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Syntheses of Mercaptobenzoic Acids and Mercaptopyridines Using Elemental Sulfur in the Presence of NaOH–KOH

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Mercaptobenzoic acids and mercaptopyridines were synthesized by using mercaptylation of halogeno compounds with elemental sulfur in the presence of molten salts (NaOH–KOH). This procedure was also applied to the preparation of selenoaryl compounds by using elemental selenium. Based on the behavior of the molten salts and sulfur, Na_2S and K_2S were considered to be the active species for the mercaptylation.

Keywords——mercaptylation; molten salt; *o*-mercaptobenzoic acid; *o*-selenobenzoic acid; 2-mercaptopyridine

Mercaptobenzoic acids are useful intermediates for syntheses of medicines and thioindigoid dyes. In one well-known method, *o*-mercaptobenzoic acid (**5**) is obtained by the reduction of salicylic disulfide, prepared from the diazonium salt of anthranilic acid and sodium disulfide.[1] Several other methods, including the carboxylation of thiophenol,[2] and the mercaptylation of *o*-chlorobenzoic acid (**1**) with sodium hydrosulfide in the presence of copper sulfate,[3] have been reported. Elemental sulfur has been used for mercaptylation in the presence of aryl lithium or a Grignard reagent.[4]

We have found a convenient method for the preparation of mercaptobenzoic acids and selenobenzoic acids from aryl halides by using elemental sulfur or selenium in the presence of molten alkali metal hydroxides (Chart 1). In this paper, the role of the molten salts and the nature of the active species are discussed.

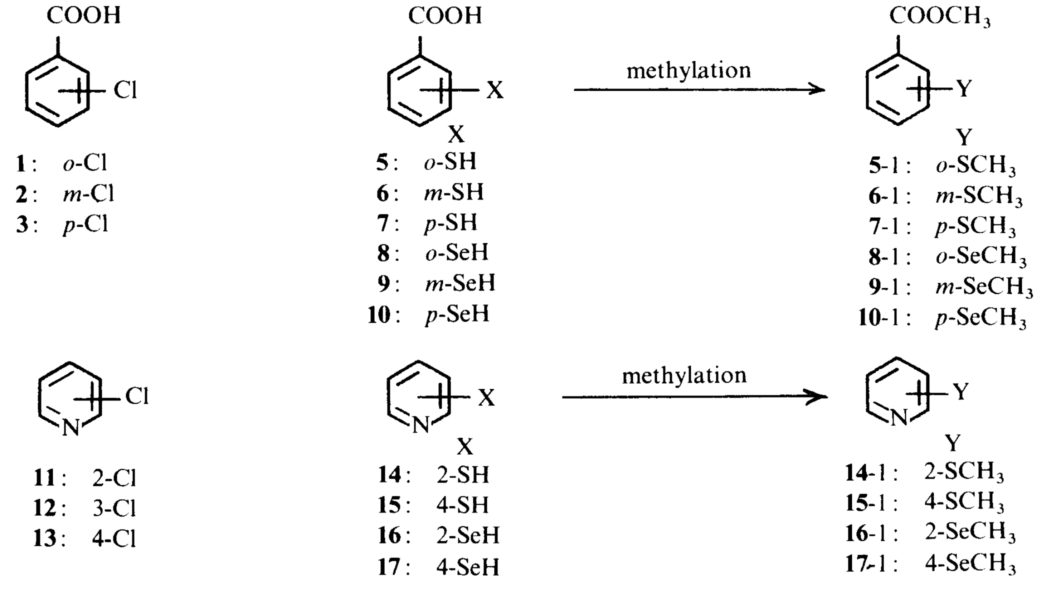

Chart 1

Results and Discussion

Mercaptylation of Chlorobenzoic Acids

The mercaptylation of **1** was carried out using elemental sulfur and alkali metal hydroxides. The products were **5** and 2,2′-dithiodibenzoic acid in a molar ratio of 5 : 1. Therefore, the yields of **5** were evaluated after the reduction of the disulfide to the mercaptan. The results are shown in Table I. When sodium hydroxide or potassium hydroxide was used independently, a poor yield of **5** and a small amount of salicylic acid (**4**) were obtained together with a trace amount of benzoic acid. However, the binary hydroxides of alkali metals such as NaOH–KOH (1 : 1 molar ratio) gave an excellent yield (81.1%) of **5** accompanied with **4** (4.0%) at 270 °C for 3 min. The reaction proceeded under a homogeneous melt, and the reaction mixture solidified after a few minutes. The conversion increased with increasing reaction time and saturated after 6 min. On the other hand, the yield of **5** reached a maximum after such a short period as 3 min and decreased gradually after the peak because of the decomposition of **5** once formed. The mercaptylation was also performed with chlorobenzoic acids (**2** and **3**), and chloropyridines (**11**, **12** and the hydrochloride of **13**); these results are shown in Table II. Chlorobenzoic acids gave the corresponding mercaptobenzoic acids in good yields. In the reaction of **2**, two products, *m*-mercaptobenzoic acid (**6**) and the *p*-isomer (**7**), were obtained in yields of 44.0 and 0.3%, respectively. 3-Chloropyridine (**12**) was not

TABLE I. Mercaptylation of **1** Using Elemental Sulfur in the Presence of Various Molten Salts

MOH (g)	Time (min)	Yield (%)	
		4	**5**
NaOH (4.0)	3.0	9.2	1.9
KOH (4.0)	3.0	8.6	19.5
LiOH·H_2O (2.0)–NaOH (2.0)	3.0	0	0
LiOH·H_2O (2.0)–KOH (2.8)	3.0	0	0
NaOH (2.0)–KOH (2.8)	1.5	3.4	26.8
	3.0	4.0	81.1
	4.5	4.2	55.1
NaOH (2.0)–RbOH (5.1)	3.0	5.6	7.3
NaOH (2.0)–CsOH (7.5)	3.0	3.7	8.7
KOH (2.8)–RbOH (5.1)	3.0	3.9	16.0
KOH (2.8)–CsOH (7.5)	3.0	11.1	8.4

1, 1.0 g; sulfur, 2.0 g; 270 °C.

TABLE II. Mercaptylation of Chlorobenzoic Acids and Chloropyridines Using Sulfur and Molten Salt (NaOH–KOH)

Substrate (g)	NaOH–KOH (Molar ratio, g)	Temp. (°C)	Time (min)	Product	Yield (%)	Yield (Isolated, g)
1 (1.0)	1 : 1 (4.8)	270	3.0	**5**	81.1	0.76
2 (0.5)	1 : 3 (4.1)	360	3.0	**6**	44.0	0.18
3 (1.0)	1 : 3 (3.9)	340	3.0	**7**	60.8	0.52
11 (1.0)	1 : 1 (1.5)	200	5.0	**14**	53.5	—
12 (1.0)	1 : 1 (4.8)	200	5.0		0	
13 (1.0)	1 : 1 (4.8)	210	2.0	**15**	71.4	—

Sulfur, 2.0 g.

TABLE III. Reaction of Chlorobenzoic Acids and Chloropyridines Using Elemental Selenium and Molten Salt (NaOH–KOH)

Substrate (g)	Se (g)	NaOH–KOH (Molar ratio, g)	Temp. (°C)	Time (min)	Product	Yield (%)
1 (0.5)	2.5	1 : 1 (2.4)	350	3.0	**8**	73.4
					9	12.3
2 (0.5)	3.5	1 : 3 (4.1)	340	3.0	**8**	8.8
					9	33.7
					10	10.9
3 (0.5)	2.5	1 : 1 (2.4)	360	3.0	**9**	1.0
					10	41.1
11 (1.0)	3.0	1 : 1 (2.4)	280	2.0	**16**	5.2
12 (1.0)	3.0	1 : 1 (2.4)	280	5.0		0
13 (1.0)	3.0	1 : 1 (2.4)	250	2.0	**17**	10.8

mercaptylated under our reaction conditions. Chlorobenzoic acids or chloropyridines were also treated with selenium under the conditions of the mercaptylation to give the corresponding selenobenzoic acids (Table III), except in the case of **12**. It should be noted that the reaction of **2** with selenium gave *m*-selenobenzoic acid (**9**) as the main product, and *o*-selenobenzoic acid (**8**) and *p*-selenobenzoic acid (**10**) as minor products. These by-products may be obtained by the addition of selenium to benzynes which are formed by the elimination of hydrochloride from **2**. In contrast, the reactions of chloropyridines with selenium gave poor yields of the corresponding selenoderivatives because of the evaporation of the raw materials and the decomposition of the products. The reactivity of **12** with selenium was poor under our reaction conditions.

Active Species and the Role of Molten Salt

Studies on the active species of the mercaptylation and on the role of molten salt were examined. The effect of the amount of sulfur on the yields of **4** and **5** is shown in Table IV. The yield of **5** increased with increasing amount of sulfur up to 0.64 mol eq to alkali. However, further addition of sulfur decreased the yield. On the other hand, the yield of **4** decreased with increasing amount of sulfur, and **4** was not detected at 1 : 0.97 molar ratio of sulfur and alkali. The maximum yield of **5** was observed at 0.64 molar ratio of sulfur to alkali metal hydroxide. Therefore, the composition of the active species was suggested to be M_2S (M = Na, K). To confirm this hypothesis, we examined various mercaptylation agents such as sodium sulfide (Na_2S, $Na_2S \cdot H_2O$ or $Na_2S \cdot 9H_2O$), potassium sulfide and sodium hydrosulfide instead of sulfur and the molten salt (Table V). All these agents gave negative results. However, an excellent result was obtained when a mixture of anhydrous sodium sulfide and potassium sulfide was used in the form of molten salt (1 : 1 molar ratio). This procedure was performed under anhydrous conditions since Na_2S is very sensitive to moisture. The effect of the amount of sulfur relative to the molten salt of Na_2S and K_2S on the yield of **5** is shown in Fig. 1. With increase in sulfur content, the yield of **5** decreased gradually. This tendency suggests that M_2S is a more plausible candidate than M_2S_n for the active species. Although our molten salt and the mixed sulfides (Na_2S and K_2S) gave almost the same yields in the mercaptylation of **1**, the former is easier to handle and is inexpensive. Figure 2 shows the effect of the composition of the molten salt of sodium hydroxide and potassium hydroxide on the yield of **5**. The activity increased with increasing ratio of potassium hydroxide to sodium hydroxide up to 50%, but further addition decreased the yield. The maximum yield was obtained at a 1 : 1 molar ratio of potassium hydroxide to sodium hydroxide. Depression of melting point was observed in the binary salts: a mixture of NaOH–KOH (1 : 1 molar ratio) showed a melting point of 161—

TABLE IV. The Effect of the Amount of Sulfur on the Yields of **4** and **5**

Sulfur (g)	S/NaOH–KOH (Molar ratio)	Yield (%)	
		4	**5**
0	—	18.9	0
0.5	0.16	17.9	8.7
1.0	0.32	15.1	18.9
1.5	0.49	10.6	63.2
2.0	0.64	5.6	76.1
3.0	0.97	0	37.6

1, 1.0 g; NaOH–KOH, 2.0—2.6 g; 270 °C; 3 min.

TABLE V. Mercaptylation of **1** Using Various Mercaptylation Agents

Agent (g)	NaOH–KOH (g)	Temp. (°C)	Conv. (%)	Yield (%)	
				4	**5**
NaSH (2.6)	0	250	41.5	0	0.5
NaSH (2.6)	0.6–0.6	260	29.5	Trace	2.4
K_2S (3.5)	0	260	76.1	0	6.5
$Na_2S \cdot 9H_2O$ (5.0)	0	270	29.0	0	0
$Na_2S \cdot H_2O$ (3.0)	0	270	50.5	0	0.6
Na_2S (2.5)	0	290	64.5	0	32.0
Na_2S–K_2S (1.25–1.75)	0	290	95.7	0	80.0

1, 0.5 g; 3 min.

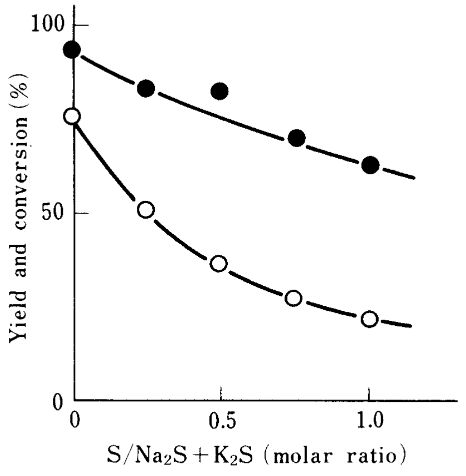

Fig. 1. The Effect of the Molar Ratio of Sulfur to Molten Salts (Na_2S and K_2S) on the Yield of **5**

1, 0.5 g; Na_2S:K_2S (1 : 1 molar ratio), 31.9 mmol; 290 °C; 3 min. —●—, conversion; —○—, yield.

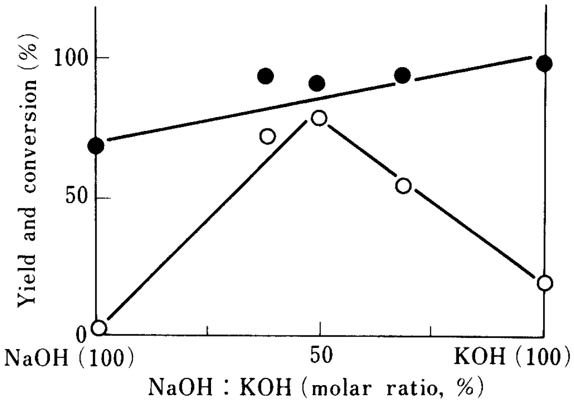

Fig. 2. The Effect of the Composition of Molten Salt (Sodium Hydroxide and Potassium Hydroxide) on the Yield of **5**

1, 1.0 g; S, 2.0 g; NaOH+KOH, 0.1 mol; 270 °C; 3 min. —●—, conversion; —○—, yield.

165 °C,[5] though the melting points of sodium hydroxide and potassium hydroxide were 318 and 380 °C, respectively. A significant correlation was observed between the yield of **5** (Fig. 2) and the fall in melting point.

Therefore, it was considered that sodium hydroxide and potassium hydroxide reacted at first with elemental sulfur to form sulfides, followed by nucleophilic substitution of sulfide anions at electron-deficient carbon. The fall in melting point was advantageous for this reaction due to the fall in reaction temperature, which reduced the decomposition of products.

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Gas-

TABLE VI. Analytical Data for Synthesized Compounds

Compound	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (ppm)	MS (*m*/*e*)	mp (°C)
		C	H	N			
5	$C_7H_6O_2S$	54.53	3.92	—	6.90 (m, 3H)	—	164—166.5
		(54.13	3.86)		7.40 (m, 1H)		
5-1	$C_9H_{10}O_2S$	59.32	5.53	—	2.45 (s, 3H)	182	50—51
		(59.18	5.42)		3.85 (s, 3H)		
					7.40 (m, 3H)		
					7.90 (m, 1H)		
6	$C_7H_6O_2S$	54.53	3.92	—	7.50 (m, 4H)	—	232—234
		(54.49	3.71)				
6-1	$C_9H_{10}O_2S$	59.32	5.53	—	2.35 (s, 3H)	182	Liquid
		(59.48	5.42)		3.60 (s, 3H)		
					7.40 (m, 4H)		
7	$C_7H_6O_2S$	54.53	3.92	—	7.60 (d, 2H)	—	225—228
		(54.72	3.80)		8.10 (d, 2H)		
7-1	$C_9H_{10}O_2S$	59.32	5.53	—	2.50 (s, 3H)	182	73—75
		(59.07	5.47)		3.80 (s, 3H)		
					7.30 (d, 2H)		
					7.80 (d, 2H)		
8-1	$C_9H_{10}O_2Se$	47.18	4.40	—	2.25 (s, 3H)	229	55—58
		(47.19	4.49)		3.90 (s, 3H)		
					7.35 (m, 3H)		
					8.00 (m, 1H)		
9-1	$C_9H_{10}O_2Se$	47.18	4.40	—	2.35 (s, 3H)	229	Liquid
		(47.45	4.41)		3.90 (s, 3H)		
					7.60 (m, 4H)		
10-1	$C_9H_{10}O_2Se$	47.18	4.40	—	2.35 (s, 3H)	229	72—75
		(47.30	4.56)		3.85 (s, 3H)		
					7.35 (d, 2H)		
					7.85 (d, 2H)		
14-1	C_6H_7NS	57.57	5.64	11.19	2.60 (s, 3H)		Liquid
		(57.75	5.22	11.26)	7.26 (m, 3H)		
					8.45 (m, 1H)		
15-1	C_6H_7NS	57.57	5.64	11.19	2.45 (s, 3H)		Liquid
		(57.19	5.86	10.96)	7.13 (d, 2H)		
					8.32 (d, 2H)		
16-1	C_6H_7NSe	41.87	4.10	8.14	2.40 (s, 3H)		Liquid
		(—	—	—)[a]	7.30 (m, 3H)		
					8.48 (m, 1H)		
17-1	C_6H_7NSe	41.87	4.10	8.14	2.36 (s, 3H)		Liquid
		(—	—	—)[a]	7.29 (d, 2H)		
					8.30 (d, 2H)		
					8.30 (d, 2H)		

a) See ref. 9.

liquid chromatography (GLC) was carried out on a Shimadzu GC-3BF instrument by using a column packed with 20% polyethyleneglycol 20M on Shimalite (80—100 mesh) (2 m). High-performance liquid chromatography (HPLC) was run on a Hitachi 633A instrument equipped with a ultraviolet (UV) detector (638-41, Hitachi Ltd.) using a 2.6 mm × 500 mm column packed with Hitachi gel #3011 and a mobile phase of methanol–acetonitrile 7 : 3 (v/v). The flow rate was maintained at 1 ml/min. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Hitachi R-600 instrument in $CDCl_3$, with tetramethylsilane as an internal standard. The abbreviations used are s (singlet), d (doublet) and m (multiplet). The gas chromatography-mass spectrometry (GC-MS) data were obtained on a Shimadzu GCMS-7000A mass spectrometer equipped with a 1% Silicone OV-1 glass column (3 mm × 2 m); column temperature 180 °C; flow rate 30 ml/min.

General Procedures and Products Analyses——The halogeno compound, elemental sulfur, sodium hydroxide and potassium hydroxide were placed in a test tube (Pyrex, 18 mm × 180 mm). The test tube was heated in an electric furnace and the materials were mixed vigorously with a glass rod. After the reaction, the reaction mixture was dissolved in water, and reduced with sodium borohydride. The solution was acidified with diluted hydrochloric acid and the products were extracted with ether. The extracts were methylated with diazomethane, and then analyzed by GLC with diphenyl as an internal standard.

Isolation of 5,6 and 7——The reaction mixture was treated with sodium borohydride and the polysulfides were reduced to the mercaptans. To remove unreacted sulfur, an excess amount of zinc chloride was added to the solution. Next, the solution was made strongly alkaline by the addition of about 10% ammonium hydroxide solution. Zinc sulfide that precipitated was filtered off and washed once with diluted ammonium hydroxide solution. Compound **5** was precipitated from the filtrate by the addition of a sufficient amount of aqueous hydrochloric acid. The product was filtered off, washed with water, and dried in a desiccator. The crude product was dissolved in hot alcohol and the solution was allowed to cool. After removal of the insoluble material, **5** was obtained by evaporation of the alcohol. Yield 0.76 g (76%), mp 164—165.5 °C (lit.[1] 163—164 °C). Analytical data are presented in Table VI. Compounds **6** and **7** were also isolated according to this procedure.

Quantitative Analyses of 14 and 16——After the reaction, the products were diluted with water and unreacted material (**11** or **13**) was analyzed in an aliquot of the solution by HPLC using triphenylmethane as an internal standard. On the other hand, the products were reduced *in situ* with sodium borohydride. The solution was acidified with acetic acid and extracted with chloroform.[6,7] The products in the extract were subsequently analyzed by using HPLC.

Quantitative Analyses of 15 and 17——The reaction products in solution were reduced with sodium borohydride. Water was removed by evaporation under reduced pressure. The residue was dissolved with alcohol, and then methylated with methyl iodide.[8] The methyl derivatives (**15**-1 and **17**-1) were analyzed by means of HPLC.

References and Notes

1) C. F. H. Allen and D. D. Mackey, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, 1943, p. 580.
2) V. K. Parmeswaran, M. L. Khorana and H. P. Tipnis, *Indian J. Pharm.*, **30**, 124 (1968).
3) Cassella and Company, Ger. Patent 189200 (1906) [*Chem. Abstr.*, **2**, 607 (1908)].
4) H. Wuyst, *Bull. Soc. Chim. Fr.*, **5**, 405 (1909).
5) Y. Takahashi, M. Kamimoto, R. Sakamoto, K. Kanari and T. Ozawa, *Nippon Kagaku Kaishi*, **103**, 1049 (1982).
6) J. R. Thirtle, *J. Am. Chem. Soc.*, **68**, 342 (1946); A. Albert and G. B. Barlin, *J. Chem. Soc.*, **1959**, 2384.
7) H. G. Mautner, S. Chu and C. M. Lee, *J. Chem. Soc.*, **1962**, 3671.
8) H. King and L. L. Ware, *J. Chem. Soc.*, **1939**, 873.
9) **16** and **17** were too unstable for elemental analysis to be possible.