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Hantzsch ester triggered metal-free cascade approach to isoindolinones

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ABSTRACT

Disclosed herein is an expedient synthesis of biologically important isoindolinone derivatives from reactions of 2-formylbenzoic acids with various amines. This method operates via a deliberately designed catalyst-free tandem reductive amination/cyclization cascade event triggered by a transfer hydrogenation process with easily available Hantzsch ester as the organic hydride source. The ease of operation, mild reaction conditions, facile accessibility of the starting materials, and easy scalability of the current method distinguish it from the other precedent protocols, thus enable it a practical approach to the syntheses of valuable isoindolinone-incorporated drugs.

Introduction

Owing to the profound biological activities of this ubiquitous isoindolinone motif found in a wide variety of natural products[1] and synthetic drugs,[2] i.e., the anti-inflammatory drug of indoprofen, the anti-tumor agent of deoxythalldomide, the tumor necrosis factor (TNF-α) production inhibitor of DWP201190, and also the mouse glutathione reductase 1 (mGR-1) antagonist of triazol-isoindolinone, (as shown in Fig. 1),[3] inspired by this unarguable fact, thus the construction of such a skeleton has increasingly gained considerable momentum over the past decades. As a consequence, an array of viable methods has been developed toward the efficient syntheses of biologically relevant isoindolinone-incorprated devatives. Traditional methods including the Gabriel approach,[4a] Grignard procedure,[4b] lithiation process,[4c] Diels–Alder reaction,[4d] Wittig reaction,[4e] rearrangement process[4f] and even photochemical reaction[4g] have been historically documented.

Apart from these stereotyped while practical methods, there are also some modern synthetic approaches that have been elegantly established. In 2005, Khan and co-workers[5] achieved a Heck/Michael addition cascade using 2-iodo-*N*-substituted benzamides and acrylic esters as the qualified substrates with palladium catalysis, a series of *N*-substituted-3-alkylisoindolinone esters were facilely synthesized. Undoubtedly, the direct selective monoreduction of phthalimides (Scheme 1, a),[6] intramolecular amidation of 2-methyl-*N*-substituted benzamides (Scheme 1, c)[7] and intramolecular C(sp^3)-H activation of *ortho*-halogenated benzamides (Scheme 1, e)[8] provide the most straightforward approaches to the isoindolinone derivatives. Moreover, an intermolecular carbonylation of 2-halo-*N*-alkylbenzylamines under transition metal catalysis also provides an alternative method for the syntheses of such an important motif (Scheme 1, b).[9] Besides, the transition-/coinage-metal-catalyzed reductive amination/condensation cascade approaches from 2-formyl-benzoic acids and amines have also been innovatively developed (Scheme 1, d).[10] Among aforementioned methods,[11] either precious transition metals or unavailability issue of the starting materials or toxic CO or flammable H_2 is indispensible for the transformations, which greatly limit the practicality of these methods. Hence, the development of a new method, of which the use of costly transition metal catalysts and intractable reagents could be circumvented, is still in high demand. To this end, we disclose herein our most recent endeavor on the development of methodology towards the syntheses of biologically important indolinone derivatives.

Nicotinamide adenine dinucleotide (NADH), as a coenzyme found in all living cells, serves as a hydride co-factor for a broad range of reductions.[12] Among all the NADH-involved transformations in nature, the glutamate dehydrogenase catalyzed reductive amination of 2-ketoglutarate to form the amino acid glutamate represents one of the most typical examples.[13] Stimulated by this precisely established process by nature, chemists have recently found that Hantzsch esters can undertake the similar reductive process as that of the NADH.[14] As a result, numerous biomimetic transformations involving the Hantzsch esters reduction have been impressively established.[15] Given the importance of this isoindolinone motif, we envisioned that a similar biomimetic strategy

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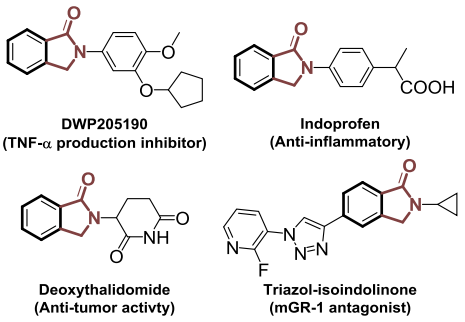


Fig. 1. Biologically active *N*-substituted isoindolinones.

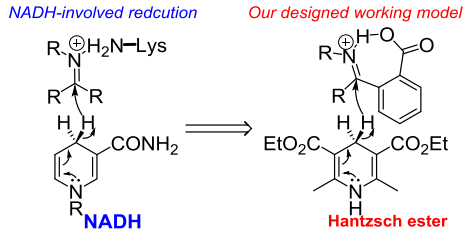


Fig. 2. NAD(P)H-mediated reduction and our design.

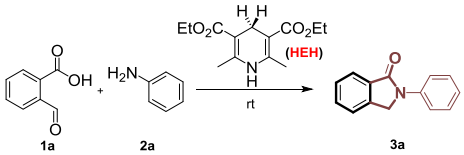
could be applied in the syntheses of isoindolinones from 2-formyl benzoic acids, amines and Hantzsch ester under catalyst-free conditions, as showed in Fig. 2.

Results and discussion

To prove the feasibility of our working hypothesis, we first investigated the reductive amination/cyclization of phthalaldehydic acid (**1a**) and aniline (**2a**) using HEH as the hydride source under various conditions (Table 1). To our delight, the direct reductive amination/cyclization reaction took place under this catalyst-free condition and the desired isoindolinone **3a** was obtained in DCM at room temperature in 86% yield (Table 1, entry 1). Encouraged by this preliminary result, several solvents, such as chloroform, DCE, toluene, DMF, 1,4-Dioxane, THF, MeCN, DMSO and MeOH, were systematically screened. As shown in Table 1, it was found that the solvent exerted a significant effect on the reaction, only commonly used chlorinated solvent or toluene used as the reaction media can afford the desired product in satisfactory yields (entries 2–4). However, to our surprise, other used solvents delivered no desired product at all, even at an expense of a prolonged reaction time (entries 5–10). Furthermore, reducing the loading of HEH from 1.2 equiv to 1.0 equiv, a slight erosion of the yield of product **3a** was observed, whereas increasing the amount of HEH loading to 1.5 equiv still failed to further improve the yield (entries 11–12).

With optimized conditions in hand, the reactions of various amines with phthalaldehydic acid (**1a**) were immediately examined and the results were summarized in Table 2. Aromatic amines bearing electron-donating groups at the *para*- or *meta*-positions such as CH_3–, CH_3O– groups reacted smoothly to afford the corresponding isoindolinone **3** in good to excellent yields (Table 2, entries 2–5). The fluoro-, chloro-, bromo-, and iodo-substitutions at the *para*-position of aromatic amines were all well tolerated, giving the desired isoindolinone **3** in over 80% yields (Table 2, entries 6–9). It should be noted that the aromatic amines with halogen substitution at the *meta*-position generally afforded better

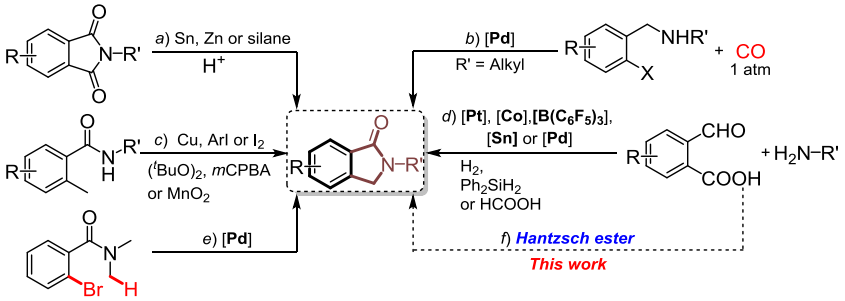
Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	HEH (equiv)	Time (h)	Yield (%)[b]
1	DCM	1.2	5	86
2	$CHCl_3$	1.2	5	85
3	DCE	1.2	6	76
4	Toluene	1.2	12	82
5	DMF	1.2	24	–
6	1,4-Dioxane	1.2	24	–
7	THF	1.2	24	–
8	MeCN	1.2	24	–
9	DMSO	1.2	24	–
10	MeOH	1.2	24	–
11	DCM	1	8	75
12	DCM	1.5	5	85

[a] Unless otherwise noted, the reaction is performed using phthalaldehydic acid **1a** (1.0 mmol), amine **2a** (1.1 mmol), and Hantzsch ester in 3.0 mL of solvent at room temperature under N_2.
[b] Isolated yield.

results than the ones with a *para*-substitution pattern (Table 2, entries 10–12). And other electron-withdrawing groups like CF_3–, CF_3O–, EtOOC– and NC– worked equally well (Table 2, entries 13–16). However, a dramatically decreased yield of 46% was observed when using 2-naphthylamine as the substrate (Table 2, entry 17). This phenomenon could be reasonably ascribed to the steric hindrance exerted by the amine substrate. And such a notion has been subsequently reinforced by the use of *ortho*-substituted aromatic amine as the substrate (Table 2, entry 18). Interestingly, heteroaromatic amines like 2-aminopyridine furnished the corresponding product **3r** in 70% yield, albeit a slightly higher temperature of 50 °C was a prerequisite condition for the success (Table 2, entry 19). Apart from the above-mentioned aromatic amines,



Scheme 1. Strategies for the syntheses of biologically relevant isoindolinones.