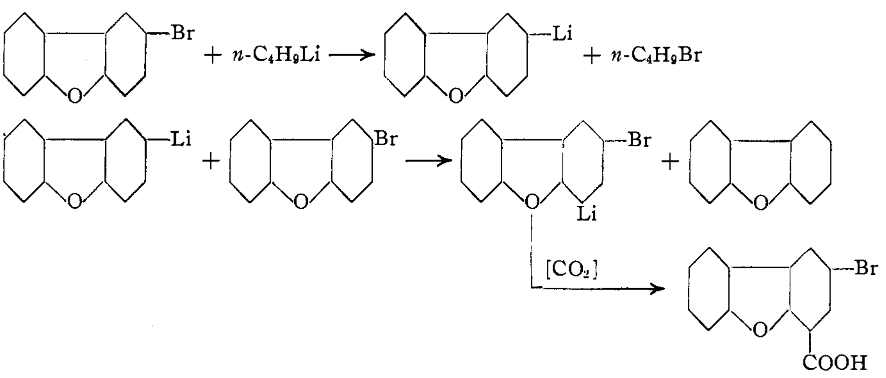
[Contribution from the Chemical Laboratory of Iowa State College, and Panhandle Agricultural and Mechanical College]

Dibenzofuran. XVI. The Two-Stage Metalation of 2-Bromodibenzofuran[1]

By Henry Gilman, Wright Langham and H. B. Willis

In an earlier study,[2] incidental to an attempt to prepare 2-bromo-6-dibenzofurancarboxylic acid, it was shown that metalation of 2-bromodibenzofuran by *n*-butyllithium gave, subsequent to carbonation, 2-bromo-4-dibenzofurancarboxylic acid.[2] The isolation from that reaction of appreciable quantities of dibenzofuran suggested that a halogen–metal interconversion first took place and that this reaction was followed by metalation as follows.



(I)

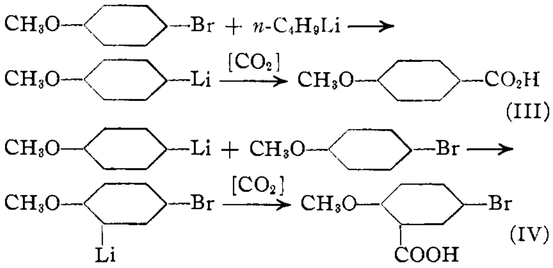
(II)

We are now presenting evidence in support of this two-stage metalation. When 2-bromodibenzofuran is treated with *n*-butyllithium for a short time, reaction (I) occurs predominantly, and carbonation results in the formation of excellent yields of 2-dibenzofurancarboxylic acid to the exclusion of any 2-bromo-4-dibenzofurancarboxylic acid. The bromo-acid probably results in accordance with reaction (II) when the reaction mixture (with equivalent quantities of reactants) is heated for a relatively long period.[2]

The preliminary reaction involving a halogen-metal interconversion is now known to take place quite readily when the halogen is bromine or iodine. This interconversion reaction is not limited to halogenated ethers, but has been observed with simple and multiple halogenated derivatives of aromatic hydrocarbons[3] and with *m*- and *p*-bromodimethylanilines.[4] The first report on such a reaction with *n*-butyllithium was probably the study by Marvel and co-workers[5] with *o*- and *m*-bromotoluenes.[6] The other reported studies on the interconversion reaction have been with *ortho*-bromo ethers.[7]

It is uncertain whether a halogen–metal interconversion precedes all metalations of halogen containing compounds. An examination of the results of metalation, particularly by *n*-butyllithium, of bromo- and iodo-ethers, reveals that in almost every case a halogen–metal interconversion first takes place.[8] However, there is no unequivocal case for interconversion preceding metalation when the nuclear halogen is chlorine or fluorine. In such cases, the rate of direct metalation is apparently decidedly greater than the rate of halogen–metal interconversion.

Two other illustrations of interconversion preceding metalation are the reactions of *p*-bromoanisole and *p*-iodoanisole with *n*-butyllithium. Under conditions reported earlier,[9] carbonation



(III)

(IV)

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[1] Paper XV, This Journal, **61**, 3149 (1939).

[2] Gilman, Cheney and Willis, *ibid.*, **61**, 951 (1939).

[3] See p. 1372 of Gilman, Willis and Swislowsky, *ibid.*, **61**, 1371 (1939), for studies by W. Langham.

[4] Gilman and Banner, *ibid.*, **62**, 344 (1940).

[5] Marvel, Hager and Coffman, *ibid.*, **49**, 2323 (1927).

[6] Under their conditions (Ref. 5) of long-timed reactions in sealed tubes and with petroleum ether as a medium, they observed that *p*-bromotoluene and *n*-butyllithium gave *p*-*n*-butyltoluene on hydrolysis. With our experimental conditions (short-time, non-sealed containers, and ether as a medium) interconversion took place as usual to give *p*-toluic acid subsequent to carbonation.

[7] Citations to the earlier literature are given in Ref. 3.

[8] Illustrations with some bromo-ethers of dibenzofuran are given in the accompanying paper by Gilman, Swislowsky and Brown, This Journal, **62**, 348 (1940).

[9] Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938); Gilman, Langham and Jacoby, This Journal, **61**, 106 (1939).

of the reaction mixture of *p*-bromoanisole and *n*-butyllithium gave 5-bromo-2-methoxybenzoic acid [reaction (IV)]. We are now reporting that by employing a large excess of *n*-butyllithium, and milder conditions, the *p*-methoxybenzoic acid is formed exclusively and in good yields [reaction (III)].

When equivalent quantities of halide and organolithium compound are used, the reaction time is the most important factor in determining the products which result. This is strikingly illustrated in the reaction of *p*-iodoanisole with *n*-butyllithium. In this case, the *p*-methoxybenzoic is formed predominantly if not exclusively in thirty minutes, whereas after six hours only 5-iodo-2-methoxybenzoic acid is isolated. Also, when equivalent quantities of *p*-bromoanisole and *n*-butyllithium are added dropwise and separately to a reaction chamber and then allowed to react but one minute prior to carbonation, a 10% yield of *p*-methoxybenzoic acid (free from any bromo acid) results. It is rather certain that even with a long period of reaction, interconversion is the main reaction when a large excess of *n*-butyllithium is used.

Experimental Part

2-Bromodibenzofuran and *n*-Butyllithium.—To a solution of 2 g. (0.0081 mole) of 2-bromodibenzofuran in 25 cc. of benzene was added approximately 0.009 mole of *n*-butyllithium in 25 cc. of ether. The solution was refluxed for thirty minutes, and then poured upon dry-ice and ether. The yield of the crude 2-dibenzofurancarboxylic acid was 1.7 g. (87.3%). One recrystallization from glacial acetic acid gave a product which melted at 241–242°.

The methyl ester, prepared from the acid and diazomethane in ether, melted at 81–82° after crystallization from dilute alcohol. A mixed melting point with an authentic specimen of methyl 2-dibenzofurancarboxylate was not depressed. Incidentally, the melting point of methyl 2-dibenzofurancarboxylate is 82–83° and not 73–74° as reported previously.[10]

Anal. Calcd. for $C_{14}H_{10}O_3$: OCH_3, 13.72. Found: OCH_3, 13.45.

In a check experiment, the yield of 2-dibenzofurancarboxylic acid was 84.5%.

In another experiment 2-dibenzofuryllithium was prepared as described above, from 0.0081 mole of 2-bromodibenzofuran and 0.009 mole of *n*-butyllithium, and after fifteen minutes an additional 0.032 mole of 2-bromodibenzofuran was added. Upon carbonation after six hours of refluxing, the only acid isolated was 2-bromo-4-dibenzofurancarboxylic acid.

With three equivalents of *n*-butyllithium to one of 2-bromodibenzofuran, in a 1:1 ether–benzene mixture heated for six hours at 50°, the yield of 2-dibenzofurancarboxylic acid was 64%, and no 2-bromo-4-dibenzofurancarboxylic acid was isolated.

***p*-Bromoanisole and *n*-Butyllithium.**—When an ether solution of equivalent quantities of *p*-bromoanisole (0.1 mole) and *n*-butyllithium was heated at 34° for twenty hours and then carbonated, the acids obtained were *p*-methoxybenzoic (10%) and 5-bromo-2-methoxybenzoic (10%). Under corresponding conditions, but with a more concentrated mixture which permitted refluxing at 50°, the yield of 5-bromo-2-methoxybenzoic acid was 28%. In a third experiment, a mixture of 0.05 mole of *p*-bromoanisole and 0.05 mole of *n*-butyllithium in a 1:1 ether–benzene solvent was refluxed for twenty hours at 50°, and then carbonated to yield 22% of 5-bromo-2-methoxybenzoic acid.

In a fourth experiment, two equivalents of *p*-bromoanisole were used. A mixture of 0.18 mole of *p*-bromoanisole and 0.09 mole of *n*-butyllithium in 150 cc. of ether was refluxed for a few minutes; then 150 cc. of dry benzene was added and the temperature of refluxing was 50°. Carbonation of 50-cc. aliquots of the reaction mixture after refluxing for one hour, five hours and ten hours gave 47, 47, and 52%, respectively, of 5-bromo-2-methoxybenzoic acid. Carbonation of the remainder of the reaction mixture after a total of twenty hours of refluxing reduced the average yield to 45%. Possibly some of the organolithium compound is used up in ether cleavage in the extended period of refluxing.

In a fifth experiment two equivalents of *n*-butyllithium were used and the reaction was run in ether at room temperature for ten minutes. From 0.02 mole of *p*-bromoanisole and 0.04 mole of *n*-butyllithium there was obtained 1.6 g. (52%) of crude *p*-methoxybenzoic acid (m. p. 168–171°). Pure *p*-methoxybenzoic acid melts at 183–184°. The crude acid gave a qualitative test for bromine, but no bromo acid was isolated.

In a sixth experiment 0.02 mole of *p*-bromoanisole and 0.02 mole of *n*-butyllithium were added separately and dropwise to a reaction chamber and carbonation was effected at intervals after the reactants had been in contact for one minute. This method gave a total yield of 0.3 g. (10%) of *p*-methoxybenzoic acid which melted at 178–180° and showed no qualitative test for bromine.

***p*-Iodoanisole and *n*-Butyllithium.**—A solution of 0.03 mole of *p*-iodoanisole and 0.03 mole of *n*-butyllithium in 100 cc. of ether was allowed to stand for thirty minutes with no external heating. Carbonation of a 25-cc. aliquot gave a 52% yield of crude *p*-methoxybenzoic acid melting at 176–180°. After one hour of refluxing, carbonation of a 25-cc. aliquot gave a 52% yield of crude *p*-methoxybenzoic acid melting at 172–175°. After six hours of heating, a 25-cc. aliquot yielded 0.45 g. of acidic material with a melting point range of 154–165°. At the end of ten hours of heating there was obtained a 35% yield of 5-iodo-2-methoxybenzoic acid.

The 5-iodo-2-methoxybenzoic acid was identified by a mixed melting point determination with an authentic specimen.[11]

Anal. Calcd. for $C_8H_7O_3I$: neut. equiv., 278. Found: neut. equiv., 278.

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[10] Gilman and Van Ess, THIS JOURNAL, **61**, 1365 (1939).

[11] For the preparation of 5-iodo-2-hydroxybenzoic acid see Hübner, *Ber.*, **12** 1347 (1879); Goldberg, *J. prakt. Chem.*, [2] **19**, 368 (1879).

In a second experiment, carbonation at the end of fifteen minutes gave a 50% yield of crude *p*-methoxybenzoic acid, melting at 170–174°. From a third experiment in which the reaction mixture was heated at 50° in a 1:1 ether–benzene solvent for five hours, the yield of pure 5-iodo-2-methoxybenzoic acid was 24%.

Orienting experiments have shown that it is possible to metalate alcohols (like benzyl alcohol), phenols, and primary and secondary amines. Also, halogen–metal interconversions take place with a variety of bromo and iodo compounds containing, in addition, other functional groups like amino, hydroxy, and acids and their derivatives. For example, *o*-bromophenol and *n*-butyllithium give, subsequent to carbonation and hydrolysis, a 60% yield of salicylic acid; and under corresponding conditions *o*-bromoaniline gives a 36% yield of anthranilic acid.

Summary

It has been shown that the metalations reported previously of some halogenated ethers involve a two-stage procedure. First, there is a halogen–metal interconversion, and, second, the organometallic compound formed in this manner then metalates the original halogenated ether. The interconversion reaction is more rapid. For example, in fifteen minutes, 2-bromodibenzofuran reacts with *n*-butyllithium to give excellent yields of 2-dibenzofuryllithium. Upon protracted refluxing, this RLi compound then metalates 2-bromodibenzofuran to give 2-bromo-4-dibenzofuryllithium.

Related observations are reported with *p*-bromoanisole and *p*-iodoanisole.

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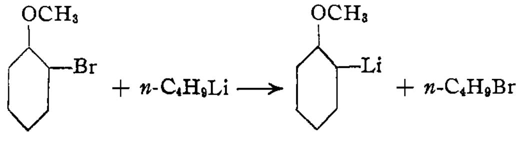
GOODWELL, OKLAHOMA RECEIVED DECEMBER 7, 1939

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

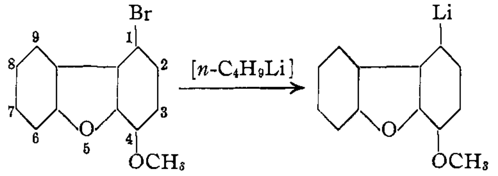
Dibenzofuran. XVII. The Reaction of Bromo-Ethers with *n*-Butyllithium[1]

BY HENRY GILMAN, JACK SWISLOWSKY AND GEORGE E. BROWN

The recent availability of a series of bromomethoxy derivatives of dibenzofuran has provided essential material for an examination of the scope of halogen–metal interconversion reactions. In the first published illustrations of this reaction with bromo-ethers,[2] the bromine replaced by lithium was always *ortho* to an ether linkage. A typical simple illustration is



We are now reporting reactions of *n*-butyllithium with a series of bromomethoxydibenzofurans in which the bromine atoms are disposed in most of the important positions with respect to the ether linkages. In these eight compounds, a bromine atom is not only *ortho*, *meta* and *para* to a methoxy group, but also *ortho* and *meta* to the oxygen bridge in dibenzofuran. We have found that in every case the predominant reaction is a halogen–metal interconversion.



Some of the reactions reported are synthetically valuable. For example, 1-bromo-3,4-dimethoxydibenzofuran has not as yet yielded either an organomagnesium[3] or an organolithium[4] compound when treated with the respective metals under general conditions for the formation of these organometallic compounds. However, *n*-butyllithium reacts promptly with 1-bromo-3,4-dimethoxydibenzofuran to give a satisfactory yield of 3,4-dimethoxy-1-dibenzofuryllithium.

The structures of the several reaction products were established by conventional procedures involving carbonation to the corresponding acids which were in turn compared with authentic specimens. The acid resulting from 1-bromo-3,4-dimethoxydibenzofuran was shown to be identical with 3,4-dimethoxy-1-dibenzofurancarboxylic acid prepared as follows

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(1) Paper XVI, THIS JOURNAL, **62**, 346 (1940).

(2) General references on this reaction are contained in the accompanying papers: (a) Gilman and Banner, *ibid.*, **62** 344 (1940), and (b) Gilman, Langham and Willis, *ibid.*, **62**, 346 (1940).

(3) The activated magnesium-copper alloy was not used.

(4) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).