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METHOXYMETHYL ETHERS. AN ACTIVATING GROUP FOR RAPID AND REGIOSELECTIVE METALATION

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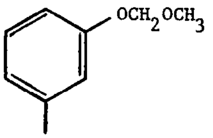
The preparation of aryllithium reagents from aryl-alkyl ethers by lithium-hydrogen exchange with readily available lithium reagents such as phenyl- or butyllithium is a well established synthetic procedure even though the metalation reaction often requires elevated temperatures for extended periods and frequently results in mixtures of isomers from reaction at the various ortho centers.[1,2] Furthermore, when applied toward the preparation of phenols there is the added difficulty of removing stable alkyl ether protecting groups. To avoid this problem Christensen[3] recently reported that certain phenyl methoxymethyl ethers could be metalated with n-butyllithium-tetramethylethylene diamine (TMEDA) and then the phenolic hydroxyl subsequently unmasked by mild acid hydrolysis.

In the course of synthetic work directed toward some ortho alkyl phenols it was found that the methoxymethoxy group is not only a convenient phenol protecting group,[4] but that it also serves to enhance, perhaps by internal chelation,[5] the susceptibility of the ortho positions toward hydrogen-metal exchange. Furthermore, it was found that substitution of tert-butyllithium, without any added complexing agents, for n-butyllithium-TMEDA, resulted in rapid and extremely regioselective metalation.

Thus, when m-cresol methoxymethyl ether 1 (bp. 91-2°/14mm) in petroleum ether at 0° was treated with 1.1 equivalents of t-butyllithium in a nitrogen atmosphere a rapid formation of the aryllithium reagent as a copious, off-white precipitate ensued. Within 2 hrs at 0° the metalation was complete as determined by quenching with D_2O or CO_2. When the anion was carbonated and the resulting acid esterified with diazomethane a 90-95% yield of ester 2 was obtained.[6] By vpc analysis 2 was the sole isomer to the extent of at least 99.5%.



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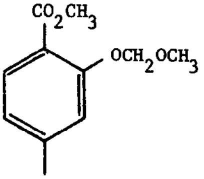

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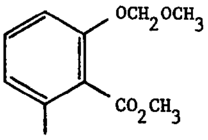

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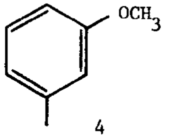
In contrast, under the same conditions with n-butyllithium-TMEDA, 1 was converted in 88% yield to an 80:20 mixture of 2 and 3.[6] The n-butyllithium-TMEDA complex is a more powerful metalating agent than t-butyllithium requiring only 1 hr to convert 1 to its anion. Without the addition of TMEDA the metalation is very slow, but by employing ether as a cosolvent at room temperature the reaction is accelerated significantly and complete reaction is observed within 4-5 hrs. There is no appreciable change in the ratio of 2 and 3 with or without the TMEDA. The metalation of 1 with n-butyllithium is considerably more selective than that observed for the methyl ether 4. Shirely and Hendrix found that treatment of 4 with n-butyllithium in ether resulted in a 60:40 mixture of ortho isomers.[2]

That the methoxymethyl group is serving to enhance the reactivity of the aryl ethers toward metalation is best seen in the comparison with the corresponding methyl ethers. When the methyl ether of m-cresol 4 was treated under the aforementioned conditions with t-butyllithium less than a 1% yield of nonvolatile acids was obtained after carbonation. Even after overnight treatment at room temperature less than a 10% conversion to the anion was observed. At room temperature 1 is metalated by t-butyllithium within 15 min.



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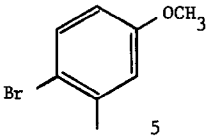

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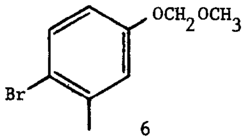

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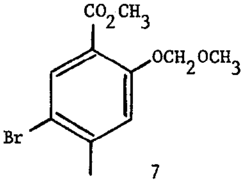

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By substituting phenyllithium for butyllithium to avoid halogen-metal exchange the reaction can be extended to some bromoethers.[7] Yamada[8] and Mirrington[9] reported that reaction of 2-bromo-5-methoxytoluene 5 with phenyllithium in ether occurs principally at the ortho positions. The reaction, however, required refluxing for several hours and only a 30-40% conversion was observed. With the corresponding methoxymethyl ether 6 (Bulb to bulb distillation, 70°/0.05mm) in 1:1 ether-petroleum ether complete metalation by phenyllithium took place in 4 hrs at room temperature to afford a 93% yield of esters after carbonation and esterification. By vpc and nmr analysis the major product 7 was contaminated with only about 8% of the other ortho isomer. Even with t-butyllithium, which reacts with halides principally by halogen-metal exchange, a 20% yield of 7 could be obtained which also demonstrates the significant activating ability of the methoxymethyl ether group for ortho metalation.

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11) The author acknowledges the Research Corporation for partial support of this work.