

The Effect of Ortho-Alkyl Substituents in the Metalation Reactions of Substituted Anisoles

Thomas E. Harmon* and David A. Shirley

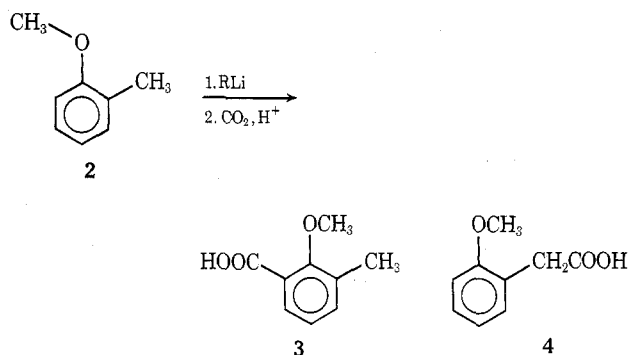
Department of Chemistry, University of Tennessee,
Knoxville, Tennessee 37916

Received February 15, 1974

In order to determine the role played by oxygen coordination in the metalation of anisole, Slocum and Koonsvitsky¹ recently investigated the lithiation of *o*-*tert*-butylanisole (1). Metalation of 1 with *n*-butyllithium in ether solvent gave only a 7.5% yield upon carbonation, whereas anisole² itself gave a 65% yield of ortho metalation under similar conditions. When 1 equiv of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was added, a 30% yield of ortho metalation of 1 was observed. These results were attributed to the steric interference of the *tert*-butyl group reducing the possibility for *n*-butyllithium coordination with the ether oxygen of 1 compared to that with anisole. The higher yield of metalation with *n*-butyllithium-TMEDA was attributed to the higher reactivity of this reagent.

Results and Discussion

Recent investigations in this laboratory do not support the above conclusions. The metalation of a similar substrate, *o*-methylanisole (2), has been studied in hydrocarbon solvent under various conditions and compared to similar metalations of anisole. Letsinger and Schnizer³ previously studied the metalation of 2 with *n*-butyllithium. These workers isolated the carboxylic acid products by fractional crystallization and reported the products to consist of approximately equal amounts of 3 and 4. The same



products were obtained in our investigations but the relative percentages of each varied according to the reaction conditions. The product distribution was determined in each case by gas chromatographic analysis of the corresponding methyl esters.

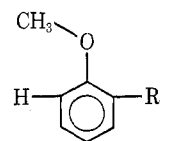
Metalation of 2 with *n*-butyllithium in refluxing cyclohexane for 10 hr followed by carbonation gave a 57% yield of carboxylic acid products. Analysis of the product composition revealed that one-third of these products, or 19%, resulted from ortho metalation. Under similar conditions, anisole was converted to the ortho acid in 40% yield. When 2 was metalated with *tert*-butyllithium for 10 hr in refluxing cyclohexane-pentane, an 81% yield was found of which 34% was ortho metalation product. Anisole was metalated under similar conditions to give a 51% yield of ortho metalation⁴ product. When the metalation of 2 was carried out for 10 hr at room temperature with *n*-butyllithium-TMEDA in cyclohexane solvent, a 72% yield of acidic product was obtained including 54% of the ortho metalation product. Ani-

sole was metalated to give only 54% yield of the ortho acid with *n*-butyllithium-TMEDA under these conditions.⁵

In order to compare the relative amounts of ortho metalation obtained in the reactions with anisole and 2 as indicated above, a statistical factor must be applied to the anisole results, since there are two ortho positions available for metalation *vs.* one ortho position in 2. Therefore metalation of anisole with *n*-butyllithium, *tert*-butyllithium, and *n*-butyllithium-TMEDA resulted in 20, 26, and 27% yields of metalation per ortho position compared to the 19, 34, and 54% yields of ortho metalation observed with 2. These results indicate that the methyl group does not reduce the ortho metalation reactivity of 2 compared with anisole and that any steric hindrance to alkyllithium coordination in 2 is not an important factor.

Complexation of *n*-butyllithium with donor molecules has been shown to produce an upfield shift in the nmr signal of the α -methylene protons of *n*-butyllithium. The magnitude of these shifts is taken as a measure of the degree of complexation. Thus, the coordination of ethyl ether and *n*-butyllithium in hexane produced a 9.0-Hz upfield shift for the methylene protons α to lithium.⁶ Ellison and Kotsonis⁷ obtained evidence for a 1:1 complex with anisole and *n*-butyllithium by observing a maximum upfield shift of 4.0 Hz at this mole ratio. The metalation of 1 was carried out by Slocum and Koonsvitsky¹ in ethyl ether solvent, as was the metalation of anisole² to which they referred. In such an excess of ether, it appears unlikely that complexation of *n*-butyllithium with 1 or anisole would be important in determining the rate and yield of metalation of these substrates. Certainly when TMEDA⁸ is present, very little if any complexation of the *n*-butyllithium with the anisole substrate occurs. The above authors correctly stated that the reactive *n*-butyllithium-TMEDA species need not form a complex with oxygen of 1 to effect metalation.

A recent investigation⁹ of the metalation of 3-alkyl- and 3,5-dialkylanisoles as well as other substrates has pointed to the importance of the oligomer size of the attacking alkyllithium species and the steric environment of the ortho hydrogens of each substrate in determining the yield and position of metalation. We believe that the results of Slocum and Koonsvitsky¹ can be interpreted using these same concepts. In hydrocarbon solvent *n*-butyllithium is known to be hexameric¹⁰ and *n*-butyllithium-TMEDA is monomeric.⁸ *n*-Butyllithium exists as a tetramer¹⁰ in ethyl ether. It is reasonable to assume that the steric requirement of the reactive *n*-butyllithium oligomer is greater than that of the *n*-butyllithium-TMEDA monomer. Owing to the steric effect of the *o*-*tert*-butyl group, the conformation of 1 would be fixed as shown in 5. The large *n*-butyllithium oli-

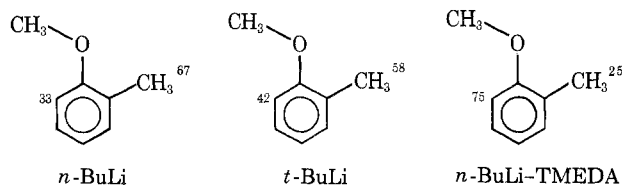


5, R = *tert*-butyl
6, R = methyl

gomer would be sterically hindered from attacking the ortho hydrogen of 5, whereas no such steric interference would occur with anisole. This steric effect plus the deactivating inductive effect¹¹ of the *tert*-butyl group would account for the rate and yield difference in the metalation of these substrates noted by Slocum and Koonsvitsky.¹ Furthermore, in the metalation of 1 with the monomeric *n*-butyllithium-TMEDA, the lower steric requirement of this metalation reagent would be expected to lead to a higher yield as was observed.¹

* E. I. du Pont de Nemours and Co., Chattanooga, Tenn. 37401.

Interesting product distribution shifts were observed in the above metalations of **2** with *n*-butyllithium, *tert*-butyllithium, and *n*-butyllithium-TMEDA as indicated below.



The numbers indicate the percentage of total metalation observed at each position. These results are also explainable in terms of the steric environment of the ortho hydrogens and the oligomer size of the alkyllithium reagent. The expected stable conformation of **2** would also be **6**.¹² Since *tert*-butyllithium is tetrameric¹⁰ in hydrocarbon, the oligomer size of the metalation reagents would be expected to decrease in the order *n*-BuLi > *t*-BuLi > *n*-BuLi-TMEDA. The product distributions observed in these metalation reactions of **2** are consistent with the concept of the alkyllithium reagent with the least steric requirement effecting the largest amount of metalation at the hindered ortho position.

These product distribution results may also be rationalized in terms of the base strength of the reagents, which increases in the order *n*-BuLi < *t*-BuLi < *n*-BuLi-TMEDA.^{8,13} A correlation is observed which indicates that the ratio of ring to lateral metalation increases with the base strength of the metalation reagent. The same conclusion was reached by Broaddus⁵ concerning the metalation of toluene with *n*-butyllithium-TMEDA. He believed that the metalation reaction was controlled by proton abstraction processes and compared his data to the results of base-catalyzed isotopic exchange reactions of toluene. These results revealed a decreasing reactivity of benzylic positions relative to ring positions with increasing base strength. Broaddus rationalized his results in terms of the principle¹⁴ that the C-H bond will be broken to the largest extent in the transition state involving the weakest base. Therefore, it may be reasonably proposed that electron delocalization stabilizing factors will also be largest with the weakest base. When more charge is developed on carbon, delocalization is a more important factor and thus reaction is favored at benzylic positions relative to ring positions.⁵

In any case the degree of complexation of the alkyllithium reagent with the oxygen of **2** does not appear to be the predominant factor in determining the yield or position of metalation. This argument seems even clearer for the metalations of anisole² and **1**¹ in ether solvent, where the coordination between *n*-butyllithium and the anisole substrates would be negligible based on the cited nmr data.^{6,7}

Experimental Section

A. General Considerations. Solutions of *n*-BuLi in cyclohexane and *t*-BuLi in pentane were obtained from Foote Mineral Co. The concentration of the organolithium reagents used was determined by the method of Gilman and Cartledge.¹⁵ Cyclohexane was refluxed for several hours over lithium aluminum hydride, distilled, and stored over freshly cut sodium. TMEDA (Aldrich Chemical Co.) was distilled from LiAlH₄ and stored over Linde MS-4A molecular sieve. *o*-Cresol was obtained from Eastman Chemical Co. and used without further purification.

B. Metalation of *o*-Methylanisole. *o*-Methylanisole was prepared from *o*-cresol with sodium hydroxide and dimethyl sulfate using the standard procedure.¹⁶ Following fractional distillation *in vacuo* no impurities were detected by gc analysis and an nmr spectrum was consistent with expectation.

The general apparatus and procedure for the metalation reactions, carbonation, and conversion of the products to their methyl esters has been previously described.⁹ The product methyl esters

were analyzed on a Varian Aerograph 711 using an FFAP column at 210° and a carrier gas flow rate of 400 cc/min. All of the chromatograms exhibited two peaks with retention times of 22.3 and 29.1 min which varied in size according to the reaction conditions. The components responsible for these peaks were isolated by preparative scale gc and identified by their nmr spectra. The nmr spectrum of the component with the retention time of 22.3 min showed a singlet of three protons at δ 2.28, a singlet of three protons at δ 3.77, a singlet of three protons at δ 3.84, and a complex multiplet of three protons at δ 6.74–7.65. This spectrum is clearly representative of methyl 2-methoxy-3-methylbenzoate, the product of metalation ortho to the methoxy group. The nmr spectrum of the component appearing at 29.1 min exhibited a singlet of two protons at δ 3.54, a singlet of three protons at δ 3.62, a singlet of three protons at δ 3.79, and a complex multiplet of four protons at δ 6.62–7.36. This spectrum is interpretable only for methyl *o*-methoxyphenylacetate, the product of metalation of the methyl group.

The product composition of these reactions was determined by the relative peak areas of the chromatograms as measured by a Disc integrator.

Registry No.—**2**, 578-58-5; **3** methyl ester, 52239-62-0; **4** methyl ester, 27798-60-3.

References and Notes

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2,6-Dinitro-*N*-(2-imidazolyl)-*p*-toluidine

John C. Grivas* and Krishna C. Navada

Chicago Chemicals Laboratory, Sherwin Williams Chemicals,
The Sherwin-Williams Company, Chicago, Illinois 60628

Received May 23, 1974

During the course of other work it became necessary to prepare 2,6-dinitro-*N*-(2-imidazolyl)-*p*-toluidine (**3**) for biological screening. This preparation could not be achieved by the direct displacement of chloride ion from 4-chloro-3,5-dinitrotoluene (**1**) by 2-aminoimidazole. Although such a displacement by aliphatic and aromatic amines^{1,2} as well as alkoxide ions³ is well known, our initial few attempts to condense **1** with 2-aminoimidazole, and another more stable heterocyclic amine, were not successful. For example, heating **1** with 2-aminoimidazole in dimethylformamide at 135° for 7 hr gave an intractable mixture of at least four major components. On the other hand, when the same reactants were heated under reflux in ethanol for 8 hr, nearly all **1** was recovered unchanged. Treating **1** with 2-aminopyrimidine (1:2 molar ratio) in glycol at 135° for 24 hr resulted in little change. Unexpectedly, at higher temperatures **1** reacted completely to afford 2,6-dinitro-*p*-toluidine (**1** → **5**) and a substantial amount of tar. A possible