



Catalyst-free Mannich-type reactions in water: Expedient synthesis of naphthol-substituted isoindolinones

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ABSTRACT

An environmentally benign while efficient approach to the synthesis of isoindolinones by three-component reactions of 2-formylbenzoic acids, primary amines, 2-naphthols via a Mannich-cyclization reaction sequence in water under catalyst-free conditions is described here. This protocol features wide substrate scope, ease of operation, the use of naturally abundant while environmentally benign water as a reaction medium and the formation of only water as the sole byproduct in the transformation.

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Introduction

Isoindolinone skeleton is widely found in an array of natural products¹ and biologically active compounds,² as exemplified in Fig. 1.³ Hence, the synthesis of isoindolinone derivatives has attracted much attention during the past decades. Traditional approaches to the synthesis of substituted isoindolinone derivatives were mainly restricted to the use of Wittig reaction,⁴ Grignard reagents,⁵ Heck cyclization,⁶ reduction processes,⁷ Diels–Alder approach,⁸ reactions of acyliminium ion,⁹ and various enantioselective methods.¹⁰ (See Scheme 1).

Owing to the inherent merits such as reasonably shortened reaction steps, circumvention of intermediates separation and purification, one-step multiple chemical bonds formation and also diverse while usually complex molecules construction, a multi-component reaction strategy has recently attracted increasing attention from both the organic synthesis and pharmaceutical science communities.¹¹ During the past decades, chemists have made great endeavor on developing the efficient multi-component reactions to construct complex molecules. In this regard, step-economic one-pot three-component reactions of 2-formylbenzoic acids, primary amines with a wide variety of nucleophiles have been applied to prepare valuable chemicals in high efficiency, and thus in principle to provide a much more straightforward approach towards the synthesis of isoindolinone derivatives.¹² It

should be noted that, during the preparation of our manuscript, a transition-metal-catalyzed C–H activation approach¹³ to prepare the isoindolinone derivatives was elegantly reported, where the 3-hydroxyisoindolinones and 2-naphthol were used as the reaction partners.¹⁴ In view of the importance of the isoindolinone motif and the limited efficient approaches to such a useful target, it is still highly desirable to establish the practical method that could start from the easily accessible chemicals employing especially the most naturally abundant water as the reaction media.¹⁵ As part of our continuing research interest on the synthesis of heterocyclic compounds,¹⁶ we report herein our most recent endeavor on the development of methodology that could streamline the synthesis of 2-naphthol-substituted isoindolinones from a three-component Mannich-cyclization cascade reaction of 2-formylbenzoic acid, primary amine and 2-naphthol under catalyst-free conditions.

Results and discussion

To substantiate the feasibility of our designed synthetic route, phthalaldehydic acid **1a** (1.0 mmol), benzylamine **2a** (1.1 mmol), and 2-naphthol **3a** (1.0 mmol) were firstly utilized as the model substrates. As shown in Table 1, the reaction proceeded smoothly at 120 °C in water for 1 h, affording the desired product **4a** in 90% isolated yield. When the reaction temperature was reduced from 120 °C to 80 °C, an obvious decreased yield of product **4a** was observed even with a prolonged reaction time. When the reaction was carried out at 100 °C, 78% yield of **4a** was obtained. To our surprise, the replacement of the environmentally benign water by

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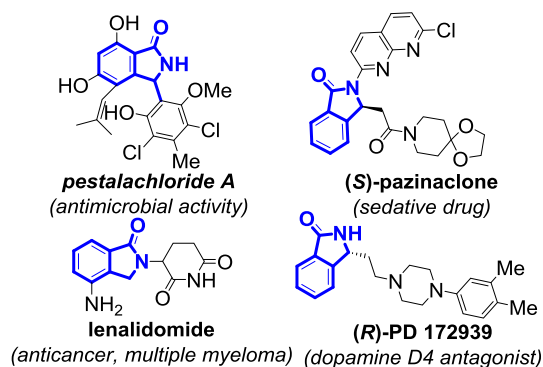
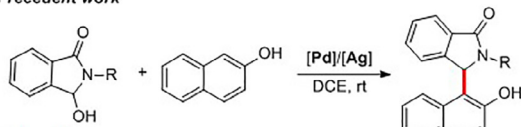
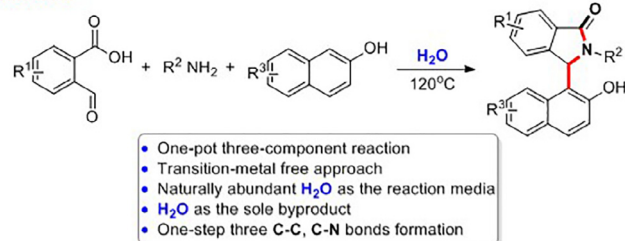


Fig. 1. Selective examples that incorporate isoindolinone motif.

Precedent work



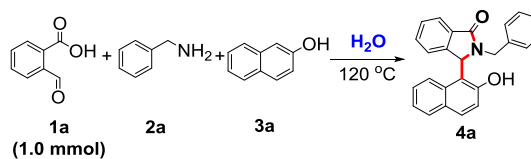
This work



Scheme 1. Synthetic approaches to the 3-substituted isoindolinones.

Table 1

Optimization of the reaction conditions^a.



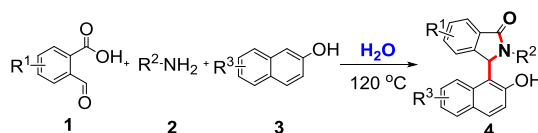
Entry	Deviation from the standard conditions	Time (h)	Yield(%) ^b
1	None	1	90
2	At 80 °C	10	62
3	At 100 °C	7	78
4	DMF instead of H ₂ O at 110 °C	24	20
5	Toluene instead of H ₂ O at 110 °C	24	30
6	1,4-Dioxane instead of H ₂ O at 80 °C	24	20
7	THF instead of H ₂ O at 70 °C	24	42
8	MeCN instead of H ₂ O at 80 °C	24	40
9	DMSO instead of H ₂ O at 110 °C	24	54
10	EtOH instead of H ₂ O at 80 °C	24	70
11	EtOH instead of H ₂ O at 120 °C	10	80
12	Neat, at 110 °C	6	50
13	Neat, at 120 °C	6	71

^a Unless otherwise noted, the reaction is performed in a closed vessel using phthalaldehydic acid **1a** (1.0 mmol), amine **2a** (1.1 mmol), and 2-naphthol **3a** (1.0 mmol) in 4.0 mL of solvent. ^b Isolated yield.

any other commonly used solvents, such as DMF, toluene, 1,4-dioxane, THF, DMSO, or MeCN, delivered no improvement of the desired product on the yield. Noteworthy, when the protic solvent of ethanol was employed, product **4a** was isolated in 70% yield at 80 °C for 24 h. Further increment of the reaction temperature to 120 °C led to an improved yield of product **4a** (80%) after 10 h. Moreover, the reaction could also work well under neat conditions in an acceptable yield at 120 °C.

Table 2

Scope for the synthesis of 3-(2-hydroxynaphthalen-1-yl)isoindolin-1-one **4** in water^a.



Entry	R ¹	R ²	R ³	Time (h)	Product 4	Yield (%) ^b
1	H	benzyl	H	1	4a	90
2	H	4-Cl-benzyl	H	1	4b	83
3	H	4-F-benzyl	H	1	4c	84
4	H	3-CF ₃ -benzyl	H	1	4d	81
5	H	3,4-di-Cl-benzyl	H	2	4e	91
6	H	2-Cl-benzyl	H	1	4f	92
7	H	4-OMe-benzyl	H	2	4g	88
8	H	2,4-OMe-benzyl	H	1	4h	86
9	H	furfuryl	H	1	4i	82
10	H	2-phenylethyl	H	0.5	4j	84
11	H	4-phenylbutyl	H	1	4k	88
12	H	1-butyl	H	1	4l	83
13	H	1-octyl	H	4	4m	77
14	H	1-dodecyl	H	4	4n	86
15	H	isopropyl	H	1	4o	32
16	H	tert-butyl	H	12	4p	0
17 ^c	H	H	H	2	4q	73
18	H	4-MeO-Phenyl	H	2	4r	61
19	H	Phenyl	H	12	4s	0
20	H	benzyl	6-Br	2	4t	62
21	H	benzyl	6-CO ₂ Me	5	4u	74
22	6-NO ₂	benzyl	H	8	4v	68
23	4-CN	benzyl	H	6	4w	77

^a Conditions: phthalaldehydic acid **1a** (1.0 mmol), benzylamine **2a** (1.1 mmol), and 2-naphthol **3a** (1.0 mmol) and H₂O (4.0 mL) at 120 °C in a closed vessel.

^b Isolated yield.

^c 4ml 28% ammonium hydroxide was used as the ammonia gas precursor and the reaction was performed at 80 °C.

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