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A Parham cyclization approach to diaryl-fused seven-membered ring heterocyclic ketones

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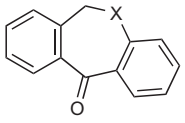
ABSTRACT

Aryl-fused seven membered heterocyclic frameworks appear in a variety of pharmaceutically pertinent compounds. However, only a very few methods for their preparation have been described. This work describes a novel synthesis route to diaryl-fused seven membered heterocyclic ketones through the generation of functionalized aryllithiums by bromine–lithium exchange, followed by intramolecular cyclization onto an electrophilic nitrile functional group. The resulting *N*-lithioimine can then be hydrolyzed to the desired ketone, generally in good yields. The order of addition of *n*-butyllithium is crucial to the process with inverse addition proving to mitigate side product formation and increase yields.

Introduction and discussion

Polycyclic ring systems having 5,7,6-, 6,7,6-, or 6,6,6-fused tricyclic structural motifs have been widely recognized as structures with a myriad of pharmaceutical applications. The benzo-fused seven-membered heterocyclic ketones have been shown to possess central nervous system pharmacological activity while products derived from diaryl-fused 6,7,6 heterocyclic compounds have been shown to have utility in a variety of different therapeutic applications including treatment of cognitive disorders such as Alzheimer's disease and Huntington's disease through inhibition of histone deactylase,[1] the treatment of sleep disorders,[2–4] antimicrobial agents,[5] and agonists of the peroxisome proliferator-activated receptor[6] to name a few (Fig. 1). The versatility and spectrum of biological activities of these compounds continues to make these derivatives and their corresponding precursors valuable synthesis targets.

Current methods for synthesizing these compounds involve highly acidic or comparably harsh reaction conditions.[7] As such, these reaction conditions prohibit the inclusion of particular functional groups. The goal of the work described herein is the development a new method of preparing these compounds that would enable the preparation of novel derivatives that may contain functional groups precluded under Friedel–Crafts conditions.



X= NR, O,S

Figure 1. 6,7,6 diaryl-fused ring heterocyclic ketones.

Despite the large number of compounds containing this framework, processes by which these compounds are prepared are limited. Current synthesis methods involve several reaction steps or restrictive reaction conditions such as strongly acidic media (intramolecular Friedel–Crafts) which preclude the incorporation of reactive functional groups.[5,8,9] Based primarily on work directed toward the preparation of symmetrical dibenzosuberones via intramolecular Parham cyclizations described by Reames et al.[10] We have found that the Parham protocol is well-suited for the preparation of a variety of these classes of compounds.[11] This Letter describes a general protocol for a straightforward synthesis of diaryl-fused seven-membered heterocyclic ketones under Parham conditions.[12]

The starting materials (**3a**–**g**) were prepared by reacting an *o*-bromophenol, *o*-bromothiophenol, or an appropriately *N*-substituted aniline (**2a**–**g**) with 2(bromomethyl)benzonitrile (**1**). Alternatively, alkylation of 2-hydroxybenzonitrile (**5**) with *o*-bromobenzyl bromide (**4**) provides **6**. Carrying out a low temperature (−78 °C) bromine–lithium exchange with *n*-butyllithium in anhydrous THF afforded the aryllithium which then cyclizes to

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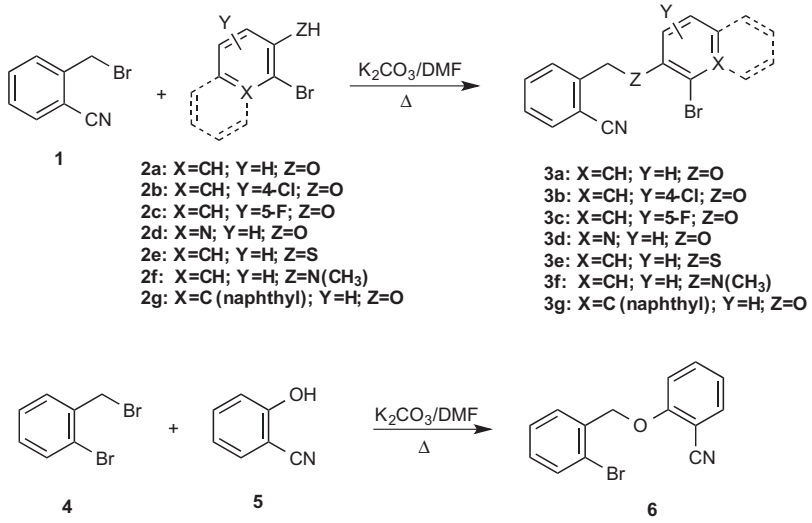
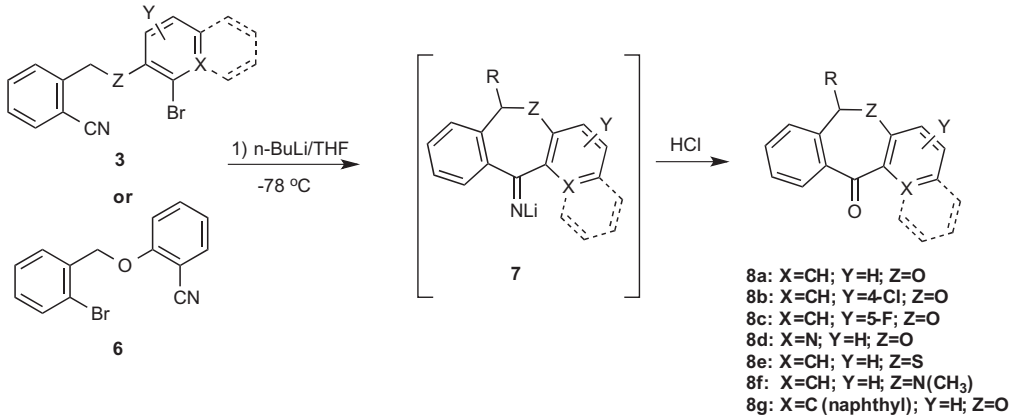
form an intermediate a *N*-lithioimine salt (**7**). Conversion to the ketone is achieved by an acidic work-up and extraction. Purification was achieved by flash chromatography on silica gel eluting with hexanes/ethyl acetate (Schemes 1 and 2).

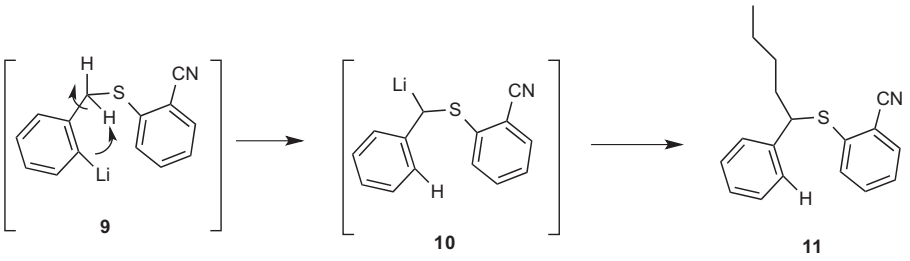
The most problematic reaction studied in this series entailed the preparation of thioether **8e**. Under standard reaction conditions (addition of 1.2 equiv of *n*-butyllithium relative to starting material **3e** at −78 °C), the desired product was formed, albeit in very low yield with a major by-product identified as the α-butylated material **11** (Scheme 3). Inverse addition (addition of starting material **3e** to 1.2 equiv of *n*-butyllithium) sharply increased the amount of the desired **8e** while significantly suppressing the formation of butylated products. However, yields of **8e** were the lowest observed among the substrates in this study no doubt due to the ability of the sulfur to stabilize the α-benzylic anion, a factor responsible for by-product formation which is absent in the other substrates investigated in this study (see Table 1).[13]



Scheme 1.

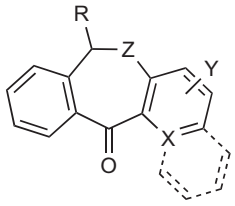


Scheme 2.



Scheme 3.

Table 1
6,7,6 diaryl-fused heterocyclic ketones prepared in this study



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Compound	X	Y	Z	R	% yield	
					Normal	Inverse
8a (from **3**)	CH	H	O	H	56	73
8a (from **6**)	CH	H	O	H	54	74
8b	CH	2-Cl	O	H	48	63
8c	CH	3-F	O	H	42	71
8d	N	H	H	H	18	48
8e	CH	H	S	H	8	38
8f	CH	H	NCH_3	H	63	78
8g (naphthyl)	CH	H	O	H	58	92

Conclusion

A new Parham cyclization methodology has been developed for the preparation of diaryl fused oxapin-4-ones, thiooxapin-4-ones, and azapin-4-ones that may permit entry to derivatives bearing electrophilic functional groups difficult to prepare under the normally employed Friedel–Crafts acylation conditions. One possible limitation for this process is poor yields for systems that can form stabilized α-anions at the benzylic position thereby leading to butylated by-products as observed for the thiooxapin-4-ones.

Acknowledgements

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12. *I. General procedure for synthesis of compounds **3a–e**; **3g** and **6***
A 250 mL round bottom flask equipped with a magnetic stir bar was charged with 100 mL dimethyl sulfoxide and 10 mmol of 2-bromophenol (**2a**), 2-bromo-2-chlorophenol (**2b**), 2-bromo-5-flourophenol (**2c**), 2-bromo-3-pyridinol (**2d**), 2-bromobenzene thiol (**2e**), or 1-bromo-2-napthol (**2g**) and 1.33 mol equiv of K_2CO_3. An equimolar amount of 2-cyanobenzylbromide (**1**) or 2-bromobenzyl bromide (**4**) was added to the solution. The reaction mixture was stirred at ambient temperature under a $CaCl_2$ drying tube overnight. The solution was poured into 200 mL of water and was stirred for 2 h. The mixture was then extracted with ethyl acetate (3 × 100 mL) and the organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product, which was recrystallized with methanol.
*II. Procedure for the synthesis of compound 2-(((2-bromophenyl)(methyl)-amino)methyl)benzonitrile **3f***
A 250 mL round bottom flask equipped with a magnetic stir bar was charged with 100 mL of methanol, 2-bromo-*N*-methylaniline (**2f**; 2.00 g; 10.75 mmol), 1.1 equiv of 2-(bromomethyl)benzonitrile (**1**; 2.31 g; 12.07 mmol), and 1.1 equiv of triethylamine (1.82 mL; 1.33 g; 13.10 mmol). The mixture was allowed to stir overnight and was then concentrated in vacuo and 100 mL of diethyl ether was added to the residue. The resulting precipitate was removed using vacuum filtration and the filtrate was again concentrated in vacuo to provide crude **2f** (2.55 g; 78.8%) as an oil which was purified using flash chromatography on silica gel eluting with hexanes/EtOAc to provide the pure product as a water–white oil, yield = 0.785 g (24.3%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56 (s, NCH_3; 3H), 4.25 (s, $ArCH_2$, 2H), 7.73–6.77 (m, ArH, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.2, 58.0, 111.8, 118.8, 120.4, 122.4, 125.0, 127.6, 128.3, 129.4, 132.6, 132.9, 134.0, 142.1, 151.1. IR: 2228 cm^{-1}; Anal. Calcd for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.35; Br, 26.53; N, 9.30. Found: C, 59.49; H, 4.00; Br, 26.51; N, 9.16.
*III. General Procedure for synthesis of **8a–g** using normal addition*
A dry three-neck-250 mL round bottom flask equipped with a temperature probe, magnetic stirrer, and nitrogen inlet was charged with 100 mL of anhydrous THF. The starting material (**3a–g** or **6**; 5 mmol) was added to the reaction flask and the resulting solution was cooled under N_2 to −78 °C using a dry/ice acetone bath. *n*-Butyllithium (1.2 equiv) was added via syringe at such a rate so as to maintain the temperature at or below −70 °C. The reaction mixture was kept at or below −70 °C for 1 h, and then allowed to slowly warm to room temperature overnight. The reaction mixture was quenched using 5% HCl and stirred for an hour. For the preparation of **8d**, sufficient 10% NaOH solution was added to turn the solution basic and mixed for an additional hour to account for the protonation of the pyridine moiety. The reaction mixture was then extracted using ethyl acetate. The organic extracts were concentrated to dryness and the desired product was separated from the crude mixture using flash chromatography on a silica gel column eluting with hexanes/EtOAc.
*IV. General procedure for synthesis of compounds **8a–g** using inverse addition*
A dry three-neck-250 mL round bottom flask equipped with a temperature probe, magnetic stirrer, and nitrogen inlet was charged with 100 mL of anhydrous tetrahydrofuran. The reaction mixture was cooled to −78 °C using a dry/ice acetone bath and 6 mmol (1.2 equiv) of *n*-butyllithium were added to the reaction flask. To the chilled solution was added 5 mmol of one of the compounds elected from **3a–g** dissolved in 30 mL of anhydrous THF dropwise. The reaction mixture was kept at or below −70 °C for 1 h, and then allowed to slowly warm to room temperature overnight. The reaction mixture was quenched using 5% HCl and stirred for an hour. For the preparation of **8d**, sufficient 10% NaOH solution was added to turn the solution basic and mixed for an additional hour to account for the protonation of the pyridine ring. The reaction mixture was then extracted using EtOAc. The organic extracts were concentrated to dryness and the desired product was separated from the crude mixture using flash chromatography on a silica gel column eluting with hexanes/EtOAc.
13. *Data for* **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (t, J = 6.3 Hz, CH_3, 3H), 1.01–1.38 (m, CH_2, 4H), 1.70–1.85 (m, CH_2, 2H), 4.30 (t, J = 6.9 Hz, benzylic –CH), 6.99–7.40 (m, ArH, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.4, 29.6, 35.7, 51.1, 112.5, 117.8, 127.4, 125.0, 127.6, 127.8, 128.1, 128.9, 132.4, 133.0, 133.2, 133.5, 146.6. IR: 2213 cm^{-1}; Anal. Calcd for $C_{18}H_{19}NS$: C, 76.82; H, 6.81; N, 4.98; N, 11.39. Found: C, 76.58; H, 6.88; N, 4.73; S, 11.78.