Synthetic Methods

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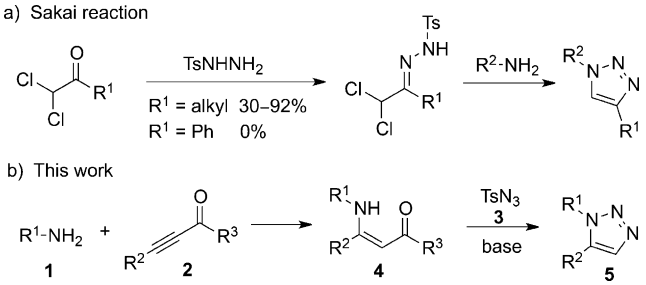
A Metal-Free Multicomponent Cascade Reaction for the Regiospecific Synthesis of 1,5-Disubstituted 1,2,3-Triazoles**

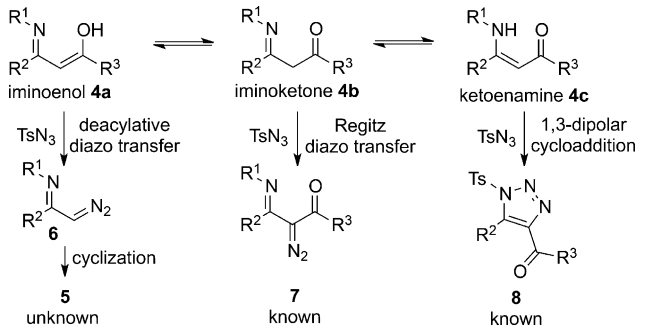
*Guolin Cheng, Xiaobao Zeng, Jinhai Shen, Xuesong Wang, and Xiuling Cui**

The thermal Huisgen 1,3-dipolar cycloaddition of organic azides and alkynes to build 1,2,3-triazoles usually requires elevated temperatures and provides a mixture of regioisomers.[1] The copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC)[2] and ruthenium(II)-catalyzed azide–alkyne cycloaddition (RuAAC)[3] have been developed as powerful strategies for the regiospecific assembly of 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazoles, respectively. These reliable processes have quickly found many applications in organic synthesis, chemical biology, and materials science.[4] Nevertheless, the contamination of heavy metals limits their potential application in the pharmaceutical industry. Several metal-free methods, including the azide–enamine cycloaddition,[5] the condensation of azides with phosphonium ylides,[6] and the addition of acetylide species to azides,[7] have also been developed for the regiospecific synthesis of 1,2,3-triazoles. Considerable drawbacks, however, exist with these processes, such as poor functional-group tolerance or requiring functionalized substrates. Westermann recently reported an improved Sakai reaction to synthesize 1,4-disubstituted triazoles from primary amines and α,α-dichlorotosylhydrazones (Scheme 1 a).[8] This procedure is limited to the synthesis of 1,4-disubstituted regioisomers. Therefore, a general and metal-free procedure to synthesize 1,5-disubstituted triazoles from readily available substrates under mild reaction conditions is still of considerable interest. Herein we report the synthesis of the 1,5-disubstituted triazoles **5** from a three-component reaction of aliphatic amines (**1**), propynones (**2**), and TsN_3 by a Michael addition/deacylative diazo transfer/cyclization sequence (Scheme 1 b).



Scheme 1. A proposed route to 1,5-disubstituted triazoles. Ts = 4-toluenesulfonyl.

Theoretically, the enaminone compounds **4** may exist as three tautomers: the iminoenol **4a**, iminoketone **4b**, and ketoenamine **4c**.[9] The α-diazo iminoketone **7**[9] and 1-tosyl triazole **8**[5] could be obtained from the Regitz diazo transfer of **4b** and 1,3-dipolar cycloaddition of **4c** with TsN_3, respectively. We assumed that, in the presence of suitable bases, **4a** might react with TsN_3 to give the α-diazoimine intermediate **6**, which could further cyclize to afford the triazole **5** (Scheme 2).



Scheme 2. Reactions between enaminones and sulfonyl azides.

To verify this hypothesis, 1,3-diphenyl-3-(*n*butylamino)-2-propen-1-one (**4a**) and the sulfonyl azides **3** were chosen as the substrates to screen bases (Table 1). No reaction was observed when weak bases, such as Et_3N or K_2CO_3, were used (Table 1, entries 1 and 2). However, in the presence of strong bases, 1-*n*butyl-5-phenyl-1*H*-1,2,3-triazole (**5aa**) could be obtained from **4a** and tosyl azide (Table 1, entries 3–6) as we expected. LiO*t*Bu gave the best result, thus affording **5aa** in 86% yield (Table 1, entry 4). Further investigation showed that this transformation was highly solvent dependent (Table 1, entries 7–12). Higher yields were achieved in CH_2Cl_2 and toluene (Table 1, entries 4 and 7), while other solvents, such as 1,4-dioxane, CH_3CN, EtOH, DMF, and DMSO, led to no reaction or lower yield (Table 1, entries 8–

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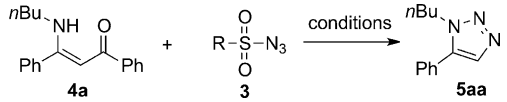
Table 1: Optimization of the reaction conditions for the reaction of 1,3-diphenyl-3-(*n*-butylamino)-2-propen-1-one (**4a**) with the sulfonyl azides **3**.[a]



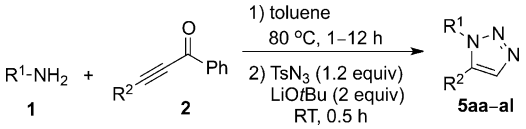
Entry	Solvent	Base	R	Yield [%][b]
1	CH_2Cl_2	Et_3N	4-MeC_6H_4	0
2	CH_2Cl_2	K_2CO_3	4-MeC_6H_4	0
3[c]	CH_2Cl_2	NaOEt	4-MeC_6H_4	10
4	CH_2Cl_2	LiO*t*Bu	4-MeC_6H_4	86
5	CH_2Cl_2	NaO*t*Bu	4-MeC_6H_4	78
6	CH_2Cl_2	KO*t*Bu	4-MeC_6H_4	63
7	toluene	LiO*t*Bu	4-MeC_6H_4	86
8	1,4-dioxane	LiO*t*Bu	4-MeC_6H_4	41
9	CH_3CN	LiO*t*Bu	4-MeC_6H_4	0
10	EtOH	LiO*t*Bu	4-MeC_6H_4	0
11	DMF	LiO*t*Bu	4-MeC_6H_4	0
12	DMSO	LiO*t*Bu	4-MeC_6H_4	0
13[d]	CH_2Cl_2	LiO*t*Bu	4-MeC_6H_4	78
14	CH_2Cl_2	LiO*t*Bu	4-$NO_2C_6H_4$	84
15	CH_2Cl_2	LiO*t*Bu	Me	61

[a] Reaction conditions: except where otherwise noted, all of the reactions were performed with **4a** (0.5 mmol), **3** (0.6 mmol), and base (1 mmol) in solvent (2 mL) at RT for 0.5 h. [b] Yield of isolated product based on **4a**. [c] The reaction was performed for 24 h. [d] Used 0.75 mmol base. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

12). Decreasing the amount of LiO*t*Bu from 2 equivalents to 1.5 equivalents slightly lowered the yield (Table 1, entry 13). Other commercially available sulfonyl azides did not give better results (Table 1, entries 14 and 15).

As the enaminones **4** could be readily prepared from the Michael addition of the aliphatic amines **1** to propynones **2** in nonpolar solvents, we employed a straightforward one-pot strategy to synthesize the desired products **5** directly from the aliphatic amines and propynones, without isolating the intermediate enaminones **4** (Table 2). A mixture of **1** and **2** in toluene (2 mL) was stirred at 80 °C under an air atmosphere until the starting materials were consumed completely, as monitored by TLC. After the reaction mixture was cooled to ambient temperature, TsN_3 and LiO*t*Bu were added. The resulting mixture was then stirred at room temperature for 30 minutes. To our delight, the deacylative diazo transfer/cyclization products **5** were obtained in similar yields to those of the two-step reaction (Table 2, entries 1–6). A number of functional groups, such as methoxy, allyl, and 1*H*-indol-3-yl, were tolerated in this transformation. Notably, the azido group was well tolerated and the desired product **5ac**, which is difficult to be synthesized by a 1,3-dipolar cycloaddition, could be obtained in 81% yield. The mono(triazole) product **5ah** was obtained in 78% yield using 4-aminophenylethylamine as a substrate, thus showing good chemoselectivity of an aliphatic amine over aniline (Table 2, entry 8). Furthermore, the scope of the propynones was also examined and both aryl- and aliphatic-substituted propynones gave the corresponding triazoles in good yields (Table 2, entries 6, 9–12).

Table 2: Scope of the aliphatic amines **1** and propynones **2**.[a]

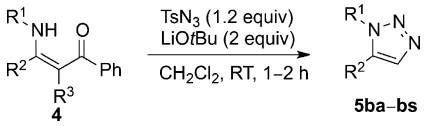


Entry	R^1	R^2	5	Yield [%][b]
1	*n*-butyl	Ph	**5aa**	85 (86)[c]
2	3-methoxypropyl	Ph	**5ab**	81 (84)[c]
3	2-azidoethyl	Ph	**5ac**	81 (83)[c]
4	allyl	Ph	**5ad**	83 (84)[c]
5	benzyl	Ph	**5ae**	80 (86)[c]
6	benzyl	Me	**5af**	70 (74)[c]
7	2-(1*H*-indol-3-yl)ethyl	Ph	**5ag**	75
8	2-(4-$NH_2C_6H_4$)ethyl	Ph	**5ah**	78
9	benzyl	4-MeC_6H_4	**5ai**	80
10	benzyl	4-$MeOC_6H_4$	**5aj**	78
11	benzyl	4-FC_6H_4	**5ak**	78
12	benzyl	*n*Bu	**5al**	76

[a] Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), 2 mL toluene, at 80 °C. After the reaction mixture was cooled to RT, TsN_3 (0.6 mmol), and LiO*t*Bu (1 mmol) were added. [b] Yield of isolated product based on **2**. [c] Yield of isolated product for the two-step reaction, based on **4**.

Since the conjugate addition of anilines to propynones proceeds extremely slowly in nonpolar solvents because of their lower nucleophilicity, the required *N*-aryl enaminones **4** were synthesized separately in EtOH in excellent yields.[11] As shown in Table 3, various *N*-aryl enaminones could be employed to form the corresponding 1,5-disubstitute triazoles **5ba–br** in good to excellent yields. Compared with RuAAC, the tolerance of an ethynyl group displayed another undeni-

Table 3: Scope of *N*-aryl enaminones **4**.[a]

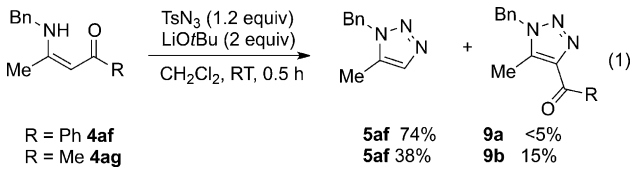


Entry	R^1	R^2, R^3	5	Yield [%][b]
1	Ph	Ph, H	**5ba**	91
2	4-MeC_6H_4	Ph, H	**5bb**	87
3	4-$MeOC_6H_4$	Ph, H	**5bc**	88
4	4-FC_6H_4	Ph, H	**5bd**	80
5	4-ClC_6H_4	Ph, H	**5be**	75
6	4-BrC_6H_4	Ph, H	**5bf**	78
7	4-IC_6H_4	Ph, H	**5bg**	71
8	3-EthynylC_6H_4	Ph, H	**5bh**	83
9	2-Me-3-$MeOC_6H_4$	Ph, H	**5bi**	96
10	1-Naphthalenyl	Ph, H	**5bj**	81
11	Ph	2-MeC_6H_4, H	**5bk**	82
12	Ph	3-MeC_6H_4, H	**5bl**	87
13	Ph	4-MeC_6H_4, H	**5bm**	93
14	Ph	4-$MeOC_6H_4$, H	**5bn**	99
15	Ph	4-FC_6H_4, H	**5bo**	82
16	Ph	4-ClC_6H_4, H	**5 bp**	87
17	Ph	Me, H	**5bq**	77
18	Ph	*n*Bu, H	**5br**	85
19	Ph	Me, Ph	**5bs**	trace

[a] Reaction conditions: **4** (0.5 mmol), TsN_3 (0.6 mmol), and LiO*t*Bu (1 mmol) in 2 mL CH_2Cl_2, RT. [b] Yield of isolated product based on **4**.

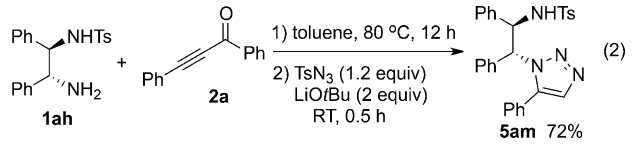
able advantage of this procedure (Table 3, entry 8). The transformation was slightly influenced by electronic effects. The substrates with electron-donating groups (Me, MeO) gave higher yields than those with electron-withdrawing (F, Cl, Br, I) groups. The reaction was not significantly affected by steric hindrance at the β-position (Table 3, entries 9–11), however, the 2-phenyl enaminone **4bs**, which has a phenyl substituent at the α-position, failed to provide the desired product (Table 3, entry 19).

Next, a benzoylated substrate and acetylated substrate were compared [Eq. (1)]. When the benzoyl group was

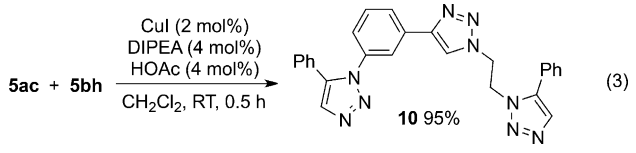


replaced by an acetyl group, the corresponding triazole **5af** was generated in lower yield and the Regitz diazo transfer product **9b** was observed to be the side product. These results suggested that the electron-donating effect of the methyl group significantly made the enolization step more difficult.

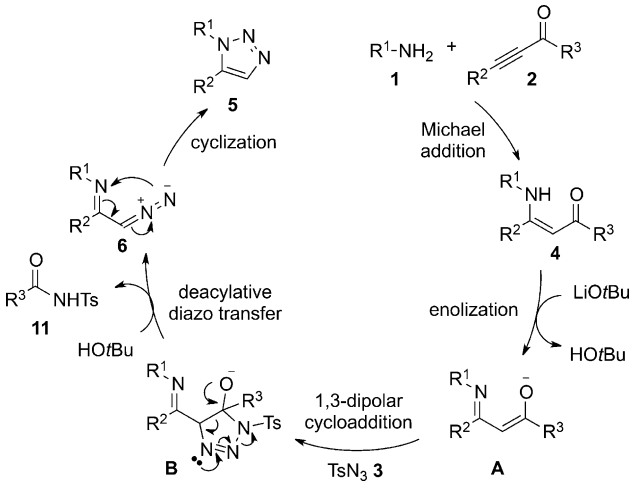
Synthesis of optically active triazoles is still a challenge.[12,13] Notably, our procedure could be employed to modify the useful biologically active compounds and synthetically important ligands containing chiral α-amines. For example, the monosulfonylated diamine **1ah** was modified by this strategy and provided the chiral triazole **5am** in 72% yield as a single diastereomer, which could be used as a new ligand in asymmetric synthesis [Eq. (2)].[14]



Moreover, the novel tri(triazole) compound **10** containing two 1,5-disubstituted triazoles and one 1,4-disubstituted triazole scaffold could be generated in 95% yield from **5ac** and **5bh** by a CuAAC.[15] The product **10** might be applied in materials science, organic synthesis, and chemical sensing [Eq. (3); DIPEA = diisopropylethylamine].



A possible reaction pathway was proposed according to the results obtained (Scheme 3). The initial Michael addition of primary amines and propynones provides the enaminones **4**. Subsequent deprotonation of **4** by LiO*t*Bu generates the iminoenolate intermediates **A**. 1,3-Dipolar cycloaddition of **A** with the tosyl azide **3** leads to the intermediates **B**, which further gives the α-diazoimines **6** and **11** by deacylative diazo transfer. At last, the final products **5** were formed spontaneously by cyclization of **6**.



Scheme 3. Proposed reaction pathway.

In conclusion, we have developed a simple and efficient synthetic methodology for preparing 1,5-disubtituted 1,2,3-triazoles based on an unprecedented cascade Michael addition/deacylative diazo transfer/cyclization reaction of primary amines, propynones, and sulfonyl azides. Various functional groups, such as a terminal alkynes and azides, are well tolerated in this transformation compared with the 1,3-dipolar azide–alkyne cycloadditon. Moreover, chiral triazoles could be obtained in high yield from readily available chiral α-amines. This protocol could be expected to find wide applications in synthetic chemistry and chemical biology.

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Keywords: amines · cyclization · heterocycles · multicomponent reactions · synthetic methods

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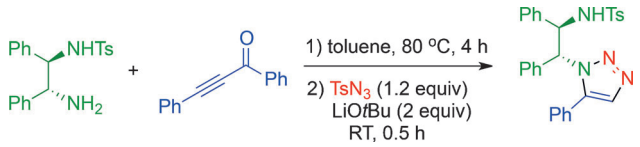
Communications

Synthetic Methods

G. Cheng, X. Zeng, J. Shen, X. Wang, X. Cui* ——— ■■■■–■■■■

A Metal-Free Multicomponent Cascade Reaction for the Regiospecific Synthesis of 1,5-Disubstituted 1,2,3-Triazoles



About specifics: A method for the regiospecific synthesis of the title compounds through an unprecedented Michael addition/deacylative diazo transfer/cyclization sequence has been established. The simple and practical method can be used for the modification of primary amines including chiral α-amines. The process involves the formation three covalent bonds and the cleavage of two covalent bonds (see scheme, Ts = 4-toluenesulfonyl).