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Base-Promoted Ecofriendly Synthesis of Trisubstituted Pyrazoles from α,β-Alkynyl *N*-Tosylhydrazones under Metal- and Solvent-Free Conditions

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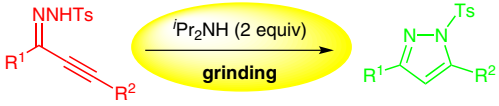

- **23 examples, 61–94% yield**
- **gram scale**
- **metal- and solvent-free conditions**
- **R^1 = aryl, alkyl; R^2 = H, aryl, alkyl, TMS**

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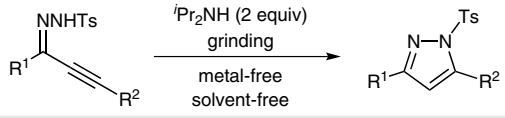
Abstract A simple and green method is described for the synthesis of trisubstituted pyrazoles from α,β-alkynyl *N*-tosylhydrazones under metal- and solvent-free conditions. Notably, only diisopropylamine is required as a promoter, and the reaction can be easily performed at room temperature and on a gram scale.

Keywords hydrazones, green chemistry, pyrazoles, cyclizations

Pyrazoles are among the most important N-heterocycles and are found in many natural products and pharmaceutically active molecules; they are also frequently used as ligands for metal-catalyzed cross-coupling reactions in materials science and in organic synthesis.[1] Substituted pyrazoles, for example, are associated with a broad range of biological activities, such as antiviral,[2] antidiabetic,[3] antibacterial,[4] antiobesity,[5] antiinflammatory,[6] and antitumor activities.[7] In addition, some pyrazole derivatives are present as core frameworks in a wide variety of leading drugs and pesticides, such as celecoxib (Celebrex), sildenafil (Viagra), zometapine, cyenopyrafen, and fenpyroximate.[8] Their diverse pharmacological and biological activities have stimulated substantial interest in the preparation of these important heterocycles.

In recent decades, several methods have been developed for the synthesis of substituted pyrazoles.[9] Typical strategies for the synthesis of pyrazoles involve a 1,3-dipolar cycloaddition reaction of diazo compounds and alkynes,[10] the cyclocondensation of hydrazines with 1,3-dicarbonyl compounds or their equivalents,[11] transition-metal-catalyzed C–N or C–C cross-coupling reactions,[12] or one-pot reactions through a propargylic substitution–cyclization cascade sequence from propargylic alcohols and hydrazines.[13] Recently, α,β-alkynyl hydrazones[14] have been explored as good precursors for the synthesis of polyfunctionalized pyrazoles with high efficiencies and high regioselectivities. However, these syntheses have several drawbacks, including the use of hazardous transition metals, harsh reaction conditions, poor regioselectivity, and laborious workup procedures. In particular, it is desirable that polyfunctionalized pyrazoles prepared for their biological or pharmaceutical activities are free of residues of metal catalysts in the final products; consequently, considerable attention has to be paid to product purification and to the detection of impurities. To overcome these drawbacks, more convenient and more environmentally benign approaches to these N-heterocycles are required.[15]

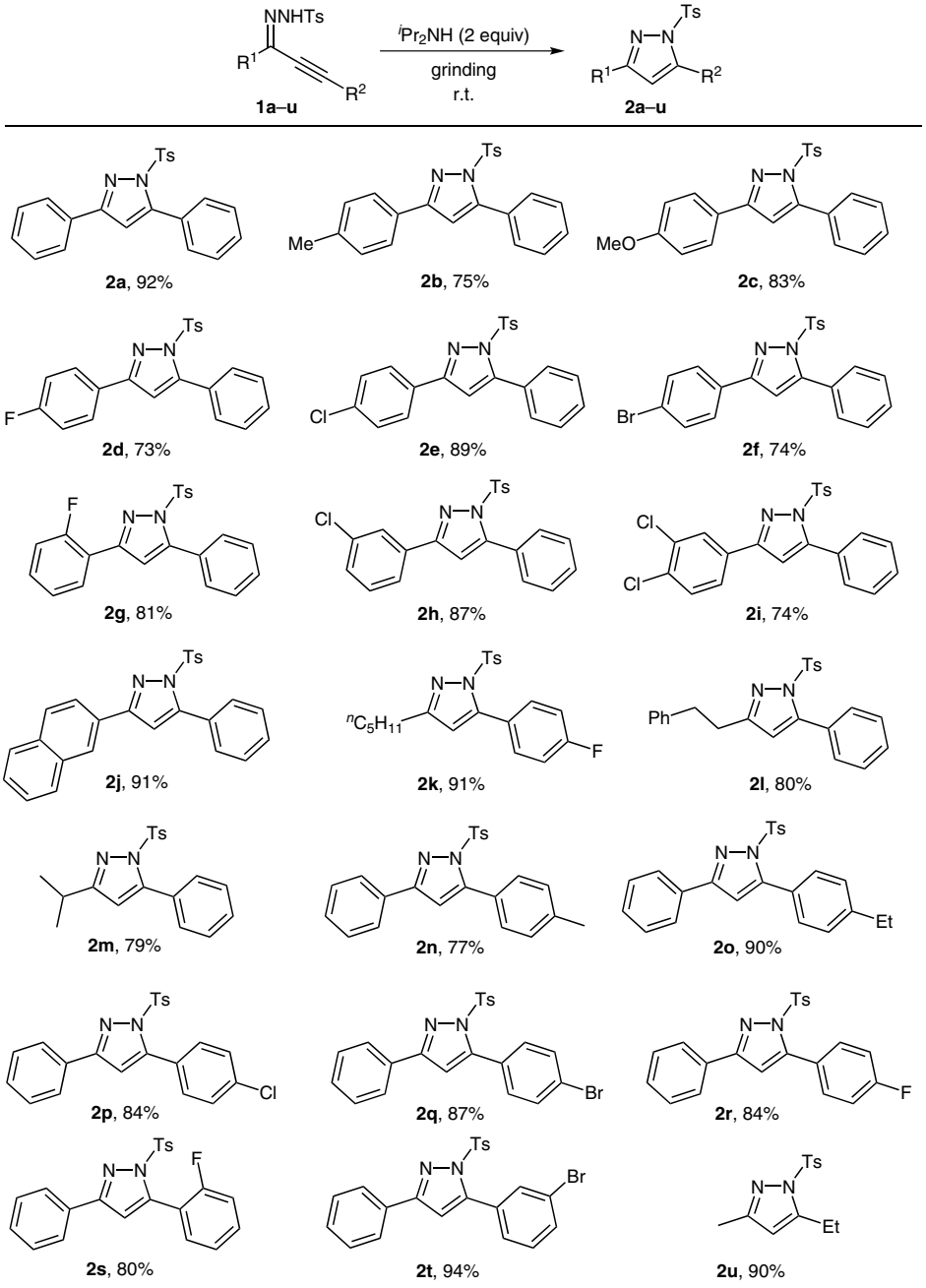
As a continuation of our ongoing efforts to develop environmentally benign synthetic reactions[16] and our interest in the synthesis of heterocycles,[17] we developed a simple and green method for the synthesis of trisubstituted pyrazoles from α,β-alkynyl *N*-tosylhydrazones under metal- and solvent-free conditions (Scheme 1). Only diisopropylamine is required as a promoter, and the reaction can be easily performed at room temperature and on a gram scale. This approach has several advantages over the conventional methods, such as a shorter reaction time, mild reaction temperatures, high isolated yields, and ease of purification of the products.



Scheme 1 Synthesis of pyrazoles under metal- and solvent-free conditions

Because solvent-free synthesis has attracted a great deal of interest, it was imperative to investigate the reaction under solvent-free conditions. First, we employed the α,β-

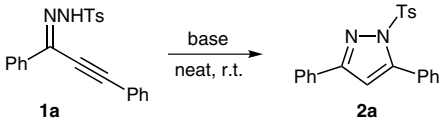
alkynyl *N*-tosylhydrazone **1a** as a substrate and investigated its electrophilic cyclization reaction under metal- and solvent-free conditions. The reaction proceeded successfully in a porcelain mortar and pestle with K_2CO_3 as the promoter, without any catalyst, to give the corresponding pyrazole **2a** in 79% yield at room temperature in 30 minutes (Table 1, entry 1). Next, we carefully examined the effectiveness of various bases in the reaction. The inorganic bases Cs_2CO_3, Na_2CO_3, and KOH behaved similarly to K_2CO_3, giving the corresponding pyrazole **2a** in 48, 27, and 44% yield, respectively (entries 2–4). However, only a trace of **2a** was detected when *t*-BuOK was used under the same reaction conditions (entry 5). Interestingly, when DBU was used as the promoter, a 78% yield of **2a** was obtained (entry 6). Although the use of Et_3N resulted in an increased yield of **2a** (entry 7), *i*-Pr_2NH was found to be the most effective base for this re-



Scheme 2 Diisopropylamine-promoted metal- and solvent-free synthesis of pyrazoles. All the reactions were carried out on a 0.3 mmol scale of **1** in the presence of 0.6 mmol of *i*-Pr_2NH under air at room temperature with grinding for 30 minutes. Isolated yields are reported.

action (entry 8). Increasing the loading of *i*-Pr_2NH did not improve the yield of the product (entry 9). Finally, for comparison, we attempted the reaction in the absence of a base, but no reaction occurred under these conditions (entry 10).

Table 1 Effect of the Base on the Electrophilic Cyclization Reaction of the α,β-Alkynyl *N*-Tosylhydrazone **1a** under Metal- and Solvent-Free Conditions[a]



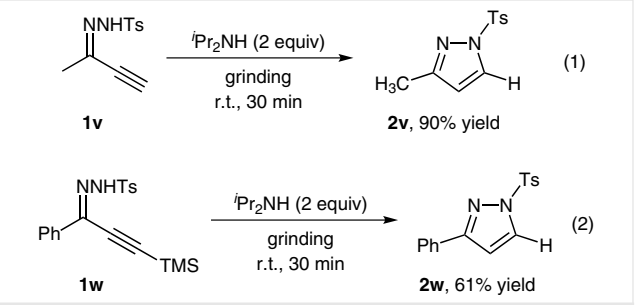
1a **2a**

Entry	Base (mol%)	Time (min)	Yield[b] (%)
1	K_2CO_3 (200)	30	79
2	Cs_2CO_3 (200)	30	48
3	Na_2CO_3 (200)	60	27
4	KOH (200)	60	44
5	*t*-BuOK (200)	30	trace
6	DBU (200)	30	78
7	Et_3N (200)	30	88
8	*i*-Pr_2NH (200)	30	92
9	*i*-Pr_2NH (300)	30	92
10	–	60	NR[c]

[a] Reactions conditions: **1a** (0.15 mmol), r.t.
[b] Yield of the isolated pure product.
[c] No reaction; the starting materials were recovered.

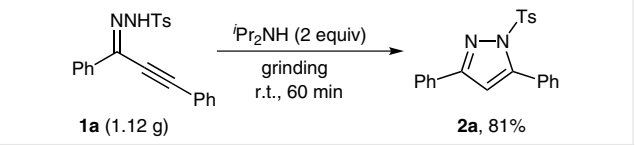
To examine the scope of the present procedure, we performed the reaction with a variety of α,β-alkynyl *N*-tosylhydrazones **1** under metal- and solvent-free conditions (Scheme 2).[18] We found that the reaction proceeded smoothly with a wide range of substrates to give the corresponding pyrazoles **2** in high yields. Among the R^1 groups on the α,β-alkynyl *N*-tosylhydrazones **1**, substituents containing a phenyl ring bearing an electron-donating group or halogen were tolerated and generally gave the desired products **2** in high yields (**2b**–**i**). Interestingly, the reaction proceeded smoothly with α,β-alkynyl *N*-tosylhydrazone bearing a 2-naphthyl substituent, affording the corresponding product **2j** in excellent yield. In addition, replacement of the aryl groups R^1 with alkyl groups also led to the desired **2k**–**m** in good yields. Next, we investigated effects of a substituent at the alkyne terminus (**2n**–**t**). The reaction was not significantly affected by the presence of substituents on the aromatic ring of the R^2 group of α,β-alkynyl *N*-tosylhydrazones **1n**–**t**; both electron-donating and halogen groups were tolerated under the reaction conditions. Besides, we were pleased to discover that substrate **1u**, in which both R^1 and R^2 are alkyl groups, was also compatible with this transformation, giving the desired pyrazole product **2u** in excellent yield. Moreover, note that the reaction proceeded readily when fluoro-containing substrates were used in this transformation (**2d**, **2g**, **2k**, **2r**, and **2s**).

More interestingly, when an α,β-alkynyl *N*-tosylhydrazone **1v** with a terminal alkyne moiety was used in the reaction, the corresponding pyrazole **2v** was successfully obtained in excellent yield (Scheme 3, eq 1). Furthermore, substrate **1w**, bearing a trimethylsilyl substituent at the alkyne terminus, also reacted smoothly, with concomitant elimination of the TMS group, to afford product **2w** in moderate yield (Scheme 3, eq 2).



Scheme 3

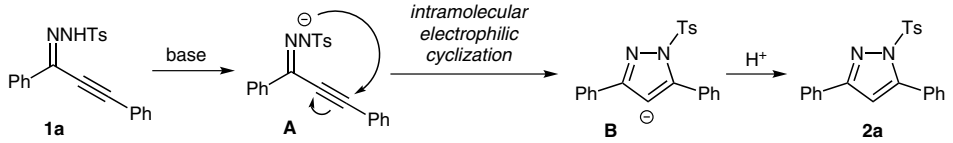
To examine the practical utility of this reaction, we performed it on a large scale. When we chose the α,β-alkynyl *N*-tosylhydrazone **1a** as a substrate for a gram-scale synthesis, the reaction proceeded smoothly to give the pyrazole **2a** in 81% isolated yield under metal- and solvent-free conditions (Scheme 4).



Scheme 4 Large-scale reaction

Scheme 5 shows our proposed mechanism for the formation of pyrazole **2a** through an intramolecular electrophilic cyclization process. An initial base-promoted deprotonation of alkyne **1a** gives intermediate **A**, which then undergoes intramolecular electrophilic cyclization to provide intermediate **B**. Protonation of intermediate **B** affords the final product **2a**.

In conclusion, we have developed a straightforward and green method for the synthesis of pyrazoles in good to excellent yields from α,β-alkynyl *N*-tosylhydrazones, promoted by *i*-Pr_2NH under metal- and solvent-free reactions at room temperature. This metal- and solvent-free reaction readily permits the ecofriendly synthesis of novel trisubstituted pyrazole derivatives that might have widespread applications in the synthesis of bioactive natural products or pharmaceuticals. Additionally, this method can be performed on a large scale without any problems.



Scheme 5 Possible mechanism for the formation of pyrazole **2a** by an intramolecular electrophilic cyclization reaction

Acknowledgements

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561853.

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(18) **Pyrazoles 2; General Procedure**
i-Pr_2NH (0.6 mmol) and the appropriate *N*-tosylhydrazone **1** (0.3 mmol) were thoroughly ground with a pestle and mortar for 30 min. When the reaction was complete, the mixture was purified by crystallization from CH_2Cl_2 or by column chroma-

tography (silica gel, EtOAc–PE) to give the pure pyrazole product **2**.

3,5-Diphenyl-1-tosyl-1*H*-pyrazole (**2a**)

White solid; yield: 103 mg (92%; gram scale: 81%); mp 122–124 °C. IR (KBr): 3029, 2921, 2855, 1594, 1558, 1459, 1382, 1195, 1177, 761, 660, 598 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 6.60 (s, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.35–7.45 (m, 8 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.84 (d, *J* = 7.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.69, 109.54, 126.48, 127.84, 128.04, 128.72, 129.33, 129.49, 129.62, 129.67, 130.02, 131.37, 134.88, 145.35, 149.48, 155.21. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{19}N_2O_2S$: 375.1167; found: 375.1161.