Synthetic Methods

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Transition-Metal-Free Multicomponent Reactions Involving Arynes, N-Heterocycles, and Isatins**

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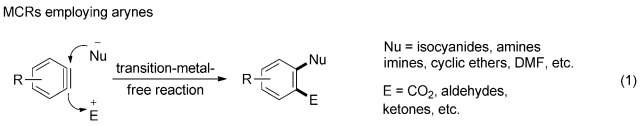
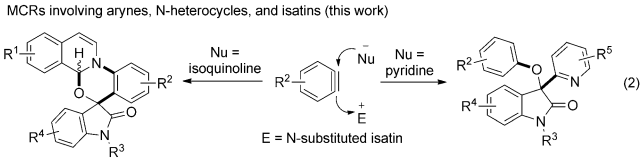
Dedicated to Dr. Vijay Nair

Arynes have been recognized as highly reactive intermediates and they have played significant role in various fundamental organic transformations.[1] Owing to the pronounced electrophilicity of arynes and the highly strained triple bond in the ring system, arynes have found widespread applications in various bond-forming reactions, including pericyclic reactions,[2] insertion reactions,[3] transition-metal-catalyzed reactions[4] and multicomponent reactions (MCRs).[5] Recent developments in aryne chemistry have been dedicated to transition-metal-free reactions, which mainly involve the initial addition of nucleophiles to arynes followed by the interception of the aryl anion intermediate with electrophiles. If the nucleophile and electrophile are separate entities, the overall process is a unique three-component reaction, where the aryne is inserted between the other two coupling partners [Eq. (1)].[6] Isocyanides are commonly used nucleophiles in



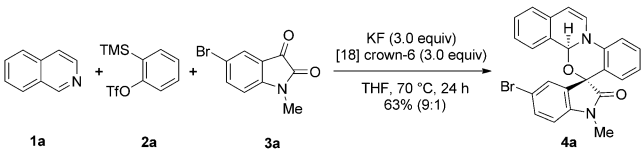
(1)

aryne MCRs;[5,7] however, the utility of imines,[8] amines,[9] cyclic ethers,[5f] DMF,[5c,d] and others as nucleophiles is also known, and the trapping agents used are usually carbonyl compounds, including carbon dioxide.[7–9] Despite this, the synthetic utility of N-heterocycles as nucleophiles in the realm of aryne MCRs has received only scant attention.[10] Herein, we report aryne MCRs triggered by N-heterocycles (pyridine, isoquinoline, and quinoline) and with N-substituted isatins[11] as the electrophilic component. Gratifyingly, with isoquinoline as the nucleophilic trigger, the reaction afforded spirooxazino isoquinoline derivatives, and proceeds through a 1,4-dipolar intermediate.[12] With pyridine as the nucleophile, the reaction furnished indolin-2-one derivatives, with the reaction is likely proceeding through a pyridylidene intermediate [Eq. (2)].[13]



(2)

The present study was initiated by treating isoquinoline **1a** and N-substituted isatin **3a** with the aryne generated in situ from 2-(trimethylsilyl)aryl triflate **2a**[14] using KF and [18]crown-6. A facile reaction occurred, leading to the formation of the spirooxazino isoquinoline derivatives as an inseparable mixture of diastereomers in 63% yield and a 9:1 ratio (Scheme 1).[15] The major diastereomer **4a** was separated by crystallization and its structure and stereochemistry was confirmed by single-crystal X-ray analysis.[16]



Scheme 1. MCR involving isoquinoline, aryne, and *N*-methyl isatin.

Encouraged by this new three-component coupling reaction, we then examined the substrate scope of this isoquinoline-triggered aryne MCR. The reaction tolerated various substituents on the isatin nitrogen, leading to an inseparable mixture of spirooxazino isoquinoline derivatives in 60–77% yield and moderate diastereoselectivity (**4b**–**4e**; Scheme 2). Moreover, electron-donating and -withdrawing groups on the carbocyclic ring of isatin resulted in smooth conversions (**4f**–**4h**). Additionally, electronically different 4,5-disubstituted symmetrical arynes readily afforded the spirooxazino isoqui-

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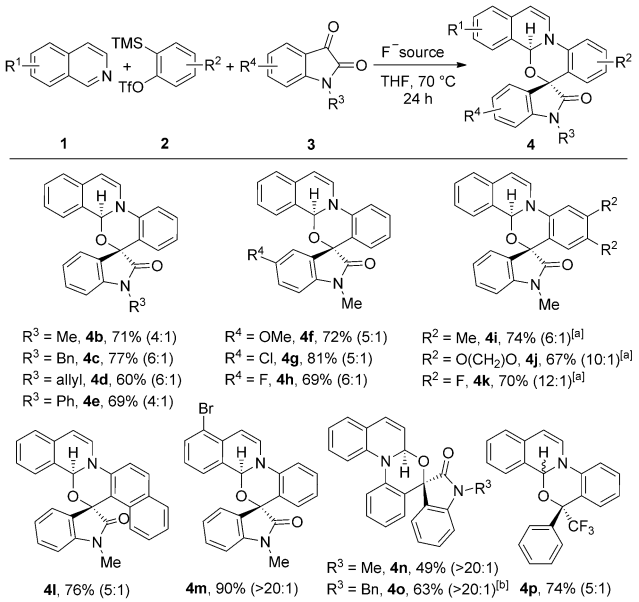
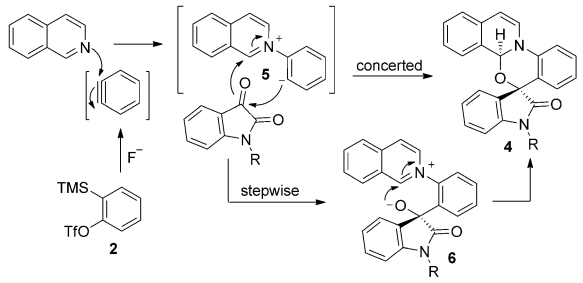


Scheme 2. Reaction scope of the MCR involving isoquinoline, arynes, and N-substituted isatins. General conditions: **1** (0.5 mmol), **2** (0.75 mmol), **3** (0.5 mmol) KF (1.5 mmol), [18]crown-6 (1.5 mmol), THF (2.0 mL), 70°C, 24 h. Total yields of both diastereomers are given and the major diastereomer is shown. Diastereomeric ratios are given in parentheses and were determined by ^{1}H NMR analysis of crude reaction mixture. [a] Reaction was run on a 0.25 mmol scale. [b] Reaction run using quinoline (2.0 equiv) and **2a** (2.0 equiv). Bn = benzyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

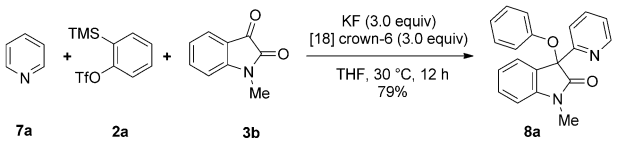
noline derivatives in good yields and diastereoselectivities (**4i**–**4k**). An unsymmetric aryne generated from 1-(trimethylsilyl)-2-naphthyltriflate furnished the desired product in 76% yield and a 5:1 ratio of diastereomers (**4l**). In this case, the observed regioselectivity may be due to the addition of isoquinoline to the least hindered position of naphthalyne.[17] Furthermore, this unique MCR is not limited to isoquinoline; 5-bromoisoquinoline and quinoline both worked well, leading to the formation of the desired products in moderate to good yields (**4m**–**4o**). The isatin component of the reaction can also be replaced with trifluoroacetophenone, leading to a good yield of the trifluoromethylated product, and thereby significantly expanding the scope of this MCR (**4p**).

Mechanistically, the reaction can be considered to proceed through the initial generation of the 1,4-dipolar intermediate **5** from isoquinoline and aryne (generated from **2**; Scheme 3). The zwitterion **5** can add to the electrophilic carbonyl group of isatin in a concerted manner, leading to the formation of **4**. Alternatively, in a step-wise path, **5** can add to isatin, generating the tetrahedral intermediate **6**, which undergoes cyclization to produce **4**. The observed diastereoselectivity in the process suggests a step-wise path.

Prompted by these interesting results, we then focused our attention on pyridine derivatives as the nucleophilic source for the aryne MCRs with a expectation that the reaction would afford the analogous pyridooxazino derivatives. Surprisingly, however, treating pyridine **7a** and *N*-methyl isatin **3b** with the aryne generated from **2a** through the use of KF and [18]crown-6 furnished the indolin-2-one derivative **8a** in



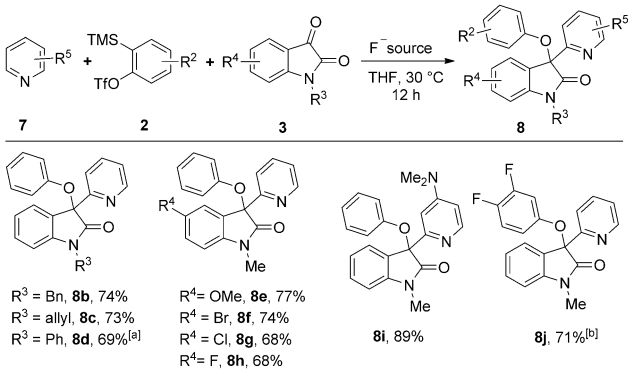
Scheme 3. Proposed reaction mechanism.



Scheme 4. MCR involving pyridine, aryne, and *N*-methyl isatin.

79% yield (Scheme 4). The reaction proceeds through a conceptually new heteroarylation followed by the arylation of isatin, which involves C–H bond functionalization of pyridine and an intramolecular aryl transfer reaction. No product derived from the interception of an initially formed 1,4-dipolar intermediate (from pyridine and aryne; analogous to **5**) with isatin was observed.[18] The structure of **8a** was unambiguously confirmed by single-crystal X-ray analysis.[16]

With the optimized reaction conditions in hand, we then examined the substrate scope of this unprecedented aryne MCR initiated by pyridine (Scheme 5). Various substituents

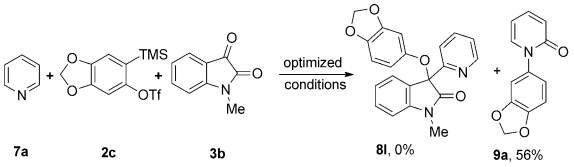


Scheme 5. Reaction scope of the MCR involving pyridine, arynes and N-substituted isatins. General conditions: **7** (0.75 mmol), **2** (0.75 mmol), **3** (0.5 mmol) KF (1.5 mmol), [18]crown-6 (1.5 mmol), THF (2.0 mL), 30°C, 12 h. Yields of isolated products are given. [a] Yield determined by ^{1}H NMR spectroscopy. [b] Reaction run on a 0.25 mmol scale.

on the isatin nitrogen resulted in smooth conversion into the indolin-2-one derivatives (**8b**–**8d**). Moreover, electron donating and -withdrawing groups on the carbocyclic ring of isatin were well tolerated, leading to the desired products in moderate to good yields (**8e**–**8h**). The nucleophile 4-dime-

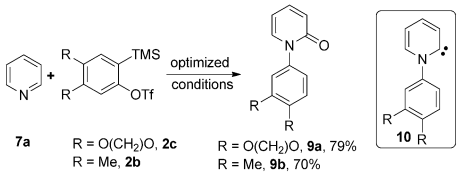
thylamino pyridine (DMAP) can also be used, affording the indoline 2-one **8i** in 89% yield. Furthermore, 4,5-difluorobenzyne furnished the desired product in 71% yield, demonstrating the versatility of the present reaction.

When the reaction was carried out using 4,5-disubstituted symmetrical aryne precursor **2c**, it did not afford the expected indolin 2-one derivative (**8l**), but instead furnished the *N*-aryl pyridin-2-one derivative (**9a**) in moderate yield [Eq. (3)]. As



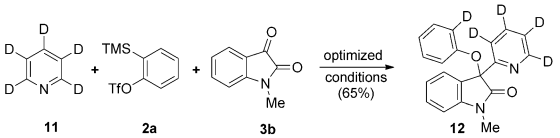
(3)

9a was formed from pyridine and aryne without incorporating isatin, we carried out additional experiments without adding isatin.[19] As expected, just mixing pyridine and the aryne precursor **2c** under the optimized conditions afforded **9a** in 79% yield [Eq. (4)].[16] Similar results were obtained with



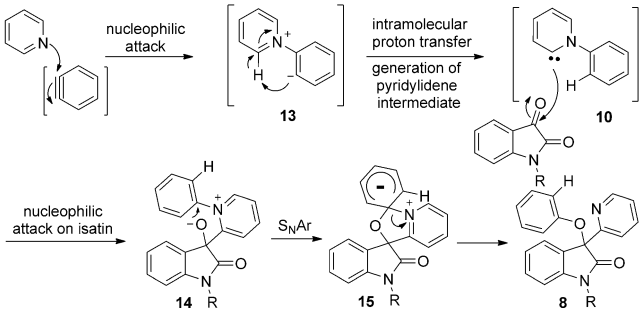
(4)

aryne precursor **2b**. These results tend to indicate that the initially generated 1,4-dipolar intermediate between pyridine and aryne (instead of adding to isatin) undergo an intramolecular proton transfer to form highly nucleophilic pyridylidene intermediate **10**, which was likely quenched by atmospheric oxygen to form the pyridine-2-one derivatives.[20,21] Moreover, to obtain further mechanistic insight into the participation of pyridylidene **10** in this reaction, an experiment was carried out using [D_5]pyridine **11**; delightfully, the reaction furnished **12** in 65% yield with incorporation of deuterium at the 2 position of the aryl group [Eq. (5)].



(5)

Based on the results of our preliminary mechanistic investigation into this MCR, we propose the mechanism outlined in Scheme 6. First, nucleophilic attack of pyridine on aryne generates the 1,4-dipolar intermediate **13**. In the absence of an external proton source, **13** undergoes an intramolecular proton transfer to generate pyridylidene intermediate **10**. The nucleophilic intermediate **10** adds to isatin to generate tetrahedral intermediate **14**, which undergoes an intramolecular nucleophilic aromatic substitution



Scheme 6. Tentative mechanism for the pyridine-initiated MCR.

(S_NAr) reaction to furnish indolin-2-one **8** via the σ-complex **15**.[22]

In conclusion, we have developed a conceptually new MCR involving arynes, N-heterocycles and N-substituted isatins. When isoquinoline is used as the nucleophile, the reaction furnished spirooxazino isoquinoline derivatives and proceeded through 1,4-dipolar intermediates. When pyridine was used as the nucleophilic trigger, the reaction afforded indolin-2-one derivatives and likely proceeded through a pyridylidene intermediate.[23]

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Keywords: isatins · multicomponent reactions · oxindoles · synthetic methods

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[15] For details, see the Supporting Information.

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[21] Additionally, treating pyridine and aryne with elemental sulfur under degassing conditions resulted in the formation of 1-phenylpyridine-2(1*H*)-thione in 16% yield. Although the yield is low, this is also an indication of the generation of a pyridylidene intermediate.

[22] It is reasonable to assume, in the case of electronically different aryne precursors **2b** and **2c**, that the electron-rich aryl ring (intermediate **14**, Scheme 6) may hamper the S_NAr reaction, hence the corresponding indolin-2-ones were not formed in these cases [Eq. (3)].

[23] The mechanistic difference in the reactivity of isoquinoline and pyridine towards aryne and isatin may be due to the less aromatic nature of the heterocyclic ring of isoquinoline, which facilitates the formation of spirooxazino derivatives. Owing to the relatively high aromaticity of pyridine, the corresponding spirocyclization is less favored in this case.

Communications

Synthetic Methods

A. Bhunia, T. Roy, P. Pachfule, P. R. Rajamohanan, A. T. Biju* _____ ■■■■–■■■■

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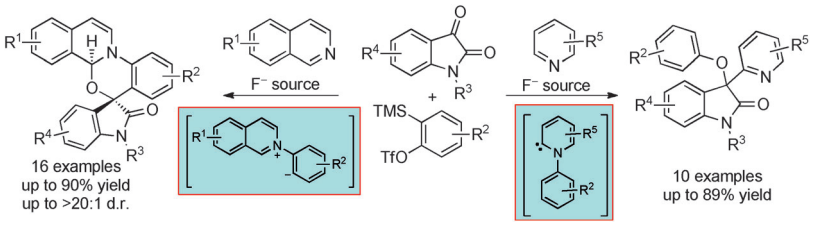

Mix and match: With isoquinoline as the nucleophilic trigger, multicomponent reactions afforded spirooxazino isoquinoline derivatives, proceeding through 1,4-dipolar intermediates. The use of pyridine as a nucleophile furnished indolin-2-one derivatives, with the reaction likely proceeding through a pyridylidene intermediate.