

Oxidation of Some Dihydropyridine Derivatives to Pyridine Via Different Methods

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Abstract

Three different methods were used for the oxidation of dihydropyridines into pyridine derivatives. In first method DMSO was used as a solvent as well as catalyst, whereas in second method few drops of nitric acids were used but in third method bleaching powder (calcium hypochlorite) was used. All the three methods are found efficient for the oxidation purpose. The yields obtained was moderate to good (25% to 64%). By using these oxidation methods, we synthesized ten derivatives which were characterized by different available spectroscopic techniques like mass spectrometry, nuclear magnetic spectroscopy (¹H & ¹³C) and elemental analysis. All the synthesized derivatives were mostly yellow in shade and were stable solids at room temperature. From this data it was confirmed that in all oxidative derivatives –NH peak disappeared in proton NMR spectra.

Keywords: Dihydropyridine, Hantzsch reaction, pyridine, oxidation, dihydropyridine.

I. Introduction

The oxidation of Hantzsch 1, 4-dihydropyridines to corresponding pyridines has been extensively studied in view of the pertinence of the reaction to the metabolism of Hantzsch esters and the calcium channel blocking drugs used in the treatment of various cardiovascular disorders (Abdel-Mohsen, Conrad, & Beifuss, 2012; McCluskey et al., 1992). Some of the representative compounds of this class possess acaricidal, insecticidal, bactericidal and herbicidal activities (Khadilkar & Borkar, 1998). The oxidation of 1, 4-dihydropyridines to the corresponding pyridine derivatives occurs initially during the first pass metabolism in the liver. The pyridine derivatives are then further metabolized leading to the cleavage of the ester groups (Abdoli-Senejani & Karami, 2020; Boecker & Guengerich, 1986). Hantzsch 1, 4-dihydropyridine derivatives are often regarded as the model of the natural reduced nicotinamide adenine dinucleotide (NADH) coenzyme which functions as redox reagent for biological reactions by transferring an electron or a hydride ion to the surrounding substrate and hence their oxidation behavior under various conditions assumes greater significance (Brewster et al., 1989; Safaiee et al., 2018). Oxidation of dihydropyridines is one of the ubiquitous issues in organic chemistry (Safaiee et al., 2018). In recent years several research groups have reported new oxidation methods which includes oxidation with ferric nitrate on a solid support (Balogh, Hermeicz, Ménszáros, & Laszlo, 2004), manganese dioxide or DDQ (Zolfigol, Sadeghi, Mohammadpoor-Baltork, Choghmarani, & Taqian-Nasab, 2001), nitric oxide (Itoh, Nagata, Matsuya, Miyazaki, & Ohsawa, 1997), bismuth nitrate pentahydrate (Mashraqui & Karnik, 1998), PCC (Vanden Eynde, Mayence, & Maquestiau, 1992), tetra kis-pyridine cobalt (II) dichromate (TPCD) (Safaiee et al., 2018), nicotinium dichromate (Loupy, Sansoulet, Díez-Barra, & Carrillo, 1992), N₂O₄ complex of 18-crown-6 (Zolfigol, Zebarjadian, et al., 2001), MClx/ NaNO₂/wet SiO₂ (Paul, Sharma, Gupta, Choudhary, & Gupta, 2007), silica chloride/NaNO₂/wet SiO₂ (Ali Zolfigol, Shirini, Choghmarani, & Mohammadpoor-Baltork, 2003), H₂O₂ Co(OAc)₂ (Zolfigol, Sadeghi, et al., 2001), MCM-41 silica supported HPF₆ (Ray, Brown, Bhaumik, Dutta, & Mukhopadhyay, 2013),

NaHSO₄/Na₂Cr₂O₇/wet SiO₂ (Zolfigol, Sadeghi, et al., 2001), peroxy-disulfatecobalt (II), Zr(NO₃)₄ (Sabitha, Kumar Reddy, Reddy, Fatima, & Yadav, 2003), hypervalent iodine reagents (Son, Truong, Mishra, Mishra, & Kim, 2018), Co(II) catalyzed auto-oxidation (Chavan, Kharul, Kalkote, & Shivakumar, 2003), Silica-supported ceric ammonium nitrate (CAN) (Kumar et al., 2019), Au/TiO₂ nanoparticles (Stratakis, Fragkiadakis, Kidonakis, & Zorba, 2020), sodium nitrite or nitrates (Monier, Abdel-Latif, El-Mekabaty, & Elattar, 2019) and heteropolyacid/NaNO₂/wet SiO₂ (Niknam, Zolfigol, Razavian, & Mohammadpoor-Baltork, 2005).

Due to the importance of oxidative derivatives of dihydropyridines, here we use three different methods for oxidation of dihydropyrides to synthesize ten derivatives and characterized using EIMS, NMR and CHN.

2. Methods and Materials

The reagents and chemicals used were commercially available from Merck or Fluka and were used as such some were synthesized in laboratory (Zafar et al., 2017). However, when needed, were purified using normal techniques. The solvents used were distilled and dried. Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. ¹HNMR and ¹³CNMR spectra were taken on Bruker DPX instrument at 300 and 400 MHz.

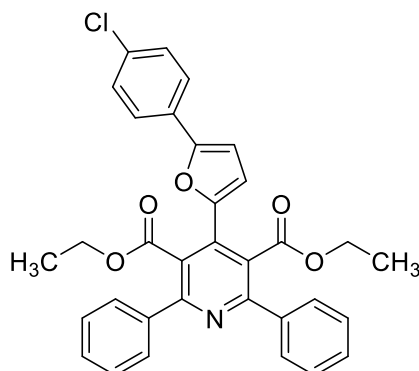
The methods that have been used for aromatization are as under:

1st procedure (A): 0.002 mmol of dihydropyridine was taken along with 5-6 mL DMSO as oxidizing agent, heated on water bath for 2-3 hours. The proceeding of the reaction was monitored by TLC. The reaction mixture was poured in chilled water. Precipitates were filtered and washed with water and cold ethanol. Then purity was checked by TLC, melting point was taken and percentage yield was calculated.

2nd Procedure (B): 0.002 mmol of dihydropyridine was taken along with 5-6 mL DMSO and a few drops of Conc. Nitric acid, heated on water bath for 2-3 hours. The proceeding of the reaction was monitored by TLC. The reaction mixture was poured in chilled water. Precipitates were filtered, washed with water and cold ethanol. Then purity was checked by TLC, melting point was taken and percentage yield was calculated.

3rd Procedure (C): Equimolar quantities of dihydropyridine and bleaching powder were taken along with 5 mL of water and 5 mL of ethyl acetate. The mixture was stirred at room temperature for 5 minutes, and then extracted with water and ethyl acetate. Precipitates were filtered, washed with water and cold ethanol. Then purity was checked by TLC, melting point was taken and percentage yield was calculated (Holla, Akberali, & Shivananda, 2001).

Diethyl 4-(5'-(4'-chlorophenyl) furan-2'-yl)-2, 6 diphenylpyridine-3, 5-dicarboxylate (1)



Color: yellow, **Physical appearance:** solid, **Molecular formula:** C₃₃H₂₆ClNO₅, **M.P** = 128^oC, **Yield** 1st = 44%. **Yield** 2nd = 31%. **Yield** 3rd = 40%. **Mass Spectra m/z (%):** 551.2 (M), 493.2 (3.93) (M-2C₂H₅), 480.2 (M-COO C₂H₅), 445.1 (3.15) (M-CO-OC₂H₅-Cl), 418.1 (5.15) (M-COOC₂H₅-Cl- C₂H₅), 380.1 (30) (M- C₆H₅-2 C₂H₅-Cl), 339.1 (5.46) (M- C₆H₅- C₂H₅-Cl-COOC₂H₅), 278.1 (7.31) (M-C₆H₄Cl- C₆H₅-COOC₂H₅-CH₃), 215.1

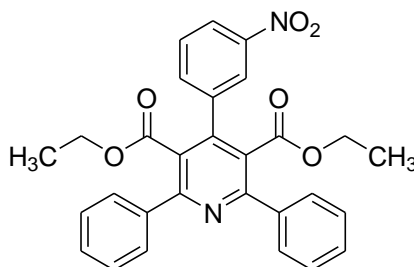
(10.22) (M-C₆H₄Cl-2 C₆H₅-COO C₂H₅), 105.1 (100) (M-C₁₀H₆ClO-2C₆H₅-COO C₂H₅- C₂H₅O), 77.0 (47.12) (C₆H₅).

¹H-NMR: (300MHz) (DMSO): δ: 1.42 (t, 6H, 2CH₃CH₂, J=10.5 Hz), 4.238 (q, 4H, 2CH₃CH₂, J=15.93 Hz), 6.605 (d, 1H, H-3, J=2.52 Hz), 6.759 (d, 1H, H-4, J=2.58 Hz), 7.479 (d, 2H, H-2, 6), 7.230(d, 2H, H-3, 5, J=1.989 Hz), 8.058 (d, 4H, H-2, 6, 2, 6, J= 5.64 Hz), 7.50 (t, 4H, H-3, 5, 3, 5, J=2.22 Hz), 7.117 (t, 2H, H-4,4, J=2.99 Hz).

¹³C-NMR: (75MHz) (DMSO): δ: 14.104 (2CH₃), 61.493 (2CH₂), 108.102 (2C), 127.753 (4CH), 128.854 (3CH), 129.247 (6CH-aromatic), 136.502 (2C), 148.810 (2C), 156.481 (2C), 165.026 (2C=O).

CHN micro analysis: calculated: C, 71.80; H, 4.75; N, 2.54; **Found:** C, 71.56; H, 4.70; N, 2.40.

Diethyl 4-(3'-nitrophenyl)-2, 6-diphenylpyridine-3, 5-dicarboxylate (2)



Color: bright yellow, **Physical appearance:** solid, **Molecular formula:** C₂₉H₂₄N₂O₆, **M.P** = 125°C, **Yield 1st** = 39%, **Yield 2nd** = 22%, **Yield 3rd** = 35%.

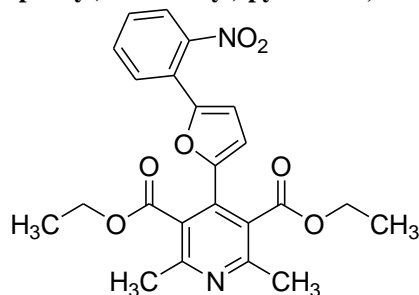
Mass Spectra m/z (%): 496.2 (18.71) (M), 467.2 (100) (M-C₂H₅), 421.1 (7.51) (M-COOC₂H₅), 395.0 (20.29) (M-COO C₂H₅- C₂H₅), 348.1 (13.45) (M-2COO C₂H₅), 304.2 (12.66) (M- C₆H₅-COO C₂H₅-NO₂), 200.1 (15.21) (M-2 C₆H₅-2COO C₂H₅), 77.1 (26.14) (C₆H₅).

¹H-NMR: (300MHz) (DMSO): δ: 0.737 (t, 6H, 2CH₃CH₂COO, J=8.4 Hz), 3.850 (q, 4H, 2 CH₃CH₂COO, J=10.9 Hz), 8.354(s, 1H, H-2'), 8.151 (d, 1H, H-4', J=0.9 Hz), 7.508 (t, 1H, H-5', J=3.9 Hz), 7.801 (d, 1H, H-6', J=1.8 Hz), The phenyl groups present at 2- and 6-positions show the following 1HNMR values: 7.793 (d, 4H, H-2, 6-of both phenyl groups, J=0.9 Hz), 7.509 (t, 2H, H-4- of both phenyl groups, J=3.9 Hz), 7.668 (t, 4H, H-2, 6-of both phenyl groups, J=3.0 Hz).

¹³C-NMR: (75MHz) (DMSO): δ: 13.04 (2CH₃CH₂COO), 61.48 (2CH₃CH₂COO), 166.30 (2CH₃CH₂COO), 155.79 (2C, C-2, 6), 122.88 (2C, C-3, 5), 147.25 (C-4), 138.23 (C-1'), 123.82 (2C, C-2', C-4'), 144.67 (C-3'), 130.15 (C-5'), 134.88 (C-6'), the phenyl groups of amide show following peaks: 136.31 (2C, C-1 of both phenyl groups), 126.72 (6C, C-2, 4, 6 of both phenyl groups), 129.49 (4C, C-3, 5 of both phenyl groups).

CHN micro analysis: calculated: C, 70.45; H, 4.66; N, 4.98; **Found:** C, 70.09; H, 4.59; N, 4.68.

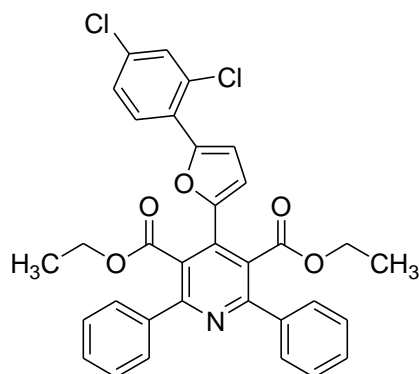
Diethyl 2, 6-dimethyl-4-(5'-(2''-nitrophenyl) furan-2'-yl) pyridine-3, 5-dicarboxylate (3)



Color: yellowish brown, **Physical appearance:** solid, **Molecular formula:** C₂₃H₂₂N₂O₇, **M.P** = 130°C, **Yield 1st** = 25%. **Yield 2nd** = 19%. **Yield 3rd** = 23%. **Mass Spectra m/z (%):** 438.1 (7.72) (M), 408.9 (92.12) (M-2CH₃), 337.0 (3.13) (M-2CH₃-COOC₂H₅), 293.1 (7.52) (M-2COO C₂H₅), 230.0 (6.31) (M-2COOC₂H₅-NO₂-CH₃), 204.0 (100) (M-C₁₇H₁₅N₂O₅-C₆H₄NO₂), 132.0 (49.62) (M-C₁₇H₁₅N₂O₅-C₆H₄NO₂-COO C₂H₅), 104.0 (40.91) (M-C₁₀H₆NO₃-C₁₃H₁₆NO₄-COO C₂H₅), 77.0 (34.13) (C₆H₅). **¹H-NMR: (300MHz) (DMSO):** δ: 2.490 (s, 6H, 2CH₃), 1.078 (t, 6H, 2CH₃CH₂COO, *J*=10.1 Hz), 4.163 (q, 4H, 2CH₃CH₂COO, *J*=10.20 Hz), 6.753 (d, 1H, H-3', *J*=3.6 Hz), 6.966 (d, 1H, H-4', *J*=3.0 Hz), 7.965 (d, 1H, H-3'', *J*=8.1 Hz), 7.627 (t, 1H, H-4'', *J*=3.9 Hz), 7.656 (t, 1H, H-5'', *J*=5.4 Hz), 7.797 (d, 1H, H-6'', *J*=3.6 Hz). **¹³C-NMR: (75MHz) (DMSO):** δ: 13.560 (2CH₃CH₂COO), 61.795 (2CH₃CH₂COO), 166.984 (4C, 2CH₃CH₂COO, C-2, 6), 22.385 (2CH₃), 114.166 (2C, C-3, 5), 146.905 (C-4), 155.503 (2C, C-2', 5'), 112.088 (C-3', 4'), 130.082 (C-1''), 146.905 (C-2''), 121.987 (C-3''), 128.826 (2C, C-4'', 6''), 132.907 (C-5'').

CHN micro analysis: calculated: C, 63.01; H, 5.06; N, 6.39 **Found:** C, 62.60; H, 4.95; N, 6.39

Diethyl 4-(5'-(2'', 4''-dichlorophenyl) furan-2'-yl)-2, 6-diphenylpyridine-3, 5-dicarboxylate (4)

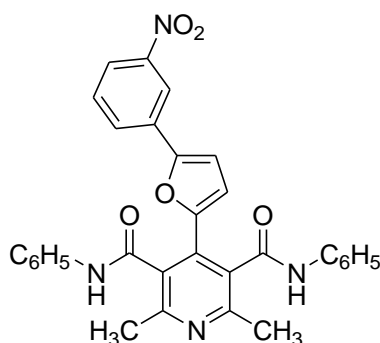


Color: bright yellow, **Physical appearance:** solid, **Molecular formula:** C₃₃H₂₅Cl₂N₂O₅, **M.P** = 132°C, **Yield 1st** = 28%. **Yield 2nd** = 19%. **Yield 3rd** = 27%. **Mass Spectra m/z (%):** 418.1 (4.66) (M-2C₆H₅-CH₃), 368.8 (6.37) (M-C₆H₃Cl₂-C₃H₅O₂), 339.9 (14.75) (M-C₆H₃Cl₂-C₃H₅O₂-C₂H₅), 305.0 (5.94) (M-2Cl-2C₆H₅-C₂H₅-CH₃), 269.1 (4.23) (M-C₁₀H₅Cl₂O-C₆H₅-C₂H₅), 249.0 (5.90) (M-2Cl-C₃H₅O₂-C₂H₅O-2C₆H₅), 215.1 (7.11) (M-C₆H₃Cl₂-2C₆H₅-C₃H₅O₂), 172.9 (45.25) (M-C₆H₃Cl₂-2C₆H₅-C₃H₅O₂-C₂H₅O), 105.1 (100) (M-C₁₀H₅Cl₂O-2C₆H₅-C₃H₅O₂-C₂H₅O), 77.1 (55.59) (M-C₂₇H₂₀Cl₂NO₅). **¹H-NMR: (300MHz) (DMSO):** δ: 1.147 (t, 6H, 2CH₃CH₂COO, *J*=14.10 Hz), 4.179 (q, 4H, 2CH₃CH₂COO, *J*=2.10 Hz), 6.775 (d, 2H, H-3, 4, *J*=8.7 Hz), 7.212 (d, 1H, H-5, *J*=3.6 Hz), 7.301 (d, 2H, H-3, 6, *J*=6.9 Hz), the phenyl groups positioned at 2 and 6, showed the following values in proton spectrum: 7.977 (d, 4H, H-2, 6, of both phenyl groups), 7.324 (t, 4H, H-3, 5, of both phenyl groups), 7.237 (t, 2H, H-4 of both phenyl groups, *J*=7.5 Hz). **¹³C-NMR: (75MHz) (DMSO):** δ: 14.008 (2C, CH₃CH₂COO), 61.208 (2C, CH₃CH₂COO), 164.196

(2C, CH₃CH₂COO), 114.173(2C, C-3, 5), 148.543 (C-4), 151.628 (2C, C-2', 5'), 135.735 (2C, C-1'', 4''), 133.605 (C-2''), 130.319 (2C, C-3'', 6''), 127.269 (C-5''), the two phenyl groups present at 2- and 6-positions show the following peaks: 135.735 (C-1 of both the phenyl rings), 127.556 (C-2, 4, 6 of both the phenyl rings), 129.174(C-3, 5 of both the phenyl rings)

CHN micro analysis: calculated: C, 67.58; H, 4.30; N, 2.39; **Found:** C, 67.52; H, 4.02; N, 2.23.

2, 6-dimethyl-4-(5'-(3''-nitrophenyl) furan-2'-yl)-N3, N5-Diphenylpyridine-3, 5- dicarboxamide (5)



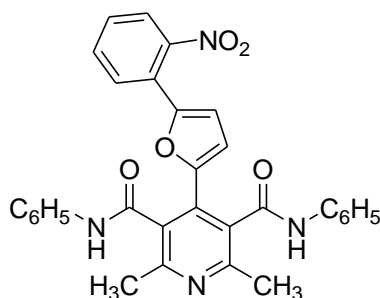
Color: Brown, **Physical appearance:** Solid, **Molecular formula:** C₃₁H₂₄N₄O₅, **M.P** = 201^oC, **Yield 1st** = 32%. **Yield 2nd** = 40%. **Yield 3rd** = 26%.

Mass Spectra m/z (%): 532.3 (9.87) (M), 440.1 (59.36) (M-C₆H₅-CH₃), 376.1 (14) (M-2C₆H₅), 333.1 (10.62) (M-C₇H₆NO-C₆H₅), 242.0 (100) (M-C₆H₄NO₂-2C₆H₅-CH₃), 196.1 (32.80) (M-C₆H₄NO₂- C₇H₆NO-2CH₃), 93.1 (82.55) (M- C₂₅H₁₈N₃O₅), 65.1 (100) (M- C₆H₄NOC₂₁H₁₈N₃O₂).

¹H-NMR: (300MHz) (DMSO): δ: 2.490 (s, 6H, 2CH₃), 8.258 (2, 2H, 2NH-amide), 6.209 (d, 2H, H-3', 4', J=3.3Hz), 8.229 (s, H-2''), 7.866 (d, H-4'', J=7.8Hz), 7.686 (t, H-5'', J=7.8Hz), 7.686 (d, H-6'', J=4.2Hz), the phenyl groups of two amides show the following values at ¹H-NMR spectrum: 7.626 (d, 4H, H-2, 6 of both the phenyl groups, J=7.5 Hz), 7.255 (t, 4H, H-3, 5 of both the phenyl rings, J=7.8 Hz), 7.000 (d, 2H, H-4 of both phenyl rings, J=14.4 Hz) **¹³C-NMR: (75MHz) (DMSO):** δ: 17.462 (2CH₃), 167.430 (2C=N), 125.123 (2C-C=O), 167.430 (2C=O), 148.458, 119.536, 130.0249, 123.470, 121.198 (12C-Ar), 107.311 (4C-furan), 130.341, 122.802, 139.599, 119.638, 128.872 and 132.029 (6C-Ar-NO₂).

CHN microanalysis: calculated: C, 69.92; H, 4.54; N, 10.52; **found:** C, 69.91; H, 4.55; N, 10.50.

2, 6-dimethyl-4-(5'-(2''-nitrophenyl) furan-2''-yl)-N3, N5-diphenylpyridine-3, 5-dicarboxamide (6)



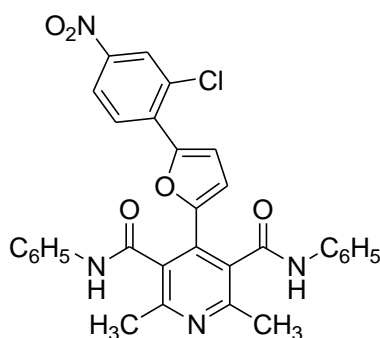
Color: Brown, **Physical appearance:** solid, **Molecular formula:** C₃₁H₂₄N₄O₅, **M.P** = 193^oC, **Yield 1st** = 42%. **Yield 2nd** = 60%. **Yield 3rd** = 49%.

Mass Spectra m/z (%): 532.0 (4.97) (M), 502.1 (2.1) (M-2CH₃), 439.9 (13.80) (M-C₆H₅-CH₃), 398.0 (23.40) (M-C₇H₆NO-CH₃), 279.0 (52.87) (M-2C₇H₆NO- CH₃), 267.0 (8.68) (M-2 C₇H₆NO-2 CH₃), 146.0 (16.13) (M-C₂₁H₁₆N₃O₄- CH₃), 93.0 (89.23) (M-C₂₅H₁₈N₃O₅), 77.1 (100) (C₆H₅).

¹H-NMR: (300MHz) (DMSO): δ : 7.853 (2H, s, NHCO), 2.490 (6H, s, CH₃), 7.699 (1H, *J*=7.8, d, Ar-H), 7.242 (1H, *J*=7.8, t, Ar-H), 7.00 (1H, *J*=7.2, t, Ar-H), 7.268 (1H, *J*=7.8, t, Ar-H), 7.673 (1H, *J*=7.8, d, Ar-H), 6.211-6.200 (2H, *J*=3.3, d, Furan ring), 8.299 (1H, d, Ar-NO₂), 7.493 (1H, *J*=9.6, t, Ar-NO₂), 7.729 (1H, *J*=4.2, t, Ar-NO₂), 7.743 (1H, *J*=4.2, d, Ar-NO₂).
¹³C-NMR: (75MHz) (DMSO): δ : 17.588 (2CH₃), 167.157 (2C=N), 124.994 (2C-C=O), 167.157 (2C=O), 132.227, 120.312, 130.025, 124.134, 128.877, 122.792 (2-phenyl rings), 139.739, 102.120 (4C-furan), 131.812, 139.283, 123.609, 128.495, 128.166, 127.368 (6C-Ar-NO₂).

CHN Microanalysis: Calculated: C, 69.92; H, 4.54; N, 10.52 **Found:** C, 69.90; H, 4.54; N, 10.51.

N3, N5-diphenylpyridine-4--(5'-(2''-chloro-4''-nitrophenyl) furan-2'-yl)-2, 6- dimethyl- 3, 5-dicarboxamide (7)



Color: Yellowish brown, **Physical appearance:** solid, **Molecular formula:** C₃₁H₂₃ClN₄O₅, **M.P** = 135°C, **Yield 1st** = 34%. **Yield 2nd** = 42%. **Yield 3rd** = 38%.

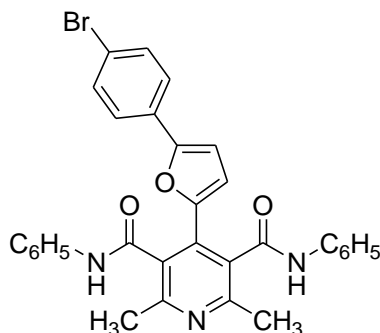
Mass Spectra m/z (%): 568.1 (7.0) (M+2), 566.1 (13.2) (M), 536.2 (14.8) (M-2CH₃), 474.1 (94.9) (M-C₆H₅-CH₃), 440.1 (6.2) (M- C₆H₅-CH₃-Cl), 398.1 (100) (M-C₆H₅-C₆H₆N), 354.1 (9) (M-C₇H₆NO- C₆H₆N), 316.1 (7.6) (M- C₁₀H₅ClNO₃-2CH₃), 279.1 (80.7) (M- 2C₇H₆NO-CH₃), 253.1 (13.0) (M-2C₇H₆NO-CH₃-NO₂), 156.0 (7.0) (M-C₂₅H₂₀N₃O₃), 132.1 (21.3) (MC₁₀H₅ClNO₃-C₇H₆NO-C₆H₆N), 93.1 (19.9) (M-C₁₀H₅ClNO₃-2C₇H₆NO-CH₃), 44.0 (19.2) (MC₂₄H₁₇ClN₃O₄-C₆H₅).

¹H-NMR: (300MHz) (DMSO): δ : 2.541 (s, 6H, 2CH₃), 6.698 (1H, H-3', *J*=3.9 Hz), 6.889 (d, 1H, H-4', *J*=3.9 Hz), 10.599 (s, 2H, 2NH-amides), 7.999 (s, 1H, H-3''), 7.995 (d, 1H, H-5'', *J*=2.1 Hz), 7.561 (d, 1H, H-6'', *J*=9.0 Hz). The two phenyl groups of amide groups show the following peaks on ¹H-NMR spectra: 7.561 (d, 4H, H-2, 6, of both the phenyl groups, *J*=9.0 Hz), 7.279 (t, 4H, H-3, 5, of both the phenyl groups, *J*=14.6 Hz), 7.065 (t, 2H, H-4, of both the phenyl groups, *J*=13.2 Hz)

¹³C-NMR: (75MHz) (DMSO): δ : 22.10 (2CH₃), 165.34 (4C, C-2, 6, 2C=O), 125.37 (2C, C-3, 5), 146.64 (C-4), 154.33 (2C, C-2', 5'), 112.32 (2C, C-3', 4'), 138.71 (C-1''), 133.78 (C-2''), 123.82 (C-3''), 149.03 (C-4''), 119.08 (C-5''), 129.53 (C-6''). The two phenyl groups of amide groups show the following peaks on ¹³CNMR spectra: 133.14 (2C, C-1 of both the phenyl groups), 119.77 (4C, C-2, 6 of both the phenyl groups), 130.88 (4C, C-3, 5 of both the phenyl groups), 125.37 (2C, C-4 of both the phenyl groups).

CHN Microanalysis: Calculated: C, 65.67; H, 4.09; N, 9.88 **Found:** C, 65.64; H, 4.10; N, 9.85.

4-(5'-(4''-bromophenyl) furan-2'-yl)-2, 6-dimethyl-N3, N5-diphenylpyridine-3, 5-dicarboxamide (8)



Color: Yellow, **Physical appearance:** solid, **Molecular formula:** C₃₁H₂₄BrN₃O₃, **M.P** = 198°C, **Yield 1st** = 53%. **Yield 2nd** = 47%. **Yield 3rd** = 64%.

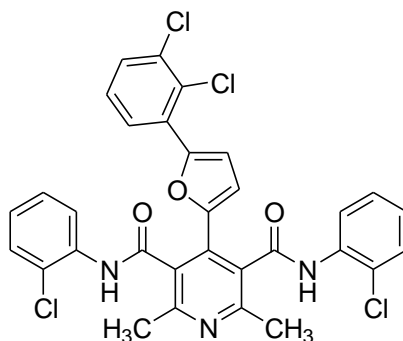
Mass Spectra m/z (%): 567.2 (15) (M+2), 565 (10) (M⁺), 242.3 (1.5) (M-C₁₀H₆BrO-C₆H₆N-CH₃), 179.1(100) (M-C₁₀H₆BrO-C₆H₆N-C₆H₅), 157.1 (56.5) (M-C₂₅H₂₂N₃O₃)

¹H NMR (300MHz) (DMSO): δ: 10.714(2H, s, NHCO), 7.670-7.643(d, 4H, J=8.1, Ar-H), 7.481-7.451(d, 4H, J=9, Ar-H), 7.349-7.298 (m, H-6, J=15.1, Ar-H), 7.122-7.073 (m, J=14.7, H=3, Ar-H), 6.979-6.966(d, J=3.9, 2H, Furan part), 2.590(s, 6H, 2CH₃).

¹³C NMR: (75MHz) (DMSO): δ: 20.963(2CH₃), 165.286(2C=N), 125.8(2C=C), 164.8(2C=O), 138.7, 121.427, 128.953, 124.122, 131.909, 119.499 (2-phenyl) 109.352(2C-furan), 128.672, 127.934, 132.723, 119.855, 131.520, 127.934(p-Br Phenyl)

CHN Microanalysis: Calculated: C, 65.73; H, 4.27; N, 7.42; **Found:** C, 65.75; H, 4.25; N, 7.40.

N3, N5-bis (2-chlorophenyl)-4-(5'-(2'', 3''-dichlorophenyl) furan-2'-yl)-2, 6- dimethylpyridine-3, 5-dicarboxamide (9)



Color: Yellowish orange, **Physical appearance:** solid, **Molecular formula:** C₃₁H₂₁Cl₄N₃O₃, **M.P** = 167°C, **Yield 1st** = 41%. **Yield 2nd** = 34%. **Yield 3rd** = 53%.

Mass Spectra m/z (%): 629.0 (2.6) (M+6), 628.0 (3.3) (M+5), 627.0 (10.3) (M+4), 626.0 (7.0) (M+3), 625.0 (20.8) (M+2), 623.0 (15.1) (M), 499.0 (100) (M-C₆H₅ClN), 461.0 (2.6) (MC₆H₅ClN-Cl), 372.0 (3.1) (M-2C₆H₅ClN), 335.0 (3.6) (M-C₆H₅Cl₂-C₆H₄Cl-Cl), 289.1 (1.7) (MC₁₀H₅Cl₂O-C₆H₅ClN), 261.1 (1.9) (M-C₁₀H₅Cl₂O-C₆H₅ClN-2CH₃), 174.9 (6.8) (M-C₁₀H₅Cl₂OC₁₀H₁₀ClN₂O-Cl), 127.0 (1.8) (M-C₂₅H₁₆Cl₃N₂O₃), 91.0 (1.8) (M-C₁₀H₅Cl₂O-2C₇H₅ClNO-CH₃).

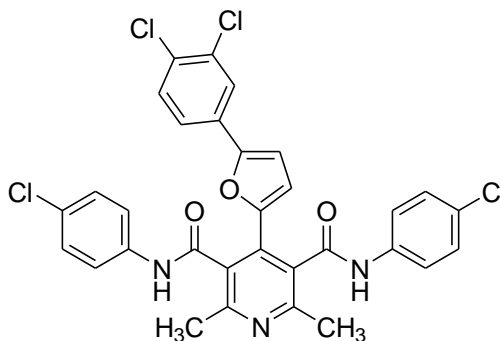
¹H-NMR: (300MHz) (DMSO): δ: 2.496 (s, 6H, 2CH₃), 10.270 (s, 2H, 2NH-amide), 6.997 (d, 2H, H-3, 4, J=6.3Hz), 7.184 (d, 1H, H-4, J=7.5Hz), 7.034 (t, 1H, H-5, J=8.1Hz), 7.377 (d, 1H, H-6, J=4.5Hz), The protons of 2-chlorophenyl of amide present at 3- and 5-positions show following values: 7.220 (d, 2H, H-3-of both the phenyls, J=1.8 Hz), 7.013 (t, 2H, H-4-of both the phenyls,

$J=7.8$ Hz), 7.197 (t, 2H, H-5-of both the phenyls, $J=6.0$ Hz), 7.588 (d, 2H, H-6-of both the phenyls, $J=6.6$ Hz).

$^{13}\text{C-NMR}$: (75MHz) (DMSO): δ : 14.14 (2CH₃), 166.52 (4C, C-2, 6, 2C=O), 126.50 (2C, C-3, 5), 134.14 (C-4), 154.42 (2C, C-2', 5'), 114.09 (2C, C-3', 4'), 134.14 (2C, C-1'', 3''), 129.57 (3C, C-2'', 4'', 5''), 127.80 (C-6''). The 2-chlorophenyl groups of two amides at 3- and 5-positions show following values: 134.14 (2C, C-1 of both phenyl groups), 126.50 (2C, C-2 of both phenyl groups), 127.00 (2C, C-3 of both phenyl groups), 126.71 (2C, C-4 of both phenyl groups), 129.45 (4C, C-5, 6 of both phenyl groups).

CHN Microanalysis: calculated: C, 59.54; H, 3.38; N, 6.72 **Found:** C, 59.52; H, 3.35; N, 6.70.

N3, N5-bis (4-chlorophenyl)-4-(5'-(3'', 4''-dichlorophenyl) furan-2'-yl)-2, 6-dimethylpyridine-3, 5-dicarboxamide (10)



Color: Dull yellow, **Physical appearance:** solid, **Molecular formula:** C₃₁H₂₁Cl₄N₃O₃, **M.P** = 175°C, **Yield 1st** = 32%. **Yield 2nd** = 27%. **Yield 3rd** = 54%.

Mass Spectra m/z (%): 630.1 (1.1) (M+7), 629.1 (2.9) (M+6), 628.1 9 (3.3) (M+5), 627.1 (10.3) (M+4), 626.1 (7.1) (M+3), 625.1 (19.5) (M+2), 623.0 (14.3) (M), 497.1 (100) (M-C₆H₅ClN), 468.1 (1.7) (M-C₇H₅ClNO), 450.1 (2.5) (M- C₆H₅ClN-Cl-CH₃), 413.1 (1.8) (M- C₆H₅ClN-2ClCH₃), 370.0 (5.0) (M- 2C₆H₅ClN), 344.1 (1.6) (M- C₆H₅ClN- C₇H₅ClNO), 324.1 (4) (M-2 C₆H₅ClN-Cl-CH₃), 287.1 (6.3) (M- 2C₇H₅ClNO-2CH₃), 207.0 (1.4) (M- C₂₁H₁₃Cl₃NO₂), 111.0 (2.8) (M-C₂₅H₁₇Cl₃N₃O₃), 44.0 (4.3) (M- C₆H₄Cl-C₂₄H₁₆Cl₃N₂O₂)

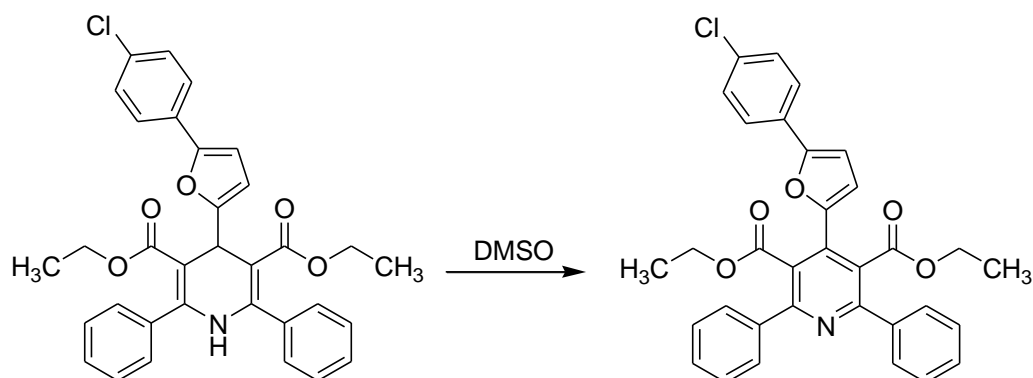
$^1\text{H-NMR}$: (300MHz) (DMSO): δ : 2.529 (s, 6H, 2CH₃), 10.767 (s, 2H, 2NH-amide), 6.850 (d, 2H, H-3', 4', $J=3.3$ Hz), 7.749 (s, 1H, H-2''), 7.148 (d, 1H, H-5'', $J=3.6$ Hz), 7.344 (d, 1H, H-6'', $J=8.7$ Hz), The two phenyl groups present at 2- and 6-positions show following $^1\text{H-NMR}$ values: 7.663 (d, 4H, H-2, 6 of both phenyl groups, $J=8.7$ Hz), 7.148 (d, 4H, H-3, 5 of both phenyl groups, $J=3.6$ Hz).

$^{13}\text{C-NMR}$: (75MHz) (DMSO): δ : 22.067 (2CH₃), 166.314 (4C, 2C=O, C-2, 6), 154.459 (3C, C-4, C-2', 5'), 128.792 (9C, C-1'', 2'', 6'', C-3, 4, 5 of two phenyl groups present at 2, and 6-position), 130.850 (3C, C-3'', 4'', 5''), 137.778 (2C, C-1 of both phenyl groups).

CHN Microanalysis: Calculated: C, 59.54; H, 3.38; N, 6.72; **Found:** C, 59.52; H, 3.35; N, 6.74.

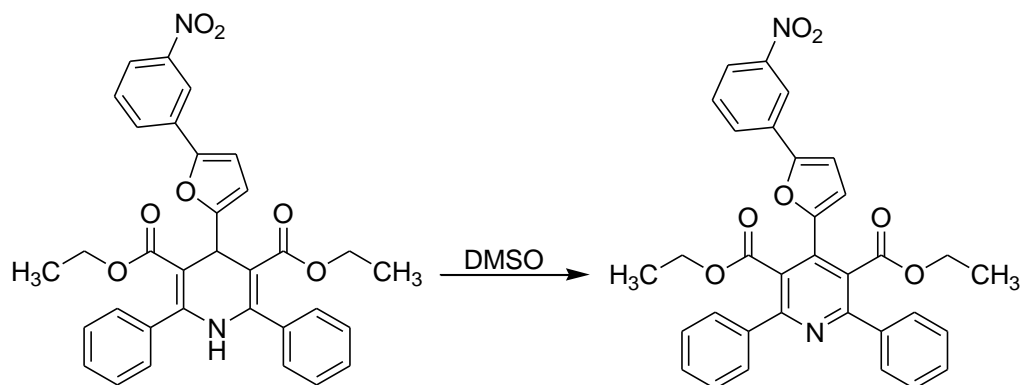
3. Results and Discussion

Diethyl 4-(5'-(4'-chlorophenyl) furan-2'-yl)-2, 6 diphenylpyridine-3, 5-dicarboxylate (1)



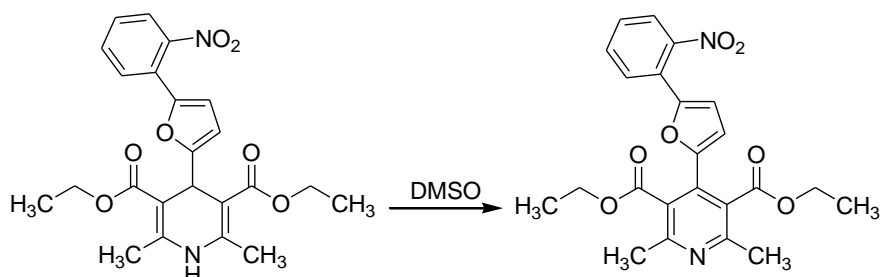
Compound **(1)** presented highest yield via 1st procedure where only DMSO used as oxidizing agent as well as solvent. Compound **1** was yellow solid and reaction was monitored by TLC (ethyl acetate: n-hexane) as solvent system. The product was confirmed through EIMS, ¹³CNMR and ¹HNMR. The melting point was 128^oC. EIMS confirmed the molecular mass of the compound which is 551.2. ¹³CNMR confirmed the structure as it showed C=O at 165.026 ppm, the ethyl group of ester showed the signals at 14.104 ppm and 61.493 ppm (CH₃ and CH₂ respectively). The ¹HNMR showed the ester protons at 1.42 ppm in the form of a triplet that showed that it is methyl groups of 2-ester substituents, and the methylene protons of the ester appeared at 4.238 ppm in the form of the quartet. The 14 aromatic protons appeared at expected places.

Diethyl 4-(3'-nitrophenyl)-2, 6-diphenylpyridine-3, 5-dicarboxylate (**2**)



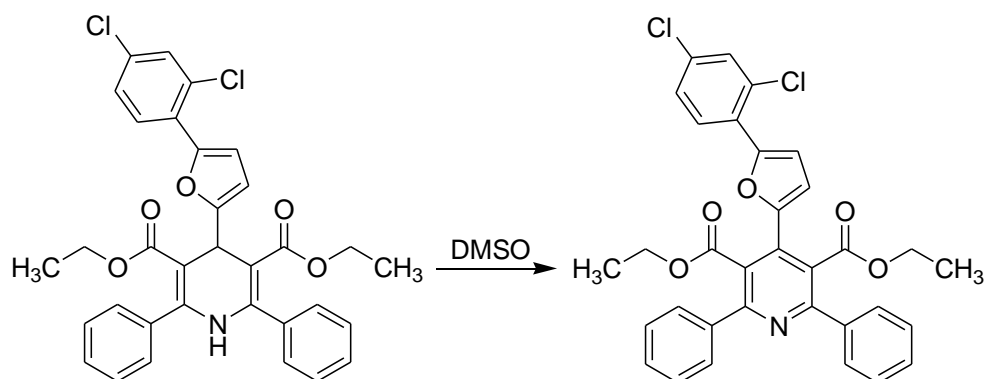
Diethyl 4-(3'-nitrophenyl)-2, 6-diphenyl dihydropyridine-3, 5-dicarboxylate (**2**) was being oxidized via all three procedures. Procedure 1 gave the highest yield 39% whereas method 2 gave lowest yield 22%. The resulting pyridine was light yellow in color and solid in nature, was confirmed through molecular ion peak and fragmentation peaks in EIMS. ¹³CNMR spectra showed the ester carbons CH₃, CH₂ and C=O at 13.04 ppm, 61.48 ppm and 166.30 ppm respectively. The ¹HNMR spectra of the compound showed the six protons of two ester methyl at 0.737ppm, four protons of methylene at 3.850 ppm. Other protons of the furan and the phenyl group are also at their respective positions.

Diethyl 2, 6-dimethyl-4-(5'-(2''-nitrophenyl) furan-2'-yl)pyridine-3, 5-dicarboxylate (3)



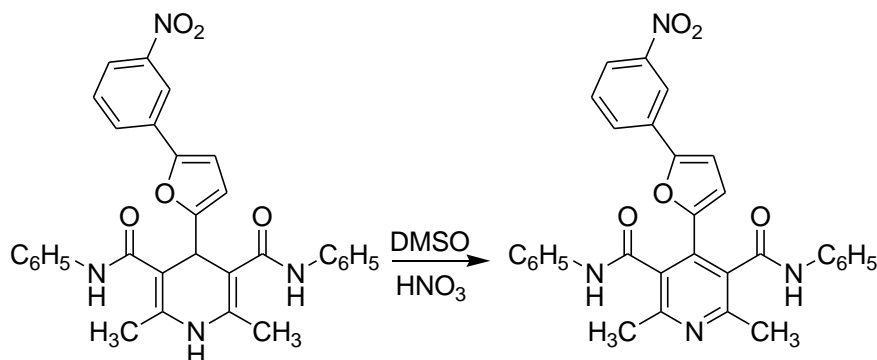
Here again DMSO was being used as oxidizing agent for the aromatization of the above mentioned compound (3) and gave the highest yield 25% whereas other both methods gave relatively less yield 19% and 23%. EIMS confirmed the molecular weight of the compound. ¹HNMR showed the signals of the ester protons at 1.078 ppm a triplet of methyl protons and at 4.163 ppm a quartet of methylene protons. All other peaks of the compound protons are at expected positions and discussed in experimental section. The ¹³CNMR showed the signals of ester carbons at 13.560 ppm, 61.795 ppm and 166.984 ppm CH₃, CH₂ and C=O respectively. All other carbons of the pyridines are at expected positions. Compound 3.

Diethyl 4-(5'-(2'', 4''-dichlorophenyl) furan-2'-yl)-2, 6-diphenylpyridine-3, 5-dicarboxylate (4)



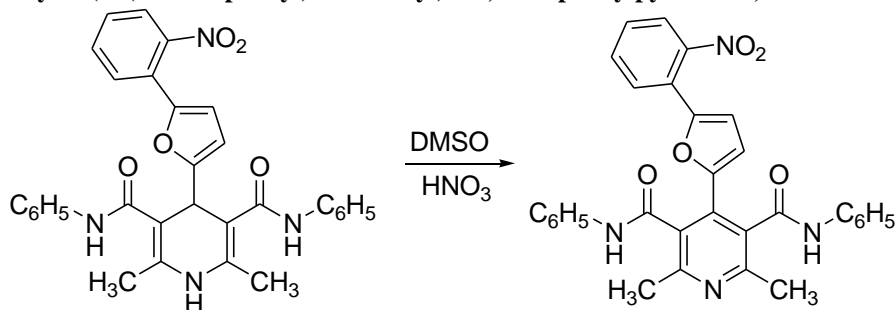
Procedure 1 presented the highest yield 28% of bright yellow colored product (4). ¹³CNMR spectra confirmed all the carbons of the molecule. The ester carbons CH₃, CH₂ and C=O appeared at 14.008 ppm, 61.208 ppm and 164.196 ppm respectively. As far as the ¹HNMR spectra is concerned the protons of ester appeared at 1.147 ppm (CH₃) in the form of triplet and at 4.179 ppm (CH₂) as quartet. The aromatic protons were at their respective positions.

2, 6-dimethyl-4-(5'-(3''-nitrophenyl) furan-2'-yl)-N3, N5-Diphenylpyridine-3, 5- dicarboxamide (5)



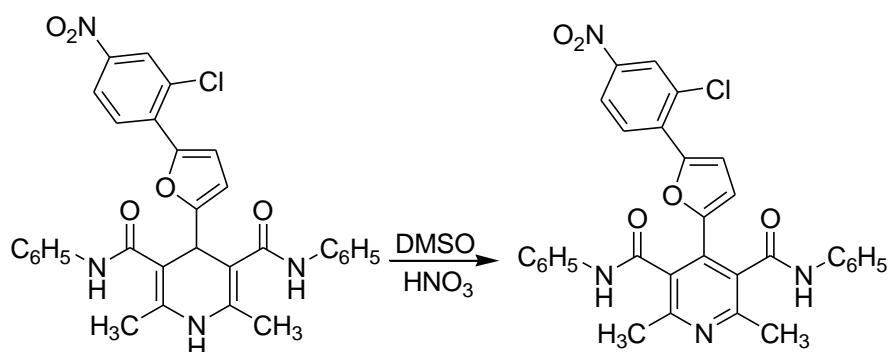
Brown colored compound 5 was prepared via all three mentioned methods. These methods gave 32%, 40% and 26% respectively. The resulting pyridine was confirmed and characterized through its EIMS, ¹HNMR and ¹³CNMR techniques. EIMS confirmed the molecular mass of the compound which is 532.2. ¹HNMR spectra confirmed the number and position of protons. 6-protons of 2-methyl groups present at 2- and 6-position of the pyridine nucleus appeared as singlet at 2.490 ppm, 2-protons of NH of both the amide groups at 8.299 ppm as singlet. Rest of the protons are aromatic and they appeared at the expected positions. ¹³CNMR spectra showed the two methyl carbons of 2- and 6-position at 17.462 ppm. Amide carbonyl appeared at 167.1430 ppm.

2,6-dimethyl-4-(5'-(2''-nitrophenyl)furan-2''-yl)-N3,N5-diphenylpyridine-3,5-dicarboxamide (6)



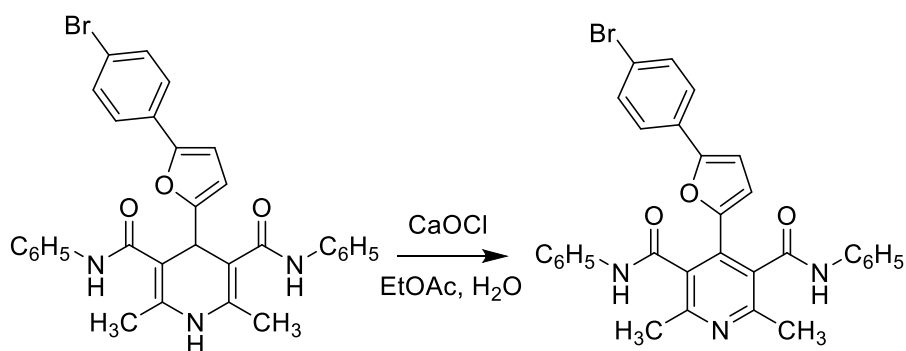
Highest yield was carried out via DMSO and HNO₃ method (method 2) while other both methods gave relatively less yield 42% and 49% as compared to method 2. The resulting pyridine was confirmed and characterized via EIMS, ¹³CNMR and ¹HNMR spectroscopic techniques. EIMS confirmed the molecular mass of the compound which is 532.0. The ¹HNMR spectra showed the protons of amide NH at 7.853 ppm as singlet. The singlet of six protons of two methyl group at 2- and 6-positions appeared at 2.490 ppm. The furan protons and aromatic protons appeared at the expected positions and are given in the experimental section. ¹³CNMR spectra showed the carbons of methyl groups at 17.588 ppm, C=O of amide appeared at 167.157 ppm.

N3, N5-diphenylpyridine-4--(5'-(2''-chloro-4''-nitrophenyl) furan-2'-yl)-2, 6-dimethyl- 3, 5-dicarboxamide (7)



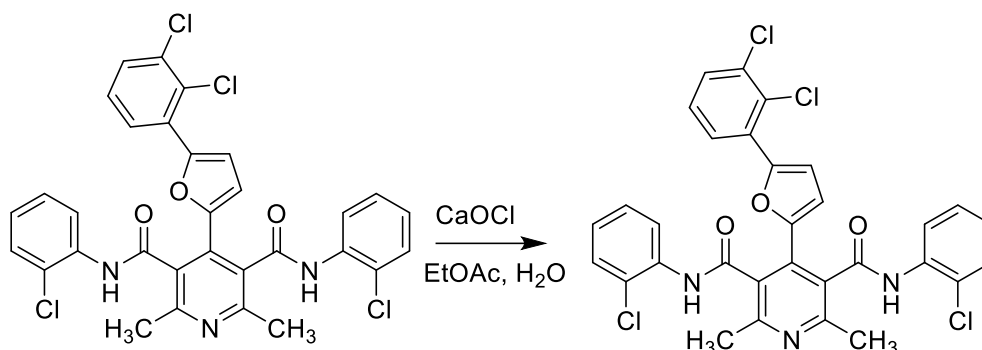
The product (7) was **brown colored solid, stable at room temperature and was** confirmed through EIMS, ¹HNMR and ¹³CNMR techniques. EIMS confirmed the molecular mass of the compound; the fragmentation confirmed the major substituents of the compound. ¹HNMR showed the protons of the compound. 6-protons of 2-methyl groups present at 2- and 6-position of the nucleus appeared at 2.541ppm in the form of the singlet. NH protons of amide appeared at 10.599 ppm as singlet. All other protons also appeared at their respective positions thus confirming the structure of desired compound. ¹³CNMR spectra of the compound showed the 2-carbons of both the methyl groups at 2- and 6-position at 22.10 ppm. Carbonylic carbon of amide moiety appeared at 165.34 ppm.

4-(5'-(4''-bromophenyl) furan-2'-yl)-2, 6-dimethyl-N3, N5-diphenylpyridine-3, 5-dicarboxamide (8)



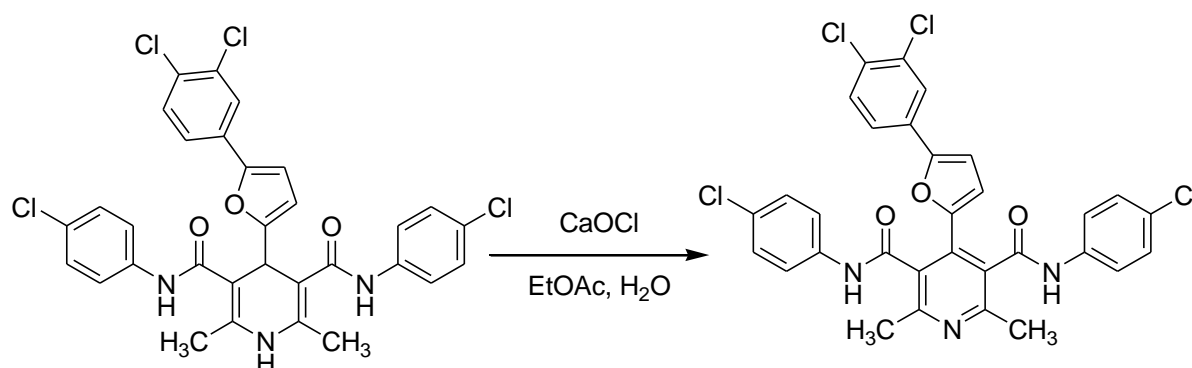
Compound 8 gave less yield by using procedure 1 & 2 but showed highest yield 64% with bleaching powder. EIMS showed the molecular mass as 567.2(M+2). This value of molecular mass is due to the presence of bromo substituent. ¹³CNMR spectroscopic results showed the two methyl carbons 20.963 ppm, two carbonylic carbons of the amide groups appeared at 164.8ppm.

N3, N5-bis (2-chlorophenyl)-4-(5'-(2'', 3''-dichlorophenyl) furan-2'-yl)-2, 6-dimethylpyridine-3, 5-dicarboxamide (9)



This reaction of aromatization has the same reaction conditions as the last reaction i.e, using method 3 that gave highest yield 53%. The product pyridine (9) was confirmed through ^{13}C NMR and ^1H NMR. ^{13}C NMR showed the carbons of methyl groups at 13.14 ppm, carbonylic carbons of amide at 166.52 ppm. All other carbons appeared at respective positions and are given written in experimental part. ^1H NMR showed the protons of two methyl groups at 2.496 ppm as singlet. NH protons of amide appeared at 10.270 ppm as singlet. The detail of results is given in experimental part.

N3, N5-bis (4-chlorophenyl)-4-(5'-(3'', 4''-dichlorophenyl) furan-2'-yl)-2, 6-dimethylpyridine-3, 5-dicarboxamide (10)



The product (10) presented the highest yield 54% via method 3 and was confirmed through EIMS, ^{13}C NMR and ^1H NMR. EIMS confirmed the molecular mass of the compound. ^1H NMR showed the six protons of two methyl groups at 2- and 6-position at 2.529 ppm as singlet. Two protons of NH of amide linkage is appeared at 10.676 ppm as singlet, and ^{13}C NMR spectra showed two carbons of methyl groups at 22.067 ppm and carbonylic carbons appeared at 166.314 ppm.

4. Conclusion

Ten dihydropyridines were successfully oxidized to yield corresponding pyridines (compound 1-10) via Hantzsch reaction using three different methods. In one method only DMSO was used as solvent and as catalyst, in second method nitric acid was used in addition of DMSO while in third method bleaching powder in a mixture of ethyl acetate and water was used. All the synthesized pyridine derivatives (compounds 1-10) were yellow to brown colored solids and stable at room temperature.

These were soluble in almost all organic solvent on heating while solubility is less at room temperature. These were characterized through available analytical techniques like thin layer chromatography, melting point, mass spectrometry, proton NMR, carbon-13 NMR and elemental analysis. From all the three methods, third method is supposed to be better due to less reaction time only stirring for 5 mint at room temperature. In some cases, (compound 8-10) product yield was highest while in others comparable yields as compared to other methods. This will be a useful approach for oxidation of dihydropyridines to pyridine.

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