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Four-component strategy for selective synthesis of azepino[5,4,3-*cd*]indoles and pyrazolo[3,4-*b*]pyridines†

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A novel four-component strategy for the selective synthesis of fused azepino[5,4,3-*cd*]indoles and pyrazolo [3,4-*b*]pyridines has been established. The bond-forming efficiency, accessibility of starting materials and substrate scope provide invaluable access to tetra-, and bis-heterocyclic scaffolds.

Functionally diverse azepino[5,4,3-*cd*]indole skeletons commonly exist in natural and unnatural products;[1] they are found in indole alkaloids, such as Aurantioclavine (I),[2] Rucaparib (II),[3] Hyrtiazepine (III)[4] and Hyrtimomines F[5] (Fig. 1), which exhibit biological activity as 5-HT1 agonists[6] and PARP inhibitors.[3] Aurantioclavines have served as key building blocks during the biosynthesis of complex polycyclic alkaloids of the communesin family.[7,8] The construction of these compounds and their structural analogues has attracted much attention in the synthetic community.[1–5] To the best of our knowledge, an efficient construction of the tetracyclic azepino[5,4,3-*cd*]indole skeleton through sequential cyclizations *via* a multicomponent domino reaction (MDR) has not yet been documented.

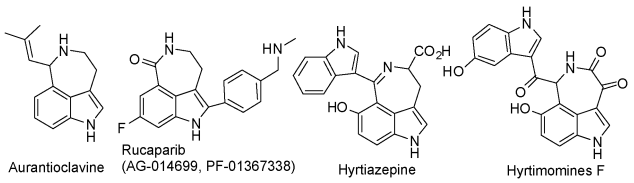

Fig. 1 Several representative natural products.

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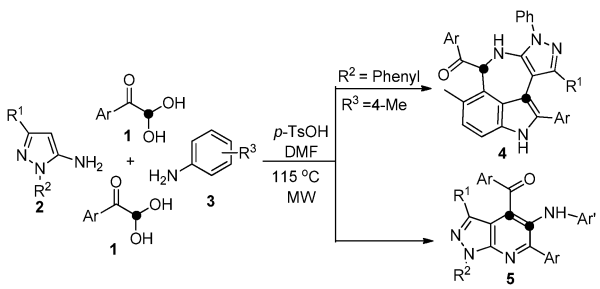
† Electronic supplementary information (ESI) available. CCDC 977865 (**4a**) and 977866 (**5g**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00740a

In recent years, multicomponent domino reactions have played an important role in synthetic methodologies, and can implement cascade reactions in the total synthesis of natural products.[9] Our groups[10] and several others[11,12] have developed a series of MDRs for the synthesis of unique heterocycles and natural mimetic compounds of chemical and pharmaceutical importance. To continue our efforts on this project, we now discovered a novel ABC_2 type domino reaction of arylglyoxal monohydrate **1** with electron-rich pyrazol-5-amines **2** and aromatic amines **3**, leading to the formation of pyrazolo[4′,3′:6,7]azepino[5,4,3-*cd*]indoles and pyrazolo[3,4-*b*]-pyridines under microwave (MW) heating (Scheme 1). The former reaction occurred through (3 + 2)/(3 + 2 + 1 + 1) bis-cyclizations to give tetracyclic pyrazolo[4′,3′:6,7]azepino[5,4,3-*cd*]indoles in a straightforward manner, which are normally difficult to obtain in a single operation. Both the 2- and 3-positions of *p*-toluidine **3a** simultaneously served as nucleophilic centers to enable the following domino cyclizations that are rarely encountered in organic reactions. Interestingly, the direct C–C formation between two electrophilic centers of arylglyoxal monohydrates can be smoothly performed through four-component [3 + 2 + 1] heteroannulation without the use of any metal catalysts.

To optimize the reaction conditions, we began by examining the reaction of 2,2-dihydroxy-1-phenylethanone (**1a**), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2a**) and *p*-toluidine (**3a**) in DMF at 100 °C (Table S1, entry 1, see ESI.†). When this reaction was performed in the presence of *p*-TsOH for 15 min, a 38% yield of

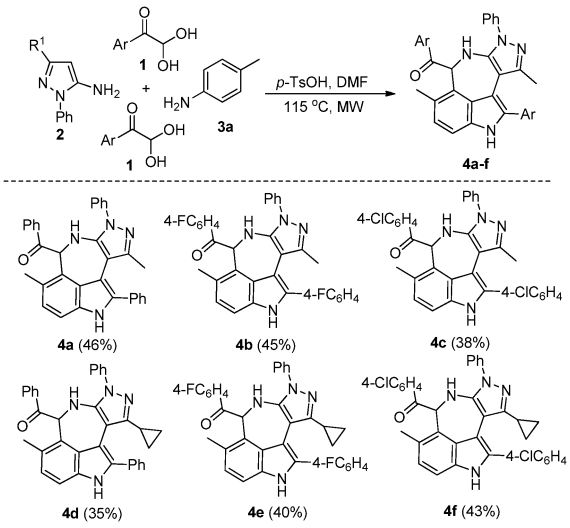


Scheme 1 Multicomponent synthesis of compounds **4** and **5**.

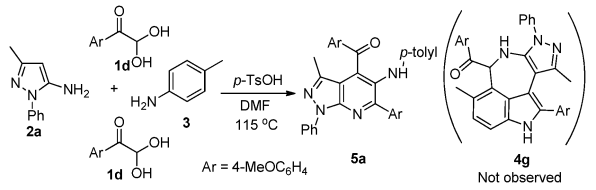
azepino[5,4,3-*cd*]indole (**4a**) was obtained. The structure of **4a** has been determined by spectroscopic and X-ray crystallographic analysis (see ESI†). We next screened different Brønsted acids and Lewis acids as catalysts (entries 1–5). As shown in Table S1 (see ESI†), the reaction did not proceed in the presence of Brønsted acids, such as H_2SO_4 and CF_3COOH. Lewis acids, such as $FeCl_3$ and $ZnCl_2$, also failed to improve the yield (entries 4 and 5). A variety of both polar and nonpolar solvents were also examined, and DMF was the most suitable solvent for this reaction (entry 1). To verify the role of *p*-TsOH either as a catalyst or a promoter, we conducted two sets of reactions by loading *p*-TsOH at 1.5 equiv. (entry 10) and 30 mol% (entry 11), respectively. We found that both conditions failed to give yields greater than 30%. The reaction was then performed in DMF at different temperatures in a sealed vessel under microwave irradiation for 15 min. The yield of product **4a** increased to 46% when the temperature was increased to 115 °C (entry 13).

With the above conditions in hand, the generality and scope of the reaction were investigated for a range of arylglyoxal monohydrates **1** and electron-rich pyrazol-5-amines **2** (Scheme 2). A variety of functional groups of substituted arylglyoxal monohydrates were found to be well tolerated under the above conditions to give azepino[5,4,3-*cd*]indole products (**4a–f**); even cyclopropyl substitution at the 3-position of pyrazol-5-amines **2** can be employed for this reaction. Surprisingly, when the strong electron-donating group MeO– was placed at the C4 position of the phenyl ring of **1**, the reaction did not give the expected azepino[5,4,3-*cd*]indoles; instead, it led to formation of multifunctionalized pyrazolo[3,4-*b*]pyridines **5a** (Scheme 3). When electronically poor 4-chloroaniline (**3b**) was utilized to replace *p*-toluidine (**3a**) to react with **1** under this system, pyrazolo[3,4-*b*]pyridine could still be formed. This interesting observation of the 1-phenyl-pyrazol-5-amine-based domino reaction indicated that the electronic effect of arylglyoxals and aromatic amines may control the reaction pathways chemoselectively.

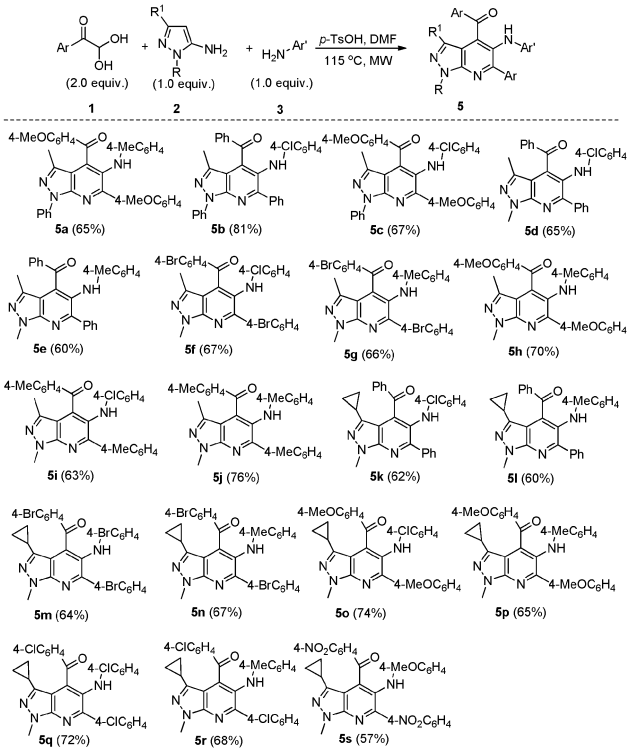
Due to the importance of pyrazolo[3,4-*b*]pyridines in organic synthesis and drug design in the pharmaceutical sciences,[13] we then focused on the feasibility of the latter reaction (Scheme 4). We found that a variety of functional groups in arylglyoxals **1** can



Scheme 2 Domino formation of azepino[5,4,3-*cd*]indoles **4a–4f**.



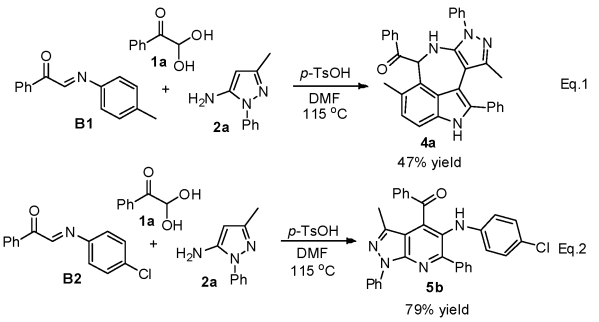
Scheme 3 Domino formation of pyrazolo[3,4-*b*]pyridines **5a**.



Scheme 4 Domino synthesis of pyrazolo[3,4-*b*]pyridines **5**.

enable the reaction to occur smoothly. Reactions involving methyl-, or chloro-substituted phenylglyoxal monohydrate **1** with **2** and **3** all worked efficiently to give the bicyclic pyrazolo[3,4-*b*]pyridines in moderate to good yields under microwave irradiation as shown in Scheme 4. This reaction also tolerated the substrate of arylglyoxal **1** attached by strong electron-withdrawing nitro group and can smoothly proceed to give pyrazolo[3,4-*b*]pyridines **5s** in 57% yield. The substituents on the N1 or C3 positions of pyrazole and on aromatic amines **3** were well tolerated to afford pyrazolo[3,4-*b*]-pyridine **5** within short times in good yields. However, *ortho*-substituted anilines, such as 2-nitroaniline (**3f**) or *o*-toluidine (**3g**), failed to give the desired pyrazolo[3,4-*b*]pyridines **5.** The structures of the resulting products **5** have been unambiguously confirmed by IR, NMR and HR-MS spectral analysis. In addition, one of them (**5g**) has been determined by X-ray diffractional analysis (see ESI†).

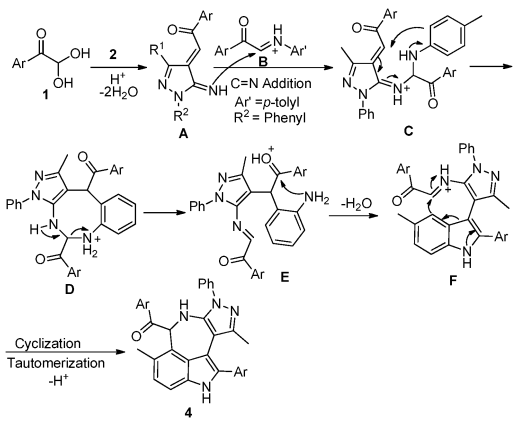
To understand the mechanism of reaction, 1-phenyl-2-(*p*-tolylimino)ethanone **B1** and 2-(4-chlorophenylimino)-1-phenylethanone **B2** were subjected to reaction with **1a** and **2a** under the standard conditions. The corresponding azepino[5,4,3-*cd*]indoles **4a** and pyrazolo[3,4-*b*]pyridines **5b** were generated in 47% and 79% yields, respectively (Scheme 5). These observations prove that the



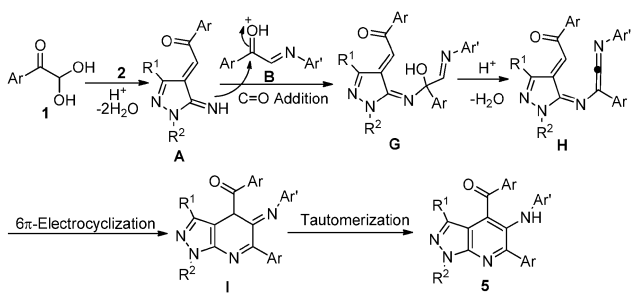
Scheme 5 Control experiments for mechanistic hypothesis.

electronic effect of aromatic amines plays a key role in controlling the reaction pathways.

On the basis of this experiment, mechanisms for these two domino reactions are proposed as shown in Schemes 6 and 7. In the former, arylglyoxal monohydrates **1** were protonated by *p*-TsOH and dehydration occurred, which was followed by an addition reaction with electron-rich pyrazol-5-amines **2** leading to intermediate **A.** The intermolecular C=N addition of intermediate **B** and intramolecular cyclization resulted in macrocyclic intermediate **D.** Ring-opening of **D** promoted by *p*-TsOH afforded imine intermediate **E** which underwent consecutive intramolecular cyclizations and tautomerization to give azepino[5,4,3-*cd*]indoles **4** (Scheme 6). Similar to the former, the latter reaction occurred to give the intermediate **A** at an early stage. Due to the electronic effect of imines **B**, the carbonyl addition reaction of intermediate **A** with imines **B** proceeded to generate enone intermediate **G,** which was then transformed into active allene intermediate **H.** The following intramolecular 6π-electrocyclization and tautomerism result in the formation of pyrazolo[3,4-*b*]pyridines **5** as the final product (Scheme 7).



Scheme 6 Proposed mechanism for forming azepinoindoles **4**.



Scheme 7 Proposed mechanism for forming pyrazolopyridines **5**.

In conclusion, we have established novel chemoselective four-component domino reactions for rapid access to azepino-[5,4,3-*cd*]indoles **4** and pyrazolo[3,4-*b*]pyridines **5**. The reactions are easy to perform under concise conditions under microwave irradiation. The mechanisms for these two new reactions were proposed and partially confirmed by control experiments. The reactions show good substrate scope, particularly the simultaneous formations of two C–N and two C–C bonds through a key 6π-electrocyclization in the latter reaction. Further study of these two new reactions and their applications will be conducted in our laboratories in due course.

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