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PII: S0040-4039(17)30525-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.04.073
Reference: TETL 48865

To appear in: *Tetrahedron Letters*

Received Date: 3 March 2017
Revised Date: 21 April 2017
Accepted Date: 24 April 2017

Please cite this article as: Zhou, Y., Chen, P., Lv, X., Niu, J., Wang, Y., Lei, M., Hu, L., A facile and efficient method for the synthesis of *N*-substituted isoindolin-1-one derivatives under $Pd(OAc)_2$/HCOOH system, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.04.073

Graphical Abstract

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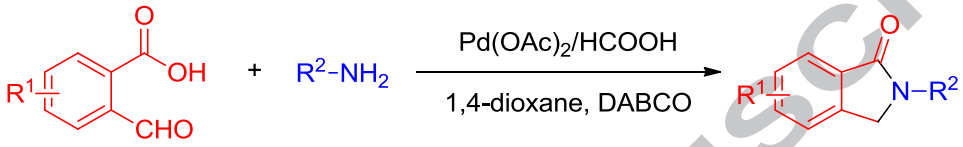


Tetrahedron Letters
journal homepage: www.elsevier.com

A facile and efficient method for the synthesis of *N*-substituted isoindolin-1-one derivatives under $Pd(OAc)_2$/HCOOH system

Yang Zhou [a], Ping Chen [a], Xue Lv [b], Junxing Niu [b], Yingying Wang [b], Min Lei [b,*] and Lihong Hu [b,c,*]

[a]*Wuhan Polytechnic University, School of Biological and Pharmaceutical Engineering, Wuhan, PR China*
[b]*Shanghai Institute of Materia Medica, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai, PR China*
[c]*Jiangsu Key Laboratory for Functional Substance of Chinese Medicine, Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, Stake Key Laboratory Cultivation Base for TCM Quality and Efficacy, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, PR China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
2-Formylbenzoic acid
Isoindolin-1-one
$Pd(OAc)_2$
Hydrogenation
Cyclization

ABSTRACT

A facile and efficient method for the synthesis of *N*-substituted isoindolin-1-one derivatives from 2-formylbenzoic acid and amine under $Pd(OAc)_2$/HCOOH system has been described. The whole process was carried out in ligand-free conditions and furnished the desired products by reductive intramolecular cyclization. Furthermore, this procedure is applied successfully for the modification of natural products, such as vindoline and estrone.

Isoindolin-1-ones are one of the most prevalent heterocyclic compounds, which are present as the basic cores in many alkaloids.[1] For example, a lot of natural products, such as narceineimide, fumaridine, fumaramine and aristoyagonine, are contain isoindolin-1-one unit.[1,2] In recent years, much attention has been focused on isoindolin-1-ones due to their significant biological activity.[3] As shown in Figure 1, lenalidomide is a clinically used drug for the treatment of multiple myeloma.[4] Compound **CC3052** is reported as a potent inhibitor of TNF-α production.[5] Indoprofen is a non-steroidal antiinflammatory drug which can increase production of the survival of the motor neuron protein.[6] Thus, efficient synthesis of this heterocyclic nucleus has been of great interest in recent years.

Due to the importance of the isoindolin-1-ones, many methods for preparing these compounds have been developed: (i) 2-bromobenzaldehyde and amine catalyzed by $PdCl_2(PhCN)_2$;[7] (ii) 1-(bromomethyl)-2-iodobenzene and amine catalyzed by $Pd(OAc)_2$;[8] (iii) isobenzofuran-1(3*H*)-one and amine under high temperature;[9] (iv) 2-formylbenzoic acid and amine under hydrogenation conditions,[10] (v) and other methods.[3f,7,11] Although, a number of modified methods under improved ~~conditions~~ have been reported, many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, and long reaction time, and the use of expensive reagents. Therefore, there is a need to develop efficient methods for the synthesis of isoindolin-1-ones under mild and green conditions.

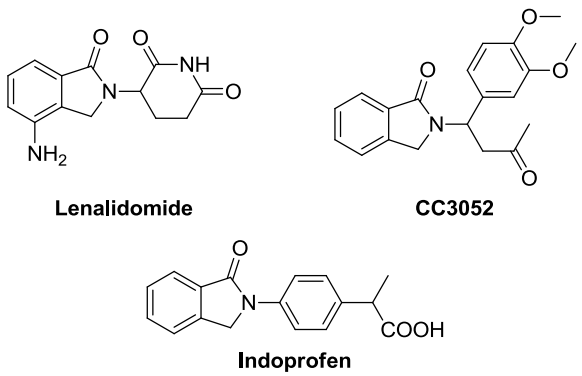


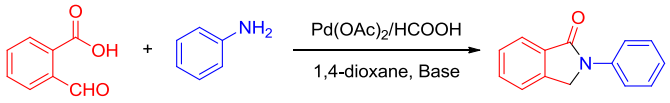
Figure 1. Examples of clinically used isoindolin-1-ones.

Our group has long been engaged in the research of the synthesis of heterocyclic compounds.[12] In the previous study, we

* Corresponding author.
E-mail address: mlei@simm.ac.cn (M. Lei)
* Corresponding author.
E-mail address: lhhu@simm.ac.cn (L. Hu)

have reported several efficient procedures for the synthesis of 2,3-disubstituted isoindolin-1-one derivatives under mild conditions.[13] It was reported that organic groups, such as olefin, nitro, could be reduction under [Pd]/HCOOH system.[14] Therefore, we wanted to know whether the reaction of 2-formylbenzoic acid and amine could proceed to form isoindolin-1-ones in the presence of [Pd]/HCOOH as reductant.

Table 1. Base screen[a]



1a **2a** **3a**

Entry	Base (equiv)	Yield of **3a** (%)[b]
1	/	60
2	Et_3N (2.0)	93
3	DIPEA (2.0)	94
4	Py (2.0)	ND[c]
5	DABCO (2.0)	99 (94)[d]
6	DMAP (2.0)	30
7	K_2CO_3 (2.0)	94
8	Na_2CO_3 (2.0)	93
9	DABCO (0.5)	79
10	DABCO (1.0)	88
11	DABCO (1.5)	91

[a]Reaction conditions: **1a** (300 mg, 2.0 mmol), **2a** (224 mg, 2.4 mmol, 1.2 equiv), base, HCOOH (0.5 mL), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 5 mol%), 1,4-dioxane (2 mL), 80 °C for 1 h.

[b]Yields were determined by LC-MS.

[c]No product were determined.

[d]Isolated yield.

Initially, we studied the reaction of 2-formylbenzoic acid (**1a**) (2 mmol) and aniline (**2a**) (2.4 mmol) under $Pd(OAc)_2$/HCOOH in 1,4-dioxane (2 mL) at 80 °C for 1 h to obtain the desired product **3a** in 60% yield. Further study revealed that base could improve the yields significantly. Therefore, the model reactions were carried out under different bases and the results are summarized in Table 1. As shown in Table 1, various bases such as Et_3N, DIPEA, Py, DABCO, DMAP, K_2CO_3, and Na_2CO_3 were applied to facilitate this model reaction. All the bases studied on this reaction showed good effect in terms of the yields of **3a** (93-99%) but pyridine (**3a** was not determined) and DMAP (30%). By screening of bases, DABCO was found to be the superior one than others to afford **3a** in 99% yield determined by LC-MS and in 94% isolated yield. Therefore, DABCO was chosen as the base for all further reactions. Furthermore, we found that the yields of **3a** were improved as the amount of DABCO increased from 0.5 to 2.0 equiv (Table 1, entries 5, 9-11). In addition, to investigation the solvent effect, various solvents such as EtOH, THF, MeCN, 1,4-dioxane, DMF, DMSO, and EtOAc were applied to promote this transformation. The results showed that amongst these solvents, 1,4-dioxane was the solvent of choice in terms of yield.

Furthermore, to screen the Pd-Cat, various catalysts such as $Pd(OAc)_2$, $Pd(TFA)_2$, $PdSO_4$, $PdCl_2$, and $Pd(PPh_3)_4$ were applied to this model reaction (Table 2). Among the Pd-Cats screened, $Pd(OAc)_2$ showed excellent activity in terms of yield in producing the required product (99%). In addition, the amount of $Pd(OAc)_2$ was also optimized (Table 2). No desired product **3a** was formed when the reaction was carried out in absence of $Pd(OAc)_2$ (Table 2, entry 6).The yields of **3a** was improved as the amount of $Pd(OAc)_2$ increased from 1 to 5 mol %. The use of 5 mol% $Pd(OAc)_2$ in model reaction led to quantitatively the target **3a** (Table 2, entry 1). Hence, 5 mol% of $Pd(OAc)_2$ was considered to be the most suitable.

Table 2. Pd-Cat screen[a]

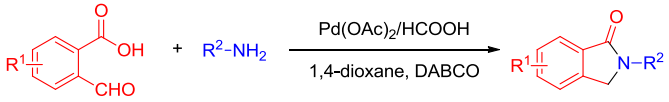
Entry	Pd-Cat (mol%)	Yield of **3a** (%)[b]
1	$Pd(OAc)_2$ (5)	99
2	$Pd(TFA)_2$ (5)	82
3	$PdSO_4$ (5)	24
4	$PdCl_2$ (5)	27
5	$Pd(PPh_3)_4$ (5)	41
6	$Pd(OAc)_2$ (0)	0
7	$Pd(OAc)_2$ (1)	50
8	$Pd(OAc)_2$ (2)	75
9	$Pd(OAc)_2$ (3)	90
10	$Pd(OAc)_2$ (4)	94
11	$Pd(OAc)_2$ (6)	98

[a]Reaction conditions: **1a** (300 mg, 2.0 mmol), **2a** (224 mg, 2.4 mmol, 1.2 equiv), DABCO (448 mg, 2 equiv), HCOOH (0.5 mL), Pd-Cat, 1,4-dioxane (2 mL), 80 °C for 1 h.

[b]Yields were determined by LC-MS.

Having established the optimized reaction conditions, we then successfully synthesized a variety of isoindolin-1-one derivatives **3** and the results were summarized in Table 3.

Table 3. Synthesis of isoindolin-1-ones [a]



1 **2** **3**

Entry	R^1	R^2	Time (h)	Product **3**	Yield (%)[b]
1	H **1a**	C_6H_5 **2a**	1	**3a**	94
2	H **1a**	4-$CH_3OC_6H_4$ **2b**	1	**3b**	91
3	H **1a**	3-$CH_3OC_6H_4$ **2c**	1	**3c**	92
4	H **1a**	2-$CH_3OC_6H_4$ **2d**	5	**3d**	83
5	H **1a**	4-$CH_3C_6H_4$ **2e**	1	**3e**	93
6	H **1a**	3-$CH_3C_6H_4$ **2f**	1	**3f**	93
7	H **1a**	2-$CH_3C_6H_4$ **2g**	5	**3g**	82
8	H **1a**	4-ClC_6H_4 **2h**	1	**3h**	70 (20)[c]
9	H **1a**	4-FC_6H_4 **2i**	1	**3i**	92
10	H **1a**	4-NCC_6H_4 **2j**	5	**3j**	93
11	H **1a**	4-$HOOCC_6H_4$ **2k**	5	**3k**	94
12	H **1a**	4-$EtOOCC_6H_4$ **2l**	1	**3l**	91
13	H **1a**	3,4-$(CH_3O)_2C_6H_3$ **2m**	1	**3m**	88
14	H **1a**	3,4-$(OCH_2O)C_6H_3$ **2n**	1	**3n**	85

15	H **1a**	1-naphthyl **2o**	5	**3o**	73
16	H **1a**	$C_6H_5CH_2$ **2p**	1	**3p**	91
17	H **1a**	*n*-butyl **2q**	1	**3q**	90
18	H **1a**	cyclohexyl **2r**	1	**3r**	93
19	4-CN **1b**	C_6H_5 **2a**	1	**3s**	90
20	4-CN **1b**	4-$CH_3OC_6H_4$ **2b**	1	**3t**	92

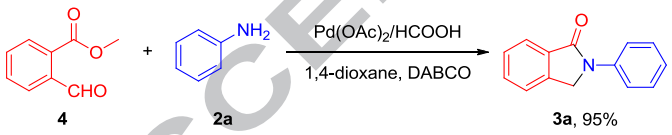
[a]Reaction conditions: **1** (2.0 mmol), **2a** (224 mg, 2.4 mmol, 1.2 equiv), DABCO (448 mg, 2 equiv), HCOOH (0.5 mL), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 5 mol%), 1,4-dioxane (2 mL), 80 °C.

[b]Isolated yields.

[c]Dechlorinated product **3a** was determined.

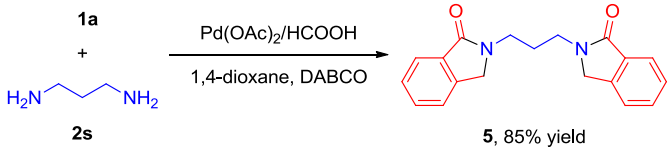
As shown in Table 3, aromatic amines carrying substituents (CH_3- and CH_3O-) at the *meta* or *para* position could react efficiently to give the corresponding products without significant differences (91-93%) (Table 3, entries 2, 3, 5 and 6). In contrast, the use of *ortho* substituted amines led to medium yields (82-83%) (Table 3, entries 4 and 7). It was noteworthy to mention that dechlorinated product **3a** (20%) was formed when using 4-chloroaniline **2h** as the substrate (Table 3, entry 8).

The results presented in Table 2 indicated that the electronic effect from the aromatic amines had no significant impact on the overall yields of the products **3**. The aromatic amines with either electron-donating (CH_3- and CH_3O-) or electron-withdrawing groups (NC-, HOOC-, and CH_3CH_2OOC-) afforded the corresponding products **3** in 91-94% yields (Table 3, entries 2, 5, 10-12). Furthermore, alkyl amines, such as benzylamine (**2p**), *n*-butylamine (**2q**), and cyclohexylamine (**2r**), were also selected as substrates for the synthesis of isoindolin-1-ones, and the corresponding products were obtained in 91, 90, and 93% yields, respectively. Furthermore, 4-cyano-2-formylbenzoic acid (**1b**) was also used as starting material, and the reaction could proceed smoothly to obtain the corresponding products in good yields (Table 3, entries 19 and 20).



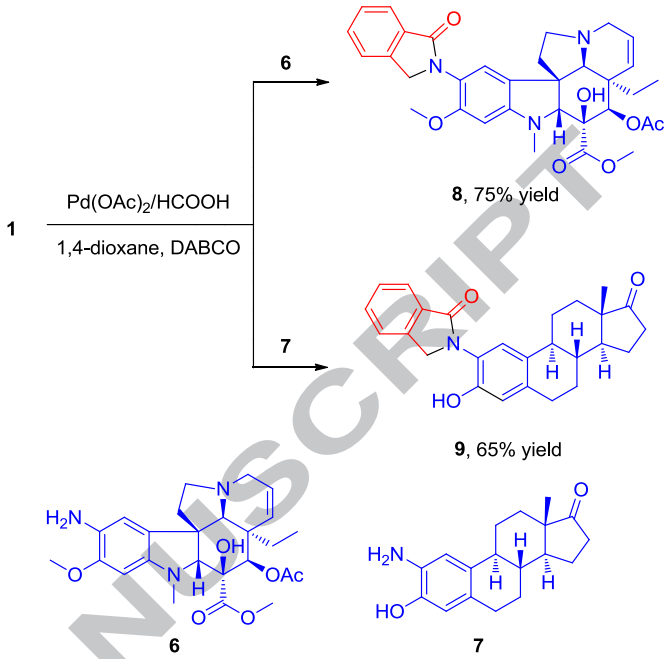
Scheme 1. The reaction of methyl 2-formylbenzoate (**4**) and aniline (**2a**).

As shown in Scheme 1, we also carried out the reaction using methyl 2-formylbenzoate (**4**) instead of 2-formylbenzoic acid (**1a**) under similar reaction conditions for 1 h, finding desired product **3a** was formed in 95% yield.



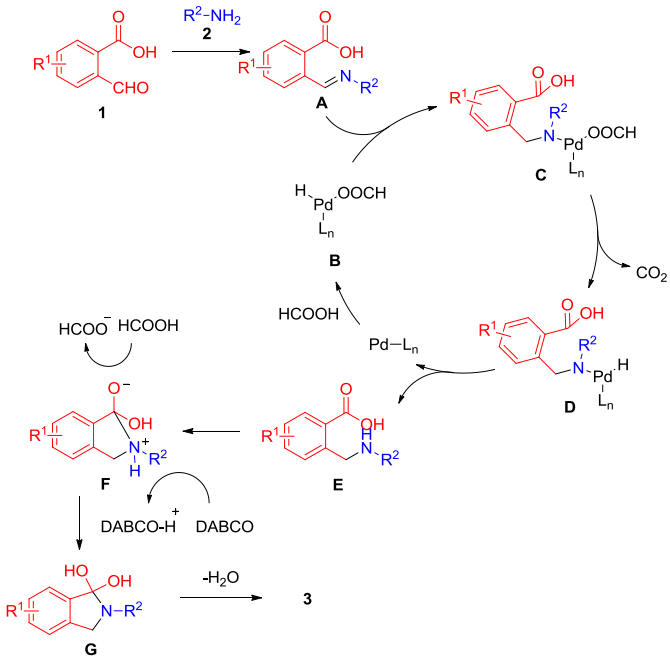
Scheme 2. The reaction of 2-formylbenzoic acid (**1**) and propane-1,3-diamine (**2s**).

As shown in Scheme 2, the propane-1,3-diamine (**4**) was chose as substrate under the similar reaction conditions, and the corresponding product **5** was obtained in 85% yield.



Scheme 3. The reaction of 2-formylbenzoic acid (**1**) and with natural products **6** or **7**.

Furthermore, this reaction was also applied in natural products (Scheme 2). At first, vindoline and estrone were chosen as starting materials, and 15-amino vindoline (**6**)[15] and 2-amino estrone (**7**)[16] were synthesized according to the reported method. Then, the reaction of **6** or **7** with 2-formylbenzoic acid (**1**) was carried out under standard conditions for 5 h. The corresponding products **8** and **9** were obtained in 75% and 65% yields, respectively.



Scheme 4. Plausible mechanism for the formation of *N*-substituted isoindolin-1-ones.

A tentative mechanism to rationalize the products **3** formation is shown in scheme 4. Initially, **1** reacts with **2** to form imine intermediate **A**, then, addition of **A** and formic acid on Pd-Cat led to the formation of key intermediate palladium hydride complex **C**. **A** new hydrido palladium complex **D** is formed from **C** by releasing carbon dioxide. Upon reduction elimination, complex **D** gave the intermediate **E** with regeneration of Pd-Cat. At last, desired product 3 is formed by intramolecular dehydration from **E**.

In conclusion, we have developed an efficient, green and convenient method for the synthesis of *N*-substituted isoindolin-1-ones via the reaction of 2-formylbenzoic acid and amine under $Pd(OAc)_2$/HCOOH system. This procedure is also suitable for the modification of natural products. Moreover, the mild reaction conditions, short reaction times, high yields of the products, ease of work-up, compatibility with various functional groups, and the ecologically clean procedure, will make the present method a useful and important addition to the present methodologies for the synthesis of *N*-substituted isoindolin-1-ones.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant: 81473110), Special Fund for Strategic Pilot Technology Chinese Academy of Sciences (XDA12040303), Shanghai Science & Technology Support Program (13431900401).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Highlights

1. The isoindolin-1-ones are synthesized from 2-formylbenzoic acid and amine under $Pd(OAc)_2$/HCOOH system.
2. This procedure is green, efficient, and high yields.
3. This method is also suitable for the modification of natural products.