Tetrahedron Letters 54 (2013) 3639–3642

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A simple and expeditious synthesis of 2,3,6-trisubstituted tetrahydropyrans through (3,5)-oxonium-ene cyclization using molecular iodine

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ARTICLE INFO

Article history:
Received 10 January 2013
Revised 26 April 2013
Accepted 28 April 2013
Available online 3 May 2013

Keywords:
Molecular iodine
Oxonium-ene reaction
Aldehydes
Alkenols
3-Isopropenyl-6-methyltetrahydropyrans

ABSTRACT

A variety of aldehydes undergo a smooth coupling with 6-methylhept-5-en-2ol in the presence of molecular iodine to afford the 2,3,6-trisubstituted tetrahydropyrans in good yields through 3,5-oxonium-ene cyclization under mild and neutral conditions. This method is simple, convenient, and cost-effective.

The tetrahydropyran ring is a core unit in a large number of natural products.[1] Prins cyclization is a powerful reaction to construct tetrahydropyran scaffolds.[2] In addition, oxonium-ene cyclization also provides tetrahydropyrans with high selectivity.[3] Recently, Mikami and Shimizu have made an extensive study on oxonium-ene cyclizations.[4] Typically, Lewis acids are known to catalyze this reaction.[5] In some cases, Bronsted acids are also found to be effective.[6] However, many of them require strong acids, extended reaction times, and also produce a mixture of regioisomers. Recently an elegant approach has been reported for the preparation of functionalized tetrahydropyrans through a sequential olefin migration and Prins-type cyclization.[7]

Molecular iodine has received considerable attention in organic synthesis because of its high tolerance to air and moisture, low-cost, nontoxic nature, and ready availability, affording the corresponding products with high selectivity in excellent yields. The mild Lewis acidity associated with iodine has led to its use in organic synthesis using catalytic to stoichiometric amounts.[8] Therefore, the use of simple, convenient, cost effective, and readily available reagent would extend the scope of oxonium-ene cyclization in natural product synthesis.

Following our interest on the catalytic application of molecular iodine for various transformations,[9] we herein report for the first time a metal-free approach for the synthesis of substituted tetrahydropyrans via oxonium-ene cyclization. Initially, we attempted the coupling of 6-methylhept-5-en-2ol (**1**) with *n*-hexanal (**2**) in the presence of a stoichiometric amount of molecular iodine in dichloromethane. The reaction proceeded smoothly at 25 °C and the desired 3-isopropenyl-6-methyl-2-pentyl tetrahydropyran **3a** was obtained in 90% yield (Table 1, Scheme 1).

Similarly, other aliphatic aldehydes such as *n*-butanal, *n*-decanal, isovaleraldehyde, and *n*-heptanal underwent smooth coupling with 6-methylhept-5-en-2-ol (**1**) to give the respective tetrahydropyrans in good yields (Table 1, entries b, j, k, and l). Interestingly, 3-phenylpropionaldehyde and benzaldehyde also participated well in this reaction (Table 1, entries d and n). Remarkably, acid sensitive aldehydes such as cinnamaldehyde and furfuraldehyde also afforded the desired products reasonably in good yields (Table 1, entries m and e). Other alkenols such as 6-methyl-2-phenyl hept-5-en-2-ol and 2,6-dimethylhept-5-en-2-ol also participated well in this reaction to afford the isopropenyl-6-methyl-6-phenyltetrahydropyran and 3-isopropenyl-6,6-dimethyltetrahydropyran derivatives, respectively (Table 1, entries f–i). In all cases, the desired six-membered tetrahydropyrans were formed exclusively in good yields with high selectivity (Table 1). The structures of all the compounds were determined by ^{1}H NMR, ^{13}C NMR, IR, and DEPT experiments. It should be noted that aliphatic aldehydes gave higher yields than aromatic aldehydes. The reaction proceeds through a stepwise manner via carbocation intermediate, but not in a concerted fashion, which is evident from the result obtained

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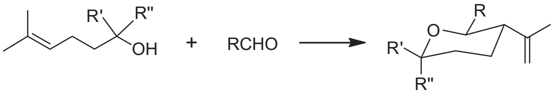
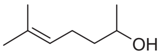
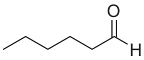
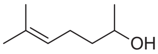
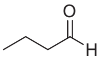
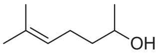
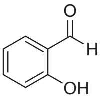
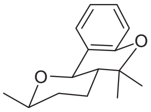
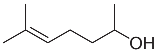
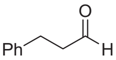
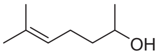
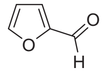
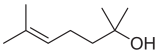
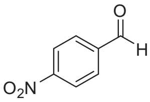
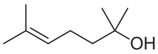
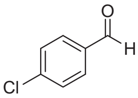
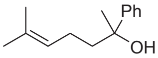
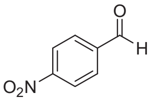
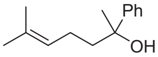
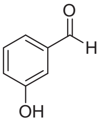
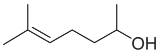
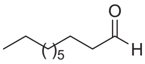
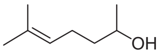
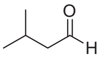
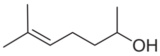
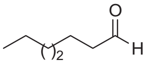
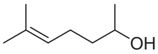
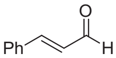
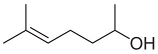
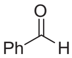
http://dx.doi.org/10.1016/j.tetlet.2013.04.104

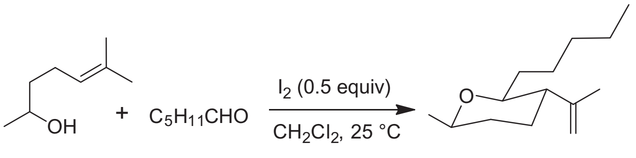
Table 1
Iodine-promoted (3,5)-oxonium-ene cyclization



Entry	Alcohol	Aldehyde	Product[a] (**3**)		Time (h)	Yield[b] (%)
a			R = Pentyl; R′ = Me; R″ = H	**3a**	2.0	90
b			R = Propyl; R′ = Me; R″ = H	**3b**	2.5	84
c				**3c**	1.0	95
d			R = Phenethyl; R′ = Me; R″ = H	**3d**	3.0	79
e			R = 2-Furyl; R′ = Me; R″ = H	**3e**	3.5	75
f			R = *p*-$NO_2C_6H_4$; R′ = Me; R″ = Me	**3f**	2.5	79
g			R = *p*-ClC_6H_4; R′ = Me; R″ = Me	**3g**	4.0	70
h			R = *p*-$NO_2C_6H_4$; R′ = Me; R″ = Ph	**3h**	2.0	82
i			R = *m*-HOC_6H_4; R′ = Me; R″ = Ph	**3i**	3.5	77
j			R = Nonyl; R′ = Me; R″ = H	**3j**	3.0	83
k			R = Isopropyl; R′ = Me; R″ = H	**3k**	2.5	87
l			R = Hexyl; R′ = Me; R″ = H	**3l**	2.5	85
m			R = Styryl; R′ = Me; R″ = H	**3m**	3.0	82
n			R = Phenyl; R′ = Me; R″ = H	**3n**	2.5	89

[a] The products were characterized by IR, NMR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.

from salicylaldehyde and 6-methylhept-5-en-2ol (**1**). In the case of salicylaldehyde, the intermediate carbocation could be successfully trapped with *ortho*-hydroxyl group affording the tricyclic compound, that is, 2,5,5-trimethyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-pyrano(3,2-*c*)chromene (Table 1, entry c). This observation suggests that oxonium-ene cyclization proceeds in a stepwise manner via carbocation intermediate.



1 **2** **3a**

Scheme 1. Preparation of 3-isopropenyl-6-methyl-2-pentyltetrahydropyran **3a**.

The catalytic efficiency of various Lewis acids such as $InCl_3$, YCl_3, and $SmCl_3$ was tested for this transformation. Of these catalysts, molecular iodine was found to be superior in terms of conversion. In the absence of the catalyst, the reaction did not proceed even after a long reaction time (24 h). This clearly indicates that molecular iodine is essential to facilitate the reaction. As a solvent, dichloromethane appeared to give the best results. The scope and generality of this process is illustrated with respect to various alke-