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Divergent synthesis of dual 1,4-dihydropyridines with different substituted patterns from enaminones and aldehydes through domino reactions†

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A concise and efficient protocol for the regioselective synthesis of dual 1,4-dihydropyridines with several substituted patterns has been developed from a cascade cyclization of enaminones and aldehydes in different media (EtOH/CH₃CN). The one-pot cascade reaction involves at least five reactive sites and generates multiple C–C and C–N bonds. The established protocol explores the chemistry of enaminones by employing their three reactive sites. The method has several advantages including mild conditions, operational simplicity, and high bond-forming efficiency. It may offer promise in a variety of biochemical applications.

Introduction

Molecularly diverse and complex heterocycles play an important role in both organic synthesis and discovery of new pharmaceutical reagents.¹ 1,4-Dihydropyridines (1,4-DHPs) derivatives represent one of the most important classes of heterocycles due to their application in biological activities and molecular functions. For example, 1,4-DHPs are contained in marketed drugs such as the calcium channel blockers nifedipine, felodipine, nicardipine, and nimodipine. During the last several decades, it has been demonstrated that 1,4-DHPs are involved in various biological applications, *i.e.* antibacterial,² anticonvulsant,³ anti-HIV,⁴ anti-tumour,⁵ radioprotective,⁶ and neuroprotection⁷ activities; they could also act as adenosine-A3 receptor antagonism⁸ and sirtuin inhibitor.⁹ In view of their high significance, numerous methodologies for 1,4-DHPs have been introduced.¹⁰ However, few strategies have been successfully developed for efficient and concise access to highly functionalized and molecularly diverse target products. Therefore, it is of great importance to build libraries of target compounds in a parallel manner.

Multicomponent domino reactions (MCDRs) are powerful tools in modern organic synthesis because they enable more than

two building blocks to combine in a single-step operation to generate complex structures through the simultaneous formation of multiple bonds.¹¹ With their inherent characteristics, *i.e.*, step efficiency, atom economy, target molecules diversity, operational simplicity. MCDRs have become an essential tool for generating complex molecular libraries in the screening of biologically and pharmacologically active candidates.

As a group of versatile and powerful synthons, enaminones have been used for construction of diverse heterocyclic systems.¹² These compounds include acridines,¹³ indoles,¹⁴ naphthyridines,¹⁵ quinolones,¹⁶ pyrroles,¹⁷ thiazines,¹⁸ pyridines,¹⁹ and thiazoles.²⁰ Some of these heterocycles which are synthesized from enaminones also demonstrate promising biological activity.²¹ So far, a number of natural product-like heterocycles have been successfully synthesized based on enaminones. Their synthetic methodology and associated medicinal activity should be engaged in the chemistry community.

In pursuit of our research interests regarding the development of MCRs based on enaminones, we report a convenient and efficient protocol for the regioselective synthesis of two libraries of 1,4-DHPs **3** and **4** *via* a tandem annulation of enaminones **1** and aldehydes **2** in EtOH and CH₃CN, respectively (Scheme 1). At least five distinct reactive sites participate in this process.

Results and discussion

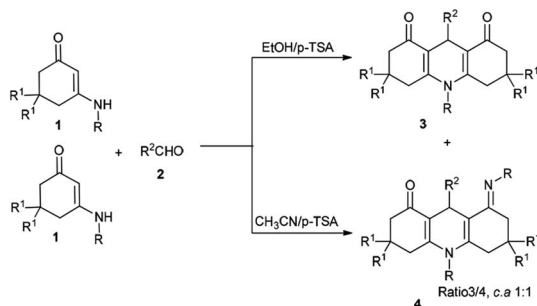
On the basis of our recent work, we examined the domino reaction which employed *N*-*p*-F-Ph substituted enaminone **1a** and 4-chlorobenzaldehyde **2a** as the substrates (Table 1).

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Scheme 1 Proposed mechanism for the construction of 1,4-DHPs 3 and 4.

First, the reaction was executed without any catalyst in anhydrous ethanol at reflux; no reaction occurred even within 3 hours (Table 1, entry 1). Next, different types of organic bases, such as piperidine, Et₃N, DBU, and DABCO, were employed as catalysts, but no transformation was observed (Table 1, entries 2–5). Nevertheless, when *p*-TSA (0.2 equiv.) was added, compound 3a was obtained in a yield of 66% (Table 1, entry 6). Other acids, such as TFA, HOAc and L-proline were also investigated, but could not generate the reaction efficiently (Table 1, entries 7–9). The reaction conditions were then optimized by screening several solvents. When *p*-TSA was added to a solution of 1a and 2a in CH₃CN (Table 1, entry 10), a new compound 4a

Table 1 Optimization of the reaction conditions for the model reaction^a

Entry	Solvent	Catalyst ^b	Time (h)	Yield ^c (%)	
				3a	4a
1	EtOH	—	4	n.r	n.r
2	EtOH	Piperidine	3	n.r	n.r
3	EtOH	Et ₃ N	3	n.r	n.r
4	EtOH	DBU	3	n.r	n.r
5	EtOH	DABCO	3	n.r	n.r
6	EtOH	<i>p</i> -TSA	3	66	n.r
7	EtOH	TFA	2	64	n.r
8	EtOH	HOAc	2	n.r	n.r
9	EtOH	L-proline	2	n.r	n.r
10	CH ₃ CN	<i>p</i> -TSA	2	43	36
11	CH ₃ CN	TFA	2	50	34
12	CH ₃ CN	TfOH	2	n.r	Trace
13	1,4-Dioxane	<i>p</i> -TSA	2	30	25
14	DMF	<i>p</i> -TSA	2	45	28
15	CH ₃ OH	<i>p</i> -TSA	2	n.r	n.r

^a The reaction was performed with 1a (1.0 mmol), 2a (0.6 mmol), and the solvent (15 mL) was under reflux temperature. ^b Catalyst (0.3 mmol) was added to the reaction. ^c Isolated yields were based on enaminone 1a.

was generated in 36% yield. In order to efficiently obtain a single final product, additional attempts were made. For example, three types of solvents, *i.e.*, 1,4-dioxane, DMF, and CH₃OH, and acidic catalysts TFA, and TfOH were used in the reaction. However, the yields of 3a and 4a were decreased, and likewise, the vying preference for the formation of 4a was unsatisfied (Table 1, entries 11–15). Thus, ethanol was the best medium for selectively obtaining product 3a. It was discovered that the optimum reaction conditions for the synthesis of 3a include *p*-TSA as the catalyst and EtOH as the medium at reflux for 3 h. Conversely, the best conditions for the preparation of 4a are conducted in CH₃CN.

With the optimal reaction conditions, the synthesis of 1,4-DHPs 4 was tested by using a range of readily available enaminones and different substituted aldehydes. As shown in Table 2, for precursors 1 and 2 bearing either electron-withdrawing or electron-donating substituents on the aromatic ring, or the aromatic groups (for 2) with diverse substitution patterns (*para* or *meta*), all reactions proceeded smoothly to provide the corresponding 1,4-DHPs derivatives. The reaction was also investigated by using alkyl enaminone 1h, which yielded the corresponding target molecule 3m.

After completing the synthesis of compounds 3, the domino reaction was studied for preparing other target molecules 4 (Scheme 2). First, the scope of substrates 1 was tested by using 3-amino-5,5-dimethylcyclohex-2-enones. The reaction results of various 3-aminocyclohex-2-enonephenyls with aldehydes

Table 2 Substrate scope of 1 and synthesis of target molecules 3^a

Entry	1 (R/R ¹)	2 (R ²)	3	Yield ^b (%)
1	1a (4-FC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3a	66
2	1a (4-FC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3b	58
3	1b (3-FC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3c	62
4	1c (3-ClC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3d	63
5	1c (3-ClC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3e	68
6	1d (4-BrC ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3f	65
7	1d (4-BrC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3g	62
8	1e (3-BrC ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3h	60
9	1f (C ₆ H ₅ /CH ₃)	2a (4-ClC ₆ H ₅)	3i	65
10	1f (C ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3j	63
11	1f (C ₆ H ₅ /CH ₃)	2c (4-OCH ₃ C ₆ H ₅)	3k	64
12	1g (3-CH ₃ C ₆ H ₅ /CH ₃)	2b (C ₆ H ₅)	3l	62
13	1h (<i>n</i> -butyl/CH ₃)	2a (4-ClC ₆ H ₅)	3m	70
14	1i (4-ClC ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3n	71
15	1j (3-ClC ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3o	72
16	1k (3-BrC ₆ H ₅ /H)	2c (4-OCH ₃ C ₆ H ₅)	3p	68
17	1l (4-CH ₃ C ₆ H ₅ /H)	2a (4-ClC ₆ H ₅)	3q	60
18	1a (4-FC ₆ H ₅ /CH ₃)	2d (<i>n</i> -propyl)	3r	62

^a The reaction was performed with 1 (1.0 mmol), 2 (0.6 mmol), and *p*-TSA (0.3 mmol) in EtOH (15 mL) at reflux for 3 hours. ^b Isolated yields based on enaminones 1.



demonstrate that the process tolerates both 3-amino-5,5-dimethylcyclohex-2-enones **1** and aromatic aldehydes **2** bearing either electron-donating or electron-withdrawing substituents on the aryl group. However, as both compounds **3** and **4** are generated from this reaction, the yields of **4** would be relatively low (yields **3** : **4**, *c.a.* 1 : 1).

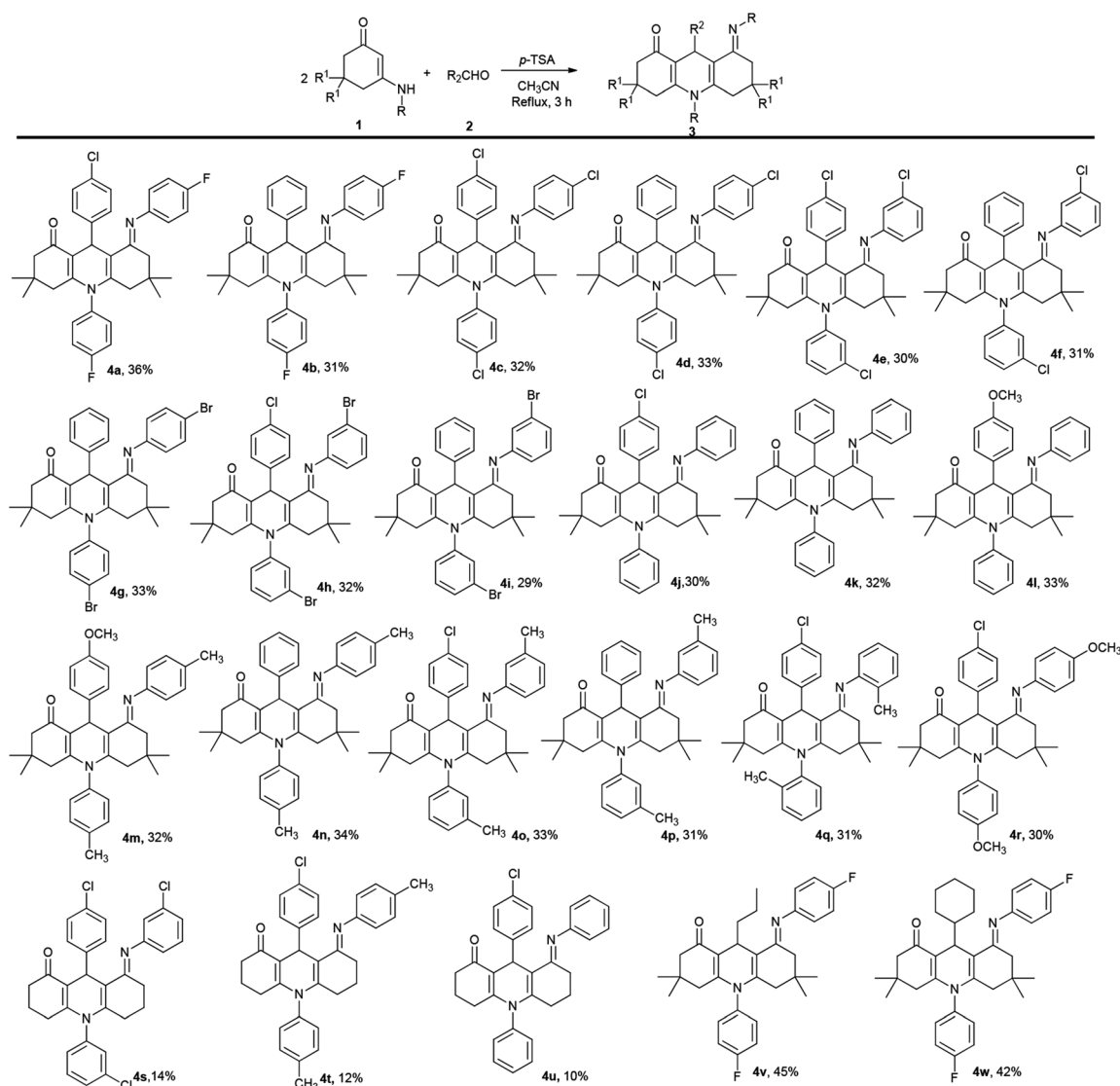
Next, the reaction was examined using *N*-substituted 3-aminocyclohex-2-enonephenyls. Unfortunately, the results did not yield much success. Most of the *N*-substituted 3-aminocyclohex-2-enonephenyls generated a low yield of **4** but a high yield of **3** (Scheme 2, **4s–4u**). It is worthwhile noting that compounds **4** are difficult to separate by conventional methods, like column chromatography and recrystallization. Hitherto, only three compounds were readily obtained by using *N*-substituted 3-aminocyclohex-2-enonephenyls.

Finally, aliphatic aldehydes butyraldehyde and cyclohexanecarboxaldehyde were also employed in this process, and both reactions proceeded well giving the corresponding 1,4-DHPs

4v and **4w**. And it was observed that the aliphatic aldehydes gave the major compounds **4** while products **3** were scarcely generated.


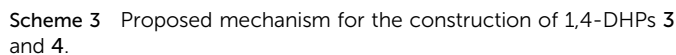
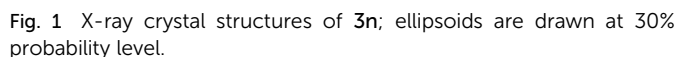
The chemical structures of 1,4-DHPs **3** and **4** were characterized by IR, ¹H NMR, ¹³C NMR, and HRMS, and unequivocally confirmed by X-ray diffraction analysis of a monocrystal of **3n** (Fig. 1, CCDC 1819954).

The possible mechanism for the formation of products **3/4** is shown in Scheme 3. Take aromatic aldehyde as the example. First, the benzaldehyde **2** accepts a proton to form **5**. Enaminone **1** serves as a heteroene component to react with **5** accompanying the loss of one molecule of H₂O to generate intermediate **6** *via* an aza-ene reaction. Following this, compound **6** undergoes imine-enamine tautomerization to produce **7**. Intermediate **7** accepts a proton to form **8**, and the elimination of water from intermediate **7** gives iminium ion **9**. Enaminone **1** then participates in a Michael addition with compound **9** to form intermediate **10**. Two potential reactions then occur in intermediate **10**. In pathway 1, the –NH group



Scheme 2 Substrate scope of the reaction for 1,4-DHPs **4**. The reaction was performed with **1** (1.0 mmol), **2** (0.6 mmol), and *p*-TSA (0.3 mmol) in CH₃CN (10 mL) at reflux for 2 h. The yields were isolated based on enaminones **1**.





solution (2 mL) and extracted with ethyl acetate (40 mL). The organic phase were dried over Mg_2SO_4 , and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate = 1 : 1) giving a yellow solid **4**.

(E)-9-(4-chlorophenyl)-10-(4-fluorophenyl)-8-((4-fluorophenyl)imino)-3,3,6,6-tetramethyl-3,4,5,6,7,8,9,10-octahydroacridin-1(2H)-one (4a). Yellow solid; mp 260–262 °C; IR (KBr): 2959, 1649, 1500, 1371, 1226, 846 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.41 (t, J = 8.0 Hz, 2H, ArH), 7.17–7.27 (m, 6H, ArH), 6.87–6.93 (m, 2H, ArH), 6.41–6.47 (m, 2H, ArH), 5.54 (s, 1H, CH), 5.25 (d, J = 32.4 Hz, 1H, CH), 1.92–2.24 (m, 6H, 3 \times CH_2), 1.67–1.83 (m, 2H, CH_2), 0.95 (s, 3H, CH_3), 0.85 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ = 195.8, 162.4 (d, $^1J_{\text{C-F}}$ = 245.0 Hz), 158.8 (d, $^1J_{\text{C-F}}$ = 238.5 Hz), 150.3, 148.0, 145.4, 142.0, 145.4, 142.0, 135.4, 131.4, 131.1, 129.6, 127.8, 120.7 (d, $^3J_{\text{C-F}}$ = 7.5 Hz), 120.6 (d, $^3J_{\text{C-F}}$ = 7.5 Hz), 117.0 (d, $^2J_{\text{C-F}}$ = 21.5 Hz), 115.4 (d, $^2J_{\text{C-F}}$ = 21.9 Hz), 115.1 (d, $^2J_{\text{C-F}}$ = 21.9 Hz), 114.6, 113.1, 50.2, 41.9, 40.8, 33.2, 32.4, 31.4, 29.9, 29.6, 26.7; HRMS (ESI-TOF): m/z calcd for $\text{C}_{35}\text{H}_{34}\text{ClF}_2\text{N}_2\text{O}^+[(\text{M} + \text{H})^+]$, 571.2322; found, 571.2323.

(E)-10-(4-fluorophenyl)-8-((4-fluorophenyl)imino)-3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,8,9,10-octahydroacridin-1(2H)-one (4b). Yellow solid; mp 233–234 °C; IR (KBr): 2957, 1644, 1579, 1367, 1267, 853 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ = 7.51 (d, J = 8.0 Hz, 2H, ArH), 7.24–7.28 (m, 6H, ArH), 7.15–7.11 (m, 1H, ArH), 6.91–6.95 (m, 2H, ArH), 6.48 (d, J = 8.0 Hz, 2H, ArH), 5.63 (s, 1H, CH), 2.01–2.27 (m, 6H, 3 \times CH_2), 1.81–1.87 (m, 2H, CH_2), 0.99 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.74 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ = 195.9, 162.3 (d, $^1J_{\text{C-F}}$ = 249.0 Hz), 158.8 (d, $^1J_{\text{C-F}}$ = 238.0 Hz), 150.19, 148.21, 146.69, 141.85, 135.57, 135.53, 131.59, 128.18, 127.69, 125.57, 120.72 (d, $^3J_{\text{C-F}}$ = 8.0 Hz), 116.9 (d, $^2J_{\text{C-F}}$ = 21.3 Hz), 115.3 (d, $^2J_{\text{C-F}}$ = 22.0 Hz), 115.1 (d, $^2J_{\text{C-F}}$ = 22.0 Hz), 114.9, 113.4, 50.3, 41.9, 41.8, 40.8, 33.5, 32.4, 31.5, 30.0, 29.6, 26.8, 26.69; HRMS (ESI-TOF): m/z calcd for $\text{C}_{35}\text{H}_{35}\text{F}_2\text{N}_2\text{O}^+[(\text{M} + \text{H})^+]$, 537.2712; found, 537.2713.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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