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Ruthenium(II)-catalyzed *N*-substituted phthalimide synthesis via C–H activation/[3+2] annulation

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ABSTRACT

Ruthenium-catalyzed intermolecular [3 + 2] annulation pathway for aromatic acids with isocyanates to afford *N*-substituted phthalimide in one step is demonstrated, which provides an efficient process to direct preparation of phthalimide from commercially available starting materials and environmentally benign catalysts. This cascade cyclization involves the direct functionalization of an *ortho* C–H bond and the subsequent intramolecular nucleophilic substitution. There is no theoretical waste except for water generated in the reaction.

Introduction

N-Substituted phthalimides are well known as a core structure of numerous natural products and important biologically compounds [1]. They also make a vital contribution in the treatment of acquired immunodeficiency syndrome (AIDS) [2], leprosy [3], and other diseases [4]. Moreover, phthalimide derivatives have been found important applications as synthetic intermediates in pesticides [5], liquid crystals [6], and functional materials [7], polymer industries [8]. As a result, the synthesis of this privileged structure has attracted considerable attention. Typically, phthalimide derivatives are synthesized via the condensation of phthalic acids or anhydrides and amines [9]. However, the limited availability of differently substituted phthalic acids, mostly due to the harsh reaction conditions in their preparation, calls for alternative protocols. Alternative approaches include carbonylative cyclization of *ortho*-dihaloarenes or *ortho*-halobenzoates and primary amines [10]; cycloaminocarbonylation of *ortho*-dihaloarenes, *ortho*-halobenzoic acids, and *ortho*-haloesters with formamides [11]; reaction between 1,2-phenylenedimethanol and amines [12]; coupling of isocyanates with *ortho*-iodobenzoates [13]. Despite their advantages, these methods have a drawback in common: they require starting materials that are not readily available.

In recent years, the selective functionalization of C–H bonds in directing group-containing arenes has attracted a substantial interest attributable to the potential shortening of synthetic steps [14]. Meanwhile, the chelation-assisted transition metal-catalyzed C–H activation–annulation reaction has become one of the most important and powerful approaches for the construction of heterocyclic compounds in organic synthesis [15]. Employing this strategy, Chatani and Rovis developed sequentially ruthenium and rhodium catalyzed oxidative carbonylation phthalimide synthesis via C–H/N–H activation [16]. However, commercially unavailable starting reagents and the using of poisonous gas of carbon monoxide are the most disadvantages in these two reports. Very recently, direct synthesis of *N*-substituted phthalimides by amidation of benzoic acids was described [17]. But this method required an expensive rhodium catalyst and long reaction time.

Up to now, the use of Ru(II) complexes as inexpensive, readily available and environmentally benign catalysts for C–H activation reactions has received considerable attention [18]. Yet, there is only one report that utilized Ru catalyst in C–H activation directed by carboxyl group [19]. Our continuous interest in the metal-catalyzed functionalization of C–H promoted us to explore the ruthenium-catalyzed reactions of aromatic acids with isocyanates. Herein, the ruthenium-catalyzed C–H activation/annulation reaction for

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0022-328X/

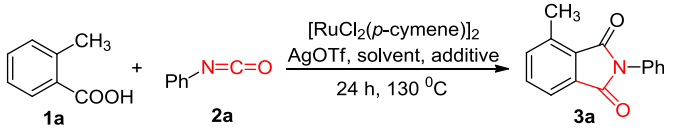
the facile preparation of *N*-substituted phthalimides via [3 + 2] annulation reaction from commercially available starting materials is presented.

Results and discussion

The cyclization reaction was carried out by using *o*-toluic acid and phenyl isocyanate as the starting materials. Gratifyingly, when *o*-toluic acid (**1a**) was treated with 2 equiv of phenyl isocyanate (**2a**) in the presence of 5 mol% $[RuCl_2(p\text{-cymene})]_2$, 25 mol% AgOTf and 2 equiv NaOAc at 130 °C for 24 h, the desired product was obtained in 39% yield (Table 1, entry 2). Control experiment revealed that the reaction did not proceed in the absence of ruthenium. However, there was no target product formed without NaOAc, suggesting that the salt is very crucial for the success of the present catalytic reaction. Therefore, a series of salts were examined for the reaction. Unfortunately, the uses of other alkali metal salts such as Na_2CO_3, K_2HPO_4 and Na_2HPO_4 exclusively decreased the yield of target product (Table 1, entries 3–5). Alternatively, acetates of metals other than sodium such as AgOAc, $Cu(OAc)_2$, $Cu(OAc)_2\cdot H_2O$, KOAc and CsOAc displayed a low or no catalytic activity (Table 1, entries 6–10). Ag_2CO_3 and Cs_2CO_3 also failed to give the target product (Table 1, entries 11 and 12).

A screening of solvents revealed that common solvent such as 1,4-dioxane, THF, PhCl, toluene and xylene also can be used in the titled reaction in addition to acetonitrile (Table 1, entries 13–17). 1,4-Dioxane is the best solvent for this transformation, in which **3a** is obtained in 55% yield. Subsequently, various conditions concerning the reaction time, the amount of isocyanate and additives was examined to optimize the formation of this cyclization product with 1,4-dioxane as the solvent. The yield of **3a** could be enhanced to 65% by increasing the amount of phenyl isocyanate from 2 equiv to 2.5 equiv (Table 1, entry 20). Then, the introduction of 25% CuI and CuBr as an additive increased the yield greatly to 81% and 78%, respectively (Table 1, entries 21 and 22).

Table 1
Selected results for the optimal reaction conditions.[a]



Entry	Additive (equiv)	Solvent	Yield[b] (%)
1	None	CH_3CN	0
2	NaOAc (2.0)	CH_3CN	39
3	K_2HPO_4 (2.0)	CH_3CN	10
4	Na_2CO_3 (2.0)	CH_3CN	7
5	Na_2HPO_4 (2.0)	CH_3CN	8
6	AgOAc (2.0)	CH_3CN	4
7	$Cu(OAc)_2$ (2.0)	CH_3CN	ND[c]
8	$Cu(OAc)_2\cdot H_2O$	CH_3CN	ND
9	CsOAc (2.0)	CH_3CN	ND
10	KOAc (2.0)	CH_3CN	ND
11	Ag_2CO_3	CH_3CN	ND
12	Cs_2CO_3	CH_3CN	ND
13	NaOAc (2.0)	1,4-Dioxane	55
14	NaOAc (2.0)	THF	43
15	NaOAc (2.0)	Toluene	24
16	NaOAc (2.0)	C_6H_5Cl	34
17	NaOAc (2.0)	Xylene	35
18[d]	NaOAc (2.0)	1,4-Dioxane	26
19[e]	NaOAc (2.0)	1,4-Dioxane	54
20[f]	NaOAc (2.0)	1,4-Dioxane	65
21[f]	NaOAc (2.0), CuBr (0.25)	1,4-Dioxane	78
22[f]	NaOAc (2.0), CuI (0.25)	1,4-Dioxane	81(76)[g]

[a] Reaction conditions: **1a** (0.1 mmol), **2b** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), AgOTf (25 mol%), additive, solvent (0.5 mL), 130 °C for 24 h, under argon in pressure tubes.
[b] Determined by ^1H NMR analysis of the crude reaction mixture using mesitylene as internal standard.
[c] ND = not detected.
[d] Run at 115 °C.
[e] Run at 150 °C.
[f] Phenyl isocyanate (0.25 mmol) was used.
[g] Isolated yield.

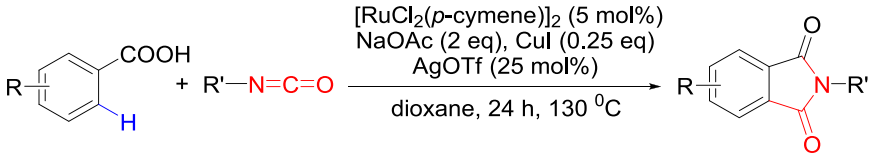
Having these satisfactory results, the substrate scope was examined with respect to the benzoic acid derivatives and phenyl isocyanate (Table 2, compounds **3b**–**3m′**). A significant electronic effect of the substituent on the reactivity was observed. Benzoic acid afforded the *N*-substituted phthalimide in 55% (**3b**). The strong electron withdrawing group such as NO_2, obviously restrained the reaction and could not afford the desired product under the standard reactions. It was found that the moderate yields of cyclization products were obtained when methyl was introduced to the aromatic acid ring (**3c**–**3g**). Contrary to our previous report [17], 2-methoxylbenzoic acid was found to be compatible in this catalysis system and provided the desired products in 33% (**3h**).

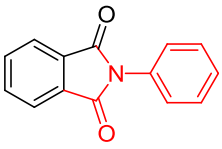
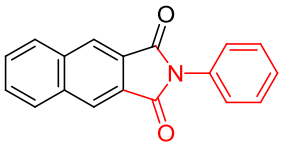
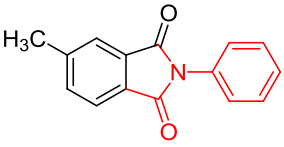
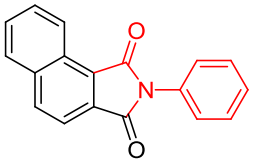
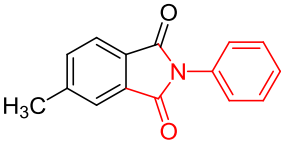
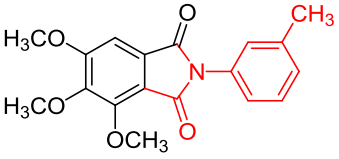
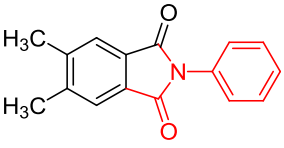
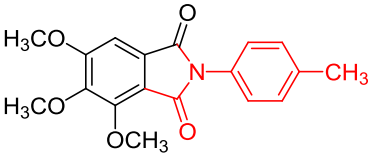
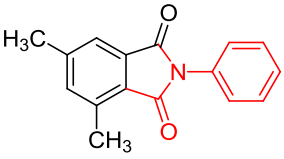
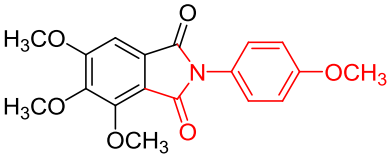
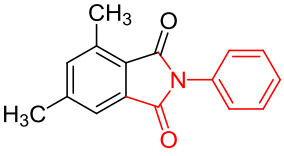
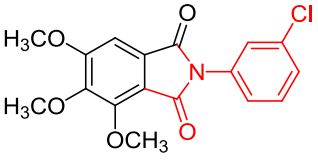
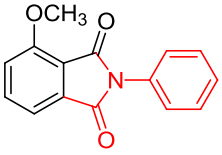
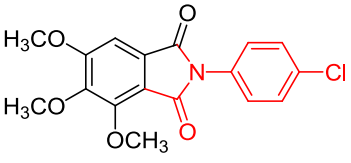
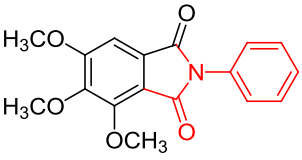
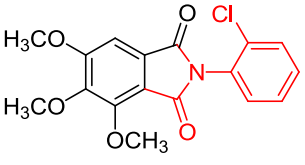
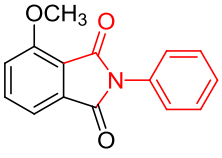
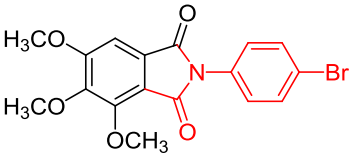
Compared with other benzoic acids, *meta*-alkoxy and *meta*-boc-amino substituted benzoic acids were easily converted into the corresponding products in a higher yield, and non-symmetrical *meta*-substituted benzoic acids afforded two isomers (**3i**–**3l′**). In this case, there are two possible C–H activation sites: C2 and C6. For example, 76% yield of desired product was isolated using 3,4,5-trimethoxylbenzoic acid (**3i**). Piperonylic acid produced a 9:5 (**3k**, **3k′**) mixture of products and 3-methoxylbenzoic acid gave two regioisomers in a ratio of 39:35 (**3j**, **3j′**). As for *meta*-Boc-amino benzoic acid, the activation occurred at the sterically less hindered C6 rather than C2 (**3l**, **3l′**). In addition, 2-naphthoic acid also underwent the reaction to generate the two corresponding products **3m** and **3m′**.

To further explore the scope of the reaction, we investigated the reactions of various isocyanates with 3,4,5-trimethoxylbenzoic acid under the optimized conditions (**3n**–**3x**). 3-Methyl, 4-methyl, 4-methoxyl phenylisocyanates afforded the corresponding products in good yields of 70%, 64%, and 52%, respectively (**3n**, **3o**, **3p**). This reaction was also compatible with halogen-substituted phenylisocyanates furnishing the respective products in good yields (**3q**–**3t**). Particularly noteworthy was that halo groups (Cl, Br) on the aromatic ring of isocyanate remained intact in the product, which provided the possibility for the further useful transformations through common cross-coupling strategies. This transformation tolerated dual-substitution, for example, 3,5-dimethylphenyl isocyanate and 3,4-dichlorophenyl isocyanate proceeded smoothly to afford products in 55% and 68% yields, respectively (**3u**, **3v**). However, 4-nitrophenyl isocyanate only gave a low yield (20% ^1H NMR yield) of desired product. The *N*-substituents are not limited to aryl groups. *N*-Butyl, *N*-2-chloroethyl substracts also can react with 3,4,5-trimethoxylbenzoic acid in somewhat lower yield (**3w**, **3x**).

Based on the known metal-catalyzed, directing-group assisted C–H bond activation reactions, a possible mechanism to account for this reaction is proposed in Scheme 1. First dissociation of the dimer precatalyst $[RuCl_2(p\text{-cymene})]_2$ gives the coordinatively unsaturated monomer, which undergoes a ligand exchange with AgOTf to give the species **A**. With the help of NaOAc, five-membered intermediate **C** is formed by an O-metalation C–H activation with concomitant formation of trifluoroacetic acid. After coordination with isocyanate and insertion of C=N bond to the intermediate C, the ruthenium alkoxide E is generated together with the formation of a new C–C bond. The intramolecular nucleophilic substitution of ruthenium alkoxide E provides the final product F and regenerates the active Ru species.

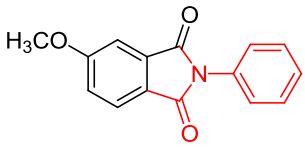
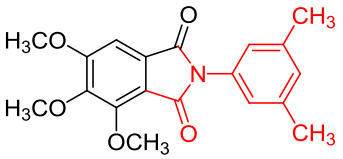
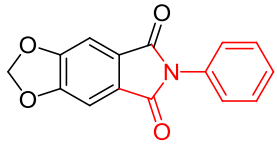
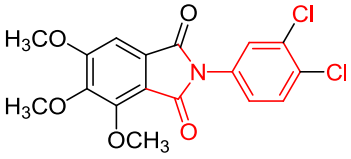
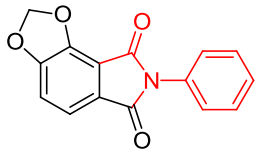
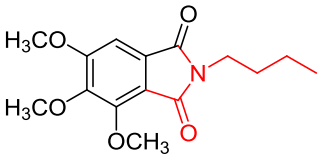
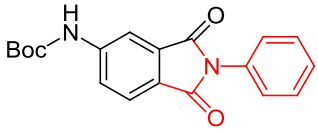
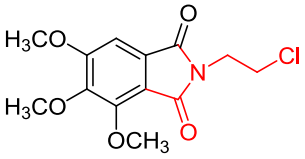
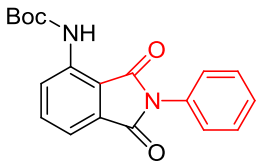
Table 2
Substrate scope for the synthesis of phthalimides via C–H functionalization.[a]



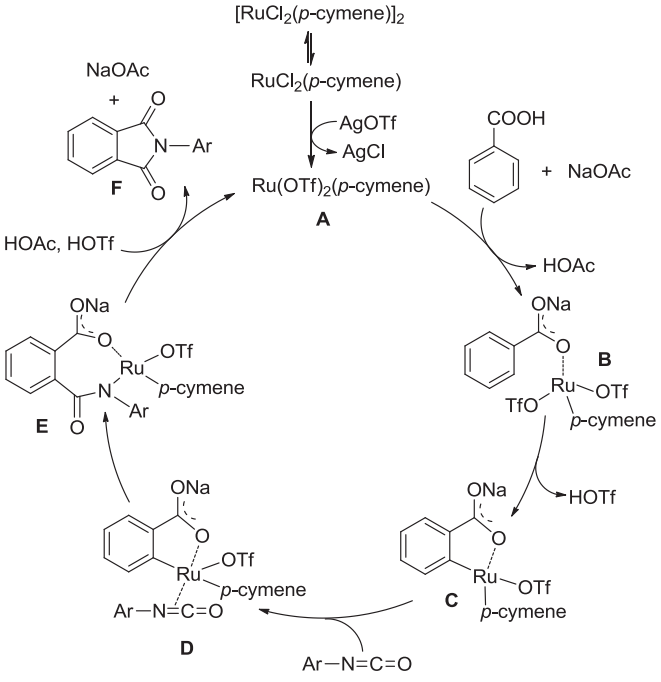
Entry	Product		Yield (%)	Entry	Product		Yield (%)
1		**3b**	55	12		**3m**	52 (22:30)
2		**3c**	50			**3m′**	
3		**3d**	43	13		**3n**	70
4		**3e**	52	14		**3o**	64
5		**3f**	56	15		**3p**	52
6		**3g**	45	16		**3q**	62
7		**3h**	33	17		**3r**	80
8		**3i**	76	18		**3s**	73
9		**3j**	74 (39:35)	19		**3t**	63

(*continued on next page*)

Table 2 (*continued*)

Entry	Product		Yield (%)	Entry	Product		Yield (%)
		**3j′**		20		**3u**	55
10		**3k**	70 (45:25)	21		**3v**	68
		**3k′**		22		**3w**	33
11		**3l**	77 (67:10)	23		**3x**	27
		**3l′**					

[a] Reaction conditions: substituted benzoic acid (0.2 mmol), isocyanate (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), AgOTf (25 mol%), NaOAc (2 equiv), CuI (0.25 equiv), solvent (1.0 mL), 130 °C for 24 h, under argon in pressure tubes. Yield of purified product is reported.



Scheme 1. Plausible mechanism for the ruthenium-catalyzed cascade cyclization.

Conclusion

In summary, we have developed a Ru(II)-catalyzed [3 + 2] cascade cyclization reaction of aromatic acids with isocyanates. This protocol, which provides a convenient access to the synthesis of useful *N*-substituted phthalimides derivatives, allows us to use cheap Ru(II) as catalyst, readily available acids and isocyanates as starting materials. This methodology is expected to be an important route for the synthesis of natural products and biological active substance.

Experimental section

General

All commercials were used as received without further purification. ^{1}H NMR spectra were measured on a 300 MHz, 400 MHz or 500 MHz spectrometer, ^{13}C NMR spectra were measured on a 500 MHz spectrometer or 600 MHz spectrometer (^{13}C NMR 125 MHz or 150 MHz), with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in hertz (Hz). High-resolution mass spectra (HRMS) were obtained from a Bruker Avance Mass Spectrometer (maXis, ESI).

General experimental procedure for the synthesis of N-substituted phthalimide

A mixture of $[RuCl_2(p\text{-cymene})]_2$ (6.1 mg, 0.01 mmol, 5 mol%) and AgOTf (12.8 mg, 0.05 mmol, 25 mol%) in 0.1 mL dioxane in an oven-dried tube was stirred at room temperature for about 30 min. Then, substituted benzoic acid (0.2 mmol), isocyanates (0.5 mmol), NaOAc (32.8 mg, 0.4 mmol, 200 mol%), and CuI (9.5 mg, 0.05 mmol, 25 mol%) were added. After the tube was evacuated and purged with argon three times, the remaining dioxane was added to the system by syringe. The mixture was stirred at 130 °C for 24 h. When the reaction completed, the resulting mixture was cooled to room temperature, filtered through a short silica gel pad, transferred to silica gel column directly and eluted with hexane and dichloroethane or dichloroethane to give the products.

Charaterization data of the desired products

*4-Methyl-2-phenylisoindoline-1,3-dione (**3a**) [20]*

White solid (76% yield, 18.0 mg): mp 150–151 °C, R_f = 0.7 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.78 (d, J = 7.32 Hz, 1H), 7.64 (t, J = 7.54 Hz, 1H), 7.54–7.48 (m, 3H), 7.44–7.38 (m, 3H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 168.1, 167.3, 138.5, 136.7, 133.9, 132.2, 131.7, 129.1, 128.4, 128.0, 126.7, 121.4, 17.8. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_2$, [M+Na] 260.0687; found: 260.0675.

*2-Phenylisoindoline-1,3-dione (**3b**) [21]*

White solid (55% yield, 24.5 mg): mp 197–199 °C, R_f = 0.6 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.98–7.94 (m, 2H), 7.82–7.77 (m, 2H), 7.53–7.50 (m, 2H), 7.45–7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.3, 134.4, 131.7, 131.6, 129.1, 128.1, 126.6, 123.7. HRMS (ESI) m/z: calculated for $C_{14}H_9NO_2$, [M+Na] 246.0531; found: 246.0521.

*5-Methyl-2-phenylisoindoline-1,3-dione (**3c**) [21]*

White solid (50% yield, 23.7 mg): mp 213–214 °C, R_f = 0.7 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83 (d, J = 7.64 Hz, 1H), 7.76 (s, 1H), 7.58 (d, J = 7.64 Hz, 1H), 7.52–7.47 (m, 2H), 7.44–7.38 (m, 3H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.5, 167.4, 145.8, 135.0, 132.1, 131.7, 129.13, 129.09, 128.0, 126.6, 124.2, 123.7, 22.1. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_2$, [M+Na] 260.0687; found: 260.0677.

*5-Methyl-2-phenylisoindoline-1,3-dione (**3d**) [21]*

White solid (43% yield, 20.3 mg): mp 213–214 °C, R_f = 0.7 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83 (d, J = 7.64 Hz, 1H), 7.76 (s, 1H), 7.58 (d, J = 7.64 Hz, 1H), 7.52–7.47 (m, 2H), 7.44–7.38 (m, 3H), 2.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.5, 167.4, 145.8, 135.0, 132.1, 131.7, 129.13, 129.09, 128.0, 126.6, 124.2, 123.7, 22.1. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_2$, [M+Na] 260.0687; found: 260.0677.

*5,6-Dimethyl-2-phenylisoindoline-1,3-dione (**3e**) [10a]*

White solid (52% yield, 26.1 mg): mp 196–197 °C, R_f = 0.6 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.61 (s, 2H), 7.44–7.30 (m, 5H), 2.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 167.6, 144.1, 132.0, 129.7, 129.0, 127.8, 126.5, 124.6, 20.6. HRMS (ESI) m/z: calculated for $C_{16}H_{13}NO_2$, [M+Na] 274.0844; found: 274.2747.

*4,6-Dimethyl-2-phenylisoindoline-1,3-dione (**3f**) [17]*

White solid (56% yield, 28.1 mg): mp 122–123 °C, R_f = 0.8 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.59 (s, 1H), 7.51–7.48 (m, 2H), 7.43–7.37 (m, 3H), 7.33 (s, 1H), 2.70 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 168.0, 167.5, 145.1, 138.2, 137.2, 132.5, 131.8, 129.0, 127.8, 126.6, 125.8, 122.0, 21.8, 17.6. HRMS (ESI) m/z: calculated for $C_{16}H_{13}NO_2$, [M+H] 252.1052; found: 252.1013.

*4,6-Dimethyl-2-phenylisoindoline-1,3-dione (**3g**) [17]*

White solid (45% yield, 22.6 mg): mp 122–123 °C, R_f = 0.8 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.58 (s, 1H), 7.51–7.47 (m, 2H), 7.43–7.38 (m, 3H), 7.33 (s, 1H), 2.69 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 168.0, 167.5, 145.1, 138.2, 137.2, 132.5, 131.8, 129.0, 127.8, 126.6, 125.8, 122.0, 21.8, 17.6. HRMS (ESI) m/z: calculated for $C_{16}H_{13}NO_2$, [M+H] 252.1052; found: 252.1013.

*4-Methoxy-2-phenylisoindoline-1,3-dione (**3h**) [17]*

White solid (33% yield, 16.7 mg): mp 177–179 °C, R_f = 0.3 (*n*-hexane/dichloroethane = 1:2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.85 (d, J = 8.31 Hz, 1H), 7.53–7.50 (m, 2H), 7.48–7.37 (m, 4H), 7.23 (dd, J = 8.31 Hz, 2.31 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.1, 167.0, 164.9, 134.3, 131.8, 129.0, 127.9, 126.5, 125.4, 123.5, 120.4, 108.1, 56.1. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_3$, [M+Na] 276.0637; found: 276.0629.

*4,5,6-Trimethoxy-2-phenylisoindoline-1,3-dione (**3i**) [17]*

White solid (76% yield, 47.6 mg): mp 149–150 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.52–7.47 (m, 2H), 7.42–7.36 (m, 3H), 7.27 (s, 1H), 4.19 (s, 3H), 4.01 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.7, 165.3, 158.9, 151.8, 146.5, 131.7, 129.0, 128.4, 127.8, 126.5, 114.6, 102.7, 62.6, 61.5, 56.7. HRMS (ESI) m/z: calculated for $C_{17}H_{15}NO_5$, [M+Na] 336.0848; found: 336.0846.

*4-Methoxy-2-phenylisoindoline-1,3-dione (**3j**) [22]*

White solid (39% yield, 19.7 mg): mp 177–179 °C, R_f = 0.3 (*n*-hexane/dichloroethane = 1:2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.85 (d, J = 8.31 Hz, 1H), 7.53–7.50 (m, 2H), 7.48–7.37 (m, 4H), 7.23 (dd, J = 8.31 Hz, 2.31 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.1, 167.0, 165.0, 134.3, 131.7, 129.0, 127.9, 126.5, 125.4, 123.5, 120.4, 108.1, 56.1. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_3$, [M+Na] 276.0637; found: 276.0629.

*5-Methoxy-2-phenylisoindoline-1,3-dione (**3j′**) [17]*

White solid (35% yield, 17.7 mg): mp 182–183 °C, R_f = 0.4 (*n*-hexane/dichloroethane = 1:2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.73 (dd, J = 8.34 Hz, 7.35 Hz, 1H), 7.55–7.38 (m, 6H), 7.26 (d, J = 8.4 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.0, 165.8, 157.0, 136.5, 133.8, 131.6, 129.0, 127.9, 126.6, 117.7, 116.9, 115.8, 56.3. HRMS (ESI) m/z: calculated for $C_{15}H_{11}NO_3$, [M+Na] 276.0637; found: 276.0642.

*6-Phenyl-5H-[1,3]dioxolo [4,5-f]isoindole-5,7(6H)-dione (**3k**) [17]*

White solid (45% yield, 24.0 mg): mp 80–82 °C, R_f = 0.7 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.51–7.47 (m, 2H), 7.42–7.36 (m, 3H), 7.31 (s, 2H), 6.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.7, 153.0, 131.8, 129.0, 127.9, 127.3, 126.4, 104.0, 103.1. HRMS (ESI) m/z: calculated for $C_{15}H_9NO_4$, [M+H] 268.0610; found: 268.0597.

*7-Phenyl-6H-[1,3]dioxolo [4,5-e]isoindole-6,8(7H)-dione (**3k′**) [17]*

White solid (25% yield, 13.4 mg): mp 245–247 °C, R_f = 0.6 (dichloroethane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.53–7.47 (m, 3H), 7.43–7.37 (m, 3H), 7.10 (d, J = 7.76 Hz, 1H); 6.28 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.3, 164.3, 154.4, 144.0, 131.6, 129.1, 128.1, 126.6, 124.9, 119.3, 112.2, 111.7, 104.0. HRMS (ESI) m/z: calculated for $C_{15}H_9NO_4$, [M+H] 268.0610; found: 268.0598.

*tert-Butyl(1,3-dioxo-2-phenylisoindolin-5-yl)carbamate (**3l**) [17]*

White solid (67% yield, 45.3 mg): mp 181–183 °C, R_f = 0.3 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.99 (d, J = 1.83 Hz, 1H), 7.85 (d, J = 8.19 Hz, 1H), 7.75 (dd, J = 8.22 Hz, 1.92 Hz, 1H), 7.52–7.36 (m, 5H), 6.96 (s, 1H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.9, 166.88, 151.9, 144.5, 133.5, 131.8, 129.0, 128.0, 126.5, 125.3, 124.9, 122.6, 112.9, 82.0, 28.2. HRMS (ESI) m/z: calculated for $C_{19}H_{18}N_2O_4$, [M−H] 337.1188; found: 337.1192.

*tert-Butyl(1,3-dioxo-2-phenylisoindolin-4-yl)carbamate (**3l′**) [17]*

Yellow solid (10% yield, 6.8 mg): mp 125–127 °C, R_f = 0.7 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.91 (s, 1H), 8.58 (d, J = 8.46 Hz, 1H), 7.73–7.68 (m, 1H), 7.55–7.53 (m, 3H), 7.43–7.41 (m, 3H), 1.54 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 169.0, 166.8, 152.2, 138.6, 136.1, 131.30, 131.27, 129.1, 128.1, 126.3, 123.5, 117.2, 114.5, 81.8, 28.2. HRMS (ESI) m/z: calculated for $C_{19}H_{18}N_2O_4$, [M+H] 339.1345; found: 339.1335.

*2-Phenyl-1H-benzo[f]isoindole-1,3(2H)-dione (**3m**) [17]*

Yellow solid (22% yield, 12.0 mg): mp 285–287 °C, R_f = 0.6 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.46 (s, 2H), 8.10–8.09 (m, 2H), 7.74–7.72 (m, 2H), 7.54–7.493 (m, 5H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm) 167.2, 135.6, 132.4, 130.8, 129.9, 129.3, 128.8, 127.84, 127.76, 125.3. HRMS (ESI) m/z: calculated for $C_{18}H_{11}NO_2$, [M+H] 274.0868; found: 274.0862.

*2-Phenyl-1H-benzo[e]isoindole-1,3(2H)-dione (**3m′**) [17]*

Yellow solid (30% yield, 16.4 mg): mp 170–171 °C, R_f = 0.8 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.01 (d, J = 8.28 Hz, 1H), 8.24 (d, J = 8.24 Hz, 1H), 8.01–7.95 (m, 2H), 7.79–7.67 (m, 2H), 7.56–7.49 (m, 4H), 7.45–7.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 168.5, 167.8, 136.8, 135.4, 131.3, 131.0, 129.7, 129.1, 128.9, 128.8, 128.1, 127.9, 126.9, 126.6, 125.1, 118.7. HRMS (ESI) m/z: calculated for $C_{18}H_{11}NO_2$, [M+H] 274.0868; found: 274.0859.

*4,5,6-Trimethoxy-2-(m-tolyl)isoindoline-1,3-dione (**3n**)*

White solid (70% yield, 45.8 mg): mp 139–140 °C, R_f = 0.5 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.37 (t, J = 7.68 Hz, 1H), 7.25 (s, 1H), 7.20–7.18 (m, 3H), 4.18 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.8, 165.4, 158.9, 151.8, 146.5, 138.9, 131.6, 128.8, 128.5, 127.2, 123.7, 114.6, 102.7, 62.6, 61.5, 56.7, 21.3. HRMS (ESI) m/z: calculated for $C_{18}H_{17}NO_5$, [M+H] 328.1185; found: 328.1187.

*4,5,6-Trimethoxy-2-(p-tolyl)isoindoline-1,3-dione (**3o**) [17]*

White solid (64% yield, 41.9 mg): mp 169–170 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.27 (s, 4H), 7.24 (s, 1H), 4.17 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.9, 165.4, 158.8, 151.7, 146.4, 137.9, 129.6, 129.0, 128.5, 126.4, 114.6, 102.6, 62.5, 61.4, 56.7, 21.1. HRMS (ESI) m/z: calculated for $C_{18}H_{17}NO_5$, [M+H] 328.1185; found: 328.1177.

*4,5,6-Trimethoxy-2-(4-methoxyphenyl)isoindoline-1,3-dione (**3p**) [17]*

White solid (52% yield, 35.7 mg): mp 163–164 °C, R_f = 0.17 (dichloroethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.30 (d, J = 9.0 Hz, 2H), 7.25 (s, 1H), 7.00 (d, J = 9.0 Hz, 2H), 4.18 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 167.0, 165.6, 159.1, 158.8, 151.8, 146.4, 128.5, 127.9, 124.4, 114.6, 114.4, 102.7, 62.6, 61.5, 56.8, 55.5. HRMS (ESI) m/z: calculated for $C_{18}H_{17}NO_6$, [M+H] 344.1134; found: 344.1136.

*2-(3-Chlorophenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3q**)*

White solid (62% yield, 43.0 mg): mp 164–166 °C, R_f = 0.2 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.48–7.46 (m, 1H), 7.34–7.31 (m, 2H), 7.36–7.25 (m, 1H), 7.20 (s, 1H), 4.11 (s, 3H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.2, 164.7, 159.0, 152.0, 146.6, 133.3, 130.8, 130.5, 130.4, 129.8, 128.6, 127.7, 114.7, 102.9, 62.7, 61.5, 56.8. HRMS (ESI) m/z: calculated for $C_{17}H_{14}ClNO_5$, [M+Na] 370.0458; found: 370.0469.

*2-(4-Chlorophenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3r**) [17]*

White solid (80% yield, 55.5 mg): mp 187–188 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.44 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 4.17 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.5, 164.9, 159.1, 151.8, 146.6, 133.5, 130.3, 129.1, 128.2, 127.6, 114.5, 102.8, 62.5, 61.5, 56.8. HRMS (ESI) m/z: calculated for $C_{17}H_{14}ClNO_5$, [M+H] 348.0639; found: 348.0636.

*2-(2-Chlorophenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3s**)*

White solid (73% yield, 50.7 mg): mp 137–139 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.54–7.53 (m, 1H), 7.41–7.37 (m, 2H) 7.33–7.31 (m, 1H), 7.26 (s, 1H), 4.18 (s, 3H), 3.98 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.1, 164.6, 158.9, 151.9, 146.4, 133.2, 130.7, 130.4, 130.2, 129.7, 128.5, 127.6, 114.6, 102.8, 62.5, 61.4, 56.7. HRMS (ESI) m/z: calculated for $C_{17}H_{14}ClNO_5$, [M+Na] 370.0458; found: 370.0453.

*2-(4-Bromophenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3t**)*

White solid (63% yield 49.3 mg): mp 158–159 °C, R_f = 0.5 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.61 (d, J = 8.58 Hz, 2H), 7.32 (d, J = 8.58 Hz, 2H), 7.25 (s, 1H), 4.17 (s, 3H), 4.00 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.4, 164.9, 159.1, 151.9, 146.7, 132.1, 130.9, 128.3, 127.9, 121.5, 114.6, 102.8, 62.6, 61.5, 56.8. HRMS (ESI) m/z: calculated for $C_{17}H_{14}BrNO_5$, [M+H] 392.0134; found: 392.0128.

*2-(3,5-Dimethylphenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3u**)*

White solid (55% yield, 37.5 mg): mp 152–153 °C, R_f = 0.5 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.25 (s, 1H), 7.02 (s, 1H), 6.99 (s, 2H), 4.18 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.0, 165.5, 158.9, 151.8, 146.5, 138.8, 131.5, 129.9, 128.6, 124.5, 114.7, 102.7, 62.6, 61.5, 56.8, 21.3. HRMS (ESI) m/z: calculated for $C_{19}H_{19}NO_5$, [M+Na] 364.1161; found: 364.1155.

*2-(3,4-Dichlorophenyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3v**)*

White solid (68% yield, 51.8 mg): mp 226–228 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.61 (d, J = 2.10 Hz, 1H), 7.56 (d, J = 8.58 Hz, 1H) 7.34 (dd, J = 8.58 Hz, 2.16 Hz, 1H), 7.26 (s, 1H), 4.18 (s, 3H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 166.2, 164.6, 159.3, 152.0, 146.9, 132.9, 131.8, 131.2, 130.6, 128.2, 125.5, 114.4, 102.9, 62.6, 61.6, 56.9. HRMS (ESI) m/z: calculated for $C_{17}H_{13}Cl_2NO_5$, [M+Na] 404.0068; found: 404.0073.

*2-Butyl-4,5,6-trimethoxyisoindoline-1,3-dione (**3w**) [17]*

Yellow oil (33% yield, 19.3 mg): R_f = 0.2 (dichloroethane); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 7.14 (s, 1H), 4.14 (s, 3H), 3.95 (s, 3H), 3.89 (s, 3H), 3.60 (t, J = 7.26 Hz, 2H), 1.63–1.58 (m, 2H), 1.36–1.30 (m, 2H), 0.92 (t, J = 7.32 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 167.9, 166.5, 158.5, 157.4, 146.0, 128.9, 114.9, 102.3, 62.4, 61.4, 56.6, 37.7, 30.6, 20.0, 13.6. HRMS (ESI) m/z: calculated for $C_{15}H_{19}NO_5$, [M+Na] 316.1161; found: 316.1155.

*2-(2-Chloroethyl)-4,5,6-trimethoxyisoindoline-1,3-dione (**3x**)*

White solid (27% yield, 16.1 mg): mp 124–126 °C, R_f = 0.4 (dichloroethane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.18 (s, 1H), 4.17 (s, 3H), 4.01–3.98 (m, 5H), 3.92 (s, 3H), 3.74 (t, J = 6.33 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.4, 165.9, 158.8, 151.6, 146.3, 128.5, 114.6, 102.6, 62.5, 61.4, 56.7, 40.8, 39.3. HRMS (ESI) m/z: calculated for $C_{13}H_{14}ClNO_5$, [M+Na] 322.0429; found: 322.0455.

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