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Four-Component Domino Reaction Leading to Multifunctionalized Quinazolines

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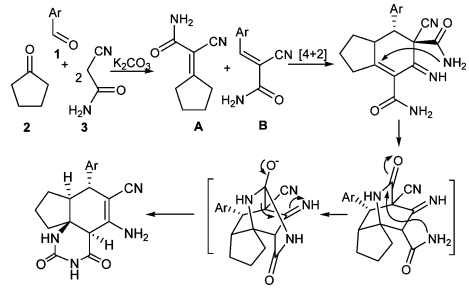
Creation of molecular complexity and diversity from common starting materials while combining economic and environmental aspects constitutes a great challenge in modern organic chemistry from academic and industrial perspectives.[1−4] In these contexts, multicomponent domino reactions for use in total syntheses of natural products and synthetic building blocks are highly desirable.[4,5] 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 cascade reactions is a continuing challenge at the forefront of organic chemistry.

In the past several years, we have been involved in the development of new multicomponent reactions (MCRs) from cyano compounds that provide easy access to novel lead structures of chemical and pharmaceutical interest.[7] A large variety of cyano compounds, such as methyl cyanoacetate and cyanoacetamide, have been utilized in several MCR processes.[8] To date, the simultaneous utilization of two electrophilic and two nucleophilic centers of cyanoacetamide in a one-pot operation has not been achieved. However, the resulting polyfunctionalized cyclopenta[*i*]-, benzo[*i*]-, and cyclohepta[*i*]quinazoline and pyrido[3,4-*i*]quinazoline derivatives are important scaffolds for drug design and synthesis and can directly serve in pharmaceutical research.[9] In this communication, we report a novel multicomponent domino reaction that employs simple aldehydes, cycloketones, and cyanoamides as both substrates and nucleophiles to give important scaffolds with a highly functionalized 2,4-dioxocyclopenta[*i*]quinazoline-6-carbonitrile skeleton (Scheme 1). The key steps of this new methodology involve tandem formation of two different Knoevenagel intermediates **A** and **B** that are trapped by two nucleophiles; one of these, **B**, results from functionalization of an aldehyde.

Scheme 1



The reaction of 4-chlorobenzaldehyde **1a** with cyclopentanone **2a** and cyanoacetamide **3** was initially investigated using various bases, such as K_2CO_3, Et_3N, piperidine, pyrrolidine, and *N*,*N*-dimethyl-4-aminopyridine (DMAP) under microwave (MW) irradiation. Although cyclohexenone **4a** can be generated in the presence of all of these bases (Scheme 2), only K_2CO_3 resulted in a high chemical yield. The reaction medium, amount of K_2CO_3, and temperature were then examined carefully. The reaction was found to proceed in three solvents (acetonitrile, ethylene glycol, and DMF) under several conditions. Among them, ethylene glycol was proven to be the best solvent and was thus selected for further investigation under an enhanced temperature of 120 °C (Table 1).

Scheme 2

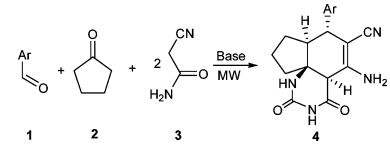


Table 1. Reaction of **1a** with **2a** and **3** under Various Conditions

entry	solvent	equiv of K_2CO_3	*T* (°C)	time (min)	yield (%)[a]
1	CH_3CN	0.5	80	15	trace
2	DMF	0.5	80	15	11
3	ethylene glycol	0.5	80	16	19
4	ethylene glycol	1.0	80	16	33
5	ethylene glycol	1.0	100	14	80
6	ethylene glycol	1.0	120	12	87

[a] Isolated yield

Under the above optimized conditions, the scope of this new MCR process was next examined using various readily available starting materials. As revealed in Table 2, a range of invaluable pyrido[3,4-*i*]quinazoline derivatives can be synthesized in good to excellent yields. The reaction is easy to perform simply by microwave heating of a mixture of aromatic aldehydes **1**, various cyclic carbonyl compounds **2**, and cyanoacetamide **3** in ethylene glycol in the presence of K_2CO_3. It is anticipated that 1 equiv of K_2CO_3 acts as the base, dehydrating agent, and heterogeneous activator for the initial Knoevenagel condensation/[4 + 2] cyclization/intramolecular Michael addition/nucleophilic reaction sequence shown in Scheme 1.

The use of acyclic ketones for this reaction did not show any useful efficiency. Interestingly, when aliphatic isobutyraldehyde was employed as the substrate, the reaction proceeded in another direction that is currently being studied in our laboratories.

The resulting highly functionalized pyrido[3,4-*i*]quinazoline derivatives offer great flexibility for structural modifications. For example, the use of cyclopentanone **2a** in combination with aldehydes **1a**−**f** led to the formation of tricyclic 2,4-dioxocyclopenta[*i*]quinazolines **4a**−**f**, while the use of cyclohexanone **2b** and cycloheptanone **2c** yielded polycyclic compounds **4g**−**m** and **4n**−**p**, respectively, from different aldehydes. Alternatively, N-substituted piperidin-4-ones **2d** and **2e** allowed a one-pot access to polycyclic 2,4-dioxopyrido[3,4-*i*]quinazolines **4q**−**z** in good yields. In all cases, the complexity of the products resulting from this new reaction

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illustrate the remarkable chemo-, regio-, and stereoselectivity of the sequence starting from very simple and easily accessible substrates. The structural elucidation and attribution of relative stereochemistry were unequivocally determined by NMR analysis and X-ray diffraction of single crystals that were obtained by slow evaporation of the solvent, as in the case of 2,4-dioxocyclopenta[*i*]quinazoline **4e** (Figure 1).[10]

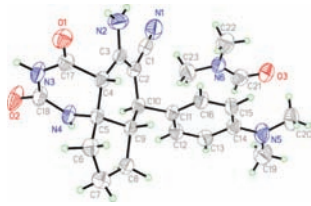
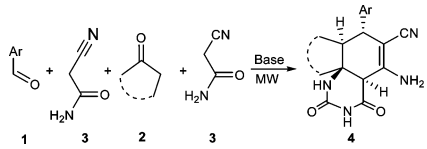
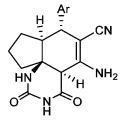
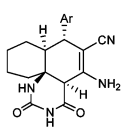
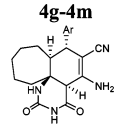
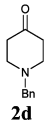
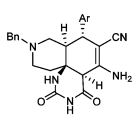
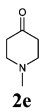
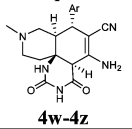


Figure 1. X-ray structure of **4e**.

Table 2. Domino Reaction under Microwave Irradiation[a]



2	Product **4** [b]	Ar =	Yield [b]	Time [c]
 **2a**	 **4a-4f**	**4a**, 4-Chlorophenyl (**1a**)	87	12
		4b, 2,4-Dichlorophenyl (**1b**)	89	14
		4c, 4-Bromophenyl (**1c**)	85	12
		4d,Benzo[*d*][1,3]dioxol-5-yl (**1d**)	82	14
		4e, 4-Dimethylaminophenyl (**1e**)	84	16
		4f, Thien-2-yl (**1f**)	79	16
2b	 **4g-4m**	**4g**, 4-Chlorophenyl (**1a**)	90	14
		4h, 4-Bromophenyl (**1c**)	89	16
		4i, Benzo[*d*][1,3]dioxol-5-yl (**1d**)	84	18
		4j, 4-Dimethylaminophenyl (**1e**)	81	18
		4k, Thien-2-yl (**1f**)	76	20
		4l, 4-Tolyl (**1g**)	79	16
		4m, 4-Methoxyphenyl (**1h**)	82	17
 **2c**	 **4n-4p**	**4n,** 4-Chlorophenyl (**1a**)	76	24
		4o, 4-Bromophenyl (**1c**)	79	24
		4p, 4-Fluorophenyl (**1i**)	74	22
 **2d**	 **4q-4v**	**4q**, 4-Chlorophenyl (**1a**)	85	18
		4r, 2,4-Dichlorophenyl (**1b**)	87	16
		4s, Benzo[*d*][1,3]dioxol-5-yl (**1d**)	81	18
		4t, 4-Dimethylaminophenyl (**1e**)	79	18
		4u, 4-Methoxyphenyl (**1h**)	76	20
		4v, 4-Fluorophenyl (**1i**)	84	14
 **2e**	 **4w-4z**	**4w**, 4-Chlorophenyl (**1a**)	84	20
		4x, 4-Bromophenyl (**1c**)	86	18
		4y,Benzo[*d*][1,3]dioxol-5-yl (**1d**)	81	18
		4z, 4-Methoxyphenyl (**1i**)	78	20

[a] Reagents and conditions: K_2CO_3 (1.0 equiv), 120 °C, ethylene glycol, microwave heating. [b] Isolated yield. [c] Time in minutes.

It is amazing that all four stereogenic centers can be controlled well in this *intermolecular* four-component process consisting of in situ steps and that one of these stereogenic centers gave a quaternary amine functionality. *This observation is truly rare and very interesting in organic chemistry*. Complete stereoselectivity and good to excellent yields were obtained in all cases that were examined. Furthermore, the reaction occurred very rapidly, in all cases finishing within 12−24 min. In comparison, conventional heating required 120 min to finish the reaction for most of the substrates and gave lower chemical yields. Water is nearly the sole byproduct, which makes workup convenient. In most cases, the products precipitated out when cold water was poured into the reaction mixture. The continuing work on this reaction will focus on the development of its asymmetric version through following strategies: (1) using chiral organic bases instead of K_2CO_3; (2) changing the cyanide group to a chiral electron-withdrawing group; (3) using chiral Lewis acids to control the [4 + 2] cycloaddition under milder conditions; and (4) last but not least, using a chiral amide in place of **3**, although the reaction may stop at the [4 + 2] cycloaddition step after this modification is made.

In conclusion, a novel four-component domino reaction has been discovered. The reaction is easy to perform simply by mixing four common reactants and K_2CO_3 in ethylene glycol under microwave irradiation. The reaction is very fast and can be finished within 10−24 min with water as the major byproduct, making workup convenient. Four stereogenic centers with one quaternary carbon−amino function are controlled very well; the stereochemistry was unequivocally determined by X-ray structural analysis. The resulting pyrido[3,4-*i*]quinazoline derivatives are of importance for organic and medicinal research.

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Supporting Information Available: Complete experimental procedures and characterizations and crystallographic data for **4e** and **4l** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The single-crystal growth was carried out in DMF at room temperature. Crystal data for **4e**: $C_{23}H_{30}N_6O_3$; $M = 438.53$; triclinic; space group $P1$; $a = 7.2741(7)$ Å, $b = 1.9560(10)$ Å, $c = 13.775(2)$ Å; $V = 1145.6(2)$ Å^3; $Z = 2$; $T = 298(2)$ K; $\mu = 0.087$ mm^{-1}; 5977 measured reflns, 3981 unique reflns, $R = 0.0476$, $R_w = 0.1083$.

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