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Highly stereoselective synthesis of *cis*-β-enaminones mediated by diethyl azodicarboxylate†

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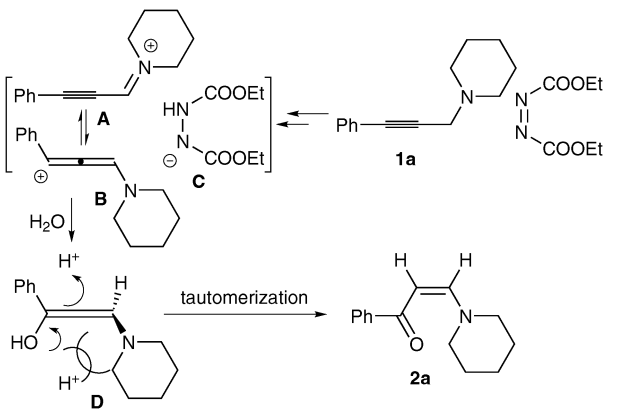
Promoted by diethyl azodicarboxylate, a novel and highly stereoselective synthesis of *cis*-β-enaminones *via* oxidative dehydrogenation and hydration of the substituted propargylamines was realized. The possible mechanism was also proposed.

β-Enaminones have attracted much attention over the past decades owing to their intrinsic biological properties.[1] Moreover, they have been widely used as versatile synthetic and pharmaceutical intermediates for the preparation of a variety of heterocyclic derivatives including natural products and analogues, such as indoles, pyridines and pyrroles.[1,2] In coordination chemistry, some can be used as good chelating ligands for main group and transition metals.[3] The classical methods[2] for the synthesis of such compounds mainly rely on the condensation of amines with carbonyl compounds, addition reaction of metal enolates to unsaturated carbon–nitrogen bonds, and cleavage of heterocycles in addition to some novel unconventional routes.[4] According to their structural features, *cis*- and *trans*-forms of β-enaminones exhibited different chemical reactivities and electronic characters in synthetic and coordination chemistry.[2] However, upon checking the literatures, reports about the synthesis of the *cis*-form were very rare.[2a,5] As far as the *cis*-form was concerned, there is no synthetic method reported up to date for the synthesis of 2,3-dihydrogen-*cis*-β-enaminone derivatives.

Diethyl azodicarboxylate (DEAD) has been widely used in organic synthesis.[6] Mediated by DEAD, a lot of efficient and excellent chemical transformations such as Mitsunobu reaction, carbon–nitrogen bond formation, oxidative coupling have been accomplished. Recent studies in our group have focused on the usability of diethyl azodicarboxylate on the oxidative application of tertiary amine.[7] Due to the structural diversity of tertiary amines, different structures and chemical characters of zwitterionic intermediates initiated by DEAD could be generated. Recently, the reaction of 1.2 equiv. of propargylamine **1a** with equal amount of DEAD and water using wet CH_3CN as a solvent was tried, and it was found that 2,3-dihydrogen-*cis*-β-enaminone **2a** was unexpectedly isolated in 15% yield. We note that the stereoselectivity of the addition reaction was excellent, and the *cis*-form isomer **2a** was formed exclusively. According to its structural feature and the reported Meyer–Schuster rearrangement mechanism,[8] the possible route for the formation of **2a** might be as follows: initially, DEAD reacted with propargylamine **1a** by nucleophilic attack and then hydrogen transfer to afford an ion pair consisting of first generated imine cation **A** or its subsequently-formed equilibrium substituted allene cation **B** and 1H-DEAD **C**. 1,4-Addition of the intermediate **A** or **B** with one molecule of water could take place to form the intermediate **D**, which subsequently underwent stereoselective enol–keto tautomerization to afford the final product **2a**. The selective formation of *cis*-isomer **2a** could be explained by the more favorable electrophilic attack of proton from the direction of less steric hindrance and the effect of intramolecular hydrogen bonding.[2a,5] From the proposed mechanism, maybe there are two activated reaction intermediates **A** and **B** coexisting, which competed with the attacking nucleophilic reagent. 1,2-Hydration addition of intermediate **A** produced the undesired side product propargyl aldehyde (Scheme 1).

Then several elements were surveyed to suppress the 1,2-addition reaction in order to enhance the 1,4-addition selectively (Table 1). Lots of solvents such as THF, DMF, DMSO, ether,



Scheme 1 Proposed mechanism.

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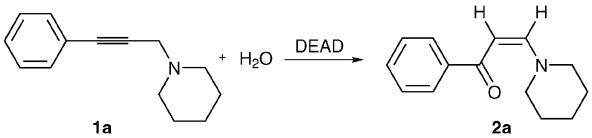
† Electronic supplementary information (ESI) available: General procedure for synthesis of compounds **2a–2k**, characterization data for compounds **2a–2k**, and ^1H and ^{13}C NMR spectra of compounds **2a–2k**. See DOI: 10.1039/c2cc16997e

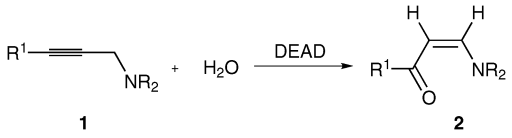
Table 1 Synthesis of **2a** under various conditions[a]



Entry	Mol ratio of **1a** : H_2O : DEAD	Solvent (2 mL)	Yield[b] (%)
1	1 : 1.2 : 1.2	CH_3CN	15
2	1 : 1.2 : 1.2	DMF	12
3	1 : 1.2 : 1.2	DMSO	15
4	1 : 1.2 : 1.2	THF	16
5	1 : 1.2 : 1.2	Toluene	23
6	1 : 1.2 : 1.2	$CHCl_3$	28
7	1 : 1.2 : 1.2	CH_2Cl_2	39
8	1 : 1.2 : 1.2	DCE	45
9	1 : 1.2 : 1.2	—	39
10	1 : 1.5 : 1.5	DCE	25
11	1 : 1.2 : 1.5	—	36
12	1 : 2 : 1.2	—	32
13	1 : 1.5 : 1.5	—	55
14	1 : 1.5 : 2	—	36

[a] The reaction was carried out at 0–10 °C for 6 h. [b] Isolated yield based on **1a**.

Table 2 Synthesis of **2** under optimized conditions[a]



Entry	Propargylamines **1**	R^1	NR_2	Yield[b] (%)
1	**1a**	Ph	Piperidyl	55 (**2a**)
2	**1b**	4-$CH_3OC_6H_4$	Piperidyl	48 (**2b**)
3	**1c**	4-FC_6H_4	Piperidyl	57 (**2c**)
4	**1d**	4-ClC_6H_4	Piperidyl	55 (**2d**)
5	**1e**	4-BrC_6H_4	Piperidyl	55 (**2e**)
6	**1f**	3-ClC_6H_4	Piperidyl	54 (**2f**)
7	**1g**	Ph	Morpholinyl	38 (**2g**)
8	**1h**	Ph	Diethylamine	18 (**2h**)[c]
9	**1i**	Ph	Dibutylamine	35 (**2i**)[d]
10	**1j**	$CH_3(CH_2)_4$	Piperidyl	51 (**2j**)
11	**1k**	3-Thienyl	Piperidyl	41 (**2k**)
12	**1l**	2-Pyridyl	Piperidyl	—[e]

[a] Propargylamine **1** (1 mmol), DEAD (1.5 mmol), H_2O (1.5 mmol) at 0–10 °C under neat conditions for 6 h; please see ESI for details. [b] Isolated yields. [c] About 10% *trans*-form isomer was detected. [d] Less than 5% *trans*-form was detected. [e] Complex mixture.

CH_2Cl_2 were examined. It was found that the high polarity solvents, such as DMF or DMSO, have no positive effect and lower yield of the desired product was obtained (entries 2–3). The other solvents for instance THF or toluene observed no obvious assistance (entries 4–5). Slightly better results came from the use of a chlorinated hydrocarbon solvent, and for example, 45% yield of the desired product could be obtained when DCE was used as the solvent (entries 6–8). Further screening of the ratio of reactants established the optimal reaction conditions: 1.5 equiv. of DEAD and H_2O under neat conditions at 0–10 °C for 6 h with 55% yield of **2a** (entry 13). In all cases, the 1,2-addition reaction could not be fully excluded.

To explore the substrate scope and limitations of this reaction, a range of propargylamines were then examined under the optimized reaction conditions. As shown in Table 2, in all successful cases except **1h** and **1i**, the *cis* selectivities for the formation of β-enaminones were excellent. It was found that the electronic property of the substituents on the aryl ring of propargylamines has little effect on the reaction (entries 2–6). Electron-donating as well as electron-withdrawing substituents are well accommodated. It was noteworthy that pentyl substituted propargylamine **1j**, an aliphatic alkyne substrate, was also subjected to the reaction, and the desired product **2j** was obtained in moderate yield (entry 10). 3-Thienyl substituted substrate **1k** acted as the appropriate candidate successfully (entry 11). On the other hand, several structural diversity types of amines, such as piperidyl, morpholinyl, diethylamine, and dibutylamine substituted substrates, could also be employed in this reaction. For less steric hindrance diethylamine substituted propargylamine **1h**, about 10% yield of the *trans*-form isomer was obtained except for the desired product **2h**, which may further support the proposed mechanism (entry 8). Compared with the results of entry 8, dibutyl substituted propargylamine **1i** showed good results, which was in accordance with our previous reports (entry 9).[7] However, using 2-pyridyl substituted propargylamine **1l** as the substrate, no desired product was obtained under the identical conditions (entry 12).

In conclusion, a highly stereoselective synthesis of 2,3-dihydrogen-*cis*-β-enaminones using propargylamines and DEAD has been successfully established. Further investigations concerning the scope of enaminones, applications, and mechanistic details are currently ongoing in our laboratory and will be published in due course.

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