[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Metalation Reactions in Tetrahydrofuran

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Dibenzofuran, dibenzothiophene, and *N*-ethylcarbazole have been metalated with methyl-, *n*-butyl-, and phenyllithium in diethyl ether, a mixture of diethyl ether and tetrahydrofuran, and in tetrahydrofuran alone. In almost every case the use of tetrahydrofuran as the solvent was shown to give significantly higher yields of the metalated product as compared to those obtained in diethyl ether or the mixed diethyl ether-tetrahydrofuran solvent. Metalation with *n*-butyllithium in ether-tetrahydrofuran was extended to include triphenylamine and naphthalene.

Recent work has shown the advantage of using tetrahydrofuran as the solvent for metalation reactions. Dibenzofuran has been metalated in mixed ether-tetrahydrofuran in yields of 83–86% under conditions milder than previously employed.[1] Tetrahydrofuran has been used also as the solvent for the metalation of fluorene[2a] and triphenylmethane[2b] with lithium metal.

This study concerns the metalation of dibenzofuran, dibenzothiophene, *N*-ethylcarbazole, triphenylamine, and naphthalene with several organolithium reagents with particular interest in the role of the solvent on the reaction. To this end, the metalation of the three heterocycles was studied using diethyl ether, ether-tetrahydrofuran, and tetrahydrofuran alone as the solvents, the yield of acid upon carbonation being used as the criterion of reaction.

Dibenzofuran has been shown to react with *n*-butyllithium in diethyl ether to yield 4-dibenzofuryllithium and upon carbonation yields of 1–76% of 4-dibenzofurancarboxylic acid were realized.[3,4] Metalation with methyllithium gave the acid in 3% yield;[4c,5] using phenyllithium, a 31% yield of acid was obtained.[4c] Dibenzofuran has also been metalated with ethyl-,[4c,6] *n*-propyl-,[4b] *iso*-butyl-,[4c] *sec*-butyl-,[4c] *tert*-butyl-,[4c] 4-dibenzothienyl-,[7] and 2,4,6-triphenylphenyllithium,[8] in most cases in less than 50% yield.

The metalation of dibenzothiophene with *n*-butyllithium followed by carbonation has resulted in yields of 40–90% of 4-dibenzothiophenecarboxylic acid.[4b,4c,9] Yields of 7–64% were obtained when derivatizing agents other than carbon dioxide were used.[10] Dibenzothiophene has also been metalated with ethyl-,[4b] *n*-propyl-,[4b] phenyl-,[11] β-naphthyl-,[11] and 1-*N*-ethylcarbazolyllithium.[4b] The reactions were generally carried out in refluxing diethyl ether.

Very little work has been done on the metalation of *N*-ethylcarbazole with organolithium reagents. However, it has been metalated with *n*-butyllithium to give a 23% yield of 9-ethylcarbazole-1-carboxylic acid.[12]

In this study each of the above compounds was metalated with methyl-, *n*-butyl-, and phenyllithium in diethyl ether, a mixture of diethyl ether and tetrahydrofuran, and in tetrahydrofuran alone. The reactions were carried out under as similar conditions as possible, any variations being noted in Table I. When carrying out the reactions in the mixed solvent, the diethyl ether-tetrahydrofuran ratio was maintained approximately constant at 6:5. In the work-up of the reaction mixtures the acids were not obtained in an optimum degree of purity, since we were primarily interested in the relative amounts obtained in the different experiments.

The metalations with *n*-butyllithium in tetrahydrofuran alone were carried out at the low temperatures indicated in Table I in order to insure its stability.[13] As with methyllithium and phenyllithium the use of tetrahydrofuran alone gave greater yields than the diethyl ether-tetrahydrofuran mixture at the same temperature.

A few additional reactions not listed in Table I were carried out with dibenzofuran. Dibenzofuran

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[1] H. Gilman and R. D. Gorsich, *J. Org. Chem.*, **22**, 687 (1957).

[2] (a) H. Gilman and R. D. Gorsich, *J. Org. Chem.*, **23**, 550 (1958); (b) B. J. Gaj, unpublished studies.

[3] (a) W. G. Bywater, Doctoral Dissertation, Iowa State College, 1934; (b) D. M. Hayes, M.S. Thesis, Iowa State College, 1934.

[4] (a) H. B. Willis, *Iowa State Coll. J. Sci.*, **18**, 98 (1943) [*Chem. Abstr.*, **38**, 739 (1944)]; (b) H. Gilman and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **67**, 877 (1945); (c) H. Gilman, F. W. Moore, and O. Baine, *J. Am. Chem. Soc.*, **63**, 2479 (1941).

[5] H. Gilman and R. V. Young, *J. Am. Chem. Soc.*, **56**, 1415 (1934).

[6] H. Gilman and R. V. Young, *J. Org. Chem.*, **1**, 315 (1936).

[7] H. Gilman, M. W. Van Ess, H. B. Willis, and C. G. Stuckwisch, *J. Am. Chem. Soc.*, **62**, 2606 (1940).

[8] J. W. Morton, Jr., unpublished studies.

[9] H. Gilman and R. L. Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939).

[10] (a) H. Gilman and A. L. Jacoby, *J. Org. Chem.*, **3**, 108 (1938); (b) H. Gilman and J. F. Nobis, *J. Am. Chem. Soc.*, **67**, 1479 (1945); (c) S. Avakian, Doctoral Dissertation, Iowa State College, 1944; (d) H. Gilman and J. F. Nobis, *J. Am. Chem. Soc.*, **72**, 2629 (1950).

[11] A. L. Jacoby, *Iowa State Coll. J. Sci.*, **13**, 70 (1938) [*Chem. Abstr.*, **34**, 99 (1940)].

[12] H. Gilman and R. H. Kirby, *J. Org. Chem.*, **1**, 146 (1936).

[13] H. Gilman and B. Gaj, *J. Org. Chem.*, **22**, 1165 (1957).

TABLE I

THE METALATION OF VARIOUS HETEROCYCLES

Compound Metalated	Solvent	RLi-Solvent	Addition Conditions	Reaction Conditions	Yield, %	
					Crude	Pure
Dibenzofuran	Ether	CH_3Li-Ether	Room temp.	Room temp., 24 hr.	2.2	1.8
	THF[a]	CH_3Li-Ether	Ice bath	Room temp., 3 hr.	19.5	11.9
	THF	CH_3Li-THF	Ice bath	Room temp., 3 hr.	37.0	29.2
	Ether	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	57.3	52.0
	THF	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	87.4	68.7
	THF	n-C_4H_9Li-Ether	−30°C.	−30°C., 5 hr.	46.4	42.3
	THF	n-C_4H_9Li-THF	−30°C.	−30°C., 5 hr.	83.0	75.0
	Ether	C_6H_5Li-Ether	Ice bath	Room temp., 5 hr.	10.6	7.9
	THF	C_6H_5Li-Ether	Ice bath	Room temp., 5 hr.	51.5	43.6
	THF	C_6H_5Li-THF	Ice bath	Room temp., 5 hr.	61.2	55.3
Dibenzothiophene	Ether	CH_3Li-Ether	Room temp.	Room temp., 5.5 hr.	Trace	—
	THF	CH_3Li-Ether	Room temp.	Room temp., 5.5 hr.	12.0	5.0
	THF	CH_3Li-THF	Ice bath	Room temp., 5 hr.	16.0	12.2
	Ether	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	30.7	24.8
	THF	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	90.0	60.0
	THF	n-C_4H_9Li-Ether	−30°C.	−30°C., 5 hr.	12.2	10.1
	THF	n-C_4H_9Li-THF	−30°C.	−30°C., 5 hr.	48.5	41.0
	Ether	C_6H_5Li-Ether	Slight cooling	Room temp., 5 hr.	1	—
	THF	C_6H_5Li-Ether	Ice bath	Room temp., 5 hr.	18.1	12.4
	THF	C_6H_5Li-THF	Ice bath	Room temp., 5 hr.	50.0	47.0
N-Ethylcarbazole	Ether	CH_3Li-Ether	Room temp.	Room temp., 5.5 hr.	—	—
	THF	CH_3Li-Ether	Room temp.	Room temp., 5 hr.	1	—
	THF	CH_3Li-THF	Ice bath	Room temp., 5 hr.	1	—
	Ether	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	4.6	2.4
	THF	n-C_4H_9Li-Ether	Ice bath	Room temp., 5 hr.	43.3	20.5
	THF	n-C_4H_9Li-THF	−30°C.	−30°C., 5 hr.	1.2	1.2
	Ether	C_6H_5Li-Ether	Ice bath	Room temp., 5 hr.	—	—
	THF	C_6H_5Li-Ether	Ice bath	Room temp., 5 hr.	—	—
	THF	C_6H_5Li-THF	Ice bath	Room temp., 5 hr.	19.0	9.6

[a] THF is an abbreviation for tetrahydrofuran.

was metalated with methyllithium in a mixture of diethyl ether and tetrahydrofuran under reflux conditions. Refluxing the reaction mixture for 2 hours resulted in a yield of 4-dibenzofurancarboxylic acid comparable to that obtained when the reaction was run for 22 hours at room temperature. Refluxing the reaction mixture for 4 hours increased the yield to 71% as compared to the 46% yield after refluxing for 2 hours.

The results of this study have shown that the use of tetrahydrofuran as a solvent increases the reactivity of methyl-, *n*-butyl- and phenyllithium in the metalation of dibenzofuran, dibenzothiophene, and *N*-ethylcarbazole. The increase in reactivity with respect to the solvent, as determined by increased yields of the carbonation product, is in the order ether <ether-tetrahydrofuran <tetrahydrofuran. The increase in the yield of metalated product with respect to the RLi compound in the mixed ether-tetrahydrofuran solvent and in tetrahydrofuran alone is of the same order as in ether;[4c] that is, methyl-, phenyl-, *n*-butyllithium. Likewise, the order of increasing influence of the hetero atoms in ether-tetrahydrofuran and in tetrahydrofuran is the same as in ether;[9] *i.e.*, N, S, O. The use of tetrahydrofuran as the solvent instead of ether has no effect on the position of metalation.

It is important to note that the reaction time of these experiments was much shorter than that previously used, and if the time were extended, increased yields of metalated product might possibly result. Furthermore, all the metalation reactions shown in Table I were carried out at room temperature or below.

While only these three heterocyclic compounds and three organolithium reagents were used in this study, the results seemed significant enough to warrant the use of tetrahydrofuran as a solvent for other types of metalation reactions. Therefore metalation with *n*-butyllithium in the mixed ether-tetrahydrofuran solvent was extended to triphenylamine. Ordinarily nuclear metalation by organoalkali compounds occurs *ortho* to the hetero atom.[14] A variety of primary, secondary, and tertiary amines such as aniline,[15] *N*-*n*-butylaniline,[15] diphenylamine,[15] *N*,*N*-dimethylaniline,[9,16] carbazole,[12] *N*-ethylcarbazole,[12] and *N*-phenylcarbazole[17] have been found to conform to this rule. However, the metalation of triphenylamine has been found to be anamolous, metalation occurring *meta* to the

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[14] H. Gilman, *Organic Chemistry,* 2nd edition, John Wiley and Sons, Inc., New York, 1943, Vol. I, p. 536.

[15] H. Gilman, G. E. Brown, F. J. Webb, and S. M. Spatz, *J. Am. Chem. Soc.*, **62**, 977 (1940).

[16] A. A. Morton and I. Hechenbleikner, *J. Am. Chem. Soc.*, **58**, 2599 (1936).

[17] H. Gilman, C. G. Stuckwisch, and A. R. Kendall, *J. Am. Chem. Soc.*, **63**, 1758 (1941).

nitrogen atom.[18] The reaction of triphenylamine with *n*-butyllithium in refluxing diethyl ether yielded 7% of *N*,*N*-diphenyl-*m*-aminobenzoic acid.[15,18] The reason proposed for this anamolous metalation is that of steric hindrance,[19] free rotation of the phenyl groups hindering approach to the *ortho* position. It is interesting to compare triphenylamine with *N*-phenylcarbazole; in the latter compound the joining of the two phenyl groups to form the more rigid carbazole nucleus leaves a greater space about the phenyl group which then can undergo *ortho* metalation. If this is truly a steric effect, then changing the solvent and/or reaction conditions should not effect the position in which metalation occurs.

In two experiments, treatment of triphenylamine with *n*-butyllithium gave a dicarboxylic acid as the major product. The structure of this acid has not been rigorously established, but its infrared spectrum indicated that the two carboxyl groups are not on the same ring, and that both are probably *meta* substituted with respect to the nitrogen. Since previous metalations of triphenylamine yielded only the *meta* substituted carboxylic acid, it is not unreasonable to expect 3,3′-dicarboxytriphenylamine to be a product of the reaction.

Naphthalene was also metalated with *n*-butyllithium in ether–tetrahydrofuran. In the few instances reported, quite low yields have been obtained in the metalation of naphthalene by RLi compounds. Refluxing naphthalene with *n*-butyllithium in ether for 15 hours resulted in a 13% yield of a mixture of α-naphthoic and β-naphthoic acids.[9] Extension of the reflux time to 36 hours increased the yield to 20%. The ratio of α- to β-naphthoic acid was roughly 2.5 to 1. The reaction with phenyllithium in ether for 48 hours gave an estimated 5% yield of a mixture of α- and β-naphthoic acids.[9]

When we carried out the metalation in a mixed ether-tetrahydrofuran solvent at room temperature, the crude yields of the mixtures of α- and β-naphthoic acids after 16 and 36 hours were 25 and 38.2%, respectively. When the reaction mixture in the mixed solvent was refluxed for 3 hours, a crude yield of the mixture of acids of 22.8% was realized. Again the use of tetrahydrofuran as the solvent has given significantly increased yields of metalated product.

The reactions which were run at room temperature for 16 hours and at reflux for 3 hours gave approximately the same α-β ratio, 1.6 and 1.7 respectively, to 1. The reaction which was run at room temperature for 36 hours gave a much lower ratio, 0.87 to 1. Although some material was lost in the separation of the isomers, it is felt that the difference in these ratios is great enough to be significant.

We have found that the best working conditions for *n*-butyllithium metallations is to prepare the lithium reagent in ether and to use tetrahydrofuran as the solvent for the compound being metalated. Carrying out the reactions in tetrahydrofuran alone seems to give a decrease in yield rather than an increase, particularly for the less reactive compounds. This was shown to be primarily a temperature effect, but the instability of *n*-butyllithium in tetrahydrofuran[13] must also be taken into account. Furthermore, it has been shown that methyl- and *n*-butyllithium, in a mixture of ether and tetrahydrofuran, may be refluxed for a short period of time to give a yield of metalated product comparable to that obtained at room temperature for a long period of time.

EXPERIMENTAL[20]

Illustrative examples of the metalations of dibenzofuran, dibenzothiophene and *N*-ethylcarbazole are given below. They are divided into three sections, metalations in ether, metalations in ether-tetrahydrofuran, and metalations in tetrahydrofuran. A complete tabulation of all the reactions carried out with the three heterocyclies is given in Table I.

Metalations in ether. (*a*) *Methyllithium.* Methyllithium was prepared in ether by the reaction of methyl iodide with lithium wire.[21] The yields as determined by single acid titration were 83–89%.

In a typical reaction, 59.0 ml. of a 0.68*M* methyllithium solution in ether, was added dropwise to a stirred 50-ml. ether solution of 6.0 g. (0.035 mole) of dibenzofuran. The addition was carried out at room temperature during 1 hr. with no refluxing of the solvent. The reaction mixture was stirred at room temperature for 24 hr. then carbonated and hydrolyzed. From the work-up of the water layer was obtained 0.17 g. (2.2%) of crude 4-dibenzofurancarboxylic acid. Recrystallization from ethanol-water gave 1.8% of the acid melting over the range 200–204°. Pure 4-dibenzofurancarboxylic acid melts at 211–213°.

Dibenzothiophene and *N*-ethylcarbazole were metalated with methyllithium in ether in a similar manner using the conditions indicated in Table I.

(*b*) *n-Butyllithium.* Metalation of the three heterocycles with *n*-butyllithium in ether was carried out in a manner similar to that used with methyllithium. All variations in procedure are included in Table I. The *n*-butyllithium used in these reactions was prepared in a conventional way.[22]

(*c*) *Phenyllithium.* The three heterocyclic compounds were metalated with phenyllithium in ether as indicated in Table I. The preparation of phenyllithium in ether was carried out in the usual manner.[21]

Metalations in ether-tetrahydrofuran. In all cases of metalation in the mixed solvent, the RLi compound was

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[18] H. Gilman and G. E. Brown, *J. Am. Chem. Soc.*, **62**, 3208 (1940).

[19] H. Gilman and S. M. Spatz, *J. Org. Chem.*, **17**, 860 (1952).

[20] All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen, and all melting points are uncorrected. The diethyl ether was dried by standing over sodium wire. The tetrahydrofuran was dried and purified by refluxing over sodium metal for several hours, and finally distilling, during the day of its use, from lithium aluminum hydride.

[21] H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Am. Chem. Soc.*, **55**, 1251 (1933).

[22] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

prepared in ether and added to a tetrahydrofuran solution of the compound being metalated.

In a typical reaction, to a 50-ml. tetrahydrofuran solution of 8.0 g. (0.035 mole) of dibenzothiophene was added 28 ml. of ether in order to attain a final ether-tetrahydrofuran ratio of 6:5. To this solution was added 33 ml. of a 1.23*M* *n*-butyllithium solution in ether. The addition was carried out using an ice bath during 15 min. After the reaction mixture had stirred at room temperature for 5 hr., it was carbonated and hydrolyzed. Work-up of the water layer resulted in the isolation of 8.8 g. of crude 4-dibenzothiophenecarboxylic acid. Recrystallization from glacial acetic acid gave 5.9 g. (60%) of the acid melting at 261-264°.

Dibenzofuran, dibenzothiophene and *N*-ethylcarbazole were metalated with methyl-, *n*-butyl- and phenyllithium in the mixed ether-tetrahydrofuran solvent using the conditions shown in Table I.

Metalations in tetrahydrofuran. (*a*) *Phenyllithium.* Phenyllithium was prepared in tetrahydrofuran in yields of 81-82% according to a published procedure.[13] After the addition of the phenyl bromide was completed, the mixture was stirred at −60° for 1-2 hr., allowed to warm up to −35°, and then decanted into a jacketed addition funnel previously cooled to −20°.

In a typical reaction, to a 50-ml. tetrahydrofuran solution of 6.8 g. (0.035 mole) of *N*-ethylcarbazole cooled by an ice bath was added 55 ml. of a 0.68*M* phenyllithium solution in tetrahydrofuran during 20 min. The reaction mixture was stirred at room temperature for 5 hr., then carbonated and hydrolyzed.

The water layer was boiled to remove any dissolved solvent, acidified with concentrated hydrochloric acid, and filtered hot. A crude yield of 19% of 9-ethylcarbazole-1-carboxylic acid was obtained. Recrystallization from carbon tetrachloride resulted in 9.6% of the acid melting at 163-165°.

Dibenzofuran and dibenzothiophene were also metalated with phenyllithium in tetrahydrofuran as indicated in Table I.

(*b*) *Methyllithium.* The three heterocycles were metalated with methyllithium in tetrahydrofuran using the conditions given in Table I. Methyllithium was prepared in tetrahydrofuran by bubbling methyl chloride gas through a tetrahydrofuran suspension of an excess of lithium wire.[13]

(*c*) *n-Butyllithium.* The metalations of dibenzofuran, dibenzothiophene and *N*-ethylcarbazole were carried out with *n*-butyllithium in tetrahydrofuran. The results of these reactions are shown in Table I. The preparation of *n*-butyllithium in tetrahydrofuran was carried out according to a published procedure.[13]

Metalation of naphthalene with n-butyllithium. Run I. To a 100-ml. tetrahydrofuran solution of 12.8 g. (0.1 mole) of naphthalene was added 182 ml. of a 1.34*M* *n*-butyllithium solution in ether. The addition was carried out at 0° over a period of 45 min. The reaction mixture was stirred at room temperature for 16 hr., carbonated, and hydrolyzed. From the acidified water layer was isolated 4.3 g. (25%) of a mixture of α- and β-naphthoic acids. The crude acid was dissolved in ammonium hydroxide and a 5% solution of calcium chloride added to precipitate the calcium salt of the β-naphthoic acid. Filtration and acidification gave 1.0 g. (5.8%) of material which melted over the range 165-180°. Upon recrystallization from aqueous acetic acid there was obtained 0.76 g. (4.4%) of β-naphthoic acid melting at 178-182°. A mixture of this material with an authentic sample (m.p. 184-185°) melted at 181-183°. The α-naphthoic acid obtained from the acidification of the filtrate from the β-isomer was found to contain a small amount of the β-naphthoic acid, therefore the calcium chloride procedure was repeated. The α-naphthoic acid was also recrystallized from aqueous acetic acid and yielded 8.2% of acid melting at 155-159°. A mixture of this material with an authentic sample (m.p. 158-160°) melted at 155-159°.

Run II. The preceding reaction was repeated extending the time of metalation to 36 hr. A crude yield of 38.2% of the mixture of acids was realized. As in the first experiment, a large amount of material was lost in the separation and purification procedure. The final yields were 8.9% α-naphthoic acid and 9.3% β-naphthoic acid.

Run III. A third run was made in which the reaction mixture was refluxed for 3 hr. The crude yield of the mixture of acids was 22.8%. Pure α-naphthoic acid was isolated in a yield of 6%, and pure β-naphthoic acid in a yield of 3%.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Copolymers of Anthracene with Styrene and *p*-Chlorostyrene[1]

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Anthracene has been copolymerized with styrene and *p*-chlorostyrene, and 2-chloroanthracene has been copolymerized with styrene. Anthracene could not be copolymerized with acrylonitrile, methyl acrylate, or vinyl chloride.

Earlier work in this laboratory has shown that anthracene and butadiene can be copolymerized[2] and that the anthracene is incorporated in the polymer chain as a 9,10-dihydroanthracene derivative. In this communication are described successful copolymerizations of anthracene with styrene and *p*-chlorostyrene.

One difficulty in obtaining satisfactory incorporation of anthracene in the earlier copolymer resulted from its very low solubility in the comonomer and benzene was added to the system to in-

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[1] The work discussed herein was performed under contract AF-33(616)-3772 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio; Lt. L. E. Coleman and Lt. Paul D. Shaw, project engineers.

[2] C. S. Marvel and W. S. Anderson, *J. Am. Chem. Soc.*, **75**, 4600 (1953).