Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 7765–7767

Tetrahedron Letters

Regioselective boron trichloride-mediated aromatic Claisen rearrangement of resorcinol allyl ethers

Fumihiro Ito, Takuya Kumamoto* and Tsutomu Ishikawa

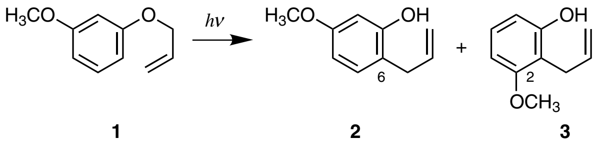
Graduate School of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi, Inage, Chiba 263-8522, Japan

Received 16 July 2005; revised 29 August 2005; accepted 7 September 2005
Available online 22 September 2005

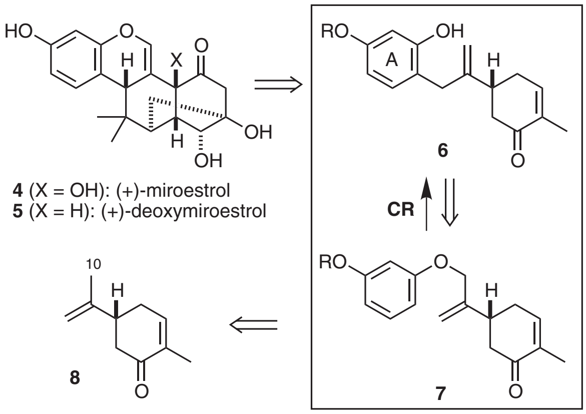
Abstract—The regioselective Claisen rearrangement of resorcinol allyl ethers with boron trichloride was achieved with good selectivity (ca. 13:1) to afford the 6-isomer as major product.

Claisen rearrangement (CR)[1] is one of versatile carbon–carbon bond forming reactions and its aromatic version is most useful for the preparation of 2-allylphenols. However, the non-selective introduction of carbon unit is usually encountered when the resorcinol derivatives **1** are used as substrates for the rearrangement (Scheme 1).[2] Syamaia and Ramamurthy [3] reported the regioselective photo-CR of **1**–α-cyclodextrin complex to 6-isomer **2**, but this system is not suitable for gram-scale preparation. In this letter, we report the regioselective boron trichloride (BCl_3)-mediated aromatic CR of resorcinol allyl ethers.

As a part of our chemical approaches to Thai miracle herb 'kwao keur' (*Pueraria mirifica*),[4] we have started the synthetic studies toward strong phytoestrogens (+)-miroestrol (**4**)[5] and (+)-deoxymiroestrol (**5**), in which regioselective aromatic CR of resorcinol allyl ethers **7** is the key step for the introduction of the A ring at the 10-position of (*R*)-carvone (**8**) (Scheme 2).



Scheme 1.



Scheme 2.

Starting resorcinol ally ethers **7** were prepared as follows: direct displacement of the chlorine atom of 10-chlorocarvone (**10**)[6] with methyl **9b** and benzoyl resorcinol **9d** afforded the corresponding allyl ethers **7b** and **7d**, respectively; however, in the latter case partial hydrolysis to phenol **7a** was observed during reaction course. Thus, the allyl ether **7a** was prepared in 70% yield from **10** by reaction with **9d** followed by hydrolysis. 2-Propyl **7c** and *tert*-butyldiphenylsilyl (TBDPS) ether **7e** were obtained by alkylation or silylation of **7a** (Scheme 3).[7]

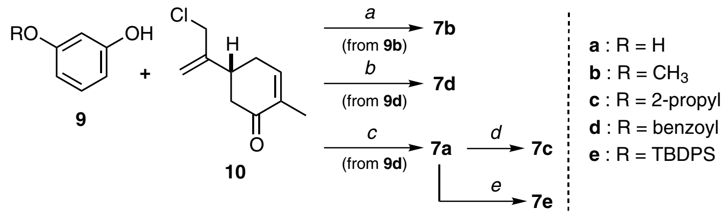
At first, we tried thermal CR (Table 1). Heating the methyl ether **7b** in *N*,*N*-diethylaniline ($PhNEt_2$) afforded the rearranged products **6b** and **11b** in moderate total yield and poor selectivity, the ratio was 1.2:1 with **6b** as a major product (run 1). Reaction proceeded much

---

Keywords: Claisen rearrangement; Regioselectivity; Boron trichloride; Resorcinol allyl ether.

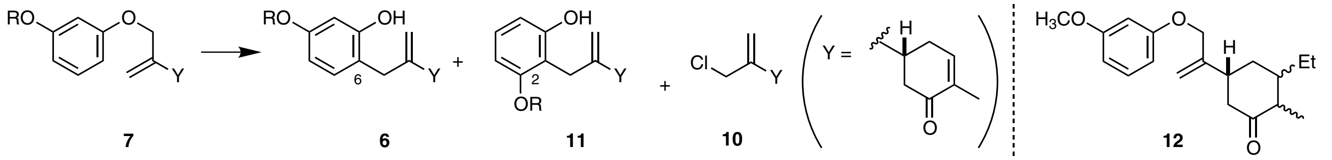
* Corresponding author. Tel./fax: +81 43 290 2911; e-mail: tkuma@p.chiba-u.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.028



Scheme 3. Reagents and conditions: (a) K_2CO_3, DMF, 70 °C, 9 h (77% from **10**); (b) K_2CO_3, DMF, 60 °C, 6 h (40% from **10** as isolated); (c) (1) K_2CO_3, DMF, 60 °C, 6 h; (2) KOH, CH_3OH, 0 °C, 30 min (70% from **10**); (d) 2-bromopropane, K_2CO_3, DMF, 50 °C, 4 h (85%); (e) TBDPSCl, imidazole, DMF, rt, 4 h.

Table 1. CR of the resorcinol ally ethers **7**



Run	R in **7**	Additive	Solvent	Conditions	Yield (%)[a]		
					6	**11**	**10**
1	**7b**: CH_3	None	$PhNEt_2$	140–220 °C, 9.5 h	27	22	0
2	**7b**: CH_3	None	$PhNEt_2$	Microwave, 250 °C, 40 min	44	34	0
3	**7a**: H	None	$PhNEt_2$	Microwave, 200 °C, 45 min	38	28	0
4	**7c**: 2-Propyl	None	$PhNEt_2$	Microwave, 250 °C, 30 min	34	18	0
5	**7d**: Benzoyl	None	$PhNEt_2$	Microwave, 250 °C, 50 min	28	28	0
6	**7e**: TBDPS	None	$PhNEt_2$	Microwave, 250 °C, 40 min	42[b]	24[b]	0
7	**7b**: CH_3	BCl_3	CH_2Cl_2	−50 to −20 °C, 3 h	54	10	19

[a] Isolated yields from corresponding **7** unless otherwise noted.

[b] Isolated yields from **7a** in two steps.

faster under microwave condition and afforded better chemical yields,[8] but regioselectivity was not improved (run 2). Reactions with varying electronic and steric factors on the *meta* substituents showed the same kind of regioselectivities in the range of 1:1 to 2:1 (runs 3–6). Next, we examined the rearrangement of the methyl ether **7b** in the presence of additives. No reaction occurred in the presence of montmorillonite K10 (MK10)[4c,d] in refluxing benzene. The reaction with diethylaluminum chloride[9] in dichloromethane (CH_2Cl_2) gave an ethyl-inserted product **12** in 47% yield as a 2.3:1 mixture of diastereomers in place of rearranged products. The reaction with aluminum trichloride in CH_2Cl_2 gave **6b** in only 33% yield.[10] So we next turned to the utilization of BCl_3, which had been reported as a good Lewis acid for regioselective CR of 4-allyloxy-2-methoxycinnamate.[11] A mixture of **7b** and BCl_3 in CH_2Cl_2 was stirred at −50 to −20 °C for 3 h. The rearranged products **6b** and **11b** were smoothly obtained and the desired 6-isomer **6b** was formed as the major isomer in a ratio of ca. 5:1, albeit the concomitant production of a cleaved product **10** (run 7). Thus, it was found that BCl_3 could effectively control the CR of the allyl ether **7b**.

The BCl_3-mediated CR was further examined (Table 2). Nearly the same results were obtained when compound **7a** was used as substrate (run 2) while the selectivity was lowered in the reaction with benzoyloxy-substituted allyl ether **7d** (run 3). 2-Propyl ether **7c** gave a complex mixture containing small amount of **6c**, **11c**, and **10** because of lability of 2-propyl group in acidic condition (run 4). Fortunately, it was found that the yield and the regioselectivity were improved (**6e**/**11e** = 13:1, 76% yield for **6e**) when TBDPS ether **7e** was used (run 5).

Table 2. BCl_3-mediated CR of the resolcinol allyl ethers **7**

Run	R in **7**	Conditions	Yield (%)[a]		
			6	**11**	**10**
1[b]	**7b**: CH_3	−50 to −20 °C, 3 h	54	10	19
2	**7a**: H	−50 °C, 3 h	51	9	8
3	**7d**: Benzoyl	−50 °C, 1 h	23	9	33
4	**7c**: 2-Propyl	−50 °C, 1 h	5[c]		17
5	**7e**: TBDPS	−50 °C, 1 h	76[d]	6[d]	0

[a] Isolated yields from corresponding **7** unless otherwise noted.

[b] The data from run 7 in Table 1.

[c] A 4:1 mixture of **6c** and **11c**.

[d] Isolated yields from **7a** in two steps.

Regioselectivity of the BCl_3-mediated CR using resorcinol methyl ether **1** was estimated by ab initio calculation based on B3LYP hybrid functional together with the 6-31+G(d) basis set using Gaussian 98 (Fig. 1). Two stable transition structures for each regioisomer were obtained and it was calculated that the transition structure (HOMO) for the 6-isomer was more stable than that for the 2-isomer in about 3 kcal/mol.[12] These

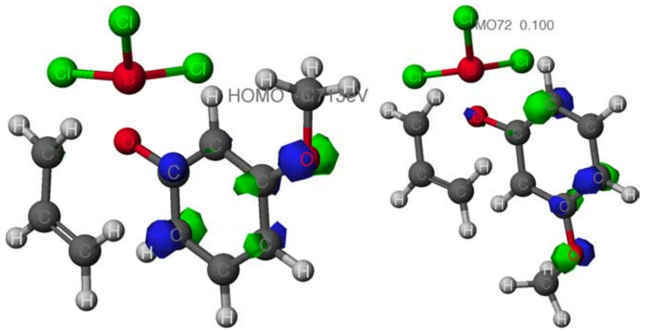


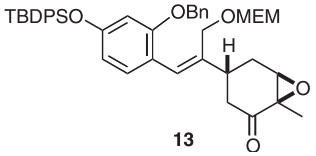
Figure 1. Calculated HOMO of transition structures of BCl_3-mediated CR of **1**; left: rearrangement at the 6-position, right: rearrangement at the 2-position.

results could suggest the origin of this regioselectivity observed in the BCl_3-mediated CR. Although the reason of the improved regioselectivity on the TBDPS ether **7e** is not clear, the electron density of the 2-position of benzene ring would be more diminished by siloxy group than by methoxy group.

In conclusion, it was found that the regioselectivity of CR of resorcinol allyl ethers **7**, especially the TBDPS ether **7e**, could be controlled by BCl_3. Further mechanistic approaches for the CR and the synthetic studies toward miroestrols are under investigation.[13]

References and notes

1. Recent review: Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
2. Gozzo, F. C.; Fernandes, S. A.; Rodorigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *J. Org. Chem.* **2003**, *68*, 5493–5499.
3. Syamaia, M. S.; Ramamurthy, V. *Tetrahedron* **1988**, *44*, 7223–7233.
4. (a) Chansakaow, S.; Ishikawa, T.; Seki, H.; Sekine, K.; Okada, M.; Chaichantipyuth, C. *J. Nat. Prod.* **2000**, *63*, 173–175; (b) Chansakaow, S.; Ishikawa, T.; Sekine, K.; Okada, M.; Higuchi, Y.; Kudo, M.; Chaichantipyuth, C. *Planta Med.* **2000**, *66*, 572–575; (c) Iwasaki, M.; Watanabe, T.; Ishikawa, T.; Chansakaouw, S.; Higuchi, Y.; Tahara, S. *Heterocycles* **2004**, *63*, 1375–1392; (d) Ito, F.; Iwasaki, M.; Watanabe, T.; Ishikawa, T.; Higuchi, Y. *Org. Biomol. Chem.* **2005**, *3*, 674–681.
5. Total synthesis of (+)-miroestrol: Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327–9328.
6. Weinges, K.; Schwarz, G. *Liebigs Ann. Chem.* **1993**, 811–814.
7. Compound **7e** was obtained as a mixture of side product derived from TPDPSCl.
8. Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166–3167.
9. Microwave reaction apparatus: CEM Discover. Conditions: 300 W, 100 psi.
10. The generation of **11b** was not observed in this reaction.
11. Cairns, N.; Harwood, L. M.; Astles, D. P.; Orr, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3095–3100.
12. It has been reported that there is no difference between two transition-state energy levels for both reaction pathways from **1** to **2** and **3** in thermal condition: see Ref. 2.
13. Compound **6b** has been converted to methoxyethoxymethyl (MEM) ether **13** (Bn: benzyl) in seven steps. The details will be reported elsewhere.



13