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 these reagents to brominated phthalimide derivatives such as 1a-c have not been studied.

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 electrophilicity 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-butyl-lithium on the imide carbonyl group (Compound 3a-c, Figure 2).

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.

Figure 2. The major product cleanly formed in each case was the addition product arising from attack of the n-butyl-lithium on the imide carbonyl group.

While the reaction of Grignard reagents with phthalimides is well known and has proven to be a valuable method for the preparation of alkylidene-thalimines,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
is not due to rotational barriers since this was not observed in the $^{13}$C NMR spectrum.

**Experimental**

**General**

Melting points were determined on a Mel-Temp heating block in open capillary tubes and are uncorrected. $^{1}$$H$ NMR spectra were obtained on a Varian Gemini 300 MHz NMR with tetramethylsilane as an internal reference. $^{13}$C NMR spectra (75MHz) were obtained utilizing CDCl$_3$ 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. Tetracydrofuran was dried over lithium aluminum hydride.

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

To a 500 mL Erlenmeyer flask equipped with a magnetic stirrer were added o-bromo-aniline (20.40g; 0.119mol), phthalic acid (19.69g; 0.119mol), and acetic acid (150mL) and the resulting mixture was heated with stirring to 100°C (oil bath) for 14h. The mixture was then allowed to cool and was poured into water (400mL). The resulting crystalline precipitate was collected by vacuum filtration and was air-dried to constant weight (32.83g, 91%). The compound was purified by recrystallization from ethanol-chloroform (1:1) to provide purified 1a as white needles (31.24 g, 87%), mp 126-27.5°C; IR (KBr): 1673cm$^{-1}$; $^{1}$$H$ NMR (300MHz, CDCl$_3$): 8.72-8.12 (m, 1 ArH); 3.83 (t, 2, J=8Hz, benzylic CH$_2$); 1.20-1.82 (m, 4, CH$_2$). Anal. Calcd for C$_{12}$H$_{8}$BrNO$_2$: C, 55.63; H, 2.65; Br, 26.49; N, 4.64. Found: C, 55.65; H, 2.79; Br, 26.57; N, 4.48.

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

To a solution of o-bromobenzyl bromide (32.45g; 0.13mol) in DMF (75mL) in a 500 mL Erlenmeyer flask equipped with a magnetic stirrer was added potassium phthalimide (25.90g; 0.14mol). An exothermic reaction ensued (70°C within 8min), and stirring was continued until the mixture cooled to room temperature (4h). The mixture was then diluted with chloroform (200mL) and the resulting mixture was poured into water (300mL). The aqueous phase was separated and was extracted with chloroform (2x250mL). 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 1b (32.00 g, 78%), mp 162-64°C; IR (KBr): 1609cm$^{-1}$; $^{1}$$H$ NMR (300MHz, CDCl$_3$); 8.31-7.60 (m, 2 ArH); 7.50-7.67 (m, 1 ArH); 7.80-8.12 (m, 4 ArH). Anal. Calcd for C$_{15}$H$_{10}$BrNO: C, 56.84; H, 3.12; Br, 25.53, 35.93, 41.39, 91.81, 122.59, 122.93, 123.51, 127.48, 128.71, 129.56, 130.08, 130.66. 132.55, 137.09, 146.90, 168.02. Found: C, 56.84; H, 3.12; Br, 25.32; N, 4.43. Found: C, 56.84; H, 3.12; Br, 25.41; N, 4.27.

**Preparation of N-(o-bromo-$\beta$-phenylethyl) phthalimide (1c)**

o-Bromo-$\beta$-phenylethyl bromide (90.65g; 0.343mol) was placed in a 1L Erlenmeyer flask equipped with a magnetic stirrer and oil bath and was dissolved in DMF (280mL). To the stirred solution was added potassium phthalimide (66.64g; 0.360mol) and the resulting mixture was heated to 90°C with stirring for 15h. The mixture was allowed to cool and was diluted with chloroform (400mL). The mixture was transferred to a separatory funnel containing water (300mL). After vigorous mixing, the aqueous phase was removed and extracted with chloroform (2x250mL). The combined chloroform layers were washed sequentially with aqueous NaOH (0.2N, 300mL) and water (300mL). The organics were dried, filtered, and concentrated in vacuo to afford 1c as a pale yellow solid (32.83g, 91%). The compound was purified by recrystallization from benzene-petroleum ether (1:3) to provide purified 1c as white needles (32.83g, 91%). The compound was purified by recrystallization from benzene-petroleum ether (1:3) to provide purified 1c as white needles (32.83g, 91%). The compound was purified by recrystallization from benzene-petroleum ether (1:3) to provide purified 1c as white needles (32.83g, 91%). The compound was purified by recrystallization from benzene-petroleum ether (1:3) to provide purified 1c as white needles (32.83g, 91%). The compound was purified by recrystallization from benzene-petroleum ether (1:3) to provide purified 1c as white needles (32.83g, 91%).
1310, 1280, 1060, 1010, 750 cm\(^{-1}\); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 0.77-1.32 (m, 7, CH\(_2\)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 (br s, 1, OH), 6.92-7.57 (m, 8, ArH); \(^1^C\) NMR (75 MHz, CDCl\(_3\)): 61.38, 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 \(^1^C\) 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.

**Acknowledgements**

None.

**Conflict of interest**

Author declares that there is no conflict of interest.

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