ORGANIC LETTERS

2002
Vol. 4, No. 13
2269−2271

Stereoselective Synthesis of Polysubstituted 2,5-Dihydrofurans from Reaction of 1,4-Dilithio-1,3-dienes with Aldehydes

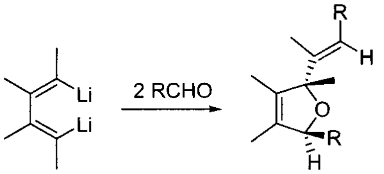
Jinglong Chen, Qiuling Song, Pixu Li, Hairong Guan, Xianglin Jin, and Zhenfeng Xi*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

zfxi@pku.edu.cn

Received May 7, 2002

ABSTRACT



Reaction of 1,4-dilithio-1,3-diene derivatives with 2 equiv of aldehydes affords polysubstituted 2,5-dihydrofurans in good to high yields with perfect regio- and stereoselectivities. Hexa-2,4-diene-1,6-dialcoholates are proposed as the first intermediates, which undergo a cyclization and subsequent elimination of Li_2O to generate the 2,5-dihydrofuran derivatives.

Among fundamental heterocycles, 2,5-dihydrofurans are important intermediates in organic synthesis.[1−5] Some natural products have been characterized to have this structural unit.[6,7] Therefore, development of synthetically useful methodology for 2,5-dihydrofurans, especially for polysubstituted ones, has attracted and continues to attract much attention.

Reaction of organolithium compounds with carbonyl groups is normally straightforward and affords alcohols after hydrolysis or α-deprotonation.[8] As an organolithium reagent, 1,4-dilithio-1,3-diene derivatives **1** can be easily prepared in situ from lithiation or lithium−halogen exchange reaction of their corresponding readily available 1,4-diiodo-1,3-dienes.[9,10] In this paper, we would like to report a conceptually new preparative method for polysubstituted 2,5-dihydrofurans by applying the simple and fundamental

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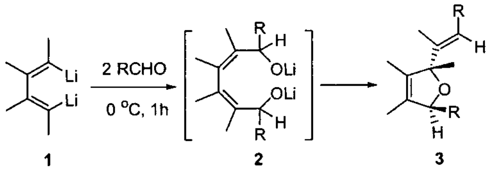
10.1021/ol0261478 CCC: $22.00

reaction pattern of organolithium compounds with aldehydes (Scheme 1). Two molecules of an aldehyde react with the two alkenyllithium moieties in **1**, affording the corresponding 1,6-dialcoholates **2**, which undergo intramolecular rearrangement and sequential cyclization to generate 2,5-dihydrofuran derivatives **3** in good to high yields with excellent regio- and stereoselectivities (Scheme 1). To the best of our knowledge, the transformation shown in Scheme 1 is the first example of such a reaction.

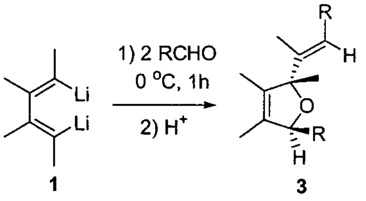
Scheme 1

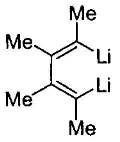
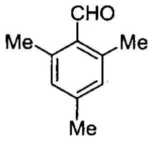
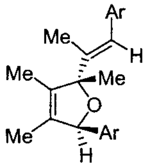
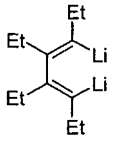
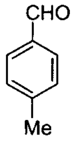
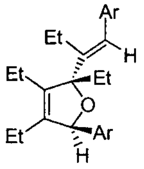
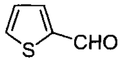
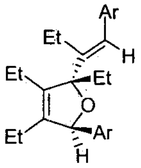
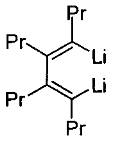
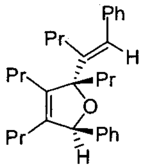
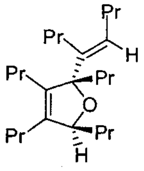
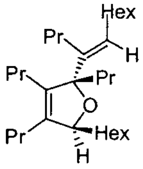
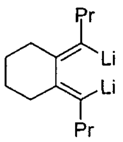
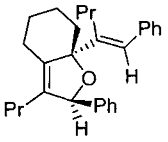


We have recently reported that 1,4-dilithio-1,3-diene derivatives **1** react with 1 equiv of aldehydes at −78 °C to afford cyclopentadiene derivatives via deoxygenation of the C═O double bond in aldehydes.[10b] Because we expected that aldehydes might react with **1** in the normal way to afford 1,6-diols after hydrolysis,[11] we investigated the reaction conditions. Finally, we found that 2 equiv of aldehydes did react with **1** in the normal way, when the reaction was carried out at 0 °C instead of −78 °C. However, to our surprise, the final products obtained after hydrolysis were not the expected 1,6-diols but 2,5-dihydrofuran derivatives. Cyclopentadiene derivatives were not formed at all in most cases.

Listed in Table 1 are representative examples of 2,5-dihydrofuran derivatives **3** obtained by hydrolysis of the reaction mixture of aldehydes with **1**. All of these compounds are formed highly selectively. In all these cases, no 1,6-diols were detected. Reaction of **1a** with 2,4,6-trimethylbenzaldehyde afforded **3a** as colorless crystals in 88% isolated yield. The structure of **3a** was determined by single-crystal X-ray analysis (Figure 1).

Table 1. Reactions of Aldehydes with Dilithio Compounds **1**



dilithio compound **1**		aldehyde	product **3**		yield of **3**/%[a]
	**1a**			**3a**[b]	88
	**1b**			**3b**[c]	71
1b				**3c**[d]	61
	**1c**	PhCHO		**3d**	57
1c		PrCHO		**3e**	54
1c		HexCHO		**3f**	51
	**1d**	PhCHO		**3g**	49

[a] Isolated yields. [b] Ar = 2,4,6-trimethylphenyl. [c] Ar = 4-methylphenyl. [d] Ar = 2-thiophenyl.

Initially, we assumed that two molecules of an aldehyde react with the two alkenyllithium moieties in **1**, affording the corresponding 1,6-dialcoholates **2**, which form their corresponding 1,6-diols **4** upon hydrolysis. Then, acid-promoted allylic rearrangement and sequential cyclization of 1,6-diols **4** might form 2,5-dihydrofuran derivatives **3** in the acidic media. To obtain evidence to understand the

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(9) For preparative methods for 1,4-diiodo-1,3-diene derivatives, see: (a) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829−2832. (b) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. K.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336−3346. (c) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870−2874. (d) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911−2924. (e) Yamaguchi, S.; Jin, R.; Tamao, K.; Sato, F. *J. Org. Chem.* **1998**, *63*, 10060−10062. (f) Xi, C.; Huo, S.; Afifi, T. H.; Hara, R.; Takahashi, T. *Tetrahedron Lett.* **1997**, *38*, 4099−4102.

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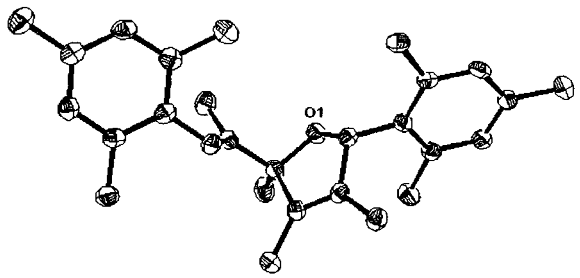
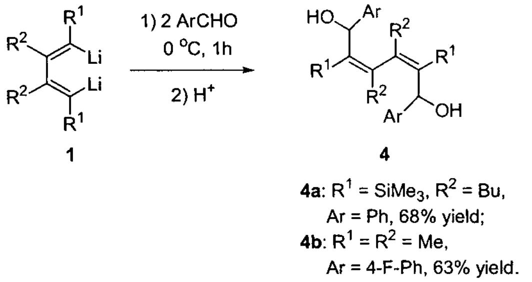


Figure 1. X-ray structure of **3a**.

reaction mechanisms, the following experiments were carried out.

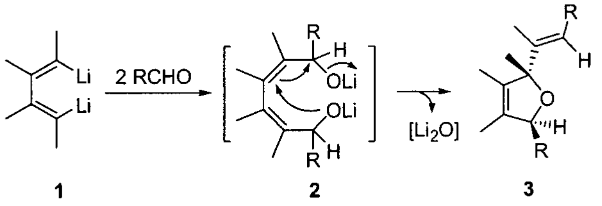
First, 1,4-dilithio-1,3-dienes bearing bulky substituents such as **1e** (Scheme 2, $R^1 = SiMe_3$, $R^2 = n$-Bu) were applied, with the expectation that steric hindrance may prevent 1,6-diols from cyclization. As expected, reaction of **1e** with 2 equiv of benzaldehyde afforded the corresponding 1,6-diol **4a** in 68% isolated yield (Scheme 2). Similarly, when **1a** was treated with 2 equiv of 4-fluorobenzaldehyde, the corresponding 1,6-diol **4b** was isolated in 63% yield. No formation of 2,5-dihydrofuran derivatives was detected in either case. Further treatment of these 1,6-diols with even stronger acids, however, did not result in the formation of 2,5-dihydrofuran derivatives **3**. Instead, messy mixtures were obtained.

Scheme 2



Second, 2 equiv of Me_3SiCl (or MeI) were added to the reaction mixture of **1b** (or **1c**) with PhCHO, with the expectation of trapping 1,6-dialcoholates **2**. However, no formation of the expected 1,6-bis(trimethylsilyl)ethers was obtained. Instead, 2,5-dihydrofuran derivatives **3** were formed. In fact, NMR spectra of the reaction mixture of **1a** with 2,4,6-trimethylbenzaldehyde without hydrolysis showed that 2,5-dihydrofuran derivatives **3a** had been already formed. All of these experimental results indicate that our initial assumption is unlikely. Although further investigation is necessary, a proposed reaction mechanism shown in Scheme 3 might be involved. Aldehydes react with **1** to afford 1,6-dialcoholates **2** as the intermediates. Intramolecular nucleophilic attack by one of the oxygen anions followed by elimination of Li_2O might result in the formation of 2,5-dihydrofuran derivatives. Further investigation into the reaction mechanism, scope, and limitations is in progress.

Scheme 3



Acknowledgment. This work was supported by the National Science Fund for Distinguished Young Scholars (29825105), the Major State Basic Research Development Program (G2000077502-D), and the National Natural Science Foundation of China (29702001 and 20172003). Cheung Kong Scholars Program and Qiu Shi Science & Technologies Foundation are gratefully acknowledged.

Supporting Information Available: Experimental details and full characterization and copies of ^1H and ^{13}C NMR spectra of all new compounds, including the crystal data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0261478