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TiI₄ Mediated Prins-Type Cyclization of Homoallylic Alcohols and Epoxides: An Efficient Method for the Synthesis of 4-Iodotetrahydropyran Derivatives

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ABSTRACT

The cyclization reaction between homoallylic alcohols and epoxides using Titanium (IV) Iodide generates 4-Iodo tetrahydropyran derivatives with good yields under mild reaction conditions.

Keywords: Tetrahydropyran; Epoxide; Homoallylic alcohol; Iodo; Titanium (IV) Iodide

INTRODUCTION

Oxygen- and nitrogen-containing heterocyclic systems such as pyran and piperidine systems occur in many natural products and are important intermediates for the synthesis of complex molecules [1-3]. In particular, these ring systems with labile groups such as halogen and hydroxyl prove useful for further functionalization [4-6]. In particular, iodine substitution on pyran and piperidine systems proves useful due to their labile functionality [7-9]. The Prins reaction, which involves acid-catalyzed aldehyde or epoxide-olefin condensation, is one of the most common and simplest methods for the synthesis of pyran and piperidine systems [10-13]. Many synthetic methods are available in the literature for the synthesis of iodine-substituted tetrahydropyrans, but their application is limited due to low yield, prolonged reaction time, and high reagent loading [14-19].

Because of their wide application, the development of improved methods that minimize reaction time and reagent loading is highly desirable. In this regard, titanium (IV) iodide proves to be more effective for the synthesis of tetrahydropyran due to its low catalyst loading and shorter reaction time with good yield. In the literature, titanium (IV) iodide has been widely used for carbon-carbon bonding reactions such as Diels-Alder reactions, Mukaiyama Aldol reactions, and carbonyl-ene reactions [20-22]. In this report, we would like to describe the synthesis of iodo-tetrahydropyrans by the Prins-type cyclization reaction between homoallylic alcohols and epoxides using titanium (IV) iodide.

EXPERIMENTAL

Material and Methods (2)

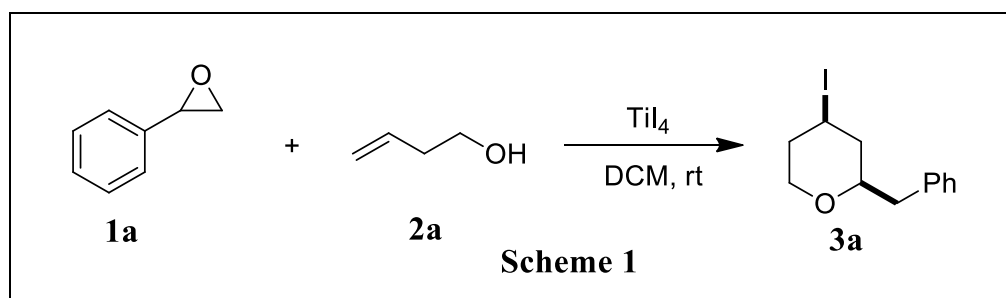
The chemicals used for these reactions were purchased from Sigma-Aldrich and used as received. All epoxides were prepared from the relevant olefins according to the methods described in the literature. For TLC, silica gel 60 F₂₅₄ coated on aluminium sheets was used and purchased from Merck. Silica gel with 60-120 meshes was used for column chromatography. ¹HNMR and ¹³CNMR spectra were recorded on a Bruker 300-MHz NMR spectrometer using trimethylsilane as an internal standard on a δ-scale of parts per million. Mass spectra were recorded using a Waters G2-XS QToF mass spectrometer. IR Spectra were recorded using the Nexus 670 Thermo Nicolet Fourier transform infrared spectrometer.

Representative Procedure (2.1)

To a magnetically stirred mixture of styrene oxide (200 mg, 1.66 mmol) and 3-buten-1-ol (96 mg, 1.33mmol) in anhydrous methylene dichloride (10 mL) under nitrogen atmosphere was added titanium (IV) iodide (230 mg, 0.4 mmol) and stirred for 15 minutes at room temperature (25-30°C). TLC monitoring after 15 minutes indicated the completion of the reaction. The reaction mixture is then poured onto crushed ice, extracted with dichloromethane and concentrated. The reaction mixture was purified by silica gel column chromatography and the product was eluted with an ethyl acetate-hexane mixture (2:8) as the mobile phase, yielding 290 mg of compound **3a** as light yellow oil.

RESULTS AND DISCUSSION


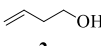
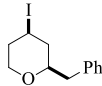
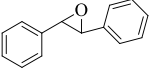
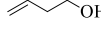
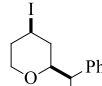

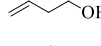
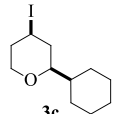

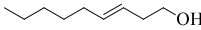
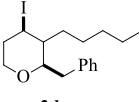
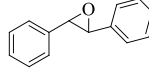
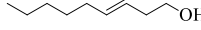
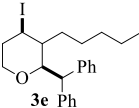
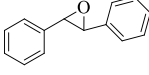
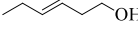
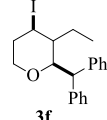
The applicability of this method was first investigated by stirring a mixture of 3-buten-1-ol and styrene oxide with Titanium (IV) Iodide in anhydrous dichloromethane under a nitrogen atmosphere at ambient temperature (25-30°C). TLC was monitored on the progress of reaction, and after 15 minutes the disappearance of the starting materials was observed. Then the reaction mixture was poured into ice, extracted with DCM and concentrated. The product was isolated by column chromatography over silica gel and eluted with ethyl acetate and hexane as mobile phase. After purification, the product was analyzed by NMR (¹H & ¹³C), IR and mass spectroscopy. All spectroscopic analysis confirmed the formation of compound **3a**, and the data obtained are comparable to literature reports [16-19] (Scheme 1).



Scheme 1: Spectroscopic analysis confirmed the formation of compound **3a**

Based on the above results, the feasibility of this method was extended to various combinations of epoxides and homoallyl alcohols. The reaction with all combinations gave corresponding tetrahydropyrans derivatives. This demonstrates the wide applicability of this method for the synthesis of a variety of Iodo-tetrahydropyrans using epoxides as starting materials (Table 1).

Table 1: Titanium (IV) Iodide mediated synthesis of 4-Iodo tetrahydropyrans

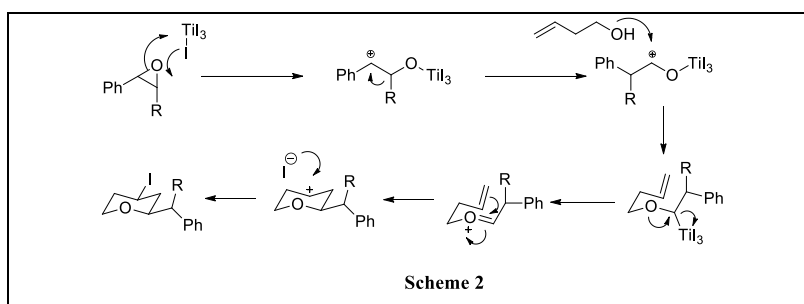
| Entry | Epoxide | Alcohol | Products ^{a, b} | Time (min) | Yield (%) ^c |
|-------|--|--|--|------------|------------------------|
| 1 |  1a |  2a |  3a | 15 | 72 |
| 2 |  1b |  2a |  3b | 30 | 65 |
| 3 |  1c |  2a |  3c | 60 | 40 |
| 4 |  1a |  2b |  3d | 30 | 68 |
| 5 |  1b |  2b |  3e | 30 | 70 |
| 6 |  1b |  2c |  3f | 30 | 70 |

^aAll the products were characterized by ¹H, ¹³C NMR, IR and mass spectroscopy.

^bThe minor isomers of THP products were not isolated.

^cYields are only isolated *cis* isomer after column chromatography.

It is observed that steric hindrance plays an important role in the reaction time and product yield. For example, the reaction of substituted epoxides with substituted homoallyl alcohols gave lower yield with longer reaction time compared to unsubstituted epoxides and homoallyl alcohols. The reaction of methylene cyclohexane oxide with 3-buten-1-ol took longer with lower yield than aryl epoxides. This could be due to the tertiary and hindered formation of cyclohexyl carbonium ions. The reaction is stereo-selective and the formation of a *cis-trans* isomer mixture was observed. The major product was *cis*-stereo chemistry and the *trans* minor isomer was not isolated. The formation of the *cis*-isomer was confirmed by ¹HNMR spectroscopy and compared with literature data. The important formation of *cis*-stereoisomer is likely due to thermodynamic stability. The expected mechanism of this reaction is possibly initiated by the ring opening of the epoxide with the Lewis acid TiI₄ to the more stable carbonium ion. Subsequently, the carbonium ion is added to the iodide nucleophile of TiI₄ to form the 4-iodo-tetrahydropyran derivative (**Scheme 2**)



Scheme 2: This reaction is possibly initiated by the ring opening of the epoxide with the Lewis acid TiI_4 to the more stable carbonium ion. Subsequently, the carbonium ion is added to the iodide nucleophile of TiI_4 to form the 4-iodo-tetrahydropyran derivative.

CONCLUSION

Briefly, we have invented an improved and simple method for the synthesis of 4-iodo-tetrahydropyrans by the cyclization reaction between homoallylic alcohols and epoxides with Lewis acid Titanium (IV) Iodide. The mild reaction conditions, low reagent usage and improved yield make this method more useful than the existing methods for the synthesis of iodotetrahydropyran derivatives.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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