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Multicomponent Reactions for Diverse Synthesis of *N*-Substituted and NH 1,4-Dihydropyridines

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The multicomponent reactions of aldehydes, electron deficient alkynes and amines have been successfully performed to yield a number of symmetrical 2,6-unsubstituted 1,4-dihydropyridines (1,4-DHPs). This method has been found generally applicable for the synthesis of both *N*-substituted and *N*-unsubstituted 1,4-DHPs by employing secondary amine to activate the alkyne component via enaminoester intermediates. The present method runs through an enamine type activation, which is different from the known approach employing AcOH as solvent.

Keywords multicomponent reactions, enamine activation, enaminoester, 1,4-dihydropyridine, diversity

Introduction

Molecular diversity consists one of the core issues in modern organic chemistry. In the last decade, under the inspiration of diversity-oriented-synthesis (DOS),[1-3] numerous efforts have been devoted to find powerful synthetic tools for rapidly accessing maximum molecular diversity with minimum cost. In the toolbox enabling DOS for generating molecular libraries, multicomponent reactions (MCRs)[4-9] are now recognized as one of the most useful and powerful strategies. Following the rapid progress in the research area of MCRs, widespread application has been found in many different areas such as chemical biology, natural product synthesis, pharmaceuticals as well as agrochemistry. Among the numerous types of organic products having been provided by MCRs, 1,4-DHPs were known as a class of significantly important and broadly concerned heterocyclic scaffolds. Owing to their splendid pharmaceutical and biological profiles, 1,4-DHPs have kept attracting worldwide interests from chemical and medicinal communities. For example, as simple 1,4-DHPs derivatives, Nifedipine, Felodipine, Amlodipine, Cilnidipine *etc*. have been known as most frequently utilized calcium channel blockers in treating cardiovascular diseases.[10] What's more, recent researches have revealed many new bioactivities[11] with 1,4-DHPs, including neuroprotective[12] phosphodiesterase 4 (PDE4) inhibitory,[13] P-glycoprotein (P-gp)[14] and anticoagulant[15] activities, to name but a few.

As privileged heterocycles, the great potential of 1,4-DHPs in drug discovery also stimulated the sustaining interests in their synthetic research, especially in designing efficient synthetic routes accessing new 1,4-DHPs derivates. Hantzsch reaction, which involves in the multicomponent condensation of aldehydes, β-ketoesters and amines/ammonium has been known as the most classical method in the synthesis of 1,4-DHPs.[16] This method is able to provide 1,4-DHPs via facile operation, but suffers from the limit on product diversity since only 1,4-DHPs with symmetrical structure are accessible. Following the daily increasing requirement on molecular diversity of biologically relevant molecules, developing new MCRs providing 1,4-DHPs containing novel or unprecedented substructures has become an issue of central importance.[17]

Among the newly designed MCRs towards 1,4-DHPs synthesis, those reactions employing enaminones or enaminoesters have been found highly efficient and flexible for synthesizing different types of 1,4-DHPs, including those with symmetrical and unsymmetrical structures.[18-25] However, a disadvantage of enaminone/enaminoester-based MCRs was that enaminones and enaminoesters are not commercially available, prior preparation of enaminones and enaminoesters is required for related synthesis. Therefore, reactions using commercially available substrates such as electron deficient alkynes have attracted chemists' attention. Several different protocols of alkyne-based MCRs have been recently developed for the synthesis of 1,4-DHPs. For example, Wang and co-workers[26] have reported the three-component synthesis of 1,4-DHPs employing electron deficient alkynes (alkyl propiolates),

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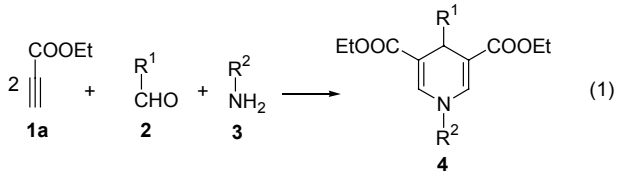
primary amines and salicylaldehydes with the catalysis of TFA, but using other aryl aldehydes rather than salicylaldehyde has been found not applicable because of the indispensable activation effect of hydroxyl group. Later on, Yan and co-workers[27] have established the multicomponent synthesis of different 1,4-DHPs by employing alkynes to incorporate aldehydes, amines and cyanomethylene substrates or cyclic dicarbonyl methylene substrates,[28] respectively. On the other hand, Jiang and co-workers[29] have found that *L*-proline catalyzes the multicomponent reactions of acyclic 1,3-dicarbonyl compounds, aldehydes, amines and alkynes to yield also 1,4-DHPs, and the three-component synthesis of polysubstituted 1,4-DHPs involving primary amines, dialkyl acetylenedicarboxylates and methyl (arylmethylidene) pyruvates has been recently achieved.[30] Interestingly, in despite of their frequent application in 1,4-DHPs synthesis, directly employing electron deficient alkynes to incorporate aldehydes and amines to access symmetrical 1,4-DHPs is rarely available. Currently, the dominant methods of this type are performing the reactions of **1a**, aldehydes **2** and amines **3** in acetic acid to yield 1,4-DHPs of type **4** (Eq. 1), and usually under the harsh reaction conditions of refluxing AcOH.[31-39] This kind of 1,4-DHPs have also been recently found achievable by using similar starting materials under microwave irradiation, but with narrow application scope.[40] As particular example, alkynes of type **1** have been found capable of acting as aldehyde alternatives for the construction of 1,4-DHPs by incorporating *β*-ketoesters and primary amines.[41] In the type of 1,4-DHPs synthesis involving aldehydes, propiolates and amines, the key factor is the formation of enaminoester intermediates via the addition of amines to propiolates. The direct addition of primary amines to propiolates, however, was not easy. Therefore, to achieve corresponding 1,4-DHPs via this method, highly excessive amount of acids (AcOH as solvent) or harsh conditions were usually required. Considering the fact that present methods in the synthesis of 1,4-DHPs of type **4** are still limited, an efficient and generally applicable approach that allows the synthesis of **4** under milder conditions is highly desirable.[42]



During our efforts on exploring effective MCRs for heterocycle synthesis,[18,24,43,44] we have discovered that the multicomponent synthesis of 1,4-DHPs **4** could be achieved by employing the activation of secondary amines as shown in Eq. 1. And we report herein this synthetic method towards various 2,6-unsubstituted symmetrical 1,4-DHPs of type **4**.

Experimental

Synthesis of 1,4-DHPs 4 and 6

General procedure To a 10 mL round-bottle flask with a stir bar were added alkyl propiolate (0.5 mmol), aldehyde (0.3 mmol), amines (0.3 mmol), piperazine (0.15 mmol) and TMSCl (0.45 mmol) in 2 mL DMF. Then the mixture was stirred at 90 ℃ for 12 h (TLC). After cooling down to r.t., 5 mL H_2O was added to the flask, and the resulting mixture was extracted with ethyl acetate (10 mL×3). The combined organic phase was dried over anhydrous sodium sulfate and filtered. The solvent was then removed and the residue was subjected to preparative silica TLC using mixed ethyl acetate and petroleum ether as eluent (*V*/*V*=1/10).

Diethyl-4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a) 73 mg, 71%; pale yellow solid; m.p. 144−146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.67 (s, 2H), 7.47 (t, *J*=7.8 Hz, 2H), 7.32−7.30 (m, 5H), 7.23 (d, *J*=8.0 Hz, 2H), 4.95 (s, 1H), 4.11 (q, *J*=6.8 Hz, 4H), 1.20 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 166.6, 144.7, 143.1, 135.7, 132.3, 130.0, 129.8, 128.2, 126.5, 120.8, 110.6, 60.4, 37.3, 14.2; IR (KBr) *v*: 3028, 2980, 1701, 1666, 1580, 754 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{23}ClNO_4$ $[M+H]^+$: 412.1316, found 412.1317.

Diethyl-4-(4-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4b) 51 mg, 45%; yellow solid; m.p. 131−132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.66 (s, 2H), 7.47 (t, *J*=7.6 Hz, 2H), 7.38 (d, *J*=8.0 Hz, 2H), 7.31−7.28 (m, 3H), 7.25 (d, *J*=8.0 Hz, 2H), 4.94 (s, 1H), 4.11 (q, *J*=7.2 Hz, 4H), 1.20 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 166.6, 145.2, 143.1, 135.7, 131.1, 130.1, 130.0, 126.5, 120.8, 120.5, 110.6, 60.3, 37.4, 14.2; IR (KBr) *v*: 3019, 2986, 1711, 1659, 1583, 696 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{23}BrNO_4$ $[M+H]^+$: 456.0810, found 456.0811.

Diethyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c) 62 mg, 56%; orange solid; m.p. 138−139 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.61 (s, 2H), 7.46−7.38 (m, 6H), 7.25−7.22 (m, 3H), 4.97 (s, 1H), 4.03 (q, *J*=6.8 Hz, 4H), 1.12 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 166.4, 143.1, 136.0, 130.0, 128.7, 126.6, 125.1 (d, J_{C-F}=3.4 Hz, 1C), 120.8, 110.4, 60.4, 37.8, 14.2; IR (KBr) *v*: 3025, 2985, 1710, 1663, 1584, 1150 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{23}F_3NO_4$$[M+H]^+$: 446.1579, found 446.1588.

Diethyl-1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (4d) 70 mg, 74%; yellow solid; m.p. 150−151 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.67 (s, 2H), 7.45 (t, *J*=3.6 Hz, 2H), 7.37 (d, *J*=6.8 Hz, 2H), 7.31−7.24 (m, 5H), 7.15 (t, *J*=6.4 Hz, 1H), 4.97 (s, 1H), 4.10 (q, *J*=6.8 Hz, 4H), 1.19 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 166.8, 146.1, 143.2, 135.5, 129.9, 128.4, 128.0, 126.6, 126.3, 120.8, 111.1, 60.2, 37.8, 14.2; IR (KBr) *v*: 3027, 2977, 1706, 1667, 1584 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{24}NO_4$ $[M+H]^+$:

378.1705, found 378.1713.

Diethyl-1-phenyl-4-*p*-tolyl-1,4-dihydropyridine-3,5-dicarboxylate (4e) 52 mg, 53%; yellow solid; m.p. 110－111 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (s, 2H), 7.37 (t, J=7.6 Hz, 2H), 7.19 (q, J=8.0 Hz, 5H), 6.98 (d, J=7.6 Hz, 2H), 4.85 (s, 1H), 4.02 (q, J=6.4 Hz, 4H), 2.21 (s, 3H), 1.12 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 143.3, 143.2, 136.0, 135.4, 129.9, 128.8, 128.2, 126.3, 120.7, 111.2, 60.2, 37.2, 21.1, 14.2; IR (KBr) v: 3034, 2987, 1693, 1664, 1584, 1389, 1200, 061, 736 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{26}NO_4$ $[M+H]^+$: 392.1862, found 392.1864.

Diethyl-4-(4-methoxyphenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4f) 74 mg, 73%; orange solid; m.p. 145－146 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (s, 2H), 7.45 (t, J=7.2 Hz, 2H), 7.29 (t, J=7.6 Hz, 5H), 6.80 (d, J=7.6 Hz, 2H), 4.91 (s, 1H), 4.11 (q, J=6.4 Hz, 4H), 3.76 (s, 3H), 1.21 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 158.3, 143.3, 138.7, 135.3, 129.9, 129.3, 126.3, 120.7, 113.4, 111.3, 60.2, 55.1, 36.8, 14.2; IR (KBr) v: 3014, 2987, 1705, 1664, 1582 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{26}NO_5$ $[M+H]^+$: 408.1811, found 408.1807.

Diethyl-4-(2-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4g) 86 mg, 84%; yellow solid; m.p. 176－177 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 2H), 7.45 (t, J=7.2 Hz, 2H), 7.38 (d, J=7.6 Hz, 1H), 7.31－7.25 (m, 4 H), 7.18 (t, J=7.2 Hz, 1H), 7.08 (t, J=7.2 Hz, 1H), 5.42 (s, 1H), 4.08 (q, J=7.6 Hz, 4H), 1.17 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 143.7, 143.1, 136.3, 133.4, 131.7, 129.9, 129.4, 127.7, 126.8, 126.4, 120.7, 110.5, 60.3, 35.4, 14.2; IR (KBr) v: 3021, 2984, 1705, 1664, 1573, 751 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{23}ClNO_4$ $[M+H]^+$: 412.1316, found 412.1321.

Diethyl-4-(2-bromophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4h) 90 mg, 79%; yellow solid; m.p. 173－174 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (s, 2H), 7.49 (d, J=7.6 Hz, 1H), 7.45 (d, J=8.0 Hz, 1H), 7.38 (d, J=7.6 Hz, 1H), 7.33－7.22 (m, 5H), 7.01 (t, J=7.6 Hz, 1H), 5.41 (s, 1H), 4.11 (q, J=7.2 Hz, 4H), 1.19 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 145.6, 143.1, 136.3, 132.8, 131.7, 129.9, 127.9, 127.5, 126.4, 123.7, 120.7, 110.8, 60.3, 37.6, 14.3; IR (KBr) v: 3025, 2981, 1709, 1663, 1579, 679 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{23}BrNO_4$ $[M+H]^+$: 456.0810, found 456.0808.

Diethyl-4-(3-hydroxyphenyl)-1-phenyl-1,4-dihydro pyridine-3,5-dicarboxylate (4i) 50 mg, 51%; pale yellow solid; m.p. 199－200 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 2H), 7.41 (t, J=7.20 Hz, 2H), 7.28 (t, J=3.6 Hz, 1H), 7.23 (d, J=8.4 Hz, 2H), 7.14 (t, J=7.6 Hz, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.93 (s, 1H), 6.68 (d, J=8.0 Hz, 1H), 6.33 (brs, 1H), 4.93 (s, 1H), 4.09 (t, J=7.2 Hz, 4H), 1.21 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.1, 156.1, 147.7, 143.0, 135.7, 129.9, 129.1, 126.2, 120.6, 115.5, 113.8, 110.9, 60.5, 37.6, 14.2; IR (KBr) v: 3341, 3024, 2981, 1705, 1662, 1583 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{24}NO_5$ $[M+H]^+$: 394.1654, found 394.1658.

Diethyl-4-(2,4-dichlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4j) 68 mg, 61%; yellow solid; m.p. 164－165 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 2H), 7.46 (t, J=7.2 Hz, 2 H), 7.34－7.26 (m, 5H), 7.17 (d, J=8.4 Hz, 1H), 5.39 (s, 1H), 4.09 (q, J=6.8 Hz, 4H), 1.20 (t, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 143.0, 142.4, 136.6, 134.1, 132.6, 132.5, 130.0, 129.1, 127.1, 126.6, 120.7, 110.0, 60.4, 35.2, 14.2; IR (KBr) v: 3021, 2987, 1712, 1659, 1592, 742 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{22}Cl_2NO_4$ $[M+H]^+$: 446.0926, found 446.0926.

Diethyl-4-(furan-2-yl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4k) 47 mg, 51%; brown solid; m.p. 104－106 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (s, 2H), 7.37 (t, J=7.8 Hz, 2H), 7.22－7.19 (m, 4H), 6.20－6.19 (m, 1H), 6.05 (d, J=3.2 Hz, 1H), 5.07 (s, 1H), 4.10 (q, J=7.2 Hz, 4H), 1.17 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 157.3, 143.2, 141.2, 136.5, 129.9, 126.4, 121.0, 110.4, 107.8, 105.7, 60.3, 31.3, 14.3; IR (KBr) v: 3056, 2978, 1706, 1668, 1585 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{21}NNaO_5$ $[M+Na]^+$: 390.1317, found 390.1317.

Diethyl-1,4-bis(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4l) 71 mg, 64%; yellow solid; m.p. 118－121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (s, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.25－7.22 (m, 4H), 4.94 (s, 1H), 4.11 (q, J=7.2 Hz, 4H), 1.20 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 144.4, 141.6, 135.2, 132.4, 132.0, 130.0, 129.8, 128.2, 122.0, 111.1, 60.4, 37.3, 14.2 cm^{-1}; IR (KBr) v: 3029, 2979, 1679, 1666, 1577, 756; ESI-HRMS calcd for $C_{23}H_{22}Cl_2NO_4$ $[M+H]^+$: 446.0926, found 446.0919.

Diethyl-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4m) 45 mg, 41%; yellow solid; m.p. 119－120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (s, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 4H), 6.96 (d, J=8.8 Hz, 2H), 4.95 (s, 1H), 4.10 (q, J=7.2 Hz, 4H), 3.83 (s, 3H), 1.19 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 158.3, 145.0, 136.6, 136.5, 132.2, 129.8, 128.1, 122.9, 115.0, 109.9, 60.2, 55.6, 37.2, 14.2; IR (KBr) v: 3011, 2979, 1711, 1666, 1582, 757 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{25}ClNO_5$ $[M+H]^+$: 442.1421, found 442.1422.

Diethyl-4-(4-chlorophenyl)-1-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4n) 46 mg, 40%; orange solid; m.p. 152－153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, J=8.4 Hz, 2H), 7.69 (s, 2H), 7.37 (d, J=8.4 Hz, 2H), 7.21－7.15 (m, 4H), 4.88 (s, 1H), 4.05 (q, J=7.2 Hz, 4H), 1.15 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.0, 147.3, 144.9, 143.5, 133.5, 132.7, 129.8, 128.3, 125.8, 119.4, 113.3, 60.8, 37.5, 14.2; IR (KBr) v: 3041, 2984, 1712, 1648, 1593, 1519, 752 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{21}ClN_2NaO_6$ $[M+Na]^+$: 479.0986, found 479.0983.

Diethyl-1-(3-chlorophenyl)-4-(4-chlorophenyl)-

1,4-dihydropyridine-3,5-dicarboxylate (4o) 83 mg, 75%; pale solid; m.p. 109－110 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62 (s, 2H), 7.39 (t, J=8.0 Hz, 1H), 7.31－7.28 (m, 4H), 7.24－7.19 (m, 3H), 4.94 (s, 1H), 4.12 (q, J=7.2 Hz, 4H), 1.21 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4, 144.3, 144.0, 135.7, 135.0, 132.4, 131.0, 129.8, 128.2, 126.5, 120.9, 118.7, 111.4, 60.5, 37.3, 14.2; IR (KBr) v: 3025, 2983, 1703, 1659, 1584, 739 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{22}Cl_2NO_4$ $[M+H]^+$: 446.0926, found 446.0923.

Diethyl-4-(4-chlorophenyl)-1-(2-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4p) 67 mg, 61%; pale yellow solid; m.p. 143－144 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (s, 1H), 7. (s, 1H), 7.40 (s, 2H), 7.36 (d, J=7.8 Hz, 1H), 7.28－7.25 (m, 3H), 7.05 (t, J=7.2 Hz, 2H), 4.95 (s, 1H), 4.10 (q, J=7.2 Hz, 4H), 3.93 (s, 3H), 1.21 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 154.1, 145.4, 138.2, 132.1, 132.0, 129.9, 129.2, 128.0, 126.0, 121.2, 112.3, 108.9, 60.1, 55.9, 37.0, 14.2; IR (KBr) v: 3019, 2989, 1708, 1671, 1586, 751 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{25}ClNO_5$ $[M+H]^+$: 442.1421, found 442.1419.

Diethyl-4-(4-chlorophenyl)-1-(2-iodophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4q) 64 mg, 48%; yellow solid; m.p. 170－172 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J=7.8 Hz, 1H), 7.51－7.44 (m, 3H), 7.34 (s, 1H), 7.32 (s, 2H), 7.25 (d, J=8.0 Hz, 2H), 7.12 (t, J=7.8 Hz, 1H), 4.97 (s, 1H), 4.09 (q, J=6.8 Hz, 4H), 1.19 (t, J=7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 145.6, 144.9, 140.6, 137.3, 132.2, 130.3, 130.0, 129.9, 128.1, 127.4, 109.4, 95.8, 60.3, 37.1, 14.2; IR (KBr) v: 3021, 2985, 1701, 1660, 1581, 751, 605 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{22}ClINO_4$ $[M+H]^+$: 538.0282, found 538.0281.

Diethyl-1-(2-bromophenyl)-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4r) 67 mg, 55%; faint yellow solid; m.p. 169－171 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.0 Hz, 1H), 7.47 (t, J=8.0 Hz, 3H), 7.33 (d, J=7.8 Hz, 1H), 7.31 (s, 2H), 7.25 (d, J=8.0 Hz, 2H), 7.13 (t, J=7.8 Hz, 1H), 4.97 (s, 1H), 4.09 (q, J=7.2 Hz, 4H), 1.19 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 145.5, 144.9, 140.6, 137.3, 132.2, 130.3, 130.0, 129.9, 128.1, 127.3, 109.4, 95.8, 60.3, 37.1, 14.2; IR (KBr) v: 3029, 2989, 1709, 1667, 1586, 761, 663 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{22}BrClNO_4$ $[M+H]^+$: 490.0421, found 490.0428.

Diethyl-1-benzyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4s) 72 mg, 68%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44－7.37 (m, 3H), 7.27 (d, J=7.2 Hz, 4H), 7.20 (q, J=7.6 Hz, 4H), 4.90 (s, 1H), 4.58 (s, 2H), 4.07 (q, J=6.0 Hz, 4H), 1.12 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 145.1, 137.7, 136.1, 132.1, 129.6, 129.2, 128.5, 128.0, 127.2, 108.8, 60.1, 58.3, 37.0, 14.2; IR (KBr) v: 3030, 2979, 1702, 1661, 1582, 750 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{25}ClNO_4$ $[M+H]^+$: 426.1472, found 426.1478.

Diethyl-4-(4-chlorophenyl)-1-cyclohexyl-1,4-dihydropyridine-3,5-dicarboxylate (4t) 83 mg, 80%; yellow solid; m.p. 118－119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (s, 2H), 7.23－7.17 (m, 4H), 4.87 (s, 1H), 4.07 (q, J=7.2 Hz, 4H), 3.27－3.19 (m, 1H), 1.98－1.76 (m, 4H), 1.74 (t, J=12.4 Hz, 2H),1.60－1.50 (m, 2H), 1.34 (q, J=12.8 Hz, 2H), 1.19 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 145.6, 136.1, 131.9, 129.5, 128.0, 108.1, 63.7, 60.0, 37.5, 32.6, 25.6, 25.0, 14.3; IR (KBr) v: 3019, 2979, 1702, 1663, 1573, 758 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{29}ClNO_4$ $[M+H]^+$: 418.1785, found 418.1795.

Diethyl-4-(4-chlorophenyl)-1-isobutyl-1,4-dihydropyridine-3,5-dicarboxylate (4u) 82 mg, 84%; yellow solid; m.p. 129－131 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (d, J=7.2 Hz, 2H), 7.20 (d, J=8.4 Hz, 2H), 7.17 (s, 2H) 4.87 (s, 1H), 4.07 (q, J=7.2 Hz, 4H), 3.19 (d, J=5.6 Hz, 2H), 2.02－1.96 (m, 1H), 1.19 (t, J=7.2 Hz, 6H), 0.98 (d, J=6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 145.3, 138.0, 132.0, 129.6, 128.0, 107.8, 62.6, 60.1, 36.9, 29.4, 19.7, 14.2; IR (KBr) v: 3028, 2984, 1712, 1665, 1590, 756 cm^{-1}; ESI-HRMS calcd for $C_{23}H_{27}ClNO_4$ $[M+H]^+$: 392.1629, found 392.1638.

Dimethyl-4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4v) 60 mg, 63%; yellow solid; m.p. 149－152 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (s, 2H), 7.37 (t, J=8.0 Hz, 2H), 7.22 (t, J=8.4 Hz, 5H), 7.15 (d, J=8.4 Hz, 2H), 4.88 (s, 1H), 3.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.9, 144.5, 143.0, 135.9, 132.4, 130.0, 129.6, 128.3, 126.6, 120.7, 110.4, 51.5, 37.2; IR (KBr) v: 3035, 2984, 1705, 1668, 1576, 751 cm^{-1}; ESI-HRMS calcd for $C_{21}H_{19}ClNO_4$ $[M+H]^+$: 384.1003, found 384.1003.

Dimethyl-4-(3-methoxyphenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4w) 28 mg, 30%; pale yellow solid; m.p. 129－130 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (s, 2H), 7.45 (t, J=8.0 Hz, 2H), 7.30－7.28 (m, 3H), 7.19 (t, J=8.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 1H), 6.94 (s, 1H), 6.73 (t, J=8.0 Hz, 1H), 4.96 (s, 1H), 3.78 (s, 3H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 159.5, 147.4, 143.1, 135.8, 130.0, 129.1, 126.4, 120.8, 120.6, 114.3, 111.8, 110.6, 55.1, 51.5, 37.5; IR (KBr) v: 3022, 2989, 1705, 1664, 1583 cm^{-1}; ESI-HRMS calcd for $C_{22}H_{22}NO_5$ $[M+H]^+$: 380.1498, found 384.1486.

Diethyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6a) 38 mg, 45%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (d, J=5.6 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.8 Hz, 2H), 6.55 (brs, 1H), 4.80 (s, 1H), 4.00 (q, J=7.2 Hz, 4H), 1.12 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 145.5, 133.8, 132.1, 129.7, 128.1, 108.2, 60.1, 37.2, 14.2; IR (KBr) v: 3335, 3019, 2985, 1706, 1659, 1586, 741 cm^{-1}; ESI-HRMS calcd for $C_{17}H_{19}ClNO_4$ $[M+H]^+$: 336.1003, found 336.1003.

Diethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6b) 45 mg, 54%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, J=5.6 Hz, 2H),

7.17 (d, J=8.8 Hz, 2H), 6.70 (d, J=8.4 Hz, 2H), 6.62 (brs, 1H), 4.76 (s, 1H), 4.00 (q, J=7.2 Hz, 4H), 3.67 (s, 3H), 1.12 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 158.1, 139.5, 133.4, 129.3, 113.3, 108.8, 60.0, 55.1, 36.7, 14.2; IR (KBr) v: 3329, 3025, 2984, 1706, 1664, 1583 cm^{-1}; ESI-HRMS calcd for $C_{18}H_{21}NNaO_5$ $[M+Na]^+$: 354.1317, found 354.1327.

Diethyl-4-(2-bromophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6c) 46 mg, 49%; orange solid; m.p. 138−141 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J=6.8 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.23 (d, J=5.6 Hz, 2H), 7.16−7.12 (m, 1H), 6.92−6.88 (m, 1H), 6.75 (brs, 1H), 5.26 (s, 1H), 4.00 (q, J=7.2 Hz, 4H), 1.10 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 146.8, 134.3, 132.5, 131.6, 127.8, 127.5, 123.2, 108.6, 60.1, 37.3, 14.3; IR (KBr) v: 3324, 3029, 2981, 1707, 1665, 1584, 665 cm^{-1}; ESI-HRMS calcd for $C_{17}H_{19}BrNO_4$ $[M+H]^+$: 380.0497, found 380.0483.

Diethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6d) 57 mg, 66%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.95 (d, J=7.2 Hz, 1H), 7.66 (d, J=6.8 Hz, 1H), 7.36−7.31 (m, 3H), 6.89 (brs, 1H), 4.96 (s, 1H), 4.00 (q, J=7.2 Hz, 4H), 1.20 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 149.0, 148.4, 134.8, 134.4, 128.7, 123.3, 121.7, 107.6, 60.3, 37.8, 14.2; IR (KBr) v: 3319, 3025, 2985, 1709, 1684, 1515 cm^{-1}; ESI-HRMS calcd for $C_{17}H_{18}N_2O_6$ $[M+H]^+$: 347.1243, found 347.1246.

Diethyl-4-(2,4-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6e) 37 mg, 40%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36−7.31(m, 4H), 7.17 (d, J=8.4 Hz, 1H), 6.77 (brs, 1H), 5.35 (s, 1H), 4.08 (q, J=7.2 Hz, 4H), 1.20 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.0, 143.6, 134.5, 133.4, 132.5, 132.4, 128.8, 127.2, 107.8, 60.2, 34.7, 14.2; IR (KBr) v: 3321, 3022, 2984, 1701, 1661, 1581, 747 cm^{-1}; ESI-HRMS calcd for $C_{17}H_{18}Cl_2NO_4$ $[M+H]^+$: 370.0613, found 370.0611.

Synthesis of intermediate 7a

To a 25 mL round bottom flask was added ethyl propiolate (0.6 mmol) and piperazine (0.3 mmol), 1.5 mL DMF was added and the mixture was stirred at r.t. for 8 h (TLC). Upon completion, 10 mL water was added and the resulting mixture was extracted with EtOAc (10 mL×3). The combined organic layer was dried with anhydrous Na_2SO_4. After filtering out the solid, evaporation on solution gave product **6a** as white solid.

(2*E*,2'*E*)-Diethyl 3,3'-(piperazine-1,4-diyl) diacrylate (7a) 76 mg, 90%; white solid, m.p. 206−207 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J=13.2 Hz, 2H), 4.65 (d, J=13.2 Hz, 2H), 4.07 (q, J=6.8 Hz, 4H), 3.20 (s, 8H), 1.19 (t, J=6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.17, 151.02, 87.11, 59.17, 47.47, 14.51; IR (KBr) v: 2977, 2916, 1685, 1378 cm^{-1}; ESI-HRMS calcd for $C_{14}H_{23}N_2O_4$ $[M+H]^+$: 283.1658, found 283.1650.

Results and Discussion

Initially, the reaction of ethyl propiolate **1a**, *p*-chlorobenzaldehyde **2a** and aniline **3a** was selected as model reaction for optimizing reaction conditions. The control experiments employing only trimethylsilyl chloride (TMSCl) or morpholine were first carried out, respectively. And no target transformation forming **4a** was observed in neither Entry after heating at 90 ℃ for 12 h (Scheme 1). While simultaneously employing both species in the reaction gave **4a** with 53% yield (Entry 1, Table 1). Further optimization was then conducted based on the fact that both acid and secondary amine were required for the reaction. Firstly, on TMSCl loading, reaction temperature and catalyst species demonstrated that the combination of piperazine (0.5 equiv.) and TMSCl (1.5 equiv.) in DMF at a brief screening on different secondary amines and reaction media implied that piperazine was more efficient in promoting the reaction with 50 mol% loading (Entries 2−8, Table 1).

Scheme 1 Control experiments on single catalyst system

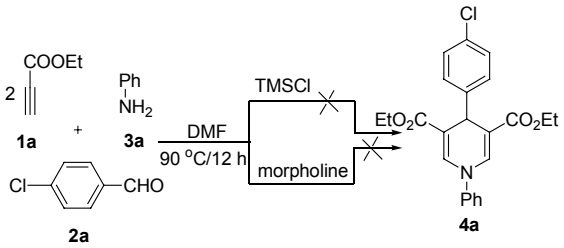


Table 1 Optimization on reaction conditions[a]

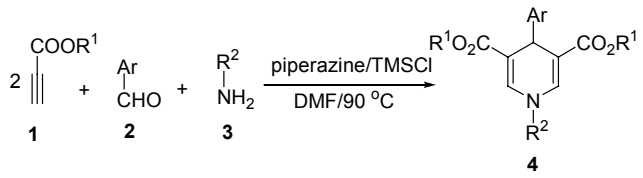
Entry	Amine	Catalyst	Solvent	T/℃	Yield[b]/%
1	Morpholine	TMSCl	DMF	90	53
2	Pyrrolidine	TMSCl	DMF	90	44
3	Piperazine	TMSCl	DMF	90	63
4	Piperazine	TMSCl	EtOH	90	34
5	Piperazine	TMSCl	Toluene	90	34
6	Piperazine	TMSCl	H_2O	90	36
7[c]	Piperazine	TMSCl	DMF	90	43
8[c]	Piperazine	TMSCl	DMF	90	63
9[d]	Piperazine	TMSCl	DMF	90	71
10[d]	Piperazine	TMSCl	DMF	90	58
11[d]	Piperazine	TMSCl	DMF	80	58
12[d]	Piperazine	*p*-TSA	DMF	90	48
13[d]	Piperazine	AcOH	DMF	90	Trace
14[d]	Piperazine	CF_3COOH	DMF	90	61

[a] Unless otherwise specified, the reaction conditions are: **1a** (0.5 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), 0.5 equiv. secondary amine and 2.0 equiv. TMSCl in 2.0 mL solvent and stirred for 12 h. [b] Yield of purified products based on **1a**. [c] Piperazine was used in 0.3 equiv. and 0.6 equiv. for Entries 7 and 8, respectively. [d] The acid catalyst was employed in 1.0 equiv. for Entry 10, and 1.5 equiv. for Entries 9 and 11−14.

Later on, the optimization temperature of 90 ℃ is the best condition among all the investigated Entries (Entry 9, Table 1).

Under the standard conditions from optimization experiments, the general applicability of this multicomponent protocol was then investigated by subjecting a number of different aldehydes, amines and alkynes. The results on the synthesis of different 1,4-DHPs were shown in Table 2. In general, benzaldehydes possessing various substitution groups such as halides, alkyl, alkoxyl, fluorinated alkyl in different sites and heteroaryl aldehydes were tolerable to this transformation. All these aldehydes incorporated ethyl propiolate and aniline to afford corresponding 1,4-DHPs with moderate to good yields without showing evident impact of substituents (Entries 1—11, Table 2). Similar results have been obtained in the Entries using different aryl amines (Entries 12—18, Table 2). An interesting point of the protocol was that alkyl amines were also tolerated well as aryl amines, and corresponding *N*-alkyl 1,4-DHPs were provided with good to excellent yields (Entries 19—21, Table 2). When methyl propiolate was employed instead of ethyl propiolate, corresponding 1,4-DHPs **4w** and **4y** were acquired smoothly with reasonable yield as expected (Entries 22, 23, Table 2). The Entry employing aliphatic aldehyde, however, was not successful under present conditions (Entry 24, Table 2). All products have been fully characterized with standard spectroscopic analysis, and the X-ray single crystal diffraction on **4r** further confirmed the structures of synthesized 1,4-DHPs (Figure 1).[45]

Table 2 Multicomponent synthesis of different *N*-substituted 1,4-DHPs[a]



Entry	Ar	R^1	R^2	Product	Yield[b]/%
1	4-ClC_6H_4	Et	Ph	**4a**	71
2	4-BrC_6H_4	Et	Ph	**4b**	45
3	4-$CF_3C_6H_4$	Et	Ph	**4c**	56
4	Ph	Et	Ph	**4d**	74
5	4-MeC_6H_4	Et	Ph	**4e**	53
6	4-$MeOC_6H_4$	Et	Ph	**4f**	73
7	2-ClC_6H_4	Et	Ph	**4g**	84
8	2-BrC_6H_4	Et	Ph	**4h**	79
9	3-HOC_6H_4	Et	Ph	**4i**	51
10	2,4-$Cl_2C_6H_3$	Et	Ph	**4j**	61
11	Furan-2-yl	Et	Ph	**4k**	51
12	4-ClC_6H_4	Et	4-ClC_6H_4	**4l**	64
13	4-ClC_6H_4	Et	4-$CH_3OC_6H_4$	**4m**	41
14	4-ClC_6H_4	Et	4-$O_2NC_6H_4$	**4n**	40
15	4-ClC_6H_4	Et	3-ClC_6H_4	**4o**	75
16	4-ClC_6H_4	Et	2-$CH_3OC_6H_4$	**4p**	61
17	4-ClC_6H_4	Et	2-IC_6H_4	**4q**	48
18	4-ClC_6H_4	Et	2-BrC_6H_4	**4r**	55
19	4-ClC_6H_4	Et	$PhCH_2$	**4s**	68
20	4-ClC_6H_4	Et	Cyclohexyl	**4t**	80
21	4-ClC_6H_4	Et	*i*-Butyl	**4u**	84
22	4-ClC_6H_4	Me	Ph	**4v**	63
23	3-$MeOC_6H_4$	Me	Ph	**4w**	30
24[c]	Et	Et	Ph	—	nr

[a] Unless otherwise specified, the reaction conditions are: **1** (0.5 mmol), **2** (0.3 mmol) and **3** (0.3 mmol), TMSCl (1.5 equiv.) and piperazine (0.5 equiv.) in 2 mL DMF, stirred at 90 ℃ for 12 h. [b] Yield of purified products based on **1.** [c] No reaction was observed.

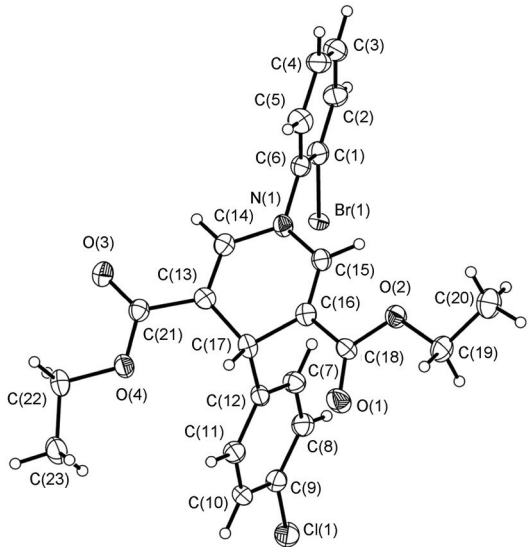


Figure 1 X-ray single crystal structure of **4r**.

In order to further demonstrate the application scope of the protocol, the reactions utilizing ammonium salt as hetero *N* resource have also been performed. To our delight, a class of different 1,4-DHPs **6a**—**6e** containing free NH group were given when ammonium acetate was subjected to react with ethyl propiolate and different aryl aldehydes, albeit with moderate yields (Scheme 2). These results further confirmed the general applicability of the present method for 1,4-DHPs synthesis.

In order to explore the possible functions of secondary amine, the control experiments on reaction of alkyne with secondary amine and subsequent transformation of obtained intermediate with aldehyde and amines have been carried out. As outlined in Scheme 3, the incorporation of piperazine with ethyl propiolate could be easily performed to give enaminoester intermediate **7a**. The subsequent assembly of **7a** with *p*-chlorobenzaldehyde and aniline under standard conditions without using secondary amine led to production of 1,4-DHP **4a** in 72% yield. These data, together with the results shown

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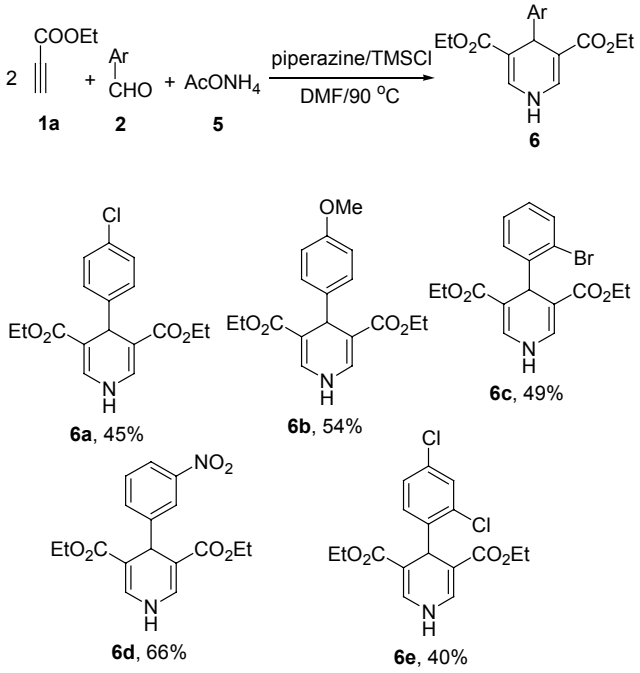
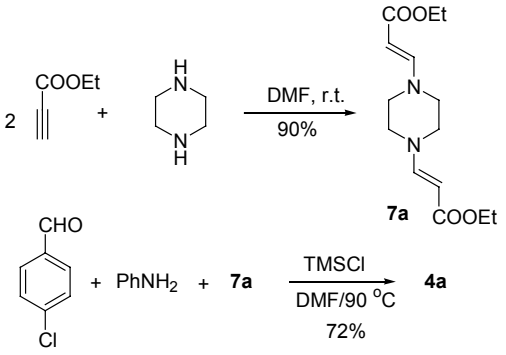
Scheme 2 Multicomponent synthesis of NH-containing 1,4-DHPs



Conditions: **1a** (0.5 mmol), **2** (0.3 mmol), **5** (0.3 mmol), TMSCl (1.5 equiv.) and piperazine (0.5 equiv.) in 2 mL DMF, stirred at 90 ℃ for 12 h. And the yields were reported as purified products based on **1**.

in Scheme 1, clearly proved that the enamine-type activation of secondary amine to electron deficient alkynes was crucial for the present multicomponent reaction.[46] A proposed mechanism for the present multicomponent reactions involving the activation of secondary amine to propiolates was outlined in Scheme 4. At first, the fast addition of secondary amine to propiolates gave enaminoesters **7**. Under the activation of TMSCl, the nucleophilic intermediates **7** incorporated aldehydes to provide **8** via aldol-type reaction. Subsequently, the dehydration condensation of **8** with another molecule of **7** generated intermediates **9**.[47] The transamination between *N*,*N*-dimethylamino functionalized **9** and primary amines readily ran at the acidic reaction conditions to provide intermediates **10**.[48] And the intramolecular transamination of **10** finally led to the production of 1,4-DHPs as products.

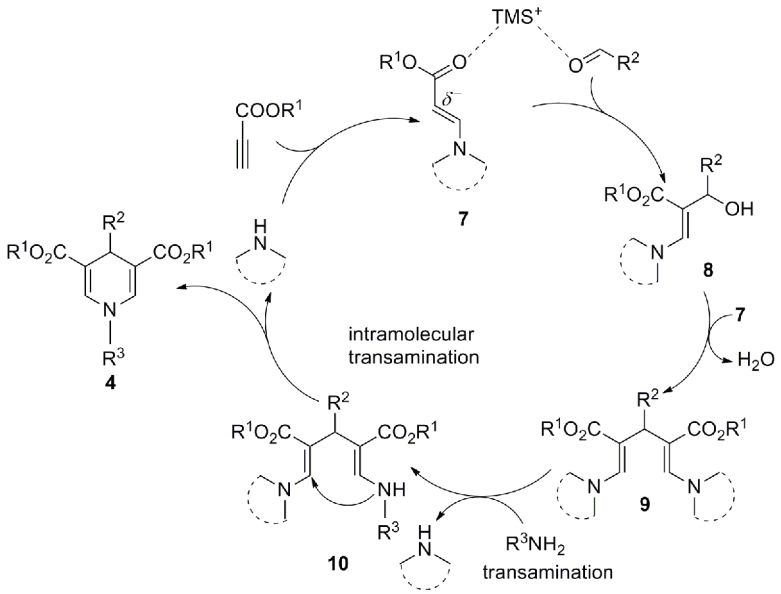
Scheme 3 Function of secondary amines in the 1,4-DHPs synthesis



Conclusions

In conclusion, a multicomponent tactic employing alkyl propiolates, aldehydes and amines/ammonium has been successfully established for the synthesis of diverse 1,4-DHPs. The key factor initiating the reaction was the activation of secondary amine to the electron deficient alkynes. This method allows the synthesis of 2,6-unsubstituted 1,4-DHPs starting from a variety of different aldehydes, primary amines/ammonium and alkyl propiolates. Considering the broad application

Scheme 4 Proposed reaction mechanism



scope as well as the easy availability of all reactants, this method can be an interesting option for 1,4-DHPs synthesis for the sake of finding new 1,4-DHP-based lead compounds.

Acknowledgement

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