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Regioselectivity Differentiation in Metalations of 3,5-Dichloro-Tertiary versus Secondary Benzamides

Francesca Khani, Tina Fleming, Carleton Collins, Erica Tabakin, Lynn M. Bradley*, David A. Hunt

Department of Chemistry, The College of New Jersey, Ewing, USA
Email: *Bradley@tcnj.edu

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Abstract

Metalation regioslectivity of 3,5-dichlorobenzamides is a function of the type of amide (secondary versus tertiary) used in the sequence. Metalation at the 2-position (adjacent to the carboxamide functional group) occurs when the secondary benzamide is metalated with *sec*-butyllithium/TMEDA mediated through complex-induced proximity effects (CIPE) process, whereas metalation with *sec*-butyllithium/TMEDA occurs exclusively at the 4-position when the tertiary benzamide is used under identical reaction conditions.

Keywords

Directed Ortho-Metalation, Complex-Induced Proximity Effects (CIPE), 3,5-Dichlorobenzamides

1. Introduction

Among the most powerful techniques for the introduction of electrophilic functional groups onto an aromatic or heteroaromatic ring system is that of Directed *ortho*-Metalation (DoM) [1]. Many review articles have been written on the technique over the past three decades describing both synthetic and mechanistic studies [2]-[7]. The importance of this effect has been amply illustrated by adoption of Directed *ortho*-Metalation as a key synthetic methodology over the past 30 years.

We have previously reported an unexpected regioselectivity observation for the metalation of 3,5-dichloro-*N*,*N*-diethylbenzamide **1** [8]. Addition of *sec*-butyllithium to a diethyl ether solution of the benzamide at −78˚C using benzaldehydes as electrophiles afforded the 4-substituted 3,5-dichlorobenzamides **3** in moderate to good

*Corresponding author.

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yields with no detectable product arising from metalation *ortho* to the tertiary amide (**Scheme 1**). Possible explanations proposed for this observation involve steric control, electronic control, or a combination of the two. In an effort to shed light on the physicochemical and/or mechanistic basis for this observation, we turned our attention to the metalation of the corresponding 3,5-dichloro-*N*-ethylbenzamide (**4**). This paper summarizes the difference between the metalation proclivities of 3,5-dichloro tertiary benzamides versus the corresponding secondary benzamides due to differences in the degree of complex-induced proximity effects (CIPE).

2. Results and Discussion

For the case of tertiary benzamide systems (**Scheme 1**), 1.0 - 1.2 molar equivalents of *sec*-butyllithium is typically employed for metalation, whereas the secondary benzamide requires a minimum of 2.0 molar equivalents of metalating agent, the first equivalent consumed in the generation of the anion **5** resulting from the acid-base reaction with the carboxamide functional group (**Scheme 2**). Through complex-induced proximity effects [4] [9] the metalated carboxamide functional group (**5**) directs the *ortho*-metalation through intermolecular complexation with the second equivalent of metalating agent. Since complexation has been shown to be an acidifying event [5], we felt that this chelation control effect may substantially alter any directing effects exerted by the chlorine atoms in the 3- and 5-positions, thereby resulting in metalation at the 2-position relative to the secondary carboxamide functional group for 3,5-dichloro-N-ethylbenzamide **4**.

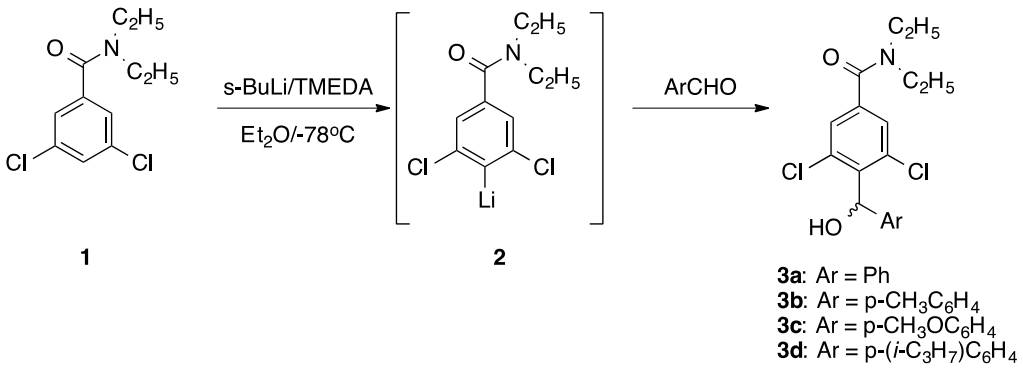
As before, *sec*-butyllithium was employed as the metalating agent with aromatic aldehydes used as electrophiles. However, in this case we isolated isobenzofuranones of the type **6** resulting from sequential *ortho*-metalation to form the bis-metalated intermediate **5** followed by nucleophilic addition to the aldehyde and subsequent intramolecular cyclization [10]-[14]. None of the product arising from metalation in the 4-position was detected (**Scheme 2**).

3. Conclusion

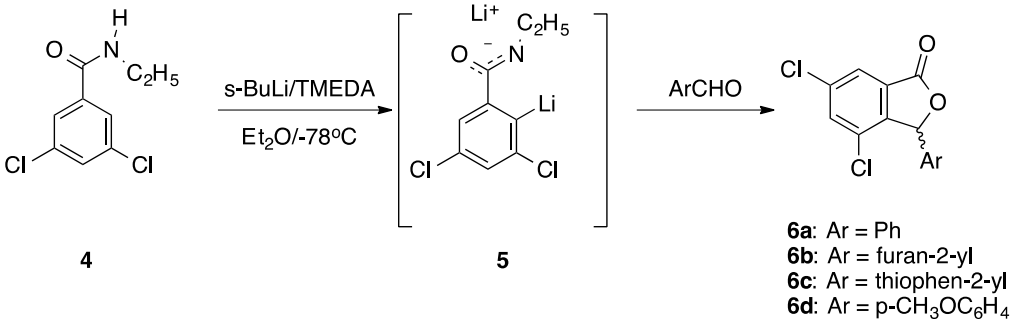
This study reveals that there are substantial differences in the degree of complexation (CIPE) of the metalating agent to the secondary versus tertiary carboxamide functional group in poly-substituted aromatic systems bearing other directing groups. These differences can and do play a major role in the regiospecificity of metalation reactions [16]. Studies detailing the behavior of the comparable 3,5-difluoro derivatives will be reported in due course.

4. Experimental

General. Tetrahydrofuran was purchased as anhydrous (Fluka) and was stored under a nitrogen blanket and over molecular sieves. *Sec*-Butyllithium (1.3 M in cyclohexane/hexane) was purchased from Acros Organics or Sigma-Aldrich. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data were obtained from a Varian Gemini 300 nuclear magnetic resonance spectrometer referencing tetramethylsilane and utilized $CDCl_3$ lock. IR data were obtained from a Perkin-Elmer Model Spectrum 2000 FT-IR spectrometer. GC/MS data were obtained from an Agilent Technologies 6850 GC/5973 MSD. Microanalyses were performed by Intertek, Whitehouse, NJ. All melting points were obtained from a Mel-Temp heating block apparatus and are uncorrected.



Scheme 1. *Para*-Metalation/elaboration of a tertiary 3,5-dichlorobenzamide.



Scheme 2. *Ortho*-Metalation/elaboration of a secondary 3,5-dichlorobenzamide.

Metalation of 3,5-Dichloro-*N*,*N*-Diethylbenzamide: General Reaction Procedure for the Preparation of 3a-d. 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 drop wise 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, CDCl3) 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˚C - 131˚C; MS: m/z = 351, 353, 355 (M^+). 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˚C - 155˚C; MS: m/z = 365, 367, 369 (M^+). 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, $CDCl_3$) ä 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˚C - 118˚C; MS: m/z = 381, 383, 385 (M^+). 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}CNMR (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˚C - 157˚C; MS: m/z = 393, 395, 397 (M^+). 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.

Metalation of 3,5-Dichloro-N-Ethylbenzamide: General Reaction Procedure for the Preparation of 6a-d.

To a 100 mL three-neck oven-dried flask equipped with a stir bar, nitrogen inlet, and low temperature thermocouple were added the 3,5-dichloro secondary benzamide (1.00 mmol), anhydrous THF (5 mL), and TMEDA (290 mg; 2.5 mmol) in anhydrous THF (5 mL). The mixture was cooled to −78˚C using a dry ice/acetone bath, and *sec*-butyllithium (2.5 equivalents relative to the starting benzamide) was added while the temperature was

maintained at or below −70˚C. The reaction was stirred for 30 min at which point a solution of 1.5 equivalents of an aromatic aldehyde in anhydrous THF (2 mL) was added. The reaction was allowed to warm to room temperature overnight under nitrogen and the mixture was quenched with water (100 mL). The mixture was then extracted with ethyl acetate (3 × 40 mL), with occasional use of saturated brine (35 mL) to alleviate emulsion formation. The organic layer was washed with a solution of saturated ammonium chloride (40 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude product. Purification was achieved by chromatography on silica gel (9:1 hexanes/MTBE) or a combination of trituration/chromatography.

4,6-Dichloro-3-phenylisobenzofuran-1(3H)-one (6a) was isolated as a white solid (chromatography), ^{1}H nmr ($CDCl_3$): δ 7.85 (d, $J_{m\text{-H}}$ = 1.7 Hz, 1, ArH), 7.60 (d, $J_{m\text{-H}}$ = 1.7 Hz, 1, ArH), 7.40 - 7.16 (m, 5, ArH), 6.35 (s, 1, CHO). ^{13}C nmr ($CDCl_3$): δ 168.1, 144.9, 137.1, 135.0, 133.8, 130.8, 130.1, 129.9, 129.2, 128.4, 124.4, 82.7; IR: 1776 (lactone) cm^{-1}; mp. 118˚C - 120˚C; MS: m/z = 278, 280, 282 (M^+). *Anal*. Calcd for $C_{14}H_8Cl_2O_2$; C, 60.24; H, 2.89. Found: C, 60.46; H, 2.71.

4,6-Dichloro-3-(furan-2-yl)isobenzofuran-1(3H)-one (6b) was isolated as an off-white solid (chromatography), ^{1}H nmr ($CDCl_3$): δ 7.83 (d, $J_{m\text{-H}}$ = 1.5 Hz, 1, ArH), 7.63 (d, $J_{m\text{-H}}$ = 1.5 Hz, 1, ArH), 7.38 (dd, $J_{\text{furanH2,H3}}$ = 2.0 Hz, $J_{\text{furanH2,H4}}$ = 0.8 Hz, 1, ArH) 6.50 (dd, $J_{\text{furanH4,H3}}$ = 3.3 Hz, $J_{\text{furanH4,H2}}$ = 0.6 Hz, 1, ArH), 6.40 (s, 1, CHO), 6.39 (dd, $J_{\text{furanH3,H4}}$ = 3.6 Hz, $J_{\text{furanH3,H2}}$ = 1.8 Hz, 1, ArH). ^{13}C nmr ($CDCl_3$): δ 167.5, 146.1, 144.5, 142.1, 137.4, 134.8, 130.8, 130.2, 124.5, 112.6, 111.1, 74.8; IR: 1778 (lactone) cm^{-1}; mp. 115.5˚C - 117˚C; MS: m/z = 268, 270, 272 (M^+). *Anal*. Calcd for $C_{12}H_6Cl_2O_3$; C, 53.56; H, 2.25. Found: C, 53.27; H, 2.25.

4,6-Dichloro-3-(thiophen-2-yl)isobenzofuran-1(3H)-one (6c) was isolated as an off-white solid (trituration/chromatography), ^{1}H nmr ($CDCl_3$): δ 7.84 (d, $J_{m\text{-H}}$ = 1.8 Hz, 1, ArH), 7.64 (d, $J_{m\text{-H}}$ = 1.5 Hz, 1, ArH), 7.38 (dd, $J_{\text{H2,H3}}$ = 5.4 Hz, $J_{\text{H2,H4}}$ = 0.9 Hz, 1, ArH), 7.14 (dd, $J_{\text{H4,H3}}$ = 3.6 Hz, J = 1.2 Hz, 1, ArH), 7.01 (dd, $J_{\text{H3,H2}}$ = 5.1 Hz, $J_{\text{H3,H4}}$ = 3.6 Hz, 1, ArH), 6.63 (s, 1, CHO). ^{13}C nmr ($CDCl_3$): δ 167.3, 144.1, 137.4, 136.4, 135.0, 130.9, 129.4, 128.2, 127.3, 127.1, 124.4, 77.2; IR: 1774 (lactone) cm^{-1}; mp. 107.5˚C - 109.5˚C; MS: m/z = 284, 286, 288 (M^+). *Anal*. Calcd for $C_{12}H_6Cl_2O_2S$; C, 50.54; H, 2.12. Found: C, 50.83; H, 2.31.

4,6-Dichloro-3-(4-methoxyphenyl)isobenzofuran-1(3H)-one (6d) was isolated as a white solid (trituration/chromatography),; ^{1}H nmr ($CDCl_3$): δ 7.84 (d, $J_{m\text{-H}}$ = 1.5 Hz, 1, ArH), 7.59 (d, $J_{m\text{-H}}$ = 1.8 Hz, 1, ArH), 7.10 (d, $J_{a,b}$ = 9.0 Hz,2, ArH), 6.86 (d, $J_{b,a}$ = 9.0 Hz, 2, ArH), 6.32 (s, 1, CHO), 3.79 (s, 3, OCH_3). ^{13}C nmr ($CDCl_3$): δ 169.0, 160.8, 145.0, 136.9, 134.8, 130.7, 129.8, 129.7, 125.6, 124.2, 114.4, 82.4, 55.5; IR: 1773 (lactone) cm^{-1}; mp. 107.5˚C - 109˚C;. MS: m/z = 308, 310, 312 (M^+). *Anal*. Calcd for $C_{15}H_{10}Cl_2O_3$; C, 58.28; H, 3.26. Found: C, 58.30; H, 3.31.

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