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# Stereoselective synthesis of 6-oxabicyclo[3.2.1]octene via (3,5)-oxonium-ene reaction

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ABSTRACT

Oxabicyclo[3.2.1]octene can efficiently be synthesized by the reaction of (−)-terpinen-4-ol and aldehyde or epoxide catalyzed by indium triflate (In(OTf)$_3$) in good yields. The reaction is stereoselective and proceeds via (3,5)-oxonium-ene-type reaction.

## 1. Introduction

Oxonium-ene reactions are important in organic synthesis due to its ability to construct various cyclic ethers.[1] Recently, several cyclic ethers, such as tetrahydrofurans, tetrahydropyrans and oxabicyclic compounds have been synthesized using this protocol.[2] Several oxabicyclic compounds exhibit biological activity. Oxabicyclo[3.3.1]nonene and its derivatives are known to behave as oestrogen receptor ligands.[3] We have synthesized oxabicyclo[3.3.1]nonanone and -nonene using (3,5)-oxonium-ene cyclization reaction starting from readily available naturally occurring terpenoids *trans-p*-menth-6-ene-2,8-diol and geraniol, respectively.[2d,e] The chemistry of 8-oxabicyclo[3.2.1]octane and -octene (Fig. 1, A) is extensively studied[4] and are found to be a basic unit of many natural products.[5] But the chemistry of 6-oxabicyclo[3.2.1]octane and -octene (Fig. 1, B) is still in its initial stage. A few methodologies for the synthesis of 6-oxabicyclo[3.2.1]octane and -octene have been reported in the literature.[6] Recently, Xu and co-workers have reported the presence of 6-oxabicyclo[3.2.1]octane moiety in natural products.[7] Naturally occurring terpenoids are precursors of biologically active compounds[8] and intermediates in asymmetric synthesis.[9] The (−)-terpinen-4-ol is found to be a main constituent of *Melaleuca alternifolia* (Tea Tree) oil, which possess antimicrobial and other medicinal properties.[10] This is also used for the synthesis of some stereoisomers of *p*-menthane-1,2,4-triol.[11] Herein, we wish to disclose a methodology for the synthesis of 6-oxabicyclo[3.2.1]octene via (3,5)-oxonium-ene reaction from the reaction of aldehydes or epoxides with commercially available (−)-terpinen-4-ol catalyzed by indium triflate.

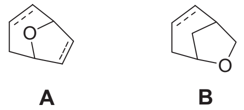

**Fig. 1.** Different types of oxabicyclo[3.2.1]octane/octene.

## 2. Results and discussion

Initially (−)-terpinen-4-ol (1 equiv), **1** was reacted with benzaldehyde (1 equiv), **2a** in dry toluene under boron trifluoride etherate (1 equiv) at 0 °C and the desired cyclization product **3a** was obtained in 32% yield along with some decomposed products. Further lowering the temperature to −30 °C resulted in the same yield. The reaction was also performed in the presence of other Lewis acids and the results are summarised in Table 1. These results showed that indium triflate (In(OTf)$_3$) was the efficient Lewis acid, which acted as a catalyst for this transformation. No reaction was observed when scandium triflate or indium trichloride was used. Among the solvents studied, dichloromethane was found to be the best solvent, whereas acetonitrile was found to be ineffective.

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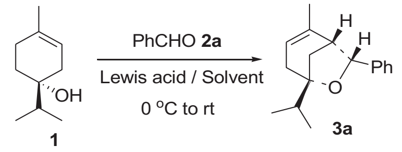
**Table 1**
Reaction with different Lewis acids and solvents

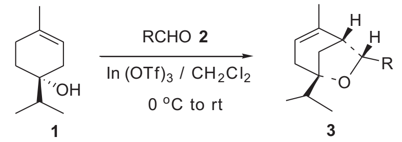


| Entry | Lewis acid (equiv) | Time/h | Solvent | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $BF_3 \cdot Et_2O$ (1) | 0.5 | $CH_2Cl_2$ | 32 |
| 2 | Sc $(OTf)_3$ (0.1) | 24 | $CH_2Cl_2$ | 0 |
| 3 | In $(OTf)_3$ (0.1) | 24 | Toluene | 45 |
| 4 | In $(OTf)_3$ (0.1) | 6 | $CH_2Cl_2$ | 75 |
| 5 | In $(OTf)_3$ (0.1) | 24 | $CH_3CN$ | 0 |
| 6 | In $(OTf)_3$ (0.05) | 24 | $CH_2Cl_2$ | 40 |
| 7 | Bi $(OTf)_3$ (0.1) | 24 | $CH_2Cl_2$ | 52 |
| 8 | Bi $(OTf)_3$ (0.1) | 24 | Toluene | 38 |
| 9 | $InCl_3$ (0.1) | 24 | $CH_2Cl_2$ | 0 |
| 10 | $InCl_3$ (0.2) | 24 | $CH_2Cl_2$ | 0 |

[a] Yields refer to isolated yield. The compound is characterized by IR, $^1H$, $^{13}C$ NMR and Mass spectroscopy.

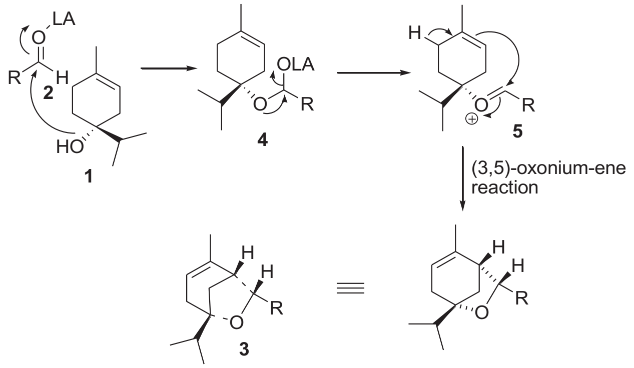
Therefore, In$(OTf)_3$ in dry $CH_2Cl_2$ was considered as the best combination for this reaction and the scope of the reaction was investigated using various aldehydes (Table 2). In all of the cases studied, 6-oxabicyclo[3.2.1]octenes **3a**–**p** could be obtained in high purity without any side products as determined from $^1H$ to $^{13}C$ NMR spectrum of the crude product. Both aliphatic and aromatic aldehydes gave the corresponding products in good yields. The substituents on the aromatic ring have a promising effect on this reaction. The aromatic aldehydes having electron-donating groups on the aromatic ring gave higher yields compared to the electron-withdrawing groups on the ring. On the other hand, aliphatic aldehydes are better substrates than the aromatic aldehydes. This might be due to the better stability imparted to the oxocarbenium ion **5** (Scheme 1) by the aliphatic, and aromatic aldehydes having electron-donating groups on the aromatic ring, which in turn is attacked by the double bond efficiently. On the other hand, aromatic aldehydes having electron-withdrawing groups on the ring destabilize the oxocarbenium ion **5**. The reaction is stereoselective, and in all the cases the fusion between two rings is cis-fusion. The structure and stereochemistry of the compound was determined by NOE experiment and X-ray crystallographic analysis (Fig. 2).[12] There is a strong NOE between $H_1$ and $H_7$ protons of **3l**, which confirms that they are cis to each other (**3l**, Fig. 3). This structure is further confirmed by the fact that the olefinic methyl protons at C-2 position are resonating at higher field in the case of *endo* aromatic substituents at C-7 position than the corresponding aliphatic substituents. This indicates that the methyl protons are in the shielding region of the aromatic ring.

**Table 2**
Synthesis of 6-oxabicyclo[3.2.1]octene



| Entry | RCHO **2** | Time (h) | Product **3** | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5CHO$ **2a** | 6 | **3a** | 75 |
| 2 | *p*-Me–$C_6H_4CHO$ **2b** | 5 | **3b** | 82 |
| 3 | *p*-MeO–$C_6H_4CHO$ **2c** | 6 | **3c** | 80 |
| 4 | *p*-Cl–$C_6H_4CHO$ **2d** | 7 | **3d** | 68 |
| 5 | *p*-Br–$C_6H_4CHO$ **2e** | 7 | **3e** | 65 |
| 6 | *m*-Br–$C_6H_4CHO$ **2f** | 8 | **3f** | 64 |
| 7 | *p*-F–$C_6H_4CHO$ **2g** | 6 | **3g** | 66 |
| 8 | *p*-$MeO_2C$–$C_6H_4CHO$ **2h** | 7 | **3h** | 60 |
| 9 | *p*-$NO_2$–$C_6H_4CHO$ **2i** | 7 | **3i** | 62 |
| 10 | *o*-$NO_2$–$C_6H_4CHO$ **2j** | 7 | **3j** | 64 |
| 11 | $CH_3CH_2CHO$ **2k** | 5 | **3k** | 94 |
| 12 | $CH_3(CH_2)_2CHO$ **2l** | 5 | **3l** | 92 |
| 13 | $(CH_3)_2CHCH_2$ CHO **2m** | 4 | **3m** | 88 |
| 14 | $CH_3(CH_2)_5CHO$ **2n** | 5 | **3n** | 85 |
| 15 | *cyclo*-$C_6H_{11}CHO$ **2o** | 7 | **3o** | 84 |
| 16 | $C_6H_5CH_2CHO$ **2p** | 7 | **3p** | 82 |

[a] Yields refer to isolated yield. The compounds are characterized by IR, $^1H$, $^{13}C$, $^{19}F$ NMR and Mass spectroscopy.



**Scheme 1.** Mechanism of the reaction.

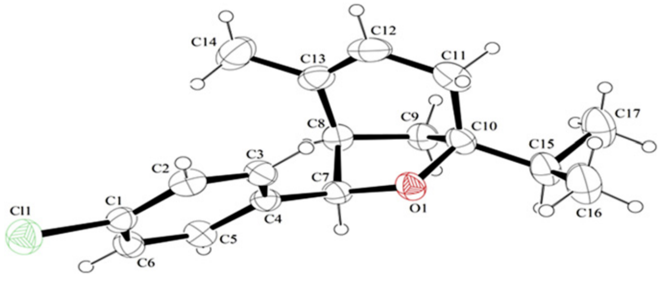


**Fig. 2.** ORTEP diagram of (1*R*,5*R*,7*R*)-7-(4-chlorophenyl)-5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene (**3d**).

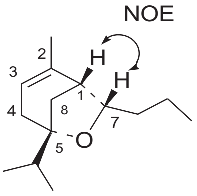


**Fig. 3.** NOE diagram of compound **3l**.

The mechanism of the reaction can be explained as follows. Lewis acid activates the aldehyde **2** for the nucleophilic attack by alcohol **1** to give acetal **4**, which after decomposition forms oxocarbenium ion **5**. The oxocarbenium ion **5** undergoes (3,5)-oxonium-ene cyclization reaction to give final product **3** (Scheme 1).

The reaction can also be extended to epoxides (Table 3). The epoxides under Lewis acid conditions rearrange to aldehyde equivalent.[13] The results in Table 3 showed that monosubstituted terminal epoxides (entry 1) are unreactive, whereas the 2,2-disubstituted and styrene oxides give the corresponding products in good to moderate yields. This is attributed to the lower stability of the carbocation **7**, formed from monosubstituted epoxides, compared to 2,2-disubstituted epoxides and styrene oxides, where carbocation **7** is better stabilized due to the tertiary and benzylic centres, respectively.