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RESEARCH ARTICLE

Synthesis of a new class of 4-pyrazole substituted 1,4-dihydropyridines by multicomponent reactions

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Abstract

1,4-Dihydropyridines (DHPs) are synthesized by the Hantszch method, which involves cyclocondensation of aldehyde, β-ketoester and ammonia either in acetic acid at room temperature or refluxing in alcohol. Here we developed a one pot synthesize of a new class of 1,4 -dihydropyridine derivatives from cyclocondensation of pyrazole aldehyde, acetylacetone and ammonium acetate in acetic acid at room temperature.

INTRODUCTION

1,4-Dihydropyridines (DHPs) are a class of nitrogen containing heterocycles having a six membered ring , which are the most powerful calcium channel blockers, have received much attention due to their wide range of pharmaceutical and biological properties such as inhibition of human cytochrome P450 enzyme,[1] angiotensine-converting enzyme inhibition and blood pressure control on chronic, nondiabetic nephropathies.[2] Nifedipine[3] and nitrendipine[4] are used for the treatment of hypertension and angina pectoris. Nisoldipine is a potent vasodilator and nimodipine[5] exhibits selectivity for cerebral vasculature.[6] A number of DHP derivatives are employed as a potential drug for the treatment of congestive heart failure.[7] Recently much effort has been expended to develop more efficient methods for the synthesis of 1,4-DHPs using microwave,[8] metal triflates as catalyst,[9] reaction in ionic liquid,[10] p-TSA,[11] HY-Zeolite [12] and $HClO_4$-SiO_2.[13]

In continuation of our interest in the Hantszch pyridine synthesis[14], multicomponent reactions[15] and considering the importance of the pyrazole and 1,4-dihydropyridine frameworks in biologically important compounds especially their calcium channel activity and anti-tubercular activity, we investigated a three-component reaction involving pyrazole aldehyde, 1,3-diketone and ammonium acetate in order to synthesize a new class of 1,4 -dihydropyridine derivatives.

2. Materials and Methods

2.1 Chemicals and reagents.

All chemicals were purchased from Sigma-Aldrich U.S.A. Analytical TLC was performed on precoated aluminium sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany.)

2.2 Equipments and analytical instruments

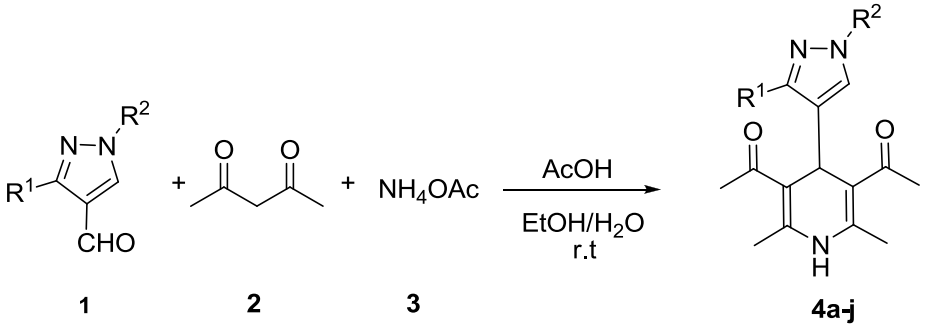
^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Bruker spectrometer at 400 MHz and 100 MHz respectively. The mass spectra (LCMS) were recorded by using an Electrospray Ionisation method with Thermo Finnigan mass spectrometer with both negative mode and positive mode. Elemental analyses were recorded using a Thermo Finnigan FLASH EA1112 CHN analyzer.

2.3 General procedure of the synthesis of pyridine derivatives 4a-j

A mixture of pyrazole aldehyde (1 mmol), acetylacetone (2 mmol) and ammonium acetate (1 mmol) in ethyl alcohol - water mixture (15ml) was stirred at room temperature for the appropriate time (**Table4.3)**. After completion of the reaction as evidenced by TLC, the reaction mixture was diluted by addition of water (20 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated in vacuum. The crude was purified by column chromatography on silica gel (Merck, 100-200 mesh) with 10% ethyl acetate-petroleum ether (bp. 60–80 ^{o}C) to afford pure Pyrazolyl pyridines **4a-j.**

3. Result and Discussion

The strategy we have developed begins with multi component reaction of pyrazole aldehyde **1**, acetyl acetone **2** and ammonium acetate **3** in ethanol-water mixture at room temperature in the presence of acetic acid. The reaction undergoes smoothly within 2 hours yielding 85 % of the product (**Scheme 4.1**). The solid product was filtered, extracted with ethyl acetate and column chromatographed with 10% ethyl acetate–petroleum ether (bp. 60–80 ^{o}C) mixture to afford pure product. These products were thoroughly characterized with various spectroscopic techniques like ^{1}H and ^{13}CNMR spectroscopy, mass spectrometry and elemental analysis as described in the experimental section. The results are summarized in table **4.3.**



Scheme 4.1 Synthesis of 1,4-dihydropyridine

Initially, we examined the effect of` various catalyst for the synthesis of 1,4-dihydropyridine from pyrazole aldehyde, acetyl acetone and ammonium acetate. After careful systematic screening (**Table 4.1**), acetic acid was found to be the catalyst of choice.

Table 4.1.Screening of catalyst

Entry	Catalyst (one eq)	Time (h)	Yield[a] (%)
1	No catalyst	72	Trace
2	$SnCl_2.H_2O$	24	20
3	$SnCl_4$	24	30
4	Acetic acid	2	85
5	Boric acid	6	25
6	$InCl_3$	3	60
7	$H_4TiW_{12}O_{40}$	10	40

[a]Isolated yield

In another attempt the preliminary screening of solvents was carried out to make the reaction greener one. The reaction was carried out with various solvents and the best result was obtained in ethanol-water mixture (60:40) (**Table4. 2**).

Table 4.2.Screening of solvents

Entry	Solvent	Yield[a] (%)
1	Neat	Trace
2	Water	Trace
3	Acetonitrile	20
4	Ethanol	80
5	Ethanol-water mixture	85

[a]Isolated yield

The ^{1}H NMR spectrum of compound **4a** exhibited a two singlet at 5.63 and 5.91 ppm reveals that the former one corresponds to pyridine proton and the later one corresponds to -NH proton. The singlet at 7.57 ppm was assigned to pyrazole ring proton. Twelve protons, doublet at 2.25 ppm was assigned to the protons of the methyl groups at positions 2 and 5 in pyridine ring and two ketonic groups **(fig 4.1)**

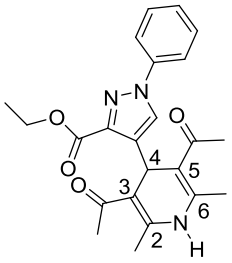
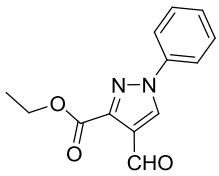
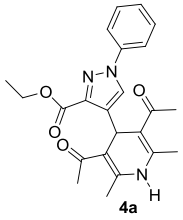
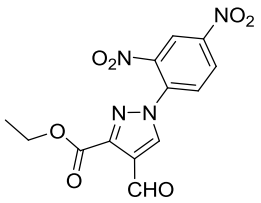
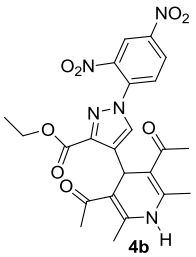
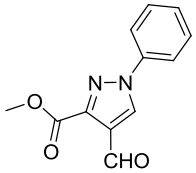
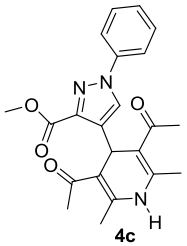
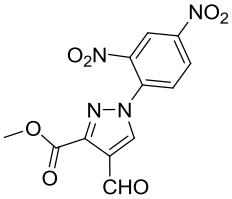
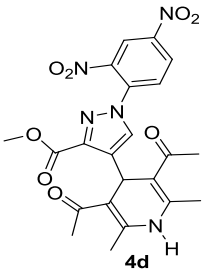
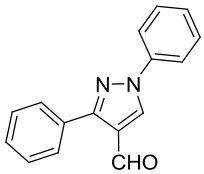
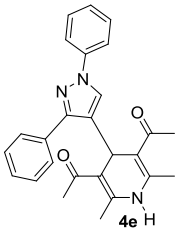
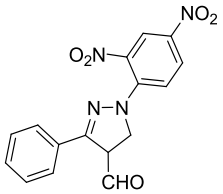
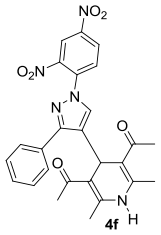
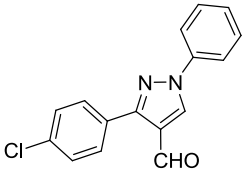
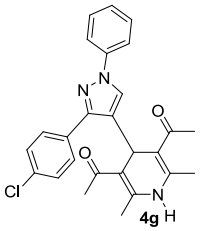


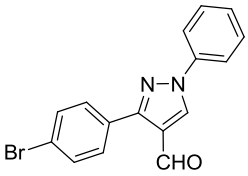
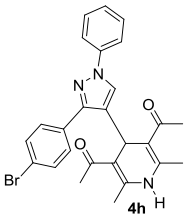
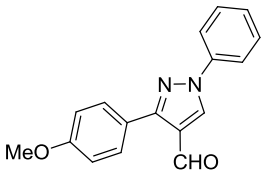
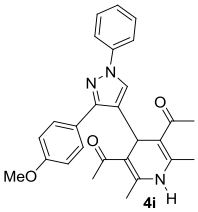
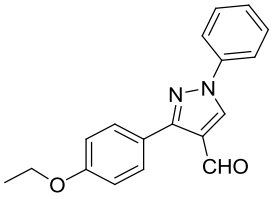
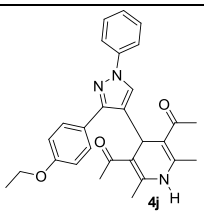
Figure 4.1 Structural diagram of compound 4a

Three protons, triplet at 1.36 ppm and two protons, quartet at 4.43 ppm clearly shows that the presence of typical ethyl ester group (CH_3-CH_2-O-CO-). The multiplet at 7.25-7.57 ppm was attributed to aromatic protons. In the ^{13}C NMR spectra, the peaks at 196 ppm and the range between 119-140 ppm were assigned to carbonyl carbon of ketonic group and aromatic ring carbons respectively. The peak at 161 ppm was attributed to ester carbonyl carbon. The peak at 148 ppm was assigned to carbons 2 and 6 of pyridine ring. The carbons at position 3&5 and 4 of pyridine ring are appeared at 113 and 35 ppm respectively. The mass spectrum showed the molecular ion peak $(M-H)^{+}$ at m/z 406 (negative mode **fig 4.2**). The formation of the product was further confirmed by elemental analysis.

Table 4.3 Synthesis of 1,4-dihydropyridine

Entry	Pyrazole aldehyde	Time (h)	Product 4[a]	Yield[b] (%)
1		1.5	 4a	85

2		2.0	 4b	75
3		1.5	 4c	78
4		2.0	 4d	74
5		2.0	 4e	79
6		2.0	 4f	72
7		1.5	 4g	76

8		1.5		73
9		1.0		79
10		1.0		76

[a]All products were characterized by [1]HNMR, [13]CNMR and mass spectroscopy
[b]Isolated yield after column chromatography.

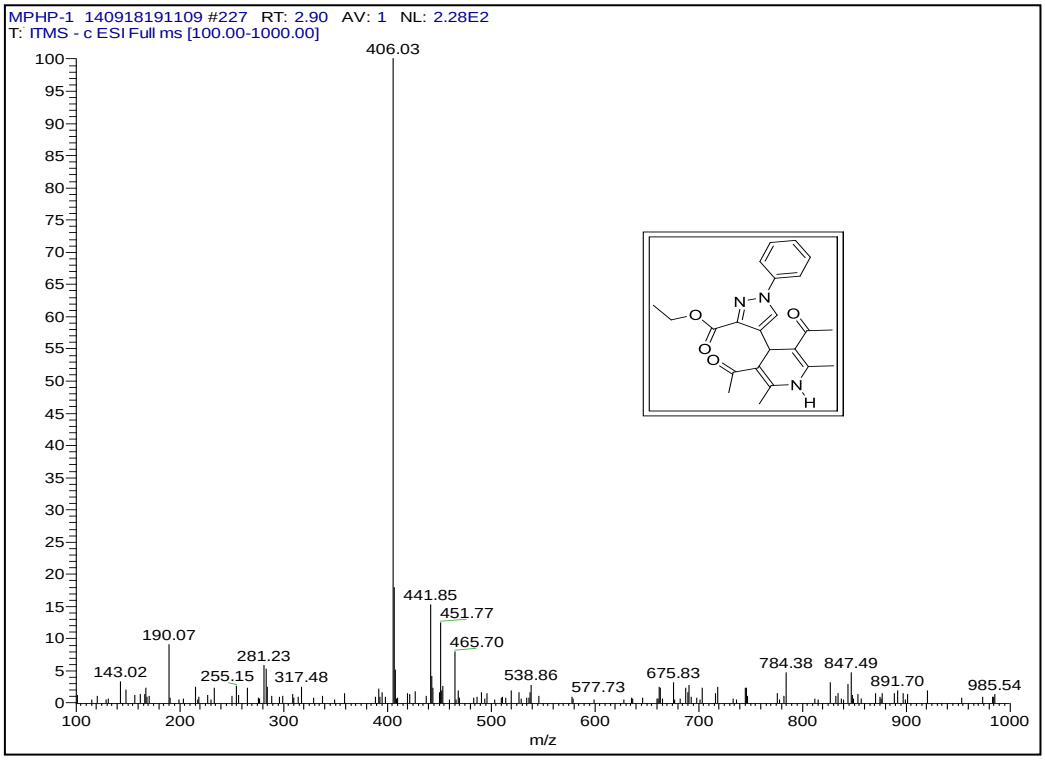


Figure 4.2 Mass spectrum of compound 4a

Characterization of compounds 4a-j

Compound 4a; Ethyl4-(3,5-diacetyl-2-methyl-1,4-dihydropyridin-4-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate, Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.36 (3H, t, *J* = 6.50 Hz), 2.25 (12H, d), 4.43 (2H, q, *J* = 7.45 Hz), 5.63 (1H, S), 5.91(1H, S), 7.25-7.57 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.3, 19.2, 27.3, 35.8, 60.6, 113.1, 119.1, 121.6, 126.2, 139.1, 142.5, 148.8, 161.3, 196.5; LC-MS (m/z):407 (M-H); Anal. (%) for $C_{23}H_{25}N_3O_4$ Calcd. C, 67.80; H, 6.18; N, 10.31; O, 15.71; Found: C, 67.78; H, 6.20; N, 10.29; O, 15.67.

Compound 4b; Ethyl 4-(3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridin-4-yl)-1-(2,4-dinitrophenyl)-1*H*-pyrazole-3-carboxylate, Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23 (3H, t, *J* = 6.65 Hz), 2.30 (12H, s), 4.41 (2H, q, *J* = 7.65 Hz), 5.53 (1H, S), 6.10 (1H, S), 7.50 (1H, S), 7.69-7.82 (2H, m), 7.89 (1H, S); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.1, 22.0, 25.4, 37.8, 63.6, 110.9, 117.4, 122.5, 126.4, 136.5, 141.1, 143.5, 149.7, 162.0, 198.2; LC-MS (m/z):498 (M+H); Anal.(%) for $C_{23}H_{23}N_5O_8$ Calcd. C, 55.53; H, 4.66; N, 14.08; O, 25.73; Found: 55.50; H, 4.61; N, 14.02; O, 25.68.

Compound 4c; Methyl 4-(3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridin-4-yl)-1-phenyl-1*H*-pyrazole-3-carboxylate, White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.28 (12H, s), 3.95 (3H, s), 4.89 (1H, S), 6.63 (1H, S), 7.42-7.68 (5H, m), 7.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.7, 28.8, 35.5, 52.3, 111.0, 118.2, 122.4, 127.0, 130.6, 138.1, 143.4, 146.5, 164.8, 197.2**;** LC-MS (m/z):394 (M+H); Anal. (%) for $C_{22}H_{23}N_3O_4$ Calcd. C, 67.16; H, 5.89; N, 10.68; O, 16.27; Found: C, 67.12; H, 5.78; N, 10.60; O, 16.18.

Compound 4d; Methyl 4-(3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridin-4-yl)-1-(2,4-dinitrophenyl)-1*H*-pyrazole-3-carboxylate, Yellow solid; Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.32 (12H, s), 3.41 (3H, s), 4.81 (1H, s) 6.30 (1H, S), 7.62 (1H, S), 8.52-8.74 (2H, m), 8.97 (1H, S); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 18.9, 27.2, 37.1, 51.9, 112.2, 120.3, 121.7, 125.9, 127.8, 138.9, 141.8, 146.8, 148.6, 162.2, 197.1; LC-MS (m/z):484 (M+H); Anal.(%) for $C_{22}H_{21}N_5O_8$ Calcd. C, 54.66; H, 4.38; N, 14.49; O, 26.48; Found: C, 54.63; H, 4.35; N, 14.47; O, 26.42.

Compound 4e; 1,1'-(4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, Pale yellow; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.26 (12H, s), 4.75 (1H, S), 6.39 (1H, S), 7.42-7.72 (10H, m), 7.82 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.3, 27.8, 34.3, 112.0, 118.8, 119.6, 122.9, 126.4, 127.9, 128.7, 130.1,132.9, 138.6, 147.1, 149.4, 198.0**;** LC-MS (m/z):412 (M+H); Anal. (%) for $C_{26}H_{25}N_3O_2$ Calcd. C, 75.89; H, 6.12; N, 10.21; O, 7.78; Found: C, 75.67; H, 6.08; N, 10.16; O, 7.69.

Compound 4f; 1,1'-(4-(1-(2,4-dinitrophenyl)3-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.13 (12H, s), 4.61 (1H, S), 6.21 (1H, S), 7.55-7.81 (5H, m), 7.89 (1H, s) 8.76 (1H. s), 8.85 (2H, d); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.0, 27.1, 35.1, 112.0, 117.5, 118.6, 121.8, 126.5, 128.2, 129.7, 132.7, 139.5, 146.5, 147.8, 150.0, 199.1; LC-MS (m/z):502 (M+H); Anal. (%) for $C_{26}H_{23}N_5O_6$ Calcd. C, 62.27; H, 4.62; N, 13.97; O, 19.14; Found: C, 62.21; H, 4.59; N, 13.86; O, 19.12.

Compound 4g; 1,1'-(4-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.22 (12H, s), 4.65 (1H, S), 6.22 (1H, S), 7.21-7.45 (5H, m), 7.68 (d, 2H, *J*=7.25 Hz), 7.95 (d, 2H, *J*=7.45 Hz), 8.02 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.9, 27.2, 33.1, 111.5, 117.6, 118.9, 122.0, 125.3, 126.8, 128.3, 130.3, 131.8, 137.5, 146.2, 148.3, 198.9**;** LC-MS (m/z):446 (M+H); Anal. (%) for $C_{26}H_{24}ClN_3O_2$ Calcd. C, 70.03; H, 5.42; Cl, 7.95; N, 9.42; O, 7.18; Found: C, 70.01; H, 5.39; Cl, 7.91; N, 9.40; O, 7.13.

Compound 4h; 1,1'-(4-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.25 (12H, s), 4.61 (1H, S), 6.21 (1H, S), 7.19-7.53 (5H, m), 7.71 (d, 2H, *J*=7.50 Hz), 7.90 (d, 2H, *J*=7.65 Hz), 8.13 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 19.7, 27.1, 32.9, 110.9, 117.2, 119.0, 121.2, 124.6, 126.1, 128.7, 130.6, 131.9, 136.3, 146.3, 148.8, 199.0**;** LC-MS (m/z):490 (M+H); Anal. (%) for $C_{26}H_{24}BrN_3O_2$ Calcd. C, 63.68; H, 4.93; Br, 16.29; N, 8.57; O, 5.53; Found: C, 63.60; H, 4.91; Br, 16.26; N, 8.51; O, 5.49.

Compound 4i; 1,1'-(4-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.20 (12H, s),3.41 (3H, s) 4.56 (1H, S), 6.10 (1H, S), 7.22-7.61 (5H, m), 7.79 (d, 2H, *J*=7.45 Hz), 7.91 (d, 2H, *J*=7.25 Hz), 8.10 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ =

20.1, 23.5, 39.1, 59.1, 113.6, 117.9, 119.8, 122.3, 124.4, 126.7, 127.7, 130.8, 132.9, 135.8, 146.7, 148.0, 198.1**;** LC-MS (m/z):440 (M-H); Anal. (%) for $C_{27}H_{27}N_3O_3$ Calcd. C, 73.45; H, 6.16; N, 9.52; O, 10.87; Found: C, 73.39; H, 6.16; N, 9.51; O, 10.82.

Compound 4j; 1,1'-(4-(3-(4-ethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)diethanone, White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.38 (3H, t, *J* = Hz), 2.26 (12H, s), 4.13 (2H, q, J = Hz) 4.58 (1H, S), 6.01 (1H, S), 7.52-7.79 (5H, m), 7.85 (d, 2H, *J*=7.45 Hz), 7.99 (d, 2H, *J*=7.25 Hz), 8.23 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 15.2, 20.1, 27.5, 36.1, 65.7, 114.2, 116.6, 118.4, 121.2, 122.6, 126.9, 128.2, 131.0, 132.1, 134.2, 146.5, 147.8, 200.1**;** LC-MS (m/z):456 (M+H); Anal.(%) for $C_{28}H_{29}N_3O_3$ Calcd. C, 73.82; H, 6.42; N, 9.22; O, 10.54; Found: C, 73.77; H, 6.38; N, 9.20; O, 10.51.

4. Conclusion

In conclusion, we have demonstrated a new, one-pot multi component reaction via Hantszch pyridine synthesis that offers a simple method for the synthesis of highly substituted 1,4-dihydropyridines from pyrazole aldehyde, acetylacetone and ammonium acetate. We also made an attempt to make the reaction eco-friendly using various solvents and catalyst. The better result was obtained with ethanol-water mixture and acetic acid as a catalyst. The synthesized compounds were well characterized by various spectroscopic techniques. It was expected that the calcium channel activity of 1,4-dihydropyridines may be enhanced by incorporating pyrazole unit.

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