$CeCl_3 \cdot 7H_2O/LiI$: A Novel Reagent System for the Synthesis of 4-Iodotetrahydropyrans via Prins Cyclization

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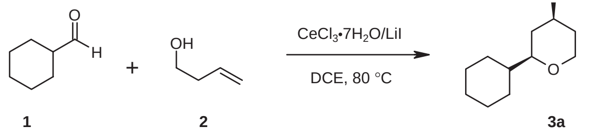
Homoallylic alcohols undergo smooth coupling with a variety of aldehydes in the presence of $CeCl_3 \cdot 7H_2O$–LiI reagent system in refluxing dichloroethane under neutral conditions to produce the corresponding 4-iodotetrahydropyran derivatives in high yields. The spirocyclic-4-iodotetrahydropyrans are obtained in case of cyclic ketones.

The Prins cyclization is a powerful synthetic route for the construction of six-membered tetrahydropyran derivatives.[1] The tetrahydropyran ring system is a core unit in a number of natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, and acutiphycins.[2] Tetrahydropyran derivatives are generally prepared through the Prins cyclization using acid catalysis.[3,4] Recently, indium halides are found to be useful for this transformation.[5] However, many of these classical methods often involve the use of expensive reagents, extended reaction times, strong acidic conditions, and also produce a mixture of products.[3] Therefore, the development of simple, convenient, and efficient protocol using inexpensive and readily available cerium reagents would extend the scope of the Prins cyclization in natural products synthesis.[6] Furthermore, the development of cost-effective and environmentally benign catalytic systems is one of the main themes of contemporary organic synthesis. In this context, lanthanide salts are unique Lewis acids[7] that are currently of great research interest. In particular, cerium reagents are relatively non-toxic, readily available at low cost and are fairly stable to water. Owing to its unique properties, $CeCl_3$ has been extensively used for a variety of organic transformations.[8]

In continuation of our interest on the use of cerium(III) reagents for various organic transformations,[9] we herein report an efficient Prins cyclization for the synthesis of highly substituted tetrahydropyrans from homoallylic alcohols and aldehydes using $CeCl_3 \cdot 7H_2O$–LiI reagent system under neutral conditions. Accordingly, treatment of cyclohexanecarboxaldehyde with 3-buten-1-ol in the presence of cerium(III) chloride heptahydrate–lithium iodide in dichloroethane at 80 °C gave the corresponding 2-cyclohexyl-4-iodotetrahydropyran (**3a**) in 91% yield with cis selectivity (Scheme 1).

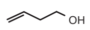
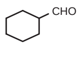
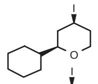
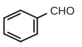
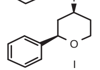
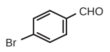
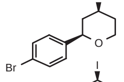
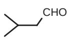
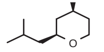
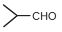
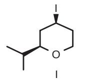
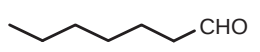
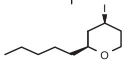
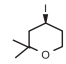
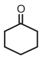
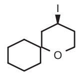
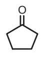
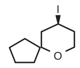
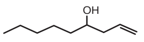
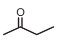
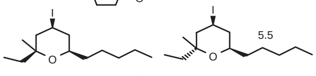
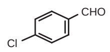
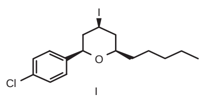
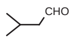
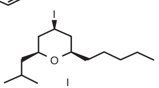
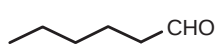
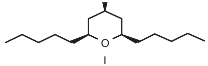
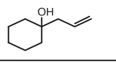
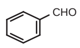
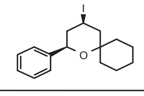
The reaction proceeded smoothly by $CeCl_3 \cdot 7H_2O$–LiI in refluxing dichloroethane under neutral conditions. The combination of cerium(III) chloride with LiI works efficiently to afford the corresponding 4-iodotetrahydropyran derivatives in excellent yields (Entries **A**–**N**, Table 1). Interestingly, various carbonyl compounds such as benzaldehyde, *p*-bromobenzaldehyde, isovaleraldehyde, isobutyraldehyde, *n*-hexanal, acetone, cyclohexanone, and cyclopentanone reacted well with 3-buten-1-ol to produce the corresponding iodopyrans in high yields (**A**–**I**, Table 1). In case of ketones, the reactions required long reaction times to furnish spirocyclic-4-iodotetrahydropyrans (Entries **G**–**J**, Table 1, Scheme 2).

Substituted homoallylic alcohols such as 1-nonen-4-ol, and

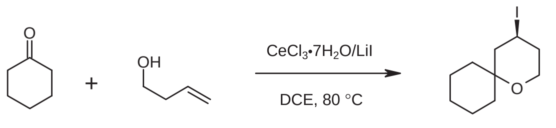


Scheme 1.

Table 1. $CeCl_3 \cdot 7H_2O$/LiI-promoted synthesis of 4-iodotetrahydropyran derivatives

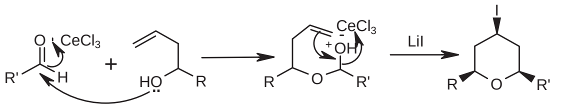
Entry	Homoallylalcohol	Aldehyde	Iodopyran[a]	Time/h	Yeild/%
A				4.0	91
B	"			4.5	90
C	"			4.5	88
D	"			4.0	92
E	"			4.5	89
F	"			4.5	90
G	"			5.5	85
H	"			5.0	90
I	"			5.5	87
J				5.5	90[c]
K	"			4.5	91
L	"			4.0	90
M	"			4.5	92
N				4.5	85

[a] All products were characterized by ^{1}H NMR, IR, and mass spectrometry. [b] isolated and unoptimized yield. [c] Cis/trans ratio 2:1.



1 2 3

Scheme 2.



Scheme 3.

1-allyl-1-cyclohexanol also coupled smoothly with aldehydes to give the respective 4-iodopyrans. In the absence of LiI, 4-chlorotetrahydropyrans were obtained in good yield. Interestingly, no chlorinated byproducts were observed in the presence of LiI. Therefore, addition of 1.5 equiv. of LiI is crucial to obtain 4-iodotetrahydropyrans. Furthermore, CeI$_3$ was found to be an equally effective for this conversion. Among various metal salts such as NaI, KI, and LiI tested, LiI was found to be superior in terms of conversion. For example, cyclohexanecarboxaldehyde and 3-buten-1-ol in the presence of LiI, NaI, and KI gave the product in 91, 73, and 62% yields respectively. However, no reaction was observed in the absence of catalyst even after a long reaction time (12 h). In all cases, the reactions proceeded smoothly by CeCl$_3$•7H$_2$O–LiI in dichloroethane at 80 °C and the products were obtained in excellent yields with high diastereoselectivity. Only a single isomer was obtained in each reaction, the structure of which was confirmed by ^{1}H NMR and also by comparison with authentic samples.[4] The formation of the products may be further explained by hemi-acetal formation and subsequent the Prins-type cyclization (Scheme 3).

The nature of the substituents on the aromatic ring shows some effect on this conversion. It should be noted that aliphatic, simple aromatic and moderately activated aldehydes like chloro-, and bromo-substituted benzaldehydes gave higher yields of products compared to strongly activated or deactivated aldehydes. To know the efficiency of this procedure, we have also carried out the reactions with other cerium salts such as cerium(III) triflate and ceric ammonium nitrate. Among these catalysts, cerium(III) chloride was found to be the most effective reagent and giving the best results. Furthermore, low conversions (10–15%) were obtained with CAN. Both 4-hydroxyl-, and 4-iodo-tetrahydropyrans were obtained when the reactions were carried out using Ce(OTf)$_3$/LiI. As solvent, dichloroethane appeared to give the best results. Furthermore, we have examined the possibility of CeCl$_3$•7H$_2$O functioning catalytically or at least, in less than stoichiometric amounts. But best results were obtained with an equimolar ratio of CeCl$_3$•7H$_2$O. There are many advantages in the use of cerium(III) chloride for this transformation, which avoids the use of strongly acidic conditions. The method does not require the use of expensive or corrosive reagents and no precautions need to be taken to exclude moisture from the reaction medium. The scope and generality of this procedure is illustrated with respect to various aldehydes and homoallylic alcohols and the results are summarized in the Table 1.[10]

In summary, we disclose a simple and efficient procedure for the preparation of 4-iodotetrahydropyrans from homoallylic alcohols and aldehydes using CeCl$_3$•7H$_2$O/LiI as the novel reagent system under neutral conditions. The notable features of this procedure are high conversions, simplicity in operation, cleaner reaction profiles, greater selectivity, and ready availability of reagents at low cost which make it a useful and attractive strategy for the synthesis of highly substituted tetrahydropyran derivatives.

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10 General procedure. To a mixture of homoallyl alcohol (1 mmol) and aldehyde (1 mmol), CeCl$_3$•7H$_2$O (1.0 mmol) and LiI (1.5 mmol) in dichloroethane (5 mL) was stirred at reflux temperature for a specified time as required to complete the reaction (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure 4-iodotetrahydropyran. The products thus obtained were characterized by IR, NMR spectroscopy, and physical constants. The characterization data was found to be consistent with the authentic samples.

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