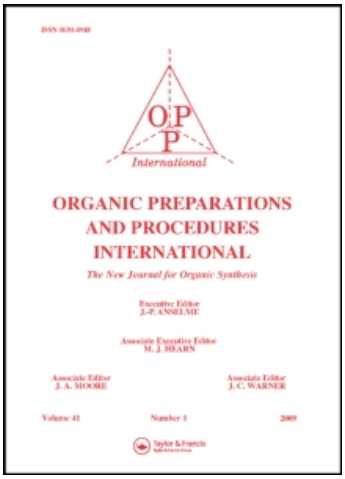

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Expedient Preparation of 4,6-Dihalo-3-arylisobenzofuran-1(3H)-ones from 3,5-Dihalo-*N*-ethylbenzamides

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Expedient Preparation of 4,6-Dihalo-3-arylisobenzofuran-1(3H)-ones from 3,5-Dihalo-*N*-ethylbenzamides

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3,5-Dihalobenzoic acid derivatives have long been known as scaffolds for compounds exhibiting a variety of biological activities. For example, compounds incorporating this moiety exhibit phytotoxicity,[1] selective inhibition of 11β-HSD1 for the treatment of metabolic syndrome,[2] MCH 1 receptor antagonism,[3] and serve as intermediates in the preparation of liquid crystals, fungicides, organo-tin antitumor compounds, insecticides, and quinolones possessing antibiotic activity.[4]

While our previous studies have shown that 3,5-dichloro tertiary benzamides are metalated *para* to the carboxamide group,[5] we have found that use of secondary amides derived from 3,5-dihalobenzoic acids (**1**, X = Cl, F) result in exclusive *ortho*-metalation. In light of the paucity of methods available to prepare highly ring-functionalized derivatives of 3,5-dihalobenzoic acids, coupled with recent studies documenting the unique antitumor properties of benzolactones,[6] we now describe the application of the chelation-controlled directed *ortho*-metalation reaction in this series as a useful method for the preparation of 4,6-dihalo-3-arylisobenzofuran-1(3H)-ones.

Metalation of 3,5-dihalo secondary benzamides (**1**) with *sec*-butyllithium resulted in exclusive *ortho*-directed metalation. Use of an aromatic aldehyde as the electrophile results in a lithioalkoxy intermediate (**3**) which undergoes nucleophilic attack upon the adjacent amide carbonyl during work-up with a concomitant loss of ethylamine, resulting in the formation of an aryl substituted dihalobenzofuranone (**4**, *Table 1*). This methodology should be applicable to a wide variety of both aromatic and aliphatic aldehydes based on reported reactions of aldehydes with aryllithium reagents generated by the directed *ortho*-metalation strategy.[7] Studies of these systems as well as the scope and limitations of this process will be the focus of future investigations.

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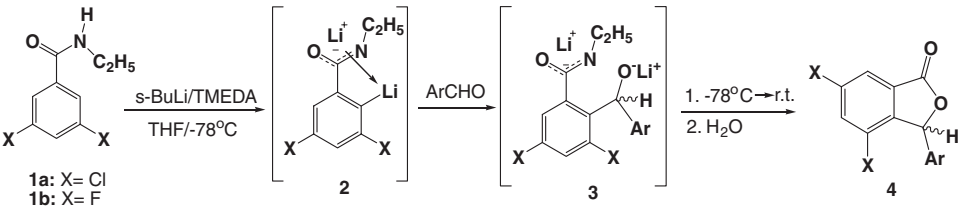

Experimental Section

Tetrahydrofuran was purchased as anhydrous (Fluka) and was stored under nitrogen. *sec*-Butyllithium (1.3 M in cyclohexane/hexane) was purchased from Acros Organics (the actual concentration was determined by colorimetric titration[8] prior to use). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data were acquired in $CDCl_3$ on a Varian Gemini 300 nuclear magnetic resonance spectrometer using tetramethylsilane (TMS) as internal standard $CDCl_3$ lock. IR data were determined 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 carried out by Quantitative Technologies, Inc., Whitehouse, NJ. All melting points were determined on a Mel-Temp heating block apparatus and are uncorrected.

General Procedure

The 3,5-dihalogenated secondary benzamide (1 mmol), anhydrous THF (5 mL), and TMEDA (290 mg; 2.5 mmol) in anhydrous THF (5 mL) were charged to a 100 mL three-neck oven-dried flask equipped with a stir bar, nitrogen inlet, and low temperature thermocouple. 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 below −70°C. The reaction mixture was stirred for 30 min at which point a solution of 1.5 equivalent of the aromatic aldehyde in anhydrous THF (2 mL) was added, it was allowed to warm to room temperature overnight under nitrogen

Table 1
Preparation of 4,6-Dihalo-3-arylisobenzofuran-1(3H)-ones

Compound	X	Ar	Yield (%)
4a	Cl	phenyl	90
4b	F	phenyl	88
4c	Cl	2-furyl	91
4d	F	2-furyl	64
4e	Cl	2-thienyl	97
4f	F	2-thienyl	77
4g	Cl	*p*-anisyl	73
4h	F	*p*-anisyl	98

and was quenched with water (100 mL). The mixture was then extracted with ethyl acetate (3 × 40 mL), with occasional use of a saturated sodium chloride solution (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), recrystallization, trituration (hexanes/MTBE), or a combination of trituration/chromatography.

4,6-Dichloro-3-phenylisobenzofuran-1(3H)-one (4a) was isolated as a white solid (chromatography), mp. 118–120°C; IR: 1776 (lactone) cm^{-1}; ^1H 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, Ar*H*), 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. Mass Spec: m/z = 279 (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-Difluoro-3-phenylisobenzofuran-1(3H)-one (4b) was isolated as a pale yellow solid (trituration), mp. 70–72°C. IR: 1765 (lactone) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (dd, $J_{H,F} = 6.6$ Hz, $J_{m\text{-}H} = 1.8$ Hz, 1, ArH), 7.40–7.24 (m, 5, ArH), 7.08 (td, $J_{H\text{-}F} = 8.7$ Hz, $J_{m\text{-}H} = 2.1$ Hz, 1, ArH), 6.46 (s, 1, CHO). ^{13}C nmr ($CDCl_3$): δ 168.2, 164.1, 157.2, 134.7, 129.9, 129.2, 128.4, 127.2, 126.4, 110.4, 108.8, 80.7. Mass Spec: m/z = 246 (M^+).

Anal. Calcd for $C_{14}H_8F_2O_2$: C, 68.29; H, 3.25. Found: C, 68.63; H, 3.56.

4,6-Dichloro-3-(2-furyl)isobenzofuran-1(3H)-one (4c) was isolated as an off-white solid (chromatography), [9].mp. 115.5–117°C; IR: 1778 (lactone) cm^{-1}; ^1H 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, $J_{furanH2,H3} = 2.0$ Hz, $J_{furanH2,H4} = 0.8$ Hz, 1, ArH) 6.50 (dd, $J_{furanH4,H3} = 3.3$ Hz, $J_{furanH4,H2} = 0.6$ Hz, 1, ArH), 6.40 (s, 1, CHO), 6.39 (dd, $J_{furanH3,H4} = 3.6$ Hz, $J_{furanH3,H2} = 1.8$ 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. Mass Spec: m/z = 268 (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-Difluoro-3-(2-furyl)isobenzofuran-1(3H)-one (4d) was isolated as a pale yellow oil (chromatography); IR: 3525 (hydrate); 1777 (lactone) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.47 (dd, $J_{H,F} = 6.6$ Hz, $J_{m\text{-}H} = 1.8$ Hz, 1, ArH), 7.41 (m, 1, $furan_{H2}$), 7.13 (td, $J_{H,F} = 8.6$ Hz, $J_{m\text{-}H} = 1.8$ Hz, 1, ArH), 6.48 (s, 1, CHO), 6.46 (d, $J_{furanH4,H3} = 3.3$ Hz, 1, ArH), 6.39 (dd, $J_{furanH3,H4} = 3.3$ Hz, $J_{furanH3,H2} = 1.8$ Hz, 1, ArH). ^{13}C nmr ($CDCl_3$): δ 168.0, 164.5, 157.3, 146.1, 144.6, 129.0, 128.4, 111.5, 111.2, 110.1, 108.9, 73.3. Mass Spec: m/z = 236 (M^+).

Anal. Calcd for $C_{12}H_6F_2O_3 \cdot 1/3H_2O$: C, 59.55; H, 2.76. Found: C, 59.77; H, 3.25.

4,6-Dichloro-3-(2-thienyl)isobenzofuran-1(3H)-one (4e) was isolated as an off-white solid (trituration/chromatography), mp. 107.5–109.5°C; IR: 1774 (lactone) cm^{-1}; ^1H 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, $J_{H2,H3} = 5.4$ Hz, $J_{H2,H4} = 0.9$ Hz, 1, ArH), 7.14 (dd, $J_{H4,H3} = 3.6$ Hz, J = 1.2 Hz, 1, ArH), 7.01 (dd, $J_{H3,H2} = 5.1$ Hz, $J_{H3,H4} = 3.6$ 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. Mass Spec: m/z = 284 (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-Difluoro-3-(2-thienyl)isobenzofuran-1(3H)-one (4f) was isolated as a yellow oil (chromatography); IR: 1774 (lactone) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.46 (dd, $J_{H,F} = 6.6$ Hz, $J_{m\text{-}H} = 2.1$ Hz, 1, ArH), 7.37 (dd, $J_{thiopheneH2,H_2} = 5.1$ Hz, $J_{thiopheneH2,H4} = 1.2$ Hz, 1, ArH),

7.16 (dd, $J_{thiopheneH4,H3} = 3.0$ Hz, $J_{thiopheneH4,H2} = 1.2$ Hz, 1, ArH), 7.13 (td, $J_{H,F} = 6.6$ Hz, $J_{m\text{-}H} = 2.1$ Hz, 1, ArH), 7.02 (dd, $J_{thiopheneH3,H2} = 5.1$ Hz, $J_{thiopheneH3,H4} = 3.0$ Hz, 1, ArH), 6.72 (s, 1, CHO). ^{13}C nmr ($CDCl_3$): δ 167.4, 164.4, 157.3, 151.0, 137.1, 130.4, 128.8, 127.9, 127.5, 110.5, 108.9, 75.8. Mass Spec: m/z = 252 (M^+).

Anal. Calcd for $C_{12}H_6F_2O_2S \cdot 1/3C_6H_{14}$: C, 59.86; H, 3.80. Found: C, 59.91; H, 3.81.

4,6-Dichloro-3-(*p*-anisyl)isobenzofuran-1(3H)-one (4g) was isolated as a white solid (trituration/chromatography), mp. 107.5–109°C; IR: 1773 (lactone) cm^{-1}; ^{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. Mass Spec: m/z = 308 (M^+).

Anal. Calcd for $C_{15}H_{10}Cl_2O_3$: C, 58.28; H, 3.26. Found: C, 58.30; H, 3.31.

4,6-Difluoro-3-(*p*-anisyl)isobenzofuran-1(3H)-one (4h) was isolated as a white solid (chromatography), mp. 100–103°C. IR: 1764 (lactone) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.45 (dd, $J_{H,F} = 6.6$ Hz, $J_{m\text{-}H} = 2.1$ Hz, 1, ArH), 7.16 (d, $J_{a,b} = 9.0$ Hz, 2, ArH), 7.07 (td, $J_{H\text{-}F} = 8.6$ Hz, $J_{m\text{-}H} = 2.0$ Hz, 1, ArH), 6.88 (d, $J_{b,a} = 9.0$ Hz, 2, ArH), 6.42 (s, 1, CHO), 3.79 (s, 3, OCH_3). ^{13}C nmr ($CDCl_3$): δ 168.3, 166.6, 160.9, 157.7, 131.5, 129.6, 128.8, 126.5, 114.6, 110.3, 108.7, 80.7, 55.6. Mass Spec: m/z = 276 (M^+).

Anal. Calcd for $C_{15}H_{10}F_2O_3$: C, 65.22; H, 3.62. Found: C, 65.44; H, 3.59.

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