JOC*Note*

Novel Regioselectivity: Three-Component Cascade Synthesis of Unsymmetrical 1,4- and 1,2-Dihydropyridines

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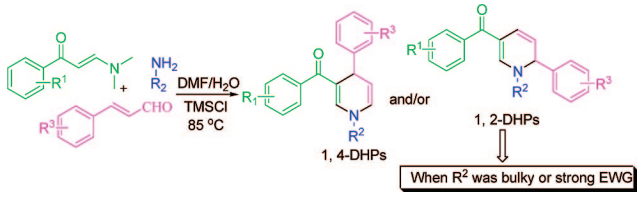

The three-component sequential reaction of α,β-unsaturated aldehydes, amines, and enaminones proceeded smoothly to give 1,3,4-trisubstituted 1,4-dihydropyridines in aqueous DMF. Moreover, the unexpected regioselective formation of 1,2-dihydropyridines has been observed for the first time in such an approach. On the basis of a systematic study, the novel regioselectivity could be assigned both to steric and electronic effects originating from the amine partner.

Nitrogen-containing heterocyclic skeletons are prevalent in pharmaceuticals and biologically functional molecules. The 1,4-dihydropyridine (1,4-DHP) skeleton is one of the most versatile heterocyclic pharmacophores since it has been found as the central fragment in many clinical pharmaceuticals.[1] The most notable examples are the series of 1,4-DHP-based calcium channel blocker drugs such as nifedipine, felodipine, and nicardipine (Figure 1), which are widely used for the treatment of hypertension and related cardiovascular diseases.[1,2] In addition, the splendid results obtained from the study with 1,4-DHPs as an α_{1a} adrenoceptor-selective antagonist suggested their promising potential in treating benign prostatic hyperplasia.[3] What is more, 1,4-DHPs have been reported with miscellaneous new pharmacological functions in recent years. To list but a few, radioprotection, cerebral anti-ischemic agents, platelet antiaggregatory agents, neuroprotection, as well as HIV protease inhibition, etc.[4] Moreover, in terms of synthetic chemistry, the high reactivity endowed 1,4-DHPs with widespread application in the synthesis of useful chemicals.[5]

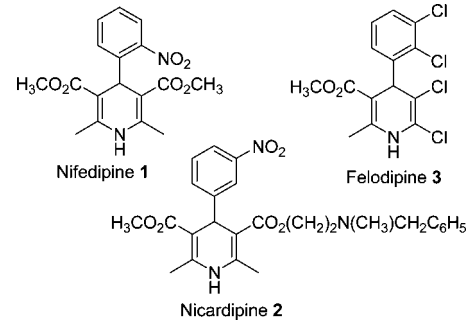

FIGURE 1. 1,4-DHP drugs for cardiovascular diseases.

Multicomponent reactions (MCRs) represent one of the most powerful strategies in modern organic synthesis. Compared to the traditional multistep methods of heterocycle synthesis, MCRs require substantially simpler materials and operations, while providing significantly higher efficiency and molecular complexity. Most importantly yet, the huge compound libraries perfectly cater to the requirement of high throughput screening in modern drug discovery.[6] The most classical synthesis of symmetrical 1,4-DHPs is the three-component condensation of aryl aldehydes, ammonia, or amines and 2 equiv of β-keto esters, which was reported in 1882 by Hantzsch.[7] Despite the long history, sustaining interests in more advanced synthetic methodology of 1,4-DHPs have been triggered by the prolific pharmacological properties imbedded in 1,4-DHPs.[8,9]

The symmetrical DHP unit, although present in many commercial drugs, is not a requirement of receptors but the consequence of the Hantsch synthetic methodology. Actually, unsymmetrical 1,4-DHPs also represent effective drug moieties (Felodipine **3**, for example) or sometimes display even better pharmacological activities.[10] Therefore, the synthesis of unsymmetrical 1,4-DHPs justifies equal importance as for the symmetrical 1,4-DHPs in terms of drug discovery. However, the nature of the Hantsch reaction employing two identical β-keto

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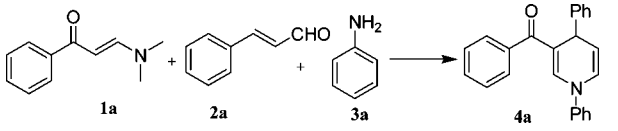
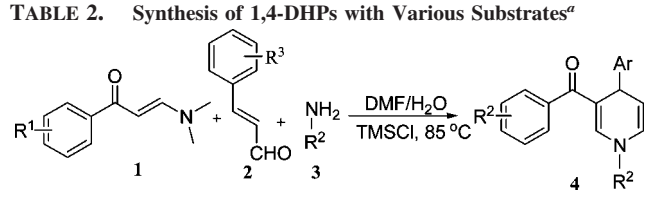
TABLE 1. Different Conditions for the Synthesis of 1,4-DHP 4a[a]



entry	catalyst	sovent(s)[b]	temp (°C)	yield (%)[c]
1	HCl[d]	DMF	85	27
2	TFA	DMF	85	32
3	PTSA	DMF	85	45
4	ACOH	DMF	85	trace
5	$InCl_3$	DMF	85	
6	$FeCl_3 \cdot 6H_2O$	DMF	85	
7	TMSCl	DMF	85	63
8	TMSCl	H_2O	85	trace
9[e]	TMSCl	H_2O/EtOH	85	
10[f]	TMSCl	H_2O/DMF	85	34
11[f]	TMSCl	H_2O/DMF	85	40
12[f]	TMSCl	H_2O/DMF	85	61
13[f]	TMSCl	H_2O/DMF	85	41
14	TMSCl	H_2O/DMF	85	67
15	TMSCl	H_2O/DMF	100	39
16	TMSCl	H_2O/DMF	70	<15

[a] Reaction conditions: enaminone (0.3 mmol), aniline (0.3 mmol), and cinnamaldehyde (0.35 mmol) in 1 mL of solvent, unless specified, the catalyst was used in 1 equiv mol and reaction time was 10 h. [b] 0.5 mL of H_2O and 0.5 mL of EtOH/DMF were used in those mixed solvents. [c] Isolated yield based on enaminone. [d] 37% commercial HCl solution was used. [e] No target product was detected. [f] The catalyst amounts used in entries 10−13 were 2.5, 2.0, 1.5, and 0.5 equiv mol, respectively.

TABLE 2. Synthesis of 1,4-DHPs with Various Substrates[a]



entry	R^1	R^2	R^3	DHP	yield (%)[b]
1	H	Ph	H	**4a**	67
2	H	4-MeC_6H_4	H	**4b**	80
3	H	4-$MeOC_6H_4$	H	**4c**	76
4	H	4-FC_6H_4	H	**4d**	72
5	H	4-ClC_6H_4	H	**4e**	64
6	H	4-BrC_6H_4	H	**4f**	66
7	H	4-AcC_6H_4	H	**4g**	61
8	H	3-ClC_6H_4	H	**4h**	83
9	4-Cl	Ph	H	**4i**	57
10	4-MeO	3-ClC_6H_4	H	**4j**	56
11	4-Cl	4-FC_6H_4	H	**4k**	68
12	4-Cl	4-BrC_6H_4	H	***4l***	76
13	4-MeO	4-FC_6H_4	H	**4m**	71
14	4-NO_2	4-$MeOC_6H_4$	H	**4n**	62
15	4-NO_2	4-FC_6H_4	H	**4o**	59
16	H	4-FC_6H_4	2-Cl	**4p**	63
17	4-Cl	4-BrC_6H_4	2-Cl	**4q**	60
18	H	$PhCH_2$	H	**4r**	68
19	H	cyclopropyl	H	**4s**	57
20	4-Cl	isopropyl	H	**4t**	<10

[a] General conditions: 0.3 mmol of enaminone **1**, 0.35 mmol of aldehyde **2**, 0.3 mmol of amine **3**, and 0.3 mmol of TMSCl mixed in 1 mL of solvents (0.5 mL of H_2O + 0.5 mL of DMF), stirred at 85 °C for 10 h. [b] Isolated yield based on enaminone.

esters predetermined the symmetrical structure of the products. The use of different β-keto esters or analogues to prepare unsymmetrical 1,4-DHPs suffers from the intervention of side reactions due to homo-condensations.[11]

A practical strategy to exclude these side reactions is the two-step method, in which the amine/ammonia is reacted with active methylene ketones to form the enamino ester intermediates prior to further incorporation of the aldehydes and the other active methylene ketones.[8a,12] Recently, α,β-unsaturated aldehydes have been disclosed as good reaction partners to incorporate the enamino intermediate generated from β-keto esters and an amine, to give unsymmetrical 5- or 5,6-unsubstituted 1,4-DHPs.[13] Although elegant results have been obtained in those works, most of the endeavors still focus on the improvement of the catalyst system in the same reaction and the diversity of products was not actually widely expanded. To the best of our knowledge, few alternative strategies in the unsymmetrical 1,4-DHP syntheses are currently available in the literature.[14] Thus, in terms of designing and screening new lead compounds, searching for new and facile MCRs to prepare 1,4-DHPs with new functional substituents is highly desirable work. Our group has been engaged in recent years in developing new MCRs to synthesize novel functional heterocyclic compounds.[15] On the basis of our previous approach in this field, we report herein a facile three-component synthesis of novel 1,3,4-trisubstituted unsymmetrical 1,4-DHPs and the first observed regioselective synthesis of 1,2-DHPs during an α,β-unsaturated aldehyde-promoted DHP synthesis.

Our study began with the simultaneous use of enaminone **1a**, cinnamaldehyde (**2a**), and aniline (**3a**) in 0.3 mmol scale in DMF by employing 1.0 equiv mol TMSCl as promoter. After10 h at 85 °C conversion was completed (TLC) and the 1,4-DHP (**4a**) was isolated in 63% yield (entry 7, Table 1). To improve the yields, we examined this reaction using different Brønsted and Lewis acids (entries 1−6). However, the screened candidates did not display the expected improvements. Subsequently, we further turned to testing the effect of solvents. EtOH, CH_3CN, or toluene showed no superiority to DMF.

Interestingly, it has been found that employing aqueous DMF as the medium slightly improved the yield of the reaction (entry 14), while no product was observed in aqueous EtOH (entry 9). Finally, by using TMSCl as the promoter, optimal conditions (1.0 equiv of TMSCl, 85 °C in aqueous DMF) were found.

To validate the generality of this new synthetic protocol, various substrates have been subjected to the reaction. Both

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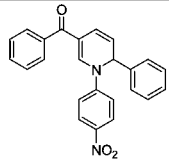
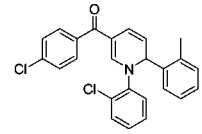
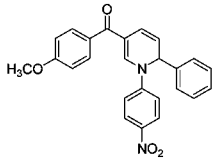
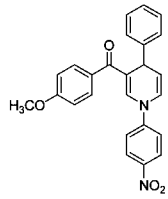
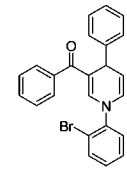
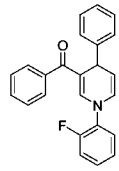
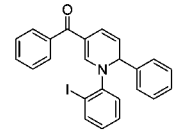
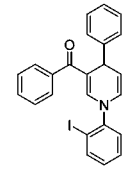
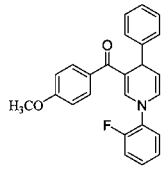
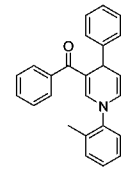
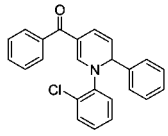
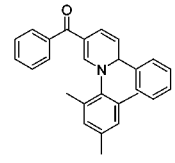
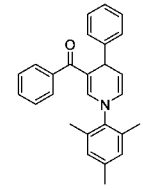
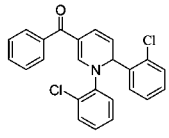
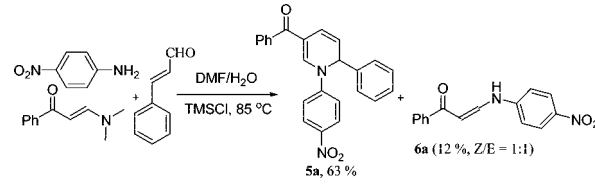
TABLE 3. Regioselective Synthesis of 1,4-DHPs and 1,2-DHPs[a]

Entry	1,2-DHP/1,4-DHP		Yield (%)[b]	Entry	1,2-DHP/1,4-DHP		Yield (%)[b]
1	 **5a**	-	63/nd[c]	7	 **5g**	-	60/nd
2	 **5b**	 **7b**	53/14	8	-	 **7h**	<10/46
3	-	 **7c**	nd/70	9	 **5i**	 **7i**	51/27
4	-	 **7d**	nd/61	10	-	 **7j**	nd/65
5	 **5e**	-	59/nd	11	 **5k**	 **7k**	51/<10
6	 **5f**	-	52/nd				

[a] Identical conditions as used in Table 2. [b] Isolated yield based on enaminone. [c] nd = not detected.

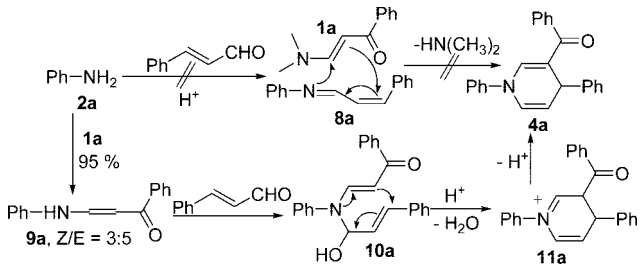
aromatic (Table 2, entries 1−17) and aliphatic amines (entries 18−19) were able to afford the corresponding 1,4-DHPs smoothly. The results displayed in Table 2 confirmed that reactants with diversified substituents tolerated the protocol well. However, unexpected products were observed when sterically hindered aromatic amines or amines with strong electron withdrawing groups were used. In the case of *p*-nitroaniline, the observed product was not, as in the previous cases, the 1,4-DHP but the 1,2-DHP **5a** (eq 1), while **6a** was isolated as a side product. Similarly, the 1,2-DHP was observed in the subsequent reaction employing *o*-chloroaniline as the substrate. The structure of these 1,2-DHPs was clearly assigned on the basis of spectral analysis and X-ray crystal diffraction (see the Supporting Information for the crystal structure determination of **5e**). To the best of our knowledge, such a regioselective synthesis of 1,2-DHPs had not been reported previously.



(1)

To examine the factors contributing to the selectivity, a series of reactions, applying *p*-nitroaniline and ortho-substituted anilines, have been implemented. The results are highlighted in Table 3. As displayed by the results, both 1,2-DHPs and/or

SCHEME 1. Preliminary mechanistic investigations



1,4-DHPs could be furnished depending on the properties of the substituent. *p*-Nitroaniline mainly offered 1,4-DHPs as products, while the results with different *o*-anilines indicate that the regioselectivity was affected by both the size and the electronic profiles of the ortho groups. In the reaction of 2-haloanilines, fluoro- and bromoaniline led to 1,4-DHP as the dominant product (entries 3, 4, and 8), while 2-chloroaniline gave 1,2-DHP as the only isolated product (entries 5−7). Integrating the 1,2- and/or 1,4-DHP furnished in the 2-iodoaniline, 2-methylaniline, and 2,4,6-trimethylaniline entries (entries 9−11), it is evident that the bulky ortho group is important, but not the only inducing factor for 1,2-DHP formation. What is notable is that the sequence of adding the reactants did not make a visible difference in the regioselectivity of the reactions.

To explore the possible pathways of these cascade transformations, we attempted to prepare likely intermediates. Two potential pathways might account for the DHP formation: one is the formation of an imine intermediate **8a**, the other is the formation of an enaminone **9a** (Scheme 1). At first, aniline **2a** and cinnamaldehyde were subjected to the standard reaction conditions. However, the reaction led to the formation of a paste-like residue, the ESI-MS analysis of which did not indicate the presence of **8a**. Moreover, adding enaminone **1a** to the mixture did not provide the target product **4a**, either. Conversely, however, the enaminone intermediate **9a** was immediately formed upon addition of TMSCl to the mixture of enaminone **1a** and aniline at room temperature. The isolated **9a** was then subjected to standard catalysis condition with cinnamaldehyde to give the 1,4-DHPs **4a** in 70% yield. Thus, the formation of **9a** plausibly served as the key step in this multicomponent cascade reaction (Scheme 1).

In conclusion, we have presented a facile and novel three-component version for the synthesis of a new class of unsymmetrical 1,4-DHPs. Also, the interesting regioselective formation of 1,2-DHPs has been disclosed and systematically surveyed for the first time during the α,β-unsaturated aldehyde-based DHPs synthesis.

Experimental Section

General Procedure for the Synthesis of 1,4-DHPs and 1,2-DHPs. Enaminone **1** (0.3 mmol) and amine **3** (0.3 mmol) were placed in a round-bottomed flask. Cinnamaldehyde (**2**) (0.35 mmol) was subsequently added together with 0.5 mL of DMF and 0.5 mL of H_2O. Finally, 0.04 mL of TMSCl (∼0.3 mmol) was injected into the mixture. The mixture was stirred at 85 °C for 10 h. After being cooled to room temperature, the reaction mixture was extracted with 3 × 10 mL of ethyl acetate and the combined organic layer was dried with anhydrous Na_2SO_4. The corresponding 1,4- and 1,2-DHPs were then obtained by silica gel chromatography.

1,4-Diphenyl-3-benzoyl-1,4-dihydropyridine (4a): colorless crystal; mp 135−138 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.55 (d, 2 H, J = 6.8 Hz), 7.45−7.36 (m, 8 H), 7.34−7.27 (m, 4 H), 7.19−7.16 (m, 2 H), 6.75 (d, 1 H, J = 7.8 Hz), 5.26 (dd, 1 H, J = 7.8, 4.8 Hz), 4.81 (d, 1 H, J = 4.8 Hz); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 195.0, 148.1, 144.2, 143.2, 140.5, 131.8, 131.0, 129.5, 129.3, 128.7, 127.3, 126.4, 126.2, 120.7, 115.3, 112.4, 38.6; IR (KBr, cm^{-1}) 3027, 2853, 1672, 1627, 1591, 1493, 1331, 1260, 1134, 937, 839, 720, 693; HRMS calcd for $C_{24}H_{19}NONa$ ([M + Na]$^+$) 360.1359, found 360.1346.

1-(2-Chlorophenyl)-2-phenyl-5-benzoyl-1,2-dihydropyridine (5e): colorless crystal; mp 182−185 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.54 (d, 2 H, J = 6.6 Hz), 7.46−7.41 (m, 5 H), 7.32 (d, 5 H, J = 10.0 Hz), 7.28−7.24 (m, 3H), 7.03 (s, 1 H), 6.71 (d, 1 H, J = 10.1 Hz), 5.84 (d, 1 H, J = 4.2 Hz), 5.53 (dd, 1 H, J = 10.1 Hz, 4.2 Hz); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 190.7, 151.2, 142.4, 142.3, 140.5, 131.8, 131.4, 130.8, 130.4, 129.9, 129.8, 129.6, 129.5, 129.3, 129.2, 128.6, 120.0, 119.6, 109.2, 65.0; IR (KBr, cm^{-1}) 3050, 3026, 1638, 1608, 1557, 1480, 1416, 1320, 1263, 1060, 910, 777, 698; HRMS calcd for $C_{24}H_{18}ClNONa$ ([M + Na]$^+$) 394.0969, found 394.0964.

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Supporting Information Available: General experimental procedure, copies of ^{1}H and ^{13}C NMR spectra, analytical data for all products, the ORTEP structure of **5e**, as well as a cif file. This material is available free of charge via the Internet at http://pubs.acs.org.

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