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Base-Promoted Synthesis of *N*-Substituted 1,2,3-Triazoles via Enaminone−Azide Cycloaddition Involving Regitz Diazo Transfer

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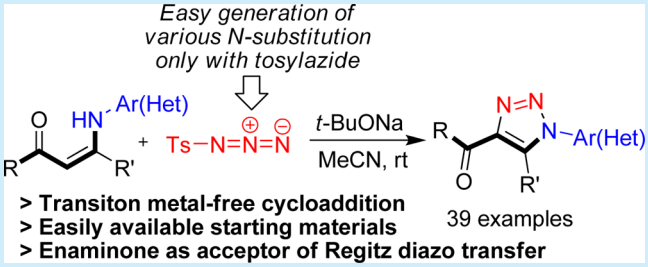
Supporting Information

ABSTRACT: The domino reactions between NH-based secondary enaminones and tosyl azide have been developed for the synthesis of various *N*-substituted 1,2,3-triazoles by employing *t*-BuONa as the base promoter. Through a key Regitz diazo-transfer process with tosyl azide, the reactions proceed efficiently at room temperature with good substrate tolerance.

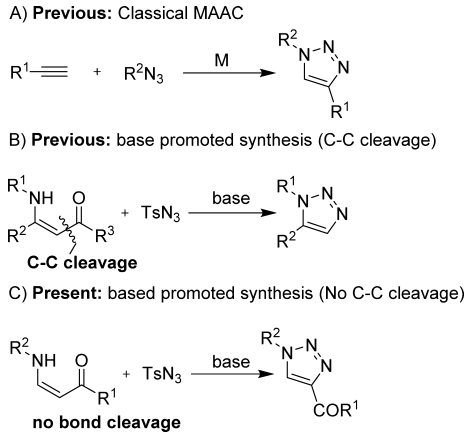


Over the past several decades, the chemistry of 1,2,3-triazoles has become a prominent area of chemical research owing to their application in organic synthesis, chemical biology, medicinal chemistry, and new materials synthesis.[1] Thanks to the landmark discovery of the alkyne azide cycloaddition (AAC) reactions disclosed by Huisgen,[2] Sharpless[3] and Meldal,[4] respectively, research both in the synthesis as well as the application of 1,2,3-triazoles has to date reached unprecedented sophistication and height. Representatively, the syntheses of 1,2,3-triazoles with improved sustainability and product diversity by means of metal catalysis,[5] metal-free AAC,[6] and alternative azide-free synthetic methodologies[7] constitute the major contemporary interests in 1,2,3-triazole synthesis.

In the available sites allowing substructural variation, the *N*-substitution of 1,2,3-triazoles is a key point in the generation of molecular diversity, which is highly crucial for biological investigations. In the classical AAC model, the synthesis of *N*-substituted 1,2,3-triazoles relies on the utilization of different organo azide starting materials,[8] which are well known for their limited commercial availability and challenging synthetic preparation (A, Scheme 1).[9] Domino reactions involving the *N*-alkylation of in situ generated *NH*-1,2,3-triazoles by use of alkyl halides as electrophiles are also able to provide *N*-substituted 1,2,3-triazoles.[10] However, this approach suffers from the restriction of tolerating only highly active benzyl halides and a few other alkyl halides. On the other hand, employing commercially available azides such as sodium azide or tosyl azide only gives *NH* or *N*-sulfonyl 1,2,3-triazoles.[11] In this context, devising alternative synthetic methodologies that are capable of providing various *N*-substituted 1,2,3-triazoles without relying on various organo azides remains highly desirable.

Recently, Cui and co-workers reported that *NH*-functionalized enaminones bearing a *β*-substituent react with sulfonyl azides to provide 1,5-disubstituted 1,2,3-triazoles under metal-free conditions[12] to afford *N*-aryl/alkyl-1,2,3-triazoles via a key

Scheme 1. Different Cycloaddition Reactions for 1,2,3-Triazole Synthesis



C−C bond cleavage in an enaminone substrate (B, Scheme 1). During our research on enaminone-based organic synthesis, we have identified a transamination between *N*,*N*-disubstituted enaminones and primary amines that has been proved to be a highly practical tactic for the generation of *NH*-functionalized enaminones, which enables the designation of various domino reactions toward the synthesis of diversified organic products.[13] Inspired by this facile *NH*-enaminone generation process, we envisioned that the synthesis of 1,2,3-triazoles with enriched *N*-substitution from the *NH*-enaminones could derive from enaminone−azide cycloaddition.[14]

Unlike the transformations involving a C−C bond cleavage in Cui's work, we have now identified a new route to 1,4-disubstituted 1,2,3-triazoles that does not involve C−C bond cleavage during the reaction (C, Scheme 1). Herein, we report

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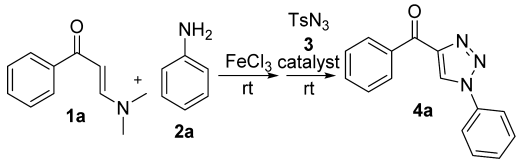
our results on this novel transition-metal-free cycloaddition reaction of enaminones and tosyl azide for the synthesis of various *N*-substituted 1,2,3-triazoles.

In an initial effort, the reaction of enaminone **1a**, aniline **2a**, and tosyl azide **3** was tentatively run in a one-pot stepwise operation. Although the transamination between **1a** and **2a** was known to proceed well with the catalysis of various Brønsted and Lewis acids,[15] $FeCl_3$ was selected as the first-step catalyst since a base promoter was required as the second-step catalyst. While the first-step transformation was easy and highly efficient, optimization experiments focused on the second cycloaddition step. As outlined in Table 1, after the transamination of **1a** and **2a**, the reaction providing 1,2,3-triazole product **4a** was found to run well in the presence of *t*-BuONa in different reaction media, with MeCN being determined to be the best medium (entries 1−6, Table 1). Subsequent variation of the base additive indicated that Et_3N was not practical, and entries utilizing MeONa, EtONa, NaOH, and KOH as well as Cs_2CO_3 gave significantly inferior product yields than the entry with *t*-BuONa (entries 7−12, Table 1). Finally, a change in the loading of the base proved that neither reducing nor increasing the amount of *t*-BuONa was positive (entries 13−15, Table 1).

Table 1. Optimization of Reaction Conditions[a]

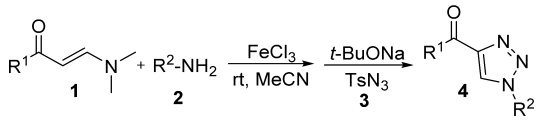


entry	catalyst	solvent	yield[b] (%)
1	*t*-BuONa	CH_2Cl_2	62
2	*t*-BuONa	EA	53
3	*t*-BuONa	CH_3CN	86
4	*t*-BuONa	EtOH	25
5	*t*-BuONa	$ClCH_2CH_2Cl$	63
6	*t*-BuONa	dioxane	56
7	Et_3N	CH_3CN	trace
8	MeONa	CH_3CN	14
9	EtONa	CH_3CN	17
10	KOH	CH_3CN	56
11	NaOH	CH_3CN	43
12	Cs_2CO_3	CH_3CN	47
13[c]	*t*-BuONa	CH_3CN	67
14[d]	*t*-BuONa	CH_3CN	86
15[e]	*t*-BuONa	CH_3CN	41

[a]General conditions: **1** (0.3 mmol), **2** (0.4 mmol), $FeCl_3$ (0.15 mmol) in 2 mL of solvent, stirred for 2 h at rt. Then **3** (0.4 mmol) and base (0.6 mmol) were added followed by stirring at rt for 2 h. [b]Yield of isolated products based on **1**. [c]*t*-BuONa (0.3 mmol). [d]*t*-BuONa (0.45 mol). [e]*t*-BuONa (0.75 mol).

The scope of this metal-free synthesis of 1,2,3-triazoles **4** was investigated by employing various enaminones **1** and primary amines **2**. The results acquired from this study (Table 2) suggested generality for this synthetic protocol. First, the enaminone component exhibited tolerance when both aryl and alkyl substructures were involved where the alkyl-functionalized enaminone gave the corresponding product with lower yield (**4x**, Table 2). Heteroaryl-based enaminones also smoothly participated in the transformation to provide heteroaryl-functionalized triazole products with good yield (**4v** and **4w**,

Table 2. Synthesis of Different 1,2,3-Triazoles[a]



entry	R^1	R^2	product	yield[b] (%)
1	Ph	Ph	**4a**	86
2	Ph	4-MeC_6H_4	**4b**	83
3	Ph	4-$MeOC_6H_4$	**4c**	84
4	Ph	2,4-$Me_2C_6H_3$	**4d**	81
5	Ph	3-ClC_6H_4	**4e**	72
6	Ph	2-MeC_6H_4	**4f**	80
7	Ph	2-$MeOC_6H_4$	**4g**	79
8	4-MeC_6H_4	4-MeC_6H_4	**4h**	85
9	4-MeC_6H_4	4-$MeOC_6H_4$	**4i**	81
10	4-$MeOC_6H_4$	4-MeC_6H_4	**4j**	84
11	2-MeC_6H_4	4-MeC_6H_4	**4k**	81
12	4-FC_6H_4	4-MeC_6H_4	**4l**	75
13	3,4-$CH_2O_2C_6H_3$	2-MeC_6H_4	**4m**	84
14	3-$MeOC_6H_4$	4-MeC_6H_4	**4n**	84
15	3-$MeOC_6H_4$	Ph	**4o**	85
16	3-$MeOC_6H_4$	2-ClC_6H_4	**4p**	75
17	3-$MeOC_6H_4$	4-BrC_6H_4	**4q**	70
18	4-BrC_6H_4	Ph	**4r**	66
19	4-$CF_3C_6H_4$	Ph	**4s**	75
20	naphth-1-yl	4-$MeOC_6H_4$	**4t**	70
21	naphth-2-yl	2,4-$Me_2C_6H_3$	**4u**	75
22	thiophene-2-yl	4-MeC_6H_4	**4v**	74
23	furan-2-yl	2-MeC_6H_4	**4w**	66
24	Me	Ph	**4x**	59
25[c]	Ph	Bn	**4y**	63

[a]General conditions: enaminone **1** (0.3 mmol), amine **2** (0.4 mmol), and $FeCl_3$ (0.15 mmol) in 2 mL of MeCN stirred for 2 h at rt. Then TsN_3 **3** (0.4 mmol) and *t*-BuONa (0.45 mmol) were added followed by stirring at rt for 2 h. [b]Yields of isolated products based on **1**. [c]*N*-Benzyl-*NH*-enaminone (0.3 mmol) prepared from **1a** and benzylamine was directly used as starting material.

Table 2). As for the amine component, anilines containing substituents of different properties in *ortho*-, *meta*-, as well as *para*-sites generally afforded target products. While the transamination between enaminone **1** and alkylamine was not practical, employing a prior prepared *N*-alkyl compound such as the *N*-benzyl *NH* enaminone could give the corresponding *N*-alkylated 1,2,3-triazole product (entry 25, Table 2), but the yield was lower than equivalent entries using *N*-aryl enaminones.

On the other hand, when 2-aminopyridine, a typical heteroarylamine, was employed, the expected *N*-pyridinyl-1,2,3-triazole was not acquired via the one-pot operation. Instead, directly utilizing the previously prepared *N*-pyridinyl enaminones **5** and tosyl azide was found to afford a practical route for the synthesis of *N*-pyridinyl-1,2,3-triazoles **6** under the standard cycloaddition conditions. As shown in Table 3, the direct cycloaddition between enaminones **5** and tosyl azide displayed satisfactory efficiency and diversity for the synthesis of *N*-pyridinyl-1,2,3-triazoles **6**.

To further demonstrate the application scope of the present method for additional 1,2,3-triazole syntheses, *NH*-enaminones **7** and **9**, which contained *β*-substitution, were employed with tosyl azide, and the corresponding 1,4,5-substituted 1,2,3-triazoles **8** and **10** were smoothly obtained under the standard

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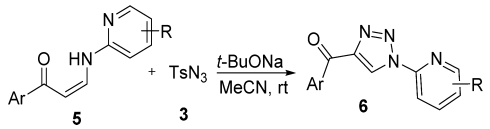
Table 3. Synthesis of 1,2,3-Triazoles[a]

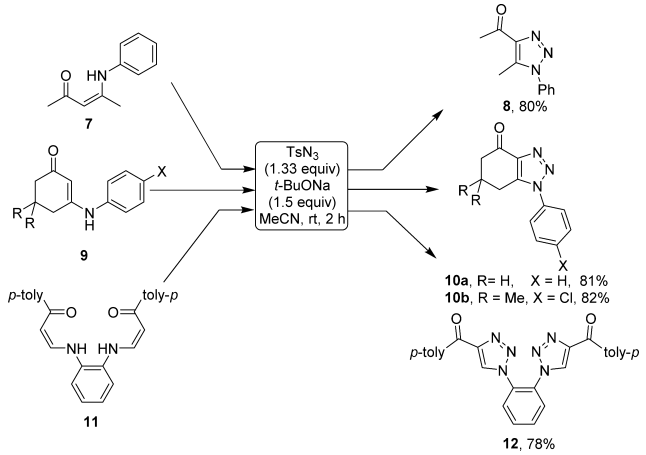


entry	Ar	R	product	yield[b] (%)
1	4-MeOC$_6$H$_4$	H	**6a**	90
2	thiophene-2-yl	H	**6b**	86
3	4-BrC$_6$H$_4$	H	**6c**	83
4	naphth-2-yl	H	**6d**	88
5	3,4-(MeO)$_2$C$_6$H$_3$	H	**6e**	91
6	4-ClC$_6$H$_4$	4-Cl	**6f**	84
7	4-MeC$_6$H$_4$	4-Me	**6g**	90
8	4-ClC$_6$H$_4$	4-Me	**6h**	84
9	naphth-2-yl	6-Me	**6i**	85
10	3,4-Cl$_2$C$_6$H$_3$	4-Me	**6j**	80

[a]General conditions: enaminone **5** (0.3 mmol), TsN_3, **3** (0.4 mmol), and *t*-BuONa (0.45 mmol) in 2 mL of MeCN were stirred for 2 h at rt. [b]Yields of isolated products based on **5**.

reaction conditions (Scheme 2). In addition, use of bis-*NH*-enaminone **11** afforded the useful bis-1,2,3-triazole product **12** in satisfactory yield (Scheme 2).

Scheme 2. Synthesis of Additional 1,2,3-Triazoles



In addition to full spectroscopic characterization, the structure of the products was further confirmed by the X-ray analysis on the single crystal of **4b** (Figure 1).[16]

According to the known literature on the reactions involving the *NH*-enaminones and related azide cycloaddition,[12,14,15,17] a possible mechanism for the present 1,2,3-triazole formation has been proposed, as outlined in Scheme 3. First, *NH*-enaminones of type **5** resulting from the transamination of **1** and **2** could afford the anion **14** in the presence of base via the tautomer **13**.

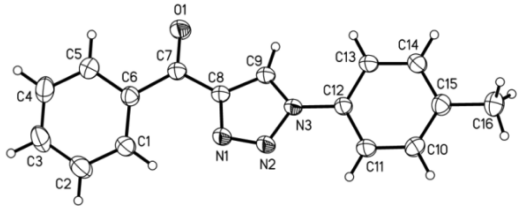
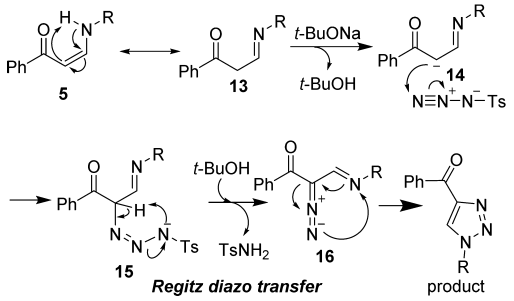


Figure 1. X-ray crystal structure of **4b**.

Scheme 3. Postulated Reaction Mechanism



The nucleophilic addition of anion **14** to the N−N triple bond in tosyl azide could then yield intermediate **15**. The diazo intermediate **16** would then be generated via a typical Regitz diazo transfer.[17] Finally, the 1,2,3-triazole products would be produced via the intramolecular cyclization of intermediate **16**.

In conclusion, by employing the *NH*-enaminones and tosyl azide as easily available starting materials, we have accomplished the synthesis of 1,2,3-triazoles via cycloaddition reactions mediated by *t*-BuONa. The generation of various *N*-substitutions in the products via *N*-substituted enaminones rather than organo azides, as well as the metal-free, room-temperature operation, demonstrate it to be a highly useful complementary strategy for the synthesis of 1,2,3-triazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02975.

Experimental procedures, characterization data, $^1H/^{13}C$ NMR spectra of all products (PDF)
Crystallographic data of **4b** (CIF)

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Notes

The authors declare no competing financial interest.

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(16) CCDC 1504366 contains the supplementary crystallographic data for this paper (**4b**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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