

Yohji Nakatsuji, Tadashi Mizuno, and Mitsuo Okahara*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka,
Japan 565

Received May 18, 1981

A variety of alkyl- or phenyl-substituted thia-crown ethers were prepared in two or three steps *via* bromoalkoxylation reactions of olefins. Dialkyl- and phenyl-substituted mono- and dithia-crown ethers were obtained as single compounds, whereas monoalkyl-substituted derivatives were a mixture of two positional isomers reflecting the isomeric mixture formation in the bromoalkoxylation reaction.

J. Heterocyclic Chem., **19**, 733 (1982).

Olefins are easily bromoalkoxylated with *N*-bromosuccinimide (NBS) and alcohols (1,2). In the case of oligoethylene glycols both the bromo group and the hydroxy group are introduced into the ends of molecule (3). The cyclization of these types of compounds in basic conditions gave substituted crown ethers (4). On the other hand, oligoethyleneglycols were cyclized to crown ethers in basic conditions by using arenesulfonyl chloride (5,6). Aza crown ethers were also prepared according to this method (7,8).

As thia-crown ethers interact with soft cations in difference from normal crown ethers (9-11), the development of new synthetic methods of preparing a variety of their analogues has been desired from the viewpoint of the effective use of their features. Although unsubstituted thia-crown ethers were successfully prepared by Bradshaw *et al.*, (12-14), the convenient methods of preparing substituted thia crown compounds were scarcely known (15).

In the present study, we attempted the synthesis of substituted mono- and dithia-crown ethers by the combination of bromoalkoxylation and intra- or intermolecular cyclization.

Results and Discussion.

Oligoethylene glycol β -bromoalkyl ethers (**1**) were prepared according to the conventional method (3) (Table 1). They were treated with 2-mercaptoethanol in the presence of sodium hydroxide in ethanol to give the corresponding sulfide **2**. The crude compounds **2** were successively cyclized without further purification by using benzenesulfonyl chloride and sodium hydroxide in dioxane.

The reaction temperature was determined to be 80-90° by the analogy with the optimum temperature in the synthesis of unsubstituted monothia-crown ethers (16). The results of synthesis of substituted monothia-crown ethers **3** are shown in Table 2.

In the bromoalkoxylation reaction, an isomeric mixture of two adducts (Markownikoff and anti-Markownikoff) was obtained except in the cases of styrene (**1b,g,h**) and 2-methyl-1-pentene (**1f**), in which only Markownikoff ad-

Scheme 1

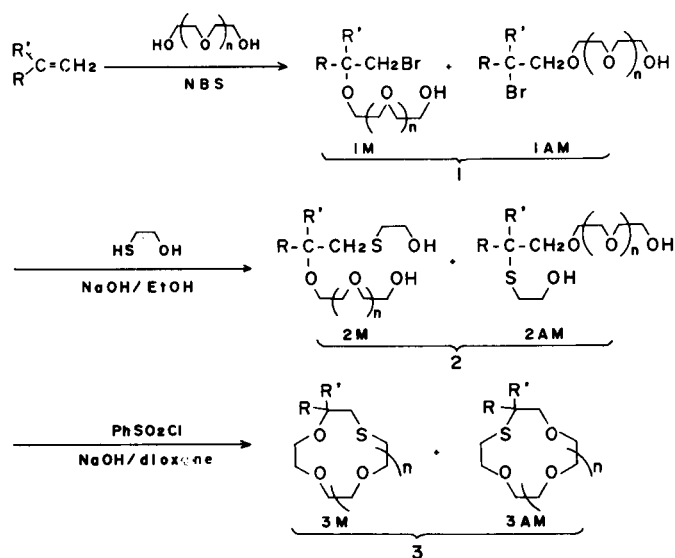


Table 1

Synthesis of Oligoethylene Glycol β -Bromoalkyl Ethers (**1**)

Compound	R	R'	n	Yield (%)	Halogen Found (Calcd.) (%)
1a	C ₄ H ₉	H	1	75	29.6 (29.7)
1b	Ph	H	1	40 (a)	27.4 (27.6)
1c	C ₂ H ₅	H	2	71	28.2 (28.2)
1d	C ₆ H ₁₃	H	2	37 (a)	23.2 (23.4)
1e	C ₈ H ₁₇	H	2	88	22.0 (21.6)
1f	C ₃ H ₇	CH ₃	2	65	25.6 (25.5)
1g	Ph	H	2	69	24.2 (24.0)
1h	Ph	H	3	71	21.5 (21.2)

(a) Purified by distillation.

ducts were formed. Although the isomeric mixture **1** gives only one type of substituted crown ether when it is cyclized (4), the corresponding sulfur derivative **2** is naturally expected to give a mixture of two different thia-crown ether, which have the substituent on the α or β carbon atom of sulfur, respectively. The nmr spectral analyses showed that the products (**3a,c,d,e**) are the mixtures of **3M** and **3AM**, though the former was largely predominant (3-5 to

Table 2

Compound	R	Synthesis of Substituted Monothia Crown Ethers (3)					NMR (δ , Carbon Tetrachloride)
		R'	n	Yield (%) (a)	MS (m/e)		
3a	C ₄ H ₉	H	1	5	248 (M ⁺)	0.90 (t, 3H), 1.10-1.68 (m, 6H)	
3b	Ph	H	1	10	268 (M ⁺)	2.30-3.04 (m, 4H), 3.10-4.04 (m, 11H)	
3c	C ₂ H ₅	H	2	30	264 (M ⁺)	2.40-3.08 (m, 4H), 3.36-4.00 (m, 10H)	
3d	C ₆ H ₁₃	H	2	25	320 (M ⁺)	4.64-4.84 (d.d., 1H), 7.20 (s, 5H)	
3e	C ₈ H ₁₇	H	2	16	348 (M ⁺)	0.88 (t, 3H), 1.24-1.76 (m, 2H)	
3f	C ₃ H ₇	CH ₃	2	26	292 (M ⁺)	2.38-3.00 (m, 4H), 3.40-3.80 (m, 15H)	
3g	Ph	H	2	20	312 (M ⁺)	0.89 (t, 3H), 1.28 (s, 10H)	
3h	Ph	H	3	28	356 (M ⁺)	2.32-2.96 (m, 4H), 3.36-3.80 (m, 15H)	
						0.88 (t, 3H), 1.28 (s, 14H)	
						2.32-2.96 (m, 4H), 3.40-3.80 (m, 15H)	
						0.90 (t, 3H), 1.16 (s, 3H), 1.24-1.64 (m, 4H), 2.54-2.92 (m, 4H), 3.44-3.84 (m, 14H)	
						2.44-3.02 (m, 4H), 3.38-3.84 (m, 14H)	
						4.32-4.56 (d.d., 1H), 7.26 (s, 5H)	
						2.44-3.04 (m, 4H), 3.36-3.80 (m, 18H)	
						4.30-4.56 (d.d., 1H), 7.23 (s, 5H)	

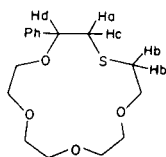
(a) Overall Yield, **1** - **3**.

Table 3

Compound	R	R'	Synthesis of β -Bromoalkyl β' -Chloroethyl Ethers (4)		Halogen Found (Calcd.) (%)
			Yield (%)	Bp ($^{\circ}$ C/Torr)	
4a	C ₂ H ₅	H	37	56/1.0	53.3 (53.5)
4b	C ₄ H ₉	H	50	62/0.2	47.0 (47.4)
4c	C ₆ H ₁₃	H	54	83/0.1	42.2 (42.5)
4d	C ₈ H ₁₇	H	53	115/0.5	38.3 (38.5)
4e	C ₁₀ H ₂₁	H	50	130/0.08	34.9 (35.2)
4f	C ₁₄ H ₂₉	H	80*(a)	—	30.4 (30.0)
4g	CH ₃	CH ₃	39	60/0.05**(b)	53.4 (53.5)
4h	C ₃ H ₇	CH ₃	44	77/0.04**(b)	47.3 (47.4)
4i	Ph	H	99*(a)	—	44.1 (43.8)

(a) Crude Yield. (b) Distillation with Kugelrohr apparatus.

1). On the contrary, phenyl thia-crown ethers (**3b,g,h**) and methyl propyl crown ether **3f** were found to be the pure compounds. For instance the nmr spectrum of **3g** was assigned as follows: δ 2.46-2.64 (H_a, d.d., 1H, J_{ac} = 14 Hz, J_{ad} = 4 Hz), 2.79 (H_b, t, 2H, J = 7 Hz), 2.79-3.00 (H_c, d.d., 1H, J_{ac} = 14 Hz, J_{cd} = 7 Hz), 3.38-3.84 (m, 14H), 4.43-4.56 (H_d, d.d., 1H), and 7.26 ppm (s, 5H).

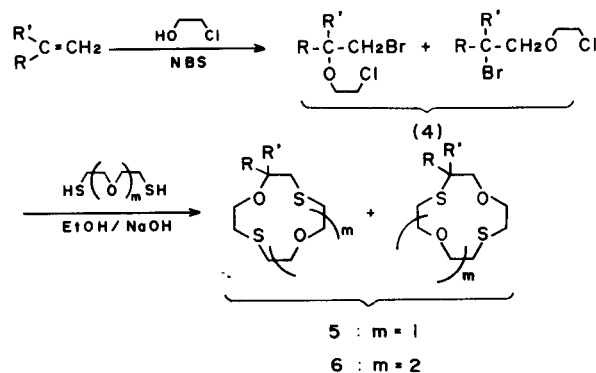


By decoupling H_d peak, the dd signals of H_a and H_c changed to doublets respectively. The ¹H nmr spectrum of **3h** also showed the similar typical ABX coupling pattern.

On the other hand, β -Bromoalkyl β' -chloroethyl ether (**4**)

was prepared by the bromoalkoxylation reaction of olefin with NBS and ethylene chlorohydrin at 45-50 $^{\circ}$ (Table 3). The ethanol solution of **4** and oligoethylene glycol dimercaptan was added drop-wise to the ethanol suspension of sodium hydroxide at the reflux temperature to give substituted 1,7-dithia crown ether.

Scheme 2



The results of 1,7-dithia-12-crown-4 (**5**) and 1,7-dithia-15-crown-5 (**6**) are shown in Tables 4 and 5, respectively. The presence of two isomers, which have alkyl substituent on the α or β carbon atom to the sulfur atom, was confirmed by ¹H-nmr and ¹³C-nmr in the case of R = Alkyl, R' = H. For example, ¹³C-nmr spectral data of **6a** (deuteriochloroform, 10% solution) showed the presence of two peaks at 9.7 and 11.3 ppm which are assigned to methyl carbons of 3-ethyl and 2-ethyl isomers respectively. In addition, methyl proton signals in ¹H-nmr of **6a** separated into two triplets in the presence of shift reagent (Europium Trisdipivaloylmethanate) and the composition of two isomers can be determined to be α : β = 26:74. On the other hand, ¹³C-nmr of **6i** showed the single structure.

Table 4
Synthesis of Substituted 1,7-Dithia-12-crown-4 (5)

Compound	R	R'	Yield (%)	MS (m/e)	NMR (δ , Carbon Tetrachloride)
5a	C ₂ H ₅	H	20	236 (M ⁺)	0.94 (t, 3H), 1.16-1.84 (m, 2H), 2.34-3.10 (m, 8H), 3.40-4.08 (m, 7H)
5b	C ₄ H ₉	H	26	264 (M ⁺)	0.93 (t, 3H), 1.16-1.80 (m, 6H), 2.36-3.12 (m, 8H), 3.44-4.06 (m, 7H)
5c	C ₆ H ₁₃	H	16	292 (M ⁺)	0.91 (t, 3H), 1.30 (s, 10H), 2.32-3.08 (m, 8H), 3.44-4.04 (m, 7H)
5d	C ₈ H ₁₇	H	23	320 (M ⁺)	0.88 (t, 3H), 1.28 (s, 14H), 2.34-3.10 (m, 8H), 3.44-4.08 (m, 7H)
5e	C ₁₀ H ₂₁	H	23	348 (M ⁺)	0.88 (t, 3H), 1.27 (s, 18H), 2.36-3.04 (m, 8H), 3.40-4.00 (m, 7H)
5f	C ₁₄ H ₂₉	H	26	404 (M ⁺)	0.88 (t, 3H), 1.24 (s, 26H), 2.36-3.04 (m, 8H), 3.44-4.00 (m, 7H)
5i	Ph	H	12	284 (M ⁺)	2.48-3.12 (m, 8H), 3.34-4.08 (m, 7H), 4.48-4.68 (d.d., 1H), 7.23 (s, 5H)

Table 5
Synthesis of Substituted 1,7-Dithia-15-crown-5 (6)

Compound	R	R'	Yield (%)	MS (m/e)	NMR (δ , Carbon Tetrachloride)
6a	C ₂ H ₅	H	34 (53%) (a)	280 (M ⁺)	0.92 (t, 3H), 1.28-1.80 (m, 2H), 2.32-3.02 (m, 8H), 3.32-3.86 (m, 11H)
6b	C ₄ H ₉	H	35	308 (M ⁺)	0.92 (t, 3H), 1.16-1.76 (m, 6H), 2.34-3.00 (m, 8H), 3.36-3.88 (m, 11H)
6c	C ₆ H ₁₃	H	34	336 (M ⁺)	0.90 (t, 3H), 1.30 (s, 10H), 2.34-3.02 (m, 8H), 3.32-3.92 (m, 11H)
6d	C ₈ H ₁₇	H	30	364 (M ⁺)	0.89 (t, 3H), 1.29 (s, 14H), 2.30-3.04 (m, 8H), 3.30-3.92 (m, 11H)
6e	C ₁₀ H ₂₁	H	30	392 (M ⁺)	0.90 (t, 3H), 1.28 (s, 18H), 2.36-3.00 (m, 8H), 3.32-3.88 (m, 11H)
6f	C ₁₄ H ₂₉	H	36	448 (M ⁺)	0.89 (t, 3H), 1.26 (s, 26H), 2.44-2.96 (m, 8H), 3.36-3.88 (m, 11H)
6h	C ₃ H ₇	CH ₃	11	308 (M ⁺)	0.93 (t, 3H), 1.26 (s, 3H), 1.28-1.76 (m, 4H), 2.48-2.94 (m, 8H), 3.40-3.90 (m, 10H)
6i	Ph	H	25	328 (M ⁺)	2.36-3.10 (m, 8H), 3.36-3.84 (m, 10H), 4.40-4.56 (d.d., 1H), 7.20 (s, 5H)

(a) Determined by glc.

EXPERIMENTAL

The ¹H-nmr and ¹³C-nmr spectra were taken at 100 MHz on a JEOL JNM-PS-100 spectrometer and at 15 MHz on a JEOL JNM-FX-60S spectrometer, respectively, using tetramethylsilane as the internal standard. The infrared spectra were obtained on a Hitachi 260-10 spectrometer. The mass spectra were measured with a Hitachi RMU-6E mass spectrometer at an ionization potential of 70 eV. The molecular weights were determined with a Hitachi-Perkin Elmer vapour-pressure osmometer in chloroform, with bibenzyl as the calibration standard.

Oligoethylene Glycol β -Bromoalkyl Ethers (1).

They were prepared according to the procedures reported in the previous paper (3).

Monothia Alkyl- or Phenyl-substituted Oligoethylene Glycol (2).

The ethanol solution (30 ml) of **1** (0.05 mole) was added drop-wise to the stirred solution of 2-mercaptoethanol (0.075 mole) and sodium hydroxide (0.08 mole) in ethanol (120 ml) over a period of 2-3 hours at the reflux temperature. The solvent was evaporated under reduced pressure

and then ether was added to the residue. Insoluble salt was removed by filtration and the ether was evaporated to give the crude product **2**. Compound **2** was used as the starting material for the next reaction without further purification. Only **2e** was purified in a 52% yield by using silica gel column chromatography (ethanol) and distillation *in vacuo*; compound **2e** ir (neat): 3400 (s), 2920 (s), 2845 (s), 1460 (m), 1345 (m), 1285 (w), 1240 (w), 1100 (s), 925 (w), and 875 cm⁻¹ (w); ms: m/e 335 (M⁺-CH₂OH), 275; nmr (carbon tetrachloride): δ 0.88 (t, 3H), 1.26 (s, 14H), 2.50-2.98 (m, 4H), and 3.30-4.14 ppm (m, 17H).

Substituted Monothia Crown Ether (3).

The dioxane solution (30 ml) of **2** (0.02 mole) and benzenesulfonyl chloride (0.022 mole) was added drop-wise to the stirred suspension of sodium hydroxide (0.08 mole) in dioxane (120 ml) over a period of 2-3 hours at 80-90°. The mixture was stirred for 2-3 hours at that temperature. After cooling to room temperature, the mixture was neutralized by hydrochloric acid and ether was added. The salt was removed by filtration and the solvent was concentrated. The residue was extracted with hexane by using liquid-liquid continuous extraction apparatus, followed by distillation (Kugelrohr) *in vacuo* or silica-gel col-

umn chromatography (hexane:acetone = 20:1) to give pure monothia-crown ether **3**. The results are shown in Table 2.

A mixture of 2-Octyl- and 3-Octyl-1-thia-15-crown-5 (**3e**).

This mixture had the following properties: ir (neat): 2920 (s), 2860 (s), 1460 (m), 1350 (m), 1295 (m), 1250 (w), 1120 (s), 980 (w), and 940 (w) cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{36}\text{SO}_4$: C, 62.04; H, 10.41; S, 9.20; mol. wt., 348.52. Found: C, 61.80; H, 10.63; S, 9.57; mol. wt., 338.

3-Methyl-3-propyl-1-thia-15-crown-5 (**3f**).

This compound had ir (neat): 2960 (s), 2920 (s), 2860 (s), 1460 (m), 1360 (m), 1295 (m), 1240 (w), 1110 (s), 1010 (w), 960 (w), and 940 cm^{-1} (w); ms: (m/e) 292 (M^+); nmr (carbon tetrachloride): δ 0.90 (t, 3H), 1.16 (s, 3H), 1.24-1.64 (m, 4H), 2.54-2.92 (m, 4H), and 3.44-3.84 ppm (m, 14H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{28}\text{SO}_4$: C, 57.50; H, 9.65; S, 10.96; mol. wt. 292.42. Found: C, 57.65; H, 9.90; S, 10.98; mol. wt. 297.

β -Bromoalkyl β' -Chloroethyl Ether (**4**).

The Olefin (0.2 mole) was added drop-wise to the stirred suspension of NBS (0.2 mole) and ethylene chlorohydrin (1.0 mole) at 45-50°. The mixture was then stirred at that temperature until the positive halogen had been consumed (2-3 hours). Ether (400 ml) was added to the mixture, and washed with water (100 ml \times 3). The ether layer was dried over magnesium sulfate and concentrated to give the crude product. The product was purified by distillation under reduced pressure except for **4f** and **4i**, which decomposed in the course of distillation. The results are shown in Table 3. The nmr spectrum of 4-bromomethyl-1-chloro-4-methyl-3-oxaheptane (**4h**) was as follows in carbon tetrachloride δ 0.96 (t, 3H), 1.28 (s, 3H), 1.29-1.85 (m, 4H), 3.32 (s, 2H), and 3.44-3.72 ppm (m, 4H).

Substituted 1,7-Dithia-12-crown-4 (**5**).

Compound **4** (0.04 mole) in ethanol (45 ml) and diethylene glycol dimercaptan (0.04 mole) in ethanol (45 ml) was simultaneously added drop-wise to the stirred ethanol (120 ml) suspension of sodium hydroxide (0.1 mole) over a 10 hour period at the reflux temperature; the mixture was then further stirred for 1 hour. The salt was removed by filtration and the solvent was evaporated. The residue was dissolved in a small amount of methanol and extracted with hexane by using liquid-liquid continuous extraction apparatus to give the crude product. The crude product was distilled in Kugel-rohr apparatus to give substituted 1,7-dithia-12-crown-4 (**5**) (Table 4).

A mixture of 2-Butyl- and 3-Butyl-1,7-dithia-12-crown-4 (**5b**).

This mixture had ir (neat): 2930 (s), 2860 (s), 1460 (m), 1410 (m), 1360 (m), 1290 (m), and 1110 cm^{-1} (s).

Anal. Calcd. for $\text{C}_{12}\text{H}_{24}\text{S}_2\text{O}_2$: C, 54.54; H, 9.15; mol. wt. 264.44. Found: C, 54.52; H, 9.43; mol. wt. 265.

3-Phenyl-1,7-dithia-12-crown-4 (**5i**).

This compound had ir (neat): 3060 (w), 2930 (s), 2860 (s), 1500 (m), 1455 (m), 1410 (m), 1360 (m), 1290 (m), 1205 (m), 1110 (s), 725 (w), and 695 cm^{-1} (m).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{S}_2\text{O}_2$: C, 59.14; H, 7.09; mol. wt. 284.43. Found: C, 58.74; H, 7.41; mol. wt. 292.

Substituted 1,7-Dithia-15-crown-5 (**6**).

Substituted 1,7-dithia-15-crown-5 (**6**) was prepared by the reaction of **4** with NBS and triethylene glycol dimercaptan according to the synthetic procedure for **5** except that the addition time of reagents was 6 hours. The results are summarized in Table 5.

A Mixture of 2-Ethyl- and 3-Ethyl-1,7-dithia-15-crown-5 (**6a**).

This mixture had ir (neat): 2920 (s), 2870 (s), 1460 (m), 1410 (w), 1350 (m), 1290 (m), and 1100 cm^{-1} (s).

Anal. Calcd. for $\text{C}_{12}\text{H}_{24}\text{S}_2\text{O}_3$: C, 51.44; H, 8.63; mol. wt. 280.44. Found: C, 51.25; H, 8.82; mol. wt. 277.

3-Phenyl-1,7-dithia-15-crown-5 (**6i**).

This mixture had ir (neat): 3060 (w), 2920 (s), 1500 (w), 1460 (m), 1410 (m), 1360 (m), 1295 (m), 1205 (w), 1110 (s), 1030 (w), 910 (w), 735 (w), and 700 cm^{-1} (m).

Anal. Calcd. for $\text{C}_{16}\text{H}_{24}\text{S}_2\text{O}_3$: C, 58.55; H, 7.37; mol. wt. 328.49. Found: C, 58.31; H, 7.24; mol. wt. 336.

REFERENCES AND NOTES

- (1) A. Iovchev, H. Reinheckel, K. Haage and R. Pomakova, *Monatsh. Chem.*, **97**, 1620 (1966).
- (2) I. Michev, N. Khristova, R. Pomakova, B. Ponnitova and A. Iovchev, *Z. Chem.*, **15**, 191 (1975).
- (3) M. Okahara, M. Miki, S. Yanagida, I. Ikeda, and K. Matsushima, *Synthesis*, 854 (1977).
- (4) T. Mizuno, Y. Nakatsuji, S. Yanagida and M. Okahara, *Bull. Chem. Soc. Japan*, **53**, 481 (1980).
- (5) P.-L. Kuo, M. Miki and M. Okahara, *J. Chem. Soc. Chem. Commun.*, 504 (1978).
- (6) I. Ikeda, S. Yamamura, Y. Nakatsuji and M. Okahara, *J. Org. Chem.*, **45**, 5355 (1980).
- (7) P.-L. Kuo, M. Miki, I. Ikeda and M. Okahara, *Tetrahedron Letters*, 4273 (1978).
- (8) P.-L. Kuo, M. Miki, I. Ikeda and M. Okahara, *J. Am. Oil. Chem. Soc.*, **57**, 227 (1980).
- (9) H. K. Frensdorff, *J. Am. Chem. Soc.*, **93**, 600 (1971).
- (10) R. M. Izatt, R. E. Terry, L. D. Hansen, A. G. Avondet, J. S. Bradshaw, N. K. Dally, T. E. Jensen and J. J. Christensen, *Inorg. Chim. Acta*, **30**, 1 (1978).
- (11) J. D. Lamb, R. M. Izatt, C. S. Swain and J. J. Christensen, *J. Am. Chem. Soc.*, **102**, 475 (1980).
- (12) J. S. Bradshaw, J. Y. Hui, B. L. Haymore, J. J. Christensen, and R. M. Izatt, *J. Heterocyclic Chem.*, **10**, 1 (1973).
- (13) J. S. Bradshaw, J. Y. Hui, Y. Chan, B. L. Haymore, R. M. Izatt and J. J. Christensen, *ibid.*, **11**, 45 (1974).
- (14) J. S. Bradshaw, R. A. Reeder, M. D. Thompson, E. D. Flanders, R. L. Carruth, R. M. Izatt and J. J. Christensen, *J. Org. Chem.*, **41**, 134 (1976).
- (15) S. Inokuma, N. Aoki, E. Kameyama, and T. Kuwamura, *Yukagaku*, **29**, 767 (1980).
- (16) Y. Nakatsuji, Y. Watanabe and M. Okahara, *Bull. Chem. Soc. Japan.*, **55**, 627 (1982).