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Transition-Metal-Free Synthesis of 2-Arylimidazolones via Cascade Reaction between Arynes and α,α′-Disubstituted α-Isocyanoacetamides

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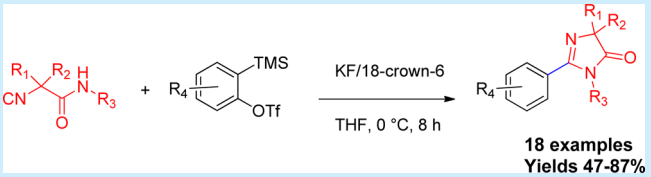
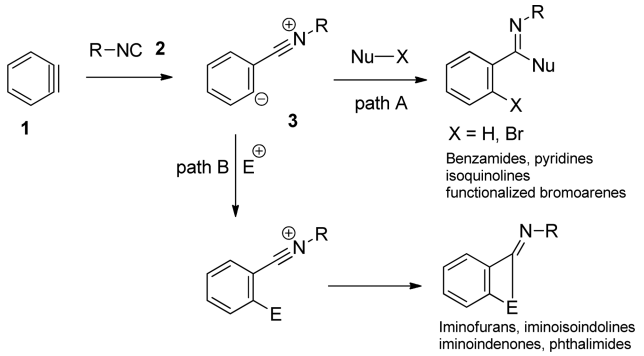
Supporting Information

ABSTRACT: The reaction between arynes and secondary α,α′-disubstituted α-isocyanoacetamides was developed to access 2-arylimidazolones of structural diversity and complexity in a straightforward manner.



Aryne chemistry has been extensively explored over the past decades,[1] and recent developments have been dedicated to transition-metal-free reactions, which mainly involve coupling between arynes and nucleophiles. Indeed, arynes display a highly electrophilic character because of their low-lying LUMO, and even neutral nucleophiles such as ureas,[2] imines,[3] *N*-heterocycles,[4] and diazene[5] can easily couple with them. In this context, isocyanides have been reported as efficient nucleophilic partners in coupling transformations with arynes, serving as key building blocks in transition-metal-free C−C bond-forming reactions.[6] In particular, the reaction of benzyne **1** with isocyanide **2** generates the zwitterion **3** and can then proceed in two different ways: (a) trapping of the nitrilium ion by a nucleophile (Scheme 1, path A)[7] and (b) interception

Scheme 1. Reaction of Benzyne with Isocyanides



of the aryl anion by an electrophile and subsequent intramolecular cyclization (Scheme 1, path B).[8] Both events lead to the direct construction of diversity-enriched structures through three-component coupling reactions, identifying isocyanides as useful nucleophiles in aryne multicomponent reactions (MCRs).[9]

While much attention has been paid to varying the third component involved in these coupling processes, to the best of our knowledge no functionalized isocyanide has ever been exploited in the reaction with arynes. In order to expand the synthetic possibilities of reacting isocyanides with aryne intermediates and in the context of our continued interest in the α-isocyanoacetamide chemistry,[10] our strategy involved the use of this bifunctional substrate as the coupling partner. To test the idea, we initially performed the reaction of benzyne **1**, generated in situ from 2-(trimethylsilyl)phenyl triflate **4a** in the presence of KF and 18-crown-6, with α-nonsubstituted and α-monosubstituted α-isocyanoacetamides.

Unfortunately, only complex reaction mixtures were obtained, suggesting that the pronounced acidity of the α-methylene proton may have interfered with the success of the reaction. Thus, we investigated the reaction of **1** with α,α′-dimethyl α-isocyanoacetamide **5a** in THF at 0 °C. Delightfully, we observed the formation of imidazolone **6a** in 60% yield (Scheme 2, a). The product was likely formed by a cascade process in which the trapping of benzyne from isocyanide triggers the subsequent intramolecular cyclization.

The formation of product **5a** encouraged us to pursue this project, since it provides an expeditious route to 2-arylimidazolones. This scaffold represents the main core of several bioactive compounds, especially in the realm of FAS (fatty acid synthase) inhibitors[11] and CGRP (calcitonin gene-related peptide) receptor antagonists.[12] The synthesis of 2-arylimidazolones is mainly based upon a ring-closing condensation of α-amidoamides,[13] but this methodology is affected by the difficult preparation of the appropriately functionalized starting material. Recently, Bischoff et al. have reported the C−H arylation under Pd(0)/Cu(I) bis-catalysis of the imidazolone ring **8** synthesized by condensation of methyl isocyanoacetate **7** with benzylamine and subsequent 4,4′-

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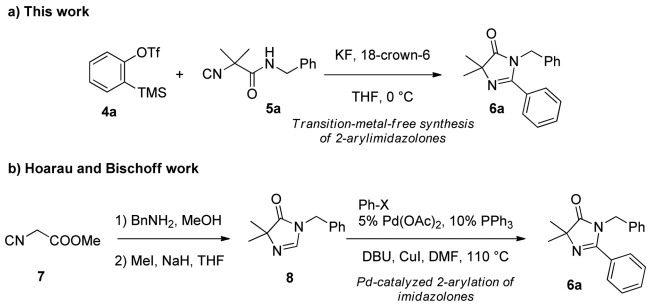
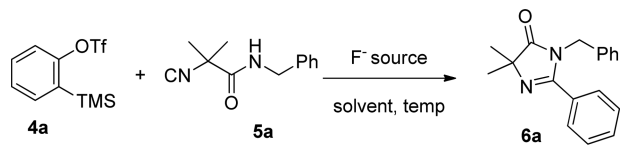
Scheme 2. Previous and Proposed Access to 2-Arylimidazolones



dimethylation (Scheme 2, b).[14] Besides being metal-catalyzed, this synthetic process is still fairly harsh and not widely applicable. Thus, an efficient and concise method to 2-arylimidazolones is highly desirable.

Encouraged by the aforementioned result, other reaction conditions were investigated, as summarized in Table 1. The

Table 1. Optimization of the Reaction Conditions[a]



entry	fluoride source	solvent	temp (°C)	yield[b] (%)
1	CsF	MeCN	82	25
2	CsF	THF	66	28
3	TBAF	THF	rt	36
4	TBAT	THF	rt	12
5	**KF, 18-crown-6**	**THF**	**0**	**60**
6	KF, 18-crown-6	THF	rt	55
7	KF, 18-crown-6	THF	40	38

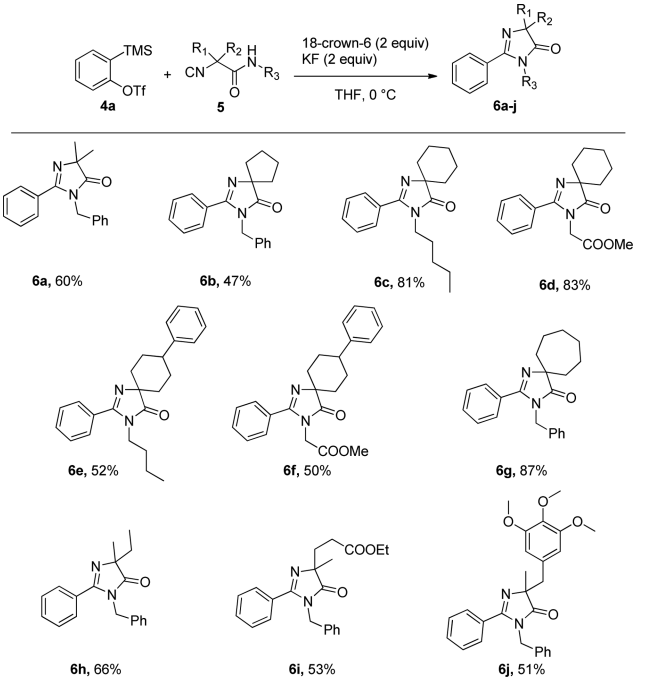
[a]Reaction conditions: **4a** (0.67 mmol, 2 equiv), **5a** (0.34 mmol, 1 equiv), fluoride source (2 equiv), 18-crown-6 (2 equiv), and solvent (3 mL) for 8 h. [b]Yields based on isolated product after gravimetric chromatography are given.

desired product **6a** was furnished with lower yields when the reaction proceeded in the presence of fluoride sources other than KF/18-crown-6 (entries 1−4). Additionally, increasing the temperature failed to offer any further improvement in yield (entries 6−7), revealing that 0 °C was the best choice for the reaction (entry 5).

After investigating the reaction conditions, we explored the scope of this transformation (Scheme 3). Diverse isocyanides were well tolerated, leading to 2-arylimidazolones **6a−j** in moderate to excellent yields. The reaction turned to be quite general, and a variety of functionalities such as methoxy, methyl, and ethyl esters were compatible with the reaction conditions.[15]

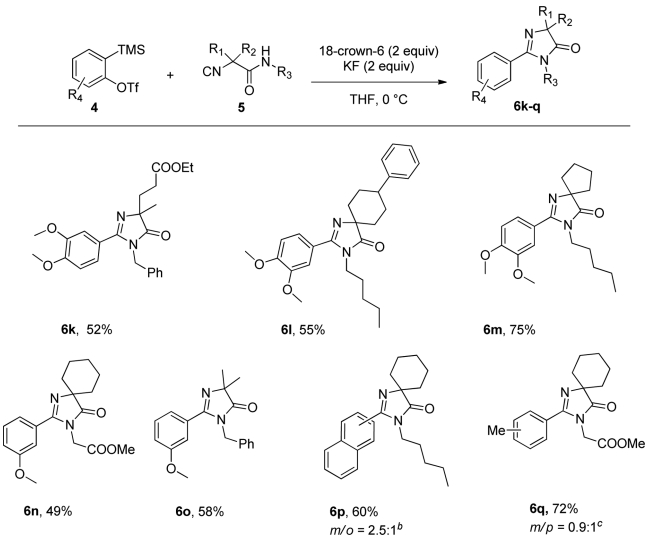
We then examined the scope of the reaction with various substituted 2-(trimethylsilyl)aryl triflates **4** (Scheme 4). A 4,5-dimethoxybenzyne was applicable to the reaction to give the corresponding 2-arylimidazolones **6k−q**. The reaction with 3-methoxyaryne took place with perfect regioselectivity due to steric and electronic effects (**6n**,**o**), while when 1-(trimethylsilyl)-2-naphthyl triflate was used an inseparable mixture of two regioisomers (**6p**) formed in 60% yield. The nucleophilic attack at the more sterically accessible 2-position was favored (ratio

Scheme 3. Reaction Involving Benzyne Precursor 4a and Isocyanoacetamides 5: Scope of Isocyanoacetamides 5[a]



[a]Reaction conditions: **4a** (0.67 mmol, 2 equiv), **5** (0.34 mmol, 1 equiv), 18-crown-6 (0.67 mmol, 2 equiv), KF (0.67 mmol, 2 equiv), THF (3 mL), 0 °C, 8 h. Yields based on isolated product after gravimetric chromatography are given.

Scheme 4. . Reaction Involving Aryne Precursors 4 and Isocyanoacetamides 5: Scope of Aryne Precursors 4[a]



[a]Reaction conditions: **4** (0.67 mmol, 2 equiv), **5** (0.34 mmol, 1 equiv), 18-crown-6 (0.67 mmol, 2 equiv), KF (0.67 mmol, 2 equiv), THF (3 mL), 0 °C, 8 h. Yields based on isolated product after gravimetric chromatography are given. [b]Regioisomeric ratio determined by HPLC analysis. [c]Regioisomeric ratio determined by ^{1}H NMR analysis.

2.5:1), in agreement with previous literature.[16] The reaction of 4-methylbenzyne furnished almost equal amounts of the regioisomeric products (**6q**) in 72% yield as steric and electronic effects are in this case negligible.

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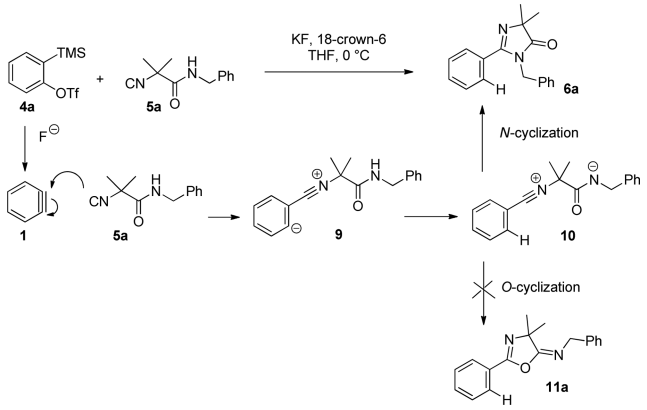
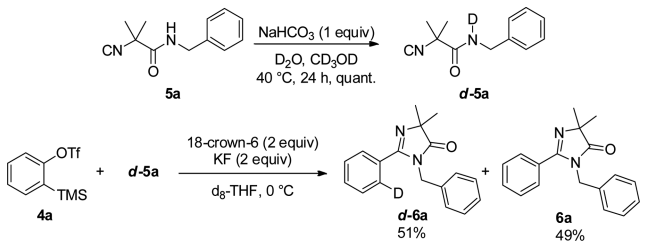
As anticipated, a plausible scenario for the formation of **6a** can be delineated as follows (Scheme 5). The reaction is

Scheme 5. Plausible Cascade Process for the Formation of 2-Arylimidazolone 6a



initiated by the nucleophilic addition of isocyanide **5a** to benzyne **1** to form the zwitterionic intermediate **9**. Subsequent abstraction of the secondary amide hydrogen by the resulting aryl anionic moiety occurs.[17] Finally, trapping of the nitrilium intermediate **10** by the internal amide nitrogen produces the imidazolone **6a**. The depicted reaction mechanism explains our experimental observation that α-nonsubstituted and α-monosubstituted isocyanoacetamides under the same reaction conditions led only to complex mixtures. In addition, to further substantiate the described intramolecular proton transfer, we conducted deuterium-labeling experiments (Scheme 6). The

Scheme 6. Deuterium-Labeling Experiments

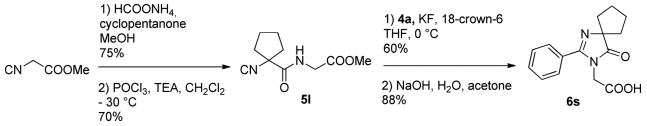


acidic proton of α-isocyanoacemide **5a** was exchanged for deuterium to afford the deuterated substrate ***d*-5a**. Upon treatment of ***d*-5a** with the benzyne precursor **4a**, we observed that there was incorporation of deuterium at the *ortho* position of the respective product ***d*-6a**.

Interestingly, the alternative nucleophilic attack by oxygen leading to 5-iminooxazoline **11a**[18] was not observed (Scheme 5). The exclusive formation of the imidazolone ring is not surprising, as the attack of the amide nitrogen to the nitrilium ion to yield imidazolones has been reported under strong basic conditions (sodium hydride, *n*-butyllithium, or potassium *tert*-butoxide),[19] which in this case are fulfilled by the aryl anion formation. The structure of **6a** was confirmed through careful NMR spectroscopy and by its stability to hydrolysis under acidic conditions.[20]

The synthetic potential of this transformation was demonstrated by the synthesis of imidazolone **6s** (Scheme 7), which is a key intermediate in the preparation of CGRP receptor antagonists (calcitonin gene-related peptide) developed by

Scheme 7. Synthesis of Imidazolone 6s, a Key Intermediate in the Preparation of CGRP Receptor Antagonists



researchers of Merck Sharp & Dohme Corp.[12] Ugi reaction proceeded in high yield, followed by dehydration to give the α-isocyanoacetamide. Treatment with the benzyne precursor **4a** in the presence of a fluorine source and subsequent hydrolysis of the methyl ester **6r** afforded the final 2-phenylimidazolone **6s**, demonstrating that this synthetic approach represents a novel and useful route to access 2-arylimidazolones. Indeed, it leads to the target compound in four synthetic steps and is characterized by an excellent average atom economy, compared to the five-step synthesis reported in the patent (73% versus 59%).

In conclusion, we have demonstrated that α,α'-disubstituted α-isocyanoacetamides are efficaciously coupled with arynes to offer direct and metal-free access to 2-arylimidazolones. Further studies focused on the extension of the reaction scope are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00580.

Experimental procedures and full characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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