Directed Metalation Reactions. III.[1] Contribution of Oxygen Coordination in the Lithiation of *o-tert*-Butylanisole

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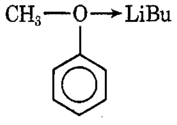
In order to ascertain the role played by coordination of the lithium ion with the oxygen atom in the metalation of anisole, *o-tert*-butylanisole was metalated with *n*-butyllithium and the position of metalation was determined. *o-tert*-Butylanisole was found to undergo metalation ortho to the methoxy group in 7.5% yield under similar conditions, which gave a 65% yield of ortho metalation of anisole itself. Addition of tetramethylethylenediamine (TMEDA), a reagent known to increase the metalating ability of *n*-butyllithium, brought about 30% metalation of *o-tert*-butylanisole. These results are attributed to steric interference by the *tert*-butyl group with the relevant coordinated intermediate; the fact that a small amount of ortho metalation was still observed is suggested to arise from the inductive effect of the methoxy group at that position.

There has been considerable speculation concerning the mechanism of the directed metalation reaction, this being one in which the alkali metal atom replaced a hydrogen at a position adjacent to the substituent on an aromatic ring. One of the primary questions raised has been the role that the heteroatom plays in such metalations. In 1946[2] it was proposed that during these metalations a coordinated complex, **1**, was formed between the heteroatom and alkyllithium reagents. Finnegan and Altshuld[3] viewed such coordination of the metal atom with the donor atom as increasing the electron-withdrawing inductive effect of the coordinating substituent. A transition state, **2**, was drawn which seemed to imply both coordination and concertedness. Thus both coordination and induction have been suggested to explain the role of the heteroatom in directed metalations.



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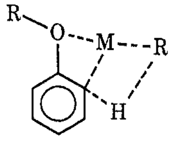

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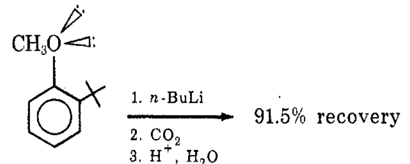
Shirley and Hendrix[4] investigated the metalation of anisole and *tert*-butyl phenyl ether with *n*-butyllithium and *tert*-butyllithium. The virtually exclusive ortho metalation observed in these reactions was interpreted to mean that such reactions had low steric requirements. These workers proposed that this low steric requirement of the metalation reaction was in disagreement with the concept of a cyclic transition state formed from a coordination complex of RLi with the heteroatom and have suggested a mechanism involving prior ionization of the metalating reagent with subsequent formation of a radical anion of the aromatic ring. This mechanism was felt to offer a better explanation of the apparent lack of steric effect observed in these systems.

Three alternative interpretations of these results of Shirley and Hendrix[4] are also possible. First, *n*-butyllithium is known to exist as a tetramer or hexamer in solution and *tert*-butyllithium has been found to be a tetramer in solution.[5] If the metalation reaction takes place with these polymeric species, rather than with the monomer, then there is very little steric difference between *n*-butyllithium and *tert*-butyllithium. Second, the greater base strength of *tert*-butyllithium may balance its possibly greater steric demand. Third, models have shown that if the methyl group of anisole is replaced by a *tert*-butyl group, there is very little additional steric interaction with the alkyllithium oligomer.

In order to ascertain the role coordination plays in the metalation reaction in the anisole system, it was decided to metalate a compound in which the possibility for coordination had been markedly reduced with respect to anisole. The compound chosen was *o-tert*-butylanisole (**3**). Space-filling models of this compound showed that the *o-tert*-butyl group restricts the possible conformers of **3** and should result in a steric hindrance to complexation.

Results and Discussion

Metalation of *o-tert*-butylanisole (**3**) with *n*-butyllithium in refluxing ether for 22 hr and condensation with Dry Ice resulted in a 91.5% recovery of starting material (eq 1). Under similar conditions, anisole is converted to the ortho acid in 65% yield.[6] This is a marked reduction in reactivity relative to anisole.



3 (1)

Similarly, ether **3** was metalated under the same conditions and treated with trimethylsilyl chloride. The product which was isolated by vpc in 7.5% yield, was identified as a 1,2,3-trisubstituted benzene by absorptions at 5.20, 5.40, and 5.70 μ in its ir spectrum. Differentiation between **4** and **5** could not be made on these grounds. On steric grounds, however, the structure **5** is most unlikely.[7] A metalation was run for 10 hr with otherwise identical experimental conditions to check

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[1] For parts I and II of this series *cf.* (a) D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971); (b) D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organometal. Chem.*, **38**, 125 (1972).

[2] J. D. Roberts and D. Y. Curtin, *J. Amer. Chem. Soc.*, **68**, 1658 (1946).

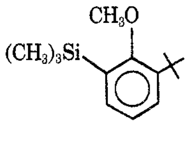
[3] R. A. Finnegan and J. W. Altshuld, *J. Organometal. Chem.*, **9**, 193 (1967).

[4] D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 217 (1968).

[5] L. D. McKeever and R. Waack, *Chem. Commun.*, 751 (1969).

[6] D. A. Shirley, J. R. Johnson, Jr., and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 209 (1968).

[7] C. D. Broaddus, *J. Org. Chem.*, **35**, 10 (1970).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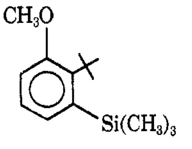
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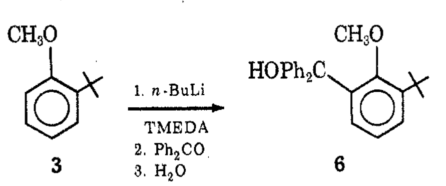
that metalation was not taking place over a shorter period, but no product was detected by vpc analysis.

The reaction of ether **3** with *n*-butyllithium and an equimolar amount of TMEDA gave a 30% yield of this same product after a 1-hr metalation period. This is in agreement with the results of Slocum, Book, and Jennings,[8] who found that TMEDA significantly increased the rate and yields of a number of directed metalation reactions.

The metalation of ether **3** with *n*-butyllithium and TMEDA followed by condensation with benzophenone gave a 25% yield of **6** (eq 2). The structure of **6** was determined by a number of observations. Molecular models show that the anisotropic effect of two phenyl groups of an ortho-situated diphenylhydroxymethyl group should exert a distinct upfield shift on neighboring methyl resonances.[9] In the case of **6**, an upfield shift of τ 0.73 was noted for the methoxy group relative to the methoxy group of *o-tert*-butylanisole itself, supporting the validity of the structure assigned. An ir spectrum of this product showed absorptions at 5.10, 5.31, and 5.53 μ, indicative of 1,2,3-trisubstitution. This also reinforces our arguments for structure **4** being the product of the reaction of metalated ether **3** with trimethylsilyl chloride.



3 6 (2)

Concern may be expressed that the large reduction in rate of metalation of *o-tert*-butylanisole (**3**) with respect to anisole might be due to the electronic effect of the *tert*-butyl group. Although there are a number of examples of the reduction of the yields of a metalation reaction by the introduction of an alkyl substituent,[10,11] there is no precedent for an effect as large as observed here. The extreme reduction in the rate of metalation of *o-tert*-butylanisole (**3**) as compared to anisole represents another example of a reaction where a lower conversion may be explained by steric hindrance to complexation. The fact that metalation of ether **3** still occurred ortho to the methoxy group can be explained as a result of the inductive effect of the methoxy group. The increase in the rate and yield of metalation with TMEDA is probably due to the reactivity of the TMEDA-complexed (monomeric) alkyllithium being much greater than that of polymeric *n*-butyllithium. This reactive species may not need to form a complex with the heteroatom to effect metalation. The site of metalation is still ortho to the methoxy group, probably as a result of the fact that the inductive effect of the oxygen atom is strongest at that position.

Experimental Section

General.—*n*-Butyllithium (1.6 *M* in hexane) was purchased from the Foote Mineral Co. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA), bp 120–122° (Aldrich Chemical Co.), was distilled and the fraction of bp 120.5–121.0° was collected. The redistilled TMEDA was stored over Linde 4A molecular sieves. The 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. Gas chromatography was performed on a 6-ft, 6% Apiezon L on 60–80 mesh Chromosorb W column at 155°, helium flow rate 60 cc/min. All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord using the 6.246-μ band of polystyrene as a reference. The nmr spectra were obtained on a Varian A-56/60 spectrometer and a Varian HA-100 using TMS as an internal standard.

Metalation of *o-tert*-Butylanisole[12] (3). Condensation with Dry Ice.—In a flame-dried flask were placed *o-tert*-butylanisole (**3**) (3.28 g, 0.02 mol) and ether (100 ml). Under an argon atmosphere, 12 ml (0.019 mol) of 1.6 *M* *n*-butyllithium in hexane was slowly dripped in and the mixture was refluxed for 22 hr. The reaction mixture was cooled to −70° and poured into a Dry Ice–ether slush. The mixture was allowed to come to room temperature and the ether layer was separated and washed with base. The ether layer was dried over $MgSO_4$ and stripped to give *o-tert*-butylanisole (**3**) (recovery 2.98 g, 91.5%). The basic wash was acidified and extracted with ether and the ether layer was dried over $MgSO_4$ and stripped. An nmr spectrum of the resultant oil showed faint signals around τ 3, ample signals in the alkyl region, and a strong odor of valeric acid.

Metalation of *o-tert*-Butylanisole (3). Condensation with Trimethylsilyl Chloride to Produce 2-*tert*-Butyl-6-trimethylsilylanisole (4).—*o-tert*-Butylanisole (**3**) (3.28 g, 0.02 mol) was dissolved in 100 ml of dry ether. Under an argon atmosphere, 12 ml (0.019 mol) of 1.6 *M* *n*-butyllithium in hexane was added and the mixture was refluxed for 22 hr. The mixture was cooled to 0° and trimethylsilyl chloride (3.0 g, 0.0278 mol) was added over a 15-min period. The reaction was allowed to come to room temperature and was stirred for an additional 5 hr. After the reaction had been hydrolyzed with approximately 20 ml of water, the ether layer was separated and dried over $MgSO_4$ and the solvent was stripped. The resulting liquid was analyzed by vpc. The first peak was identified by its retention time as recovered *o-tert*-butylanisole (**3**). The peak whose retention time was 8.0 min with respect to *o-tert*-butylanisole was isolated. Nmr and elemental analysis data of this compound were consistent with the structure 2-*tert*-butyl-6-trimethylsilylanisole (**4**) (yield 7.2% by vpc analysis): ir 8.00 ($-OCH_3$), 8.20 [$C(CH_3)_3$], 5.20, 5.40, 5.70 μ (1,2,3-trisubstituted benzene); nmr (CCl_4) τ 2.66–3.25 (multiplet, 3.2 protons, C_6H_3-), 6.28 (singlet, 2.9 protons, $-OCH_3$), 8.59 [singlet, 9.1 protons, $-C(CH_3)_3$], 9.62 [singlet, 8.8 protons, $Si(CH_3)_3$].

Anal. Calcd for $C_{14}H_{24}OSi$: C, 70.91; H, 10.20. Found: C, 71.05; H, 10.30.

Metalation of *o-tert*-Butylanisole (3) with *n*-Butyllithium and TMEDA. Condensation with Trimethylsilyl Chloride to Produce 2-*tert*-Butyl-6-trimethylsilylanisole (4).—*o-tert*-Butylanisole (**3**) (3.28 g, 0.02 mol) and TMEDA (2.22 g, 0.0192 mol) were dissolved in 50 ml of dry ether. Under an argon atmosphere, 12 ml (0.0192 mol) of 1.6 *M* *n*-butyllithium in hexane was added. The mixture was refluxed for 1 hr and cooled to 0° and 3.0 g (0.0278 mol) of trimethylsilyl chloride was added slowly. After the mixture was stirred for an additional 4 hr at room temperature, the reaction was hydrolyzed with 20 ml of water, the layers were separated, and the ether layer was dried over $MgSO_4$ and stripped. The first peak was identified by its retention time (3.1 min with respect to ether), which was identical with that of *o-tert*-butylanisole (**3**). The peak whose retention time was 8 min with respect to *o-tert*-butylanisole was identified as 2-*tert*-butyl-6-trimethylsilylanisole on the basis of this retention time and on the fact that its nmr and ir spectra were identical with those of **4** prepared above (yield 28.8% by vpc analysis).

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[8] D. W. Slocum, G. Book, and C. A. Jennings, *Tetrahedron Lett.*, 3443 (1970).

[9] D. W. Slocum and C. A. Jennings, *J. Chem. Soc. Chem. Commun.*, 54 (1972).

[10] D. A. Shirley and E. A. Lehto, *J. Amer. Chem. Soc.*, **79**, 3481 (1957).

[11] M. Hallet and R. Huls, *Bull. Soc. Chim. Belg.*, **61**, 33 (1952).

[12] I. J. Borowitz and G. J. Williams, *J. Org. Chem.*, **31**, 603 (1966).

Metalation of *o-tert*-Butylanisole (3) with *n*-Butyllithium and TMEDA. Condensation with Benzophenone to Produce 2-*tert*-Butyl-6-diphenylhydroxymethylanisole (6).—*o-tert*-Butylanisole (3) (3.28 g, 0.02 mol) was dissolved in 50 ml of dry ether. TMEDA (2.22 g, 0.0192 mol) was added, and under an argon atmosphere 12 ml (0.0192 mol) of 1.6 *M* *n*-butyllithium was slowly added. The mixture was stirred for 1 hr and treated with benzophenone (3.5 g, 0.0192 mol) in 20 ml of ether. The mixture was stirred for 4 hr and hydrolyzed with 20 ml of water. The ether layer was separated, washed with water, dried over $MgSO_4$, and stripped. The resulting oil was purified by heating in a steam bath overnight at 0.01 mm to remove unreacted *o-tert*-butylanisole (3) and benzophenone. An ir of the resulting oil indicated that some benzophenone still remained. The oil was subjected to steam distillation until an ir spectrum of the residue indicated that all the benzophenone had been removed. The absence of any definitive absorptions in an nmr spectrum of this residue indicated that it was contaminated by some paramagnetic material, probably a result of the steam distillation. The oil was dissolved in ether and washed through a column of sand and magnetic stirring bars. Upon removal of the solvent an oil resulted and the nmr and elemental analysis data given below were consistent with the structure 2-*tert*-butyl-6-diphenylhydroxymethylanisole (6) (yield 1.73 g, 25%): ir 2.94 (–OH), 5.10, 5.31, 5.53 (1,2,3-trisubstituted benzene), 7.90 ($-OCH_3$), 8.20 μ [$-C(CH_3)_3$]; nmr ($CDCl_3$) τ 2.59–3.63 (multiplet, 13.9 protons, $HO(C_6H_5)_2CC_6H_3-$), 6.96 (singlet, 3.2 protons, $-OCH_3$), 8.58 [singlet, 8.9 protons, $-C(CH_3)_3$].

Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.02; H, 7.56. Found: C, 82.96; H, 7.75.

Registry No.—**3**, 2944-48-1; **4**, 38661-99-3; **6**, 38662-00-9; trimethylsilyl chloride, 75-77-4.

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Directed Metalation Reactions. IV.[1] 2-Metalation of N-Substituted Ferrocenecarboxamides

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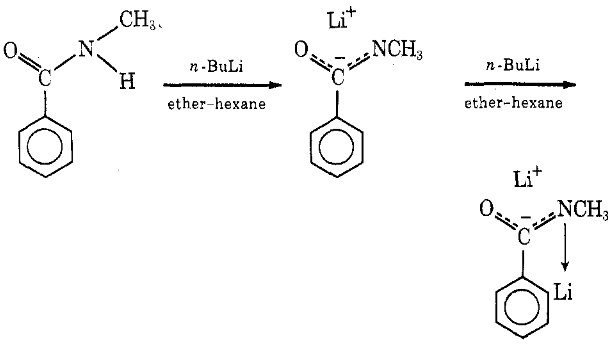
Demonstration of the 2-metalating ability of the N-substituted carboxamide group in ferrocene is presented. By means of the 2-lithiated intermediate a series of 1,2-disubstituted ferrocenes, where one of the substituents is the carboxamide group, has been prepared. That this procedure will be useful for the preparation of 2-substituted ferrocenecarboxylic acids has been shown by the three-step synthesis, starting from ferrocene, of 2-methylferrocenecarboxylic acid.

Puterbaugh and Hauser in 1963[2] demonstrated the interesting phenomenon of the directing ability of the methyl amide substituent in the 2-metalation of the benzene nucleus. This served to extend the original observation from the Hauser group of the directing ability of the dimethylaminomethyl substituent in both the benzene[3] and ferrocene[4] systems. Metalation of the amide functional group was postulated to occur by successive removal of two protons: the first from the monosubstituted amide group to produce a resonance-stabilized anion; the second from the 2 position of the benzene ring, with a coordinated lithio intermediate similar to that described for the 2-lithiation of aromatics containing the dimethylaminomethyl substituent being proposed (Scheme I). The resonance-stabilized anion which was produced by the removal of the nitrogen proton was felt to significantly reduce the tendency of the carbonyl group to undergo nucleophilic attack. Hence electrophilic attack of the more reactive second position of metalation, *i.e.*, the 2 position of the aromatic ring, could be observed.

In these laboratories we have observed that directed metalation reactions of monosubstituted benzenes can be made to occur in their ferrocene counterparts, often with greater facility.[5] These observations, coupled with our desire to examine methods of synthesizing 2-substituted ferrocene derivatives, prompted an investigation of the use of the directed metalation of *N*-ethylferrocenecarboxamide (1).

SCHEME I



Results and Discussion

N-Ethylferrocenecarboxamide (1) was metalated with 1.5 equiv of *n*-butyllithium and condensed with various reagents in order to test the suitability of the procedure as a method of synthesizing 1,2-disubstituted ferrocenes. The *N*-ethyl derivative was chosen for examination because of its recorded preparation;[6] the

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[1] For part III, *cf.* D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).

[2] W. H. Puterbaugh and C. R. Hauser, *J. Amer. Chem. Soc.*, **85**, 2467 (1963).

[3] (a) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963); (b) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

[4] D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965).

[5] *Cf.*, for example, D. W. Slocum, C. A. Jennings, T. R. Engelmann, B. W. Rockett, and C. R. Hauser, *J. Org. Chem.*, **36**, 377 (1971); D. W. Slocum, B. P. Koonsvitsky, and C. R. Ernst, *J. Organometal. Chem.*, **38**, 125 (1972).

[6] M. D. Rausch, P. Shaw, D. Mayo, and A. M. Lovelace, *J. Org. Chem.*, **23**, 505 (1958).