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Protic Solvent Mediated Cycloisomerization of Quinoline and Isoquinoline Propargylic Carbinols: Syntheses of (±)-3-Demethoxyerythratidinone and (±)-Cocculidine

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Novel nitrogen-containing rings (azacycles) are particularly valuable in the arenas of alkaloid synthesis and medicinal chemistry. To that end, our group has been engaged in the development of cycloisomerization strategies of pyridine propargylic carbinols (e.g., **1**, Figure 1) for the generation of indolizines and indolizines using both Pt(II)- and In(III)-catalysts.ⁱ Similarly, others have shown that a wide variety of π -acids can mediate the cycloisomerization of pyridine propargylic carbinols to indolizines.ⁱⁱ Unfortunately, benzannulated variants of these underutilized scaffolds (especially benz[e]indolizines or benz[g]indolizines) that would arise from quinoline or isoquinoline carbinols, respectively (see **2** and **3**, Figure 1), are not formed efficiently under the metal promoted cycloisomerization conditions that were effective for the synthesis of indolizines and indolizines. In this communication, we demonstrate that benzindolizines can be produced in high yields by the cycloisomerization of quinoline or isoquinoline carbinols mediated by protic solvents (e.g., ethanol or *n*-propanol), which presumably form a H-bonding network that activates the substrate.

Surprisingly, the benzindolizine framework has gone virtually unexplored, with only scattered reports of benz[e]indolizinesⁱⁱⁱ and only a single report of the isomeric benz[g]indolizine^{iv} appearing in the literature prior to the work that is described herein. To demonstrate the utility of the unique azacyclic products that can now be effectively realized using protic solvent mediated cycloisomerization, we have applied the benz[g]indolizine scaffold to short syntheses of the *Erythrina* alkaloids^v (±)-3-demethoxyerythratidinone (**4**)^{vi} and (±)-cocculidine (**5**).^{vii}

The basis of our current studies rests on the concurrent discovery by Kim et al. and our group that simple protic solvents can mediate cycloisomerizations of pyridine propargylic carbinols to yield indolizines and indolizines.^{viii,ix} This observation suggested a potential

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route to access benzindolizinones given that the metal-mediated cycloisomerization conditions (e.g., **6a** to **7a**, Scheme 1) proceed only in low yield (36%) due to a competing ejection of the acetylide unit to give a ketone (e.g., **8a**) and hexyne.^x Alternatively, as demonstrated by Kim and coworkers,^{xi} subjecting quinoline propargylic carbinol **6b** to iodocycloisomerization conditions results in the formation of iodo pyrrolo[1,2-a]quinoline **9** and not the expected benzindolizinone (i.e., **7b**) or its iodinated derivative.

We hypothesized that protic solvents, unlike π -Lewis acids, would be less likely to effect the ejection of acetylides from substrates such as **6**. As such, protic solvent mediated cycloisomerization could provide a possible solution to the unsolved problem of access to benzindolizinones from propargylic carbinols. Support for this assertion is evident in the effectiveness of protic solvent mediated cycloisomerization conditions (*n*-PrOH, 120 °C, 40 h) that leads to the formation of benz[g]indolizinone **7a** in 91% isolated yield from quinoline carbinol **6a**.

As shown in Scheme 2, aryl, alkyl and alkenyl groups function as migrating groups when terminal alkyne bearing quinoline propargylic carbinol substrates (i.e., **3**) are employed to give the desired products in good to excellent yields. Generally, these reactions were conducted at 100 °C in sealed vessels with ethanol as the solvent. The observed reaction rates approximately correlate with the nature of the migrating group (aryl > alkenyl > alkyl). However, the rate of benzindolizinone formation does not appear to correlate with the electronics of the aryl migrating groups. Notably, saturated azacycles such as a protected piperidine (see **10h**) also serve competently as migrating groups. Additionally, in the case of alkenyl-alkynyl carbinol substrates (i.e., R = alkenyl in **3**), complete chemoselectivity for cycloisomerization involving the alkyne group was observed (see **10d**).

The most significant impact on the facility of the cycloisomerization of quinoline carbinols to form benz[e]indolizinones appears to arise in situations where significant peri-strain develops en route to the product as demonstrated in Scheme 3. Thus, for internal alkyne substrates (e.g., **6a** and **11**), cycloisomerization proceeds only slowly at 100 °C (e.g., 50% conversion of **6a** to **7a** after heating in ethanol for 40 h). Gratifyingly, increasing the reaction temperature to 120 °C (which necessitated a switch to the higher boiling solvent *n*-PrOH) leads to complete conversion over the same time period. Similarly, aryl substituted carbinol **11** undergoes complete conversion over 9 h at 120 °C to afford a 95% yield of **12**. Importantly, our observation that methyl-substituted quinoline propargyl carbinol substrate **13**, which possesses a terminal alkyne group is slow to react at 100 °C and only proceeds to full conversion upon raising the reaction temperature to 120 °C, demonstrates that the lower reactivity of **6a** and **11** is likely because of peri-strain in slowing the progress of the reaction and not because these are internal alkyne substrates.

Analogous to the developments using *quinoline* propargylic carbinols to access benz[e]indolizinones (Scheme 2), *isoquinoline* propargylic carbinols serve as effective substrates for the synthesis of benz[g]indolizinones. As illustrated in Scheme 4, aryl and alkyl groups are competent as migrating groups to afford the benz[g]indolizinones in excellent yield. Qualitatively, cycloisomerizations to afford benz[g]indolizinones proceed more quickly than the corresponding formation of benz[e]indolizinones.

As shown in Scheme 5, the benzindolizinone frameworks that can now be effectively accessed may be selectively manipulated. For example, oxidation level adjustments can be performed chemoselectively by exploiting differences in electronic bias between the vinylogous amide, enamide, or alkene groups (see **17**, **18**, **20** and **21**, respectively).^{xii} Alternatively, iodination can be effected using *N*-iodosuccinimide to afford **19** and **22** as the major products from **10e** and **16b**, respectively.^{xiii}

Finally, substituted benzindolizinones (e.g., methoxy benz[g]indolizinone **23**, Eq. 1; prepared in 93% yield from the requisite propargylic alcohol) can also undergo selective hydrolysis to provide, for example, **24**, which possesses a carbonyl group that may be further manipulated.

(1)

As a testament to the utility of the benzindolizinone scaffolds that can now be accessed using our cycloisomerization approaches, we have employed benz[g]indolizinones in syntheses of the *Erythrina* alkaloids 3-demethoxyerythratidinone (**4**) and cocculidine (**5**). The synthesis of **4** (Scheme 6) commenced with the preparation of benzindolizinone **29**, which is available from iodo-isoquinoline **25**^{xiv} in three steps. The union of **25** and Weinreb amide **26** provides ketone **27**.^{xv} Treatment of **27** with ethynylmagnesium bromide affords propargylic carbinol **28** in 68% yield over the two steps. Cycloisomerization of **28** to the desired benzindolizinone (**29**) proceeds in quantitative yield over 1 h by heating the propargylic alcohol substrate in ethanol. Of note, enantiopure **28** (>99% ee; obtained by preparative chiral HPLC)^{xvi} affords enantiopure **29** (>99% ee) demonstrating excellent enantiospecificity in the chirality transfer for the cycloisomerization step. Following a survey of various reduction protocols (including hydrogenation and the use of hydride reagents such as sodium borohydride and diisobutyl aluminium hydride) we found that under carefully controlled conditions, an ionic reduction of both the enamine and vinylogous amide moieties of **29** could be effected with attendant deprotection of the pendant ketone group in a single pot to give **30**. Overall, this cycloisomerization/reduction sequence provides a powerful alternative to the Pictet-Spengler approach that has historically been employed for the synthesis of intermediates such as **30** in many syntheses of *Erythrina* alkaloids.^{xvii} Diketone **30** was then converted to (±)-3-demethoxyerythratidinone (**4**) using a base-mediated aldol condensation as previously reported by Simpkins and coworkers.^{xviii} Thus, the synthesis of **4** was achieved in five steps from **25** and **26**.

Using a similar approach to that employed in the synthesis of **4**, we have prepared cocculidine (**5**) as illustrated in Scheme 7 in five steps from iodoisoquinoline **31**^{xix} and Weinreb amide **32**.^{xx} The sequence began with the coupling of **31** and **32** to afford ketone adduct **33**. Ethynylation of **33** proceeds in quantitative yield but with modest diastereoselectivity (1.2:1 d.r.) to give **34** as the major product. Because the mixture of

propargylic alcohol diastereomers is not easily separated using flash chromatography, the mixture was subjected to the cycloisomerization conditions to give a quantitative yield of the diastereomeric benzindolizinsonone products (i.e., **35b** and its diastereomer). The diastereomers can be readily separated at this stage to give 53% yield of **35b**. On the basis of the observations made during the cycloisomerization of enantiopure **28** to **29** (Scheme 6), we believe that excellent chirality transfer from the propargylic stereocenter in **34** to the ring fusion position in **35b** occurs even in the presence of the methoxy bearing stereocenter. In line with our previous studies, the enamide and enamine double bonds of benzindolizinsonone **35b** can be readily reduced (in the presence of the terminal olefin group) to give **36b**. Following a survey of numerous direct and indirect ring closing tactics,^{xxi} we found that a carbonyl-ene ring closing metathesis reaction using the Schrock molybdenum complex **37**^{xxii,xxiii} provided the best way to convert **36b** to cocculidine (**5**). This synthesis constitutes the shortest reported synthesis of cocculidine, which highlights the significance of the benzindolizinsonone framework as a starting point for the synthesis of the *Erythrina* alkaloids. Synthetic **5** provided spectral data that is in full agreement with that reported previously. Furthermore, its structure was unambiguously confirmed by single crystal X-ray analysis (see Figure 2 for an ORTEP representation of **5**).

In conclusion, we report the development of protic solvent mediated conditions for the synthesis of benz[e]indolizinsonones and benz[g]indolizinsonones from quinoline propargylic carbinols and isoquinoline propargylic carbinols, respectively. These unusual heterocycles can be selectively manipulated to afford partially saturated variants (e.g., benzindolizidinones). These observations have been applied to short syntheses of the *Erythrina* alkaloids (±)-3-demethoxyerythratidinone and (±)-cocculidine. In our synthesis of (±)-cocculidine, we have also demonstrated a rare example of the utility of the Schrock molybdenum complex **37** to accomplish a carbonyl/ene ring closing reaction in the context of a natural product synthesis. Our future studies are aimed at the application of benzindolizinsonone azacycles in the syntheses of other complex natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Cycloisomerization approaches to indolizines, indolizinones and benzindolizinones.

Scheme 1.

Development of effective cycloisomerization conditions for benzindolizinone formation

Scheme 2.
Migrating group scope for benz[e]indolizinone formation

Scheme 3.

The influence of peri-strain on reactivity

Scheme 4.

Cycloisomerization of isoquinoline propargylic carbinols. (ORTEP of **16b** shown at 50% probability of thermal ellipsoids. Hydrogens removed for clarity).

Scheme 5.

Selective manipulation of benzindolizinones.

Scheme 6.

Synthesis of (±)-3-demethoxyerythratinone (**4**). Reagents and conditions: a) *i*-PrMgCl, **25**, THF, 0 °C, 2 h; **26**, THF, 0 °C to rt, overnight; b) HCCMgBr (2 equiv), THF, rt, 2 h, 68% over two steps; c) EtOH, 100 °C, 1 h, 98%; d) TFA, MeOH, NaBH₃CN (2.3 equiv), 0 °C; acetone; 1 M HCl, 64%. THF = tetrahydrofuran, TFA = trifluoroacetic acid.

Scheme 7.

Synthesis of (±)-cocculidine (**5**). Reagents and conditions: a) *i*-PrMgCl, **25**, THF, -10 °C, 1 h; **32**, THF, 0 °C to rt, overnight, 71%; b) HCCMgBr (1.1 equiv), THF, -10 °C to rt, overnight, quantitative (1.2 : 1 dr); c) EtOH, 100 °C, 1 h, 99% combined yield (53% yield of **35b** over two steps); d) TFA, MeOH, NaBH₃CN (2.1 equiv), 0 °C, 2 h, 51%; e) **37** (1.02 equiv), PhH, 30 °C, 15 h, 84%; THF = tetrahydrofuran, TFA = trifluoroacetic acid, PhH = benzene.

Figure 2.

ORTEP representation of the X-ray crystallography data for cocculidine (Thermal ellipsoids shown at the 50% probability level.
Most hydrogens removed for clarity)