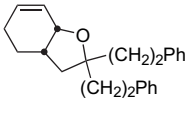
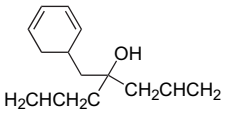
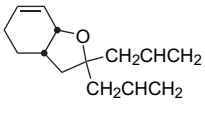
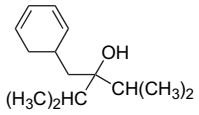
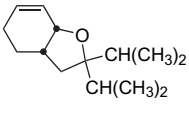
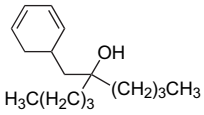
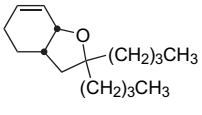
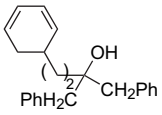
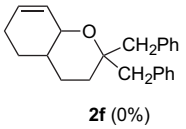
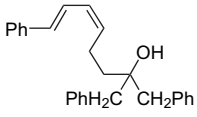
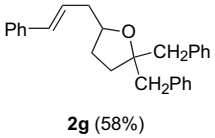
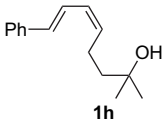
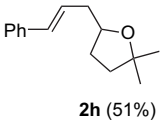
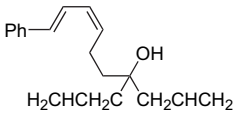
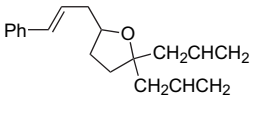
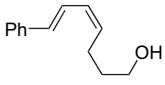
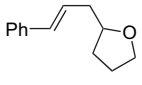
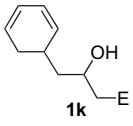
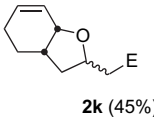
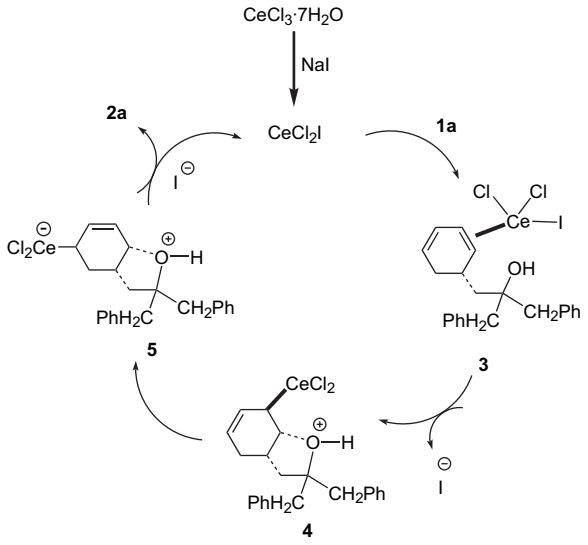
doi:10.1016/j.tet.2006.05.026

**Table 1**. Intramolecular addition reactions of 7-hydroxy-1,3-dienes via Scheme 1[a]

| Entry | 7-Hydroxy-1,3-dienes | Products (yield[b]) |
|---|---|---|
| 1 |  **1a** |  **2a** (58%) |
| 2 |  **1b** |  **2b** (48%) |
| 3 |  **1c** |  **2c** (56%) |
| 4 |  **1d** |  **2d** (22%) |
| 5 |  **1e** |  **2e** (12%) |
| 6 |  **1f** |  **2f** (0%) |
| 7 |  **1g** |  **2g** (58%) |
| 8 |  **1h** |  **2h** (51%) |
| 9 |  **1i** |  **2i** (48%) |
| 10 |  **1j** |  **2j** (70%) |
| 11 |  **1k** |  **2k** (45%) |

[a] All intramolecular addition reactions were performed in refluxing $CH_3CN$ using 10 mol % of $CeCl_3\cdot 7H_2O$–NaI as the catalyst.
[b] Isolated yields after silica-gel column chromatography.

reaction of **1a** with $CeCl_3\cdot 7H_2O$ alone failed to produce **2a** and alcohol **1a** was recovered almost quantitatively. This is consistent with the failure of cyclization of unsaturated 3-hydroxy esters using $CeCl_3\cdot 7H_2O$ as the sole catalyst reported in the literature.[9a] Based upon the above results, it is reasonable to state that both $CeCl_3$ and NaI are required in the catalytic process. Our proposed reaction mechanism for the $CeCl_3\cdot 7H_2O$–NaI-mediated hydroalkoxylation is shown in Scheme 2. Reaction of $CeCl_3$ with NaI would give $CeCl_2I$. The catalyst $CeCl_2I$ coordinated on the β-face of the proximal double bond of **1a** to give **3**, which was then attacked by the oxygen-nucleophile on the opposite face. This afforded the postulated $\eta^1$-allylic intermediate **4** with the newly formed carbon–oxygen bond positioned trans to the cerium–carbon bond. Due to the steric congestion caused by the cerium fragment adjacent to the bicyclic ring juncture, intermediate **4** may undergo $\eta^1$–$\eta^3$–$\eta^1$ allylic rearrangement to the $\eta^1$-allylic intermediate **5**. Subsequent protonation of **5** resulted in formation of the 1,4-hydroalkoxylation product **2a** and regeneration of the $CeCl_2I$ catalyst. The addition of an oxygen and a metal across a double bond was found for indium,[8a] palladium,[6b] and cerium[9a] in the literature.




**Scheme 2**.

Under the same reaction conditions, intramolecular addition reactions of tertiary alcohols **1b–e** using 10 mol % equiv of $CeCl_3\cdot 7H_2O$–NaI in boiling acetonitrile gave hexahydrobenzofurans **2b–e** as single diastereomer in each case (entries 2–5, Table 1). In general, yields of hexahydrobenzofurans are fair (ca. 50%). The fair yields might be due to the fact that $CeCl_3\cdot 7H_2O$–NaI is an efficient reagent for the conversion of tertiary alcohols into alkyl iodides. Moreover, the problem of the competing elimination found in tertiary alcohols reduced the yield of cyclization.[9d] It is important to mention that unlike successful formation of tetrahydrofuran ring, six-membered ring of tetrahydropyran cannot be formed. Thus, intramolecular addition reaction of a substrate with one more methylene unit on the tethered failed and 8-hydroxy-1,3-diene **1f** (entry 6, Table 1) was recovered quantitatively even after refluxing in acetonitrile for 24 h. The failure in the formation of tetrahydropyranyl rings might be attributed to unfavorable formation of the *cis*-decalin intermediate **6**, which contained the bulky cerium fragment adjacent to the bicyclic ring juncture (Chart 1). It is important to mention that cyclization of 3-hydroxy esters