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An Expeditious Oxidative Aromatization of Hantzsch 1,4-Dihydropyridines to Pyridines Using Cetyltrimethylammonium Peroxodisulfate: A Phase Transferring Oxidant

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A new approach to the use of potassium peroxodisulphate as an oxidizing reagent is proposed and applied to the case of oxidative aromatization of 1, 4-dihydropyridines with cetyltrimethylammonium peroxodisulfate, a phase transfer oxidant. We demonstrate how it is possible to increase the reactivity of potassium peroxodisulphate in the presence of phase transfer catalyst. Dealkylation in case of 4-*n*-alkyl/*n*-alkenyl was not obtained.

Key Words: Oxidative aromatization, Cetyltrimethylammonium peroxodisulfate (CTAPDS), Phase transfer catalyst, 1,4-DHP, Cetyltrimethyl ammonium bromide

Introduction

The pyridine nucleus is of substantial significance as this ring is the key component in a variety of bioactive compounds, both naturally occurring and synthetic.[1] Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed.[2] Among these, one of the very convenient approaches which attracted our attention is the oxidative aromatization of 1,4-DHP. The 1,4-dihydropyridine (1,4-DHP) L-type voltage sensitive calcium ion channel represents an important drug target that possesses specific binding sites for both antagonist and agonist ligands that modulate the closed or open conformational state of the channel.[3] These compounds generally undergo oxidative metabolism in the liver by the action of cytochrome p-450 to form the corresponding pyridine derivatives.[4] These ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-DHPs. A variety of reagents has been utilized for this oxidative conversion: S-nitrosoglutathion,[5] N_2O_4 complex of 18-crown-6,[6] photochemical oxidation,[7] $Zr(NO_3)_4$,[8] tetrakis-(pyridine)cobalt(II) dichromate,[9] nicotinum dichromate,[10] cytochrome P-450,[11] electrochemical catalysis,[12] urea nitrate,[13] peroxydisulfate-Co(II),[13] $Mn(OAc)_3$,[14] Vanadium salts,[15] tetra-*n*-butylammonium periodate,[16] $AlCl_3$,[17] benzyltriphenylphosphonium peroxymonosulfate,[18] Mn(TPP)Cl-PSI/$NaIO_4$,[19] urea-H_2O_2,[20] Fe$(ClO_4)_3$/AcOH,[21] $H_6PMo_9V_3O_{40}$,[22] pyridinium chlorochromate,[23] K_2FeO_4,[24] iodine,[25] silica modified sulfuric acid/$NaNO_2$,[26] $KBrO_3$/$SnCl_4{\cdot}5H_2O$,[27] silica Chromate,[28] MnO_2,[29] hypervalent iodine.[30-35] In spite of an overabundance of methods for this conversion, limitations like extended reaction times, poor yields and use of strong or toxic oxidant has led to the investigation of many alternative procedures.

Therefore, it is of practical importance and need of the hour to develop and introduce a convenient, milder and efficient method for the oxidation of 1,4-dihydropyridines to the corresponding pyridines. The peroxodisulfate ion is one of the strongest oxidizing agents known in aqueous solution. The standard oxidation-reduction potential for the reaction is estimated to be −2.01 V. The oxidative application of peroxodisulfate ion in organic synthesis has been widely investigated.[36]

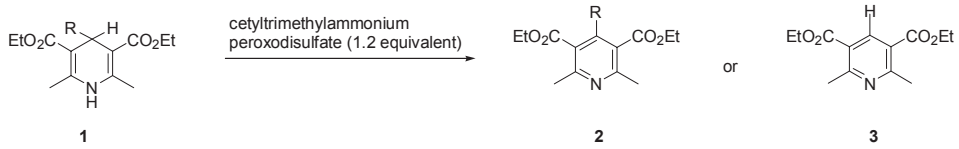
The main disadvantage associated with the use of potassium peroxodisulphate is the difficulty encountered to solubilize the peroxodisulfate ion in organic solvents. The phase transfer oxidant, tetrabutylammonium peroxodisulfate[36(j)] and cetyltrimethylammonium peroxodisulfate (CTAPDS), can be used for oxidation of various organic substrates and as free radical generator in organic solvents.

Cetyltrimethylammonium peroxodisulphate,[37] CTAPDS, a mild, efficient, stable, and cheap reagent, is a white powder quite soluble in most organic solvents such as methanol, ethanol, dichloromethane, chloroform, ethyl acetate, dioxane, benzene, acetone and acetonitrile. This reagent is easily prepared by addition of an aqueous solution of cetyltrimethylammonium bromide to a solution of potassium peroxodisulfate in water.

Result and Discussion

In continuation to our work on aromatization of 1,4-DHP,[34,35] we report herein oxidation of 1,4-DHP to corresponding pyridine derivative using cetyltrimethylammonium peroxodisulfate, a phase transfer oxidant (Scheme 1). Results are summarized in Table 1.

In preliminary experiments to study the oxidizing efficiency of reagent CATPDS and substituents effect, we selected the reactions of 4-methoxyphenyl, 4-phenyl and 4-nitrophenyl substituted 1,4-DHP as model reactions with reagent CATPDS in various solvents such as hexane, CH_2Cl_2, $CHCl_3$, CH_3CN and THF at room temperature and refluxing conditions. The oxidative aromatization of 1,4-DHP was not successful at room

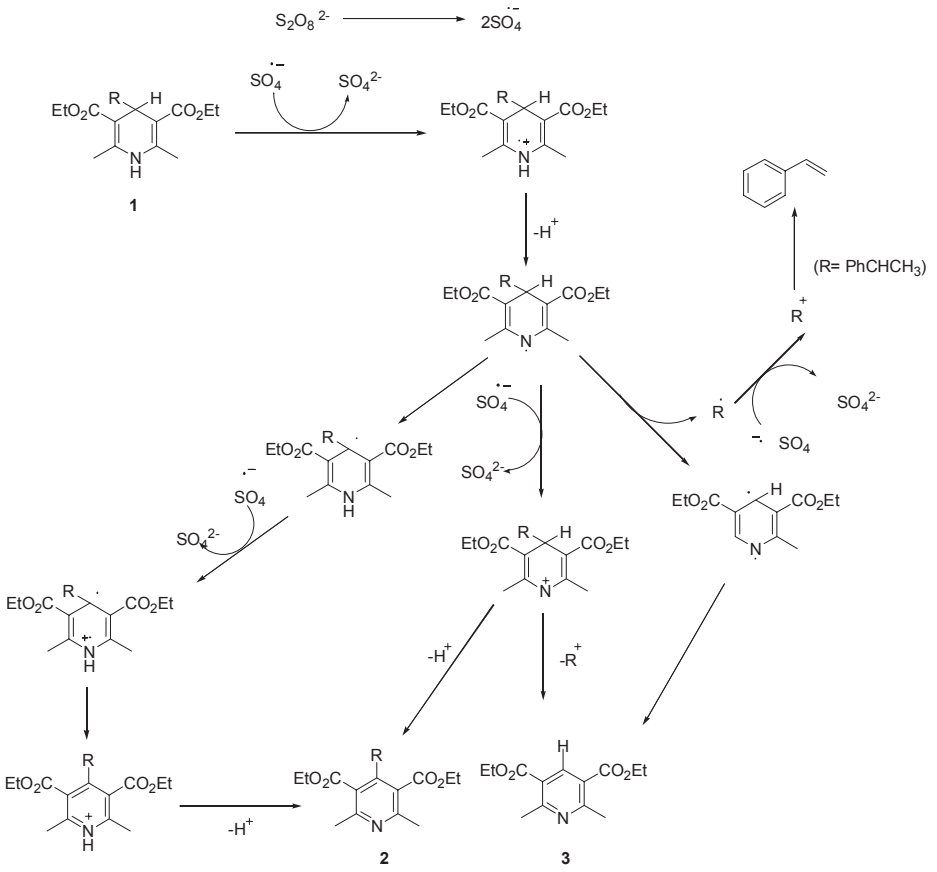


1 **2** **3**

1. R = (a) C_6H_5; (b) 4-$NO_2C_6H_4$; (c) 3-$NO_2C_6H_4$; (d) 2-$NO_2C_6H_4$; (e) 4-$MeOC_6H_4$; (f) 3,4$(OCH_3)_2C_6H_3$; (g) 4-$CH_3C_6H_4$; (h) 4-ClC_6H_4; (i) 2,4-$Cl_2C_6H_3$; (j) 3-BrC_6H_4; (k) 3-$PhCOO\text{-}C_6H_4$; (l) $C_6H_5CH{=}CH$; (m) $CH_3CH{=}CH$; (n) 2-Furyl; (o) 3-Pyridyl; (p) 2-Thienyl; (q) CH_3; (r) C_2H_5; (s) $CH_3CH_2CH_2$; (t) $CH_3CH_2CH_2CH_2$; (u) C_6H_{13}; (v) $(CH_3)_2CH$; (w) $C_6H_5CH_2$; (x) C_6H_{11} (cyclohexyl); (y) C_6H_9 (cyclohex-3-enyl); (z) $C_6H_5\text{-}CH\text{-}CH_3$; (aa) H.

2. R = (a) C_6H_5; (b) 4-$NO_2C_6H_4$; (c) 3-$NO_2C_6H_4$; (d) 2-$NO_2C_6H_4$; (e) 4-$MeOC_6H_4$; (f) 3,4$(OCH_3)_2C_6H_3$; (g) 4-$CH_3C_6H_4$; (h) 4-ClC_6H_4; (i) 2,4-$Cl_2C_6H_3$; (j) 3-BrC_6H_4; (k) 3-$PhCOO\text{-}C_6H_4$; (l) $C_6H_5CH{=}CH$; (m) $CH_3CH{=}CH$; (n) 2-Furyl; (o) 3-Pyridyl; (p) 2-Thienyl; (q) CH_3; (r) C_2H_5; (s) $CH_3CH_2CH_2$; (t) $CH_3CH_2CH_2CH_2$; (u) C_6H_{13}.

Scheme 1



Scheme 2. Proposed mechanism for CTAPDS catalyzed oxidative aromatization of 1,4-DHPS

temperature but at reflux conditions it gave 100% conversion (TLC) within 10 min. Acetonitrile was superior to other solvents as reaction failed to continue after some conversion in other solvents. The reactions were smooth and the effect of an electron donating or an electron-withdrawing group on the aromatic ring of the 1,4-DHP was not observed.

To establish the generality of the reagent CATPDS, various alkyl, aryl, and heterocyclic substituted Hantzsch 1,4-DHP were oxidized under the above cited conditions. The oxidation proceeded smoothly with 1,4-dihydropyridine substrates bearing substituents at the 4-position such as hydrogen, methyl, *n*-alkyl/alkenyl, aryl and heterocyclic groups. However, in the case of oxidation of the 1,4-DHP with isopropyl/benzyl/cyclohexyl/cyclohex-3-enyl/1-phenylethyl group at 4-position gave exclusively dealkylated/debenzylated pyridine derivatives (**3**) (Table 1). These substituents are debarred with the formation of dealkylated/debenzylated product either due to stability of radical cation formed during the reaction *via* single electron mechanism (SET) or electron donating ability of the corresponding radicals (Scheme 2). This mechanism is further confirmed by isolation of styrene (Table 1, Entry 26).

The application of peroxodisulphate ion with Co(II) or without Co(II) in the oxidative aromatization of 1,4-dihydropyridines has already been reported.[13,38] To the best of our knowledge, cetyltrimethylammonium peroxodisulphate (CATPDS) is not used in oxidation of 1,4-DHP. Thus, we hoped that the CATPDS would be superior to the previously reported other peroxodisulphate oxidants because of i) less reaction time (ii)

Table 1. Oxidative aromatization of 1,4-DHPs derivatives with cetyltrimethylammonium peroxodisulfate (1.2 equivalent)

Entry	R	Product	Reaction Time t (min)	Yield[a] (%)	mp[b] (°C)
1	C_6H_5	**2a**	6	97	62 - 63
2	4-$NO_2C_6H_4$	**2b**	7	95	112 - 113
3	3-$NO_2C_6H_4$	**2c**	7	94	61 - 62
4	2-$NO_2C_6H_4$	**2d**	7	94	73 - 75
5	4-$MeOC_6H_4$	**2e**	7	95	51 - 52
6	3,4$(OCH_3)_2C_6H_3$	**2f**	5	95	100 - 101
7	4-$CH_3C_6H_4$	**2g**	5	94	71 - 72
8	4-ClC_6H_4	**2h**	7	95	69 - 71
9	2,4-$Cl_2C_6H_3$	**2i**	8	95	112 - 113
10	3-BrC_6H_4	**2j**	8	92	70 - 72
11	3-PhCOO-C_6H_4	**2k**	10	90	260 - 261
12	C_6H_5CH=CH	**2l**	9	95	161 - 162
13	CH_3CH=CH	**2m**	8	92	oil
14	2-Furyl	**2n**	7	93	oil
15	2-Pyridyl	**2o**	7	94	90 - 92
16	2-Thienyl	**2p**	7	91	78 - 79
17	CH_3	**2q**	5	94	oil
18	C_2H_5	**2r**	5	95	oil
19	$CH_3CH_2CH_2$	**2s**	5	95	oil
20	$CH_3CH_2CH_2CH_2$	**2t**	6	95	oil
21	C_6H_{13}	**2u**	6	92	oil
22	$(CH_3)_2CH$	**3**	5	94	70 - 71
23	$C_6H_5CH_2$	**3**	6	95	70 - 71
24	C_6H_{11} (cyclohexyl)	**3**	10	96	70 - 71
25	C_6H_9 (cyclohex-3-enyl)	**3**	10	96	70 - 71
26	C_6H_5-CH-CH_3	**3**	5	95	70 - 71
27	H	**3**	3	93	70 - 71

[a]Yields are isolated. [b]Melting points are uncorrected and compared with literature reports.

high yield (iii) no dealkylation of 4-*n*-alkyl/alkenyl substituents of 1,4-DHP i.e., selective oxidation (iv) avoidance of toxicity of many transition metal involved in such process (v) solubility in most organic solvent (vi) commercial availability.

Experimental Section

All chemicals used in this study were purchased from local venders and used without further purification. Melting points were determined on a buchi oil heating melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on Brucker-300 Hz spectrometer using TMS as internal standard (chemical shift in δ, ppm). IR spectra were taken on a Perkin Elmer 1600, FTIR spectrophotometer using KBr pellets and peaks are reported in cm^{-1}.

1,4-Dihydropyridine were prepared according to described procedures.[30-35]

Preparation of cetyltrimethylammonium peroxodisufate. Potassium peroxodisulphate (0.01 mol) in 10 mL water was added slowly to an aqueous solution of cetyltrimethylammonium bromide (0.025 mol) with continuous stirring on a magnetic stirrer. A light yellow coloured compound appeared slowly. Stirring was continued for 30 min. The resulting light yellow coloured compound was filtered, washed with water for several times until no trace of bromide ion was detected in the filtrate. It was vacuum dried and kept in a dark bottle inside desiccator, yield 93%. ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 7.6 Hz, 6H); 1.25-1.32 (multiplet, 52H); 1.81 (multiplet, 4H), 3.38-3.46 (multiplet, 22H). *m/z* 760.57. Anal. Calcd. for $C_{38}H_{84}N_2O_8S_2$: C, 59.96; H, 11.12; N, 3.68. Found: C, 60.17; H, 11.23; N, 3.78%.

General procedure for oxidation of Hantzsch 1,4-DHPs. In a 50 mL round bottom flask, cetyltrimethylammonium peroxodisulfate (1.2 mmol), Hantzsch-1,4-dihydropyridime (1.0 mmol) in 20 mL acetonitrile was added. The reaction mixture was refluxed on water bath for the time indicated in Table 1. The progress of reaction was monitored by TLC (hexane/ethylacetate = 9/1). After completion of reaction, solvent was evaporated and the crude reaction mixture was purified by column chromatography using ethyl acetate-hexane (1:8).

The characterization and spectral data for selected products.

Diethyl-4-phenyl-2,6-dimethylpyridine-3,5-dicarboxylate (2a): IR (KBr) 3014, 2986, 1723, 1591, 1498, 1302, 1250, 1170, 791, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, J = 7.12 Hz, 6H, CH_3), 4.26 (q, J = 7.12 Hz, 4H, OCH_2), 2.65 (s, 6H, CH_3), 7.18 (m, 2H), 7.30 (m, 3H). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.83; H, 6.38; N, 4.32.

Diethyl-4-(4-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2b): IR (KBr) 3012, 2977, 1723, 1557, 1518, 1349, 1116, 865, 843, 745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7.10 Hz, 6H, CH_3), 2.69 (s, 6H, CH_3), 4.27 (q, J = 7.10 Hz, 4H, OCH_2), 7.41(d, J = 8.2 Hz, 2H)–8.22 (d, J = 8.2 Hz, 2H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.31; H, 5.36; N, 7.50.

Diethyl-4-(3-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2c): IR (KBr) 3015, 2980, 1716, 1590, 1555, 1520, 1358, 1280, 1183, 870, 785, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, J = 7.11 Hz, 6H, CH_3), 2.70 (s, 6H, CH_3), 4.25 (q, J = 7.11 Hz, 4H, OCH_2), 7.58-8.28 (m, 4H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.15; H, 5.49; N, 7.33.

Diethyl-4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2d): IR (KBr) 3005, 2983, 1725, 1605, 1548, 1512, 1358, 1278, 1191, 762, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.19 (t, J = 7.11 Hz, 6H, CH_3), 2.70 (s, 6H, CH_3), 4.28 (q, J = 7.11 Hz, 4H, OCH_2), 7.48-8.25 (m, 4H). Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.08; H, 5.22; N, 7.63.

Diethyl-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2e): IR (KBr) 3030, 2973, 1729, 1614, 1557, 1291, 1107, 857, 835, 779 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7.12 Hz, 6H, CH_3), 4.25 (q, J = 7.12 Hz, 4H, OCH_2), 2.66 (s, 6H, CH_3), 3.82 (s, 3H, OCH_3), 6.89 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H). Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.05; H, 6.40; N, 3.88.

Diethyl-4-(3,4-dimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2f): IR (KBr) 3030, 2973, 1729, 1614, 1557, 1291, 1107, 857, 835, 779 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7.12 Hz, 6H, CH_3), 4.25 (q, J = 7.12 Hz, 4H, OCH_2), 2.66 (s, 6H, CH_3), 3.86 (s, 6H, OCH_3), 6.95 (m, 2H), 7.21 (m, 1H). Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 65.25; H, 6.61; N, 3.77.

Diethyl-4-(4-methylphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2g): IR (KBr) 3013, 2983, 1727, 1571, 1446,

1239, 1033, 821, 856, 775 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, J = 7.12 Hz, 6H, CH_3), 2.37 (s, 3H, CH_3), 2.64 (s, 6H, CH_3), 4.29 (q, J = 7.12 Hz, 4H, OCH_2), 7.11(d, J = 6.8 Hz, 2H), 7.21 (d, J = 6.8 Hz, 2H). Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.23; H, 6.56; N, 4.33.

Diethyl-4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2h): IR (KBr) 3025, 2984, 1729, 1580, 1231, 1104, 1044, 858, 658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, J = 7.12 Hz, 6H, CH_3), 4.27 (q, J = 7.12 Hz, 4H, OCH_2), 2.69 (s, 6H, CH_3), 7.13 (d, J = 9.01 Hz, 2H), 7.32 (d, J = 9.01 Hz, 2H). Anal. Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 62.97; H, 5.44; N, 4.03.

Diethyl-4-(2,4-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2i): IR (KBr) 3008, 2986, 1730, 1560, 1480, 1280, 1228, 1108, 856, 775, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, J = 7.13 Hz, 6H, CH_3), 4.33 (q, J = 7.13 Hz, 4H, OCH_2), 2.67 (s, 6H, CH_3), 7.15-7.42 (m, 3H). Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53. Found: C, 57.77; H, 5.00; N, 3.49.

Diethyl-4-(3-bromophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2j): IR (KBr) 3026, 2986, 1726, 1561, 1278, 1230, 1108, 1035, 865, 787, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.22 (t, J = 7.11 Hz, 6H, CH_3), 4.31 (q, J = 7.11 Hz, 4H, OCH_2), 2.66 (s, 6H, CH_3), 7.20-7.44 (m, 4H). Anal. Calcd. for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.30; H, 5.10; N, 3.27.

Diethyl 4-(3-(benzoyloxy)phenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (2k): IR (KBr) 3014, 2986, 1735, 1723, 1574, 1498, 1380, 1250, 1170, 791, 760 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, J = 7.11 Hz, 6H, CH_3), 4.26 (q, J = 7.11 Hz, 4H, OCH_2), 2.63 (s, 6H, CH_3), 7.33-7.77 (m, 7H), 8.20 (m, 2H). Anal. Calcd. for $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13. Found: C, 69.83; H, 6.38; N, 4.32.

Diethyl 2,6-dimethyl-4-cinnamylpyridine-3,5-dicarboxylate (2l): IR (KBr) 3067, 2966, 2835, 1729, 1588, 1552, 1466, 1240, 1230, 1108, 1035, 962, 835, 739 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7.13 Hz, 6H, CH_3), 4.29 (q, J = 7.13 Hz, 4H, OCH_2), 2.64 (s, 6H, CH_3), 6.65 (d, J = 15.3 Hz, 1H); 7.18 (d, J = 15.3 Hz, 1H); 7.30-7.60 (m, 5H). Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.41; H, 6.66; N, 4.11.

Diethyl 2,6-dimethyl-4-(prop-1-enyl)pyridine-3,5-dicarboxylate (2m): IR (KBr) 2978, 2834, 1721, 1588, 1566, 1466, 1245, 1230, 1108, 861 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.78 (t, J = 6.8 Hz, 3H); 1.22 (t, J = 7.11 Hz, 6H, CH_3), 4.27 (q, J = 7.11 Hz, 4H, OCH_2), 2.62 (s, 6H, CH_3), 6.01-6.12 (m, 1H); 6.42 (d, J = 16.1 Hz, 1H). Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.11; H, 7.33; N, 5.00.

Diethyl 4-(2-thienyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2p): IR (KBr) 3101, 2972, 2827, 1722, 1566, 1466, 1242, 1102, 1022, 860, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.11 (t, J = 7.11 Hz, 6H), 2.44 (s, 6H), 4.18 (q, J = 7.11 Hz, 4H), 7.17 (m, 1H), 7.40-7.50 (m, 2H).

Diethyl 4-(2-pyridyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2o): IR (KBr) 3111, 2991, 2855, 1729, 1611, 1522, 1457, 1241, 1111, 859, 710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.15 (t, J = 7.12 Hz, 6H), 2.62 (s, 6H), 4.15(q, J = 7.4 Hz, 4H), 7.0-7.8 (m, 3H), 8.51 (d, J = 5.2 Hz, 1H).

Diethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2p): IR (KBr) 3121, 2988, 2840, 1727, 1571, 1241, 1109, 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.18 (t, J = 7.0 Hz, 6H), 2.59 (s, 6H), 4.21 (q, J = 7.0 Hz, 4H,), 6.56-6.66 (m, 2H), 7.42 (m, 1H).

Diethyl 2,6-dimethyl-4-methylpyridine-3,5-dicarboxylate (2q): IR (KBr) 2981, 2870, 1726, 1568, 1446, 1285, 1220, 1106, 1045, 871, 777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, J = 7.10 Hz, 6H, CH_3), 2.19 (s, 3H, CH_3), 2.51 (s, 6H, CH_3), 4.25 (q, J = 7.10 Hz, 4H, OCH_3). Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.23; H, 7.32; N, 5.01.

Diethyl 2,6-dimethyl-4-ethylpyridine-3,5-dicarboxylate (2r): IR (KBr) 2992, 2879, 1731, 1576, 1438, 1286, 1112, 1045, 923, 847, 751 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.08 (t, J = 7.5 Hz, 3H, CH_3), 1.25 (t, J = 7.11 Hz, 6H, CH_3), 2.49 (s, 6H, CH_3), 2.78(q, J = 7.5 Hz, 2H, CH_2), 4.25 (q, J = 7.11 Hz, 4H, OCH_3). Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.78; H, 7.78; N, 4.94.

Diethyl 2,6-dimethyl-4-*n*-hexylpyridine-3,5-dicarboxylate (2u): IR (KBr) 2989, 2879, 1726, 1569, 1445, 1222, 1102, 1044, 917, 756 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.08 (t, J = 6.6 Hz, 3H), 1.24 (t, J = 7.10 Hz, 6H, CH_3), 1.32-1.42 (m, 8H); 1.56 (t, J = 6.6 Hz, 2H); 2.48 (s, 6H, CH_3), 4.22 (q, J = 7.10 Hz, 4H, OCH_3). Anal. Calcd. for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.19; H, 8.78; N, 4.23.

Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (3): IR (KBr) 2974, 1721, 1588, 1555, 1298, 1254, 1123, 1022, 777 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.35 (t, J = 7.11 Hz, 6H, CH_3), 2.74 (s, 6H, CH_3), 4.28 (q, J = 7.11 Hz, 4H, OCH_3). Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.92; H, 7.02; N, 5.44.

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