BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (8), 2437—2438 (1978)

Catalytic Activities of Salicylaldehyde Derivatives. VII. Synthesis and Catalytic Activity of (2-Formyl-3-hydroxyphenyl)dimethylsulfonium Salt in the Racemization of L-Glutamic Acid

Makoto ANDO* and Sakae EMOTO

The Institute of Physical and Chemical Research, Wako-shi, Saitama 351

(Received January 10, 1978)

Synopsis. The title compound (**1**) was prepared from 6-nitro-*o*-anisidine *via* 2-bromo-*m*-anisidine, 2-bromo-3-(methylthio)anisole, 6-methylthio-*o*-anislaldehyde, and 6-(methylthio)salicylaldehyde. Compound **1** was found to be the most inactive catalyst among the dimethylsulfonio derivatives of salicylaldehyde, but the most active catalyst among the other salicylaldehyde derivatives examined in the racemization of L-glutamic acid at pH 10 and at 80 °C in the presence of copper(II) ion in the initial stage of the reaction.

Since salicylaldehyde derivatives having a dimethylsulfonio group at 3-, 4-, and 5-positions have been found to be active catalysts in the racemization of L-glutamic acid,[1] 6-isomer (**1**) may also actively catalyze the racemization.

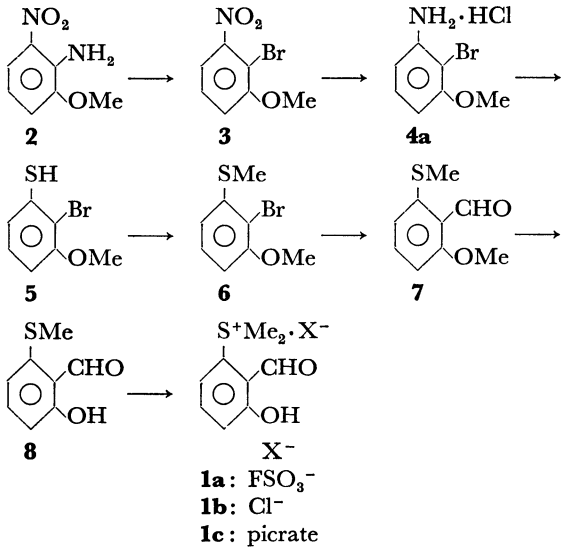
Here we describe a synthesis of **1** from 6-nitro-*o*-anisidine (**2**)[2,3] and the catalytic activity of **1** in the racemization of L-glutamic acid. 2-Bromo-3-nitroanisole (**3**) was prepared from **2** in the usual way. Most of the reagents tested for the reduction of **3** to give 2-bromo-*m*-anisidine (**4**) brought about undesirable debromination. With hydrazine hydrate over Raney nickel W-2,[4] however hydrochloride of **4** (**4a**) was obtained in a good yield. In the usual way, **4a** was converted into 2-bromo-3-methoxybenzenethiol (**5**). *S*-Methylation of **5** afforded 2-bromo-3-(methylthio)anisole (**6**), which gave 6-methylthio-*o*-anisaldehyde (**7**) by the Grignard reaction with diethyl phenyl orthoformate. *O*-Demethylation of **7** to 6-(methylthio)salicylaldehyde (**8**) was successful with boron tribromide in dichloromethane, but not with hydrogen bromide in acetic acid. Although *S*-methylation of **8** was unsuccessful with methyl *p*-toluenesulfonate, methyl fluorosulfate gave the fluorosulfate of **1** (**1a**) which was converted into the chloride (**1b**) *via* the picrate (**1c**).

Following the earlier work,[5,6] the racemization of L-glutamic acid catalyzed by **1b** was carried out at 80 °C and at pH 10 in the presence of copper(II) ion.

As Table 1 shows, the catalytic activity of **1b** decreased gradually during the course of the reaction by its decomposition, similarly to the other dimethylsulfonio derivatives of salicylaldehyde.[1] At an early stage of the reaction, however **1b** was found to be a more active catalyst than the trimethylammonio derivatives of salicylaldehyde,[5,6] but a less active catalyst than the other dimethylsulfonio derivatives of salicylaldehyde.[1]

Table 1. Racemization yield and catalytic activity catalyzed by **1b**

Time min	Racemization yield $100\,(\alpha_0-\alpha_t)/\alpha_0$, (%)	Catalytic activity $(\log \alpha_0/\alpha_t)/t$, ($min^{-1}$)
20	22.6	5.57×10^{-3}
40	34.0	4.50
60	40.6	3.77
120	55.3	2.92
240	69.7	2.16
480	87.0	1.85



Experimental

All the melting points and boiling point are uncorrected. Silica gel 60 (Merck No. 7734) was used for column chromatography. UV, IR, and PMR spectra were recorded on a Hitachi 124, a Shimadzu IR-27G, and a Varian HA-100D spectrometer, respectively.

2-Bromo-3-nitroanisole (3). A solution of 6-nitro-*o*-anisidine (**2**) (56.0 g) in concentrated sulfuric acid (230 ml) was diluted with water (460 ml) and diazotized with $NaNO_2$ (25.0 g) in water (40 ml). The solution was added to a mixture of CuBr (27.0 g), 48% HBr (60 ml), and water (340 ml) with stirring at 60 °C over a period of 1 h and then refluxed for 1 h. The resulting precipitate was recrystallized from ethyl acetate, giving 66.7 g of **3**. Additional **3** in the filtrate was recovered by passing it through a column of silica gel (360 g). Elution with benzene gave 2.6 g of **3** (total yield, 90%): mp 93—94 °C; IR (KBr) 1530 and 1280 cm^{-1}. Found: C, 36.36; H, 2.69; Br, 34.34; N, 5.89%. Calcd for $C_7H_6BrNO_3$: C, 36.24; H, 2.61; Br, 34.44; N, 6.04%.

2-Bromo-m-anisidine Hydrochloride (4a). To a mixture of **3** (78.4 g), Raney Ni W-2 (6.0 ml), and methanol (1.5 l), a solution of 100% hydrazine hydrate (42.3 g) in methanol (50 ml) was added over a period of 90 min under reflux with stirring. After stirring for another 2 h, the cold mixture was filtered and the filtrate was concentrated to a syrup and extracted with benzene and NaOH solution. The concentrated benzene layer was extracted with hot 1 M HCl. The

extract was treated with charcoal and concentrated to give 74.1 g of **4a** (92%): mp 201—202 °C dec. Found: C, 35.37; H, 3.90; Br+Cl, 48.10; N, 5.86%. Calcd for $C_7H_9BrClNO$: C, 35.25; H, 3.80; Br+Cl, 48.36; N, 5.87%.

2-Bromo-3-methoxybenzenethiol (5). A solution of diazonium salt prepared from **4a** (56.4 g) in 2 M HCl (300 ml) with $NaNO_2$ (16.5 g) in water (30 ml) was adjusted to pH 5 by addition of crystalline sodium acetate (60 g) and then added to a solution of potassium *O*-ethyl dithiocarbonate (76.0 g) in water (80 ml) at 60 °C over a period of 30 min with stirring. After being kept at 80 °C for 2 h, the mixture was extracted with ethyl acetate and the ethyl acetate layer was evaporated to a syrup. A mixture of the syrup and NaOH (30.0 g) in 90% aqueous ethanol (300 ml) was refluxed for 6 h and then extracted with ethyl acetate and water. The aqueous layer was acidified with HCl and the resulting oily product was extracted with ethyl acetate. The extract was dried ($MgSO_4$) and distilled under nitrogen atmosphere to give 22.3 g of **5** (42%) and some polymerized residue: mp 36—37 °C; bp 113 °C/3 mmHg. Found: C, 38.28; H, 2.97; Br, 36.59; S, 14.75%. Calcd for C_7H_7BrOS: C, 38.73; H, 3.22; Br, 36.47; S, 14.64%.

2-Bromo-3-(methylthio)anisole (6). To a stirred solution of distilled **5** (22.1 g) and NaOH (20.0 g) in water (200 ml), dimethyl sulfate (25 ml) was added over a period of 20 min at 70 °C and the mixture was then refluxed for 2 h. The resulting precipitate was recrystallized from methanol to give 22.1 g of **6** (94%). The use of undistilled **5** was better in the overall yield (59% based on **4a**) than the use of purified **5**: mp 73 °C; IR (KBr) 1590 and 1270 cm^{-1}. Found: C, 41.49; H, 3.75; Br, 34.53; S, 13.74%. Calcd for C_8H_9BrOS: C, 41.22; H, 3.89; Br, 34.37; S, 13.75%.

*6-Methylthio-*o*-anisaldehyde (7).* To a Grignard reagent of **6** (16.3 g) in dry THF (160 ml) with magnesium (1.7 g), diethyl phenyl orthoformate (15.2 g) in dry THF (30 ml) was added at room temperature over a period of 10 min with stirring and refluxed for 20 h. The cooled mixture was treated with a 20% NH_4Cl solution (120 ml) and extracted with benzene. The extract was dried ($MgSO_4$), concentrated, and hydrolyzed in a hot ethanol (150 ml)–2.4 M HCl (100 ml). Recrystallization of the resulting precipitate from methanol gave 9.7 g of **7**. The mother liquor was concentrated and packed on a column of silica gel (75 g). Elution with benzene gave 0.5 g of **7** (total yield, 81%): mp 98 °C; UV_{max} (MeOH) 372 (ε 19000), 298 (ε 24900), and 236 nm (ε 74600); IR (KBr) 1660, 1590, and 1270 cm^{-1}; PMR ($CDCl_3$) δ=10.56 (1H, s, CHO), 3.92 (3H, s, OCH_3), and 2.42 (3H, s, SCH_3). Found: C, 59.42; H, 5.42; S, 17.53%. Calcd for $C_9H_{10}O_2S$: C, 59.33; H, 5.53; S, 17.60%.

6-(Methylthio)salicylaldehyde (8). A solution of boron tribromide (25.0 g) in dry dichloromethane (20 ml) was added with stirring to a solution of **7** (16.5 g) in the same solvent (330 ml) over a period of 20 min at −55—−65 °C. The mixture was kept for another 30 min at the same temperature and then at room temperature for 2 h and concentrated below 30 °C. To the residue ethanol (300 ml) and then sodium acetate trihydrate (16.5 g) in water (80 ml) were added. The mixture was refluxed for 2 h, concentrated, and extracted with benzene and water. From the benzene layer, which was washed with NaOH solution and then with water, 1.0 g of **7** was recovered. The aqueous layer was acidified with HCl and extracted with benzene. The extract was dried ($MgSO_4$) and concentrated, giving crude **8** which was recrystallized from methanol to give 8.7 g of **8**. The mother liquors of **8** were concentrated and chromatographed on a silica-gel column (250 g). Elution with benzene gave 2.6 g of **8** (total yield, 74%): mp 71—72 °C; UV_{max} (MeOH) 353 (ε 23800), 296 (ε 27000), and 237 nm (ε 99000); IR (KBr) 1650 and 1450 cm^{-1}; PMR ($CDCl_3$) δ=11.94 (1H, s, OH), 10.48 (1H, s, CHO), and 2.52 (3H, s, SCH_3). Found: C, 56.89; H, 4.56; S, 18.99%. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79; S, 19.06%.

(2-Formyl-3-hydroxyphenyl)dimethylsulfonium Picrate (1c) and Chloride (1b). A solution of methyl fluorosulfate (5.7 g) and **8** (8.4 g) in dry dichloromethane (50 ml) was stirred for 1 h and allowed to stand for 4 days at room temperature. The resulting precipitate of crude fluorosulfate (**1a**) (mp 158—162 °C) was dissolved in methanol, treated with picric acid (11.0 g), and concentrated to give crude **1c**. Its recrystallization from methanol–acetone gave 9.7 g of **1c** (49%): mp 181—182 °C. Found: C, 43.67; H, 3.31; N, 10.00; S, 7.72%. Calcd for $C_{15}H_{13}N_3O_9S$: C, 43.80; H, 3.19; N, 10.22; S, 7.79%.

In the usual way, **1b** was prepared from **1c** in a 84% yield. It was slightly soluble in water and methanol: mp 173—174 °C dec; UV_{max} (H_2O) 380 (shoulder, ε 5500), 332 (ε 20900), and 255 nm (ε 21300); IR (KBr) 1670 cm^{-1}. Found: C, 49.25; H, 5.05; Cl, 15.98; S, 14.70%. Calcd for $C_9H_{11}ClO_2S$: C, 49.43; H, 5.07; Cl, 16.21; S, 14.66%.

Procedure of the Racemization. The racemization was carried out as described previously.[5]

The authors wish to thank Dr. Haruo Homma of this Institute and his staff for the elementary analyses and Mr. Jun Uzawa and Mrs. Tamiko Chijimatsu of this Institute for the measurements of PMR spectra. The work was partially supported by a Research Grant for Biosciences given by this Institute.

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