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Highly Efficient Synthesis of *N*-Substituted Isoindolinones and Phthalazinones Using Pt Nanowires as Catalysts

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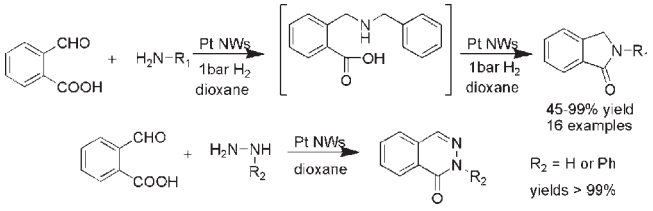
ABSTRACT



A series of *N*-substituted isoindolinones have been successfully synthesized through the reductive C−N coupling and intramolecular amidation of 2-carboxybenzaldehyde and amines. This one-pot synthesis gives excellent yields using ultrathin Pt nanowires as catalysts under 1 bar of hydrogen. These unsupported catalysts can also be used for the synthesis of phthalazinones in high yield when hydrazine or phenyl hydrazine is used instead of amines.

The importance and widespread use of the isoindolinone skeleton in many drugs, of natural and synthetic origin, has led to interest in its synthesis.[1] Much effort has been focused toward preparing 3-substituted isoindolinones.[2] *N*-Substituted isoindolinones are common compounds with important biological activities (Scheme 1).[3] Norman et al.[4] described a number of synthetic strategies to obtain this skeleton, such as the condensation of aminoalkanols with phthalide, reacting 2-(bromomethyl)benzoate with primary amines, and the monoreduction of phthalimide followed by alkylation of the isoindolinone. Beller[5] developed a novel monoreduction of phthalimide using low-cost polymethylhydrosiloxane and fluoride ions as a catalyst, giving up to 78% yield. Transition metal catalysis like palladium (Pd) have also been used in their synthesis. Kollár[6] reported the Pd-catalyzed cycloaminocarbonylation of 2-iodobenzylbromide and 2-iodobenzylamine. Cho's group[7] used 2-bromobenzaldehyde and amines as the substrates for *N*-substituted isoindolinones synthesis

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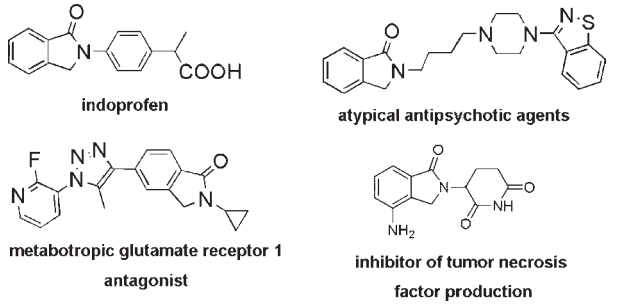
with carbon monoxide (CO) in the presence of a Pd catalyst. Alper[8] described two approaches for the systhesis of isoindolinone derivatives in phosphonium salt ionic liquids through Pd-catalyzed carbonylation–hydroamination reactions of 1-halo-2-alkynylbenzene and amines. Rousseaux[9] devoloped a Pd-catalyzed intramolecular alkylation at aliphatic positions adjacent to a nitrogen atom in amides to obtain the isoindolinone derivatives. Platinum chloride ($PtCl_2$) was also used as the catalyst in cycloisomerization reactions using *o*-halobenzyl- or *o*-halobenzoylynamides.[10] These methods were encouraging; however there remained considerable scope for improvement, such as a more suitable catalyst and reaction conditions which prevent catalyst leakage, avoiding the use of highly toxic CO, and obtaining higher yields.

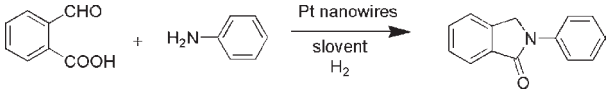
Scheme 1. Examples of N-Substituted Isoindolinones with Biological Activities[3]



Inspired by our previous research on Pt nanowires (NWs) catalyzed C–N coupling reactions between aldehydes and amines,[11] and amidation reactions between amines and carboxyl acids,[12] we designed a simple path to prepare *N*-substituted isoindolinones from 2-carboxybenzaldehydes. They would replace the 1,2-disubstituted benzenes such as *o*-phthalaldehyde, *o*-halobenzoic amides, and *o*-haloalkynylbenzenes as substrates. The process requires the amination and intramolecular amidation of 2-carboxybenzaldehyde and amines in one pot using Pt NW as catalyst under a hydrogen atmosphere.

Pt NWs were obtained from the acidic etching of FePt NWs in air followed by multiple washings with methanol as reported in our previous work.[11,12] These Pt NWs are several hundred nanometers in length and average 1.5 nm in diameter with a very narrow distribution (between 1.3 and 1.7 nm), which is calculated from the analysis of high-resolution TEM (HR-TEM) images (Figure S1). Fe was almost completely removed with no Fe detected by inductive coupling plasma mass spectrometry (ICP-MS). The powder X-ray diffraction (pXRD) pattern and HR-TEM proved the Pt NWs to be single crystals with an interplane distance of 0.23 nm, which agrees with the (111) plane of *fcc* phase of bulk Pt crystals.

Table 1. 2-Phenylisoindolin-1-one Formation in a Series of Reaction Conditions[a]



entry	catalyst	solvent	H_2 (bar)	temp (°C)	time (h)	yield (%)[b]
1	–	1,4-dioxane	1	80	18	N.D.[c]
2	Pt NW	1,4-dioxane	–	80	18	N.D.[c]
3	Pt NW	CH_3OH	1	40	18	80.1
4	Pt NW	$CHCl_3$	1	40	18	75.0
5	Pt NW	C_2H_5OH	1	70	18	96.4
6	Pt NW	H_2O	1	80	24	38.4
7	Pt NW	1,4-dioxane	1	80	18	98.1 (95)
8	Pt NW	DMF	1	80	18	1.4
9	Pt NW	1,4-dioxane	1	40	18	98.1
10	Pt NW	1,4-dioxane	1	100	18	97.1
11	Pt NW	1,4-dioxane	2	80	6	99.8
12	Pt NW	1,4-dioxane	4	80	3	95.2

[a] All reactions were carried out with 1 mg of Pt NW, 1 mmol of 2-carboxybenzaldehyde, 1.1 mmol of aniline, and 2 mL of solvent at the appropriate temperature under a hydrogen atmosphere. [b] GC yield. [c] Not detected. The values in parentheses are the yields of the isolated products.

For the initial screening, we tested six solvents (Table 1, entries 3–8) under 1 bar of initial hydrogen pressure. In 1,4-dioxane, Pt NWs show the greatest catalytic activity and obtained the target product 2-phenylisoindolin-1-one in a yield of 98.1%. The strongly polar solvents DMF and water gave only 1.4% and 38.4% of the target product, and most of the substrate was converted to 2-((phenylimino) methyl)benzoic acid. The reaction temperature was also investigated at 40 and 100 °C; the catalyst shows excellent catalytic activity and gave the product in 98.1% and 97.1% yield respectively. When no catalyst or hydrogen was used under these conditions, the product obtained was 2-((phenylimino)methyl)benzoic acid, proving the Pt NW and hydrogen are crucial factors for this reaction. Higher pressure tends to increase the hydrogenation reaction rates, and in this reaction, the product was obtained in 6 h at 2 bar and 3 h at 4 bar.

This catalyst can be recycled easily, and the reaction solution was detected by Inductively Coupled Plasma (ICP); no Pt ion was detected. The recycled catalyst was also detected by TEM, and no morphogenetic change was observed. The catalytic activities of recycled catalysts were investigated, and it is found that the yields were kept constant at ~98% (Figure S3).

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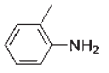
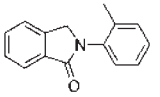
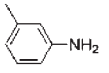
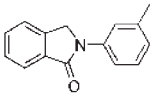
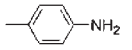
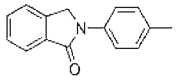
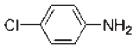
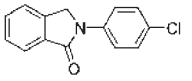
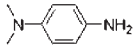
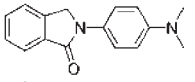
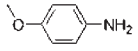
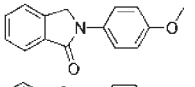
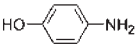
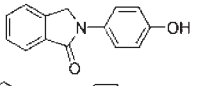
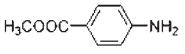
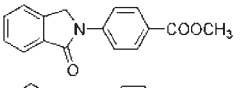
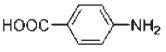
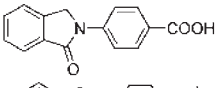
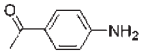
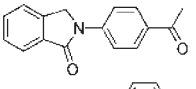
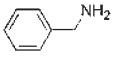
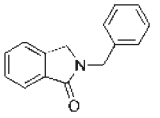
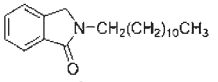
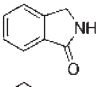
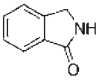
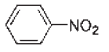
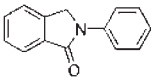
Table 2. *N*-Substituted Isoindolinones Prepared Using Different Amines over Pt NWs[a]

entry	amine	product	yield (%)[b]
1			85.4 (84)
2			99.4 (94)
3			99.5 (95)
4			85.8 (82)
5			93.9 (88)
6			99.8 (96)
7			99.2 (89)
8			84.9 (81)
9			69.3 (65)
10			64.6 (62)
11			95.6 (93)
12	$CH_3(CH_2)_{10}CH_2NH_2$		97.8 (96)
13[c]	$NH_3 \cdot H_2O$		73.0 (64)
14	CH_3COONH_4		45.0 (38)
15			99.5 (98)

[a] All reactions were carried out with 1 mg of Pt NW, 1 mmol of 2-carboxybenzaldehyde, 1.1 mmol of amine (or ammonium acetate, nitrobenzene), and 2 mL of 1,4-dioxiane at 80 °C under a hydrogen atmosphere. [b] GC yield. [c] Ammonium hydroxide (2 mL) was used as the substrate and solvent at 40 °C. The values in parentheses are the yields of the isolated products.

After achieving the optimal reaction conditions, we set out to explore its application with other substrates. A wide range of amines, as well as nitrobenzene, were investigated, and the results are summarized in Table 2. Gratifyingly, both aromatic and aliphatic amines were found to be suitable substrates and produced the corresponding *N*-substituted isoindolinones in good to excellent yields. For aromatic amines (Table 2, entries 1 to 10), electron-donating substituents show excellect results in these reactions and the yields are above 85%. The amines with electron-withdrawing groups can also be used, and the yields are good to excellent. Sterically constrained amines with *ortho*-substituents on the benzene ring have only a small reduction in yield. Both linear and α-branched aliphatic amine compounds gave good yields without any apparent byproducts (Table 2, entries 11, 12). Futher investigation revealed that less reactive ammonia sources like ammonium hydroxide and ammonium acetate can also be used as the substrates, albeit in reduced yields.

In our previous reports, Pt NWs proved to be highly active catalysts for the hydrogenation of nitro-aromatics to the corresponding amines under hydrogen.[12] Encouraged by these results, we considered the possibility of using nitrobenzene instead of amines. Under the same reaction conditions, nitrobenzene gave the target product with an excellent yield of 99.5%.

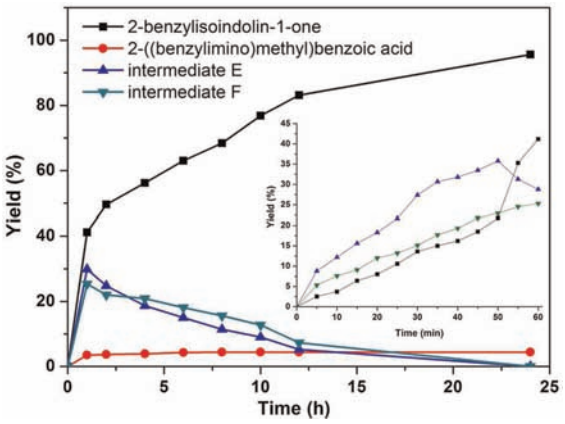


Figure 1. Time−conversion plot for the model reaction between the 2-carboxybenzaldehyde and benzylamine with Pt NWs (insert: the first hour results).

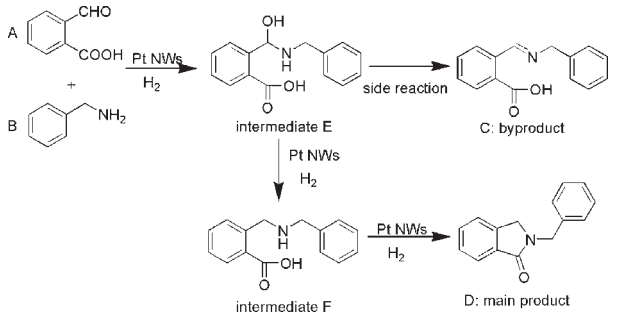
To obtain more information about the mechanism of this catalytic process, GC measurements were carried out to study the model reaction between the 2-carboxybenzaldehyde and benzylamine with Pt NWs as the catalyst over time (Figure 1). The results indicate that the substrates are quickly converted to two intermediates along with the target product (2-phenylisoindolin-1-one) in the first hour. Then the two intermediates are more slowly converted to

(13) (a) Betti, L.; Zanelli, M.; Giannaccini, G.; Manetti, F.; Schenoned, S.; Strappaghetti, G. *Bioorg. Med. Chem.* **2006**, *14*, 2828. (b) Chollet, A.-M.; Diguarher, T. L.; Kucharczyk, N.; Loynel, A.; Bertrand, M.; Tucker, G.; Guilbaud, N.; Burbridge, M.; Pastoureau, P.; Fradin, A.; Sabatini, M.; Fauchèrea, J.-L.; Casara, P. *Bioorg. Med. Chem.* **2002**, *10*, 531. (c) Pan, J.; Li, K.; Chuayprakong, S.; Hsu, T.; Wang, Q. *ACS Appl. Mater. Interfaces* **2010**, *2*, 1286. (d) Norman, M. H.; Rigdon, G. C.; Navas, F.; Coopel, B. R. *J. Med. Chem.* **1994**, *37*, 2552. (e) Cesari, N.; Biancalani, C.; Vergelli, C.; Piaz, V. D.; Graziano, A.; Biagini, P.; Ghelardini, C.; Galeotti, N.; Giovannoni, M. P. *J. Med. Chem.* **2006**, *49*, 7826. (f) Wu, L.; Huang, C.; Woo, J.-J.; Wu, D.; Yun, S.-H.; Seo, S.-J.; Xu, T.; Moon, S.-H. *J. Phys. Chem. B* **2010**, *114*, 13121.

2-phenylisoindolin-1-one. Focusing on the first hour of the reaction revealed 95% of 2-carboxybenzaldehyde was consumed in the first hour and 42% of 2-phenylisoindolin-1-one was obtained.

The proposed reaction mechanism of the reaction between 2-carboxybenzaldehyde and benzylamine is shown in Scheme 2. Benzylamine first couples with the aldehyde group, and two intermediates (**E** and **F**) are obtained. This is similar to our previous results of C−N bond formation reaction between benzaldehyde and amines.[11] The intermediate **F** can convert to the target product in the reaction conditions. However, trace amounts of 2-((phenylimino) methyl)benzoic acid (**C**) were also obtained through intramolecular water elimination of **E**. This product cannot convert to the target product through the amidation, as there is no active N−H bond to undergo amidation.

Scheme 2. Proposed Mechanism for the Reaction of 2-Carboxybenzaldehyde and Benzylamine

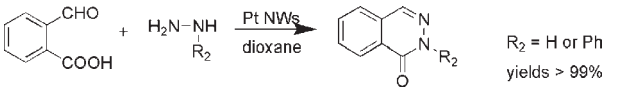


This reaction can be upscaled successfully. When 3 g of 2-carboxybenzaldehyde was used as the substrate, we can obtain 3.8 g of 2-phenylisoindolin-1-one (91%) (Table S2). Although the yield is a little lower than that of the 1 mmol scale, it can be used for multigram-scale isoindolinone synthesis.

Phthalazinones are also important skeletons in many natural products, fine chemicals, and pharmaceuticals.[13]

(14) (a) Heravi, M. M.; Baghernejad, B.; Oskooie, H. A. *J. Heterocycl. Chem.* **2009**, *46*, 351. (b) Outerbridge, V. M.; Landge, S. M.; Tamaki, H.; Török, B. *Synthesis* **2009**, *40*, 1801. (c) Wharton, C. J.; Wrigglesworth, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 809.

Scheme 3. Synthesis Route for Phthalazinones



In our catalytic system, this phthalazinon skeleton can be obtained in high yields when hydrazine or phenyl hydrazine is used as the ammonia source instead of amines under a nitrogen atomosphere (Scheme 3). The reaction requires only 0.5 h using Pt NWs as the catalyst which is more active than reported solid-acid catalysts or other catalysis procedures.[14]

In conclusion, *N*-substituted isoindolinones and phthalazinones have been successfully synthesized from the amination and intramolecular amidation of 2-carboxybenzaldehyde and amines or hydrazines in one pot using highly active and stable Pt NWs as the catalyst. The reaction is simple, efficient, and environmentally friendly which facilitates the preparation of cyclic amides. Further study of this catalytic system for wider application is under investigation in our laboratory.

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Supporting Information Available. Experimental procedures include Pt NWs synthesis, characterization, and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.