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Graphical Abstract

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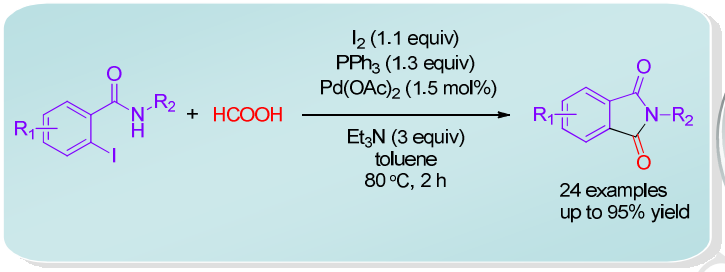

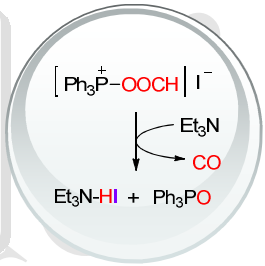

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PPh_3/I_2/HCOOH: an efficient CO source for the synthesis of phthalimides

Yingying Wang [a,b,1], Yang Zhou [a,b,1], Min Lei [a,b,*], Jinjun Hou [a,b], Qinghao Jin [a,b], Dean Guo [a,b] and Wanying Wu[a,b,*]

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ABSTRACT

A straightforward and general method has been developed for the synthesis of phthalimide derivatives from 2-iodobenzamides and PPh_3/I_2/HCOOH in the presence of a catalytic amount of $Pd(OAc)_2$. The reaction results demonstrate that PPh_3/I_2/HCOOH is a facile, efficient and safe CO source. The whole process is carried out in toluene at 80 °C and furnishes the desired products in good to excellent yields.

1. Introduction

Phthalimides are a category of important compounds because of their significant biological activities as well as wide-ranging utility in organic synthesis.[1] For example, the Gabriel synthesis, a famous named reaction first reported by S. Gabriel in 1887,[2] is an efficient method for the synthesis of primary amines from alkyl halides and phthalimide.[3] In recent years, phthalimides also apply in synthesis of dyestuff,[4] pesticide,[5] and rubber.[6] Due to the importance mentioned above, the synthesis of phthalimides towards milder reaction conditions and improved yields receives widespread attention.

Recently, methods have been discovered to synthesis of phthalimides: (a) *o*-phthalic anhydride with nitrogen source;[7] (b) phthalic acid with nitrogen source;[8] (c) hydration of phthalonitrile;[9] (d) 2-iodobenzoic acid with DMF/$POCl_3$;[10] (e) 1,2-diiodobenzene with DMF/$POCl_3$;[11] (f) coupling with CO;[12] (g) and other methods.[13] 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 times, and the use of expensive or toxic reagents. For example, $Fe(CO)_5$ is highly volatile, tough handle and very toxic. Therefore, searching for more facile and practical synthetic routes to synthesis of phthalimides is still highly desirable work.

CO is an important C1 source which applies in industrial manufacture widely. However, laboratorial utilization of gaseous CO suffers from storage, transportation, handling as well as safety regulations. Recently, although several C1 sources are reported, such as N-formylsaccharin,[14] 9-methylfluorene-9-carbonyl chloride,[15] acetic formic anhydride,[16] $Fe(CO)_5$,[17] etc,[18] these reagents have one or more drawbacks in using. Therefore, there has been considerable interest to explore more facile and practical agent as C1 source in organic synthesis.

During the course of our studies, we found PPh_3/I_2/HCOOH could release CO efficiently and rapidly (Scheme 1). This result inspired us that PPh_3/I_2/HCOOH might be as CO precursor used in organic synthesis. In order to examine our idea, we carried out the model reaction of 2-iodobenzamide and PPh_3/I_2/HCOOH in the presence of $Pd(OAc)_2$ in toluene at 80 °C for 2 h. To our delight that the desired product phthalimide was obtained in 78%

[1] These three authors attributed equally to this work.

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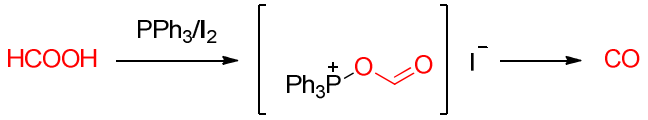
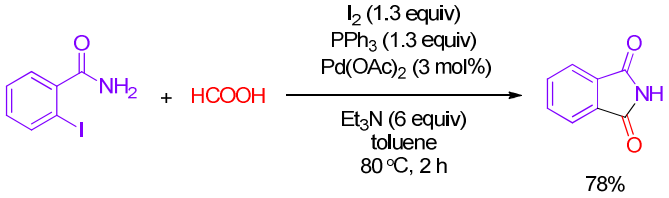
yield (Scheme 2). Hence, we would like to report a simple, efficient and practical method for the synthesis of phthalimides using PPh_3/I_2/HCOOH as CO source.



Scheme 1. PPh_3/I_2/HCOOH is an efficient CO precursor.



Scheme 2. Synthesis of phthalimide using PPh_3/I_2/HCOOH as CO precursor.

2. Results and Discussion

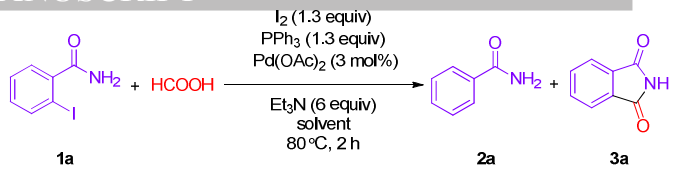
For further improve the yields of this synthetic reaction, the model reaction was carried out under different conditions. Initially, to investigate the solvent effects, the reaction was carried out in different solvents, and the results are summarized in Table 1. De-iodo product **2a** was obtained in 96% and 90% yields in DMSO and DMF as slolvents, respectively. While the desired product **3a** was obtained with low yields (2% and 8% yields, respectively). These results indicated that high polar solvents were not suitable for this model reaction (Table 1, entries 1 and 2). Moderate yields of **3a** (36–68%) were obtained when the reaction carried out in MeCN, THF, EtOAc (Table 1, entries 3–5). In all examined solvents, toluene showed the best solvent effect, and the desired product **3a** was obtained in 78% yield (Table 1, entry 6). Hence, toluene was chosen as the solvent for all further reaction.

Then, the other factors, such as equivalences of HCOOH and Et_3N, were also investigated, and the results showed that 2 equivalences of HCOOH and 3 equivalences of Et_3N were more suitable (see Tables S2 and S3 in the SI). In addition, Pd catalysts were also examined and the results are summarized in Table 2.

Among the Pd catalysts screened, $Pd(OAc)_2$ showed excellent activity in terms of yield (88%) in producing the required product (Table 2, entry 5). Next, we optimized the amount of $Pd(OAc)_2$ in the model reaction, and the optimum amount of $Pd(OAc)_2$ was found to be 1.5 mol % (Table 2, entry 8).

Furthermore, the amount of I_2 and PPh_3 was also optimized (see Table S5 in the SI). After extensive experimentation (see Tables S1-S5 in the SI), the optimal condition was established as HCOOH (2 equiv), Et_3N (3 equiv), $Pd(OAc)_2$ (1.5 mol %), I_2 (1.1 equiv), PPh_3 (1.3 equiv) in toluene at 80 °C for 2 h. Moreover, 92% isolated yield of **3a** was obtained under the optimal condition.

Table 1. Screen of solvent[a]



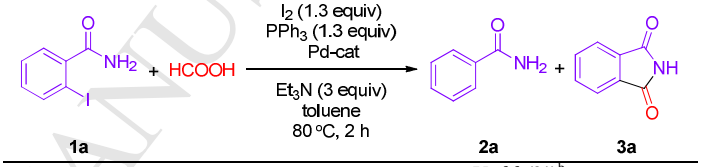
1a 2a 3a

Entry	Solvent	Yield (%)[b]		
		1a	**2a**	**3a**
1	DMSO	2	96	2
2	DMF	2	90	8
3	MeCN	36	28	36
4	THF	14	32	54
5	EtOAc	1	31	68
6	toluene	1	21	78

[a]Reaction conditions: **1a** (1 mmol), HCOOH (4 mmol, 4 equiv), I_2 (1.3 mmol, 1.3 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$ (0.03 mmol, 3 mol%), Et_3N (6 mmol, 6 equiv), solvent (4 mL), 80 °C for 2 h.

[b]Yields were determined by LC-MS.

Table 2. Screen of Pd catalyst[a]



1a 2a 3a

Entry	[Pd] (mol %)	Yield (%)[b]		
		1a	**2a**	**3a**
1	$PdSO_4$ (3)	23	2	75
2	$Pd(TFA)_2$ (3)	2	14	84
3	$Pd(PPh_3)_4$ (3)	11	1	88
4	$PdCl_2$ (3)	9	3	88
5	$Pd(OAc)_2$ (3)	3	5	92
6	$Pd(OAc)_2$ (2.5)	3	4	93
7	$Pd(OAc)_2$ (2)	1	4	95
8	$Pd(OAc)_2$ (1.5)	1	2	97
9	$Pd(OAc)_2$ (1)	10	1	89

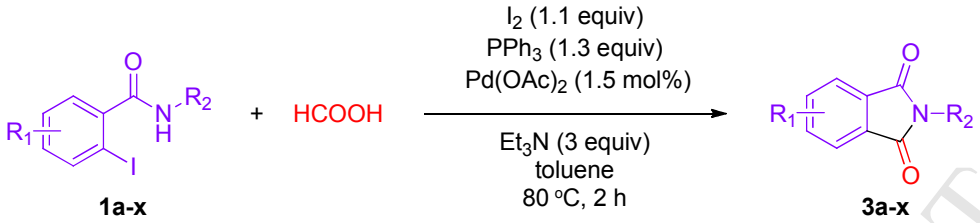
[a]Reaction conditions: **1a** (1 mmol), HCOOH (2 mmol, 2 equiv), I_2 (1.3 mmol, 1.3 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$, Et_3N (3 mmol, 3 equiv), toluene (4 mL), 80 °C for 2 h.

[b]Yields were determined by LC-MS.

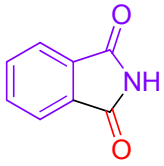
In order to gauge the scope of the conditions, a series of 2-iodobenzamide derivative were examined under the optimized conditions (Table 3). At first, a series of N-alkyl, N-benzyl and N-aryl substituted 2-iodobenzamides were synthesized as starting materials. As shown in Table 3, except for **3f** (47%), all the N-alkyl and N-benzyl substituted substrates could react smoothly to obtain the desired products **3** in good yields (84–95%). Most importantly, aryl carrying either electron-donating or electron-withdrawing substituents reacted efficiently giving excellent yields (83–95%). Heteroaryl substrate was also synthesized and used for the reaction, and desired product **3t** was obtained in 83% yield. Furthermore, 2-iodo-5-methylbenzamide and 4-chloro-2-iodobenzamide were also examined under the optimized conditions to obtain the desired products **3w** and **3x** in 95% and

75% yields, respectively. Obviously, the yield of **3x** was much lower than **3w** under similar reaction conditions in that de-chloro product **3a** was formed when using 4-chloro-2-iodobenzamide as substrate. Moreover, **1d** was selected as substrate to synthesis of **3d** under gram-scale, and desired product **3d** was obtained in 85% yield.

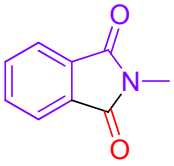
Table 3. Synthesis of phthalimide derivatives[a,b]



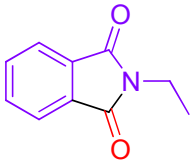
1a-x **3a-x**



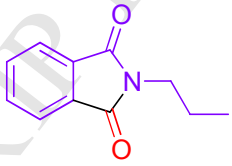
3a, 92%



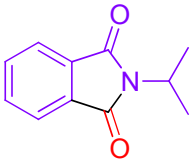
3b, 95%



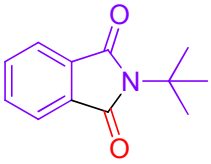
3c, 95%



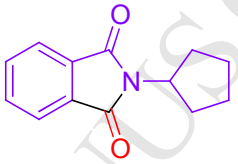
3d, 94%



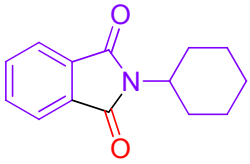
3e, 92%



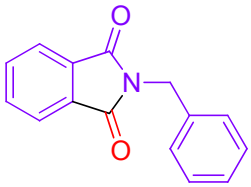
3f, 47%[c]



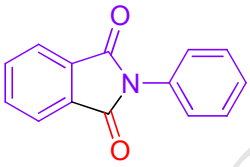
3g, 87%



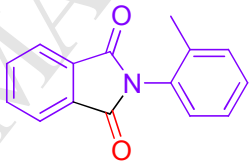
3h, 84%



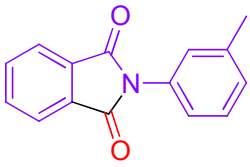
3i, 88%



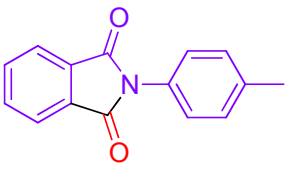
3j, 92%



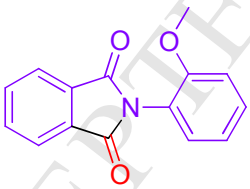
3k, 94%



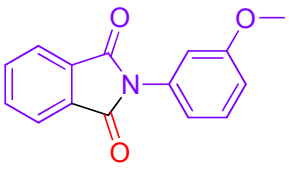
3l, 95%



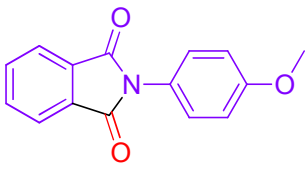
3m, 94%



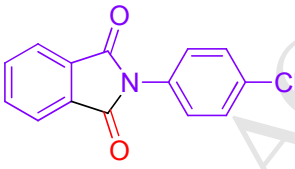
3n, 94%



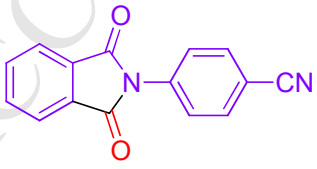
3o, 94%



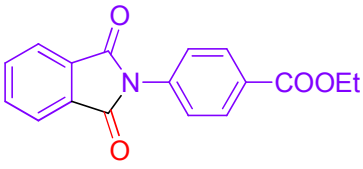
3p, 94%



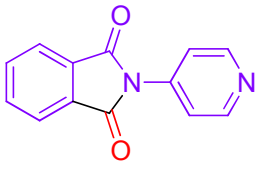
3q, 91%



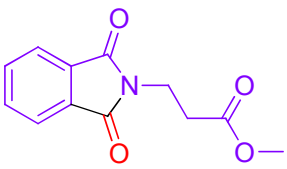
3r, 95%



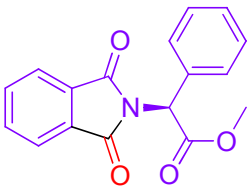
3s, 87%



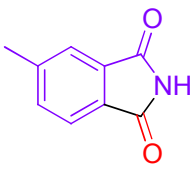
3t, 83%



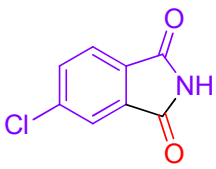
3u, 94%



3v, 93%



3w, 95%



3x, 75%

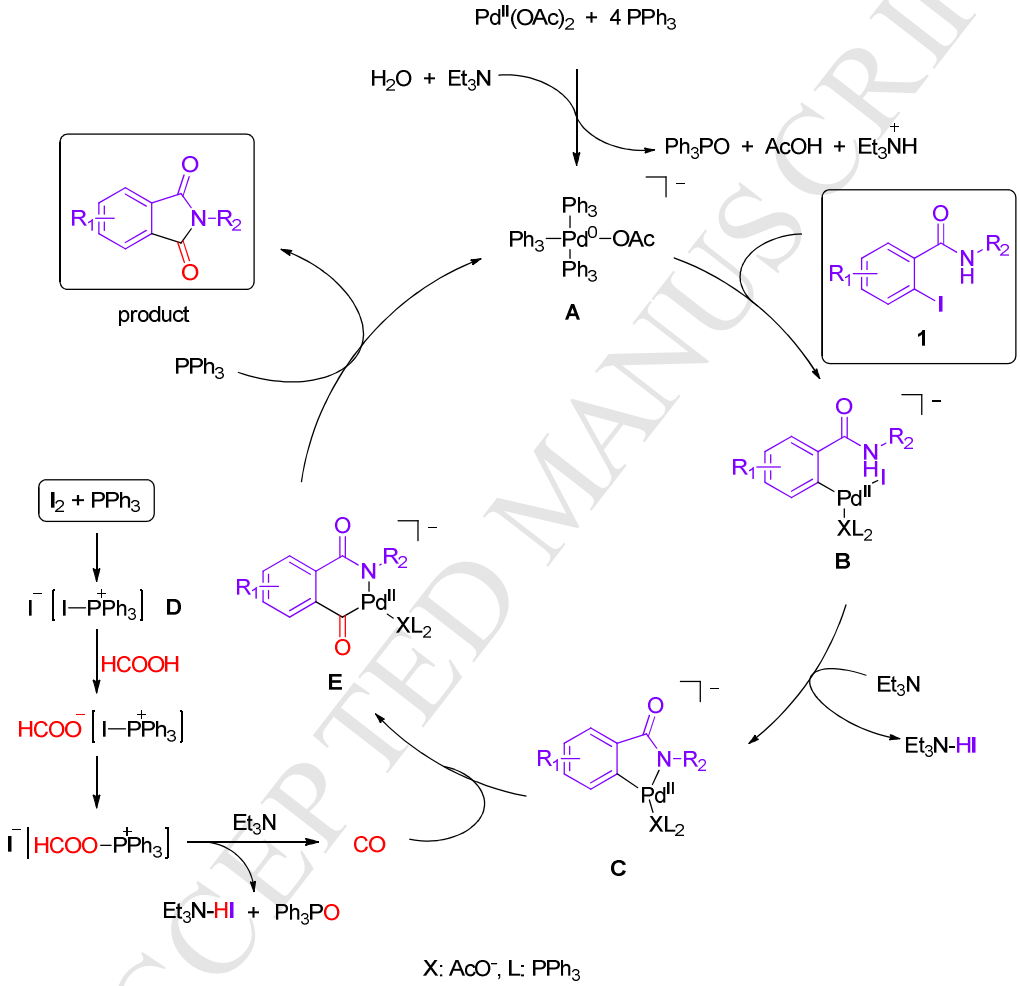
[a]Reaction conditions: **1a** (1 mmol), HCOOH (2 mmol, 2 equiv), I_2 (1.1 mmol, 1.1 equiv), PPh_3 (1.3 mmol, 1.3 equiv), $Pd(OAc)_2$ (1.5 mol %), Et_3N (3 mmol, 3 equiv), toluene (4 mL), 80 °C for 2 h.

[b]Isolated Yields.

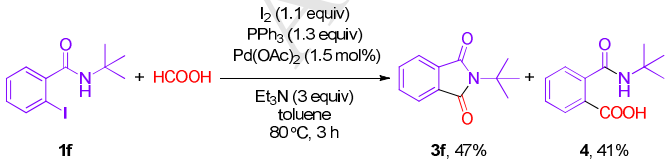
[c]The reaction proceeded for 3 h.

For the further study why the yield of **3f** was much lower than other cases, we carried out the reaction of N-(*tert*-butyl)-2-iodobenzamide (**1f**) and PPh_3/I_2/HCOOH under the optimized conditions. The reaction used LC-MS to track and monitor. The result showed that a main by-product with m/z 222.7 $[M + H]^+$ was formed. Then, the by-product (**4**) was isolated and the structure was established by NMR (Scheme 3). The main reason for phenomenon might result from large steric hindrance of *tert*-butyl which effected the intramolecular cyclization.

Based on the experimental results and previous reports, a plausible reaction mechanism was proposed (Scheme 4).[19] Pd^{II} was reduced by PPh_3 to form Pd^0 complex **A**.[19] Through a oxidative addition process of aryl iodide to Pd^0 to form Pd^{II} complex **B**. Then, HI was released under the action of base to form **C**. At same time, I_2 and PPh_3 formed complex **D**, which promated the release of CO from formic acid. Then, CO was captured by palladium intermediate **C** to form **E**. Upon reduction elimination, complex **E** gave the final product **3** and Pd^0 that launched another catalytic cycle.



Scheme 4. Plausible mechanism for the formation of phthalimides.



Scheme 3. Reaction of **1f** with PPh_3/I_2/HCOOH.

3. Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of phthalimide derivatives from from 2-iodobenzamides and PPh_3/I_2/HCOOH in the presence of a catalytic amount of $Pd(OAc)_2$. The main advantages of this methodology are: (a) operational simplicity, (b) short reaction times, (c) high yields of products, and (d) the use of relatively non-toxic reagents. The present study provided a useful supplement for the synthesis of phthalimides.

4. Experimental section

4.1. General information

All reactions were performed in flame-dried glassware using sealed tube. Liquids and solutions were transferred with syringes. All solvents and chemical reagents were obtained from commercial sources and used without further purifications. ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference at 400 MHz and 101 MHz, respectively.

Spectra were referenced to the residual solvent peak of $CDCl_3$ or DMSO-d_6 unless otherwise noted. Low and high-resolution mass spectra were obtained in the ESI mode. Flash column chromatography on silica gel (200-300 mesh) was used for the routine purification of reaction products. The column output was monitored by analytical thin-layer chromatography (TLC) on silica gel (100-200 mesh) precoated on glass plates (15 x 50 mm), and spots were visualized by ultraviolet light at 254 or 365 nm. Melting points were recorded on a WRS-1B melting point apparatus and are uncorrected. Commercially available chemicals were obtained from *Acros Organics, Strem Chemicals, Alfa Aesar, Adamas-beta, J&K and TCI.*

4.2. Experimental procedure for the synthesis of compound 3a-x

PPh_3 (1.3 mmol, 1.3 equiv), I_2 (1.3 mmol, 1.3 equiv) and toluene (4 mL) were added to a 20 mL test tube equipped with a stir bar, which was stirred for 10 min at room temperature. Then 2-iodo-benzamide (**1**) (1 mmol), $Pd(OAc)_2$ (0.015 mmol, 1.5 mol%), and Et_3N (3.0 mmol, 3.0 equiv) were added into the solution. At last, HCOOH (2 mmol, 2 equiv) was added, and the tube was immediately sealed and stirred at 80 °C for 2 h (3 h for **1f**). After completion of the reaction, the mixture was cooled to room temperature, and diluted with DCM (20 mL). The solid was removed by filter, and the filtrate was washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/acetone = 8/1, v/v) to afford the product **3a-x**.

*4.2.1. Phthalimide (**3a**).*

Yield: 135 mg (92%); white solid; mp: 244.4–246.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 7.81–7.80 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.19, 134.28, 132.59, 122.89; MS (ESI) *m/z* 148.6 $[M+H]^+$.

*4.2.2. N-Methylphthalimide (**3b**).*

Yield: 153 mg (95%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.82 (m, 2H), 7.70–7.68 (m, 2H), 3.17 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.58, 133.98, 132.33, 123.27, 24.05; MS (ESI) *m/z* 162.6 $[M+H]^+$.

*4.2.3. N-Ethylphthalimide (**3c**).*

Yield: 167 mg (95%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.81 (m, 2H), 7.70–7.68 (m, 2H), 3.73 (q, *J*=7.2 Hz, 2H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.15, 133.80, 132.21, 123.07, 32.87, 13.94; MS (ESI) *m/z* 176.4 $[M+H]^+$.

*4.2.4. N-Propylphthalimide (**3d**).*

Yield: 178 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H), 7.68–7.66 (m, 2H), 3.62 (t, *J*=7.2 Hz, 2H), 1.67 (h, *J*=7.2 Hz, 2H), 0.91 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.41, 133.86, 132.17, 123.14, 39.61, 21.96, 11.38; MS (ESI) *m/z* 190.6 $[M+H]^+$.

*4.2.5. N-Isopropylphthalimide (**3e**).*

Yield: 173 mg (92%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H), 7.69–7.68 (m, 2H), 4.59–4.44 (m, 1H), 1.48 (dd, *J*=7.2, 0.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.34, 133.77, 132.13, 122.98, 43.00, 20.15; MS (ESI) *m/z* 189.5 $[M+H]^+$.

*4.2.6. N-(tert-Butyl)phthalimide (**3f**).*

Yield: 95 mg (47%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.67–7.62 (m, 2H), 1.68 (s, 9H)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.76, 133.75, 132.26, 122.66, 57.93, 29.20; MS (ESI) *m/z* 204.5 $[M+H]^+$.

*4.2.7. N-Cyclopentylphthalimide (**3g**).*

Yield: 187 mg (87%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (m, 2H), 7.69–7.66 (m, 2H), 4.61 (p, *J*=8.4 Hz, 1H), 2.13–2.01 (m, 2H), 1.98–1.88 (m, 4H), 1.66–1.61 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.40, 133.72, 132.08, 122.92, 50.90, 29.56, 25.09; MS (ESI) *m/z* 216.6 $[M+H]^+$.

*4.2.8. N-Cyclohexylphthalimide (**3h**).*

Yield: 192 mg (84%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.70–7.66 (m, 2H), 4.10 (tt, *J*=12.4, 4.0 Hz, 1H), 2.20 (qd, *J*=12.4, 3.2 Hz, 2H), 1.90–1.83 (m, 2H), 1.74–1.67 (m, 3H), 1.40–1.24 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.58, 133.85, 132.22, 123.12, 51.04, 30.01, 26.16, 25.26; MS (ESI) *m/z* 230.7 $[M+H]^+$.

*4.2.9. N-Benzylphthalimide (**3i**).*

Yield: 209 mg (88%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H), 7.72–7.69 (m, 2H), 7.49–7.41 (m, 2H), 7.35–7.32 (m, 2H), 7.30–7.28 (m, 1H), 4.87 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.04, 136.44, 134.01, 132.17, 128.72, 128.65, 127.86, 123.36, 41.65; MS (ESI) *m/z* 238.9 $[M+H]^+$.

*4.2.10. N-Phenylphthalimide (**3j**).*

Yield: 205 mg (92%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.95 (m, 2H), 7.80–7.78 (m, 2H), 7.54–7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.38, 134.50, 131.88, 131.81, 129.22, 128.21, 126.69, 123.86; MS (ESI) *m/z* 224.7 $[M+H]^+$.

*4.2.11. N-(o-Tolyl)phthalimide (**3k**).*

Yield: 223 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H), 7.81–7.77 (m, 2H), 7.40–7.30 (m, 3H), 7.21 (d, *J*=7.6 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.47, 136.68, 134.44, 132.17, 131.29, 130.73, 129.58, 128.86, 127.01, 123.90, 18.18; MS (ESI) *m/z* 238.7 $[M+H]^+$.

*4.2.12. N-(m-Tolyl)phthalimide (**3l**).*

Yield: 225 mg (95%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–791 (m, 2H), 7.77–7.75 (m, 2H), 7.39 (t, *J*=7.6 Hz, 1H), 7.26–7.15 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.36, 139.12, 134.37, 131.81, 131.58, 129.04, 128.95, 127.29, 123.78, 123.69, 21.43; MS (ESI) *m/z* 238.8 $[M+H]^+$.

*4.2.13. N-(p-Tolyl)phthalimide (**3m**).*

Yield: 223 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.90 (m, 2H), 7.78–7.74 (m, 2H), 7.31 (s, 4H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.43, 138.17, 134.35, 131.86, 129.80, 129.06, 126.50, 123.69, 21.26; MS (ESI) *m/z* 238.8 $[M+H]^+$.

*4.2.14. N-(2-Methoxyphenyl)phthalimide (**3n**).*

Yield: 238 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.91 (m, 2H), 7.79–7.74 (m, 2H), 7.48–7.39 (m, 1H), 7.26 (dd, *J*=7.6, 1.6 Hz, 1H), 7.13–6.97 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.41, 155.49, 134.17, 132.30, 130.72, 130.04, 123.69, 120.91, 120.35, 112.22, 55.88; MS (ESI) *m/z* 254.7 $[M+H]^+$.

*4.2.15. N-(3-Methoxyphenyl)phthalimide (**3o**).*

Yield: 238 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.93 (m, 2H), 7.80–7.77 (m, 2H), 7.41 (t, *J*=8.0 Hz, 1H), 7.03 (d, *J*=8.0 Hz, 1H), 7.00–6.90 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.33, 160.17, 134.52, 132.79, 131.87, 129.91, 123.87, 118.99, 114.24, 112.49, 55.56; MS (ESI) *m/z* 254.6 $[M+H]^+$.

*4.2.16. N-(4-Methoxyphenyl) phthalimide (**3p**).*

Yield: 238 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.88 (m, 2H), 7.76–7.73 (m, 2H), 7.36–7.29 (m, 2H), 7.01–6.99 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 159.28, 134.38, 131.83, 128.01, 124.29, 123.71, 114.51, 55.57; MS (ESI) *m/z* 254.4 $[M+H]^+$.

*4.2.17. N-(4-Chlorophenyl) phthalimide (**3q**).*

Yield: 234 mg (91%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2H), 7.82–7.78 (m, 2H), 7.48–7.46 (m, 2H), 7.42–7.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.05, 134.66, 133.84, 131.64, 130.27, 129.37, 127.75, 123.93; MS (ESI) *m/z* 258.8 $[M+H]^+$.

*4.2.18. N-(4-Cyanophenyl)phthalimide (**3r**).*

Yield: 236 mg (95%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.95 (m, 2H), 7.84–7.81 (m, 2H), 7.78 (d, *J*=8.4 Hz, 2H), 7.67 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.54, 135.98, 135.03, 133.02, 131.40, 126.55, 124.19, 118.35, 111.34; MS (ESI) *m/z* 249.9 $[M+H]^+$.

*4.2.19. Ethyl 4-(1,3-dioxoisoindolin-2-yl)benzoate (**3s**).*

Yield: 257 mg (87%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J*=8.6 Hz, 2H), 7.91 (dd, *J*=5.4, 3.1 Hz, 2H), 7.77 (dt, *J*=5.4, 3.4 Hz, 2H), 7.56 (d, *J*=8.6 Hz, 2H), 4.37 (q, *J*=7.1 Hz, 2H), 1.38 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.73, 165.75, 135.76, 134.63, 131.49, 130.28, 129.53, 125.87, 123.83, 61.17, 14.33; MS (ESI) *m/z* 296.6 $[M+H]^+$.

*4.2.20. N-(4-Pyridyl)phthalimide (**3t**).*

Yield: 186 mg (83%); white solid; mp: 247.2–248.3 ^{o}C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J*=5.4 Hz, 2H), 8.02–8.00 (m, 2H), 7.95–7.93 (m, 2H), 7.59 (d, *J*=5.4 Hz, 2H) ; ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.19, 150.45, 139.52, 135.01, 131.38, 123.69, 120.64; MS (ESI) *m/z* 225.7 $[M+H]^+$; HRMS (ESI) calcd for $C_{13}H_9N_2O_2$ $[M+H]^+$ 225.0659, found225.0655.

*4.2.21. Methyl 2-(1,3-dioxoisoindolin-2-yl)propanoate (**3u**).*

Yield: 229 mg (94%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 2H), 7.59–7.54 (m, 2H), 3.81 (t, *J*=7.2 Hz, 2H), 3.51 (s, 3H), 2.57 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.29, 168.04, 134.12, 132.11, 123.42, 51.99, 33.85, 32.87; MS (ESI) *m/z* 234.4 $[M+H]^+$.

*4.2.22. (S)-N-Phthaloylphenylglycine methyl ester (**3v**).*

Yield: 275 mg (93%); white solid; mp: 107.9–110.1 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.76 (m, 2H), 7.62–7.60 (m, 2H), 7.59–7.53 (m, 2H), 7.39–7.27 (m, 3H), 6.05 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.99, 166.50, 134.06, 133.77, 131.18, 129.24, 128.13, 128.06, 123.06, 77.16, 55.29, 52.53; MS (ESI) *m/z* 296.7 $[M+H]^+$; HRMS (ESI) calcd for $C_{17}H_{14}NO_4$ $[M+H]^+$ 296.0917, found 296.0921.

*4.2.23. 4-Methylphtalimide (**3w**).*

Yield: 151 mg (95%); white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 7.73–7.53 (m, 3H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.26, 169.17, 145.13, 134.65, 132.96, 129.99, 123.28, 122.80, 21.32; MS (ESI) *m/z* 160.6 $[M-H]^-$.

*4.2.24. 4-Chlorophthalimide (**3x**).*

Yield: 134 mg (75%); white solid; mp: 228.7–229.3 ^{o}C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 8.03–7.56 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.26, 167.87, 139.08, 134.61, 134.05, 131.16, 124.69, 122.98; MS (ESI) *m/z* 180.5 $[M-H]^-$; HRMS (ESI) calcd for $C_8H_5ClNO_2$ $[M+H]^+$ 182.0003, found 182.0006.

*4.2.25. 2-(tert-Butylcarbamoyl)benzoic acid (**4**).*

Yield: 90 mg (41%); white solid; mp: 158.1–158.6 ^{o}C ; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (brs, 1H), 7.84 (s, 1H), 7.79 (d, *J*=7.2 Hz, 1H), 7.54 (t, *J*=7.2 Hz, 1H), 7.47 (t, *J*=7.2 Hz, 1H), 7.37 (d, *J*=7.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.52, 168.13, 139.98, 131.23, 130.40, 129.28, 128.67, 127.90, 50.76, 28.63; MS (ESI) *m/z* 222.7 $[M+H]^+$; HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $[M+H]^+$ 222.1125, found 222.1125.

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