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Diastereoselective Multicomponent Reaction in Water: Synthesis of 2-Azapyrrolizidine Alkaloid Analogues

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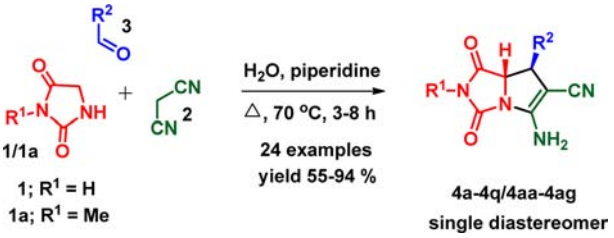
ABSTRACT



Synthesis of the 2-*aza* analogues of the pyrrolizidine alkaloid motif with two contiguous stereocenters has been achieved with high regio-, chemo-, and diastereoselectivity by an innovative multicomponent reaction in water. This elegant tactic has integrated the principles of privileged substructure-based Diversity Oriented Synthesis (pDOS) and Biology Oriented Synthesis (BIOS) to access a biologically relevant scaffold.

Highly functionalized small organic molecules[1] mimicking privileged natural products are promising candidates as probes in chemical biology to investigate biological phenomena and for drug development. Diversity Oriented Synthesis (DOS)[2] is a dazzling area of research in synthetic organic chemistry to address the demand posed by chemical biology for a huge number of small molecules. Biology Oriented Synthesis (BIOS)[3] and privileged-substructure-based Diversity Oriented Synthesis (pDOS)[4] are two emerging complementary DOS approaches with the focus on diversifying natural product scaffolds which have been prevalidated for biological activity by evolution or biologically relevant non-natural scaffolds.

Integrating the strategies of DOS[5] into the realm of Multi-Component Reactions (MCRs) in water can be visualized as an elegant synthetic approach to achieve diverse molecular skeletons. We have created skeletal diversity and complexity by integrating the Single Reactant Replacement[6] (SRR) strategy with our MCR in water.[7] Hydantoin can be considered as the SRR variant of pyrrozol-4-one. Hydantoins and their bi- and tricyclic derivatives are reported[8] to be an important class of biologically active molecules with broad medicinal[9] and agrochemical[10] applications.

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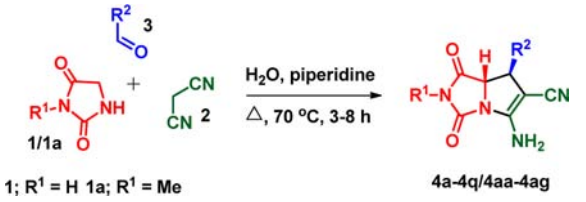
Scheme 1. Reaction between **1**/**1a**, **2**, and **3**



As a pDOS–MCR approach (Scheme 1), a three-component reaction between hydantoin **1**, malononitrile **2**, and benzaldehyde **3** was performed in water to obtain a biologically relevant scaffold. The reaction resulted in (*trans*-7,7a)-5-amino-7-phenyl-1,3-dioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carbonitrile **4a** which was confirmed unambiguously by single crystal X-ray crystallography (Figure 1). This product is the 2-*aza* analogue of the biologically important pyrrolizidine alkaloid motif.

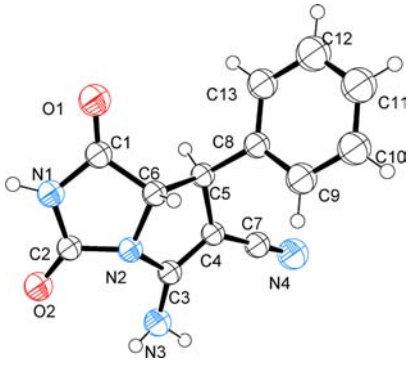


Figure 1. ORTEP diagram of compound **4a**.

Pyrrolizidine alkaloids are widespread in nature and possess noteworthy biological and pharmacological responses.[11] Plants containing pyrrolizidine alkaloids are being used as important herbs in traditional chinese medicine which is popular in China and widely accepted the world over[12] (Figure 2). Substituting one or more ring carbons with heteroatoms is known to significantly modify biological properties.[13]

Table 1

entry	product	R^1	R^2	time (h)	yield (%)[a]
1	**4a**	H	-Ph	3.0	94
2	**4b**	H	-2′-F-Ph	5.0	78
3	**4c**	H	-4′-F-Ph	4.0	89
4	**4d**	H	-2′-Cl-Ph	7.0	79
5	**4e**	H	-4′-Cl-Ph	4.0	87
6	**4f**	H	-2′-Br-Ph	6.0	70
7	**4g**	H	-3′-Br-Ph	3.5	91
8	**4h**	H	-4′-Br-Ph	4.0	88
9	**4i**	H	-4′-Me-Ph	4.0	90
10	**4j**	H	-3′-MeO-Ph	4.0	90
11	**4k**	H	-4′-MeO-Ph	4.0	85
12	**4l**	H	-3′-O_2N-Ph	3.0	89
13	**4m**	H	-3′-MeO, 5′-MeO-Ph	8.0	55
14	**4n**	H	-2′-Cl, 6′-F-Ph	8.0	56
15	**4o**	H	-2′-Cl, 6′-Cl-Ph	8.0	20
16	**4p**	H	-2′-furyl	3.0	90
17	**4q**	H	-2′-thienyl	3.0	91
18	**4aa**	Me	-4′-Me-Ph	4.0	90
19	**4ab**	Me	-4′-HO-Ph	4.0	91
20	**4ac**	Me	-4′-MeO-Ph	3.5	90
21	**4ad**	Me	-4′-Cl-Ph	5.0	87
22	**4ae**	Me	-4′-Br-Ph	4.0	80
23	**4af**	Me	-2′-furyl	4.0	92
24	**4ag**	Me	-2′-thienyl	4.0	91

[a] Isolated yield.

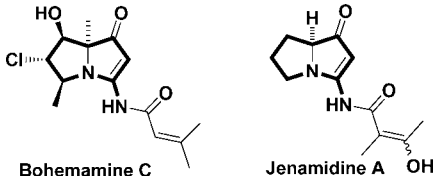


Figure 2. Naturally occurring bioactive pyrrolizidine scaffolds.

The MCR reaction depicted in Scheme 1 leads to the generation of two chiral centers in which the rings are *cis*-fused and vicinal hydrogens are *trans*. Small organic motifs with contiguous multiple stereogenic centers exist in plenty of natural and non-natural products that exhibit pronounced biological activity.[14] This three-component reaction has occurred with high regio-, chemo-, and diastereoselectivity. Use of **1** in this MCR is like tossing a coin. The reaction might follow either a 5-*exo*-*dig* or 6-*exo*-*dig*

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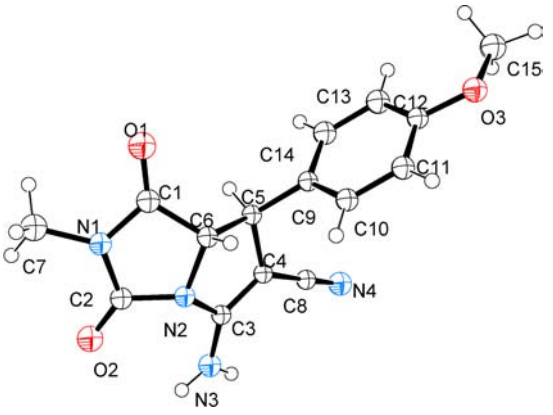


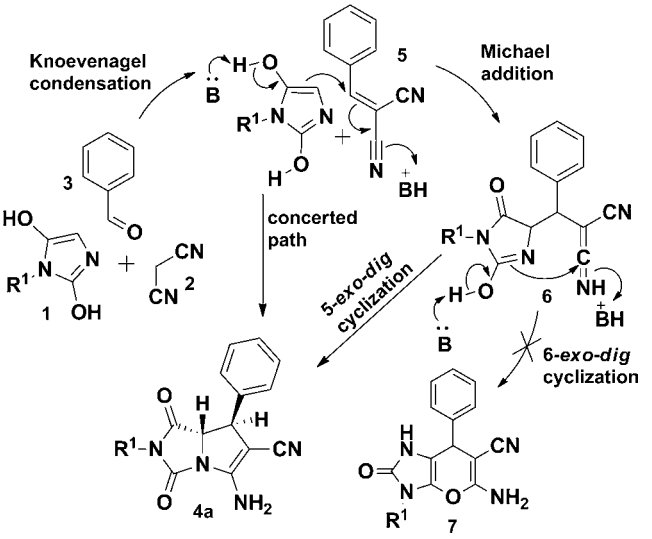
Figure 3. ORTEP diagram of compound **4ac**.

cyclization pathway yielding pyrrolo[1,2-*c*]imidazole or pyrano[2,3-*d*]imidazole derivatives, respectively (Scheme 2). Formation of **5** (but no other intermediates) was noticed on TLC during the course of the reaction. The high selectivity observed in the reaction indicates either a concerted path reaction between **1** and **5** or a two-step reaction through intermediate **6**. The nucleophilic carbon of **1** reacts in an intermolecular Michael addition with **5**, and of the other two heteroatom nucleophiles, nitrogen reacts with nitrile in 5-*exo-dig* cyclization to afford the azapyrrolizidine scaffold **4a**. A two-component reaction between **1** and **5** also afforded **4a** only. If the reaction is suggested to proceed *via* a stepwise pathway, formation of the Michael adduct is probably the rate-limiting step, with the 5-*exo-dig* cyclization being very fast.

The reaction showed similar selectivity when different aldehydes were used as oxo building blocks (Table 1). The use of 3-methylhydantion **1a** in this MCR occurred with similar selectivity, affording the single diastereomer of 2-methylazapyrrolizidines, for example **4ac** (Figure 3).

Overall, we have invented a highly regio-, chemo-, and diastereoselective multicomponent reaction protocol conforming to the guiding principles of pDOS and BIOS.

Scheme 2. Plausible Mechanism



This synthesis accesses privileged natural product analogues with contiguous stereocenters by integrating the SRR strategy with our MCR in water.

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Supporting Information Available. General experimental procedure and characterization data for all products, including copies of ^{1}H and ^{13}C NMR spectra. X-ray structural information (CIF) of **4a** (CCDC 884626) and **4ac** (CCDC 894865) from The Cambridge Crystallographic Data Centre can be accessed via www.ccdc.cam.ac.uk/data_request/cif. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.