

REACTION OF THERMOLABILE ARYLITHIUM REAGENTS WITH N-METHYLISATOIC ANHYDRIDE

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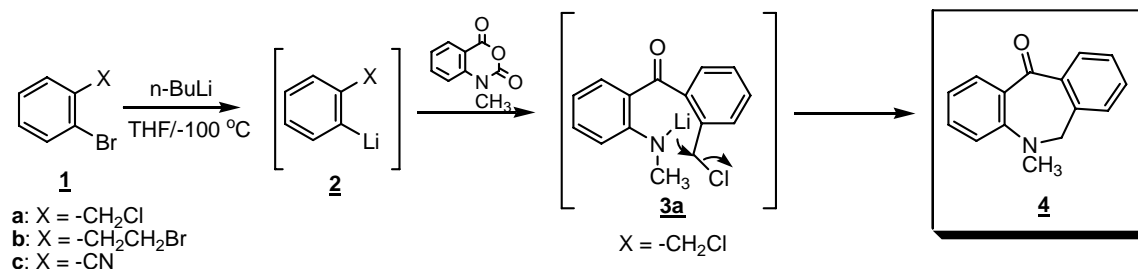
ABSTRACT

Aryllithium reagents functionalized with pendant electrophilic functional groups react with N-methylisatoic anhydride to provide highly functionalized *o*-N-methylamino- benzophenones which would be difficult to prepare by other methods. However, intramolecular capture of the intermediate N-lithio intermediate to form tricyclic nitrogen heterocycles failed. A rationale for this observation is provided based on spectroscopic evidence.

INTRODUCTION

Isatoic anhydrides are known to be extremely versatile reagents, useful in the preparation of a variety of heterocyclic ring systems.¹ Previous studies have shown that these compounds react efficiently with carbanions. One study focused on a two-step process utilizing the reaction of an aryllithium reagent with isatoic anhydride to form *o*-aminobenzophenones.² However, to the best of our knowledge, there have been no studies detailing reactivity of isatoic anhydride and related derivatives with functionalized organometallics, specifically thermolabile aryllithium reagents of the Parham type (compounds of the type **2**; Scheme 1).³ This one-pot reaction sequence could provide a novel entry to tricyclic structures of the type **4** *via* nucleophilic attack of the nitrogen onto the internal electrophilic center (**3**→**4**). This study will describe our work toward demonstrating the feasibility of this chemistry toward the development of a new cyclization methodology.

Scheme 1



EXPERIMENTAL

General

All reactions involving organolithium reagents were conducted under an atmosphere of nitrogen. Tetrahydrofuran was purchased as "dry" (OmniSolv) and was stored under a nitrogen blanket. Reaction temperatures of -100 °C were achieved with a liquid nitrogen-toluene bath; reaction temperatures of -78 °C were achieved with an acetone-dry ice bath. All organic residues were dried over anhydrous magnesium sulfate. Crude product yields are reported.

¹H NMR (300 MHz) and ¹³C NMR (75 MHz) data were obtained from a Varian Gemini 300 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane. ¹³C NMR data utilized CDCl₃ lock; IR data were obtained from a Perkin-Elmer Model Spectrum 2000 FT-IR

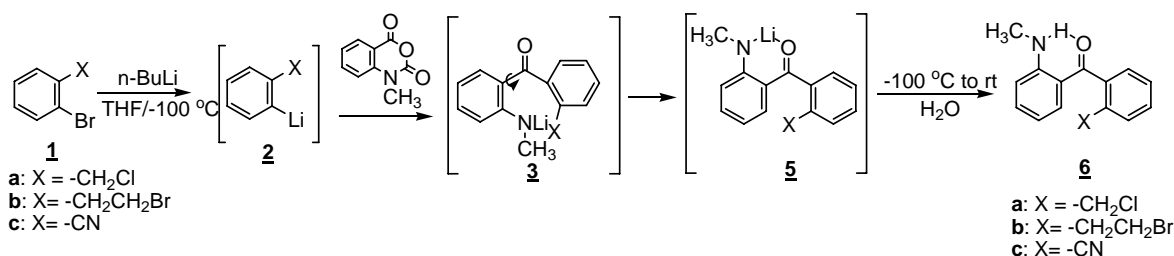
spectrometer; mass spectra were obtained from a Varian Model CP-3800 gas chromatograph interfaced to a Varian Saturn 2000 GC/MS/MS.

Microanalyses were performed by Quantitative Technologies, Inc., Whitehouse, N. J. All melting points were obtained from a Mel-Temp heating block apparatus and are uncorrected.

General Procedure

To produce the initial aryllithium intermediate, the halogen-metal exchange was conducted on the aryl halide (5.64 mmol) with one equivalent of *n*-butyllithium (3.9 mL of 1.6 M in hexanes; 6.24 mmol) in dry THF while maintaining the temperature at -90 to -100 °C in a liquid nitrogen-toluene bath.⁵ This solution was then allowed to stir for 30 minutes. A pink color was observed during this step, indicative of the functionalized aryllithium. N-Methylisatoic anhydride (1.00 g; 5.64 mmol) was then added to this solution in the same flask, while maintaining the temperature at -100 °C. During the addition of N-methylisatoic anhydride to the carbanion, a color change was always observed and was a function of the specific functionalized aryllithium used in the reaction sequence. The reaction mixture was stirred under an atmosphere of nitrogen while slowly warming to room temperature and was then added to water. The aqueous mixture was extracted with ethyl acetate and the organics were separated, dried (MgSO₄), and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel eluting with hexanes/EtOAc.

Scheme 2



2-Chloromethyl-2'-methylaminobenzophenone [Scheme 2 - (**6a**) 1.12 g, 77%] was isolated as a viscous yellow oil; ¹H NMR (CDCl₃) □□2.88 (d,3H,-NHCH₃□, 4.51 (s, 2H, -CH₂Cl), 6.36 (tt,1H,ArH), 6.64 (d,1H,ArH), 7.12-7.44 (m,6H,ArH), 8.78 (br s1H,-NH); ¹³C NMR (CDCl₃) □ 29.50, 43.54, 111.24, 113.94, 117.43, 127.92, 128.30, 129.77, 130.40, 135.32, 135.49, 140.51, 153.15, 199.64; IR (nujol) 1678 cm⁻¹

2-Bromoethyl-2'-methylaminobenzophenone [Scheme 2 - (**6b**) 0.542 g, 30%] was isolated as a dark yellow oil; ¹H NMR (CDCl₃) □□2.88 (d,3H, -NHCH₃), 3.02 (t,2H,-CH₂), 3.42 (t,2H,-CH₂), 6.32 (t,1H,ArH), 6.64 (d,1H,ArH), 7.09-7.31 (m,6H,ArH), 8.80 (br s1H,-NH); ¹³C NMR (CDCl₃) □ 29.51, 32.85, 37.04, 111.31, 112.24, 113.94, 114.41, 126.48, 128.02, 129.39, 130.56, 131.42, 135.91, 136.78, 153.12, 200.58; mass spectrum (70 eV), m/z 319 (M⁺; ⁸¹Br isotope), 317 (M⁺; ⁷⁹Br isotope).

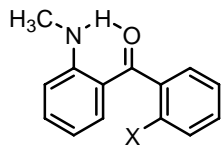
2-[2'-(Methylamino)benzoyl]benzonitrile [Scheme 2 - (**6c**) 1.33 g, 100%] was isolated as a yellow oil; ¹H NMR (d₆-acetone) □□2.88 (d,3H, -NHCH₃), 6.53 (t,1H,ArH), 6.75 (d,1H,ArH), 7.36-7.82 (m,6H,ArH), 8.80 (br s1H,-NH); IR (nujol) 2306 cm⁻¹

RESULTS

Initial results (Table 1) indicate that the functionalized aryllithium reagents of the type **2** do indeed react with N-methylisatoic anhydride in the predicted fashion to afford functionalized *o*-(lithioamino) benzophenones of the type **3**. No products of the type **4** were detected upon quenching the reaction mixture after warming to room temperature; rather, the functionalized aminobenzophenones **6** were isolated in low to moderate yields. Analysis of the spectral data revealed the clear presence of an intramolecular hydrogen

bond, indicating that the formation of the intramolecular chelated intermediate **5** is no doubt favored. The non-nucleophilic nature of **5** would preclude cyclization onto the pendant electrophilic center. Attempts to utilize **6** as a synthon for the preparation of cyclized derivatives will be the focus of a future study.

Table 1



<u>X</u>	<u>-NH (δ, ppm)</u>
-CH ₂ Cl	8.78
-CH ₂ CH ₂ Br	8.80
-CN	8.59

CONCLUSION AND FUTURE WORK

The feasibility study of the reaction of the functionalized aryllithium reagents of the type **2** with N-methylisatoic anhydride proved successful. However, because of the non-nucleophilic nature of the intermediate N-lithio salts **5** which formed, the only products isolated were the functionalized aminobenzophenone derivatives **6**. However, this method may well be of use in the design and synthesis of pharmacologically useful *o*-aminobenzophenones which would be difficult to prepare by other means.⁴ While the feasibility study proved successful, the reactions require further optimization and additional studies need to be conducted to determine the full scope of this chemistry.

ACKNOWLEDGEMENTS

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