Pergamon

Tetrahedron, Vol. 52, No. 11, pp. 3889-3896, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00056-7

SELECTIVE AND ONE-POT FORMATION OF PHENOLS BY ANODIC OXIDATION[1)]

Kazuo Fujimoto,† Yuichiro Tokuda,† Hirofumi Maekawa,
Yoshiharu Matsubara,† Takumi Mizuno, and Ikuzo Nishiguchi*

Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Jyoto-ku, Osaka 536
†Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University, 3-4-1, Kowakae, Higashi-osaka 577

Abstract: Direct monohydroxylation of benzene and substituted benzenes was successfully performed by anodic oxidation to form the corresponding phenol derivatives in good yields. The anodic oxidation was generally carried out in a mixed solvent of trifluoroacetic acid and dichloromethane containing triethylamine using a divided cell equipped with a platinum plate as the anode, a carbon rod as the cathode. Benzene derivatives having electron withdrawing groups were suitable for the present electrochemical oxidation. It was clarified that aryltrifluoroacetates were formed as the initial products from the reaction of the radical cations, generated by one electron transfer from the substrates, with trifluoroacetic acid, followed by hydrolysis during work-up to give the corresponding phenols.

Introduction

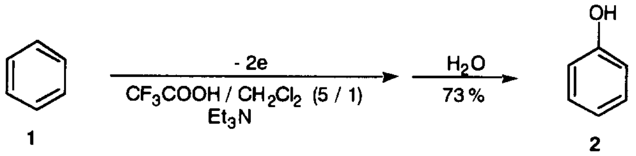
Phenols were important principle chemicals for a variety of industrial and organic materials such as phenol resins and bisphenol A. Numerous synthetic methods of phenols such as classical sulfonation followed by alkali fusion, metal-catalyzed air-oxidation[2)] and electrooxidative methods[3a), 3b)] have been reported while the so-called Cumene process is widely utilized as the most practical industrial process. Synthetic utilities of most of direct methods for oxidative formation of phenols have been considerably limited because of a difficult, principle but inevitable problem that the introduced hydroxyl group activates the benzene ring and makes it further prone to oxidation to the corresponding benzoquinones. Therefore, the reaction must be generally stopped at the stage of low conversion of benzenes to obtain high selectivity in phenols' production.

Recently selective monohydroxylation of only some of aromatic compounds such as chloro- and trifluoromethyl benzenes has been attained using electrooxidation in trifluoroacetic acid (TFA) containing sodium trifluoroacetate and trifluoroacetic anhydride followed by hydrolysis[3c~3f)], although phenol itself was formed through anodic oxidation of benzene under the similar conditions only in a 27%[4)] or a 12% yield[5)].

In this study, we wish to present efficient and selective monohydroxylation of benzene (**1**) and substituted benzenes (**3** and **5**) through anodic oxidation in a mixed solvent of TFA and dichloromethane followed by work-up using water to give the corresponding phenols (**2**, **4** and **6**) in good yields. This method may be characterized by high selectivity and good yield of the products, phenols, even at the high consumption of the starting benzene derivatives, and simple procedure of one-pot introduction of a hydroxyl group.

Results and Discussion

At first, our attention was mainly concentrated on efficient anodic transformation of benzene itself (**1**) to phenol (**2**) since hitherto known methods[4), 5)] did not give satisfactory results. It was found that transformation from **1** to **2** was largely influenced by many factors of reaction conditions, such as relative ratio of TFA and CH_2Cl_2, nature and an amount of a supporting electrolyte, a kind of electrodes, an amount of electricity and current density. The typical results were summarized in Scheme 1 and Table 1, in which **2** was isolated in a 67% yield based on used **1** under the optimum conditions (entry 8 and Experimental).



Scheme 1.

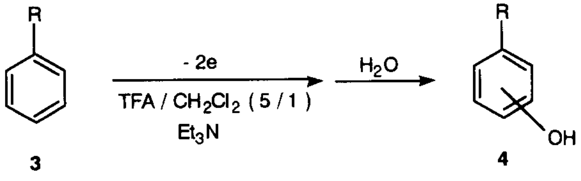
Table 1. Anodic Monohydroxylation of Benzene (1)[a)]

Entry	Relative Ratio	S. E.[b)]	C. D.[c)]	B. C.[d)]	Isolated Yield of Phenol
	CF_3COOH / CH_2Cl_2	(mol / l)	mA / cm^2	mol / l	%
1	100 / 0	nBu_4NCl (0.2)	7.5	0.20[e)]	15
2	100 / 0	Et_4NOTs (0.6)	7.5	0.20[e)]	2
3	100 / 0	NaOAc (0.6)	7.5	0.20[e)]	45
4	100 / 0	Et_3N (1.0)	7.5	0.33	49
5	83/17	Et_3N (2.0)	7.5	0.33	62
6	83/17	Et_3N (4.0)	7.5	0.33	60
7	83/17	Et_3N (2.0)	3.8	0.33	50
8	83/17	Et_3N (2.0)	11.3	0.33	67
9	83/17	Et_3N (2.0)	11.3	0.33	72[f)]
10	83/17	Et_3N (2.0)	15.0	0.33	62
11	34/66	Et_3N (2.0)	11.3	0.33	50
12	83/17	Et_3N (2.0)	11.3	0.66	73[g)]
13	83/17	Et_3N (2.0)	11.3	1.65	48[g)]

a) An amount of electricity passed through the system was 3860 coulombs, which corresponds to the theoretical amount (2.0 F/mol) for 20 mmole of **1**. b) Supporting electrolyte.
c) Current density. d) Benzene concentration in 60 ml of a solvent.
e) Benzene concentration in 100 ml of CF_3COOH.
f) Current efficiency when 1930 coulombs (2.0 F/mol for 10 mmole of **1**) passed through the system.
g) Current efficiency when 3860 coulombs (2.0 F/mol for 20 mmole of **1**, which is a half or one fifth of used benzene) passed through the system.

It may be interesting that the presence of 2.0 mole equivalents excess of **1** based on the theoretical amount of electricity brought about some increase in the current efficiency (72~73% in entries 9 and 12) while that of more than 2.0 eq. moles of **1** resulted in the considerable decrease (entry 13). In this reaction, the addition of CH_2Cl_2 to TFA led to increase in solubility of the substrate. Furthermore, employment of a large amount of a salt between Et_3N and TFA as a supporting electrolyte resulted in large increase in concentration of CF_3COO^- anion. Good yield of **2** may be attributed to these factors.

Anodic monohydroxylation proceeded smoothly for a variety of monosubstituted benzenes (**3**) possessing an electrowithdrawing group rather than ones with an electrodonating group to give the positional mixtures (ortho, meta, para) of the corresponding phenols (**4**) effectively accompanying quite little formation of the corresponding hydroquinones (Scheme 2)[6].



Scheme 2.

3a, 4a R = Cl
3b, 4b R = Br
3c, 4c R = F
3d, 4d R = CF_3
3e, 4e R = $COCH_3$
3f, 4f R = CO_2Et
3g, 4g R = CHO
3h, 4h R = CN
3i, 4i R = NO_2

Among many benzene derivatives **3a~i**, the reaction of bromobenzene (**3b**) and ethyl benzoate (**3f**) brought about the most efficient hydroxylation to give the mixtures of the three positional isomers (ortho-, meta-, para-) of bromophenol (**4b**) and ethyl hydroxy benzoate (**4f**) in excellent yields of 87% and 89%, respectively, as shown in the following Table 2.

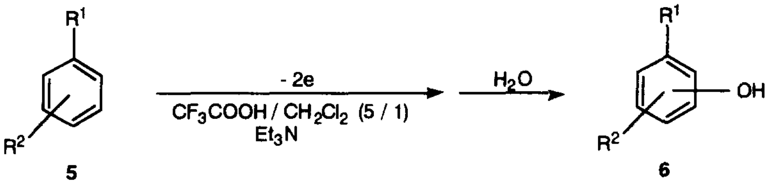
Table 2. Hydroxylation of Mono-Substituted Benzenes (**3**)

Substrate	Supplied electricity	Yield[a)]	Isomer ratio / %
	F / mol	%	o / m / p
3a	2	67	32 / 8 / 60
3b	2	87 (82)[b)]	30 / 9 / 61
3c	2	50	67 / 7 / 26
3d	2	61	23 / 63 / 14
3e	3	43 (41)[b)]	47 / 33 / 20
3f	3	89	44 / 34 / 22
3g	3	33	29 / 47 / 24
3h	4	40	43 / 27 / 30
3i	5	18	44 / 27 / 29

a) Yield of each products was determined by VPC method using nitrobenzene or *p*-cresol as an internal standard. b) Isolated yield after purification by silica gel column chromatography.

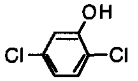
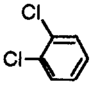
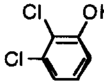
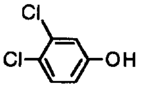
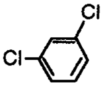
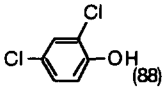
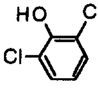
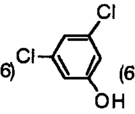
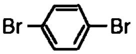
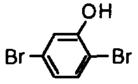
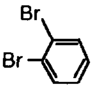
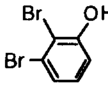
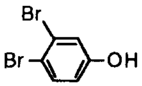
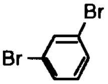
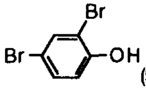
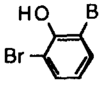
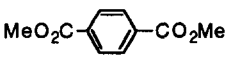
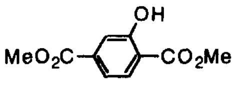
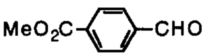
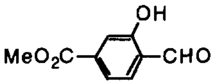
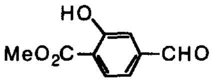
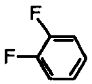
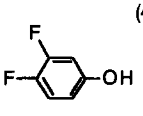
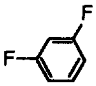
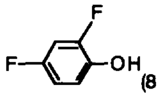
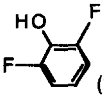
Moreover, it was found that anodic oxidation of dihalogenobenzenes (ortho-, meta-, para-) and diethyl terephthalate (**5g**) gave the corresponding phenols (**6**), as shown in the following Scheme 3 and Table 3.

In these reactions, *m*-dichlorobenzene (**5c**) and *m*-dibromobenzene (**5f**) were transformed to 2.4-dihalogenophenols with high selectivity in good yields, although anodic hydroxylation of *o*- or *p*-dihalogenobenzenes did not necessarily give good results.



Scheme 3.

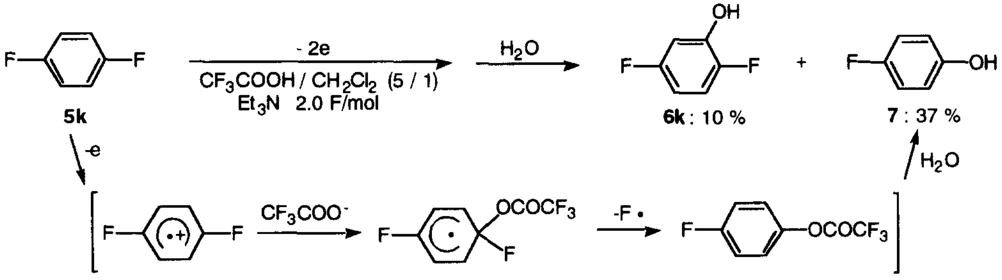
Table 3. Anodic Hydroxylation of Di-Substituted Benzenes (**5a**~**j**)

Substrate		S. E.[a] (F / mol)	Products Yield[b] / %	(Isomer ratio)
	**5a**	2.0	57	 (100)
	**5b**	2.0	68	 (24)  (76)
	**5c**	2.0	78	 (88)  (6)  (6)
	**5d**	2.0	48	 (100)
	**5e**	2.0	62	 (30)  (70)
	**5f**	2.0	72	 (93)  (7)
	**5g**	3.0	47	 (100)
	**5h**	3.0	53	 (42)  (58)
	**5i**	2.0	69	 (100)
	**5j**	2.0	52	 (81)  (19)

a) Supplied electricity. b) Isolated yield.

Unexpectedly, *p*-difluorobenzene (**5k**) gave the defluorinated *p*-fluorophenol (**7**) as the main product rather than the corresponding difluorophenol (**6k**) even under the same conditions, which was quite different from those of other disubstituted benzenes (Scheme 4). The similar phenomenon was observed in the formation of tetrafluorobenzoquinone from anodic oxidation of hexafluorobenzene in TFA[7]. This defluorinated hydroxylation may be initiated by ipso-substitution to a cation radical species generated from **5k** by electron transfer, as shown in Scheme 4.

It may be noteworthy that no use of water in the work-up procedure of the reaction mixture led to some formation of phenyl trifluoroacetate (**1c**; 35-40% yield) accompanying **2** (25-30% yield). This fact indicated that the real product of the present anodic oxidation was not **2** but **1c**, which was found to be readily hydrolyzed to **2** during the work-up using water.



Scheme 4.

Also cyclic voltammetry of anisole derivatives (**8**)[8] in acetonitrile and TFA provided us with significant informations to study the reason why this electrooxidation gave no benzoquinone, the further oxidation product, as shown in Table 4.

Table 4. Anodic Potential of Anisole and Benzene Derivatives (**8**)[a]

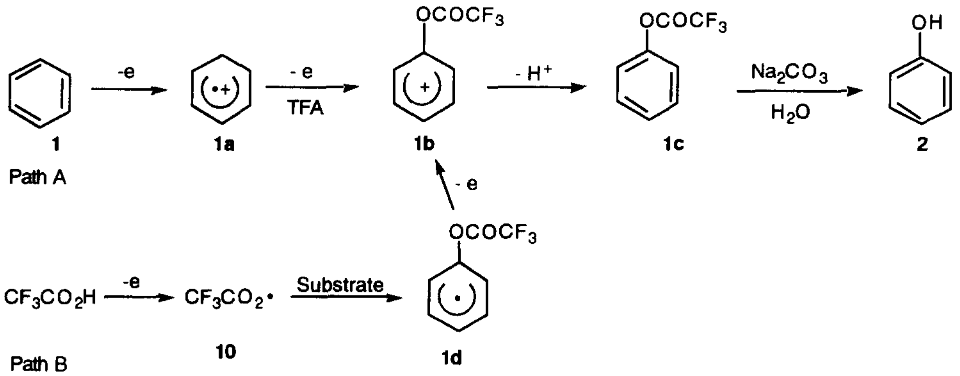
Substance		Ep vs Ag / AgCl	
		CH_3CN / Et_4NClO_4 [V]	CF_3COOH / Et_3N [V]
Anisole	**8a**	1.93	1.70
p-Methoxyphenol	**8b**	1.14	0.92
p-Acetoxyanisole	**8c**	1.65	1.42
p-Methoxyphenyl trifluoroacetate	**8d**	2.2 - 2.5	1.92
Benzene	1	-	2.2 - 2.5
Phenyl trifluoroacetate	1c	-	> 3.0

a) Pt^+ - Pt^-, Sweep Rate 500 mV/s

Thus, introduction of a hydroxyl or an acetoxy group into the benzene ring brought about some decrease in oxidation potential in proportion with the electron-donating ability of the introduced substituent while oxidation potential of **8d** increased to some extent from the parent anisole, indicating that **8d** was less easy to oxidize electrochemically than the parent anisole because of electron-withdrawing character of a trifluoromethyl group. In a similar manner, the study on oxidation potential indicated that phenyl trifluoroacetate (**1c**) was more difficult to oxidize than benzene (**1**) although the results were not so clear-cut as those in the case of anisole derivatives.

The following scheme 5 shows two plausible paths (A and B) for the anodic hydroxylation of **1**. In the reaction path A, **1** is initially subjected to one-electron transfer on the anode to generate a radical cation (**1a**). Nucleophilic addition of a trifluoroacetoxy anion to **1a** followed by the second one-electron oxidation gives the corresponding cation (**1b**), which was subject to deprotonation to afford **1c**. Path B shows the first one-electron oxidation of a trifluoroacetoxy anion to give a trifluoroacetoxy radical (**10**). Radical addition of **10** to **1** followed by the second one-electron oxidation of the aromatic radical species (**1d**) provides **1b** as that shown in path A.

From these experimental results, considerably lowering[9),10)] of oxidation potentials in TFA from those in acetonitrile may support that electron transfer from aromatic compounds to the anode initiated the present anodic oxidation to form aromatic cationic species (path A) rather than electrochemical oxidation of a trifluoroacetoxy anion to generate a trifluoroacetoxy radical (path B).



Scheme 5.

Furthermore, the difficulty in electrochemical oxidation of phenyl trifluoroacetate (**1c**) relative to benzene[11)] may also support the preference of path A leading to the present selective monohydroxylation.

Anyhow, from the viewpoint of simple procedure, high selectivity and satisfactory yield, the present electrochemical monohydroxylation may possess high potentiality for synthesis of some kinds of phenols having halogen atoms or electron-withdrawing substituents.

Experimental Section

General Comments Gas chromatography (GLC) were performed using a Hitachi 163 and a Shimadzu GC-12A. ^{1}H NMR spectra were obtained by a JEOL JNM-EX270 spectrometer. Infrared spectra (IR) were recorded on a JASCO A-3 spectrometer. Mass spectra were recorded on a JEOL JMX-DX 303HF spectrometer.

Reagents All the chemicals of the starting benzene derivatives (**1**, **1c**, **3a~i**, **5a~k**, and **8a~b**) and all the positional isomers of the products phenols (**2**, **4a~i**, **6a~d**, **6f**, **6i~k**, and **7**) were purchased from Nacalai Tesque, Aldrich Chemical Inc., or Tokyo Kasei Organic Chemicals and used as received. Dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Trifluoroacetic acid (98 % pure) was used without any pre-treatment after purchase.

Typical Procedure of electrolysis of benzene derivatives (1, 3a~i and 5a~k) The reaction was carried out in a divided electrolysis cell (100 cm^3) equipped with a ceramic cylinder (25 cm^3) as the diaphragm, a platinum plate (70 x 40 x 0.1 mm) as the anode, and a carbon rod (diameter : 0.8 cm) as the cathode. A mixed solvent (60 cm^3) of TFA and dichloromethane (volume ratio : 5/1) containing triethylamine (120 mmol) was divided into the anodic (ca. 45 cm^3) and the cathodic (ca. 15 cm^3) solutions, and one of benzene derivatives (**1**, **3a~i** and **5a~k**) (20 mmol) was added to the anolyte. The electrolysis was carried out at room temperature under the constant-current conditions (current density : 11.3 mA/cm^2) with stirring until 2.0 F/mol of electricity passed through the system. Then the anolyte was poured into 200 ml of water and the mixture was extracted with three 100 cm^3 portions of ether. The combined ethereal solution was neutralized with 10% aqueous $NaHCO_3$ solution, and dried over anhydrous $MgSO_4$. After removal of the drying agent and evaporation of the solvent, distillation of the residue gave a mixture of ortho-, meta-, para-positional isomers of the corresponding monohydroxylated products. All of the products were isolated by preparative gas chromathography (OV-1, 2 m) and/or column chromathography (silicagel), and identified by comparison of their gas chromathographic and spectroscopic behaviors (^{1}H NMR, IR, UV) with those of the authentic samples.

Dibromophenols (6e)

2,3-dibromophenol M.p. 67-69 °C (Lit.$^{13)}$ M.p. 68-69 °C)

3,4-dibromophenol M.p. 70-71 °C (Lit.$^{14)}$ M.p. 71-73 °C)

Hydroxy dimethyl terephthalate (6g)$^{15)}$ M.p. 94 °C; IR (neat) 3200 (-OH), 1720 (C=O), 1670 (C=O), 1440, and 1200 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) δ 3.92 (3H, s), 3.98 (3H, s) and 7.50-7.91 (3H, m, Ar*H*) ppm.; ^{13}C NMR ($CDCl_3$) δ 52.55, 52.68, 118.43, 119.02, 119.77, 130.09, 136.56, 161.42, 166.04, and 170.03 ppm.; FAB-MS; m/z (%) 211(M^++H 100).

Hydroxy methyl terephthalaldehydates (6h)

Methyl 4-formyl-2-hydroxybenzoate M.p. 77 °C (Lit.$^{16)}$ M.p. 76-77 °C)

Methyl 4-formyl-3-hydroxybenzoate M.p. 134-136 °C (Lit.$^{17)}$ M.p. 135-135.5 °C)

***p*-acetoxyanisole (8c)**$^{18)}$ **8c** was prepared from *p*-methoxyphenol and acetic anhydride in a 91% yield as colorless oil: M.p. 32 °C; IR (neat) 2950, 1750 (C=O), 1510, and 1030 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) δ 2.26 (3H, s, $OCOCH_3$), 3.81 (3H, s, OCH_3), and 6.85-7.01 (4H, m, Ar*H*) ppm.

***p*-methoxyphenyl trifluoroacetate (8d)**$^{19)}$ **8d** was prepared from *p*-methoxyphenol and trifluoroacetic anhydride in a 65% yield as colorless oil: B.p. 196-199 °C; IR (neat) 2950, 1795 (C=O), 1500, and 1030 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) δ 3.81 (3H, s, OCH_3), and 6.91-7.14 (4H, m, Ar*H*) ppm.; ^{13}C NMR ($CDCl_3$) δ 55.68, 114.82(q, *J*=285.5 Hz), 114.87, 121.43, 142.95, 156.21(q, *J*=43.9 Hz), and 158.37 ppm.

Acknowledgment

This work was supported by the Grant-in-Aid for Scientific Research on Priority Area of Electroorganic Chemistry No. 05235107 from the Ministry of Education, Science and Culture, Japan.

References and Notes

1 A preliminary communication : Fujimoto, K.; Maekawa, H.; Tokuda, Y.; Matsubara, Y.; Mizuno, T.; Nishiguchi, I. *SYNLETT*, **1995**, 661-662.

2 Kitano, T.; Kuroda Y.; Mori, M.; Ito, S.; Sasaki, K.; Nitta, M. *J. Chem. Soc. Perkin Trans. 2*, **1993**, 981-985, and references therein.

3 a) Eberson, L. *J. Am. Chem. Soc.*, **1967**, *89*, 4669-4677 ; b) Wellmann, J.; Steckhan, E. *Chem. Ber.*, **1977**, *110*, 3561-3571 ; c) Weinberg, N. L.; Wu, C. N. *Tetrahedron Lett.*, **1975**, *39*, 3367-3370 ; d) Weinberg, N. L. (Hooker Chem.), U. S. P., 4,024,032, **1976** [*Chem. Abstr.*, **1977**, *87*, 13507s] ; e) Bockmair, G.; Fritz, H. P.; Gebauer, H. *Electrochimica Acta.*, **1978**, *23*, 21-23 ; f) So, Y-H.; Becker, J. Y.; Miller, L. L. *J. Chem. Soc. Chem. Commun.*, **1975**, 262-263.

4 Blum, Z.; Cedheim, L.; Nyberg, K. *Acta. Chem. Scand.*, **1975**, *B29*, 715-716.

5 Baudouin, M.; Michelet, D. (Rhone-Poulenc), F. R., 2,422,733, **1977** [*Chem. Abstr.*, **1980**, *92*, 146427r].

6 The reactions using an undivided cell under the similar conditions resulted in quantitative recovery of the starting substrates **1** and **3a~i**.

7 Blum, Z.; Nyberg, K. *Acta. Chem. Scand.*, **1979**, *B33*, 73-75.

8 Since **1** and **1c** did not show any peak potentials (Ep) in their cyclic voltammetry in CH_3CN/Bu_4NClO_4 up to 2.5 V(vs. Ag/Ag^+), oxidation potentials of **8** were measured and shown in Table 4.

9 Oxidation potentials of hydrocarbons in TFA or TFA/CH_2Cl_2 were reported to considerably decrease in comparison with those in CH_3CN and so on.10)

10 Clark, D. B.; Fleischmann, M.; Pletcher, D. *J. Chem. Soc. Perkin 2*, **1973**, 1578-1581, Fritz, H. P.; Würminghausen, T. *J. Chem. Soc. Perkin 1*, **1976**, 610-613.

11 The peak potential of **1** was reported12) to be 2.4 V (vs. SCE) at a Pt-foil electrode and 2.75 V (vs. SCE) at a Pt-film electrode.

12 Osa, T.; Yildiz, A.; Kuwana, T. *J. Am. Chem. Soc.*, **1969**, *91*, 3994-3995.

13 Henley, R.V.; Turner, E. E. *J.Chem. Soc.*, **1930**, 928-940.

14 Liedholm, B. *Acta. Chem. Scand.*, **1984**, *B38*, 877-884.

15 Schulz, L. *Chem. Abstr.*, **1942**, *36*, 7015.

16 Dyke, S. F.; White, A. W. C.; Hartley, D. *Tetrahedron* , **1973**, *29*, 857-862.

17 Wasserman, H. H.; Ackerman, H. W.; Wotiz, H. H.; Liu, T. C. *J. Am. Chem. Soc.*, **1955**, *77*, 973-979.

18 Cavill, G. W. K.; Solomon, D. H. *J.Chem. Soc.*, **1955**, 1404-1407.

19 Kurz, M. E.; Hage G. W. *J. Org. Chem.*, **1977**, *42*, 4080-4084.

(*Received in Japan* 6 *November* 1995; *accepted* 10 *January* 1996)