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PAPER

New domino heteroannulation of enaminones: synthesis of diverse fused naphthyridines†

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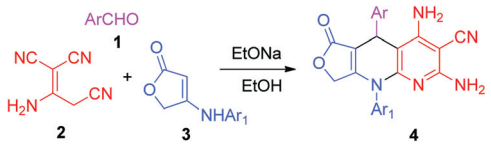
A series of new poly-functionalized fused naphthyridine derivatives were synthesized *via* a three-component reaction of aldehyde, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and enaminone in EtOH using EtONa as a base. During these reaction processes, the domino construction of fused naphthyridine skeleton with concomitant formation of two new pyridine rings was readily achieved *via* base promoted three-component reactions in a one-pot operation. The procedures are facile, avoiding time-consuming and costly syntheses, tedious work-up and purifications of precursors.

Introduction

Functionalized naphthyridines and their benzo/heterofused analogues are present in numerous products of marine origin[1] and possess a wide range of biological activities such as antiproliferative activity[2] and HIV-1 integrase inhibition.[3] They can also act as allosteric inhibitors of Akt1 and Akt2,[4] antitumor agents,[5] and selective antagonists of 5-HT4 receptors.[6] Because of the biological activities they exhibit, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus the synthesis of these molecules has attracted considerable attention.[7,8] A survey of the literature shows that the majority of the strategies involve either multistep sequences,[7] or expensive catalysts,[7c–f,8] inert atmosphere,[7b,c,e,8a] anhydrous conditions, lengthy reaction times,[7c,d] and laborious workup.[7b–d] Therefore, a simple and novel method for synthesizing naphthyridines, especially polysubstituted fused naphthyridines, is highly desirable and has practical benefits.

On the other hand, the derivatives of tetronic acid (tetrahydrofuran-2,4-dione) are yet another nucleus known to be part of many biologically active compounds, occupying a unique position in medicinal and pharmaceutical chemistry by serving as anti-inflammatory,[9] antifungal,[10] antibiotic,[11] insecticidal,[12] analgesic,[13] anticoagulant,[14] and antiepileptic[15] agents. Thus, a hybrid of these two motifs could potentially lead to a series of structurally and biologically interesting compounds.

Multicomponent domino reactions (MDRs) have gained considerable popularity in the synthetic community. They provide efficient access to complex molecules from readily available starting materials.[16] They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, *e.g.*, ligands for catalysis or bioactive compounds. Recently, we have been engaging in the development of new multi-component 'domino' reactions that can provide easy access to new core structures of chemical and pharmaceutical interest.[17,18] During our continuous efforts on the development of useful multi-component domino reactions, herein, we would like to report another highly efficient approach to multi-functionalized furo[3,4-*b*][1,8]naphthyridine derivatives through new three-component domino reactions of aldehyde **1** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** and enaminones **3** under microwave (MW) heating (Scheme 1). The great aspect of the present domino reaction is shown by the fact that the domino construction of fused naphthyridine skeleton with concomitant formation of two new pyridine rings was readily achieved *via* base promoted three-component reactions in a one-pot operation. To the best of our knowledge, the one-pot formation of two new pyridine rings and construction of such furonaphthyridine skeleton with two NH_2 groups residing in 2 and 4-positions of fused naphthyridine nucleus, respectively, have not been achieved so far.



Scheme 1 The synthesis of furo[3,4-*b*][1,8]naphthyridines.

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Results and discussion

We have planned to link two biologically important nuclei, naphthyridines and furans, to generate a new set of compounds, furo[3,4-*b*][1,8]naphthyridine analogues, using three-component domino [3 + 2 + 1]/intramolecular six-membered heterocyclization of aldehydes **1** with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** and enaminones **3**. It should be mentioned that enaminones are versatile and readily obtainable reagents, and their chemistry has received considerable attention in recent years.[17a,b,19] We started this study by subjecting a preformed enaminone **3a** and 4-bromobenzaldehyde **1a** to the reaction with 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** in ethanol at 100 °C under microwave irradiation, using different bases (1.5 equiv.). Unfortunately, the reaction scarcely proceeded in the presence of KOH or NaOH. The incomplete reaction was observed using Et_3N or NaOMe as a base catalyst. Sodium ethylate (EtONa) was proven to be the best base (Table 1, entry 5). Subsequently, the reaction catalyzed by NaOEt was performed and repeated many times in different temperatures in a sealed vessel under microwave irradiation for 16 min. The best yield of product **4a** (83%) was obtained in ethanol as the reaction temperature was increased to 120 °C.

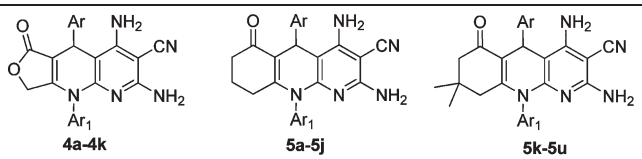
With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse aromatic aldehydes and enaminones were investigated, and a series of new multi-functionalized furo[3,4-*b*]-[1,8]naphthyridines were afforded in good yields. As shown in Table 2, at the beginning, we made a search for the aldehyde

Table 1 Optimization of the catalyst in the synthesis of **4a** under MW

Entry	Base	*T* (°C)	Time (min)	Yield[a] (%)
1	NaOH	100	16	Trace
2	KOH	100	16	Trace
3	MeONa	100	16	38
4	Et_3N	100	16	42
5	EtONa	100	16	57
6	EtONa	120	16	83

[a] Isolated yield.

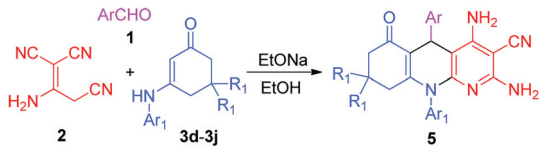
Table 2 Three-component domino synthesis of products **4** and **5** under MW irradiation



4a-4k **5a-5j** **5k-5u**

Entry	Product	**3**	Ar	Time (min)	Yield[a] (%)
1	**4a**	4-Chlorophenyl (**3a**)	4-Bromophenyl (**1a**)	16	83
2	**4b**	4-Chlorophenyl (**3a**)	4-Chlorophenyl (**1b**)	18	81
3	**4c**	4-Chlorophenyl (**3a**)	2,3-Dichlorophenyl (**1c**)	20	80
4	**4d**	4-Chlorophenyl (**3a**)	Phenyl (**1f**)	20	78
5	**4e**	4-Bromophenyl (**3b**)	4-Bromophenyl (**1a**)	18	84
6	**4f**	4-Bromophenyl (**3b**)	4-Chlorophenyl (**1b**)	20	82
7	**4g**	4-Bromophenyl (**3b**)	Phenyl (**1f**)	22	79
8	**4h**	4-Bromophenyl (**3b**)	4-Tolyl (**1g**)	20	80
9	**4i**	4-Tolyl (**3c**)	4-Bromophenyl (**1a**)	18	79
10	**4j**	4-Tolyl (**3c**)	4-Chlorophenyl (**1b**)	20	78
11	**4k**	4-Tolyl (**3c**)	Phenyl (**1f**)	22	75
12	**5a**	4-Bromophenyl (**3d**)	4-Bromophenyl (**1a**)	18	82
13	**5b**	4-Bromophenyl (**3d**)	4-Chlorophenyl (**1b**)	19	80
14	**5c**	4-Bromophenyl (**3d**)	4-Tolyl (**1g**)	18	78
15	**5d**	4-Chlorophenyl (**3e**)	4-Bromophenyl (**1a**)	20	83
16	**5e**	4-Chlorophenyl (**3e**)	3,4-Dichlorophenyl (**1d**)	17	81
17	**5f**	4-Chlorophenyl (**3e**)	4-Chlorophenyl (**1b**)	18	76
18	**5g**	4-Chlorophenyl (**3e**)	4-Tolyl (**1g**)	20	72
19	**5h**	Phenyl (**3f**)	4-Chlorophenyl (**1b**)	24	80
20	**5i**	Phenyl (**3f**)	Phenyl (**1f**)	20	74
21	**5j**	Phenyl (**3f**)	4-Tolyl (**1g**)	22	77
22	**5k**	4-Fluorophenyl (**3g**)	4-Chlorophenyl (**1b**)	16	82
23	**5l**	4-Fluorophenyl (**3g**)	4-Bromophenyl (**1a**)	25	84
24	**5m**	4-Chlorophenyl (**3h**)	4-Chlorophenyl (**1b**)	24	81
25	**5n**	4-Chlorophenyl (**3e**)	2,3-Dichlorophenyl	26	71
26	**5o**	4-Chlorophenyl (**3e**)	2-Chlorophenyl (**1e**)	26	69
27	**5p**	4-Chlorophenyl (**3e**)	Phenyl (**1f**)	18	76
28	**5q**	4-Bromophenyl (**3i**)	2,3-Dichlorophenyl (**1c**)	17	72
29	**5r**	4-Bromophenyl (**3i**)	Phenyl (**1f**)	18	75
30	**5s**	4-Bromophenyl (**3i**)	4-Tolyl(**1g**)	17	79
31	**5t**	4-Tolyl (**3j**)	3,4-Dichlorophenyl (**1d**)	22	80
32	**5u**	4-Tolyl (**3j**)	4-Chlorophenyl (**1b**)	20	79

[a] Isolated yield.



Scheme 2 The synthesis of benzo[*b*][1,8]naphthyridines.

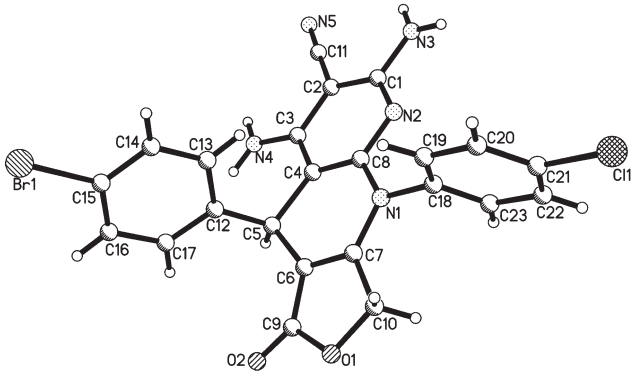
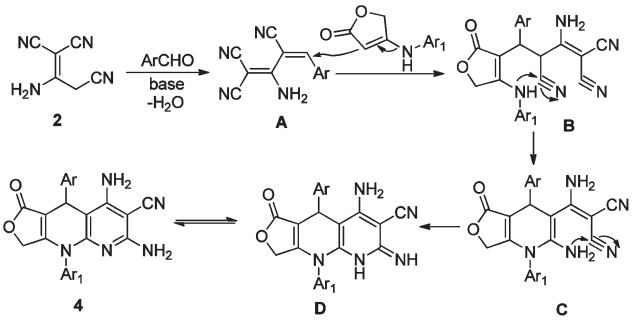


Fig. 1 X-Ray structural of **4a**.



Scheme 3 The proposed mechanism for the formation of products **4**.

substrate scope, enaminone **3a** and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** were used as model substrates (Table 2, entries 1–4), and the results indicated that aromatic aldehydes bearing chloro, or bromo group were suitable for the synthesis of compound **4**. The bulky *o*-substituted aldehyde **1c** was converted into the corresponding furo[3,4-*b*][1,8]naphthyridines **3c** in 80% yield. Subsequently, the enaminone scope of this interesting transformation was investigated (Table 2). Several different *N*-substituents were compared and substituents bearing electron-withdrawing (4-bromophenyl, **3b**) or electron-donating (4-tolyl, **3c**) groups were found to be suitable for this domino reaction. Furthermore, using various aldehydes together with different *N*-substituted enaminones **3d–j** resulted in the cyclization to corresponding substituted benzo[*b*][1,8]naphthyridine **5a–u** smoothly (Scheme 2). The results exhibit the scope and generality of the novel multicomponent domino reaction with respect to a range of enaminone and aldehyde substrates. Indeed, the protocol provides a straightforward pathway to construct highly substituted fused naphthyridine, which are generally prepared *via* multi-step reactions.[7]

Similar to our previous multi-component domino process,[17,18] the present reaction also showed the following attractive characteristics: (1) fast reaction rates which enable the reaction to be completed within 16–26 min; (2) the environmentally friendly process in which water is the major by-product; (3) the convenient work-up which only needs simple filtration since the products directly precipitate out after the reaction is finished and when its mixtures are diluted with cold water; (4) readily available starting materials of aldehydes, 2-aminoprop-1-ene-1,1,3-tricarbonitrile and preformed enaminone. Moreover, during these domino processes, up to two pyridine rings and four sigma-bonds were formed accompanied by C=O bond cleavage of the aryl aldehydes, and two cyano groups of compound **2** were converted into two amine groups in a one-pot intermolecular manner. This observation is very interesting and important in organic chemistry. Only microwave irradiation can make the present multi-component domino reaction to occur rapidly and efficiently, while normal heating diminished both yield and speed. The structures of all the obtained compounds were based on their spectroscopic data. Furthermore, the structure of the product **4a** has been unequivocally determined by X-ray structural analysis (Fig. 1).

On the basis of all the above results, possible mechanism has been proposed for the formation of furo[3,4-*b*][1,8]naphthyridines as shown in Scheme 3. The reaction involves the ring closure cascade reactions that consist of initial Knoevenagel condensation (**2** to **A**), Michael addition (**A** to **B**), intramolecular cyclization (**B** to **C**), and intramolecular second cyclization and isomerization (**C** to **4**).

Conclusion

In summary, we have described three-component domino [3 + 2 + 1]/intramolecular six-membered heterocyclization as an alternative method for the synthesis of a set of furo[3,4-*b*][1,8]-naphthyridines and benzo[*b*][1,8]naphthyridines with concomitant formation of two new pyridine rings in one-pot manner. This MDR provides a general and efficient strategy for construction of structurally diverse fused naphthyridine skeleton. The ready accessibility of the starting materials, the broad compatibility of *N*-substituted enaminone substrates, and the generality of this process make the reaction highly valuable in view of the synthetic and medicinal importance of fused heterocycles of this type. The features of this strategy include mild conditions, convenient one-pot operation, short reaction periods of 16–26 min, and excellent atom economy. Further investigations are in progress in our laboratory to improve our understanding of this asymmetric version, to evaluate the process with a broader range of substrates, and to synthesize more complex products and test their biological activity.

Experimental

General

Microwave irradiation was carried out with Initiator from Biotage Company, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were taken on a FT-IR Tensor 27 spectrometer in KBr pellets and reported in

inverse centimeters. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz (^{13}C NMR, 100 MHz) spectrometer in DMSO-d_6 with chemical shifts (δ) given in parts per million relative to TMS as an internal standard. HRMS (ESI) was determined by using microTOF-Q II HRMS/MS instrument (Bruker). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the synthesis of compounds 4 and 5

Microwave heating: in a 10 mL reaction vial, an aldehyde (1 mmol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (1 mmol), EtOH (1.5 mL) were mixed and stirred at room temperature for 3 min. Then an enaminone (1 mmol) and EtONa (1.5 mmol) was added into the mixture, and the system was heated for given time at 120 °C under microwave irradiation. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The resulting suspension was neutralized with diluted hydrochloric acid solution. Then the mixture was stirred for 5 min. The solid product was collected by Büchner filtration and washed with water and EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give the pure product.

2,4-Diamino-9-(4-chlorophenyl)-5,6,8,9-tetrahydro-6-oxo-5-phenylfuro[3,4-*b*][1,8]naphthyridine-3-carbonitrile (4d)

Pale yellow solid, mp: 243–244 °C. IR (KBr, ν, cm^{-1}): 3468 (νNH$_2$), 3357 (νNH$_2$), 3244 (νNH$_2$), 2206 (νCN), 1748 (νC═O). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.56 (d, J = 8.8 Hz, 2H, ArH), 7.46 (d, J = 8.8 Hz, 2H, ArH), 7.41 (d, J = 7.2 Hz, 2H, ArH), 7.29 (t, J = 7.6 Hz, 2H, ArH), 7.19 (t, J = 7.2 Hz, 1H, ArH), 6.20 (s, 2H, NH$_2$), 6.17 (s, 2H, NH$_2$), 5.08 (s, 1H,CH), 4.58 (d, J = 16.0 Hz, 1H, CH$_2$), 4.50 (d, J = 16.4 Hz, 1H, CH$_2$). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 174.1, 158.8, 158.7, 156.0, 151.7, 144.2, 137.7, 132.1, 129.8, 128.4, 128.2, 127.5, 118.6, 116.5, 100.0, 92.0, 70.6, 65.2, 33.8. HRMS (ESI) m/z: calc. for $C_{23}H_{16}ClN_5O_2$: 428.0914; [M − H$^-$] found: 428.0947.

2,4-Diamino-5,10-bis(4-bromophenyl)-5,6,7,8,9,10-hexahydro-6-oxobenzo[*b*][1,8]naphthyridine-3-carbonitrile (5a)

Pale yellow solid, mp: >300 °C. IR (KBr, ν, cm^{-1}): 3473 (νNH$_2$), 3441 (νNH$_2$), 3362 (νNH$_2$), 3241 (νNH$_2$), 2200 (νCN), 1607 (νC═O). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.68 (d, J = 7.6 Hz, 2H, ArH), 7.41 (d, J = 7.2 Hz, 2H, ArH), 7.35 (d, J = 7.6 Hz, 2H, ArH), 7.27 (d, J = 7.2 Hz, 2H, ArH), 6.29 (s, 2H, NH$_2$), 5.93 (s, 2H, NH$_2$), 5.26 (s, 1H, CH), 2.18 (s, 3H, CH$_2$), 1.94 (d, J = 17.2 Hz, 1H, CH$_2$), 1.79 (s, 1H, CH$_2$), 1.57 (s, 1H, CH$_2$). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.3, 158.4, 155.3, 153.5, 151.6, 145.3, 138.5, 131.9, 130.8, 129.8, 121.1, 119.0, 116.7, 112.5, 92.5, 70.3, 36.1, 32.1, 28.3, 20.7. HRMS (ESI) m/z: calc. for $C_{25}H_{19}Br_2N_5O$: 563.9854; [M − H$^-$] found: 563.9844.

2,4-Diamino-5,10-bis(4-chlorophenyl)-5,6,7,8,9,10-hexahydro-8,8-dimethyl-6-oxobenzo[*b*][1,8]naphthyridine-3-carbonitrile (5m)

Pale yellow solid, mp: >300 °C. IR (KBr, ν, cm^{-1}): 3446 (νNH$_2$), 3397 (νNH$_2$), 3343 (νNH$_2$), 3237 (νNH$_2$), 2198 (νCN), 1609 (νC═O). ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 7.57 (d, J = 8.4 Hz, 2H, ArH), 7.43 (d, J = 8.4 Hz, 2H, ArH), 7.30 (q, 4H, ArH), 6.30 (s, 2H, NH$_2$), 5.93 (s, 2H, NH$_2$), 5.25 (s, 1H, CH), 2.20 (q, 2H, CH$_2$), 1.99 (d, J = 16.0 Hz, 1H, CH$_2$), 1.77 (d, J = 17.2 Hz, 1H, CH$_2$), 0.87 (s, 3H, CH$_3$), 0.67 (s, 3H, CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 194.0, 158.3, 155.2, 151.8, 151.3, 145.6, 138.1, 132.5, 129.1, 127.9, 127.4, 126.0, 111.9, 93.2, 70.3, 49.5, 41.4, 32.7, 31.9, 29.2, 25.9. HRMS (ESI) m/z: calc. for $C_{27}H_{22}Cl_2N_5O$: 502.1201; [M − H$^-$] found: 502.1193.

Acknowledgements

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