

Available online at www.sciencedirect.com



CHINESE Chemical Letters

Chinese Chemical Letters 21 (2010) 511-514

www.elsevier.com/locate/cclet

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

Dan Feng Huang*, Hai Feng Wang, Chang Ming Xu, Teng Niu, Yu Lai Hu*

College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China Received 7 September 2009

Abstract

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

© 2009 Dan Feng Huang. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

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 2,5disubstituted 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

* Corresponding authors.

E-mail addresses: huangdf@nwnu.edu.cn (D.F. Huang), huyl@nwnu.edu.cn (Y.L. Hu).

^{1001-8417/\$ –} see front matter © 2009 Dan Feng Huang. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved. doi:10.1016/j.cclet.2009.12.026



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 BF₃·Et₂O as Lewis acid.

Entry	Lactone	R'ZnBr	Product		Yield (%) ^a	Ratio of trans/cis ^b
1	n-C7H15	ZnBr	n-C7H15	3a	64	57/43
2	n-C4H9 O	ZnBr	n-C4H9 0	3b	69	56/44
3	Ph	ZnBr	Ph	3c	77	37/63
4	n-C ₇ H ₁₅	ZnBr	n-C7H15	3d	63	53/47
5	n-C4H9 O	ZnBr	n-C4H9	3e	58	55/45
6	Ph Ph O	ZnBr	Ph OPh O	3f	82	50/50

^a Isolated yield [12].

^b The ratio of *trans/cis* was determined by GC.

Table 2			
Effects of different L	ewis acids o	on the	reaction.

Entry	Lewis acid	Isolated yield 3a (%)	Ratio of trans/cis ^a	
1	ZnBr ₂	59	56/44	
2	$ZnCl_2$	88	50/50	
3	BF ₃ ·Et ₂ O	64	57/43	
4	SnCl ₄	59	57/43	
5	CeCl ₃	91	46/54	

^a The ratio of *trans/cis* was determined by GC.

Preparation of 2, 5-disubstituted tetrahydrofurans from lactones and organozinc boromides using CeCl₃ as lewis acid.



Entry	R	R′	Product	Isolated yield (%)	Ratio of trans/cis ^a
1	<i>n</i> -C ₇ H ₁₅	Allyl	3a	91	46/54
2	$n-C_4H_9$	Allyl	3b	86	47/53
3	Ph	Allyl	3c	90	39/61
4	<i>n</i> -C ₇ H ₁₅	Proparyl	3d	76	40/60
5	n-C ₄ H ₉	Proparyl	3e	71	55/60

^a The ratio of *trans/cis* was determined by GC.

In order to improve the yield, we examined the reaction with various Lewis acids using 5-heptanyllactone as representative substrate (Table 2). The model reaction proceeded smoothly in the presence of $ZnBr_2$, $ZnCl_2$, $BF_3 \cdot Et_2O$, $SnCl_4$ or $CeCl_3$, respectively. Among them, $CeCl_3$ showed the best reactivity and the yield of the product reached 91% (Table 2, entry 5). Based on the optimized reaction conditions, we tried the reaction with different substrates using $CeCl_3$ as Lewis acid. Compared with the results in Table 1, the yields of all products were greatly improved (Table 3).

1. Experimental

Table 3

The solution of lactone (2.5 mmol) in THF (10 mL) was cooled to -78 °C and DIBAL (5 mL, 1 mol/L) was added dropwise in 15 min under nitrogen. The mixture was then stirred for 45 min at -78 °C. A solution of pyridine (7.5 mmol) and DMAP (5 mmol) in CH₂Cl₂ (8 mL) was added into the mixture, and then Ac₂O (15 mmol) was added. After being stirred for 12 h, the mixture was allowed to warm to 0 °C, and then saturated aqueous NH₄Cl (20 mL) and potassium sodium tartrate (10 mL) were added. The mixture was stirred at 0 °C for 30 min and extracted with CH₂Cl₂ (10 mL ×3). The combined organic layers were dried and concentrated to afford acetoxy derivative which was used directly in the next step.

Organozinc halides (7.5 mmol) (prepared following Knochel's procedure) [13] in THF (5 mL) was added at -78 °C dropwise into the solution of acetoxy derivative of lactol prepared above in CH₂Cl₂ (6 mL) under nitrogen. The mixture was stirred for 10 min, and then anhydrous CeCl₃ (5 mmol) was added. The mixture was stirred at -78 °C for 3 h. After completion of the reaction, the reaction mixture was warmed to room temperature and saturated aqueous NH₄Cl (15 mL) was added. The mixture was stirred for 10 min and then extracted with CH₂Cl₂ (15 mL ×3). The combined organic layers were dried over MgSO₄ and concentrated in vacuum. The pure products were obtained by column chromatography on silica gel using petroleum–ethylacetate as eluent.

In conclusion, an efficient method for synthesis of 2,5-disubstituted tetrahydrofurans from organozinc halides and lactones via lactols or their acetoxy derivatives has been developed. Allylzinc and propargylzinc bromides can react with lactols or their acetoxy derivatives prepared *in situ* from lactones to give the 2,5-disubstituted tetrahydrofurans in high yield in the presence of Lewis acids. CeCl₃ is the best Lewis acid. Acetoxy derivatives of lactols give better results than the corresponding lactols.

Acknowledgments

The work was supported by the National Natural Science Foundation of China (No. 20472068), Specialized Research Fund for the Doctoral Program of Higher Education (No. 200807360001), Key Laboratory of Eco-Environment-Related Polymer Materials of Ministry of Education (Northwest Normal University).

References

- (a) J.R. Alali, X.X. Liu, J.L. Mclaughlin, J. Nat. Prod. 62 (1999) 504;
 (b) M.C. Zafra-Polo, B. Figadère, T. Gallardo, Phytochemistry 48 (1998) 1087.
- [2] (a) J.A. Gladysz, Chem. Rev. 105 (2005) 4235;
 (b) G.M. Cragg, P.G. Grothaus, D.J. Newman, Chem. Rev. 109 (2009) 3012.
- [3] (a) M.C. Elliott, J. Perkin Trans. 1 (2002) 2301;
 (b) P.D. Pohlhaus, S.D. Sanders, A.T. Parsons, J. Am. Chem. Soc. 130 (2008) 8642;
 - (c) B. Lü, X. Jiang, C. Fu, et al. J. Org. Chem. 74 (2009) 438.
- [4] (a) C.H. Larsen, B.H. Ridgway, J.T. Shaw, J. Am. Chem. Soc. 121 (1999) 12208;
- (b) K. Miura, S. Okajima, T. Hondo, J. Am. Chem. Soc. 122 (2000) 11348.
- [5] K. Tomooka, K. Matsuzawa, K. Suzuki, et al. Tetrahedron Lett. 28 (1987) 6339.
- [6] X. Frank, R. Hocquemiller, B. Figadère, Chem. Commun. (2002) 160.
- [7] (a) R.A. Pilli, V.B. Riatto, I. Vencato, Org. Lett. 2 (2000) 53;
 (b) G. Jalce, M. Seck, X. Franck, J. Org. Chem. 69 (2004) 3240.
- [8] M. Hayashi, M. Sugiyama, T. Toba, J. Chem. Soc. Chem. Commun. (1990) 767.
- [9] H.U. Reissig, A. Schmitt, Synlett (1990) 40.
- [10] P. Knochel, R.D. Singer, Chem. Rev. 93 (1993) 2117.
- [11] (a) J.X. Wang, Y. Fu, Y. Hu, Angew. Chem. Int. Ed. 41 (2002) 2757;
 (b) Y. Hu, J. Yu, S. Yang, Synlett (1998) 1213;
 (c) D.F. Huang, J.X. Wang, Synlett (2007) 2272.
- [12] Compound **3a**: colorless oil. IR (KBr): 3074, 2926, 2857, 1644, 1082, 998, 912 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 5.85–5.76 (m, 1H), 5.10–5.03 (m, 2H), 4.02–3.78 (m, 2H), 2.39–1.88 (m, 4H), 1.66–1.28 (m, 14H), 0.93–0.86 (t, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 135.1, 116.6, 79.6, 79.0, 78.4, 77.8, 40.5, 40.4, 36.1, 36.0, 31.9, 31.8, 31.4, 30.9, 30.4, 29.7, 29.3, 26.2, 22.6, 14.1. HRMS (ESI, Pos.) *m/z* calcd. for C₁₄H₃₀NO [M+NH₄]⁺: 228.2322, found 228.2319.
- [13] P. Knochel, M.C.P. Yeh, S.C. Berk, J. Talbert, J. Org. Chem. 52 (1988) 2390.