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Highly Selective Domino Multicyclizations for Forming Polycyclic Fused Acridines and Azaheterocyclic Skeletons

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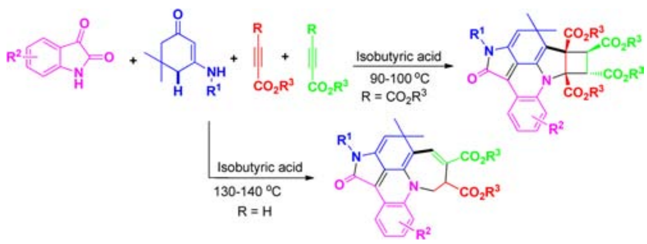
ABSTRACT



Highly selective four-component domino multicyclizations for the synthesis of new fused acridines and azaheterocyclic skeletons have been established by mixing common reactants in isobutyric acid under microwave irradiation. The reactions proceeded at fast rates and were conducted to completion within 20−30 min. Up to seven new chemical bonds, four rings, and four stereocenters were assembled in a convenient one-pot operation. The resulting hexacyclic and pentacyclic fused acridines and their stereochemistry have been fully characterized and determined by X-ray structural analysis.

The assembly of complex polycyclic skeletons of chemical and biomedical importance has become a challenging and hot topic in modern organic chemistry.[1,2] Among these skeletons, a unique pyrrolo-fused acridine parent ring system commonly exists in natural alkaloids and has been represented by Stellettamine,[3] Cyclodercitin,[3,4] and Plakinidines[5] (Figure 1); it shows a broad range of biological activities. These complex architectures have inspired our interest on creating new synthetic strategies for total synthesis and methodologies.[6]

Highly efficient syntheses usually reflect the sum of enormous efforts aimed at atom-economic and environmental elements and remarkable chemo-, stereo-, and regioselective control of multiring construction.[7] Domino multicyclizations (DMCs) have been successfully applied to the total synthesis of natural and natural-like products

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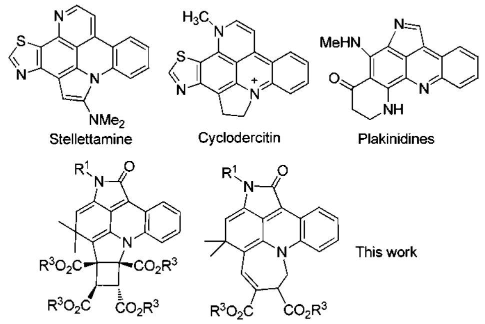


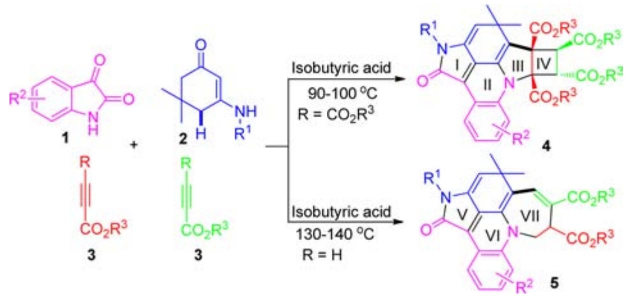
Figure 1. Several representative natural products.

by controlling multiring-junction frameworks.[8] These reactions not only enable the construction of complex structures in a single operation but also avoid tedious isolation and purification workup.[9] Among these methodologies, various DMCs toward the formation of polycyclic fused azaheterocycles have been extensively studied.[10] However, more efficient methodologies for the total synthesis of azaheterocyclic products from readily available reactants remain extremely challenging.

In the past several years, we and others have developed a series of domino reactions for the construction of multiple functional ring structures of chemical and pharmaceutical importance.[11,12] During our continuous effort on this domino project, we now discovered novel domino multicyclization reactions of enaminones with isatin and electron-deficient alkynes divergently leading to the formation of polyfunctionalized hexacyclic and pentacyclic fused acridines **4** and **5** in good yields and excellent stereoselectivity (Scheme 1). The resulting polyfunctionalized multicyclic fused acridines are important scaffolds for drug design and discovery and can serve in pharmaceutical research.[1]

The attractive aspects of these domino reactions are demonstrated by the fact that up to seven new chemical bonds and four new rings (tetracyclic 5−6−5−4 skeleton including pyrrole (I and III), pyridine (II), and cyclobutane

Scheme 1. Two Novel Domino Multicyclization Reactions



(IV)) were readily formed in domino fashion that involved novel sequential [3 + 2]/[4 + 2]/[2 + 2 + 1]/[2 + 2] cyclizations in a one-pot operation. The four newly formed stereocenters including two quaternary centers were also well controlled in a one-pot operation. Very interestingly, by changing the terminal groups of alkynes, the reaction can be controlled toward formation of tricyclic 5−6−7 skeletons including pyrrole (V), pyridine (VI), and azepine (VII) via another novel sequential [3 + 2]/[4 + 2]/[2 + 2 + 2 + 1] cyclization mechanism. In addition, the direct conversion of allylic C−H bonds into C−C bonds was achieved in this domino system without the use of any metal catalysts. To the best of our knowledge, the synthetic strategy and mechanistic sequences described in this communication have not been reported so far.

We began our investigation on the multicyclization reaction of unsubstituted indoline-2,3-dione **1a**, *N*-(4-chlorophenyl) enaminones **2a**, and symmetrical diethyl but-2-ynedioate **3a**. When these components were mixed in a ratio of 1:1:2.2 and subjected to microwave irradiation in acetic acid (HOAc) at 110 °C, an intermolecular hexacyclic product, cyclobuta[4,5]pyrrolo [3,2,1-*de*]pyrrolo-[4,3,2-*mn*]acridines **4a**, was obtained in 45% yield. Its structure was unambiguously determined by X-ray diffraction analysis (see Supporting Information (SI)). This unprecedented observation prompted us to further optimize the reaction conditions. Various acidic solvents, such as formic acid (HCOOH), trifluoroacetic acid (TFA), propanoic acid (EtCOOH), *n*-butyric acid ($CH_3(CH_2)_2COOH$), and isobutyric acid ($(CH_3)_2CHCOOH$), were thus employed as microwave irradiation media. Among these

Table 1. Optimization for the Synthesis of **4a** under MW

entry	solvent	temp (°C)	time (min)	yield[a]%
1	acetic acid	100	20	45
2	formic acid	120	25	trace
3	trifluoroacetic acid	120	25	trace
4	propanoic acid	100	20	47
5	*n*-butyric acid	100	20	51
6	isobutyric acid	100	20	59

[a] Isolated yield.

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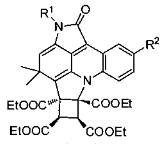
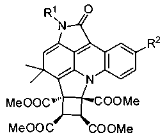
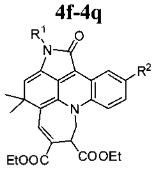
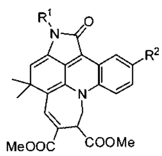
Table 2. Domino Synthesis of Fused Acridines **4** and **5**

entry	product 4 and 5[a]		substrate (1)	2(R[1])	3	time/min	yield[b]/%
1		**4a**	Indoline-2,3-dione (**1a**)	4-Chlorophenyl (**2a**)	**3a**	20	59
2		**4b**	Indoline-2,3-dione (**1a**)	Phenyl (**2b**)	**3a**	24	54
3		**4c**	Indoline-2,3-dione (**1a**)	4-Tolyl (**2c**)	**3a**	30	61
4		**4d**	Indoline-2,3-dione (**1a**)	3,4-Dimethoxyphenyl (**2d**)	**3a**	20	50
5		**4e**	5-Fluoroindoline-2,3-dione (**1b**)	4-Tolyl (**2c**)	**3a**	25	46
6		**4f**	Indoline-2,3-dione (**1a**)	4-Chlorophenyl (**2a**)	**3b**	20	53
7	**4a-4e**	**4g**	Indoline-2,3-dione (**1a**)	Phenyl (**2b**)	**3b**	22	56
8		**4h**	Indoline-2,3-dione (**1a**)	4-Tolyl (**2c**)	**3b**	24	59
9		**4i**	Indoline-2,3-dione (**1a**)	3,4-Dimethoxyphenyl (**2d**)	**3b**	26	51
10		**4j**	Indoline-2,3-dione (**1a**)	4-Methoxyphenyl (**2e**)	**3b**	30	48
11		**4k**	Indoline-2,3-dione (**1a**)	Carboxymethyl (**2f**)	**3b**	28	52
12		**4l**	5-Methylindoline-2,3-dione (**1c**)	4-Chlorophenyl (**2a**)	**3b**	26	58
13		**4m**	5-Methylindoline-2,3-dione (**1c**)	Phenyl (**2b**)	**3b**	25	62
14	**4f-4q**	**4n**	5-Methylindoline-2,3-dione (**1c**)	4-Tolyl (**2c**)	**3b**	26	64
15		**4o**	5-Methylindoline-2,3-dione (**1c**)	4-Methoxyphenyl (**2e**)	**3b**	30	49
16		**4p**	5-Methylindoline-2,3-dione (**1c**)	4-Bromophenyl (**2g**)	**3b**	30	52
17		**4q**	5-Chloroindoline-2,3-dione (**1d**)	4-Chlorophenyl (**2a**)	**3b**	28	45
18		**5a**	Indoline-2,3-dione (**1a**)	Phenyl (**2b**)	**3c**	30	48
19		**5b**	Indoline-2,3-dione (**1a**)	4-Tolyl (**2c**)	**3c**	20	51
20		**5c**	Indoline-2,3-dione (**1a**)	4-Methoxyphenyl (**2e**)	**3c**	30	46
21	**5a-5e**	**5d**	Indoline-2,3-dione (**1a**)	3,5-Dichlorophenyl (**2g**)	**3c**	30	43
22		**5e**	Indoline-2,3-dione (**1a**)	4-Chlorophenyl (**2a**)	**3c**	28	40
23		**5f**	Indoline-2,3-dione (**1a**)	Phenyl (**2b**)	**3d**	25	50
24		**5g**	Indoline-2,3-dione (**1a**)	4-Tolyl (**2c**)	**3d**	28	52
25		**5h**	Indoline-2,3-dione (**1a**)	3,4-Dimethoxyphenyl (**2d**)	**3d**	28	45
26		**5i**	Indoline-2,3-dione (**1a**)	4-Methoxyphenyl (**2e**)	**3d**	30	42
27		**5j**	Indoline-2,3-dione (**1a**)	Carboxymethyl (**2f**)	**3d**	30	46
28	**5f-5m**	**5k**	Indoline-2,3-dione (**1a**)	3-Chlorophenyl (**2h**)	**3d**	28	52
29		**5l**	5-Methylindoline-2,3-dione (**1c**)	4-Tolyl (**2c**)	**3d**	28	55
30		**5m**	5-Methylindoline-2,3-dione (**1c**)	4-Methoxyphenyl (**2e**)	**3d**	30	50

[a] Conditions: the synthesis of products **4**, $(CH_3)_2CHCOOH$ (1.5 mL), 90−100 °C, microwave heating; the synthesis of products **5**, $(CH_3)_2CHCOOH$ (1.5 mL), 130−140 °C, microwave heating. [b] Isolated yield.

solvents, the first two acids (HCOOH and TFA) led to poor yields of product **4a** even at an enhanced temperature of 120 °C. Instead, only intermediate **D** (Table 1, entries 2−3 and Scheme 2) was observed. The other two solvents, propanoic acid and *n*-butyric acid, resulted in product **4a** in 47% and 51% isolated yield, respectively. The best yield of 59% was achieved when the reaction was performed in isobutyric acid. In an attempt to enhance the yield further, metal triflates such as $Sc(OTf)_3$, $Cu(OTf)_2$, and $Zn(OTf)_2$ were then employed to promote the reaction.[14] Unfortunately, complex mixtures were formed, making purification very difficult. It was found that acetic acid can serve not only as a suitable media but also as an adequate Brønsted acid promoter for the present multicyclizations shown in Scheme 1. It should be noted that, for four-component reactions, this yield would be interpreted as a very good one.

With this optimization in hand, we next examined the substrate scope of this reaction by using various readily available starting materials. As revealed in Table 2, various starting materials can be employed for this reaction and result in highly functionalized fused acridine derivatives that offer flexibility for structural modifications. For enaminone substrates, a variety of *N*-substituents bearing electron-withdrawing or -donating groups can all tolerate the reaction conditions. Meanwhile, various substituted isatins, such as 5-F (**1b**) 5-Me (**1c**), and 5-Cl (**1d**), can also be utilized and result in corresponding hexacyclic fused acridines **4b**−**4q** smoothly. With the importance of *N*-substituted amino acids considered,[15] the preformed *N*-carboxymethyl enaminone **2f** was subjected to the reaction with **1a** and **3b**, providing the corresponding polycyclic substituted amino acid derivative **4k**. As shown in Table 2, the present intermolecular domino multiple cyclilaztions showed a broad substrate scope to give hexacyclic products in excellent stereoselectivity. Essentially, only a single diastereomer was detected by ^{1}H and ^{13}C NMR spectroscopic analysis.

During our investigation on alkyne substrates, we found when unsymmetrical electron-deficient alkynes, propargyl esters **3c**−**d**, were subjected to the reaction with indoline-2,3-diones **1** and *N*-substituted enaminones **2a**−**2h** in acetic acid at 130−140 °C, propargyl esters were consumed

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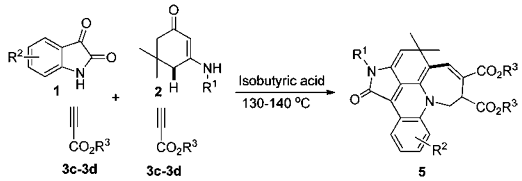
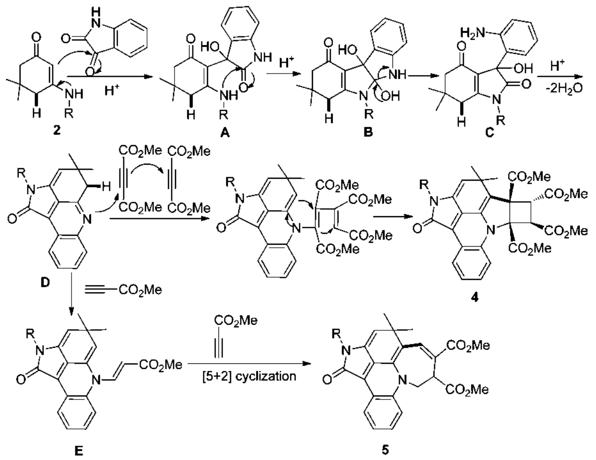
Scheme 2. Domino Synthesis of Pentacyclic Fused Acridines **5**



Scheme 3. Mechanism Hypothesis for Forming **4** and **5**



within 20−30 min. Surprisingly, the reaction occurred toward another direction to give multifunctionalized pentacyclic fused acridines **5** that belong to another family of important scaffolds for organic and pharmaceutical sciences (Scheme 2).[16] Two molecules of unsymmetrical electron-deficient alkynes **3c**−**d** were introduced into the final pentacyclic fused acridine products (Scheme 2). The structural elucidation and attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystals that were obtained by slow evaporation of the solvents (**4a** and **5i**; see SI). The results are summarized in Table 2. Both electron-deficient and -rich aromatic groups on the *N*-substituted enaminones gave very good chemical yields (**5a**−**5m**) for this reaction. Furthermore, halogen functional groups (Cl and Br) were tolerated well under the current conditions and can provide opportunities for further functional manipulations via cross-couplings.[17] Similar to the former reaction, the latter also resulted in multiple rings and chemical bonds rapidly in a one-pot operation. Besides the characteristic of a high reaction rate, these two reactions can be both worked out conveniently, in which water is a major byproduct and the products can precipitate out after cold water was poured into the reaction mixture, which makes workup very convenient simply by filtration/washing.

The mechanism for these two domino cyclizations are proposed and shown in Scheme 3. The former involves the ring closure cascade reactions that consist of initial nucleophilic addition (**2** to **A**), intramolecular cyclization (**A** to **B**), and ring-opening of indoline-2,3-dione **1** (**B** to **C**), recyclization and dehydration (**C** to **D**), and second intermolecular double nucleophilic additions and third double cyclizations (**D** to **4**). Similar to the former, the latter underwent the same sequent processes to give intermediate **D**, which is followed by a subsequent intermolecular nucleophilic addition with one molecular propargyl ester leading to the formation of *N*-vinylethenamines **E**. The [5 + 2] cycloaddition between *N*-vinylethenamines **E** and propargyl ester occurred to yield thermodynamically stable pentacyclic products **5**. This mechanism has been partially supported by an experiment in which the isolated intermediate **D** was subjected to the reaction with **3a** in isobutyric acid; the hexacyclic product **4a** was generated in 58% yield.

In summary, novel four-component domino [3 + 2]/[4 + 2]/[2 + 2 + 1]/[2 + 2] and [3 + 2]/[4 + 2]/[2 + 2 + 2 + 1] multicyclizations have been discovered for selectively diverse constructions of hexa- and pentacyclic fused acridines and polycyclic fused azaheterocyclic skeletons. The ready accessibility of starting materials and the broad compatibility of *N*-substituted enaminones make these reactions highly valuable for organic and biomedical fields. Other attractive features of these reactions include mild conditions, convenient one-pot operation, short reaction times of 20−30 min, and excellent regio- and stereoselectivity. The continuing work on this project will be focused on the development of asymmetric versions of these reactions and applications of the resulting highly conjugate systems.

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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.

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The authors declare no competing financial interest.