Metalation of a 3,5-Dichloro-Tertiary Benzamide. An Unusual Regioselectivity Observation

Maria Demas, Gary J. Javadi, Lynn M. Bradley,* and David A. Hunt

Department of Chemistry, The College of New Jersey, Ewing, New Jersey 08628-0718

bradley@tcnj.edu

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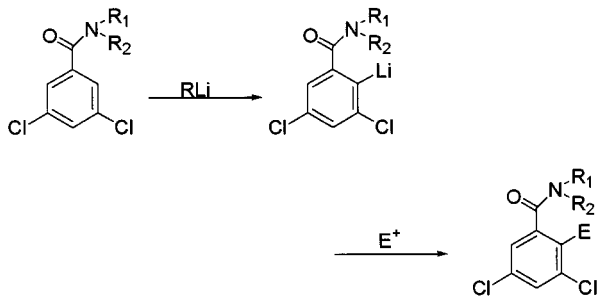
The use of directed *ortho*-metalation in the elaboration of aromatic rings has become a staple of synthesis over the past three decades.[1,2] The carboxamide moiety is one of the more powerful *ortho*-directing functional groups extensively used, exploited not only for its *ortho*-directing capability but also serving as a latent electrophilic reaction center for cyclization chemistry, particularly in the case of tertiary carboxamides.[3] Since we recently had occasion to prepare a variety of 2-substituted-3,5-dihalo-tertiary benzamides in support of a study targeting specific analogues for biological evaluation, we determined that the *ortho*-metalation method was best suited for the preparation of this series of compounds (Scheme 1).

Evaluation of the starting benzamide **1** reveals only two positions are available for metalation: the equivalent 2- and 6-positions *ortho* to the carboxamide and the 4-position adjacent to both chlorine atoms. Of these possibilities, conventional wisdom based on competitive metalation studies with both 4-chloro-*N*,*N*-diethylbenzamide[3] and 3,5-dimethoxy-*N*,*N*-diethylbenzamide[4] indicates the *ortho*-positions would be favored as the regioselective site of metalation due to the strong directing effect of the carboxamide compared with the moderate directing effect of chlorine and the methoxy group.

While the *ortho*-directing property of secondary benzamides in arene metalation reactions has been thoroughly investigated and is well understood, tertiary benzamides in comparable systems have been less widely studied. The seminal work of Beak and Brown utilizing *sec*-butyllithium as the metalating agent with inverse addition (substrate addition to *sec*-BuLi) has proven to be the best method for the *ortho*-metalation of tertiary benzamides.[3] Taking these findings into account, utilizing the conditions outlined by Beak and Brown, and using benzaldehydes as electrophiles, we were surprised to isolate the 4-substituted-3,5-dichlorobenzamides **3** in moderate to good yields with no detectable product arising from metalation *ortho* to the tertiary amide (Scheme 2). Determination of metalation regioselectivity was based on ^{1}H and ^{13}C NMR spectroscopy of the diaryl methanols.

A comparable phenomenon has been observed with the metalation behavior of compounds **4** and **5**, *N*-(pivaloyl)- and *N*-(*tert*-butoxycarbonyl)-3,5-difluoroaniline.[5] In both cases, metalation is directed exclusively by both fluorine atoms versus the N-containing functional group and a fluorine atom (Scheme 3).

Scheme 1



Possible explanations proposed for this observation involve steric control, electronic control, or a combination of the two. Regarding sterics, regioselectivity may lie in the mechanistic basis for the *ortho*-metalation process. Initial coordination of the *sec*-butyllithium with **1** can occur with the lone pairs of electrons residing on one of two functional groups: chlorine or the carboxamide. Crystal structure determinations of *ortho*-lithiated species with a variety of directing groups indicate that complexes involve tetrameric aggregates with a high degree of lithium−heteroatom coordination.[6] For the complex formed between *sec*-butyllithium and the tertiary carboxamide, adding to the sterics of the aggregate is the chlorine atom flanking the *ortho*-position relative to the tertiary amide−*sec*-butyllithium complex.[1] By comparison, once the relatively unencumbered chlorine−*sec*-butyllithium complex is formed, acidity of the 4-H is enhanced since complexation has been demonstrated to be an acidifying event.[7]

Yet another plausible rationale for these results may lie in electronic inductive effects based on the potential additive effect of metalation between halogen atoms *meta* to one another. An example of the additive enhancement of fluorine atoms has been documented. Thus, while fluorobenzene can be metalated in the 2-position, 1,3-difluorobenzene is metalated in the 2-position much faster.[8] Regarding this study, a more pertinent observation illustrating an additive effect is the 2-metalation of 1,3-dichlorobenzene.[9] While it is difficult to anticipate the expected regioselectivity of metalation due to the paucity of metalation studies on comparable 1,3,5-trisubstituted arenes, it is clear that the determining factors are related to electronic effects, steric effects, or a combination of both.

This study illustrates that through judicious choice of metalation-directing functional groups in polysubstituted

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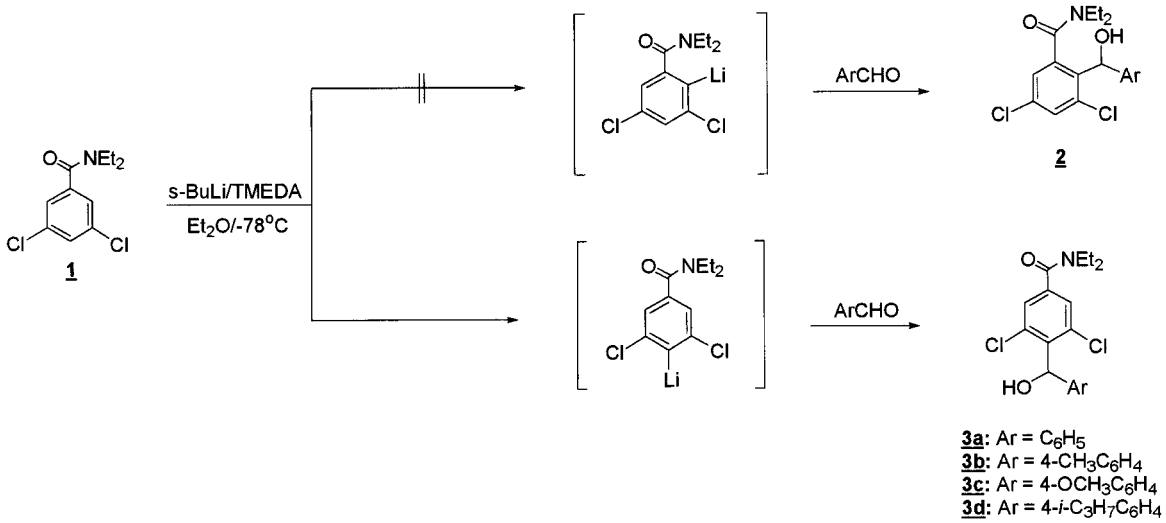
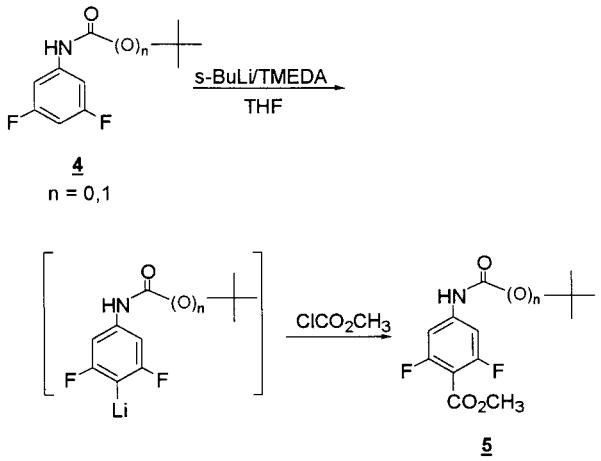
Scheme 2



Scheme 3



arenes, it may be possible to design substrates for regiospecific metalation based on steric control, electronic control, or a combination of both in preference to functional group directional ability alone. Furthermore, care needs to be taken selecting a directing group for *ortho*-metalation strategies when multiple metalation sites are possible.

Experimental Section

General Procedures. All reactions with organolithium reagents were conducted at −78 °C (dry ice−acetone slush bath) under a dry nitrogen atmosphere. Elemental analyses were obtained from Quantitative Technologies, Inc., Whitehouse, NJ.

General Reaction Procedure. To a flask containing 246 mg (1.00 mmol) of 3,5-dichloro-*N*,*N*-diethylbenzamide and 5 mL of anhydrous diethyl ether was added a solution of TMEDA (1.2 equiv) in 2 mL of anhydrous diethyl ether. The resulting solution was cooled with magnetic stirring to −78 °C. To the resulting white suspension was added 1.2 equiv of *sec*-BuLi in cyclohexane dropwise. The resulting yellow suspension was stirred at −78 °C for 30 min, at which point the aryl aldehyde (1.5 equiv) in 2 mL of anhydrous ether was added dropwise to the reaction mixture. The resulting mixture was allowed to slowly warm to ambient temperature and was stirred an additional 2 h. The mixture was quenched by addition to water. The ether layer was separated, sequentially washed with water and 2 N HCl, dried ($MgSO_4$), filtered, and concentrated. The residue was triturated with petroleum ether to afford the final product.

3,5-Dichloro-*N*,*N*-diethyl-4-(hydroxyphenylmethyl)benzamide (**3a**) was obtained as a colorless solid (152 mg; 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (br m, 3H), 1.26 (br m, 3H), 3.23 (br m, 2H), 3.52 (br m, 2H), 6.65 (s, 1H), 7.26−7.36 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.3, 39.6, 43.4, 72.1, 125.5, 127.4, 128.4, 135.5, 138.5, 138.9, 141.0, 167.9; IR (KBr) 3411, 2990, 1612, 1541, 1285, 1070 cm^{-1}; mp 129−131 °C. Anal. Calcd for $C_{18}H_{19}NO_2Cl_2$: C, 61.37; H, 5.44; N, 3.98; Cl, 20.13. Found: C, 61.36; H, 5.37; N, 4.01; Cl, 20.23.

3,5-Dichloro-*N*,*N*-diethyl-4-(hydroxy-*p*-tolylmethyl)benzamide (**3b**) was obtained as an off-white solid (161 mg; 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (br m, 3H), 1.26 (br m, 3H), 2.35 (s, 3H), 3.23 (br m, 2H), 3.52 (br m, 2H), 6.61 (s, 1H), 7.16 (bs, 4H), 7.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.3, 21.2, 39.6, 43.4, 72.2, 125.4, 127.2, 129.1, 135.4, 137.2, 137.9, 138.4, 138.8, 167.9; IR (KBr) 3409, 1612, 1495, 1274, 1070 cm^{-1}; mp 154−155 °C. Anal. Calcd for $C_{19}H_{21}NO_2Cl_2$: C, 62.30; H, 5.78; N, 3.82; Cl, 19.36. Found: C, 61.83; H, 5.74; N, 3.63; Cl, 19.25.

3,5-Dichloro-*N*,*N*-diethyl-4-[hydroxy-(4-methoxyphenyl)methyl)benzamide (**3c**) was obtained as an off-white solid (174 mg; 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (br m, 3H), 1.26 (br m, 3H), 3.23 (br m, 2H), 3.52 (br m, 2H), 3.81 (s, 3H), 6.58 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.3, 39.6, 43.4, 55.3, 72.1, 113.8, 126.8, 127.2, 132.9, 135.4, 138.5, 138.8, 159.0, 167.9; IR (KBr) 3384, 1607, 1510, 1251, 1050 cm^{-1}; mp 117−118 °C. Anal. Calcd for $C_{19}H_{21}NO_3Cl_2$: C, 59.70; H, 5.54; N, 3.66; Cl, 18.55. Found: C, 59.54; H, 5.44; N, 3.60; Cl, 18.86.

3,5-Dichloro-*N*,*N*-diethyl-4-[hydroxy-(4-isopropylphenyl)-methyl)benzamide (**3d**) was obtained as an off-white solid (153 mg; 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (br m, 3H), 1.26 (br m, 3H), 1.25 (d, J = 3.4 Hz, 6H), 2.91 (m, 1H), 3.23 (br m, 2H), 3.52 (br m, 2H), 6.61 (s, 1H), 7.20 (bs, 4H), 7.36 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9, 14.3, 33.7, 39.6, 43.4, 72.3, 125.5, 126.5, 127.2, 135.4, 138.2, 138.5, 138.8, 148.1, 167.9; IR (KBr) 3422, 2965, 1615, 1541, 1283, 1079 cm^{-1}; mp 154−157 °C. Anal. Calcd for $C_{21}H_{25}NO_2Cl_2$: C, 63.96; H, 6.39; N, 3.55; Cl, 17.98. Found: C, 63.89; H, 6.41; N, 3.48; Cl, 17.67.

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