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Transition-Metal-Free Synthesis of *N*-(1-Alkenyl)imidazoles by Potassium Phosphate-Promoted Addition Reaction of Alkynes to Imidazoles

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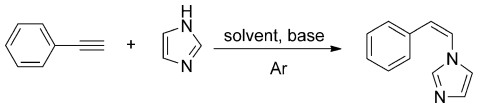
Abstract: The addition reaction of alkynes to *N*-heterocycles by simply heating in DMSO with potassium phosphate is reported. Good yields with high stereoselectivity could be achieved for a range of substrates. The scope is quite general for both amines and phenylacetylenes. In addition, internal alkynes and α-bromostyrene were also examined in this reaction. This process is efficient and useful for the synthesis of (*Z*)-*N*-(1-alkenyl)imidazoles and related *Z* products. Thus, the reaction is useful because of the importance of the imidazole scaffold.

N-(1-Alkenyl)imidazoles are versatile intermediates in organic synthesis and widely present in many biologically active molecules.[1] The antifungal and antiparasitic properties of these compounds are widely applied in medicine and agriculture.[2] Over the past few decades, a number of methods to synthesize such compounds have been reported.[3,4] Among these methods, vinylation reactions of imidazoles with vinyl halides were the most efficient and straightforward, because the traditional methods are not able to control the geometry of the double bond and suffer from harsh reaction conditions.[4]

Recently, we were interested in the stereoselectivity of the vinylation of imidazoles.[5] Interestingly, we found that just 10 mol% of CuI could effectively catalyze the coupling reaction of nitrogen-containing heterocycles with vinyl bromides and chlorides to afford exclusive *E* products under ligand-free and Pd-free conditions.[5a] However, when 10 mol% of $FeCl_3$ was employed as the catalyst, *Z* products were obtained predominantly.[5b] But how can we gain access to the *Z* products exclusively? It is noteworthy that the base is important for the stereoselectivity of the addition reaction of alkynes and *N*-heterocycles, particularly for *Z* products.[6]

The reaction system, KOH/DMSO (DMSO = dimethyl sulfoxide), has been extensively applied in many synthetic reactions, including the addition of alkynes to pyrroles.[6e,f,7] Therefore, we selected the addition of imidazole to phenylacetylene in the presence of KOH/DMSO as the model reaction. Unfortunately, the product could only be obtained in 34% yield (*Z*/*E* = 75:25; Table 1, entry 1). Therefore, we deduced that the known protocol was not suitable for this addition reaction. In DMSO, different, commonly used bases were investigated under similar reaction conditions (120 °C and 24 h), such as K_2CO_3, Cs_2CO_3, K_3PO_4, *t*BuOK, and Et_3N (Table 1, entries 2–6). To our surprise, a satisfactory result was achieved when K_3PO_4 was used as the base (94% yield, *Z*/*E* > 99:1; Table 1, entry 4). Therefore, we deduced that the inorganic bases are more suitable than the organic bases for the addition reaction. Various solvents such as *N*,*N*-dime-

Table 1. Screening various catalytic conditions for the addition of phenylacetylene to imidazole.[a]



Entry	Solvent	Base	*t* [h]	*Z*/*E*	Yield [%][b]
1	DMSO	KOH	24	75:25	34
2	DMSO	K_2CO_3	24	>99:1	26
3	DMSO	Cs_2CO_3	24	>99:1	91
4	DMSO	K_3PO_4	24	>99:1	94
5	DMSO	*t*BuOK	24	35:65	9
6	DMSO	Et_3N	24	–	0
7	DMF	K_3PO_4	24	83:17	26
8	Toluene	K_3PO_4	24	–	0
9	NMP	K_3PO_4	24	–	0
10	1,4-dioxane	K_3PO_4	24	–	0
11[c]	DMSO	K_3PO_4	24	>99:1	68
12[d]	DMSO	K_3PO_4	24	>99:1	19
13	DMSO	K_3PO_4	5	>99:1	78
14	DMSO	K_3PO_4	12	>99:1	83
15	DMSO	K_3PO_4	30	>99:1	84
16[e]	DMSO	K_3PO_4	24	75:25	91
17[f]	DMSO	K_3PO_4	24	75:25	78
18[g]	DMSO	K_3PO_4	24	65:35	80
19	DMSO	–	24	–	NR

[a] Catalytic conditions: Phenylacetylene (0.4 mmol), imidazole (0.48 mmol), solvent (2 mL), base (2 equiv), 24 h, 120 °C, Ar. [b] Isolated yield based on phenylacetylene. [c] 100 °C. [d] 60 °C. [e] 1 equiv of K_3PO_4 was employed. [f] 3 equiv of K_3PO_4 was employed. [g] 0.2 equiv of K_3PO_4 was employed. NR = no reaction.

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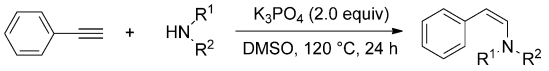
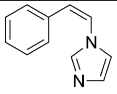
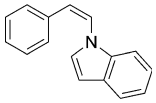
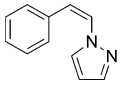
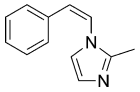
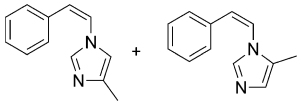
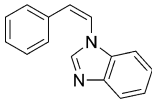
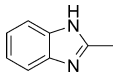
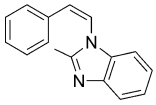
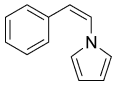
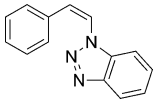
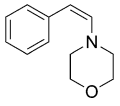
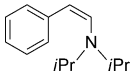
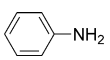
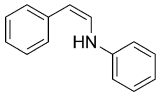
thylformamide (DMF), toluene, *N*-methyl pyrrolidone (NMP), and 1,4-dioxane were tested (Table 1, entries 7–10), and DMF afforded the desired product in low yield (Table 1, entry 7). Next, we optimized the reaction conditions in terms of temperature, time, and the amount of K_3PO_4 employed (Table 1, entries 11–18). In a control experiment, no product was detected in the absence of base, as expected (Table 1, entry 19). Finally, the best reaction conditions were those shown in entry 4 (Table 1).

Under these optimized reaction conditions, a variety of amine substrates were examined in the addition reaction and the results are shown in Table 2. We were delighted to find that the addition reaction of phenylacetylene to various *N*-heterocycles proceeded smoothly to give the *Z* isomers in good to excellent yields (83–99%; Table 2, entries 1–6). Interestingly, unsymmetrically substituted 4-methylimidazole afforded a mixture of 1,4- and 1,5-trisubstituted imidazoles, but the overall conversion of the reaction was good (97%; Table 2, entry 5).[8] Subsequently, other *N*-heterocycles, such as pyrrole (38%; Table 2, entry 8), indole (84%; Table 2; entry 2), benzimidazole (78–83%; Table 2; entries 6 and 7), and benzotriazole (13%; Table 2; entry 9) were also tested as substrates and afforded the desired products. It was demonstrated that our method can be successfully applied for various *N*-containing heterocycles. However, the addition reactions of phenylacetylene to aliphatic amines including morpholine, diisopropylamine, or aniline were unsuccessful (Table 2, entries 10–12).

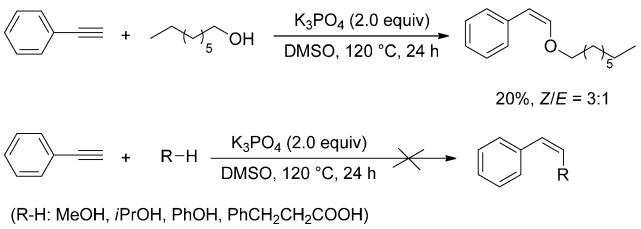
Table 2. Addition reactions of phenylacetylene to various amines under transition metal-free conditions.[a]



Entry	Amine	Product	*Z*/*E*	Yield [%][b]
1			>99:1	94
2			>99:1	84
3			>99:1	92
4			>99:1	>99
5			55:45 (or vice versa)	97
6			>99:1	83
7			>99:1	78
8			>99:1	38
9			>99:1	13
10			–	NR
11	iPr_2NH		–	trace
12			–	trace

[a] Reaction conditions: Phenylacetylene (0.4 mmol), amine (0.48 mmol), DMSO (2 mL), K_3PO_4 (2 equiv), 24 h, 120 °C, Ar. [b] Yield of isolated product based on phenylacetylene. NR = no reaction.

Furthermore, the addition reactions of phenylacetylene to alcohols or carboxylic acids were investigated. However, only when *n*-octanol was employed as the addition reagent, the desired product could be obtained in 20% yield, as shown in Scheme 1.

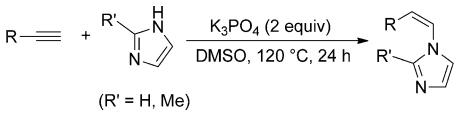


Scheme 1. Addition reaction of phenylacetylene to various alcohols or acid using the K_3PO_4/DMSO system.

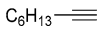
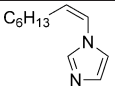
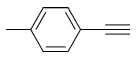
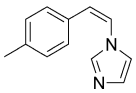
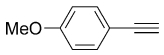
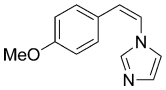
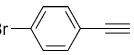
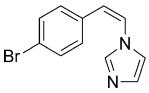
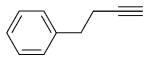
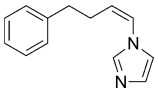
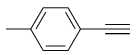
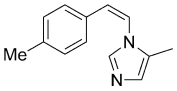
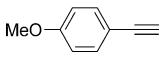
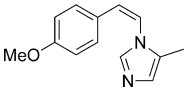
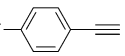
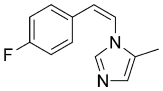
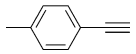
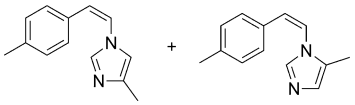
The scope of this addition reaction is substantially extended to both aromatic and aliphatic alkynes, as shown in Table 3. The addition products were not obtained when aliphatic alkynes were used as the substrates (Table 3, entries 1 and 5). However, the addition products of imidazole to aromatic alkynes were obtained with good yields (73–85%; Table 3, entries 2–4) and the addition reactions of 2-methylimidazole with aromatic alkynes afforded the desired products in moderate to good yields (43–99%, Table 3, entries 6–8). Interestingly, unsymmetrically substituted 4-methylimidazole afforded a mixture of 1,4- and 1,5-trisubstituted imidazoles. However, the overall conversion of the reaction was good (88%; Table 3, entry 9).[8]

Imidazole- or benzimidazole-fused isoquinoline polyheteroaromtaic compounds showed biological activities, such as anticancer and antifungal properties.[9] Retrosynthetic analysis showed that these compounds came from *N*-(1-alkenyl)imidazoles through two sequential C–H activations. Recently, Bao and co-workers reported an *N*-arylation of (*Z*)-β-bromostyrene and *N*-heterocycles with good yields.[10] Herein, our alternative to prepare *N*-(1-alkenyl)imidazoles is through the direct addition of readily available alkynes to *N*-heterocycles, as shown in Scheme 2.

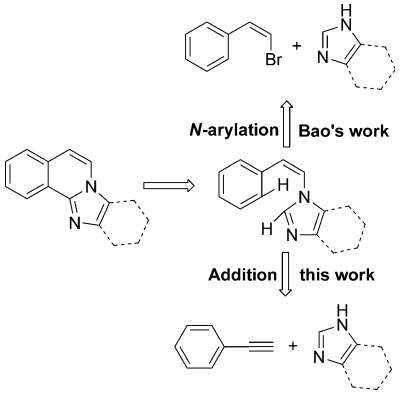
Table 3. Transition-metal-free addition reactions of various terminal alkynes to 1*H*-imidazoles.[a]



(R' = H, Me)

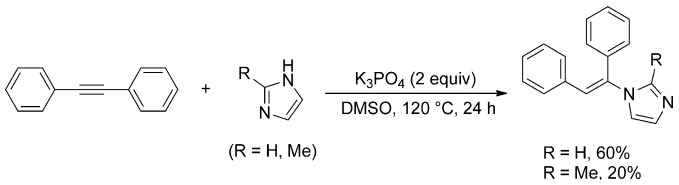
Entry	Alkyne	Product	*Z*/*E*	Yield [%][b]
1			–	NR
2			>99:1	85
3			>99:1	73
4			>99:1	74
5			–	trace
6			>99:1	>99
7			>99:1	84
8			>99:1	43
9			60:40 (or vice versa)	88

[a] Reaction conditions: alkyne (0.4 mmol), amine (0.48 mmol), DMSO (2 mL), K_3PO_4 (2 equiv), 24 h, 120 °C, Ar. [b] Yield of isolated product based on alkyne.



Scheme 2. Retrosynthetic analysis of imidazole- or benzimidazole-fused isoquinoline compounds.

To further expand the range of substrates, addition reactions of internal alkynes to imidazoles were examined. As shown in Scheme 3, when diphenylacetylene was used as an alkyne substrate, a single isomer was obtained successfully.



Scheme 3. Addition reaction of diphenylacetylene to imidazoles using the K_3PO_4/DMSO system.

Scheme 4. Addition of α-bromostyrene to imidazole using the K_3PO_4/DMSO system.

To extend the application of our method, we applied the K_3PO_4/DMSO catalytic system to other addition reactions, such as the addition of α-bromostyrene to imidazole. To our delight, the desired product could also be afforded in 80% yield, as shown in Scheme 4.

Although the actual active species is unknown until now,[6] one can deduce from the above results that both solvent and base play an important role in the chemical reactivity and the stereoselectivity of this addition reaction. For this reaction, K_3PO_4 was employed not only as the base but also as the catalyst. In those cases where the combination of K_3PO_4 and DMSO exclusively affords the *Z* products, we propose that these adducts are initially formed as the *Z* isomers owing to kinetic control, according to the classic *trans*-nucleophilic addition rule.[11] Then, as a result of thermodynamic control, in some instances, the *Z* isomers isomerized to give the *E* isomers until reaching a state of equilibrium. Studies on the reaction mechanism were performed in our laboratory.

In summary, an efficient ligand-free and transition-metal-free protocol has been developed for the addition reaction of alkynes to *N*-heterocycles. These reactions were opera-

tionally simple, and gave good yields with high stereoselectivities. Thus, the low-cost, benign character, and easy availability of the catalyst makes this method potentially useful, which could be amenable to scale-up. Efforts are under way to investigate the compatibility with representative functional groups, and this should be advantageous for practical applications of this method.

Experimental Section

General experimental

All reactions were carried out under an atmosphere of argon. Various alkynes and *N*-heterocycles were purchased from Aldrich, Acros, or Alfa. Column chromatography was generally performed on silica gel (100–200 mesh) and reactions were monitored by thin-layer chromatography (TLC) using UV light (254 nm) to visualize the course of the reactions. The ^{1}H (300 MHz or 400 MHz) and ^{13}C NMR spectroscopic (75 MHz or 100 MHz) data were recorded on Varian 300 MHz or 400 MHz spectrometers, respectively, using $CDCl_3$ as a solvent. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{1}H NMR spectra were recorded with tetramethylsilane ($\delta = 0.00$ ppm) as an internal reference; ^{13}C NMR spectra were recorded with $CDCl_3$ ($\delta = 77.000$ ppm) or [D_6]DMSO ($\delta = 39.500$ ppm) as an internal reference. ESI-MS and HRMS were performed by the State-authorized Analytical Center in Soochow University.

General procedure for the transition-metal-free addition of phenylacetylene to imidazole

A mixture of phenylacetylene (43.9 mg, 0.4 mmol), imidazole (33.3 mg, 0.48 mmol), K_3PO_4 (171.2 mg, 2 equiv), and DMSO (2 mL) in a Schlenk tube was stirred under an argon atmosphere at 120 °C for 24 h. Then, the mixture was poured into ethyl acetate, washed with water, extracted with ethyl acetate, dried by anhydrous Na_2SO_4, filtered, and evaporated under vacuum, and then the residue was purified by flash column chromatography (petroleum ether or petroleum ether/ethyl acetate, 1:2) to afford the corresponding coupling products.

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