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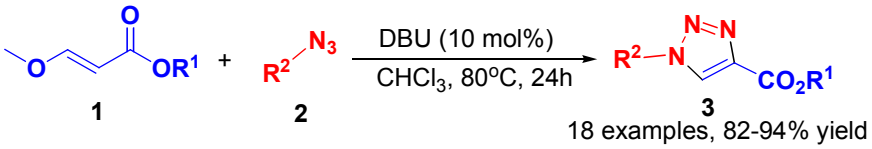

Direct Access to 1,4-Disubstituted 1,2,3-Triazole through Organocatalytic 1,3-Dipolar Cycloaddition Reaction of α, β-Unsaturated Ester with Azide

DBU-catalyzed organocatalytic 1,3-dipolar cycloaddition reactions of α, β-unsaturated esters with azides have been developed. This strategy could generate 1,4-disubstituted 1,2,3-triazoles in high yields and high level of regioselectivities. It is demonstrated that some of these products can be transformed into pharmaceutical important agents.

Direct Access to 1,4-Disubstituted 1,2,3-Triazole through Organocatalytic 1,3-Dipolar Cycloaddition Reaction of α, β-Unsaturated Ester with Azide

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DBU-catalyzed organocatalytic 1,3-dipolar cycloaddition reactions of α, β-unsaturated esters with azides have been developed. This strategy could generate 1,4-disubstituted 1,2,3-triazoles in high yields and high level of regioselectivities. It is demonstrated that some of these products can be transformed into pharmaceutical important agents.

The 1,2,3-triazole core is a privileged scaffold that is featured in a abundant number of bioactive molecules and they have exhibited considerably biological activities.[1] As showed in Fig 1, Tazobactam has been identified as β-lactum antibiotic tazobactum.[2] Cefatrizine could exhibit antibacterial activity.[3] Rufinamide is an anticonvulsant drug developed in 2004 by Novartis pharmaceutical company.[4] It is normally used to treat Lennox-Gastaut syndrome and other disorders. 1,2,3-Triazole moieties can also behave as an antimicrobial agent.[5]

The widely used protocol to synthesize 1,2,3-triazole is the Huisgen 1,3-dipolar cycloaddition.[6] However, this method requires high temperatures and proceed with limited regioselectivity. In recent years, chemists have developed metal-catalyzed (copper,[7] ruthenium,[8] iridium[9]) azide–terminal alkyne cycloaddition (AAC). Although this strategy could provide a mild and efficient synthesis of 1,4-disubstituted 1,2,3-triazoles, the metal ions are potentially toxic for living organisms and could induce degradation of viruses.[10] In recent years, Ramachary,[11] Bressy[12] and our group[13] independently reported the organocatalytic regioselective synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through *in situ* enamine intermediate. This methodology provides a novel pathway to generate 1,2,3-triazoles in high yields and regioselectivities. However, these approaches are restricted to ketone or cyclic enone substrates and can only produce 1,4,5-trisubstituted 1,2,3-triazoles. Inspired by the

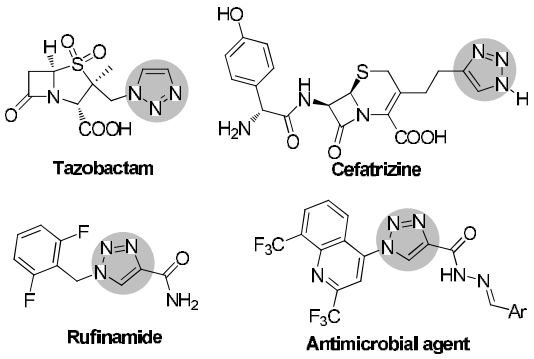


Fig 1: Examples of important 1,2,3-triazoles.

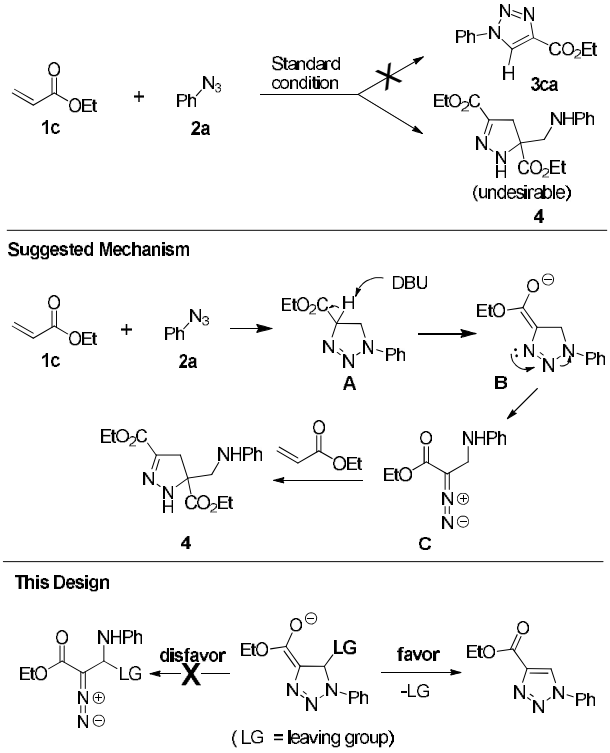


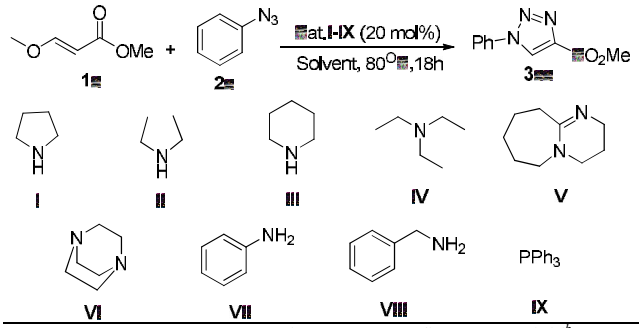
Fig 2: Exploration of 1,4-Disubstituted 1,2,3-Triazoles.

success of the 1,4,5-trisubstituted 1,2,3-triazole synthesis,[14] our efforts are moved to another highly important class of 1,4-disubstituted 1,2,3-triazoles. As exemplified in Figure 1**,** rufinamide and antimicrobial agent have been identified as very important pharmaceuticals. In the beginning, we speculate that the reaction of ethyl acrylate **1c** with azide **2a** would give the 1,4-disubstituted 1,2,3-triazole **3ca** under standard conditions. Surprisingly, the product arising from this reaction was undesirable pyrazoline **4** (Fig 2). In this transformation (Fig 2), the postulated mechanism suggested that the cycloaddition intermediate **A** of acrylate **1c** and azide **2a** would undergo an arrangement to generate the diazoester intermediate **C**,[15] which further react with second acrylate **1c** to finally form undesirable pyrazoline **4**. In order to achieve the triazole structure, we behave to circumvent the ring opening step to avoid the conversio between **B** and **C**. After being confronted with this challenge, a thermodynamic control strategy has been taken to solve above problem. As indicated in Figure 2 (this design), we can bear a suitable leaving group (LG) on C5 position, which probably stimulates the competitive elimination reaction to eventuall induce the reaction to directly construct the desire product 1,4

disubstituted 1,2,3-triazoles driven by the force of electron delocalization and aromaticity.

We began our initial investigation by employing active α, β-unsaturated esters **1a** and phenyl azide **2a** in the precence of various amine or phosphine catalysts. The screening results indicated that tertiary amine **V** was the best catalyst for this reaction (Table 1, entry 5). Other amine catalysts (**I-IV, VI-VIII**) can also give the desired product but the yields were not very high (Table 1, entries 1-4, 6-8). While if we utilized triphenylphosphine **IX** as the catalyst, no desired product was obtained (Table 1, entry 9). After identifying the catalyst **V** as the best catalyst, we next further screened the reaction mediums to improve yield. Further experimental results revealed that the solvent was one of the crucial factors for this reaction. The efficency of reaction exhibited great difference between different solvents. For instance, when we conducted the reaction in DMF or DMA, the solvent gave the positive influence on the reaction and the yields of desired product **3aa** were improved to 61% and 63% (Table 1, entries 10-11). However, when we changed the solvents as methanol, toluene and CH_3CN, only moderate yields (42%, 53% and 56%) were observed (Table 1, entries 12-14). To our delight, when we utilized THF as the reaction medium, the yield would increase to 89% remarkably (Table 1, entry 15). Further experiment revealed that $CHCl_3$ was the best solvent for this transformation. When we conducted the reaction using $CHCl_3$ as the solvent, the excellent yield (93%) was observed (Table 1, entry 16). Further extensive screening of temperature indicated that decreased T ^oC led to a slow conversion (entry 17, 50 ^oC, 53%, 48 h). It is worth to note that lowering the catalyst loading to 10 mol% resulted in a longer reaction time (24h) with the yield of product **3aa** maintained (Table 1, entry 18). Further reducing the catalyst loading to 5 mol% would reduce the decrease of yield to 82% after 48h (Table 1, entry 19). Finally, optimization of reaction parameters led us to identify DBU as a superb catalyst and $CHCl_3$ as an ideal medium for the desired transformation to give adduct **3aa** in essentially high yield. Moreover, adduct **3aa** could be obtained in absolute regioselectivity, which may be contributed to the energy coincidence of frontier molecular orbital between α, β-unsaturated esters **1a** and phenyl azide **2a**.

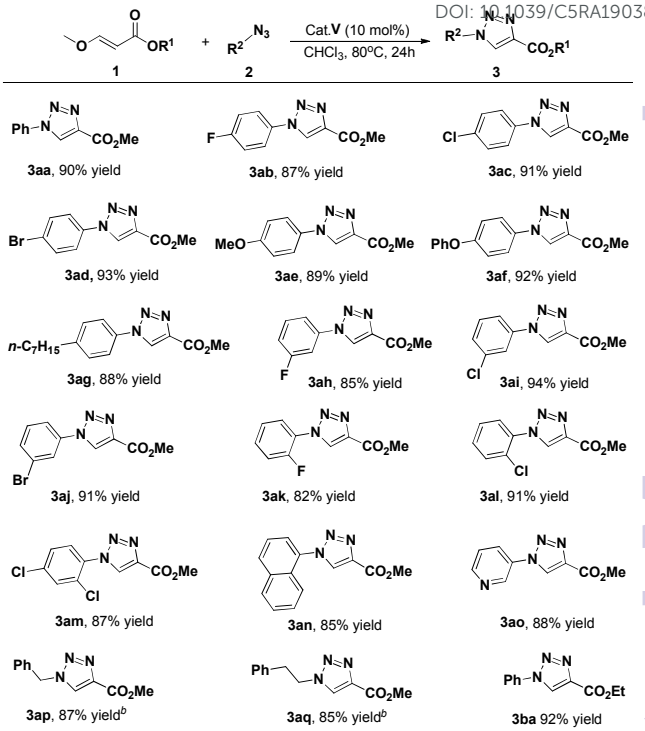
Table 1: Optimization of the Reaction Conditions.[a]



Entry	Cat.	Solvent	t/h	Yield[b](%)
1	**I**	DMSO	18	38
2	**II**	DMSO	18	41
3	**III**	DMSO	18	45
4	**IV**	DMSO	18	37
5	**V**	DMSO	18	54
6	**VI**	DMSO	18	21
7	**VII**	DMSO	18	31
8	**VIII**	DMSO	18	28
9	**IX**	DMSO	18	<5
10	**V**	DMF	18	61
11	**V**	DMA	18	63
12	**V**	MeOH	18	42
13	**V**	Toluene	18	53
14	**V**	CH_3CN	18	56
15	**V**	THF	18	89
16	**V**	$CHCl_3$	18	93
17[c]	**V**	$CHCl_3$	48	53
18[d]	**V**	$CHCl_3$	**24**	**90**
19[e]	**V**	$CHCl_3$	48	82

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **2a** (0.20 mmol) and catalyst (20 mol%) in the solvent (0.3 mL) was stirred at 80 ^oC for 18h. [b] Isolated yield. [c] The reaction was conducted at 50 ^oC. [d] 10 mol% catalyst used. [e] 5 mol% catalyst used.

Table 2: Synthesis of 1,4-Disubstituted 1,2,3-Triazoles.[a]

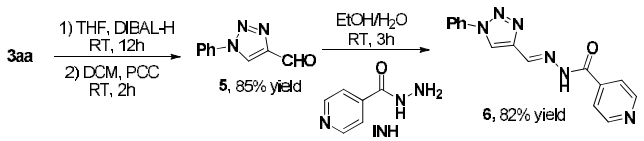


[a] Reaction conditions: A mixture of **1** (0.10 mmol), **2** (0.20 mmol) and **V** (10 mol%) in $CHCl_3$ (0.3 mL) was stirred at 80 ^oC for 24h. [b] neat, 80 ^oC, 48 h.

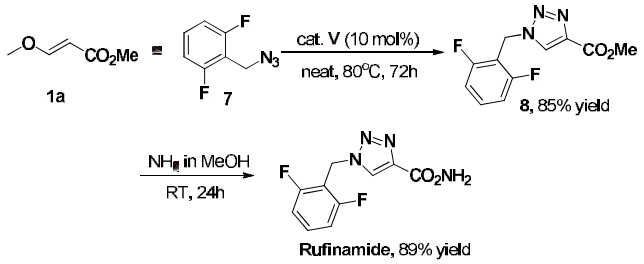
With the optimized conditions in hand, the generality of substrate scope of 1,4-disubstituted 1,2,3-triazole synthesis was explored. As shown in table 2, a diverse set of azides involves in the transformation to produce the 1,4-disubstituted 1,2,3-triazoles in high to excellent yields. After obtaining the product **3aa** in 90% yield, various aryl azides, regardless of electron-donating groups or electron-withdrawing groups in *o*, *m*, *p*-position, all led to the desire products **3aa**–**am** (Table 2, 82–94%). To our delight, aryl azides, which contained naphthalene ring and heterocyclic rings, could be also general for this transformation to afford the desired products **3an** and **3ao** in 85% and 88% yields respectively. It is worth to note that alkyl azides also afforded expected

adducts in high chemical yields, but under neat condition (**3ap** and **3aq**, 87% and 85%, respectively). The configuration of the products was assigned based on single-crystal X-ray analysis of **3ad**.[16]

To further demonstrate the utility of this methodology, we have performed a late-stage modification on several triazole analogues. As shown in scheme 1, isonicotinoyl hydrazide **6** exhibited antimycobacterial activity against mycobacterium tuberculosis H37Rv Strain.[17] DIBAL-H reduction of **3aa** followed with an efficient PCC oxidation to yield the key intermediate aldehyde **5** (85% overall yield, 2 steps). Then aldehyde **5** reacted with isonicotinohydrazide (INH) at room temperature for 3 h to yield the desired isonicotinoyl hydrazide **6** in 82% yield.

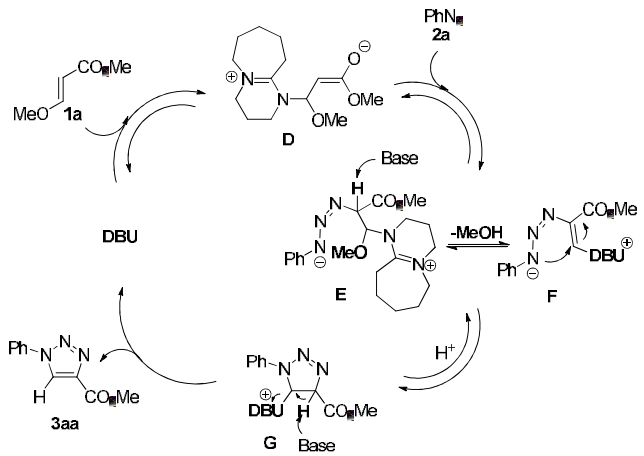


Scheme 1. Synthesis of Isonicotinoyl Hydrazide **6**.



Scheme 2. Synthesis of Rufinamide.

After accomplishing the above synthesis, we embarked on the total synthesis of rufinamide, an anticonvulsant drug. The synthetic route to rufinamide started with the DBU–catalyzed [3+2] reaction (Scheme 2). Azide **7** reacted with α, β-unsaturated ester **1a** to give triazole **8** in 85% yield (approximately 80°C and 72 h). Next, ammonolysis of triazole **8** gave the corresponding rufinamide (89% yield, rt, 24 h).



Scheme 3. Plausible mechanism.

The details of the postulated mechanism are illustrated in scheme 3. **1a** bearing a LG group (MeO) was chosen to demonstrate the reaction process. DBU would firstly react with **1a** to form zwitterion **D**. Next addition of zwitterion intermediate **D** to phenyl azide **2a** forms intermediate **E**. Elimination of **E** allows to produce intermediate **F**, which undergoes a cascade sequence of electrocyclization and subsequent elimination to finally generate the cycloaddition product **3aa**.

In summary, a DBU-catalyzed organocatalytic 1,3-dipolar cycloaddition of active α, β-unsaturated ester to azide has been developed. This methodology provides a straight-forward pathway to generate 1,4-disubstituted 1,2,3-triazoles, which exhibit considerably biological activities, in high yields and regioselectivities. Compared with the metal-based catalytic AAC systems, this methodology makes an important complementary. Notably, the reaction proceeds efficiently by a simple and cheap catalyst. Considering the ready availability of the starting materials (α, β-unsaturated esters) and the operational simplicity, we believe that this work will draw more research interests in organocatalytic synthesis of substituted 1,2,3-triazole and other biologically active heterocycles. Such studies are actively under way in our laboratory, and more results will be reported in due course.

Notes and references

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General procedure for 1,3-dipolar cycloaddtions of α,β-unsaturated esters with azides: To a solution of $CHCl_3$ (0.3 mL) were added α,β-unsaturated esters **1** (0.10 mmol), azides **2** (0.20 mmol) and catalyst **V** (0.01 mmol). The reaction mixture was stirred at 80 °C for 24h and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product **3**.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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16 CCDC 1021699 (**3ad**) 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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