Reaction of o-bromoaryl- and o-bromoarylalkyl phthalimides with n-butyllithium at low temperatures

Abstract

In a study designed to determine chemoselectivity of nucleophilic addition versus bromine-lithium exchange, addition of n-butyllithium to o-bromoaryl- and o-bromoarylalkyl phthalimides at low temperature results in clean addition to the imide carbonyl in lieu of bromine-lithium exchange thereby affording good to excellent yields of 3-n-butylydroxyisoindolin-1-ones containing a bromoarene moiety. This methodology has potential for the preparation of a variety of highly functionalized nitrogen heterocycles.

Keywords: o-bromoaryl phthalimides, o-bromoarylalkyl phthalimides, bromine-lithium exchange studies, 2-bromoaryl-3-n-butyloxyisoindolin-1-ones, 2-bromoarylalkyl-3-n-butyloxyisoindolin-1-ones

Introduction

The work of Parham, Jones and Sayed,1 which demonstrates that bromine-lithium exchange, occurs in preference to carbonyl addition in aromatic amide derivatives of o-bromo-β-phenylpropionic acid, led to the consideration of using o-bromoaryl phthalimides 1a-c as precursors for the preparation of multi-ring nitrogen heterocycles and for elaborations of aromatic systems requiring an amine-protecting group (Figure 1). While the chemistry of the addition of Grignard and organolithium reagents to phthalimides is well known,2 to the best of our knowledge, attempts to carry out the addition of the these reagents to brominated phthalimide derivatives such as 1a-c have not been studied.

Figure 1 o-bromoaryl phthalimides 1a-c as precursors for the preparation of multi-ring nitrogen heterocycles and for elaborations of aromatic systems requiring an amine-protecting group.

Results and discussion

Even at low temperatures (ca. -100°C), bromine-lithium exchange to provide intermediate 2 proved fruitless in each case, presumably due to the greater electro-philicity of the imide carbonyl system compared to the aryl bromide. The major product cleanly formed in each case was the addition product arising from attack of the n-butyllithium on the imide carbonyl group (Compound 3a-c, Figure 2).

While the reaction of Grignard reagents with phthalimides is well known and has proven to be a valuable method for the preparation of alkylidene phthalimidines,3 heating is typically necessary for the reaction. In the case of the low temperature exchange attempts of these systems, aliquotting experiments revealed that substantial butylation had occurred after 30 minutes at -100°C. Compound 3a was determined to be a mixture of rotamers based on 13C NMR analysis, presumably due to steric inhibition of free rotation about the phenyl C-N bond. The homologs 3b and 3c did not exhibit this behavior based of 13C NMR analysis. The 1H NMR spectrum of 3b revealed the presence of an AB pattern for the benzylic protons. Presumably, this
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Experimental

General

Meling points were determined on a Mel-Temp heating block in open capillary tubes and are uncorrected. 1H NMR spectra were obtained on a Varian Gemini 300 MHz NMR with tetramethylsilane as an internal reference. 13C NMR spectra (75MHz) were obtained utilizing CDCl3, lock. IR data were recorded on a Perkin-Elmer 2000 FT-IR spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. All starting material, reagents, and solvents were reagent grade and were used without additional purification. Tetrachlorofuran was dried over lithium aluminum hydride.

Preparation of N-(o-bromophenyl) phthalimide (1a)4

To a 500mL Erlenmeyer flask equipped with a magnetic stirrer were added o-bromo-aniline (20.40g; 0.119mol), phthalic acid (19.69g; 0.14mol), and acetic acid (150mL) and the resulting mixture was allowed to cool and was poured into water (200mL). The organic phase was separated and was extracted with chloroform (2x50mL). The combined organics were then washed sequentially with aqueous NaOH (0.2N, 300mL) and water (300mL). The organics were dried, filtered, and concentrated in vacuo to afford 1a as white needles (31.24 g, 87%), mp 126-127.5°C; IR (KBr): 3360, 3050, 2925, 1665, 1610, 1470, 1380, 1110, 1020, 860, 830, 760cm-1; 1H NMR (300MHz, CDCl3): δ: 8.02 (s, 1, H NMR (300MHz, CDCl3); 8.02-8.32 (m, 3 ArH), 7.12-7.43 (m, 3 ArH), 3.97 (s, 1, OH), 4.60 (AB pattern, 2, J=15Hz, benzylic CH2), 1.87-2.16 (m, 2, CH2), 1.36-1.78 (m, 2, CH2), 0.93-1.36 (m, 7, CH3). Found: C, 60.99; H, 5.40; Br, 21.44; N, 3.49.

Preparation of N-(o-bromobenzyl) phthalimide (1b)4

To a solution of o-bromobenzyl bromide (32.45g; 0.13mol) in DMF (75mL) in a 500mL Erlenmeyer flask equipped with a magnetic stirrer was added potassium phthalimide (25.90g; 0.14mol), and the resulting mixture was cooled to -100°C, and n-butyllithium (1.0molar equivalent) was added at such a rate so as to maintain the temperature below -95°C. After the addition was complete, the mixture was stirred at -100°C for 1h. The mixture was then allowed to warm to room temperature (2h) and was poured into water (200mL). The organic phase was separated from the aqueous phase and the aqueous phase was extracted with diethyl ether (3x125mL). The combined organics were dried (MgSO4), filtered and concentrated in vacuo. The crude products were purified by recrystallization.

Compounds 3a-c

2-(2-Bromophenyl)-3-butyl-3-hydroxyisoindolin-1-one (3a) (mixture of rotamers) was isolated as white needles (33.47g, 82%) as a brown semisolid, which was triturated with diethyl ether to provide 1a as white needles (31.24 g, 87%), mp 126-127.5°C; IR (KBr): 1675cm-1; 1H NMR (300MHz, CDCl3): δ: 8.07-8.32 (m, 3 ArH), 7.12-7.43 (m, 3 ArH), 3.97 (s, 1, OH), 4.60 (AB pattern, 2, J=15Hz, benzylic CH2), 1.36-1.78 (m, 2, CH2), 0.93-1.36 (m, 7, CH3). Found: C, 60.99; H, 5.40; Br, 21.98; N, 3.60.

General procedure for the reaction of n-butyllithium with N-(o-bromophenyl) phthalimides. Preparation of Compounds 3a-c

The bromo phthalimide (1a-c) was dissolved in anhydrous THF (125mL) and hexane6 (30mL), and the resulting solution was placed into a three-neck 250mL round bottom flask equipped with an overhead stirrer, addition funnel, low temperature thermometer and N2 inlet, and low temperature (LN2/diethyl ether) bath. The mixture was cooled to -100°C, and n-butyllithium (1.0molar equivalent) was added at such a rate as to maintain the temperature below -95°C. After the addition was complete, the mixture was stirred at -100°C for 1h. The mixture was then allowed to warm to room temperature (2h) and was poured into water (200mL). The organic phase was separated from the aqueous phase and the aqueous phase was extracted with diethyl ether (3x125mL). The combined organics were dried (MgSO4), filtered and concentrated in vacuo. The crude products were purified by recrystallization.

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1310, 1280, 1060, 1010, 750 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 0.77-1.32 (m, 7, CH\(_3\)CH\(_2\)CH\(_2\))2.11 (t, 2, J=8 Hz, CH\(_2\)), 3.03-3.80 (m, 4, CH\(_2\), benzylic CH\(_2\)), 3.76 (bd s, 1, OH), 6.92-7.57 (m, 8, ArH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 61.84, 22.42, 25.60, 35.09, 35.87, 38.66, 91.42, 121.69, 123.12, 124.55, 126.31, 127.61, 128.19, 129.36, 131.11, 132.22, 132.81, 138.65, 146.90, 167.76. Anal. Calcd for C\(_{20}\)H\(_{22}\)BrNO\(_2\): C, 61.86; H, 5.67; Br, 20.62; N, 3.61. Found: C, 62.04; H, 5.78; Br, 20.77; N, 3.43.

**Conclusion**

Hydroxphthalimidines 3a-c were obtained in good yields with no perceptible halogen-metal exchange by low temperature addition of n-butyllithium to N-(o-bromophenyl)-phthalimide and N-(o-bromophenylalkyl)phthalimides and were characterized by \(^1\)H and \(^{13}\)C NMR, IR, and elemental analysis. This methodology may provide an entry to a variety of heterocyclic systems that may utilize the latent functionalization that subsequent bromine-lithium exchange can provide.

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None.

**Conflict of interest**

Author declares that there is no conflict of interest.

**References**

6. Practical grade, stored over 4Å molecular sieves.