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Directed Metalation Reactions. 7.[1] Directed Metalation of Methoxymethylferrocene: 2- and 1′-Metalated Ferrocene Intermediates

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Received August 13, 1974

A unique regiospecific metalation of a substituted ferrocene has been observed in the lithiation of methoxymethylferrocene (MMF, 1). Approximately equal amounts of 2- and 1′-monometalated intermediates were produced as judged by derivatization experiments. Among the most interesting of the new compounds isolated were 2- and 1′-chloromercurimethoxymethylferrocene (2-ClHg-MMF) and (1′-ClHg-MMF). 1′-ClHg-MMF underwent a transmetalation reaction with *n*-butyllithium to produce a unique ferrocenyllithium derivative, namely, 1′-lithiomethoxymethylferrocene (1′-Li-MMF). Also found to undergo 2 lithiation were ethyoxymethylferrocene (EMF, 5) and α-methoxyethylferrocene (MEF, 6). These results are interpreted in terms of coordination of oxygen with a lithium ion in the metalated intermediate.

The displacement of a hydrogen atom from a carbon–hydrogen bond by an alkali metal to give an organometallic intermediate, i.e., metalation, has become of increasing interest to organic chemists. In recent years, the ability of certain groups on aromatic systems to direct lithiation at a position "ortho" to the substituent has been demonstrated to be of synthetic utility, since such a procedure enables a chemist to produce "ortho" disubstituted products virtually uncontaminated by other isomers.[3] More recently, ortho metalation of aromatic systems by various transition metal derivatives has also received attention.[4]

Although many of the early reports focused on the directing ability of amines, several articles dealing with directed metalation of aromatic ethers also appeared. Notable among these were the early studies of Gilman and co-workers on the directed lithiation of dibenzofuran, anisole, and related ethers.[3a] Subsequent papers by other workers have contained suggested mechanism(s)[5a,b,6] and caveats[5c] for the observed ortho lithiation of aryl ethers and these contain estimates of contributions of coordination by oxygen to the overall transition state. In the preceding paper,[1] the methoxy group was found to be intermediate in directing ability among the group of nine directing substituents studied. Moreover, the methoxy group has also been found to direct metalation in other systems, namely, ferrocene[7] and naphthalene.[8] Some evidence for the importance of coordination in the mechanism of directed lithiation by the methoxy group has been inferred from the observed significant decrease in the extent of lithiation of the anisole nucleus by the presence of an ortho *tert*-butyl group.[9]

In our opinion, no unequivocal demonstration of a coordinating direction of lithiation by oxygen has ever been accomplished. Such an example is provided herein, namely, the formation of 2-Li-MMF and 1′-Li-MMF upon metalation of MMF with *n*-butyllithium. Both the regiospecificity of the metalation (no 3 metalation) as well as the observation that the rate is much faster and the extent greater than metalation of ferrocene itself under these conditions[10] dictate a decided

Table I. Time Study of the Metalation of Methoxymethylferrocene (MMF) and Condensation with Benzonitrile

Metalation period, h	% 1,2-disubstituted product isolated	% 1,1′-disubstituted product isolated
0.5	24.5	24.5
1	27.5	24.6
2	32.3	31.1
5	32.4	30.0
10	30.5	26.3
20	25.1	24.5

influence of the methoxymethyl group on the course of the reaction. The fact that the oxygen atom is "insulated" from the ferrocene residue by the presence of a methylene group rules out significant contribution of any type of through-bond electronic effect to the mechanism. Only a coordination contribution is left.

It is also interesting to note that no Wittig rearrangement products were detected during the course of these metalations. Such products have been isolated from lithiation of benzyl ethers.[6]

Results and Discussion

In the dimethylaminomethyl-,[11a] dimethylaminoethyl-,[11b] and *N*-ethylcarboxamidoferrocene systems,[12] metalation with *n*-butyllithium resulted in partitioning between the 2-metalated and 2,1′-dimetalated specie. For this reason, the expected products from the lithiation of MMF were to arise from 2-Li-MMF and 2,1′-diLi-MMF. In addition to products arising from the expected 2-lithio-MMF, concomitant 1′ metalation occurred as indicated by the isolation of six 1′-substituted MMF's in from 11 to 35% yield. This significant 1′ metalation of MMF appears to be a unique metalation pattern which presents the possibility of a new route to 1,1′-heteroannular disubstituted ferrocenes. These observations modify somewhat an earlier communication of ours[13] on this topic, a necessity which has already been alluded to in a paper by Valkovich, Gokel, and Ugi.[14]

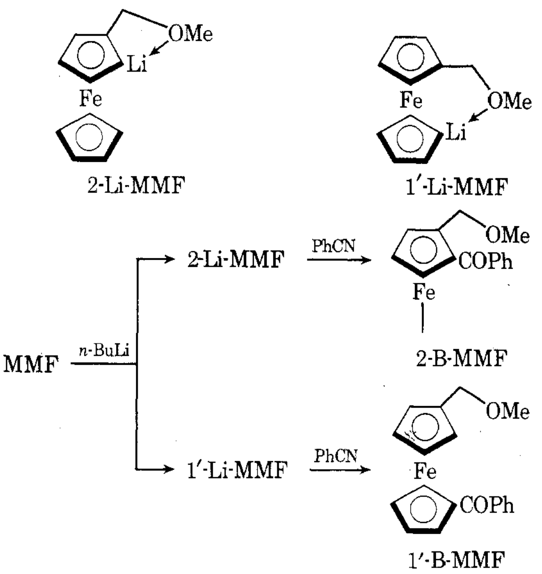
A time study of the metalation of MMF (Table I) indicated that the 2- and the 1′-lithio-MMF were formed at comparable rates and that these intermediates, once formed, were stable within periods of from 0.5 to 20 h. Surprisingly, no significant amounts of products stemming from 2,1′-dilithio-MMF were detected. These data were obtained by isolation of the two monobenzoyl derivatives, 2-B-MMF and 1′-B-MMF, since these isomers could be cleanly separated on a chromatography column. The inferred reaction sequence is outlined in Scheme I.

Condensation with phenyl isocyanate gave a 28% yield of 2-(*N*-phenylcarboxamido)methoxymethylferrocene (2-PC-MMF) and a 17.3% yield of 1′-(*N*-phenylcarboxamido)-methoxymethylferrocene (1′-PC-MMF). The lower yield observed in this reaction is more a demonstration of the difficulty encountered in the purification of these products than of the efficacy of the condensation itself.

The NMR spectrum of 2-PC-MMF displayed an AB quartet for the methylene protons. Magnetic nonequivalence of the methylene-group protons of 1,2-disubstituted ferrocenes was first examined in detail by Smith, McLesky, and Slocum[15] and renders support for the assignment of 1,2 disposition of the substituents in 2-PC-MMF. Magnetic nonequivalence was not observed in the other 1,2-disubstituted products because the resonances for the methylene protons were obscured by the resonances of the ferrocene moiety.

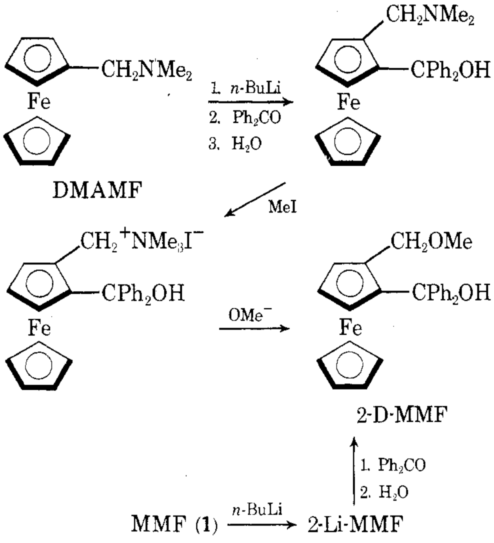
Condensation of the lithio intermediates with benzophenone was reexamined; this reaction also resulted in a mixture of the products from 2 and 1′ metalation. This is in contrast to our original report[13] in which it was claimed that only 2 lithiation of MMF was observed. The 1,1′ structure for 1′-(α,α-diphenylhydroxymethyl)methoxymethylferrocene was assigned on the basis of its elemental analysis, which indicated that the compound contained one diphenylhydroxymethyl group per molecule, and the absence of absorptions in the 9 and 10 μ region of its ir spectrum. Absorptions at 9 and 10 μ in the ir spectrum of a substituted ferrocene are indicative of the presence of at least one unsubstituted cyclopentadienyl ring.[16]

Scheme I



The 1,2 structure for 2-(α,α-diphenylhydroxymethyl)-methoxymethylferrocene (2-D-MMF) was assigned on the basis of its elemental analysis, the presence of absorptions at 9 and 10 μ in its ir spectrum,[16] and its identity with a sample of the known compound prepared by a route involving the 2 metalation of dimethylaminomethylferrocene (DMAMF).[11a] Since 2 metalation of DMAMF has been unequivocally demonstrated,[11a] the identity of the carbinol ethers prepared by both routes provides additional proof of the 2 metalation of MMF (1). Scheme II outlines both routes used in the synthesis of 2-D-MMF.

Scheme II



In the condensation with carbon dioxide and subsequent reaction with diazomethane, only 1′-(carbomethoxy)hydroxymethylferrocene (1′-C-HMF) was identified. Another

Table II. Products from the Metalation of Methoxymethylferrocene (MMF) and Condensation with Various Electrophilic Reagents

Condensing agent	2 or 1′ derivative	Metalation time, h	Condensation time, h	Yield, % 1,2	Yield, % 1,1′
PhCOPh	$-CPh_2OH$	2.5	4	32.5	34.9
$HgCl_2$	$-HgCl$	5.0	16	37.5	33.0
PhCN	$-COPh$	1.0	2	32.4	30.0
PhNCO	$-CONHPh$	2.0	16	28.8	17.3
1. CO_2 2. CH_2N_2	$-CO_2Me$[a]	3.0	1		15.0
$CH_2CH_2ONO_2$	$-NO_2$	2.5	2.5		10.7

[a] Methoxymethyl group was hydrolyzed during course of reaction and workup to hydroxymethyl group.

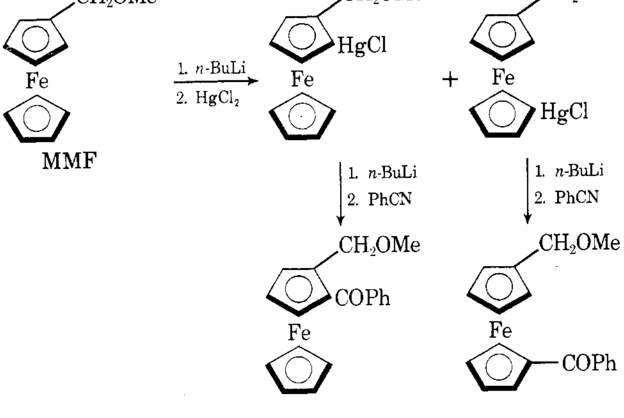
product, presumably the 1,2-disubstituted isomer, was isolated and an ir spectrum obtained, but the compound proved to be too unstable for further analysis. It is not known whether the methoxymethyl group in 1′-C-HMF was cleaved during carbonation, acidification, or chromatography of the product. It is interesting to note here that other attempts to cleave the ether function of several substituted methoxymethylferrocenes by acid or by reaction with lithium metal failed. The spontaneous cleavage which resulted in 1′-C-HMF appears to be a result of the inherent instability of this particular compound relative to its methyl ether under the reaction or isolation conditions utilized and does not constitute a general method of cleavage for ferrocenylmethyl ethers.

Another instance, where only the product resulting from 1′ metalation was isolated, was the condensation with ethyl nitrate to give 1′-nitromethoxymethylferrocene (1′-N-MMF). The 1,1′ structure was assigned on the basis of (1) an NMR spectrum which displayed two downfield two-proton triplets which were assigned to the four protons on the nitro-substituted ring and (2) the absence of absorptions at 9 and 10 μ in its ir spectrum. As was the case in the condensation with carbon dioxide, the isolation of only the 1,1′ derivative was probably due to the instability of the 1,2-disubstituted compound.

Derivatization with mercuric chloride produced 2-(chloromercuri)methoxymethylferrocene (2-ClHg-MMF) and 1′-(chloromercuri)methoxymethylferrocene (1′-ClHg-MMF). These compounds were particularly interesting because they were stable, crystalline solids. More important, the isolation of 1′-ClHg-MMF presented the possibility of the synthesis of 1,1′-disubstituted ferrocenes uncontaminated by the corresponding 1,2-disubstituted compound. It is known that the chloromercuri group in the ferrocene series can be transmetalated by *n*-butyllithium to give the corresponding lithio intermediate.[17]

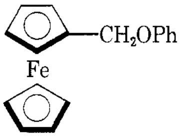
1′-ClHg-MMF was transmetalated by treatment with *n*-butyllithium to give 1′-Li-MMF uncontaminated by the 2-lithio isomer as demonstrated by derivatization with benzonitrile (Scheme III). No materials other than MMF and 1′-B-MMF were isolated from the chromatographic workup procedure. Use of 1′-ClHg-MMF as an intermediate in the synthesis of 1,1′-disubstituted ferrocenes thus appears feasible. Presumably, 2-ClHg-MMF could be utilized similarly.

Scheme III

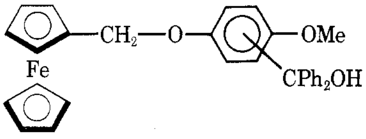


In none of the metalations of MMF were any products isolated which would have resulted from a Wittig rearrangement. Ustynyuk, Perevalova, and Nesmeyanov[18] have shown that the ferrocenylmethyl group stabilizes a carbanionic center to a lesser extent than does the benzyl group. It appears that the ring metalated intermediates formed from lithiation of MMF are more stable than the intermediate, α-Li-MMF, which would be formed prior to Wittig rearrangement. This is exactly the opposite of the stabilities of the anions in the corresponding benzene compounds.[19] A summary of the products from the metalation of MMF can be found in Table II.

In order to investigate the electronic requirements for the metalation of ferrocenylmethyl ethers, a number of related compounds were prepared, treated with *n*-butyllithium, and condensed with electrophilic reagents. Phenoxymethylferrocene (2) was allowed to react with *n*-butyllithium for from 2 to 22 h in several experiments, and was condensed with benzophenone or dry ice. From these reactions only phenoxymethylferrocene itself was recovered. An attempt was made to increase the coordinating ability of the phenoxy group by the placing of a *p*-methoxy electron-donating group of the phenyl nucleus. *p*-Methoxyphenoxymethylferrocene (3) was found to undergo metalation only in the benzene ring to give, upon condensation with benzophenone, the carbinol **4.** It is probable that metalation took place ortho to the methoxy group, since the methoxy group is a known director, but this assignment cannot be substantiated at present.



2



4

Ethoxymethylferrocene (EMF, **5**) was metalated and condensed with benzophenone. The derivative was found to be 2-(α,α-diphenylhydroxymethyl)ethoxymethylferrocene by its identity with a compound previously studied in our group.[20] No 1′-substituted product was isolated from this reaction.

Substitution of one of the α hydrogens in MMF as in the compound α-methoxyethylferrocene (**6**) apparently brought significant steric hindrance to the transition state for 2 metalation. Only a 1.7% yield of this lithio intermediate could be detected by carbonation.[21]

Experimental Section

General. All lithiation reactions were run under an atmosphere of argon. *n*-Butyllithium (1.6 M in hexane) used in the following reactions was purchased from the Foote Mineral Co. *N,N,N′N′*-

Tetramethylethylenediamine (TMEDA) (bp 120–122 °C) was obtained from Aldrich Chemical Co. and was redistilled. The fraction of bp 120.5–121.0 °C was collected and was stored over Linde 4A molecular sieves. Ether used as a reaction solvent was Matheson Coleman and Bell "absolute" grade and was stored over Linde 4A molecular sieves.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratory, Mulheim, West Germany. Melting points were determined on a Hoover melting point apparatus and were corrected. Column chromatographies were performed on Matheson Coleman and Bell activated alumina using distilled solvents.

All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord spectrometer using the 6.246-μ band of polystyrene as a reference. NMR spectra were obtained on a Varian A-56/60 spectrometer and a Varian HA-100 using Me_4Si as an internal standard. Physical data of the new compounds isolated can be found in Table III and ir and NMR spectral data for these compounds in Table IV (see paragraph at end of paper regarding supplementary material).

General Lithiation and Condensation Procedure. Methoxymethylferrocene (MMF, 5 mmol) in 100 ml of dry ether was treated dropwise with 8 mmol of 1.6 M *n*-butyllithium in hexane and metalation was allowed to proceed with stirring at 25 °C for 1–5 h. At this point, the condensing agent (8 mmol) in 25 ml of ether was added; the solution was then stirred for an additional 1–15 h. After hydrolysis with 25 ml of water, the aqueous layer was separated and extracted twice with ether and the combined ether extracts dried over anhydrous $MgSO_4$. After removal of the ether the oils were chromatographed on alumina with methylene chloride/petroleum ether as eluent.

Transmetalation of 1′-ClHg-MMF. Condensation with Benzonitrile. 1′-ClHg-MMF (0.46 g, 1.0 mmol) in dry ether was treated with 1 ml (1.6 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred for 1 h whereupon 0.3 g (3.0 mmol) of benzonitrile was introduced. After stirring for 2 h the reaction mixture was hydrolyzed with 20 ml of water. The aqueous and ether layers were separated, the aqueous layer extracted twice with ether, and the combined ether extracts dried over anhydrous $MgSO_4$. This solution was filtered and the solvent stripped under vacuum to afford a brown oil which was chromatographed on alumina II with CH_2Cl_2/petroleum ether as eluent. MMF (0.15 g, 65%) was eluted with 10% CH_2Cl_2/petroleum ether. A second fraction which was eluted with 30% CH_2Cl_2/petroleum ether gave a red oil upon removal of solvent. An ir spectrum of this oil was identical with that of 1′-B-MMF prepared via the original lithiation route. The yield was 0.1 g (30%).

***p*-Methoxyphenoxymethylferrocene (3). A. Preparation of *p*-Methoxyphenoxymethylferrocene (3).** *p*-Methoxyphenol (70.25 g, 0.566 mol) in a minimum amount of dry ether was lithiated with 100 ml (0.16 mol) of 1.6 M *n*-butyllithium in hexane. This solution was added to a mixture of the methiodide of dimethylaminomethylferrocene (56.25 g, 0.146 mol)[24] in 1 l. of water. The ether was evaporated, and the resulting mixture refluxed for 5 h and allowed to cool. This mixture was extracted several times with ether, and the combined extracts were washed with 5% NaOH solution.

After evaporation of this ether solution under vacuum, a solid was obtained which was recrystallized from hexane (yield 25.5%).

B. Metalation of *p*-Methoxyphenoxymethylferrocene (3). Condensation with Benzophenone to Produce the Diphenylcarbinol Derivative 4. *p*-Methoxyphenoxymethylferrocene (1.61 g, 5.0 mmol) dissolved in 125 ml in dry ether was treated with 1.6 M *n*-butyllithium (3.1 ml, 4.8 mmol) in hexane. The mixture was stirred for 5.5 h, whereupon an ether solution of benzophenone (3.64 g, 20 mmol) was added with stirring being continued overnight. Water was added and the layers were separated. The aqueous layer was extracted twice with ether and the combined ether extracts were dried over anhydrous $MgSO_4$. After filtration and stripping of the solvent, an oil was obtained which was chromatographed on alumina III with CH_2Cl_2/petroleum ether as eluent. After a forerun of benzophenone, a fraction was eluted with 10% CH_2Cl_2/90% petroleum ether which was found to be ether 3 (recovery 0.30 g, 19%). Fraction 2 which was eluted with 30% CH_2Cl_2/70% petroleum ether gave a yellow solid upon evaporation, mp 139–141 °C, after being chromatographed several times and then recrystallized from hexane (yield 0.25%). NMR and elemental analysis data indicated that condensation and, therefore, metalation had taken place on the benzene ring to produce diphenylcarbinol 4.

Lithiation of Ethoxymethylferrocene (5). Condensation with Benzophenone to Produce 2-(α,α-Diphenylhydroxymethyl)-ethoxymethylferrocene (2-D-EMF). EMF (2.44 g, 10 mmol) in 100 ml of dry ether was treated with 10 ml (16 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred at room temperature for 5 h. After this time, benzophenone (5.9 g, 32 mmol) in ether was added. After the solution had been stirred for 4 h, water was added, the layers separated, the aqueous layer extracted twice with ether, and the ether combined extracts dried over anhydrous $MgSO_4$. The solution was filtered and stripped of solvent with the resulting oil being crystallized by trituration with petroleum ether. A yellow solid was obtained (yield 31%). Its ir spectrum was identical with that of a known sample of 2-D-EMF.[20]

Table III. Physical Data

Registry no.	Compd[a]	Molecular formula	Mp, °C
59922-65-5	2-B-MMF	$C_{19}H_{18}O_2Fe$	Oil
59922-66-6	1′-B-MMF	$C_{19}H_{18}O_2Fe$	Oil
59922-67-7	2-PC-MMF	$C_{19}H_{19}O_2NFe$	Oil
59922-68-8	1′-PC-MMF	$C_{19}H_{19}O_2NFe$	Oil
32914-68-4	2-D-MMF	$C_{25}H_{24}O_2Fe$	109–111
51178-07-5	1′-D-MMF	$C_{25}H_{24}O_2Fe$	Oil
59922-69-9	1′-C-HMF	$C_{13}H_{14}O_3Fe$	Oil
59922-70-2	1′-N-MMF	$C_{12}H_{13}O_3NFe$	64–66
59922-71-3	1′-ClHg-MMF	$C_{12}H_{13}OClHgFe$	105.5–106.5
59922-72-4	2-ClHg-MMF	$C_{12}H_{13}OClHgFe$	152–154
59922-73-5	3		98–100
59922-79-1	4		139–141
59922-74-6	2-D-EMF		123–125.5
59922-75-7	2-ME-FCA		202 dec

[a] All materials except 2-D-EMF and 2-ME-FCA purified by column chromatography. [b] Satisfactory analytical data (±0.3% for C, H, and in certain cases for N, Fe, and Cl) were obtained with the following exceptions: 2-D-MMF, Fe, 13.09 (13.55); 4, C, 73.24 (73.67). Elemental analyses were not obtained for 2-PC-MMF, 2-D-EMF, and 2-ME-FCA.

Metalation of α-Methoxyethylferrocene (MEF, 6). Condensation with Carbon Dioxide to Produce 2-(α-Methoxyethyl)-ferrocene carboxylic Acid (2-ME-FCA). MEF[25] (4.9 g, 0.02 mol) in 200 ml of absolute ether was treated with 25 ml (0.04 mol) of 1.6 M *n*-butyllithium in hexane and the resulting solution stirred for 4 h. The reaction mixture was poured over dry ice/ether and after a time extracted with base. This basic solution was then washed with ether. The combined ether extracts were dried, filtered, and evaporated under vacuum. An oil was obtained which was redissolved in ether. Upon cooling this solution a precipitate appeared which was isolated by suction filtration. Ir and NMR data were consistent with the structure 2-(α-methoxyethyl)ferrocenecarboxylic acid (yield 17%). An analysis was not obtained.

Acknowledgments. We are grateful for partial support of this research by the Office of Research and Projects, Southern Illinois University, and to Dr. C. A. Jennings for help in the preparation of this manuscript.

Registry No.—**1**, 12153-89-8; **2**, 34871-88-0; **5**, 31724-98-8; **6**, 12512-90-2; carbon dioxide, 124-38-9; benzophenone, 119-61-9; ethyl nitrate, 625-58-1; mercuric chloride, 7487-94-7; *p*-methoxyphenol, 150-76-5; dimethylaminomethylferrocene methiodide, 12086-40-7; phenyl isocyanate, 103-71-9; benzonitrile, 100-47-0.

Supplementary Material Available. Table IV, ir and NMR spectral data of 1,2- and 1,1-disubstituted ferrocenes (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) For part 6 in this series, cf. D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, preceding paper in this issue.

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(21) Mention must be made here that Valkovitch et al.[14] also metalated ether **6** with *n*-butyllithium and have reported isolation of significant yields of all three possible ring metalated derivatives upon condensation with benzophenone. Such discrepancy in yields from the same metalated intermediate is not as unusual as it may seem. We are prompted to report here some unpublished studies[22] involving carbonation of commercial phenyllithium (Ventron Corp.). Repeated attempts to effect this carbonation, either by bubbling CO_2 through the phenyllithium or by pouring the phenyllithium solution over dry ice/ether, afforded only low yields of benzoic acid (<20%). On the other hand, condensation of this same phenyllithium solution with benzophenone under various conditions brought routinely yields of 60–70% of triphenylcarbinol. A similar study by Gilman and co-workers[23] has been published.

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Directed Metalation Reactions. 8.[1] Directed Metalation of 3-Mono- and 2,5-Disubstituted Thiophenes

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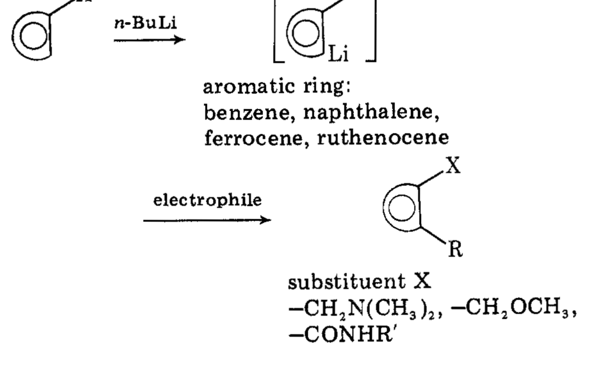
Received August 13, 1974

Regiospecific 2 metalation of thiophene has long been known. In this study we have examined the metalation with *n*-butyllithium of thiophenes containing a substituent that directs metalation such that a competition between the directing properties of the sulfur and the substituted group was set up. Results were as follows: (1) 2-Substituted thiophenes were lithiated in the 5 position, i.e., the sulfur atom controlled the site of metalation; (2) if the 5 position was blocked, 3 lithiation was observed; (3) 3-substituted thiophenes were lithiated in the 2 position, a site common to the directing properties of both the substituent and the sulfur moiety. Each of these metalations was surprisingly regiospecific. These lithiation pathways were explored via a number of derivatization and cyclization experiments and can be utilized in the synthesis of a wide variety of 2,3-disubstituted thiophenes. An intriguing dimerization of *N,N*-dimethyl-3-thiophenecarboxamide (**5**) in the presence of *n*-butyllithium to 4,8-dehydrobenzo[1,2-*b*:4,5-*b′*]dithiophene-4,8-dione (**5a**) was discovered.

Directed metalation of *N,N*-dimethylbenzylamine,[3] its ferrocene analogue,[4] and a number of related amines with subsequent treatment with electrophilic reagents has provided a general route to a variety of aromatic amines substituted exclusively in the 2 position.[5] In the preceding paper of this series[1] similar results are recorded for the directed lithiation of methoxymethylferrocene, thereby establishing unequivocally that the ether analogue of the dimethylaminomethyl group can also direct metalation. The 2-metalating ability of the N-substituted carboxamide group on benzene[6] and ferrocene[7] has also been reported. A generalized picture of these transformations is summarized in eq 1.



(1)

The ability of the directed metalation reaction to produce ortho-disubstituted products uncontaminated by other isomers would possess significant synthetic potential for other aromatic systems, notably heterocycles. In this study the utility of this method for the preparation of specific di- and trisubstituted thiophenes is described. These results can be contrasted to those for the electrophilic substitution of thiophenes. Generally for 2-substituted thiophenes, varying amounts of 2,5- or 2,4-disubstituted compounds are obtained depending on the competitive directing influence of the ring sulfur and the 2 substituent.[8] The yield of 2,3-disubstituted thiophenes is improved somewhat for 3-substituted compounds containing ±I + M substituents. For example, 3-methylthiophene gives upon acylation a mixture consisting of 80% 3,2 isomer and 20% 3,5 isomer.[9]

Ideally, directed metalation of a 2-substituted thiophene to give a 3-lithio intermediate would be most desirable, since 2-substituted thiophenes are much more readily available as starting materials. In no instance during this study was this lithiation pattern for 2-substituted thiophenes realized; rather 5 metalation was observed. This suggests that the thiophene sulfur is a stronger director than the carboxamide and dimethylaminomethyl groups, which are among the strongest directors known.[10] Likewise the 2-alkylsulfonamides were found to be weaker directors than the thiophene sulfur, although other reactions at times ensued upon metalation of