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ORTHO-METALATION OF p-CHLOROANISOLE: A MEDIA STUDY

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Abstract: As the chlorophenyl group is a pharmacophore, its stability toward metalation conditions in conjunction with the methoxy substituent was assessed. For p-chloroanisole metalation ortho to the methoxy group was achieved in high yield using increments of THF in cyclohexane; numerous other regimes afforded lower yields and a competing benzyne pathway.

The ideal media for directed ortho-metalation (DoM) reactions would be hydrocarbon solvents (n-hexane, cyclohexane, toluene, etc.). These solvents avoid the plagues associated with common ether solvents (volatility, peroxides, adventitious moisture, reactivity with organolithium reagents), but suffer from the fact that organolithium reagents are relatively unreactive in such media. This diminished reactivity is commonly associated with the predominance of higher oligomer structures. Amine additives are known to increase the reactivity of such reagents in hydrocarbon solvents. Recently, we have observed that increments of tetramethylethylenediamine (TMEDA)[1] and increments of THF[2] in n-hexane dramatically accelerate the rate and significantly boost the extent of metalation of anisole. Such observations are of importance since they portend that conditions that approach a 1:1 correspondence of H-atom transfer and aryl organolithium intermediate formation can be achieved[3] by fine-tuning the solvent medium.

Metalation of the haloanisoles poses a problem of long-standing; that of p-fluoroanisole (p-FA) has been complicated by two competing sites of metalation[4] and that for p-BrA and p-IA by a competing halogen-metal exchange.[5] Only p-ClA has been cleanly ortho-metalated, but either relatively low yields have been achieved using ether as solvent[6a-c] or intensive conditions have been employed.[6d] Herein we report our study of the DoM of p-ClA, a study that has reinforced our contention of the efficacy of THF in hydrocarbon solvents as a valuable medium for certain metalation reactions.

Attempts to metalate p-ClA in n-hexane and cyclohexane using increments of TMEDA (0.1 equiv. TMEDA vs. 1.0 equiv. n-BuLi) afforded black solutions GC/MS analysis of which revealed products resulting from formation of a benzyne intermediate. Surprisingly, a similar observation was made when the metalation was attempted in neat THF (dried over molecular sieves). Inspection of the GC/MS of sequential samples from this latter reaction after quenching with excess chlorotrimethylsilane (ClTMS) revealed no incorporation of the TMS moiety in two peaks with m/z of 248 with an M+2 (1/3 intensity) at 250; TMS was incorporated in the lower m/z product at 214 with M+2 (1/3 intensity) at 216 (Figure I). The latter is the ortho TMS-product from derivatization of p-ClA while the former can be assigned to the brace of biphenyl derivatives that can be formed by the competing metalation of the site ortho to the chloro substituent, benzyne formation and capture by the more-rapidly-formed ortholithio intermediate (equation) (Figure I).[7]

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FIGURE I

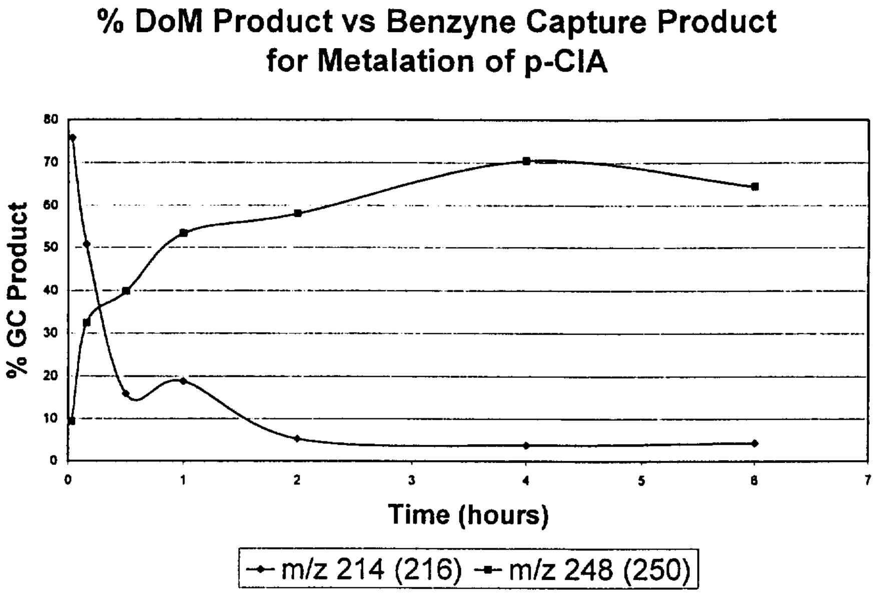
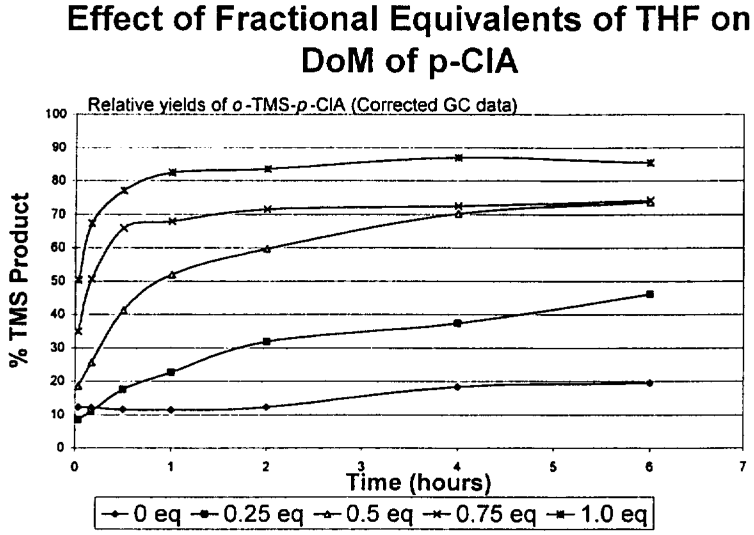
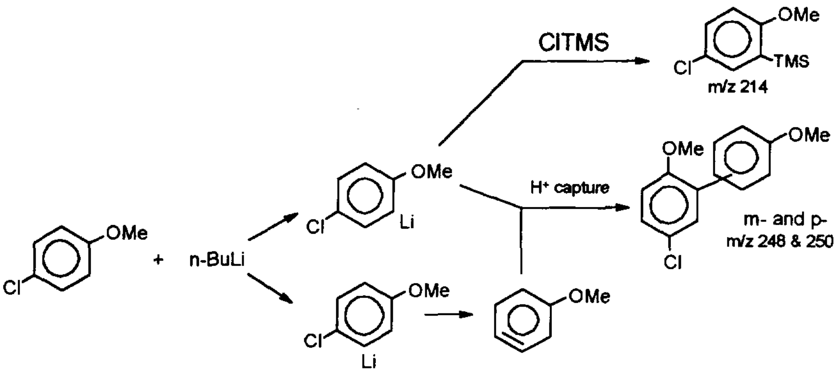


FIGURE II



THF in 30 ml cyclohexane at 25 degrees C, Containing .04 mole each (1 eq) of *p*-ClA and n-BuLi.



Fractional equivalents of THF in cyclohexane containing about 1.3 M each of p-ClA and n-BuLi provide a medium wherein only a modest yellowing of the homogeneous solution is observed with no evidence of products of benzyne formation.[8] One equivalent of THF in 30 mL of cyclohexane affords 86-88% ortho-metalation after 4 h (Figure II). Use of 2 equiv. of THF (not shown) produces a slightly higher extent of metalation. These observations are remarkable in that other media (neat THF, TMEDA/hydrocarbon solvent, TMEDA/ether) each afford benzyne intermediate formation. Use of diethylether itself, or diethylether, dioxolane, methyl t-butyl ether or dioxane in cyclohexane produce homogeneous media which provide significantly slower rates and lower extents of metalation. Use of up to four equiv. of THF in cyclohexane affords little additional benefit; use of five or more equiv. of THF causes contribution from the benzyne intermediate mechanism.

One last observation can be made. Comparison of the rates of metalation of p-ClA and anisole[2] under comparable conditions reveals that p-ClA undergoes metalation at a much faster rate. This observation has already been made for p-FA.[9] For p-ClA greater validity can be ascribed to our contention that an electronic effect is operating in this reaction since there are no competing benzyne formation products as there are in the metalation of p-FA. This effect can either be ascribed to an opposing-π-resonance effect,[10] a -I effect or a combination of both. Much the same analysis has been made by M. Schlosser et al. in the metalation of certain methylanisoles.[11]

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7. Comparison of the products from benzyne formation upon metalation of p-ClA and p-FA reveal significant differences. Study of GC/MS spectra of the product solutions resulting from metalation of p-FA, treatment with ClTMS followed by aqueous work-up indicate the following: (1) arenes resulting from the addition of n-BuLi across the 3,4-benzyne and either -H or -SiMe$_3$ capture (4 products); (2) biphenyls from coupling of the 3,4-benzyne and the aryllithiums resulting from addition of n-BuLi across the 3,4-benzyne followed by -H or -SiMe$_3$ capture (4 products); (3) fluorine-containing biphenyls resulting from o-Li-p-FA adding across the 3,4-benzyne followed by H- or -SiMe$_3$ capture(4 products). All twelve of these possible products were detected from p-FA yet under similar conditions only the two biphenyls illustrated in the equation were produced from p-ClA.
8. Experimental

   0.04 mol of p-ClA and 3.2 mL (0.04 mol, 1.0 equiv.) of THF dried over molecular sieves (Aldrich, 4A, 4-8 mesh) are added to 20 mL of dry cyclohexane in a one-neck flask purged with N$_2$ and sealed with a septum. To this solution is added 10 mL (0.04 mol) of 2.0 M n-BuLi in cyclohexane to bring the volume of cyclohexane to 30 mL. Other runs use exactly the same procedure exept that 0.01 mol (0.25 equiv.), 0.02 mol (0.5 equiv.), 0.03 mol (0.75 equiv) of THF are utilized. The flask is placed in a constant temperature bath maintained at 25°C. The plots of percentage metalation vs. time are constructed by extracting about 1 mL samples with a syringe from the reaction solution after 2, 10, 30 min., 1, 2, 4, 6, 24 h, or other periods as necessary, and quenching with a solution of excess chlorotrimethylsilane (ClTMS) in n-hexane. After aqueous workup each sample is subjected to GC analysis (HP 5890 A with OV-17 packed glass column). Identities of products are checked by GC-MS analysis (HP 5890 A gas chromatograph coupled with an HP 5970 series mass selective detector). Analysis of corrected spectra of TMS derivative(s) provides an estimate of the extent of metalation as measured by the lithio intermediate's capture of the TMS moiety.
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