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STUDIES OF METHOXYMETHYL-DIRECTED METALATION[1]

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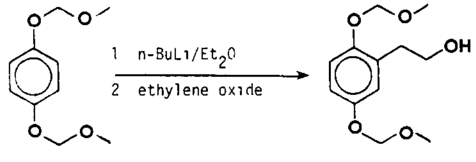
Abstract: *To explore the use of methoxymethyl groups to elaborate simple benzenoid precursors to more complex polyketide-derived natural products, the reaction of phenolmethoxymethyl ether ortho-anion was investigated with a number of electrophiles.*

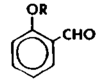
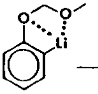
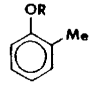
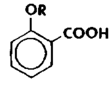
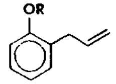
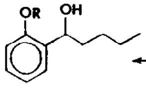
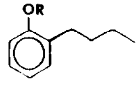
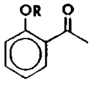
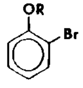
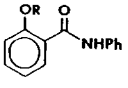
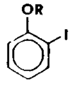
Stern, English and Cassidy[2] appear to have been the first to recognize and apply methoxymethyl groups both as an easily removed phenol protecting group and as a functionality to direct ortho-metalation[3] and subsequent reaction with an electrophile; i.e. 1→2 (85% yield). In the intervening years isolated examples have appeared wherein simply substituted aryl methoxymethyl ethers have been metalated and reacted with dimethylformamide[4] or carbon dioxide[5] to give the corresponding aldehydes or carboxylic acids, respectively. In the past year conceptual extentions of these earlier observations have been reported in syntheses of 11-deoxyanthracyclinones[6] and (—)-aplysin.[7]



1 2

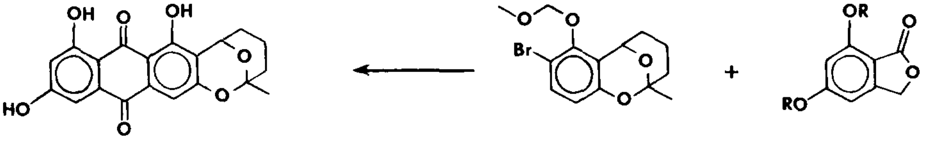
Apart from ethylene oxide, however, the electrophile in all of these reactions has been a carbonyl derivative. In the course of work to develop a total synthesis of averufin 3,[8] a key intermediate in aflatoxin biosynthesis,[9] we have been led to explore the scope of methoxymethyl-directed aryl metalation. We report herein our findings using methoxymethylphenol as a simple model system and, as detailed in Table 1, the reactions of its ortho-lithiated species with the indicated electrophiles under constant conditions of anion formation.[10]

Table 1. Methoxymethylphenol ortho-anion and reactions with electrophiles.

Entry	Yield[a]		Electrophile		Electrophile		Yield[a]	Entry
1	78%		DMF/1 9 eq r t /30 min		MeI/3 0 eq r t /30 min		59%	6
2	76%		CO$_2$/excess r t /5 min		Br⌒⌒/1 4 eq r t /45 min		52%	7[d]
3	67%		n-C$_4$H$_9$CHO/1 2 eq r t /30 min		n-C$_4$H$_9$I/1 5 eq /r t 20% HMPA/5 hr		51%	8[d]
4[b]	68%		Ac$_2$O/3 0 eq 0°/1 5 hr		BrCN/1 0 eq r t /5 min		78%	9
5[c]	73%		PhNCO/1 3 eq r t /30 min		I$_2$/1 2 eq r t /1 min		73%	10

(a) All Reactions on tlc analysis showed clean conversion of starting material to product (except entries 5, 7 and 8 — see c and d) Given are the isolated yields of chromatographically homogeneous products having satisfactory spectral properties obtained after conventional work up in ether and Kugelrohr distillation (b) Acetylchloride gave product in inferior yield and purity (c) Tlc analysis indicated four products, the major component being the desired anilide which readily crystallized on work up, m p 87-88 5° (d) After work up, both alkylation products were separated from unreacted starting material by plc (silica, hexane ether 4 1)

As a class, polyketide-derived natural products[11] are frequently characterized by polyhydroxylated aromatic rings. A direct and versatile strategy for their synthesis is the elaboration of properly oxygenated benzenoids to more complex systems. Although notable exceptions exist, in general, avoidance of steps requiring the introduction or removal of aryl oxygen is normally observed. Methoxymethyl, therefore, provides at once a phenol protecting group easily removed for ultimate liberation of the target natural product; and, as indicated by the reactions in Table 1, allows the synthetic elaboration of simple oxygenated benzenoid precursors in a variety of ways. Entries 1-4 show the formation of new C-C bonds at a range of oxidation states at the benzylic position in the biogenetically correct relation to the ring oxygen. Particularly useful is the direct synthesis of an anilide (entry 5) employing phenylisocyanate as electrophile. Secondary and tertiary amides, usually obtained from the corresponding acids, are excellent *ortho*-metalation directors[3] and have been used extensively in recent years.[12] Entries 6-8 indicate simple alkylation reactions in good yields and entries 9 and 10 show that in our hands cyanogen bromide and iodine[13] were the best means to introduce bromine and iodine, respectively. In a similar fashion bicyclic ketal bromide 4 has been synthesized and its *in situ*-generated benzyne trapped by the anion of 5,7-dimethoxymethyl phthalide 5 (R=CH_2OCH_3) to afford, after oxidation and deprotection, (±)-averufin 3.[8]



3 4 5

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