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Studies into the generation and Diels–Alder reactions of 7,8-quinolyne with furan dienes

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Abstract—Reaction of an appropriate *ortho*-halo tosylate precursor with organolithium reagents provides the first conclusive route to the intermediate, 7,8-quinolyne. The transient existence of this hetaryne was confirmed by Diels–Alder reactions with furan derivatives that provide endoxide adducts. Chemical induced rearrangement of these adducts allows entry to key compounds of 10-hydroxy[*h*]benzoquinoline and its 7-substituted derivatives in modest yields.
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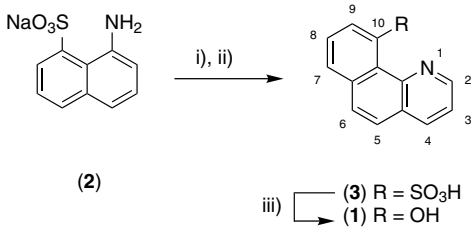
The element beryllium (Be) and its composite materials are important due to their physical properties. Beryllium alloys and ceramics are lightweight, durable, conductive and have neutron moderating characteristics. Such materials have found use in specialized applications in the electronic, nuclear, aerospace, and defense industries, as well as day to day use in golf clubs, bicycle frames, anti-sparking tools, and dental prostheses. Unfortunately, despite its widespread use, beryllium possesses extreme toxicity. Beryllium and its compounds are classified as a Group 1 carcinogen to humans. In addition, inhalation of micro-sized particles of beryllium into the lung can lead to the debilitating respiratory problem, known as Chronic Beryllium Disease (CBD); there is currently no cure for this disease.[1]

In an effort to develop new chemical methods to detect or sequester beryllium, and possibly treat people suffering from CBD, we have reviewed known Be coordination complexes. Initially our attention was drawn to the unique chemical and photophysical properties of 10-hydroxybenzo[*h*]quinoline (10-HBQ) (**1**)[2] and its metal complexes. Under alkaline aqueous-alcoholic conditions, 10-HBQ forms a neutral 2:1 complex with $BeSO_4$; this stable complex has been used in an OLED to produce one of the most electroluminescent devices known to date.[3] Following these findings, Matsumiya et al. have reported that a water soluble derivative of 10-HBQ forms a complex with aqueous Be that also exhibits enhanced fluorescence emission.[4]



Scheme 1. Reagents and conditions: (i) H_3PO_4, glycerol, nitrobenzene, heat; (ii) aqueous $Na_2Cr_2O_7$, heat; (iii) KOH, NaOH, 260–270 °C.

We considered that 10-HBQ would serve as a practical platform from which functionalized derivatives could easily be obtained and used in our specific studies. Initially, 10-HBQ was commercially available from TCI, but during 2002 this item was discontinued. A search of the literature, surprisingly, revealed only a 1944 preparation of 10-HBQ.[5] Employing Skraup and classical alkali hydroxide substitution conditions, sodium 8-aminonaphthalene sulfonate (**2**) was transformed into (**1**) via two steps in only 12% overall yield (Scheme 1). In addition, attempts to selectively incorporate functionality in the phenolic system of 10-HBQ via electrophilic aromatic substitution were inefficient. Iodination[6a,b] or formylation[6b] of 10-HBQ resulted in poor regioselectivity

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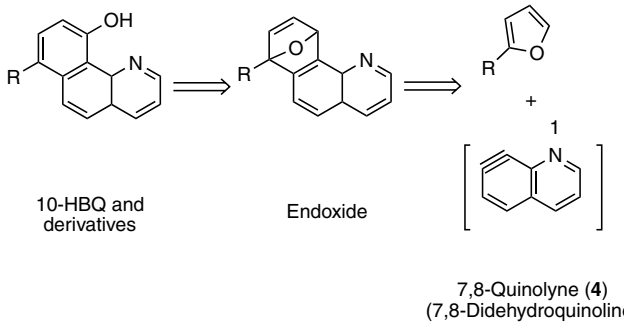
and afforded mixtures of *ortho*-, *para*-, and 7,9-di-substituted products.

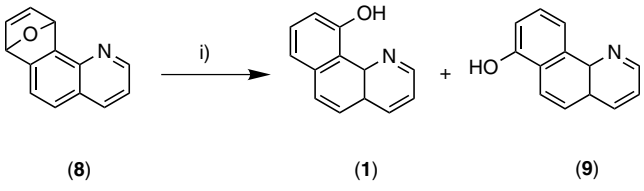
Since we were interested in controlling functionality at the position *para* to the phenolic group to avoid interference with the binding site, we designed a divergent synthesis to 10-HBQ and 7-substituted derivatives. As shown below, the success of this approach was dependent on two key processes; the trapping of 7,8-quinolyne (**4**)[7] with 2-substituted furans and the subsequent regioselective rearrangement of the ethereal bridge of the endoxide adduct. Apart from kinetic data proposing the intermediacy of (**4**),[8] there is no information regarding the stability or propensity of this hetaryne to undergo Diels–Alder reactions.



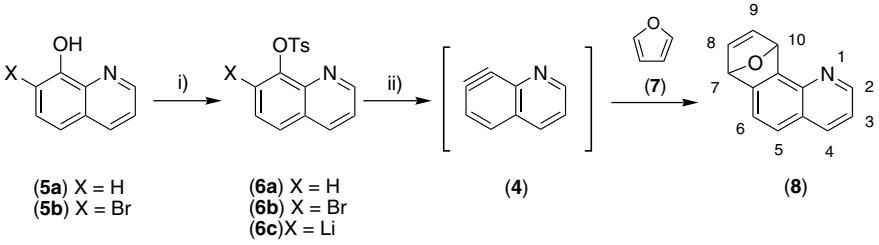
A number of strategies have been developed for the synthesis of arynes and we considered the simplest would be the base induced 1,2-elimination of an appropriate sulfonate ester.[9] Attempts to convert 8-hydroxyquinoline (**5a**) to the tosylate (**6a**) by employing *p*-TsCl in neat triethylamine[10] gave complex reaction mixtures that made purification tedious and inefficient. Instead, it was determined that phase transfer conditions with *p*-TsCl, tetraethylammonium bromide, DCM, and aqueous NaOH gave the required product as a white solid in near quantitative yields (Scheme 2). Treatment of this tosylate (**6a**) and furan (**7**) at −78 °C with LDA, followed by slow warming to 0 °C, gave a dark brown viscous oil after normal aqueous work-up. Analysis of the crude mixture by ^{1}H NMR spectroscopy in an attempt to identify the adduct (**8**), or any major constituent, was unsuccessful and therefore this approach was abandoned.

Alternatively, arynes have been generated under mild conditions via the reaction of *ortho*-halo aryltosylates with organolithium reagents.[11,12] Thus, 7-bromo-8-hydroxyquinoline (**5b**)[13] was easily converted to the analogous tosylate (**6b**) in high yield using the biphasic conditions described earlier. Initial treatment of bromo-tosylate (**6b**) with *n*-BuLi at low temperatures in the presence of furan resulted in formation and isolation of the desired endoxide (**8**) in 42% yield. Repeating the reaction using PhLi instead of *n*-BuLi gave cleaner reactions, which resulted in an improved yield (50%) of (**8**). This was accompanied by the formation of trace amounts of (**6a**). Presumably, metal–halogen exchange of (**6b**) with organolithium reagents is rapid, affording (**6c**) which can either undergo the desired elimination to form 7,8-quinolyne or proton abstraction to give (**6a**). The ^{1}H NMR spectrum of (**8**) is consistent with the structure of the Diels–Alder adduct. With the aid of a COSY experiment and coupling constants, all signals were easily assigned. Most noticeable are the broad singlets at 6.54 and 5.95 ppm which are due to the bridgehead protons 7 and 10, respectively, while an apparent AB quartet in the aromatic region is the result of protons 5 and 6.[14]

With satisfactory quantities of the endoxide in hand, the rearrangement of the oxabicyclic system was examined. Reaction of (**8**) under typical conditions with catalytic concentrated HCl heated in ethanol[11,12] only afforded unreacted starting material. Instead, it was determined that excess acid and long reaction times were essential to cause the rearrangement that gave a mixture of regioisomers (Scheme 3). Encouragingly, analysis of the proton NMR spectrum indicated that the ring opening was favored toward the desired compound 10-HBQ (**1**) (65%)[15,16] rather than 7-HBQ (**9**) (27%).[17,18] The ^{1}H NMR spectra of these two isomers are easily differentiated by the location and appearance of the phenolic protons in aprotic solvents. The phenolic proton of 7-HBQ is observed at 10.29 ppm as a broad signal.[18] However, the sharp singlet of the phenolic proton of 10-HBQ is deshielded at 14.82 ppm, presumably a result of hydrogen bonding.[16] X-ray crystallographic data of 10-HBQ



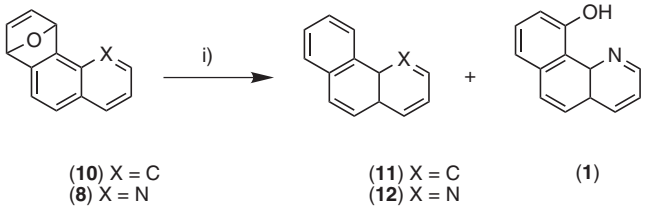
Scheme 3. Reagents and conditions: (i) ethanol, excess concd HCl, reflux.



Scheme 2. Reagents and conditions: (i) *p*-TsCl, NEt_4Br, aq NaOH, DCM; (ii) RLi, THF, −78 °C to rt, furan (**7**).

in the solid state confirms that intramolecular hydrogen bonding exists between the phenolic proton and nitrogen atom.[19]

The reluctance of (**8**) to rearrange to the phenol under aqueous conditions led us to investigate the feasibility of employing mild Lewis acids under aprotic conditions. Failure to affect the ring opening with anhydrous TMSBr or $ZnCl_2$[20] in dichloromethane once again indicated the robust nature of this endoxide. Jung and Koreeda have shown that subjecting the carbocyclic endoxide (**10**) to TMSI instead results in deoxygenation to afford phenanthrene (**11**) in near quantitative yield (Scheme 4).[12] Treatment of adduct (**8**) under these conditions affords surprisingly small amounts of the aromatized product benzo[*h*]quinoline (**12**); instead the main product is 10-HBQ (**1**). From these reactions, it is unclear whether the nitrogen atom in (**8**) is a cause of this unusual reactivity. Further work is directed at understanding the mechanisms that operate so that the yields of the desired product can be optimized.



Scheme 4. Reagents and conditions: (i) TMSI, MeCN, rt.

In order to determine whether 7,8-quinolyne (**4**) would serve as a versatile intermediate, another target was investigated. Our attention was directed at the recent synthetic efforts to form aza-quinonoid compounds, benzo[*g*]quinoline-5,10-dione and benzo[*g*]isoquinoline-5,10-dione,[21] as both these simple compounds have been shown to exhibit biological activity.[22] With this in mind, we considered that quinonoid compounds, such as (**16**), might have interesting metal-binding, redox, and biological properties. Hetaryne (**4**) was generated as described previously, but the diene 2-methoxyfuran (**13**) was substituted instead (Scheme 5). No attempt was made to isolate the Diels–Alder adducts, as previous reports with other endoxide derivatives[11,23] indicated that such strained adducts readily decompose on handling. Instead, the crude reaction mixture was subjected to an immediate acidic aqueous work-up to induce the desired rearrangement. Analysis of the crude sample by proton NMR unexpectedly indicated only one methoxy signal. Subjection of this crude mixture to column chromatography allowed isolation of only one product that was determined to be regioisomer (**16**) (35%) based on NMR characterization.[24] The key features are the phenolic proton that occurs at 14.49 ppm as a sharp singlet and the methoxy signal which occurs at 4.01 ppm.[24] From this information it seems that the cycloaddition favors the formation of only one regioisomer (**16**), as (**17**) could not be detected. However, it is unclear as to whether electronic or steric factors are the driving force in the initial cycloaddition.

In conclusion, these results clearly indicate that 7,8-quinolyne (**4**) can be generated and trapped with furan in moderate yield. Treatment of the endoxide (**8**) using typical acidic conditions or aprotic conditions with Lewis acids results in a rearrangement to afford acceptable yields of the desired compound, 10-HBQ (**1**). Encouragingly, trapping 7,8-quinolyne (**4**) with 2-methoxyfuran (**13**) affords only one regioisomer; more importantly, this method enables the controlled introduction of functionality at the 7-position. Currently, a range of quinonoid derivatives are being synthesized for binding and biological studies with Be. Future work will also address whether hetaryne (**4**) can be trapped by a range of other 2-substituted furan compounds. Thus, we have shown that this Diels–Alder approach serves as an alternative to conventional condensation protocols to construct functionalized benzo[*h*]quinoline compounds.

Acknowledgements

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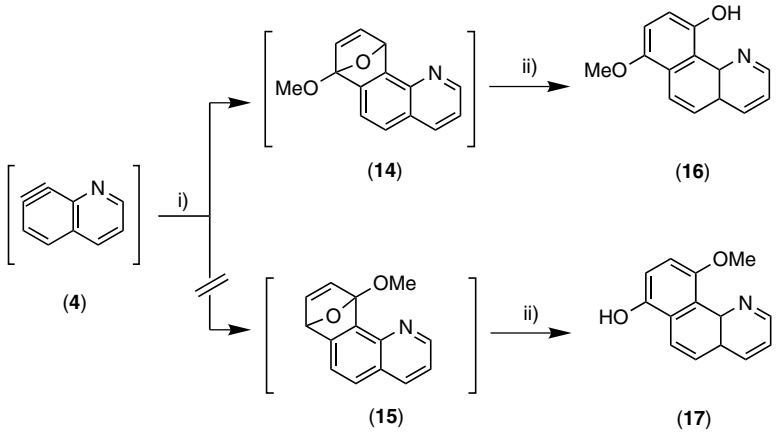

Scheme 5. Reagents and conditions: (i) 2-methoxyfuran (**13**), −78 °C, THF; (ii) aq HCl.

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14. Selected data for endoxide (**8**); mp 115 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (dd, 1H, J = 4.1, 1.6 Hz, H2); 8.12 (dd, 1H, J = 8.4, 1.6 Hz, H4); 7.59 (A part of ABq, 1H, J = 7.8 Hz, H6); 7.55 (B part of ABq, 1H, J = 7.8 Hz, H5); 7.33–7.25 (m, 2H, H3 and 8); 7.20 (dd, 1H, J = 5.5, 1.8 Hz, H9); 6.54 (br s, 1H, H7); 5.95 (br s, 1H, H10). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.2, 150.9, 148.8, 144.4, 144.2, 142.0, 136.7, 126.7, 125.8, 120.5, 119.9.
15. The ^{1}H, ^{13}C NMR and melting point of this compound is in agreement with that of the TCI sample.
16. Selected data for 10-HBQ (**1**); mp 101–102 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.82 (s, 1H, OH); 8.99 (dd, 1H, J = 4.7, 1.6 Hz, H2); 8.59 (dd, 1H, J = 8.1, 1.6 Hz, H4); 7.96 (A part of ABq, 1H, J = 8.9 Hz, H6); 7.88 (B part of ABq, 1H, J = 8.9 Hz, H5); 7.80 (dd, 1H, J = 8.1, 4.7 Hz, H3); 7.66 (app t, 1H, H8); 7.52 (br d, 1H, J = 7.8 Hz, H7); 7.16 (dd, 1H, J = 7.8, 0.9 Hz, H9). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 158.7, 147.2, 145.9, 137.1, 134.7, 129.9, 128.7, 125.9, 125.1, 121.7, 118.1, 115.0, 113.3.
17. Although a synthesis for this compound has been cited, it contains no experimental or characterization data; Tulagin, V.; Coles, R. F. *Chem. Abstr.* **1957**, 914.
18. Selected data for 7-HBQ (**9**); mp 254 °C decomposes, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.29 (br s, 1H, OH); 8.98 (dd, 1H, J = 4.3, 1.7 Hz, H2); 8.65 (d, 1H, J = 8.2 Hz, H10); 8.38 (dd, 1H, J = 8.0, 1.7 Hz, H4); 8.18 (d, 1H, J = 9.1 Hz, H6); 7.78 (d, 1H, J = 9.1 Hz, H5); 7.65 (dd, 1H, J = 8.0, 4.3 Hz, H3); 7.54 (app t, 1H, H9); 7.15 (dd, 1H, J = 7.7, 1.0 Hz, H8). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 153.5, 148.9, 145.6, 136.0, 132.3, 127.5, 126.1, 123.9, 123.4, 122.2, 121.4, 114.5, 111.8.
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24. Selected data for (**16**); mp 134 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 14.49 (s, 1H, OH); 8.85 (dd, 1H, J = 4.6, 1.7 Hz, H2); 8.30 (d, 1H, J = 9.1 Hz, H6); 8.27 (dd, 1H, J = 8.0, 1.7 Hz, H4); 7.66 (d, 1H, J = 9.1 Hz, H5); 7.59 (dd, 1H, J = 8.0, 4.6 Hz, H3); 7.19 (A part of ABq, 1H, J = 8.6 Hz, H9); 7.14 (B part of ABq, 1H, J = 8.6 Hz, H8); 4.01 (s, 3H, OMe).