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Synthesis of 2,5-disubstituted tetrahydrofurans from organozinc halides and lactones

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Abstract

2,5-Disubstituted tetrahydrofurans were obtained from lactones and organozinc halides in moderate to high yield in the presence of Lewis acids.

Keywords: Organozinc halides; Lactones; Lactols; 2,5-Disubstituted tetrahydrofurans; Lewis acid

2,5-Disubstituted tetrahydrofurans are often found in many biologically active natural products such as acetogenins [1] and polyether antibiotics [2]. Thus, there has been a long-standing interest in the preparation of 2,5-disubstituted tetrahydrofurans and a variety of methods have been achieved [3]. Among them conversion of lactols to 2,5-disubstituted tetrahydrofurans by organometallic reagents is an efficient method. For example, organosilane has been extensively investigated [4]. Organoaluminium, organostanne [5], Grignard reagents [6], and enolates [7] are also used as nucleophiles to convert lactols to 2,5-disubstituted tetrahydrofurans. As for the organozinc reagents, only Reformatsky reagents [8] and dialkylzinc (R_2Zn) [5,9] are used in this transformation. There are no reports for the formation of 2,5-disubstituted tetrahydrofurans from organozinc halides (FG-RZnX). As it is known, organozinc halides are more convenient to be prepared, and more useful in organic synthesis because they can tolerate a broad range of functionalities, but can react with various electrophiles to give multi-functional molecules [10]. Lots of work on organozinc halides has been done in our group [11]. Thus, we wondered if organozinc halides would be able to convert lactols to 2,5-disubstituted tetrahydrofurans. If so, functionalized 2,5-disubstituted tetrahydrofurans can be obtained and further incorporated into the natural products through the functional group. Firstly, allylzinc bromide was used. As expected, the reaction occurred. We will report here that the allylzinc and propargylzinc bromides can react with lactols prepared *in situ* or their acetoxy derivatives to give the 2,5-disubstituted tetrahydrofurans in the presence of Lewis acids.

Initially, we got lactol **2** from lactone **1**, which was not separated from reaction mixture and used directly in the next step. Allylzinc bromide was then reacted with lactol **2** in the presence of $BF_3{\cdot}Et_2O$. Unfortunately, the desired product **3a** was obtained only in 19% yield, the ring opening diol **4** was major product in 76% yield (Scheme 1). We envisioned

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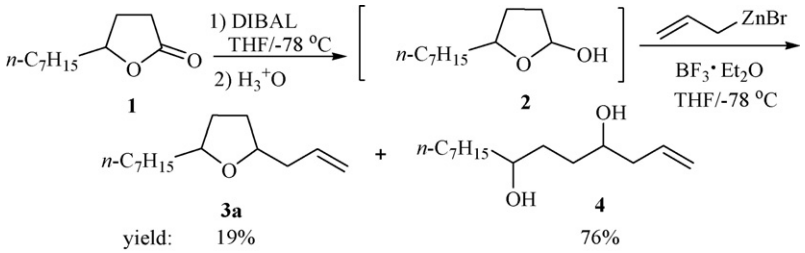
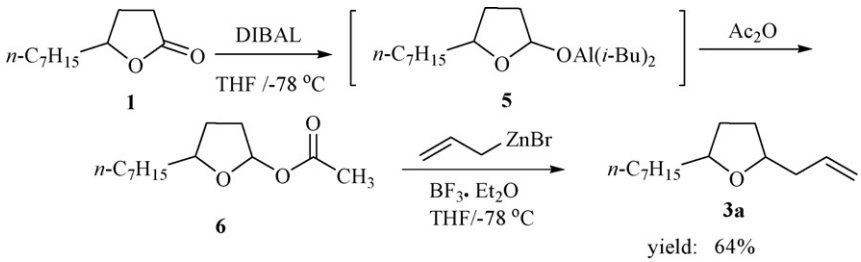


Scheme 1.

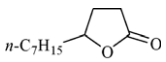
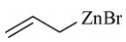
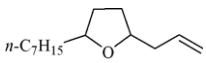
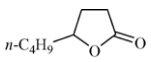
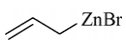
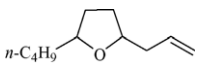
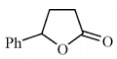
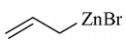
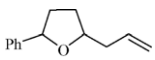
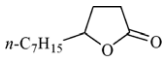
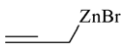
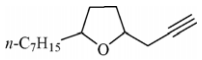
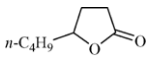
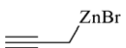
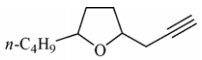
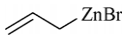
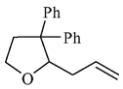


Scheme 2.

that the hemiacetal **2** maybe too reactive. So we captured the aluminium hemiacetal intermediate **5** *in situ* with Ac_2O to give acetoxy derivative **6** (Scheme 2), which was then reacted with allylzinc bromide. To our delight, the reaction gave the expected product **3a** in 64% yield.

To investigate the applicability of the method, various substituted lactones were further employed. As shown in Table 1, the reaction with allylzinc bromides gave the desired 2,5-disubstituted tetrahydrofurans (Table 1, entries 1–3). The reaction with propargylzinc bromides also produced the corresponding 2,5-disubstituted tetrahydrofurans (Table 1, entries 4–5). In addition, when the hendered lactone with substituents at 3-position was used, the reaction also afforded the product **3f** in 82% yield (Table 1, entry 6).

Table 1
Preparation of 2,5-disubstituted tetrahydrofurans from lactons and organozinc bromides using $BF_3 \cdot Et_2O$ as Lewis acid.

Entry	Lactone	R′ZnBr	Product		Yield (%)[a]	Ratio of *trans*/*cis*[b]
1				**3a**	64	57/43
2				**3b**	69	56/44
3				**3c**	77	37/63
4				**3d**	63	53/47
5				**3e**	58	55/45
6				**3f**	82	50/50

[a] Isolated yield [12].
[b] The ratio of *trans*/*cis* was determined by GC.