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Regioselective Synthesis of 1,3,5-Trisubstituted Pyrazoles from *N*-Alkylated Tosylhydrazones and Terminal Alkynes

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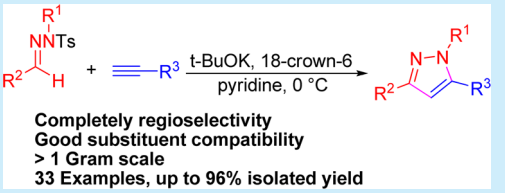
Supporting Information

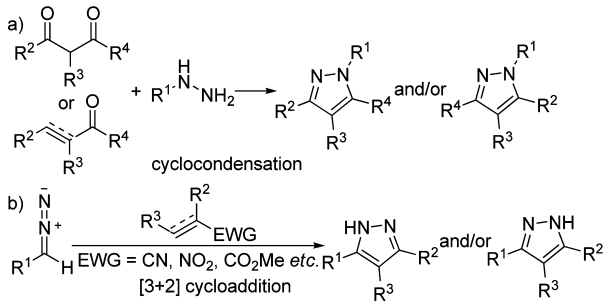
ABSTRACT: An efficient synthesis of 1,3,5-trisubstituted pyrazoles from *N*-alkylated tosylhydrazones and terminal alkynes was developed. The protocol was applied to a wide range of substrates and demonstrated excellent tolerance to a variety of substituents, including both electron-donating and -withdrawing groups. In comparison with the common approaches for substituted pyrazole syntheses, this methodology proceeded with complete regioselectivity, especially, in the cases that R^2 and R^3 are similar substituents.



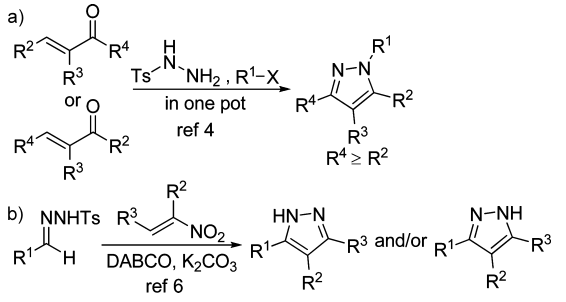
As an important class of heteroaromatic ring systems, pyrazoles have found widespread application in the agrochemical, material, and especially pharmaceutical industries.[1] The syntheses of pyrazoles have received considerable attention from organic chemists because of their diverse bioactivities.[2]

Of the many methods developed, the Knorr pyrazole synthesis, the cyclocondensation of hydrazines with a 1,3-dicarbonyl compound or surrogates thereof, has been adapted as the standard method for its convenience and versatility.[3] However, the lack of regiospecificity and somewhat limited substrate scope greatly reduce the attractiveness of this method. Especially, in the cases that R^2 and R^4 are similarly substituted

Scheme 1. Two General Methods for the Pyrazole Synthesis



Scheme 2. Our Previous Reported Work in Pyrazole Synthesis



Scheme 3. Preparation of *N*-Alkylated Tosylhydrazones in a One-Pot Version

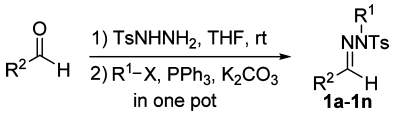
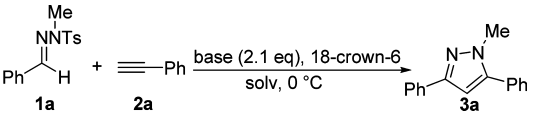


Table 1. Screening the Reaction Conditions[a]



entry	2a (equiv)	base	18-crown-6 (equiv)	solvent	time	yield (%)[b]
1	4	*t*-BuOK	0	pyridine	12 h	58
2	4	*t*-BuOK	0.1	pyridine	3.5 h	67
3	4	*t*-BuOK	0.5	pyridine	15 min	76
4	3	*t*-BuOK	0.5	pyridine	15 min	69
5	1.5	*t*-BuOK	0.5	pyridine	15 min	52
6	1.5	*t*-BuOK	0.5	pyridine	25 min	51[c]
7	4	*t*-BuOK	0.5	pyridine	15 min	64[d]
8	4	NaH	0.5	pyridine	36 h	20
9	4	NaOMe	0.5	pyridine	24 h	trace
10	4	KOH	0.5	pyridine	24 h	trace
11	4	Cs_2CO_3	0.5	pyridine	24 h	–
12	4	*t*-BuOK	0.5	THF	10 h	20
13	4	*t*-BuOK	0.5	DMSO	24 h	14[d]
14	4	*t*-BuOK	0.5	DMF	10 h	trace
15	4	*t*-BuOK	0.5	dioxane	10 h	36

[a]Reactions were performed with **1a** (0.18 mmol) in 1 mL of solvent. [b]Isolated yields. [c]The reaction was performed with **1a** (4.0 mmol) in 5 mL of pyridine. [d]The reaction was carried out at room temperature.

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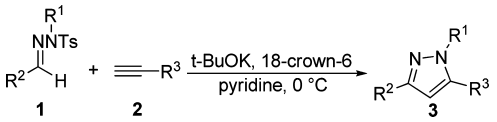
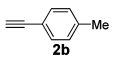
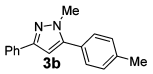
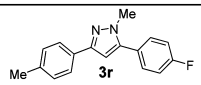
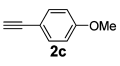
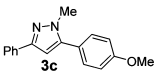
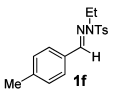
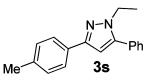
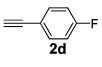
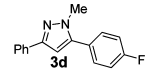
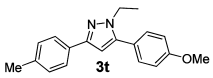
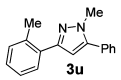
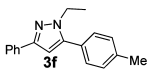
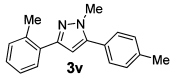
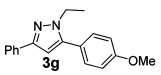
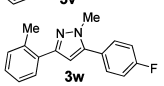
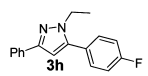
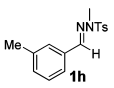
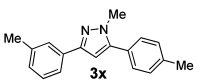
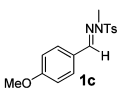
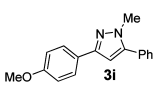
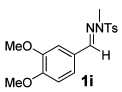
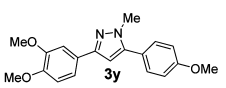
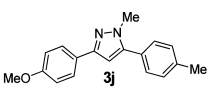
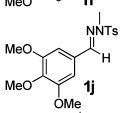
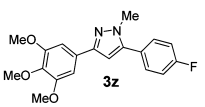
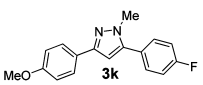
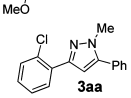
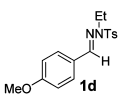
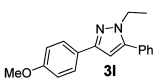
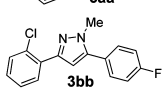
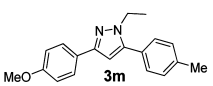
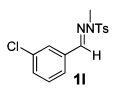
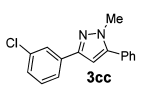
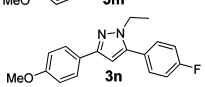
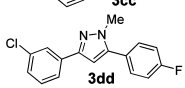
Table 2. Regioselective Synthesis of 1,3,5-Trisubstituted Pyrazoles from *N*-Alkylated Tosylhydrazones and Terminal Alkynes[a]



entry	sub. **1**	sub. **2**	prod. **3**	yield (%)[b]	entry	sub. **1**	sub. **2**	prod. **3**	yield (%)[b]
1	**1a**	 **2b**	 **3b**	52	17	**1e**	**2d**	 **3r**	84
2	**1a**	 **2c**	 **3c**	47	18	 **1f**	**2a**	 **3s**	57
3	**1a**	 **2d**	 **3d**	79	19	**1f**	**2c**	 **3t**	51
4	 **1b**	**2a**	 **3e**	67	20	 **1g**	**2a**	 **3u**	60
5	**1b**	**2b**	 **3f**	70	21	**1g**	**2b**	 **3v**	49
6	**1b**	**2c**	 **3g**	52	22	**1g**	**2d**	 **3w**	73
7	**1b**	**2d**	 **3h**	85	23	 **1h**	**2b**	 **3x**	61
8	 **1c**	**2a**	 **3i**	96	24	 **1i**	**2c**	 **3y**	60
9	**1c**	**2b**	 **3j**	74	25	 **1j**	**2d**	 **3z**	70
10	**1c**	**2d**	 **3k**	65	26	 **1k**	**2a**	 **3aa**	47
11	 **1d**	**2a**	 **3l**	80	27	**1k**	**2d**	 **3bb**	54
12	**1d**	**2b**	 **3m**	89	28	 **1l**	**2a**	 **3cc**	58
13	**1d**	**2d**	 **3n**	86	29	**1l**	**2d**	 **3dd**	64
14	**1e**	**2a**	**3o**	83	30	**1m**	**2a**	**3ee**	66
15	**1e**	**2b**	**3p**	62	31	**1m**	**2d**	**3ff**	64
16	**1e**	**2c**	**3q**	50	32	**1n**	**2a**	**3gg**	48

[a]Reactions were performed with *N*-alkylated tosylhydrazones **1** (0.18 mmol), alkynes **2** (0.72 mmol), *t*-BuOK (0.38 mmol), and 18-crown-6 (0.09 mmol) in pyridine (1 mL) at 0 °C. [b]Isolated yields.

with only minor differences both electronically and sterically, complete control of the regioselectivity becomes a daunting task (Scheme 1a). Recently, we reported an efficient one-pot synthesis of substituted pyrazoles, in which we used $TsNHNH_2$ and halides instead of monosubstituted hydrazines. And compared with the Knorr pyrazole synthesis, the reaction we developed could give a different type of product (Scheme 2a).[4]

Another prevalent strategy for constructing pyrazole rings is the 1,3-dipolar cycloaddition of diazo compounds to alkenes or alkynes (Scheme 1b).[5] Usually, the significant electronegativity difference of the two C atoms of the alkenes or alkynes allows better control of the regioselectivity. But the difficulty in preparing diazo compounds and handling reactive 1,3-dipolars often limits their synthetic application. We developed a

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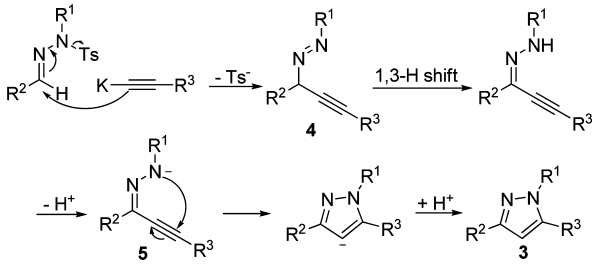
Scheme 4. Proposed Pathway for Pyrazole Formation



DABCO-promoted synthesis of pyrazoles from tosylhydrazones and nitroalkenes. Compared to the 1,3-dipolar cycloaddition reaction, the corresponding diazo intermediates were not formed and the regioselectivity was reversed in this approach (Scheme 2b).[6]

As an *in situ* source of diazo compounds,[7] tosylhydrazones have been reported to react with terminal alkynes to produce pyrazoles under basic conditions[8] and a TfOH mediated cycloaddition reaction of tosylhydrazones and terminal alkynes has also been reported.[9] Using *N*-monosubstituted hydrazones reacted with nitroalkenes, Deng et al. developed a novel regioselective synthesis of pyrazoles under neutral, acidic, or basic conditions.[10] However, to our knowledge, *N*-alkylated tosylhydrazones (**1**), which can be prepared according to our recently reported procedure[11] in an improved one-pot version easily (Scheme 3),[12] have not been used in pyrazoles syntheses. In continuance of our interest in the regioselective synthesis of pyrazoles, herein, we describe our endeavor toward the synthesis of 1,3,5-trisubstituted pyrazoles from *N*-alkylated tosylhydrazones and terminal alkynes with complete regioselectivity.

In an initial experiment, we conducted the reaction between the *N*-methyl tosylhydrazone (**1a**) and phenylacetylene (**2a**) in pyridine and in the presence of *t*-BuOK at 0 °C (Table 1). After 12 h, pyrazole **3a** was given in 58% yield (entry 1). In order to accelerate the reaction rate and improve the yield, we added 18-crown-6 to the reaction mixture. Delightfully, the use of 0.1 equiv of 18-crown-6 could significantly shortened the reaction time, and the reaction could be completed within 15 min in the presence of 0.5 equiv of 18-crown-6 with a yield of 76% (entry 3). Decreasing the amount of **2a** resulted in lower yields (enties 4, 5). To investigate the reaction's practical utility, we also performed the reaction with 4 mmol of **1a**, and the yield was not affected (entry 6). Furthermore, the reaction could be carried out at room temperature, but the yield was lower (entry 7). Of the bases screened, NaH, NaOMe, KOH, and Cs_2CO_3 all gave unsatisfactory results (entries 8−11). Next, a variety of different solvents were also evaluated; however, use of THF, DMSO, DMF, and dioxane resulted in poor yields of **3a** (entries 12−15).

Under the above optimized conditions, we then attempted to synthesize a variety of pyrazoles to test the generality and scope of the method (Table 2). First, the scope of the reaction was evaluated with regard to the structure of the alkynes. In general, the electronic effect on the aromatic ring had little influence on the reaction, and the alkynes bearing electron-donating (**2b**, **2c**) or -withdrawing substituents (**2d**) all resulted in good yields. And the reaction is also general for all types of *N*-alkylated aromatic aldehyde tosylhydrazones; *N*-alkylated tosylhydrazones derived from benzaldehyde featuring electron-donating (**1c**−**1j**) or -withdrawing (**1k**−**1n**) substituents in an aromatic ring all gave the corresponding pyrazole derivatives in good to high yields. However, a slightly lower yield was observed with electron-withdrawing substituents (entries 26−32), possibly due to their instability under the basic conditions. Additionally, aliphatic terminal alkynes and *N*-alkylated aliphatic aldehyde tosylhydrazones afforded the corresponding product in extremely poor yield.

As shown in Table 2, the main favorable characteristics of this reaction included the following: remarkably, our reaction conditions show good compatibility with different substituents. It was effective for a wide scope of substrates, and a series of 1,3,5-trisubstituted pyrazole derivatives were synthesized in good yields; more importantly, complete control of the regioselectivity was achieved, especially, in the cases that R^2 and R^3 are similar substituents with only minor differences, such as the products **3j** (entry 9), **3t** (entry 19), **3v** (entry 21), **3x** (entry 23), **3bb** (entry 27), **3dd** (entry 29), **3ff** (entry 31), etc. which were prepared in good yields and are not easily accessible with complete regioselectivity from other routes. Additionally, by adjusting the structures of substrates **1** and **2**, the two regioisomers can be prepared respectively, for example, as products **3b** (entry 1) and **3o** (entry 14), **3c** (entry 2) and **3i** (entry 8), **3f** (entry 5) and **3s** (entry 18), **3g** (entry 6) and **3l** (entry 11), **3j** (entry 9) and **3q** (entry 16), **3m** (entry 12) and **3t** (entry 19), which are usually prepared as a mixture of regioisomers.

A simple mechanism was proposed as shown in Scheme 4. The reaction was initiated by the nucleophilic addition of alkynyl potassium to *N*-alkylated tosylhydrazones resulting in intermediate **4** by the loss of a *p*-toluenesulfinic acid anion and then a 1,3-H shift, with deprotonation producing the anion **5**, which subsequently went through an intramolecular cyclization and protonation to form pyrazoles **3**.

In summary, we have reported a simple and efficient procedure for the regioselective preparation of 1,3,5-trisubstituted pyrazole derivatives. The protocol was applied to a wide range of substrates and demonstrated excellent tolerance to a variety of substituents, including both electron-donating and -withdrawing examples. In addition, compared with the 1,3-dipolar cycloaddition reactions of diazo compounds with terminal alkynes, the corresponding diazo intermediates were not formed and the reaction is amenable to gram-scale synthesis of pyrazoles and proceeded with complete regioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) For details, see Supporting Information.

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