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One-Pot Three-Component Approach to the Synthesis of Polyfunctional Pyrazoles

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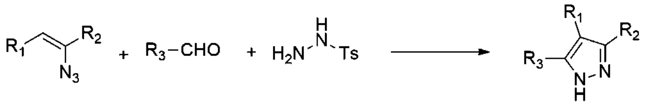
ABSTRACT



20 examples
54-95% yield

A simple, multicomponent, and straightforward reaction of vinyl azide, aldehyde, and tosylhydrazine affords the construction of 3,4,5-trisubstituted 1*H*-pyrazoles regioselectively in the presence of base with moderate to excellent yields. A range of functionality could be tolerated in this methodology, and a possible mechanism is proposed.

Pyrazoles are one of the most important heterocyclic compounds that possess a range of biological activities, such as antibacterial,[1] antileukemic,[2] antitumor,[3] antiobesity,[4] and anti-inflammatory.[5] Polysubstituted pyrazoles have also been utilized as useful ligands for some cross-coupling reactions.[6] Due to pyrazoles' important utility, numerous approaches have been developed over the past decades including the reaction of 1,3-diketones with hydrazine and hydrazine derivatives,[7] the coupling of *N*-arylhydrazones and nitroolefins,[8] and 1,3-dipolar cycloaddition of hydrazines to alkynes.[9] However, it is still challenging to prepare polysubstituted pyrazoles.

Recently, vinyl azides have emerged as important synthons although they were once regarded as "sleepers" of the reactive azido species for a long time. In recent years, our group[10] and others[11] have developed numerous nitrogen-containing heterocycles from vinyl azides. Based on the previous result, herein, we demonstrate a simple, multicomponent, and straightforward approach to provide 3,4,5-trisubstituted 1*H*-pyrazoles regioselectively in the presence of base with good to excellent yields from vinyl azides, benzaldehyde, and tosylhydrazine. The azido group in vinyl azides serves as a leaving group.[12]

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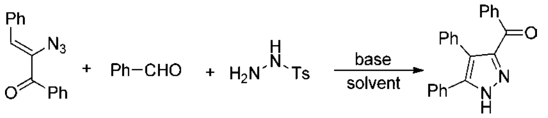
Initially, vinyl azide **1a**, benzaldehyde **2a**, and tosylhydrazine **3** were selected as model reagents to optimize the reaction conditions (Table 1). No corresponding product was observed in the absence of base (Table 1, entry 1). However, the expected transformation occurred in the presence of 1.5 equiv of NaOH at 60 °C. The desired compound **4a** was obtained as the major product with 49% yield (Table 1, entry 2). Gratifyingly, the yield was notably increased when more equivalents of base were added into the reaction mixture (Table 1, entries 2–5). A perfect isolated yield was obtained when the reaction was performed in the presence of 5 equiv of NaOH in 2 h (Table 1, entry 4), while continuously increasing the amount of base (7 equiv) did not give a significant change (Table 1, entry 5).

Further, other bases were also tested for the reaction, which revealed that NaOH was the most efficient one (Table 1, entry 8–13), while DMF was considered as the most preponderant solvent (Table 1, entries 14–17). Temperature screening showed that 60 °C was optimal to obtain the maximum yield of the product. On the basis of the above studies, the most favorable reaction conditions for the formation of **4a** were established. The vinyl azides were readily prepared according to literature[13] (Scheme 1).

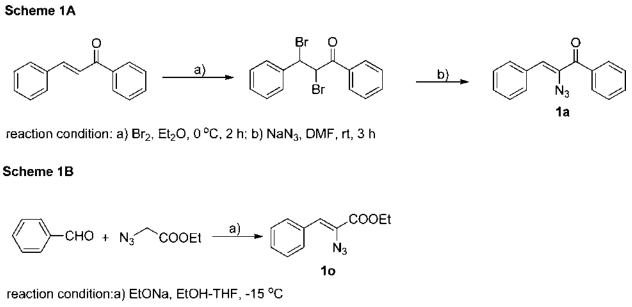
Table 1. Optimization of Reaction Conditions[a]



entry	solvent	base (equiv)	t (h)	conversion (%)[b]
1	DMF	–	12	n.r
2	DMF	NaOH(1.5)	12	49
3	DMF	NaOH(3)	2	74
4	**DMF**	**NaOH**(5)	**2**	**89 (83)**[c]
5	DMF	NaOH(7)	2	88
6	DMF	NaOH(5)	5	71[d]
7	DMF	NaOH(5)	1	85[e]
8	DMF	KOH(5)	2	85
9	DMF	^{t}BuOK(5)	2	54
10	DMF	Cs_2CO_3(5)	2	75
11	DMF	NaOMe(5)	12	49
12	DMF	DABCO(5)	12	trace
13	DMF	DBU(5)	2	n.r
14	dioxane	NaOH(5)	2	46
15	toluene	NaOH(5)	2	74
16	ethanol	NaOH(5)	2	25
17	acetonitrile	NaOH(5)	2	86

[a] Reaction conditions: vinyl azide (0.25 mmol, 1.0 equiv), benzaldehyde (0.25 mmol, 1.0 equiv), tosylhydrazine (0.25 mmol, 1.0 equiv), 2 mL of solvent, 60 °C. n.r. = no reaction. [b] Determined by HPLC, based on the disappearance of the starting vinyl azide. The most successful entry is highlighted in bold. [c] Isolated yield. [d] The reaction temperature is 40 °C. [e] The reaction temperature is 80 °C.

Scheme 1. Synthesis of Vinyl Azides



Scheme 1A

1a

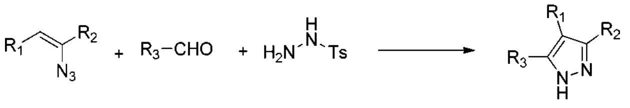
reaction condition: a) Br_2, Et_2O, 0 °C, 2 h; b) NaN_3, DMF, rt, 3 h

Scheme 1B

1o

reaction condition:a) EtONa, EtOH-THF, -15 °C

Table 2. Reactions Scope of Vinyl Azides, Aldehyde, and Tosylhydrazine[a]



1 2 3 4

entry	R₁	R₂	R₃	product	yield (%)[b]
1	Ph	Ph-CO	Ph	**4a**	83
2	Ph	Ph-CO	4-MePh	**4b**	78
3	Ph	Ph-CO	4-BrPh	**4c**	89
4	Ph	Ph-CO	3-BrPh	**4d**	85
5	Ph	Ph-CO	4-NO_2Ph	**4e**	92
6	Ph	Ph-CO	4-pyridinyl	**4f**	82
7	Ph	Ph-CO	piperonyl	**4g**	63
8	Ph	4-MePh-CO	4-MePh	**4h**	74
9	Ph	4-MePh-CO	Ph	**4i**	74
10	Ph	4-ClPh-CO	Ph	**4j**	87
11	4-BrPh	Ph-CO	Ph	**4k**	88
12	Ph	4-ClPh-CO	4-NO_2Ph	**4l**	95
13	Ph	4-MePh-CO	3-BrPh	**4m**	91
14	Ph	4-MePh-CO	4-pyridinyl	**4n**	71
15	Ph	COOEt	4-NO_2Ph	**4o**	75[c]
16	4-OMePh	COOEt	4-NO_2Ph	**4p**	59[c]
17	4-BrPh	COOEt	4-NO_2Ph	**4q**	69[c]
18	4-NO_2Ph	COOEt	4-NO_2Ph	**4r**	77[c]
19	*n*-propyl	COOEt	4-NO_2Ph	**4s**	54[c]
20	H	Ph	Ph	**4t**	56[c,d]
21	H	Ph	4-MePh	**4u**	63[c,d]
22	Ph	4-ClPh-CO	*n*-propyl	–	–

[a] Reactions were carried out in DMF (2.0 mL) with **1** (0.25 mmol, 1.0 equiv), **2** (0.25 mmol, 1.0 equiv), **3** (0.25 mmol, 1.0 equiv), NaOH (1.25 mmol, 1.0 equiv), 60 °C. [b] Isolated yield. [c] Reactions were carried out with 5.0 equiv of Cs_2CO_3. [d] Reaction temperature was 80 °C for 12 h.

Based on the optimal conditions, the scope of the reaction was studied using a series of vinyl azides **1** and aldehydes.

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As shown in Table 2, various substituted vinyl azides worked well with aldehydes and hydrazide to provide the corresponding 3,4,5-trisubstituted 1*H*-pyrazoles with moderate to excellent yields. The reaction could tolerate vinyl azides with aromatic substitution and aldehydes with various steric and electronic properties.

At the R_3 position, various groups on the aryl ring were compatible with the reaction. Notably, aldehydes bearing an electron-withdrawing group at the aryl ring afforded the desired products with excellent efficiency (Table 2, entry 5). We also found that the reaction could tolerate heteroaryl motifs (Table 2, entry 6). However, no desired product was observed when butaraldehyde was employed (Table 2, entry 22). It was most likely due to the instability of the hydrazone intermediate generated from butyraldehyde.

Instead of arylcarbonyl substituted vinyl azides, the reaction of vinyl azide (Table 2, entries 15−19) bearing an ester group at the α-position gave the desired products with moderate yields. Meanwhile, vinyl azide with an alkyl group at the R_1 position can also tolerate the reaction (Table 2, entry 19). The reaction of α-azidostyrene (Table 2, entries 20 and 21) was sluggish, requiring a higher temperature and longer reaction time.

The structures of the 3,4,5-trisubstituted 1*H*-pyrazoles were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (ESI). In order to explore in more detail the structure of our product and the mechanism, we performed an X-ray study of **4n** (shown in Figure 1). More details related to the X-ray crystal structure can be found in the Supporting Information.

To gain information on the mechanistic aspects of the reaction, control reactions were examined (Scheme 2). The reaction of benzaldehyde with 1 equiv of tosylhydrazine in DMF at room temperature gave the known hydrazone. Further reaction of hydrazone with 1 equiv of vinyl azide **1a** afforded the corresponding **4a** in 83% yield.

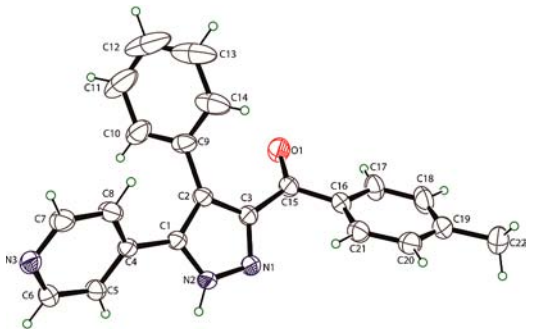
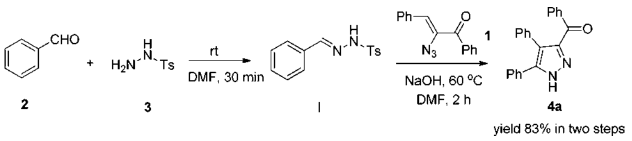
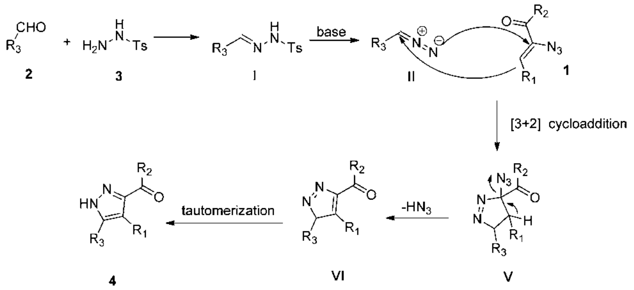


Figure 1. X-ray crystal structure of **4n**.

Scheme 2. Control Reaction



Scheme 3. Proposed Reaction Mechanism



On the basis of the above experimental results, the following possible mechanism for this cycloaddition reaction is proposed. As outlined in Scheme 3, the initial condensation of aromatic aldehyde **2** and tosylhydrazine **3** gave the corresponding hydrazone intermediate **I**, which subsequently generated diazomethane **II** upon heating in the presence of base.[14] Intermediate **II** was then reacted with vinyl azide **1** via a [3 + 2] cycloaddition to afford the intermediate **V** with elimination of the azido group. Finally, the desired product **4** was obtained via the proton transfer of intermediate **VI**.

In conclusion, we have developed a simple and straightforward one-pot reaction from vinyl azide, aryl aldehyde, and tosylhydrazine to provide trisubstitued-1*H*-pyrazoles in the presence of base with good to excellent yields. The azido group serves as a leaving group in this approach.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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