Selective Mono- and Dibromination of Thymol by Electrolysis in Acetonitrile and Methanol

Isao TANIGUCHI,* Kouzou TAKADA, Hiroko YAMAGUCHI, and Kazuo YASUKOUCHI
Department of Industrial Chemistry, Faculty of Engineering, Kumamoto University, Kurokami, Kumamoto 860

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Synopsis. For anodic bromination of thymol, MeCN and MeOH were suitable solvents for mono- and dibromination respectively. In MeCN, no dibrominated product was observed even when four Faradays per mole of thymol were passed.

Regioselective halogenation is one of the attractive subjects in electroorganic synthesis. Electrochemical chlorination of benzene derivatives in aqueous solutions was developed by Osa *et al.*1) by using an α-cyclodextrin immobilized electrode. Gileadi *et al.*2) have shown that the product ratio of bromophenols for anodic bromination of phenol depended on the charge consumed in aqueous solutions. In nonaqueous solvents, regioselective halogenation takes place at ordinary anodes. Matsuda *et al.*3) have recently reported that para-preferential chlorination of alkoxybenzenes proceeded at a Pt electrode in *N,N*-dimethylacetamide and *N,N*-dimethylformamide, whereas in methanol, 2,4-dichlorophenetole was the product.4) We have also reported5) that anisole was easily brominated in high para-selectivity in acetonitrile. Recentrly, Becker6) and Torii7) reviewed studies of anodic halogenation. However, information on selective halogenation in nonaqueous solvents is still limited.8)

Hence we have examined anodic bromination of thymol (*p*-cymene-3-ol) in acetonitrile (MeCN) and methanol (MeOH), because thymol derivatives are useful for medicinal materials.

Experimental

Controlled-potential electrolysis (CPE) was carried out at 25 °C by using a two-compartment cell. The amount of charge consumed was measured by a Hokuto Denko HF-201 coulometer. The working (5×8 cm^2) and the counter electrodes were Pt plates. The anolyte was 50 cm^3 in volume. An Ag/0.01 M $AgClO_4$ in MeCN or MeOH was used as a reference electrode. Anode potentials for CPE were determined from the cyclic voltammograms of the test solutions. The products were analyzed gas chromatographically. The column used was 2 m×3 mmϕ SUS packed with 5% polyethylene glycol 20 M on Uniport HP. Authentic samples of bromothymols donated from Kohjin Co., were identified by mass spectrometry. No significant difference in product distribution was observed when CPE was undertaken at temperatures between 0 and 40 °C. Throughout this paper 1 M=1 mol dm^{-3}.

Results and Discussion

Figure 1 shows the change in the yield of product as a function of the amount of charge passed for anodic bromination of thymol. In MeCN, thymol was brominated to 6-bromothymol at a current efficiency of more than 90% when up to one equivalent charge (two Faradays per mole of thymol) was passed. Further electrolysis caused a slight decrease in the amount of 6-bromothymol, but no dibrominated product was obtained. On the other hand, in MeOH, the initial product was 6-bromothymol, as in MeCN, and was further brominated to 2,6-dibromothymol with high selectivity in a yield of *ca.* 90% at two equivalent charges. Typical results of CPE are summarized in Table 1. In MeCN, neither the anode potential nor the concentration ratio of thymol to bromide ion affected the selective monobromination (runs 1—10).

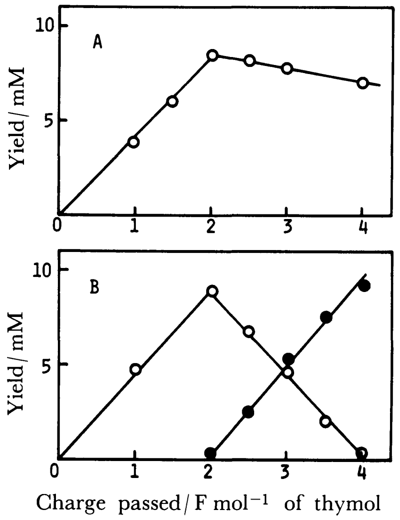

Fig. 1. Change in the yields of products as a function of the amount of charge passed for anodic bromination of thymol in MeCN (A) and MeOH (B). ○; 6-bromothymol and ●; 2,6-dibromothymol. Electrolyses were carried out in solutions consisted of 10 mM thymol, 20 mM bromide and 0.1 M perchlorate.

In MeOH, the total yield and the selectivity of brominated products decreased at potentials more positive than 0.55 V (*vs.* Ag/Ag$^+$ in MeOH). This is because oxidation of thymol itself and of the solvent both occurred (runs 11—18). No significant influence of the counter ion of the bromide ion source on the bromination behavior was observed (runs 11, 12, and 19—24). Thus, clearly, selective mono- and dibromination of thymol can be performed in MeCN and MeOH, respectively; an excess amount of bromide with respect to thymol is preferable for effective bromination in high selectivity (runs 7—10, 13, and 14).

A possible explanation for the difference in regioselectivity in MeCN and MeOH can be given as follows: (i) Since MeOH is a strong electron-acceptor (acceptor number, *AN*=41.39)), anodically generated bromine would be more polarized, $Br\xrightarrow{\delta^+}Br\xrightarrow{\delta^-}S$ where S is the solvent, in MeOH than in MeCN (*AN*=19.39)), and bromine molecules in MeOH become much more active than in MeCN. (ii) In MeCN, Br_3^- which is not active for bromination5,10) is stable and the equilibrium of $Br_2+Br^-=Br_3^-$ lies to the right (pK=$-7$11)), while unstability of Br_3^- in an amphiprotic solvent such as

Table 1. Anodic bromination of thymol

Run	Anolyte[a]	Anode potential[b]	Charge passed/ equivalent[c]	Yield of product[d]/% (Selectivity/%) 6-Bromothymol	2,6-Dibromothymol
1	MeCN–Et$_4$NBr	0.85	1	85.9(100.0)	0(0)
2			2	71.6(100.0)	0(0)
3		1.0	1	89.9(100.0)	0(0)
4[e]			2	65.9(100.0)	0(0)
5		1.2	1	79.0(100.0)	0(0)
6[e]			2	64.5(100.0)	0(0)
7[f]		0.85	1	98.1(100.0)	0(0)
8[f]			2	96.4(100.0)	0(0)
9[g]		0.85	1	94.2(100.0)	0(0)
10[g]			2	97.5(100.0)	0(0)
11	MeOH–NaBr	0.35	1	88.5(98.4)	1.4(1.6)
12			2	3.7(4.0)	87.9(96.9)
13[f]		0.35	1	93.1(98.7)	1.2(1.3)
14[f]			2	0(0)	93.8(100.0)
15		0.55	1	70.0(92.8)	5.4(7.2)
16[h]			2	8.7(10.1)	77.7(89.9)
17		0.75	1	68.4(93.4)	4.8(6.6)
18[h]			2	10.1(14.7)	58.6(85.3)
19	MeOH–LiBr	0.35	1	85.2(95.6)	3.9(4.4)
20			2	8.8(9.0)	89.3(91.0)
21	MeOH–NH$_4$Br	0.35	1	80.0(96.3)	3.1(3.7)
22			2	0.1(0.1)	88.3(99.9)
23	MeOH–Et$_4$NBr	0.35	1	85.5(97.9)	1.8(2.1)
24			2	7.4(8.1)	83.5(91.9)

a) 50 cm^3 of solution consisted of 10 mM thymol, 20 mM bromide and 0.1 M perchlorate as a supporting electrolyte, except runs 7—10, 13, and 14. b) V *vs.* Ag/0.01 M AgClO$_4$ in MeCN or in MeOH. Potentials for CPE were chosen at which bromine was produced. c) One equivalent charge is 96.5 C (=2 F/mol of thymol). d) Based on 10 mM thymol. The yields were calculated from gas chromatographic data. The values also indicate the current efficiencies for the bromination. e) Oxidation of 6-bromothymol also occurred. f) 10 mM thymol and 50 mM bromide. g) 10 mM thymol and 100 mM bromide. h) Oxidation products of thymol itself were also detected.

MeOH shifts the equilibrium far to the left (pK= -2.2[11]). Thus, the actual concentration of Br$_2$ during electrolysis is larger in MeOH than in MeCN. (iii) Moreover, bulky bromine molecules may be solvated in MeCN through the dispersion force between solvent and bromine molecules, but the solvation would be unlikely in MeOH because of low acceptability of hydrogen-bond of Br$_2$; thus the active bromine would be larger in size in MeCN than in MeOH. Accordingly, these kinetic and steric factors make dibromination (the second bromination at 2-position) of thymol favorable in MeOH, but not in MeCN.

The following results also support the difference in regio-selectivity in MeCN and MeOH. Chlorination of anisole in MeCN gave monochlorinated products,[8] whereas in MeOH, 2,4-dichloroanisole was obtained as well, as reported by Matsuda *et al.*[4] For bromination of phenol, di- and tribromophenols were obtained in MeOH, but only in small amounts in MeCN.

On the other hand, exceptions were also observed. Bromination and iodination of anisole gave *p*-halogenoanisole in high para-selectivity and no dihalogenation took place at all, even in MeOH. This can be explained in terms of the steric hindrance at the ortho position by the methoxyl group for larger halogen molecules.

Finally, MeCN and MeOH are, rather generally, promising solvents for mono- and di- (and/or multi) halogenation of aromatic compounds, respectively.

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