TABLE II

-5-PHENYLISOXAZOLE

Subs.	M. p., °C.	Formula	Analyses, % Calcd.	Found
3-(4-Iodoanilino)-	148–149	$C_{15}H_{11}IN_2O$	I, 35.5	I, 35.4
3-(4-Iodoanilino)-4-bromo-[2]	172–173	$C_{15}H_{10}BrIN_2O$	Br, 18.1	Br, 18.5
3-(4-Iodoanilino)-4-chloro-	151–152	$C_{15}H_{10}ClIN_2O$	Cl, 8.9	Cl, 8.6
3-(4-Iodoanilino)-4-nitro-	243–244	$C_{15}H_{10}IN_3O_3$	I, 31.2	I, 31.6
3-(2-Bromo-*p*-toluidino)-4-bromo-	130–131	$C_{16}H_{12}Br_2N_2O$	Br, 39.2	Br, 38.8
3-(2,6-Dichloro-*p*-toluidino)-4-chloro-	229–230	$C_{16}H_{11}Cl_3N_2O$	Cl, 30.1	Cl, 29.7
3-(4-Phenylanilino)-	176–177	$C_{21}H_{16}N_2O$	C, 80.5	C, 80.1
			H, 4.8	H, 4.5

TABLE III

-5-PHENYLPYRAZOLE

Subs.	M. p., °C.	Formula	Analyses, % Calcd.	Found	Calcd.	Found
3-(4-Iodoanilino)-	175–176	$C_{15}H_{12}IN_3$	I, 35.1	I, 35.3		
3-(2-Bromo-4-iodoanilino)-4-bromo-	201–202	$C_{15}H_{10}Br_2IN_3$	Br, 30.8	Br, 30.8		
3-(4-Iodoanilino)-4-chloro-	206–207	$C_{15}H_{11}IN_3Cl$	Cl, 8.9	Cl, 8.5		
3-(3-Bromoanilino)	205–206	$C_{15}H_{12}BrN_3$	Br, 25.5	Br, 25.4		
3-(3-Bromoanilino)-4-bromo-	178–179	$C_{15}H_{11}Br_2N_3$	Br, 40.7	Br, 40.5		
3-(*p*-Toluidino)-	157–158	$C_{16}H_{15}N_3$	C, 77.1	C, 76.8	H, 6.1	H, 5.9
3-(2-Bromo-*p*-toluidino)-4-bromo-	181–182	$C_{16}H_{13}Br_2N_3$	Br, 39.4	Br, 39.5		
3-(2,6-Dinitro-*p*-toluidino)-4-nitro-	245–247	$C_{16}H_{12}N_6O_6$	C, 50.0	C, 49.9	H, 3.1	H, 3.0
3-(4-Phenylanilino)	219–220	$C_{21}H_{17}N_3$	C, 81.1	C, 80.9	H, 5.5	H, 5.3

The product contained tarry material best removed by ethylene chlorohydrin after which it was crystallized from alcohol several times, eventually separating as nearly colorless needles; yield 20–30%. Bromine and chlorine reacted smoothly in chloroform solution, producing after crystallization from alcohol colorless hair-like crystals. The toluidino derivative separated as plates. The nitration went less smoothly, while the products separated from glacial acetic acid as yellow crystals. Only slight evidence of isoxazole formation was found with the naphthyl or the phenetidine derivatives.

Pyrazole formation was also accompanied by considerable tar formation, best purified in the manner indicated for the isoxazoles and forming eventually colorless needles or plates. The chlorine and bromine derivatives were obtained in good yield as colorless needle-like crystals. Nitration did not go so smoothly, the products apparently consisting of mixtures not easily separated.

Summary

Certain derivatives of 3-anilino-5-phenylisoxazole and -pyrazole have been prepared and their reactions with chlorine, bromine and nitric acid studied.

MEDFORD, MASS.

RECEIVED OCTOBER 24, 1938

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[2] The value for bromine was reached by first subtracting from the weight of the mixed silver halides the theoretical value for silver iodide.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

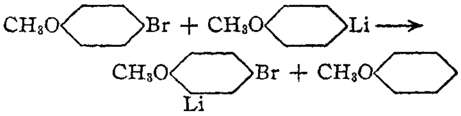
Metalation as a Side Reaction in the Preparation of Organolithium Compounds

BY HENRY GILMAN, WRIGHT LANGHAM AND ARTHUR L. JACOBY

Introduction

It was reported recently that the extent of metalation of dibenzothiophene by a series of organolithium compounds varied quite regularly with the rates of cleavage of organometallic compounds by hydrogen chloride. In that study, *p*-methoxyphenyllithium behaved anomalously, for the acid obtained subsequent to carbonation was 5-bromo-2-methoxybenzoic acid. This acid undoubtedly was formed from 5-bromo-2-methoxyphenyllithium, which in turn was formed, in all probability, by auto-metalation in accordance with the following sequence of reactions[1]

$$p\text{-}CH_3OC_6H_4Br + 2Li \longrightarrow p\text{-}CH_3OC_6H_4Li + LiBr \quad (I)$$



(II)

That is, part of the original *p*-bromoanisole was metalated as a side reaction in the preparation of

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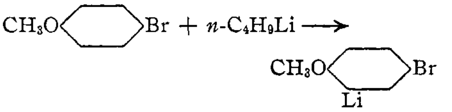
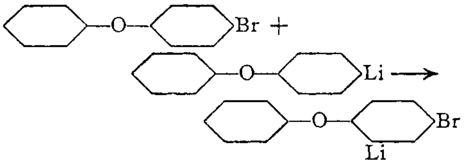
[1] Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938). See p. 109 of that article for the identification of 2-methoxy-5-bromobenzoic acid and for the mechanism of its formation.

p-methoxyphenyllithium. There are two pieces of evidence confirming the interpretation proposed. First, anisole is formed as a product of metalation (Reaction II). Second, metalation by a different organolithium compound gives the same product

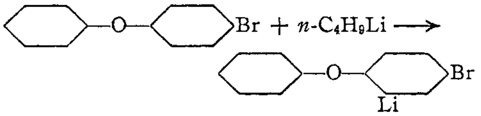


(III)

Furthermore, a related series of reactions was observed with *p*-bromodiphenyl ether



(IV)



(V)

Selective Nuclear Substitution.—Reaction (V) leading to the introduction of nuclear substituents in positions *ortho* to the ether linkage is unusual because Brewster[2] and others have shown that reactions like nitration, halogenation, etc., do not involve those positions. This is an additional illustration[3] of the utility of metalation for the introduction of nuclear substituents into positions otherwise not accessible by the older nuclear substitution reactions. The selective nature of some metalations is shown with the parent type, phenyl ether. Metalation of phenyl ether by organoalkali compounds introduces the alkali metal in the 2-position;[4] however, mercuration involves the 4-position.[5]

Interconversion of Organoalkali Compounds.—There are numerous illustrations of the formation of a new organometallic compound by interaction of an organometallic compound with a metal or a compound. One of these involves the moderately reactive Grignard reagent[6]

$$C_6H_5CH{=}CHCH_2Br + C_2H_5MgBr \longrightarrow C_6H_5CH{=}CHCH_2MgBr + C_2H_5Br$$

When *o*-bromoanisole is metalated by a filtered solution of *n*-butyllithium, the acid obtained subsequent to carbonation is *o*-methoxybenzoic acid. This indicates that the following interconversion occurred

$$o\text{-}CH_3OC_6H_4Br + n\text{-}C_4H_9Li \longrightarrow o\text{-}CH_3OC_6H_4Li + n\text{-}C_4H_9Br$$

This transformation is quite unlike that shown by *p*-bromoanisole (Reaction III). Furthermore, the acid obtained by carbonating the reaction mixture of *o*-bromoanisole and lithium was *o*-methoxybenzoic acid, unaccompanied by a bromo-substituted methoxybenzoic acid. That is, *o*-bromoanisole does not show metalation under conditions observed for the metalation of *p*-bromoanisole. Likewise, *p*-bromotoluene and lithium give an organolithium compound which on carbonation yields the normally expected *p*-toluic acid. Other limitations of the secondary metalation reaction in the preparation of organometallic compounds are being examined.

Competitive Metalations.—One might have predicted that the metalation of *p*-bromodiphenyl ether (Reactions IV and V) would have involved the unsubstituted nucleus rather than the nucleus having a relatively negative substituent like bromine. However, when equimolecular quantities of anisole and *p*-bromoanisole were allowed to compete for *n*-butyllithium under forced conditions, the product formed was 5-bromo-2-methoxybenzoic acid. Under milder conditions, the acids isolated were 5-bromo-2-methoxybenzoic acid and *p*-methoxybenzoic acid. The formation of *p*-methoxybenzoic acid is anomalous, because metalation of anisole by *n*-butyllithium, followed by carbonation, is known to yield *o*-methoxybenzoic acid.[4]

The secondary reaction of auto-metalation is not confined to organolithium compounds. Carbonation of the organosodium compounds obtained from chlorobenzene and sodium yields benzoic and chlorobenzoic acids.[7] Also, Challenger and Miller[8] have shown recently that anisole and phenetole can be metalated under forced conditions by some Grignard reagents to yield the corresponding *o*-methoxyphenyl- and *o*-ethoxyphenylmagnesium bromides. It is possible that the unusual reaction reported recently by Dubinin[9] also may be due in part to a secondary metalation by a Grignard reagent. He found that the

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[2] Brewster and Strain, This Journal, **56**, 110 (1934).

[3] Gilman and Young, *ibid.*, **56**, 1415 (1934) and **57**, 1121 (1935); Gilman and Kirby, *J. Org. Chem.*, **1**, 146 (1936).

[4] Gilman and Bebb, This Journal, **61**, 109 (1939).

[5] Schroeder and Brewster, *ibid.*, **60**, 751 (1938).

[6] Prevost, *Bull. soc. chim.*, **49**, 1372 (1931); Wuyts, *Compt. rend.*, **199**, 1317 (1934); Scheibler and Schmidt, *Ber.*, **67**, 1514 (1934).

[7] Private communication from Dr. George F. Wright.

[8] Challenger and Miller, *J. Chem. Soc.*, 894 (1938). See, also, Houben and Freund, *Ber.*, **42**, 4815 (1909).

[9] Dubinin, *J. Gen. Chem.* (U. S. S. R.), **7**, 2209 (1937); [*C. A.*, **32**, 516 (1938)].

organomagnesium compound prepared from 5-bromo-3-methoxytoluene reacted normally with carbon dioxide to give 3-methyl-5-methoxybenzoic acid, but when boiled at 100° with *t*-butyl bromide or iodide formed 4-butyl-3-methoxytoluene.

In a report just published by Wittig, Pockels and Dröge[10] are results in agreement with ours[1] on the reaction between *p*-bromoanisole and lithium. It is also interesting to note that our interconversion reaction between *o*-bromoanisole and *n*-butyllithium has a counterpart in a reaction reported by them. They observed that phenyllithium reacted with 2,4-dimethoxy-1,5-dibromobenzene to give 2,4-dimethoxy-5-bromophenyllithium and bromobenzene.

Experimental Part

Preparation and Carbonation of *p*-Methoxyphenyllithium.—The organolithium compound was prepared in essential accordance with the "A-conditions" described earlier[11] from 1.52 g. (0.22 g. atom) of finely cut lithium and 18.7 g. (0.1 mole) of *p*-bromoanisole. After all the halide had been added, the mixture was stirred for forty-five minutes, filtered through glass wool or a sintered glass plate, and carbonated by adding it jet-wise to powdered solid carbon dioxide. Repeated fractional crystallization of the mixture of acids gave a 12% yield of *p*-methoxybenzoic acid and a 5.2% yield of 5-bromo-2-methoxybenzoic acid.

Anal. Calcd. for $C_8H_7O_3Br$: C, 41.22; H, 3.23; neut. equiv., 233. Found: C, 41.56; H, 3.06; neut. equiv., 231.

All solid products reported were identified by mixed melting point determinations with authentic specimens. From the non-acidic portion there was isolated a 9.4% yield of anisole.

From another experiment in which the reaction was refluxed for twenty hours before carbonating, there was obtained an 8.2% yield of *p*-methoxybenzoic acid and a 9.2% yield of 5-bromo-2-methoxybenzoic acid.

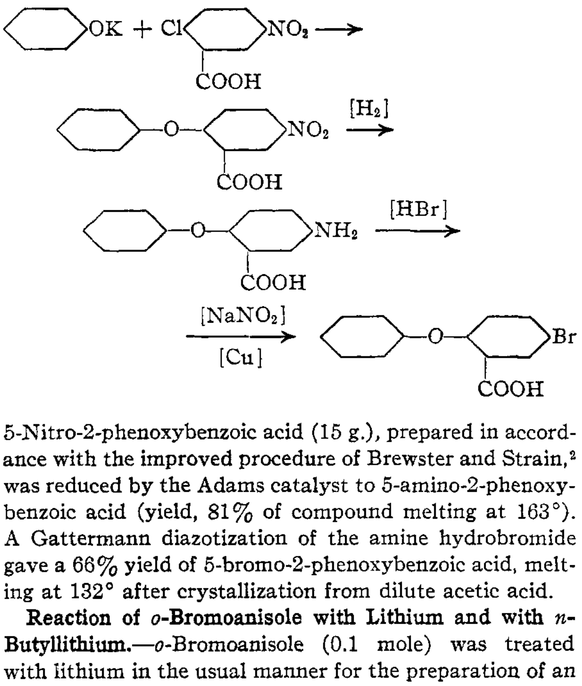
In a third experiment, the organolithium solution was filtered through a sintered glass filter (subsequent to the initial forty-five minute period of stirring), and then part of the ether was removed by distillation so that the total volume was 50 cc. Ten cc. of this solution was carbonated to yield a mixture of *p*-methoxybenzoic and 5-bromo-2-methoxybenzoic acids. The remainder of the solution was then refluxed for twenty hours, diluted to 150 cc. with ether and carbonated to yield 28% of 5-bromo-2-methoxybenzoic acid and 16% of anisole.

Metalation of *p*-Bromoanisole by *n*-Butyllithium.—To a clear solution of 0.195 mole of *n*-butyllithium was added 0.1 mole of *p*-bromoanisole in ether. After the initial heat of reaction (sufficient to cause refluxing for ten minutes) was dissipated, the solution was concentrated to 55 cc., refluxed for twenty hours, diluted with 150 cc. of ether and carbonated to yield 31% of 5-bromo-2-methoxybenzoic acid and a trace of anisole.

Reaction of *p*-Bromodiphenyl Ether with Lithium and with *n*-Butyllithium.—The acid obtained by reaction, in the customary manner, of *p*-bromodiphenyl ether and lithium was 5-bromo-2-phenoxybenzoic acid. A very small quantity of the coupling product, 4,4'-diphenoxybiphenyl,[12] was isolated.

The filtered metalation mixture of *n*-butyllithium and 0.1 mole of *p*-bromodiphenyl ether was refluxed for twenty hours and then carbonated to yield 20% of 5-bromo-2-phenoxybenzoic acid and 0.25 g. of 4,4'-diphenoxybiphenyl. No *o*- or *p*-phenoxybenzoic acids were isolated.

An authentic specimen of the 5-bromo-2-phenoxybenzoic acid was prepared as follows



5-Nitro-2-phenoxybenzoic acid (15 g.), prepared in accordance with the improved procedure of Brewster and Strain,[2] was reduced by the Adams catalyst to 5-amino-2-phenoxybenzoic acid (yield, 81% of compound melting at 163°). A Gattermann diazotization of the amine hydrobromide gave a 66% yield of 5-bromo-2-phenoxybenzoic acid, melting at 132° after crystallization from dilute acetic acid.

Reaction of *o*-Bromoanisole with Lithium and with *n*-Butyllithium.—*o*-Bromoanisole (0.1 mole) was treated with lithium in the usual manner for the preparation of an organolithium compound. After refluxing for twenty hours the mixture was carbonated to yield 58% of *o*-methoxybenzoic acid, 16% of *o,o'*-dimethoxybenzophenone and 15% of recovered *o*-bromoanisole.

Metalation by *n*-butyllithium of 0.1 mole of *o*-bromoanisole in ether, followed by carbonation, yielded 47% of *o*-methoxybenzoic acid.

Preparation and Carbonation of *p*-Tolyllithium.—The *p*-tolyllithium, prepared in the customary manner from 0.15 mole of *p*-bromotoluene, was filtered, heated for twenty hours, and then carbonated to yield 56.8% of *p*-toluic acid and 16.3% of di-*p*-tolyl ketone. The relatively high yields of ketone in this experiment and in the experiment with *o*-bromoanisole are in accordance with results of earlier studies on the carbonation of organolithium compounds.[13]

Competitive Metalation of Anisole and *p*-Bromoanisole.—To 0.03 mole of a filtered solution of *n*-butyllithium

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[10] Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938).

[11] Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

[12] Davis and Morris, *J. Chem. Soc.*, 2881 (1932).

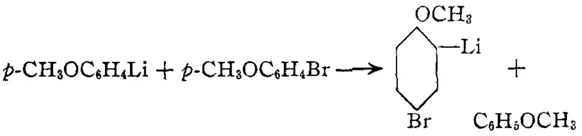
[13] Gilman and Van Ess, THIS JOURNAL, **55**, 1258 (1933).

was added equivalent amounts of anisole and *p*-bromoanisole. The mixture was then concentrated to 55 cc., refluxed for twenty hours, and carbonated to yield 30% of 5-bromo-2-methoxybenzoic acid. From a related experiment in which the ether solution was not concentrated, there was isolated a mixture of 5-bromo-2-methoxybenzoic acid and *p*-methoxybenzoic acid.

Acknowledgment.—The authors are grateful to Dr. Ray Q. Brewster for suggestions and samples of some phenyl ether derivatives.

Summary

1. Incidental to the preparation of *p*-methoxyphenyllithium, varying amounts of 5-bromo-2-methoxyphenyllithium are formed by autometalation



A related reaction takes place with *p*-bromodiphenyl ether.

2. When *o*-bromoanisole is metalated by *n*-butyllithium the following interchange occurs

$$o\text{-}CH_3OC_6H_4Br + n\text{-}C_4H_9Li \longrightarrow o\text{-}CH_3OC_6H_4Li + n\text{-}C_4H_9Br.$$

AMES, IOWA RECEIVED OCTOBER 19, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

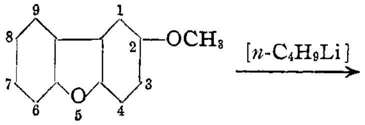
Relative Reactivities of Organometallic Compounds. XX.* Metalation

BY HENRY GILMAN AND ROBERT L. BEBB

Introduction

This paper reports results on the lateral and the nuclear metalations of some compounds, using a variety of organometallic compounds and different media.

2-Methoxydibenzofuran.—The metalation of dibenzofuran by metals, inorganic salts and organometallic compounds invariably has involved the otherwise inaccessible 4-position.[1] Subsequent studies[2] confirmed the pronounced tendency of metalation to take place ortho to an ether linkage. Substituti[illegible]ethoxy in the 2-position should make mono-metalation possible in the 1-, 3- or 4-position. We have now shown that metalation does not take place in the expected 4-position. The 60% yield of methoxy acid, formed subsequent to carbonation, was found to consist of about four parts of 2-methoxy-1-dibenzofurancarboxylic acid (m. p. 156°) to one part of 2-methoxy-3-dibenzofurancarboxylic acid (m. p. 206–207°).[3]



$2\text{-}CH_3O[C_{12}H_6O]Li\text{-}1$ and $2\text{-}CH_3O[C_{12}H_6O]Li\text{-}3$

Ethers and Thioethers.—The acids obtained after carbonating the RM products of metalation of anisole, phenyl ether and phenyl sulfide were *o*-methoxybenzoic, *o*-phenoxybenzoic and *o*-phenylmercaptobenzoic acids, respectively.

Metalation of anisole by *n*-butyllithium in ether for twenty hours gave 19%[4] of acid; by *n*-butylsodium in petroleum ether (b. p., 60–68°) for four days gave a 42% yield; by phenylsodium in benzene for twenty-four hours gave a 44% yield; and by phenylsodium in benzene for forty-eight hours gave a 64% yield.

Metalation of phenyl ether in liquid ammonia by means of ethynylsodium gave as the only acidic material a small quantity of *o*-phenylphenol. The same product was obtained earlier by Späth when phenyl ether was heated with ethylmagnesium bromide at elevated temperatures.[5] Apropos the series of extremely weak acids,[6] phenyl ether was not metalated by triphenylmethylsodium. Using *n*-butyllithium the yield of *o*-phenoxybenzoic acid in petroleum ether was 7% at the end of twenty hours and in ether the yields were 54 and 60% at the end of six hours and twenty hours, respectively.

Metalation of phenyl sulfide, by *n*-butyllithium in ether for six hours gave 24% of *o*-phenylmercaptobenzoic acid; by *n*-butyllithium in ether for twenty hours gave 30% of

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(*) Paper XIX, THIS JOURNAL, **60**, 2334 (1938).

(1) Gilman and Young, *ibid.*, **56**, 1415 (1934); **57**, 1121 (1935).

(2) Gilman, Langham and Jacoby, *ibid.*, **60**, 106 (1938); Gilman and Bradley, *ibid.*, **60**, 2333 (1938); Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938).

(3) The authors are grateful to P. R. Van Ess for authentic specimens of these two acids.

(4) An unusually high yield (40%) of di-*o*-methoxyphenyl ketone was isolated. Under corresponding conditions of carbonation, the yield of benzophenone from phenyllithium is 15.4%; Gilman and Van Ess, THIS JOURNAL, **55**, 1258 (1933).

(5) Späth, *Monatsh.*, **35**, 319 (1914).

(6) Conant and Wheland, THIS JOURNAL, **54**, 1212 (1932); McEwen, *ibid.*, **58**, 1124 (1936).