



# Synthesis of phthalimides through 1,3-dipolar cycloaddition of CO<sub>2</sub> with isocyanides and arynes

Yi Fang, Shun-Yi Wang\*, Shun-Jun Ji\*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

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## ABSTRACT

A new practical synthesis of phthalimides through 1,3-dipolar cycloaddition of CO<sub>2</sub> with isocyanides and *in situ* generated arynes is reported here. A series of phthalimide derivatives are observed in moderate to good yields under mild conditions.

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## 1. Introduction

Phthalimides is a class of amide compounds with broad applications in agriculture, industry and pharmaceutical industry.<sup>1</sup> They have important biological activities (Fig. 1),<sup>2</sup> such as anti-inflammatory,<sup>3</sup> anti-epileptic,<sup>4</sup> anti-bacterium<sup>5</sup> and anti-tumor<sup>6</sup> activities. The synthesis of phthalimides has received much concern at present.<sup>7</sup>

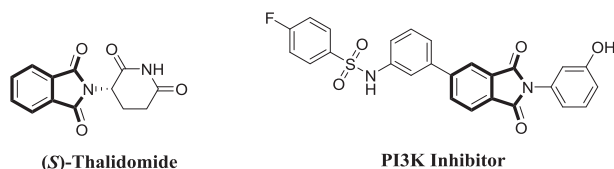


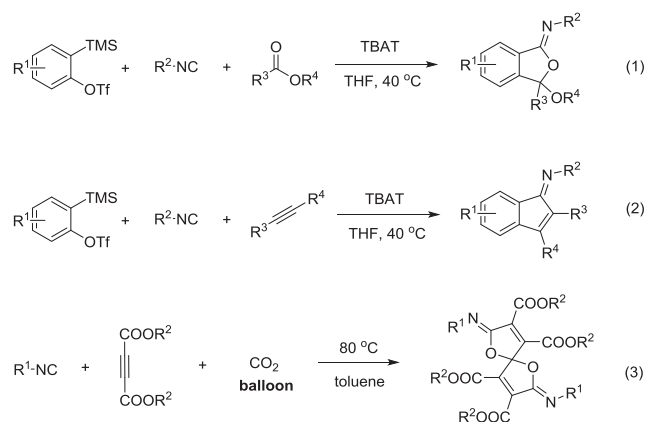
Fig. 1. Biologically active structures of phthalimide derivatives.

The highly active arynes intermediates generated *in situ* have been an intriguing synthon due to their remarkable diversities. In recent years, a lot of multicomponent reactions involving arynes have been reported.<sup>8</sup> For example, the Stoltz group<sup>9</sup> reported isocyanides incorporated reactions using arynes, with esters and alkynes as electrophilic partners to generate phenoxy iminoisobenzofurans and iminoindenones, respectively (Scheme 1, eq. 1, 2).

\* Corresponding authors. Fax: +86 512 65880307; e-mail addresses: [shunyi@suda.edu.cn](mailto:shunyi@suda.edu.cn) (S.-Y. Wang), [shunjun@suda.edu.cn](mailto:shunjun@suda.edu.cn) (S.-J. Ji).

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Scheme 1. MCRs involving arynes and isocyanides.

Carbon dioxide (CO<sub>2</sub>) is the most abundant C1 feedstock in nature. It has attracted the attention of the scientists how to take full advantage of CO<sub>2</sub> and convert into substances useful to humanity and the planet.<sup>10</sup> Recently, CO<sub>2</sub> has been successfully used for the synthesis of carbonic ether,<sup>11</sup> carboxylic acid,<sup>12</sup> coumarins<sup>13</sup> and isocoumarins<sup>14</sup> etc. Based on our previous works on the dual 1,3-dipolar cycloaddition of CO<sub>2</sub><sup>15</sup> (Scheme 1, eq. 3), we reason that phthalimide derivatives can be generated through 1,3-dipolar cycloaddition of CO<sub>2</sub> with isocyanides and *in situ* generated arynes.

Herein, we report a three-component reactions of 2-(trimethylsilyl) aryl triflates, isocyanides, with CO<sub>2</sub> as the third component to generate phthalimides under transition-metal-free conditions.

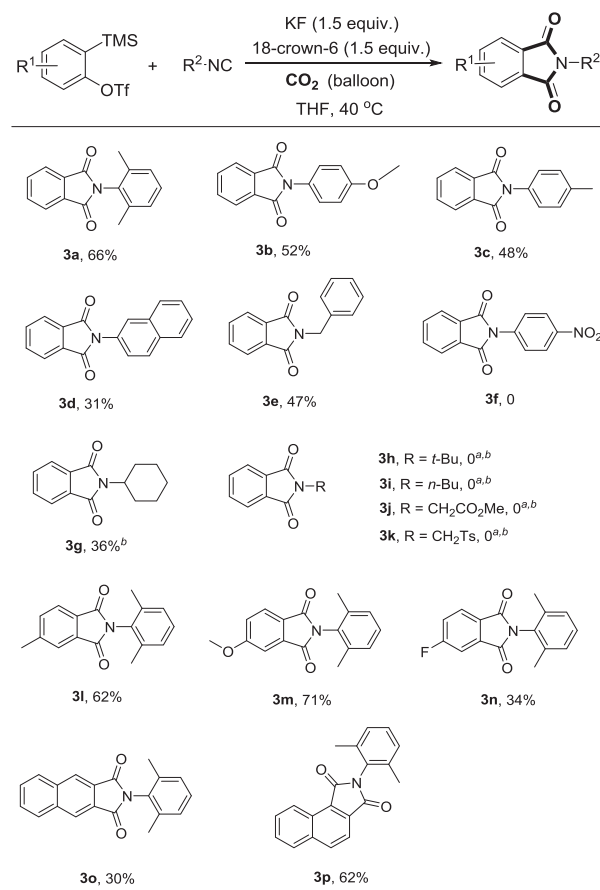
When we are preparing this paper, the Biju group<sup>16</sup> has reported a similar work. However, our reaction conditions are different with them. The isocyanides show different reaction activities under Biju's and our reaction conditions, respectively. The aryl isocyanides react better under our reaction conditions.

## 2. Results and discussion

We initiated the study by treating 2-(trimethylsilyl)aryl triflate **1a** and 2,6-xylyl isocyanide **2a** with stoichiometric amounts of KF and 18-crown-6 in THF at rt under a balloon pressure of CO<sub>2</sub>. After 12 h, fortunately, the *N*-2,6-xylyl phthalimide **3a** was obtained in 27% yield. Inspired by this result, we screened several reaction conditions to increase the yield of **3a**. It was found that the reaction temperature had great influence on the yield of **3a**. Either higher or lower temperature would decrease the yield of **3a** (Table 1, entries 1–3). Further screening the solvents showed that DMF inhibited the reaction (Table 1, entry 4) and lower yields of **3a** were obtained when the reaction was carried out in MeCN, 1,4-dioxane, methyl *tert*-butyl ether (MTBE) and 2-MeTHF, respectively (Table 1, entries 5–8). The yield of **3a** could be increased to 66% yield when the reaction time was prolonged to 18 h (Table 1, entry 9). More longer reaction time could not further increase the yield of **3a** (Table 1, entry 10). When more KF and 18-crown-6 were used in the reactions, the yield of **3a** decreased dramatically (Table 1, entries 11–12). Attempting to increase the yield, DBU (1 equiv) was added as an additive. However, the reaction was completely inhibited by the addition of DBU. Finally, we found that the optimal reaction conditions were 2-(trimethylsilyl)aryl triflate (**1a**, 1.5 equiv), 2,6-xylyl isocyanide (**2a**, 1.0 equiv), KF (1.5 equiv) and 18-crown-6 (1.5 equiv) in THF at 40 °C under a balloon pressure of CO<sub>2</sub>.

With the optimal conditions in hand, we investigated other isocyanides such as substituted aryl isocyanides, benzyl isocyanides and alkyl isocyanides with aryl in the presence of CO<sub>2</sub>. The results are summarized in Table 2. It was found that the desired products **3b–e** could be observed in moderate yields. Unfortunately, no

**Table 2**  
Substrate scope of reaction<sup>a</sup>



<sup>a</sup> Reaction conditions: **1a** (0.45 mmol), **2a** (0.3 mmol), KF (0.45 mmol), 18-crown-6 (0.45 mmol), THF (3mL), under a balloon pressure of CO<sub>2</sub>, 40 °C, 18h.

<sup>b</sup> TBAT (1.5 equiv.) was used.

**Table 1**  
Optimization of the reaction conditions<sup>a</sup>

Entry	Solvent	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>
1	THF	rt	12	27
2	THF	40	12	50
3	THF	Reflux	12	32
4	DMF	40	12	Trace
5	Dioxane	40	12	34
6	MTBE	40	12	10
7	2-MeTHF	40	12	20
8	MeCN	40	12	32
9	THF	40	18	66
10	THF	40	24	57
11 <sup>c</sup>	THF	40	18	48
12 <sup>d</sup>	THF	40	18	34
13 <sup>e</sup>	THF	40	18	N.D.

<sup>a</sup> Reaction conditions: **1a** (0.45 mmol), **2a** (0.3 mmol), KF (0.45 mmol), 18-C-6 (0.45 mmol), solvent (3 mL), under a balloon pressure of CO<sub>2</sub>.

<sup>b</sup> Isolated yield.

<sup>c</sup> KF (0.45 mmol), 18-crown-6 (0.45 mmol).

<sup>d</sup> KF (0.90 mmol), 18-C-6 (0.90 mmol).

<sup>e</sup> DBU (0.30 mmol) was added. N.D.=Not detected.

desired product **3f** was isolated, when aryl isocyanide with electron withdrawing group NO<sub>2</sub> was subjected to the reaction. Cyclohexyl isocyanide **2g**, *tert*-butyl isocyanide **2h** and *n*-butyl isocyanide **2i** failed to give the desired products **3g–i** under previous optimal reaction conditions. It should be noted that the reaction of cyclohexyl isocyanide **2g** led to **3g** in 36% yield when tetrabutylammonium triphenyldifluorosilane (TBAT) was utilized instead of KF/18-crown-6. However, methyl 2-isocyanoacetate **2j** and 1-(isocyano-methylsulfonyl)-4-methylbenzene **2k** didn't react well to afford the desired products under several reaction conditions. Next, we evaluated the scope of aryl precursors. The electron-rich substrates was more efficient than the electron-deficient ones. The reactions of 5-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate and 5-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate under the optimized conditions led to the desired products **3l** and **3m** in 62% and 71%, respectively.

Based on the results above and the literature reports,<sup>15–17</sup> a plausible mechanism is illustrated in Scheme 2. Initially, a benzyne **A** is generated in situ by 1,2-elimination of 2-(trimethylsilyl) aryl triflate **1** with KF/18-crown-6. Then a highly reactive zwitterionic intermediate **B** is formed by the nucleophilic addition reaction of isocyanide **2** with benzyne **A**. In rapid sequence, the 1,3-zwitterionic intermediate **B** adds to one of the carbonyl groups of CO<sub>2</sub> and concert to the isophthalimide intermediate **C**. According to the literature reports, a thermally rearrangement (*path a*) is supposed to happen and lead to the final product phthalimide **3**.

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