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Gallium(III) Iodide Mediated Mild and Efficient Method for Synthesis of 4-Iodotetrahydropyrans by Cross-Cyclization of Epoxides and Homoallylic Alcohols

K. KAMESU[1,2], G.V. KRISHNAMOHAN[2] and K. RAJASEKHAR[1,*]

[1]Ragas Pharmaceuticals Private Limited (OPC), IDA Cherlapally, Hyderabad-500 051, India
[2]Department of Chemistry, K L University, Vaddeswaram, Guntur-522 502, India

*Corresponding author: E-mail: koorella.rajasekhar@gmail.com

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The synthesis of 4-iodotetrahydropyran derivatives has been achieved *via* gallium(III) iodide mediated cyclization of epoxides and homo-allylic alcohols. This is a single step diastereoselective method for the preparation of 4-iodotetrahydropyrans.

Keywords: Epoxides, Homoallylic alcohols, Tetrahydropyrans, Gallium(III) iodide.

INTRODUCTION

Tetrahydropyrans are the common structural units, which appears in many natural products like tubulexin A [1], (-)-centrolobine [2] and (-)-dactylolide [3]. Especially, tetrahydropyrans having labile group at the 4th position are much useful for the construction of macrocyclic ring system. In this context, 4-iodotetrahydropyrans could be considered as useful intermediates due to the presence of labile iodo-substituent which can easily be converted to different functionalities [4]. Zurwerra *et al*. [5] reported the synthesis of (-)-dactylolide from 4-iodotetrahydropyran derivative. Even though there is considerable demand for 4-iodotetrahydropyrans, limited methods are available in the literature [6-11]. Among the existing methods, Prins cyclization is the common and widely used method for the tetrahydropyrans synthesis. Prins reaction is the reaction of aldehydes or ketones with homo-allylic alcohol in the presence of an acid. Due to the importance of Prins reaction in the tetrahydropyran ring formation, many modified Prins cyclization methods were reported [12-15]. Among them, Lewis acid mediated cross-cyclization of epoxides and homoallylic alcohols has received little attention. Epoxides are the convenient starting materials for various synthetic trans-formations because of their ease of formation, wide reactivity and ability to undergo regio-selective reactions [16-21]. Although other methods are reported, many of these methods require more than stoichiometric amounts of Lewis acids, longer reaction times and low yields of products [11,14,15]. Therefore, the develo-pment of an efficient method that successfully minimizes the use of Lewis acid would still be useful. In this aspect, Gallium(III) iodide has been found as an efficient Lewis acid because of ease of handling, moisture stability and economic viability [22-34]. In the ever-increasing quest for exploration of an efficient and versatile method, GaI_3 is found as a mild and efficient Lewis acid for the synthesis of 4-iodotetrahydropyrans using epoxides and homo allylic alcohols. Herein, we wish to report our results of gallium(III) iodide mediated synthesis of 4-iodotetrahydropyrans using epoxides and homo allylic alcohols.

EXPERIMENTAL

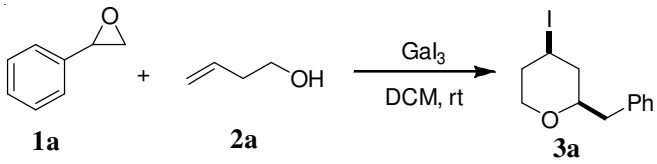
^{1}H NMR, ^{13}C NMR spectra were recorded on Bruker 300 NMR spectrometer and Mass spectra were recorded at 70 eV.

General procedure: To a stirred solution of 3-buten-1-ol (200 mg, 2.77 mmol), styrene oxide (500 mg, 4.16 mmol) in anhydrous dichloromethane (10 mL) under nitrogen atmosphere, was added GaI_3 (623 mg, 1.38 mmol) and continued stirring at 25-30 ºC for 45 min. After 45 min, TLC indicated the complete consumption of both starting materials. Then the reaction mixture was quenched with water (10 mL) and the aqueous layer was extracted twice (2 × 10 mL) with dichloromethane. The combined organics were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (60-120 mesh) by eluting with ethylacetate:hexane mixture (2:7) to afford 686 mg of 4-iodotetrahydropyran (**3a**) (Yield 82 %).

RESULTS AND DISCUSSION

In order to check feasibility of the reaction, 3-buten-1-ol and styrene oxide was taken in anhydrous dichloromethane

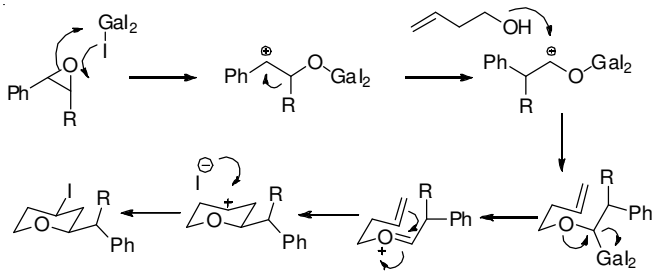
under nitrogen atmosphere. To this, GaI_3 was added at room temperature under stirring. The reaction mixture was monitored by TLC. After 45 min, TLC indicated complete consumption of starting materials. After workup, the product was isolated by silica-gel column chromatography (**Scheme-I**). Characterization of product by ^{1}H NMR and mass analysis indicated the formation of compound **3a**. The spectroscopic analysis was further compared with literature data [14] and confirmed the product as compound **3a**.



Scheme-I

The method was further applied to stilbene oxide and other homoallylic alcohols. In all these cases, reaction proceeded effectively under the same reaction conditions indicating wide applicability of this method (Table-1). The substitution on homoallylic alcohols shows effect on the yield. It has been observed that the reaction of 4-alkyl substituted homoallylic alcohols with epoxides afforded lower yield compared to unsubstituted homoallylic alcohols. Similarly, slight lower yield was observed in case of stilbene oxide compared to styrene oxide. This may be due to the steric factors of bulky groups during tetrahydropyran ring formation. The role of GaI_3 is to acts as Lewis acid and also providing the iodide nucleophiles to tetrahydropyran carbonuim species.

The tentative mechanism for this transformation can be explained by GaI_3 promoted opening of epoxide ring followed by intra-molecular migration of hydrogen in the case of compound **1a** and aryl group in the case of compound **1b** to afford acyclic carbonium species. After reaction of carbonium ion with homoallylic alcohol and after rearrangement gives cyclic carbonium ion, which is being attacked by iodide neucleophile to afford 4-iodotetrahydropyran derivative. The stereochemistry for the tetrahydropyrans formation with *cis* selectivity could be explained by the formation of stable (*E*)-oxocarbenium ion with chair-like transition state, which places the hydrogen atom at C4 in a pseudoaxial position. This transition state favours the equatorial attack of iodide nucleophiles leading to the formation of 2,4-cis substituted tetrahydropyran derivatives (**Scheme-II**).



Scheme-II

Conclusion

In summary, a simple and convenient protocol is described for the preparation of 4-iodotetrahydropyrans by the cyclization of epoxides and homoallylic alcohols using GaI_3. The

TABLE-1
GaI_3 MEDIATED CYCLIZATION OF EPOXIDES WITH HOMOALLYLIC ALCOHOLS

Entry	Epoxide	Alcohol	Products[a,b]	Time (min)	Yield (%)[c]
1	**1a**	**2a**	**3a**	45	82
2	**1a**	**2b**	**3b**	75	76
3	**1b**	**2a**	**3c**	60	79
4	**1b**	**2c**	**3d**	90	74
5	**1b**	**2b**	**3e**	90	70

[a]All the products were characterized by ^{1}H NMR and mass spectroscopy. [b]The minor isomers of THP products were not isolated. [c]Isolated yield after column chromatography.

advantages of this process are mild reaction conditions, cleaner reactions with improved yield makes it a useful process for the synthesis of 4-iodotetrahydropyran derivatives.

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