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PRODUCT DISTRIBUTION IN THE METALATION OF SOME AROMATIC SUBSTRATES WITH n-BUTYLLITHIUM

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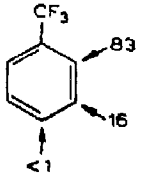
INTRODUCTION

The reaction of metalation by organolithium reagents received intensive study following its introduction by Gilman and by Wittig prior to 1940[1]. A wide variety of the simpler aromatic substrates were studied before the advent of vapor phase chromatographic techniques and this work, with rare exceptions, involved only isolation and identification of the major product.

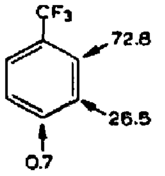
We are carrying out a series of studies of the metalation of substituted aromatic rings for the determination of major and minor product distribution. The objectives of this work have been to observe the degree and nature of position selectivity exhibited by the metalating agent, the degree of steric control exercised by ring substituents, and the relationship of these data to the present ideas of the mechanism of the reaction. In an earlier paper[2], which is a part of this study, the metalation of 1-methoxynaphthalene was examined.

RESULTS AND DISCUSSION

One early example of careful study of product distribution in the metalation reaction was by Roberts and Curtin[3] who found the results as shown in (I) in the metalation (ether reflux, 6 h) of benzotrifluoride by n-butyllithium. In the presentation of this and most subsequent data in this paper, total metalation at ring and side chain position is given a value of 100% and the numbers at the various positions are expressed in percentages of the total. The above data were obtained[3] by conversion of the aryllithium mixture formed in the metalation to the corresponding carboxylic acids and the separation of the acids by crystallization techniques. We initiated our study by a repetition, under similar conditions, of the metalation of benzotrifluoride with conversion to the carboxylic methyl esters and VPC analysis of the mixed esters. The results are as indicated in (II).



(I)

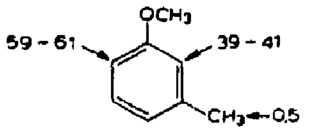


(II)

Roberts and Curtin used n-butyllithium prepared from n-butyl chloride and lithium in ether while in the present study commercial n-butyllithium in hexane was used. We have noted earlier[2] that product composition in the metalation of 1-methoxynaphthalene differs in a manner apparently dependent upon whether the preparation of n-butyllithium is in ether or in alkane solvent.

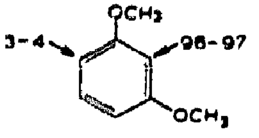
Anisole was metalated with phenyllithium[4] and n-butyllithium[5] in the early work on metalation, and only *ortho* substitution was recorded. In our re-examination of this reaction, no metalation could be detected in the methoxyl group, at the *meta*-position or at the *para*-position, and it was demonstrated that as little as 0.1 % could have easily been detected at any of these positions. Thus *ortho*-position attack by the metalation agent represents essentially all of the acidic products. Many reactions of aromatic substitution tend toward lower position selectivity with increase in reaction temperature. The above results were obtained at reflux temperature of the ether solvent and two additional runs were made, one in which tetrahydrofuran was the solvent and the other in which excess anisole was the solvent. Reaction product from runs at the reflux temperature of each of these solvents also showed essentially 100 % *ortho*-metalation. The yields (based on n-BuLi) of *o*-methoxybenzoic acid in these metalations were about 65 % in ether, 26 % in tetrahydrofuran and 5 % in excess anisole. Cleavage of THF by the n-BuLi was apparently faster than metalation, as was cleavage of anisole in the experiment at the reflux temperature of anisole.

The metalation of *m*-cresol methyl ether has apparently never been reported. Analysis of carboxylic acid esters from a metalation at ether reflux (3.75 h, 53 % conversion of *m*-cresol methyl ether) showed product distribution as shown in (III). It has been demonstrated in a number of systems[6] that methyl and other alkyl groups deactivate a ring toward metalation, and ring positions nearest the alkyl group are most deactivated. The above results exhibit the operation of this effect of the methyl group in directing the greater amount of substitution to the more remote of the two positions which are adjacent to methoxyl. It could be considered that steric hindrance to substitution in the position between the methyl and methoxyl groups could also account for the results; however, the data discussed below, and in the following paper, demonstrate the low steric requirement of the metalation reaction.

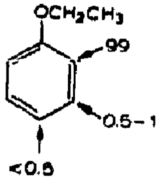


(III)

Resorcinol dimethyl ether was shown earlier[4,7] to metalate between the methoxyl groups in 50–70 % conversion. A careful analysis of product compositions resulting from metalations with n-BuLi in both ether and cyclohexane solvents at the reflux temperature of the respective solvents gave the results shown in (IV). No products were detected representing metalation at the remaining ring position or in the methoxyl groups. Conversions observed were in the range of 60–75 %.



(IV)

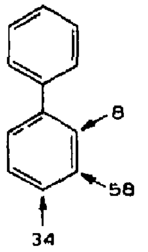


(V)

Phenetole has apparently never been metalated. The product distribution from equimolar amounts of reactants in ether at the reflux temperature are shown in (V). The product was examined carefully for evidence of α-metalation in the ethoxyl group and none was found. Three reactions were run under the same conditions except for reaction times of 3.5, 6 and 27 hours. The conversions of phenetole to carboxylic acid were 32, 39 and 63 % respectively. It is of interest that composition of the product from each of the three runs did not vary from the figures given above. It is apparent that the metalation of phenetole goes with high position selectivity in favor of the *ortho*-position, but the process is somewhat less selective than with anisole.

It has been long recognized[4,8] that the principal factor in the metalation reaction which determines the position of the entering lithium atom is the relative "acidity" of the ring hydrogen atoms as influenced by the inductive effects of ring substitutents. This quite simple concept allows an effective correlation of the vast majority of accumulated data on the metalation of both aromatic and heterocyclic substrates with alkylalkali compounds. A significant exception to this concept has been the report by Gilman and Bebb[5] that biphenyl metalates with n-BuLi in the *para*-position. Since a phenyl substituent has an inductive effect of electron attraction, it would be expected that the *ortho*-position would be the principal point of attack.

We carried out the metalation of biphenyl in ether for 48 hours at the reflux temperature. This substrate is attacked only slowly by n-BuLi (but faster than benzene), since only a 12 % conversion to mixed carboxylic acid resulted. The composition (±1 %) of this mixture is shown in (VI).



(VI)

The earlier workers[5] had apparently concentrated the least soluble *para*-carboxylic acid by crystallization techniques and missed the fact that the *meta* isomer predominates in the mixture. Taking into account the statistical factor, the above results indicate that the *para*-position is attacked to a greater degree than the *meta* which is attacked to a greater degree than the *ortho*-position. These results, however, continue to point up the anomalous pattern of biphenyl metalation. This situation will be dealt with further in the following paper.

It was considered possible that biphenyl underwent a rapid metalation in the *ortho*-position followed by a slower distribution of metal among the three ring positions either by (1) intramolecular rearrangement of metal or (2) metalation by *o*-lithiobiphenyl in the *meta*- and *para*-positions of biphenyl molecules. A situation similar to route (2) has apparently been observed[9] in the metalation of isopropylbenzene with n-amylsodium and n-amylpotassium in which initial ring metalation is followed by formation of the product with the metal atom in the α-position. In order to test for movement of the lithium atom between ring positions in biphenyl, we prepared

2-lithiobiphenyl by halogen–metal interconversion[10] of 2-bromobiphenyl with n-BuLi, and allowed this to react with biphenyl (ether, reflux) for 48 hours. The biphenylcarboxylic acids produced contained 99.7% *o*-isomer with the remaining 0.3% consisting of the *m*- and *p*-isomers. Thus it seems unlikely that a product of rapid metalation in the *ortho*-position is a precursor of the *m*- and *p*-metalation products. In an earlier paper[2] from this laboratory, it was demonstrated that in the metalation of 1-methoxynaphthalene there is concurrent attack at the 2- and 8-positions with the 2-position being attacked more rapidly. This conclusion was in opposition to an earlier proposal[11] that 2-position substitution followed the rapid introduction of the lithium atom into the 8-position.

EXPERIMENTAL

All n-butyllithium used was Foote Mineral Company product in hexane. Concentration of n-BuLi was determined by hydrolysis of the clear solution and titration with standard acid. Unless otherwise indicated, all vapor phase chromatographic (VPC) analyses were performed on a Perkin–Elmer Model 154D "Vapor Fractometer" on 2 meters × 0.25 inch columns. Elemental analyses were by Galbraith Laboratories of Knoxville, Tennessee.

Anisole metalation and product analysis

Many of the operations used in this work are exemplified in the experiments with anisole, and this system will be described in greater detail than the others.

A 500 ml three-necked flask fitted with dropping funnel, stirrer and condenser was flame dried and allowed to cool with a stream of dry nitrogen passing through the apparatus. A solution of 11.34 g (0.105 mole) of anisole in 125 ml of dry ether was heated under reflux and 0.10 mole of n-BuLi solution was added (15 min). The mixture was heated and stirred for 21 h and then poured slowly into a slurry of 50 ml of ether and 20 g of crushed solid carbon dioxide. The mixture was allowed to stand until it reached room temperature, after which it was extracted with 2% aqueous sodium hydroxide solution. Acidification (HCl) of the extract precipitated carboxylic acid. The conversion to carboxylic acid, based on n-BuLi and assuming it to be a methoxybenzoic acid, was 65%. Another run of 10 h duration gave a 39% conversion.

A solution of the carboxylic acid in ether was treated with an ethereal solution containing a 40% molar excess of diazomethane generated[12] from N-nitroso-N-methyl-*p*-toluenesulfonamide. The ether and excess diazomethane were allowed to evaporate in the hood. No residual unreacted carboxylic acid could be detected in the product. The resulting methyl ester(s) were analyzed by VPC. In description of all VPC analyses, no mention will be made of peaks representing volatile components such as residual ether solvent and methyl valerate from the n-BuLi. These peaks appeared at less than 5 min retention time. A Perkin–Elmer analytical "P" column was used for the analysis. This column contained a polyester of succinic acid and diethylene glycol on "GC-22" 60–80 mesh support material. The column was used at 210° and a helium flow rate of 70 ml/min with samples of 10 μl and a thermal conductivity detector operated at 8 V. Retention times were measured from sample injection to the beginning of component appearance.

Only two components appeared on the chromatogram. A large component at 15.0 min was methyl *o*-methoxybenzoate and a much smaller peak at 9.0 min was phenol. The peaks were identified by addition of authentic samples. A synthetic mixture was made up consisting of methyl *o*-, *m*- and *p*-methoxybenzoate. Analysis showed retention times of 14.9, 13.0 and 16.7 min respectively for the above isomers. It was demonstrated that as little as 0.1 % of the *meta*- or *para*-isomers could have been detected in the presence of the *ortho*-isomer. The amount of phenol was rather small and its quantitative estimation was not attempted, since part had undoubtedly been lost in the extractions used in the work-up procedure. Phenol would arise from cleavage of the anisole by n-BuLi.

A metalation was performed in tetrahydrofuran and a Gilman test II[13] for alkyllithium was negative after 2 h and only 26 % of carboxylic acid was isolated indicating rather rapid consumption of n-BuLi by cleavage of THF. A 4 h reaction time at the boiling point of excess anisole as solvent gave only 5 % of carboxylic acid. Product analysis in both these latter runs again showed only metalation *ortho* to the methoxyl group.

Vapor phase chromatographic analysis of products from other metalations

In metalation of all the other substrates, more than one ring substituted isomer was found. In these cases product compositions were determined by making up three different synthetic mixtures of known compositions approximating the unknown. The areas under the VPC peaks of the knowns were determined, and correction factors calculated for direct conversion of peak area ratios to mole ratios. These factors were then applied to the unknown mixtures.

Metalation of m-cresol methyl ether

The metalation and work-up was carried out as described above for anisole, with the same molar amounts of n-BuLi and substrate in ether solvent for 3.75 h.

The VPC analysis was carried out on the mixed methyl esters in the same column and with the same operating parameters as for the anisole system. Four peaks were observed, two large at 13.4(a) and 17.8(b) min and two small peaks at 11.2(c) and 17.3(d) min. The compounds producing the two large peaks (a and b) were isolated by use of a "preparative" column and the Perkin–Elmer 154D Vapor Fractometer. This column is 1 inch × 3 m and contained "Apiezon L" grease as the liquid phase. It was operated at 225° with a 0.5 ml sample. Again four peaks were observed, and samples of the two large peaks from the "prep" column were injected into the analytical column to determine that the two large peaks were coming from the two columns in the same order. Samples corresponding to the large peaks from the "prep"column were collected and separately hydrolyzed by reflux with aqueous alcoholic KOH solution. The recovered acids were recrystallized and the one from peak (a) melted at 139.5–141° and the one from peak (b) melted at 103–104.5°. Literature values for the m.p. of 6-methoxy-2-methylbenzoic acid are 139°[14] and 141°[15]. Literature values for the m.p. of 2-methoxy-4-methylbenzoic acid are 103–104°[16], 104°[17] and 103°[18].

The two acids from the preparative VPC column were oxidized by 20 min reflux periods with a dilute aqueous solution of $KMnO_4$ and NaOH. The resulting dicarboxylic acid from peak (a) exhibited a variable melting point depending on rate of heating. The sample was held at 65° *in vacuo* for five hours after which it melted at 158°. An infrared spectrum showed two bands in the carbonyl stretch region (5.42 μ and 5.62 μ) in accord with listed values[19] (5.42 μ and 5.64 μ) for phthalic anhydride. The literature value[20] for the melting point of 3-methoxyphthalic anhydride is 160–161°. The dicarboxylic acid produced by oxidation of the acid from peak (b) melted at 271–273° after recrystallization from ethanol-benzene. The melting point of methoxyterephthalic acid is reported[21] as 270–280° and several[16,22] intermediate values. These results clearly indicate that peak (a) represented methyl 6-methoxy-2-methylbenzoate and (b) represented methyl 2-methoxy-4-methylbenzoate.

Peak (c) above was identified as *m*-cresol from cleavage of the ether by n-BuLi and peak (d) represented methyl *m*-methoxyphenylacetate. The latter compound was formed as a result of metalation on the ring methyl group of *m*-cresol methyl ether.

Metalation of benzotrifluoride

This reaction was performed at ether reflux for 9 h with 0.126 mole of benzotrifluoride to 0.120 mole of n-BuLi. Conversion to mixed carboxylic acid was 33%. Conversion to the methyl ester mixture was followed by VPC analysis at 180° on the column described above. Samples of the methyl *o*-, *m*- and *p*-trifluoromethylbenzoates were prepared from the commercially available trifluoromethylbenzoyl chlorides (Columbia Organic Chemical Co.) and a mixture put through the analytical VPC column. It was found that the column would not separate the *meta*- and *para*-isomers, both having retention times of 3.9 min, compared with 6.4 min for the *ortho*-isomer. The mixed methyl esters from the metalation showed two peaks (3.9 and 6.4 min). Analytical columns containing "Apiezon-L", polypropylene glycol, silicone grease and "DEGA" polyester also did not separate the *meta*- and *para*-isomers. The separation was achieved in the laboratories of the Chemical Products Division of the Chemetron Corporation at Newport, Tennessee by use of a ¼" × 15' column at 170° containing polypropylene glycol. Under these conditions the *ortho*-isomer came at 30 min, the *meta*- at 43 min and the *para*-isomer at 55 min. Analysis on this column of the mixture from the metalation showed only a small amount of *para*-isomer estimated by use of only the relative peak areas to be 0.7%. The relative amounts of the *ortho*- and *meta*-isomers were then determined as described earlier to give the relative amounts of nuclear substitution indicated in the discussion section.

Metalation of resorcinol dimethyl ether

The reaction was performed in ether solvent for 20 h at reflux temperature and 0.10 mole each of n-BuLi and resorcinol dimethyl ether were used. The conversion to the crude acid mixture was 74% and this was converted to the mixed methyl esters. Analysis of the mixture was by use of a Wilkens Model A-700 "Autoprep" using a 20% silicone (SE-30) analytical column supplied by the Wilkens Co., at a column temperature of 250°. Methyl 2,6-dimethoxybenzoate, m.p. 88.5–89°[23], and methyl 2,4-dimethoxybenzoate, b.p. 124° at 0.9 mm[24], were synthesized as it was anticipated that these isomers would be present in the metalation product. Analysis of the metalation product showed only two peaks beyond 5 min, and these were shown to be the expected methyl 2,6-dimethoxybenzoate at 6.7 min and methyl 2,4-dimethoxybenzoate at 8.2 min. Two small peaks in the 3 to 5 min range were identified as resorcinol and resorcinol monomethyl ether. Metalation in the methoxyl groups was excluded by synthesis of *m*-methoxyphenoxyacetic acid[25] and observation of the retention time of its methyl ester in the VPC column as 6.9 min in a mixture with methyl 2,6-dimethoxybenzoate.

A metalation in cyclohexane solvent at the reflux temperature for 30 min gave a 62% conversion to crude acid, which had the same composition, within experimental error, as the product from the runs conducted in ether.

Metalation of phenetole

Reaction involved ether solvent, 0.10 m each of n-BuLi and phenetole, at the reflux temperature. In three runs metalation times were 3.5, 6 and 27 h and conversions to crude acid after carbonation were 32%, 39% and 63%, respectively.

Methyl *o*-ethoxybenzoate and methyl *p*-ethoxybenzoate were prepared from the commercially available acids (Eastman Organic Chemicals) and diazomethane. *m*-Hydroxybenzoic acid was converted to *m*-ethoxybenzoic acid with diethyl sulfate and aqueous sodium hydroxide. Methyl *m*-ethoxybenzoate has apparently never been reported before. It was made from the acid and diazomethane by the procedure indicated above. It boiled at 100° at 1.75 mm (Found: C, 66.49; H, 6.71. $C_{10}H_{12}O_3$ calcd.: C, 66.68: H, 6.72%.)

The mixed esters from the metalation were analyzed on a column (Perkin-Elmer Co.) containing 20% Ucon oil LB-550-X on 60–80 mesh GC-22 support, at a temperature of 200°. Peaks beyond 5 min appeared at (a) 6.5 min, (b) 14.9 min, (c) 15.8 min, (d) 17.2 min, and (e) 19.0 min. Peak (a) was due to phenol; peak (b), which was very large, was due to methyl *o*-ethoxybenzoate. Peak (c) was due to methyl *m*-ethoxybenzoate, and (e) due to methyl *p*-ethoxybenzoate. Peak (d) was considered likely to be methyl 2-phenoxypropionate from metalation in the α-carbon of the ethoxy group. This compound has apparently not been reported and was synthesized from the corresponding acid[26] and diazomethane. It boiled at 80° at 0.5 mm. (Found: C, 66.86; H, 6.74. $C_{10}H_{12}O_3$ calcd.: C, 66.68; H, 6.72%.)

This ester showed a single peak (10.5 min) from the VPC column operated under the same conditions as above. Peak (d) which was small in relative size remained unidentified.

The relative amounts of attack at the various ring positions of phenetole, indicated in the discussion section, were found to be the same in the products of each of the three runs at different metalation times.

Metalation of biphenyl

Metalation at ether solvent reflux of 0.10 mole of biphenyl with 0.10 mole of n-BuLi for 48 h produced 12% of crude carboxylic acids which were methylated for VPC analysis.

The three isomeric methyl phenylbenzoates were synthesized. The *ortho*- and *para*-isomers were obtained from the commercially available acids, and the *meta*-acid was made from methyl *m*-aminobenzoate by the method of Hey *et al.*[27]. Analysis of the methyl ester mixture from the metalation was on the Wilkens Model A-700 "Autoprep" with a 30% silicone (SE-30) column at 210°. Peaks appearing at 11.9, 17.8 and 19.0 min were shown to be due to methyl *o*-phenylbenzoate, methyl *m*-phenylbenzoate and methyl *p*-phenylbenzoate respectively. A small peak appearing at 20.9 min was not identified.

SUMMARY

The following compounds were metalated with n-butyllithium in ether and product isomer ratios determined with the aid of vapor phase chromatographic techniques: anisole, trifluoromethylbenzene, phenetole, *m*-cresol methyl ether, resorcinol dimethyl ether and biphenyl. The data with all substrates except biphenyl are in accord with the view of relative rate of attack of different ring positions controlled by inductive effects of ring substituent on the "acidity" of ring carbon-to-hydrogen bonds.

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