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New pathway to pyrrolidinones and pyrrolizidinones using aryl aldehydes, 3-phenyl-5-isoxazolone and secondary amino acids

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ABSTRACT

A novel and efficient approach to pyrrolidinones and pyrrolizidinones via a one-pot multicomponent reaction of aryl aldehydes, 3-phenyl-5-isoxazolone, sarcosine and L-proline, respectively in methanol under reflux condition is reported.

MCRs which employ three or more reactants to furnish products containing structure or substructure of all starting materials in one-pot and one set of fixed reaction conditions are such examples with powerful productivity. They also form an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality, for example, ligands for catalysis or bioactive compounds.[1] Therefore, the design of efficient MCRs to achieve our desired compounds is a challenge in organic chemistry. Recently, our research group was involved in various multicomponent reactions that can provide easy access to important polyfunctionalized ring structures of chemical and pharmaceutical interest.[2]

The vast majority of biologically active organic compounds are N-heterocyclic in nature, a fact that has been heavily exploited by the pharmaceutical industry.[3] The pyrrolidin-2-one structure is one of the most popular N-heterocycles incorporated into the structure of many complex natural products and pharmaceutical compounds. It is known that many pyrrolidinone-containing compounds exhibit a wide spectrum of biological activities on various drug targets, such as aspartic protease, β-amyloid cleaving enzyme (BACE), progesterone receptor (PR), human melanocortin-4 receptor, factor Xa and HIV-1 integrase.[4]

The development of facile synthesis of pyrrolidinones has been the focus of much research for several decades and continues to be an active and rewarding research area. However, most of the existing methods suffer from tedious synthetic routes, long reaction time, drastic reaction conditions, as well as narrow substrate scope.[5] We have recently developed a new pathway for spiropyrrolidinone oxindoles by a multicomponent reaction of isatin, sarcosine, 3-phenyl-5-isoxazolone via cleavage of the 3-phenyl-5-isoxazolone ring by sarcosine.[2e] During our continuous efforts on the research towards novel multicomponent reactions,[2] herein, we wish to utilize this unusual mechanistic pathway of spiropyrrolidinone oxindoles as a novel route to achieve functionalized pyrrolidinones[2e] by employing aromatic and heteroaromatic aldehydes. It is also noteworthy to mention that the exploitation of a multicomponent strategy combined with cleavage of the lactone ring for the construction of a pyrrolidinone skeleton has not been achieved so far. Here, the highly conjugated 4-arylidene-3-phenyl-5-isoxazolone formed in situ by Knoevenagel condensation between aryl aldehyde and 3-phenyl-5-isoxazolone plays a major role in the synthesis of pyrrolidinones.

In a prototype experiment, a three-component reaction of benzaldehyde **1a**, 3-phenyl-5-isoxazolone **2** and sarcosine **4** in methanol under reflux condition was investigated (Scheme 1). Initially, the reaction mixture was colourless. After 10 min, the solution turns into a yellow colour which indicates the formation of the intermediate 4-arylidene-3-phenyl-5-isoxazolone **3a** and the reflux was continued until the completion of the reaction as evidenced by TLC. The reaction mixture turns into a white colour which infers the completion of the reaction. The reaction mixture was cooled to room temperature in which the white solid precipitated from the reaction was filtered and recrystallized from methanol to furnish pyrrolidinone **5a** as a single product.

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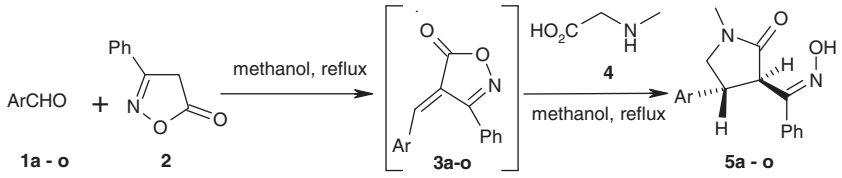
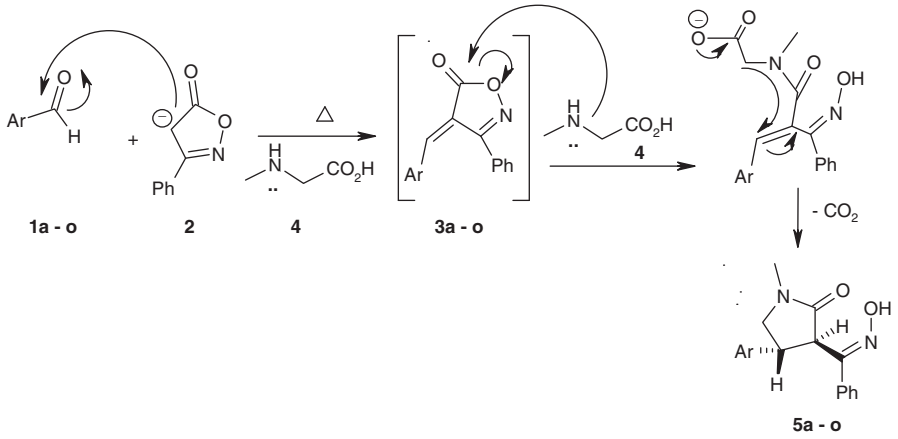


Scheme 1. Synthesis of 4-arylpyrrolidinones **5a**–**o**.



Scheme 2. Plausible mechanism for 4-arylpyrrolidinones **5a**–**o**.

On the basis of the above results, a tentative mechanistic interpretation to explain the formation of the product **5a** is proposed (Scheme 2). The aromatic aldehyde **1a** easily undergoes Knoevenagel condensation with 3-phenyl-5-isoxazolone **2** to provide 4-arylidene-3-phenyl-5-isoxazolone **3a** as intermediate[6] which was isolated and confirmed by NMR spectroscopy.[7] In **3a**, the lactone part which has two bulky moieties adjacent to the isoxazolone ring may be cleaved[8] by sarcosine **4**[9] and the decarboxylation and subsequent Michael addition could facilitate cyclization to furnish 4-arylpyrrolidinone **5a** in good yield (78%).

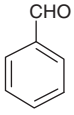
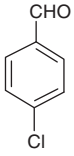
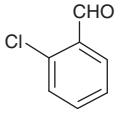
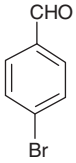
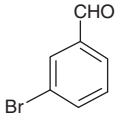
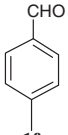
In order to explore the applicability of the reaction over a wide range of compounds, various derivatives of aromatic and heteroaromatic aldehydes **1a**–**o**, 3-phenyl-5-isoxazolone **2** and sarcosine **4** were subjected to same reaction conditions to achieve a library of 4-aryl pyrrolidinones **5a**–**o** in good yields. The results are summarized in Table 1.

The structures of the compounds **5a**–**o** were characterized by spectroscopic studies and elemental analysis. The IR spectrum of the compound **5j** showed peaks at 3218 and 1714 cm^{-1} for –OH of the oxime group and the amide carbonyl group, respectively. The ^1H NMR spectrum of compound **5j** exhibited two characteristic singlets at δ 2.85 and 11.66 ppm for –NCH_3 protons and –O*H* proton of the oxime group (D_2O exchangeable), respectively. The amide carbonyl carbon atom of the pyrrolidinone ring displayed a peak at δ 171.5 ppm in ^{13}C NMR spectrum. A distinguishing peak was observed at *m*/*z* 345.0 in the mass spectrum for (M^++1) ion.[10] The relative stereochemistry of the products **5a**–**o** was established through single-crystal X-ray analysis of the compound **5k** (Fig. 1).[11]

Delighted by these results, we then focused our attention to prepare 1-aryl pyrrolizidinone derivatives **7a**–**o** by replacing sarcosine **2** by L-proline **6** under identical reaction conditions (Scheme 3). The reaction proceeded smoothly with a series of aromatic and heteroaromatic aldehydes **1a**–**o** to provide a collection of 1-aryl pyrrolizidinone derivatives **7a**–**o**. The results are summarized in Table 2.

In IR spectrum of the compound **7a**, the absorptions at frequencies 3424 and 1733 cm^{-1} correspond to –OH of the oxime group and the amide carbonyl group, respectively. In the ^1H NMR spec-

Table 1
Synthesis of 4-aryl pyrrolidinone derivatives **5a**–**o**

Entry	ArCHO (**1a**–**o**)	Product[a] (**5**)	Time (min)	Yield[b] (%)
1	 **1a**	**5a**	40	78
2	 **1b**	**5b**	30	80
3	 **1c**	**5c**	30	81
4	 **1d**	**5d**	30	78
5	 **1e**	**5e**	30	77
6	 **1f**	**5f**	40	78