



Cite this: *RSC Adv.*, 2021, 11, 38933

Received 13th November 2021
Accepted 29th November 2021

DOI: 10.1039/d1ra08322h

rsc.li/rsc-advances

Synthesis of vinyl-1,2,3-triazole derivatives under transition metal-free conditions†

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Herein, we describe a novel and green route for the direct synthesis of vinyl triazole derivatives with alkynes and triazoles promoted by an inorganic base under transition metal-free conditions. The base shows great catalytic activity for the anti-Markovnikov stereoselective hydroamination of alkynes. Moreover, good yields with excellent functional group tolerance are successfully achieved for a range of substrates, including aryl and heteroaryl groups, terminal alkynes and internal alkynes, and various triazole derivatives. This work presents an advanced concept for the synthesis of alkenyl triazole with a versatile and cost-efficient approach.

Introduction

1,2,3-Triazole compounds are an important class of nitrogen-containing heterocyclic compounds that are often introduced into existing drugs or lead compounds as pharmacodynamic groups to improve their pharmacological activity.^{1,2} In addition, their derivatives have a variety of biological activities, such as antibacterial,³ anti-malaria,⁴ anti-HIV,⁵ anti-fungal,⁶ anticancer⁷ and anti-inflammatory,⁸ activities (Fig. 1), which are indispensable in the field of new drug research and development.

When vinyl is used as a substituent in triazole, its desirable features including aromaticity, acid-base stability, large dipole moment, structural diversity of substituents, vinyl functional groups and regioisomers have attracted increasing attention.⁹ Therefore, vinyl-1,2,3-triazole is used as an important precursor for functionalized polymers in industry. The industrial production of electron-rich polymers can be realized by using the properties of high activity and easy polymerization, which are widely used in the production of polymerizable functional materials and polymer materials.¹⁰ Therefore, vinyl-1,2,3-triazole shows great application potential in the application of cations in biomaterials, ion exchange membranes, drug delivery, and metal-containing polymers for depollution and metal recovery.¹¹

At present, a well-known method for the synthesis of 1,2,3-triazole compounds, azide-alkyne click chemistry (CuACC

reaction), is considered to be the most extensive approach and has the characteristics of simple operation, high yields and compatibility with functional groups (Scheme 1a).^{10d} Such methodologies rely on Cu-catalyzed cycloaddition reactions as a key step and form vinyl substituents through elimination or Wittig-type reactions (Scheme 1c).¹² However, this method, which uses organic azide or sodium azide as raw materials for synthesis, is potentially explosive and is not suitable for large-scale industrial production.¹³ Therefore, there is academic and practical significance for the development of alternative methods other than azide-alkyne click chemistry. Vinyl triazole has been prepared using diazonium as a raw material. Yan prepared a variety of *N*-vinyl-1,2,3-triazole monomers from 2-aminoethanol and α -diazo- β -oxoamides through modified Wolff's cyclocondensation reactions (Scheme 1d). This method

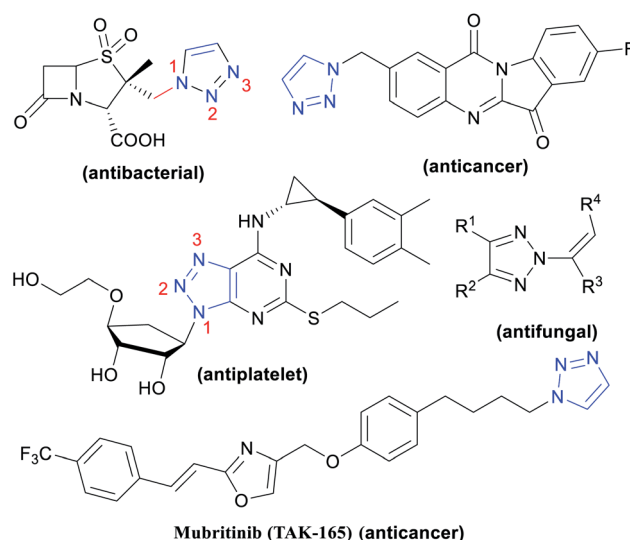


Fig. 1 Biologically active compounds featuring 1,2,3-triazole.

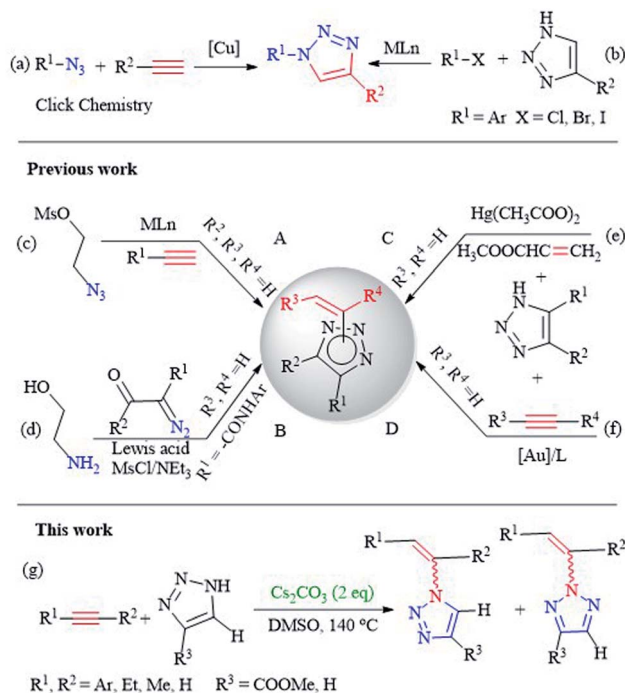
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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra08322h





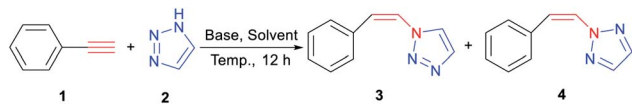
Scheme 1 Previous and present synthesis of vinyl-1,2,3-triazole.

enjoys not only the advantages of Wolff's 1,2,3-triazole cyclocondensation but also replacement for click chemistry due to its high yields and feasibility.⁹ To date, 1,2,3-triazole as a substrate is also an effective method for the direct synthesis of triazole derivatives (Scheme 1b).¹⁴ Kizhnyaev reported that 1,2,3-triazole and alkenyl compounds are directly reacted to synthesize *N*-vinyl-1,2,3-triazole derivatives under the catalysis of mercury acetate. Unfortunately, a toxic mercury acetate catalyst is used in the reaction, and the reaction easily generates unknown nitro byproducts.¹⁵ Duan, Zhao studied the use of precious metal complexes to add 1,2,3-triazole to alkynes (Scheme 1e and f).¹⁶ Besides, alkali metal hydroxides as have already been employed for the addition of nitrogen derivatives to alkynes, such as anilines, imidazoles and pyrroles.¹⁷ However, the synthesis of alkenyl triazoles without transition metal promoted has not yet been studied.

Our research is mainly devoted to the development of environmentally friendly and waste minimization procedures without metal conversion and aims to report the transition metal-free hydrogenation amination of 1,2,3-triazole on alkynes.

Results and discussion

To commence our studies, reaction conditions were examined in the reaction of 1,2,3-triazole (2a) with aryl acetylene (1a) (Table 1). Initially, the reaction was screened in DMSO under the catalyzed conditions for the organic bases piperidine and triethylamine, but no reaction was observed at 120 °C for 24 hours (Table 1, entries 1 and 2). Then, the reaction was explored in the presence of KOH, EtONa and Cs₂CO₃ under the

Table 1 Optimization of the reaction conditions^a


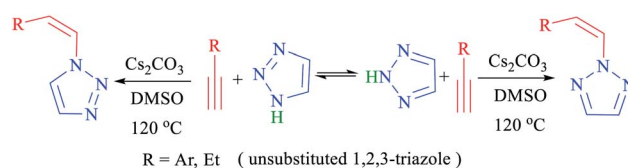
Entry	Base	Base	T (°C)	Yield ^b (%)	3aa : 4aa ^c
1	Pyridine (2 eq.)	DMSO	120	None	—
2	Et ₃ N (2 eq.)	DMSO	120	None	—
3	KOH (2 eq.)	DMSO	120	21	47 : 53
4	EtONa (2 eq.)	DMSO	120	42	80 : 20
5	Cs ₂ CO ₃ (2 eq.)	DMSO	120	73	88 : 12
6	Cs ₂ CO ₃ (0.1 eq.)	DMSO	120	22	44 : 56
7	Cs ₂ CO ₃ (1 eq.)	DMSO	120	47	69 : 31
8	Cs ₂ CO ₃ (1.5 eq.)	DMSO	120	54	86 : 14
9	Cs ₂ CO ₃ (2 eq.)	DMSO	140	92	81 : 19
10	Cs ₂ CO ₃ (2eq.)	DMSO	150	69	73 : 27
11	Cs ₂ CO ₃ (2 eq.)	DMSO	100	6	—
12	Cs ₂ CO ₃ (2 eq.)	DMSO	80	14	—
13	Cs ₂ CO ₃ (2eq.)	DMF	140	59	85 : 15
14	Cs ₂ CO ₃ (2eq.)	NMP	140	24	—
15	Cs ₂ CO ₃ (2eq.)	DMA	140	65	86 : 14
16	—	DMSO	140	None	—

^a Reactions were performed by using 1a (0.5 mmol), alkyne 2a (1 mmol), and base (0.05–1 mmol) in solvent (2 mL) at 80–150 °C for 12 h. ^b Yield of mixture of isolated product. ^c Regioselective isomer ratio.

abovementioned conditions (Table 1, entries 3–5). The results show that with Cs₂CO₃ (2 eq.) as the base catalyst, the yield is 73%, and the 3a : 4a ratio is equal to 88 : 12 (Table 1, entry 5). Unsubstituted 1,2,3-triazole is well known for rapid tautomerization. When 1*H*-1,2,3-triazole was used, mixtures of tautomeric addition products were obtained, mainly *N*-1 substituted products (Scheme 2). When the reaction equivalent of Cs₂CO₃ was changed, the yield was significantly reduced (Table 1, entries 6–8).

We examined the influence of different temperatures on the formation of 3a and 4a (Table 1, entries 9–12). To our surprise, a satisfactory result was achieved when Cs₂CO₃ was used as the base at 140 °C (92% yield, 3aa : 4aa = 81 : 19; Table 1, entry 9). Then, various solvents, such as *N,N*-dimethylformamide (DMF), *N*-methyl pyrrolidone (NMP) and *N,N*-dimethylacetamide (DMA), were tested (Table 1, entries 13–15), and the yields were not significantly improved. In a control experiment, no product was detected in the absence of the base, as expected (Table 1, entry 16). Finally, the best reaction conditions were determined to be those shown in entry 9 (Table 1).

With the optimized conditions in hand, we then explored the substrate scope for synthesis of vinyl-1,2,3-triazole derivatives

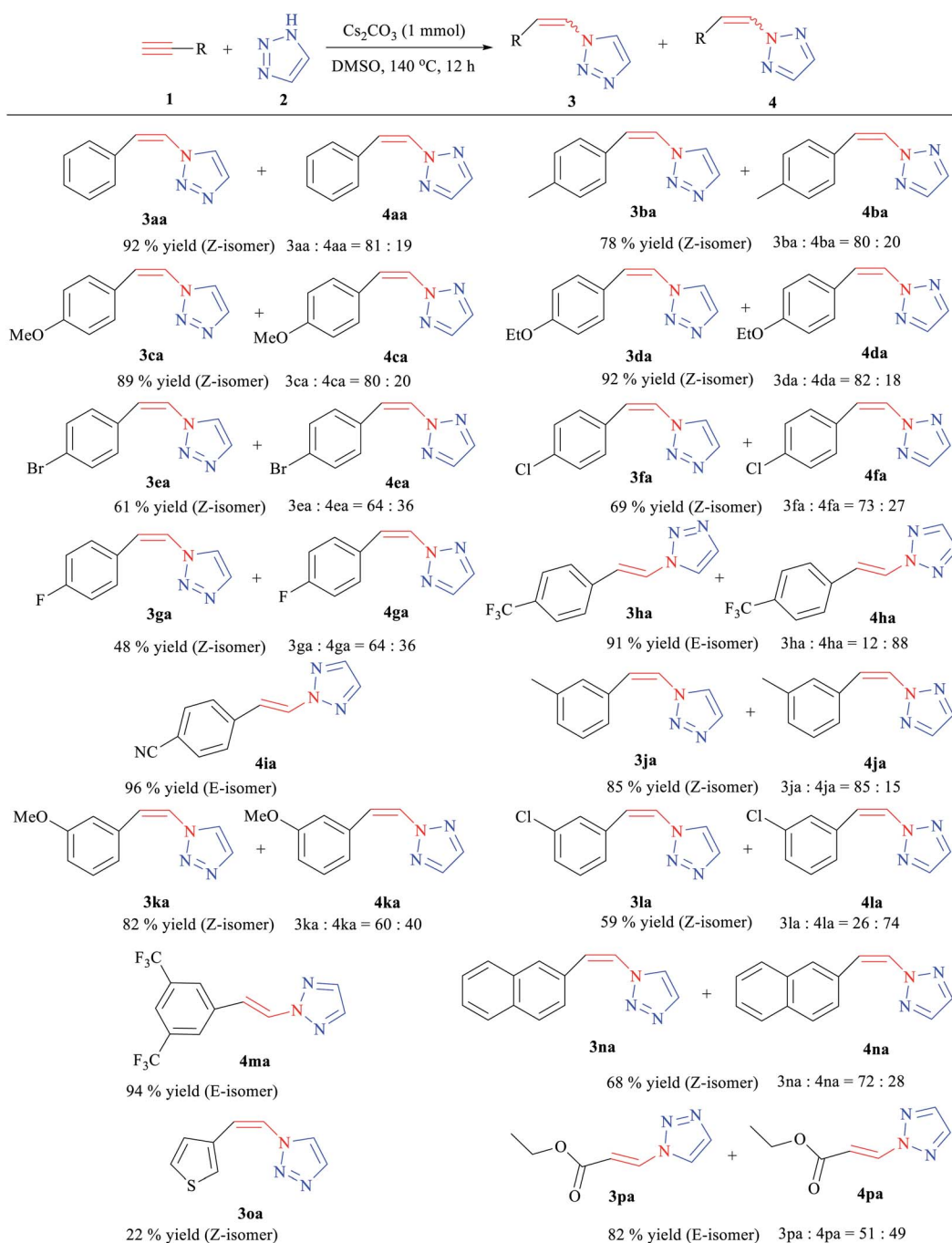


Scheme 2 Tautomerization in unsubstituted 1,2,3-triazole.



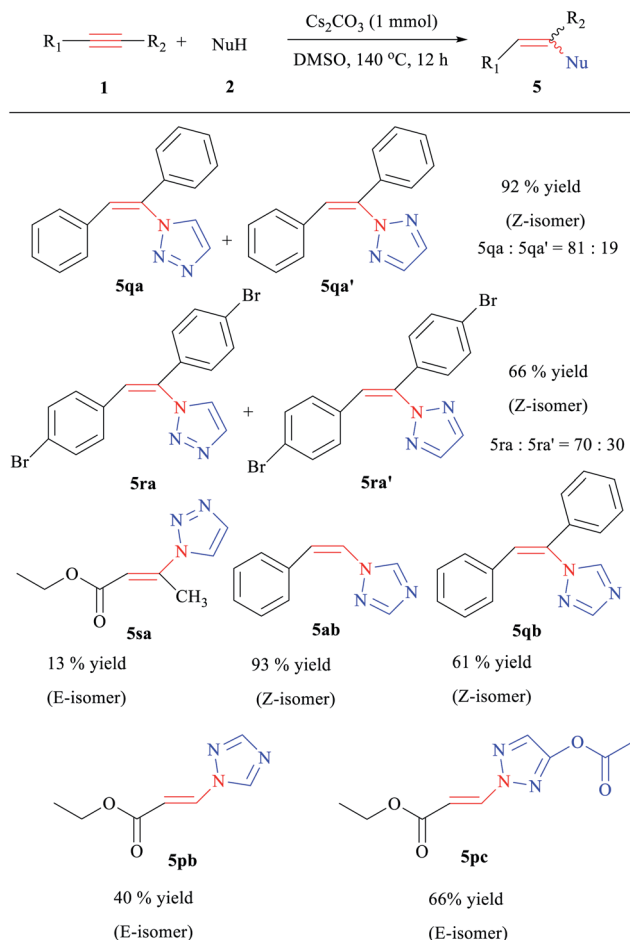
via a variety of aromatic alkynes and triazole derivatives. In all cases, anti-Markovnikov products were formed, and alkynes with electron-rich and electron-deficient substituents were well tolerated (Scheme 3). Alkynes containing electron-donating groups on the phenyl ring gave the corresponding better yield. With the enhancement of electron donation, products were obtained in moderate to good yields (Scheme 3, 3/4ba–da, 78%, 89% and 92% yield). The *N*-1/*N*-2 ratio for the addition products was approximately 80/20 in terms of location selectivity. When alkynes with electron-drawing groups were used, the reaction

proceeded with moderate conversion values (Scheme 3, 3/4ea–ga, 61%, 69% and 48% yield). However, the *N*-1/*N*-2 ratio for the addition products with electron withdrawing groups trends towards the conversion of *N*-2-vinyl-triazole. Interestingly, the addition of alkyne with stronger electron withdrawing substituents –CF₃ and –CN on the phenyl ring afforded *E*-isomer products completely (Scheme 3, 3/4ha–ia, 91% and 96% yield), presumably due to the decreased electron density at the distal end of the C–C bond. The cyano-substituted product was regioselectively obtained as the *N*-2 substitution product. We



Scheme 3 1,2,3-Triazolation of terminal alkynes.





Scheme 4 Triazolation of internal alkynes and alkenylation of triazole.

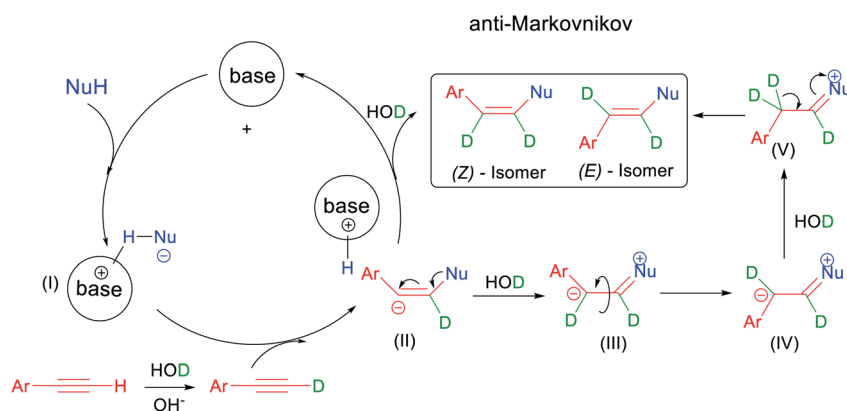
can see that the strength of the electron withdrawing group on the phenyl ring directly affects the stereoselectivity and regioselectivity of the product. Similarly, the addition product for alkyne with disubstituted trifluoromethyl groups only produces *N*-2-vinyl-triazole, and the yield is as high as 94% (Scheme 3, **4ma**). We also investigated the effect of substituting substrates at different positions on the phenyl ring. The yield of the meta-

substituent alkyne addition product is relatively low compared to the para-substituent alkyne (Scheme 3, **3/4ja-la**, 85%, 82% and 59% yield). In addition to aryl acetylenes, we also studied the reaction of aliphatic alkynes with triazoles. Alkynes containing ester groups completely generate *trans* products with poor position selectivity (Scheme 3, **3/4pa**, 82% yield).

The addition of heteroaromatic alkynes was studied for their potential applications in bioactive molecules and synthetic drugs. When the reaction was conducted using bulkier 2-ethynyl-naphthalene, products were obtained in 68% yield with *N*-1-vinyl-triazole regioselectivity (Scheme 3, **3/4na**). Consistent with above results, alkyne with electron-donating thiophene group gave completely *Z*-stereoselective and *N*-1-regioselective adducts (Scheme 3, **3oa**).

N-Functionalised azoles are important molecular scaffolds for pharmaceuticals and natural products, show excellent biological activity. To our delight, we used internal alkynes as the source of alkynes to synthesis with triazole derivatives and got better results. At first, diphenylacetylene and bis(4-bromophenyl) acetylene were reacted with 1,2,3-triazole lead to the corresponding *Z*-products **5qa/5qa'** and **5ra/5ra'** in good yields (Scheme 4, 92% and 66% yield). The reaction afforded preferentially the *N*-1 addition product **5qa**, the *N*-2 tautomer product **5qa'** being minor. The ethyl 2-butynoate with 1,2,3-triazole only afforded *E*-isomers, but the yield is 13% (Schemes 4 and **5 sa**).

To expand the universality, a variety of triazole substrates were examined in the addition reaction under these optimized reaction conditions. We were delighted to find that the addition reaction of 1,2,4-triazole to phenylacetylene and diphenylacetylene proceeded smoothly to give the *Z*-isomers in good to excellent yields (Scheme 4 **5ab**, **5qb**, 93% and 61% yield). Subsequently, methyl 1,2,3-triazole-4-carboxylate was also tested as a substrate and afforded the desired products with ethyl propiolate. This result is consistent with the previous conclusion that ester groups as alkynes afford *E*-isomer products in moderate yields (Scheme 4 **5pb**, **5pe**, 40% and 66% yield). However, reaction with aromatic acetylenes did not give products.



Scheme 5 Proposed reaction mechanism.



To explore the reaction mechanism, we used DMSO- d_6 as a solvent to mark the styryl position of compound **1a/h**. The results show that the source of the styrene matrix proton in the addition reaction is H in the solvent. Therefore, we preliminarily deduced the possible reaction mechanism: the base can efficiently activate *N*-nucleophiles and DMSO- d_6 under alkaline conditions. Then, kinetically stable alkenyl anion **III** is initiated by the attack of ion pair **I** on alkyne- d_6 , prioritizing conversion to the *Z*-isomer. In addition, intermediate **II** is converted into intermediate **III** after deuterium substitution due to migration of the triazole lone pair toward the adjacent carbon. Intermediate **V** was formed *via* bond transformation and deuteration. Furthermore, the migration of the triazole lone pair for intermediate **V** generated the compound *E*-isomer. The transformation of *Z*-isomers and *E*-isomers proceeds in an anti-Markovnikov fashion. The possible reason for this is that intermediate **III** is more stable.

Conclusions

In summary, an efficient base-mediated stereoselective and regioselective addition method for imidazoles (electron-deficient heterocycles) onto alkynes involves the synthesis of a broad range of functionalized vinyl triazole derivatives. This approach utilizes a simple and economical basic system composed of Cs_2CO_3 /DMSO for the addition of terminal and internal alkynes, avoiding the use of expensive catalysts and ligands. The catalytic system, which is low cost, benign and easily available, makes this method of potential practical value. The present process represents a safe, green and atom-economical alternative approach for existing synthesis methods to assemble a variety of functional vinyl triazole derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Center for Instrumental Analysis, Tongji University, China.

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