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Nitrogen Heterocycles

Metal-Free C–N- and N–N-Bond Formation: Synthesis of 1,2,3-Triazoles from Ketones, *N*-Tosylhydrazines, and Amines in One Pot

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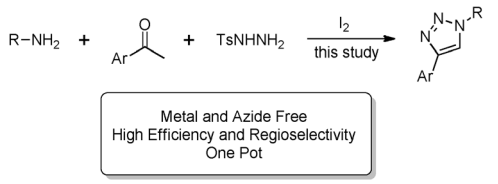
Abstract: A novel synthetic approach toward 1,4-disubstituted 1,2,3-triazoles by C–N- and N–N-bond formation has been established under transition-metal-free conditions. Complete control of the regioselectivity was successfully achieved. Commercially available anilines, ketones, and *N*-tosylhydrazine were treated with molecular iodine in one pot to allow the regioselective generation of 1,4-disubstituted 1,2,3-triazoles in high yields without the use of azides.

Introduction

1,2,3-Triazoles are key structural moieties in functional materials, bioactive products, and pharmaceutical agents.[1] Therefore, the development of chemical methods that allow the selective construction of this five-membered heterocyclic framework is an important research field in organic synthesis. In 1963, Huisgen and co-workers explored the synthesis of triazoles by uncatalyzed thermally induced dipolar cycloaddition of alkynes with organic azides.[2] The disadvantages of the Huisgen-type reaction include the limited substrate scope and low regioselectivity. Later, the groups of Sharpless[3] and Meldal[4] established the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, which remarkably increases the reaction rate and regioselectivity of the 1,4-disubstituted triazole isomer. The CuAAC reaction has had a huge impact on organic synthesis as a premier example of click chemistry and has been widely utilized, both in industry and academia.[5] Other metal catalysts[6] and organocatalysts[7] have also been investigated for the synthesis of 1,2,3-triazoles.

However, all of the above methods involve the use of sodium azides or organic azides, which are toxic and difficult to handle, especially on a large scale. Recently, we reported a copper-mediated method for the synthesis of 1,2,3-triazoles from *N*-tosylhydrazones and amines, which provides an alternative route to access of 1,2,3-triazoles without the use of azides.[8] Although the efficiency and regioselectivity of our recently developed procedure is good, a significant amount of copper salt must be applied. Considering the wide application of 1,2,3-triazoles in pharmaceutical and life sciences research, the development of metal-free methodology is highly desirable to avoid possible metal contamination of the heterocyclic products; trace residues of copper may spoil further property investigation in many cases. However, achievement of the precise synthesis of 1,2,3-triazoles without the use of metals is a significant challenge. It is known that the spontaneous regioselective formation of C–N and N–N bonds is quite difficult without the help of transition metals.[9] Recently, a metal-free method for the synthesis of 1,2,3-triazoles by condensation of α,α-dichlorotosylhydrazones with primary amines was reported by Westermann and co-workers.[10] This method has aroused much attention and has been used broadly for the construction of 1,2,3-triazoles, although the preparation and handling of α,α-dichlorotosylhydrazones is not convenient.[11] Herein, we report a metal-free, mild, operationally simple, and practical approach to access to 1,4-disubstituted 1,2,3-triazoles from anilines **1**, ketones **2**, and *N*-tosylhydrazine (**3**) in one pot (Scheme 1). More significantly, complete regiocontrol was achieved for the spontaneous formation of C–N and N–N bonds by the choice of easy-to-handle and inexpensive molecular iodine as the activator. Control experiments were performed to gain insight into the nature of this new reaction.



Scheme 1. Metal-free approach to 1,2,3-triazoles.

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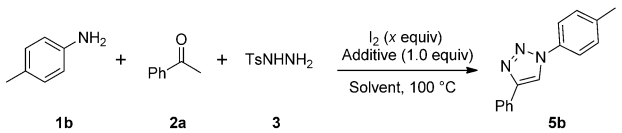
Results and Discussion

Molecular iodine has been widely used as the activator for a range of transformations due to its low toxicity and cost.[12] We began our study by optimizing the amount of iodine required for the reaction (Table 1). A solution of *p*-toluidine (**1b**), acetophenone (**2a**), and **3** in DMSO was treated with iodine (0.5 equiv) at 100 °C for 12 h. A clean 1,4-disubstituted isomer 4-phenyl-1-*p*-tolyl-1*H*-1,2,3-triazole (**5b**) was obtained in 34% yield (Table 1, entry 1). Further studies revealed that the addition of iodine (1.5 equiv) showed the best efficiency and gave the triazole **5b** in 86% yield (Table 1, entries 2–4). Further increases of the amount of iodine led to a decrease of the yield (Table 1, entries 5 and 6). Iodine proved to be crucial to the reaction and no reaction was observed in the absence of iodine (Table 1, entry 7). The use of solvents other than DMSO, such as toluene, CH_3CN, 1,4-dioxane, DMF, and 1,2-dichloroethane (DCE), resulted in lower yields (Table 1, entries 8–12). A temperature screen revealed that the transformation at 100 °C delivered the highest isolated yield (Table 1, entries 13–15). Interestingly, a compatible yield could be obtained by the use of iodine (50 mol%) in the presence of *tert*-butylhydroperoxide (TBHP, 1.0 equiv) (Table 1, entry 16). Oxidant additives, such as 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), *N*-fluorobenzenesulfonimide (NFSI), benzoquinone (BQ), and $PhI(OAc)_2$, had a detrimental effect on the reaction (Table 1, entries 17–20). Oxone and $K_2S_2O_8$ promoted the reaction, but afforded lower yields (Table 1, entries 21–22). The reaction gave a 45% yield under an oxygen atmosphere (Table 1, entry 23). Because TBHP is expensive and difficult to handle on a large scale, the optimal reaction conditions were determined as: iodine (1.5 equiv), DMSO, 100 °C, 12 h. The reaction promoted by 1 or 1.5 equivalents of iodine under a nitrogen atmosphere was conducted (Table 1, entry 24 and 25). The efficiency of the reaction is related to the amount of iodine under an inert atmosphere: the use of iodine (1 equiv) gave 48% of **5b**, whereas iodine (1.5 equiv) afforded a higher yield of 64%. These results indicate that oxygen is involved in the reaction as an oxidant.

Table 1. Optimization of the reaction conditions[a]



1b 2a 3 5b

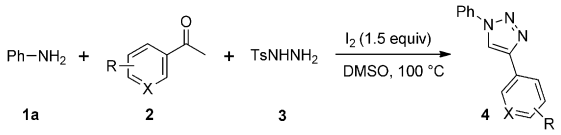
Entry	I_2 [equiv]	Additive	Solvent	Yield[b] [%]
1	0.5	–	DMSO	34
2	1.0	–	DMSO	65
3	1.2	–	DMSO	70
4	**1.5**	**–**	**DMSO**	**86**
5	2.0	–	DMSO	62
6	3.0	–	DMSO	27
7	–	–	DMSO	0
8	1.5	–	toluene	15
9	1.5	–	CH_3CN	trace
10	1.5	–	1,4-dioxane	10
11	1.5	–	DMF	55
12	1.5	–	DCE	trace
13	1.5	–	DMSO	30[c]
14	1.5	–	DMSO	76[d]
15	1.5	–	DMSO	81[e]
16	0.5	TBHP	DMSO	76
17	0.5	TEMPO	DMSO	0
18	0.5	NFSI	DMSO	18
19	0.5	BQ	DMSO	trace
20	0.5	$PhI(OAc)_2$	DMSO	15
21	0.5	Oxone	DMSO	62
22	0.5	$K_2S_2O_8$	DMSO	58
23	0.5	O_2	DMSO	45
24	1.0	–	DMSO	48[f]
25	1.5	–	DMSO	64[f]

[a] Reaction conditions: **1b** (0.6 mmol), **2a** (0.5 mmol), **3** (0.75 mmol), additive (0.5 mmol), solvent (2 mL), 100 °C, 12 h. [b] Isolated yield. [c] $T=60$ °C. [d] $T=80$ °C. [e] $T=120$ °C. [f] Under N_2 atmosphere.

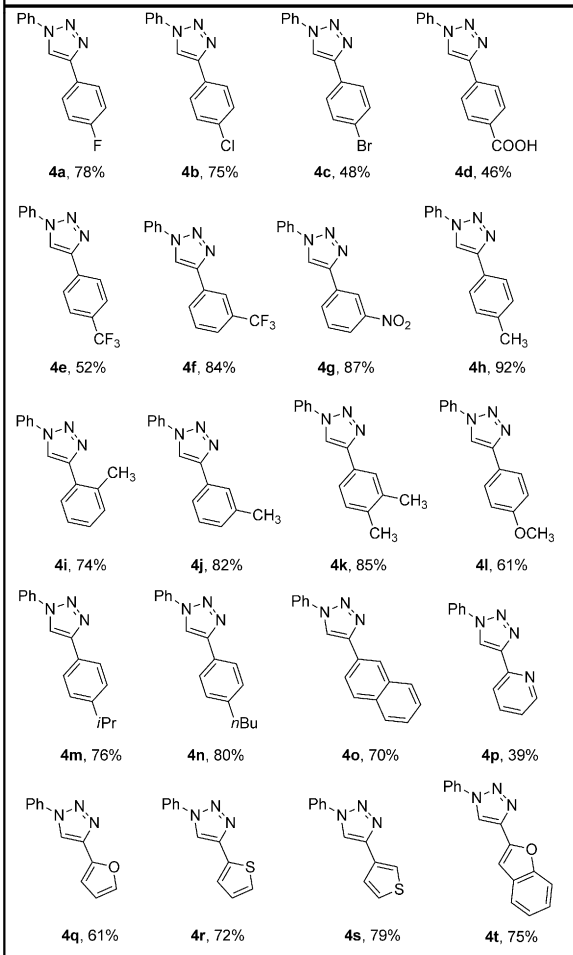
With the newly developed metal-free protocol, a variety of arylketones **2** were subjected to the optimized conditions (Table 2). The results are especially remarkable when compared to the synthesis of 1,2,3-triazoles from *N*-tosylhydrazones and amines, reported previously by us,[8] in which *N*-tosylhydrazones with electron-withdrawing substituents on the aryl ring showed very low reactivity and *N*-tosylhydrazones with substituents such as trifluoromethyl on the aryl ring failed to give the corresponding triazoles. To our delight, the metal-free system displayed good tolerance towards a range of electron-withdrawing groups, including $-CF_3$, $-NO_2$, and $-COOH$, to give the corresponding triazoles in good yields (**4a**–**g**, 46–87%). However, the aryl ketones that bore electron-donating groups still showed better reactivity and gave higher yields (**4h**–**n**, 61–92%). Steric hindrance played little role in this transformation, both *ortho*- and *meta*-substituted aryl ketones presented excellent reactivity (**4h**–**j**, 74–92%). A disubstituted aryl ketone participated smoothly in the reaction to afford **4k** in 85% isolated yield. 1-(Naphthalen-2-yl)ethanone worked well in this transformation to smoothly give **4o**. It should be noted that the heterocycle-substituted triazoles **4p**–**t** could be obtained in moderate-to-good yields from the corresponding heterocyclic ketones (39–79%). However, extension of the reaction to aryl, alkyl ketone precursors with a longer alkyl chain, such as aryl propanones or 1-phenylpropan-2-one, to form 1,4,5-trisubstituted triazoles failed.

We subsequently applied this new method with a range of anilines, as shown in Table 3. The electron-rich anilines, including methyl, methoxyl, *tert*-butyl, and phenyl could be smoothly converted to the desired triazole products in high yields (**5a**–**h**, 79–93%). Electron-deficient anilines also showed better reactivity relative to our previous copper-mediated system.[8] For example, anilines that bear halogen substituents were well tolerated and the corresponding triazole products were isolated in good yields (**5i**–**k**, 72–80%). Although the strongly electron-deficient aniline 4-aminobenzonitrile was inactive in our copper-mediated system, the corresponding triazole **5l** was isolated under the present optimized conditions in an acceptable yield (46%). Notably, strongly electron-withdrawing groups in the *meta*-position exhibited good-to-excellent reactivity (**5m**–**n**, 75–90%). Naphthalen-1-amine and isoquinolin-8-amine participated efficiently in the reaction to give the correspond-

Table 2. Synthesis of 1,2,3-triazoles from a variety of ketones.[a,b]

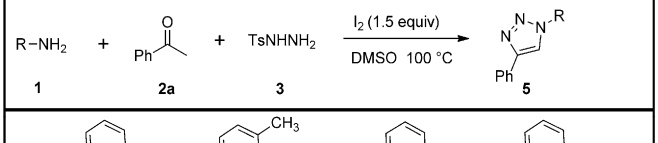


1a 2 3 4

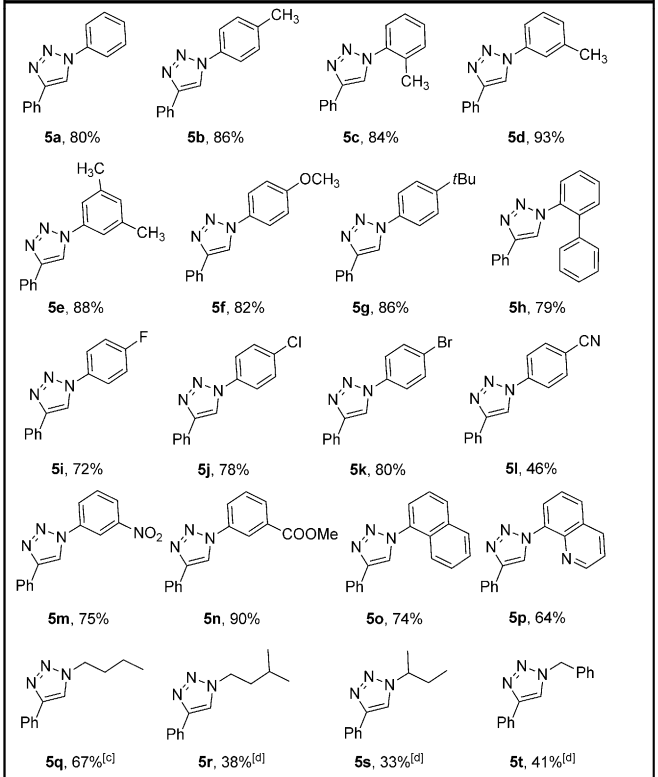


[a] Reaction conditions: **1a** (0.6 mmol), **2** (0.5 mmol), **3** (0.75 mmol), I_2 (0.75 mmol), DMSO (2 mL), 100 °C, 12 h. [b] Isolated yield.

Table 3. Synthesis of 1,2,3-triazoles from diverse amines.[a,b]



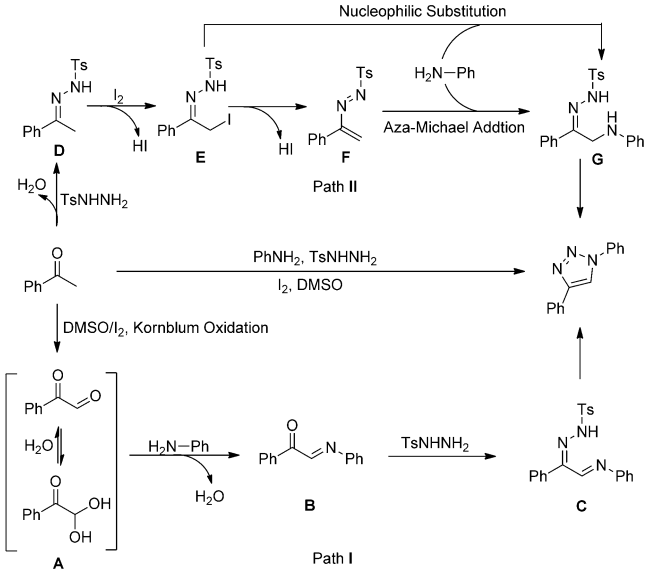
1 2a 3 5



[a] Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol), **3** (0.75 mmol), I_2 (0.75 mmol), DMSO (2 mL), 100 °C, 12 h. [b] Isolated yields. [c] I_2 (0.25 mmol), TBHP (0.5 mmol, 70% in water), 1,4-dioxane (2 mL), 100 °C, 12 h. [d] I_2 (0.25 mmol), Oxone (0.5 mmol), 1,4-dioxane (2 mL), 100 °C, 12 h.

ing triazoles in good yields (**5o–p**, 64–74%). In the case of aliphatic amines, a complex mixture was produced and the desired triazoles were quite difficult to isolate. Gratifyingly, experimentation revealed that butyl amine afforded the desired triazole **5q** in 67% yield when the reaction conditions were switched to iodine (50 mol%) and TBHP (1 equiv). However, other amines tested failed to give the corresponding triazoles under these conditions. After further optimization of the reaction conditions, we obtained alkyl-substituted triazoles **5r--t** by the combination of iodine (50 mol%) and Oxone (1 equiv), albeit in lower yields.

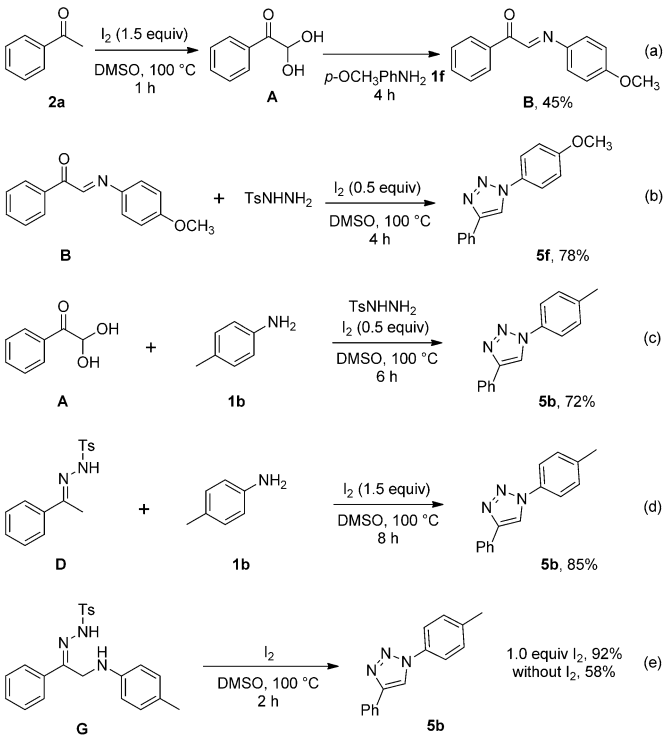
Two plausible pathways are proposed (Scheme 2). Phenylglyoxal intermediate **A** formed in the presence of iodine and DMSO by Kornblum oxidation[13] undergoes condensation with the aniline to form the C-acyl imine intermediate **B**. Subsequent condensation of intermediate **B** with *N*-tosylhydrazine



Scheme 2. A plausible mechanism.

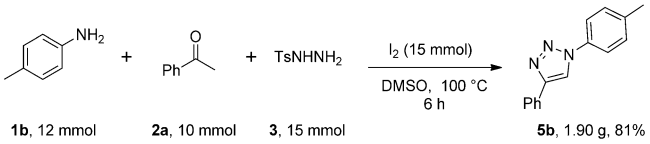
affords intermediate **C**, which undergoes cyclization and aromatization in the presence of molecular iodine or O_2 to generate the triazole product (Path I). Another possible pathway is the formation of *N*-tosylhydrazone **D** by the reaction of an arylketone with *N*-tosylhydrazine. Subsequent α-iodogenation of the *N*-tosylhydrazone forms intermediate **E**. Elimination of HI from **E** gives the key intermediate 1-tosyl-2-vinyldiazene **F**,[14] which undergoes aza-Michael addition with the aniline to generate intermediate **G**. Oxidative cyclization and aromatization of intermediate **G** in the presence of iodine affords the triazole product (Path II). Direct nucleophilic attack of aniline onto intermediate **E** is another possible route for the formation of intermediate **G**.

To gain further insight into the reaction mechanism, we performed the control experiments illustrated in Scheme 3. It was found that treatment of **2a** with molecular iodine and DMSO



Scheme 3. Control experiments.

first produced intermediate **A**, and subsequent addition of **1f** generated C-acyl imine intermediate **B** (Scheme 3a). The reaction of intermediate **B** with **3** gave the triazole product **5f** in 78% yield (Scheme 3b). The reaction of intermediate **A**, **1b**, and **3** in one pot also afforded the triazole product **5b** in 72% yield (Scheme 3c). These results provide evidence for Path I. On the other hand, we prepared *N*-tosylhydrazone **D** and treated it with **1b** under the standard reaction conditions (Scheme 3d). The desired triazole product **5b** was obtained in 85% yield, indicative that the triazole can also be formed by Path II. Importantly, we found that intermediate **G**, which was prepared by a literature method,[8] could be smoothly cyclized

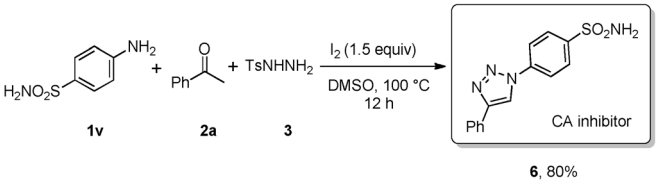


Scheme 4. Scaleup of the reaction.

by formation of a N–N bond to afford the final triazole **5b** in the presence or absence of iodine (Scheme 3e).

We performed the reaction on a gram scale (Scheme 4) and were pleased to find that the triazole product **5b** was obtained in 81% yield. This satisfactory result presents the possibility for large-scale applications of this methodology.

The sulfonamide moiety is the core structure of carbonic anhydrase (CA) inhibitors.[15] The CA inhibitor properties can be readily tuned with respect to structure–property and structure–activity parameters by covalently tethering a tail fragment onto an established primary sulfonamide CA-recognition pharmacophore, as in compound **6** (Scheme 5).[15a] By the use of



Scheme 5. Synthetic utilization of the metal-free method.

our method, the "tail approach" can be easily achieved with high efficiency from commercially available chemicals in one pot. This metal-free method provides straightforward access to useful bioactive molecules.

Conclusion

A new synthetic method for the construction of C–N and N–N bonds under metal-free conditions has been demonstrated. More significantly, the transformation is operationally simple and executed in one pot from commercially available reagents to regioselectively afford 1,4-disubstituted 1,2,3-triazoles in high yields under mild conditions. The substrate scope is broad and the reaction can be readily scaled up to gram scale, which thereby offers a practical approach for the production of diverse 1,2,3-triazoles. Further investigations to extend the reaction scope and elucidate the possible mechanism are in progress.

Experimental Section

Representative procedure for the formation of 1,2,3-triazoles

I_2 (0.75 mmol) was added to a mixture of **1b** (0.6 mmol), **2a** (0.5 mmol), and **3** (0.75 mmol) in DMSO (2 mL). The mixture was

stirred at 100 °C under air for 4–12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature and water (30 mL) was added to the mixture, which was then extracted with EtOAc (3×50 mL). The extract was washed with 10% *w/w* $Na_2S_2O_3$ (aq), dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum to provide the crude product, which was purified by column chromatography on silica gel to afford **5b** as a light-yellow solid (86%).

Acknowledgements

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Keywords: anilines · ketones · metal-free reactions · synthetic methods · 1,2,3-triazoles

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FULL PAPER

Nitrogen Heterocycles

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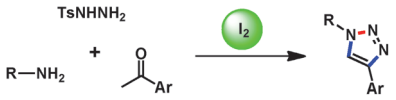
Metal-Free C–N- and N–N-Bond Formation: Synthesis of 1,2,3-Triazoles from Ketones, *N*-Tosylhydrazines, and Amines in One Pot



Metal and Azide Free
High Efficiency and Regioselectivity
One Pot

A novel synthetic approach toward 1,4-disubstituted 1,2,3-triazoles by C–N- and N–N-bond formation has been established under transition-metal-free conditions (see scheme). Complete control of regioselectivity was successfully achieved and anilines, ketones, and *N*-tosylhydrazines were treated with molecular iodine in one pot to allow the formation of 1,4-disubstitued 1,2,3-triazoles in high yields without the use of azides.