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SOME OBSERVATIONS PERTAINING TO THE MECHANISM OF METALATION OF AROMATIC SUBSTRATES WITH ALKYLLITHIUM REAGENTS

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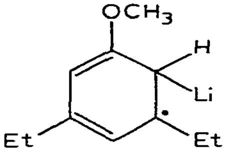
Summary

Metalation of 3,5-diethylanisole with carbon-14 labelled ethyllithium has demonstrated that an adduct of EtLi to the ring is not an intermediate in the process; an alternative radical and radical anion route involving capture of a hydrogen atom by $R^{\bullet}$ (from RLi) from



is not ruled out by the labelling experiments, but negative CIDNP results did not support the idea of the intermediacy of radical species in the metalation reaction with six different substrates.

A number of metalation results were obtained with n-BuLi and t-BuLi in non-polar solvents in the presence and in the absence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) on substrates selected for showing different steric environments in the same molecule. The large majority of the data could be correlated with the concept that the steric requirement of the RLi was related to the oligomer size and that the decreasing order of steric requirement was n-BuLi in hydrocarbon > t-BuLi in hydrocarbon > n-BuLi in ether > n-BuLi—TMEDA in hydrocarbon.

A case of particularly facile dimetalation was observed with a substrate in which the second lithium atom substituted in a methyl group adjacent to the position of substitution on the ring by the first lithium, e.g.,

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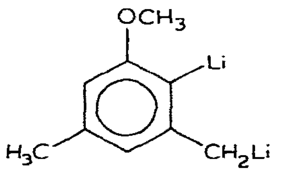


This reaction outcome seemed to correlate with the association of the product of the first metalation with the RLi oligomer which brought the nearby methyl group into close association with the oligomer surface, thus facilitating a second attack with introduction of the lithium atom at that point. Metalation in the presence of TMEDA did not allow this facile dimetalation probably because of the absence of the oligomer in the presence of the chelating amine.

Several observations point to heretofore unrealized possibilities for synthetic utility of RLi metalations under certain conditions.

Introduction

A report from this laboratory [1] in 1968 proposed in some detail a multi-step route of metalation of aromatic substrates with alkyllithium reagents. In main outline the mechanism proposed consisted of (1) a single electron transfer from an alkyl anion derived from RLi or RLi oligomer to the aromatic substrate, (2) lithium cation capture by the resulting radical anion giving a neutral radical, (3) alkyl radical capture by the radical from (2) resulting in overall RLi addition to the π system of the aromatic ring, and (4) a rate-determining loss of RH from the adduct. A number of experimental observations in support of this mechanism were collected. While no single type of observation was compelling, there seemed to emerge a sufficient amount of data to justify the radical anion mechanism as a better approach than had been proposed in earlier work. Some principal lines of evidence may be summarized in the following points: (1) well documented [1—3] hydrogen isotope effect studies showing cleavage of the aromatic C—H bond in the rate-determining step, (2) the studies of Dixon and coworkers [4] who isolated the adducts of t-butyllithium to naphthalene and biphenyl, (3) the observation [5] by ESR spectroscopy of the pyrene radical anion from the action of n-butyllithium on pyrene and the easy metalation of pyrene [6] under these conditions, and (4) the apparent low steric requirement of the reaction as seen in orientation of the entering lithium atom in many metalation reactions [1] indicating that rate-determining and product-determining steps were probably different. Earlier mechanistic ideas on the metalation reaction [1] required a single step that was both product- and rate-determining. It has been our objective to subject the proposed mechanism to a number of experimental tests.

Results and discussion

A. Probes for intermediate free radicals

A mixture of equimolar amounts of naphthalene, n-butyllithium and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) at room temperature exhibited a well resolved ESR spectrum. Analysis of the hyperfine structure indicated the presence of the naphthalene radical anion in close association with the lithium cation. There was clear evidence for a splitting of the 25 line spectrum of the naphthalene radical anion by the lithium-7 component of the lithium cation with a coupling constant of 0.9 gauss. Such coupling constants have been shown to be solvent and temperature dependent and a value of 0.5 for naphthalene radical anion-Li^+ at room temperature in 2-methyltetrahydrofuran has been reported [7]. Since closely associated ions are favored by the low dielectric of the cyclohexane solvent, the enhanced value of the lithium-7 coupling constant seems supported. A reaction mixture made up in the same way as the one sampled for the ESR experiments showed a 68% yield of naphthalenecarboxylic acids upon treatment with CO_2.

Similar ESR experiments were run with biphenyl and anisole substrates, but no paramagnetic species were observed. The use of t-butyllithium with anisole at varying temperatures down to —60° did not yield an ESR signal.

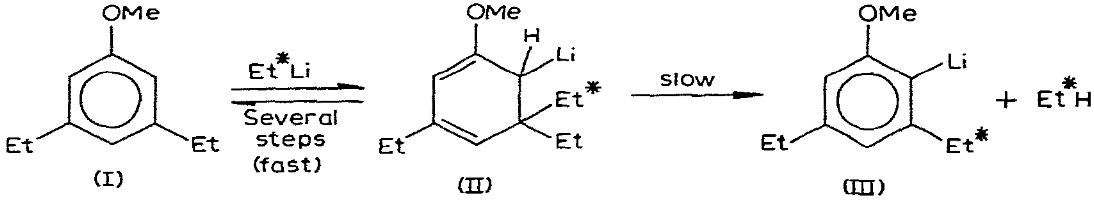
While the radical intermediate proposal seems supported by the experiment with naphthalene, the naphthalene radical anion-Li^+ ion pair could come from traces of lithium metal possibly present in the alkyllithium solutions. This well known electron transfer process could have been the source of the ion pairs in sufficient concentration to give the ESR signal, even though clear solutions of RLi in cyclohexane were used.

We next turned to another sensitive method for demonstrating the presence of free radicals in systems undergoing reaction. This is the technique of chemically induced dynamic nuclear polarization (CIDNP) [8]. Ward and Lawler [9] have demonstrated the presence of radical intermediates in the reaction of alkyllithium reagents with alkyl halides by use of CIDNP. The technique requires that radical pairs be formed within solvent cages and remain together at certain critical distances for certain times. Therefore CIDNP signals from a reacting system, usually seen in product molecules, is a strong positive indicator of radical intermediates, but the absence of the signal does not rule against the presence of these species.

We examined six aromatic substrates undergoing metalation in hydrocarbon and ether solvents for CIDNP signals. The aromatic proton region was used, since solvent tended to obscure other significant regions. Expected changes in the basic NMR signals derived from the progressing metalation reaction were observed, but no excess signal absorptions or emissions characteristic of the CIDNP process were found.

B. Test for an intermediate adduct

The mechanism proposed earlier from this laboratory [1] applied to 3,5-diethylanisole (I) reacting with ethyllithium would involve a species such as (II). If (II) were formed, use of carbon-14 labelled ethyllithium would introduce radioactive ethyl groups into products derived from the 2-lithio-3,5-diethylanisole (III) and possibly into "unreacted" substrate (I). Such an experiment was conducted using ethyllithium-1-^{14}C and three different sets of reaction conditions all known by prior experiments to lead to good yields of (III). No significant level of radioactivity was observed in unreacted (I) or in carboxylic acid derived from (III) and CO_2.



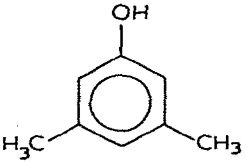
C. Tests for steric factors in the metalation process

An examination of the large amount of data which have accumulated on the metalation process with alkyllithium compounds [10] would indicate that the process has a low steric requirement. While attack at crowded positions has usually been adjacent to atoms having non-bonding electrons, the steric insensitivity is sometimes striking [1, 11].

I. Metalation of 3-alkyl- and 3,5-dialkylanisoles

We have reopened the question of steric effects on the metalation of alkyl aryl ethers with examination of the metalation of a series of 3-alkyl- and 3,5-dialkylanisoles. Such types yield two positions *ortho* to methoxy which are under quite different steric but similar electronic environments.

We first examined metalation of 3,5-dimethyl- and 3,5-diethylanisole, the latter in connection with the metalation studies with labelled ethyllithium referred to above. 3,5-Dimethylanisole with n-BuLi in cyclohexane at reflux temperature for 10 h gave a 40% yield of carboxylic acid. Analysis of total acidic products showed a product distribution 24% IV, 51% V and 30% VI. The high proportion of dimetalation product (VI) is surprising in view of the absence of product representing monometalation in a methyl group.



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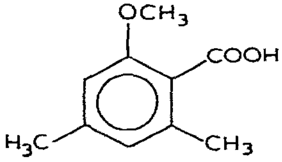

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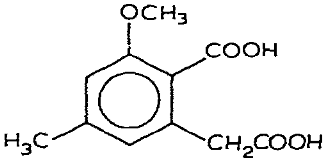
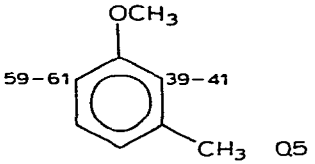


(VI)

Similar metalation conditions except with an equivalent of TMEDA present gave only the cleavage product IV in 35% yield. However, the same amounts of reactant at room temperature gave no IV or VI with the sole acidic product in the monometalation product V, and this was formed in 73% yield. Note the sharp gain in product selectivity in the presence of TMEDA.

m-Methylanisole was reported [11] to metalate with n-BuLi in ether solution as shown in (VII). Replacing the ether with cyclohexane gave the results of duplicate experiments shown in (VIII). Use of t-BuLi in cyclohexane gave the results (single experiment) of IX and with n-BuLi and TMEDA in cyclohexane the results (duplicate experiments) of X.



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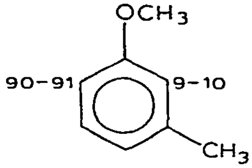

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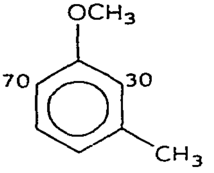

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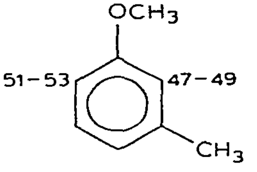
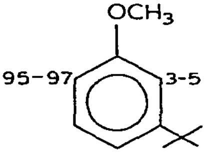


(X)

These results may be correlated by use of a concept of a steric effect depending on the probable size of the RLi oligomer present under the different reaction conditions. In hydrocarbon solvents n-butyllithium is hexameric [12] and t-butyllithium is tetrameric [13]. n-Butyllithium in ether is dimeric [14] and in the presence of TMEDA is monomeric [15]. While it is uncertain just what the electron donor properties of the anisole do to these relationships, particularly those in hydrocarbon solvent, it seems likely that the oligomer size of the reactive species decreases in the order n-BuLi in hydrocarbon > t-BuLi in hydrocarbon > n-BuLi in ether > n-BuLi—TMEDA. Note that in the above metalation results, reaction at the sterically hindered position between the methoxy and methyl groups increases in the same order with the least amount of attack with the largest oligomer and the largest amount with the smallest oligomer. Indeed in the case of n-BuLi—TMEDA there is little discrimination between the two positions *ortho* to methoxyl.

A more stringent test of this idea is provided by *m*-t-butylanisole due to the larger size of the t-butyl group compared with methyl. Here three conditions were tried with the results shown: n-BuLi in cyclohexane (XI), t-BuLi in cyclohexane (XII) and n-BuLi—TMEDA (XIII). The ring t-butyl group is apparently large enough to discourage major amounts of adjacent metalation under any conditions, but the order of increasing amount of substitution in the sterically hindered position is the order of decreasing size of the RLi oligomer.



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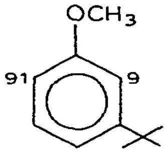

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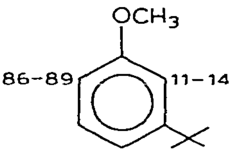
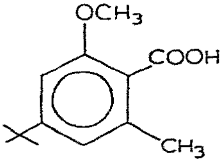


(XIII)

We next turned to 3-methyl-5-t-butylanisole to look at the degree of steric competition between methyl and t-butyl. The use of n-BuLi in cyclohexane at reflux for 10 h, (2 runs) gave the products XIV—XVI in 24—25, 12 and 63—64%, respectively. One experiment using n-BuLi—TMEDA in cyclohexane at room temperature for 10 h, gave the product distribution 97, 3 and 0%. Both the large amount of dimetalation in the former case and its complete absence in the latter is surprising. Also we expected that the n-BuLi—TMEDA reagent, if truly less sterically demanding than n-BuLi alone, would show a greater amount of metalation between the t-butyl and methoxy groups. Actually, less metalation in this more sterically hindered position is evident with the TMEDA complexed reagent.



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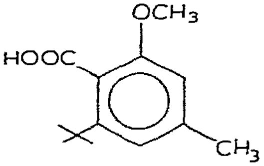

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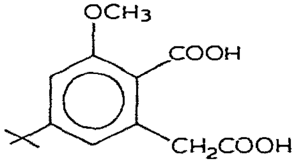
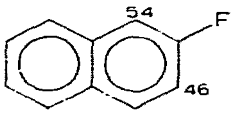


(XVI)

II. Metalation of 2-methoxynaphthalene

2-Methoxynaphthalene offers two different steric environments at the positions adjacent to the methoxy group. This substrate has been investigated by Sunthanker and Gilman [16] and Huisgen and Rist [17] who reported only 3-position metalation and by Gay and Hauser [18] who showed by thin layer chromatography the presence of two products which were not further identified as to structure or amounts. With n-BuLi in ether—hexane we found 14% 1- and 86% 3-metalation. The use of n-BuLi and TMEDA in cyclohexane showed a shift to 33% 1- and 67% 3-metalation.

These results with the alkoxynaphthalenes should be examined in terms of the concept of the size of the RLi oligomer which was introduced above. Note that n-BuLi in the presence of ether attacks preferentially the less hindered 3-position but that the smaller n-BuLi—TMEDA reagent gives a significant increase in attack at the more hindered 1-position. Some related results reported by Kinstle and Bechner [19] are of interest in this regard. These workers metalated 2-fluoronaphthalene with n-BuLi and t-BuLi at −65° in tetrahydrofuran with the results shown in XVII and XVIII respectively. Eastham and coworkers [20] have shown that both n-BuLi and t-BuLi in tetrahydrofuran are solvated dimers. Thus t-BuLi should be the more sterically demanding reagent where the oligomer size is the same. Note that this latter reagent metalates the more hindered 1-position to the lesser degree.



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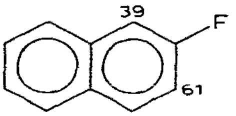
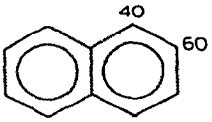


(XVIII)

III. Miscellaneous metalations

We have studied several additional substrates and these should be mentioned in connection with the idea of RLi oligomer size as it relates to position of metalation.

Metalation of naphthalene has been reported [21, 22] to involve both the 1- and 2-positions in varying amounts. Our results with n-BuLi in ether—hexane are shown in XIX and with n-BuLi—TMEDA, n-BuLi—TEEDA, t-BuLi—TMEDA (total of 5 runs) in XX. These results are in line with the view that the larger n-BuLi oligomer discriminates against the more crowded 1-position while the smaller monomeric RLi in the amine systems is less selective.



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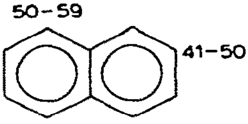
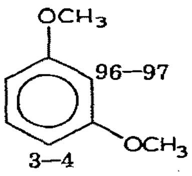


(XX)

Biphenyl has been metalated by earlier workers [11, 21] and our recent work [11] showed with n-BuLi in ether a product distribution of 8% *ortho*, 58% *meta* and 34% *para*. We repeated this experiment using a GLC column (Apiezon L) for separation of the mixed carboxylic acid methyl esters which gave a better separation than obtained earlier on a 30% silicone column. The new results are similar but indicated 5% *ortho*, 66% *meta* and 29% *para*. Change of reaction conditions to n-BuLi—TMEDA in cyclohexane gave 15% *ortho*, 58% *meta* and 27% *para*. This increase of metalation in the hindered *ortho* position is in line with the use of the sterically less demanding RLi monomer complex.

Another use of n-BuLi—TMEDA in re-examination of a substrate was with 1,3-dimethoxybenzene. Earlier results [11] with both n-BuLi in ether and in cyclohexane are shown in XXI. Repetition of the n-BuLi cyclohexane conditions gave nearly the same results (XXII), but use of n-BuLi—TMEDA in cyclohexane showed a significant shift to even greater attack at the highly hindered position between the methoxy groups (XXIII). Thus this result is also in line with a lesser steric requirement of the n-BuLi—TMEDA reagent.



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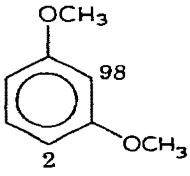

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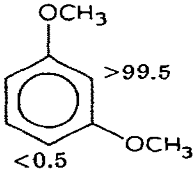


(XXIII)

It should be pointed out that the preceding ideas on steric effects due to RLi oligomer size serve to explain an experimental result reported earlier from this laboratory [1]. This is the competitive metalation of phenyl t-butyl ether with equimolar amounts of n-BuLi and t-BuLi in cyclohexane in which it was found that t-BuLi was consumed faster in the *ortho* metalation process. Also a recent observation by Grocock and coworkers [23] is of interest. These workers found that metalation of 1,3-bis(trifluoromethyl)benzene with n-BuLi in the presence of TMEDA occurred exclusively in the 2-position, while use of n-BuLi in ether gave an unresolved mixture of acidic products subsequent to carbonation. Here again the n-BuLi—TMEDA reagent improved attack selectivity in favour of the more sterically hindered position.

Recent results of Slocum and Koonsvitsky [24] indicate that *o*-t-butylanisole metalates with n-BuLi adjacent to the methoxy group at a sharply reduced rate compared with anisole. However in the presence of TMEDA the sterically hindered substrate undergoes a more rapid metalation than in the absence of the amine. These authors point specifically and correctly to the fact that the apparent steric effect of the *o*-t-butyl group in slowing metalation compared to anisole is in contrast to the earlier claim from this laboratory [1] of the low steric requirement of the metalation reaction. At the same time the Slocum and Koonsvitsky results fall clearly in line with the ideas presented in this paper, namely, that the steric requirement of n-BuLi—TMEDA is quite low compared to n-BuLi alone.

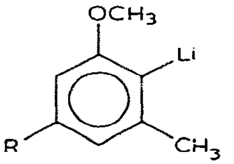
D. Discussion

One matter emerges clearly from the results reported above and that is the sometimes high degree of synthetic utility of the n-BuLi—TMEDA reagent. This was first observed [25] in the remarkably selective 2-metalation of 1-methoxynaphthalene. Later Slocum and coworkers [26] demonstrated a marked changed in position of metalation of *p*-methoxy-*N*,*N*-dimethylaniline from adjacent to $(CH_3)_2N$ with n-BuLi alone to adjacent to CH_3O with n-BuLi—TMEDA. Additional cases of potential synthetic utility of this reagent are (a) the absence of dimetalation with 3,5-dimethylanisole and 3-methyl-5-t-butylanisole and (b) the increased selectivity for 2-metalation in 1,3-dimethoxybenzene.

In dealing with the many types of changes in positions of metalation with changes in reaction conditions, it should be emphasized that there is little possibility that the results are simply interplays between kinetic and equilibrium phases of a substitution process or rearrangement of the metallic atom between different ring positions. In a number of cases where tests for this have been devised [2, 11, 27], it has been found that competition for metalation of various ring positions is strictly under kinetic control. The same is apparently true in metalation of side chain alkyl groups at the α-position with alkyllithium reagents [28—30].

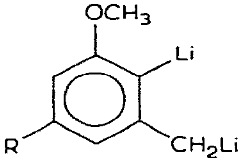
We should like to point out the results of a series of observations involving dimetalation of various substrates. In the vast majority of metalations with alkyllithium reagents not involving tertiary amine coordination, introduction of a second lithium atom into the ring is much slower than the first. An example is thiophene undergoing metalation by n-BuLi in ether where the interrelationship between mono- and dimetalation was examined carefully [2]. However Hendrix [31] observed that t-BuLi in hydrocarbon solvent reacts with thiophene giving major amounts of 2,5-dimetalation along with 2-position monometalation. Hendrix suggested [31] that this was perhaps due to a specially facile cross association of 2-thienyllithium with t-BuLi in a mixed organolithium oligomer, in which the 5-position was in a favorable position for attack within the oligomer. Such mixed oligomers are known to form readily and to undergo facile dissociation and reassociation for rapid exchange of the organolithium components [32—34].

In the metalation of 3,5-dimethylanisole equimolar amounts of n-BuLi and substrate in cyclohexane gave the large amount of dimetalation shown in V and VI with the second metal atom entering the methyl group. A similar situation with even more dimetalation was observed in the case of 3-methyl-5-t-butylanisole. On the other hand 3-methylanisole under corresponding conditions shows only a trace of metalation in the methyl group. These facts may be reconciled by the cross-association of the initially formed ring metalated product (XXIV), and attack within the oligomer aggregate on the adjacent exposed methyl group to form XXV. There is perhaps a particularly favorable geometry for methyl attack, with the methyl group held on or near the surface of the aggregate. The remaining methyl group in XXIV (R = CH_3) is thereby held away from the surface and no dimetalation involving this group is found. The absence of appreciable dimetalation in 3-methylanisole can be rationalized by the results shown in VIII in which the position between methoxyl and methyl is metalated at only about one-tenth the rate of the other position adjacent to methoxyl. Cross-association of this more abundant product keeps the methyl group away from the surface of the RLi aggregate with a sharply lesser vulnerability to attack. These geometries assume that the electron donor properties of the methoxyl group are also involved in the cross-associated complex, and thus the aromatic ring is probably edgewise in the aggregate leaving the groups on the other side of the ring well away from the oligomer surface.



(XXIV)

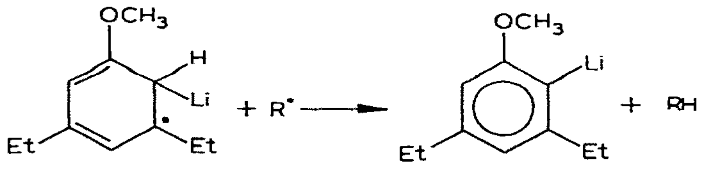
R = CH_3 or t-butyl



(XXV)

It should be pointed out that these ideas also account for the lack of dimetalation in the process in which n-BuLi—TMEDA was used on 3,5-dimethylanisole. Here the n-BuLi and the product organolithium are likely monomeric and no cross-association occurs. Similarly no dimetalation was observed in the n-BuLi—TMEDA metalation of 3-methyl-5-t-butylanisole.

The data accumulated in this research seem not to point to any "new" mechanism for the metalation process. The radical anion mechanism proposed earlier [1] seems to be not supported. Certainly the addition—elimination mechanistic route in the case of 3,5-diethylanisole metalation is unequivocally eliminated. However the original work of Hendrix [31] presented the radical-ion mechanism as not involving an intermediate adduct corresponding to II but rather hydrogen atom abstraction by R$^•$ from the radical precursor of II (eqn. 1).

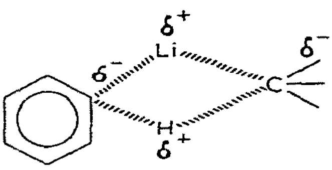


(1)

(XXVI) (III)

The carbon-14 labelling experiments do not rule out this path. The CIDNP experiments, in which we were looking at the aromatic proton region of product molecules, might have been sensitive to this possibility; however, it is hardly eliminated by the negative CIDNP results.

The one step "protophilic" mechanism for metalation proposed [35] many years ago may be valied. However, the data presented herein support the view that a RLi oligomer is the reactive species in metalation reactions and not the alkyllithium monomer. The proposed transition state for the "protophilic" mechanism (XXVII), as well as a more recent version (XXVIII) [36], seems crowded in the case of many substrates and attacking RLi oligomers. At the same time such transition states would be sensitive to the steric effects pointed out in this paper. In any event it seems that in the past too little attention has been given to the size of the RLi oligomer, as modified under the conditions of particular reactions by donor groups in the substrate, donor solvents, tertiary amine "catalysts", and product cross-association within the RLi oligomer.



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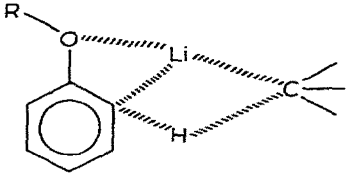

(XXVIII)

Experimental

A. General considerations

Solutions of n-BuLi in cyclohexane, t-BuLi in pentane and EtLi in benzene were obtained from Foote Mineral Co. Solutions of t-BuLi in pentane were also obtained from Alfa Inorganic Inc. Anhydrous ethyl ether (Fisher Scientific Co. or Matheson Chemical Co.) was used from freshly opened small containers and was used without further purification since GLC analysis showed no other components. Benzene and cyclohexane were refluxed for several hours over lithium aluminum hydride, distilled and stored over freshly cut sodium. TMEDA (Aldrich Chemical Co.) was distilled from $LiAlH_4$ and stored over Lind MS-4A molecular sieve. Lithium wire (1/8") containing 1% sodium was obtained from Lithium Corporation of America and a 50% dispersion of finely divided lithium in pentane was supplied by Matheson, Coleman and Bell. Ethyl bromide containing carbon-14 in the α-position was obtained from Mallinckrodt Nuclear Co.

The concentration of organolithium reagents used was determined by the method of Gilman and Cartledge [37].

Element microanalyses were performed by Galbraith Laboratories of Knoxville, Tenn.

NMR spectra including the CIDNP experiments were obtained on a Varian A-60 instrument. IR spectra were obtained on a Beckman IR-5A instrument. GLC data were obtained on the following instruments: Varian-Aerograph 90-P, Varian-Aerograph 711 and a Wilkins A-700. Peak areas were measured with a disc integrator on all non-overlapping peaks and by manual triangulation on partially overlapping peaks. Retention times were measured from peak injection to the time corresponding to the peak maximum.

The aryllithium compounds obtained in a metalation run were converted to carboxylic acids with CO_2 and the mixed acids converted to methyl esters with diazomethane. Methyl ester mixtures were chromatographed for qualitative and quantitative analysis. The techniques used have been fully described in earlier work from this laboratory [11] with the exception that a number of the runs in this paper report percentages of isomeric carboxylic esters which were obtained directly from relative GLC peak areas. Thus we did not chromatograph a variety of known mole ratios of known isomers to obtain the correction factors by which peak area ratios are converted to mole ratios. The reason for use of the simpler technique was twofold (1) experience [11] with determination of correction factors for a number of isomeric mixed esters showed factors within a few percent of unity as long as the mole ratio of two isomers present in the mixture was no greater than about 4 or 5 to 1 and (2) the compositions of product mixtures obtained were within a few percent, normally within 1—2%, of the correct values and this accuracy was sufficient to define the trends in product composition as related to reaction conditions. Duplicate metalation runs were made for virtually all of the data reported.

Qualitative identifications of the GLC peaks were made by addition of an authentic supposed component, and this was facilitated by the fact that most systems studied had only a few major carboxylic ester product isomers and the possible structures of these could be predicted with reliability.

Melting points reported are uncorrected and were taken on either a Mel-Temp or a Thomas-Hoover Model 6406-H apparatus.

B. General apparatus and procedure of metalation reactions

A 500 ml three-neck round-bottom flask was fitted with a reflux condenser, a 250 ml pressure compensating dropping funnel capped with a rubber septum, and an inlet and outlet system to maintain an inert atmosphere of dry argon or nitrogen. The equipment was previously dried in a 140° oven and assembled while hot. It was then flame dried while a rapid flow of inert gas was maintained. A solution of 0.1 mole of substrate in 100 ml of cyclohexane was introduced into the flask. This solution was brought to reflux with a heating mantle and stirred with a magnetic stirrer. The alkyllithium reagent (0.1 mole) was introduced into the dropping funnel using a syringe, and subsequently dropped into the reaction mixture over a 15 min period. The reaction mixture was then refluxed with stirring for 10 h under an argon or nitrogen atmosphere.

A slightly modified procedure was used for metalation reactions carried out in the presence of TMEDA. The same apparatus was employed with a septum cap replacing the dropping funnel. After drying as before, 0.1 mole of TMEDA in 50 ml of cyclohexane was introduced into the reaction flask via a syringe. This solution was stirred at room temperature while 0.1 mole of the alkyllithium reagent was added slowly via syringe. To the resultant solution of the alkyllithium—TMEDA complex was added 0.1 mole of the substrate in 50 ml cyclohexane also with a syringe. The reactants were then stirred at room temperature under an argon or nitrogen atmosphere for 10 h.

At the end of the reaction period, the metalation reaction mixture was carbonated by slowly pouring onto a slurry of powdered dry ice in ether with vigorous stirring. A large excess of ether was necessary to obtain good yields of carbonation products from the metalation reactions in the presence of TMEDA. Approximately 200 ml of ether was added in excess of that required to cover the powdered dry ice for the carbonation of these reactions. When an insufficient amount of ether was utilized in the carbonation of the metalation reactions in the presence of TMEDA, the yields were sharply lowered. The carbonation of the metalation reactions in which TMEDA was not employed showed no sensitivity of the amount of ether employed.

C. Metalation of 3,5-diethylanisole with ethyllithium-1-^{14}C

3,5-Diethylphenol was prepared by the procedure of Jannasch and Rathjen [38] and was followed without modification. The crude product was recrystallized in petroleum ether (b.p. 40—60°) to give a 27% yield of white needles melting at 75—76°. Literature values for the melting point of 3,5-diethylphenol are 76° [39] and 77° [38].

The 3,5-diethylphenol was methylated according to a normal procedure [40] using sodium hydroxide and dimethyl sulfate. This product was purified by distillation in vacuo, and a center fraction collected from 138—140° at 16 mm represented a 91% yield. A literature boiling point was 115° at 16 mm [39]. GLC indicated the clear liquid product was pure and the NMR spectra confirmed the structure.

A glass breakseal ampule containing 50 microcuries of ethyl-1-^{14}C bromide was cooled in a dry ice—acetone bath. The seal was broken and the contents were rinsed successively with five ml portions of ethyl bromide until the volume was made up to 25.0 ml in a volumetric flask. A sample was counted by liquid scintillation and the specific activity calculated to be 9.75×10^8 counts/min/mole.

A mixture consisting of 4.4 g of a 50% by weight lithium dispersion (0.31 g atom) in pentane and 40 ml of cyclohexane was introduced into the reaction flask. This mixture was stirred rapidly while 9.0 ml (0.12 mole) of ethyl-1-^{14}C bromide in 30 ml of cyclohexane was dropped in over a 45 min period. An ice bath was applied when the reaction became too vigorous. After the addition of the ethyl-1-^{14}C bromide, the reactants were stirred at room temperature for 2 h. At this time 100 ml of cyclohexane was added, and the purple solution heated to dissolve a maximum of the sparingly soluble alkyllithium compound. The resultant solution was filtered through a glass wool plug into a 250 ml flask which had previously been dried and purged with argon. The flask was capped with a rubber septum and the straw-colored solution of ethyllithium-1-^{14}C analyzed to indicate that the 125 ml solution contained 0.09 moles of ethyllithium-1-^{14}C for a 75% yield based on starting ethyl-1-^{14}C bromide.

The metalation apparatus and procedure was employed as previously described. Two metalation reactions were carried out with 3,5-diethylanisole and ethyllithium-1-^{14}C in benzene solvent, one at the reflux temperature for 8 h (reaction A) and the other in like manner for 48 h (reaction B).

The metalation products were carbonated and worked up as described earlier. The crude carboxylic acid product from reaction A was recrystallized in pentane—carbon tetrachloride giving light yellow granular crystals with a melting point of 105—107°. After two sublimations at 92—93° and 0.1 mm, white crystals were obtained which melted at 107—108°. The literature melting point for the expected 2,4-diethyl-6-methoxybenzoic acid is reported to be 112.5—113.5° [41]. An NMR spectrum of the product in carbon tetrachloride confirmed the above structural assignment.

The unreacted 3,5-diethylanisole was recovered from the base insoluble organic phase. This fraction was evaporated to a small volume and distilled in vacuo. A product consisting of 1.83 g of 3,5-diethylanisole was collected at 118—119° and 4.7 mm.

The product 2,4-diethyl-6-methoxybenzoic acid and unreacted 3,5-diethylanisole were isolated from reaction B in similar fashion.

The labelled ethyl-1-^{14}C bromide, metalation product 2,4-diethyl-6-methoxybenzoic acid, and recovered 3,5-diethylanisole were counted on a Packard Tri-Carb Liquid Scintillation Spectrometer.

Both the 2,4-diethyl-6-methoxybenzoic acid and the recovered 3,5-diethylanisole showed a low but significant amount of activity. An additional sublimation of the acid from reaction A reduced the activity to approximately one-half of its former value. Since the ethyllithium-1-^{14}C had a high specific activity, a small amount of residual propionic-2-^{14}C acid was suspected to be responsible for the observed activity. The acid was dissolved in propionic acid and evaporated to dryness in vacuo several times. The resultant acid was twice sublimed at 95° and 0.1 mm to give white crystals with a melting point of 108—109°. The measured specific activity decreased significantly by this procedure and was only 3.6×10^5 counts/min/mole or 0.037% of the activity level of the starting ethyl bromide.

A somewhat higher level of activity was found in the recovered 3,5-diethylanisole (1.98×10^7 counts/min/mole or about 2.4% of the ethyl bromide activity). No detectable impurity was observed by GLC, NMR, or IR and the recovered 3,5-diethylanisole appeared identical to the authentic material. The sample was chromatographed through a Barber Coleman Series 5000 instrument with the Model 5190 radioactivity monitoring system. The radioactivity peaks were found not to coincide with the peak for 3,5-diethylanisole. In order to detect minute impurities the instrument was operated at a high sensitivity where the 3,5-diethylanisole peak was driven far off-scale. A small peak with a retention time of 16.2 min was found to contain approximately 70% of the measured radioactivity. The remainder of the detected activity was contained in a very small peak with a retention time of 14.0 min. The large peak for 3,5-diethylanisole occurred at a retention time of 19.8 min. The radioactivity monitor recorded no activity in this peak. Therefore, minute radioactive impurities were responsible for the activity found in the recovered 3,5-diethylanisole. The nature of these impurities was not been determined. The ethyl-1-^{14}C bromide was also analyzed by the above technique and no spurious activity peaks were observed.

The samples for reaction B were prepared and counted in an analogous fashion with results similar to those from reaction A.

A portion of each of the crude acid products from reactions A and B was methylated with diazomethane as previously described. The methyl esters were chromatographed on the Varian Aerograph 90-P with the SE-30 column operating at 185° and a flow rate of 150 cc/min. The gas chromatogram for reaction A exhibited a single peak with a retention time of 20.6 min. This peak was shown to be the methyl ester of 2,4-diethyl-6-methoxybenzoic acid. The chromatogram for reaction B exhibited a small peak with a retention time of 9.7 min and a much larger peak at 20.7 min. The small peak was identified as 3,5-diethylphenol using an authentic sample of the phenol. The large peak was again assigned to methyl 2,4-diethyl-6-methoxybenzoate. Thus the only position of attack in the metalation of 3,5-diethylanisole is in the 2-position.

A similar experiment in which 3,5-diethylanisole was metalated with the labelled EtLi in the presence of TMEDA showed similar results.

D. Metalation of m-t-butylanisole

The metalations were carried out as described under section A. Three conditions were evaluated (1) n-BuLi in cyclohexane, (2) t-BuLi in cyclohexane and (3) n-BuLi—TMEDA.

The crude carboxylic acid product from condition (1) was formed in 53% yield. The crude acid product was extracted with boiling hexane. Upon cooling, the solution deposited light yellow crystals with a melting point of 55—56°. Recrystallization from hexane gave white granular crystals with a melting point of 57—58°. An NMR spectrum of this material in carbon tetrachloride solution indicated its structure to be 2-methoxy-4-t-butylbenzoic acid. The spectrum exhibited a nine proton singlet for the t-butyl group at δ 1.33, a singlet of three protons at δ 3.99 assigned to the methoxy group, a complex multiplet of two protons at δ 6.86—7.13 and a one proton doublet centered at δ 7.86 for the aromatic protons, and a singlet of one proton at δ 10.30 for the carboxylic acid proton. The one proton doublet (J 8.5 Hz) at δ 7.86 was assigned to the proton on C-6, adjacent to the carboxyl group, based on its chemical shift. This proton is coupled with the proton on C-5, since it appears as a doublet with a coupling constant of 8.5 Hz which is characteristic of *ortho* aromatic protons. The proton on C-5 should also appear as a doublet. A complex multiplet at δ 6.86—7.13 consisted of a doublet at δ 6.98 superimposed on a doublet of doublets centered at δ 6.97. The doublet of doublets was assigned to the proton on C-5, since it has a coupling constant of 8.5 Hz arising from its coupling with the proton on C-6, and further fine splitting (J 1.5 Hz) from its interaction with the proton on C-3. The coupling constant of 1.5 Hz for the fine splitting is characteristic of *meta* coupling of aromatic protons. The doublet at δ 6.98 (J 1.5 Hz) also exhibited a proper coupling constant value for *meta* coupling and was assigned to the proton on C-3. These data are consistent with the expected product of *ortho*-metalation away from the t-butyl group, 2-methoxy-4-t-butylbenzoic acid. It should be pointed out that these NMR data are also consistent with 2-t-butyl-4-methoxybenzoic acid. However, the literature melting point for this compound is 113—114° [42] eliminating it as a possibility.

Since the 2-methoxy-4-t-butylbenzoic acid has apparently never been reported, a carbon—hydrogen analysis was obtained (Found: C, 69.34; H, 7.86 and C, 69.20; H, 7.69. $C_{12}H_{16}O_3$ calcd.: C, 69.21; H, 7.74%).

Yield of crude carboxylic acid mixture from conditions (2) was 73% and two runs under conditions (3) gave yields of 65 and 73%.

Product composition data (given in the discussion section) were obtained from GLC analysis of the mixed methyl esters using the Varian Aerograph 90-P with SE-30 column. The column temperature was 190° and the carrier gas flow rate was 125 cc/min. The chromatograms all showed a small peak with a retention time of 14.1 min and a much larger peak at 18.5 min. The large peak was attributed to methyl 2-methoxy-4-t-butylbenzoate, since the corresponding acid was isolated and characterized as above as the major reaction product. The smaller peak at 14.1 min was assigned to the other likely metalation product, methyl 2-methoxy-6-t-butylbenzoate, although direct experimental evidence was not obtained.

E. Metalation of 3-t-butyl-5-methylanisole

The 3-t-butyl-5-methylphenol was prepared by alkylation of *m*-cresol according to Chichibabin and Barkovsky [43] without modification. GLC analysis of the crude product revealed other isomers were present. The crude product was distilled in vacuo and a center fraction was collected from 130—145° at 5.0 mm. This fraction was redistilled using a six inch vigreux column. The center fraction of this distillation, collected at 150—155° and 10.5 mm, represented a 24% yield. This material gave a single peak on GLC analysis. NMR and IR data were consistent with the expected product. This compound was an oil and is reported in the literature as melting at 50° [43] and 40—41° [44].

Methylation to 3-t-butyl-5-methylanisole was by the usual procedure [40]. The crude product, isolated in 93% yield, was purified by distillation in vacuo through an 18 inch vigreux column. A center fraction was collected at 112—116° and 4.2 mm representing a 79% yield. However, GLC analysis revealed a slight impurity at a high retention time. A second distillation was carried out and a center fraction was collected at 120° and 8.0 mm. This fraction was shown to be pure by GLC analysis and was used for the subsequent metalation reactions. The literature boiling point for 3-t-butyl-5-methylanisole is 225—227° at 760 mm [45]. NMR data were consistent with 3-t-butyl-5-methylanisole.

Metalations were carried out with n-BuLi in cyclohexane in the presence and in the absence of TMEDA. Yields of crude carboxylic acid were 36 and 38% in duplicate runs without TMEDA and 59% in one run in the presence of the base.

The crude acid product from the metalations in the absence of TMEDA was extracted with boiling hexane which dissolved only a small amount of the material. The remaining product was recrystallized in benzene giving white granular crystals with a melting point of 177—178°. NMR data were used to assign the structure of this compound as the product of dimetalation, 2-carboxy-3-methoxy-5-t-butylphenylacetic acid. The NMR spectrum in trifluoroacetic acid exhibited a singlet of nine protons at δ 1.42 attributed to the t-butyl group. Two partially superimposed singlets appeared at δ 4.17 and 4.23 which integrated for a total of five protons. The singlet at δ 4.17 was approximately twice the intensity of the other and was assigned to the methoxy group. The lower intensity singlet at δ 4.23 was assigned to the benzylic protons. Two doublets of one proton each appeared at δ 7.21 and 7.32 and were assigned to the aromatic protons at C-4 and C-6. The *meta* coupling of 1.5 Hz for these doublets agree with this assignment. The signals for the acid protons were obscured by the solvent.

In order to observe the carboxylic acid protons, an additional NMR spectrum was obtained in acetone. This spectrum showed a nine proton singlet at δ 1.30 for the t-butyl group, a two proton singlet at δ 3.75 for the benzylic protons, a singlet of three protons at δ 3.86 for the methoxy group, a two proton singlet at δ 7.02 for the aromatic protons, and a broad singlet integrating for two protons at δ 8.08 assigned to the two carboxylic acid protons. The signal at δ 8.08 disappeared after the addition of one drop of deuterium oxide. The chemical shift of δ 8.08 for these carboxylic acid protons is an unusually high field position for acid protons.

The chemical shift of the benzylic proton signal provides evidence supporting the assigned structure. The chemical shift for the analogous protons of *m*-methoxyphenylacetic acid appear at δ 3.58 [46]. The observed chemical shifts of δ 4.23 and 3.75 for the benzylic protons of the product dicarboxylic acid indicate that the carboxyl group must be on the adjacent carbon, C-2. This deshielding effect would be absent in 3-methoxy-4-carboxy-5-t-butylphenylacetic acid and the benzylic proton signal would not be expected to appear at such a low field position as was observed. Therefore the NMR data are consistent only with the assigned structure of 2-carboxy-3-methoxy-5-t-butylphenylacetic acid.

Since no reference was found to this compound in the literature, a carbon—hydrogen analysis was obtained (Found: C, 63.27; H, 6.80. $C_{14}H_{18}O_5$ calcd.: C, 63.15; H, 6.81%.)

Conclusive chemical evidence for the assigned structure was obtained by the formation of the corresponding cyclic anhydride. Using the procedure of Price, Lewis and Meister [47], 0.4 g of 2-carboxy-3-methoxy-5-t-butylphenylacetic acid was refluxed in 2.0 g of acetyl chloride for 2 h. The resulting solution was cooled and the solid anhydride which precipitated was filtered and washed with pentane. The product was crystallized in hexane giving white needles with a melting point of 164—165°. The yield was 0.24 g representing a 64% conversion (Found: C, 67.78; H, 6.52. $C_{14}H_{16}O_4$ calcd.: C, 67.73; H, 6.50%.)

The crude product from metalation in the presence of TMEDA was soluble in boiling hexane. Upon cooling the solution yielded white crystals with a melting point of 138—140°. An additional recrystallization from hexane gave white needles melting at 144—145°. An NMR spectrum of a carbon tetrachloride solution of this product showed a singlet of nine protons at δ 1.29 for the t-butyl group, a three proton singlet at δ 2.40 for the methyl group, a singlet of three protons at δ 3.82 for the methoxy group, a singlet of two protons at δ 6.76 for the two aromatic protons, and a singlet of one proton at δ 12.4, assigned to the carboxylic acid proton. From the chemical shift of the methyl group, this product was identified as 2-methyl-4-t-butyl-6-methoxybenzoic acid. The methyl signal is shifted downfield by 6.0 Hz relative to the methyl signal in the NMR spectrum of 3-t-butyl-5-methylanisole. The chemical shift of the t-butyl signal was unaffected. Therefore, the carboxyl group must be adjacent to the methyl group as in the assigned structure. This compound has apparently never been reported (Found: C, 70.21; H, 8.30. $C_{13}H_{18}O_3$ calcd.: C, 70.24; H, 8.16%.)

The methyl esters from the metalation reactions were analyzed on the

Varian Aerograph 90-P using the Ap-L column. The column temperature was 220° and the carrier gas flow rate was 150 cc/min. The chromatograms of reactions carried out in the absence of TMEDA both showed a peak with a retention time of 56.6 min, a smaller peak at 61.2 min, and a much larger peak at 140.0 min. The large peak at 140.0 min was attributed to the methyl ester of the major reaction product, 2-carboxy-3-methoxy-5-t-butylphenylacetic acid. The chromatogram of the methyl esters of the metalation in the presence of TMEDA showed a large peak with a retention time of 56.6 min and a very small peak at 63.5 min. The large peak at 56.6 min represented the major reaction product, methyl 2-methyl-4-t-butyl-6-methoxybenzoate. The peak with the identical retention time of 56.6 min in the chromatograms of reactions in the absence of TMEDA was also shown to arise from methyl 2-methyl-4-t-butyl-6-methoxybenzoate by the addition of some of this compound. The small peaks at 61.2 min in one chromatogram and 63.5 min in the other chromatogram were assumed to be methyl 2-t-butyl-4-methyl-6-methoxybenzoate, the remaining probable metalation product.

F. Metalation of 2-methoxynaphthalene

Metalation with n-BuLi in ether—hexane gave a 70% yield of carboxylic acid mixture which melted in the range of 118—124°. Three crystallizations from benzene including one charcoal treatment gave 3-methoxy-2-naphthoic acid, m.p. 134—136°. Literature values range from 133—136° in four different citations [48].

Authentic 2-methoxy-1-naphthoic acid, the other product from the metalation, was kindly provided by Dr. D.C. Kleinfelter of these laboratories.

Metalation with n-BuLi in the presence of TMEDA gave a 78% yield of crude carboxylic acid mixture, melting in the range 115—125°.

GLC analysis of these and related runs in the naphthalene series were by the techniques given in section A and with the results cited in the discussion section.

G. Other Metalations

Results obtained on naphthalene, biphenyl, 3,5-dimethylanisole and 1,3-dimethoxybenzene involved well-characterized and often commercially available carboxylic acids, with GLC analysis of the methyl esters as described in section A.

H. Probe for free radical intermediate by CIDNP

Equimolar mixtures of alkyllithium and substrate were placed in NMR tubes. The tubes were previously dried in an oven at 140° and flushed with argon before use. Transfer of solutions to the tube were made in a nitrogen filled glove bag. Internal TMS standard was also added, and the spectra obtained in the tightly capped tubes. The substrates studied were (1) 1,4-dimethoxybenzene, (2) 1-methoxynaphthalene, (3) anisole, (4) *o*-methylanisole, (5) 3,5-dimethylanisole and (6) naphthalene. All were examined in cyclohexane solvent and (1), (2) and (6) were also run in THF. Repetitive scans were rapidly made of the spectral region of interest, usually the aromatic proton region. After failure to observe the CIDNP signals an equimolar amount of electron donor "catalyst" was added and the scans repeated. In none of the samples examined were any signals of enhanced absorption or emission observed. In many cases, however, rapid metalation was indicated by the appearance of new lines in the spectrum which were due to the metalation products. For example, 15 min after TMEDA was added to a mixture of n-butyllithium and 1,4-dimethoxybenzene, the integration trace indicated a 50% yield of metalation. With 1-methoxy-naphthalene and n-butyllithium, a 50% conversion was indicated 30 min after the addition of TMEDA.

References

1 D.A. Shirley and J.P. Hendrix, J. Organometal. Chem., 11 (1968) 217.
2 D.A. Shirley and K.R. Barton, Tetrahedron, 22 (1966) 515.
3 S. Gronowitz and K. Halvarson, Arkiv Kemi, 8 (1955) 343.
4 J.A. Dixon, D.H. Fishman and R.S. Dudinyak, Tetrahedron Lett., (1964) 613; R.L. Eppley and J.A. Dixon, J. Amer. Chem. Soc., 90 (1968) 1606.
5 H.W. Brown and R.C. Jones, J. Chem. Phys., 37 (1962) 2809.
6 A. Berg, Acta Chem. Scand., 10 (1956) 1362.
7 P.B. Ayscough, F.P. Sargent and R. Wilson, J. Chem. Soc., B (1966) 900.
8 H.R. Ward, Accounts Chem. Res., 5 (1972) 18.
9 H. Ward and R. Lawler, J. Amer. Chem. Soc., 89 (1967) 5518; R. Lawler, J. Amer. Chem. Soc., 89 (1967) 5519.
10 J.M. Mallen and R.L. Bebb, Chem. Revs., 69 (1969) 693; H. Gilman and J.W. Morton, Organic Reactions, 8 (1954) 258.
11 D.A. Shirley, J.R. Johnson and J.P. Hendrix, J. Organometal. Chem., 11 (1968) 209.
12 H.L. Lewis and T.L. Brown, J. Amer. Chem. Soc., 92 (1970) 4664.
13 T.L. Brown, Accounts Chem. Res., 1 (1968) 23.
14 Z.K. Cheema, G.W. Gibson and J.F. Eastham, J. Amer. Chem. Soc., 85 (1963) 3517.
15 A.W. Langer, Trans. N.Y. Acad. Sci., 27 (1965) 741.
16 S.V. Sunthanker and H. Gilman, J. Org. Chem., 16 (1951) 8.
17 R. Huisgen and H. Rist, Ann., 594 (1955) 137.
18 R.L. Gay and C.R. Hauser, J. Amer. Chem. Soc., 89 (1967) 2297.
19 T.H. Kinstle and J.P. Bechner, J. Organometal. Chem., 22 (1970) 497.
20 F.A. Settle, M. Haggerty and J.F. Eastham, J. Amer. Chem. Soc., 86 (1964) 2076.
21 H. Gilman and R.L. Bebb, J. Amer. Chem. Soc., 61 (1939) 109.
22 H. Gilman and S. Gray, J. Org. Chem., 23 (1958) 1476.
23 D.E. Grocock, T.K. Jones, G. Hallas and J.D. Hepworth, J. Chem. Soc. C, (1971) 3305.
24 D.W. Slocum and B.P. Koonsvitsky, J. Org. Chem., 38 (1973) 1675.
25 D.A. Shirley and C.F. Cheng, J. Organometal. Chem., 20 (1969) 251.
26 D.W. Slocum, G. Book and C.A. Jennings, Tetrahedron Lett., (1970) 3443.
27 B.M. Graybill and D.A. Shirley, J. Org. Chem., 31 (1966) 1221.
28 A.F. Halasa, J. Organometal. Chem., 31 (1971) 369.
29 A.J. Chalk and T.J. Hoogeboom, J. Organometal. Chem., 11 (1968) 615.
30 R. West and P. Jones, J. Amer. Chem. Soc., 90 (1968) 2656.
31 J.P. Hendrix, Ph.D. Dissertation, University of Tennessee, Knoxville, Tennessee, 1965.
32 L.M. Seitz and T.L. Brown, J. Amer. Chem. Soc., 88 (1966) 2174.
33 T.L. Brown, Accounts Chem. Res., 1 (1968) 23.
34 L.M. Seitz and T.L. Brown, J. Amer. Chem. Soc., 89 (1967) 1607.
35 D. Bryce-Smith, J. Chem. Soc., (1954) 1086.
36 R.A. Finnegan and J.W. Altschuld, J. Organometal. Chem., 9 (1967) 193.
37 H. Gilman and F.K. Cartledge, J. Organometal. Chem., 2 (1964) 447.
38 P. Jannasch and A. Rathjen, Ber., 32 (1899) 2391.
39 O. Kruber and H. Lauenstein, Ber., 81 (1948) 221.
40 H. Gilman, Organic Syntheses, Coll. Vol. I, J. Wiley and Sons, New York, 1944, p. 58.
41 F.P. Doyle, J.H.C. Nayler, H.R.J. Waddington, J.C. Hanson and G.R. Thomas, J. Chem. Soc., (1963) 497.
42 J.M.A. Baas and B.M. Wepster, Rec. Trav. Chim. Pays Bas, 86 (1967) 69.
43 A.E. Chichibabin and C. Barkovsky, Ann. Chim., 17 (1942) 349.
44 E.L. Eliel and F.J. Biros, J. Amer. Chem. Soc., 88 (1966) 3334.
45 B.M. Dubinin and N.E. Kozhevnikova, Zhur. Obschei Khim., 21 (1951) 662.
46 Sadtler NMR Spectrum No. 4228, Sadtler Research Laboratories, Philadelphia, Pa., 1968.
47 C.C. Price, F.M. Lewis and M. Meister, J. Amer. Chem. Soc., 61 (1939) 2760.
48 E. Bretscher, H.G. Rule and J. Spence, J. Chem. Soc., (1928) 1493; E.L. Eliel and T.E. Hoover, J. Org. Chem., 24 (1959) 938; G.B. Jambuserwala, S. Holt and F.A. Mason, J. Chem. Soc., (1931) 373; J. Jacques, Bull. Soc. Chim. France, (1951) 271.