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Alkyl propiolates participated [3+2] annulation for the switchable synthesis of 1,5- and 1,4-disubstituted 1,2,3-triazoles containing ester side chain

Shuo Cao,[a] Yunyun Liu,[a] Changfeng Hu,[b] Chengping Wen*[b] and Jie-Ping Wan*[a]

Abstract: By means of a featured enamine activation, the alkyl propiolates have been successfully employed in the [3+2] annulation for the synthesis of 1,2,3-triazoles. The synthesis of both 1,4- as well as the hardly available 1,5-disubstituted 1,2,3-triazoles can be selectively accessed by using tosyl azide and tosyl hydrazine as nitrogen source, respectively.

Introduction

Owing to their daily increasing applications in the discovery of organic compounds with valuable biological function, designation of functional materials as well as multiple other areas, the 1,2,3-triazole heterocycle keeps receiving extensive attention and research interest from chemical community.[1] As the fundamental step before any application exploration, the synthesis of 1,2,3-triazoles occupies particularly crucial position.[2] As classical route in 1,2,3-triazole ring construction, the copper-catalyzed alkyne azide cycloaddition (CuAAC) constitutes the main tool to access 1,2,3-triazoles for a long period.[3] In order to develop complementary synthetic methods free of transition metal utilization, however, tremendous efforts have been made over the last two decades, and notable advances have been gained.[4] Among the presently known tactics enabling the metal-free 1,2,3-triazole synthesis, the enamine-based annulation has turned out to be the most reliable one. By making use of enamines as building blocks or designated intermediates, a number of methodologies have been successfully established for the synthesis of 1,2,3-triazoles with metal-free operation. More notably, besides the favorable feature of metal-free condition, enamine-based reactions also bring novel transformation pathways and selectivity to the 1,2,3-triazole synthesis.[5]

Inherently, the regioselectivity of classical CuAAC determines the style of 1,4-disubstitution in the 1,2,3-triazole products by employing terminal alkynes and organoazides as substrates. The synthesis of 1,5-disubstituted 1,2,3-triazoles, however, is hardly accessible by this protocol. To develop applicable approaches allowing the selective synthesis of 1,5-disubstituted 1,2,3-triazoles, huge endeavours has been devoted. In this regard, the synthesis employing the catalysis of transition metal species such as iridium,[6] ruthenium,[7] nickel[8] have been disclosed. The rare earth samarium has also been found as practical catalyst in catalyzing the synthesis of 1,5-disubstituted 1,2,3-triazoles.[9] Recently, by utilizing enoic acids as the reaction partners of organoazides, Kumar et al[10] accomplished the copper-catalyzed cycloaddition providing 1,5-disubstituted 1,2,3-triazoles based on a featured decarboxylation. Alternatively, the *in situ* preparation of alkynyl metal reagents such as alkynyl magnesium, alkynyl zinc, and alkynyl lithium[11] as well as aqueous NMe_4OH promoted alkyne-azide annulation[12] can also lead to the synthesis of 1,5-disubstsituted 1,2,3-triazoles. Due to the employment of transition metal catalyst, sensitive organometal reagents, restricted product diversity, and/or the harsh reaction conditions in these methods, their synthetic application does not yet meet the requirement of the 1,5-disubstituted 1,2,3-triaozoles synthesis. In this background, the enamine-based annulation reaction has been found as a powerful tool by offering metal-free and operationally practical routes towards the 1,5-disubstituted 1,2,3-triazoles. Cui and co-workers reported in 2013 a novel method on the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles via base promoted cyclization reactions of enamines with tosyl azide wherein the C(alkynyl)-C(carbonyl) bond cleavage was involved.[13] Our group has developed a different synthetic approach by employing tertiary enaminones, tosyl hydrazine and primary amines via the catalysis of molecular iodine.[14] Interestingly, During the preparation of this present work, Jiang and Du et al[15] reported their results in the synthesis of 1,5- and 1,4,5-substituted 1,2,3-triazoles via the reactions of enaminoesters and tosyl hydrazine in the presence of KI/TBAI and TBHP (Scheme 1A).

On the other hand, as commercially available and stable alkyne derivatives, alkyl propiolates have been previously employed as alkyne substrate in CuAAC, which provides classical 1,4-disubstituted 1,2,3-triazoles (Scheme 1B).[16] However, in our previous work, we have disclosed that the electron deficient alkynes such as alkyl propiolates can be easily transformed into the enamines in the presence of a secondary amine, and thereafter enable the designation of various domino reactions via the reactive enamine intermediate.[17] Therefore, we envision that such enamine activation strategy can also be used to design the synthesis of divergent 1,2,3-triazoles under metal-free conditions.[18] Herein, we report for the first time the metal-free annulation reactions of alkyl propiolates with tosyl hydrazine

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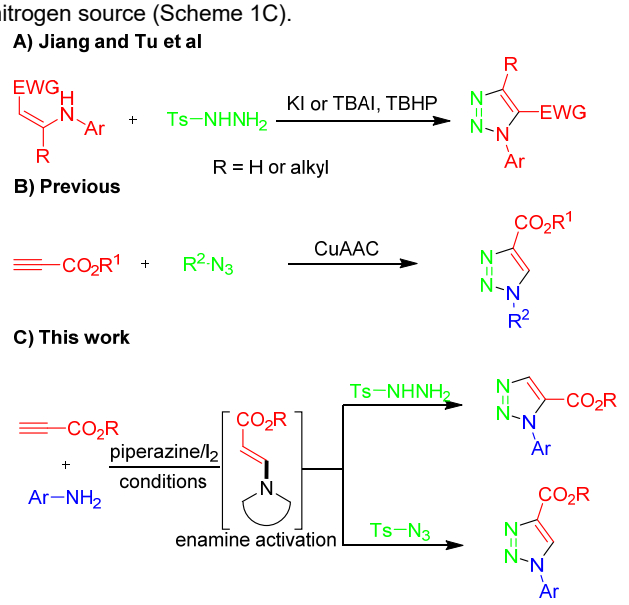
for the regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles. Notably, the switchable synthesis of 1,4-disubstituted 1,2,3-triazoles is also achieved by employing tosyl azide as the nitrogen source (Scheme 1C).

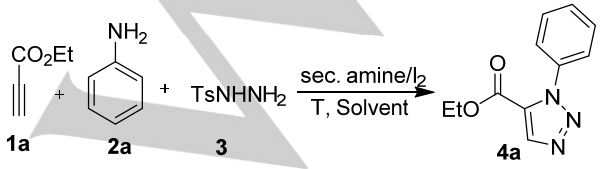


Scheme 1 Different synthetic strategies for 1,5-disubstituted and other 1,2,3-triazoles

Results and Discussion

At the beginning, the reaction of ethyl propiolate **1a**, aniline **2a** and tosyl hydrazine **3** was tentatively run in the presence of piperazine and molecular iodine in DMSO, which was found to provide the 1,5-disubstituted 1,2,3-triazole **4a** with moderate yield (entry 1, Table 1). Comparing with the parallel experiments employing different secondary amines such as morphorline, diethanolamine (DEA) and diehtylamine, piperazine was proved to be the best secondary amine in promoting the target reaction (entries 2-4, Table 1). The examination on the impact of reaction temperature indicated that 120 °C was preferred (entries 5-7, Table 1), and a control experiment without using secondary amine at this temperature did not provide product **4a** (entry 8, Table 1). Later on, the loading of piperazine and I_2 were varied, respectively, but no improved result was obtained (entries 9-13, Table 1). The requirement of relative high loading of piperazine could be ascribed to the partial deactivation of piperazine resulting from the in situ generated proton acid (see Scheme 2 for the proposed mechanism). In next step, this reaction was performed in various media with different polarity, which confirmed DMSO as the best medium (entries 14-18, Table 1).

Table 1 Optimization on the conditions providing 1,5-disubstituted 1,2,3-triazoles[a]

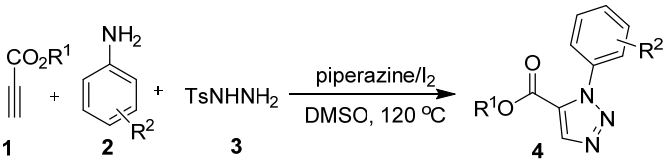


entry	sec. amine	temp. (°C)	solvent	yield (%)[b]
1	piperazine	110	DMSO	43
2	morpholine	110	DMSO	31
3	DEA	110	DMSO	trace
4	Et_2NH	110	DMSO	trace
5	piperazine	100	DMSO	31
6	piperazine	120	DMSO	62
7	piperazine	130	DMSO	56
8	-	120	DMSO	nr
9[c]	piperazine	120	DMSO	trace
10[d]	piperazine	120	DMSO	59
11[e]	piperazine	120	DMSO	nr
12[f]	piperazine	120	DMSO	54
13[g]	piperazine	120	DMSO	60
14	piperazine	120	DMF	28
15	piperazine	reflux	EtOH	trace
16	piperazine	120	ethyl lactate	nr
17	piperazine	reflux	H_2O	nr
18	piperazine	reflux	toluene	trace

[a] General conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), **3** (0.45 mmol), amine additive (0.15 mmol) and I_2 (0.24 mmol) in 2 mL of solvent stirred for 12 h. [b] Yield of isolated products based on **1a**. [c] 0.09 mmol piperazine was used. [d] 0.24 mmol piperazine was used. [e] No I_2 was employed. [f] 0.15 mmol I_2 was used. [g] 0.3 mmol I_2 was used.

To investigate the scope of the 1,5-disubstituted 1,2,3-triazole synthesis, the reactions employing different alkyl propiolates **1** and aryl amines **2** were then conducted. The results from this section were outlined in Table 2. According to the results, this method showed fine tolerance to both substrates. Anilines containing substitutions of different properties, such as alkyl, alkoxy, halogen and nitro in the *para*- site all participated the synthesis to give the expected products with moderate to good yields (**4b**, **4d**, **4g** and **4i**, Table 2). In addition, aniline substrates containing substituents in *ortho*- and *meta*-position were also well tolerated (**4c**, **4e**, **4f**, **4h** and **4j**, Table 2). On the other hand, varying the alkyl group in **1** was also allowed, and related products were given with satisfactory yields (**4k-4m**, Table 2). No notable effect of the substituent in either component **1** or **2** could be defined with the present data.

Table 2 Scope on the synthesis 1,5-disubstituted 1,2,3-triazoles[a]



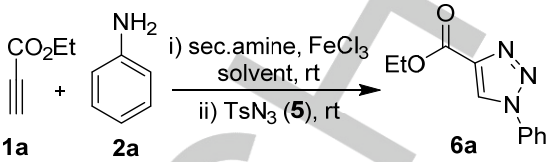
1 2 3 4

R^1	R^2	product	yield(%)[b]
Et	H	**4a**	62
Et	4-CH_3	**4b**	64
Et	2-CH_3	**4c**	61
Et	4-CH_3O	**4d**	58
Et	2-CH_3O	**4e**	54
Et	3-CH_3O	**4f**	61
Et	4-Br	**4g**	67
Et	3-Cl	**4h**	62
Et	4-Cl	**4i**	67
Et	3-NO_2	**4j**	71
Me	4-CH_3	**4k**	63
Me	4-Br	**4l**	70
Me	4-Cl	**4m**	64

[a] General conditions: propiolate **1** (0.3 mmol), primary amine **2** (0.3 mmol), tosyl hydrazine **3** (0.45 mmol), piperazine (0.15 mmol) and I_2 (0.24 mmol) in DMSO (2 mL) stirred at 120 °C for 12 h. [b] Yield of isolated products based on **1.**

Being inspired by this enamine activation-based synthesis of triazoles **4**, we envisaged that such activation pathway could also be utilized for the designation of a metal-free annulation providing 1,4-disubstituted 1,2,3-triazoles, which would thus complement the previous CuAAC in the synthesis of identical products (Scheme 1B). First, substrates **1a**, **2a** were subjected with piperazine and $FeCl_3$ since a Lewis acid was required for the transamination between the *in situ* generated tertiary enamine and the primary amine,[19] and 0.5 equiv piperazine was also employed in the reaction because of the co-presence of weakly acidic $FeCl_3$. The subsequent employment of tosyl azide **5** together with *t*-BuONa in one-pot operation enabled the formation of 1,4-disubstutituted 1,2,3-triazole **6a** with fair yield (entry 1, Table 3). In the screening of reaction medium, including AcOEt, MeCN, EtOH, 1,2-dichloroethane (DCE) and DMSO, MeCN turned out to be the most proper medium (entries 2-6, Table 3). Subsequently, different secondary amines and blank experiments were also conducted, and piperazine was found as the best candidate (entries 7-10, Table 3). On the other hand, among the tested base additives such as Et_3N, MeONa, KOH, *t*-BuOK and Na_2CO_3, *t*-BuONa was found as the most favorable promoter (entries 11-15, Table 3). No further improved result was found by varying the loading of *t*-BuONa (entries 16-18, Table 3).

Table 3 Optimization on the synthesis 1,4-disubstituted 1,2,3-triazole[a]



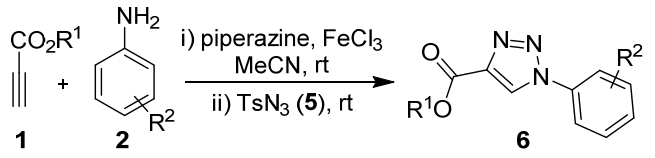
1a 2a 6a

entry	sec. amine	base additive	solvent	yield(%)[b]
1	piperazine	*t*-BuONa	acetone	57
2	piperazine	*t*-BuONa	AcOEt	57
3	piperazine	*t*-BuONa	CH_3CN	70
4	piperazine	*t*-BuONa	EtOH	trace
5	piperazine	*t*-BuONa	DCE	54
6	piperazine	*t*-BuONa	DMSO	trace
7	morpholine	*t*-BuONa	CH_3CN	54
8	DEA	*t*-BuONa	CH_3CN	52
9	Et_2NH	*t*-BuONa	CH_3CN	trace
10	-	*t*-BuONa	CH_3CN	trace
11	piperazine	Et_3N	CH_3CN	trace
12	piperazine	MeONa	CH_3CN	30
13	piperazine	KOH	CH_3CN	51
14	piperazine	*t*-BuOK	CH_3CN	55
15	piperazine	Na_2CO_3	CH_3CN	NR
16[c]	piperazine	*t*-BuONa	CH_3CN	trace
17[d]	piperazine	*t*-BuONa	CH_3CN	35
18[e]	piperazine	*t*-BuONa	CH_3CN	61

[a] General conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), secondary amine (0.15 mmol) and $FeCl_3$ (0.15 mmol) in 2 mL of solvent, stirred for 2 h at rt, then tosyl azide **5** (0.4 mmol) and base addtive (0.45 mmol), further stirred at rt for 2 h. [b] Yield of isolated products based on **1a**. [c] 0.15 mol *t*-BuONa was used. [d] 0.3 mol *t*-BuONa was used. [e] 0.6 mmol *t*-BuONa was used.

In the successive work investigating the synthetic scope, a class of different anilines were utilized to react with alkyl propiolates and tosyl azide. Correspondingly, the 1,4-disubstituted 1,2,3-triazles **6** containing various functional groups derived from anilines **2** were acquired with good to excellent yield (**6a-6l**, Table 4). The alkyl, alkoxyl, halogen and nitro in the aniline component were well suited the synthesis of target products and displayed no evident effect to the yield regardless their individual property. In addition, both ethyl and methyl propiolates could take part in the synthesis without observable distinction (**6m-6o**, Table 4), demonstrating the fine tolerance of the synthetic method to different alkyl propiolates.

Table 4 Scope on the synthesis of 1,4-disubstituted 1,2,3-triazoles[a]

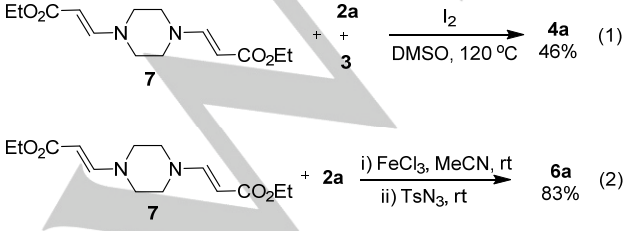


1 2 6

R^1	R^2	product	yield(%)[b]
Et	H	**6a**	70
Et	4-CH_3	**6b**	71
Et	2-CH_3	**6c**	67
Et	3-CH_3	**6d**	64
Et	4-CH_3O	**6e**	68
Et	3-CH_3O	**6f**	72
Et	4-Br	**6g**	79
Et	2-Cl	**6h**	73
Et	3-Cl	**6i**	76
Et	4-Cl	**6j**	77
Et	2,4-Me_2	**6k**	68
Et	3-NO_2	**6l**	81
Me	4-Br	**6m**	77
Me	3-Cl	**6n**	75
Me	3-CH_3	**6o**	69

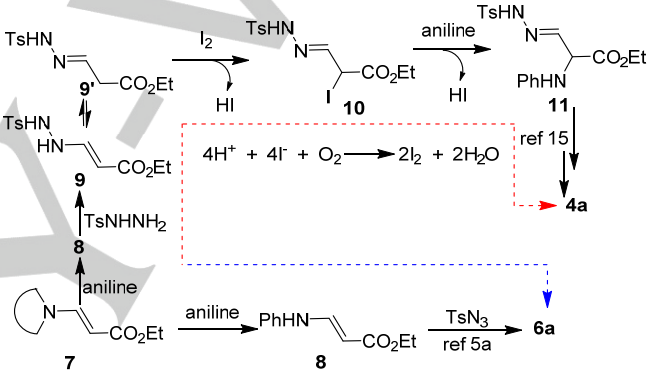
[a] General conditions: alkyl propiolate **1** (0.3 mmol), aniline **2** (0.3 mmol), piperazine (0.15 mmol) and $FeCl_3$ (0.15 mmol) in 2 mL of CH_3CN stirred for 2 h at rt. Then added Tosyl azide (0.4 mmol) and NaOtBu (0.45 mmol) stirred for 2 h; [b] Yield of isolated products based on **1**.

In previous study, we discovered that the alkyl propiolates can react fast with piperazine to provide enaminoester of type **7**,[17c] we then accordingly performed the control experiments by directly employing **7** for the potential synthesis of both **4** and **6**. Under the standard conditions without secondary amine, enaminoester **7** reacted with aniline **2a** and tosyl hydrazine **3** to provide product **4a** with 46% yield (Eq 1, Scheme 2). On the other hand, the reaction of **7**, **2a** and tosyl azide gave 1,2,3-triazole **6a** with 83% yield (Eq 2, Scheme 2). These results confirmed that the formation of enamine intermediate was the key step enabling the synthesis of these 1,2,3-triazoles.



Scheme 2 Control experiments

Correspondingly, the general reaction processes based on this enamine activation are proposed (Scheme 3). In the reactions producing 1,5-disubstituted 1,2,3-triazoles, the tertiary enamine intermediate **7** undergoes a transamination with aniline to give *NH*-enamine intermediate **8**. **8** reacts with tosyl hydrazine to provide intermediate **9**. By means of the isomeric form **9'**, an iodination reaction takes place on the acidic C(sp^3)-H bond to give intermediate **10** in the presence of iodine. Subsequently, the nucleophilic substitution of aniline to **10** could afford intermediate **11**. This intermediate undergoes similar transformations as proposed by Jiang et al[15] to provide product **4a**. On the other hand, in the reaction with tosyl azide, the formation of the *NH*-enaminoester **8** enables analogous transformations in previously reported [3+2] cycloaddition of *NH*-enaminone to provide the 1,4-disubstituted 1,2,3-triazoles **6a**.[5a] It is notable that the part of the in situ formed HI can be regenerated to molecular iodine under air atmosphere with heating, and thus promotes the completion of the reaction.[20]



Scheme 3 The proposed reaction mechanism

Conclusions

In conclusion, by making use of a key enamine activation resulting from the aza-Michael addition of secondary amine to alkyl propiolates, we successfully realized the first metal-free synthetic method toward 1,5-disubstituted 1,2,3-triazoles via the reaction of alkyl propiolates, primary amines and tosyl hydrazine. In addition, by altering tosyl hydrazine to tosyl azide, and modifying reaction conditions, the switchable synthesis of 1,4-disubstituted 1,2,3-triazoles has also been accomplished via metal-free triazole annulation. The results included herein disclose the distinctive new applications of the commercially available alkyl propiolates in the synthesis of divergent 1,2,3-triazoles.

Experimental Section

General procedure for the synthesis of 1,2,3-triazoles 4

In a 25 mL round bottom flask was successively charged with alkyl propiolate **1** (0.3 mmol), piperazine (0.15 mmol), primary amine **2** (0.3 mmol), tosyl hydrazine **3** (0.45mmol), I_2 (0.24 mmol) and DMSO (2mL).

The vessel was then stirred at 120 °C for 12 h. Upon completion (TLC), 5 mL water was added, and the resulting suspension was extracted with EA (3 × 8 mL). The organic layers were combined and dried overnight with anhydrous $MgSO_4$. After filtration, the solution was employed to reduced pressure to remove the solvent. The residue was subjected to flash silicon column chromatography to provide pure products by using mixed EA and petroleum ether (PE) as eluent (V_{PE} : V_{EA} = 10:1~6:1).

General procedure for the synthesis of 1,2,3-triazoles 6

In a 25 mL round bottom flask was charged with alkyl propiolate **1** (0.3 mmol) and piperazine (0.15 mmol), primary amine **2** (0.3 mmol), $FeCl_3$ (0.15 mmol) and MeCN (2mL). The resulting mixture was stirred at rt for 2 h. Tosyl azide **5** (0.4 mmol) and *t*-BuONa (0.45 mmol) were then added, and the vessel was further stirred for 2 h at rt. Upon completion (TLC), 5 mL water was added, and the resulting suspension was extracted with 3 × 8 mL ethyl acetate (EA). The organic layers were combined and dried overnight with anhydrous $MgSO_4$. After filtration, the solution was employed to reduced pressure to remove the solvent. The residue was subjected to flash silicon column chromatography to provide pure products by using the mixed EA and petroleum ether (PE) as eluent (V_{PE} : V_{EA} = 3:1~6:1).

Acknowledgements

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Keywords: alkyl propiolate • annulation • enamine activation • switchable • 1,2,3-triazoles

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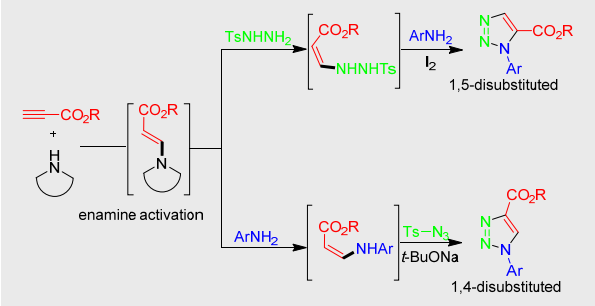

Shuo Cao, Yunyun Liu, Changfeng Hu, Chengping Wen and Jie-Ping Wan**

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Alkyl propiolates participated [3+2] annulation for the switchable synthesis of 1,5- and 1,4-disubstituted 1,2,3-triazoles containing ester side chain

Text for Table of Contents

The enamine activation on alkyl propiolates enables the switchable synthesis of 1,5- and 1,4-disubstituted 1,2,3-triazoles bearing ester side chain. The selective synthesis of 1,2,3-triazoles with different substitution styles are realized by employing different hydrogen atom sources of tosyl hydrazine and tosyl azide. The annulation of both 1,2,3-triazole rings takes place under transition metal-free condition, providing sustainable new routes in the synthesis of structurally divergent 1,2,3-triazole scaffolds.