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Novel Double [3 + 2 + 1] Heteroannulation for Forming Unprecedented Dipyrazolo-Fused 2,6-Naphthyridines

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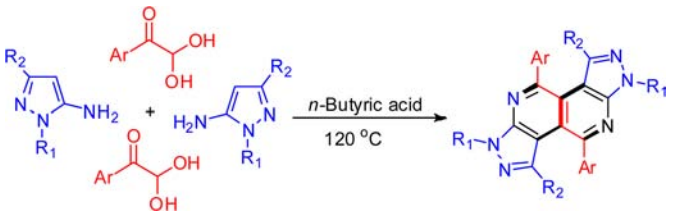
ABSTRACT



A novel four-component strategy for the efficient synthesis of unprecedented dipyrazolo-fused 2,6-naphthyridines through a double [3 + 2+1] heteroannulation has been described. The bond-forming efficiency, accessibility, and generality of this synthesis make it highly valuable to assemble tetra-heterocyclic scaffolds.

The functionalized fused naphthyridine unit is often found in many natural products of marine origin[1] that have shown a wide range of biological activities[2] such as HIV-1 integrase inhibition[3] and as antitumor agents[4] and selective antagonists of 5-HT4 receptors,.[5] In addition, a variety of synthetic fused 2,6-naphthyridines exhibited various biological properties, including selective human PKD1 inhibitor,[6] protein kinase CK2 inhibitors,[7] and antimicrobial agents.[8] Although many studies on the preparation of fused 2,6-naphthyridine derivatives have been developed,[7a−c,8] these methods suffer multistep syntheses. Thus, the development of general and efficient routes to

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regioselective synthesis of fused 2,6-naphthyridine is still challenging.

The pursuit of highly efficient synthetic strategies continues to demand enormous efforts aimed at atom-economic and environmental aspects and remarkable chemo- and regioselective control of constructing natural products or natural-like structures.[9] Multicomponent domino reactions (MDRs), being one of the most effective methods to improve synthetic efficiency, can implement reaction cascades and generate high levels of diversity giving rise to complex structures by simultaneous formation of three or more bonds from simple substrates.[10] It is obvious that such transformations can avoid tedious steps of protection and deprotection of functional groups and isolation of intermediate, thereby minimizing the generation of waste and rendering the transformations green.[11] In recent years, considerable efforts have been devoted to the development of various MDRs toward the formation of various heterocycles.[12] However, the utilization of MDRs for the construction of tetracyclic dipyrazolo-fused [2,6]naphthyridine skeleton through sequential carbon−oxygen bonds cleavage, to the best of our knowledge, has not been reported so far.

Recently, our group and others have developed a series of unique domino reactions for the construction of useful functionalized complex molecules of chemical and pharmaceutical interest.[13,14] To continue our study on this topic, herein, we discovered a novel A_2B_2 type domino reaction of arylglyoxal monohydrate **1** and electron-rich pyrazol-5-amines **2**. The unique characteristics of this chemistry are as indicated below: the domino construction of unprecedented dipyrazolo-fused 2,6-naphthyridine skeleton with concomitant formation of *two new pyridine rings* was readily achieved in domino fashion that involved double [3 + 2 + 1] heteroannulation; *up to five σ bonds* were formed in a one-pot operation from common and inexpensive starting materials (Scheme 1). In addition, the direct C−C formation between two electrophilic centers of arylglyoxal monohydrates can be easily achieved in this domino system without the use of any metal or carbene catalysts. This observation is very rare and may be useful in organic chemistry.

Scheme 1. Multicomponent Synthesis of Dipyrazolo-Fused 2,6-Naphthyridines

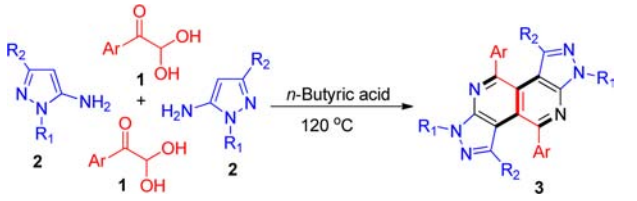

Table 1. Optimization for the Synthesis of **3a** under MW

entry	solvent	temp (°C)	time (min)	yield[a](%)
1	CH_3CN	100	20	no
2	Toluene	100	20	trace
3	CF_3COOH	100	20	trace
4	HCOOH	100	20	trace
5	HOAc	100	20	36
6	EtCOOH	100	20	44
7	*i*-PrCOOH	100	20	48
8	*n*-PrCOOH	100	20	54
9	*n*-PrCOOH	120	20	68
10	*n*-PrCOOH	130	20	67

[a] Isolated yield.

Our investigation was initiated by evaluating the domino reaction of 2,2-dihydroxy-1-phenylethanone **1a** with electron-rich pyrazol-5-amines **2a**. The reaction was tested under a variety of different conditions. The representative data were summarized in Table 1. It was found that the reaction could not proceed at 100 °C for 20 min under microwave (MW) heating using toluene, CH_3CN, HCOOH, or CF_3COOH as a solvent (Table 1, entries 1−4). An incomplete reaction was observed when HOAc was used as a solvent at 100 °C (entry 5). The identical reaction in propanoic acid (EtCOOH) at 100 °C generated slightly higher yield of **3a** (44%). It was found that acidic solvent can serve as a suitable media for the present domino cyclizations. Subsequently, other two acidic solvents, such as *n*-butyric acid (*n*-PrCOOH) and isobutyric acid (*i*-PrCOOH), were thus employed as microwave irradiation media. Isobutyric acid at 100 °C resulted in product **3a** in 48% isolated yield (enty 7). The best yield of 54% was achieved when the reaction was carried out in *n*-butyric acid. Gratifyingly, this reaction worked more efficiently

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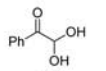
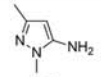
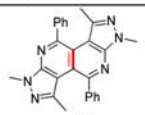
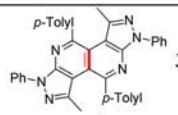
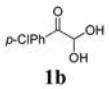
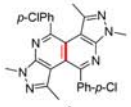
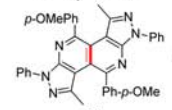
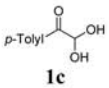
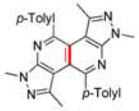
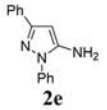
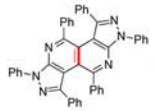
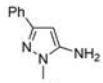
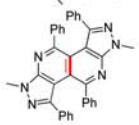
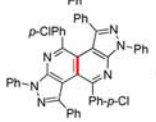
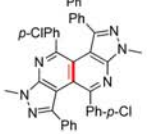
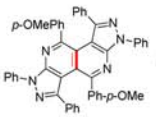
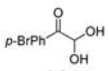
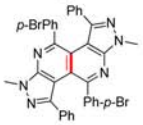
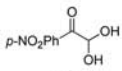
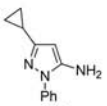
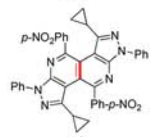
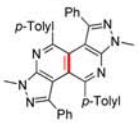
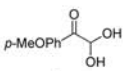
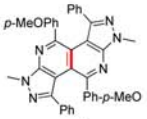
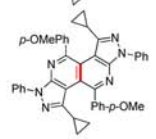
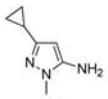
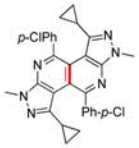
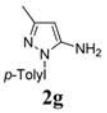
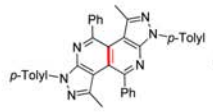
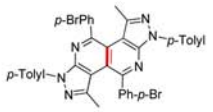
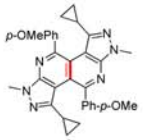
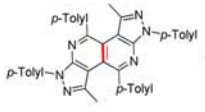
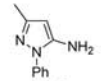
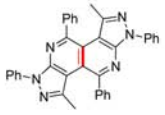
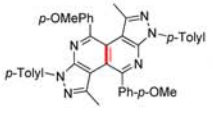
Table 2. Domino Synthesis of 2,6-Naphthyridines **3**[a]

entry	substrate (**1**)	substrate (**2**)	product (**3**)	time[b]	yield[c](%)	entry	substrate (**1**)	substrate (**2**)	product (**3**)	time[b]	yield [c](%)
1	 **1a**	 **2a**	 **3a**	20	68%	13	**1c**	**2d**	 **3m**	28	67%
2	 **1b**	**2a**	 **3b**	22	65%	14	**1e**	**2d**	 **3n**	26	69%
3	 **1c**	**2a**	 **3c**	25	71%	15	**1a**	 **2e**	 **3o**	23	74%
4	**1a**	 **2b**	 **3d**	22	69%	16	**1b**	**2e**	 **3p**	24	73%
5	**1b**	**2b**	 **3e**	20	67%	17	**1e**	**2e**	 **3q**	25	71%
6	 **1d**	**2b**	 **3f**	23	70%	18	 **1f**	 **2f**	 **3r**	23	75%
7	**1c**	**2b**	 **3g**	25	71%	19	**1c**	**2f**	 **3s**	27	68%
8	 **1e**	**2b**	 **3h**	26	65%	20	**1e**	**2f**	 **3t**	26	73%
9	**1b**	 **2c**	 **3i**	23	71%	21	**1a**	 **2g**	 **3u**	22	72%
10	**1d**	**2c**	 **3j**	22	66%	22	**1d**	**2g**	 **3v**	25	67%
11	**1e**	**2c**	 **3k**	27	68%	23	**1c**	**2g**	 **3w**	26	71%
12	**1a**	 **2d**	 **3l**	23	70%	24	**1e**	**2g**	 **3x**	25	74%

[a] Reaction conditions: **1** (1.1 mmol), **2** (1.0 mmol), *n*-butyric acid (1.5 mL), 120 °C, MW. [b] Time (min). [c] Isolated yield.

in *n*-butyric acid at an enhanced temperature of 120 °C, which afforded the corresponding product **3a** in 68% yield (entry 9). Further increase of reaction temperature failed to improve the yield of desired product **3a** (entry 10). It turned out that *n*-butyric acid can be used as an adequate Brønsted acid promoter for this double [3 + 2 + 1] heteroannulation.

With the optimal conditions in hand, we then explored the substrate scope of this domino reaction of arylglyoxal monohydrate **1** and electron-rich pyrazol-5-amines **2**.

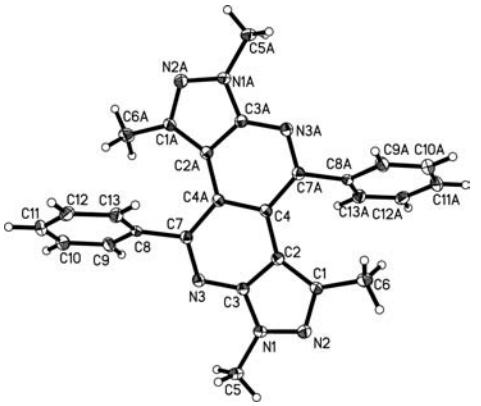
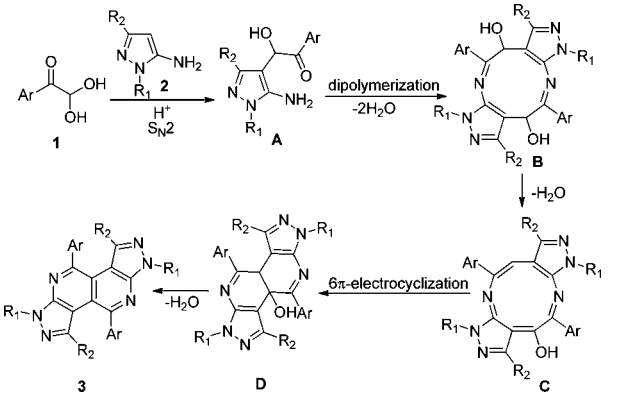


Figure 1. ORTEP drawing of **3a**.

The results were presented in Table 2. It was pleasing to find that the substituents on the aromatic ring of arylglyoxal monohydrate **1** did not hamper the reaction process. Reactions of methyl- or chloro-substituted phenylglyoxal monohydrate **1** with **2** all worked well to provide the desired products in moderate to good yields. The variation of nitrogen-tethered substituents on the pyrazole ring **2** including methyl or aryl groups all furnished the unprecedented dipyrazolo-fused 2,6-naphthyridines **3** in good yields within short times. Moreover, methyl-, phenyl-, and cyclopropyl-substituted of 3-position of pyrazol-5-amines **2** were all successfully engaged in this reaction and were readily transformed into the corresponding dipyrazolo-fused 2,6-naphthyridines **3**. The tolerance of functionalities, such as chloro and bromo, in this protocol provides the opportunity of their various further chemical manipulations in products. It is worth mentioning that the protocol provides an unusual pathway for the generation of complex tetracyclic dipyrazolo-fused 2,6-naphthyridines, which are normally difficult to prepare by other methods. Moreover, it also gives a new example for bis-heterocyclization in an economical and atom-efficient fashion, providing a valuable strategy to discover new bioactive compounds.

In general, the reaction occurred at a very fast speed; in fact, all cases can be finished within short reaction times. Water is nearly a sole byproduct, which makes the workup convenient. In most cases, the products can precipitate out after the reaction mixture was poured into cold water and was neutralized by diluted basic solution. The structural elucidation of the products was determined from its IR, ^{1}HNMR, ^{13}C NMR, and HRMS spectra. The structure of compound **3a** was unequivocally confirmed by X-ray analysis (Figure 1). During these processes, up to two new rings and five sigma-bonds were formed accompanied by cleavage of four C−O bonds and two C═O of bonds arylglyoxal monohydrates. This observation is very interesting and useful in organic chemistry.

Scheme 2. Mechanism Hypothesis for Forming **3**



On the basis of experimental results, a tentative reaction mechanism for this domino reaction is postulated in Scheme 2. First, arylglyoxal monohydrate protonated by *n*-butyric acid underwent an S_N2 type reaction of electron-rich pyrazol-5-amines **2** to convert into intermediate **A**, followed intermolecular dipolymerization of itself to yield macrocyclic dipolymer **B**. Then, second dehydration and subsequent intramolecular 6π-azaelectrocyclization of **C** occurred, affording final dipyrazolo-fused 2,6-naphthyridines **3** via third dehydration.

In conclusion, we have discovered a novel double [3 + 2+1] heteroannulation of arylglyoxal monohydrate, that led to new construction of the tetracyclic dipyrazolo-fused 2,6-naphthyridines skeleton with high regioselectivity. This cascade process involves an S_N2-type reaction/dipolymerization/6π-azaelectrocyclization sequence. Undoubtedly, this multicomponent strategy provides a straightforward and green pathway to construct the target molecules in an atom-economic manner, avoiding the use of transition metal catalysts. Other features of this tactic include the mild conditions, convenient one-pot operations, and high bond-forming efficiency. We believe this methodology may be of value to others seeking new and original synthetic fragments with unique properties for medicinal and pharmaceutical chemistry.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.