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Base-Promoted Nitrile−Alkyne Domino-Type Cyclization: A General Method to Trisubstituted Imidazoles

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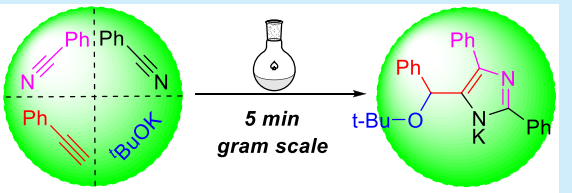
Supporting Information

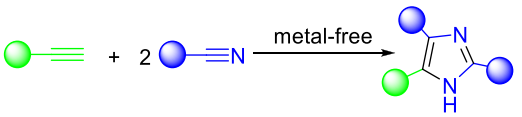
ABSTRACT: An efficient base promoted nitrile-alkyne domino-type cyclization for multicomponent assembly of imidazoles from alkynes, nitriles, and tBuOK has been developed, which could run even in the absence of solvent on a gram scale with complete atom economy. This method contributes directly to reaching the synthesis of valuable imidazole derivatives from readily available raw materials.



Multisubstituted imidazoles are one of the crucial five-membered nitrogen heterocycles used in daily life because of their biological activity (anti-inflammatory,[1] antibacterial derivatives,[2] especially anti-HIV[3]), material properties,[4] As valuable intermediates, imidazoles are generally used in organic synthesis. Imidazole contains two *N*-donor coordination sites, which made it shine in coordination chemistry, and has widely served as excellent candidates for targeted metal−organic frameworks (MOFs).[5]

Substantial advances in the development of transition-metal-catalyzed[6] and transition-metal-free[7] synthetic methods for multisubstituted imidazoles[8] have been achieved over the past few decades. Compared to transition-metal-catalyzed methods, most of these transition-metal-free reactions are eco-environmentally friendly. However, luxuriant complex substrates are required in the large reactions for the synthesis of imidazole. Therefore, the door-to-door construction of imidazole from elemental compounds is still an important research area. Alkynes, nitriles, and potassium *tert*-butylate are three classes of commercially available starting materials and generally used in organic synthesis. The atom-economical cycloaddition from these substrates is a perfect strategy to construct multi-substituted imidazole (Scheme.1). Further demand for green

Scheme 1. Nitrile−Alkyne Domino-Type Cyclization



chemistry is to design an atom-economical reaction that does not require a solvent, and the aimed product would be obtained on a gram scale within a few minutes at room temperature under air. The synthesis strategy of imidazole is still elusive. Herein, we hope to demonstrate a novel base-promoted nitrile-alkyne domino-type cyclization for a multi-component assembly of imidazole with complete atom economy and versatile compatibility.

Activating terminal alkynes seems to be the critical transformation in achieving multicomponent assembly of imidazoles through nitrile−alkyne cycloaddition. The most popular protocols of activating terminal alkynes are to form transition-metal acetylide under the catalysis of metal salts such as Mg,[9] Zn,[10] Fe,[11] Cu,[12] Pd,[13] Ag,[14] and Au[15] salts. Ligands and bases are almost essential in these methods. In 2013, oligsubstituted pyrroles were efficiently assembled through the Ag_2CO_3-mediated oxidative cyclization of alkynes with isocyanides by Bi and co-workers.[14a] Given that isocyano and nitrile have similar properties and our enthusiasm for environmentally friendly reactions, we initially tested that potassium *tert*-butylate,[16] as a robust base to replace the Ag_2CO_3, might activate terminal alkynes to complete the nucleophilic cyclization reaction directly with nitrile.[17]

Phenylacetylene (**1a**, 1.0 equiv), benzonitrile (**2a**, 3.0 equiv), and potassium *tert*-butylate were used as substrates (**3a**, 2.0 equiv), and we first examined the reaction under the conditions shown in Table 1. 2,4,5-Trisubstituted imidazole **4a** was isolated in 55% yield in heptane at 100 °C under Ar (entry 1).[18] Encouraged by this result, we continued to optimize the reaction conditions. The yield of imidazole **4a** was reduced while the amount of **2a** was reduced to 2.2 equiv or the temperatures were lowered to room temperature (entries 2 and 3). Beyond this, shortening the reaction time to 1 h led to a trace amount of imidazole **4a** (entry 4). Delightfully, by adjusting the ratio of **1a**/**2a**/**3a** to 1.0/4.0/2.5, the reaction afforded imidazole **4a** with a better yield (66%, entry 5). High yields of imidazole **4a** were achieved, while the solvents of *n*-pentane and cyclohexane were examined in this ratio (entries 6 and 7). Remarkably, cyclohexane as solvent in this nitrile−alkyne domino-type cyclization reaction afforded imidazole **4a** in 93% yield. It is noteworthy that the imidazole **4a** was still isolated with 48% yield in the absence of the solvent (entry 8). A series of bases were finally screened (entries 9−14), and the results showed that there was no more

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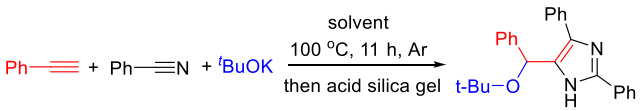
Table 1. Screening for the Reaction Conditions[a]



1a 2a 3a 4a

entry	1a/2a/3a (equiv)	base	solvent	time (h)	yield[b] of 4a (%)
1	1/3.0/2.0	tBuOK	heptane	11	55
2	1/2.2/2.0	tBuOK	heptane	11	42
3[c]	1/2.2/2.0	tBuOK	heptane	11	31
4	1/3.0/2.0	tBuOK	heptane	1	trace
5	1/4.0/2.5	tBuOK	heptane	11	66
6	1/4.0/2.5	tBuOK	hexane	11	80
7	1/4.0/2.5	tBuOK	cyclohexane	11	93
8	1/4.0/2.5	tBuOK		1	48
9	1/4.0/2.5	tBuOLi	cyclohexane	11	trace
10	1/4.0/2.5	tBuONa	cyclohexane	11	38
11	1/4.0/2.5	PhCOOK	cyclohexane	11	NR
12	1/4.0/2.5	CH_3ONa	cyclohexane	11	NR
13	1/4.0/2.5	CH_3OK	cyclohexane	11	NR
14	1/4.0/2.5	PhOK	cyclohexane	11	NR

[a]Unless otherwise noted, the reactions were performed as follows: **1a** (0.20 mmol, 1.0 equiv), **2a** (4.0 equiv), **3a** (2.5 equiv), solvent (1.5 mL), Ar. [b]Isolated yields. [c]The reaction was performed at room temperature.

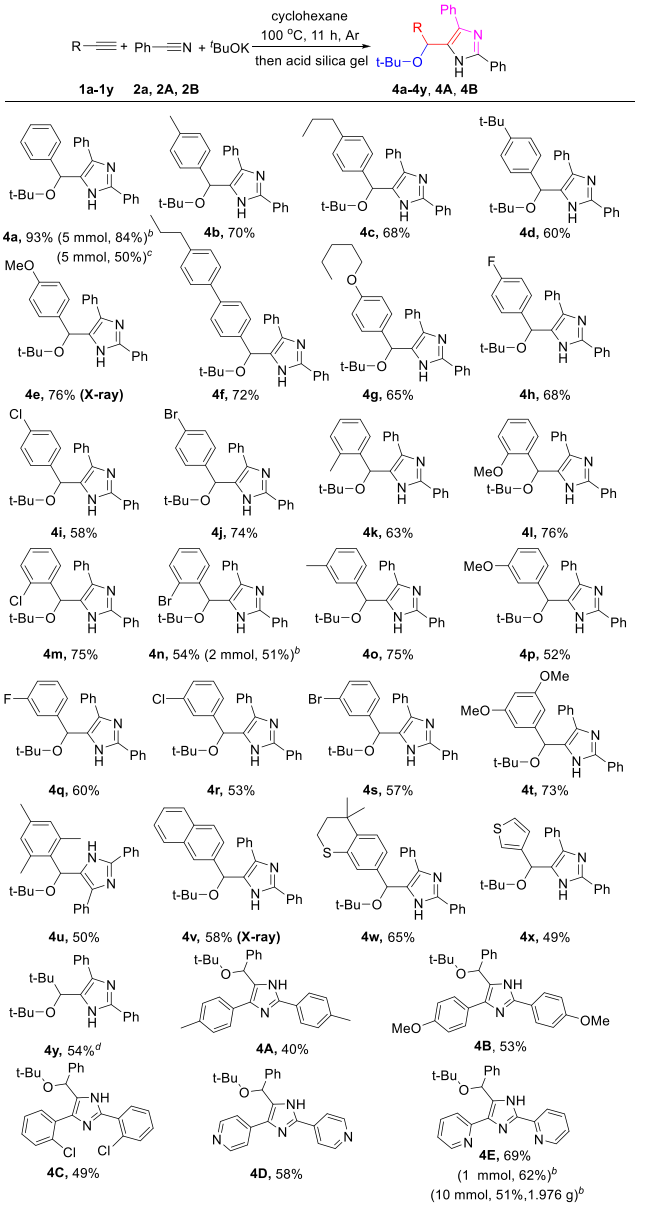
suitable base for this transformation than potassium *tert*-butylate.

Using these optimized reaction conditions (Table 1, entry 7), the nitrile–alkyne domino-type cyclization reactions with various alkynes were explored (Scheme 2). A range of substituted alkynes were investigated (**4a–4y**). Phenylacetylenes bearing different electron-donating and electron-withdrawing groups furnished the corresponding products with good yields (**4a–4w**). The position of the substituents on the phenyl ring has no effect on this reaction. The reaction also has a good response to multisubstituted phenylacetylenes (**4t–4u**). Ethynylnaphthalene, -benzothiopyran, and -thiophene participated efficiently and afforded the corresponding imidazoles **4v–4x** in 58%, 65%, and 49% yields, respectively. Remarkably, an aliphatic alkyne such as *tert*-butylacetylene was a suitable substrate, and the reaction successfully proceeded at 60 °C in THF (**4y**). In order to reveal the broadness of the reaction, *N*-heteroaryl nitriles were also examined with phenylacetylene (**1a**) for this domino-type cyclization reaction (**4A–4E**). Good results were obtained when 2- and 4-pyridylnitrile were used under the optimized reaction conditions (**4D–4E**). In particular, there is potential to employ the imidazole **4E** as a ligand to build metal-catalyzed reaction.

To further demonstrate the utility of this reaction, we performed this approach on a large scale to produce imidazole **4a**, **4n**, and **4B**. The reaction runs smoothly and gave the corresponding products in moderate yields at 100 °C in cyclohexane for 11 h (**4a**[b], **4n**[b], **4B**[b]). Importantly, the reaction still occurred and was isolated in 50% yield in the absence of solvent on a 5 mmol scale, which proceeded violently at room temperature for 5 min since a large amount of heat released during the reaction.

The drawback is that no other base has been found to be suitable for this reaction at present, and it only reacts with potassium (sodium) *tert*-butoxide to build *tert*-butyl ether compounds. Fortunately, *tert*-butyl ethers were easily converted to other ethers. The imidazoles **4a1–4a3** were isolated in mild conditions with high yields (Scheme 3), which greatly broadened the utility of this atom-economical strategy for imidazole synthesis.

Scheme 2. Substrate Scope for Nitrile–Alkyne Domino-Type Cyclization[a]



[a]Unless otherwise noted, the reactions were performed: alkyne (**1a–1y**) (0.20 mmol), benzonitrile or cyano compound (4.0 equiv), tBuOK (2.5 equiv), cyclohexane (1.5 mL), 100 °C, 11 h, Ar, isolated yields. [b]The reactions were performed on a large scale in the optimized condition reactions. [c]The 5 mmol scale reaction was run without a solvent at room temperature for 5 min, air. [d]The reaction was performed in THF (1.5 mL) as solvent at 60 °C for 11 h.

To understand the nitrile–alkyne domino-type cyclization reaction pathway better, critical mechanistic information was collected by experimental investigations (Scheme 4). First, the alkynes could easily transform to [*d*]-alkynes under the influence of tBuOK in cyclohexane at room temperature for 30 min (eq 1).[17c,d] The results reveal that an alkynyl anion could be an intermediate in the reaction. When deuterated

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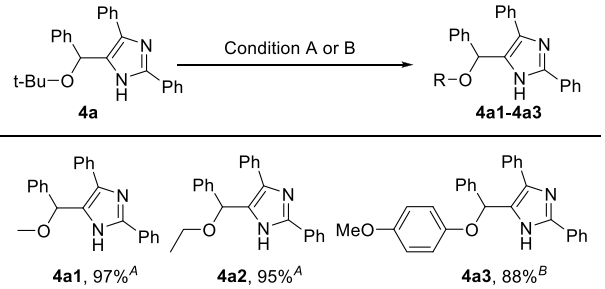
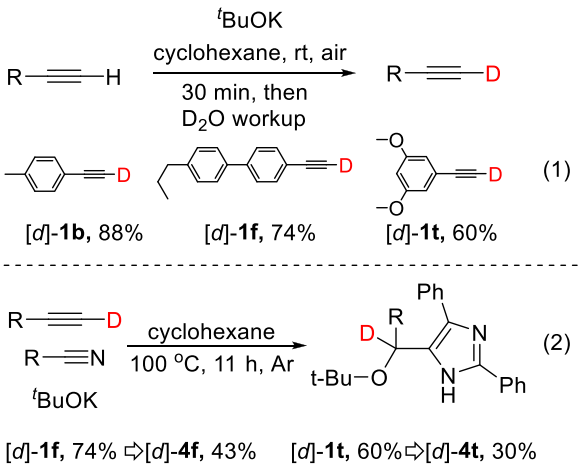
Scheme 3. Further Synthetic Derivation



[a]Conditions A: HCl/ROH = 1:7, 70 °C, 2 h, air, isolated yields. Conditions B: HCl:CH_2Cl_2 = 1:7, ROH (5.0 equiv), 60 °C, 2 h, air, isolated yield.

Scheme 4. Mechanistic Investigations

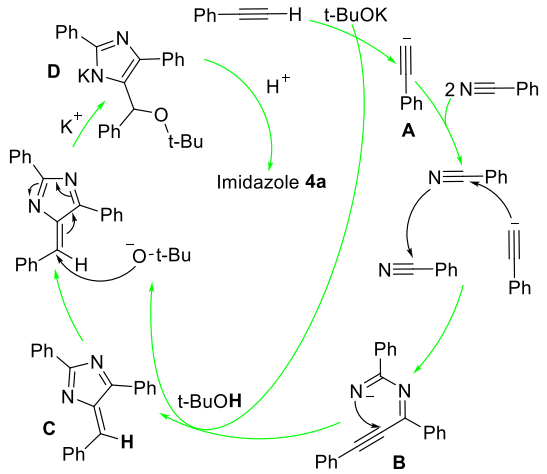


alkynes ([*d*]-**1f**, 74% deuterium content, [*d*]-**1t**, 60% deuterium content) were run with benzonitrile and potassium *tert*-butylate, 43% and 30% deuterium content for imidazoles **4f** and **4t** were observed, respectively (eq 2).

A plausible mechanism for the base-promoted nitrile−alkyne domino-type cyclization among alkynes, benzonitrile, and tBuOK is described on the basis of the above experiments and literature precedents[7a,14a,16] in Scheme 5. The reaction begins with activation of a C−H bond of alkynes with the help of tBuOK, which furnishes the alkynyl anion **A**. Then anion **A** continues to react with two molecules of benzonitrile and affords the intermediate **B**, which undergoes molecular nucleophilic addition to produce intermediate **C**. Intramolecular isomerization occurs while the tBuO anion attacks the double bond of intermediate **C** and gives product **D** with the participation of potassium ions. The desired imidazole is obtained when worked up with acid silica gel.

In summary, we have successfully developed a novel base-promoted metal-free multicomponent reaction to synthesize trisubstituted imidazole by coupling the readily available alkynes, nitriles, and tBuOK under mild conditions. The transformation features excellent functional group tolerance, simple operation, and atom-economic ability. Even without the solvent, the reaction is isolated in moderate yield at room temperature for 5 min on a gram scale, which has significant synthetic potential and is very helpful for green chemical synthesis under the current environmental protection policy.

Scheme 5. Plausible Mechanism



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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03782.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^1H and ^{13}C spectra (PDF)

Accession Codes

CCDC 1961140−1961141 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) The reactions were purified by acid silica gel column, and the imidazole **4a** was isolated, not the potassium salt of imidazole.

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