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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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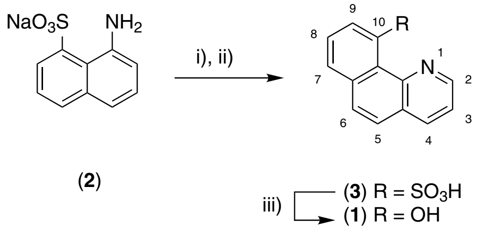
The element beryllium (Be) and its composite materials are important due to their physical properties. Beryllium alloys and ceramics are lightweight, durable, conductive and have neutron moderating characteristics. Such materials have found use in specialized applications in the electronic, nuclear, 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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Keywords: Hetaryne; Diels–Alder reaction; Furan; Endoxide rearrangement; Benzo[*h*]quinoline; 7,8-Quinolyne.

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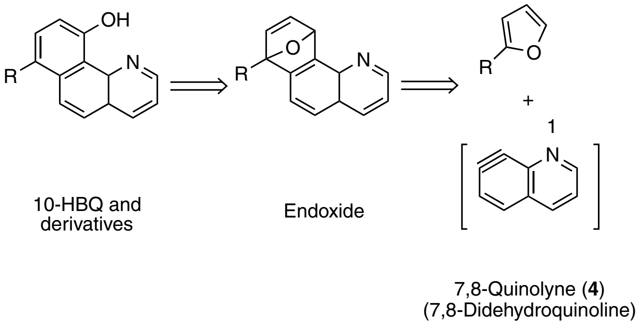
and afforded mixtures of *ortho*-, *para*-, and 7,9-di-substituted products.

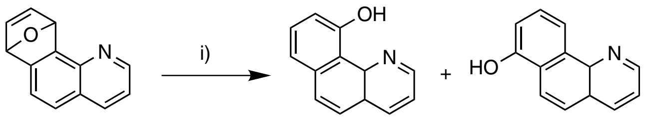
Since we were interested in controlling functionality at the position *para* to the phenolic group to avoid interference with the binding site, we designed a divergent synthesis to 10-HBQ and 7-substituted derivatives. As shown below, the success of this approach was dependent on two key processes; the 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.

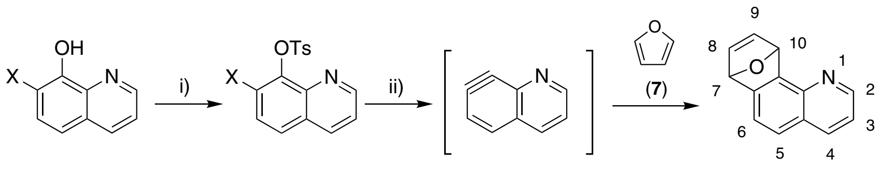
Alternatively, arynes have been generated under mild conditions via the reaction of *ortho*-halo aryltosylates with organolithium reagents.[11,12] Thus, 7-bromo-8-hydroxyquinoline (**5b**)[13] was easily converted to the analogous tosylate (**6b**) in high yield using the biphasic conditions described 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



(**8**) (**1**) (**9**)

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



(**5a**) X = H
(**5b**) X = Br

(**6a**) X = H
(**6b**) X = Br
(**6c**)X = Li

(**4**)

(**8**)

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