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Highly regioselective synthesis of *cis*-β-enaminones by 1,4-addition of propiolaldehydes

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ABSTRACT

A convenient one-pot strategy for the regioselective synthesis of *cis*-β-enaminones has been developed via the condensation of propiolaldehydes and amines in EtOH. This process has opened a new synthetic route to enamines in good yield. A possible reaction mechanism involving a Michael addition/enol tautomerization via a six-membered ring transition state is proposed.

Introduction

β-Enaminones are versatile synthetic intermediates and have a lot of synthetic applications in organic chemistry. Such compounds are key synthons for the preparation of a wide variety of nitrogen-containing heterocycles[1–4] and naturally occurring alkaloids.[5,6] They have also been employed as important precursors for the synthesis of pharmaceutical drugs with antiviral, anticonvulsant,[7–9] and larvicidal[10] properties. Due to their rich applications, many efficient approaches to these compounds have been developed. The most well-known route for the synthesis of β-enaminones is the condensation of β-dicarbonyl compounds with amines, while another general way is the condensation of active methylene ketones with dialkylamino dimethyl acetals.[11] Typically, this condensation reaction is carried out in refluxing aromatic hydrocarbons. Various modified synthetic pathways have been reported, such as the addition reaction of amines to triple bonds and metal enolates to unsaturated carbon–nitrogen bonds. Furthermore, several methods were reported for the synthesis of β-enaminones using Lewis acids, inorganic acids, ionic liquids, and transition metal catalysts.[12] In addition, β-enaminones have also been prepared by using microwave[13] and ultrasound irradiation.[14] However, these methods are associated with major or minor limitations such as the requirement of sensitive reaction conditions and expensive reagents, use of homogenous and non-recyclable catalysts, tedious workup procedures, low yields, and low selectivity. Moreover, upon checking the literature, *cis*-β-enaminone formation was really rare, especially the use of secondary amines to provide the *cis* configuration. The only example for the synthesis of 2,3-dihydrogen-*cis*-β-enaminone derivatives is the reaction using propargylamines mediated by diethyl azodicarboxylate (DEAD),[15] but the low yield of this reaction limits its further practical applications.

The development of simple, cost-effective, nonpolluting, and high-yielding routes for the construction of β-enaminones is still a great challenge to organic chemists. As part of our growing enthusiasm about developing efficient and environmentally friendly methods in organic synthesis,[16] we are very delighted to have found a simple, high-yielding, and highly stereoselective synthesis of 2,3-dihydrogen-*cis*-β-enaminones using an in situ reaction of propiolaldehydes and amines.

Results and discussion

The required propiolaldehydes can be easily prepared according to known literature procedures.[17] The lithiation of terminal alkynes with *n*-BuLi, followed by formylation with DMF, gives propiolaldehydes in excellent yields (>90%). It is noteworthy that a reverse quench into a phosphate buffer has been proven to be the key for these high-yielding formylation reactions. Propiolaldehydes can

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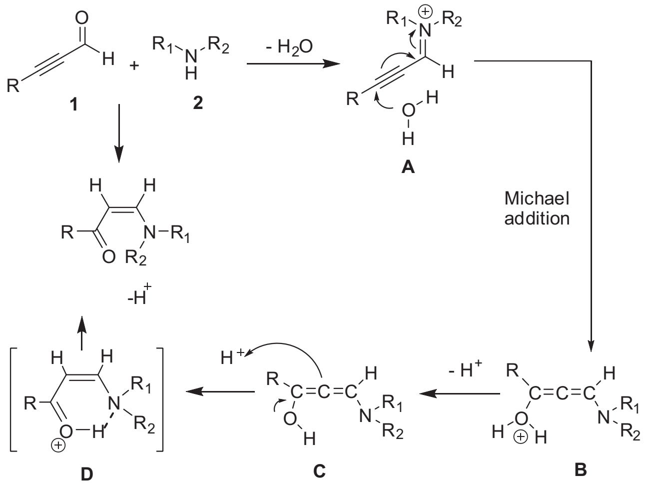

Scheme 1. Plausible mechanism.

undergo a range of reactions at different sites. In order to successfully develop an amine-promoted 1,4-addition of propiolaldehydes with nucleophiles, we surmise that the key problem is to suppress the 1,2-addition reaction.

To test the possibility of this hypothesis, initially, the direct reaction of 1 equiv of phenylpropiolaldehyde **1a** with equal amount of dipropylamine **2a** in CH_2Cl_2 was carried out at room temperature for 3 h. to afford the β-enaminone **3aa**, which was isolated in 72% yield. The structure of the β-enaminone synthesized was well characterized by NMR spectral analysis, which was in conformity with 2,3-dihydrogen-*cis*-β-enaminone. We found that the *cis*-β-enaminone **3aa** was generated exclusively, and the regioselectivity and stereoselectivity of the reaction were excellent. This could serve as a new method to prepare synthetically interesting, functionalized *cis*-β-enaminone. According to the reported enamine catalysis of nucleophilic substitution reactions[18] and the known Meyer–Schuster rearrangement mechanism,[19] our postulated reaction mechanism is summarized in Scheme 1. It is proposed that the reaction is triggered by the generation of iminium **A** via the reaction of propiolaldehydes **1** and secondary amine **2**. Then one molecule of water acts as a nucleophile for the 1,4-addition with iminium **A** to form the intermediate **B**. The subsequent stereoselective enol–keto tautomerization leads to the formation of a six-membered ring transition state **D** which is stabilized by intramolecular hydrogen bonding. The selective formation of *cis*-β-enaminone can be illustrated by electrophilic attack from the less sterically hindered direction and the effect of intramolecular hydrogen bonding to form a six-membered ring transition state.

Several elements were then investigated to optimize the reaction conditions (Table 1). Screening of different solvents in Table 1 showed that the reaction gave the highest yield in protic solvents, such as CH_3OH, C_2H_5OH, and H_2O (entries 2–4). Aprotic solvents, such as CH_2Cl_2, $CHCl_3$, DMF, CH_3CN, and THF have no positive effect and the target product **3aa** was obtained in lower yields (entries 1, 5–8). The lowest yield (<25%) of the desired product was obtained (entry 9) with the use of apolar aprotic solvents, for instance toluene. This may be due to the protic solvents being more favorable to generate iminium **A,** thus being easier to react. However, in the apolar aprotic solvent, the imine ion A was difficult to generate and the product yield was very low, which is consistent with our proposed mechanism. After identifying the suitable solvent EtOH, we attempted to optimize the reaction by varying other elements systemically. As expected, higher temperature greatly shortened the reaction time (entries 3 and 10). However, when the reaction temperature was increased to 80 °C, there was no meaningful improvement on the reaction rate (entry 11). Changing the ratio of **1a**/**2a** from 1:1.5 to 1:1 or 1:2, we found 1.5 equiv of dipropylamine (**2a**) established the optimal reaction conditions (entries 12–13).

With the optimized conditions in hand, we then investigated a variety of amines using phenylpropiolaldehyde (**1a**) at 60 °C with EtOH as the solvent. The results are summarized in Table 2. The reactions between the various secondary amines **2** and phenylpropiolaldehyde (**1a**) proceed smoothly to furnish the desired products **3** in overall good yields and high stereoselectivities. Interestingly, it was found that increasing steric hindrance of the amine slows down the reaction rate and leads to the formation of *trans*-β-enaminones. Probably, when steric hindrance increased, the branched chain connected to nitrogen cannot rotate freely and this leads to the generation of some *trans* isomer. For example, acyclic amines (e.g. long aliphatic chain based dialkyl amine) had good performance on the *cis* selectivity (entries 1–7), while several cyclic or larger sterically hindered amines, such as piperidyl, pyrrolidine, diisopropylamine, diisobutylamine, and dicyclohexylamine created significant steric effect, and they not only prolonged the reaction time, but also dramatically lowered the *cis* selectivity, further supporting the proposed mechanism (entries 8–12). However, no reaction occurred under identical conditions using propylamine and phenylamine as substrates.

To further investigate the generality and substrate scope of our approach, a wide range of propiolaldehydes (**1**) were then used in these optimized reaction conditions. As shown in Table 3, it seems that the electronic properties and steric hindrance of the substituents in the phenyl ring had significant influence on stereoselectivity and chemical yield. For example, phenylpropiolaldehyde bearing electron-donating groups (**2a**) not only dramatically decreased the *cis* selectivity, but also lowered the chemical yield (entries 6 and 7); electron-withdrawing groups mainly lowered the *cis* selectivity (entries 1–5). Perhaps the increased steric hindrance of the substituents in the phenyl ring and the push-pull electronic effect brought about a barrier of rotation around the C=C bond and decreased the *cis* selectivity.[20]

Table 1
Optimization of reaction conditions[a]

Entry	Solvent	*T* (°C)	*t* (h)	Yield[d] (%)
1	CH_2Cl_2	60	8	72
2	MeOH	60	0.25	90
3	EtOH	60	0.25	97
4	H_2O	60	0.25	82
5	$CHCl_3$	60	12	79
6	DMF	60	6	68
7	MeCN	60	3	77
8	THF	60	12	40
9	Toluene	60	12	25
10	EtOH	rt	3	92
11	EtOH	80	0.25	96
12[b]	EtOH	60	0.25	87
13[c]	EtOH	60	0.25	95

[a] Unless otherwise stated, reaction conditions are: **1a** (0.4 mmol, 1.0 equiv), **2a** (0.6 mmol, 1.5 equiv), 2.0 mL of solvent.
[b] Compound **1a**/**2a** (1:1).
[c] Compound **1a**/**2a** (1:2).
[d] Isolated yield after column chromatography.