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COMMUNICATION

New multicomponent cyclization: domino synthesis of pentasubstituted pyridines under solvent-free conditions†

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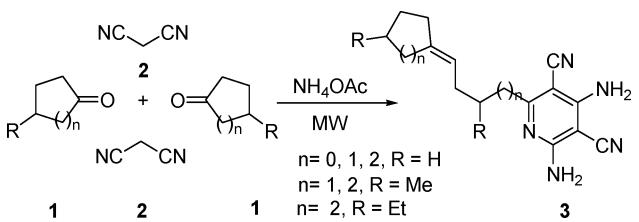
An efficient methodology for the synthesis of highly functionalized pyridine derivatives starting from readily available common reactants has been developed under microwave irradiation and solvent-free conditions. The new domino reaction enables successful assembly of five new σ bonds including two C–N bonds in a one-pot operation. A new mechanism has been proposed, which involves a novel reaction and sequence consisting of deprotonation–imine formation–anionic carbonyl addition.

The search for efficient formations of multifunctionalized complex products by using simple reactants has been an active objective in organic synthesis.[1] In this regard, multi-component domino reactions that are very useful for the total syntheses of natural products and versatile building blocks have become increasingly attractive because of their green characteristics of atom-economy, bond-forming economy and structural economy.[2–5] These reactions can avoid time-consuming and costly processes for purification of various precursors and tedious steps of protection and deprotection of functional groups. In addition, these reactions are environmentally friendly, and often proceed with excellent chemoselectivities.[6] Therefore, the design of new selective domino reactions is a continuing challenge at the forefront of organic chemistry.

It is well-known that malononitrile can serve as an exceptionally versatile compound; it has been extensively used as a reactant or intermediate in organic synthesis. It exhibits unique reactivity due to the fact that the strongly electron-withdrawing cyano group can activate the methylene CH_2 (pK_a = 11.2); its cyano group can be a good leaving group for substitution reactions with its polar multiple bonds being suitable for nucleophilic additions.[7] Both methylene group and cyano group can participate in condensation reactions to give a variety of addition products and heterocyclic compounds.[8] This exceptional behavior further makes malononitrile an important candidate for the design of new practical multicomponent syntheses serving for medicinal, industrial and agricultural research.[8–10]

In the past several years, our group and several others have developed a series of multicomponent domino reactions that provide easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest.[11–14] For example, a new four-component domino reaction was established providing an easy access to multifunctionalized quinazoline derivatives[11a] and tricyclo[6.2.2.0^{1,6}]dodecanes.[11b] Recently, we have also found that the domino reaction of Meldrum's acid, aromatic aldehydes and electron-rich heteroaryl-amines in the aqueous phase under microwave irradiation (MW) led to the formation of multifunctionalized spiro{[1,3]dioxane-pyridine}-4,6-diones with high chemo- regio- and stereoselectivity and good yields.[11d] As a continuation of our research devoted to the development of multicomponent domino reactions,[11–13] in this communication we would like to report another new four-component domino reaction for the synthesis of polyfunctionalized pyridine derivatives that are of chemical and biomedical importance. The reaction was achieved by reacting malononitrile, cycloketones and ammonium acetate in a one-pot operation under microwave irradiation (MW) in the absence of any strong acids or metal catalysts (Scheme 1).



Scheme 1

When a mixture of malononitrile, cyclopentanone and an excess amount of ammonium acetate was heated in HOAc at 150 °C for 30 min under microwave irradiation, the pyridine derivative, **3a** (2,4-diamino-6-(4-cyclopentylidenebutyl)pyridine-3,5-dicarbonitrile) was readily obtained in 57% yield. This product has been fully characterized by ^{1}H- and ^{13}C-NMR, HR-MS and IR spectral analysis. Furthermore, it has been unambiguously determined by X-ray structural analysis as shown in Fig. 1.

Encouraged by this initial result, we then made many efforts on optimizing reaction conditions. As shown in Table 1, the use of ammonium acetate allowed the direct conversion of cyclopentanone **1a** to give the corresponding polysubstituted

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† CCDC reference number 806791. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01258k

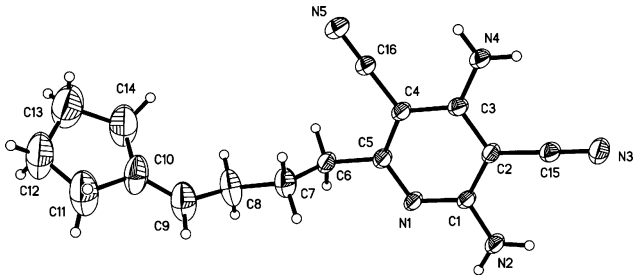
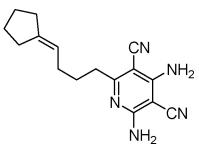


Fig. 1 The ORTEP drawing of **3a**.

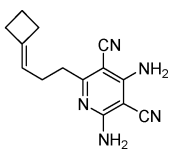
Table 1 Optimization of reaction conditions

Entry	Solvent	equiv	Time/min	Yield/%
1	HOAc	6.0	30	57
2	DMF	6.0	35	48
3	Ethylene alcohol	6.0	32	42
4	Water	6.0	30	37
5	Solvent-free	6.0	30	81

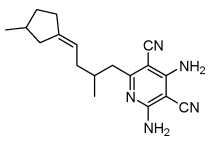
Table 2 The domino synthesis of compounds **3** at 150 °C



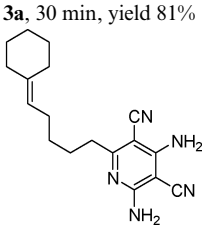
3a, 30 min, yield 81%



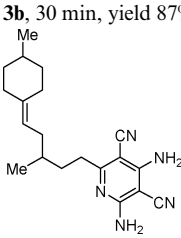
3b, 30 min, yield 87%



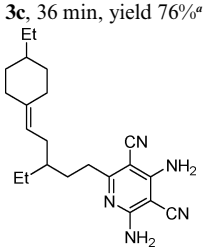
3c, 36 min, yield 76%[a]



3d, 40 min, yield 67%



3e, 45 min, yield 52%



3f, 48 min, yield 41%

[a] Yield of the mixture of two diastereoisomers.

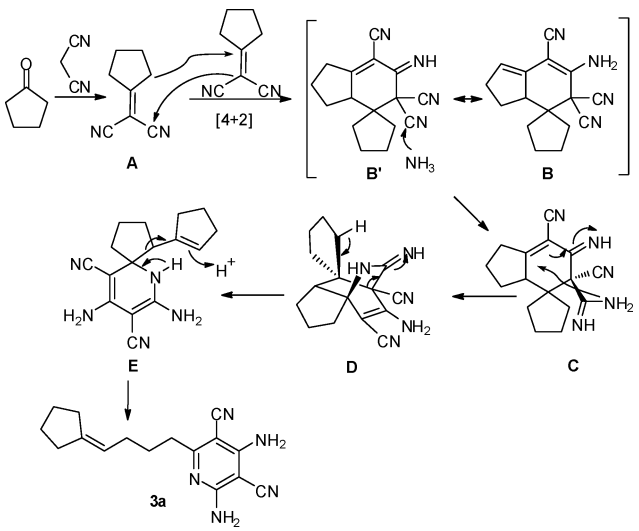
pyridines **3a** in a yield of 81% under solvent-free and microwave irradiation conditions (Table 1, entry 5). Other polar solvents, such as DMF, ethylene alcohol and water gave lower yields of 37%–57% under MW irradiation for 30 min (Table 1, entries 1–3). The use of more than 6 equiv of ammonium acetate did not result in higher chemical yields.

We next investigated the substrate scope of this domino reaction by subjecting a series of cycloketones **1b–f** to the reactions with malononitrile **2** in the presence of ammonium acetate under the optimal conditions. During the domino process of forming compounds **3**, it was interesting to observe that the smaller cycloketones such as cyclobutanone **1b** and cyclopentanones **1a**, **1c** showed faster reaction rates and led to higher chemical yields (76%–87%, Table 2) than their larger counterparts such as cyclohexanones **1d**, **1e** and **1f** that led to slower reaction rates and lower chemical yields (41%–67%, Table 2). Based on ^{1}H-NMR analysis (see spectrum in Supporting Information), the diastereoselectivity of **3c** derived from 3-methylcyclopentanone **1c** was determined to be 2.3 : 1, but the major isomer needs further investigation.

The unusual feature of forming **3a–3f** is shown by the fact that two cycloketones were simultaneously converted to a polysubstituted pyridine structure, one of them unexpectedly occurred *via* ring opening. It should be pointed out that this phenomenon has not been observed in known cyclization reactions of malononitrile during the formation of carbocyclic and heterocyclic compounds.[15–18] The use of other cyclic ketones and their functionalized counterparts for this domino reaction will be studied in due course.

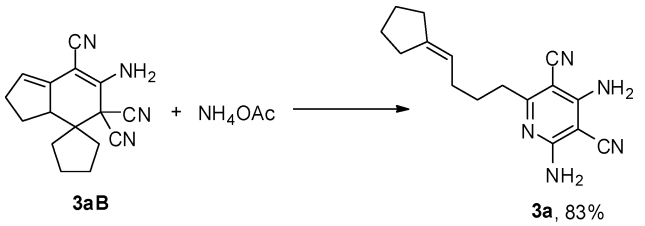
Similar to our previous four-component domino process,[7] the present reaction also showed the following attractive characteristics: (1) the environmentally friendly process in which water is the major by-product without additional use of organic solvent during the reaction process; (2) the convenient work-up which only needs simple filtration since the products directly precipitate out after the reaction is finished[19–21] and when its mixtures are diluted with cold water; (3) readily available starting materials of malononitrile, cycloketones, and ammonium acetate; (4) high atom-economy and bond-forming economy. Moreover, the two C═O bonds and one C–C bond of cycloketones were cleaved and five new σ bonds were formed. The novelty of the present domino reaction is shown by the fact that multiple chemical bonds breaking and forming were simultaneously achieved in an intermolecular manner and in a one-pot operation.

On the basis of the resulting products, a reasonable mechanism is proposed as shown in Scheme 2 and represented by the formation of **3a**. During the ring closure domino process, the condensation of malononitrile with cyclopentanone is the initial step to form intermediate **A**. The [4 + 2] cycloaddition of two molecules of **A** occurs and leads to the formation of spirocyclic intermediate **B′**, to which ammonia was added to give **C**. Intramolecular Michael addition of **C** leads to the formation of **D**, followed by isomerization of the imines which results in the ring-opening of 1,2-dihydropyridine intermediate **E** which is subjected to dehydration to give the final product **3a**. Interestingly, several similar structures to **D** have been proposed in our previous work in which final products were also confirmed by X-ray structural analysis.[11a–b] Pleasantly, an isomeric



Scheme 2

intermediate **3aB** has been successfully isolated and can support the above proposed mechanism. The reaction of isolated **3aB** with ammonium acetate under similar conditions resulted in the ring-opening product **3a** in 83% yield (Scheme 3). It should be pointed out that the tandem ring-opening from intermediate **D** is truly novel sequence which will be further studied in our labs.



3aB **3a**, 83%

Scheme 3

Conclusion

In summary, a new multicomponent domino reaction of two moles of malononitrile with two moles of cycloketones and NH_4OAc has been developed. The new reaction can be easily performed within a short period under microwave irradiation and solvent-free conditions to afford highly substituted 2,4-diaminopyridine-3,5-dicarbonitriles. A logical mechanism has proposed and supported by a successful isolation of a key intermediate. In addition, a novel reaction step of an intermediate with malononitrile was discovered.

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