Synthesis of Benzoylbenzoic Acids

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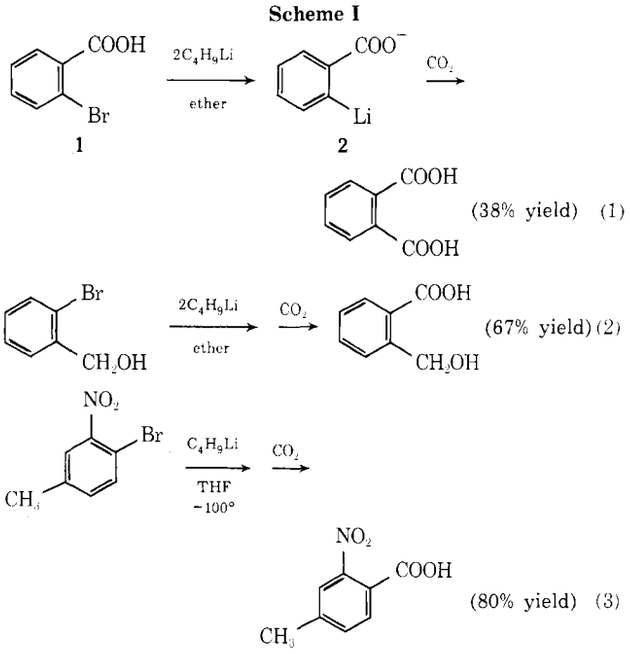
Bromine–lithium exchange in the isomeric bromobenzoic acids with *n*-butyllithium in tetrahydrofuran occurs selectively at −100°. The fate of these ions as a function of temperature has been examined. The dianions are stable at −75° but self-condense readily at −20° to give directly, and in good yield, *o*-, *m*-, and *p*-benzoylbenzoic acid, respectively. Anthraquinone is formed directly from *o*-bromobenzoic acid at higher temperature (0 to −20°).

In his pioneering work in organometallic chemistry, Gilman[1] and his coworkers established that halogen–metal interchange could be achieved with substituted halobenzene derivatives, and that the derived anions could be used as intermediates in synthesis as shown in Scheme I. A variety of halobenzene derivatives were employed in this work containing OH, CN, NH_2, SO_2NH_2, and $SO_2N(C_2H_5)_2$ functional groups; diethyl ether was used as solvent and temperatures of metalation varied from room temperature to −78°. While syntheses from organometallic intermediates of type **1** are potentially quite valuable, the procedure utilizing functionalized aryl halides has largely been overlooked, probably owing to the highly variable yields of benzoic acid derivatives (14–78%) obtained upon carbonation. In 1970, Kobrich and Buck[2] showed that *o*-nitrobromobenzene derivatives could be metalated in high yield (tetrahydrofuran at −100°) (eq 3, Scheme I) while *m*- or *p*-nitrobromobenzene derivatives undergo a redox reaction under these conditions.

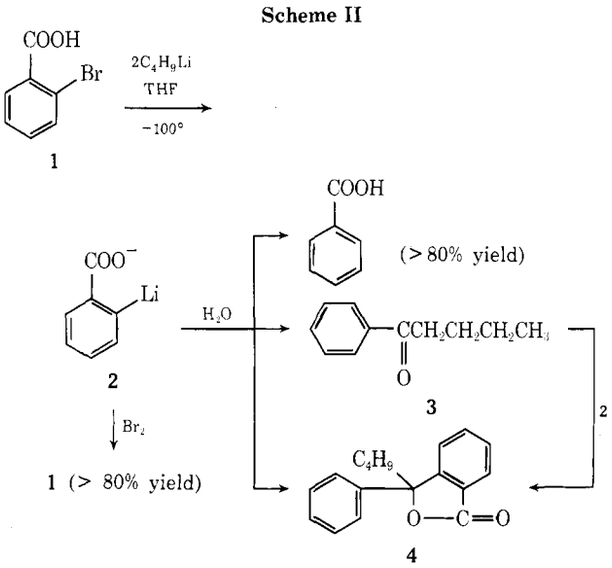
We conclude that bromine–lithium exchange should be highly selective for many substituted halobenzenes at very low temperature (−100°, liquid N_2), and that the variable yields of products previously reported were a consequence of side reactions of derived anions of type **2** with themselves or with solvent. We have, accordingly, reexamined halogen–metal interchange of the isomeric bromobenzoic acids and evaluated the product distribution as a function of temperature.

Reaction of *o*-bromobenzoic acid was studied in detail. When metalation of **1** was conducted at −100° in tetrahydrofuran and the reaction mixture maintained at −75°,

Scheme I



Scheme II



metalation was complete. The product distribution obtained subsequent to quenching the mixture with water is shown in Scheme II.

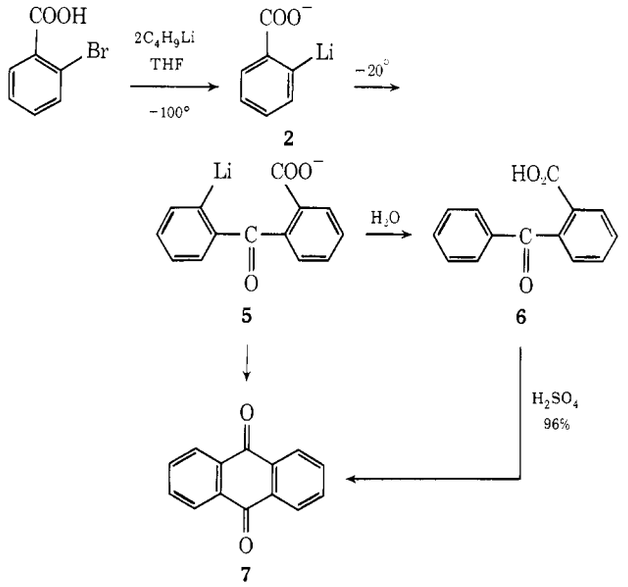
When the anion **2** was added to bromine in carbon tetrachloride, *o*-bromobenzoic acid was formed and isolated in >80% yield. Two minor side products, valerophenone (**3**, 6%) and lactone **4** (4.5%), were detected in the neutral fraction of the product obtained by addition of **2** to water. Valerophenone was undoubtedly formed by the slow addition of excess butyllithium to the anion **2**, and the lactone **4** by addition of **2** to valerophenone. Evidence supporting the latter assumption was obtained by the independent synthesis of **4** (67% yield) by addition of **2** to valerophenone.

The fate of the anion **2** was found to be quite sensitive to temperature (Scheme III). Thus, while the anion **2** is quite stable at −75°, it condenses with itself[3] as the temperature is raised to −20°. Quenching the mixture obtained at −20° with water gave benzoic acid (8.4%), formed from unreacted **2**, *o*-benzoylbenzoic acid (**6**, 63% yield, pure), anthraquinone (**7**, 2.3% yield) formed by self-condensation of **5**, valerophenone (4%), and lactone **4** (7%).

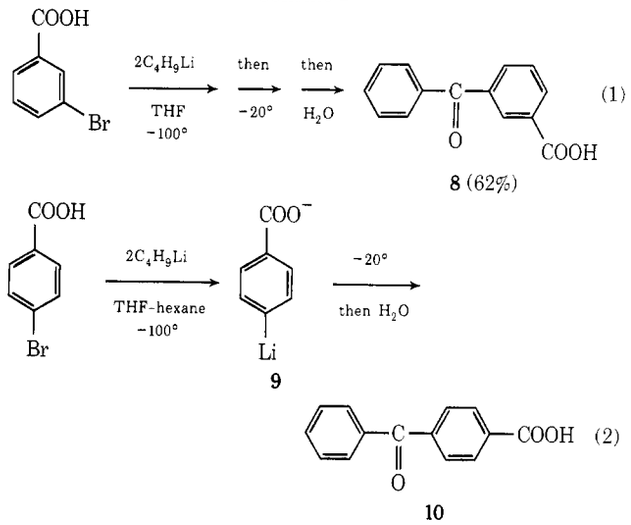
When the temperature of the above reaction mixture was brought to 0°, none of the anion **2** survived nor was there any loss of anion **2** by abstraction of hydrogen from solvent, since no benzoic acid was obtained after addition of water; the yield of anthraquinone rose only slightly to 5.6%, and the yield of *o*-benzoylbenzoic acid was not changed appreciably (64% pure **6**).

Attempts to effect a more efficient direct conversion of **5** to **7** were only partly successful, and this is attributed to interaction of **5** with solvent at higher temperature (−20°) to give the salt of **6**. Addition of bromine to the solution of

Scheme III



Scheme IV



2 prepared at −100° but then warmed up to −20° gave 6 but no detectable amount of bromo acid derived from 5. Studies with *p*-bromobenzoic acid, discussed subsequently, substantiate loss of anion by reaction with solvent. When the solution of 2, prepared at −100°, was heated at the reflux temperature (24 hr) prior to addition of water, the yield of anthraquinone was raised to only 15%; the yield of *o*-bromobenzoic acid was reduced to 58%. The stability of anion 2 does appear to be a function of tetrahydrofuran concentration, since the yield of anthraquinone was increased to 44% (26% yield of 6) when metalation was effected at −100° in a mixture of tetrahydrofuran–hexane (40:60), and the mixture subsequently brought to reflux. Direct formation of anthraquinone (7) is of little synthetic consequence, since 7 can be formed[4] essentially quantitatively by reaction of 6 with concentrated sulfuric acid; however, utilization of the derived anion 5 directly for further synthetic transformations does not appear to be feasible.

This efficient one-step synthesis of *o*-benzoylbenzoic acid is of considerable synthetic consequence, since, in view of Gilman's[1] earlier work, it is anticipated that a number of substituted *o*-bromobenzoic acids can be employed which will provide direct access to substituted *o*-benzoylbenzoic acids and, subsequently, to substituted anthraquinones. This is important since the only practical direct synthesis of anthraquinones is the phthalic anhydride synthesis,[5] which is limited by the usual orientation problems and inhibiting action of negatively substitututed benzenes associated with Friedel–Crafts acylation reactions.

The direct formation of benzoylbenzoic acids is by no means limited to *o*-benzoylbenzoic acids. Thus, we have observed (Scheme IV) that *m*-benzoylbenzoic acid (8, 62% yield) and *p*-benzoylbenzoic acid (10, 55–60% yield) can be obtained directly by obvious modification of the procedure.

The anion 9 was found to be more reactive with solvent tetrahydrofuran than the corresponding anion derived from *o*- and *m*-bromobenzoic acids. Thus, when anion 9, formed at −100° in tetrahydrofuran at the same concentration used for the preparation of 3 and 8, was warmed to −20° prior to addition of water the yield of 10 was only 40%; benzoic acid was isolated in 30% yield. When the amount of solvent was increased twofold, only benzoic acid was obtained. Optimum conversion of *p*-bromobenzoic acid to 10 (55–60%) was realized by using a mixture of tetrahydrofuran–hexane (60:40); in this case a small amount (5%) of high-melting acid was formed.

Benzoylbenzoic acids of such orientation are not readily prepared by other methods, and it is anticipated that a variety of substituted aroylbenzoic acids can now be conveniently prepared.

Experimental Section

Reaction of *o*-Bromobenzoic Acid with *n*-Butyllithium. A. *n*-Butyllithium (12.5 ml of ~2 *M* solution in hexane, ~0.025 mol) was slowly added (~1 hr) to a solution of 1 (2.5 g, 0.0125 mol) in tetrahydrofuran (50 ml, distilled from $LiAlH_4$). The mixture was maintained under nitrogen and the temperature was controlled by a liquid nitrogen–diethyl ether bath and was not allowed to rise above −95°. The mixture was then allowed to warm to −75° for 2 hr and was then poured into 5% aqueous hydrochloric acid (50 ml). The resulting mixture was extracted with chloroform (100 ml) and the chloroform extracts were washed with water (50 ml). The chloroform solution was extracted with cold 10% aqueous sodium hydroxide (25 ml) to remove acid products, and then washed with water and dried. Acidification of the alkaline extract gave essentially pure benzoic acid (1.25 g, mp 119–120°, 83% yield; 1.21 g after recrystallization from water, 79% yield, mp and mmp 120–122°).

The oil obtained from the chloroform extract was chromatographed on silica gel [preparative tlc, petroleum ether[6]–diethyl ether (80:20) as eluent] to give valerophenone (122 mg, 6%), identified by nmr and infrared, and lactone 4 as an oil; nmr showed butyl group and nine aromatic hydrogens; ir showed five-membered lactone at $\lambda_{C=O}$ 1770 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.66.

B. When the above reaction mixture was allowed to warm to −20 to −30° and maintained at this temperature for 5 hr prior to quenching, there was obtained (1) benzoic acid (8.4%), (2) *o*-benzoylbenzoic acid [6, 68% yield, mp 124–129° by chromatography, silica gel, petroleum ether[6]–ether (80:20) as eluent; 63% from benzene–petroleum ether[6], mp and mmp 128–129° (lit.[7] mp 127°)], along with the ketone 3 (4.2%), the lactone (7%), and anthraquinone (2.3%), mp and mmp 282–285°.

C. When the above mixture was maintained at room temperature for 6 hr prior to addition of water, there was obtained *o*-benzoylbenzoic acid (6, 64%), ketone 3 (4%), lactone 4 (8%), and anthraquinone (8.8%).

D. When the above mixture was heated at reflux (24 hr) prior to quenching, the yield of 6 was 55% and the yield of anthraquinone was 15%.

E. The optimum direct conversion of 1 to anthraquinone (44%) was obtained in experiments similar to D but by using tetrahydrofuran–hexane (40:60) as solvent; the yield of 6 was reduced to 26%.

Preparation of Lactone 4. Valerophenone (0.81 g, 0.005 mol) was added at −75° to a solution of 2 (~0.005 mol) as prepared in A above. The mixture was allowed to warm to room temperature. The lactone 4 was converted to the salt in warm aqueous base which was reconverted to lactone on acidification, yield of 4 67%.

Conversion of 2 to *o*-Bromobenzoic Acid. A solution of **2** was prepared as described in A and prior to quenching was added to bromine (excess in carbon tetrachloride). The acid **1** was isolated by conventional means and obtained in nearly quantitative yield.

***m*-Benzoylbenzoic acid** was prepared from *m*-bromobenzoic acid (0.0125 mol) by a procedure essentially identical with that described in B; the mixture was maintained at −20 to −10° (5 hr) prior to quenching with water. There was obtained (1) benzoic acid (mp 118–120°, 9.2%), (2) *m*-benzoylbenzoic acid [**8**, 69%, mp 155–158°; 63% from chloroform–petroleum ether,[6] mp and mmp 161–162° (lit.[8] mp 161–162°)]. The neutral fraction contained only trace quantities of products other than valerophenone (9%).

***p*-Benzoylbenzoic acid** was prepared from *p*-bromobenzoic acid as described for **8**. The acid fraction on chromatography [silica gel, petroleum ether[6]–diethyl ether (70:30) as eluent] gave *p*-benzoylbenzoic acid [40%, mp 199–201° (lit.[9] mp 197–200°)] and benzoic acid (30%).

When the amount of tetrahydrofuran was increased twofold, only benzoic acid was obtained.

When the procedure was carried out as described for **8** but with a mixture of tetrahydrofuran–hexane (60:40) the yield of *p*-benzoylbenzoic acid was 55–60% (multiple runs).

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Registry No.—**1**, 88-65-3; **2**, 51310-60-2; **4**, 51310-61-3; **6**, 85-52-9; **8**, 579-18-0; **10**, 611-95-0; *n*-butyllithium, 109-72-8; benzoic acid, 65-85-0; *m*-bromobenzoic acid, 585-76-2; *p*-bromobenzoic acid, 586-76-5.

References and Notes

(1) (a) H. Gilman and C. Arntzen, *J. Amer. Chem. Soc.*, **70**, 4178 (1948); (b) *ibid.*, **70**, 2844 (1948); (c) H. Gilman and D. S. Melstrom, *ibid.*, **63**, 2844 (1941).
(2) G. Kobrich and P. Buck, *Chem. Ber.*, **103**, 1412 (1970).
(3) The possibility that **6** was formed by a sequence involving reaction of **2** with *n*-butyl bromide to form an ester with subsequent condensation of the derived ester with **2** was not supported by the observation that the lithium salt of benzoic acid does not react with *n*-butyl bromide at −20°.
(4) (a) A. H. Gleason and G. Dougherty, *J. Amer. Chem. Soc.*, **51**, 310 (1929); (b) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957, p 159.
(5) *Cf.* E. Barnett, "Anthracene and Anthraquinones," Baillière, Tindall and Cox, London, 1921.
(6) Boiling point 30–60°.
(7) C. R. Rubidge and N. C. Qua, *J. Amer. Chem. Soc.*, **36**, 732 (1914).
(8) S. Seuff, *Justus Liebigs Ann. Chem.*, **220**, 252 (1883).
(9) E. Westheim, *J. Amer. Chem. Soc.*, **55**, 2541 (1933).

Synthesis of Isomeric Methyl Benzoylbenzoates and Substituted *o*-, *m*-, and *p*-Benzoylbenzoic Acids

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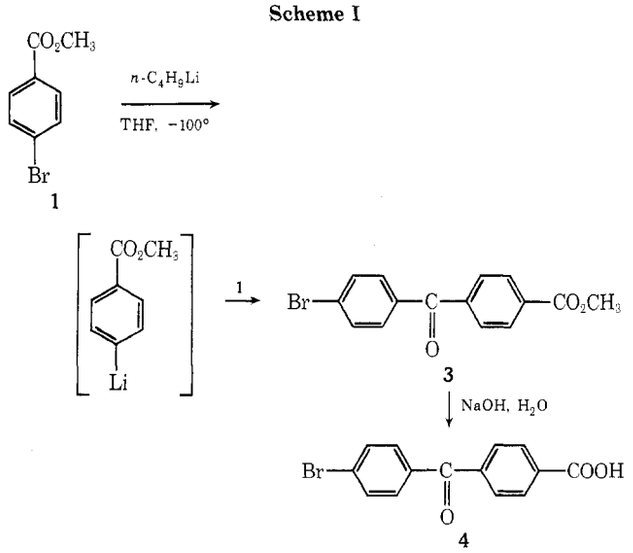
n-Butyllithium reacts selectively at −100° with isomeric methyl bromobenzoates by halogen–metal exchange. The corresponding anions derived from the meta and para isomers react readily with methyl ester functions at −100°; however, the anion derived from the ortho isomer reacts only slowly at this temperature, which permits complete metal–halogen interchange. The self-condensation of isomeric methyl bromobenzoates, and the reactions of dianions derived from the isomeric bromobenzoic acids with substituted methyl benzoates, provide ready access to a wide variety of *o*-, *m*-, and *p*-benzoylbenzoic acids.

In a previous communication[1] we reported a convenient procedure for a one-step conversion of bromobenzoic acids to *o*-, *m*-, and *p*-benzoylbenzoic acids. While it is apparent that this concept can be extended to a variety of substituted halobenzene derivatives, we were particularly interested in examining comparable reactions of the isomeric methyl bromobenzoates with *n*-butyllithium; it was anticipated that an understanding of competitive halogen–metal exchange *vs.* carbonyl addition reactions in such systems would permit a more versatile procedure for the preparation of a variety of isomeric aroylbenzoic acids.

A. Self-Condensation of Methyl Bromobenzoates. Methyl esters are considerably more reactive to anion addition reactions than carboxylate ions previously studied;[1] nevertheless, reaction of methyl *p*-bromobenzoate with *n*-butyllithium in tetrahydrofuran at −100° is selective in that the primary reaction involves halogen–metal interchange rather than addition of alkyllithium to the carbonyl ester function. The derived anion **2** did, however, react as formed at the ester function of unreacted **1**, as shown in Scheme I.

Scheme I



The principal product, methyl 4-(*p*-bromobenzoyl)benzoate (**3**), obtained pure in 63% yield when 0.75 molar equiv of *n*-butyllithium was employed, was unknown, and was further characterized by hydrolysis (~100% yield) to the corresponding acid **4**. The yield of **3** was optimum with approximately 0.75 molar equiv of *n*-butyllithium. The yield of **3** dropped to 49% when 0.6 molar equiv of *n*-butyllithium was employed, and in this case 9% of **1** was recovered unchanged; when 1 molar equiv of *n*-butyllithium was employed the yield of **3** was 57%.

The temperature of the above reaction was found to be critical if high yields of bromo ester **3** are to be obtained.