Organic Reactions

VOLUME 18

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Organic Reactions

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

Chemists who are considering the preparation of a manuscript for submission to Organic Reactions are urged to write the secretary before they begin work.

* * *

During the period when this volume was in galley proof, Dr. Margaret J. Jorgenson, one of our authors, died. Her publications in organic chemistry are well-known and her chapter in this volume is another of her outstanding contributions. The Editorial Board is saddened by her passing and she will be missed as a friend as well as a chemist.

CONTENTS

CHAPTER 1

PREPARATION OF KETONES FROM THE REACTION OF ORGANOLITHIUM REAGENTS WITH CARBOXYLIC ACIDS

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* Deceased, March 12, 1970

INTRODUCTION

The reaction of organolithium reagents and carboxylic acids constitutes a simple general method for the synthesis of ketones. Utilization of this reaction, known since 1933,[1] has received impedus in recent years from the commercial availability of numerous organolithium reagents. This preparative route is currently the method of choice for the direct conversion of carboxylic acids to ketones. Although a cursory evaluation of the reaction of methyllithium with carboxylic acids has been published,[2] no comprehensive review of the reactions of organolithium reagents with carboxylic acids has appeared. It is the purpose of this chapter to evaluate critically the scope and limitations of this reaction and to recommend optimal experimental conditions for its application.

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[1] H. Gilman and P. R. van Ess, *J. Amer. Chem. Soc.*, **55**, 1258 (1933).

[2] C. Tegner, *Acta Chem. Scand.* **6**, 782 (1952).

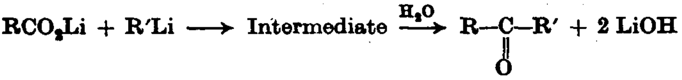
The synthetic potential of the reaction of carboxylic acids with organolithium reagents was first recognized by Gilman and Van Ess who discovered this transformation as a side reaction during studies of the carbonation of organolithium reagents.[1] From the reaction of phenyllithium with carbon dioxide, benzophenone was formed in 70% yield. It was postulated that the process involved a two-step reaction sequence *via* lithium benzoate (Eqs. 1 and 2). The high yields of ketones obtained by these authors from the reaction of lithium benzoate or lithium butyrate and phenyllithium furnished compelling support for this proposed scheme. It is evident that the reaction of organolithium reagents with carbon dioxide can serve as a useful synthesis of symmetrical ketones.

$$C_6H_5Li + CO_2 \longrightarrow C_6H_5CO_2Li \qquad \text{(Eq. 1)}$$

$$C_6H_5CO_2Li + C_6H_5Li \longrightarrow \text{Intermediate} \xrightarrow{H_2O} (C_6H_5)_2CO \qquad \text{(Eq. 2)}$$

For a general case, the reaction of 2 moles of organolithium reagent with 1 mole of carboxylic acid can be viewed as taking place in two discrete steps: the first (Eq. 3) leads to the lithium salt of the carboxylic acid; the second, the reaction of the lithium carboxylate with another mole of organolithium reagent (Eq. 4), furnishes ketone after hydrolysis.

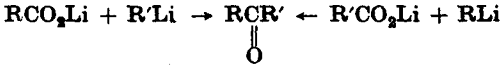
$$RCO_2H + R'Li \longrightarrow RCO_2Li + R'H \qquad \text{(Eq. 3)}$$



$$RCO_2Li + R'Li \longrightarrow \text{Intermediate} \xrightarrow{H_2O} R\text{—}\underset{\displaystyle O}{\overset{}{\underset{\|}{C}}}\text{—}R' + 2\,LiOH \qquad \text{(Eq. 4)}$$

Hence, either the free acid or the lithium carboxylate can serve as the starting material in this preparation. The relative merits of the two methods are considered in the experimental section.

The reaction of organolithium reagents with carboxylic acids is limited to the preparation of acyclic ketones. Although the objective of this reaction is, generally, the formation of an unsymmetrical ketone, the method is clearly applicable to the synthesis of symmetrical ketones. Two different routes (Eq. 5)* to the same unsymmetrical ketone are possible; the group R may be derived either from the carboxylic acid or from the organolithium reagent. In practice, one of these routes will be preferred because of the availability of the reagents or structural limitations inherent in one of the reagents. This topic is treated under "Design of Synthesis."



$$RCO_2Li + R'Li \rightarrow R\underset{\displaystyle O}{\underset{\|}{C}}R' \leftarrow R'CO_2Li + RLi \qquad \text{(Eq. 5)}$$

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* In this and subsequent reactions of organolithium reagents and carboxylic acids or their lithium salts the hydrolysis is not shown as a separate step.

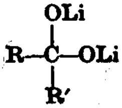
To date, the reaction has been applied only to the preparation of monoketones. However, the conversion of dilithium reagents to diketones, as exemplified in Eq. 6 for 1,5-dilithiopentane, should be viable. Such a transformation would constitute a valuable extension of this synthetic reaction, but its potential has not been explored.

$$\mathrm{Li(CH_2)_5Li} + 2\,\mathrm{RCO_2Li} \rightarrow \mathrm{R}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{(CH_2)_5}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{R} \qquad \text{(Eq. 6)}$$

MECHANISM

The singular feature believed to make the formation of ketones from carboxylic acids and organolithium reagents possible is the stability of the intermediate dilithium compounds. In this respect the reaction differs markedly from the reaction of organolithium reagents with carboxylic esters, acid chlorides, or anhydrides. With the latter three classes of compounds, the facile decomposition of the organometallic intermediate to a ketone in the reaction mixture makes tertiary alcohols rather than ketones the usual products.

The mechanistic course of the reaction of organolithium reagents and carboxylic acids, partially depicted in Eqs. 3 and 4, needs to be supplemented by a clear specification of the structure of the intermediate. This intermediate can be formulated as 1, on the basis of chemical and analytical studies conducted on the solid intermediate formed upon reaction of phenyllithium with lithium benzoate[3] and from the isolation of an intermediate of this structure when $\mathrm{R = R' = CF_3}$.[4]



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A mechanistic study of this reaction has not been undertaken. By analogy with the reaction of ketones with organolithium reagents, which has been investigated,[5] the reaction depicted in Eq. 4 can be considered to be a relatively slow nucleophilic attack by the organolithium reagent on the carbonyl carbon atom of the lithium carboxylate. The reaction between the free carboxylic acid and the organolithium reagent (Eq. 3) and the hydrolysis of 1 (Eq. 4) are very fast.

[3] H. F. Bluhn, H. V. Donn, and H. D. Zook, *J. Amer. Chem. Soc.* **77**, 4406 (1955).

[4] P. H. Ogden and G. C. Nicholson, *Tetrahedron Lett.*, **1968**, 3553.

[5] (a) C. G. Swain and L. Kent, *J. Amer. Chem. Soc.*, **72**, 518 (1950). (b) S. G. Smith, *Tetrahedron Lett.*, **1966**, 6075.

Whether the stability of the dilithio intermediate is the sole factor responsible for the high yields of ketones is not known. Some success in ketone formation has been reported, for example, from the reaction of Grignard reagents with carboxylic acids or their salts.[6] Yields from these reactions are inferior, probably owing to the better leaving-group tendency of OMg compared to OLi, so that intermediates in this reaction are less stable and give rise to alcohols. (For these reasons the reaction possesses no generality as a synthetic method.) It is reasonable to conclude that at least four factors are responsible for the higher yields of ketones from the reaction of carboxylic acids with organolithium reagents compared to those from the reaction with other organometallic reagents: the greater nucleophilicity of the organolithium reagent compared to that of organomagnesium reagents;[1] the appreciable solubility of the less ionic lithium carboxylate compared to other metal carboxylates (the critical role played by the solubility of the carboxylate salt in some reactions is discussed later); the greater susceptibility to nucleophilic attack at the carbonyl carbon atom of lithium carboxylates, compared to other metal carboxylates which have a more highly developed ionic character; and the greater stability of the dilithium intermediate 1 compared to other metal dialkoxides.

SCOPE AND LIMITATIONS

The Organolithium Reagent

General Effects on Reactivity. A comparative study of the reactivities of various alkyl- and aryl-lithium reagents with lithium carboxylates has not been undertaken. In general, reactions appear to take place readily with all organolithium reagents, since high yields of ketones are obtained after reaction at room temperature for periods as short as 10 minutes. The reactivity of various organolithium compounds with ketones[5a] and nitriles[7] conforms to the following order: phenyllithium > ethyllithium > isopropyllithium. This order differs from that recorded for the relative reactivities in the halogen-metal interchange reaction: *n*-propyl > ethyl > *n*-butyl > phenyl > methyl.[8] In the aliphatic series, methyllithium has the lowest reactivity.

In addition to electronic factors inherent in the structure of the organolithium reagent, external factors also determine the reactivity of these

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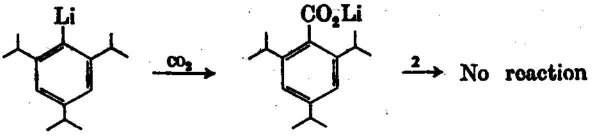
[6] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, pp. 948–960 and references therein, Prentice-Hall, Englewood Cliffs, N.J., 1954.

[7] H. Gilman, E. St. John, N. St. John, and M. Lichtenwalter, *Rec. Trav. Chim. Pays-Bas*, **55**, 577 (1936).

[8] R. R. Jones and H. Gilman, *Org. Reactions*, **6**, 339 (1951).

reagents. The solvent for the reaction determines the nucleophilic reactivity of the organolithium reagent by affecting the degree of association[9] and the degree of polarity of the carbon-lithium bond.[10] Metalations occur more readily in tetrahydrofuran than in diethyl ether,[11] probably because of a more highly developed ionic character of the organolithium reagent in the former, better cation-solvating medium. Additives also affect the nucleophilic capacity of the organolithium reagent; thus in the presence of alkoxides, *n*-butyllithium has been shown to become more reactive.[12] An extensive literature exists on the structure and behavior of organolithium reagents which should be consulted for the properties of individual organolithium reagents.

Steric effects in the organolithium reagent have not been specifically studied. Such effects are probably relatively unimportant, since *t*-butyllithium reacts readily with lithium carboxylates. It is likely that steric effects in the organolithium reagent will exert themselves only when the reagent is employed in conjunction with a highly hindered lithium carboxylate. It has been reported that the substituted phenyllithium reagents 2 and 3 carbonate normally, but do not react further to yield ketones.[13] Reaction of the intermediate lithium carboxylates with the aryllithium reagents 2 and 3 appears to be sterically precluded. It is not clear whether these reagents, 2 and 3, would react even with unhindered carboxylic acid salts. Except for the indirect evidence for a steric effect in compounds 2 and 3, no examples have been found of complete inhibition of ketone formation due to the large size of the organolithium reagent.



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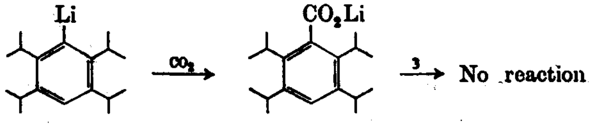

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[9] T. L. Brown R. L. Gerteis, D. A. Bafus, and J. A. Ladd, *J. Amer. Chem. Soc.*, **86**, 2135 (1964); L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *ibid.*, **90**, 3244 (1968); P. West and R. Waack, *ibid.*, **89**, 4395 (1967); T. L. Brown, *Acc. Chem. Res.*, **1**, 23 (1968).

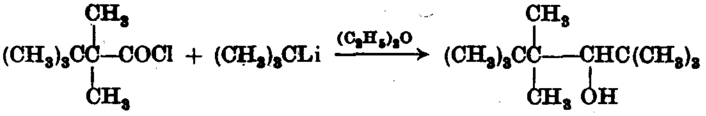
[10] R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Commun.*, 117 (1969); L. D. McKeever, R. Waack, M. A. Doran, and E. B. Baker, *J. Amer. Chem. Soc.*, **91**, 1057 (1969).

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

[12] M. Schlosser, *J. Organometal. Chem.*, **8**, 81 (1967).

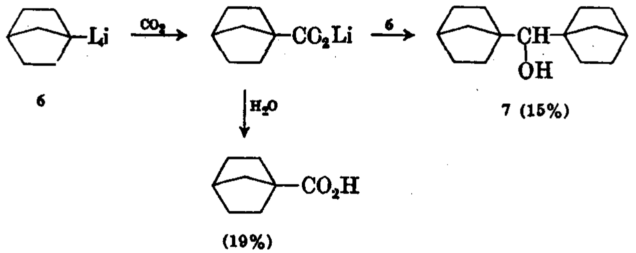
[13] G. Vavon and J. Thiec, *Compt. Rend.*, **233**, 1290 (1951).

Reduction of, rather than addition to, the carbonyl group of ketones is common with bulky organolithium reagents. A related example has been noted for the acid halide **4**; the product of this reaction, **5**, is derived from both addition and reduction by *t*-butyllithium.[14] Although no examples of the comparable reaction of *t*-butyllithium with a carboxylate salt exist in the literature, it is likely that such reactions will occur when bulky organolithium reagents react with crowded carboxylic acids. Indirect evidence for such a reaction is afforded by carbonation of the norbornyllithium reagent **6** to furnish dinorbornylcarbinol (**7**)* in addition to the expected carboxylic acid.[15]



$$(CH_3)_3C\overset{CH_3}{\underset{CH_3}{C}}-COCl + (CH_3)_3CLi \xrightarrow{(C_2H_5)_2O} (CH_3)_3C\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{CH}C(CH_3)_3$$

4 5 (74%)



6 7 (15%) (19%)

Reaction with Solvents. Reactive organolithium reagents such as *t*-butyllithium and isopropyllithium cannot be prepared or stored in common ethereal solvents at room temperature because they react with these solvents. The organolithium reagent will be destroyed and extraneous products may be obtained when reactions with carboxylic acids are conducted in these solvents. For example, carbonation of isopropyllithium in diethyl ether at ambient temperatures resulted in the formation of diisoamyl ketone as shown in the accompanying equations.[16]

$$(CH_3)_2CHLi + CH_3CH_2OCH_2CH_3 \rightarrow CH_2{=}CH_2 + CH_3CH_2CH_3 + LiOCH_2CH_3$$

$$(CH_3)_2CHLi + CH_2{=}CH_2 \rightarrow (CH_3)_2CHCH_2CH_2Li$$

$$(CH_3)_2CHCH_2CH_2Li + CO_2 \rightarrow (CH_3)_2CHCH_2CH_2\underset{\underset{O}{\|}}{C}CH_2CH_2CH(CH_3)_2$$

---

* Reduction of the ketone may have occurred by the unchanged lithium metal, present in large excess.

[14] P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955).

[15] T. Traylor and A. Sieber, unpublished observations.

[16] P. D. Bartlett, S. Friedman, and M. Stiles, *J. Amer. Chem. Soc.*, **75**, 1771 (1953).

At temperatures below −40°, solvent decomposition is sufficiently slow that *t*-butyllithium and isopropyllithium can be prepared and carbonated without complications.[16] Whether these organolithium reagents react with lithium carboxylates at these low temperatures has not been determined. At ambient temperatures, isopropyllithium[17] and *t*-butyllithium[18] have reacted in diethyl ether to give ketones, but yields were not reported. In experiments designed to define the applicability of isopropyllithium and *t*-butyllithium as organolithium reagents at room temperature, each reagent was treated with benzoic acid in diethyl ether (Eqs. 7 and 8). Isobutyrophenone was obtained in 60% yield, accompanied by 15% of tertiary alcohol, and *t*-butyl phenyl ketone was produced in 44% yield, together with 30% of a $C_{15}H_{22}O$ ketone.[19] (The latter is probably derived from the reaction of *t*-butyllithium with 2 molecules of ethylene, the decompositon product of ether, to give a new organolithium reagent whose reaction with benzoic acid furnishes the C_{15} ketone.)

$$C_6H_5CO_2H + (CH_3)_2CHLi \xrightarrow{(C_2H_5)_2O} \underset{(60\%)}{C_6H_5COCH(CH_3)_2} \qquad \text{(Eq. 7)}$$

$$C_6H_5CO_2H + (CH_3)_3CLi \xrightarrow{(C_2H_5)_2O} \underset{(44\%)}{C_6H_5COC(CH_3)_3} + \underset{(30\%)}{C_{15}H_{22}O} \qquad \text{(Eq. 8)}$$

It is evident from these examples that the reaction of isopropyllithium and *t*-butyllithium with carboxylic acids is faster than their reaction with diethyl ether. Thus reactions with these organolithium reagents can be conducted in that solvent, if extraneous ketonic products can be tolerated. For best results, however, reactions should be conducted in solvents that are more stable to the reagent. When benzene was substituted for diethyl ether in the reaction of *t*-butyllithium with benzoic acid (Eq. 9), the yield of *t*-butyl phenyl ketone was raised to 67% and complicating side reactions were averted.[20]

$$C_6H_5CO_2H + (CH_3)_3CLi \xrightarrow{C_6H_6} \underset{(67\%)}{C_6H_5COC(CH_3)_3} \qquad \text{(Eq. 9)}$$

Structural Variation and Complexities. Methyllithium is by far the most frequently employed aliphatic organolithium reagent in the

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[17] M. M. Green and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5190 (1967).

[18] J. K. Crandall and L. H. C. Lin, *J. Amer. Chem. Soc.*, **89**, 4526 (1967).

[19] M. J. Jorgenson and D. Dahlhauser, unpublished observations.

[20] C. H. Heathcock and R. Radcliffe, unpublished observations. This procedure is reproduced under "Experimental Procedures."

reaction with carboxylic acids. Ethyl-,[21–25] *n*-propyl-,[23] isopropyl-,[17–19] *n*-butyl-,[3, 23, 24] *t*-butyl-,[18–20] and *n*-pentyl-lithium[26] have been employed only occasionally. In the aromatic series, widest application has been made of phenyllithium, although *p*- and *m*-tolyllithium[27] and 2,6-difluorophenyllithium[28] have been used. Aromatic lithium reagents other than those related to phenyllithium have not been employed. Attempted reaction of 2-naphthyllithium with lithium crotonate in a variety of solvent failed to give the expected ketone.[29]

Low yields have been reported from the reaction of alkenyllithium reagents with carboxylic acids or their salts. The best yield (42%) was reported for the preparation of benzoylcyclohexene from 1-cyclohexenyllithium and lithium benzoate.[30] The yield from the reaction of isobutenyllithium with various lithium carboxylates was in the range 0–40%.[31] The yield of 40% for the reaction of lithium benzoate with isobutenyllithium[31] should be compared with the high yields of 82% for the reaction of benzoic acid with methyllithium[2] and 70% for the reaction of lithium benzoate with phenyllithium.[1] The reduced yields are due to a large degree to the formation of Wurtz coupling products during the preparation of the alkenyllithium reagent or during the course of reaction. For example, large amounts of 2,5-dimethyl-2,4-hexadiene accompanied the ketone formed from isobutenyllithium.[31] Higher yields of ketone were obtained when the alkenyllithium was generated in the presence of the carboxylate.[32] The cyclopropenyl lithium derivative **8** has been reported to react with lithium acetate to furnish the methyl ketone **9** in unstated yields.[33] (Equation on p. 10.)

Reactions of acetylenic organolithium reagents with carboxylic acids have not been investigated, although such lithium reagents react with

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[21] H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968). This procedure is reproduced under "Experimental Procedures."

[22] P. Doyle, J. R. Maclean, R. D. H. Murray, W. Parker, and R. A. Raphael, *J. Chem. Soc.* **1965**, 1344.

[23] K. Mislow and C. L. Hamermesh, *J. Amer. Chem. Soc.*, **77**, 1590 (1955).

[24] R. Ya. Levina, I. G. Bolesov, I. H. Wu, and N. P. Samoilova, *Zh. Org. Khim.*, **2**, 1897 (1966) [*C.A.*, **66**, 55179 (1967)].

[25] J. Meinwald, J. W. Wheeler, A. A. Nimetz, and J. S. Liu, *J. Org. Chem.*, **30**, 1038 (1965).

[26] H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

[27] C. K. Bradsher and S. T. Webster, *J. Amer. Chem. Soc.*, **79**, 393 (1957).

[28] T. V. Talalaeva, G. V. Kazennikova, and K. A. Kocheshkov, *Zh. Obshch. Khim.*, **29**, 1593 (1959) [*J. Gen Chem.* (*USSR*), **29**, 1566 (1959)].

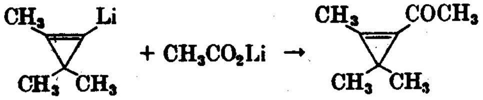
[29] M. J. Jorgenson and A. F. Thacher, unpublished observations.

[30] H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

[31] E. A. Braude and J. A. Coles, *J. Chem. Soc.*, **1950**, 2012. This procedure is reproduced, under "Experimental Procedures."

[32] E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, **1950**, 2000.

[33] G. L. Closs, in *Advances in Alicyclic Chemistry*, H. Hart and G. J. Karabatsos, Ed., Vol. 1, p. 102, Academic Press, New York, 1966.



8 9

ketones and carboxylic acid derivatives.[34–36] Lithium phenylacetylide reacts with carbon dioxide to give phenylpropiolic acid in good yield,[37] but no ketone was isolated from this reaction.[34]

Aromatic heterocycles are readily metalated with simple organolithium reagents and the reactions of these lithium reagents with carbon dioxide to give acids has received considerable attention.[38] Reactions of heterocyclic lithium reagents with carboxylic acids are much less numerous, perhaps because these organolithium reagents frequently react with esters or acid halides to give high yields of ketones.[39–43] There is no reason to believe, however, that the reaction with carboxylic acids will not produce ketones in high yield.

The quinoline acid salt **10** and pyridyllithium produced ketone **11** in 60% yield.[44] Lithiated phenothiazines are reported to give acylated products on reaction with lithium acetate, lithium propionate, or lithium benzoate.[45] A complication, characteristic for aromatic and heterocyclic compounds, arises in this case from the presence of more than one metalation site in the molecule. (The electronic factors controlling the site of metalation in such molecules have been discussed.[38]) When the organolithium reagent obtained from phenothiazine and one equivalent of *n*-butyllithium was heated with lithium acetate, no ketonic products were formed. When phenothiazine was treated first with two equivalents of *n*-butyllithium and then with lithium acetate, a 40% yield of the 1-acetyl derivative **14** was formed. With 10-methylphenothiazine only 1 mole of *n*-butyllithium was required, and subsequent reaction with lithium acetate furnished a 20% yield of the 4-acetyl derivative **15**. Similar results were obtained for other 10-alkylphenothiazine derivatives.

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[34] D. Nightingale and F. T. Wadsworth, *J. Amer. Chem. Soc.*, **69**, 1181 (1947).

[35] L. D. Bergel'son and A. N. Grigoryan, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, [2] 286 (1966) [*C.A.*, **64**, 19400 (1966)].

[36] K. Suga, S. Watanabe, and T. Suzuki, *Can. J. Chem.*, **46**, 3041 (1968).

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

[38] H. Gilman and J. W. Morton, *Org. Reactions*, **8**, 258 (1954).

[39] N. T. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, **73**, 4301 (1951).

[40] J. A. Gautier, M. Miocque, and C. Lafontaine, *Bull. Soc. Chim. Fr.*, **1960**, 1117.

[41] M. Regitz and A. Liedhegener, *Chem. Ber.*, **99**, 2918 (1966).

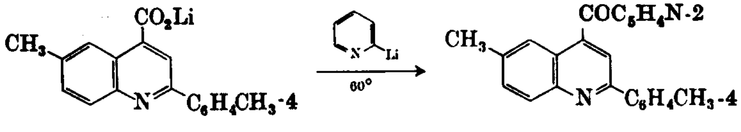
[42] N. N. Goldberg and R. Levine, *J. Amer. Chem. Soc.*, **77**, 3647, 4926 (1955).

[43] C. S. Sheppard and R. Levine, *J. Heterocycl. Chem.*, **1**, 67 (1964).

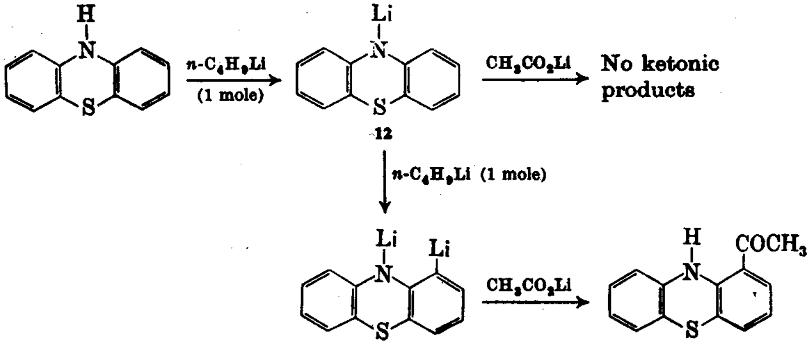
[44] D. W. Boykin, A. R. Patel, R. E. Lutz, and A. Burger, *J. Heterocycl. Chem.*, **4**, 459 (1967).

[45] G. Cauquil, M. Casadevall, and E. Casadevall, *Bull. Soc. Chim. Fr.*, **1960**, 1049; *Compt. Rend.*, **242**, 590 (1956).

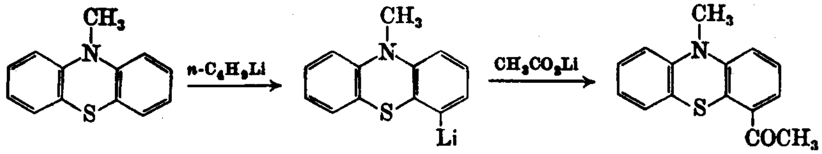
It is evident that 2 moles of butyllithium are required to convert phenothiazine, *via* **12**, to the productive dilithium reagent **13** because of the presence of an acidic hydrogen. The different direction of acylation in the two phenothiazines is striking. Minor amounts of the 3-acyl derivatives are also formed from the reaction of the lithiated 10-alkylphenothiazines.



10 **11** (60%)



12 **13** **14** (40%)



15 (20%)

Attempted lithiation of heterocycles may lead to competitive side reactions. For example, reaction of the pyrazine **16** with methyllithium gave both the desired organolithium reagent **17** and substantial amounts of products derived from addition to the heterocyclic ring.[46] (See p. 12.)

Metalation of furan proceeds smoothly to form a lithio derivative which furnishes ketones on subsequent reaction with carboxylic acids (Eq. 10).[47] By contrast, the reaction of furyllithium with carboxylic esters yielded only tertiary alcohols.[48] Reaction of 2-thienyllithium and trifluoroacetic acid at −60° furnished trifluoromethyl 2-thienyl ketone in 87%

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[46] G. P. Rizzi, *J. Org. Chem.*, **33**, 1333 (1968).

[47] C. H. Heathcock, L. G. Gulick, and T. Dehlinger, *J. Heterocycl. Chem.*, **6**, 141 (1969).

[48] V. Ramanathan and R. Levine, *J. Org. Chem.*, **27**, 1216 (1962).