An Efficient, Three-component One-pot Preparation of 1,4-Dihydropyridines Containing Novel Substituted Pyrazole under Sulfamic Acid Catalysis

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An efficient approach to 1,4-dihydropyridines containing novel substituted pyrazole is achieved via three-component reaction of pyrazolyl aldehyde, *β*-ketoester, and ammonium acetate in one-pot under sulfamic acid catalysis.

Keywords Hantzsch reaction, 1,4-dihydropyridines, pyrazole, sulfamic acid, catalysis, synthesis

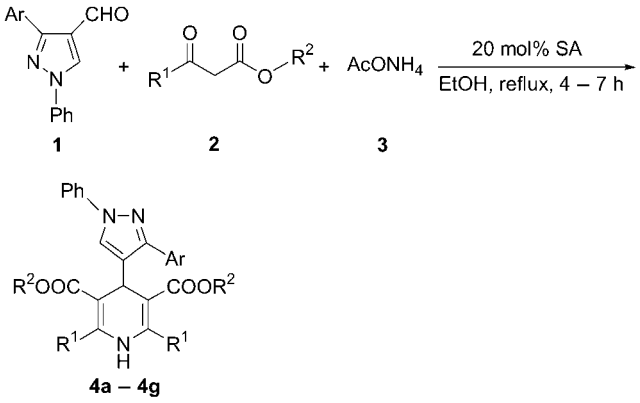
Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) constitute an important class of calcium channel blockers[1-3] and are used most frequently as cardiovascular agents for treatment of hypertension.[4] 1,4-Dihydropyridines possess a variety of biological activities,[5] such as bronchodilator, antiatherosclerotic, antitumor and antidiabetic agents. They also function as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease as antiischaemic agents.[6-8] Among 1,4-DPHs, there are also examples of drug-resistance modifiers,[9] antioxidabts[10] and a durg for the treatment of urinary urge incontinence.[11] Therefore, the development of synthetic methods for 4-substituted 1,4-dihydropyridines is very significant to both heterocycle chemistry and medicinal chemistry.

Nowadays, the pyrazole derivatives were paid much attention for their various biological activities, such as antitumor,[12,13] selective COX-2 inhibitory.[14] Besides, they can be used as cytokine inhibitors,[15] potent catalytic activity inhibitor of human telomerase.[16] Consequently, we may obtain some compounds with higher biological activities by putting the pyrazole group into the 1,4-DPHs. This might help us to develop new chemotherapeutic agents.

1,4-DPHs are generally synthesized using the Hantzsch methods,[17] which involve cyclocondensation of an aldehyde, active methylene compounds and ammonia either in acetic acid or under reflux in alcohols for long reaction time which typically leads to low yields.[18,19] Other procedures comprise the use of TMSCl-NaI,[20] $InCl_3$,[21] $Yb(OTf)_3$,[22] I_2,[23] $SiO_2/NaHSO_4$,[24] CAN,[25] $FeCl_3$•$6H_2O$ and organocatalysts.[26] However, most of these catalysts such as TMSCl-NaI, $Yb(OTf)_3$, $InCl_3$, and some organocatalysts are costly or require additional efforts to prepare. Although $FeCl_3$•$6H_2O$ and CAN were inexpensive catalysts, the reaction only afforded the desired product in moderate yields (Table 1, Entries 8 and 9). Herein, we report that sulfamic acid is an extremely efficient and inexpensive catalyst for the synthesis of 1,4-DPHs by one-pot, three-component reaction of pyrazolyl aldehyde, *β*-ketoester, and ammonium acetate (Scheme 1).

Scheme 1 SA-catalyzed synthesis of 1,4-dihydropyridines containing pyrazole



Results and discussion

To obtain the best experimental conditions, treatment of one equivalent of 4-substituted pyrazolyl aldehyde **1b** and ammonium acetate **3** with two equiv. of ethyl acetoacetate **2a** in the presence of 10 mol% of SA in etha-

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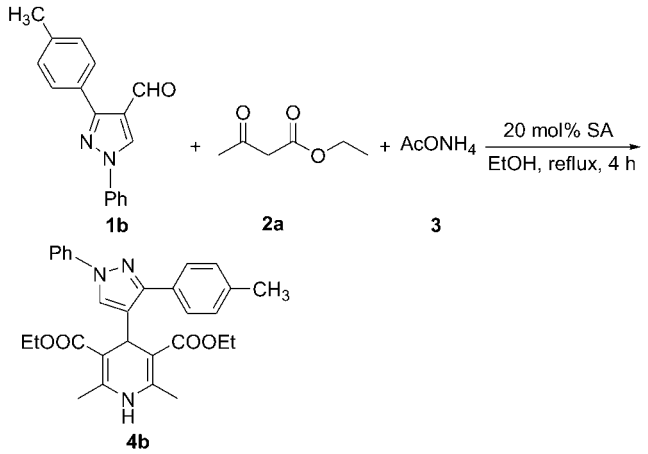
nol at reflux afforded the corresponding 1,4-dihydropyridine **4b** in 84% yield (Table 1, Entry 5). Thus, the reaction conditions were optimized. Ethanol proved to be a much better solvent in terms of yield than all the others tested including tetrahydrofuran (Entry 1), acetonitrile (Entry 2) which afforded the desired product in moderate yields (28%—47%). Neat conditions furnished 1,4-DPHs **4b** in 78% yield (Entry 3). Under the similar conditions as Entry 5, reaction with 20 mol% of SA in ethanol at reflux raised the yield to an excellent 90% (Entry 4). However, there was no improvement in the reaction rates and yields on decreasing the amount of SA to 10 or 5 mol%. To demonstrate the efficiency of our catalyst, a blank reaction was carried out in the absence of SA. After 7 h at reflux in ethanol only a 30% yield of **4b** was obtained.

Table 1 SA-catalyzed Hantzsch synthesis of 1,4-dihydropyridines containing pyrazole **4b** under different conditions[a]



Entry	Solvent	Catalyst (mol%)	Yield[b] of **4b**/%
1	THF	SA (20)	28
2	CH_3CN	SA (20)	47
3	None[c]	SA (20)	78
4	EtOH	SA (20)	90
5	EtOH	SA (10)	84
6	EtOH	SA (5)	72
7	EtOH	None	30
8	EtOH	$FeCl_3$•$6H_2O$ (20)	62
9	EtOH	CAN (20)	56

[a] 4-Substituted pyrazolyl aldehyde/ethyl acetoacetate/ammonium acetate＝1∶2∶1 (molar ratio), reflux, 4h. [b] Isolated yield. [c] Reaction at 80 ℃.

The reactions of various 4-substituted pyrazolyl aldehydes possessing either electrondonating or electron-withdrawing substituents with *β*-ketoester and ammonium acetate in the presence of a catalytic amount (20 mol%) of SA afforded good yields of the corresponding 1,4-DPHs (70%—90%) in short time. The results are presented in Table 2.

Table 2 SA-catalyzed Hantzsch synthesis of 1,4-dihydropyridines containing pyrazole **4a**—**4g**[a]

Entry	Ar	R^1	R^2	Time/h	Product	Yield[b]/%
1	C_6H_5	CH_3	CH_2CH_3	5	**4a**	73
2	4-Me-C_6H_4	CH_3	CH_2CH_3	4	**4b**	90
3	4-MeO-C_6H_4	CH_3	CH_2CH_3	4	**4c**	86
4	4-Cl-C_6H_4	CH_3	CH_2CH_3	5	**4d**	80
5	4-O_2N-C_6H_4	CH_3	CH_2CH_3	4	**4e**	84
6	4-Me-C_6H_4	CH_3CH_2	CH_3	7	**4f**	70
7	4-MeO-C_6H_4	CH_3CH_2	CH_3	7	**4g**	78

[a] 4-Substituted pyrazolyl aldehyde/*β*-ketoester/ammonium acetate＝1∶2∶1 (molar ratio), reflux, 4—7 h. [b] Isolated yield.

Experimental

General procedures

Melting points were determined with an XRC-1 micromelting point apparatus and uncorrected. NMR spectra were measured on a Bruker DPX 400 M, respectively, using TMS as the internal standard and $CDCl_3$ as the solvent. Chemical shifts (δ) were expressed downfield from the internal standand TMS and coupling constants J were given in Hz. Elemental analysis was performed on a PE-2400 Analyzer. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. The starting material, 1-phenyl-3-aryl-1*H*-pyrazole-4-carbaldehyde (**1**) was prepared according to Ref.[27]

General procedure for the synthesis of 4a—4g

A mixture of pyrazolyl aldehyde **1** (1 mmol), *β*-ketoester **2** (2 mmol), ammonium acetate **3** (1 mmol), and SA (20 mol%) was heated at reflux in ethanol (5 mL) for the appropriate time (Table 2, monitored by TLC). The reaction mixture, after being cooled to room temperature was poured into cold water and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. Then the crude products were purified by silica gel column chromatography [*V*(petroleum ether)∶*V*(ethyl acetate)＝4∶1].

Diethyl 1,4-dihydro-2,6-dimethyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarboxylate (4a) White crystal; m.p. 169—171 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.076 (t, J＝7.0 Hz, 6H, $2CH_3$), 2.230 (s, 6H, $2CH_3$), 3.761—3.824 (m, 2H, CH_2), 3.981—4.043 (m, 2H, CH_2), 5.298 (s, 1H, CH), 5.400 (s, 1H, NH), 7.229 (t, J＝7.0 Hz, 1H, ArH), 7.337 (t, J＝7.6 Hz, 1H, ArH), 7.393—7.424 (m, 4H, ArH), 7.678 (d, J＝8.0 Hz, 2H, ArH), 7.746 (s, 1H, N＝CH), 7.829 (d, J＝6.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.28, 19.53, 29.67, 59.67, 104.35, 125.92, 127.01, 127.40, 127.84, 128.52, 128.96, 129.18, 134.84, 140.06, 143.24, 151.24, 167.51. Anal. calcd for $C_{28}H_{29}N_3O_4$: C 71.32, H 6.20, N 8.91; found C 71.62, H 6.37, N 9.18.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarboxylate (4b)

White crystal; m.p. 194—195 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.075 (t, J=7.0 Hz, 6H, $2CH_3$), 2.282 (s, 6H, $2CH_3$), 2.389 (s, 3H, CH_3), 3.756—3.801 (m, 2H, CH_2), 4.005—4.049 (m, 2H, CH_2), 5.288 (s, 1H, CH), 5.408 (s, 1H, NH), 7.217 (d, J=7.6 Hz, 3H, ArH), 7.396 (t, J=7.8 Hz, 2H, ArH), 7.671 (d, J=8.4 Hz, 2H, ArH), 7.708 (s, 1H, N=CH), 7.728 (s, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.23, 19.39, 21.24, 29.60, 59.65, 104.38, 118.73, 125.84, 127.00, 128.50, 128.63, 128.75, 129.15, 131.87, 136.96, 140.09, 143.33, 151.16, 167.58. Anal. calcd for $C_{29}H_{31}N_3O_4$: C 71.73, H 6.43, N 8.65; found C 72.01, H 6.58, N 8.89.

Diethyl 1,4-dihydro-4-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2,6-dimethylpyridine-3,5-dicarboxylate (4c) White crystal; m.p. 128—130 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.088 (t, J=7.0 Hz, 6H, $2CH_3$), 2.242 (s, 6H, $2CH_3$), 3.797—3.842 (m, 2H, CH_2), 3.853 (s, 3H, OCH_3), 3.991—4.054 (m, 2H, CH_2), 5.270 (s, 1H, CH), 5.409 (s, 1H, NH), 6.957 (d, J=8.4 Hz, 2H, ArH), 7.219 (t, J=7.2 Hz, 1H, ArH), 7.399 (t, J=7.8 Hz, 2H, ArH), 7.669 (d, J=7.6 Hz, 2H, ArH), 7.729 (s, 1H, N=CH), 7.771 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.28, 19.37, 29.65, 55.34, 59.68, 104.30, 113.33, 118.70, 125.85, 127.03, 127.45, 128.57, 129.17, 130.07, 140.05, 143.39, 150.90, 159.18, 167.62. Anal. calcd for $C_{29}H_{31}N_3O_5$: C 69.44, H 6.23, N 8.38; found C 69.76, H 6.43, N 8.62.

Diethyl 4-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (4d) White crystal; m.p. 167—168 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.077 (t, J=7.0 Hz, 6H, $2CH_3$), 2.266 (s, 6H, $2CH_3$), 3.778—3.841 (m, 2H, CH_2), 3.990—4.070 (m, 2H, CH_2), 5.265 (s, 1H, CH), 5.482 (s, 1H, NH), 7.233 (d, J=7.6 Hz, 1H, ArH), 7.412 (t, J=7.8 Hz, 4H, ArH), 7.663 (d, J=8.0 Hz, 2H, ArH), 7.738 (s, 1H, N=CH), 7.855 (d, J=8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.26, 19.51, 29.63, 30.90, 59.75, 104.45, 118.82, 126.14, 127.34, 128.02, 128.86, 129.22, 130.19, 133.35, 139.93, 143.33, 167.44. Anal. calcd for $C_{28}H_{28}ClN_3O_4$: C 66.46, H 5.58, N 8.30; found C 66.86, H 6.04, N 8.62.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]pyridine-3,5-dicarboxylate (4e) Yellow crystal; m.p. 124—126 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.034 (t, J=7.2 Hz, 6H, $2CH_3$), 2.312 (s, 6H, $2CH_3$), 3.770—3.832 (m, 2H, CH_2), 3.983—4.028 (m, 2H, CH_2), 5.323 (s, 1H, CH), 5.572 (s, 1H, NH), 7.290 (d, J=7.2 Hz, 1H, ArH), 7.436 (t, J=7.6 Hz, 2H, ArH), 7.682 (d, J=8.4 Hz, 2H, ArH), 7.777 (s, 1H, N=CH), 8.238 (d, J=8.8 Hz, 2H, ArH), 8.312 (d, J=8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.28, 19.66, 29.69, 59.85, 104.65, 119.00, 123.26, 126.63, 128.05, 129.28, 129.33, 130.00, 139.73, 141.67, 143.50, 146.92, 148.14, 167.32. Anal. calcd for $C_{28}H_{28}N_4O_6$: C 65.11, H 5.46, N 10.85; found C 65.66, H 5.61, N 11.19.

Dimethyl 2,6-diethyl-1,4-dihydro-4-(1-phenyl-3-*p*-tolyl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarboxylate (4f) Faint yellow colloid; m.p. 68—70 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.190 (t, J=7.4 Hz, 6H, $2CH_3$), 2.406 (s, 3H, CH_3), 2.563—2.616 (m, 2H, CH_2), 2.832—2.886 (m, 2H, CH_2), 3.338 (s, 3H, CH_3), 5.281 (s, 1H, CH), 5.675 (s, 1H, NH), 7.234 (d, J=9.6 Hz, 2H, ArH), 7.399 (t, J=8.0 Hz, 2H, ArH), 7.648 (d, J=7.6 Hz, 2H, ArH), 7.680 (s, 1H, N=CH), 7.764 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.66, 21.26, 25.76, 29.40, 50.58, 103.59, 118.77, 125.89, 126.93, 128.45, 128.67, 128.91, 129.18, 129.45, 131.95, 136.92, 140.10, 149.27, 150.92, 167.40. Anal. calcd for $C_{29}H_{31}N_3O_4$: C 71.73, H 6.43, N 8.65; found C 72.15, H 6.69, N 8.91.

Dimethyl 2,6-diethyl-1,4-dihydro-4-[3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]pyridine-3,5-dicarboxylate (4g) Faint yellow colloid; m.p. 67—69 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.192 (t, J=7.6 Hz, 6H, $2CH_3$), 2.563—2.616 (m, 2H, CH_2), 2.835—2.888 (m, 2H, CH_2), 3.342 (s, 6H, $2CH_3$), 3.866 (s, 3H, OCH_3), 5.266 (s, 1H, CH), 5.669 (s, 1H, NH), 6.995 (d, J=8.8 Hz, 2H, ArH), 7.221 (t, J=7.6 Hz, 1H, ArH), 7.399 (t, J=8.0 Hz, 2H, ArH), 7.645 (d, J=7.6 Hz, 2H, ArH), 7.678 (s, 1H, N=CH), 7.822 (d, J=8.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.68, 25.76, 29.44, 50.66, 55.33, 103.57, 113.46, 118.73, 125.89, 126.95, 127.54, 128.84, 129.19, 129.76, 140.07, 149.30, 159.13, 167.42. Anal. calcd for $C_{29}H_{31}N_3O_5$: C 69.44, H 6.23, N 8.38; found C 69.88, H 6.47, N 8.75.

Conclusions

In summary, we have developed a simple and efficient method for the synthsis of 1,4-dihydropyridines containing novel substituted pyrazole under sulfamic acid catalysis. The present method has many obvious advantages compared to those reported in the previous literatures, including the avoidance of discharging harmful organic solvents, the simplicity of the methodology and the inexpensive catalyst.

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