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Acid-Catalyzed Multicomponent Tandem Cyclizations: Access to Polyfunctional Dihydroindolizino[8,7-*b*]indoles

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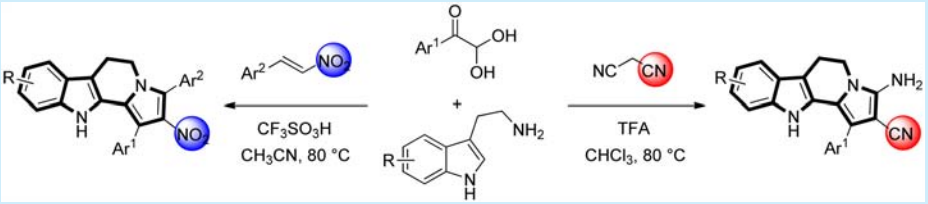
Supporting Information



ABSTRACT: An acid-catalyzed multicomponent tandem cyclization protocol has been developed for the synthesis of polyfunctional dihydroindolizino[8,7-*b*]indoles from simple and readily available arylglyoxal monohydrates, tryptamines, and *trans*-*β*-nitrostyrenes or malononitrile. This reaction represents a highly efficient and convenient methodology for the synthesis of diversely substituted heteropolycyclic scaffolds under mild, metal-free conditions.

Indolizino[8,7-*b*]indole derivatives represent a significant class of alkaloids containing the indole skeleton,[1] which can be found in numerous natural products and pharmaceutical molecules, such as harmicine (**I**),[2a] cladoniamide G (**II**),[2b] pegaharmalines B (**III**),[2c] and human CCK_1 receptor antagonists (**IV** and **V**)[2d,e] (Figure 1). In particular, dihydroindolizino[8,7-*b*]indoles have also been used as synthetic intermediates for the preparation of more complex alkaloids and biologically active molecules.[3]

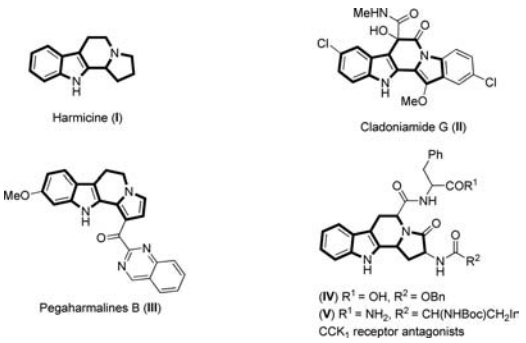
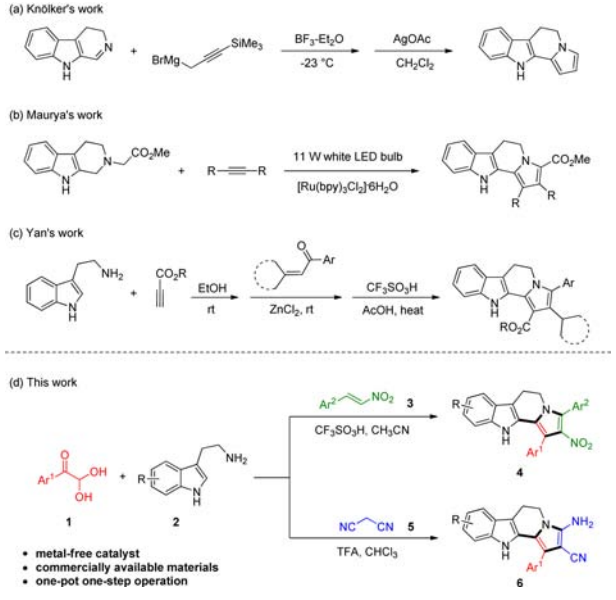


Figure 1. Selected natural products and pharmaceutical compounds with an indolizino[8,7-*b*]indole moiety.

Owing to the importance and usefulness of dihydroindolizino[8,7-*b*]indole derivatives, various approaches for their construction have been developed.[4−10] The general strategy differs, depending on how the pyrrole ring is constructed. For example, Knölker and co-workers reported a two-step procedure for the construction of the pyrrole ring by addition of a propargyl Grignard reagent to 3,4-dihydro-*β*-carboline and subsequent silver(I)-promoted oxidative cyclization (Scheme 1a).[4] The Maurya group reported a photoredox-catalyzed 1,3-dipolar cycloaddition of tetrahydro-*β*-carboline azomethine ylide with a dipolarophile to form the pyrrole ring (Scheme 1b).[5] In addition, the Yan group developed a three-step procedure for the construction of tetrahydropyridine and pyrrole rings via the Michael addition of *α*, *β*-unsaturated

Scheme 1. Strategies for the Synthesis of Dihydroindolizino[8,7-*b*]indoles



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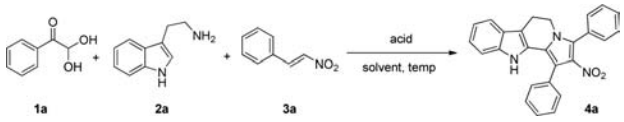
ketone and β-enamino ester generated in situ from the reaction of tryptamine and propargyl ester (Scheme 1c).[6]

Despite these significant advances made to date, the development of a highly efficient method to access diversely substituted dihydroindolizino[8,7-*b*]indole derivatives from readily available substrates would be of great value. Meanwhile, tandem cyclizations have emerged as a powerful tool for the construction of highly functionalized polycyclic ring systems in recent years.[11] These reactions not only enable the creation of molecular complexity and diversity but also omit the isolation and purification of intermediates, thus minimizing waste production.[12] Herein, we report a novel acid-catalyzed multicomponent reaction to construct two kinds of diversely substituted dihydroindolizino[8,7-*b*]indoles from easily available arylglyoxal monohydrates, tryptamines, and *trans*-β-nitrostyrenes or malononitrile in a single operation (Scheme 1d). To the best of our knowledge, this work represents the first reported example of a direct construction of tetrahydropyridine and pyrrole rings via tandem cyclizations in one step without any metal additives.

Our study commenced with the tandem cyclization reaction of phenylglyoxal monohydrate **1a**, tryptamine **2a**, and *trans*-β-nitrostyrene **3a** in the presence of different Brønsted acids and solvents to optimize the reaction conditions. To our delight, the reaction proceeded successfully to give the desired product **4a** in 66% yield when it was conducted in ethanol with 30 mol % of CF_3SO_3H (Table 1, entry 1). A series of solvents were then screened, and CH_3CN was shown to be the most effective in this reaction (Table 1, entries 2−8). Based on this encouraging result, we evaluated several other acids, but none of these performed any better than CF_3SO_3H (Table 1, entries 9−11). After screening several different amounts of CF_3SO_3H, we found that 30 mol % of CF_3SO_3H was still the most suitable for the reaction (Table 1, entries 12−16 vs entry 8). Moreover, the yield decreased slightly when the reaction was performed at a lower or higher temperature (Table 1, entries 17−20).

With the optimized conditions in hand, the generality and scope of this reaction was investigated, as shown in Table 2. It is noteworthy that the reaction demonstrated wide tolerence for diverse substituents of arylglyoxals, tryptamines, and *trans*-β-nitrostyrenes. Arylglyoxals bearing electron-neutral (4-H, 4-Me), electron-rich (4-OMe, 3-OMe, 3,4-OCH_2O), electron-deficient (4-NO_2), and halogenated (4-Cl, 4-Br, 2-Br) substituents were smoothly converted to the corresponding products in moderate to excellent yields (68−86%; entries 1−9). 1-Naphthyl and heteroaryl (3-thienyl, 2-benzofuranyl) substituents were also found to be suitable for this transformation (62−76%; entries 10−12). Furthermore, 7-methyl- and 5-methoxyl-substituted tryptamines also provided the corresponding products **4m** and **4n** in 73% and 66% yield, respectively (entries 13 and 14). In addition, a variety of *trans*-β-nitrostyrenes with different substituents, including electron-neutral, electron-rich, halogenated, sterically hindered, and heteroaryl groups, were explored and were also well tolerated under the reaction conditions to afford the expected products in satisfactory yields (52−74%; entries 15−22). The structures of **4a** and **4c** were unambiguously confirmed by X-ray diffraction analysis (see the SI).

Table 1. Optimization of the Reaction Conditions for the Synthesis of 4aa[a]

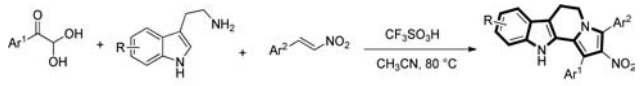


1a 2a 3a 4a

entry	solvent	acid (mol %)	temp (°C)	yield[b] (%)
1	EtOH	CF_3SO_3H (30)	80	66
2	*i*-PrOH	CF_3SO_3H (30)	80	50
3	DMF	CF_3SO_3H (30)	100	32
4	DMSO	CF_3SO_3H (30)	100	35
5	THF	CF_3SO_3H (30)	60	0
6	$CHCl_3$	CF_3SO_3H (30)	40	0
7	1,4-dioxane	CF_3SO_3H (30)	100	40
8	**CH_3CN**	**CF_3SO_3H (30)**	**80**	**78**
9	CH_3CN	CH_3SO_3H (30)	80	70
10	CH_3CN	CH_3CO_2H (30)	80	72
11	CH_3CN	CF_3CO_2H (30)	80	68
12	CH_3CN		80	trace
13	CH_3CN	CF_3SO_3H (10)	80	52
14	CH_3CN	CF_3SO_3H (60)	80	38
15	CH_3CN	CF_3SO_3H (120)	80	0
16	CH_3CN	CF_3SO_3H (150)	80	0
17	CH_3CN	CF_3SO_3H (30)	rt	37
18	CH_3CN	CF_3SO_3H (30)	40	42
19	CH_3CN	CF_3SO_3H (30)	60	68
20	CH_3CN	CF_3SO_3H (30)	100	75

[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.36 mmol, 1.2 equiv), **3a** (0.3 mmol, 1.0 equiv), and acid (*x* mol %) were heated in 3 mL of solvent in a sealed vessel for 5 h. [b]Isolated yields.

Table 2. Scope of Substances To Form 4[a]



1 2 3 4

entry	Ar^1	R	Ar^2	4	yield[b] (%)
1	C_6H_5	H	C_6H_5	**4a**	78
2	4-MeC_6H_4	H	C_6H_5	**4b**	81
3	4-$MeOC_6H_4$	H	C_6H_5	**4c**	82
4	3-$MeOC_6H_4$	H	C_6H_5	**4d**	86
5	3,4-$OCH_2OC_6H_3$	H	C_6H_5	**4e**	71
6	4-$NO_2C_6H_4$	H	C_6H_5	**4f**	68
7	4-ClC_6H_4	H	C_6H_5	**4g**	74
8	4-BrC_6H_4	H	C_6H_5	**4h**	73
9	2-BrC_6H_4	H	C_6H_5	**4i**	77
10	1-naphthyl	H	C_6H_5	**4j**	62
11	3-thienyl	H	C_6H_5	**4k**	69
12	2-benzofuryl	H	C_6H_5	**4l**	76
13	C_6H_5	7-Me	C_6H_5	**4m**	73
14	C_6H_5	5-MeO	C_6H_5	**4n**	66
15	C_6H_5	H	4-MeC_6H_4	**4o**	70
16	C_6H_5	H	4-$MeOC_6H_4$	**4p**	65
17	C_6H_5	H	4-OHC_6H_4	**4q**	68
18	C_6H_5	H	4-ClC_6H_4	**4r**	71
19	C_6H_5	H	2-ClC_6H_4	**4s**	74
20	C_6H_5	H	2-BrC_6H_4	**4t**	60
21	C_6H_5	H	1-naphthyl	**4u**	68
22	C_6H_5	H	2-thienyl	**4v**	52

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), **3** (0.5 mmol), and CF_3SO_3H (0.15 mmol) were heated in 5 mL of CH_3CN in a sealed vessel for 5 h. [b]Isolated yields.

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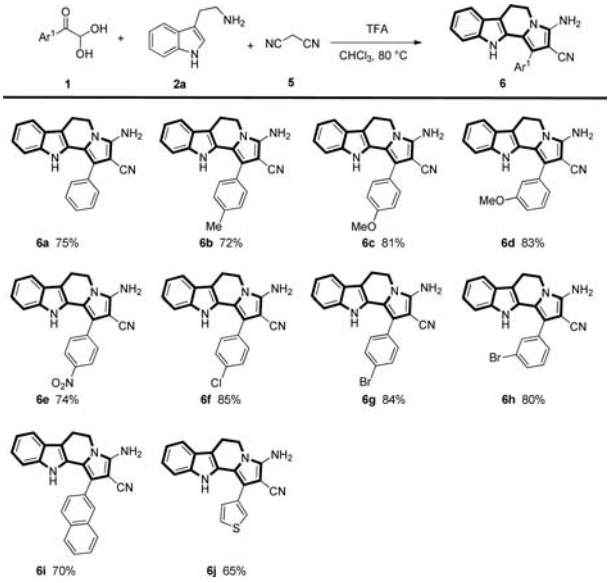
In order to obtain a diverse library of polyfunctional dihydroindolizino[8,7-*b*]indoles, our work extended to using malononitrile as a substrate instead of *trans*-*β*-nitrostyrene (Scheme 2). After optimizing the reaction conditions (see the SI), we explored the scope of this reaction. Much to our satisfaction, the electronic properties of the substituents on the arylglyoxals were shown to have little influence on the efficiency of this reaction. In general, electron-neutral (4-H, 4-Me), electron-rich (4-OMe, 3-OMe), electron-deficient (4-NO_2), and halogenated (4-Cl, 4-Br, 3-Br) groups were all found to be compatible under the optimal reaction conditions with excellent yields (72−85%; **6a**−**h**). Sterically hindered (2-naphthyl) and heterocyclic (3-thiophenyl) arylglyoxals were also tolerated in this reaction to afford the desired products **6i** and **6j** in 70% and 65% yield, respectively. Furthermore, the structure of **6g** was unambiguously confirmed by X-ray diffraction analysis (see the SI).

Scheme 2. Scope of Arylglyoxal Monohydrates To Form 6[a]

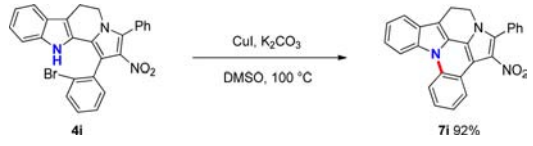


[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), **5** (0.6 mmol), and TFA (0.45 mmol) were heated in 5 mL of $CHCl_3$ in a sealed vessel for 3 h.

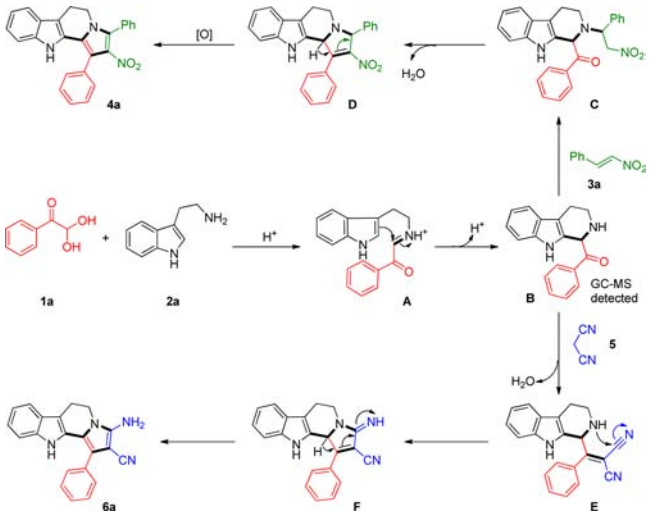
Notably, the polyfunctional dihydroindolizino[8,7-*b*]indole derivative **4i** could also be successfully applied in the convenient synthesis of the hexacyclic compound **7i**, which is an important portion of heterofullerenes $C_{34}N_2$ and $C_{48}N_2$.[13] As shown in Scheme 3, the reaction of **4i** with CuI and K_2CO_3 occurred smoothly in DMSO to afford the corresponding coupling product **7i** in 92% yield, according to the reported procedure.[14]

On the basis of the above results and previous reports,[15] a plausible mechanism for the formation of polyfunctional dihydroindolizino[8,7-*b*]indoles **4** and **6** was presented in Scheme 4 (**4a** and **6a** as examples). Initially, phenylglyoxal monohydrate **1a** reacted with tryptamine **2a** to afford

Scheme 3. Applications of Product 4i



Scheme 4. Plausible Mechanism for Forming 4 and 6 (4a and 6a as Examples)



intermediate **B** via a Pictet−Spengler cyclization. Then, Michael addition of intermediate **B** to (*E*)-(2-nitrovinyl)benzene **3a** led to intermediate **C**, which subsequently underwent intramolecular cyclization and oxidative aromatization to give the product **4a**. Meanwhile, as for the formation of product **6a**, it went through a Knoevenagel condensation of the key intermediate **B** and malononitrile **5** to furnish intermediate **E**. Afterward, intermediate **E** could be converted to intermediate **F** via an intramolecular addition reaction. Finally, **F** tautomerized to give the desired product **6a**. Given that intermediate **B** could be easily oxidized to yield dihydro-*β*-carboline[16] if there was no the third component (**3a** or **5**) to capture it, we could only detect it via GC−MS (see the SI).

In conclusion, we have developed a highly efficient multicomponent tandem cyclization protocol for the synthesis of polyfunctional dihydroindolizino[8,7-*b*]indoles from simple and readily available starting materials in a single operation. These reactions proceed under mild conditions and show good functional group compatibility. This method features in the consecutive construction of two rings in one pot without any metal additives. Further studies into the applications of this multicomponent tandem cyclization are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00281.

Experimental procedures, product characterizations, crystallographic data, and ^1H and ^{13}C NMR spectra (PDF)

X-ray crystallographic data for **4a**, **4c**, and **6g** (ZIP)

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Notes

The authors declare no competing financial interest.

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