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Highly efficient construction of pentacyclic benzo[*b*]indeno-[1,2,3-*de*][1,8]naphthyridine derivatives *via* four-component domino reaction†

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A series of new octahydrobenzo[*b*]indeno[1,2,3-*de*][1,8] naphthyridine and decahydropyrido[2,3,4-*gh*]phenanthridine derivatives were synthesized *via* a four-component domino reaction under microwave irradiation. This one-pot transformation, which involved multiple steps and did not require the use of a catalyst, constructed four new C–C bonds, two new C–N bonds, and three new rings, with efficient use of all reactants.

The efficient construction of polyheterocyclic skeletons is a challenging theme in organic synthesis.[1] 1,8-Naphthyridine derivatives have rich photochemical properties due to their rigid planar structure. Based on the bridging coordination mode they could form two centers by the two nitrogen atoms on positions, and auxiliary chelating groups could be incorporated using a special cage-like receptor as potential multidentate ligands, which made naphthyridine derivatives useful as luminescence materials in molecular recognition.[2] According to an extensive literature search, we found that naphthyridines were not only used in photochemical,[3] but also used as new drug leader[4] and anti-cancer active screening agents in new drug discovery.[5]

During the past few years, multicomponent domino reactions (MDRs), in which multiple reactions are combined into a single synthetic operation, have been extensively used in organic synthesis, as well as in combinatorial and medicinal chemistry. Obviation of the need for isolation and purification of the intermediates results in maximization of yields and reduction of waste, making these protocols ecofriendly.[6] These features make MDRs well suited for the construction of complex molecules from readily available starting materials.[7]

Recently, we and others have been developing a series of multicomponent reactions that offer easy access to polyfunctionalized heterocyclic skeletons of chemical and pharmaceutical interest.[8] As part of our ongoing research on the development of domino reaction approaches to the synthesis of heterocycles,[9] we report the efficient construction of octahydrobenzo[*b*]indeno[1,2,3-*de*]-[1,8]naphthyridine and decahydropyrido[2,3,4-*gh*]phenanthridine derivatives *via* a four-component domino reaction under microwave irradiation.

We began our studies with the four-component domino reaction of a 1 : 2 : 1 mixture of 5,5-dimethyl-3-(4-methoxyphenylamino)cyclohex-2-enone (**1a**), malononitrile (**2**), and *o*-phthalaldehyde (**3a**) in ethanol at 100 °C for 20 min under microwave irradiation, without the use of a catalyst. This afforded 7-amino-5-(4-methoxyphenyl)-3,3-dimethyl-1-oxo-1,2,3,4,5,5a^1,8a,12b-octahydrobenzo[*b*]indeno[1,2,3-*de*][1,8] naphthyridine-5a^1,8-dicarbonitrile (**4a**) in 43% LC yield. The polyhydronaphthyridine derivative **4a** was fully characterized using IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopies. Only a single diastereoisomer of **4a** was detected using ^{1}H NMR spectroscopy. The structure of **4a** was further confirmed using single-crystal X-ray diffraction analysis[10] (see ESI†). The usefulness of these domino reactions is shown by the fact that up to six new bonds (four C–C bonds and two C–N bonds) and three new rings (a tricyclic 5-6-6 skeleton consisting of cyclopentene and two pyridines) were readily formed in domino fashion. This work represents the first example of the construction of these special types of polyhydronaphthyridine skeletons in one pot. To optimize the reaction conditions, the model reaction was investigated under different reaction conditions. The results are summarized in Table 1. The addition of catalysts such as L-proline, CAN, piperidine, *p*-toluenesulfonic acid, and silica sulfuric acid did not improve the yields (Table 1, entries 2–6). DMF provided higher yields than did other organic solvents and water (compare entry 7 with entries 8–11), so DMF was chosen as the solvent for all further reactions. When the reaction was carried out at 90 °C, 100 °C, 110 °C, and 120 °C, **4a** was obtained in yields of 79%, 80%, 84%, and 80% (entries 7 and 12–14), respectively. These experiments showed that conditions of 110 °C in DMF, without a catalyst, under microwave irradiation provided the highest yield.

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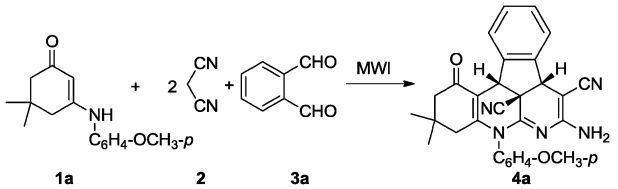
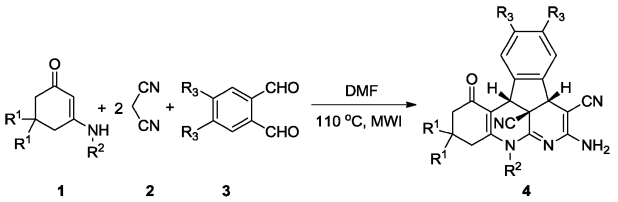
Table 1 Optimization of reaction conditions for synthesis of **4a** under microwave irradiation



Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (min)	Yield[a] (%)
1	EtOH	—	100	20	43
2	EtOH	L-Proline (10)	100	20	43
3	EtOH	CAN (10)	100	20	40
4	EtOH	Piperidine (10)	100	20	Trace
5	EtOH	*p*-TsOH (10)	100	20	Trace
6	EtOH	SSA (10)	100	20	Trace
7	DMF	—	100	20	80
8	CH_3CN	—	100	20	15
9	CH_3OH	—	100	20	6
10	$HOCH_2CH_2OH$	—	100	20	51
11	H_2O	—	100	20	21
12	DMF	—	90	20	79
13	DMF	—	110	20	84
14	DMF	—	120	20	80

[a] The yields were determined by HPLC-MS.

Table 2 Synthesis of compounds **4** under microwave irradiation



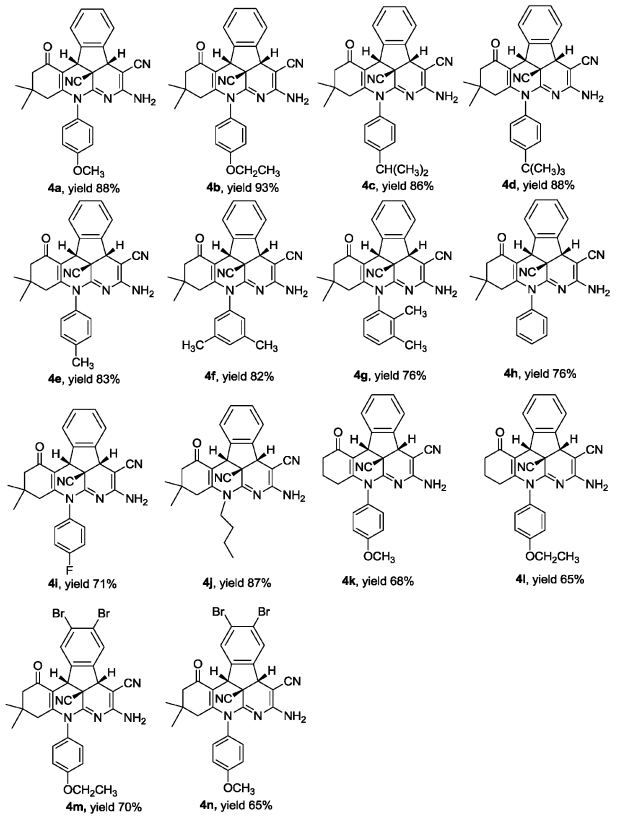
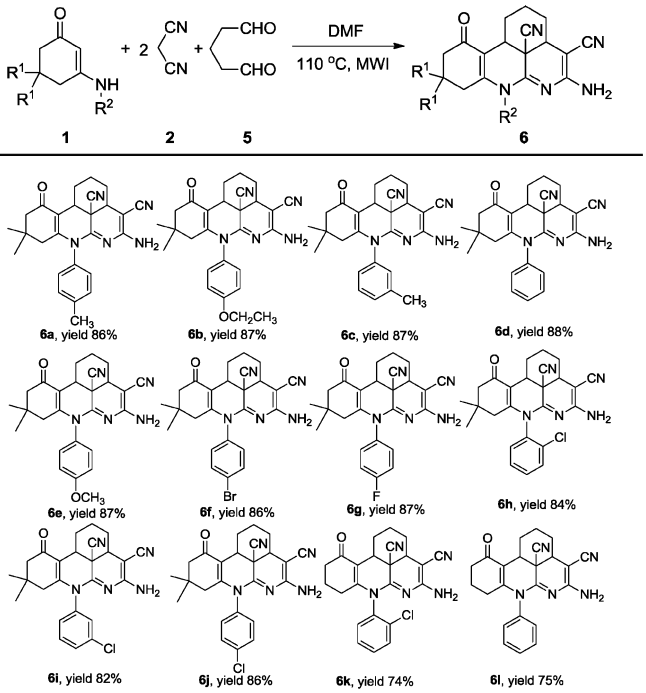
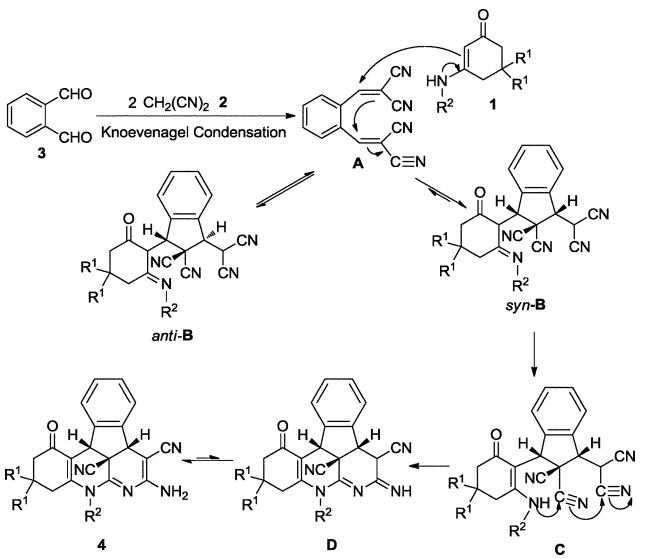


Table 3 Synthesis of compounds **6** under microwave irradiation



Using the optimal conditions, we investigated the substrate scope of the transformation. The results are summarized in Table 2. As shown in Table 2, *n*-butyl and phenyl groups bearing either electron-withdrawing or electron-donating groups on the enaminone ring were well tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 93%).

To expand the scope of the current method, glutaraldehyde (**5**) was examined as a replacement for *o*-phthalaldehyde (**3**). The desired products, decahydropyrido[2,3,4-*gh*]phenanthridine derivatives (**6**) were obtained. The results are summarized in Table 3. Phenyl groups bearing either electron-withdrawing or



Scheme 1 Proposed mechanism for formation of compound **4**.

electron-donating groups on the enaminone ring were well tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 88%). The polyhydronaphthyridine derivative **6** was fully characterized using IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopies.

A proposed mechanism for this new four-component domino reaction is shown in Scheme 1. An initial Knoevenagel condensation of *o*-phthalaldehyde (**3a**) with two malononitrile (**2**) molecules gives the intermediate **A**. The intermediate **B** is formed by Michael addition of enaminone (**1**) to intermediate **A** and cyclization. Intermediate **A** to **B** may be a reversible process. Therefore, from **A** to **B**, there may be two isomers formed. One is *syn*-**B**, the other is *anti*-**B**. The *syn*-**B** is more stable than *anti*-**B** (see ESI†). Moreover, *syn*-**B** is favored over *anti*-**B** to cyclize the third ring, so *anti*-**B** will go back to **A**. Finally all **A** is transformed to **B**. The *syn*-**B** undergoes imine–enamine tautomerization to give intermediate **C**, which subsequently reacts in an intramolecular cyclization to give intermediate **D**. In the last step, intermediate **D** undergoes imine–enamine tautomerization to give the product **4**.

In conclusion, we have developed a procedure for the facile synthesis of various potentially biologically active octahydrobenzo[*b*]indeno[1,2,3-*de*][1,8]naphthyridine and decahydropyrido[2,3,4-*gh*]phenanthridine derivatives, based on a novel four-component domino reaction. Using this method, a diverse collection of benzo[*b*]indeno[1,2,3-*de*][1,8]naphthyridine and pyrido[2,3,4-*gh*]phenanthridine derivatives were rapidly constructed with excellent yields in short reaction times by simply heating a mixture of enaminones, malononitrile, and *o*-phthalaldehyde or glutaraldehyde in DMF, without a catalyst, under microwave irradiation.

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10 CCDC 938367 (**4a**). $C_{29}H_{25}N_5O_2$, a yellow crystal (0.38 × 0.30 × 0.21 mm), T = 293(2) K, λ (Mo-Kα) = 0.71073 Å, monoclinic, space group: $P2_1/C$, a = 14.6432(17) Å, b = 7.6244(9) Å, c = 23.275(3) Å, β = 104.693(2)°, V = 2513.6(5) Å^3, R_1 = 0.0840, wR_2 = 0.1996.