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Synthesis of pyranocoumarin fused spirooxindoles via Knoevenagel/Michael/cyclization sequence: a regioselective organocatalyzed multicomponent reaction

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ABSTRACT

Synthesis of pyranocoumarin fused spirooxindole derivatives from the three-component reaction of isatin, malononitrile, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one using piperidine as organocatalyst has been reported. Replacing malononitrile by ethyl cyanoacetate and using methanol as solvent, the same protocol provides the corresponding transesterified products. The salient features of this protocol are metal-free reaction conditions, easy isolation of products, applicability to a wide range of isatins with good yields and formation of only one regioisomer among the three possible products.

The oxindole core containing a spirocyclic stereocenter at the C-3 position represents a privileged heterocyclic motif found in alkaloids as well as synthetic pharmaceuticals.[1] Spirooxindoles attached with other heterocycles have drawn significant attention to organic as well as medicinal chemists due to their wide range of biological activities such as anti-microbial,[2] anti-mycobacterial,[3] antifungal,[4] anti-tumor,[5] anti-tubercular,[6] anti-malarial,[7] and anti-oxidant activities.[8] Similar to spirooxindoles, pyranocoumarins are also found in various natural products, for example, Luvangetin,[9] Alloxanthoxyletin, 5-Methoxyseselin, and (+)-Calanolide A[10] (Fig. 1). Pyranocoumarins also exhibit diverse pharmacological properties such as anti-inflammatory,[11] anti-HIV-1,[12] anti-hepatitis B virus,[13] anti-cancer,[14] antinociceptive,[15] etc. Considering the wide spectrum of biological activities of these moieties, development of new methods for the synthesis of spirooxindoles and pyranocoumarins has drawn significant attention in recent times.[16] Multicomponent reactions (MCRs) have emerged as popular and useful tools for the easy and rapid access of diverse heterocycles. Considering the pot-, atom- and step-economy (PASE)[17] of MCRs, it is considered as a green approach in organic synthesis. Although various methods are known in the literature for the synthesis of either spirooxindoles or pyranocoumarins, methods for the synthesis of molecules having both the spirooxindole and pyranocoumarin moiety are still limited.[18] Karami et al. reported a three-component reaction of aldehydes, malononitrile, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one for the synthesis of pyranocoumarins using K_2CO_3[19] (Scheme 1). Lee and co-workers have recently reported a multicomponent reaction of isatin, malononitrile, and substituted resorcinols for the synthesis of spirooxindole pyrans using $Ca(OH)_2$.[20]

Organo-catalyzed multicomponent reactions have drawn remarkable attention as a powerful tool in organic synthesis due to its virtues over metal catalyzed reactions.[21] Recently we have developed an imidazole catalyzed multicomponent reaction for the synthesis of various carbo and heterocycles.[22] Similarly we have also reported a L-proline catalyzed multicomponent reaction for the facile access to 2*H*-benzo[*g*]pyrazolo[3,4-*b*]-quinoline-5,10(4*H*,11*H*)-dione derivatives.[23]

In continuation of our efforts toward the synthesis of spirooxindole derivatives[24] and other functionalized heterocycles[25] using MCRs, we envisioned that pyranocoumarin fused spirooxindoles could be synthesized from the three-component reaction of isatins, malononitrile, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one. Interestingly, this combination may provide a total of three regioisomers as shown in Scheme 2. To the best of our knowledge there is no method reported in the literature for the one-pot synthesis of pyranocoumarin fused spirooxindoles from the combination of isatin, malononitrile, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one.

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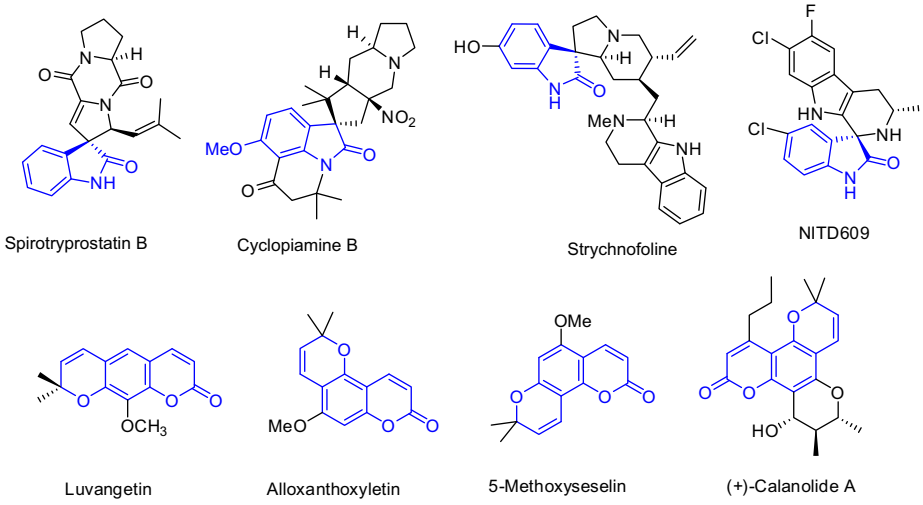
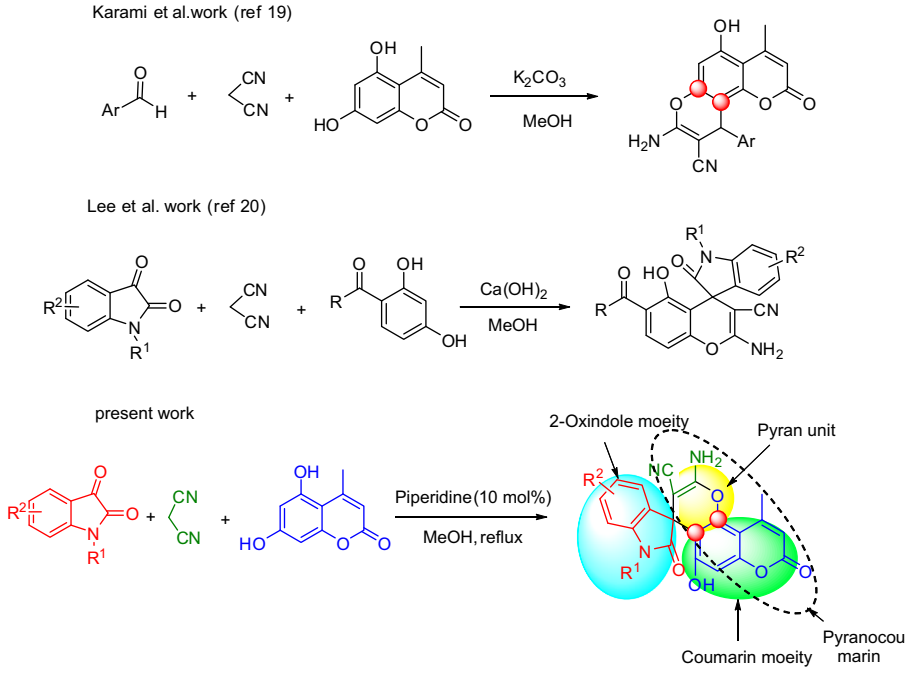
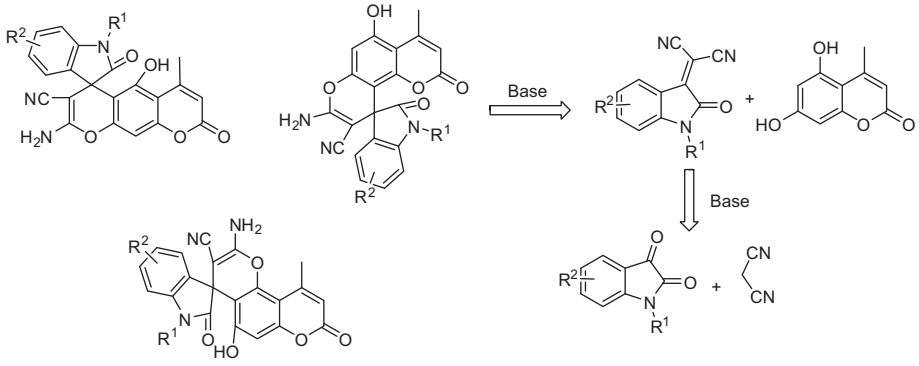


Figure 1. A few representative biologically active spirooxindoles and pyranocoumarins.



Scheme 1. Methods for the synthesis of pyranocoumarin, spirooxindole pyran, and pyranocoumarin fused spirooxindole.



Scheme 2. Proposed reaction strategy for the synthesis of pyranocoumarin fused spirooxindoles.