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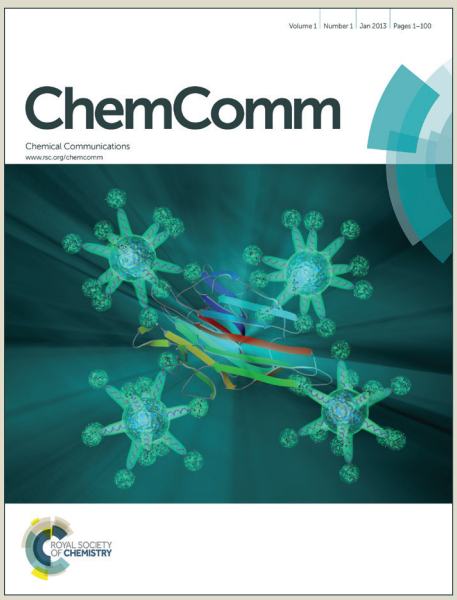

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Highly selective synthesis of functionalized polyhydroisoquinoline derivatives via a three-component domino reaction

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Two series of novel functionalized polyhydroisoquinoline derivatives have been synthesized via the three-component domino reaction of glutaraldehyde and malononitrile with a series of β-ketoamides under microwave irradiation conditions in the presence of a catalytic amount of Et_3N (10 mol%). This reaction represents the first reported process for the facile conversion of a β-ketoamide to a hydroisoquinoline via a C-N bond cleavage reaction without the need for a multistep reaction process.

Nitrogen-containing polyheterocyclic skeletons are present in a broad range of natural products and synthetic molecules with important biological activities.[1] Among them, hydroisoquinoline scaffolds have received considerable attention because of the synthetic challenges associated with their complex molecular architecture and their interesting biological properties, such as their anticancer, antibacterial, anti-inflammatory and antimalarial activities.[2] Hydroisoquinoline skeleton can be found in a wide range of natural alkaloids, such as reserpine[3] and yohimbine[4] (Figure 1). Isoquinolines have also been used as ligands in a number catalytic asymmetric transformations.[5] Although several methods have been developed for the synthesis of compounds belonging to this structural class,[6] they invariably involve long, multistep processes and provide low yields of the desired product. For this reason, there is therefore an urgent need for the discovery of new and efficient methods for the construction of these complex molecules.

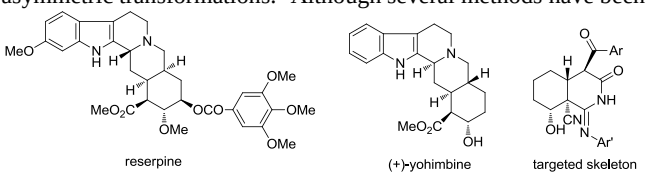

Figure 1 Hydroisoquinoline scaffolds occurring in natural products and the targeted skeleton

The creation of diverse and complex molecules from readily available starting materials is a challenging theme in modern synthetic organic chemistry.[7] Multicomponent domino reactions (MDRs) have become especially important in this regard because of their convergent character, atom economy and operational simplicity. Furthermore, MDRs can be used to introduce a high level of structural diversity in a single process, making them especially useful for the construction of complex molecules. MDRs have become increasingly important in recent years in terms of the role that they have play in the development of novel synthetic methodologies, with particular emphasis on their use in cascade reactions for the total synthesis of natural products.[8] Microwave irradiation has been widely used in organic synthesis recently because this method of energy transfer to a reaction mixture can provide impressive enhancements in product yield, selectivity and reaction rate. This technology has been used in MDRs.[9] We recently reported the development of several new MDRs that provided rapid access to a variety of nitrogen-containing heterocyclic skeletons of chemical and pharmaceutical interest, including pyrrole, 3-pyrrolyl coumarin, 1,8-naphthyridine and dispiropyrrolidine skeletons.[10] In this study, we have developed a novel three-component domino reaction for the synthesis of functionalized polyhydroisoquinoline derivatives under microwave irradiation conditions. The attractive features of this newly developed MDR include a novel strategy for the construction of hydroisoquinolines and the direct cleavage of the C-N bond of a β-ketoamide, both of which were easily achieved without the need for multistep operations.

We initially evaluated the three-component domino reaction of a 1:1:1 (mol/mol/mol) mixture of glutaraldehyde (**1**), malononitrile (**2**) and 3-oxo-3-phenyl-*N*-(*p*-tolyl)propanamide (**3a**) as a model reaction under microwave irradiation to optimize the reaction conditions (Table 1). When the reaction was carried out in EtOH for 10 min under microwave irradiation without any catalyst, the desired product **4a** was obtained in 60% yield (Table 1, entry 1). Several catalysts were evaluated in the reaction, including Na_2CO_3,

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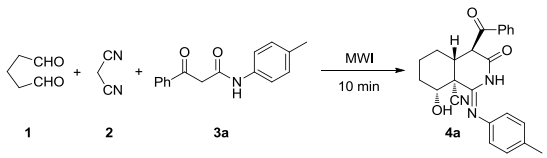
†Electronic supplementary information (ESI) available: Experimental procedures, characterization and spectral data of the Strecker-type reaction products. CCDC 1028447 and CCDC 1028776. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c000000x

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

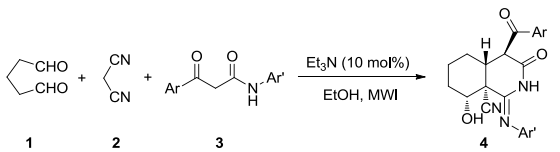


1 2 3a 4a

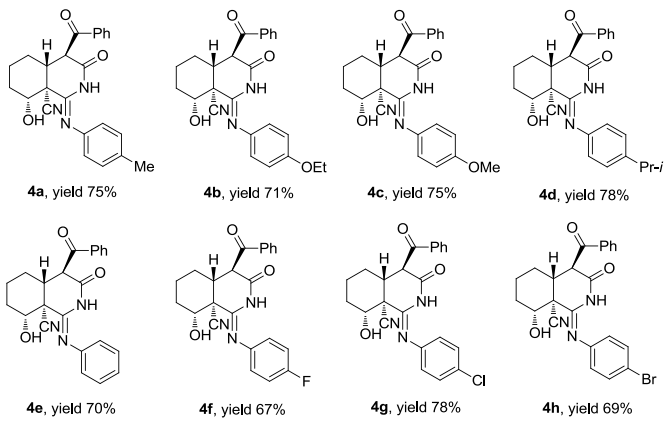
Entry	Solvent	Temp.	Catalyst	Yield[b]
1	EtOH	100	No	60
2	EtOH	100	Na_2CO_3 (10)	38
3	EtOH	100	Piperidine (10)	42
4	EtOH	100	Et_3N (10)	78
5	EtOH	100	*p*-TsOH (10)	Trace
6	THF	80	Et_3N (10)	28
7	DMF	100	Et_3N (10)	32
8	CH_3CN	100	Et_3N (10)	61
9	Toluene	100	Et_3N (10)	Trace
10	H_2O	100	Et_3N (10)	35
11	EtOH	100	Et_3N (5)	62
12	EtOH	100	Et_3N (15)	69
13	EtOH	100	Et_3N (20)	67
14	EtOH	60	Et_3N (10)	18
15	EtOH	70	Et_3N (10)	23
16	EtOH	80	Et_3N (10)	44
17	EtOH	90	Et_3N (10)	59

[a] Reactions were performed with **1** (1 mmol), **2** (1 mmol) and **3a** (1 mmol) in solvent (3 mL) under microwave irradiation. [b] The yields were determined by HPLC-MS

Table 2 Synthesis of decahydroisoquinoline derivatives **4** under microwave irradiation

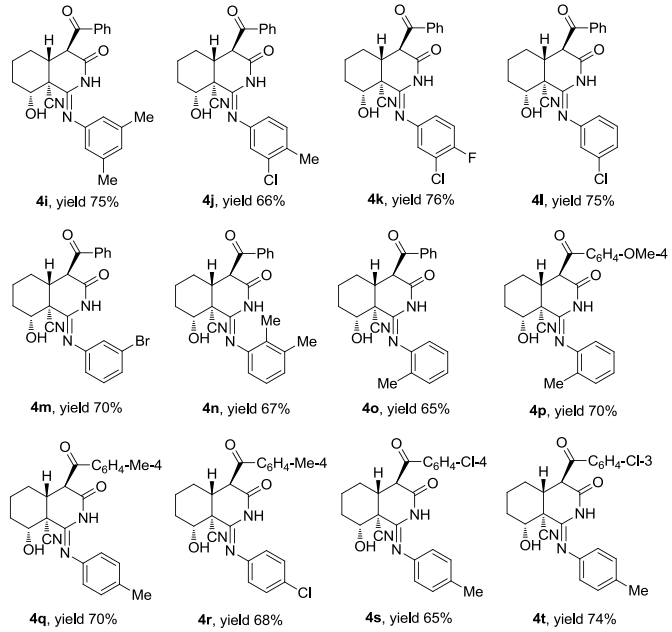


1 2 3 4



4a, yield 75% **4b**, yield 71% **4c**, yield 75% **4d**, yield 78%

4e, yield 70% **4f**, yield 67% **4g**, yield 78% **4h**, yield 69%

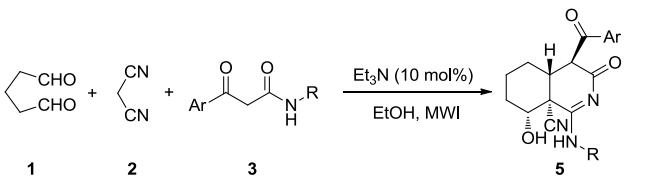


4i, yield 75% **4j**, yield 66% **4k**, yield 76% **4l**, yield 75%

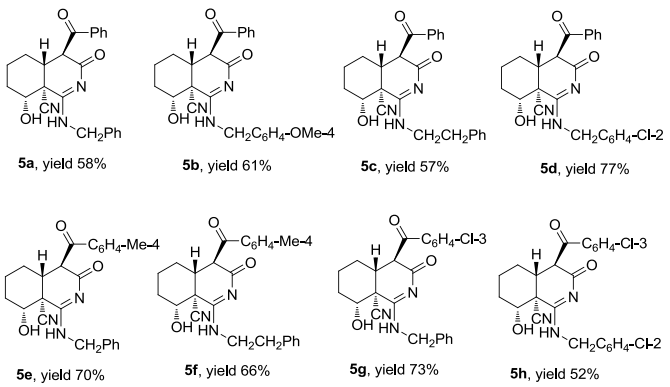
4m, yield 70% **4n**, yield 67% **4o**, yield 65% **4p**, yield 70%

4q, yield 70% **4r**, yield 68% **4s**, yield 65% **4t**, yield 74%

Table 3 Synthesis of octahydroisoquinoline derivatives **5** under microwave irradiation



1 2 3 5



5a, yield 58% **5b**, yield 61% **5c**, yield 57% **5d**, yield 77%

5e, yield 70% **5f**, yield 66% **5g**, yield 73% **5h**, yield 52%

piperidine, Et_3N and *p*-TsOH to evaluate their impact on the yield. All of these reactions were conducted in EtOH at 100 ℃ under microwave irradiation with a 10 mol% charge of the catalyst. The results of these screening experiments revealed that Et_3N provided superior catalytic efficiency compared with all of the other catalysts tested (Table 1, entries 2–5). Various solvents, including THF, DMF, acetonitrile, toluene and water, were also evaluated to identify the best solvent for the reaction (Table 1, entries 4 and 6–10). The results of these screening experiments revealed that EtOH provided the best results of all of the solvents tested in terms of the product yield.

Having identified Et_3N as the best catalyst for the transformation, we proceeded to evaluate the amount of catalyst required to affect this reaction. The results showed that a 10 mol% charge of Et_3N was sufficient for promoting the current reaction (Table 1, entries 4 and 11–13). The reaction was also carried out at a variety of different temperatures, including 60, 70, 80, 90 and 100 ℃ in EtOH under microwave irradiation in the presence of Et_3N (10 mol%) to determine the optimum temperature for this transformation (Table 1, entries 14–17 and 4), respectively. The results of these experiments revealed that the best reaction temperature was 100 ℃. However, when above reaction was carried out in ethanol for 6 h at reflux temperature without microwave irradiation, the desired product **4a** was only obtained in 58% yield. This result indicated that this reaction can be promoted by microwave. Taken together, the results of these screening experiments revealed that the optimum reaction conditions were using 10 mol% Et_3N as catalyst in ethanol at 100 ℃ under microwave irradiation.

With the optimal reaction conditions in hand, we proceeded to evaluate the scope of the transformation using a variety of different β-ketoamides. As shown in Table 2, a wide variety of different substituents were well tolerated on the phenyl ring attached to the nitrogen atom of the β-ketoamide, including methyl, methoxy, chloro, bromo and fluoro substituents. Various electron-withdrawing and electron-donating groups were also well tolerated on the benzoyl ring of the β-ketoamide, with the corresponding products being isolated in satisfactory yields. However, the replacement of malononitrile with methyl or ethyl cyanoacetate failed to provide any of the desired methyl- or ethyl-substituted products.

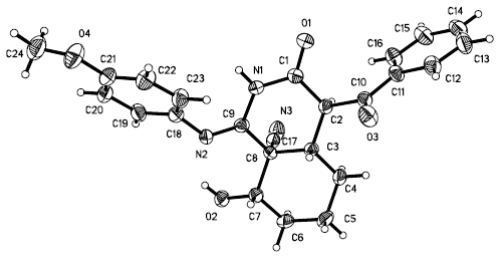


Figure 2 X-Ray crystal structure of compound **4c**

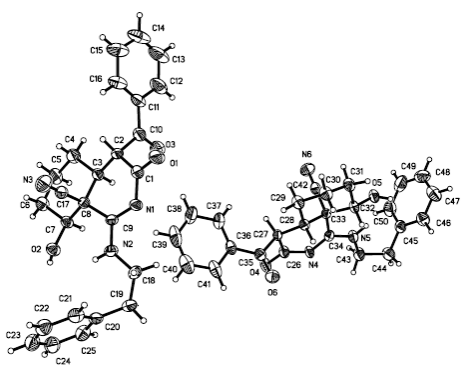
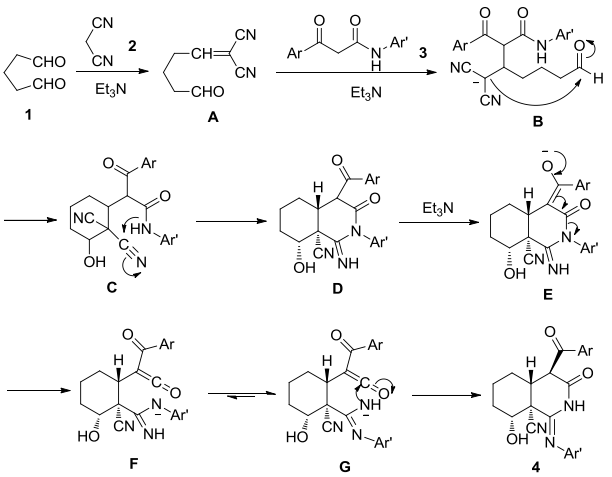


Figure 3 X-Ray crystal structure of compound **5c**

The use of 3-oxo-3-aryl-*N*-alkylpropanamide as a replacement for 3-oxo-3-aryl-*N*-arylpropanamide was also investigated to further expand the scope of the reaction. Surprisingly, however, the use of 3-oxo-3-aryl-*N*-alkylpropanamides under the optimized conditions did not provide access to the desired decahydroisoquinoline derivatives **4** but resulted instead in the formation of the corresponding isomerization products, octahydroisoquinoline derivatives **5**, in good yields (Table 3). The reaction pathways could therefore been controlled by varying the nature of the substituent attached to the β-ketoamides to provide selective access to a series of novel decahydroisoquinolines and octahydroisoquinolines.

The structures of the products synthesized in the current study were characterized from their IR, ^{1}H NMR, ^{13}C NMR spectroscopies and HRMS analysis. The structures and stereochemistry of compounds **4c** and **5c** were further confirmed by X-ray analysis (Figure 2 and 3).[11]

Scheme 1 Proposed mechanism for the synthesis of compound **4**



Based on the results of the current study, we proposed a mechanism for this novel three-component domino reaction, which is shown in Scheme 1. The Knoevenagel condensation of glutaraldehyde (**1**) with malononitrile (**2**) would give intermediate **A**. The subsequent Michael addition of β-ketoamide (**3**) to intermediate **A** would give intermediate **B**, which would undergo an intramolecular nucleophilic addition reaction to form intermediate **C**. Intramolecular cyclization of intermediate **C** would give intermediate **D**, which would undergo a Et_3N-catalyzed ring-opening reaction to give the ketene intermediate **G**. Lastly, intermediate **G** would undergo a second intramolecular nucleophilic addition reaction to give the desired product **4**.

In conclusion, we have successfully developed a straightforward, inexpensive and environmentally friendly three-component domino reaction for the synthesis of novel functionalized hydroquinoline derivatives. The key features of this new method include its mild reaction conditions, operational simplicity, high bond-forming efficiency and high stereo-selectivity. We believe that this methodology could provide a useful platform for other researchers interested in developing new structural frameworks with unique properties for medicinal and pharmaceutical chemistry.

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11 Crystallographic data for the structures of compounds **4c** and **5c** have been deposited at Cambridge Crystallographic Data Center, and the deposit numbers are CCDC-1028447 and CCDC-1028776, respectively. Copy of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336 033; e-mail deposit@ccdc.cam.ac.uk). Crystal data of compound **4c**: $C_{24}H_{23}N_3O_4$, a colorless crystal (0.27 × 0.25 × 0.12 mm), T = 298(2) K, λ (Mo-Kα) = 0.71073 Å, monoclinic, space group: $P2_1$, a = 6.8289(7) Å, b = 13.5236(12) Å, c = 12.1421(11) Å, b = 106.143(2)°, V = 1076.33(18) Å^3, R_1 = 0.0544, wR_2 = 0.0710. Crystal data of compound **5c**: $C_{25}H_{25}N_3O_3$, a colorless crystal (0.32 × 0.17 × 0.14 mm), T = 298(2) K, λ (Mo-Kα) = 0.71073 Å, monoclinic, space group: $P2_1$/c, a = 18.9871(17) Å, b = 18.0668(16) Å, c = 12.5460(11) Å, b = 94.4380(10)°, V = 4290.8(7) Å^3, R_1 = 0.0540, wR_2 = 0.0692.

