Synthetic Methods

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Diastereoselective Synthesis of C3-Quaternary Indolenines Using α,β-Unsaturated *N*-Aryl Ketonitrones and Activated Alkynes**

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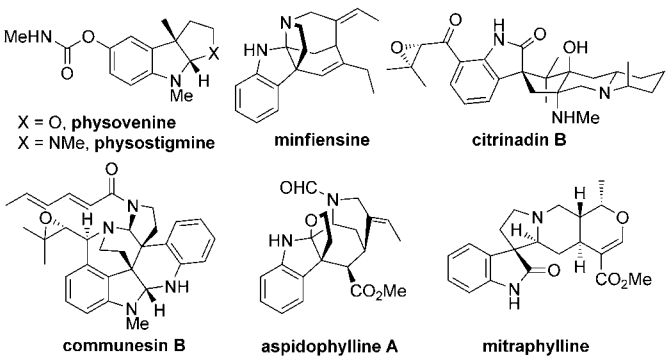
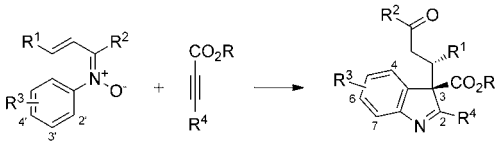
Indole-containing structures are ubiquitous in natural products, medicinal compounds, and organic materials.[1] Given their biomedical importance, synthetic methods towards these structural motifs remain relevant even after decades of innovations.[2] However, despite all the efforts toward the efficient construction of C3-quaternary indole derivatives, significant challenges remain.[3] These challenges are found in the forms of spirooxindole, pyrroloindoline, furoindoline, and other indole-containing polycycles, which exist in a large number of alkaloids, such as physovenine,[4] physostigmine,[5] minfiensine,[6] citrinadin B,[7] communesin B,[8] aspidophylline A,[9] and mitraphylline[10]. (Scheme 1). Many of the



Scheme 1. Some indole alkaloids.

existing methods form the C3 quaternary center by alkylation,[11] cycloaddition,[12] and rearrangement of 3-substituted indoles or oxindoles.[13,14] These methods are limited by the availability or the ease of preparation of the indole and oxindole starting materials, especially those that have substituents on the indole benzenoid ring. Indeed, whereas methods have been developed for syntheses of C2- and C3-substituted indoles, the selective functionalization of the indole benzenoid ring remains problematic.[15] A method that allows rapid and stereoselective synthesis of these structural motifs from simple starting materials would be of tremendous value and provide entry to the structurally diverse family of indole alkaloids. Herein, we report a remarkably simple and efficient approach that consists of combining α,β-unsaturated *N*-aryl ketonitrones and activated alkynes to form C3-quaternary indolenines with formation of the heterocycles and two contiguous quaternary and tertiary chiral centers from readily available starting materials (Scheme 2).



Scheme 2. Reaction of α,β-unsaturated *N*-aryl ketonitrones and activated alkynes.

Our preliminary investigation of the reaction of α,β-unsaturated *N*-phenyl ketonitrone **1a**, which was readily prepared from *tert*-butyl pent-2-enoate by a two-step route that we have previously described,[16] and diethyl acetylenedicarboxylate in methylene chloride showed that they readily combined to give C3-quaternary indolenine **2a** (Table 1, entry 1; and X-ray structure of Figure 1). In addition to the formation of a 3*H*-indole heterocycle, this drastic transformation also led to diastereoselective formation of two contiguous quaternary and tertiary chiral centers.

The potential of such a transformation as a general entry to C3-quaternary indolenines prompted us to examine various reaction parameters in an attempt to improve its efficiency (Table 1). The reaction was found to give better yields in nonpolar solvents (CH_2Cl_2 or toluene; Table 1, entries 1–6). The addition of both Brønsted and Lewis acids decreased the reaction efficiency or stopped the reaction completely (Table 1, entries 7–14). Elevated temperature (40

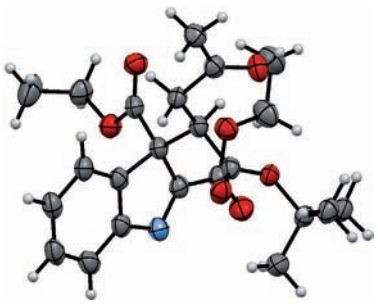


Figure 1. X-ray based ORTEP drawings of **2a** (O red, N blue). Spheres are drawn at the 50% probability level.[25]

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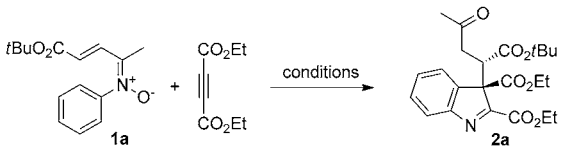
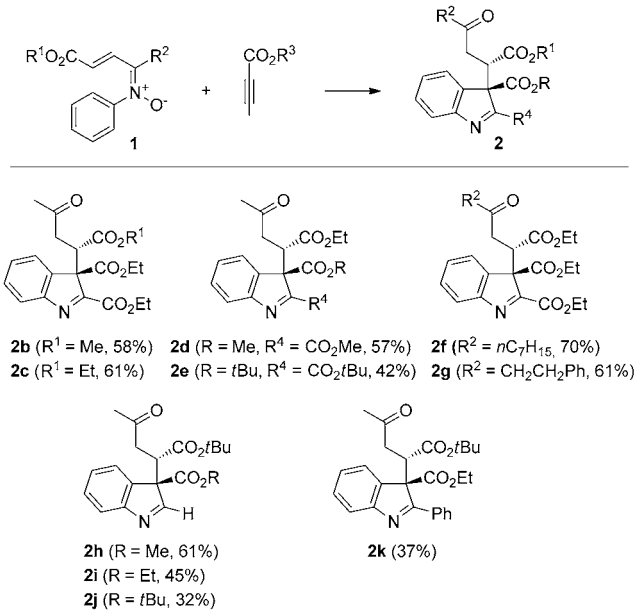
Table 1: Optimization of conditions for formation of **2a**.[a]



Entry	Solvent	Additive[b]	*T* [°C]	**2a**[c]
1	CH_2Cl_2	–	RT	64
2	THF	–	RT	48
3	ether	–	RT	21
4	DMF	–	RT	trace
5	*i*PrOH	–	RT	trace
6	toluene	–	RT	68
7[d]	toluene	HOAc	RT	7
8[d,e]	toluene	HOAc/H_2O	RT	45
9	toluene	TFA	RT	trace
10	toluene	TfOH	RT	15
11	toluene	$ZnCl_2$	RT	trace
12	toluene	$SnCl_4$	RT	trace
13	toluene	$FeCl_3$	RT	trace
14	toluene	$TiCl_4$	RT	trace
15	toluene	–	40	73
16	toluene	–	80	79

[a] All reactions were carried out using 1 equiv of **1a** and 3 equiv of diethyl acetylenedicarboxylate. [b] Unless noted otherwise, 1.2 equiv of the additive was used. [c] Yield of the isolated product. [d] 0.2 equiv of HOAc was used. [e] The reaction was carried out in a mixture of toluene/H_2O (10:1). DMF = *N*,*N*′-dimethylformamide, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.



Scheme 3. Reaction of **1** and activated alkynes. All reactions were carried out using 1 equivalent of **1** and 3 equivalents of activated alkynes at 80 °C in toluene until the reaction was complete by TLC analysis (8–12 h). The yields are of the isolated products.

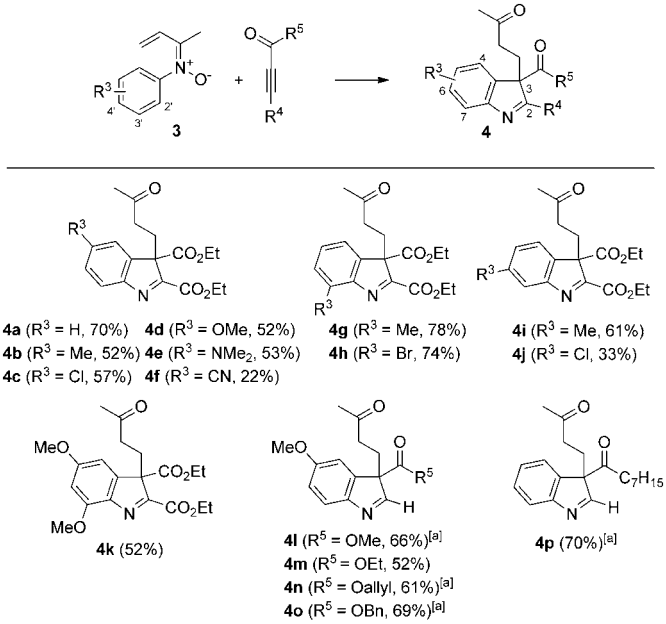
to 80 °C) not only accelerated the reaction, but led to improved yields as well (Table 1, entries 15 and 16). Thus, all subsequent reactions were carried out in toluene at 80 °C unless noted otherwise.

The scope of the reaction was investigated under the optimized reaction conditions using a range of α,β-unsaturated *N*-phenyl ketonitrones (**1**) and activated alkynes (Scheme 3). The yields of **2** were affected by the size of the alkyl ester groups of both the ketonitrones and the activated alkynes, but in opposite ways; a better yield was observed when the ketonitrone with a bulky *tert*-butyl carboxylate substituent was used (**2a** versus **2b** and **2c**), however, a lower yield was obtained when an alkyne with an ester of increased steric bulk was used (**2e** versus **2c** and **2d**). The α′-alkyl (R^2) substituent of the α,β-unsaturated ketonitrones also exerted a slight influence over the reaction efficiency (**2f** and **2g**). All these reactions appeared to be stereoselective since only the *anti* diastereomer was isolated in each of the examined cases.

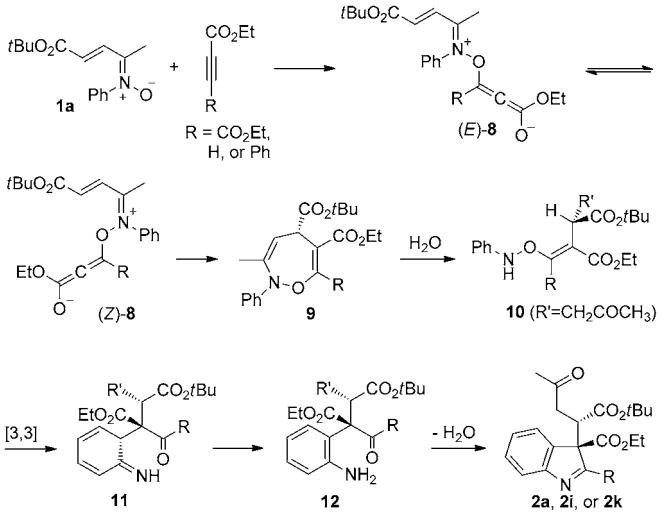
Excellent regioselectivity was observed when alkyl propiolates (R^4 = H) were used. Only the C3-quaternary indolenines (**2h**, **2i**, and **2j**) were formed upon reaction of **1a** with unsymmetrical monoactivated alkynes. The steric characteristics of the ester groups of these monoactivated alkynes had a more pronounced effect over the reaction yields than that of the ester groups of the symmetrical diactivated alkynes. For example, the reaction of **1a** with methyl propiolate led to formation of **2h** in 61 % yield whereas **2j** was obtained in only 32 % yield from the reaction of **1a** and *tert*-butyl priopiolate. A C3-quaternary indolenine (**2k**) was also formed when the monoactivated internal alkyne ethyl 3-phenylpriopiolate was used. Alkynes without activating groups (such as 6-dodecyne, phenylacetylene, and diphenylacetylene; not shown) did not participate in the reaction.

To further explore the generality of this method a series of *N*-aryl ketonitrones without β substituents (**3**) were also investigated (Scheme 4).[17] Good to moderate yields were obtained for reactions of α,β-unsaturated *N*-tolyl ketonitrones with diethyl acetylenedicarboxylate: the 6-methyl indolenine **4i** was regioselectively generated from the *N*-*meta*-tolyl ketonitrone and 5- and 7-methyl indolenines (**4b** and **4g**, respectively) were formed from the *N*-*para*-tolyl and *N*-*ortho*-tolyl ketonitrones, respectively. α,β-Unsaturated ketonitrones with 2′-bromo, 3′-chloro, and 4′-chloro-*N*-phenyl groups also reacted to give indolenines (**4h**, **4j**, and **4c**) regioselectively. Substitution of the *N*-phenyl group with the electron-donating methoxy, dimethylamino, and dimethoxy groups was found to be compatible with these reactions (**4d**, **4e**, and **4k**). Significantly reduced yield was observed when the *N*-phenyl ring was substituted with the electron-withdrawing cyano group (**4f**). Monoactivated terminal alkynes in the form of methyl, ethyl, allyl, and benzyl esters of propiolic acid readily reacted with the α,β-unsaturated *N*-4′-anisyl ketonitrone to give C3-quaternary indolenines (**4l**–**4o**). A preliminary study showed that the alkyne with a keto activating group rather than an ester group was also compatible with the reaction (**4p**).

These C3-quaternary indolenines could be easily manipulated for potential synthetic applications. For example, the indolenine moiety of **4l** could be oxidized with *m*CPBA to form oxindole **5** (Scheme 5).[18] Also reduction of **4l** with the Hantzsch ester gave **6** in 76 % yield.[19] Complex mixtures were formed when other reducing agents (such as $NaBH_4$, $NaBH_3CN$, and $NaBH(OAc)_3$/HOAc) were used. The 3-



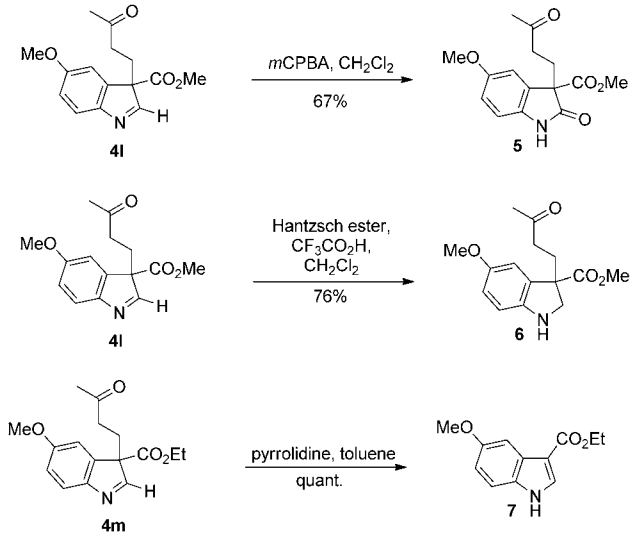
Scheme 4. Reaction of **3** with activated alkynes. All reactions were carried out using 1 equivalent of **3** and 3 equivalents of activated alkynes at 80 °C in toluene until the reaction was complete by TLC analysis (8–12 h). The yields are of the isolated products. [a] These reactions were conducted at RT. Bn = benzyl.



Scheme 6. Proposed reaction mechanism.

substituted indole **7** was quantitatively formed by the retro-Michael cleavage of one of the C3-substituents when **4m** was treated with pyrrolidine. This method provides a unique entry to substituted indoles by reaction of α,β-unsaturated *N*-aryl ketonitrones and activated alkynes.

We propose the reaction mechanism shown in Scheme 6. The [5+2] cycloaddition of **1a** with diethyl acetylenedicarboxylate (R = CO_2Et) would give a seven-membered heterocycle **9**.[20] This transformation possibly proceeds through a stepwise process initiated by the nucleophilic Michael attack of the oxygen atom of the nitrone on the activated alkyne.[21] We speculate that formation of the zwitterion (*E*)-**8** is accompanied by significant reduction of the energy barrier for C=N bond isomerization to give (*Z*)-**8**, which cyclizes to form **9**. The next step involves hydrolysis of **9** to give **10**. Further transformations of **10** through [3,3] sigmatropic rearrangement,[22] tautomerization, and intramolecular condensation lead to formation of the C3-quaternary indolenine **2a**.[23] Only a catalytic amount of water is necessary for the entire process since water is regenerated upon formation of **2a**. Such a mechanism is consistent with the stereoselective formation of the diastereomer illustrated for **2a** (Scheme 6). Specifically, minimization of the 1,3-allylic strain requires **10** to adopt the conformation shown in Scheme 6;[24] this conformation directs the [3,3] sigmatropic rearrangement to occur from the sterically less-hindered β face to give **2a** stereoselectively. Since the nucleophilic attack of the oxygen atom of the nitrone will occur at the β position of the activated alkyne, this mechanism also rationalizes the regioselectivity in the formation of C3-quaternary indolenines (such as **2i** and **2k**) when monoactivated alkynes are used.



Scheme 5. Some transformations of **4l** and **4m**. Hantzsch ester = diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

In conclusion, we have developed an expedient approach to C3-quaternary indolenines that are potentially applicable in the synthesis of complex indole alkaloids and related compounds. It features a topographically dramatic transformation of α,β-unsaturated *N*-aryl ketonitrones with activated alkynes that leads to formation of the heterocycles with concomitant generation of up to two contiguous quaternary and tertiary stereocenters without transition metal catalysis. This remarkable transformation is general and proceeds with good yields considering its complexity. This transformation also constitutes a rare example of reactions involving α,β-unsaturated ketonitrones and reveals some insights into the reactivity of these relatively unexplored species. Studies to extend the scope of the reaction, develop asymmetric variants, and validate/elucidate the reaction mechanism are underway.

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[25] CCDC 873391 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

