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A one-pot, three-component and solvent-free synthesis of 2,3-disubstituted isoindolin-1-ones

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ABSTRACT

A one-pot and three-component reaction is described for the preparation of 2,3-disubstituted isoindolin-1-ones. Heating a mixture of 2-formylbenzoic acid, a cyclic six-membered β-dicarbonyl compound, and a benzylamine under solvent-free conditions afforded the title compounds in good to excellent yields. The generality of the reaction was shown by the use of various β-dicarbonyl compounds including 1,3-cyclohexadione, dimedone, Meldrum's acid, *N*,*N*-dimethylbarbituric acid, and some benzylamine derivatives.

Multi-component reactions (MCRs), have many advantages for organic chemistry, enabling the synthesis of complex molecules in a single synthetic operation which excludes the need to isolate intermediates.[1]

Recently, isoindolin-1-ones have attracted a great deal of attention because they are common structural motifs in naturally occurring compounds such as magallanesine,[2] lennoxamine,[3] and stachybotrin C,[4] and also in important pharmaceutical compounds such as zopiclone and pagoclone (Fig. 1).[5,6] Compounds containing the isoindolin-1-one scaffold have been shown to possess a broad range of biological activities (antimicrobial,[7] anti-viral,[8] and anti HIV[9]) and have been used in the synthesis of sedative and hypnotic agents.[10] Furthermore, isoindolin-1-ones have been used in the treatment of diabetes,[11] obesity and hyperlipidemia,[12] cancer, (Fig. 1)[13] and CNS diseases.[14] Several isoindoline derivatives have been proposed as dipeptidyl peptidase DPP8/9 inhibitors in immunohistochemical studies.[15] Isoindolin-1-ones have also been used in the Diels–Alder reaction and as building blocks in asymmetric synthesis.[16,17]

Several synthetic routes toward isoindoles have been reported in the past three decades.[18,19] However, few syntheses of these heterocycles using 2-formylbenzoic acid can be found in the literature 20–24.

In accordance with the increasing need to develop new and simple methods to prepare these biologically active heterocyclic compounds, and in a continuation of our previous studies on the development of efficient methods for the synthesis of biologically active heterocyclic compounds,[25] we herein report a novel synthesis of 2,3-disubstituted isoindolin-1-ones via a one-pot, three-component reaction between 2-formylbenzoic acid, a CH-acid, and a benzylamine.

The reaction of 2-formylbenzoic acid **1**, dimedone **2a**, and benzylamine **3a** was selected as a model reaction (Scheme 1), for which the reaction conditions would be optimized. We investigated the effect of solvent, various temperatures, and reaction time on the yield of isoindolin-1-one **4a**.

At first, the reaction was carried out in different solvents and then under solvent-free conditions. In the case of EtOH and DMF, yields of up to 80% were achieved when the reaction mixture was heated at reflux for 18 and 8 h, respectively. Under solvent-free conditions the yield continued to increase with increasing temperature up to 150 °C, after which the yield started to decrease with increasing temperature. Under the optimum conditions of 150 °C and reaction times of 1 h and solvent-free, isoindolin-1-one **4a** was isolated in a maximum yield of 98%.

With the optimized conditions in hand, we decided to probe the generality of this three-component reaction. We attempted to extend the reaction by use of 2-formylbenzoic acid **1**, CH-acids **2a–d**, and benzylamines **3a–f** (Scheme 1). The reactions were

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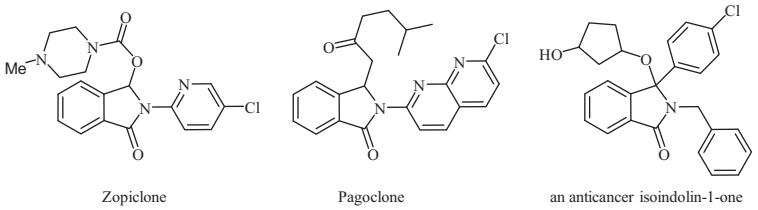
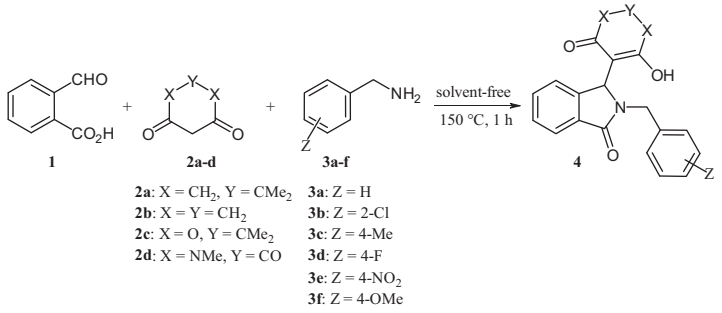
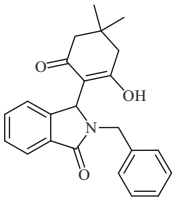
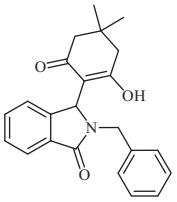
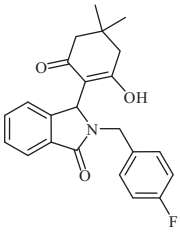
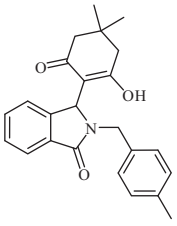
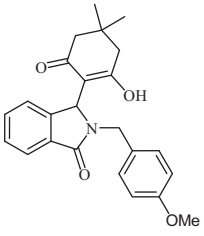
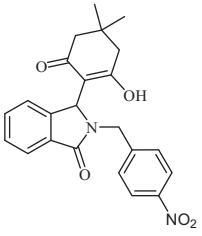
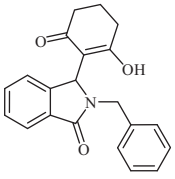
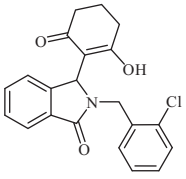


Figure 1. Examples of pharmacologically important compounds having the isoindolin-1-one core structure.



Scheme 1. Synthesis of 2,3-disubstituted isoindolin-1-ones **4**.

Table 1
Synthesis of 2,3-disubstituted isoindolin-1-ones **4a–p**[a]

Product	Structure	Yield[b] (%)	Product	Structure	Yield[b] (%)
4a		98	**4b**		87
4c		83	**4d**		90
4e		94	**4f**		95
4g		88	**4h**		90