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# REACTION OF $\alpha$ -SUBSTITUTED $\alpha$ -ETHOXY-2,6-DIMETHYL-4-METHOXYTOLUENES WITH HYDRIODIC ACID

by

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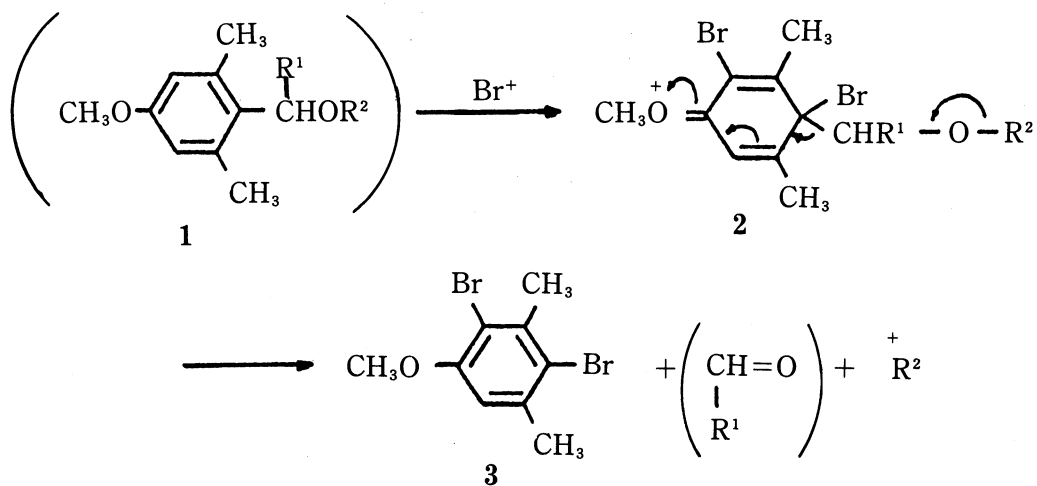
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## Abstract

The Reaction of  $\alpha$ -ethoxy-2,6-dimethyl-4-methoxytoluenes possessing electron-donating and -withdrawing groups at the benzylic position, with hydriodic acid afforded a variety of products and their formation paths were considered.

## Introduction

The reaction of bromine to 2,6-dimethyl-4-methoxybenzyl alcohol derivatives (1) possessing various electron-donating and -withdrawing substituents at the benzylic position have been studied.<sup>1)</sup> In the reaction, the oxonium intermediate

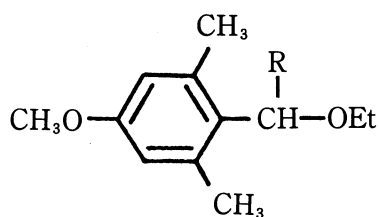


Scheme 1

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**2** from the electrophilic displacement to aromatic nuclei by bromo cation, underwent the cleavage of C-C bond to give the bromide **3**, the formation of which was observed to be strongly affected by the electronegativity of a benzylic substituent.

Hydriodic acid is generally used for the cleavage of ether linkage and the reduction of aryl compound.<sup>2)</sup> Since it is presumed that the ether cleavage reaction was in competition with the protonolysis to aromatic nuclei in the reaction of a benzyl ether with hydriodic acid, we have devoted considerable attention to the reaction of it to 2,6-dimethyl-4-methoxybenzyl ethyl ethers (**4**), especially to the effects of benzyl substituents. To compare the effect of substituent, a series of 2,6-dimethyl-4-methoxybenzyl ethyl ethers (**4**) possessing various electron-donating and -withdrawing substituents, Et, Me, CONH<sub>2</sub>, CO<sub>2</sub>Me and CN, at the benzylic position were synthesized from 3,5-xyleneol via 2,6-dimethyl-4-methoxybenzaldehyde<sup>3)</sup> and the reaction was studied in hydriodic acid.



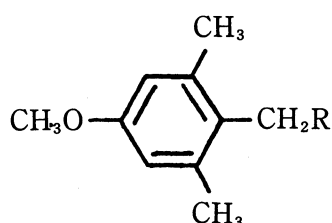
- 4 a : R=CN  
 4 b : R=CO<sub>2</sub>Me  
 4 c : R=CONH<sub>2</sub>  
 4 d : R=CH<sub>3</sub>  
 4 e : R=CH<sub>2</sub>CH<sub>3</sub>

Fig. 1

### Results and Discussion

The reaction of  $\alpha$ -substituted  $\alpha$ -ethoxy-2,6-dimethyl-4-methoxytoluenes, **4a-4e**, with 57% hydriodic acid was studied at 10°C. The ethers, **4a** (R=CN), **4b** (R=CO<sub>2</sub>Me) and **4c** (R=CONH<sub>2</sub>), possessing electronegative groups at benzylic position afforded the product **5** (yield : **5a** : 59%, **5b** : 90%, **5c** : 84%) derived from the cleavage of benzylic C-O bond, while main products from **4d** (R=Me) and **4e** (R=Et) possessing electron-donating alkyl groups were stylenes **6d** (33%) and **6e** (84%). In the reaction of **4d**, two different type dimers, 1,3-diaryl-1-butene **7** (30%) and dibenzyl ether **8** (9%), were also isolated. The structures of these products were identified by the IR and <sup>1</sup>H NMR spectra and elemental analysis, and the stereochemistry of double bonds in the stylenes **6e** and **7** were assigned as trans from their coupling constants of 17.5 and 17.0 Hz. On the other hand, the dibenzyl ether **8** was identified as the racemic isomer by the direct

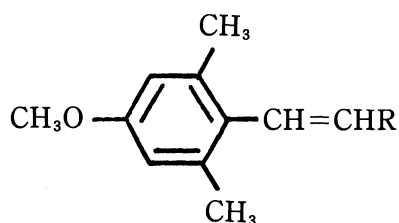
comparison with an authentic sample.<sup>4)</sup> Two isomers of bis( $\alpha$ -methyl-2,6-dimethyl-4-methoxybenzyl) ethers are accessible from 1-(2,6-dimethyl-4-methoxyphenyl)ethanol by acid dehydration reaction but the presence of the meso isomer could not be detected in the reaction products from **4d**.



**5a** : R=CN

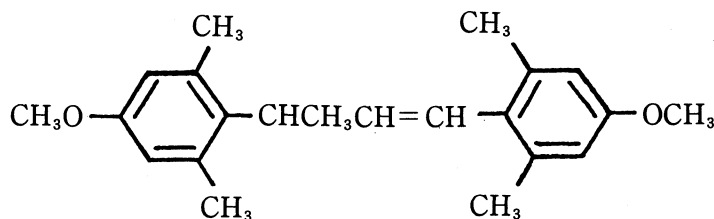
**5b** : R=CO<sub>2</sub>Me

**5c** : R=CONH<sub>2</sub>

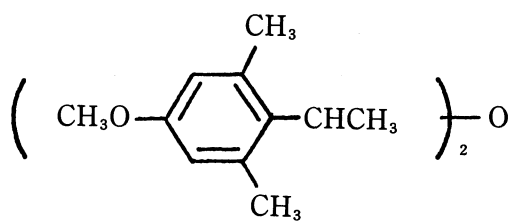


**6d** : R=H

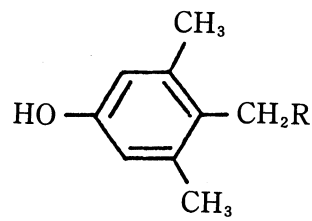
**6e** : R=CH<sub>3</sub>



**7**



**8**



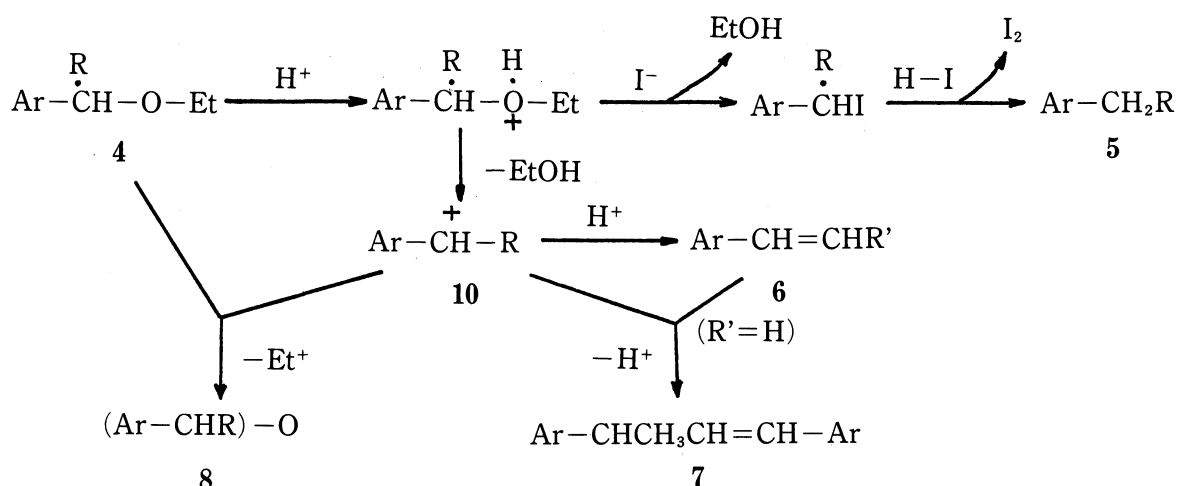
**9b** : R=CO<sub>2</sub>H

**9c** : R=CONH<sub>2</sub>

Fig. 2

Although there may be several mechanism by which the formation of the compounds 5-8 can be explained, Scheme 2. is one of simple ones. The electron-donating alkyl substituent at benzylic position stabilizes a benzyl cation 10, which easily produces the styrene 6. The attack by the cation 10 upon the styrene 6 and the ethyl ether 4 should give the dimers 7 and 8, respectively. The compound 7 was also obtained from 6d by the acid treatment, which well supported the proposed mechanism. No formation of dimers from 4e and 6e must result from their steric factors.

On the other hand, a protonolysis to aromatic nuclei was observed in the reaction of 4d and 4e under reflux to give 3,5-xylenol in 40 and 46% yields. In such reaction condition, the compounds 6d, 6e, 7 and 8 also afforded 3,5-xylenol. However, 4a-4c and 5a-5c did not afford 3,5-xylenol even under reflux but the fission of the ether linkage and the hydrolysis of cyano group alone occurred to give the corresponding phenols 9b and 9c. This is attributed to the decrease of the electron density on aromatic nuclei by the electron-withdrawing effect of the benzyl substituents.



Scheme 2

### Experimental

All melting and boiling points are uncorrected.

**Reaction Materials.** 4a<sup>1)</sup>: mp 49-50°C. 4b<sup>1)</sup>: bp 109-111°C / 7 mmHg (1 mmHg ~ 133.322 Pa). 4c<sup>1)</sup>: mp 121-122°C. 4d<sup>1)</sup>: bp 86-88°C / 7 mmHg. 4e: bp 92-93°C / 7 mmHg; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  = 0.90 (3 H, t, J = 7.3 Hz), 1.18 (3 H, t, J = 7.3 Hz), 1.78 (2 H, dq, J = 7.5 and 7.3 Hz), 2.35 (6 H, s), 3.22 (2 H, q, J = 7.3 Hz),

3.68 (3 H, s), 4.50 (1 H, d,  $J=7.5\text{Hz}$ ), 6.45 (2 H, s). Found: C, 75.50; H, 10.12%  
Calcd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$ : C, 75.63; H, 9.92%.

**General Procedure for the Reaction of the Ethers 4a-4c with Hydriodic Acid.** (i) At  $10^\circ\text{C}$ . A mixture of the benzyl ether (500 mg) in 57% hydriodic acid (15 ml) was stirred at  $10^\circ\text{C}$  for 1 h. After the addition of ice-water (30 ml), the reaction mixture was extracted with  $\text{CHCl}_3$  and the soln was washed with water, aq  $\text{Na}_2\text{S}_2\text{O}_3$  soln and water, successively. The crude product was chromatographed over silica gel. (ii) Under reflux. A mixture of the benzyl ether in 57% hydriodic acid was refluxed for 1 h with stirring. After the addition of water, the reaction mixture was treated with a similar way described above.

**Reaction Products.** **5a**: mp  $63-64^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=2.32$  (6 H, s), 3.55 (2 H, s), 3.75 (3 H, s), 6.60 (2 H, s). Found: C, 75.44; H 7.62; N, 8.17%. Calcd for  $\text{C}_{11}\text{H}_{13}\text{NO}$ : C, 75.40; H, 7.48; N, 7.99%. **5b**: bp  $115-117^\circ\text{C}/7\text{ mmHg}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=2.27$  (6 H, s), 3.60 (2 H, s), 3.64 (3 H, s), 3.73 (3 H, s), 6.55 (2 H, s). Found: C, 69.16; H, 7.92%. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_3$ : C, 69.21; H, 7.74%. **5c**: mp  $176-178^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=2.31$  (6 H, s), 3.53 (2 H, s), 3.76 (3 H, s), 5.92 (2 H, br), 6.60 (2 H, s) Found: C, 68.51; H, 7.79; N, 7.22%. Calcd for  $\text{C}_{11}\text{H}_{15}\text{O}_2$ : C, 68.37; H, 7.82; N, 7.15%. **6d**: bp  $65-67^\circ\text{C}/7\text{ mmHg}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=2.21$  (6 H, s), 3.70 (3 H, s), 5.12 (1 H, dd,  $J=18$  and 2 Hz), 5.40 (1 H, dd,  $J=11$  and 2 Hz), 6.56 (2 H, s), 6.60 (1 H, m). Found: C, 81.55; H, 8.87%. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}$ : C, 81.44; H, 8.70%. **6e**: bp  $86-89^\circ\text{C}/7\text{ mmHg}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=1.78$  (3 H, d,  $J=7\text{ Hz}$ ), 2.20 (6 H, s), 3.71 (3 H, s), 5.90 (1 H, m), 6.13 (1 H, br d,  $J=17.5\text{ Hz}$ ), 6.58 (2 H, s). Found: C, 81.80; H, 9.16%. Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}$ : C, 81.77; H, 9.15%. **7**: viscous oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta=1.48$  (3 H, d,  $J=6.6\text{ Hz}$ ), 2.20 (6 H, s), 2.34 (6 H, s), 3.72 (6 H, s), 4.12 (1 H, m), 5.84 (1 H, dd,  $J=17$  and 4.5 Hz), 6.18 (1 H, br d,  $J=17\text{ Hz}$ ), 6.54 (4 H, s). Found: 81.75; H, 8.91%. Calcd for  $\text{C}_{22}\text{H}_{28}\text{O}_2$ : C, 81.44; H, 8.70%. **8<sup>d</sup>**: mp  $102-104^\circ\text{C}$ . **9b**: mp  $157-158^\circ\text{C}$ ; methyl ester: mp  $61-62^\circ\text{C}$ . Found: C, 68.02; H, 7.17%. Calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_3$ : C, 68.02; H, 7.27%. **9c**: mp  $227-228^\circ\text{C}$ . Found: C, 67.01; H, 7.27; N, 7.72%. Calcd for  $\text{C}_{10}\text{H}_{13}\text{NO}_2$ : C, 67.02; H, 7.31; N, 7.82%. 3,5-Xylenol: mp  $62-64^\circ\text{C}$ .

**Reaction of 6d and 6e with Hydriodic Acid at  $10^\circ\text{C}$ .** In a similar manner described above **6d** and **6e** were treated with hydriodic acid at  $10^\circ\text{C}$  for 1 h. **6d** gave **7** (49%) and unchanged **6d** (42%). **6e** was recovered unchanged.

**Reaction of 6d, 6e, 7 and 8 with Hydriodic Acid under Reflux.** In a similar manner described above, **6d**, **6e**, **7** and **8** were refluxed in hydriodic acid for 1 h to give 3,5-xylenol in 40, 46, 42 and 52% yields, respectively.

**Reaction of 5a, 5b and 5c with Hydriodic Acid under Reflux.** **5a** and **5c** afforded **9c** and **5b** gave **9b**.

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