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A Facile Synthesis of 1,4-Dialkoxy-2,5-diiodobenzenes: Reaction of Dialkoxybenzenes with Iodine Monochloride in Alcoholic Solvents

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Abstract:

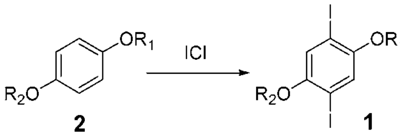
A facile synthesis of 1,4-dialkoxy-2,5-diiodobenzenes via diiodination of the corresponding dialkoxybenzenes with iodine monochloride has been developed. Employment of an alcoholic solvent as a reaction medium is crucial for attaining a high yield; the reaction in a nonalcoholic solvent usually resulted in a poor yield. The diiodobenzene derivatives are useful intermediates in the synthesis of such advanced materials as soluble phenylenevinylene polymers and dialkoxy derivatives of 7,7,8,8-tetracyanoquinodimethane.

Introduction

Dialkoxy-substituted 1,4-diiodobenzenes (**1**) are key intermediates in the syntheses of soluble phenylenevinylene polymers (PPVs) and 7,7,8,8-tetracyanoquinodimethanes (TCNQs). Extended π-electron systems of PPVs constitute very useful components in advanced materials with electroluminescent, conductive, or nonlinear optical properties.[1−4] TCNQs serve as strong electron acceptors, showing unusual molecular electromagnetic properties[5] as well as photochemical stabilizing effects.[6] Palladium-catalyzed coupling reactions of the 1,4-diiodobenzenes furnish the most straightforward syntheses of PPVs and TCNQs; reactions of 1,4-diiodo-2,5-dialkoxybenzenes (**1**) with vinylbenzenes[2,4] give PPVs, while those with malononitrile followed by oxidation[7] give TCNQs.

Dialkoxy-substituted 1,4-diiodobenzenes (**1**) have been prepared by direct diiodination of the corresponding dialkoxybenzenes (**2**). For example, the reaction of 1,4-dimethoxybenzene (**2a**) with benzyltrimethylammonium dichloroiodate−zinc(II) dichloride in acetic acid at room temperature for 15 h gave 1,4-diiodo-2,5-dimethoxybenzene (**1a**) in a 92% yield.[8] The treatment of **2a** with a mixture of molecular iodine−iodic acid−carbon tetrachloride in an acetic acid−sulfuric acid mixture afforded **1a** in an 84.4% yield.[9] The iodination of **2a** with mercury(II) oxide−iodine in dichloromethane at room temperature for 36 h gave **1a** in an 85% yield.[10] The reaction with iodine chloride in acetic acid, which appears most straightforward, gave **1a** only in a 36% yield.[11] From a practical point of view, however, the hitherto reported syntheses are still unsatisfactory: the use of mercury(II) chloride, strongly acidic solvents, or oxidative reaction conditions implies disadvantages concerning waste disposal problems. In this contribution, we report an improved practical process for diiodination of 1,4-dialkoxybenzenes (**2**) using iodine chloride in alcoholic solvents[12] (Scheme 1).

Scheme 1



Results and Discussion

Dialkoxybenzenes **2** are allowed to react with an excess amount of iodine monochloride for 4 h in refluxing methanol or in other solvents at 70 °C. Reaction conditions and isolated yields of diiodinated products **1** are listed in Table 1.

When 1,4-dimethoxybenzene **2a** was allowed to react with ICl in acetic acid according to Sargent et al.,[11] we observed development of red color reminiscent of molecular iodine in the reaction mixture. Actually, the reaction mixture showed an absorption band with a peak at 464 nm, which is identical with that of molecular iodine in acetic acid. The product analysis revealed that 2-iodo-1,4-dimethoxybenzene **3a** and 2-chloro-1,4-dimethoxybenzene **4a** in addition to the desired diiodinated product **1a** (31%) was also formed. In acetic acid, an extended reaction period failed to improve the yield of **1a**. The reaction apparently stopped in the early stages when

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(12) Iodine or ICl, which is prepared by direct reaction of I_2 and Cl_2, are recyclable: ICl-containing solution recovered from a reaction vessel has been utilized as a resource for I_2 at an iodine refinery in Japan, the second largest iodine-producing nation.

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Table 1. **Isolated yields of 1 and reaction conditions**

product	R_1	R_2	ICl/**2**[a]	solvent	yield (%)
1a	CH_3	CH_3	4.3	methanol	85.0
1a	CH_3	CH_3	4.3	2-propanol	82.0
1a	CH_3	CH_3	4.3	acetic acid	31.0
1a	CH_3	CH_3	4.1	acetonitrile	13.0[b]
1b	CH_3	C_2H_5	4.8	methanol	80.1
1c	C_2H_5	C_2H_5	4.3	methanol	89.9
1d	n-C_4H_9	n-C_4H_9	4.3	methanol	82.0
1e	C_2H_4OH	C_2H_4OH	5.0	methanol	86.0

[a] Mole ratio. [b] Not isolated: the yield was estimated based on the ^{1}H NMR of a mixture with the major product, **5a**.

I_2 formation became remarkable. These observations suggest that the conversion of ICl into less reactive molecular iodine was the cause of the low yield of the diiodo derivative **1a**. We therefore sought such conditions that would maintain the electrophilic iodinating reactivity of ICl during the reaction.

Reaction of arenes with ICl was reported to give chlorinated or iodinated products depending on the reaction conditions.[13] In view of the solvent and salt effects on the competition between chlorination and iodination in aromatic halogenation with iodine monochloride, Hubig et al. described that such polar solvents as acetonitrile favor iodination over chlorination by suppressing the formation of less reactive molecular iodine without mentioning the effect of any alcoholic solvents.[13]

In our case, however, application of acetonitrile as a reaction medium resulted in a low conversion to the diiodo derivative **1a** (13.0%); the main product was 1-chloro-4-iodo-2,5-dimetoxybenzene **5a** (58.3%). Just after the addition of 1,4-dimethoxybenzene to a solution of ICl in acetonitrile, the reaction mixture turned deep red due to I_2 formation. By contrast, a reaction in an alcoholic solvent did not show the color of I_2. When we used a polar solvent, methanol, development of red color due to molecular iodine ceased to be observed, and at the same time, the isolated yield of the diiodo derivative **1a** remarkably improved to 85%. The reaction completed within 4 h of refluxing. The workup was simple: the crystalline product, which crystallized out of the reaction mixture on cooling, was collected by filtration and rinsed with methanol. The purity by HPLC assay, 99.4% by area, was sufficient for the use in the subsequent reactions. The present process was successfully applied also to diiodination of 1-ethoxy-4-methoxybenzene (**2b**) 1,4-diethoxybenzene (**2c**), 1,4-dibutoxybenzene (**2d**), and 1,4-bis(2-hydroxyethoxy)benzene (**2e**), as shown in Table 1. Since 2-propanol in place of methanol also facilitated the diiodination reaction, the employment of alcohols as reaction media is crucial for the improvement of the yield and provides a means for avoiding acidic solvents. Although hydrogen chloride is among the byproducts of this reaction, the stoichiometric amount of the acid is far less than the amount of an acid as a solvent. In the absence of a solvent, dialkoxybenzenes and ICl react very violently: addition of 0.67 g of 1,4-dimethoxybenzene to 3.2 g of ICl at room temperature resulted in spattering of the reaction mixture. By contrast, use of a solvent is effective in suppressing the vigorous reaction: we did not observe a significant rise in temperature when we added 0.5 g of 1,4-dimethoxybenzene to 3.18 g of ICl in 30 mL of methanol at 39.5 °C.

Although mixing a halogen with an alcohol often causes highly exothermic reactions, we observed only slight evolution of heat on mixing ICl with methanol or 2-propanol; the heat evolution on mixing methanol with ICl was estimated to be ca. 9.7 kcal/mol ICl, which was well within the capacity of our reactor. We have actually repeated the reaction quite safely even at a scale of 400 mol.

As we have not yet completed safety assessment regarding the effects of contaminants and impurities in chemicals used in the present reaction, we recommend not reusing an ICl-containing solution as recovered from a reaction vessel.

Experimental Section

Proton NMR spectroscopy was determined on a Bruker ARX-300 (300 MHz) spectrometer, and the chemical shifts are quoted in ppm downfield from $SiMe_4$. IR spectra were recorded on a JASCO IR-810 spectrometer. UV/vis spectra were recorded on a Shimadzu UV-3100PC spectrophotometer. FAB mass spectra were measured with a JEOL DX-303 mass spectrometer, and m/z values obtained for the isolated compounds were consistent with the corresponding molecular formulae. HPLC was performed on a Shimadzu system with UV detection at 254 nm through a TSK-gel ODS-80 column (4.6 mm × 150 mm) eluted with aqueous acetonitrile containing 0.2 vol % of acetic acid and triethylamine.

Materials. Solvents were obtained from commercial sources and used without further purification. 1,4-Dimethoxybenzene (**2a**), 1,4-diethoxybenzene (**2c**), 1,4-dibutoxybenzene (**2d**), 1,4-bis(2-hydroxyethoxy)benzene (**2e**), and iodine monochloride were commercially available reagents. 1-Ethoxy-4-methoxybenzene (**2b)** was prepared as described in the literature.[14]

1,4-Diiodo-2,5-dimethoxybenzene (1a). *Reaction in Methanol.* Iodine monochloride (175 g, 1.08 mol) was added dropwise to 300 mL of methanol below 15 °C. To the mixture were added 35 g (0.25 mol) of **2a** below 15 °C, and then the reaction mixture was heated under reflux for 4 h. After cooling the reaction mixture to room temperature, resulting crystals were collected by filtration. The crystals were rinsed with methanol (300 mL) and air-dried to give 84 g of **1a** (85% yield). HPLC assay 99.4%. Mp 171−172 °C (lit.[15] 171 °C). ^{1}H NMR ($CDCl_3$) δ 3.82 (6H, s), 7.19 (2H, s).

Reaction in 2-Propanol. The procedure was repeated except for using 2-propanol in place of methanol, and the reaction mixture was heated at 70 °C. The yield of **1a** was 80 g (82% yield).

Reaction in Acetic Acid. Iodine monochloride (7.5 g) was dissolved in 10 mL of acetic acid. To the solution was added

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1.6 g of **2a**. The resulting solution was heated at 70 °C for 4 h and then cooled to room temperature. Deposited crystals were collected by filtration and rinsed with 10 mL of methanol to give 1.4 g (31% yield) of **1a**. From the filtrate, an oily mixture of **3a** and **4a** in a mol ratio of 1:0.35 based on the ^{1}H NMR was obtained. ^{1}H NMR ($CDCl_3$) signals due to **3a**[13] δ 3.37 (s, 3H), 3.82 (s, 3H), 6.38 (d, 1H), 6.85 (dd, 1H), 7.33 (d, 1H); signals due to **4a**[13] δ 3.76 (s, 3H), 3.84 (s, 3H), 6.74 (dd, 1H), 6.85(d, 1H), 6.94 (d, 1H). MS *m/z* 263 (**3a**).

Reaction in Acetonitrile. Iodine monochloride (18.1 g, 111 mmol) was dissolved in 30 mL of acetonitrile. To the solution was added 3.7 g (26.8 mmol) of **2a**. The resulting solution was heated at 70 °C for 4 h and then cooled to room temperature. Deposited crystals were collected by filtration and rinsed with acetonitrile to give 1.72 g of colorless crystals, the NMR of which showed two sets of signals due to **5a** and to **1a** in a intensity ratio of 1.3:1, which corresponds to 0.86 and 0.86 g, respectively. On treatment of the filtrate with a sodium sulfite solution (12 g/200 mL) were deposited colorless crystals, which were collected by filtration to give 4.3 g of a mixture of **5a** and **1a** in a mol ratio of 10:1, which corresponds to 3.8 and 0.5 g, respectively. Recrystallization of the mixture from 2-propanol gave **5a** as colorless needles, which melted at 115−116.5 °C (lit.[11] 115−116 °C). ^{1}H NMR ($CDCl_3$) δ 3.83 (3H, s), 3.85 (3H, s), 6.95 (1H, s), 7.32 (1H, s). Total yields of **5a** and **1a** were 4.66 g (58.3%) and 1.36 g (13.0%), respectively.

1-Ethoxy-2,5-diiodo-4-methoxybenzene (1b). Iodine monochloride (68.1 g, 0.419 mol) was added dropwise to 88 mL of methanol below 15 °C. To the mixture was added 13.3 g (0.087 mol) of **2b** below 15 °C, and then the reaction mixture was heated under reflux for 4 h. The reaction mixture was cooled to 5 °C. The resulting crystals were collected by filtration rinsed with methanol (40 mL) and air-dried to give 28.2 g of **1b** (80.1% yield). HPLC assay 99.4%. Mp 93 °C, recrystallization from ethanol raised the mp to 101−102 °C. IR (KBr) 3120, 3000, 2852, 1500, 1360, 1222, 1070, 942, 858, 780 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.47 (3H, t), 3.82 (3H, s) 4.04 (2H, q), 7.20 (2H, s). Calcd for $C_9H_{10}I_2O_2$ C, 26.76; H, 2.49; I, 62.83. Found C, 26.70; H, 2.37; I, 62.40.

1,4-Diethoxy-2,5-diiodobenzene (1c). According to the procedure for **1a** except for using 23.3 g of **2c** in place of 35 g of **2a**, we obtained 52.6 g (89.9% yield) of **1c**. Mp 144.5−146.5 °C (recrystallized from ethanol). IR (KBr) 2980, 2860,1488, 1352, 1205, 1058, 928, 826, 775 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (6H, t), 4.01 (4H, q), 7.19 (2H, s). Calcd for $C_{10}H_{12}I_2O_2$ C, 28.73; H, 2.89; I, 60.72. Found C, 28.50; H, 2.73; I, 60.20.

1,4-Dibutoxy-2,5-diiodobenzene (1d). According to the procedure for **1a** except for using 55 g of **2d** in place of 35 g of **2a**, we obtained 98 g (82% yield) of **1d**. Mp 83−85 °C (lit.[16] 83−85 °C).

1,4-Bis(2-hydroxyethoxy)-2,5-diiodobenzene (1e). Iodine monochloride (57 g, 0.35 mol) was added dropwise to 80 mL of methanol below 15 °C. To the mixture was added 14 g (0.07 mol) of **2e** below 15 °C, and then the reaction mixture was heated under reflux for 4 h. After cooling the reaction mixture to 5 °C, resulting crystals were collected by filtration. The crystals were rinsed with methanol (40 mL) and air-dried to give 27 g of **1e** (86% yield). HPLC assay 99.5%. Mp 163.5−165.5 °C (recrystallized from acetonitrile). IR (KBr) 3190 (broad), 2950, 1490, 1345, 1220, 1066, 935, 780 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 3.7 (4H, t), 4.00 (4H, t), 4.81 (2H, broad s), 7.38 (2H, s). Calcd for $C_{10}H_{12}I_2O_4$ C, 26.69; H, 2.69; I, 56.40. Found C, 26.40; H, 2.58; I, 56.20%.

Heat Evolution on Mixing ICl with Methanol. One milliliter (3.18 g) of ICl was added to 30 mL of methanol at 26 °C. The temperature of the solution rose to 39.5 °C. Letting the density and the heat capacity of methanol be 0.787 and 0.6 cal deg^{-1} g^{-1}, respectively, the evolved heat was estimated to be ca. 9.7 kcal/mol ICl. To the solution was added 0.5 g of 1,4-dimethoxybenzene. The temperature of the solution was 39 °C.

Registry Numbers: **2a**, 150-78-7; **2b**, 5076-72-2; **2c**, 122-95-2; **2d**, 104-36-9; **2e**, 104-38-1; **1a**, 51560-21-5; **1c**, 225243-10-7; **1d**, 145483-70-1; **1e**, 299217-85-9; **3a**, 25245-35-6; **4a**, 2100-42-7; **5a**, 90064-46-3; ICl, 7790-99-0.

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