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Oxidative Dearomatization of 4,5,6,7-Tetrahydro-1*H*-indoles Obtained by Metal- and Solvent-Free Thermal 5-*endo-dig* Cyclization: The Route to Erythrina and Lycorine Alkaloids

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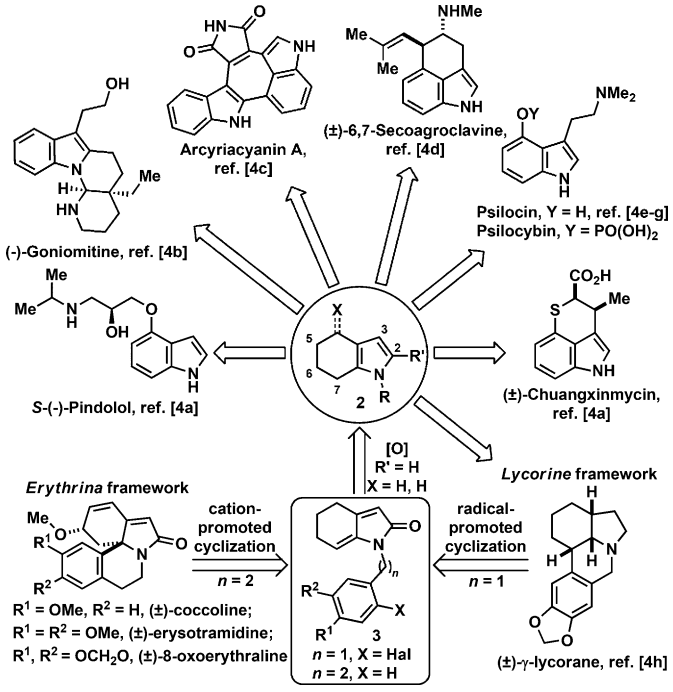
Dedicated to the academician N. S. Zefirov on the occasion of his 80th birthday

Abstract: A facile one-pot approach based on a thermally induced metal- and solvent-free 5-*endo-dig* cyclization reaction of the amino propargylic alcohols in combination with Dess–Martin periodinane-promoted oxidative dearomatization of 4,5,6,7-tetrahydroindole intermediates provides an efficient and robust access to 5,6-dihydro-1*H*-indol-2(4*H*)ones. Green, relatively mild and operationally simple characteristics of the synthetic sequence are the major advantages, which greatly amplify the developed methodology. The utility of obtained indolones as unified key precursors is demonstrated by the application of these products to the formal total syntheses of a whole pleiad of *Erythrina*- and *Lycorine*-type alkaloids, namely (±)-erysotramidine, (±)-erysotrine, (±)-erythravine, (±)-γ-lycorane, and abnormal erythrinanes (±)-coccoline and (±)-coccuvinine.

Introduction

Erythrina- and *Lycorine*-type tetracyclic alkaloids constitute two vast classes of natural products. Members of these families display remarkable biological activities and a number of pharmacological effects; *Erythrina* scaffolds exhibit sedative, hypnotic, hypotensive, antiasthmatic, spasmolytic, antineoplastic, diuretic, and central nervous system (CNS) activities,[1] while *Lycorine*-type alkaloids exhibit anticancer, acetylcholinesterase (AChE) inhibitory, antiviral, antibacterial, anticonvulsant and antidepressant activities.[2] An equal if not exciding interest has been attracted to their challenging polycyclic cores, as a plethora of synthetic approaches have been designed over the past 50 years.

According to the literature, both natural product classes can be retrosynthetically traced back to a common intermediate, 5,6-dihydro-1*H*-indol-2(4*H*)one **3**. In the case of a *Lycorine* framework: $n=1$, X = Hal[3a,b] and with respect to an *Erythrina* core: $n=2$, X = H[3a,c–e] (Scheme 1). These indolones, in turn, could be envisioned as oxygenated forms of 4,5,6,7-tetrahydroindoles **2**, which are extensively employed as highly functionalized indole precursors—valuable intermediates in the numerous syntheses of alkaloids and drugs, such as *S*-(−)-pindolol and (±)-chuangxinmycin,[4a] (−)-goniomitine,[4b] arcyriacyanin A,[4c] 6,7-secoagroclavine,[4d] psilocin and psilocybin[4e] via the intermediary of 4-hydroxyindole[4f,g] and, finally, (±)-γ-lycorane.[4h]



Scheme 1. Application of 4,5,6,7-tetrahydro-1*H*-indoles as valuable intermediates in a variety of total syntheses and their possible transformation to 5,6-dihydro-1*H*-indol-2(4*H*)ones—key precursors to both *Erythrina*- and *Lycorine*-type alkaloids.

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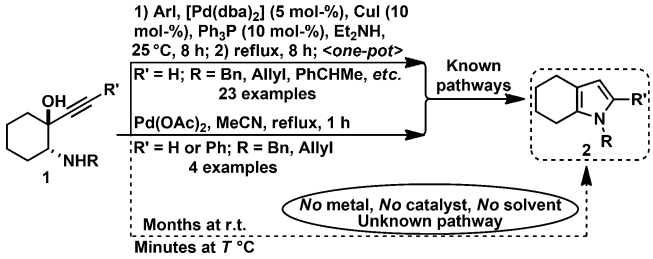
Despite the fact that 4,5,6,7-tetrahydroindoles can be readily converted into indoles, it was rather unclear if they could also be easily transformed into the requisite indolones. Nevertheless, our synthetic efforts en route to the alkaloids mentioned above should have started from the effective assembly of the required heterocycles **2**.

Results and Discussion

Recently, we have developed a two-step synthetic methodology that leads to 4,5,6,7-tetrahydroindoles possessing a wide-range of substituents both at C_2 or nitrogen atoms (including chiral moieties).[5a,b] This approach bears a general character and is readily scalable to generate sufficient amounts of material on a gram-scale in good to excellent yields (Scheme 2, the upper path). Alternatively, tetrahydroindoles **2** can be obtained directly through $Pd(OAc)_2$-promoted 5-*endo-dig* cyclization (Scheme 2, the middle path).[5a,c] Unfortunately, crude yields of such transformations in the case of C_2-unsubstituted compounds (R′ = H) are not excellent. Moreover, the overall yields are even worse when the low oxidative stabilities of these labile substances and the following chromatographic purifications are taken into account.

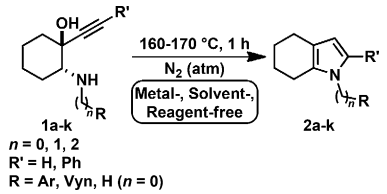


Scheme 2. Synthetic pathways leading to 4,5,6,7-tetrahydroindoles. dba = dibenzylideneacetone.

An interesting observation was noticed during the prolonged storage of amino propargylic alcohol **1b** (R = Bn, R′ = H), both as a solution in CH_2Cl_2 or neat. TLC and ^1H NMR spectroscopic analyses of the samples showed considerable amounts of tetrahydroindole **2b** (R = Bn, R′ = H). Intrigued by this fact, we wondered if this transformation could be applicable on a preparative scale and whether the reaction conditions could be mild enough to decrease reaction times from months to minutes to furnish 4,5,6,7-tetrahydroindoles **2** in appreciable yields (Scheme 2, the lower path).

Indeed, simple heating of neat **1b** in a vial at 140 °C (external oil bath temperature) produced water in the first few minutes. After approximately 30 min, the TLC control showed almost complete consumption of the starting material. Further verification of the conditions revealed the necessity of excluding air from the reaction media. Generally, to achieve full conversion on the majority of the amino propargylic alcohols **1**, temperatures of 160–170 °C were employed for a period of 1 to 3 h. The results of the novel thermally induced 5-*endo-dig* cyclization reactions on various substrates are listed in Table 1.

Table 1. Synthesis of 4,5,6,7-tetrahydroindoles **2** by metal- and solvent-free thermally induced 5-*endo-dig* cyclization.[a]



n = 0, 1, 2
R′ = H, Ph
R = Ar, Vyn, H (*n* = 0)

Entry	Amino propargylic alcohol **1**	*n* (0–2); R; R′	4,5,6,7-Tetra-hydro-indole **2**	Yield [%][b]
1	**1a**	1; Ph; Ph	**2a**	73 (66)
2	**1a′**	1; Vyn; Ph	**2a′**	75 (87)
3	**1b**	1; Ph; H	**2b**	90 (54)
4	**1b′**	1; Vyn; H	**2b′**	77 (82)
5	**1c**	1; Ph; TMS	**2c**[c]	0[d] (0)[e]
6	**1d**	0; 4-F-Ph; H	**2d**[f]	81
7	**1e**	0; H; H	**2e**	26[g]
8	**1f**	1; $CONH_2$; H	**2f**	83
9	**1g**	2; 3,4-di-OMe-Ph; H	**2g**	94
10	**1h**	2; 4-OMe-Ph; H	**2h**	88
11	**1i**	2; 3,4-OCH_2O-Ph; H	**2i**	85
12	**1j**	1; 6-Br-3,4-OCH_2O-Ph; H	**2j**[h]	58
13	**1k**	2; 2-I-4,5-di-OMe-Ph; H	**2k**[h]	68

[a] N_2 atm, 1 h, 160–170 °C (internal oil bath temperature). These are general conditions, unless otherwise stated. [b] Isolated yield after flash column chromatography. The yield in parentheses was obtained performing cyclization under previously disclosed conditions:[5a,c] $Pd(OAc)_2$ (1 mol%), MeCN (0.1 M), reflux, 1 h. [c] Reaction conditions: > 1 h; > 200 °C. [d] Only unchanged **1c** was obtained. [e] Only desilylated tetrahydroindole **2b** was obtained. [f] The reaction time was increased to 3 h at 180 °C. [g] Deviations from the general conditions both in reaction temperature or time led to decreased yields or complete decomposition. [h] The reaction time was increased to 2 h.

All of the starting amino alcohols **1** were produced according to previously reported procedures on a gram-scale.[6]

According to the table above, the majority of the 4,5,6,7-tetrahydroindoles were obtained in good to excellent yields. In the case of *N*-benzyl-substituted compounds, the outcomes of the thermal cyclization reactions were better than those using palladium (Table 1, entries 1 and 3), while *N*-allyl-substituted compounds demonstrated contrary results (entries 2 and 4). The low reactivity of silyl amino propargylic alcohol **1c** (entry 5) compared to other alkynes was anticipated and in full agreement with previous reports.[7] The low cyclization yield of **1e** (entry 7) was also expected as is always the case with N-unsubstituted amino propargylic alcohols.[5a] The moderate yield of **2j** (entry 12) could be attributed to steric factors. Nevertheless, the reaction demonstrated general character and didn't require any solvents or metal catalysts and produced water as a major byproduct.

Although the cyclization proceeded without a metal, we wanted to exclude the influence of transition-metal salts on the reaction pathway. Trace metal analysis was performed by ICP-MS of aliquots (1–2 mg) taken after the completion of the reactions, which showed that the levels of major transition

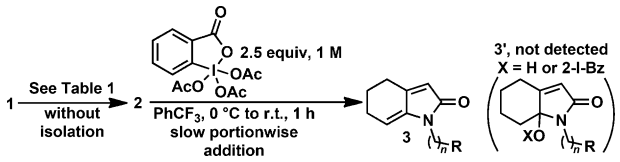
metals (Cu, Zn, Pd, Ag, Pt, Au) capable of promoting 5-*endo-dig* cyclization reactions were lower than the detection limit.[8] Other metals were detected in units of ppm, emphasizing and rigorously demonstrating the metal-free nature of designed cyclization.[9] Moreover, the reaction takes place only above 140 °C, whereas in the presence of Pd^{II} the cyclization proceeded in refluxing acetonitrile (~80 °C) or even Et_2NH (~55 °C) at relatively small concentrations (up to 1 mM of catalyst).[5a–c] Taking into the account that the thermally induced cyclization is also solvent-free, the concentration of both substrate and adventitious metals should have risen tremendously forcing the reaction to proceed at much lower temperatures. While these facts are only speculation, they additionally solidify our initial hypothesis of the absence of trace metal impurities, which could interfere with the course of the thermal cyclization.

After having established permanent and reliable access to 2-unsubstituted tetrahydroindoles **2**, the next goal was to find suitable oxidation conditions for these labile substrates.[10] Based on a study published by Smith et al.,[11] tetrahydroindoles **2** were envisioned as suitable starting materials to achieve oxidized pyrroles, oxypyrrolinones **3**, as the key intermediates in the alkaloid syntheses. These intermediates could be easily transformed into target tetracyclic cores by either radical- or cation-promoted intramolecular cyclization reactions.

Aiming to develop a one-pot approach to minimize losses, tetrahydroindole **2b** was subjected to oxidation directly upon thermal cyclization without purification. To our delight, the portionwise treatment of crude **2b** in CH_2Cl_2 with Dess–Martin periodinane (DMP) at 0 °C afforded the desired 5,6-dihydro-1*H*-indol-2(4*H*)one **3b**[12] in impure form in 56% yield after chromatographic purification. Optimization of the reaction conditions revealed a number of features. The reaction temperature during the slow portionwise addition of DMP should be approximately 0 °C (especially during the scale-up of experiments) because overheating during the exothermic oxidation reaction considerably affects the purity of the product. Reversing the order of addition does not alter the yield, but it is much less convenient than the direct addition. The final concentration of DMP in the reaction mixture could be as large as 1 M, and lower concentrations result in slightly decreased yields. Additives such as $MgSO_4$, $NaHCO_3$, and trifluoroacetic acid (TFA) particularly decrease the effectiveness of the oxidation reaction. Finally, the application of chromatographically isolated **2b** is unnecessary and also has a negative influence on the reaction outcome. This observation could be explained by the presence of one equivalent of water in the crude cyclization product, which results in the formation of acetoxyiodinane oxide upon the reaction with DMP. Acetoxyiodinane oxide is well known to be more active and efficient in promoting oxidation.[13] Consequently, varying the solvent from dichloromethane to acetonitrile and finally to benzotrifluoride ($PhCF_3$)[14] resulted in improvements in both of the purity and yield (68%) of **3b**.[15]

The obtainment of 5,6-dihydro-1*H*-indol-2(4*H*)ones **3** deserved a special attention as no formation of aroyloxy- or hydroxy- product **3′** was detected. According to the above-mentioned work of Smith et al.,[11a] oxidation of 2-substituted *N*-alkyl pyrroles under similar conditions with 2.5 equivalents of DMP afforded 5-hydroxy-γ-lactam, while the obtainment of the elimination product required an additional treatment of the intermediate reaction mixture with $BF_3{\cdot}OEt_2/Et_3SiH$. In our case, the product **3** was formed without any additional manipulations. The plausible explanation of this fact could be due to the liberation of AcOH during the oxidation, which was enough to trigger the elimination process. Moreover, the identity of ^1H NMR spectra of the crude and isolated **3b** further supported our assumption that the elimination took place exactly during the oxidation, but not upon the chromatographic purification on silica gel. Though a minor probability of dehydroxylation during the work-up procedure persisted, the TLC control of the reaction mixture before and after the basic aqueous treatment eliminated the final uncertainty as the major product spot corresponded with **3b** completely. While the exact mechanism of the oxidation is not elaborated yet, the one proposed by Smith and co-workers[11a] seems to be reasonable and applicable in our instance with the exception of the product outcome. With the optimized one-pot cyclization/oxidation conditions in hand, we then examined the scope of this novel sequence on amino propargylic alcohols **1f**–**k** (Table 2).

Table 2. One-pot syntheses of 5,6-dihydro-1*H*-indol-2(4*H*)ones **3** by successive metal- and solvent-free thermally induced 5-*endo-dig* cyclization followed by Dess–Martin periodinane-promoted oxidation of the pyrrole cores.[a]



Entry	Amino propargylic alcohol **1**	R′ = H; *n* (1 or 2); R	5,6-Dihydro-1*H*-indol-2(4*H*)one **3**	Yield [%][b]
1	**1b**	1; Ph	**3b**	68
2	**1f**	1; $CONH_2$	**3f**	0[c]
3	**1g**	2; 3,4-di-OMe-Ph	**3g**	79[d] (20)
4	**1h**	2; 4-OMe-Ph	**3h**	78[d] (60)
5	**1i**	2; 3,4-OCH_2O-Ph	**3i**	50
6	**1j**	1; 6-Br-3,4-OCH_2O-Ph	**3j**	47[d] (30)
7	**1k**	2; 2-I-4,5-di-OMe-Ph	**3k**	48

[a] N_2 atm, 1 h, 160–170 °C (internal oil bath temperature). These were general conditions, unless otherwise stated. After cooling to r.t., the crude **2** was dissolved in $PhCF_3$ and treated portionwise with DMP (2.5 equiv) at 0 °C. [b] Isolated two-step yield after flash column chromatography. The yield in parentheses was obtained after additional recrystallization from the appropriate solvent (see the Supporting Information). [c] DMF (20 vol%) was added to increase the solubility of **2f**. A complex mixture of products was obtained. [d] Average yield of the reaction.

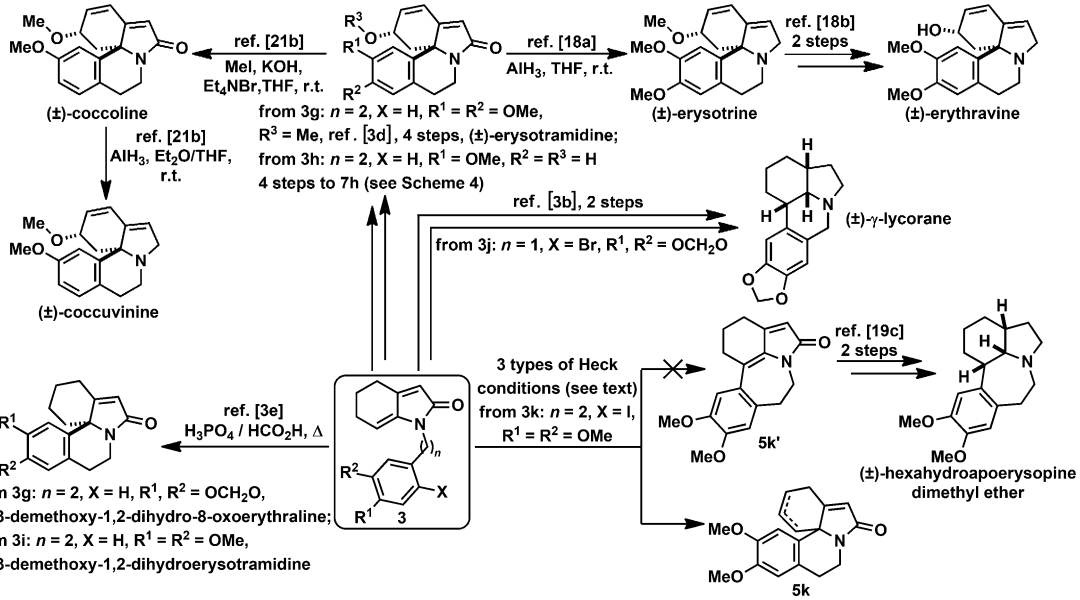
The treatment of crude **2f** with DMP produced a complex mixture of products, which contained no required product according to LCMS analysis. Presumably, primary alkyl amide reacted with the polyvalent iodine reagent through a Hofmann

rearrangement even at 0 °C.[16] Nevertheless, the oxidation of the other tetrahydroindoles proceeded smoothly and furnished the desired indolones **3g**–**k** in moderate to good yields. The reasons for the poor scalability of DMP-oxidation on a scale larger than 10 mmol are the subject of further investigations.

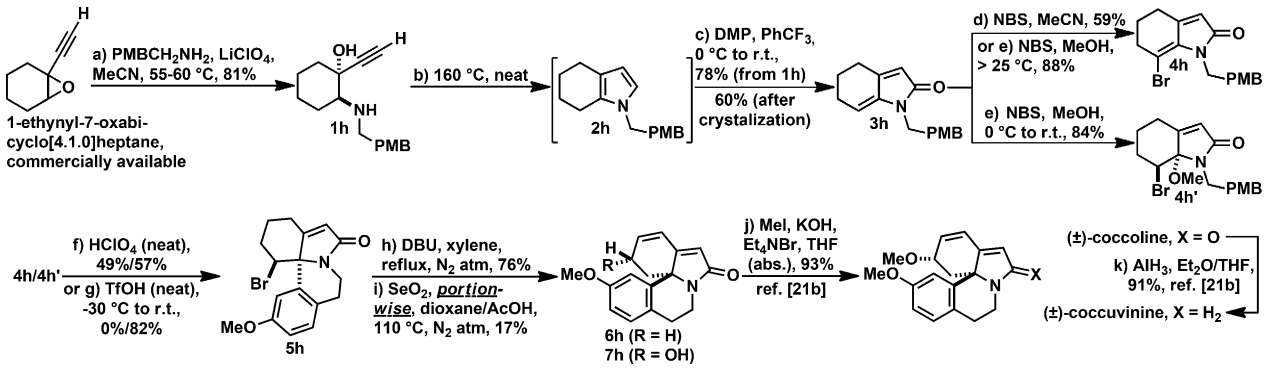
The acquirement of **3g**, **3i**, and **3j** completed the formal total syntheses of a whole pleiad of alkaloid structures,[17] namely (±)-3-demethoxy-1,2-dihydroerysotramidine and (±)-3-demethoxy-1,2-dihydroerythraline,[3e] (±)-erysotramidine,[3d] which could be further transformed into (±)-erysotrine[18a] and (±)-erythravine,[18b] and finally, (±)-γ-lycorane[3b] (Scheme 3). To achieve another formal synthesis of the rearranged alkaloid tetrahydroerythraline, hexahydroapoerysopine dimethyl ether[19] indolone **3k** was subjected to intramolecular ligand-free Heck cyclization under Jeffery conditions.[20] Unfortunately, regardless of variations in reaction conditions, erythrinane **5k** (56% yield) was obtained as an inseparable mixture of unassigned regioisomeric alkenes in ~4:1 ratio (according to ^{1}H NMR and LCMS analyses) instead of the expected apoerysopine core intermediate **5k′**.

To achieve another formal syntheses[21] of (±)-coccoline and (±)-coccuvinine, we focused our attention on the transformation of indolone **3h** into the tetracyclic intermediate **6h** (Scheme 4). Bromocyclization under conditions developed by Padwa[3d] did not result in the required cyclization product **5h**. Instead, an inseparable mixture of vinyl bromide **4h** and bromohydrin **4h′(desMe)** was obtained in 77% crude yield. An extensive search for conditions leading to the requisite **5h** revealed that a two-step procedure could be successfully utilized. First, indolone **3h** was converted into either vinyl bromide **4h** or methoxy bromide **4h′** according to the judicious choice of solvent, temperature and even the order of addition of NBS. Next, **4h** and **4h′** were both subjected to acid-mediated cyclization; **4h′** in neat trifluoromethanesulfonic acid afforded the best results on a gram-scale under very mild reaction conditions, whereas numerous elaborated cyclization approaches led to unsatisfying results.[15,22] It should be noted that this cyclization reaction eliminates the necessity of an additional electron-donating directing group that was employed in the first total synthesis of (±)-coccoline by Ju-ichi et al., thus obviating at least two low-yielding steps for the deprotective cleavage of this auxiliary.[21a] The obtained tetracyclic erythrina skeleton **5h** was smoothly converted into α,β,γ,δ-unsaturated diene amide **6h** upon treatment with DBU in refluxing *p*-xylene for approximately 20 h in 76% yield according to previously disclosed conditions.[3d]

After having established a robust and facile method to access the desired tetracyclic framework, only one simple but not easy and unevident step, namely the oxidation of the C_3-allylic position, was sufficient for the completion of the formal total syntheses of the abnormal *Erythrina*-type alkaloids (±)-coccuvinine and (±)-coccoline.[21] Reproducing Padwa's conditions[3d] exploited in the synthesis of (±)-erysotramidine verbatim proved to be ineffective in terms of the tremendously long reaction times and low conversion of the starting material. Thus, exposing **6h** to 10 equivalents of SeO_2 in a refluxing mixture of dioxane and formic acid[3d] for 8 h resulted in <3% conversion of the starting material according to LCMS analysis. To improve both conversion and reaction times, we performed an extensive screening of reagents and conditions generally employed for allylic oxidation in the field of total synthesis.[15] This exhaustive optimization showed that the employment of any alternative reagents was not helpful. Thus, we returned to utilizing selenium dioxide oxidation to carefully revise and improve the literature conditions. Several further experiments established the scope and limitations of the process and demonstrated that the temperature should not greatly exceed 100 °C, while the reaction rate was majorly increased as the concentration of **6h** rose. Conducting solid-phase ball milling-assisted oxidation disappointingly led to undesired decomposition



Scheme 3. 5,6-Dihydro-1*H*-indol-2(4*H*)ones **3** as the key intermediates en route to *Erythrina*- and *Lycorine*-type tetracyclic alkaloids.



Scheme 4. Formal syntheses of (±)-coccoline and (±)-coccuvinine: a) epoxide (1 M), 4-MeO-phenethyl amine (2 equiv), $LiClO_4$ (1.5 equiv), MeCN, 55–60 °C, 16 h; b) 160–170 °C, neat, N_2 atm, 1 h; c) **2h** (without isolation), $PhCF_3$, Dess–Martin periodinane (2.5 equiv, 1 M final concentration) portionwise addition at 0 °C→r.t., 1 h; d) NBS (1.1 equiv), MeCN (0.1 M), r.t., 1 h; e) for **4h**: NBS (1.1 equiv), MeOH (0.1 M), 25–30 °C, 30 min, **4h**/**4h**′ ≈ 10:1; for **4h**′: NBS (1.1 equiv), MeOH (0.1 M), 0 °C→r.t., 30 min, **4h**′/**4h** > 100:1; f) **4h** or **4h**′ (0.1 M), $HClO_4$ (70 wt.-%, aq.), r.t., 30 min; g) **4h**′ (0.33 M), TfOH, −30 °C→r.t., 15-20 min; h) **5h** (0.2 M), DBU (10 equiv), *p*-xylene, N_2 atm, reflux, 20 h; i) **6h** (0.5 M in dioxane) in a sealed vial with a rubber septum, N_2 atm, SeO_2 (portionwise addition, 1 equiv per hour starting from 2 equiv), AcOH (10 equiv), 110 °C (oil bath), 12–14 h; j) see ref. [19b]; k) see ref. [19b]. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DMP = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (Dess–Martin periodinane); NBS = *N*-bromosuccinimide.

products, though the reaction profile at the beginning was promising. Finally, we established an optimal set of conditions. The allylic oxidation was performed in dioxane in a sealed vial under a nitrogen atmosphere at a concentration of **6h** as high as 0.5 M at 110 °C (internal oil bath temperature). The highest conversion (approx. 88%) was achieved after 12 h of a portionwise (1 equiv every hour starting from 2 equiv) addition of SeO_2 and afforded **7h** in 17% yield after flash chromatography. The spectral characterization data for **7h** was in accordance with that obtained by Sano and co-workers.[21b,23] Thus, the formal total syntheses of (±)-coccoline and (±)-coccuvinine were accomplished in only seven and eight steps, respectively, from the commercially available epoxide 1-ethynyl-7-oxabicyclo[4.1.0]heptane, which provided the most facile access to these abnormal *erythrinanes* to date.

Conclusion

To summarize, we successfully designed a novel one-pot two-step approach leading to 5,6-dihydro-1*H*-indol-2(4*H*)ones **3** based on green and uncatalyzed thermally induced cyclization of amino propargylic alcohols **1** followed by DMP oxidation of 4,5,6,7-tetrahydroindole **2** intermediates. First of all, we have made another use of tetrahydroindoles as worth-while synthetic intermediates. On the other hand, we have extended the range of applications of pyrroles as suitable substrates for the oxidative dearomatization reactions, which culminate in synthetically useful intermediates[24] and shown the unique oxidizing power of hypervalent iodine reagents, which suggests that they could be reasonable metal-free alternatives to conventional reagents.[25] The array of synthesized indolones **3**, in turn, served as unified key intermediates in the total syntheses of alkaloids representing the *Erythrina* and *Lycorine* families. The facile obtainment of **7h** was the missing link en route to (±)-coccoline and (±)-coccuvinine, which further extended our approach to synthesizing abnormal *Erythrina* alkaloids. We hope that our exhaustive work on the optimization of the allylic oxidation conditions for **6h** will not go unnoticed, making the approach based on the late-stage installation of OH-groups to C_3-positions much more viable and applicable for the final assembly of other *erythrinanes*.

Experimental Section

Experimental procedures, product characterization data, and copies of the ^1H and ^{13}C NMR spectra are presented in the Supporting Information.

Acknowledgements

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Keywords: 4,5,6,7-tetrahydroindoles · alkaloids · green chemistry · thermally induced cyclization · total synthesis

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