Tetrahedron Letters 49 (2008) 7153–7156

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Pd(0) catalyzed intramolecular Heck reaction: a versatile route for the synthesis of 2-aryl substituted 5-, 6-, and 7-membered O-containing heterocycles

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ARTICLE INFO

Article history:
Received 22 August 2008
Revised 25 September 2008
Accepted 27 September 2008
Available online xxxx

Keywords:
Oxepine
Diene
Heterocyclic
Tetrahydropyran

ABSTRACT

An efficient and convenient method for the synthesis of 2-aryl substituted tetrahydropyran, tetrahydrofuran, and oxepine derivatives via intramolecular palladium catalyzed cyclization is developed. The two *exo*-cyclic double bonds at adjacent carbon atoms in these ring systems could serve as potential dienes for cycloaddition reactions.

1. Introduction

The intramolecular Heck reaction is a very useful approach for the synthesis of various heterocyclic and carbocyclic rings.[1] This reaction is also important for the synthesis of natural products. Substituted pyran, furan, and oxepine rings are common structural components found in many natural products such as mycalamide,[2] (+)-trans-kumasyne,[3] and roglolenyne.[4] Laulimide, a novel cancer-therapy agent which contains two pyran rings can be synthesized by nucleophilic attack on a carbopalladium complex.[5] Morphine contains a fused furan ring and has been synthesized via intramolecular Heck reaction.[6] Alternatively, an intermolecular Heck reaction is used for the synthesis of (−)-strychnine, which contains an oxepine subunit.[7] These ring systems have been prepared by various methods including radical cyclization,[8] olefin metathesis[9] and metal catalyzed cyclization.[10,11] Among these, palladium catalyzed cyclization is a very powerful method due to its tolerance of a wide variety of functional groups, thus neatly avoiding protection group chemistry. Based on previous reports utilizing pyran, furan, and oxepine ring systems as the subunit of many natural products, we propose a general method for the synthesis of these ring systems via palladium catalyzed intramolecular Heck reaction.[12–15]

In this context, we describe the intramolecular Heck cyclization of 4-(2-bromoallyloxy)-4-arylbut-1-ene, 4-(2-bromoallyloxy)-2-methyl-4-arylbut-1-ene and 3-(2-bromoallyloxy)-3-arylprop-1-ene which yields the corresponding tetrahydropyran, oxepine, and tetrahydrofuran, respectively. Herein, we report two modes of cyclization, one being the *exo* mode leading to substituted tetrahydropyran and tetrahydrofurans and the other being the *endo* mode that leads to the substituted oxepines. The main feature of the 2-aryl substituted tetrahyropyran and tetrahyrofuran rings prepared herein is the presence of two adjacent double bonds that can be utilized in cycloaddition reactions leading to 2-aryl substituted fused pyran and furan rings.[16]

First, the starting materials for the Heck reaction were prepared by *O*-2-bromo-allylation of 1-arylbut-3-en-1-ol (**2**), 1-arylbut-3-methyl-3-en-1-ol (**3**), and 1-arylprop-2-ene-1-ol (**4**). The alcohols **2** and **3** were synthesized by treating the appropriate aryl aldehyde **1** with indium metal, sodium iodide, and allyl bromide or methallyl bromide in dimethylformamide at room temperature. The alcohols **4** were synthesized by treating aryl aldehydes with vinylmagnesium bromide in tetrahydrofuran at 0 °C followed by stirring at room temperature (25–30 °C). Alcohols **2**, **3**, and **4** were reacted with 2,3-dibromopropene in the presence of sodium hydride in THF at 0 °C to give 4-(2-bromoallyloxy)-4-arylbut-1-ene (**5**), 4-(2-bromoallyloxy)-2-methyl-4-arylbut-1-ene (**6**), and 3-(2-bromoallyloxy)-3-arylprop-1-ene (**7**), respectively, as the precursors for the intramolecular Heck reaction, (Scheme 1).

Heck reaction precursors **5, 6**, and **7** (1 mmol) with $Pd(OAc)_2$ (5 mol %), PPh_3 (0.5 equiv) and Cs_2CO_3 (1.2 equiv) in dimethylformamide (8 ml) at 80–85 °C yielded the desired 4,5-dimethylene-2-aryl-tetrahydropyrans **8a–h** (Table 1, entries 1–8), 4-methyl6-methylene-2-aryl-2,3,6,7-tetrahydro-oxepines **9a–e**

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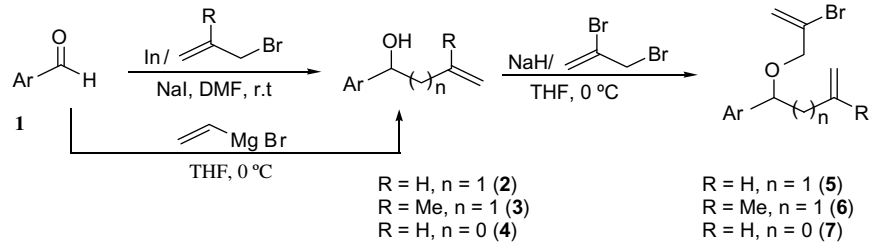
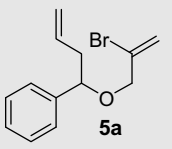
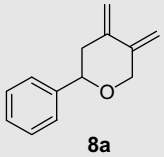
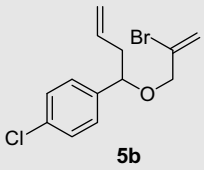
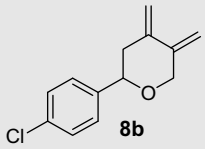
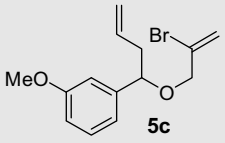
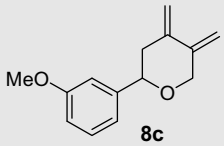
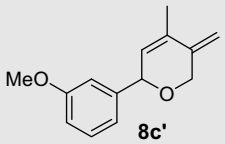
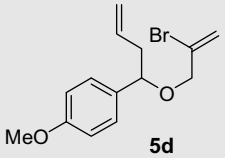
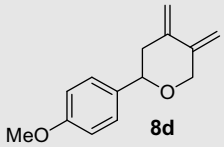
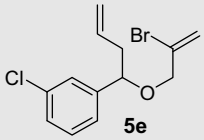
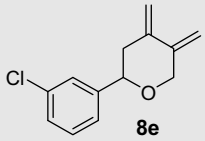
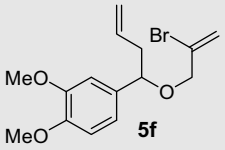
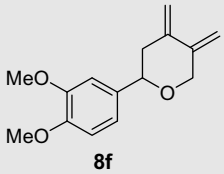
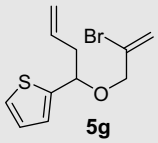
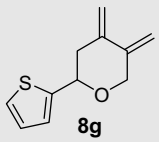
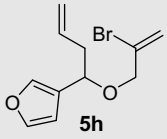
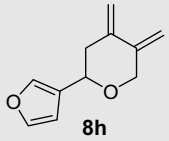
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.162



Scheme 1. Preparation of *O*-2-bromo-allylated derivatives.

Table 1
Pd-catalyzed cyclization of various 2-bromo-allylated derivatives[a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **5a**	 **8a**	1.83	80
2	 **5b**	 **8b**	1.75	70
3	 **5c**	 **8c**  **8c'**	1.5	65 + 10
4	 **5d**	 **8d**	2.0	78
5	 **5e**	 **8e**	1.5	72
6	 **5f**	 **8f**	1.5	70
7	 **5g**	 **8g**	1.5	82
8	 **5h**	 **8h**	2.0	65