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Tandem Cyclization–Annulation of α-Acidic Isocyanides with 2-Methyleneaminochalcones: Synthesis of Pyrrolo[2,3-*c*]quinoline Derivatives

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Abstract. Tandem cyclization-annulation of tosylmethyl isocyanide and isocyanoacetate with 2-methyleneaminochalcones as aza-1,5-dielectrophiles has been successfully developed. These domino transformations feature simultaneous formation of three bonds and two rings in a single operation, and represent novel protocols for the expedient synthesis of both aromatic and partially aromatic pyrrolo[2,3-*c*]quinoline derivatives from readily available precursors under metal-free conditions. Notably, tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolones that bear three adjacent stereocenters were obtained in a highly diastereoselective manner.

Keywords: tosylmethyl isocyanide; aza-1,5-dielectrophiles; pyrrolo[2,3-*c*]quinolines; tandem reactions; isocyanoacetate

During the past decade, a few marine natural products containing tricyclic 3*H*-pyrrolo[2,3-*c*]quinoline ring system have been reported (Figure 1), including marinoquinoline A–F,[1,2] aplidiopsamine A[3] and trigonoine B.[4] The alkaloids marinoquinoline A–F showed antibacterial, antifungal, and acetylcholinesterase activities.[1,2] Aplidiopsamine A was found to be a potent antimalarial agent[3] and trigonoine B displayed anti-HIV activity.[4] Furthermore, some 4-substituted pyrrolo[2,3-*c*]quinolones were found to possess antitubercular activity.[5] The rare and unique structural feature and interesting bioactive properties of these heterocycles inspired continuous interest in developing efficient protocols for their preparation.[6-11] The well-established strategy is the formation of central pyridine ring from aryl-substituted pyrroles by Morgen-Walls reaction,[6] Pictet–Spengler reaction,[7] tandem reductive cyclization reaction,[8] Pd-catalyzed

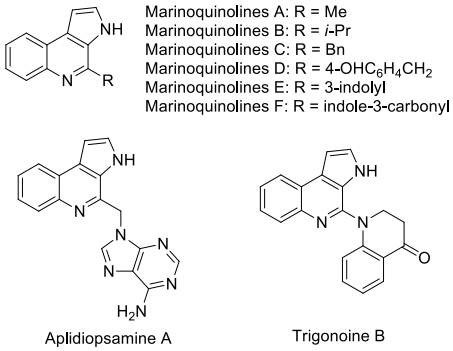
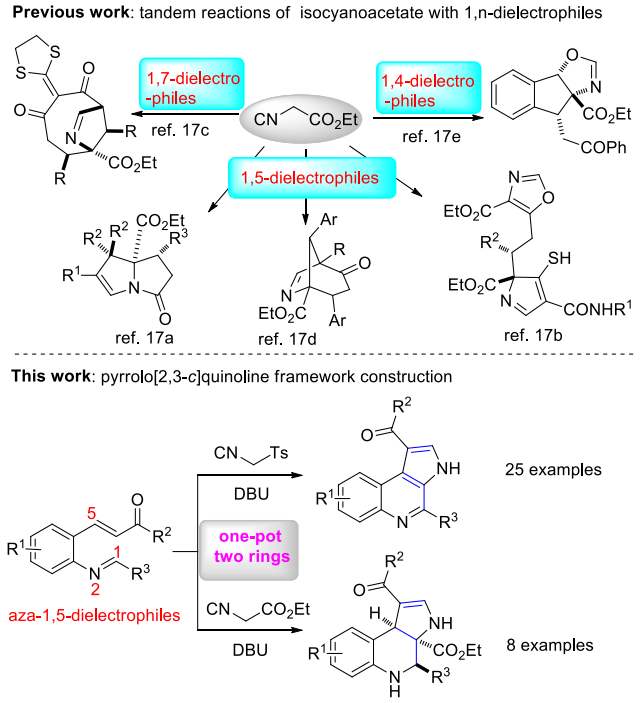


Figure 1. Natural pyrrolo[2,3-*c*]quinolone alkaloids.

imine cyclization,[9] Bischler-Napieralski-type cyclization[10] and arene–ynamide cyclization[11]. Alternatively, methods involving the synthesis of pyrrole ring by Bartoli indolization[12a] or reductive cyclization reaction[12b,c] have also been documented. However, these syntheses mainly rely on the formation of one ring with a tricyclic framework from aryl-substituted pyrrole[6-11] or quinoline derivatives[12]. Recently, a tandem cyclization-annulation protocol has emerged as an efficient and promising strategy for the construction of this tricyclic frameworks. For example, Wang, Ji and co-workers have developed an efficient synthesis of pyrrolo[2,3-*c*]quinolines by the sequential formation of the pyridine and pyrrole rings through a domino reaction of 3-(2-oxo-2-ethylidene)indolin-2-ones with alk-1-enyl substituted TosMICs.[13] Last year, we reported a tandem cyclization-annulation of azomethine ylides with methyleneaminochalcones for the facile synthesis of pyrrolo[2,3-*c*]-quinolines by the sequential formation of the pyridine and pyrrole rings.[14] Despite these great achievements, the

development of novel domino strategies for the efficient synthesis of these tricyclic scaffolds is still highly desirable.

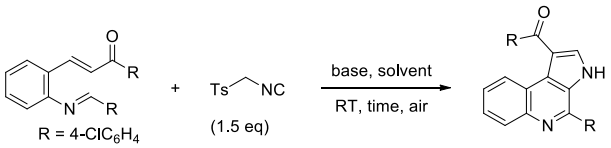
α-Acidic isocyanides such as tosylmethyl isocyanide (TosMIC) and isocyanoacetate are versatile building blocks for the synthesis of a diverse class of five-membered heterocycles through formal [3+2] cycloaddition reactions.[15] In recent years, our research efforts have been devoted to the domino transformation of functionalized isocyanides.[16,17] Accordingly, a range of structurally complex heterocycles, including pyrrolizidines,[17a] C_2-tethered pyrrole/oxazole pairs,[17b] tricyclic indolizidines,[17c] 8-azabicyclo[5.2.1]dec-8-enes[17d] and bi-/tricyclic oxazolines,[17e] were efficiently constructed from the domino reaction of α-acidic isocyanides with all-carbon 1,4-, 1,5- or 1,7-dielectrophiles (Scheme 1, top). In continuation of our studies on isocyanide-based reactions,[18] as well as inspired by Xu's work[19] wherein 2-methyleneaminochalcones were used as aza-dielectrophiles, we herein report the tandem cyclization-annulation of α-acidic isocyanides with 2-methyleneaminochalcones for the straightforward and efficient synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines and tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolines, respectively (Scheme 1, bottom). Both the aromatic and partially aromatic tricyclic pyrroloquinolines were efficiently assembled by simultaneous formation of the pyridine and pyrrole rings in a single operation. Notably, the domino reaction of isocyanoacetate with 2-methyleneaminochalcones was found to proceed in a highly diastereoselective manner, and only one of the four possible diastereomers of tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolines was obtained.



Scheme 1. Tandem reactions of α-acidic isocyanides

Initially, the reaction of 2-methyleneaminochalcone **1a** (0.2 mmol) with tosylmethyl isocyanide (TosMIC) **2a** (0.3 mmol) was studied carefully in the presence of different amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in acetonitrile at room temperature (Table 1, entries 1–3). The reactions gave 3*H*-pyrrolo[2,3-*c*]quinoline **3a** in 70% yields when 2.0 equivalent of DBU was used (Table 1, entry 3), whereas 1.2 and 1.5 equivalent of DBU led to lower yield of **3a** (Table 1, entries 1 and 2). In comparison to other bases tested, such as TMG (1,1,3,3-tetramethylguanidine), Et_3N, NaOH and K_2CO_3 (Table 1, entries 4–7), DBU proved to be the best choice with respect to the yield (Table 1, entry 3 vs entries 4–7). Different solvents were also screened (Table 1, entries 8–11). While **3a** was only obtained in 29% yield in THF (Table 1, entry 8) and a trace amount in EtOH (Table 1, entry 9), in DMF and CH_2Cl_2 it was obtained in good yield (Table 1, entries 10 and 11).

Table 1. Screening of Reaction Conditions[a]



1a 2a 3a

Entry	Base	Solvent	Time (h)	Yield of **3a** (%)[b]
1	DBU (1.2)	CH_3CN	50	38
2	DBU (1.5)	CH_3CN	46	49
3	***DBU (2.0)***	***CH_3CN***	***41***	***70***
4	TMG (2.0)	CH_3CN	41	32
5	Et_3N (2.0)	CH_3CN	41	NR
6	NaOH (2.0)	CH_3CN	41	12
7	K_2CO_3 (2.0)	CH_3CN	41	trace[c]
8	DBU (2.0)	THF	41	29
9	DBU (2.0)	EtOH	41	trace[d]
10	DBU (2.0)	DMF	41	65
11	DBU (2.0)	CH_2Cl_2	41	60

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), base and solvent (2 mL).
[b]Yields of isolated products.
[c]**1a** was recovered in 22% yield.
[d]**1a** was recovered in 10% yield.

With the optimal conditions in hand (Table 1, entry 3), various 2-methyleneaminochalcones **1** were explored to investigate the generality of this domino bicyclization reaction (Scheme 2). In general, a wide range of substrates **1a**–**y** bearing various functional groups reacted smoothly with TosMIC **2a** at room temperature, giving rise to the desired pyrrolo[2,3-*c*]quinolines **3a**–**y** in good to high yields. The R^2 group in **1** may be electron-deficient aryl (**1a**–**c**, **1h**, **1i** and **1k**), electron-neutral aryl (**1d**), electron-rich aryl (**1e**–**g** and **1j**), hetereoaryl (**1l** and **1m**) and alkyl (**1n**) groups, and the corresponding pyrrolo[2,3-*c*]quinolines **3a**–**n** were obtained in good to high yields. Various aryl and heteroaryl substituents as R^3

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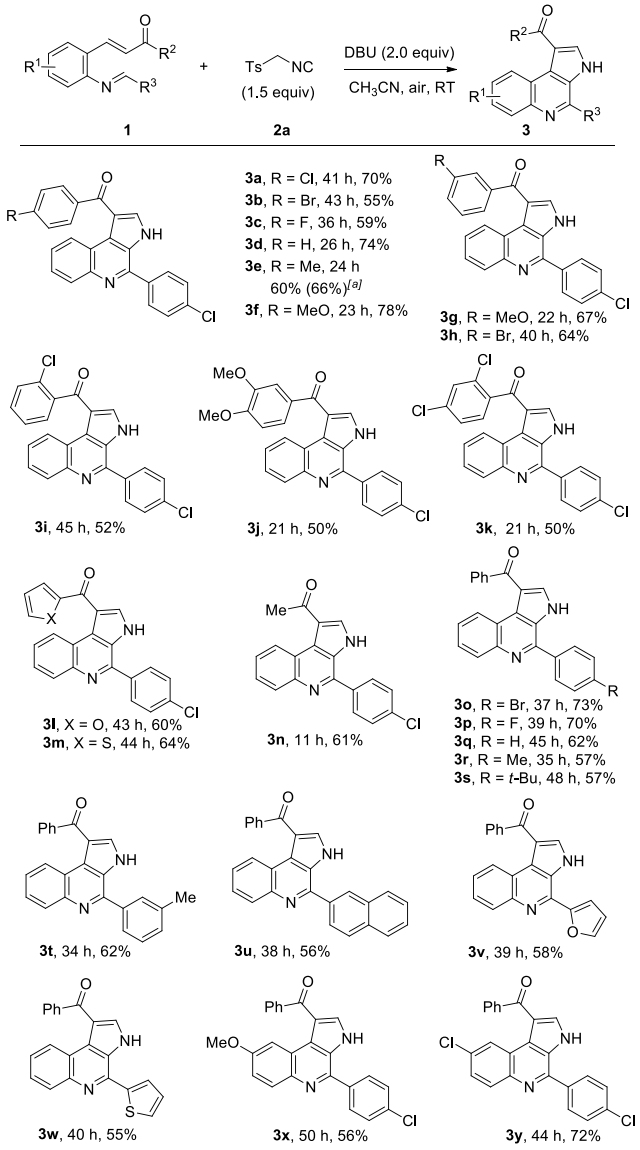
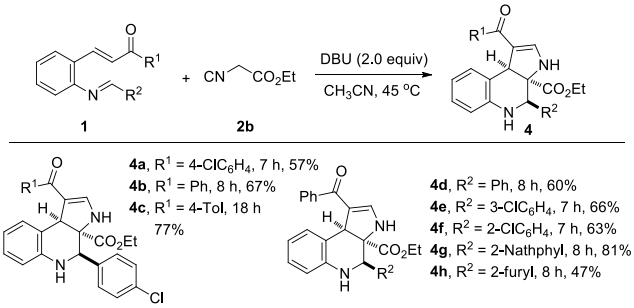
substrates **1** were also tolerated and 4-substituted pyrroloquinolines **3o**–**w** were thus obtained in good yields. Substrates **1x** and **1y** with both electron-donating and -withdrawing R^1 groups on the benzene ring afforded the desired pyrrolo[2,3-*c*]quinolines **3x** and **3y** in good yields.



Scheme 2. Synthesis of 3*H*-pyrrolo[2,3-*c*]quinoline **3.** Reactions were carried out with **1** (0.2 mmol), **2a** (0.3 mmol) and DBU (0.4 mmol) in CH_3CN (2 mL); yields of isolated product. [a] 1 mmol scale synthesis.

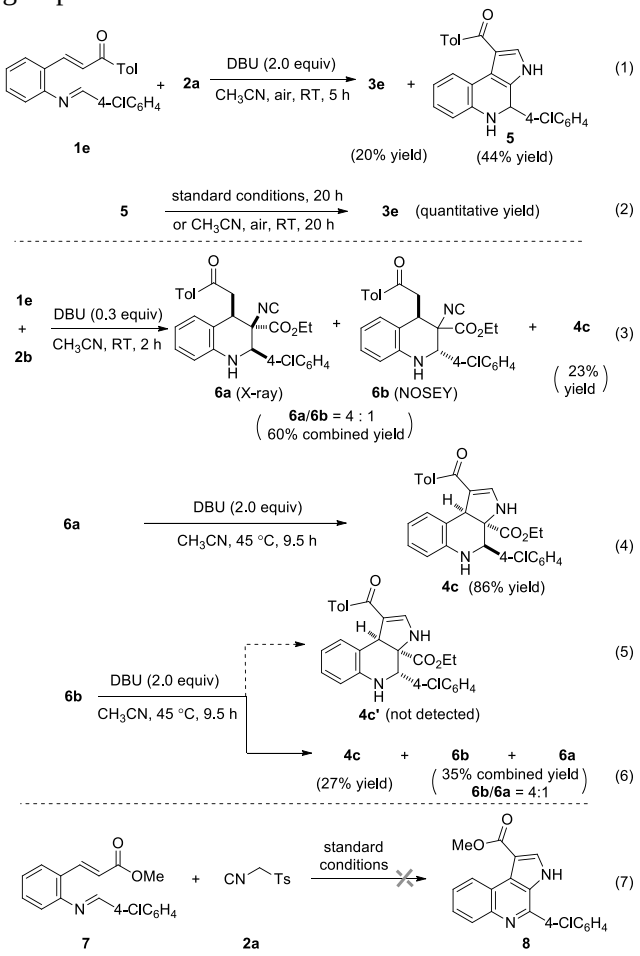
Next, the tandem cyclization-annulation of 2-methyleneaminochalcones **1** with isocyanoacetate **2b** was also investigated. As depicted in Scheme 3, the reaction of several **1** with isocyanide **2b** afforded the tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolines **4a**–**h** in good to high yields. Notably, only one of the four possible diastereomers of **4** was obtained in this reaction, indicating that this domino process proceeds in a highly diastereoselective manner. The relative configuration of **4c** was confirmed by single-crystal X-ray diffraction analysis.[20]



Scheme 3. Tandem cyclization-annulation of isocyanoacetate **2b** with 2-methyleneaminochalcones **1**. Reactions were carried out with **1** (0.2 mmol), **2b** (0.3 mmol) and DBU (0.4 mmol) in CH_3CN (2 mL); yields of isolated product.

To gain mechanistic insight of this tandem cyclization-annulation, a series of control experiments were conducted (Scheme 4). Under the optimal conditions (Table 1, entry 3), the reaction of **1e** with TosMIC **2a** for 5 h gave the pyrrolo[2,3-*c*]quinoline product **3e** and the corresponding dihydropyrrolo[2,3-*c*]quinoline **5** in 20% and 44% yields, respectively (Scheme 4, eq 1). Exposure of **5** under identical conditions or without DBU for 20 h produced **3e** in quantitative yield (Scheme 4, eq 2). These results illustrate that **5** is likely the reaction intermediate and DBU is not required for the aerobic oxidation of **5**. When the reaction of **1e** with isocyanoacetate **2b** was quenched at 2 h, tetrahydroquinolines **6a** and **6b** were obtained in a combined yield of 60% (4 : 1 d.r.), along with tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolone **4c** in 23% yield (Scheme 4, eq 3). The relative configuration of major diastereomer **6a** was unambiguously confirmed by single-crystal X-ray analysis.[20] The substituents on C2 and C4 of the minor product **6b** were assigned as *trans* by NOSEY analysis (see Supporting Information). Treatment of **6a** under the standard conditions as Scheme 3 for 9.5 h led to the formation of tetrahydro-3*H*-pyrrolo[2,3-*c*]quinoline **4c** in 86% yield (Scheme 4, eq 4). This result indicates that tetrahydroquinoline **6a** is most likely the intermediate en route to tetrahydropyrroloquinoline **4c**. In contrast, when **6b** was treated with the identical conditions, the expected product **4c'** was not detected (Scheme 4, eq 5). Instead, after quenching the reaction within 9.5 h, the same product **4c** was obtained in 27% yield, along with recovery of a mixture of **6a** and **6b** (in a ratio of 1 : 4) in 35% combined yield (Scheme 4, eq 6). These results demonstrate that intermediate **6b** could convert to **6a** and then gave the same product **4c** under the standard conditions. Furthermore, the reaction of 2-methyleneaminocinnamate **7** and TosMIC **2a** was also performed, but the desired pyrrolo[2,3-*c*]quinoline **8** could not be detected (Scheme 3, eq 7). The result suggests that this domino reaction is initiated by the attacking at the carbon-carbon double bond of 2-

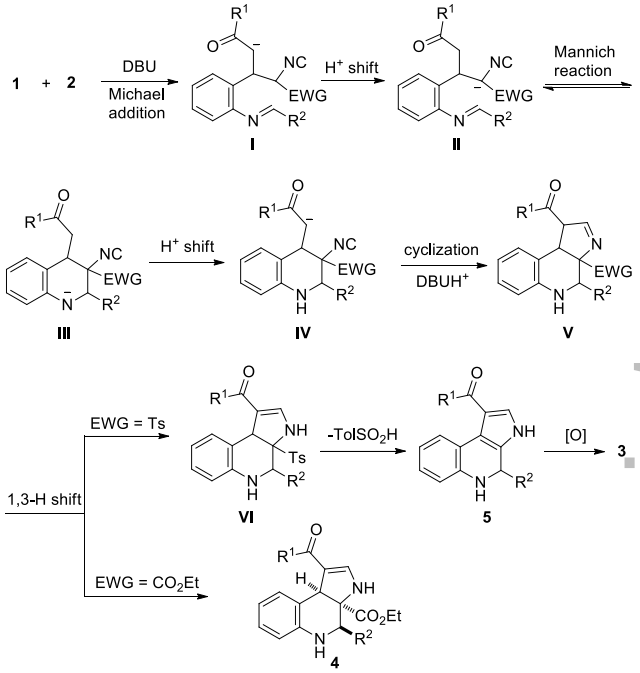
methyleneaminochalcone **1** rather than the imine group of **1**.



Scheme 4. Mechanistic studies.

On the basis of above observations and the related work,[16-19,21] a possible pathway for this domino reaction is proposed in Scheme 5. The tandem cyclization-annulation may involve the following domino sequence: Michael addition of isocyanides **2** to 2-methyleneaminochalcone **1** under basic conditions provides the anion **I**;[21] proton shift takes place to generate anion **II**, followed by intramolecular Mannich reaction to form the bicyclic nitrogen anion **III** (this step may be reversible based on the results of eq 6 in Scheme 4); sequential proton shift and cyclization give the tricyclic intermediate **V**, which undergoes 1,3-proton shift to produce tetrahydropyrroloquinolines **4** (EWG = CO_2Et) or intermediate **VI** (EWG = Ts). Then, elimination of *p*-toluenesulfinic acid from **VI** affords dihydropyrrolo[2,3-*c*]quinoline **5**.[17e,21,22] Finally, aerobic oxidative aromatization furnishes pyrrolo[2,3-*c*]quinolones **3**.[23]

In summary, a tandem cyclization-annulation of 2-metheneaminochalcones with activated methylene isocyanides was successfully developed for the efficient synthesis of diverse pyrrolo[2,3-*c*]quinoline derivatives. The sequential formation of the pyridine and pyrrole rings in a domino process represents an efficient strategy for the construction of these tricyclic frameworks. A tandem intermolecular



Scheme 5. Proposed mechanism.

Michael addition/intramolecular Mannich reaction/annulation cascade is proposed on the basis of control experiments. This reaction features high efficiency, mild reaction conditions, highly regio- and diasteroselectivity in some cases, convenient manipulation, and readily availability of starting materials.

Experimental Section

General Procedure for Synthesis of pyrrolo[2,3-*c*]quinolones 3

DBU (61 μL, 0.4 mmol) was added to a solution of 2-metheneaminochalcones **1** (0.2 mmol) and tosylmethyl isocyanide **2a** (0.059 g, 0.3 mmol) in acetonitrile (2 mL) at 25 °C, the mixture was then stirred until substrate **1a** was consumed and the intermediate was also converted to the target product **3** as indicated by TLC. The resulting mixture was concentrated in vacuo, purification of the crude product with flash column chromatography (silica gel; petroleum ether : ethyl acetate = 10 : 1-10 : 3) gave products **3**.

Acknowledgements

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UPDATE

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