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First syntheses of two quinoline alkaloids from the medicinal herb *Ruta Chalepensis via* cyclization of an *o*-iodoaniline with an acetylenic sulfone†

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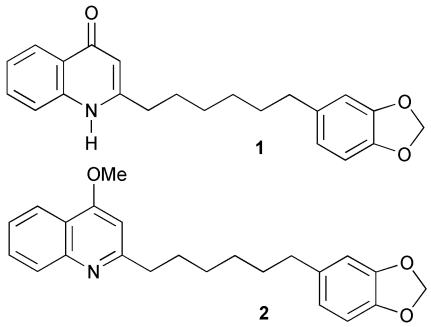
The first syntheses of two quinoline alkaloids found in the medicinal herb *Ruta chalepensis* are reported *via* the conjugate addition of an *o*-iodoaniline to an acetylenic sulfone, followed by Pd-catalyzed carbonylation, intramolecular acylation of the coresponding sulfone-stabilized carbanion, and reductive desulfonylation.

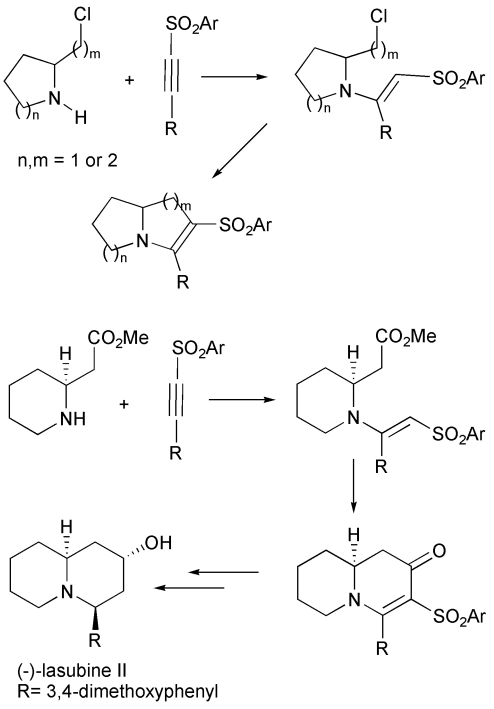
Acetylenic sulfones are useful synthetic intermediates[1] that undergo facile conjugate additions with primary or secondary amines.[1,2] When the amine contains a chloro[3] or ester[4,5] substituent, subsequent intramolecular alkylations or acylations provide a short and versatile route to the corresponding nitrogen heterocycles (*e.g.* Scheme 1). These cyclizations can be followed by further functional group manipulations and ultimately desulfonylation,[6] and have thus provided new routes to (−)-pumiliotoxin C,[4] other dendrobatid alkaloids containing indolizidine structures[3b] and the quinolizidine alkaloid (−)-lasubine II.[5] However, very few cases of conjugate additions of anilines to acetylenic sulfones have been reported[2a,f] and we wished to determine whether these much less nucleophilic amines could be employed in a similar cyclization protocol.

We now report a procedure for achieving the conjugate addition and intramolecular acylation of an appropriately *o*-functionalized aniline with an acetylenic sulfone, and illustrate the utility of the procedure in the first syntheses of the recently discovered quinoline alkaloids **1** and **2**.[7] Alkaloids **1** and **2** were isolated from the roots of *Ruta chalepensis*, a perennial herb collected from the northern Saudi desert, which is used in folk medicine as, *inter alia*, an antirheumatic and antispasmodic agent. To our knowledge, there have been no previously reported syntheses of **1** and **2**.

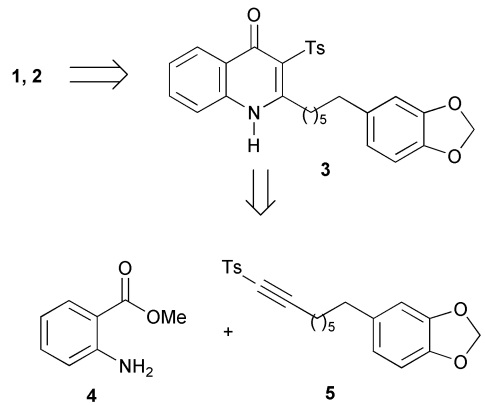


Our initial approach to quinolines **1** and **2** was based on the conjugate addition of methyl anthranilate **4** to acetylenic sulfone **5**, followed by intramolecular acylation to the expected product **3**, and desulfonylation (Scheme 2). The acetylenic sulfone was easily prepared by selenosulfonation[8] and selenoxide *syn*-elimination of the known acetylene **8**,[9] which was in turn obtained by a new route from commercially available **6**, as shown in Scheme 3.

However, neither methyl anthranilate nor its *N*-benzyl derivative was sufficiently nucleophilic to add to **5**, even under forcing conditions. When various amide and carbamate derivatives of **4** were employed in the presence of a base catalyst, only the *N*-formyl derivative **9** afforded the corresponding conjugate addition product, isolated as the allyl sulfone isomer **11**, but in low yield (Scheme 4). However, the cyclization of **11** proceeded quantitatively to afford **15** *via* acylation of the carbanion generated from the allyl sulfone moiety of **11** with lithium hexamethyldisilazide (LiHMDS), with concomitant deformylation (Scheme 4). In an effort to improve the yield of the conjugate addition step, we attempted to modify the ester substituent to make it less electron-withdrawing. Thus, for



Scheme 1



Scheme 2

† Electronic supplementary information (ESI) available: experimental data and NMR spectra. See http://www.rsc.org/suppdata/cc/b2/b205408f/

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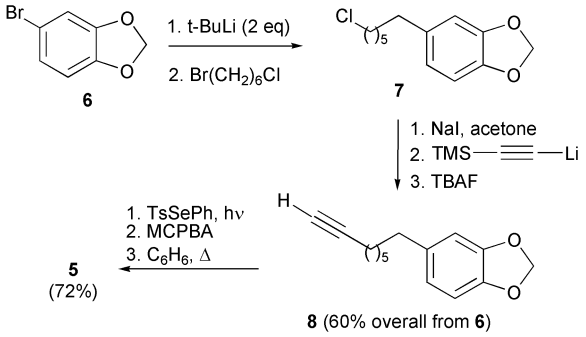
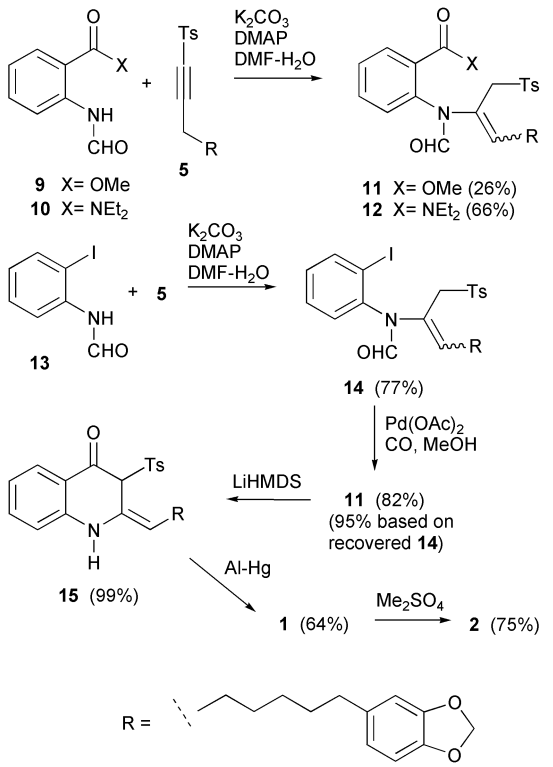


Scheme 3

example, the corresponding diethylamide **10** afforded an improved yield of 66% of the corresponding adduct **12** (Scheme 4). Unfortunately, all attempts to cyclize the latter product to **15** failed.

The most successful overall results were obtained by starting with the *o*-iodoaniline **13**, which afforded adduct **14** in 77% yield (Scheme 4). Presumably, absence of the electron-withdrawing ester group facilitated the conjugate addition. The required ester moiety was then appended by palladium-catalyzed carbonylation[10] in methanol, thus affording **11**, in a much improved yield compared to the route starting from ester **9**. After cyclization of **11** to the quinoline derivative **15**, desulfonylation with aluminium amalgam[11] was accompanied by alkene isomerization to produce alkaloid **1**.‡ *O*-Methylation of the latter compound completed the synthesis of its congener **2**.



Scheme 4

In conclusion, we have found a convenient procedure to overcome the poor reactivity of methyl anthranilate derivatives in conjugate additions to acetylenic sulfone **5**. This was achieved by employing the conjugate base of the corresponding *N*-formyl derivative, and by using the more strongly nucleophilic *o*-iodoaniline **13**, with subsequent introduction of the ester group by palladium-catalyzed carbonylation. This procedure was followed by intramolecular acylation of the corresponding sulfone-stabilized allyl carbanion and reductive desulfonylation, thereby achieving the first syntheses of the *Ruta Chalepensis* alkaloids **1** and **2** in overall yields of 40 and 30%, respectively, from **13** and **5**.

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Notes and references

‡ The ^{1}H and ^{13}C NMR spectra of **1** and **2** were in generally close agreement with the reported spectra (ref. 7). However, in the ^{1}H NMR spectrum of **1**, we noted a significant concentration dependence, particularly of the chemical shifts of the signals at δ 7.73, 7.58 and 5.87, attributed to H-8, H-7 and H-3, respectively (for complete NMR assignments, see ref. 7). These chemical shifts were also sensitive to the presence or absence of trace acids. The concentration and pH dependence may be the result of changes in the equilibrium between enaminone **1** and its corresponding pyridinol tautomer, or to changes in intermolecular hydrogen bonding.

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