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Efficient $PhB(OH)_2$-catalyzed one-pot synthesis of 3-substituted isoindolin-1-ones and isobenzofuran-1(3*H*)-ones under solvent free conditions

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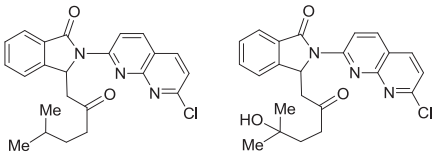
ABSTRACT

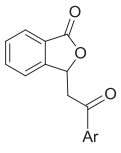
An efficient and practical one-pot synthesis of 3-substituted isoindolin-1-ones and isobenzofuran-1(3*H*)-ones has been developed under solvent free-conditions using non-toxic and cheap phenylboronic acid as excellent catalyst. This strategy involves the sequential two-step Mannich/lactamization cascade reaction of inexpensive 2-formylbenzoic acid with primary amines and a wide variety of ketones, and an aldol/lactonization cascade reaction of 2-formylbenzoic acid with a broad range of ketones.

1. Introduction

Heterocyclic compounds like 2,3-disubstituted isoindolin-1-ones are undoubtedly one of the most interesting compounds since, they are present in a great number of natural products and have attracted much attention in recent years because of their wide range of biological activities. For example, the pagoclone **1** is a partial agonist at the benzodiazepine site of the $GABA_A$ receptor, which acts as an anxiolytic agent [1], is used in the treatment of panic disorders [2], and also in the therapy for patients who stutter [3], whereas that the 5′-hydroxy pagoclone **2** acts as an anxiolytic agent [4]. On the other hand, isobenzofuran-1(3*H*)-ones represent also an important class of benzofurans, especially those that possess an acyl group at the C-3 position of the lactone ring, which exhibit a broad spectrum of pharmacological activities [5]. For example, the 3-acyl substituted isobenzofuran-1(3*H*)-one type **3** acts as an anti-tuberculosis agent [6], has a potential anti-nociceptive activity [7], cytotoxic activity against a panel of three leukemia cancer cell lines [8], and as an anti-hypertensive and anti-inflammatory agents [9]. Additionally, the isobenzofuran-1(3*H*)-ones are key intermediates in the synthesis of more complex compounds with potential applications in the pharmaceutical industry [10].



Pagoclone, **1** 5'-Hydroxy pagoclone, **2**



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Due to the high potential of the 3-substituted isoindolin-1-ones and isobenzofuran-1(3*H*)-ones, the synthesis of these compounds has received considerable attention, and in the last years significant progress has been made to develop more efficient methods for their preparation [11]. The methods for the synthesis of 2,3-disubstituted

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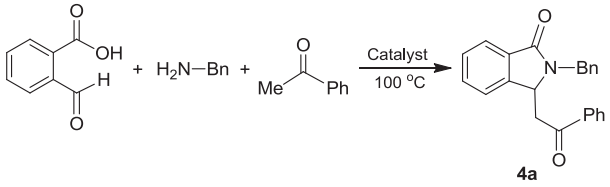
isoindolin-1-ones include the Mannich type reaction of *N*-acyliminium ions with the appropriate enols or trimethylsilyl enol ethers [12] with ylides [13], the one-pot reaction of 2-formylbenzoic acid or its methyl ester with amines and the corresponding enols or trimethylsilyl enol ethers [14], the hydration of 3-alkynyl isoindolin-1-ones obtained by alkynylation/lactamization of methyl 2-formylbenzoate [15], and the reaction of *o*-alkynyl arylaldehydes with amines [16]. On the other hand, the 3-substituted isobenzofuran-1(3*H*)-ones have been obtained by aldol/lactonization reaction [17], intramolecular oxa-Michael addition [18] and by carbonylative cyclization of *o*-bromo-benzaldehyde [19]. However, in spite of their potential utility, these procedures suffer from one or more disadvantages such as the use of strong, corrosive and harmful acids and bases, harsh conditions or tedious multistep processes are necessary for its purification.

Therefore, considering the high value of the 3-substituted isoindolin-1-ones and isobenzofuran-1(3*H*)-ones, the growing need to develop green synthetic methods in connection with our current research interest in the synthesis of 2,3-disubstituted isoindolin-1-ones [20]. and the exploration of phenylboronic acid [$PhB(OH)_2$] as a green catalyst in multi-component reactions [21], herein we describe an efficient and practical method for the synthesis of these compounds. Our synthetic strategy is based in a one-pot Mannich/lactamization cascade reaction of 2-formylbenzoic acid an essential reactant, which serves as acceptor for the Mannich reaction and also as substrate for the subsequent lactamization, with primary amines and a wide variety of ketones catalyzed with $PhB(OH)_2$ under solvent free-conditions. Additionally, here we also describe an efficient and practical method for the synthesis of 3-substituted benzofuran-1(3*H*)-ones via a $PhB(OH)_2$-catalyzed one-pot sequential aldol/lactonization reaction of 2-formylbenzoic acid with a great number of ketones under solvent free-conditions.

2. Results and discussion

For the synthesis of 2,3-disubstituted isoindolin-1-ones **4** through the Mannich/lactamization cascade reaction, we started with the design and optimization conditions of the one-pot reaction in the presence of some potential catalysts such as *p*-toluenesulfonic acid (PTSA), pyridinium *p*-toluenesulfonate (PPTS) and phenylboronic acid. For this purpose, the one-pot reaction of 2-formylbenzoic acid, benzylamine and acetophenone in 1:1:1 M proportion was examined with detail in order to find the most efficient reaction conditions. Under this context, initially the 2-formylbenzoic acid was treated with benzylamine at room temperature to obtain the corresponding imine, which was reacted with acetophenone at 100 °C under solvent and catalyst free-conditions, obtaining the 2,3-disubstituted isoindolin-1-one **4a** in only 18% yield after 4.0 h (Table 1, entry 1). In the next experiment, the imine was reacted with acetophenone at 100 °C in the presence of 10 mol% of PTSA or PPTS as catalyst, obtaining the expected 2,3-disubstituted isoindolin-1-one **4a** in 86% and 80% yield, respectively, after 3.0 and 3.5 h (Table 1, entries 2 and 3). Later, we carried out the reaction of 2-formylbenzoic acid with benzylamine followed by the treatment with acetophenone in the presence of 10 mol% of $PhB(OH)_2$ under solvent free-conditions and at 100 °C, obtaining **4a** in 91% in only 1.0 h (Table 1, entry 4). With these excellent results and in order to find the optimum amount of $PhB(OH)_2$, the reaction was performed using 5 and 20 mol%, found that using 20 mol% of $PhB(OH)_2$ the yield of the desired 2,3-disubstituted isoindolin-1-one **4a** did not improve, but using 5 mol% of catalyst the yield decreased to 75% yield (Table 1, entries 5 and 6). In addition, when the reaction was carried out at 80 °C, the yield of **4a** also decreased to 78% and longer reaction time was required (Table 1, entry 7). These results show that all catalysts tested are excellent for the synthesis of the 2,3-disubstituted isoindolin-1-one **4a** through the one-pot reaction, but we selected the $PhB(OH)_2$ as the catalyst to continue this study under solvent free-conditions because it is easy access and cheap.

Table 1
Optimization of Mannich/lactamization cascade reaction conditions.



Entry	Catalyst	(mol%)	Time (h)	Yield (%)[a]
1	none	–	4.0	18
2	PTSA	10	3.0	86
3	PPTS	10	3.5	80
4	$PhB(OH)_2$	10	1.0	91
5	$PhB(OH)_2$	5	1.5	75
6	$PhB(OH)_2$	20	1.0	90
7	$PhB(OH)_2$	10	2.5	78[b]

[a] Isolated after chromatographic purification.
[b] The reaction was carried out at 80 °C.

With the optimized Mannich/lactamization reaction conditions established above, later we turned our attention to investigate the scope and versatility of this method in the synthesis of several 2,3-disubstituted isoindolin-1-ones. Thus, the scope of this sequential Mannich/lactamization reaction was first tested with 2-formylbenzoic acid, benzylamine and a broad range of methyl aryl ketones bearing *para*-electron donating as well as electron withdrawing substituents. In all cases, the reaction proceeded efficiently affording the 2,3-disubstituted isoindolin-1-ones **4b-g** in 63–91% yield. On the other hand, recognizing that a nitrogen atom in the ketone might significantly influence the course of the reaction by protonation or coordination with the phenylboronic acid, we decided to evaluate the Mannich/lactamization reaction using 4-acetylpyridine and 2-acetylpyrrole, which react very well to give the desired 2,3-disubstituted isoindolin-1-ones **4h** and **4i** in 74 and 60% yield, respectively, demonstrating that these ketones tolerate very well these reaction conditions. We also tested the reaction using dialkyl ketones as the 2-butanone, which afforded the 2,3-disubstituted isoindolin-1-one **4j** in 49% yield. Finally, when the reaction was carried out using the 5,5-dimethyl-1,3-cyclohexanedione (dimedone), furnished the 2,3-disubstituted isoindolin-1-ones **4k** in 83% yield (Scheme 1).

Then, to ensure the efficiency and generality of this sequential Mannich/lactamization cascade reaction for the synthesis of 2,3-disubstituted isoindolin-1-ones, a variety of primary amines including *p*-methoxybenzylamine, cyclohexanemethylamine, allylamine and 2,2-dimethoxyethylamine were tested using the optimal conditions described above. For this purpose, we first evaluated the one-pot reaction of 2-formylbenzoic acid and *p*-methoxybenzylamine with acetophenone, *p*-methoxyacetophenone and *p*-methylacetophenone. In all cases, the reaction proceeded efficiently to give the 2,3-disubstituted isoindolin-1-ones **4l-n** in moderated to excellent yield (73–95%). However, when the *p*-hydroxyacetophenone was reacted under the same conditions, the isoindolin-1-one **4o** was obtained in only 45% yield, whereas the reaction with the acetylated *p*-hydroxyacetophenone derivative, gave the isoindolin-1-one **4p** in 65% yield. Again, the sequential Mannich/lactamization cascade reaction with 4-acetylpyridine or 2-acetylpirrole, produced the 2,3-disubstituted isoindolin-1-ones **4q**