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A novel application of the oxidizing properties of urea nitrate and peroxydisulfate-cobalt(II): aromatization of NAD(P)H model Hantzsch 1,4-dihydropyridines

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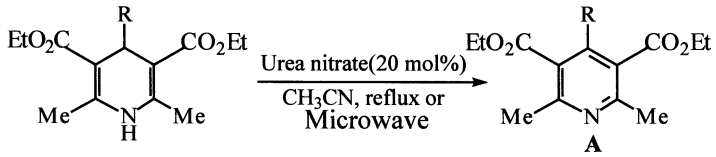
Abstract—4-Alkyl or aryl substituted derivatives of Hantzsch 1,4-dihydropyridine were readily oxidized by urea nitrate under microwave irradiation or refluxing conditions to the corresponding pyridine derivatives in quantitative yields. The oxidation reaction was also effected by peroxydisulfate in the presence of cobalt(II) in aqueous acetonitrile under refluxing conditions. When *n*-propyl, *n*-butyl and cinnamyl were the substituent groups in the 4-position, a mixture of 4-substituted and unsubstituted pyridines were formed. The catalysts used in the reaction are inexpensive and provide high yields in short reaction times.

1. Introduction

Hantzsch 1,4-dihydropyridine derivatives which contain the 1,4-dihydropyridine structure of the natural reduced nicotinamide adenine dinucleotide [NAD(P)H] coenzyme play a vital role in many bioreductions by transferring a hydride ion or an electron to the surrounding substrate[1] and possess a high biological activity as a class of useful drugs, particularly as antioxidants. The 4-substituted-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl esters have anti-hypoxic and anti-ischemic activities. Some of the representatives of this class have acaricidal, insecticidal, bactericidal and herbicidal activities.[2]

The oxidation of Hantzsch 1,4-dihydropyridines is one of the ubiquitous issues in organic chemistry and even in recent years several groups have reported various new methods for aromatization including oxidation with ferric nitrate on a solid support,[3] ceric ammonium nitrate,[4] clay-supported cupric nitrate (Claycop),[5] pyridinium chlorochromate,[6] bromo trichloromethane,[7] nitric acid,[8] nitric oxide and *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide.[9,10] According to Maquestiau et al.,[5] Claycop is not an efficient reagent for the aromatization of Hantzsch 1,4-dihydropyridines bearing an alkyl group in the 4-position even under sonication conditions.

However most of these reactions require an extended period of time for completion, utilize strong oxidants in large excess and afford only modest yields of the products. In recent times, much attention has been paid to the use of microwave irradiation in organic synthesis due to added advantages like substantial reduction in reaction time and higher heating efficiency.[11] Result and discussion in this paper, we report the development of a novel, simple and milder method for the oxidation of Hantzsch 1,4-dihydropyridines to the corresponding pyridine derivatives using urea nitrate in acetonitrile under both microwave irradiation and refluxing conditions with high yield in short reaction times (Scheme 1). Urea nitrate has been used for regioselective nitration of 4-halonitrobenzene to 4-halo-ortho-dinitro benzene[12a] and aromatic amines.[12b] Recently we reported the utility of urea nitrate as an efficient catalyst for the imino Diels–Alder reactions.[13] The suspension of



Scheme 1.

Keywords: 1,4-dihydropyridines; urea nitrate; peroxydisulphate-cobalt(II); oxidation; pyridine derivatives.
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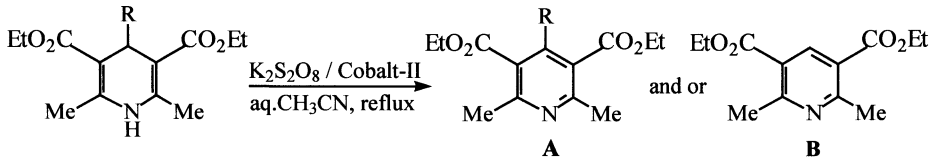


Scheme 2.

urea nitrate in solvent slowly releases nitric acid, which is involved in the oxidation reaction. Since urea nitrate is inexpensive and easy to prepare,[14] we explored its ability to catalyze the oxidation reaction effectively in shorter reaction times.

Peroxydisulfate ion is one of the versatile oxidizing agents in aqueous solution,[15] employed in many organic reactions in the presence of metal acetates,[16] cobalt(III) acetate[17] and copper ion.[18] The reactions involving this ion are generally slow at ambient temperature and the rate of peroxydisulfate decomposition increases by many folds when the temperature is raised.[15] The standard oxidation–reduction potential of the reaction is estimated to be 2.01 V.[15]

The oxidation of 4-alkyl or aryl substituted dihydropyridines with potassium peroxydisulfate in the presence of cobalt(II) in aqueous acetonitrile by refluxing on a water bath to the corresponding pyridine derivatives proceeded in high yields (Scheme 2) The results obtained with various 4-substituted 1,4-dihydropyridines are given in Table 1.

According to earlier studies, oxidation of 4-alkyl dihydropyridines containing methyl, ethyl, propyl and cinnamyl substituents produced exclusively 4-alkyl pyridine (**A**).[10,19–21] Contrary to this, we observed during our studies that 4-alkyl substituted dihydropyridines (**3**, **4** and **13**) resulted in a mixture of 4-substituted and unsubstituted pyridines (**A** and **B**). This is in agreement with the observation of Delgado et al.[22] except for 4-methyl dihydropyridine, which gave 4-methyl pyridine (**16**). The products were analyzed by GC-MS.

Investigations on the oxidation efficiency of peroxydisulfate alone at ambient temperature as well as higher temperature indicated that in the absence of metal ion, oxidation of 1,4-dihydropyridines into aromatized products by the sulfate radical anion is less effective.[23] In conclusion we opine that the peroxydisulfate-cobalt(II) nitrate reagent offers a rate enhancement, due to the presence of cobalt(II) which increases the rate of decomposition of peroxydisulfate to form a sulfate radial anion and a cobalt(III) ion, the cobalt(III) ion initiates the oxidation reaction by abstracting an electron on the nitrogen of 1,4-dihydropyridine to give Co(II) ions.[24]

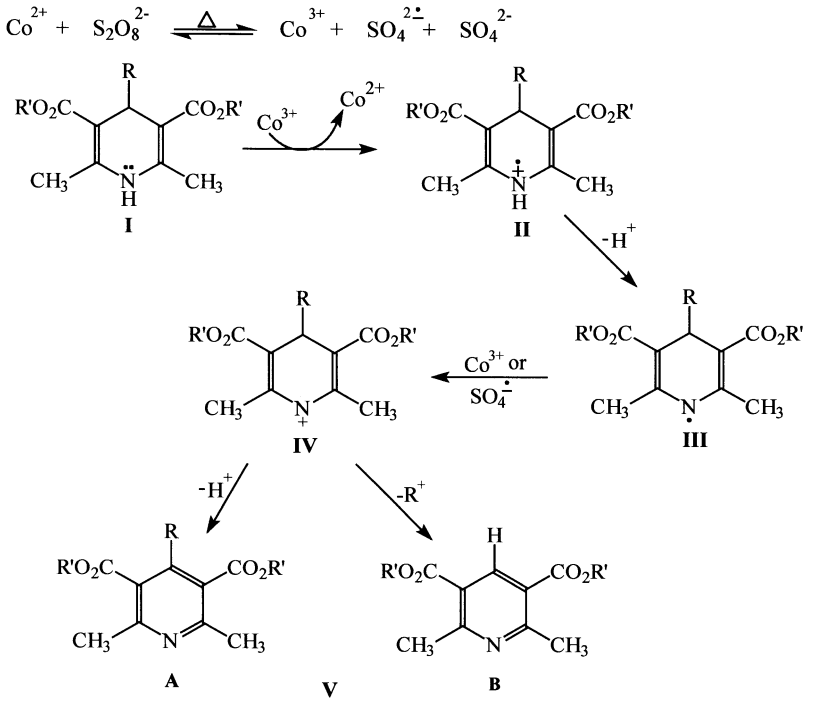
The possible mechanism of the oxidation reaction using peroxydisulfate in presence of cobalt(II) which involves an initial one electron transfer from 1,4-dihydropyridine (**I**) to the cobalt(III) ion to give radical cation **II**. This radical cation loses a proton to form an intermediate **III**, which transfers an electron to the sulfate radical anion or Co(III) to form the cation **IV**, subsequently results in the aromatized product(s) **V** by homolysis (Scheme 3).

The influence of the various solvents on the yield of the reaction was investigated using compound **1** as the substrate. The results obtained show that acetonitrile is a better choice for the oxidation reaction. This can be attributed to the enhanced solubilizing power of the solvent for the oxidant as well as the substrate (Table 2).

Table 1. Oxidation of Hantzsch 1,4-dihydropyridine with urea nitrate and peroxydisulfate-cobalt(II)

Compound	R	Product(s)[a]	Peroxydisulphate-Co(II)[b]			Urea nitrate[c]			
			Time (min)	Yields (%)[d]		Refluxing conditions		Microwave irradiation	
				A	**B**	Time (h)	Yield (%)[d]	Time (min)	Yield (%)[d]
1	H	**15**	10	–	96	1.5	92 (**B**)	0.5	98 (**B**)
2	CH_3	**16**	10	95	–	2	94	1	97
3	*n*-C_3H_7	**17**	10	78	15[e]	2	90	1	92
4	*n*-C_4H_9	**18**	15	76	20[e]	2	92	1	95
5	C_6H_5	**19**	10	96		2	91	1.5	98
6	*m*-$NO_2C_6H_4$	**20**	15	94		2.5	89	2	94
7	*p*-$NO_2C_6H_4$	**21**	15	92		3	86	2	95
8	*p*-$CH_3C_6H_4$	**22**	15	94		2	84	2	91
9	*p*-CH_3OC6H4	**23**	15	92		2	82	1	90
10	2-Thienyl	**24**	10	95		2.5	85	2	92
11	2-Furyl	**25**	15	93		2.5	80	2	89
12	*N*-Benzenesul-fonyl-3-Indolyl	**26**	15	89		3	85	2	94
13	PhCH=CH	**27**	10	18	72[e]	3	88	2	92
14	CH_3CH=CH	**28**	10	94	–	3	84	2	91

[a] All the products were characterized by IR, NMR and GC-MS.
[b] The reaction was carried out with equimolar amount of peroxydisulfate and cobalt(II) nitrate in aqueous CH_3CN under refluxing conditions.
[c] The reaction was carried out with 20 mol% urea nitrate under microwave irradiation.
[d] The yield is based on isolation by column chromatography.
[e] The yield ratio is based on GC analysis.



Scheme 3.

Table 2. Effect of the solvent medium on the reaction yield of **1** with urea nitrate and peroxydisulfate-Co(II)

Entry	Solvent	Peroxydisulphate-Co(II)[a] yield (%)[b]	Urea nitrate (20 mol%)[c] yield (%)[b]
1	$CHCl_3$	15	45
2	MeOH	72	65
3	CH_2Cl_2	30	25
4	THF	45	70
5	CH_3CN	96	98
6	Benzene	25	38

[a] The reaction was carried out with equimolar amount of peroxydisulfate and cobalt (II) nitrate under reflux for 10 min.
[b] The yield is based on isolation by column chromatography.
[c] The reaction was carried out with 20 mol% urea nitrate under microwave irradiation for 30 s.

2. Conclusion

In summary, the present work offers a simple oxidation method, employing readily available reagents and avoiding dry and inert atmospheric conditions employed previously, leading to better yield of pyridines from dihydropyridines. Of the two systems under investigation urea nitrate was found to yield only one product in contrast to peroxydisulfate-cobalt(II). In addition the catalysts employed in this reaction are cost effective and provide quantitative yield in short reaction times.

3. Experimental

4-Substituted Hantzsch 1,4-dihydropyridines were prepared using the appropriate aldehyde, ammonium acetate and ethyl acetoacetate under microwave irradiation as reported by us earlier.[11e] Potassium peroxydisulfate and cobalt (II) nitrate were obtained from E-Merck India Ltd. Reagent grade acetonitrile and other solvents were used. The percent conversion was determined by GC-MS using a Perkin–Elmer Auto System XL Gas Chromatography with Turbo Mass spectrometer (EI, 70 eV), with helium as carrier gas at a flow rate of 1.0 mL/min, Perkin Elmer Elite series PE-5, capillary column (30 m×0.25 mm×1 μm), oven programmed between 100 and 260°C at the rate of 10°C/min. Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). Fractionation of the products was performed by column chromatography with silica gel (60–120 mesh; s.d Fine chem Ltd. India). IR spectra were recorded as neat (for liquids) and as KBr pellets for solids on a Perkin Elmer Spectrum RXI FT-IR. ^{1}H NMR spectra were recorded on a Bruker instrument at 300 MHz in $CDCl_3$ and the chemical shifts are given in δ relative to the internal standard TMS. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ and the chemical shifts are given in δ relative to the solvent (77.0).

3.1. Oxidation of Hantzsch 1,4-dihydropyridines with urea nitrate (20 mol%): general procedure

(i) To a solution of 1,4-dihydropyridine (2 mmol) in 20 mL of acetonitrile, urea nitrate (0.0735 g, 20 mol%) was added. The resulting mixture was refluxed on a water bath for the appropriate time. (ii) Identical quantities of the substrate, reagent and solvent were taken in a 250 mL of open conical flask and subjected to microwave irradiation. After ascertaining the completion of the reaction by TLC, the reaction mixture was extracted with CH_2Cl_2 (30 mL×2). The combined organic layer was dried using anhydrous

Na_2SO_4 and the solvent was distilled. The product was purified by short silica gel column using a mixture of ethyl acetate and petroleum ether (2:8) to afford the corresponding pyridine derivatives.

3.2. Oxidation of Hantzsch 1,4-dihydropyridines with peroxidisulfate-Co(II): general procedure

A solution of potassium peroxydisulphate (0.53 g, 2 mmol) and cobalt(II) nitrate (0.58 g, 2 mmol) in 5 mL of water was added to a solution of 1,4-dihydropyridine (2 mmol) in 20 mL of acetonitrile(excess) in a 100 mL RB flask. The resulting mixture was refluxed on a water bath. After ascertaining the completion of the reaction by TLC, the reaction mixture was worked up as described above.

3.2.1. Diethyl 2,6-dimethyl pyridine-3,5-dicarboxylate (15). Colorless solid; mp 69–70°C (lit.,[25] 70–71°C); IR (KBr) 2981, 2932, 1719, 1591, 1441, 1369, 1295, 1222, 1120, 1043, 771, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 4.41 (q, 4H, J=7.4 Hz), 2.84 (s, 6H), 1.42 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 162.1, 140.8, 122.9, 61.3, 24.8, 14.2; MS m/z 251 (M^+); Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57; Found: C, 62.23; H, 6.75; N, 5.48.

3.2.2. Diethyl 2,6-dimethyl-4-methylpyridine-3,5-dicarboxylate (16). Pale yellow colored oil (lit.,[26] oil); IR (KBr) 2981, 2937, 1725, 1567, 1239, 1107, 1041, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.42 (q, 4H, J=7.2 Hz), 2.53, (s, 6H), 2.28 (s, 3H), 1.40 (t, 6H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 154.9, 142.3, 127.7, 61.6, 22.8, 17.0, 14.2; MS m/z 265 (M^+); Anal. calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28; Found: C, 63.55; H, 7.30; N, 5.21.

3.2.3. Diethyl 2,6-dimethyl-4-*n*-propylpyridine-3,5-dicarboxylate (17). Pale yellow colored oil; IR (KBr) 2959, 2933, 2873, 1727, 1566, 1234, 1106, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (q, 4H, J=6.8 Hz), 2.75–2.43 (m, 2H), 2.51 (s, 6H), 1.58 (m, 2H), 1.39 (t, 6H, J=7.2 Hz), 0.93 (t, 3H, J=6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 155.1, 146.1, 141.0, 127.3, 61.6, 33.5, 24.2, 22.9, 14.2; MS m/z 293 (M^+); Anal. calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77; Found: C, 65.73; H, 7.82; N, 4.85.

3.2.4. Diethyl 2,6-dimethyl-4-*n*-butylpyridine-3,5-dicarboxylate (18). Pale yellow colored oil; IR (KBr) 2966, 2875, 1727, 1568, 1284, 1236, 1200, 1105, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (q, 4H, J=6.2 Hz), 2.65–2.58 (m, 2H), 2.51 (s, 6H), 1.58–1.20 (m, 4H), 1.39 (t, 6H, J=7.2 Hz), 0.91 (t, 3H, J=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 155.0, 146.7, 127.3, 121.5, 61.6, 33.0, 31.2, 23.1, 22.8, 14.3; MS m/z 307 (M^+); Anal. calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56; Found: C, 66.18; H, 8.31; N, 4.65.

3.2.5. Diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (19). Colorless solid; mp 63–65°C (lit.,[26] 62–64°C); IR (KBr) 2981, 2934, 1716, 1556, 1290, 1228, 1096, 1040, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (br s, 2H), 7.27 (br s, 3H), 4.01 (q, 4H, J=6.0 Hz), 2.62 (s, 6H), 0.90 (t, 6H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 155.2, 146.1, 136.4, 128.3, 127.9, 126.8, 61.2, 22.7, 13.5; MS m/z 328 (M^+); Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; Found: C, 69.82; H, 6.39; N, 4.19.

3.2.6. Diethyl 2,6-dimethyl-4-(*m*-nitrophenyl)pyridine-3,5-dicarboxylate (20). Pale yellow colored solid; mp 60–62°C (lit.,[27] 61–62°C); IR (KBr) 3084, 2982, 2935, 1726, 1534, 1352, 1290, 1234, 1105, 1041, 737, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 (m, 1H), 8.22 (m, 1H), 7.67 (m, 2H), 4.10 (q, 4H, J=7.3 Hz), 2.65 (s, 6H), 0.98 (t, 6H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 155.6, 147.4, 143.1, 137.7, 134.0, 128.9, 126.1, 122.9, 61.1, 22.5, 13.2; MS m/z 373 (M^+); Anal. calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52; Found: C, 61.39; H, 5.49; N, 7.44.

3.2.7. Diethyl 2,6-dimethyl-4-(*p*-nitrophenyl)pyridine-3,5-dicarboxylate (21). Pale yellow colored solid; mp 112–114°C (lit.,[28] 115°C); IR (KBr) 3111, 3054, 2977, 2929, 1724, 1558, 1518, 1349, 1231, 1105, 1044, 863, 747, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, 2H, J=8.8 Hz), 7.46 (d, 2H, J=8.8 Hz), 4.04 (q, 4H, J=7.2 Hz), 2.64 (s, 6H), 0.98 (t, 6H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 156.1, 147.7, 143.2, 129.3, 126.2, 123.5, 123.2, 61.6, 23.0, 13.6; MS m/z 373 (M^+); Anal. calcd for $C_{19}H_{20}N_2O_6$: C, 61.32; H, 5.39; N, 7.55; Found: C, 61.35; H, 5.43; N, 7.49.

3.2.8. Diethyl 2,6-dimethyl-4-(*p*-methylphenyl)pyridine-3,5-dicarboxylate (22). Pale yellow colored solid; mp 71–73°C (lit.,[26] 72–73°C); IR (KBr) 2981, 2930, 2872, 1728, 1555, 1289, 1233, 1104, 1042, 862, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (br s, 4H), 4.03 (q, 4H, J=7.2 Hz), 2.60 (s, 6H), 2.36 (s, 3H, $ArCH_3$), 0.95 (t, 6H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 155.2, 146.3, 138.3, 133.6, 128.8, 128.0, 127.2, 61.3, 22.8, 21.2, 13.6; MS m/z 342 (M^+); Anal. calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; Found: C, 70.51; H, 6.70; N, 3.98.

3.2.9. Diethyl 2,6-dimethyl-4-(*p*-methoxyphenyl)pyridine-3,5-dicarboxylate (23). Colorless solid; mp 56–58°C (lit.,[29] 57–59°C); IR (KBr) 2980, 2935, 2838, 1726, 1555, 1444, 1180, 1105, 1040, 862, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, 2H, J=9 Hz), 6.89 (d, 2H, J=9 Hz), 4.05 (q, 4H, J=7.2 Hz), 3.82 (s, 3H, OCH_3), 2.59 (s, 6H), 0.99 (t, 6H, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 159.8, 155.2, 145.8, 129.5, 128.7, 127.3, 113.6, 61.3, 55.3, 22.8, 13.7; MS m/z 358 (M^+); Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; Found: C, 67.34; H, 6.41; N, 3.83.

3.2.10. Diethyl 2,6-dimethyl-4-(2-thienyl)pyridine-3,5-dicarboxylate (24). Light brown colored solid; mp 78–80°C (lit.,[30] 76–79°C); IR (KBr) 3106, 2981, 2934, 1726, 1557, 1443, 1288, 1232, 1099, 1041, 859, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 7.08 (br s, 2H), 4.14 (q, 4H, J=8.4 Hz), 2.61 (s, 6H), 1.07 (t, 6H, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.7, 144.0, 127.9, 127.7, 126.0, 103.9, 59.6, 39.5, 19.3, 14.2; MS m/z 334 (M^+); Anal. calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20; Found: C, 61.09; H, 5.85; N, 4.31.

3.2.11. Diethyl 2,6-dimethyl-4-(2-furyl)pyridine-3,5-dicarboxylate (25). Yellow colored oil (lit.,[31] oil); IR (KBr) 3121, 2982, 2936, 1726, 1563, 1234, 1105, 1042, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 6.66 (br s, 1H), 6.56 (br s, 1H), 4.28 (q, 4H, J=7.1 Hz), 2.60 (s, 6H), 1.22 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 155.3, 147.6, 143.7, 133.4, 124.5, 111.7, 111.5, 61.4, 22.3, 13.6; MS *m/z* 318 (M^+); Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.14; H, 6.33; N, 4.40; Found: C, 64.32; H, 6.24; N, 4.32.

3.2.12. Diethyl 2,6-dimethyl-4-(*N*-benzenesulphonyl-3-indolyl)pyridine-3,5-dicarboxylate (26). Pale yellow colored solid; mp 132–135°C; IR (KBr) 3100, 3064, 2986, 2934, 1728, 1560, 1448, 1373, 1234, 1186, 1107, 1045, 955, 725, 685, 592 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05–7.91 (m, 3H), 7.62–7.18 (m, 7H), 3.71 (q, 4H, J=6.5 Hz), 2.62 (s, 6H), 0.54 (t, 6H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 156.0, 138.0, 137.4, 134.2, 134.0, 129.9, 129.3, 127.6, 126.9, 125.3, 124.6, 123.6, 120.8, 118.5, 113.3, 61.2, 23.0, 13.0; MS *m/z* 507 (M^+); Anal. calcd for $C_{27}H_{26}N_2O_6S$: C, 64.02; H, 5.17; N, 5.23; Found: C, 64.24; H, 5.09; N, 5.44.

3.2.13. Diethyl 2,6-dimethyl-4-cinnamylpyridine-3,5-dicarboxylate (27). Pale yellow colored solid; mp 163–165°C (lit.,[26] 162–165°C); IR (KBr) 3059, 2981, 2935, 1727, 1556, 1448, 1372, 1237, 1107, 1041, 747, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.19 (m, 5H), 7.12 (d, 1H, J=16.5 Hz), 6.82 (d, 1H, J=16.5 Hz), 4.34 (q, 4H, J=7.2 Hz), 2.59 (s, 6H), 1.29 (t, 6H, J=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 155.3, 142.5, 136.8, 135.9, 128.0, 126.8, 125.8, 122.4, 119.5, 61.7, 22.6, 14.1; MS *m/z* 354 (M^+); Anal. calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96; Found: C, 71.16; H, 6.65; N, 4.07.

3.2.14. Diethyl 2,6-dimethyl-4-chrotylpyridine-3,5-dicarboxylate (28). Yellow colored oil; IR (KBr) 2981, 2936, 1724, 1565, 1444, 1235, 1108, 1041, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, 1H, J=16 Hz), 6.09–5.95 (m, 1H), 4.37 (q, 4H, J=7.1 Hz), 2.54 (s, 6H), 1.84 (d, 3H, J=6.5 Hz), 1.36 (t, 6H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 154.6, 142.1, 134.2, 125.5, 124.8, 61.2, 22.2, 18.6, 13.8; MS *m/z* 292 (M^+); Anal. calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81; Found: C, 65.75; H, 7.36; N, 4.89.

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