DOI: 10.1002/chem.200801325

Amino Acid-Catalyzed Cascade [3+2]-Cycloaddition/Hydrolysis Reactions Based on the Push–Pull Dienamine Platform: Synthesis of Highly Functionalized *N*H-1,2,3-Triazoles

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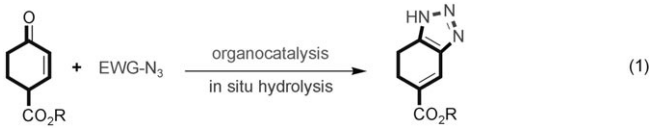
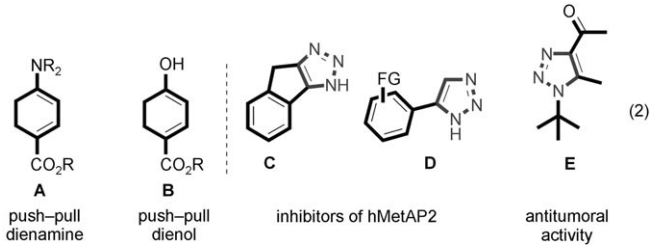
1,2,3-Triazoles are an important class of heterocycles, which display very large spectrum of biological activities and are widely used as pharmaceuticals and agrochemicals.[1] Compounds containing 1,2,3-triazoles have also found industrial applications as corrosion inhibitors, lubricants, dyes, and photostabilizers.[1] As such, the development of new and more general methods for their preparation is of significant interest.[2] The conventional method to triazoles is the Huisgen 1,3-dipolar cycloaddition of alkynes with azides. Recent discovery of the novel technology of Cu^{I}-catalyzed [3+2]-cycloaddition reactions of terminal alkynes with organic azides provided a general route to a variety of 1,4-disubstituted 1,2,3-triazoles in good yields, and it has become a paradigm of a "click chemistry" reaction.[3] The advent of click reaction technology triggered a burst of activity in the synthesis of a huge variety of differently substituted 1,2,3-triazoles as in vitro and in vivo conditions.[4]



(1)



(2)

Recently, the copper-catalyzed azide–alkyne click reaction has proven extremely valuable for attaching small molecular probes to various biomolecules in a test tube or on immobilized cells.[5] However, its use in the labeling of biomolecule in living cells or organisms is not feasible because the reaction conditions require a cytotoxic copper catalyst.[5]

As part of our program to engineer direct organocatalytic cascade reactions,[6] herein we have report the discovery of a copper-free, novel and green technology for the synthesis of highly substituted α-diazo compounds and *N*H-1,2,3-triazoles using organocatalytic cascade enamine amination/elimination (EA/E) and [3+2]-cycloaddition/hydrolysis ([3+2]-CA/H) reactions from commercially available activated enones, azides and amines/amino acid [Eq. (1)]. In this communication, we report to the best of knowledge for the first time an organocatalytic approach for the synthesis of *N*H-1,2,3-triazole products.

Over the last few years, we have been interested in amine-mediated in situ generation and application of novel push–pull dienamines/push–pull dienols [**A** and **B**, see Eq. (2)] in cascade reactions from Hagemann's esters with nitrogen-containing species for the formation of C–N bonds.[7] During our search for new coupling species for such processes, we decided to explore the potential ability of organic azides to participate in an amine/amino acid-catalyzed coupling reaction. We expected that the coupling of an organic azide with in situ generated push–pull dienamines would lead to protected 1,2,3-triazoles. However, protected 1,2,3-triazoles were not detected, but instead *N*H-1,2,3-triazoles were obtained under the standard reaction conditions. This unexpected result of the cascade reaction represents a novel methodology for the preparation of *N*H-1,2,3-triazoles and a new reactivity for amino acid catalysts. Herein, we report our findings regarding these new amino acid-catalyzed cascade reactions.

We initiated our preliminary studies of the cascade EA/E or [3+2]-CA/H reactions by screening a number of both

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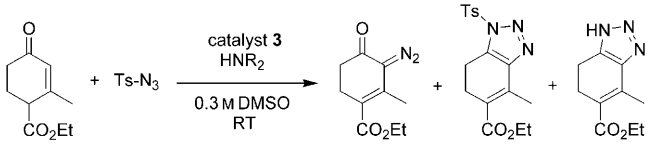
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801325.

known and new organocatalysts for the amination of Hagemann's ester **1a** by 0.5 to 1.0 equivalents of *p*-toluenesulfonyl azide (TsN_3) **2a**; some representative results are shown in Table 1. Interestingly, reaction of **1a** with 1.0 equiv of **2a** in DMSO under 20 mol% of glycine (**3a**) catalysis furnished the cascade [3+2]-CA/H product *N*H-1,2,3-triazole **6aa** as single product with only 25% yield (Table 1, entry 1). The same reaction with 20 mol% of L-proline (**3b**) catalysis also furnished the *N*H-1,2,3-triazole **6aa** as single product with 55% yield (Table 1, entry 2). Interestingly, reaction of **1a** with 1.0 equiv of **2a** under diamine **3c** catalysis generated the cascade EA/E diazo-product **4aa** with 83% yield in DMSO and there are no products from the cascade [3+2]-CA/H sequence (Table 1, entry 3). Secondary amines such as piperidine (**3d**), morpholine (**3e**), and pyrrolidine (**3f**) catalysts also furnished the cascade EA/E diazo-product **4aa** with good yields in DMSO solvent (entries 4, 5 and 6). Primary amine, benzylamine (**3g**) also catalyzed the formation of cascade diazo-product **4aa** in very good yield (entries 7–9). Benzylamine-catalyzed cascade EA/E reactions are solvent-dependent reactions, which work well in aprotic polar solvents, such as DMSO, DMF and NMP: only <15% conversion is observed in other solvents, such as EtOH, CH_3CN, $CHCl_3$, THF, H_2O and [bmim]BF_4 (Table 1, entries 11–12). Addition of 20 mol% of simple tertiary amines, such as Et_3N (**3h**), $Me_2NCH_2CH_2OH$ (**3i**), DBU (**3j**), DABCO (**3k**) and DMAP (**3l**) as the catalyst in DMSO at 25°C for 1.5 h furnished the cascade EA/E diazo-product **4aa** as single compound in 65–77% yields as shown in Table 1, entries 13–17. We envisioned the optimized condition to be 25°C in DMSO under 20–40 mol% benzylamine (**3g**) catalysis to furnish the highly substituted diazo-product **4aa** in 83–90% yield (Table 1, entries 7–9).

Reaction of **1a** with **2a** under amino acid **3b** catalysis furnished the interesting [3+2]-CA/H cascade product **6aa** as single product (Table 1, entry 2). To improve the reaction yield, we screened a number of reaction conditions for the coupling of Hagemann's ester **1a** by 0.5 to 1.0 equiv of **2a** under **3b** catalysis; some representative results are shown in Table 2. Reaction of **1a** with 1.0 equiv **2a** in EtOH under 20 mol% **3b** catalysis furnished **6aa** as single product with only 30% yield (Table 2, entry 1). Interestingly, same reaction in MeOH furnished the unhydrolyzed 1,2,3-triazole **5aa** as single product with 35% yield (Table 2, entry 2). Reaction of **1a** with 1.0 equiv of **2a** under **3b** catalysis in DMSO at 70°C for 5 h furnished **6aa** in 65% yield (Table 2, entry 4). Increasing the catalyst **3b** loading from 20 to 50 mol% or substrate **1a** loading from 1.0 to 2.0 equiv, yield of cascade product **6aa** increased drastically from 55 to 90/94% at 25°C for 24 h in DMSO solvent as shown in Table 2, entries 5–6 and 10–11. Interestingly, amino acid catalyzed cascade [3+2]-CA/H reactions are also solvent dependent reactions and performed well in aprotic polar solvents such as DMSO, DMF and NMP; only <15% conversion is observed in other solvents such as CH_3CN, $CHCl_3$, THF, H_2O and *c*-C_6H_{12} (Table 2, entries 7–9). Cascade reaction of **1a** with **2a** under **3b** catalysis in DMF at 25°C for 24 h furnished the unhydrolyzed 1,2,3-triazole **5aa** in 55% yield accompanying with product **6aa** in 10% yield as shown in Table 2, entry 7. Same cascade reaction in NMP as solvent furnished the products **5aa** and **6aa** in 60 and 10% yield, respectively (Table 2, entry 8). We envisioned the optimized

Table 1. Preliminary study for the reaction optimization.[a]

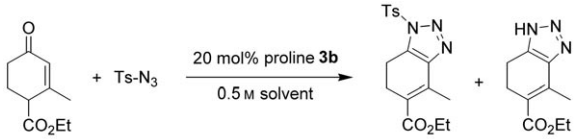


1a 2a 4aa 5aa 6aa

Entry	Catalyst **3** [20 mol%]	*t*[h]	Yield[%][b] **4aa**	**5aa**	**6aa**
1	glycine (**3a**)	96	–	–	25
2	proline (**3b**)	24	–	–	55
3	diamine (**3c**)[c]	0.75	83	–	–
4	piperidine (**3d**)	0.75	83	–	–
5	morpholine (**3e**)	0.75	73	–	–
6	pyrrolidine (**3f**)	1.0	67	–	–
7	benzylamine (**3g**)	0.75	83	–	–
8[d]	**3g**	0.75	85	–	–
9[e]	**3g**	0.70	90	–	–
10[f]	**3g**	0.75	80	–	–
11[g]	**3g**	0.75	70	–	–
12[h]	**3g**	0.75	80	–	–
13	Et_3N (**3h**)	1.5	65	–	–
14	$Me_2NCH_2CH_2OH$ (**3i**)	1.5	71	–	–
15	DBU (**3j**)	1.5	58	–	–
16	DABCO (**3k**)	1.5	77	–	–
17	DMAP (**3l**)	1.5	67	–	–

[a] Reactions were carried out in solvent (0.3 M) with 1.0 equiv of **1a** relative to the **2a** in the presence of 20 mol% of catalyst **3**. Ts=*p*-toluenesulfonyl; [b] Yield refers to the column-purified product. [c] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (**3c**). [d] 30 mol% of **3g** was used. [e] 40 mol% of **3g** was used. [f] 2.0 equiv of **1a** was used. [g] DMF used as solvent. [h] NMP used as solvent.

Table 2. Reaction optimization for the *N*H-1,2,3-triazole synthesis.



1a 2a 5aa 6aa

Entry	0.5 M Solvent	Ester **1a** [equiv]	*T* [°C]	*t* [h]	Yield [%][a] **5aa**	**6aa**
1	EtOH	1.0	25	120	–	30
2	MeOH	1.0	25	120	35	-
3	DMSO	1.0	25	24	–	55
4	DMSO	1.0	70	5	–	65
5[b]	DMSO	1.0	25	24	–	76
6[c]	DMSO	1.0	25	24	–	90
7	DMF	1.0	25	24	55	10
8	NMP	1.0	25	24	60	10
9	NMP	2.0	25	19	70	10
10	DMSO	2.0	25	24	–	94
11	DMSO	2.0	80	5	–	91
12	DMSO	0.5	80	5	–	75

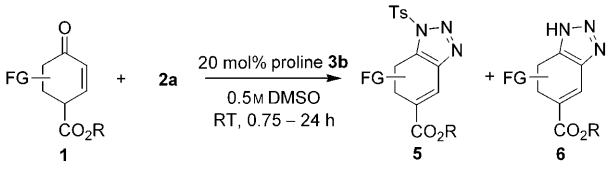
[a] Yield refers to the column purified product. [b] Proline **3b** was used as 40 mol%. [c] Proline **3b** was used as 50 mol%.

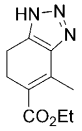
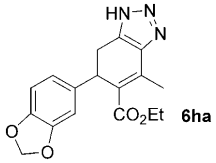
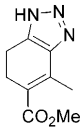
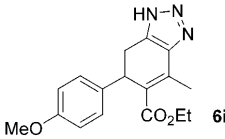
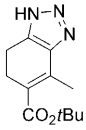
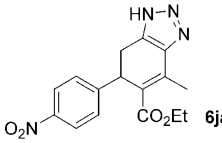
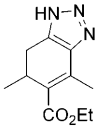
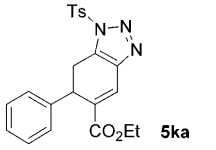
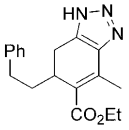
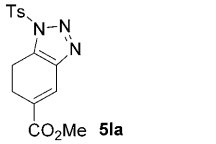
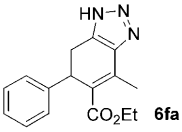
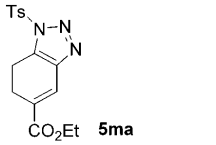
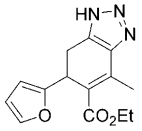
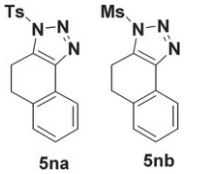
conditions to be addition of 2.0 equiv of **1a** to **2a** under 20 mol% **3b** catalysis in DMSO or NMP at 25°C for 24 h to furnish the cascade products **6aa** and **5aa** in 94 and 70% yield, respectively (Table 2, entry 9 and 10). Structure and regiochemistry of 4-methyl-1-(toluene-4-sulfonyl)-6,7-dihydro-1*H*-benzotriazole-5-carboxylic acid ethyl ester (**5aa**) and 4-methyl-6,7-dihydro-1*H*-benzotriazole-5-carboxylic acid ethyl ester (**6aa**) was also confirmed by X-ray structure analysis as shown in Figures S1 and S2 (see Supporting Information).[8]

After successful demonstration of cascade EA/E and [3+2]-CA/H reactions from **1a** with **2a** under amine or amino acid-catalysis, we also investigated the amine or amino acid catalyzed cascade reaction of **1a** with the other azides such MsN_3 (**2b**), N_3CO_2Et (**2c**), 4-$NO_2C_6H_4SO_2N_3$ (*p*NBSA) (**2d**), 2-$NO_2C_6H_4SO_2N_3$ (*o*NBSA) (**2e**), BnN_3 (**2f**) and $TMSN_3$ (**2g**), but the diazotization or *N*H-1,2,3-triazole formation of the **1a** was inferior compared to **2a** as shown in Table S1, entries 1–7 (see Supporting Information).

With the optimized reaction conditions in hand, the scope of the amino acid- and amine-catalyzed [3+2]-CA/H and EA/E cascade reactions was investigated. A series of substituted Hagemann's esters **1a–m** was reacted with 0.5 equivalents of azides **2a–b** catalyzed by 20 mol% of **3b** at 25°C in DMSO (Table 3). Both aliphatic and aromatic substituted Hagemann's esters **1** were furnished the expected *N*H-1,2,3-triazoles **6** with excellent yields (Table 3). Yields of the cascade [3+2]-CA/H products **6** were increased by the prolonging reactions time up to 24 h and also water content of the DMSO solvent. These are ideal examples for the biomimetic solvent induced cascade chemistry in organic reactions. For example, proline-mediated reaction of simple Hagemann's esters **1k**, **l** and **m** with **2a** in DMSO at 25°C for 1 h furnished the expected unhydrolyzed 1,2,3-triazoles **5ka**, **la** and **ma** in 50, 70 and 65% yield, respectively, as shown in Table 3, entries 11–13. But unfortunately we are not observed the enantioselectivity in the **3b**-mediated cascade reaction of 6-substituted Hagemann's esters **1** with **2a**. Fascinatingly, reaction of 3,4-dihydro-1*H*-naphthalen-2-one (**1n**) with azides **2a** or **2b** at 25°C for 1 h in DMSO under amino acid catalysis furnished the expected 1,2,3-triazoles **5na**/**5nb** in combination with **6na**/**6nb** in almost quantitative yields with excellent regioselectivity as shown in Table 3. Regiochemistry of cascade products **5na–nb**/**6na–nb** was

Table 3. Chemically diverse libraries of *N*H-1,2,3-triazoles **6**.



Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
1	 **6aa**	94	8	 **6ha**	70
2	 **6ba**	90	9	 **6ia**	65
3	 **6ca**	90	10	 **6ja**	55
4	 **6da**	65	11	 **5ka**	50
5	 **6ea**	75	12	 **5la**	70
6	 **6fa**	80	13	 **5ma**	65
7	 **6ga**	70	14[b] 15[b,c]	 **5na** **5nb**	80 80

[a] Yield refers to the column-purified product. For the entries 1–10, reaction time is 12–24 h and for the entries 11–15, time is 0.75–1.0 h. [b] In both reactions, 15–20% of corresponding hydrolyzed *N*H-1,2,3-triazole **6na/6nb** were isolated. [c] **2b** was used instead of **2a**.

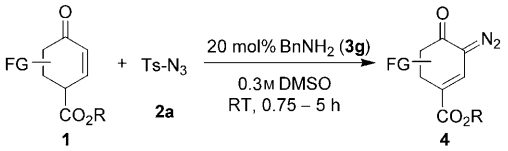
confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **5na** (see Figure S3, Supporting Information).[8] Cascade products **5na**/**6na** would be very interesting model analogues for the studies of inhibitors of hMetAP2 as shown in Equation (2).

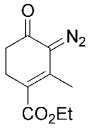
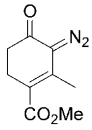
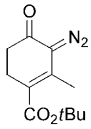
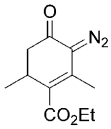
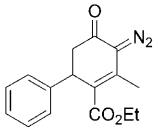
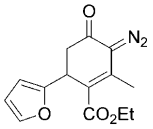
We also generated the highly functionalized diversity oriented library of cascade EA/E products **4** under primary amine catalysis. The results in Table 4 demonstrate the broad scope of this novel green methodology covering a structurally diverse group of Hagemann's esters **1a–g** and **2a** generally with very good yields compared with tertiary amine catalysis. Cascade EA/E reaction of Hagemann's esters **1a–g**, **2a** under **3g** catalysis furnished diazo products **4aa–4ga** in good yields (Table 4). Structure and regiochemistry of cascade EA/E products **4** was also confirmed by X-ray structure analysis on **4ba** (Figure S4, see Supporting Information).[8]

The possible reaction mechanism for the synthesis of cascade products **4**, **5** and **6** through reaction of Hagemann's ester **1a**, **2a** and amine/amino acid **3** is illustrated in Scheme 1. The reaction mechanism can be divided into three categories (**I**, **II** and **III**) as catalyzed by three different amines as shown in Scheme 1. In the first category (**I**), reaction of tertiary amines with Hagemann's ester **1a** generates the push–pull dienol **7** based on reaction conditions.[7b] Reaction of push–pull dienol **7** with **2a** furnish the selectively amination product **9**, which will give product **10** via keto–enol tautomerism by treatment with basic amine. Rearrangement followed by elimination of toluene-4-sulfonamide of **10** converted into highly substituted diazo-product **4aa**. In the second category (**II**), reaction of primary amine **3g** with Hagemann's ester **1a** generates the push–pull dienamine **11**,[7b] which on treatment with **2a** furnish the selectively amination product **12**, which will transform into product **13** via imine–enamine tautomerism by treatment with basic amine. Rearrangement followed by elimination of toluene-4-sulfonamide of **13** and hydrolysis of resulting imine gives to the highly substituted diazo-product **4aa**. In the third category (**III**), reaction of secondary amino acid **3b** with Hagemann's ester **1a** generates the push–pull dienamine **14**,[7b] which on treatment with **2a** furnish the selectively 7a-(2-carboxy-pyrrolidin-1-yl)-4-methyl-1-(toluene-4-sulfonyl)-3a,6,7,7a-tetrahydro-1*H*-benzotriazole-5-carboxylic acid ethyl ester (**16**) via concerted [3+2]-cycloaddition, which may transform into product **5aa** through rapid elimination of **3b**. Possible weak interactions from acid group in transition state **15** will be the driving force to undergo concerted [3+2]-cycloaddition compare to **8**/**11** transition states. The solvent (DMSO) induced in situ hydrolysis of resulting 1,2,3-triazole **5aa** gives to the *N*H-1,2,3-triazole **6aa** in good yields as shown in Scheme 1. This in situ hydrolysis step is totally influenced by the water content of the DMSO solvent and not in the workup stage.

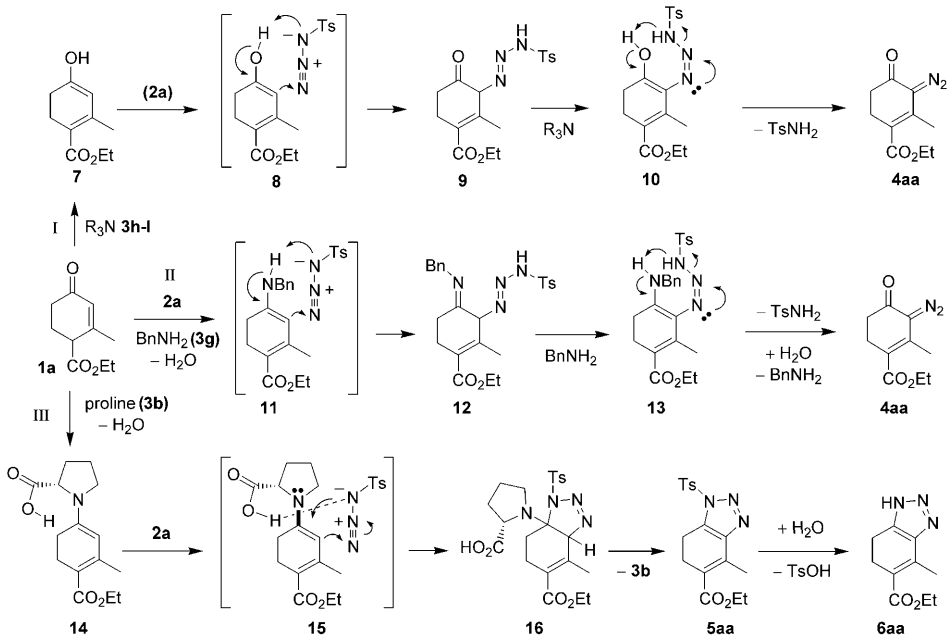
In summary, we have first time developed the synthesis of *N*H-1,2,3-triazole products **5** and **6** from simple starting materials via [3+2]-CA/H reactions under amino acid catalysis. The cascade reaction proceeds in good yields with high selectivity using proline as the catalyst. Furthermore, we have

Table 4. Chemically diverse libraries of diazo-products **4**.[a]



					
90 % (**4aa**)	80 % (**4ba**)	65 % (**4ca**)	50 % (**4da**)	50 % (**4fa**)	70 % (**4ga**)

[a] Yield refers to the column-purified product.



Scheme 1. Proposed reaction mechanism.

demonstrated the bio-mimetic solvent induced hydrolysis in amino acid-catalyzed cascade reactions. Further work is in progress to develop asymmetric version of cascade [3+2]-CA/H reactions.

Experimental Section

Experimental procedures, characterization data for new products, and complete details about the synthesis of new products are available in the Supporting Information.

Acknowledgements

This study was supported by the Department of Science and Technology (DST), New Delhi. K.R.K. and V.V.N. thank Council of Scientific and Industrial Research (CSIR), New Delhi for their research fellowships. We thank Dr. P. Raghavaiah for X-ray structural analysis.

Keywords: cascade reactions · cycloaddition · organocatalysis · push–pull dienamine · triazoles

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[8] CCDC 689189 (**5aa**), 689190 (**6aa**), 690284 (**5na**) and 689188 (**4ba**) contain 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.

Received: July 1, 2008
Published online: September 2, 2008

