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ORTHO-METHYLATION OF PHENOLS WITH ETHYL(IODOMETHYL)ZINC

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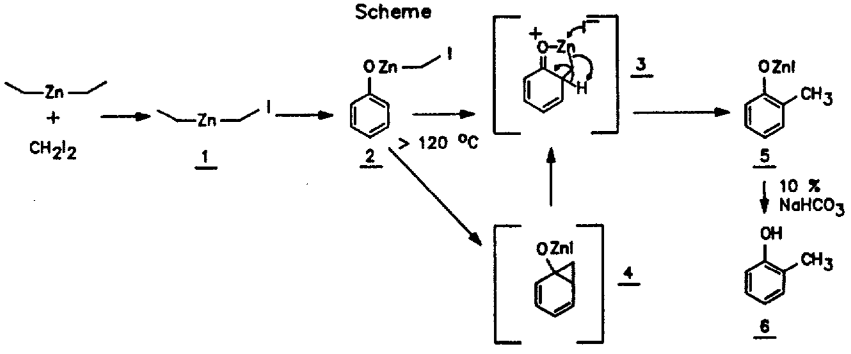
SUMMARY: The regioselective ortho-methylation of phenols by in situ generated ethyl(iodomethyl)zinc via an internal alkylation process is described.

The selectivity in O- vs C-alkylation of phenols has been the source of considerable investigation.[1] Alkylation at the oxygen site is expected upon treatment of the phenolate species with alkylating agents, as observed with sodium phenolates and alkyl halides or with diazoalkanes and the parent phenol.[2] Conversely, C-alkylation of phenols is anticipated in Friedel-Crafts alkylation procedures exemplified by the Lewis acid-catalyzed additions of olefins[3], alcohols[4], and alkyl halides[5] to the parent phenol. Other methods for the C-alkylation of phenols have employed the reaction of various metal aryloxides[4] with olefins. These methods for phenol C-alkylation often exhibit low regioselectivity in alkyl group addition to the aromatic ring, polyalkylation of the aromatic ring, and carbocationic rearrangement of the alkylating species prior to phenol alkylation. In addition, the reaction conditions required to promote C-alkylation are often strongly acidic or do not possess sufficient generality to enable extension to analogous phenol substrates. In the context of a program directed at the synthesis of phenolic natural products, we have attempted to develop methods for the C-alkylation of phenols that complement existing strategies and circumvent the limitations associated with current approaches. We report here a method for the selective ortho-methylation of phenols through the reaction of phenols with the modified Simmons-Smith reagent derived in situ from diethylzinc and diiodomethane.[5]

Our results are compiled in Table 1. The reaction of the diethylzinc/diiodomethane species gave exclusive ortho-methylation in all phenols investigated, with the exception of the electron deficient substrates, 2,4-dichlorophenol (Entry 11) and 2-carbomethoxyphenol (Entry 12). In addition, the reaction demonstrated exclusive mono-alkylation in all phenols with the exception of m-cresol (Entry 6) which underwent dialkylation to form 2,3,6-trimethylphenol as the major product. All yields in the Table represent isolated products via the "unoptimized" general procedure described below; unreacted precursor phenol represented the principal material balance and yields based on recovered reactant approached quantitative in all cases. Although our primary focus has been the development of methods for *ortho*-methylation, this methodology appears capable of extension to more complex diiodoalkane precursors, as illustrated by the ethylation of 2,5-dimethylphenol (Entry 15). Our preliminary efforts directed at alkylation of phenols using diiodoalkanes[6] [$RCHI_2$] have produced low yields.

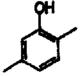
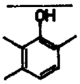
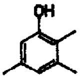
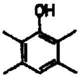
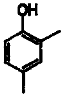
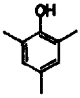
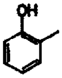
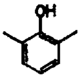
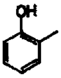
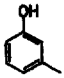
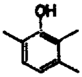
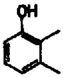
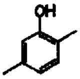
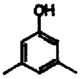
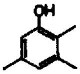
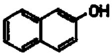
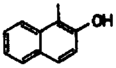
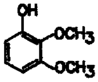
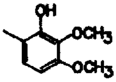
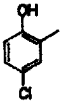
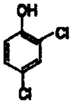
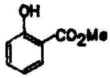
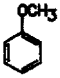
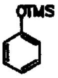
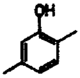
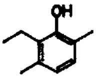
We postulate that this *ortho*-methylation process occurs *via* the sequence of reactions outlined in the Scheme. In the first step of the reaction, diethylzinc and diiodomethane undergo halogen metal exchange to produce ethyl(iodomethyl)zinc (1) and ethyliodide.[7] Subsequent deprotonation of the phenol by 1 results in rapid loss of ethane and production of the iodomethylzinc phenolate (2). The mechanism for phenol alkylation could proceed *via* two discrete pathways, which we have not been able to differentiate. In one mechanism, an internal alkylation-internal proton transfer process [eg. 2 -> 3 -> 5] is envisioned. Although the 5(endo)tet transition state for this process would appear unfavorable, this mechanism has parallels with the alkylation sequence proposed in the alkylation of phenols by olefins and ethers using triethylaluminum or aluminum triphenoxide.[7] Alternatively, a cycloalkylation-ring scission-internal proton transfer sequence [eg. 2 -> 4 -> 3 -> 5] to afford an intermediate methylphenolic zinc iodide complex (5) could occur. Subsequent protonation of the phenolate would afford the methylated phenol (6).

Scheme



Support for this sequence is derived from the following observations. The requisite formation of 1 is supported by the observation that simultaneous addition of diiodomethane and phenol to diethylzinc resulted in a 50% reduction of the yield observed with the mixing period. This suggests that the phenol and diiodomethane exhibit competitive reaction pathways with diethylzinc that result in phenol deprotonation (to ethylzinc phenolate) and metal halogen exchange (to 1). These reactions must have similar reaction rates at 0°C (eg. near diffusion-controlled) and, thus, diffusion presumably determines the percentage of reaction completion. The reduction in yield is due to formation of an ethylzinc phenolate species which, because of its reduced electrophilicity,[8] and aggregation in aromatic solvents,[9] is unable to undergo halogen metal exchange to form 2. In addition, a phenol moiety is essential for successful reaction; phenol derivatives, such as anisole or

TABLE

Entry	Starting Phenol	Diiodoalkane	Product	Product/Starting Ratio	Yield
1.		CH_2I_2		99/1	70 %
2.				99/1	80 %
3.				68/1	64 %
4.				70/1	57 %
5.				47/1	50 %
6.			  	0.82/0/0.61/1	62 %
7.				48/1	56 %
8.					20 %
9.				58/1	49 %
10.				21/1 after 8 hrs.	28 %
11.			NR		
12.			NR		
13.			NR		
14.			NR		
15.		CH_3CHI_2			25 %

phenylsilyl ethers, failed to undergo the reaction. Finally, a temperature profile of the reaction indicated that product appearance did not occur until the reaction reached a critical temperature of ≈120°C. Support for an intramolecular proton shift [eg. **3** -> **5**] was obtained from experiments in which the reaction was quenched with D_2O and the product analysis demonstrated no (<3%) incorporation of deuterium into the methyl group.

The general procedure used for this reaction follows. In a 25 mL round bottom flask, methylene iodide (0.14 mL, 2.0 eq, 1.6 mM) was dissolved in toluene (3 mL) and the solution cooled to 0°C. To a vigorously stirred solution, diethylzinc in toluene [1.2 mL of a 1.2 M solution (1.5 eq, 1.23 mM)] was added rapidly *via* syringe. After reaction of methylene iodide and diethylzinc for ~10 sec, the reactant phenol, dissolved in toluene (3 mL), was added. The reaction mixture was stirred at 0°C for 5 min. and then heated at reflux for 1.5 hr. The reaction was then cooled to 0°C and quenched with an aqueous solution of $NaHCO_3$ (10% w/w). Extraction with ether, followed by drying and concentration *in vacuo*, furnished the crude product as a dark yellow oil. Purification by chromatography gave the methylated phenol in the designated yield. **CAUTION:** Diethylzinc reacts violently with air.

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