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A Catalyst-Free One-Pot Protocol for the Construction of Substituted Isoindolinones under Sustainable Conditions

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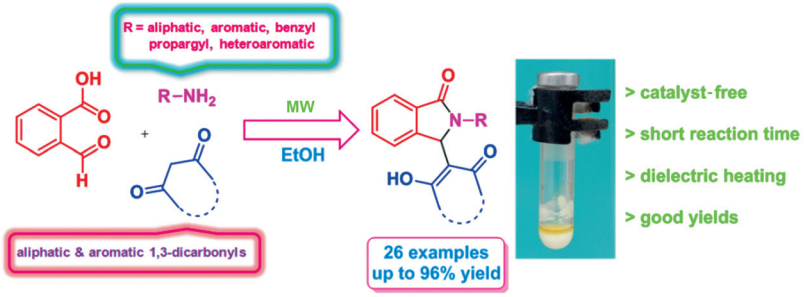

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Abstract An operationally simple, one-pot, catalyst-free method was developed for the synthesis of pharmaceutically important substituted isoindolinones by a three-component reaction of 2-formylbenzoic acid, a primary amine, and a 1,3-dione in ethanol under dielectric heating.

Key words isoindolinones, medicinal chemistry, multicomponent reaction, formylbenzoic acid, amines, diones

The isoindolinone motif is present in many natural and synthetic compounds with important biological properties.[1] A representative natural product that contains this framework is hericerin (**1**; Figure 1), isolated from the edible mushroom *Hericium erinaceus*, used in traditional Chinese medicine for the treatment of dyspepsia, gastric ulcers, and enervation.[2] Clitocybin A (**2**) is a novel isoindolinone with free-radical-scavenging activity, isolated from the culture broth of the mushroom *Clitocybe aurantiaca*.[3] Nuevamine (**3**) is an isoindolo[1,2-*a*]isoquinolinone alkaloid.[4]

The isoindolinone motif is also present in many pharmaceutically interesting compounds such as pazinaclone (**4**; Figure 1), which is used as an anxiolytic,[5] lenalidomide (Revlimid, **5**), used as an anticancer agent for the treatment of multiple myeloma,[6] and indoprofen (**6**), used as a nonsteroidal antiinflammatory drug.[7]

Consequently, the development of new and efficient methods for the synthesis of 3-substituted isoindolinones is an area of current interest.[8] General methods for the synthesis of isoindolinones include nucleophilic addition of organometallic reagents,[9] palladium-catalyzed isocyanide insertion,[10] or rhodium/ruthenium-catalyzed annulation.[11] Additionally, metal-free catalytic systems consisting of tetrabutylammonium acetate or triflic acid have also been developed for the preparation of isoindolinone-type compounds.[12] Interestingly, 2-formylbenzoic acid has been employed as a key starting material in a one-pot, three-component reaction with amines and appropriate nucleophiles such as benzimidazoles,[13a] dimethyl phosphate,[13b] or β-dicarbonyl compounds[13c] for the synthesis of isoindolinones. However, despite their significant contributions in the development of efficient methodologies, these methods suffer from one or more limitations, such as poor substrate scopes, high temperatures, or long reaction times. In addition, some of these procedures require specific nucleophilic reagents (such as Grignard reagents), harsh

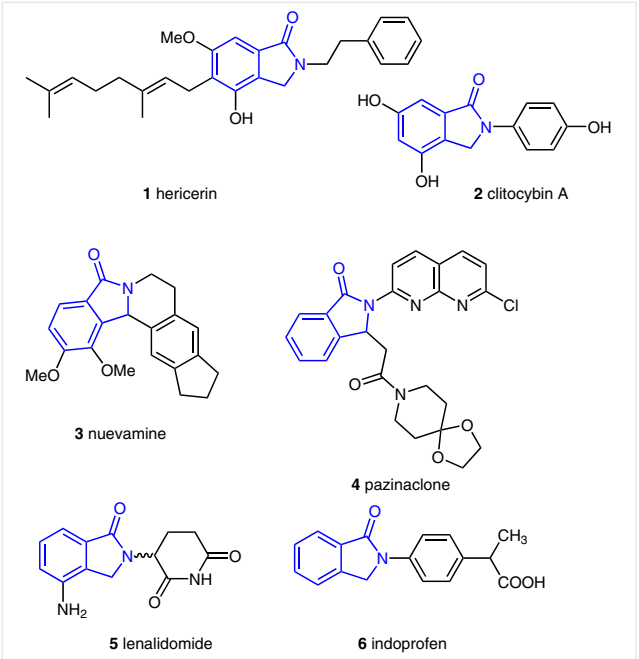


Figure 1 Examples of natural and synthetic pharmacologically active isoindolinone-containing frameworks

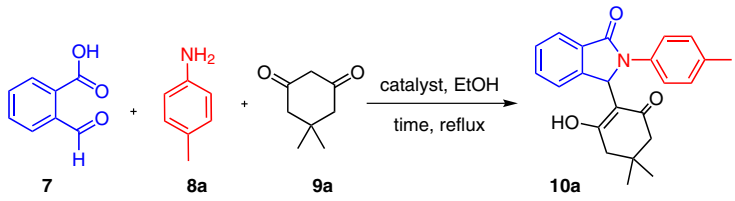
reaction conditions (such as an anhydrous environment), or expensive metal catalysts, which might prevent the elaboration of some sensitive isoindolin-1-ones. Therefore, it was imperative to develop mild and practical protocols involving easily available materials to synthesize a library of bioactive isoindolin-1-ones.

Microwave-assisted chemical synthesis is an emerging technology in medicinal chemistry because microwaves have specific effects that cannot be achieved by conventional heating.[14] Microwaves induce efficient internal heating by the interaction of the electric-field component of high-frequency electromagnetic radiation with dipoles in the reaction mixture.[15]

Multicomponent reactions have emerged as powerful tools in organic, combinatorial, and medicinal chemistry because of their high bond-forming efficiency.[16] In multicomponent cascade or domino reactions, three or more reactants proceed through multiple transformations to give complex heterocyclic compounds from simple starting materials with several new carbon–carbon or carbon–heteroatom bonds being formed in a single operation.[17] As part of our continued interest in developing novel efficient reactions for the synthesis of medicinally important heterocyclic compounds,[18] we report a successful one-pot multicomponent reaction for the synthesis of isoindolinone derivatives under sustainable reaction conditions. The three-component condensation reaction can be carried out efficiently to obtain 3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-2-phenylisoindolin-1-one derivatives in satisfactory yields from 2-formylbenzoic acid, an aromatic, heteroaromatic, or aliphatic primary amine, and a cyclohexane-1,3-dione derivative as the starting materials.

To achieve this goal, we performed preliminary experiments with 2-formylbenzoic acid (**7**), *p*-toluidine (**8a**), and 5,5-dimethylcyclohexane-1,3-dione (**9a**; dimedone) in refluxing ethanol in the absence of a catalyst, which gave isoindolin-1-one **10a** in 34% yield (Table 1, entry 1). To optimize the reaction conditions, we examined the use of the various Lewis acids (entries 2–12). To our delight, $CeCl_3·7H_2O$ effectively catalyzed the cyclization to give the isoindolin-

Table 1 Optimization of the Reaction Conditions[a]



7 **8a** **9a** **10a**

Entry	Catalyst (equiv)	Time (h)	Yield[b] (%)
1	–	5.0	34
2	$ZnCl_2$ (0.3)	5.0	40
3	$FeCl_3$ (0.3)	5.0	38
4	$AlCl_3$ (0.3)	5.0	40
5	$SnCl_2$ (0.3)	5.0	40
6	$CuCl_2$ (0.3)	5.0	35
7	$BiCl_3$ (0.3)	5.0	36
8	$CeCl_3·7H_2O$ (0.3)	5.0	90
9	$InCl_3$ (0.3)	5.0	42
10	$HgCl_2$ (0.3)	5.0	40
11	AgOTf (0.3)	5.0	41
12	$AuCl_3$ (0.3)	5.0	42
13	$CeCl_3·7H_2O$ (0.3)	4.0	88
14	$CeCl_3·7H_2O$ (0.3)	3.0	88
15	$CeCl_3·7H_2O$ (0.3)	2.0	88
16	**$CeCl_3·7H_2O$ (0.2)**	**2.0**	**88**
17	$CeCl_3·7H_2O$ (0.1)	2.0	80
18	$CeCl_3·7H_2O$ (0.2)	1.0	65

[a] Reaction conditions: 2-formylbenzoic acid (**7**; 1 mmol), *p*-toluidine (**8a**; 1 mmol), dimedone (**9a**) (1 mmol), EtOH (1 mL), 80 °C.
[b] Isolated yield.

1-one derivative **10a** in 90% yield (entry 8);[19] all the other catalysts proved less effective. Next, we screened the reaction time and catalyst loading with $CeCl_3·7H_2O$ as the catalyst (entries 13–18). The reaction occurred efficiently with 20 mol% of $CeCl_3·7H_2O$ in ethanol as solvent (entry 16). However, the yield of 34% under metal-free conditions was more interesting, and prompted us to develop a sustainable procedure that does not require the use of a catalyst.

In the field of synthetic chemistry, interest in microwave heating is increasing because it can induce fast, clean, high-yielding, and efficient reactions. We therefore carried out further optimizations under microwave conditions. We performed a control experiment under the optimized conventional reaction conditions, but with microwave irradiation to evaluate the feasibility of the process. The catalyst-containing mixture was stirred for one minute to dissolve the reactants and to obtain a clear solution, and then it was irradiated with microwaves for fifteen minutes to give a good yield of the final product (Table 2, entry 4). However, similar yields were obtained in shorter reaction times in the absence of a catalyst (entries 1–3), clearly indicating that a metal-free reaction is possible. Having identified the catalyst-free reaction, we performed solvent screening to find a suitable and relatively benign solvent, but the yields were lower than that obtained in ethanol (entries 5–13).

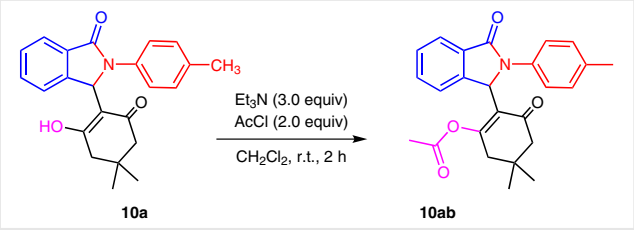
Table 2 Optimization of Microwave Reaction Conditions[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	EtOH	5	48
2	EtOH	10	72
3	**EtOH**	**15**	**92**
4[c]	EtOH	15	92
5	MeCN	15	65
6	AcOH	15	70
7	THF	15	40
8	DCE	15	58
9	PEG-400	15	52
10	acetone	15	46
11	DMF	15	75
12	H_2O	15	38
13	neat	15	–[d]

[a] Reaction conditions: 2-formylbenzoic acid (**7**; 1 mmol), *p*-toluidine (**8a**; 1 mmol), dimedone (**9a**; 1 mmol), solvent (1 mL), MW, 90 °C.
[b] Isolated yield.
[c] $CeCl_3·7H_2O$ (20 mol %) was used.
[d] Reactants were recovered along with the imine intermediate.

Isoindolin-1-one **10a** was characterized by means of spectral studies. The white solid showed a quasimolecular ion peak at *m/z* = 362.1370 in the HRMS spectrum, consistent with the molecular formula $C_{23}H_{23}NO_3$. The IR spectrum showed absorption bands for hydroxy (3404 cm^{-1}) and conjugated carbonyl (1622 cm^{-1}) functional groups. The ^{13}C and DEPT-135 NMR spectra (in pyridine-d_5) showed the presence of only twenty-one carbon resonances, corresponding to one carbonyl, one oxygenated aromatic quaternary, one amide quaternary, six sp^2 methine, four aromatic quaternary, two aliphatic methylene, two aliphatic methyl, one aromatic methyl, one aliphatic tertiary, and two aliphatic quaternary carbons. The ^1H NMR spectrum indicated the presence four protons of two methylene groups at δ = 2.27 (d, *J* = 16.6 Hz, 1 H), 2.09 (d, *J* = 16.6 Hz, 1 H), 2.01 (d, *J* = 16.8 Hz, 1 H), and 1.84 (d, *J* = 16.9 Hz, 1 H), along with three methyl groups at δ = 2.20 (s, 3 H), 0.89 (s, 3 H), and 0.49 (s, 3 H). In a COSY experiment, we observed a correlation between four *ortho*-coupled protons at δ = 7.28 (d, *J* = 7.8 Hz, 2 H) and 7.04 (d, *J* = 7.9 Hz, 2 H), indicating the presence of a 1,4-disubstituted aromatic ring, which explains the absence of two carbon signals in the ^{13}C NMR. Further, the key HMBC correlations of protons at δ_H = 6.43 (s, 1 H, H-3) with δ_C = 190.2 (C-18), 183.6 (C-22), 169.8 (C-1), 145.3 (C-9), 132.3 (C-8), 121.3 (C-4), 134.3 (C-10), and 108.5 (C-17) confirmed the formation of an isoindalone skeleton. On the basis of this spectral evidence, **10a** was confirmed to be 3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-(4-tolyl)isoindolin-1-one.

The presence of a hydroxy group in **10a** was further confirmed by the formation of its acetyl derivative in the presence of triethylamine and acetyl chloride in dichloromethane (Scheme 1).



Scheme 1 Acetylation of compound **10a**

Finally, the structure was confirmed by X-ray crystallography.[20] An ORTEP diagram of compound **10a** is shown in Figure 2.

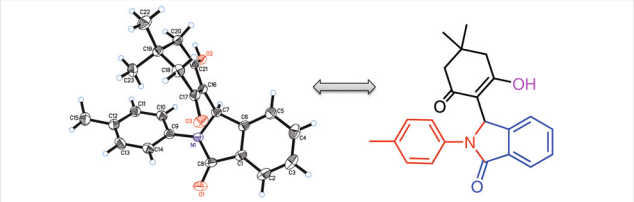
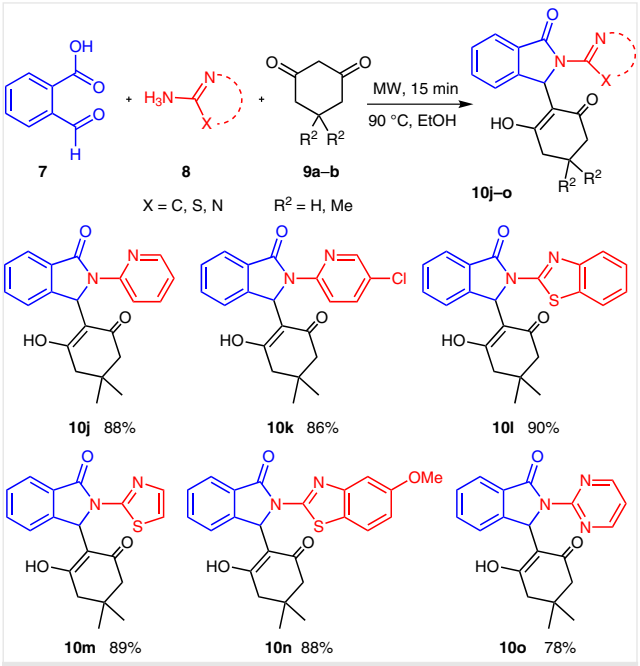


Figure 2 ORTEP diagram for compound **10a**

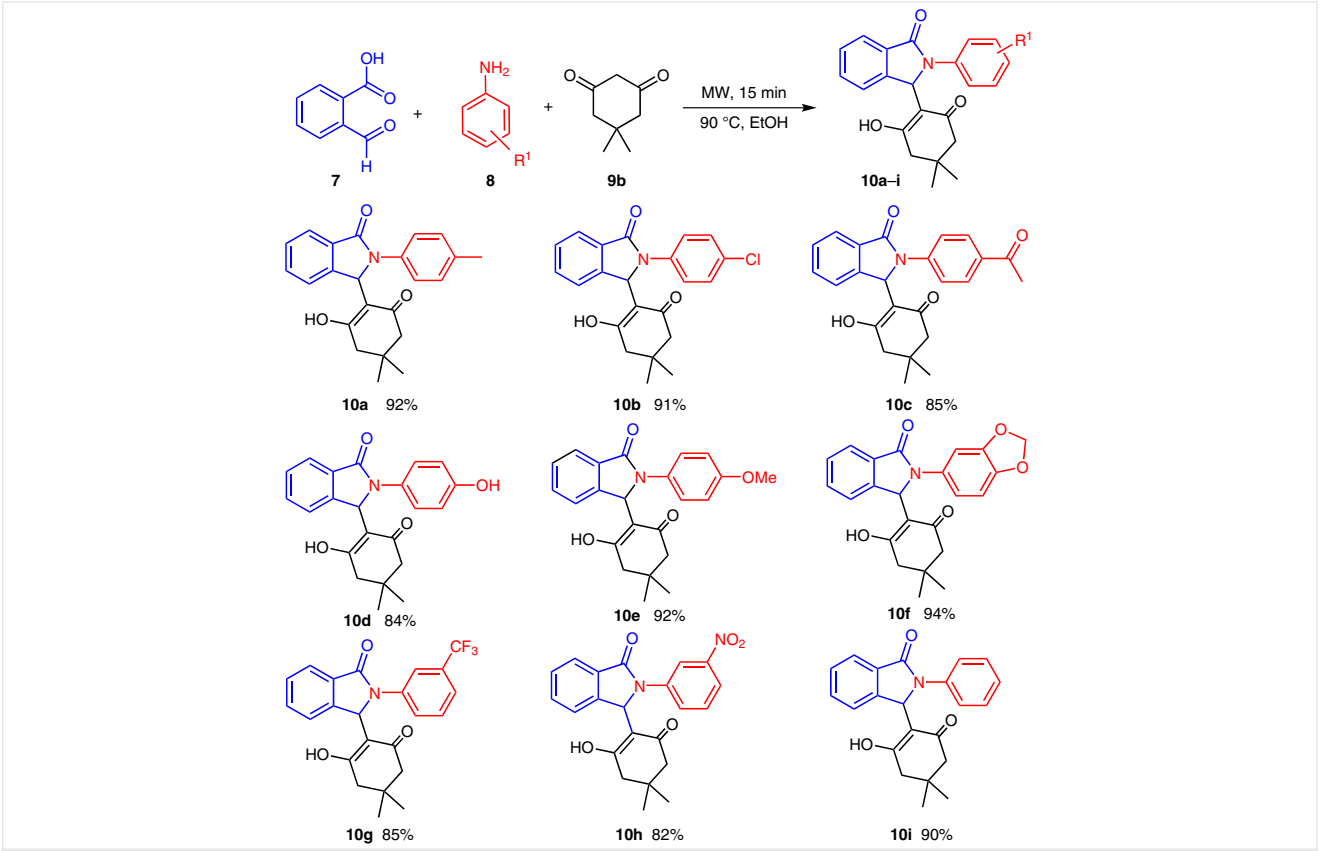
Next we screened a range of primary amines and cyclohexane-1,3-dione derivatives to test the scope of our new reaction. First, we studied the effect of substituents on the aniline reactant (Scheme 2). Under the optimized conditions, anilines containing either electron-donating or electron-withdrawing groups underwent cyclization. However, higher yields were observed in the case of anilines containing electron-donating groups. Under the same conditions, a trifluoromethyl aniline also underwent cyclization smoothly in high yield.

Next, the applicability of the reaction conditions to primary heteroaromatic amines was evaluated. Pyridin-2-amine, pyrimidin-2-amine, and various aminothiazole derivatives gave the corresponding cyclized products **10j–o** in good yields under the optimized reaction conditions (Scheme 3). Pyrimidin-2-amine gave a lower yield of the corresponding product than did pyridin-2-amine or the aminothiazoles.

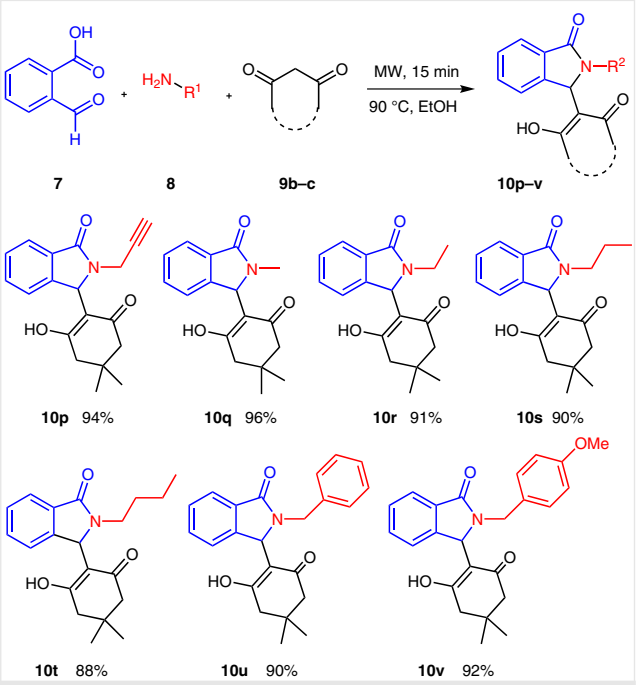
When propargyl, aliphatic, or benzylic amines were employed under the optimized reaction conditions, all gave good yields of the corresponding products (Scheme 4).



Scheme 3 Scope of heterocyclic amines under the optimized reaction conditions

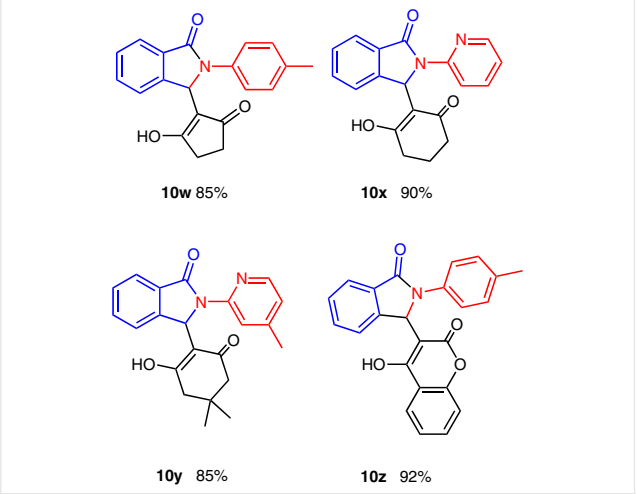


Scheme 2 Scope of aromatic amines under the optimized reaction conditions



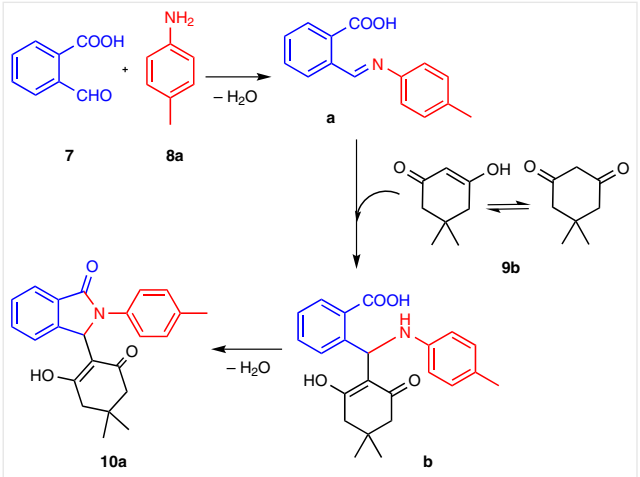
Scheme 4 Scope of amine diversification under optimized reaction conditions

It is noteworthy that five- or six-membered-ring aliphatic 1,3-diones, as well as their aromatic congeners, also worked well in this transformation (Scheme 5). After the completion of the reaction, product settled as a white solid in the reaction vial, and the pure product was obtained by simple filtration, without additional workup or column-purification steps. Homogeneous reaction mixtures were, however, purified by column chromatography.



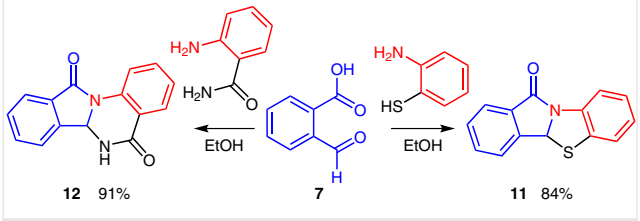
Scheme 5 Scope of 1,3-diones under the optimized reaction conditions

Our postulated mechanism for the formation of isoindolinones involves in situ formation of imine **a** from 2-formylbenzoic acid and *p*-toluidine (Scheme 6). This is followed by nucleophilic attack by the diketone on the imine to give the Michael addition product **b**. Further intramolecular nucleophilic cyclization of the amine gives the desired isoindolinone **10a**.



Scheme 6 Plausible mechanism for isoindolinone formation

The proposed mechanistic rationalization was confirmed by using 2-aminobenzenethiol or 2-aminobenzamide (which both have amine and nucleophilic groups in the same molecule) to synthesize fused isoindolinones **11** and **12** in good yields in the absence of a diketone (Scheme 7).[21] The formation of these fused isoindolinones supports our suggestion that nucleophilic attack by the diketone on the imine system occurs to form a Michael addition product.



Scheme 7 Synthesis of fused isoindolinones

In conclusion, we have successfully developed a rapid and efficient one-pot strategy for the synthesis of substituted isoindolinones through sequential multicomponent reactions. The scope of this reaction includes C–C, C–N, and C–S bond formation, resulting in a variety of substituted isoindolinones without the use of toxic heavy-metal catalysts. This cost-effective and metal-free strategy is expected to be of considerable interest to medicinal chemists for the synthesis of libraries of diverse isoindolinones for the drug-discovery

process. The simple reaction setup and the variety of commercially available starting materials are additional merits of this method.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562614.

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(19) **3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-(4-tolyl)isoindolin-1-one (10a); Typical Procedure**

A mixture of 2-formylbenzoic acid (**7**; 1.0 mmol), *p*-toluidine (**8a**; 1.0 mmol), and dimedone (**9b**; 1.0 mmol) in EtOH (1 mL) was stirred for 1 min and then subjected to microwave irradiation at 90 °C for 15 min. When the reaction was complete, the mixture was filtered and the product was dried to give a white solid; yield: 0.333 g (0.92 mmol, 92%); mp 264–266 °C; IR (KBr): 3404, 2922, 1622, 1206, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.4 Hz, 1 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.35 (t, *J* = 7.4 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 7.21 (d, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 7.9 Hz, 2 H), 6.43 (s, 1 H), 2.27 (d, *J* = 16.6 Hz, 1 H), 2.20 (s, 3 H), 2.09 (d, *J* = 16.6 Hz, 1 H), 2.01 (d, *J* = 16.8 Hz, 1 H), 1.84 (d, *J* = 16.9 Hz, 1 H), 0.89 (s, 3 H), 0.49 (s, 3 H). ^{13}C NMR (75 MHz, pyridine-d_5): δ = 190.2, 183.6, 169.4, 148.0, 138.2, 135.4, 134.9,

133.1, 130.6, 129.0, 124.4, 123.8, 123.6, 111.1, 57.6, 49.2, 47.9, 33.2, 29.7, 28.6, 22.0. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{24}NO_3$: 362.1751; found: 362.1730.

(20) CCDC 1460875 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(21) **Isoindolo[1,2-*b*][1,3]benzothiazol-11(4b*H*)-one (11); Typical Procedure**

A mixture of 2-formylbenzoic acid (**7**, 1.0 mmol) and 2-aminobenzenethiol (1.0 mmol) in EtOH (1 mL) was stirred for 1 min then subjected to microwave irradiation at 90 °C for 15 min. When the reaction was complete (TLC), the excess EtOH was evaporated under reduced pressure and the residue was purified by column chromatography [silica gel, MeOH–CH_2Cl_2 (2:98)] to give a white solid; yield: 0.200 g (0.84 mmol, 84%); mp 173–175 °C. IR (KBr): 3404, 2922, 1622, 1206, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.3 Hz, 1 H), 7.68–7.63 (m, 2 H), 7.60–7.53 (m, 2 H), 7.22–7.16 (m, 2 H), 7.11–7.06 (m, 1 H), 6.99 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 143.1, 136.6, 135.9, 133.2, 132.7, 129.9, 125.9, 125.9, 125.2, 123.6, 123.1, 118.5, 69.2. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{10}NOS$: 240.0478; found: 240.0474.