[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Dibenzofuran. XXI. Benzene and Biphenyl Intermediates for 1,9-Derivatives[1]

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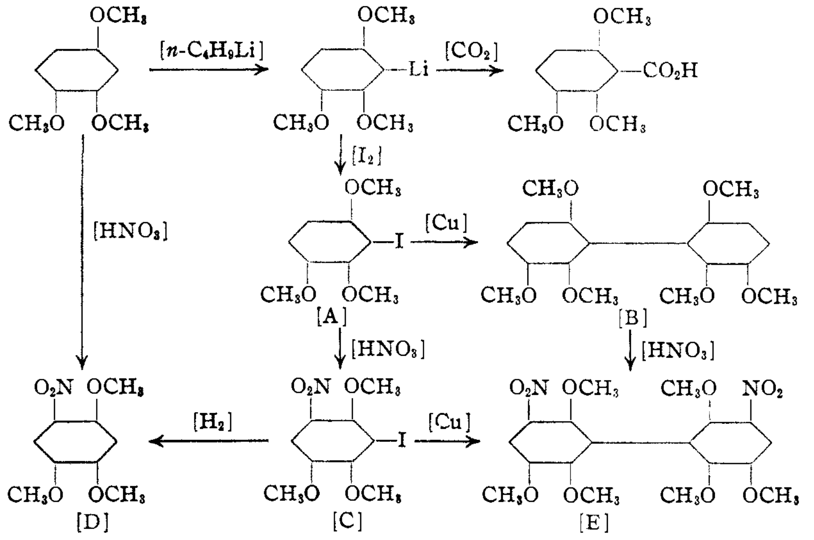
In the preparation of intermediates which, by ring-closure reactions, might give some reference 1,9-dibenzofuran derivatives, several benzene and biphenyl derivatives have been prepared. The general transformations are as follows:



Metalation of 1,2,4-trimethoxybenzene by *n*-butyllithium was shown to take place almost entirely in the 3-position. This was particularly interesting because of the possibilities of three isomeric monolithium derivatives due to the ortho-directing effect of methoxy groups in metalation. A parallel illustration is the metalation of resorcinol dimethyl ether to give, subsequent to carbonation and hydrolysis, practically exclusively 2,6-dimethoxybenzoic acid.[2]

The structure of the metalation product was established by carbonation to 2,3,6-trimethoxybenzoic acid and comparison with a sample prepared earlier by Smith and LaForge[3] by another procedure. Treatment of the lithium compound with iodine gave 2,3,6-trimethoxyiodobenzene [A] from which was obtained, by an Ullmann coupling, the 2,2',3,3',6,6'-hexamethoxybiphenyl [B]. Attempted ring closure of [B], by heating with an acetic acid solution of hydrobromic acid, gave a colored unstable polyphenolic type. Under corresponding conditions using hydrochloric acid there was recovered 85% of [B]; and with constant boiling hydriodic acid much as yet unresolved tarry material resulted.

Nitration of [A] gave 2,3,6-trimethoxy-5-nitroiodobenzene [C] the structure of which was established by hydrogenolysis to 1,2,4-trimethoxy-5-nitrobenzene [D]. The authentic specimen used to identify [D] was prepared, in accordance with the directions of Schüler,[4] by the nitration of 1,2,4-trimethoxybenzene. 2,2',3,3',6,6'-Hexamethoxy-5,5'-dinitrobiphenyl [E] was prepared by the coupling of [C] and also, in excellent yield, by the direct nitration of [B]. Inasmuch as [B] was essentially unaffected by hydrochloric acid, it was hoped that the nitro groups in [E] might preferentially labilize the ortho-methoxy groups in a cleavage reaction. However, no dibenzofuran derivative has been isolated.

Experimental

Quinone was converted to 1,2,4-triacetoxybenzene in 80% yield by the method of Thiele.[5] 1,2,4-Trimethoxybenzene was prepared in one step in 90% yield from 1,2,4-triacetoxybenzene by the procedure of Bargellini and Martegiani.[6]

2,3,6-Trimethoxyiodobenzene.—To a stirring and refluxing solution of 9.8 g. (0.0583 mole) of 1,2,4-trimethoxybenzene in 100 cc. of dry ether was added 0.0655 mole of *n*-butyllithium dissolved in 100 cc. of ether. The reaction mixture was refluxed with stirring for two hours. The system was allowed to cool under nitrogen, and a Gooch adapter was placed between the reaction flask and the reflux condenser. A Soxhlet thimble was charged with 17.8 g. (0.14 g. atom) of iodine and was supported in the adapter by means of a piece of clay plate. Stirring was continued and heating was regulated in such a manner that the iodine was dissolved slowly. The reaction of the iodine with the organolithium compound was very vigorous at the start. As the reaction heat diminished, heating was regulated to extract the iodine more rapidly. The entire extraction required forty-five minutes. Toward the end a distinct yellow to orange color due to excess iodine was noted and the white, insoluble, organolithium compound had disappeared, a clear solution resulting.

The ether solution was extracted with dil. sodium bisulfite to remove iodine and lithium iodide. After drying over calcium chloride, the ether was evaporated, leaving 10.6 g. (61.5% crude yield) of somewhat oily crystals. Recrystallization from 40 cc. of ethanol gave 8.7 g. (51%) melting at 107–108°. A second recrystallization raised the melting point to 108–108.5°.

Anal. Calcd. for $C_9H_{11}O_3I$: OCH_3, 31.63. Found: OCH_3, 31.61, 31.61.

2,3,6-Trimethoxybenzoic Acid.—Carbonation of the *n*-butyl-lithium-metalation product of 6.72 g. (0.04 mole) of 1,2,4-trimethoxybenzene by dry-ice gave, subsequent to hydrolysis, 4 g. (47%) of crystals melting at 148–149°.

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(1) Paper XX; Gilman, Swiss, Willis, and Yeoman, THIS JOURNAL, **66**, 798 (1944).

(2) Gilman, Willis, Cook, Webb and Meals, *ibid.*, **62**, 667 (1940).

(3) Smith and LaForge, *ibid.*, **53**, 3072 (1931).

(4) Schüler, *Arch. Pharm.*, **245**, 267, 276 (1907) [*Chem. Zentr.*, **78**, II, 806 (1907); see, also, *C. A.*, **2**, 1965 (1908)].

(5) Thiele, *Ber.*, **31**, 1247 (1898).

(6) Bargellini and Martegiani, *Gazz. chim. ital.*, **41**, II, 445 (1911) [*C. A.*, **6**, 625 (1912)]; *Atti. accad. Lincei*, **20**, II, 18 (1911) [*C. A.*, **5**, 3405 (1911), and *Chem. Zentr.*, **82**, II, 1026 (1911)].

Recrystallization from water raised the melting point to 149–150°. Smith and LaForge[3] reported a melting point of 145–146°, and a mixed m. p. with the sample kindly provided by them and our acid was 146–149°.

Anal. Calcd. for $C_{10}H_{12}O_5$: neut. equiv., 212. Found: neut. equiv., 219.

Methyl 2,3,6-Trimethoxybenzoate.—2,3,6-Trimethoxybenzoic acid was esterified with great difficulty. One gram was dissolved in 10 cc. of methanol and saturated with dry hydrogen chloride. After refluxing for one hour and cooling no crystals formed, but evaporation left an oil. The oil was dissolved in ether and washed twice with 10% sodium carbonate solution. From the dried ethereal solution there was obtained 0.3 g. (28%) of white crystals melting at 54–56°. Recrystallization from petroleum ether (b. p. 60–68°) raised the melting point to 57–57.5°.

Anal. Calcd. for $C_{11}H_{14}O_5$: OCH_3, 54.87. Found: OCH_3, 54.88.

Ethyl 2,3,6-Trimethoxybenzoate.—One gram of 2,3,6-trimethoxybenzoic acid was dissolved in 6 cc. of ethanol and 1 cc. of concd. sulfuric acid. After refluxing for one-half hour the reaction mixture was poured into 20 cc. of water. The solid was dissolved in ether and shaken with dilute sodium carbonate solution. After drying the ether layer over anhydrous potassium carbonate, the ether was evaporated, leaving an oil which crystallized on agitation. The crude product melted at 38–41°. Recrystallization from petroleum ether (b. p. 60–68°) raised the melting point to 42.5–43°.

Anal. Calcd. for $C_{12}H_{16}O_5$: alkoxyl, 57.50. Found: alkoxyl, 57.41.

2,2′,3,3′,6,6′-Hexamethoxybiphenyl.—Copper powder (50 g.) was purified by the method of Kleiderer and Adams.[7] After drying, an intimate mixture was made with 17.3 g. (0.0588 mole) of 2,3,6-trimethoxyiodobenzene. The mixture was heated by an oil-bath at 185–190° for three hours, in a nitrogen atmosphere. The temperature was finally raised to 210–215° for fifteen minutes.

Extraction in a Soxhlet apparatus was effected by 250 cc. of acetone. Concentration of the extract to a small volume and dilution with water gave 9.5 g. (97%) of crystals melting at 122–124°. Recrystallization from 30 cc. of hot acetone, diluted with water until crystals began to form, gave 7.5 g. (76.4%) of product melting at 125.0–125.5°.

Anal. Calcd. for $C_{18}H_{22}O_6$: OCH_3, 55.69. Found: OCH_3, 55.50, 55.68.

2,2′,3,3′,6,6′-Hexamethoxy-5,5′-dinitrobiphenyl.—This preparation is similar to the procedure used for 2,2′,6,6′-tetramethoxy-3,3′-dinitrobiphenyl.[8]

One gram (0.003 mole) of 2,2′,3,3′,6,6′-hexamethoxybiphenyl in a shell vial was dissolved in 10 cc. of acetic anhydride and 0.5 cc. of concd. nitric acid, which was prepared by warming fuming nitric acid until colorless. The mixture was heated gently on a hot-plate to start the reaction and then removed from the heat. After boiling had ceased, heating was continued at incipient boiling for five minutes. When cool, the product was isolated as follows. Six reaction mixtures were combined in an Erlenmeyer flask. Ten cubic centimeters of boiling acetic acid was used to rinse all of the shell vials. The crystals which formed were redissolved by slight warming, and 10 cc. of water was added dropwise to hydrolyze the excess acetic anhydride. The solution was kept at 0° overnight giving 6.9 g. (90.5%) of yellow crystals melting at 149–150°. Recrystallization from ethanol raised the melting point to 151–151.5°.

Anal. Calcd. for $C_{18}H_{20}O_{10}N_2$: OCH_3, 43.87. Found: OCH_3, 43.91, 43.77.

2,3,6-Trimethoxy-5-nitroiodobenzene.—A solution of 3.34 g. (0.0114 mole) of 2,3,6-trimethoxyiodobenzene in 12 cc. of glacial acetic acid at 60° was stirred while 6 cc. of concd. nitric acid in 20 cc. of acetic acid was added over a period of five minutes. Stirring was continued at 60° for fifteen minutes longer. After cooling, the crystals were filtered and washed with acetic acid and with water. Two and nine-tenths grams (75.3%) of pale yellow needles melting at 119.5–120° was obtained. Dilution of the filtrate gave 0.8 g. melting at 115–118°. Crystallization of the latter from acetic acid gave 0.45 g. more pure product. Dilution of the filtrate again and crystallization from dilute acetic acid gave an additional 0.27 g. The total yield of pure product was 3.62 g. (94.1%).

Anal. Calcd. for $C_9H_{10}O_5NI$: OCH_3, 27.43. Found: OCH_3, 27.25.

The position of the nitro group was proved by removal of the iodine atom by hydrogen and palladium–calcium carbonate catalyst. Two-tenths g. of the compound was shaken with 1 g. of the catalyst in 20 cc. of absolute ethanol at 30 pounds pressure of hydrogen for two hours. After filtering, concentrating to small volume, and cooling, crystals formed which melted at 125–127°. Recrystallization from ethanol raised the melting point to 128–129° and a mixed melting point with an authentic sample of 2,4,5-trimethoxynitrobenzene[4] was not depressed.

Coupling of 2,3,6-Trimethoxy-5-nitroiodobenzene.—An intimate mixture of 2.0 g. (0.0059 mole) of 2,3,6-trimethoxy-5-nitroiodobenzene and 6.0 g. of the specially prepared copper powder[7] was placed in a Pyrex test-tube, covered with a thin layer of copper powder, and protected from air by a closely-fitting cork stopper placed just above the reaction mixture. The tube was placed in a heating bath at 210°. Heating was continued at 210° for one hour and ten minutes. The temperature was raised to 230° and held there for thirty minutes.

The reaction mixture was extracted in a Soxhlet apparatus with acetone. Evaporation of the acetone gave 0.9 g. of a tarry material. Extraction of this product with boiling petroleum ether (b. p. 60–68°) gave 0.2 g. of yellow crystals melting at 142–149°. Recrystallization from dilute acetic acid raised the melting point to 147–149°. A recrystallization from ethanol gave pale yellow crystals melting at 149.5–151°, and a mixed melting point with the 2,2′,3,3′,6,6′-hexamethoxydinitrobiphenyl prepared by direct nitration, was not depressed. This establishes the nitro groups in the 5,5′-positions.

Summary

It has been shown that the metalation of 1,2,4-trimethoxybenzene by *n*-butyllithium gives almost exclusively 2,3,6-trimethoxyphenyllithium. This RLi compound with iodine gives the corresponding iodo compound which, when coupled by copper, yields 2,2′,3,3′,6,6′-hexamethoxybiphenyl. Nitration of the iodo compound gives 2,3,6-trimethoxy-5-nitroiodobenzene which was coupled to 2,2′,3,3′,6,6′-hexamethoxy-5,5′-dinitrobiphenyl. Neither of the polymethoxybiphenyls has yielded any 1,9-dibenzofurans.

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(7) Kleiderer and Adams, THIS JOURNAL, **55**, 4219 (1933).

(8) VanArendonk, Cupery and Adams, *ibid.*, **55**, 4225 (1933).