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Practical Synthesis of Phthalimides and Benzamides by a Multicomponent Reaction Involving Arynes, Isocyanides, and CO_2/H_2O

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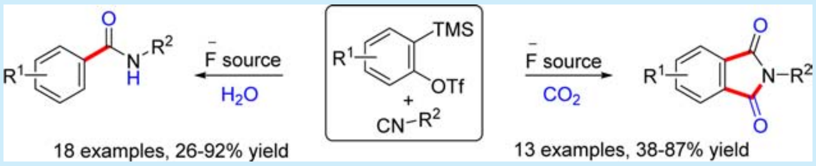
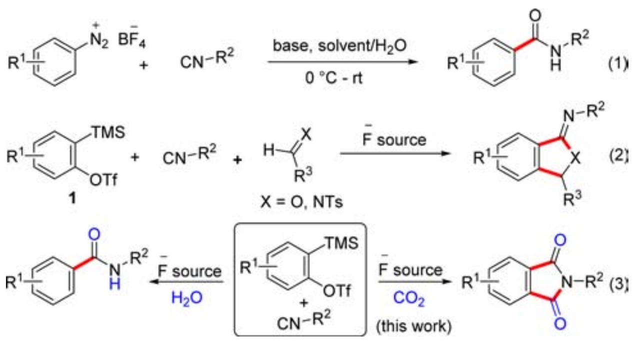
Supporting Information



ABSTRACT: Transition-metal-free multicomponent reactions involving arynes and isocyanides with either CO_2 or H_2O have been reported. With CO_2 as the third component, the reactions resulted in the formation of *N*-substituted phthalimides. The utility of water as the third component furnished benzamide derivatives in moderate to good yields. These reactions took place under mild conditions with broad scope.

The amide bond is one of the most important functional groups present in various biologically important compounds including peptides and proteins, and this moiety is present in more than 25% of the known drugs.[1] Traditionally, the construction of amide bonds has been achieved by the coupling of carboxylic acids/derivatives with amines. However, in most cases, the reaction requires coupling reagents and produces a stoichiometric byproduct.[2] Transition-metal-catalyzed methods are possible alternatives, which expanded the scope of amide synthesis by starting from various substrates other than acids.[3] Several reports to uncover efficient and environmentally benign methods to amide synthesis have appeared in the past few years.[4] Very recently, the Grimaud and Zhu groups independently disclosed an efficient and transition-metal-free synthesis of aryl substituted carboxamides from aryl diazonium salts and isocyanides, and the reaction proceeded via a radical intermediate (Scheme 1, eq 1).[5,6] Considering the widespread applications of isocyanides in multicomponent reactions (MCRs),[7] we envisioned that the isocyanide triggered MCRs with highly electrophilic arynes[8] could result in a transition-metal-free new route to the synthesis of amides. Notably, the generation of a 1,3-zwitterionic intermediate from isocyanide and aryne derived from **1**[9] and its subsequent interception with electrophiles such as aldehydes, and activated imines leading to the formation of benzannulated heterocycles, has been demonstrated by Yoshida, Kunai and co-workers (eq 2).[10,11] Herein, we report the MCR involving isocyanides and arynes, where the third component used is either CO_2 or H_2O. When CO_2 was used as the third component,[12] the reaction afforded *N*-substituted phthalimides, whereas the use of H_2O as the third component furnished benzamides (eq 3).

Scheme 1. Transition-Metal-Free Amide Bond-Forming Reactions Involving Isocyanides



The synthesis of value-added products by the efficient utilization of CO_2 as a one-carbon source has been an imperative subject in organic chemistry.[13] Intriguingly, the incorporation of CO_2 in aryne reactions has received only limited attention.[12] In this context, we began our studies by treating *tert*-butyl isocyanide **2a** with the aryne formed *in situ* from 2-(trimethylsilyl)aryl triflate **1a**[9] using CsF in MeCN at 30 °C under an atmosphere of CO_2 (balloon). Although the expected product was the iminoisobenzofuranone derivative **4a** formed by the interception of the 1:1 adduct between aryne and isocyanide with CO_2, delightfully, the *N*-*tert*-butyl phthalimide **3a** was isolated in 76% yield (Scheme 2).[14] The product **3a** was likely formed by the fluoride induced ring opening of **4a** followed by the cyclization.

With this procedure in hand, we then studied the substrate scope of this phthalimide forming aryne MCR (Scheme 3). A variety of aliphatic isocyanides underwent a smooth aryne MCR with incorporation of CO_2 leading to the formation of *N*-

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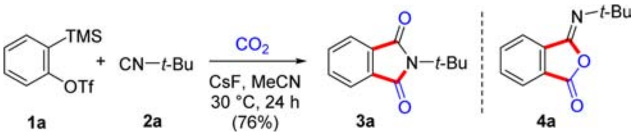
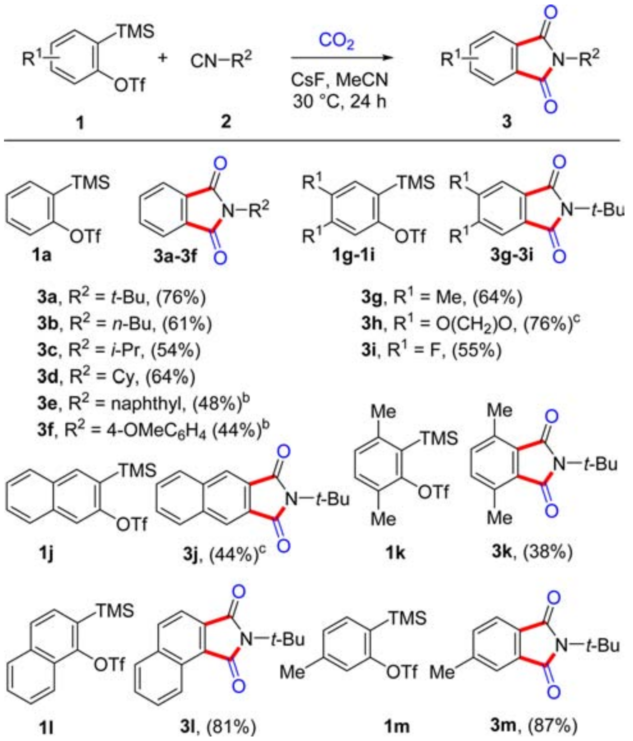
Scheme 2. MCR Involving Arynes, Isocyanides, and CO_2



Scheme 3. Substrate Scope of the MCR Involving Isocyanides, Arynes, and CO_2[a]

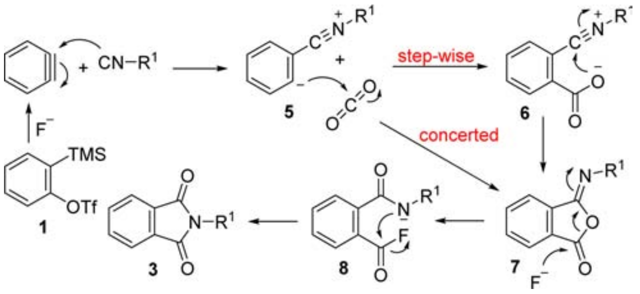


[a]General conditions: **1** (0.75 mmol), **2** (0.5 mmol), CsF (1.5 mmol), MeCN (2.0 mL), under an atmosphere of CO_2 (balloon), 30 °C, 24 h. Yields of the isolated products are given. [b] Reaction was run at 60 °C for 6 h. [c] Reaction was run on 0.25 mmol scale.

alkyl phthalimides in moderate to good yields (**3a**−**3d**). Moreover, relatively less nucleophilic aromatic isocyanides reacted very slowly at 30 °C with arynes and CO_2. However, at a high temperature of 60 °C, these reactions afforded the desired product in moderate yields (**3e**−**3f**). Then, we evaluated the scope of this reaction with various aryne precursors. As expected, electronically different 4,5-disubstituted symmetrical aryne precursors **1g**−**1i** easily resulted in the formation of phthalimides **3g**−**3i** in moderate to good yields. Additionally, the symmetrical naphthalyne derived from **1j** as well as the 3,6-dimethyl aryne derived from **1k** furnished the expected products in moderate yields (**3j**−**3k**). Interestingly, the reaction of unsymmetrical aryne derived from **1l** resulted in the formation of the expected product **3l** in 81% yield. Furthermore, the monosubstituted aryne derived from **1m** delivered the phthalimide **3m** in 87% yield, thereby expanding the scope of the aryne MCRs. It may be noted in this context that some of the *N*-substituted phthalimides are known to have anticonvulsant and neurotoxic properties.[15]

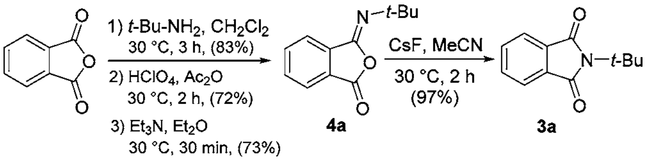
The proposed mechanism of this CO_2 incorporated aryne MCR leading to phthalimides is presented in Scheme 4. Initially, the isocyanide undergoes a nucleophilic addition to an aryne formed *in situ* from the precursor **1** leading to the generation of the 1,3-zwitterionic intermediate **5**. The nucleophilic aryl anion intermediate **5** can add to the electrophilic carbonyl group of CO_2 in a stepwise pathway furnishing the zwitterion **6**, which on ring closure results in the formation of iminoisobenzofuranone derivative **7**. Alternatively, it is also likely that the addition of aryl anion **5** to CO_2 and the subsequent cyclization can proceed via a concerted manner to form **7**. It is probable that the fluoride induced ring opening of **7** generates the acid fluoride intermediate **8**, and the latter on further cyclization affords the phthalimide derivative **3**. It is interesting to note in this context that the rearrangement of isoimide **7** to imide **3** has been documented in the literature.[16]

Scheme 4. Plausible Reaction Mechanism



To shed light on the fluoride-induced rearrangement of isoimide **7** to phthalimide **3**, we have synthesized the *N*-*tert*-butyl isoimide derivative **4a** starting from phthalic anhydride in three steps following the literature procedures.[17] Gratifyingly, treatment of **4a** with CsF resulted in the formation of the desired phthalimide derivative **3a** in 97% yield (Scheme 5).

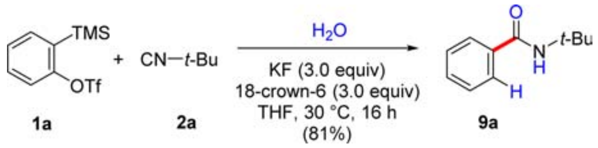
Scheme 5. Experiment to Confirm Fluoride-Induced Rearrangement



This clearly indicates the fluoride-induced rearrangement of **7** to **3** as proposed in Scheme 4. Moreover, after filtration of the reaction mixture and evaporation of solvent, the crude NMR of the reaction (^1H NMR in $CDCl_3$ using CH_2Br_2 as an internal standarad) mixture revealed an 80% yield of **3a** indicating that the rearrangement of **4a** to **3a** is not happening during purification using silica gel column chromatography.

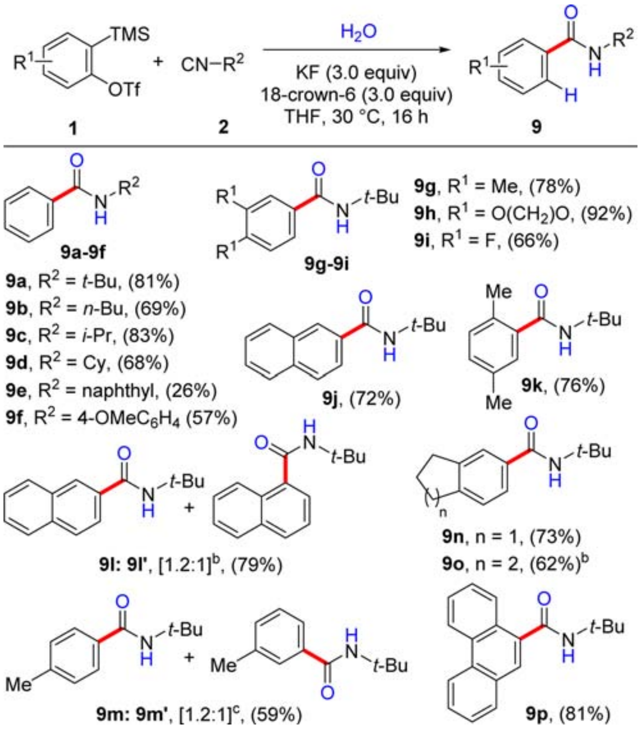
Inspired by the synthesis of phthalimides by the MCR of isocyanides and arynes with CO_2, we continued our studies using other trapping agents instead of CO_2. It was envisioned that if the trapping agent used is water, this MCR can result in the formation of aromatic amides under transition-metal-free conditions. Notably, the synthesis of aromatic amides by the reaction of isocyanides and water with an aryne generated from aryldiazonium 2-carboxylate has been shown by Rigby and Laurent.[18] However, the scope of this reaction appears narrow and the isolated yields of the product are moderate in most cases. In a pilot experiment, treatment of *tert*-butyl isocyanide **2a** with the aryne generated from 2-(trimethylsilyl)aryl triflate **1a**[9] using KF (in the presence of 18-crown-6) in THF at 30 °C followed by the addition of water resulted in the formation of *N*-(*tert*-butyl)benzamide **9a** in 81% yield (Scheme 6). During

Scheme 6. MCR Involving Arynes, Isocyanides, and H_2O



optimization studies, it was found that the other fluoride sources such as CsF (in MeCN) and tetrabutyl ammonium fluoride (TBAF) in THF furnished the desired product in reduced yields.

Scheme 7. Substrate Scope of the MCR Involving Isocyanides, Arynes, and H_2O^a

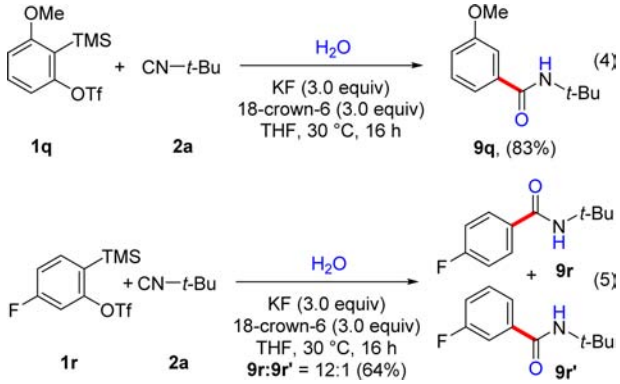


[a] General conditions: **1** (0.75 mmol), **2** (0.5 mmol), KF (1.5 mmol), 18-crown-6 (1.5 mmol), H_2O (1.0 mmol), and THF (2.0 mL), 30 °C, 16 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale. [c] The regioisomer ratio was determined by ^1H NMR analysis of the crude reaction mixture.

The scope of this transition-metal-free synthesis of aromatic amides was found to be general with various isocyanides and differently substituted arynes (Scheme 7). Diverse alkyl isocyanides were well tolerated leading to *N*-alkyl benzamides in good yields (**9a**−**9d**). In addition, aromatic isocyanides also underwent the reaction under the optimized conditions to furnish the desired product (**9e**−**9f**). Moreover, a variety of electronically diverse symmetrical arynes derived from precursors **1g**−**1k** afforded the expected product in good yields (**9g**−**9k**). As anticipated, the unsymmetrical naphthalyne generated from the precursor **1l** underwent efficient MCR with isocyanides and water to afford an inseparable mixture of regioisomers **9l** and **9l′** in a 1.2:1 ratio and in 79% yield. Furthermore, the reaction of the unsymmetrical aryne derived from **1m** resulted in the formation of inseparable regioisomers **9m**/**9m′** in a 1.2:1 ratio. Finally, this method is not limited to the synthesis of phenyl and naphthyl carboxamides, but instead, the synthesis of indane-5-carboxamide (**9n**), tetrahydronaphthalene-2-carboxamide (**9o**), and phenanthrene-9-carboxamide (**9p**) can be accomplished starting from suitably substituted symmetrical aryne precursors.[19]

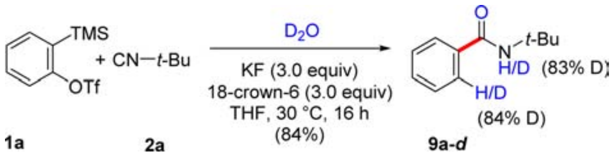
Not surprisingly, the reaction of *tert*-butyl isocyanide **2a** with unsymmetrical 3-methoxy benzyne derived from **1q** and water resulted in the formation of the aryl amide **9q** in 83% yield as a single isomer. The selective formation of **9q** may be due to the combined electron-withdrawing effect and steric effect induced by the −OMe group, which directs the selective addition of isocyanide at the *meta*-position (Scheme 8, eq 4). Moreover, 4-fluoro benzyne generated from **1r** furnished a regioisomeric mixture of aryl amides **9r** and **9r′** in the ratio 12:1 in 64% yield (eq 5). The preferential formation of **9r** in this case may be due to the enhanced stability of the intermediate (formed by the addition of **2a** on aryne generated from **1r**), where the negative charge is nearer to the electronegative fluorine atom.[20]

Scheme 8. Regioselective Synthesis of Aromatic Amides



To gain insight into the mechanism of the aryl amide forming reaction, an experiment has been performed with D_2O as the third component. This reaction resulted in the formation of the expected product **9a-*d*** in 84% yield (based on ^1H NMR) with 84% deuterium incorporation at the 2-position of the ring (Scheme 8).[14] In addition, 83% deuterium incorporation was observed at the amide functionality. This indicates that the initially formed aryl anion intermediate **5** (Scheme 4) is first protonated and the subsequent hydrolysis of the resultant iminium species results in the formation of the benzamide **9**.

Scheme 9. Reaction Using D_2O as the Third Component



In conclusion, we have reported the operationally simple and transition-metal-free MCRs involving arynes and isocyanides with either CO_2 or H_2O as the third component. When the third component used was CO_2, the reaction afforded *N*-substituted phthalimides. The desired product was formed by the construction of two new C−C bonds and a new C−N bond. Additionally, the incorporation of water as the third component resulted in the formation of aromatic amides in moderate to good yields. Further studies on related aryne MCRs are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures as well as characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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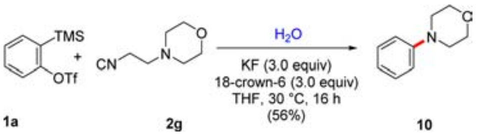

(20) For selected reports on regioselective product formation with aryne precursors **1q** and **1r**, see refs 10 and 12a.