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REACTION OF FUNCTIONALIZED ARYL LITHIUM REAGENTS WITH N-ALKYLISOTOICANHYDRIDES. A STRAIGHT FORWARD ROUTE TO 2'-SUBSTITUTED 2-N-ALKYLAMINOBENZOPHENONE DERIVATIVES

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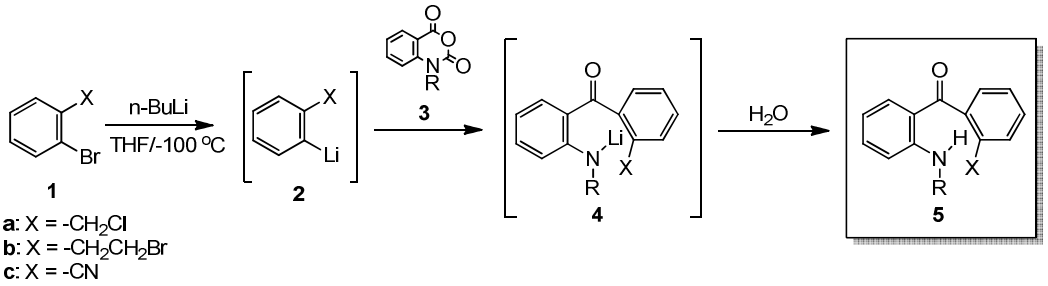
ABSTRACT
N-Substituted isatoic anhydrides have been found to cleanly undergo acylation with Parham reagents (highly elctrophillic functional group-substituted aryllithium reagents) followed by elimination of CO_2 to afford novel 2'-substituted 2-N-alkyl- aminobenzophenones difficult to prepare by standard methods. Such derivatives could prove useful as intermediates toward the preparation of novel heterocyclic systems.

KEYWORDS: Isatoic anhydrides, Parham chemistry, functionalized aryllithium reagents, 2-aminobenzophenones, 2'-substituted 2-N-alkyl-aminobenzophenones

1. INTRODUCTION
2-Aminobenzophenone derivatives have long been of value as synthetic intermediates for the preparation of a variety of heterocyclic ring systems[I]. Additionally, they also have applications as therapeutic agents with activities as anticancer agents[II] and bradykinin B1 receptor antagonists[III]. The most common methods for the preparation of 2-aminobenzo-phenones from appropriately substituted anilines entail harsh reaction conditions or expensive reagents[IV].

Isatoic anhydrides have been well documented as valuable synthons for heterocycle synthesis[V]. While nucleophilc ring opening of isatoic anhydrides is well known and has been thoroughly documented, corresponding ring opening reactions with aryllithium reagents have been detailed to a lesser extent. One of the few studies to date describing aryllithium addition to isatoic anhydrides demonstrates a two-step process using an aryllithium reagent with isatoic anhydride and 2-amino-N-methoxy-N-methylbenzamide to afford 2-aminobenzophnones[VI]. However, the reactions of isatoic anhydride and related derivatives with functionalized aryllithium reagents of the Parham type have not been reported to date (compounds of the type **2**; Scheme 1)[VII]. Utilization of this one-pot reaction process could provide a straightforward route to highly functionalized 2-amino- benzophenones of the type

8. This study describes our work toward the development of a new method for the preparation of highly functionalized 2'-substituted 2-N-alkylaminobenzophenones.



Scheme 1 - Reaction of Isatoic Anhydrideswith Functionalized Aryllithium Reagents

2. 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 ^{o}C were achieved with a liquid nitrogen-toluene bath. All organic residues were dried over anhydrous magnesium sulfate.

^{1}H NMR (300 MHz) data were obtained from a Varian Gemini 300 300MHz nuclear magnetic resonance spectrometer referencing tetramethylsilane. 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.

General Procedure for the preparation of 2'-substituted 2-N-alkylamino-benzophenones 8: Preparation of 2-Chloromethyl-2'-methylaminobenzophenone 8a. Aryllithium intermediate **2a** was prepared *via* the halogen-metal exchange of the aryl halide (1.16 g; 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[VIII]. This solution was then allowed to stir for 30 min. 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 as a solid through a powder addition funnel under N_2 while maintaining the temperature at -100 ˚C. During the addition of isatoic anhydride to the aryllithium reagent, 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 a N_2 blanket while warming to ambient temperature and was then added to water. The aqueous mixture was extracted with EtOAc (3 X 50 mL) and the organics were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was then purified by column chromatography on silica gel eluting with hexanes/EtOAc to afford **8a** (1.12 g, 77%)as a viscous yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.88 (d,J=5.1 Hz, 3H,-$NHCH_3$), 4.51 (s, 2H, -CH_2Cl), 6.36 (t,J=6.9 Hz, 1H,ArH), 6.64 (d,J=8.4 Hz, 1H,ArH), 7.12-7.44 (m,6H,ArH), 8.78 (br s,1H,-NH); IR 1621 cm^{-1} (C=O), 3313 cm^{-1} (-NH); mass spectrum (70eV) m/z223 (M^{+}-HCl)

2-Bromoethyl-2'-methylaminobenzophenone [**(8b)** 74%] was isolated as a bright yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (d, J=5.1Hz, 3H, -$NHCH_3$**)**, 3.02 (t, J=7.8 Hz, 2H, -CH_2CH_2Br), 3.42 (t, J=7.8 Hz, 2H, -CH_2Br), 6.32 (t,J= 7.1Hz, 1H), ArH, 6.64 (d, j= 8.1Hz, 1H, ArH), 7.09-7.31 (m, 6H, ArH), 8.80 (br s, 1H, -NH); IR 1616 cm^{-1} (C=O), 3320 cm^{-1} (-NH); mass spectrum (70eV) m/z 319/317 (M^{+})

2-[2'-(Methylamino)benzoyl]benzonitrile [(**8c)** 93%] was isolated as a yellow oil which crystallized on standing, mp = 128-130 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (d, J=5.4 Hz, 3H, -$NHCH_3$**)**, 6.53 (t, J= 8.2 Hz, 1H, ArH), 6.75 (d, J= 8.2 Hz, 1H, ArH), 7.36-7.82 (m, 6H, ArH), 8.59 (br s, 1H, -NH); IR 1619 cm^{-1} (C=O), 2235 cm^{-1}(-CN), 3306 cm^{-1} (-NH); mass spectrum (70eV) m/z 312 (M^+)

2-Chloromethyl-2'-ethylaminobenzophenone[(**8d**) 67%] was isolated as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J=6.9 Hz, 3H, -CH_2CH_3**)**, 3.15 (q, j= 6.9 Hz, 2H, -CH_2), 4.45 (s, 2H, -CH_2Cl), 6.25 (t, J= 6.8Hz, 1H, ArH), 6.59 (d, J= 8.1Hz, 1H, ArH), 7.04-7.40 (m, 6H, ArH), 8.69 (br s, 1H, -NH); IR 1619 cm^{-1}(C=O), 3315 cm^{-1} (-NH); mass spectrum (70eV)m/z 237 (M^+-HCl)

2-Bromoethyl-2'-ethylaminobenzophenone [(**8e)** 71%] was isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, J= 7.8 Hz, 3H, -CH_2CH_3**),** 3.08 (q, J=7.8 Hz, 2H, -$NHCH_2$), 3.02 (t, J= 7.8 Hz, 2H, -CH_2CH_2Br), 3.35 (t, J= 7.8 Hz, 2H, -CH_2Br), 6.25 (t, J= 8.1 Hz, 1H, ArH) 6.55 (d, J= 8.1 Hz, 1H, ArH), 6.98-7.22 (m, 6H, ArH), 8.68 (br s, 1H, -NH); IR 1616 cm^{-1} (C=O), 3320 cm^{-1} (-NH); mass spectrum (70eV) m/z 330/332(M^+-H)

2-[2'-(Ethylamino)benzoyl]benzonitrile [(**8f)** 93%] was isolated as a yellow oil which crystallized on standing, mp = 59-62 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.18 (t, J= 6.9 Hz, 3H, -$NHCH_2CH_3$**)**, 3.14 (overlapping d of q, 2H, -$NHCH_2CH_3$),6.30 (t, J= 8.2 Hz, 1H, ArH), 6.60 (d, J= 8.2 Hz, 1H, ArH), 7.00-7.60 (m, 6H, ArH), 8.65 (br s, 1H, -NH); IR 1618 cm^{-1} (C=O), 2233 cm^{-1}(-CN), 3309 cm^{-1} (-NH); mass spectrum (70eV**)** m/z 250 (M^+)

2-Chloromethyl-2'-benzylaminobenzophenone[(**8g**) 67%] was isolated as an orange oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, J= 5.7 Hz, 3H, -$NHCH_2$**)**, 4.46 (s, 2H, -CH_2), 4.45 (s, 2H, -CH_2Cl), 6.25 (t, J= 8.1Hz, 1H, ArH), 6.59 (d, j= 8.7 Hz, 1H, ArH), 7.04-7.40 (m, 6H, ArH), 8.69 (br s, 1H, -NH); IR 1614 cm^{-1}(C=O), 3318 cm^{-1} (-NH); mass spectrum (70eV) m/z 299 (M^+-HCl)

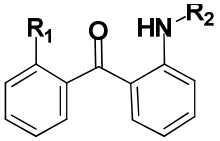
2-Bromoethyl-2'-benzylaminobenzophenone [**(8h)** 49%] was isolated as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (t, J= Hz, 2H, -CH_2CH_2Br**),** 3.35 (t, J=Hz, 2H, -CH_2CH_2Br), 4.36 (d, J= Hz, 2H, -$NHCH_2$), 6.27 (t, J= 8.1 Hz, ArH), 6.52 (d, J= 8.1 Hz, 1H, ArH), 7.04-7.20 (m, 6H, ArH), 9.19 (br s, 1H, -NH); IR 1616 cm^{-1} (C=O), 3320 cm^{-1} (-NH); mass spectrum (70eV) m/z 313 (M^+-HBr)

2-[2'-(Benzylamino)benzoyl)benzonitrile [**(8i)** 84%] was isolated as a pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (d, J= 5.4 Hz, 2H, -$NHCH_2Ph$**)**, 6.32 (t, J= 8.2 Hz, 1H, ArH), 6.55 (d, J= 8.2 Hz, 1H, ArH), 7.03-7.60 (m, 6H, ArH), 9.10 (br s, 1H, -NH); IR 1618 cm^{-1} (C=O), 2227 cm^{-1}(-CN), 3309 cm^{-1} (-NH); mass spectrum (70eV) m/z 312 (M^+)

3. RESULTS AND DISCUSSION

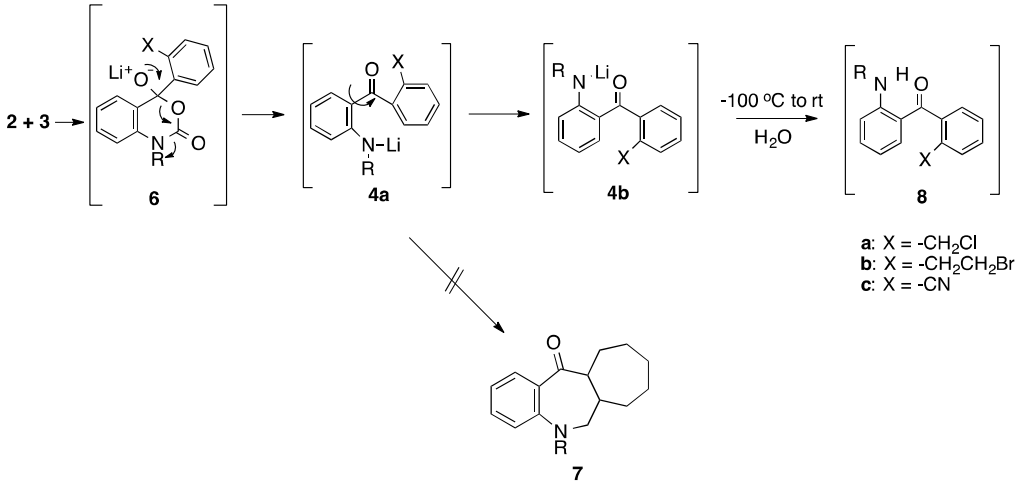
This study demonstrates that the Parham reagents **2a-c** react with N-substituted isatoic anhydrides to afford highly functionalized 2'-substituted 2-N-alkylaminobenzophenones in good yields through the intermediate *o*-(lithioamino)benzophenones of the type **4a/4b**. No fused ring tricyclic products of the type **7** resulting from intramolecular capture of the N-lithio anion were detected.

Table 1 – Functionalized 2-Aminobenzophenones Prepared



Compound	R_1	R_2	Yield
8a	CH_2Cl	CH_3	77%
8b	$(CH_2)_2Br$	CH_3	74%
8c	CN	CH_3	93%
8d	CH_2Cl	C_2H_5	67%
8e	$(CH_2)_2Br$	C_2H_5	71%
8f	CN	C_2H_5	93%
8g	CH_2Cl	Bz	67%
8h	$(CH_2)_2Br$	Bz	49%
8i	CN	Bz	84%

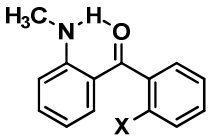
The non-nucleophilic property of the N-lithio derivative **4a**/**4b** prohibits cyclization onto the electrophilic center adjacent to the site of halogen-metal exchange that would provide compounds of the type **7**. Spectral data for all of the products **8** showed a characteristic broad singlet downfield of 8 ppm indicative of intramolecular hydrogen bonding (Table 2). This observation points to the formation of **4b** as a stabilizing intermediate prior to neutralization.



Scheme 2 – Mechanism of Formation of 2-Aminobenzophenones 8

Further applications of this chemistry to the preparation of heterocyclic systems are currently under study.

Table 2 – ^{1}H NMR Chemical Shift of Aryl N-H



X	-NH (δ, ppm)
$-CH_2Cl$	8.78
$-CH_2CH_2Br$	8.80
-CN	8.59

4. CONCLUSION

The reaction of the Parham reagents of the type **2** with N-alkylisatoic anhydrides **3** has proved to be an efficient and straightforward entry to highly functionalized 2'-substituted 2-N-alkylaminobenzophenone derivatives. Based on the non-nucleophilic property of the intermediate N-lithio salts **4b** that form, the only products detected and isolated were the functionalized 2-aminobenzophenone derivatives **8**. This methodology may be of use in the design and synthesis of 2-aminobenzophenones and heterocyclic systems derived therefrom which would otherwise be difficult to prepare [IV].

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