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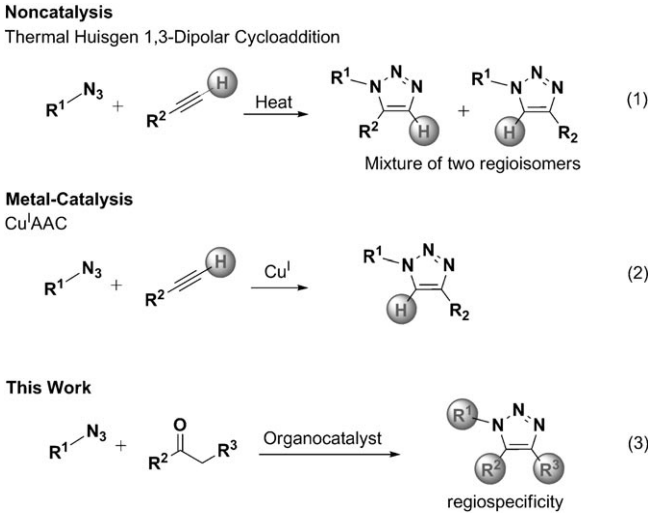
Organocatalytic Enamide–Azide Cycloaddition Reactions: Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-Triazoles

Lee Jin Tu Danence, Yaojun Gao, Maoguo Li, Yuan Huang, and Jian Wang*[a]

The emerging field of "click chemistry" has been developed as a unique approach for a set of powerful and selective reactions.[1] These powerful methods enable the chemist to rapidly construct chemical libraries under mild reaction conditions and using readily available reagents. As one of the most powerful members of "click" reactions, the Huisgen 1,3-dipolar cycloaddition has evolved into a common coupling procedure that is employed in numerous chemical reactions.[2] In particular, the Huisgen 1,3-dipolar cycloaddition reactions between azides and alkynes for the synthesis of 1,2,3-triazole compounds are considered as the "cream of the crop" of all "click" reactions.[2a,c]



Fused and nonfused 1,2,3-triazoles have been broadly utilized as photostabilizers and inhibitors.[3] Additionally, they are biologically active compounds in agrochemical research and also in medicinal chemistry.[4] A number of methods have thus far been reported to prepare *N*-substituted 1,2,3-triazoles, among which the cyclization of triazenes,[5] the synthesis of triazoles by Wolff,[6] and the cyclization of α-diazoamides.[7] However, most of these methods are not modular and require a multi-step synthesis for the precursors. Actually, the synthesis of 1,2,3-triazoles by thermal 1,3-dipolar cycloadditions [Eq. (1)] was discovered by the research group of Michael at the end of the 19th century[8a] and has been significantly developed by the research group of Huisgen in the 1960s.[8b,c] However, because of the high activation energy (ca. 24–26 kcal mol^{-1}),[9] these cycloadditions are usually very slow even at elevated temperature (80–120 °C, 12–24 h) and are likely to generate mixtures of regioisomers. The relatively poor regioselectivity of the Huisgen 1,3-dipolar cycloaddition has significantly limited the extensive utilization of this strategy. Meanwhile, the copper(I)-catalyzed Huisgen 1,3-dipolar cycloadditions of azides and alkynes (CuAAC) have been discovered and became one of the most straightforward and powerful approaches to prepare 1,5-disubstituted 1,2,3-triazoles [Eq. (2)].[4b,10] Recently, Fokin and co-workers have reported a copper(I)-catalyzed reaction for the preparation of 1,4,5-disubstituted 1,2,3-triazoles.[14] This reactions, because of the near perfect chemoselectivity and high thermodynamic driving force, is generally well-suited for click chemistry endeavors. However, the presence of the transition metal may cause copper-induced degradation of viruses or oligonucleotide strands in biological system.[11] Additionally, copper ions are potentially toxic for living organisms. Notably, the reactions are only suited for terminal alkynes [Eq. (2)]. Therefore, this limitation largely restricts the diverse application of this strategy in the preparation of 1,2,3-triazoles. In brief, the advent of novel methods that are devoid of these deficiencies would be of great value and particularly necessary to the synthetic community.

Herein, we report the development of the first organocatalytic method for the cycloaddition reaction of azides with enamine[12] to produce 1,4,5-trisubstituted-1,2,3-triazoles [Eq. (3)]. Some noteworthy attributes of this reaction include 1) simple structure of the catalyst, 2) high efficiency (high yields and short reaction time in most cases), 3) mildness (nonmetal and mild temperature), 4) regiospecificity (complete exclusion of regioisomers), 5) complexity (three substituents), and 6) functional-group tolerance (e.g., ketones, esters, nitrile, trifluoromethane, halogen, and hydroxyl groups).

To test our hypothesis, we initially explored the reaction of phenyl azide (**1a**) with ethyl acetoacetate (**2a**), in the

[a] L. J. T. Danence, Dr. Y. Gao, Dr. M. Li, Y. Huang, Prof. Dr. J. Wang
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
Fax: (+65) 6516-1691
E-mail: chmwangj@nus.edu.sg

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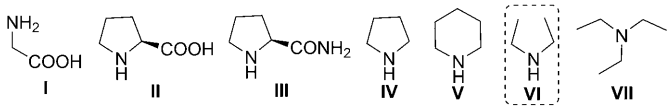
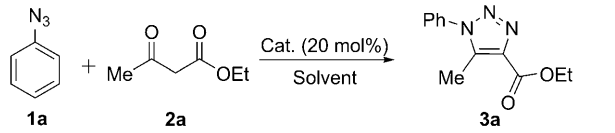


Scheme 1. Tested small organic molecules.

presence of the primary α-amino acid glycine (**I**; Scheme 1) and of the secondary α-amino acid, L-proline (**II**, Scheme 1). With this method, we obtained none of the desired 1,4,5-trisubstituted-1,2,3-triazoles (yield lower than 5 %; Table 1, entries 1 and 2). Nevertheless, a temperature increase (to 50 °C), resulted in trace amount of desired product (10 %; Table 1, entry 3). Once the temperature reached 70 °C, the reaction yield was slightly improved (24 %; Table 1, entry 4). A further increase in temperature and of the amount of phenyl azide (**1a**) had only limited effect on reaction yield (22–32 %, Table 1, entries 5–7). Later on, we examined the carboxylic acid-free catalysts **III** and **IV** (Scheme 1). Interestingly, the less bulky catalyst pyrrolidine (**IV**) afforded a 62 % yield (Table 1, entry 9). Then we examined the six-member ring piperidine (**V**) and acyclic diethyl amine catalyst **VI** (Scheme 1). It was noted that the acyclic secondary amine catalyst is essential to this reaction and leads to a higher reaction yield in a shorter time (92 %, 24 h; Table 1, entry 11). Lowering the ratio of **1a** (from 3 equiv to 1.5 equiv) did not affect the reaction rate and yield (91 %, 24 h; Table 1, entry 12). Further optimization of the catalyst loading showed that even 5 mol % of catalyst **VI** can also efficiently catalyze the reaction (90 %, 48 h; Table 1, entry 14,). In contrast to other catalysts, the tertiary amine catalyst **VII** resulted much less effective in this case (15 %, 48 h; Table 1, entry 18). Moreover, the choice of solvent was critical, in that the use of *N*,*N*-dimethylformamide (DMF), MeOH, or toluene has led to significantly lower yields (yield lower than 32 %; Table 1, entries 15–17).

The compatibility of of several substrates **2** is presented in Table 2. β-keto esters were successfully introduced to participate in the "click" reaction under the current catalytic system (Table 2, entries 1–4). High yields were achieved in 48 h (90–92 %; Table 2, entries 1–4). In the case of β-keto ester containing a phenyl group, a higher catalyst loading was required (**VI** (10 mol %); Table 2, entry 3). Another type of interesting substrates, 1,3-diketones, have also been employed in this reaction and provided high to excellent yields (88–94 %, 48 h; Table 2, entries 5–7). Most surprisingly, ketones with an electron-withdrawing group in the α-position efficiently reacted with azides to generate 1,2,3-triazoles (80–99 %, 1–24 h; Table 2, entries 9–20). Several substituted phenyl azides containing electron-donating groups (methyl, isopropyl, and methoxyl) and electron-withdrawing groups (halogen, trifluoromethyl, and nitro groups), were all compatible with this transformation under the optimal reaction conditions (87–99 %, 1–24 h; Table 2, entries 10–19). In

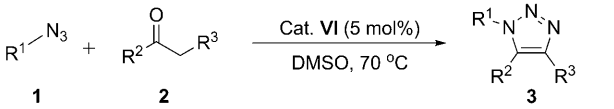
Table 1. Optimization of the reaction conditions.[a]



Entry	Cat.	T [°C]	t [h]	Yield [%][e]
1	**I**	RT[i]	48	<5
2	**II**	RT[i]	120	<5
3	**II**	50	120	10
4	**II**	70	48	24
5	**II**	100	48	22
6[b]	**II**	70	48	31
7[c]	**II**	70	48	32
8[c]	**III**	70	48	25
9[c]	**IV**	70	48	62
10[c]	**V**	70	48	62
11[c]	**VI**	70	24	92
12[d]	**VI**	70	24	91
13[d]	**VI** (10 mol %)	70	36	91
14[d]	**VI (5 mol %)**	**70**	**48**	**90**
15[f]	**VI**	70	24	23
16[g]	**VI**	70	48	32
17[h]	**VI**	70	36	<5
18[c]	**VII**	70	48	15

[a] Unless otherwise noted, the reaction conditions are: 0.5 M in DMSO, **1a**/**2a** (1:1.3). [b] 0.5 M in DMSO, **1a**/**2a** (3:1). [c] 1.0 M in DMSO, **1a**/**2a** (3:1). [d] 1.0 M in DMSO, **1a**/**2a** (1.5:1). [e] Yield of isolated product **3a**. [f] DMF as solvent. [g] Methanol as solvent. [h] Toluene as solvent. [i] RT. DMSO = dimethyl sulfoxide.

Table 2. Scope of substrates.[a]

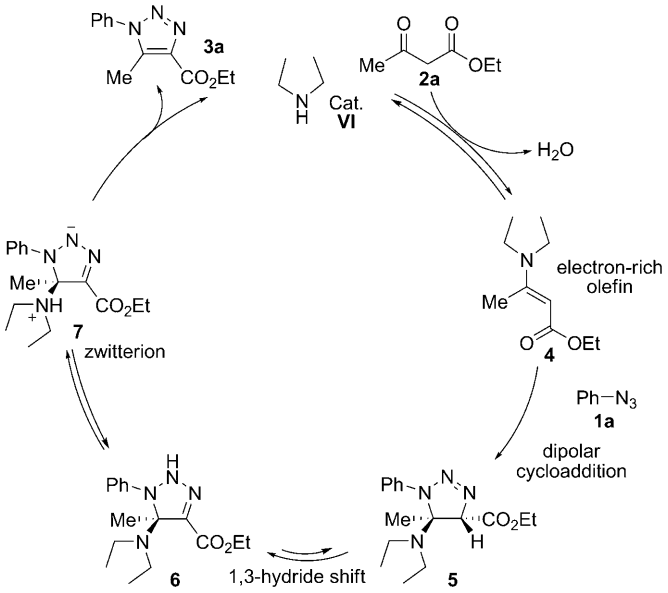


Entry	R^1	R^2	R^3	Product	t [h]	Yield [%][b]
1	Ph	Me	COOEt	**3a**	48	90
2	Ph	Et	COOEt	**3b**	48	92
3[c]	Ph	Ph	COOEt	**3c**	48	90
4	Ph	CF_3	COOEt	**3d**	24	92
5	Ph	CF_3	COPh	**3e**	48	88
6	Ph	Me	COMe	**3f**	48	94
7	Ph	Ph	COPh	**3g**	48	88
8	4-ClC_6H_4	Me	COOEt	**3h**	48	95
9	Ph	Ph	CN	**3i**	12	92
10	4-ClC_6H_4	Ph	CN	**3j**	6	96
11	3-ClC_6H_4	Ph	CN	**3k**	6	94
12	3-$CF_3C_6H_4$	Ph	CN	**3l**	1	91
13	4-$CF_3C_6H_4$	Ph	CN	**3m**	1	99
14	4-$NO_2C_6H_4$	Ph	CN	**3n**	1	94
15	3-Me,4-ClC_6H_3	Ph	CN	**3o**	6	94
16	4-$MeOC_6H_4$	Ph	CN	**3p**	24	87
17	3-OHC_6H_4	Ph	CN	**3q**	12	98
18	3,5-$Me_2C_6H_3$	Ph	CN	**3r**	12	91
19	4-*i*PrC_6H_4	Ph	CN	**3s**	12	95
20[c]	$PhCH_2$	Ph	CN	**3t**	24	80

[a] Unless otherwise noted, the reaction conditions are: 1.0 M in DMSO, **1a**/**2a** (1.5:1). [b] Yield of isolated product **3**. [c] Catalyst loading (10 mol %).

general, electron-withdrawing groups provided the desired products in a shorter time (91–99%, 1–6 h; Table 2, entries 10–15). In contrast to electron-withdrawing groups, the electron-donating groups required a relative longer time, but without affecting the yield (87–98%, 12–24 h; Table 2, entries 16–19). Appreciatively, alkyl azide was also used in the reaction and led to a good yield but requested 10 mol% of catalyst **VI** (80%, 24 h; Table 2, entry 20). The regioselectivity of product **3g** was determined by using single crystal X-ray diffraction analysis.[13]

Although the reaction mechanism is not clear at this stage, it is believed that this transformation is initiated by the formation of enamine.[12] As shown in Scheme 2, we proposed a catalytic cycle. The first step is most likely the condensation of the catalyst **VI** and the β-ketoester (**2a**) to generate an iminium ion that then tautomerizes into active enamine **4**. Enamine **4** acts as the electron-rich olefinic partner, and reacts with the aromatic azide **1a** in a Huisgen cycloaddition to form triazoline **5** with complete regioselectivity. Instead of an enamine-type cycloaddition, another competing pathway involves the catalyst functioning as a base and forming enolate. Enolates can potentially form adducts with azides. However, the results of the catalyst screening revealed that the process catalyzed by an organic base is significantly slow (15%; Table 1, entry 18), and thus this pathway represents only a minor contribution. Next, there would be an elimination step to assist the formation of the final product **3a**. In this process, we propose that such elimination might be derived from a zwitterionic intermediate (**7**), whose negative charge is stabilized by both resonance and π-network delocalization. Upon this mechanism, the nature of the electron-withdrawing group is essential in the catalytic cycle. It is responsible to create a balance in which the enamine remains reactive in the Huisgen cycloaddition and yet stabilizes the formation of the zwitterion and allows the catalytic turnover. The catalyst is the most important component and acts as an electron-donating group to facilitate complete regioselectivity, to improve the reaction rate, and additionally act as a leaving group upon protonation. Based on our experimental evidence, the rate-determining step is most probably the dipolar cycloaddition because the catalytic rates have a strong dependence on the electronic nature of the azide. The enamine (**4**) was observed by LCMS, thus suggesting that the catalytic cycle accumulates at this stage. No triazoline intermediate (**6**) was detected. In addition, intermediate zwitterion (**7**) is potentially indirectly derived from the cycloaddition adduct (**5**). Conversion of **5** into the proposed intermediate **6** is a formally 1,3-hydride shift.



Scheme 2. Proposed catalytic cycle.

In summary, we have developed the first regioselective organocatalytic enamide–azide cycloaddition reaction in the presence of a metal-free small organic molecule, diethyl amine. The reaction is applicable to a variety of azides that tolerated aryl and alkyl groups as substituents. A number of aryl ketones and ketoesters have been employed to additionally present the versatility of this method. As a result, multi-substituted 1,2,3-triazoles were obtained in high to excellent yields (80–99%). Significantly, none of the regioisomers were formed. Moreover, this catalytic system also tolerated many synthetic useful functional groups, such as nitrile, ketone, and ester functional groups which might be manipulated for accessing more sophisticated heterocyclic compounds. Further synthetic application of the catalytic system to other new reactions is under way in our laboratory.

Experimental Section

General procedure: Phenyl azide **1a** (50 mg, 0.42 mmol) was dissolved in DMSO (0.28 mL) in a small vial fitted with a screw cap. First the β-functionalized ketone (37 mg, 0.28 mmol) and then the catalyst diethylamine (1 mg, 0.014 mmol) were added to this reaction mixture. The reaction mixture was stirred at 70°C in a silicon oil bath and the reaction was monitored through thin-layer chromatography. Once the reaction reached completion, the crude product was purified by column chromatography on silica gel (hexane/EtOAc = 5:1) to afford the desired product **3a** (58 mg, 90% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.51 (m, 3H), 7.42–7.39 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.55 (s, 3H), 1.40 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 139.4, 137.3, 136.0, 130.7, 130.3, 126.0, 61.6, 15.0, 10.6 ppm; HRMS (EI) calcd for $C_{12}H_{13}N_3O_2$: 231.1008 $[M+H]^+$, found: 231.1008.

Acknowledgements

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[13] CCDC-790341 (**3g**) contains the supplementary crystallographic data for this paper. 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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