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Acid-Catalyzed Cascade Reactions of Enaminones with Aldehydes: C–H Functionalization To Afford 1,4-Dihydropyridines

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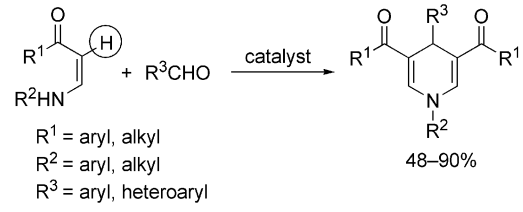
An efficient acid-catalyzed approach to the synthesis of functional 1,4-dihydropyridines from the reaction of readily available enaminones with aldehydes has been developed. This methodology was realized by a cascade reaction involving first formation of divinylmethanes and subsequent intramolecular cyclization.

Introduction

1,4-Dihydropyridines (1,4-DHPs) are very attractive heterocycles in medicinal chemistry and pharmacology due to their wide range of biological activities.[1] For example, these compounds are known as calcium channel blocker drugs,[2] and they have also been reported to be vasodilators and bronchodilators. They also possess antiatherosclerotic, antitumor, antidiabetic, or photosensitizing activities.[3] Furthermore, they are useful and versatile synthetic intermediates in organic chemistry.[4] As a result, much effort has been paid to their preparation. The Hantzsch reaction, the condensation of a β-keto ester or a 1,3-dicarbonyl compound with an aldehyde and ammonia, is one of the most well-documented methods for the formation of 1,4-DHPs, and improved procedures for the synthesis of 1,4-DHPs have been reported.[5] For example, it is known that 1,4-DHPs can be constructed through the condensation of enaminones with α,β-unsaturated aldehydes.[5b,6f] The reaction of amines and 3-(2-formylphenoxy)propenoates to 1,4-DHPs is also reported.[6e] Although these procedures are efficient for the synthesis of 1,4-DHPs, the C–H functionalization of enaminones to 1,4-DHPs remains a challenging task. In recent years, the direct conversion of C–H bonds into C–C bonds has emerged as a rapidly growing area in organic chemistry, as the process is atom economic and environmentally benign for the synthesis of useful synthetic intermediates and materials.[7] In this regard, enaminone derivatives are considered to serve as a viable C–H component for direct functionalization. Enaminones are versatile reagents that combine the ambident nucleophilicity of enamines with the ambident electrophilicity of enones. Although much progress has been made in recent years in devising new processes, especially for the synthesis of heterocycles, that involve the use of enaminones, direct carbon–carbon bond-forming reactions with carbon electrophiles is still quite limited.[8] Herein, we would like to report the stereoselective synthesis of enaminones and its cascade addition/cyclization reactions with aldehydes catalyzed by Brønsted or Lewis acids, in which a C–C bond is formed directly at the α-carbon of the enaminone (Scheme 1). This reaction offers an efficient and straightforward route to 1,4-dihydropyridines.



Scheme 1.

Results and Discussion

It is known that enaminones are prepared by direct condensation of 1,3-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons, or by the addition of amines to alkynones.[9] In recent years, transition-metal-mediated approaches have also been reported.[10] However, many of these processes suffer from limitations such as drastic reaction conditions, low yields, or lack of stereoselectivity. Here we found that *N*-substituted enaminones **2** were readily prepared through conjugate addition of anilines or aliphatic amines with terminal alkynones or ethyl propiolate (Table 1). The reaction could be carried out conveniently at room temperature or at 80 °C in toluene, and the corresponding enaminones were formed in good to high yields. It is noteworthy that the stereoselectivity of this reaction is high except for **2h**, and the *Z*-isomer was observed

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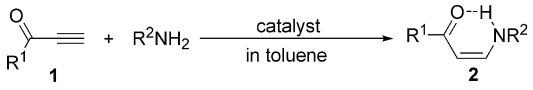
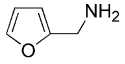
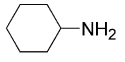
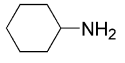
as the major isomer, possibly due to the tendency to form an intramolecular hydrogen bond. In the case of **2h**, the ratio of *Z*/*E* changed greatly, as observed in the crude reaction mixture and the isolated materials (Table 1, Entry 9). When a less nucleophilic amine such as 4-chlorobenzenamine was used, the addition of $FeCl_3$ as a catalyst accelerated the reaction, and desired **2b** was obtained in 85% yield within 1 h. Without this catalyst, a longer reaction time was required (Table 1, Entries 2 and 3). We can see from Table 1 that the desired enaminones were obtained in high yields and with excellent stereoselectivity within short reaction time.

Table 1. Stereoselective formation of enaminones.

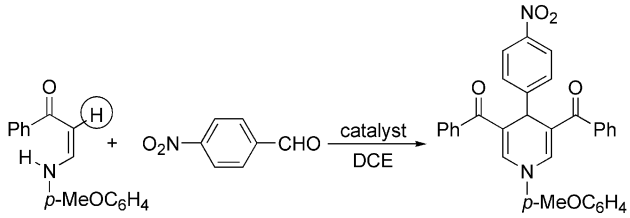


Entry	Alkynone	Amine	Catalyst	*T* [°C]	Product	Yield [%][a]
1	PhCO—≡ **1a**	*p*-$MeOC_6H_4NH_2$	–	80	**2a**	90[b] (100:0)
2	**1a**	*p*-$ClC_6H_4NH_2$	–	80	**2b**	75[c] (100:5)
3	**1a**	*p*-$ClC_6H_4NH_2$	10% $FeCl_3$	80	**2b**	85 (100:0)
4	**1a**	$PhCH_2NH_2$	–	r.t.	**2c**	96 (100:6)
5	**1a**		–	r.t.	**2d**	96 (100:6)
6	**1a**	*n*$BuNH_2$	–	r.t.	**2e**	93 (100:4)
7	**1a**		–	r.t.	**2f**	88 (100:3)
8	*n*HexCO—≡ **1b**	*p*-$MeOC_6H_4NH_2$	–	80	**2g**	59[d] (100:0)
9	EtOOC—≡ **1c**		–	r.t.	**2h**	81 (26:100)[e]
10	**1c**	*t*$BuNH_2$	–	r.t.	**2i**	80 (100:12)[f]

[a] Isolated yields. Unless noted, all the reactions were carried out for 0.5–1 h. The ratio of the *Z*/*E* isomers in the crude reaction mixture is given in parentheses. [b] Reaction time was 5 h. [c] Reaction time was 23 h. [d] Reaction time was 6 h. [e] The ratio is 100:23 in the isolated product. [f] Under solvent-free conditions.

We started our investigation with (*Z*)-3-(4-methoxyphenylamino)-1-phenylprop-2-en-1-one (**2a**). The reaction of **2a** with 4-nitrobenzaldehyde was selected as the prototypical case to screen the experimental conditions (Table 2). To our delight, it was found that in the presence of a catalytic amount of $TsOH·H_2O$, TFA, or $NaAuCl_4·2H_2O$, **2a** was smoothly transformed into desired 1,4-DHP **3a** in 75–79% yield (Table 2, Entries 2–4). It is noteworthy that increasing the amount of aldehyde from 0.75 to 1.0 equiv. not only lessened the reaction time, but also enhanced the product yield (Table 2, Entry 2 vs. 6). The best yields were achieved by employing $TsOH·H_2O$ as the catalyst (85–87%; Table 2, Entries 6 and 7). The results indicated that the use of an excess amount of aldehyde ensured efficient elimination of amine. Actually, the imine 4-methoxy-*N*-(4-nitrobenzylidene)benzenamine byproduct was observed in these experiments. The Lewis acid $FeCl_3·6H_2O$ afforded a moderate yield (48%) of **3a** (Table 2, Entry 8). In the absence of a catalyst, no reaction occurred (Table 2, Entry 9). It is worthy to note that the general and efficient approaches to 1,4-DHPs without substituents in the 2- and 6-positions are still limited,[5d,6] and most of the methods suffer from harsh reaction conditions and relatively low yields of the products, or are specific to substituted substrates. It is reported that 1,4-DHPs without substitutes in the 2- and 6-positions exhibit important pharmaceutical activities; for example, dimers of these compounds are potential inhibitors of HIV-1 protease and possess anticancer activity.[11]

Table 2. Optimization studies for the formation of 1,4-dihydropyridines.



Entry	Aldehyde [equiv.]	Catalyst (mol-%)	*T* [°C]	Time [h]	Yield [%] of **3a**[a]
1	0.75	$Sc(OTf)_3$ (5)	80	12	34
2	0.75	$TsOH·H_2O$ (10)	80	3	75
3	0.75	TFA (10)	80	5	71
4	1.0	$NaAuCl_4·2H_2O$ (5)	80	1	79
5	1.0	TFA (5)	80	20	91
6	1.0	$TsOH·H_2O$ (10)	80	1	85
7	1.0	$TsOH·H_2O$ (5)	80	1	87
8	1.0	$FeCl_3·6H_2O$ (10)	80	3	48
9	1.0	—	80	10	NR[b]

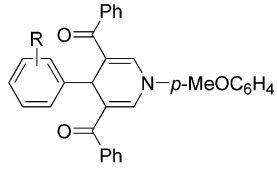
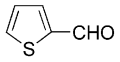
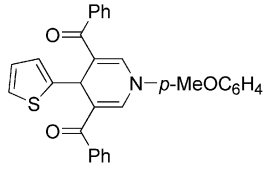
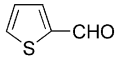
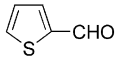
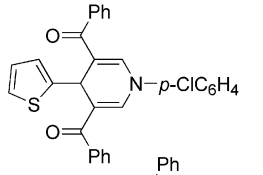
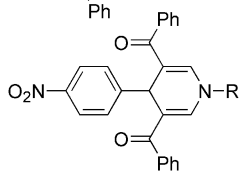
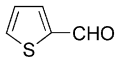
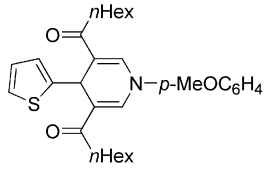
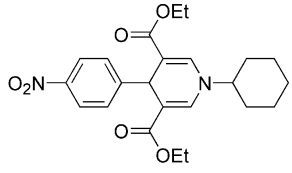
[a] Isolated yields. [b] NR = no reaction.

With the optimized reaction conditions in hand, we next examined the substrate scope of this catalytic method for the synthesis of 1,4-DHPs by using a variety of enaminones **2** and aldehydes (Table 3). We first investigated the electronic effects of the aromatic substituents on the aldehydes. It was found that an electron-withdrawing (-Cl) aryl group afforded the corresponding product **3b** in 78% yield (Table 3, Entry 1). Benzaldehyde also gave good yield of **3c** (Table 3, Entry 2). However, an electron-donating (-Me) aryl group resulted in a longer reaction time of 4 d with 80% yield of **3d** as a result of the lower reactivity of this aldehyde (Table 3, Entry 3). The use of $NaAuCl_4·2H_2O$ as catalyst reduced the reaction time dramatically to 16 h, and dihydropyridine **3d** was formed in 83% yield (Table 3, Entry 4). A heteroaryl aldehyde such as 2-thienylaldehyde was also compatible under the reaction conditions, furnishing

3f, **3g**, and **3l** in yields of 76–90% (Table 3, Entries 6–8, 13). The reaction also proceeded smoothly with *N*-alkyl-substituted enaminones **2d**–**f** to produce desired 1,4-DHPs **3i**–**k** in yields of 48–81% (Table 3, Entries 10–12). Enaminone **2g** with an alkyl substituent on the carbonyl carbon led to the formation of **3l** in 90% yield (Table 3, Entry 13). The cyclization was also successfully extended to enaminoester **2h**, and 77% yield of **3m** bearing two ester groups was obtained through the reaction with *p*-nitrobenzaldehyde (Table 3, Entry 14). However, the use of paraformaldehyde resulted in a complicated reaction mixture (Table 3, Entry 15). The structure of 1,4-DHP was further confirmed by X-ray crystallographic analysis of **3c**.[12]

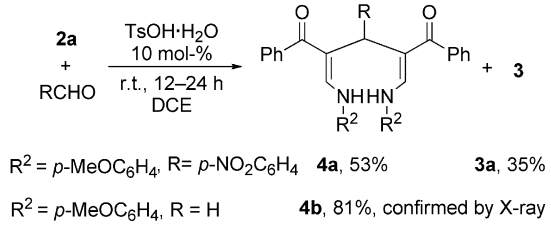
To understand the reaction mechanism, we carried out the reaction of **2a** with *p*-nitrobenzaldehyde at room temperature. It was found that divinylmethane intermediate **4a**

Table 3. Synthesis of various substituted 1,4-dihydropyridines.

Entry	Enaminone	Aldehyde	Conditions[a]	Time [h]	Product		Yield [%][b]
1	**2a**	*p*-ClC_6H_4CHO	A	22		**3b** R= *p*-Cl	78
2	**2a**	PhCHO	A	18	R = H	**3c**	81
3	**2a**	*p*-MeC_6H_4CHO	A	96	R = *p*-Me	**3d**	80
4	**2a**	*p*-MeC_6H_4CHO	B	16	R = *p*-Me	**3d**	83
5	**2a**	*p*-$MeOC_6H_4CHO$	B	32	R = *p*-MeO	**3e**	54
6	**2a**		A	29		**3f**	76
7	**2a**		B	15		**3f**	85
8	**2b**		A	22		**3g**	84
9	**2c**	*p*-$NO_2C_6H_4CHO$	A	3		**3h** R = CH_2Ph	70
10	**2d**	*p*-$NO_2C_6H_4CHO$	A	3	R = CH_2(2-furanyl)	**3i**	81
11	**2e**	*p*-$NO_2C_6H_4CHO$	A	24	R = *n*Bu	**3j**	56
12	**2f**	*p*-$NO_2C_6H_4CHO$	A	22	R= *c*Hex	**3k**	48
13	**2g**		A	24		**3l**	90
14	**2h**	*p*-$NO_2C_6H_4CHO$	A	17		**3m**	77
15	**2i**	$(CH_2O)_n$	A	12	— [c]		

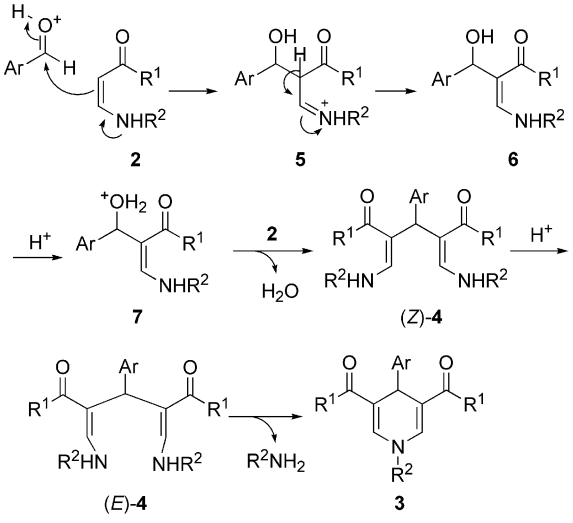
[a] Conditions A: $TsOH·H_2O$ (10 mol-%), 80 °C in DCE. Conditions B: $NaAuCl_4·2H_2O$ (10 mol-%), 80 °C in DCE. [b] Isolated yields. [c] The reaction was not clean.

was isolated in 53% yield along with 35% of desired **3a** (Scheme 2). When TFA (20 mol-%) was used as the catalyst, **4a** was obtained in a higher yield of 70% at room temperature. Isolated **4a** was subjected to standard conditions by using *p*-nitrobenzaldehyde (1 equiv.) to afford **3a** in 92% yield. Without *p*-nitrobenzaldehyde, **3a** could also be formed in 73% yield; however, a longer reaction time of 19 h was required. The results indicated that an excess amount of aldehyde could accelerate the reaction process by trapping the released amine. The formation of divinylmethane **4a** might be the key step in this cascade reaction. Interestingly, during the reaction, the double bond configuration of the enaminone changed from the *Z* form in **2a** to exclusively the *E* form in **4a**, which was verified by its NOESY spectra. In addition, the reaction of **2a** with paraformaldehyde afforded divinylmethane **4b** with the *E* form in 81% yield; the structure of **4b** was confirmed by X-ray crystallography[12] (Scheme 2).



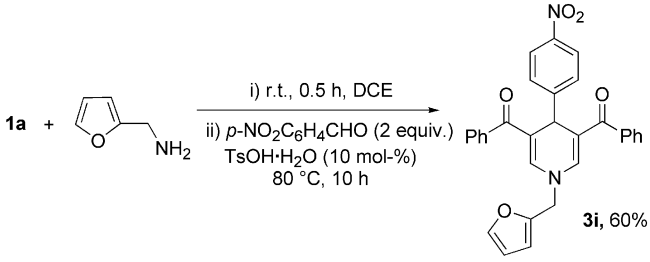
Scheme 2.

On the basis of the above observations, a possible reaction mechanism is proposed in Scheme 3. First, nucleophilic addition of enaminone **2** to the carbonyl group of the aldehyde occurs to form **6**. This process is different from the Hantzsch reaction, which includes a Michael addition of the enamine to the α,β-unsaturated carbonyl compound. Compound **6** reacts with another enaminone molecule through benzylic substitution to generate divinylmethane (*Z*)-**4**. Isomerization of (*Z*)-**4** into (*E*)-**4** followed by nucleophilic attack of the amino group to the enone moiety leads to cyclized product **3**.



Scheme 3.

To make this overall approach more convenient, a one-pot process proceeding through sequential reactions was also checked. Typically, alkynone **1a** (1 equiv.) was first treated with furan-2-ylmethanamine (1 equiv.) in DCE for 0.5 h to form compound **2** in situ, and $TsOH·H_2O$ (10 mol-%) was then added. The mixture was stirred at 80 °C for 10 h to give 1,4-DHP **3i** in 60% yield (Scheme 4).



Scheme 4.

Conclusions

In conclusion, we have successfully developed an efficient method for the synthesis of 1,4-DHPs without substituents at the C-2 and C-6 positions through an acid-catalyzed vinylation/cyclization cascade reaction, in which direct conversion of the C–H bonds of enaminones to C–C bonds was achieved. The 1,4-DHP products can also be constructed from alkynones, amines, and aldehydes by a sequential process that omits the isolation of the enaminone intermediates. Further application of this novel acid-catalyzed procedure and endeavors to extend the scope of the reaction such as for the synthesis of unsymmetrical substituted 1,4-DHPs are under progress in our group.

Experimental Section

Typical Procedure for the $TsOH·H_2O$- or $NaAuCl_4·2H_2O$-Catalyzed Synthesis of 1,4-Dihydropyridines 3 from (*Z*)-Enaminones 2 and Aldehydes: To a solution of (*Z*)-enaminone **2** (0.4 mmol) and aldehyde (0.4 mmol) in DCE (2 mL) was added $TsOH·H_2O$ (3.8 mg, 10 mol-%) or $NaAuCl_4·2H_2O$ (8.0 mg, 10 mol-%). The resulting solution was stirred at 80 °C until the reaction was complete, as monitored by thin-layer chromatography. The solvent was evaporated in vacuo, and the residue was purified by chromatography on silica gel to afford 1,4-dihydropyridine derivatives **3**.

[1-(4-Methoxyphenyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-diyl]-bis(phenylmethanone) (3a): Yield: 88 mg (85%); yellow solid, m.p. 225–226 °C. ^1H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.78 (s, 3 H, OCH_3), 5.78 (s, 1 H, 4-H), 6.89–6.93 (m, 2 H), 7.11–7.15 (m, 2 H), 7.30 (s, 2 H, 2-H), 7.36–7.40 (m, 4 H), 7.44–7.48 (m, 2 H), 7.51–7.53 (m, 4 H), 7.70–7.73 (m, 2 H), 8.12–8.16 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, Me_4Si): δ = 37.08, 55.52, 115.16, 118.67, 123.07, 123.56, 128.25, 128.32, 129.04, 131.23, 135.92, 138.51, 140.79, 146.37, 152.84, 158.68, 193.94 ppm. HRMS: calcd. for $C_{32}H_{24}N_2O_5$ 516.1685; found 516.1696.

Supporting Information (see footnote on the first page of this article): Experimental details and spectroscopic data of all new compounds.

Acknowledgments

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[12] CCDC-767582 (for **3c**) and -767583 (for **4b**) 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.

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