INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

EFFECT OF SOLVENT AND CATALYSIS ON SYNTHESIS OF DIHYDROPYRIDINE DERIVATIVES

S. Baluja* and R. Talaviya

Physical Chemical Laboratory, Chemistry Department,
Saurashtra University, Rajkot-360 005, Gujarat, India.

ABSTRACT

A facile and efficient preparation of dihydropyridine derivatives have been reported via a multi component reaction in the presence and absence of ammonium iron(II) sulphate. Further, synthesis is performed in different pure alcohols and their mixtures. A series of substituted dihydropyridine derivatives were synthesized and the structures of these compounds were established on the basis of spectral analysis. Excellent yield of compounds is observed in presence of ammonium iron(II) sulphate. Thus, ammonium iron(II) sulphate is proven to be a very efficient catalyst for synthesis of these derivatives. Further, among different alcohol mixtures, ethanol + isopropanol mixture gives higher yield and reaction time is also reduced.

Keywords: Dihydropyridine derivatives, ammonium iron(II) sulphate, methanol, ethanol.

INTRODUCTION

Dihydropyridine derivatives are among the most prevalent heterocyclic ring with various substitutions at several positions. Some of these derivatives are known to act as a multifunctional lead molecule for various biological activities such as inhibition of HMGCoA-reductase,[1] antihypertensive,[2] K^+ channel openers,[3]anticancer,[4] antihistaminic,[4]anticonvulsant,[5]calcium channel blockers,[6] antifungal,[7]analgesic,[8] anti-tubercular,[9,10] antiulcer,[11]antiplasmodial,[12] anti inflammatory[13] etc. Further, some dihydropyridine derivatives act as highly selective adenosine receptor antagonist.[14,15]Because of these pharmacological activities of dihydropyridines, the synthesis of this class of compounds is highly desirable.

Due to multifold biological properties exhibited by pyridine scaffold, various workers have reported synthesis of pyridine derivatives by various methods.[16-18] The use of catalyst in organic synthesis has many advantages such as high efficiency, easy purification, mild reaction condition, benefiting to industry[19,20] etc. Hantzsch synthesis is one of the most broadly used methods for the preparation of dihydropyridine derivatives.[21] In order to improve the efficiency of synthesis, different catalysts have been explored and many of them exhibited excellent catalytic activity.[22] Furthermore, along with the development of environmental consciousness in chemical research and industry, solvent-free reaction, microwave method and some efficient attempts have been used to build dihydropyridine scaffold.[23,24]

In the present work, synthesis of some new dihydropyridine derivatives is given. The characterization of these synthesized compounds was done by IR, ^{1}H NMR,^{13}C NMR,mass and elemental analysis.

EXPERIMENTAL SECTION

Materials

All the reagents i.e. 4-hydroxy-3-methoxy benzaldehyde (vanillin), ethyl cyanoacetate, ammonium acetate, ammonium iron(II) sulphate, methanol, ethanol and isopropanol were purchased from Spectrochem Pvt. Ltd. (Mumbai, India) and were used without further purification. Theacetophenones used in the present study were simple acetophenone and its different substituents such as 2-methoxy acetophenones, 4-methoxy acetophenones, 4-bromo acetophenones, 3,4,5-trimethoxy

acetophenone, 4-flouro acetophenones, 4-methyl acetophenones, 2-hydroxy acetophenones, 4-hydroxy acetophenones and 4-chloro acetophenones. These acetophenones were purchased from Spectrochem Pvt. Ltd. and LOBA Chemie Pvt. Ltd.

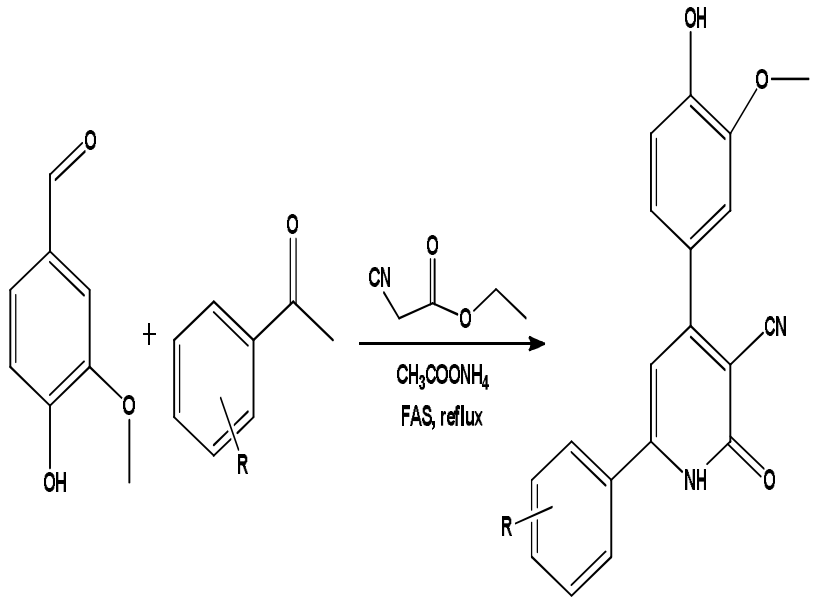
The structure confirmation of these synthesized compounds was done by IR, ^{1}H NMR, ^{13}C NMR,massand elemental analysis data. IRaffinity-1S (SHIMADZU furrier transport infrared spectrophotometer) instrument was used for infrared spectrometry study of synthesized dihydropyridine derivatives. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker AVANCE III (400 MHz). In all the cases, ^{1}H NMR and ^{13}C NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d_6) using TMS as an internal standard. The NMR signals are reported in δ ppm. Mass spectra were determined using direct inlet probe on a SHIMADZU GC-MS (Model No.-QP 2010) mass spectrometer. Elemental analysis for C, H, and N were performed using a EuroVector (Model-EA3000) analyzer. The melting points of synthesized compounds were determined using differential scanning calorimeter (SHIMADZU DSC-60) under nitrogen atmosphere. The DSC-60 was calibrated using standard lead and zirconium metal sample.

Synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives

An alcoholic solution (pure or mixture) of acetophenone (0.01mol), 4-hydroxy-3-methoxy benzaldehyde (0.01mol), cyanoethylacetate(0.01mol) and ammonium acetate (0.04mol) was refluxed. The completion of reaction was confirmed by analytical thin layer chromatography (TLC) (Performed on aluminium coated plates Gel 60F_{254} (E. Merck)) using (0.6:0.4 v/v-Hexane: Ethyl acetate) as mobile phase. After completion of reaction, the reaction mass was cooled and obtained solid was stirred with toluene for half an hour. The resultant solid was filtered, washed with methanol to remove unreacted reagents and dried under vacuum to give crude product.

Pure methanol, ethanol, isopropanol and their mixtures are used for the synthesis. The compositions of alcohol mixtures, *i.e.,* ethanol + methanol, methanol + isopropanol and ethanol + isopropanol were 80:20 (v/v).

Further, reactions were carried out both in the absence and presence of catalyst. In the present study, ammonium iron(II) sulphate(2-4% mol) was used as catalyst.



Scheme. 1: Synthesis of dihydropyridine derivatives

Spectral data

DPCE-1. IR (υ, cm^{-1}): 3524.54 (-CN), 3284.77 (O-H), 2214.28 (-CN), 1737.86 (-C=O), 1629.85, 1587.42 (-NH-), 1456.26 (-CH-), 1388.75 (-CH-), 1286.52, 1230.58, 1022.27 (C-O), 939.33 (-OH). ^{1}H NMR (400 MHz, DMSO-d_6) (δ ppm):3.8372 (s, 6H, 2-OCH_3), 6.7842 (s, 1H, CH), 6.9308-6.9414 (d, 1H, J=8.24 Hz, CH), 6.9865-6.9918 (d, 1H, J=4.24 Hz, CH), 7.2480-7.3487 (m, 2H, CH), 7.6047-7.8259 (m, 6H,CH), 7.9186 (s, 1H, CH), 9.7776 (s, 1H, OH), 12.7288 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 55.26, 56.02, 113.72, 114.91, 116.02, 118.42, 122.64, 126.98, 130.26, 147.83, 149.77, 162.28. Mass (m/ʒ): 348. Analytically calculate ($C_{20}H_{16}O_4N_2$): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.99; H, 4.71; N, 8.11.

DPCE-2. IR (υ, cm^{-1}): 3479.58 (-CN), 2924.09 (O-H), 2222.00 (-CN), 1643.35, 1597.06 (-NH-), 1496.76 1427.3, 21381.03, 1350.17 (-CH-), 1280.73, 1211.30 (C-O), 1118.71, 1087.85, 1018.41 (O-C), 902.69 (-OH). ^{1}H NMR (DMSO-d_6) (δ ppm):3.8437-3.8688 (s, 6H, 2-OCH_3), 6.7742 (s, 1H, CH), 6.9256-6.9461 (d, 1H, J=8.2 Hz, CH), 7.0740-7.0956 (d, 2H, J=8.64 Hz, CH), 7.2294-7.2496 (d, 1H, J=8.08 Hz, CH), 7.3320 (s, 1H, CH), 7.8791-7.9000 (d, 2H, J=8.36 Hz, CH), 9.7386 (s, 1H, OH), 12.5543 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 55.48, 55.73, 112.42, 114.31, 115.44, 117.28, 121.72, 126.76, 129.36, 147.47, 149.00, 161.59. Mass (m/ʒ):348. Analytically calculate ($C_{20}H_{16}O_4N_2$): C, 68.96; H, 4.63; N, 8.04. Found: C, 68.99; H, 4.70; N, 8.10.

DPCE-3. IR (υ, cm^{-1}): 3427.19 (-CN), 3087.76 (O-H), 2214.74 (-CN), 1741.39(-C=O), 1647.27, 1583.59 (-NH-), 1474.46, 1398.49, 1340.53 (-CH-), 1274.95, 1213.25, 1089.78 (C-O), 995.27 (-OH), 682.80 (C-Br). ^{1}H NMR (DMSO-d_6) (δ ppm):3.8321 (s, 3H, OCH_3), 6.7639 (s, 1H, CH), 6.8602-6.8689 (d, 1H, J=3.48 Hz, CH), 6.8952-6.9032 (d, 1H, J=3.2 Hz, CH), 7.2181-7.3083 (m, 2H, CH), 7.5822-7.5994 (d, 2H, J=6.88 Hz, CH), 7.9006 (s, 1H, CH), 9.7072 (s, 1H, OH), 12.7208 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 54.73, 111.98, 113.76, 114.12, 116.91, 121.03, 125.62, 128.27, 146.19, 148.04, 160.71. Mass (m/ʒ): 397. Analytically calculate ($C_{19}H_{13}O_3N_2Br$): C, 57.45; H, 3.30; N, 7.05. Found: C, 57.52; H, 3.42; N, 7.13.

DPCE-4. IR (υ, cm^{-1}): 3534.19 (-CN), 3082.25 (O-H), 2212.14 (-CN), 1747.51(-C=O), 1649.14, 1585.49 (-NH-), 1471.69, 1398.39, 1340.53 (-CH-), 1274.95, 1213.25, 1089.78 (C-O), 995.27 (-OH). ^{1}H NMR (DMSO-d_6) (δ ppm):3.8321 (s, 3H, OCH_3), 3.8945 (s, 3H, OCH_3), 3.4123 (s, 3H, OCH_3), 3.4289 (s, 3H, OCH_3), 6.3418 (s, 1H, CH), 6.5392 (s, 1H, CH), 6.8608-6.9034 (m, 3H, CH), 7.9016 (s, 1H, CH), 9.7072 (s, 1H, OH), 12.7214 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 57.03, 114.13, 115.98, 116.71, 119.72, 123.09, 127.98, 131.11, 134.89, 137.01, 148.18, 150.17, 163.22. Mass (m/ʒ): 387. Analytically calculate ($C_{22}H_{14}O_5N_2$): C, 64.70; H, 4.94; N, 6.86. Found: C, 64.46; H, 4.81; N, 6.89.

DPCE-5.IR (υ, cm^{-1}): 3331.22(-CN), 3078.25 (O-H), 2217.14 (-CN), 1742.52(-C=O), 1644.14, 1582.44 (-NH-), 1476.65, 1395.35, 1344.52 (-CH-), 1278.95, 1215.25, 1084.78 (C-O), 992.22 (-OH), 681.19 (C-F). ^{1}H NMR (DMSO-d_6) (δ ppm): 3.8320 (s, 3H, OCH_3), 6.7892 (s, 1H, CH), 6.8603-6.8778 (d, 2H, J=7.00 Hz, CH), 7.2180-7.3080 (m, 2H, CH), 7.5641-7.5801 (d, 2H, J=6.4 Hz, CH), 7.9301 (s, 1H, CH), 9.7070 (s, 1H, OH), 12.7218 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 56.89, 114.21, 115.28, 117.01, 119.42, 123.72, 126.21, 130.51, 148.42, 150.38, 162.92. Mass (m/ʒ): 337. Analytically calculate ($C_{19}H_{13}O_3N_2F$): C, 67.85; H, 3.90; N, 8.33. Found: C, 67.91; H, 3.94; N, 8.38.

DPCE-6. IR (υ, cm^{-1}): 3434.19 (-CN), 3083.14 (O-H), 2210.44 (-CN), 1716.65 (-C=O), 1649.14, 1598.99 (-NH-), 1490.97, 1471.69 (-CH-), 1367.53, 1334.74 (-CH-), 1288.45, 1234.44, 1074.35 (C-O), 968.27 (-OH). ^{1}H NMR (DMSO-d_6) (δ ppm) : 3.3843 (s, 3H, CH_3), 3.6621 (s, 3H, OCH_3), 6.7483 (s, 1H, CH), 6.8605-6.8685 (d, 1H, J=3.2 Hz, CH), 6.9929-7.0082 (d, 1H, J=6.12 Hz, CH), 7.1131-7.2033 (m, 2H, CH), 7.4632-7.4706 (d, 2H, J=2.96 Hz, CH), 7.9046 (s, 1H, CH), 9.7072 (s, 1H, OH), 12.7208 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 52.47, 57.02, 114.22, 115.74, 116.99, 119.09, 123.78, 127.51, 131.56, 148.89, 150.19, 162.86. Mass (m/ʒ): 332. Analytically calculate ($C_{20}H_{16}O_3N_2$): C, 72.38; H, 4.85; N, 8.43. Found: C, 72.49; H, 4.89; N, 8.49.

DPCE-7. IR (υ, cm^{-1}): 3324.69 (-CN), 3037.56 (O-H), 2215.14 (-CN), 1746.41 (-C=O), 1579.70 (-NH-), 1450.11 (-CH-), 1393.53 (-CH-), 1256.58, 1019.90 (C-N), 1291.48 (C-O), 929.33 (-OH). ^{1}H NMR (DMSO-d_6) (δ ppm) : 3.0651 (s, 3H, OCH3), 6.7384 (s, 1H, CH), 6.8835-6.8921 (d, 1H, J=3.44 Hz, CH), 6.9881-7.9958 (d, 1H, J=3.08 Hz, CH), 7.5337-7.8125 (m, 4H, CH), 7.9529 (s, 1H, CH), 9.7189 (s, 1H, OH), 9.7491 (s, 1H, OH), 12.4676 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 53.57, 113.02, 114.98, 116.09, 117.31, 122.89, 126.98, 130.16, 147.68, 149.41, 162.11. Mass (m/ʒ): 334. Analytically calculate ($C_{19}H_{14}O_4N_2$): C, 68.26; H, 4.22; N, 8.38. Found: C, 68.32; H, 4.25; N, 8.43.

DPCE-8. IR (υ, cm^{-1}): 3434.12 (-CN), 2917.56 (O-H), 2218.14 (-CN), 1747.55 (-C=O), 1579.70 (-

NH-), 1460.11 (-CH-), 1394.53 (-CH-), 1276.88, 1029.99 (C-N), 1230.58 (C-O), 939.33 (-OH). ^{1}H NMR (DMSO-d_6) (δ ppm) : 3.0651 (s, 3H, OCH_3), 6.7384-6.7462 (d, 1H, J=3.12 Hz, CH), 7.1337-7.1425 (d, 1H, J=3.52, CH), 7.4386-7.4501 (d, 1H, J=4.6 Hz, CH), 7.5853-7.9906 (m, 4H, CH), 8.0056 (s, 1H, CH), 9.7272 (s, 1H, OH), 9.7393 (s, 1H, OH), 12.7106 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 53.89, 113.67, 115.28, 116.79, 118.23, 123.51, 127.55, 130.89, 148.28, 150.01, 162.79. Mass (m/z): 334. Analytically calculate ($C_{19}H_{14}O_4N_2$): C, 68.26; H, 4.22; N, 8.38. Found: C, 68.33; H, 4.25; N, 8.43.

DPCE-9. IR (υ, cm^{-1}): 3433.69(-CN), 3083.44 (O-H), 2213.11 (-CN), 1745.51 (-C=O), 1645.28, 1595.13, 1570.06 (-NH-), 1471.69 (-CH-), 1394.53 (-CH-), 1259.52, 1024.20 (C-N), 1230.58 (C-O), 908.47 (N-H), 889.45 (C-Cl). ^{1}H NMR (DMSO-d_6) (δ ppm): 3.8622 (s,3H, OCH_3), 6.8806 (s, 1H, CH), 6.9308-6.9514 (d, 1H, J=7.84 Hz, CH), 7.2436-7.2684 (dd, 1H, CH), 7.3446-7.3487 (d, 1H, J=1.46 Hz, CH), 7.6047-7.6259 (d, 2H, J=8.48, CH), 7.9186-7.9389 (d, 2H, J=8.12 Hz, CH), 9.7776 (s, 1H, OH), 12.7288 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 55.75, 112.48, 115.47, 116.49, 121.85, 126.48, 128.86, 129.60, 135.85, 147.50, 141.14. Mass (m/z): 352. Analytically calculate ($C_{19}H_{13}O_3N_2Cl$): C, 64.69; H, 3.71; N, 7.49. Found: C, 64.75; H, 3.75; N, 7.55.

DPCE-10. IR (υ, cm^{-1}): 3424.54 (-CN), 3023.95 (O-H), 2222.00 (-CN), 1737.86 (-C=O), 1649.14, 1591.27 (-NH-), 1473.62 (-CH-), 1377.17 (-CH-), 1249.52, 1022.27 (C-N), 1228.66 (C-O), 910.48 (N-H). ^{1}H NMR (DMSO-d_6) (δ ppm): 3.0742 (s, 3H, OCH_3), 6.7569 (s, 1H, CH), 6.2892-6.3048 (d, 1H, J=6.24 Hz, CH), 6.9992-7.0111 (d, 1H, J=4.76 Hz, CH), 7.7427-8.3285 (m, 6H, CH), 9.7932 (s, 1H, OH), 12.7836 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 53.89, 111.27, 112.72, 114.82, 116.39, 120.29, 123.51, 128.03, 147.93, 147.62, 159.55. Mass (m/z): 318. Analytically calculate ($C_{19}H_{13}O_3N_2$): C, 71.69; H, 3.65; N, 7.25. Found: C, 71.76; H, 3.69; N, 7.31.

RESULTS AND DISCUSSION

All the synthesized compounds were crystallized using methanol.Overall, ten derivatives were synthesized, which are as follows:

- **DPCE-1:** 4-(4-hydroxy-3-methoxyphenyl)-6-(2-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-2:** 4-(4-hydroxy-3-methoxyphenyl)-6-(4-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-3:** 6-(4-bromophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-4:** 6-(3,4,5-trimethoxy)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-5:** 6-(4-fluorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile
- **DPCE-6:** 4-(4-hydroxy-3-methoxyphenyl)-2-oxo-6-(tolyl)-1,2-dihydropyridine-3-carbonitrile
- **DPCE-7:** 4-(4-hydroxy-3-methoxyphenyl)-6-(2-hydroxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-8**: 4-(4-hydroxy-3-methoxyphenyl)-6-(4-hydroxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-9:** 6-(4-chlorophenyl)-4-(4-hydroxy-3-methoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile
- **DPCE-10**: 4-(4-hydroxy-3-methoxyphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile

The physical properties of synthesized compounds are given in Table 1. For DPCE-2, the IR, ^{1}H NMR, ^{13}C NMR and mass spectrum are given in Figures 1 to 4.

The effect of solvent and catalyst on reaction time and % yield is graphically represented in Figures 5-8.

Figure 5 shows the % yield of all the compounds in different alcohols *i.e.,* methanol, ethanol and isopropanol in the absence and presence of catalyst. It is evident from Figure 5[A] that for all the compounds, % yield is maximum in ethanol solutions and minimum in isopropanol. The % yield is maximum for DPCE-6 in ethanol. In the presence of catalyst also, % yield is found to be higher in ethanol for all the compounds and is maximum for DPCE-3 and DPCE-9, as evident from Figure 5[B].

The effect of different solvents on reaction time is graphically presented in Figure 6. The reaction time is improved in ethanol solution for both in the absence and presence of catalyst. However, in isopropanol, reaction time is higher for all the compounds.

The % yield and reaction time are also studied in mixed alcohols. Figure 7 shows the % yield in methanol + ethanol, methanol + isopropanol and ethanol + isopropanol mixtures. It is observed that % yield is found to be maximum in ethanol + isopropanol mixture in both absence and presence of catalyst. Overall, % yield is

minimum in methanol + isopropanol. Further, % yield is maximum for DPCE-3 in ethanol + isopropanol mixture in the absence of catalyst but in the presence of catalyst, % yield is increased for all the compounds.

The effect of alcohol mixture on reaction time is shown in Figure 8. The reaction time is also found to be reduced in ethanol + isopropanol mixture. However, in methanol + ethanol mixture, the time is comparatively less than that required for methanol + isopropanol mixture for both cases *i.e.,* in the absence and presence of catalyst. In ethanol + isopropanol mixture, reaction time is minimum for DPCE-9 in the absence of catalyst whereas in the presence of catalyst, the reaction time is reduced for all compounds.

CONCLUSION

For the synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile derivatives, use of catalyst increases the % yield and reduces the reaction time. Further, comparison of % yield and reaction time in pure and mixed solvents indicates that alcohol mixture is more effective than pure alcohols and in ethanol + isopropanol mixture, % yield and reaction time are both improved.

ACKNOWLEDGEMENT

Authors are thankful to Head of Chemistry Department for providing necessary facilities. Rahul is thankful to UGC-New Delhi for BSR Fellowship in Science.

Table 1: Physical properties of 1,2-dihydropyridine derivatives

Compound Code	R substitution	Molecular formula	Molecular weight (gm/mol)	Melting points (°C)	R_f^* Value
DPCE-1	2-methoxy	$C_{20}H_{16}O_4N_2$	348	350.40	0.58
DPCE-2	4-methoxy	$C_{20}H_{16}O_4N_2$	348	298.14	0.55
DPCE-3	4-bromo	$C_{19}H_{13}O_3N_2Br$	397	340.65	0.63
DPCE-4	3,4,5-trimethoxy	$C_{22}H_{14}O_5N_2$	386	241.34	0.49
DPCE-5	4-flouro	$C_{19}H_{13}O_3N_2F$	336	342.90	0.62
DPCE-6	4-methyl	$C_{20}H_{16}O_3N_2$	332	241.34	0.60
DPCE-7	2-hydroxy	$C_{19}H_{14}O_4N_2$	334	241.55	0.53
DPCE-8	4-hydroxy	$C_{19}H_{14}O_4N_2$	334	248.77	0.51
DPCE-9	4-chloro	$C_{19}H_{13}O_3N_2Cl$	352	335.60	0.61
DPCE-10	Hydrogen	$C_{19}H_{13}O_3N_2$	318	251.98	0.59

R_f^* mobile phase; hexane:ethylacetae-0.6:0.4 v/v

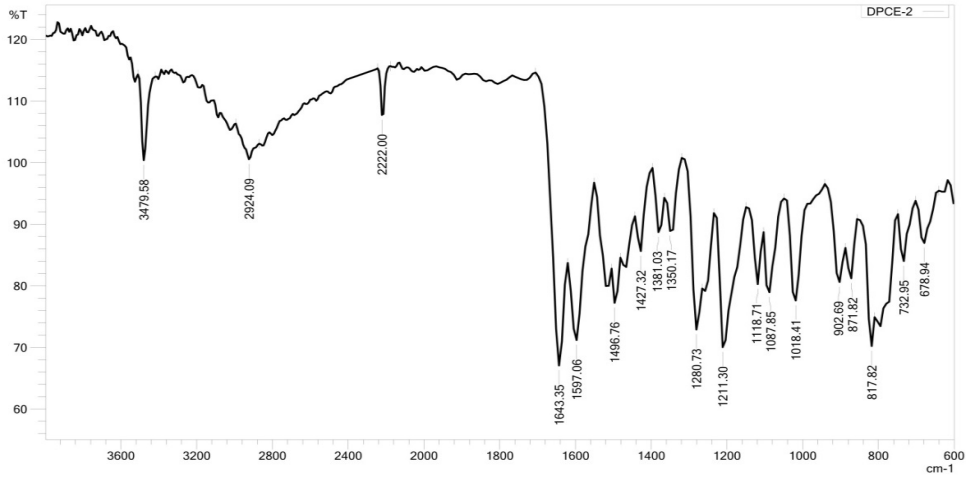


Fig. 1: IR spectrum of DPCE-2

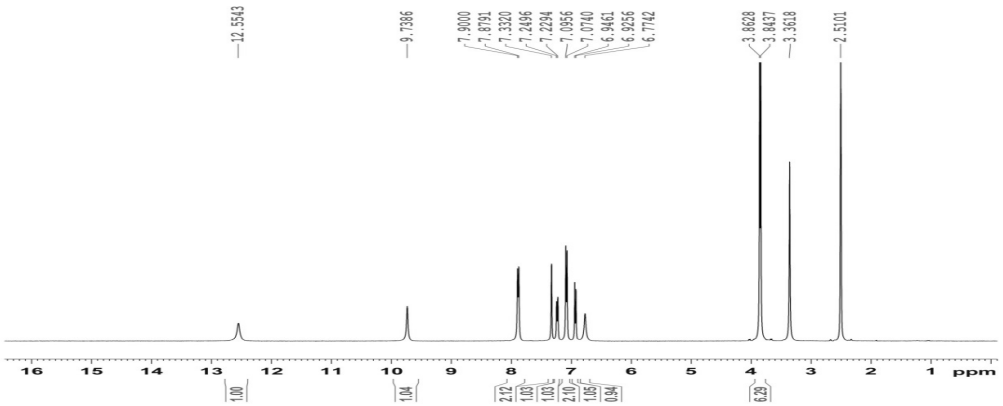


Fig. 2: ^{1}H NMR spectrum of DPCE-2

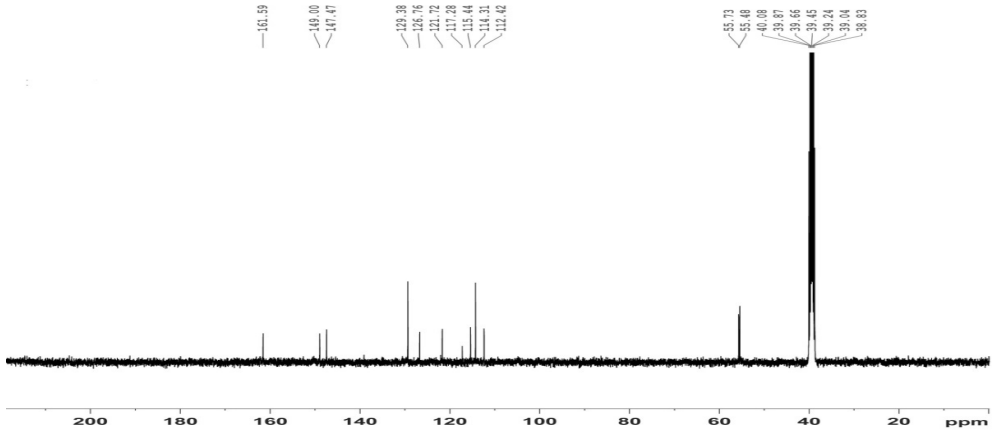


Fig. 3: ^{13}C NMR spectrum of DPCE-2

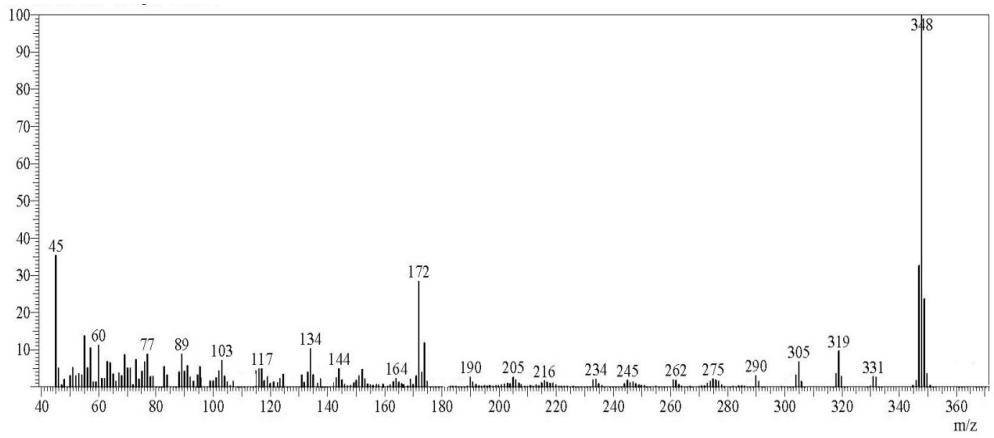


Fig. 4: Mass spectrum of DPCE-2

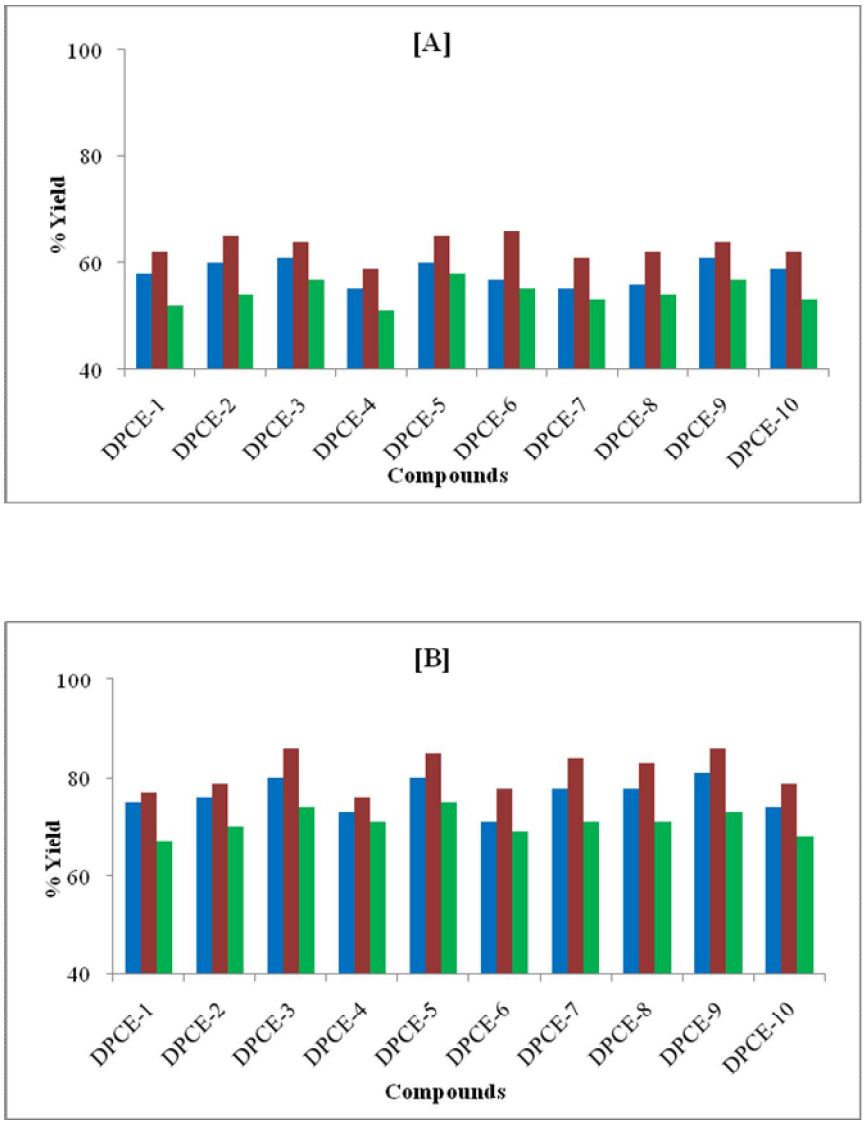


Fig. 5:% Yield of synthesized 1,2-dihydropyridine derivatives in [A] absence of catalyst and [B] presence of catalyst in pure alcohols; (■) methanol, (■) ethanol, (■) isopropanol

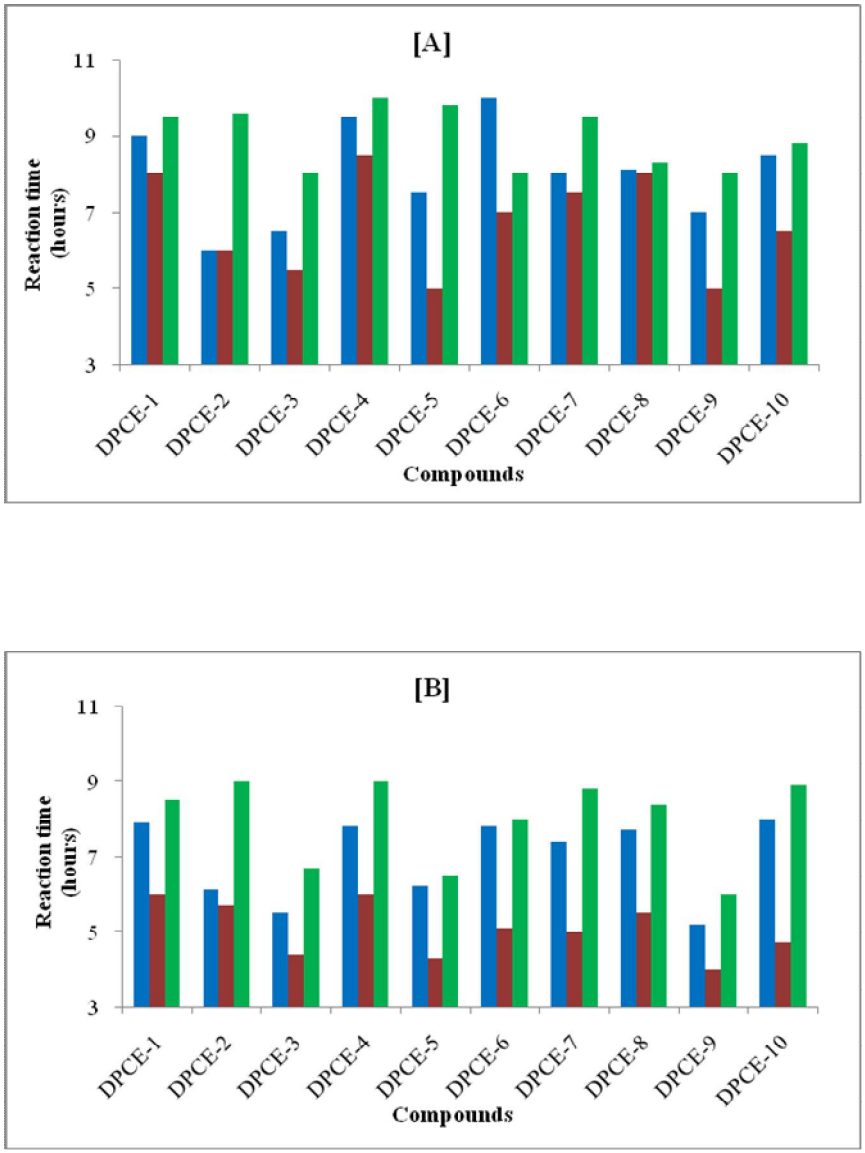


Fig. 6:Reaction time for the synthesis of 1,2-dihydropyridine derivatives in [A] absence of catalyst and [B] presence of catalyst in pure alcohols; (■) methanol, (■) ethanol, (■) isopropanol

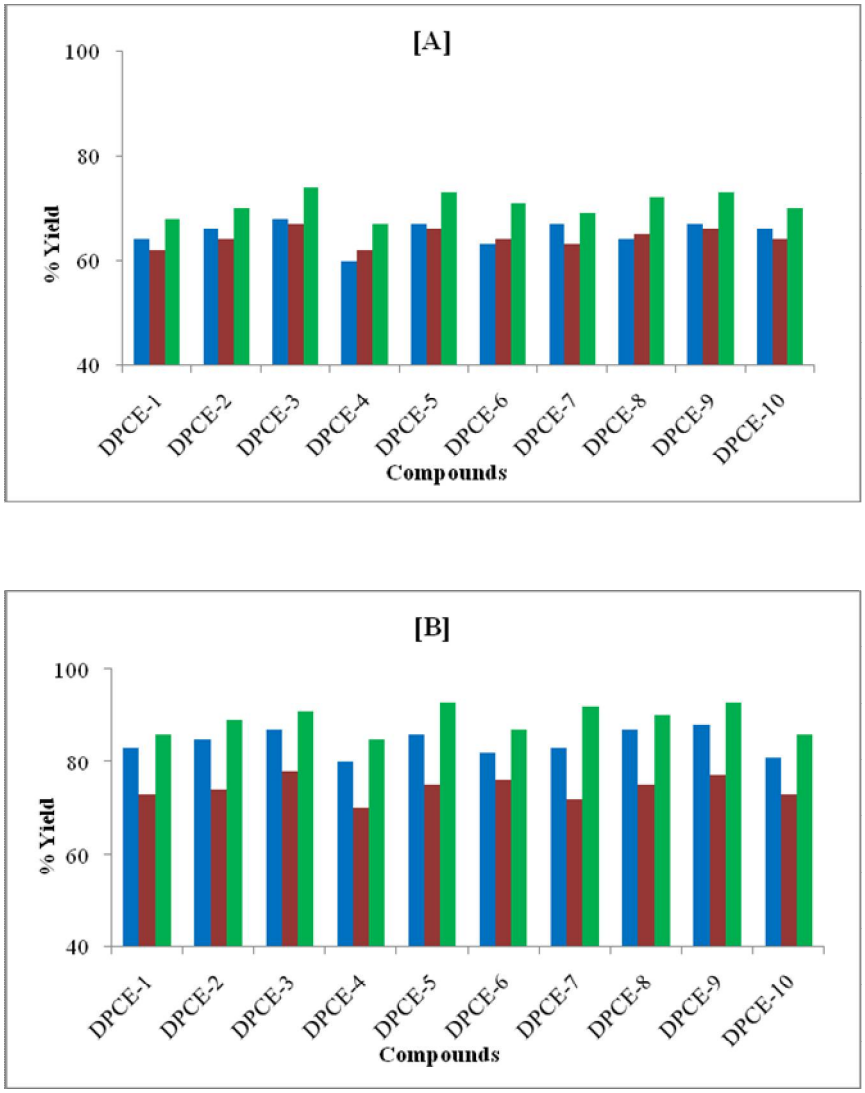


Fig. 7:% Yield of synthesized 1,2-dihydropyridine derivatives in [A] absence of catalyst and [B] presence of catalyst in binary mixture of alcohols; (■) methanol + ethanol, (■) methanol + isopropanol, (■) ethanol + isopropanol

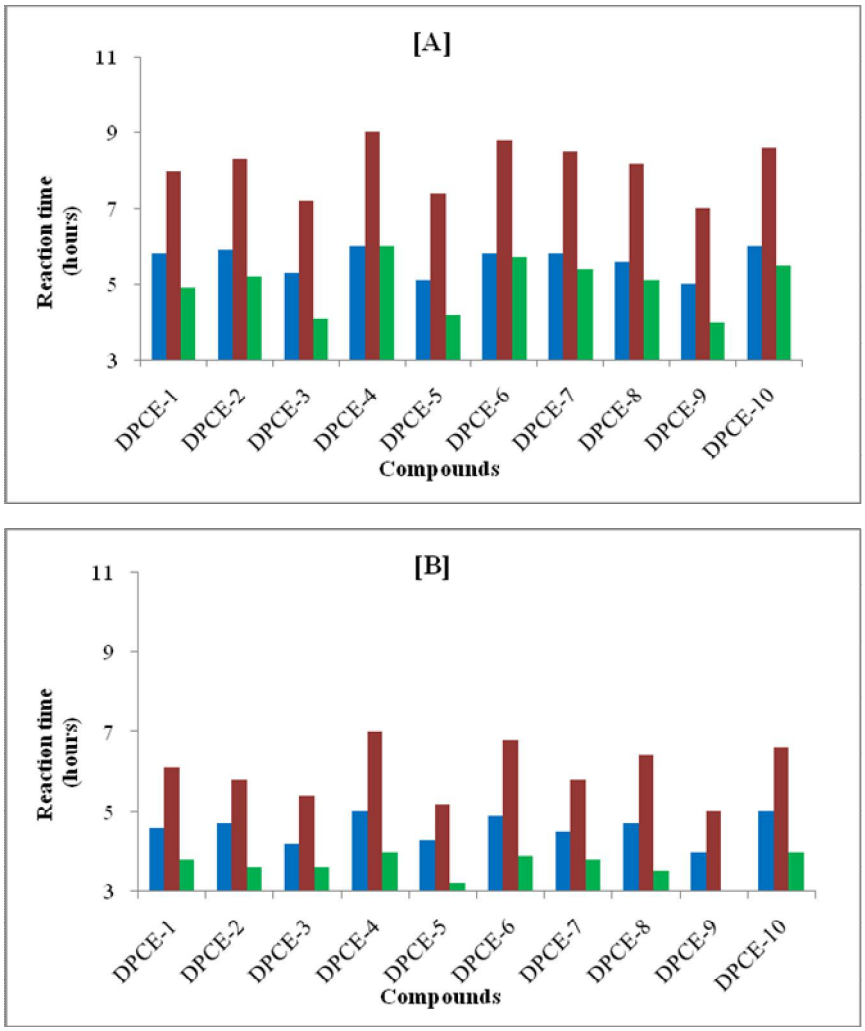


Fig. 8: Reaction time for the synthesis of 1,2-dihydropyridine derivatives in [A] absence of catalyst and [B] presence of catalyst in binary mixture of alcohols; (■) methanol + ethanol, (■) methanol + isopropanol, (■) ethanol + isopropanol

REFERENCES

1. Suzuki M, Iwasaki H, Fujikawa Y, Sakashita M, Kitaharac M and Sakoda R. Synthesis and biological evalution of condensed pyridine and condensed pyrimidine-based HMG-CoA reeducates inhibitors. Bioorg Med Chem Lett. 2001;11:1285-1288.
2. Chen Yuan K and Ming-Jung W. The synthesis of N-phenyoxyethyl-1-substituted-1,2,3,4-tetrahydroisoquinolines and their α_1 – adeenoceptor blocking activity. Eur J Med Chem. 2009;44:1271-1277.
3. Saponara S, Kawase M, Shah A, Motohas N, Molnar J, Ugocsai K, Sgaragli G and Fusi F. 3,5-Dibenzoyl-4(3-phenoxyphenyl)-1,4-dihydro-2,6-dimethylpyridine (DP7) as a new multidrug resistance reverting agent devoid of effect on vascular smooth muscle contractility. British J Pharma. 2004;141:415-422.
4. Manilal A, Idhayadhulla A, Kumar SRand Jamal abdulnaseer A.Synthesis of some new pyrrole and pyridine derivatives and their antimicrobial, anticancer activities. Int J Bio Chem. 2013;7:15-26.
5. Kumar SR, Idhayadhulla A, Jamal abdulnaseer A, Kavimani S and Indumathy S.Synthesis and anticonvulsant activity of a new series of 1,4-dihydropyridine derivatives. Ind J Pharm Sci. 2010;72:S719-725.
6. Shaldam MA, Elhamamsy MH, Esmat EA and El-Moselhy T. 1,4-dihydropyridine

calcium channel blockers: homology modeling of the receptor and assessment of structure activity relationship. Hindawi publishing corporation. ISRN MedChe. Volume 2014,Article ID 203518, pages 14.
7. ChhillarAK, Arya P, Mukherjee C, Kumar P, Yadav Y, Sharma AK, Yadav V, Gupta J, Dabur R, Jha HN, Watterson AC, Parmar VS, Prasad AK and Sharma GL. Microwave-assisted synthesis of antimicrobial dihydropyridine and tetrahydropyrimidine-2-ones: novel compounds against aspergillosis. Bioorg Med Chem. 2006;14:973-981.
8. Gullapalli S and Ramarao P. L-type Ca^{+2} channel modulation by dihydropyridinespotentiates opioid receptor agonist induced acute analgesia and inhibits development of tolerance in rats. Neuropharmacology. 2002;42:467-475.
9. Amini M, Navidpore L and Shafiee A. Synthesis and antitubercular activity of new N,N-diaryl-4(4,5-dichloroimidazole-2-yl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxamides. DARU. 2008;16:9-12.
10. Fassihi A, Azadpour Z, Delbari N, Saghaie L, Memarian HR, Sabet R, Alborzi A, Miri R, Pourabbas B, Mardaneh J, Mousavi P,Moeinifard B andHojjat S. Synthesis and antitubercular activity of novel 4-substituted imidazolyl-2,6-dimethyl-N^3,N^5-bisaryl-1,4-dihydropyridine-3,5-dicarboxamides. Eur J Med Chem. 2009;44:3253-3258.
11. Domány G, Matuz J, Sághy K and Ezer E. 1,2-dihydropyridine derivatives as potential antiulcer agents. Eur J Med Chem. 1993;28:633-636.
12. Verhaeghe P, Azas N, Gasquet M, Hutter S. Castera-Ducros C, Laget M, Rault S, Rathelota P andVanellea P. Synthesis and in vitro antiplasmodial evaluation of 4-anilino-2-trichloromethylquinazolines. Bioorg Med Chem Lett. 2009;18:4313-4322.
13. Kappe CO. 100 years of the biginellidihydropyrimidine synthesis. Tetrahedron. 1993;49:6937-6963.
14. Jacobson KA, Xie R, Li A, Xiao-Duo J, Melman N, Olah ME and Tiles GL. Selective A_3adenosine receptor antagonist: water-soluble 3,5-diaryl-1,2,4-trialkylpyridinium salts and their oxidative generation from dihydropyridine precursors. J Med Chem. 1999;42:4232-4238.
15. Jiang J, Michiel van Rhee A,Melman N, Ji X and Jacobson KA. 6-phenyl-1,4-dihydropyridine derivatives as potent and selective A_3adenisine receptor antagonists. J Med Chem. 1996;39:4667-4675.
16. Hatamjafari F and Nezhad FG. An efficient one-pot synthesisofdihydropyridines under solvent-free conditions. Oriental J Chem. 2014;30:355-357.
17. Nikoorazm M. A new method for the oxidation of 1,4-dihydropyridine derivatives by guanidinium nitrate in the presence of silica sulfuric acid under mild, heterogeneous and metal-free conditions. ScientialRanica. 2012;20:603-606.
18. Li-RongW, Zhao-Rui L, Ming L and Cao H. Solvent-free and efficient synthesis of imidazole[1,2-α]pyridine derivatives via a one-pot three-component reaction. Green Chem. 2012;14:707-716.
19. Taylor MS and Dimitrijevi E. Organoboron acids and their derivatives as catalysts for organic synthesis. ACS Catalysis. 2013;3:945-962.
20. Han J. Eco-catalysis leads the way to green synthetic chemistry. Organic Chem Curr Res. 2012;1:e114.
21. Hantzsch A. Justus Liebigs Ann Chem. 1882;215:1.
22. Run-tao L, Yu-peng L, Jin-ming L, Xin W and Tei-ming C. Multicomponent reactions leading to symmetric and asymmetric multi-substituted 1,4-dihydropyridines on montmorillonite. Tetrahedron. 2013;69:5242-5247.
23. Lee YA and Kim SC. Synthesis of 1,4-dihydropridine using microwave-assisted aza-diels-alder reaction and its application to amlodipine.J Indus Eng Chem. 2011;17:401-403
24. Bagley MC, Fusillo V, Jenkins R, Lubinu MC and Mason C. One-step synthesis of pyridines and dihydropyridines in a continuous flow microwave reactor. Beilstein J Org Chem. 2013;9:1957-1968.