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Title: TBAI or KI-Promoted Oxidative Coupling of Enamines and N-Tosylhydrazine: An Unconventional Method toward 1,5- and 1,4,5-Substituted 1,2,3-Triazoles

Authors: Huanfeng Jiang, Wei Huang, Chuanle Zhu, Minke Li, Yue Yu, Wanqing Wu, and Zhengchao Tu

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TBAI or KI-Promoted Oxidative Coupling of Enamines and *N*-Tosylhydrazine: An Unconventional Method toward 1,5- and 1,4,5-Substituted 1,2,3-Triazoles

Wei Huang[a], Chuanle Zhu[a], Minke Li[b], Yue Yu[a], Wanqing Wu[a], Zhengchao Tu[b,*], and Huanfeng Jiang[a,*]

[a] Key Laboratory of Functional Molecular Engineering of Guangdong Province, Guangdong Engineering Research Center for Green Fine Chemicals, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China.
Fax: (+86) 20-87112906; E-mail: jianghf@scut.edu.cn

[b] Drug Discovery Pipeline & Guangdong Provincial Key Laboratory of Biocomputing, Guangzhou Institutes of Biomedicine and Health, Guangzhou 510530, P. R. China.
Fax: (+86) 20-32015324; E-mail: tu_zhengchao@gibh.ac.cn

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Abstract. A novel method for the synthesis of 1,5- and 1,4,5-substituted 1,2,3-triazoles has been reported. This approach is promoted by iodine-TBHP oxidation system using enamines and *N*-tosylhydrazine as materials, which avoid the dependence of traditional methods on azides and transition metals. Through this approach, various 1,5- and 1,4,5-substituted 1,2,3-triazoles were delivered in moderate to high yields. The mechanistic study indicated that an amino exchange would be involved in the reaction process. Moreover, the product methyl 1-(2-methoxyphenyl)-4-methyl-1*H*-1,2,3-triazole-5-carboxylate is a useful precursor to anti-influenza A agent, and further application research was conducted.

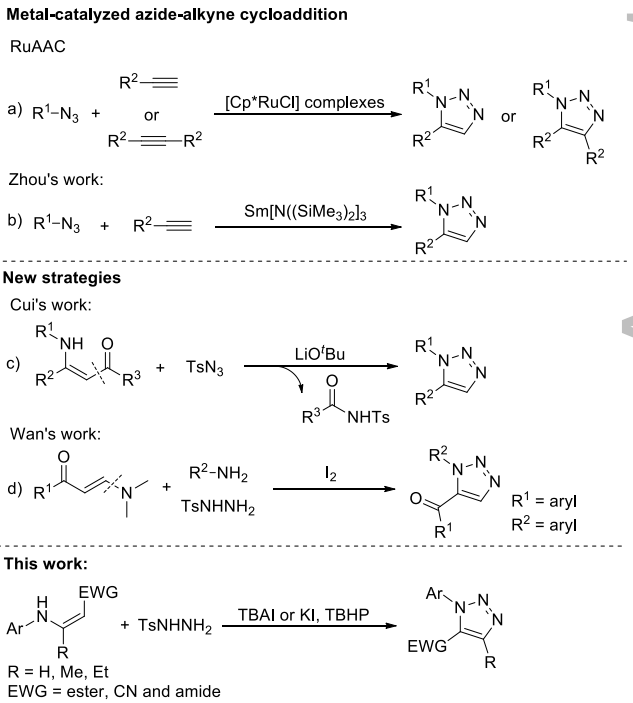
Keywords: 1,2,3-triazoles; *N*-tosylhydrazine; enamines; transition metal free; amino exchange

Introduction

1,2,3-Triazole derivatives, as an important member of the azole family have typical bioactivity and stability. They are broadly applied in pharmaceuticals, bioactive molecules and materials.[1] For example, they are key moiety of anticancer agents,[1e] anti-influenza agents[1f] and cannabinoid receptor antagonists[1g]. In addition, they are also useful building blocks and ligands in synthetic chemistry.[2-3] Due to their importance, numerous methods have been developed to construct 1,2,3-triazoles with different functional groups.

Huisgen 1,3-dipolar cycloaddition of azides and alkynes is the premier method to 1,2,3-triazoles.[4] However, the low efficiency and poor regioselectivity of this approach greatly hindered its extensive application. During past decade, great efforts have been dedicated to improve the selectivity and efficiency of Huisgen reaction and sought more efficient ways to synthesize 1,2,3-triazoles. Among them, Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) developed by Sharpless's and Meldal's group respectively is one of the most significant breakthrough,[5] which provide a general method for

Scheme 1. Strategies for the synthesis of 1,5-substituted 1,2,3-triazoles.



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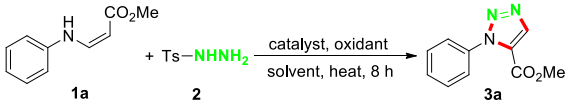
1,4-disubstituted 1,2,3-triazoles. Afterwards, various strategies to assemble 1,4-disubstituted 1,2,3-triazoles have been developed.[6, 7] Compared with the successful development of the synthesis of 1,4-disubstituted 1,2,3-triazoles, investigation on the construction of 1,5-disubstituted 1,2,3-triazoles are relatively rare.[8] The pioneering work on regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles was Ru(I)-catalyzed azide-alkyne cycloaddition (RuAAC) disclosed by Fokin and coworkers in 2005 (Scheme 1, a).[8b, 8c] After that, however, studies on the preparation of 1,5-disubstituted 1,2,3-triazole have been rarely pursued.[8d, 8e] In 2013, Zhou's group developed a rare earth metal (Sm)-catalyzed method for 1,5-disubstituted 1,2,3-triazoles (Scheme 1, b).[9] Although the transition-metal-catalyzed strategies have shown high efficiency, all these reactions need the use of expensive transition metal complexes and unstable and potential explosive organic azides. Recently, metal-free or metal- and azide-free strategies for 1,5-disubstituted 1,2,3-triazoles have been respectively reported by Cui's[10] and Wan's[11] group (Scheme 1, c and d). These works offered new perspective to the synthesis of 1,5-disubstituted 1,2,3-triazoles. However, they all suffer from the disadvantages of limitation of substrates and low atomic economy. Therefore, it is still meaningful and desirable for development of new, especially metal- and azide-free methods for 1,5-disubstituted 1,2,3-triazoles and its derivatives.

Enamines are versatile and fundamental building blocks in organic synthesis due to their multiple reaction sites and high reactivity. Over the past few decades, it has been extensively explored in the assembly of various nitrogen-containing compounds[12], especially *N*-heterocycles, such as pyrroles[12a-h], indoles[12i-k], pyrazoles[12l] and isoxazoles[12m], and so on. Based on our previous works with the synthesis of enamine derivatives[13] and exploring their synthetic applications [14], herein we report a novel and efficient strategy for the synthesis of 1,5-and 1,4,5-substituted 1,2,3-triazoles using enamines and *N*-tosylhydrazine as materials.

Results and Discussion

On the basis of our previous work, [14] we started this work with the anticipation of realizing a sulfonylation of **1a**, as *N*-tosylhydrazine (**2**) could serve as a sulfonyl radical source under oxidative conditions.[15] After several attempts, we noticed an unexpected product which was finally proved to be **3a**. Encouraged by this result, we continued to investigate this reaction (Table 1). Methyl-3-(phenylamino)-acrylate (**1a**) and *N*-tosylhydrazine (**2**) were selected as model substrates. Product **3a** was obtained in 32% GC yield in the presence of TBAI (20 mol%) and TBHP (2 equiv) in acetonitrile at 50 °C (entry 1). Subsequently, series of solvents were examined (entries 2-5). A solvent of DMF was found to be the optimal. Then, the screening of different catalysts including $AgNO_3$, CuBr, I_2, KI, NIS, showed that iodine is vital to this transformation. The use of TBAI, I_2, KI or NIS could afford the desired product **3a** in 35%-47% yields (entries 8-10), while other trans-metal catalysts did not make positive effects (entries 6, 7). Considering the sublimation and environmental impact of iodine, TBAI was chosen as the best catalyst. When the temperature was elevated to 70 °C, the yield increased to 54%, but further increasing temperature lead to a lower yield (entries 11-13). We also tried to use acid or base to promote the reaction (entries 14-18). Fortunately, the addition of 1 equiv of AcOH could increase the yield to 80% (entry 17). It is noteworthy that there is no product detected without TBHP or TBAI (entries 19-20).

Table 1. Screening reactions for the synthesis of 1,5-disubstituted-1,2,3-triazoles.[a]



Entry	Catalyst	Additive	Solvent	T (°C)	Yield [%][b]
1	TBAI	-	CH_3CN	50	32
2	TBAI	-	DMF	50	46
3	TBAI	-	DMSO	50	31
4	TBAI	-	Toluene	50	23
5	TBAI	-	THF	50	22
6	$AgNO_3$ (10 mol%)	-	DMF	50	trace
7	CuBr (10 mol%)	-	DMF	50	n.d.
8	I_2	-	DMF	50	47
9	KI	-	DMF	50	35
10	NIS	-	DMF	50	42
11	TBAI	-	DMF	60	51
12	TBAI	-	DMF	70	54
13	TBAI	-	DMF	80	25
14	TBAI	LiO^{t}Bu	DMF	70	n.d.
15	TBAI	Na_2CO_3	DMF	70	n.d.
16	TBAI	DBU	DMF	70	n.d.
17	TBAI	AcOH	DMF	70	80 (76)
18[c]	TBAI	AcOH	DMF	70	47
19[d]	TBAI	AcOH	DMF	70	n.d.
20	-	AcOH	DMF	70	n.d.

[a] Reaction conditions: all reactions were performed with **1a** (0.1 mmol), **2** (1.2 equiv), catalyst (20 mol%), TBHP (2 equiv), additive (1 equiv), solvent (1 mL), at the indicated temperature for 8 h unless otherwise noted.
[b] Determined by GC-MS using dodecane as the internal standard. The number in the parentheses is isolated yield.
[c] AcOH (2 equiv).
[d] Without TBHP.

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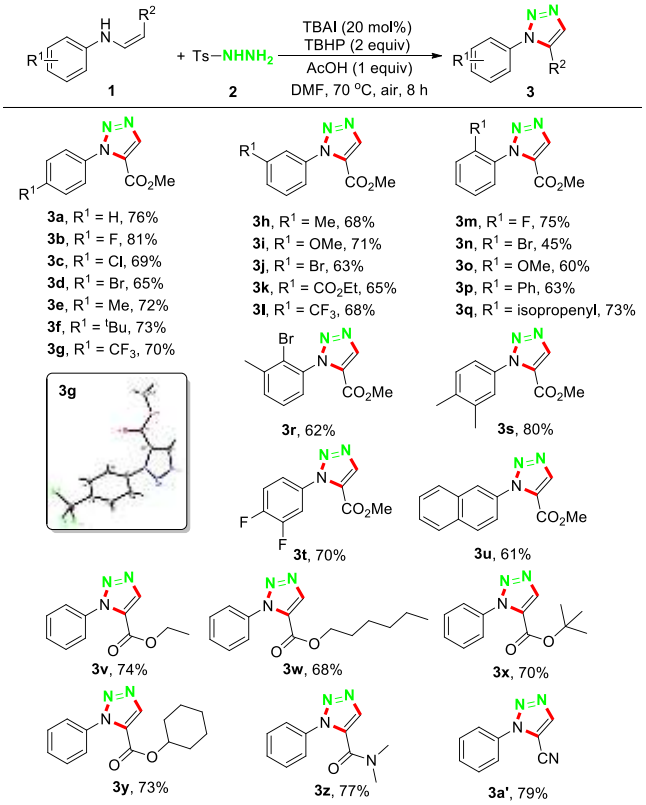
Under the optimal reaction conditions, we then examined the scope and limitations of this TBAI and TBHP motivated coupling between enamines and *N*-tosylhydrazine (Scheme 2). Generally, a wide range of enamines could react smoothly and transferred to the corresponding products in moderate to good yields. Electron-donating groups such as methyl (**3e**, **3h**), *tert*-butyl (**3f**), methoxyl (**3i**) on the *para*- or *meta*-position of the aromatic ring were well tolerated, while the electron-withdrawing groups such as halogen (**3b**, **3c**, **3d**, **3j**), trifluoromethyl (**3g**), CO_2Et (**3k**) lead to a lower yields. Large substituents on the *ortho*-position showed some steric hindrance (**3n-3p**). Particularly, 2-Br substituted substrate (**1n**) only gave a 45% yield. It was well reminded that isopropenyl was compatible to this reaction (**3q**). Multisubstituted materials and methyl 3-(naphthalen-2-ylamino)acrylate could also be used as substrates giving general and moderate yields under the standard reaction conditions (**3r-3u**). For R^2 = ethyl, *n*-hexyl, *tert*-butyl and cyclohexyl formate showed good reactivities in this reaction (**3v-3y**). Even *N*, *N*-dimethylformyl and cyano were also compatible with this approach, affording the corresponding products in good yields (**3z**, **3a'**). The molecular structure of **3g** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details).[16]

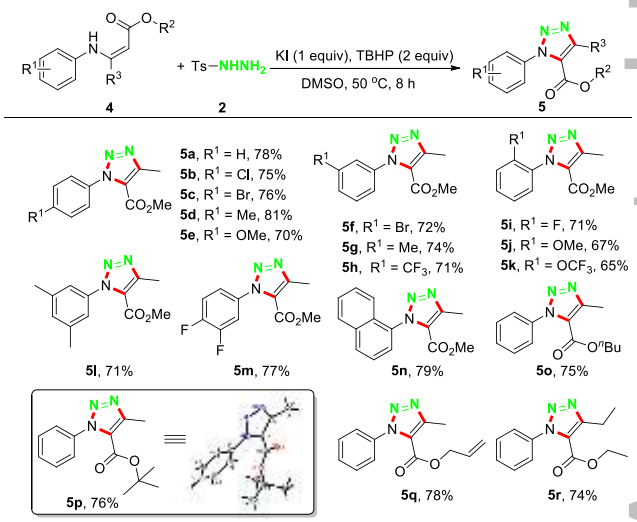
Scheme 2. Substrate scope of enamines (**1**) for the synthesis of 1,5-disubstituted-1,2,3-triazoles.[a]



[a] Reaction conditions were **1** (0.4 mmol), **2** (0.48 mmol), TBAI (20 mol%), TBHP (2 equiv) and AcOH (1 equiv) in DMF (2 mL) at 70 °C for 8 h.
[b] Isolated yield.

Interestingly, when methyl 3-(phenylamino)but-2-enoate (**4a**) was tested under this optimized reaction conditions, only a trace amount of desired 1,4,5-trisubstituted 1,2,3-triazole (**5a**) was detected. Given the importance of these 1,4,5-trisubstituted 1,2,3-triazoles[1e-g] as well as to further explore of our strategy, we further optimized the reaction conditions (see the Supporting Information for details). Under the optimized reaction conditions, various 1,4,5-trisubstituted 1,2,3-triazoles were synthesized smoothly. The results of which were shown in Scheme 3. Enamines with a variety of substituent groups on benzene ring could react smoothly and the corresponding 1-phenyl-4-alkyl-5-ester-1,2,3-triazoles were obtained in good yields (**5a-5m**). Methyl 3-(naphthalen-1-ylamino)but-2-enoate could also be used as substrate, giving corresponding product **5n** in 79% yield. Subsequently, we explored the effect of different ester. When R^2 = *n*-butyl, *tert*-butyl even allyl group, these reactions all proceeded well (**5o-5q**). The molecular structure of **5p** was confirmed by X-ray crystallographic analysis (see the Supporting Information for details).[16] In addition, we also tried to replace R^3 with other group. Pleasingly, ethyl 3-(phenylamino)pent-2-enoate (**4r**) was compatible with this approach providing **5r** in 74% yield. Unfortunately, when R^3 was isopropyl, only trace amount of desired product was detected, and when R^3 was phenyl, no desired product was obtained, and the double bond of enamines was cleaved.

Scheme 3. Substrate scope of enamines (**4**) for the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles.[a]



[a] Reaction conditions were **4** (0.4 mmol), **2** (0.48 mmol), KI (1 equiv), TBHP (2 equiv) in DMSO (2 mL) at 50 °C for 8 h.

It is particularly noteworthy that the skeleton of our product (**5j**) is a precursor to an anti-influenza A agent, which was reported by Ding's group in 2012.[1f] This drug molecule exhibits a fine effect in inhibiting the replication of viruses H3N2, H1N1 and H5N1. For the sake of seeking the practical applications of

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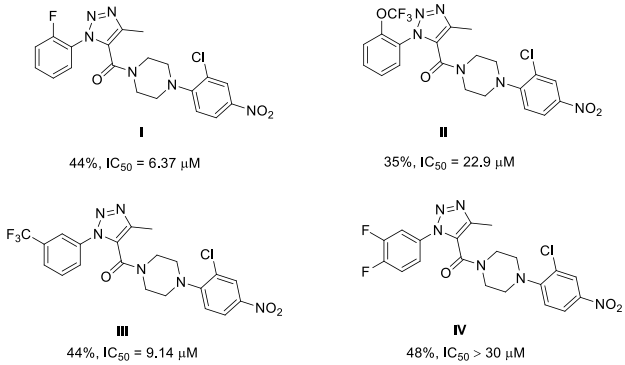
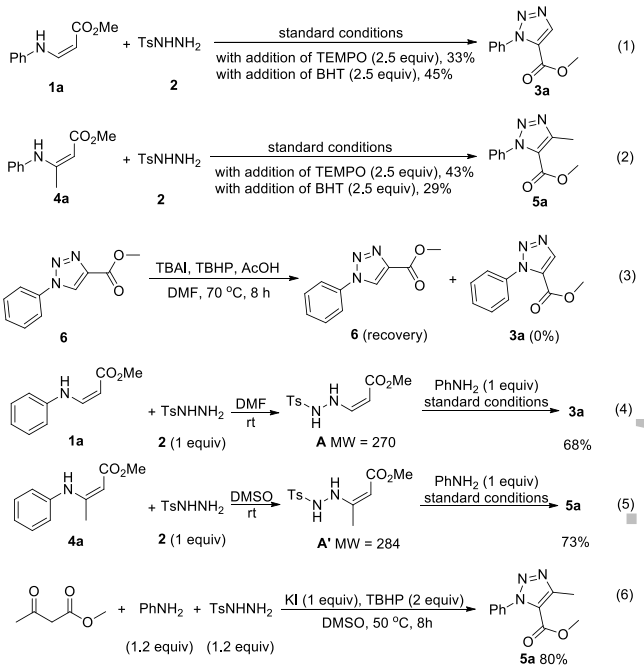
our approach and exploring the effects of fluorine[17], we selected a couple of products with fluorine substituents (**5i**, **5k**, **5h**, **5m**) and tried to synthesize potential drug molecules **I-IV** (Figure 1). Using our method, the total yields could be obtained in 35-48% and there is no problem of regional selectivity. Next, preliminary tests of the anti-H3N2 virus activities of **I-IV** were conducted. As shown in Figure 1, compound **I** displayed the best potency to inhibit the replication of H3N2 with IC_{50} value of 6.37 μM. Compound **III** was second with IC_{50} value of 9.14 μM (see the Supporting Information for details). Further researches on the application of triazoles in medicine will continue in our laboratory.

Figure 1. Anti-H3N2 virus activities of **I-IV**



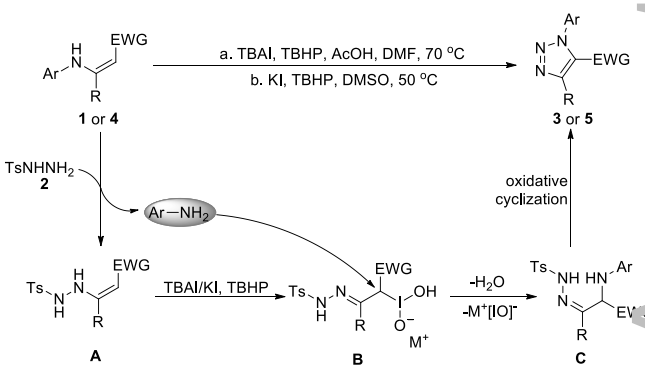
To investigate the mechanism of these cyclization reactions, several control experiments were performed (Scheme 4). Firstly, when the radical scavenger reagent TEMPO or BHT was added to the reaction systems, the reaction was not completely suppressed with the yield of 29-45% [Scheme 4, eqn (1) and (2)]. So it is inadequate to conclude that a radical process was involved. Subsequently, in order to rule out the possibility of the transformation between **3a** and **6** (methyl 1-phenyl-1*H*-1,2,3-triazole-4-carboxylate), we synthesized **6**[6g] and tested it under the standard conditions [Scheme 4, eqn (3)]. The result indicated that **6** was stable in the reaction conditions and it could not be the intermediate of this reaction. With the aim of finding the reaction intermediate, the mixture of enamines (**1a** and **4a**) and *N*-tosylhydrazine (**2**) were stirred overnight in the corresponding solvents at room temperature [Scheme 4, eqn (4) and (5)]. It was found that starting materials were converted to the amino exchange products (**A** and **A'**) almost equivalently, which were detected by LC-MS, and the structure of **A** and **A'** were verified by HRMS (see the Supporting Information for details). Then, after flash column chromatography, aniline was added to **A** and **A'** under standard conditions [Scheme 4, eqn (4) and (5)]. To our pleasure, the target products (**3a** and **5a**) were obtained in 68% and 73% yields. So, we conceived that compounds **A** and **A'** were probably the intermediates for these two reactions respectively. In addition, inspired by these results, a three-component reaction was also conducted [Scheme 4, eqn (6)] and the reaction worked well producing **5a** in 80% yield.

Scheme 4. Mechanistic studies



On the basis of the above results and previous reports, a possible mechanism is proposed in Scheme 5. Initially, an amino exchange occurred between enamines (**1** or **4**) and *N*-tosylhydrazine (**2**), producing the intermediate **A**. Under the oxidation of TBHP, TBAI or KI would be oxidized to generate $M^+[IO_2]^-$, and then reacted with **A** to afford intermediate **B**[18]. **B** undergoes a nucleophilic attack by aniline produced in the previous amino exchange to afford the key intermediate **C**. Meanwhile, the released hypoiodite ($M^+[IO]^-$) can be reoxidized by TBHP to give iodite ($M^+[IO_2]^-$), realizing its recycle. Finally, the desired product **3** or **5** was obtained by oxidative cyclization of **C**.

Scheme 5. Plausible mechanism



Conclusion

In summary, we have developed an efficient and convenient method for the synthesis of 1,5-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles through an iodine promoted coupling of enamines and *N*-tosylhydrazine. This method is featured by cheap

and available materials, easy to operate and exclusive formation of 1,5- or 1,4,5-substituted 1,2,3-triazoles. Mechanism studies indicated that the reaction is likely proceed an amino group removal and reorganization process, in which the iodine-TBHP oxidation system played an important role. Noteworthily, by hydrolysis of the ester group, products can be further transformed into various complex molecules. Several potential drug molecules have been synthesized and corresponding activity to anti-H3N2 virus have been determined. Investigations to explore the further application of this reaction will be conducted in our laboratory.

Experimental Section

General Procedure for 1,5-Disubstituted-1,2,3-Triazoles

To a test tube, a mixture of enamine **1** (0.4 mmol), *N*-tosylhydrazine **2** (0.48 mmol), TBAI (20 mol%), DMF (2 mL) was added TBHP (70% solution in water, 2 equiv, 110μL) slowly. Then the mixture was stirred at 70 °C for 8 h. After the reaction was completed (monitored by TLC), water (10 mL) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were then dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification of the residue on a preparative TLC (petroleum ether/ethyl acetate, 5:1) afforded the desired products **3**.

General Procedure for 1,4,5-Trisubstituted-1,2,3-Triazoles

To a test tube, a mixture of enamine **4** (0.4 mmol), *N*-tosylhydrazine **2** (0.48 mmol), KI (1equiv), DMSO (2 mL) was added TBHP (70% solution in water, 2 equiv, 110 μL) slowly. Then the mixture was stirred at 50 °C for 8 h. After the reaction was completed (monitored by TLC), water (10 mL) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were then dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification of the residue on a preparative TLC (petroleum ether/ethyl acetate, 5:1) afforded the desired products **5**.

Acknowledgements

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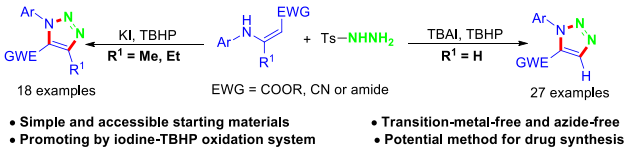
FULL PAPER

TBAI or KI-Promoted Oxidative Coupling of Enamines and *N*-Tosylhydrazines: Unconventional Methods toward 1,5- and 1,4,5-Substituted 1,2,3-Triazoles



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Wei Huang[a], Chuanle Zhu[a], Minke Li[b], Yue Yu[a], Wanqing Wu[a], Zhengchao Tu[b,*], and Huanfeng Jiang[a,*]