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One-pot multicomponent strategy for stereospecific construction of tricyclic pyrrolo[1,2-*a*]quinolines

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Abstract

A novel multicomponent strategy for the efficient synthesis of tricyclic pyrrolo[1,2-*a*]quinolines has been described. The bond-forming efficiency, accessibility and generality of this synthesis make it highly attractive to assemble tri-heterocyclic scaffolds.

The functional diverse pyrrolo[1,2-*a*]quinoline skeletons are well-represented in biologically active natural products;[1] they have been found in natural alkaloids, such as gephyrotoxin (**I**) (Figure 1), that was isolated from tropical frogs *Dendrobates histrionicus* by Daly and coworkers in 1977.[2] These compounds exhibited nearly nontoxic activity as a muscarinic antagonist[3] and an array of neurological activities.[4] In addition, pyrroloquinolines are well-known to possess various biological activities including antitumor,[5] antibacterial [6] and antifungal.[7] Because of their unique chemical and biological characteristics, the synthesis of **I** [8] and its analogues [9] has attracted much attention among the synthetic community since the first total synthesis of **I** was reported by Kishi and coworkers.[10] In Kishi's strategy, one key step was the preparation of the 6-6-5 cyclic framework in the intermediate **II** (Scheme 1). Although the construction of the 6-6-5 cyclic framework was improved by using shorter synthetic routes, the related approaches to the skeleton of **II** still suffered from multistep operations, the availability of starting materials and the usage of catalysts.[11,12] Therefore, the development of concise approaches to the special tri-heterocyclic skeleton of **II** for the synthesis of gephyrotoxin analogues of biomedical importance from common starting materials is highly desirable in modern organic and medicinal chemistry. To the best of our knowledge, the utilization of multicomponent domino strategy for the stereospecific construction of tricyclic pyrrolo[1,2-*a*]quinolin-6(7*H*)-one skeleton and its poly-functionalization residing in different positions of this unit have not been achieved so far.

Recently, our group and others have developed various multicomponent domino reactions (MDRs) that led to useful functionalized complex molecules of chemical and pharmaceutical interest from simple substrates.[13,14] To continue our study on this topic, herein, we discovered a novel ABC_2 type domino reaction [15] of 3-aryl-1- azaaryl-prop-2-en-1-one, 1,3-cyclohexanedione or 5,5-dimethylcyclohexane-1,3-dione and (pyridin-2-yl)methanamine or (pyrizin-2-yl)methanamine. The great features of this chemistry are as indicated below: simultaneously forming rings of pyridine and pyrrole and functionalizations on C1, C2, C3, C3a, and C5 positions of the pyrrolo[1,2-*a*]quinoline scaffold were readily achieved in domino fashion that involved [2+3+1]/[2+2+1] heterocyclizations; five stereocenters including a quaternary center were controlled well in a one-pot operation from common and inexpensive starting materials (Figure. 1). Since pyridine and pyrazine as heterocycles are prevalent substructures commonly found in natural

products and pharmaceuticals,[16] we anticipated that the introduction of these functional groups onto the parent ring would largely benefit to the biomedical research, particularly, to numerous chemical entities of bioscreening.

As shown in Scheme 1, the retrosynthetic analysis of **4** (R = H, X = CH) was described in details. We envisaged that the target molecules **4** would be formed *via* [3+2] cycloaddition of the intermediates **III** with 2-azaaryl substituted propenones in which **III** can be generated from **IV** through dehydration reaction. The cleavage of C3a-N and C5-C5a bonds can give 2-azaaryl substituted propenones and an enaminone intermediate which is generated by the reaction of cyclohexane-1,3-dione with (pyridin-2-yl)methanamine. Based on the above retrosynthetic analysis, we are pleased to realize this new MDRs.

Initially, we chose cyclohexane-1,3-dione (**1a)**, (pyridin-2-yl)methanamine (**2a**) and 3-(4-chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**3a)** as model substrates to optimize reaction conditions (Table 1). This model reaction was carried out under N_2 atmosphere in the absence of any catalyst in DMF at 25 °C. The mixture was stirred for a certain time (monitored by TLC). The desired compound **4a** was obtained with 40 % chemical yield by chromatographic separation and confirmed by ^{1}H NMR, ^{13}C NMR and HRMS (Table 1, entry 1). In order to further optimize the reaction conditions, the effect of solvents was also investigated. Comparing with EtOH, DMF, CH_3CN, CH_2Cl_2, $CHCl_3$, and THF, the yield of **4a** was improved when anhydrous MeOH as a solvent was used (Table 1, entry 3). Next, the influence of reaction temperature was also optimized and indicated that 45 °C let to the best result (Table 1, entry 10).

With the optimal reaction conditions in hand, we next turned our attention to the scope of this MDRs with different 2-azaaryl substituted propenones. The reactions proceeded efficiently and the corresponding products (Table 2, entries 2–8) were obtained in moderate to good yields. In view of these results, we next replaced 1,3-cyclohexanedione with 5,5-dimethylcyclohexane-1,3-dione to carry out the reactions under the above conditions. In these cases, the target compounds (Table 2, entries 9–16) were also afforded with good yields. Similarly, (pyrizin-2-yl)methanamine was converted into the corresponding pyrizin-2-yl substituted pyrrolo[1,2-*a*]quinolines under the same conditions (Table 2, entries 17–18). As shown in Table 2, all the substrates led to the corresponding pyrrolo[1,2-*a*]quinoline derivatives in 70–81% yields.

In order to determine the stereochemistry of pyrrolo[1,2-*a*]quinolines **4,** the single crystal of **4a** was obtained by slowly evaporating the solvent. Its relative stereo-configuration was established by X- ray diffraction as shown in Figure 2. The perspective diagram shows that there are five strereocenters in the molecular structure and the two aryl groups residing on C2 and C5 positions of the pyrrolo[1,2-*a*]quinoline scaffold are *anti*-configuration; this can particularly match stereo pattern of *Gephyrotoxin*.

On the basis of the above results, the possible mechanism for this new reaction was proposed and depicted in Scheme 2. The cyclohexanedione was first condensed with (pyridin-2-yl)methanamine or (pyrizin-2-yl)methanamine to generate enaminone **5**, followed by intermolecular 1,4-addition with chalones **3** to yield the intermediate **6**. Then the isomer **7** of **6** underwent intramolecular cyclization to form **8**, which was subsequently converted into the intermediate **9** *via* dehydration. The intermediate **10** was formed from the Michael addition reaction of **9** with **3**. Intramolecular addition led to the formation of the target compounds **4**. It should be noted that the pathway for the formation of **4** *via* [3+2] cycloaddition would not be excluded. The further investigation of the mechanism is to be conducted in due course.

In conclusion, a facile and convenient straightforward one-pot multicomponent strategy for the construction of pyrrolo[1,2-*a*]quinoline skeleton has been established. This protocol generated five new sigma bonds and five stereocenters by means of simple one-pot operation from commercially available common starting materials. The bond-forming efficiency, accessibility and generality make the present method a highly attractive approach to the tri-heterocyclic scaffolds of chemical and biomedical importance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. The crystal data for **4a** see CCDC- 903897

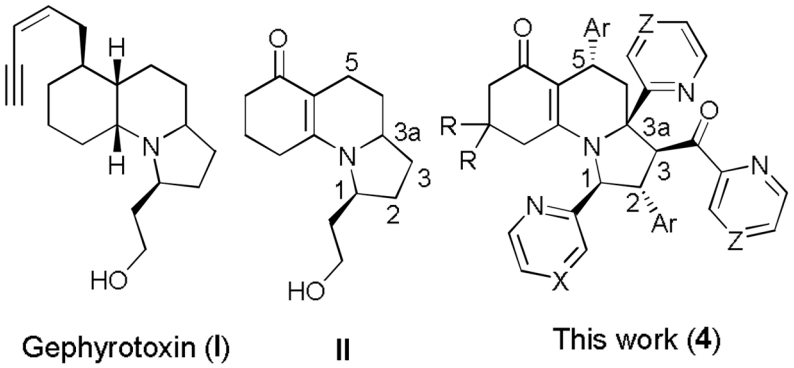


Fig. 1.

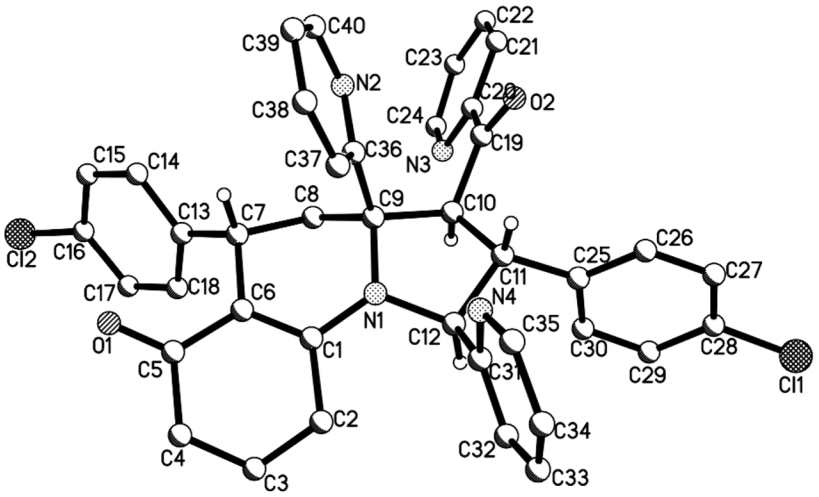
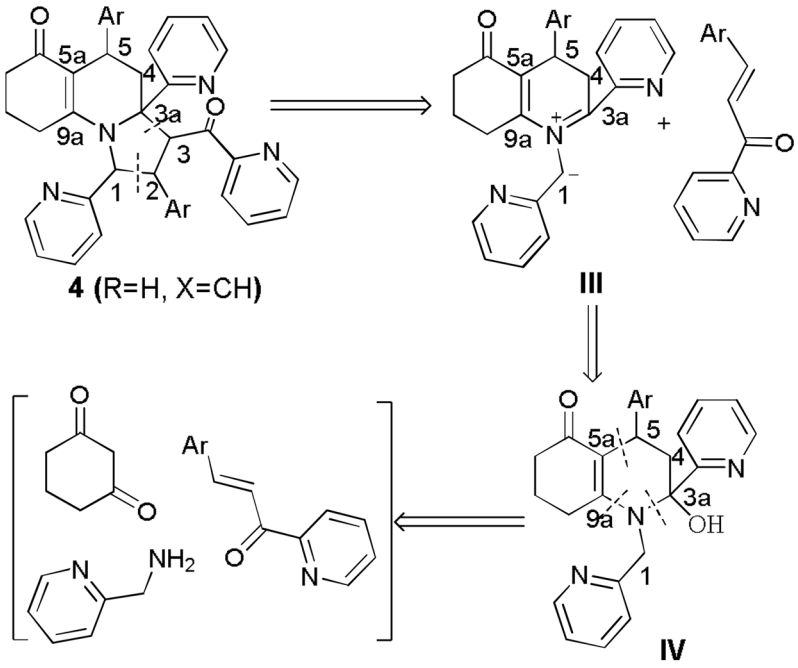
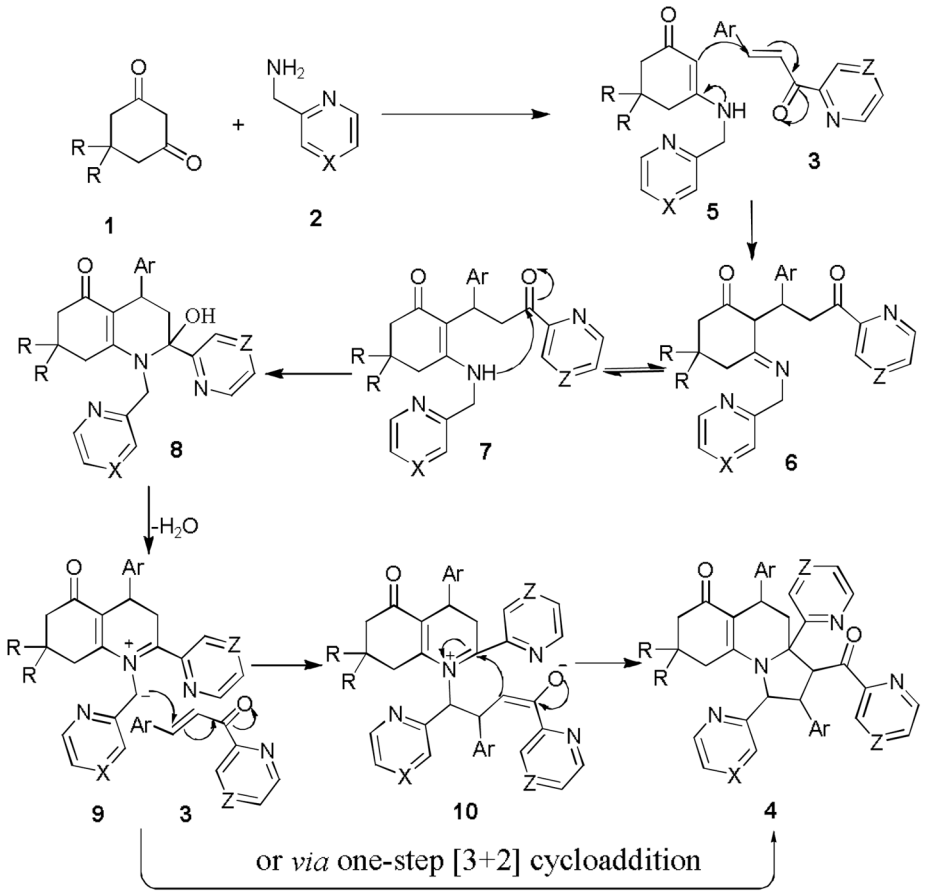


Figure 2.
Crystal structure of **4a**. All H atoms except H7, H10, H11, H12 were omitted for clarity.[17]



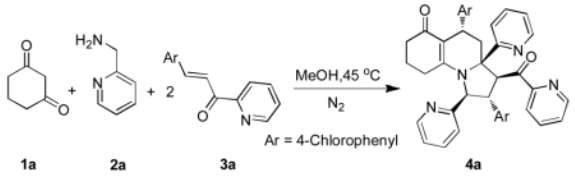
Scheme 1.
Retrosynthetic analysis of **4**



Scheme 2.
Proposed mechanism for the synthesis of **4**.

Table 1

Optimization of conditions on the model reaction



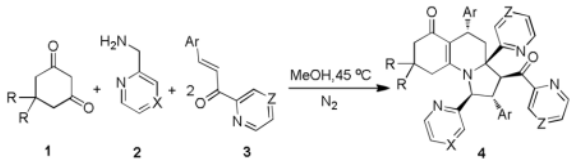
1a 2a 3a 4a

Entry	Solvent	T /°C	Time / h	Yield / %[a]
1	DMF	25	18	40
2	EtOH	25	20	38
3	MeOH	25	20	55
4	CH_3CN	25	20	25
5	$CHCl_3$	25	20	25
6	CH_2Cl_2	25	20	26
7	THF	25	18	NR
8	MeOH	35	16	60
9	MeOH	40	16	70
10	MeOH	45	14	81
11	MeOH	55	14	62
12	MeOH	65	10	40

[a]Reported yields were isolated yields

Table 2

Synthesis of compounds **4**



1 2 3 4

Entry	4	Ar	R	X/Z	Yield / %[a]
1	**4a**	4-ClC_6H_4	H	CH/CH	81
2	**4b**	4-BrC_6H_4	H	CH/CH	79
3	**4c**	4-FC_6H_4	H	CH/CH	76
4	**4d**	4-$CH_3C_6H_4$	H	CH/CH	78
5	**4e**	4-$CH_3OC_6H_4$	H	CH/CH	75
6	**4f**	2,4-$Cl_2C_6H_3$	H	CH/CH	80
7	**4g**	3,4-$Cl_2C_6H_3$	H	CH/CH	78
8	**4h**	2,3-$Cl_2C_6H_3$	H	CH/N	70
9	**4i**	4-ClC_6H_4	CH_3	CH/CH	80
10	**4j**	4-BrC_6H_4	CH_3	CH/CH	78
11	**4k**	4-FC_6H_4	CH_3	CH/CH	74
12	**4l**	4-$CH_3C_6H_4$	CH_3	CH/CH	78
13	**4m**	2,4-$Cl_2C_6H_3$	CH_3	CH/CH	76
14	**4n**	3,4-$Cl_2C_6H_3$	CH_3	CH/CH	76
15	**4o**	4-ClC_6H_4	CH_3	CH/N	72
16	**4p**	4-BrC_6H_4	CH_3	CH/N	70
17	**4q**	4-BrC_6H_4	H	N/CH	72
18	**4r**	4-ClC_6H_4	H	N/N	70

[a]Reported yields were isolated yields.