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Short Communication

# Iodobenzene diacetate (IBD) catalyzed an quick oxidative aromatization of Hantzsch-1,4-dihydropyridines to pyridines under ultrasonic irradiation

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ABSTRACT

This project was undertaken to demonstrate the potential of iodobenzene diacetate for the oxidative aromatization of Hantzch-1,4-dihydropyridines under ultrasonic irradiation. All reactions were carried out under ultrasonic irradiation and results were compared with traditional method. Sonochemical switching was observed in case of oxidative aromatization of 4-*n*-alkyl substituted 1,4-DHP. Without sonication, dealkylation occurred in case of *n*-alkyl substituted 1,4-DHP (ionic mechanism) but under ultrasonic irradiation, *n*-alkyl group was not expelled (radical mechanism). However, secondary alkyl (isopropyl) and benzyl group were expelled under both conditions.



## 1. Introduction

Hantzsch 1,4-dihydropyridines have attracted growing interest from both organic and medicinal chemists owing to their diverse range of biologic and pharmacological activities such as antihypertensive and calcium channels blocker [1–10]. These compounds generally undergo oxidative metabolism in the liver by the action of cytochrome p-450 to form the corresponding pyridine derivatives [6]. With this increasing repertoire of applications, developing efficient methods for the oxidation of 1,4-dihydropyridines has drawn much attention in recent years [11–45]. Despite these intensive efforts, the majority of them have several drawbacks such as the use of toxic and corrosive reagents, drastic reaction conditions, tedious workup, long reaction times, and poor selectivity. To overcome these difficulties, development of a convenient protocol for oxidation of 1,4-DHP is still of high importance.

Hypervalent iodine(III) reagents have become increasingly important reagents for the oxidation of organic molecules combined with their benign environmental character and easy commercial availability [39–47]. It is of great interest to explore their ability as extremely discriminating oxidants, their electrophilic properties and to develop novel reaction using hypervalent iodine compounds [48].

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the recent years [49–54]. Compared with traditional methods, this method is more convenient and can be easily controlled. The prominent features of the ultrasound approach are improved reaction rates, high yields, and easier manipulation and considered a processing aid in terms of energy conservation and waste minimization, which compared with traditional methods, this technique is more convenient taking green chemistry concepts into account [55].

## 2. Results and discussion

As a continuing interest in the development of new methodologies for oxidative aromatization of 1,4-DHP [23,41,42], herein, oxidation of 1,4-DHP to corresponding pyridine derivative using iodobenzene diacetate (IBD) under ultrasonic irradiation (Scheme 1) is reported. Results are summarized in Table 1.

The reaction of diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate with IBD was screened to optimize reaction conditions. Our initial attempts to oxidize diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate with IBD (1.2 equivalent) in dichloromethane at room temperature yielded diethyl 2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (2j) (78%) in 60 min under mechanical agitation (Table 1, entry 13). When the reaction mixture was irradiated with ultrasound, almost quantitative conversion was observed (TLC) within 10 min (Table 1, entry 13) and 2j was isolated in 95% yield. Thus the role of irradiation was definitely identified.

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**Table 1**
Oxidative aromatization of 1,4-DHPs derivatives with IBD (1.2 equivalent) under ultrasonic irradiation.

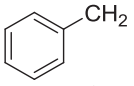
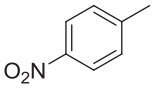
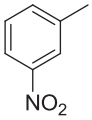
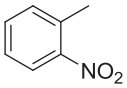
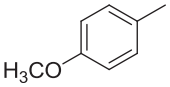
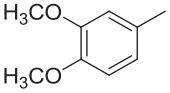
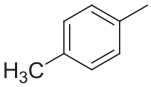
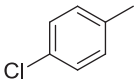
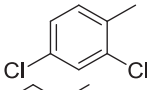
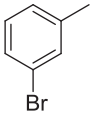
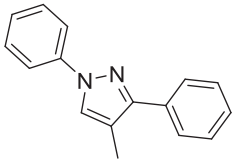
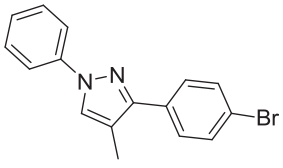
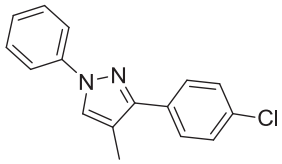
| Entry | Substrate *R* | Product | Reaction time *t* (min) | | Yield[a] (%) | | Mp[b] (°C) |
|---|---|---|---|---|---|---|---|
| | | | Under sonication | Without sonication | Under sonication | Without sonication | |
| 1. | H | 3 | 5 | 25 | 96 | 90 | 70–71 |
| 2. | $CH_3$ | 2a + 3 | 6 | 40 | 90 + 5[c] | 10[c]+75 | Oil |
| 3. | $C_2H_5$ | 2b + 3 | 6 | 40 | 89 + 5[c] | 10[c]+77 | Oil |
| 4. | $(CH_3)_2CH$ | 3 | 5 | 35 | 90 | 78 | 70–71 |
| 5. | $n$-$C_6H_{13}$ | 2c + 3 | 8 | 60 | 85 + 7[c] | 8[c]+70 | Oil |
| 6. |  | 3 | 6 | 50 | 95 | 75 | 70–71 |
| 7. |  | 2d | 9 | 70 | 91 | 78 | 112–113 |
| 8. |  | 2e | 9 | 80 | 92 | 79 | 61–62 |
| 9. |  | 2f | 9 | 80 | 95 | 78 | 73–75 |
| 10. |  | 2g | 7 | 42 | 95 | 84 | 51–52 |
| 11. |  | 2h | 5 | 30 | 94 | 80 | 100–101 |
| 12. |  | 2i | 5 | 60 | 93 | 80 | 71–72 |
| 13. |  | 2j | 10 | 60 | 95 | 78 | 62–63 |
| 14. |  | 2k | 7 | 70 | 95 | 83 | 69–71 |
| 15. |  | 2l | 10 | 75 | 91 | 79 | 112–113 |
| 16. |  | 2m | 9 | 65 | 90 | 76 | 70–72 |
| 17. |  | 2n | 10 | 85 | 92 | 78 | Oil |
| 18. |  | 2o | 10 | 90 | 96 | 75 | 84–86 |
| 19. |  | 2p | 10 | 90 | 90 | 70 | 114–116 |
| 20. |  | 2q | 10 | 90 | 91 | 71 | 116–118 |

**Table 1** (*continued*)

| Entry | Substrate *R* | Product | Reaction time *t* (min) | | Yield[a] (%) | | Mp[b] (°C) |
|---|---|---|---|---|---|---|---|
| | | | Under sonication | Without sonication | Under sonication | Without sonication | |
| 21. |  | 2r | 10 | 90 | 92 | 72 | 101–102 |

[a] Yields are isolated.
[b] Melting points are uncorrected and compared with literature reports [42,59,60].
[c] Yields are noted on GC.

**Table 2**
Effect of solvent on oxidative aromatization of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate by IBD under sonication at room temperature.

| Entry | Solvent | Reaction condition | Reaction time *t* (min) | Yield[a] (%) |
|---|---|---|---|---|
| 1. | $CH_2Cl_2$ | Sonication | 10 | 95 |
| 2. | $CHCl_3$ | Sonication | 20 | 88 |
| 3. | $CH_3CN$ | Sonication | 20 | 80 |
| 4. | THF | Sonication | 20 | 82 |

[a] Yields are isolated.

IBD is sparingly soluble in $CH_2Cl_2$ at room temperature and generates heterogeneous reaction conditions. Upon application of ultrasound, IBD was dispersed in $CH_2Cl_2$ and reacted with dissolved 1,4-DHP to give dark colored solutions, afforded the pyridine derivatives in short reaction times with very good yields.

The influence of various solvents was also investigated using $CH_2Cl_2$, $CHCl_3$, $CH_3CN$, and THF. The ultrasound promoted reaction in $CH_2Cl_2$ gave better yields than in other solvents (Table 2). Using the optimized reaction conditions, we oxidized a series of 1,4-DHP's to corresponding pyridine derivatives under ultrasonic irradiation.

4-Substituted-1,4-dihydropyridines were oxidized in excellent yield bearing substituents at the 4-position such as hydrogen, methyl, *n*-alkyl, aryl and heterocyclic groups, with a number of electron donating as well as electron withdrawing group on aromatic ring. However, in the case of oxidation of the 1,4-DHP with isopropyl/benzyl group at 4-position gave exclusively dealkylated/debenzylated pyridine derivative (3) (entry 4 and 6, Table 1). Literature survey showed that oxidative aromatization of 4-*n*-alkyl/isopropyl/benzyl-1,4-DHP by IBD–$CH_2Cl_2$ [40], dealkylated product was major while in case of hydroxy-tosyloxy-iodobenzene (HTIB) [43] only isopropyl or benzyl group was debarred. Results of this protocol are in accordance to results of HTIB. Thus, for this protocol, the reactivity of IBD under ultrasonic irradiation was found similar to HTIB. This may be due to sonochemical switching, i.e. changes of product distribution by ultrasound [55,56]. Literature survey reveals that IBD in $CH_2Cl_2$ under stirring at room temperature react *via* ionic mechanism but under ultrasonic irradiation [57] an alternative SET pathway exists in this reaction leading to the formation of *n*-alkyl substituted pyridine derivatives (Scheme 2). Moreover, the radical pathway was almost inhibited after the addition of 4-*tert*-butylcatechol (radical scavenger).

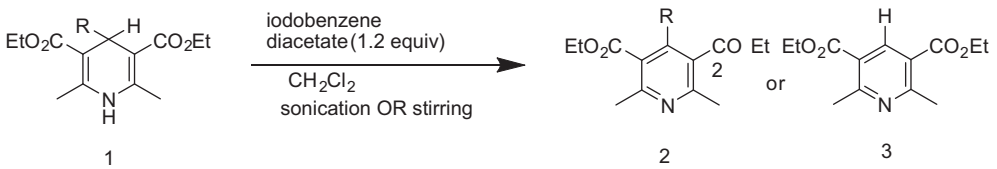
To understand the effect of ultrasonic radiation and sonochemical switching, the oxidative aromatization of diethyl 4-*n*-hexyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate was carried out with IBD in $CH_2Cl_2$ at different temperature under mechanical agitation. At higher temperature the radical pathway was favored and became predominant at 90 °C. For ultrasound mediated reaction, the temperature of reaction mixture was determined before and after the reaction, the former being lower than the later by about 6.5 °C. Then the reaction was carried out at lower temperature (10–15 °C) under ultrasonic irradiation and radical pathway being predominant gave diethyl 2,6-dimethyl-4-*n*-hexylpyridine-3,5-dicarboxylate (2c) as major product. This may be due to hot spot theory of ultrasonic cavitation [49b,55]. Literature survey also revealed that sonochemical switching occurred with variation of temperature [56]. Under sonochemical condition, the reproducibility of the results was good when the reaction conditions were kept constant.

The results of Table 1 clearly indicate the advantage of ultrasonic irradiation method over conventional method, i.e. (a) time required for oxidative aromatization of 1,4-DHPs under ultrasonic irradiation is shorter, (b) aromatization takes place at room temperature, and (c) yields are higher.

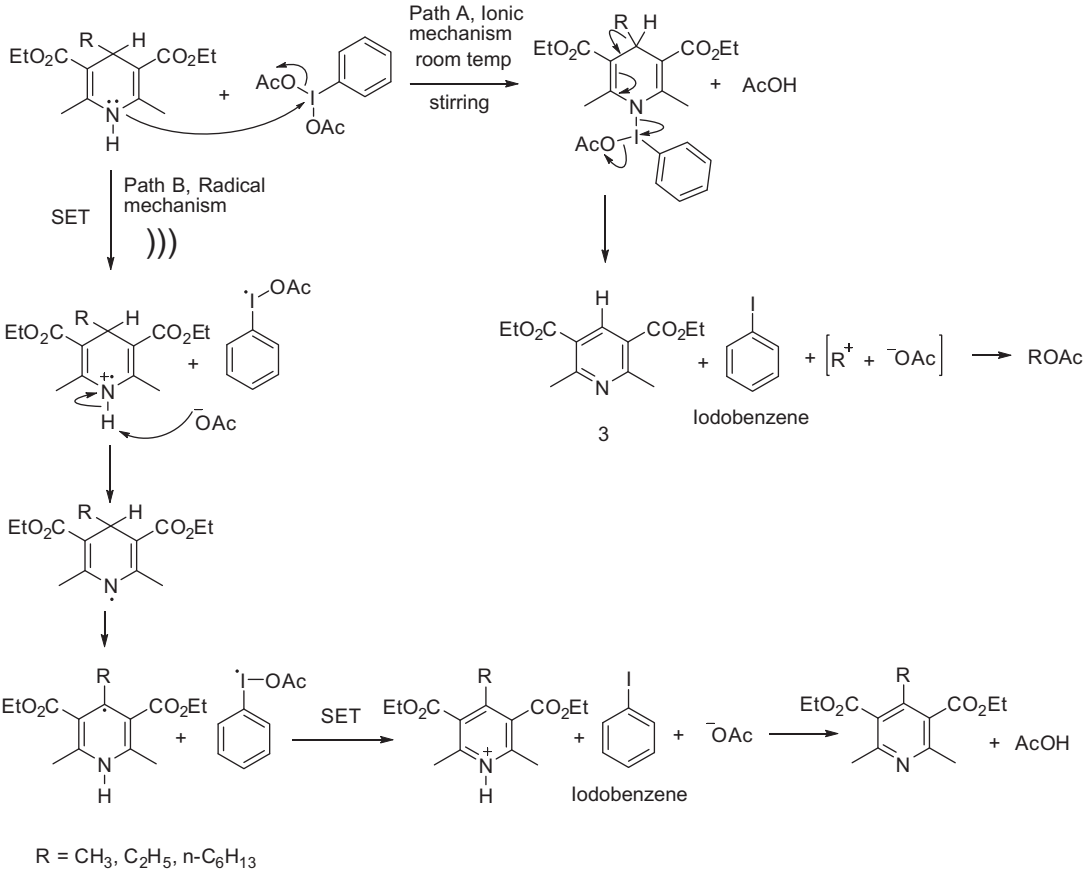
In conclusion, we have demonstrated how to increase the oxidative potential of IBD under ultrasonic irradiation and this potential is utilized for oxidative aromatization of 1,4-DHPs. The mild experimental conditions, operational simplicity, rapid conversions, and high yields of the product are the attractive feature of the present protocol. These reaction conditions are contributing to the development of sustainable techniques in organic synthesis and to the simplicity of reactions with hypervalent iodine compounds.

## 3. Experimental procedure

All chemicals used in this study were of the highest purity available and purchased from local vendors. Melting points were determined on a Buchi oil heated melting apparatus and are uncorrected. $^1$H NMR spectra were recorded in $CDCl_3$ on a Bruker-300 MHz spectrometer using TMS as an internal standard (chemical shift in $\delta$). IR spectra were taken on a Perkin–Elmer 1600 FT-IR spectrophotometer using KBr pellets and peaks are reported in cm$^{-1}$. Sonication was performed in a PCI made ultrasound cleaner with a frequency of 25 and 40 kHz through manual adjustment and an output power of




**Scheme 1.** Oxidative aromatization of 1,4-DHP.




**Scheme 2.** Proposed mechanism for oxidative aromatization of 4-*n*-alkyl-1,4-DHP.

250 W. The reaction flask was located at the center of the cleaner, and the surface of the reactants was placed slightly lower than the level of the water. The addition or removal of water controlled the temperature of the water bath. The temperature of the water bath was controlled at 25–30 °C.

1,4-Dihydropyridine was prepared according to the literature [10,41,42,58].

### *3.1. General procedure for the synthesis of pyrazole substituted-1,4-dihydropyridines 2a–g*

A mixture of pyrazole aldehyde (5 mmol), ethylacetoacetate (10 mmol), and ammonium acetate (10 mmol) in ethanol (20 mL) was heated at 90 °C for 3 h. Progress of reaction was monitored on TLC. The reaction mixture was cooled to room temperature and solid, thus separated, was filtered. A yellowish colored solid mass was obtained and it was recrystallized with ethanol to get pure diethyl 1,4-dihydro-2,6-dimethyl-4-(3-aryl-1-phenyl-4-pyrazolyl) pyridine-3,5-dicarboxylates.

### *3.2. Diethyl 1,4-dihydro-2,6-dimethyl-4-(1,3-diphenyl-4-pyrazolyl) pyridine-3,5-dicarboxylates*

M.p. 167–169 °C.

IR (KBr): 3355, 3035, 2986, 1697, 1689, 1602, 1465, 1213, 750.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 1.092 (t, $J$ = 6.9 Hz, 6H), 2.234 (s, 6H), 3.744–3.848 (m, 2H), 3.986–4.068 (m, 2H), 5.307 (s, 1H), 5.537 (s, 1H), 7.221–7.279 (m, $J$ = 6.9 Hz, $J$ = 7.5 Hz, 2H), 7.353–7.377 (d, $J$ = 7.2 Hz, 2H), 7.424–7.447 (d, $J$ = 6.9 Hz, 2H) 7.760 (s, 1H), 7.681–7.706 (d, $J$ = 7.5 Hz, 2H); 7.844–7.868 (d, $J$ = 7.2 Hz, 2H).

Anal. Calcd. for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.45; H, 6.26; N, 9.03.

### *3.3. Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-p-chlorophenyl-1-phenyl-4-pyrazolyl) pyridine-3,5-dicarboxylates*

M.p. 166–168 °C.

IR (KBr): 3344, 3074, 2979, 1697, 1682, 1603, 1470, 1222, 837.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 1.096 (t, $J$ = 7.2 Hz, 6H), 2.278 (s, 6H), 3.766–3.837 (m,2H); 3.997–4.104 (m, 2H), 5.285 (s, 1H), 5.558 (s, 1H), 7.235–7.260 (d, $J$ = 7.5 Hz, 1H), 7.406–7.454 (t, $J$ = 7.2 Hz, 4H) 7.668–7.75 (m, 2H), 7.814 (s, 1H), 7.863–7.891 (d, $J$ = 8.4 Hz, 2H).

Anal. Calcd. for $C_{28}H_{28}N_3O_4Cl$: C, 66.47; H, 5.54; N, 8.31. Found: C, 66.47; H, 5.55; N, 8.31.

### *3.4. Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-p-bromophenyl-1-phenyl-4-pyrazolyl) pyridine-3,5-dicarboxylates*

M.p. 181–182 °C.

IR (KBr): 3399, 3063, 2981, 1695, 1683, 1612, 1466, 1208, 842.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 1.096 (t, $J$ = 7.2 Hz, 6H), 2.277 (s, 6H), 3.763–3.870 (m, 2H), 3.998–4.103 (m, 2H), 5.281 (s, 1H), 5.584 (s, 1H), 7.257 (t, $J$ = 7.2 Hz, 1H), 7.400–7.451 (m, 2H); 7.575 (d, $J$ = 8.1 Hz, 2H), 7.678 (d, $J$ = 7.8 Hz, 2H) 7.753 (s, 1H), 7.820 (d, $J$ = 8.4 Hz, 2H).

Anal. Calcd. for $C_{28}H_{28}BrN_3O_4$: C, 61.10; H, 5.13; N, 7.63. Found: C, 61.22; H, 5.27; N, 7.72.

### *3.5. General procedure for the oxidative aromatization of 1,4-DHP under ultrasonic irradiation*

In a 25 mL round bottom flask, 1,4-dihydropyridine (1.0 mmol) and IBD (1.2 mmol) in 10 mL $CH_2Cl_2$ was taken. The reaction mixture was irradiated (25 kHz, 280 W) in the water bath of an ultrasonic cleaner for a period as indicated in Table 1. Sonication was

continued until the 1,4-DHP disappeared, as indicated by TLC. After completion of reaction, the organic layer was concentrated to give crude product. The pure product was obtained by column chromatography using ethyl acetate–hexane (1:6). All compounds were fully characterized by mp, IR, $^1$H NMR and elemental analysis. These data are in full agreement with those previously reported in literature [42,59–60].

### 3.6. Diethyl 2,6-dimethyl-4-methylpyridine-3,5-dicarboxylate 2a

IR (KBr): 2979, 2869, 1722, 1586, 1464, 1268, 1222, 1116, 1054, 873, 769 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.25 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.20 (s, 3H, $CH_3$), 2.49 (s, 6H, $CH_3$), 4.26 (q, $J$ = 7.11 Hz, 4H, $OCH_3$).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.19; H, 7.28; N, 5.11.

### 3.7. Diethyl 2,6-dimethyl-4-ethylpyridine-3,5-dicarboxylate 2b

IR (KBr): 2989, 1729, 1577, 1441, 1276, 1111, 1045, 923, 846, 751 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.09 (t, $J$ = 7.40 Hz, 3H, $CH_3$), 1.25 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.49 (s, 6H, $CH_3$), 2.80 (q, $J$ = 7.40Hz, 2H, $CH_2$), 4.26 (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, 64.38; H, 7.69; N, 4.96.

### 3.8. Diethyl-4-(4-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2d

IR (KBr): 3023, 2988, 1726, 1555, 1504, 1351, 1106, 866, 843, 745 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.23 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 2.63 (s, 6H, $CH_3$), 4.25 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 7.41 (d, $J$ = 8.23 Hz, 2H), 8.22 (d, $J$ = 8.23 Hz, 2H).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.44; H, 5.32; N, 7.65.

### 3.9. Diethyl-4-(3-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2e

IR (KBr): 3033, 2991, 1724, 1579, 1549, 1508, 1351, 1281, 1178, 872, 783, 717 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.24 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.69 (s, 6H, $CH_3$), 4.26 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 7.57–8.28 (m, 4H).

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.29; H, 5.41; N, 7.53. Found: C, 61.36; H, 5.36; N, 7.48.

### 3.10. Diethyl-4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2f

IR (KBr): 3029, 2991, 1725, 1608, 1548, 1511, 1353, 1278, 1192, 762, 701 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ 1.23 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.69 (s, 6H, $CH_3$), 4.27 (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, 61.46; H, 5.38; N, 7.48.

### 3.11. Diethyl-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2g

IR (KBr): 3034, 2987, 1731, 1599, 1523, 1288, 1107, 856, 834, 772 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.22 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 4.27 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 2.69 (s, 6H, $CH_3$), 3.86 (s, 3H, $OCH_3$), 6.91 (d, $J$ = 8.57 Hz, 2H), 7.11 (d, $J$ = 8.57 Hz, 2H).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.34; H, 6.54; N, 4.02.

### 3.12. Diethyl-4-(4-methylphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2i

IR (KBr): 3022, 2978, 1725, 1582, 1444, 1228, 1013, 822, 857, 776 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.234 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 2.35 (s, 3H, $CH_3$), 2.66 (s, 6H, $CH_3$), 4.28 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 7.12 (d, $J$ = 6.79 Hz, 2H), 7.23 (d, $J$ = 6.79 Hz, 2H).

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.44; H, 6.84; N, 4.28.

### 3.13. Diethyl-4-phenyl-2,6-dimethylpyridine-3,5-dicarboxylate 2j

IR (KBr): 3026, 2978, 1729, 1592, 1477, 1301, 1212, 1171, 792, 761 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.22 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 4.27 (q, $J$ = 7.11 Hz, 4H, $OCH_2$), 2.67 (s, 6H, $CH_3$), 7.18-7.23 (m, 2H), 7.30-7.32 (m, 3H).

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.88; H, 6.55; N, 4.19.

### 3.14. Diethyl-4-(4-chlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2k

IR (KBr): 3028, 2991, 1728, 1588, 1232, 1106, 1045, 857, 657 cm$^{-1}$.

$^1$HNMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.22 (t, $J$ = 7.11 Hz, 6H, $CH_3$), 4.27 (q, $J$=7.11 Hz, 4H, $OCH_2$), 2.70 (s, 6H, $CH_3$), 7.12 (d, $J$ = 8.99 Hz, 2H), 7.32 (d, $J$ = 8.99 Hz, 2H).

Anal. Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87. Found: C, 62.92; H, 5.66; N, 3.66.

### 3.15. Diethyl-4-(2, 4-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate 2l

IR (KBr): 3041, 2977, 1732, 1587, 1466, 1281, 1231, 1100, 857, 775, 701 cm$^{-1}$.

$^1$HNMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.23 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 4.29 (q, $J$ = 7.12 Hz, 4H, $OCH_2$), 2.68 (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, 57.44; H, 5.02; N, 3.66.

### 3.16. Diethyl-4-(3-bromophenyl)-2, 6-dimethylpyridine-3, 5-dicarboxylate 2m

IR (KBr): 3055, 2988, 1727, 1562, 1280, 1102, 1035, 866, 777, 697 cm$^{-1}$.

$^1$HNMR ($CDCl_3$, $\delta$, ppm): $\delta$ = 1.24 (t, $J$=7.13 Hz, 6H, $CH_3$), 4.30 (q, $J$=7.13 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, 56.32; H, 4.88; N, 3.28.

### 3.17. Diethyl 4-(1,3-diphenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3,5-dicarboxylate 2p

IR (KBr): 3055, 3033, 2989, 1737, 1618, 1591, 1470, 1212, 747.

$^1$H NMR ($CDCl_3$, $\delta$, ppm): 0.910–0.996 (t, $J$ = 7.2 Hz, 6H), 2.618 (s, 6H), 3.909–4.072 (m, 4H), 7.110–7.313 (m, 4H), 7.819 (s, 1H), 7.581–7.690 (m, 6H).

Anal. Calcd. for $C_{28}H_{27}N_3O_4$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.77; H, 5.98; N, 9.09.

### 3.18. Diethyl 4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3,5-dicarboxylate 2q

IR (KBr): 3042, 2988, 1743, 1611, 1598, 1559, 1452, 1338, 1241, 1208, 1089, 1017, 867, 757, 732, 693 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$, ppm): 0.932 (t, $J$ = 7.2 Hz, 6H), 2.612 (s, 6H), 3.909–4.098 (m, 4H), 7.310–7.371 (m, 2H); 7.470–7.522 (m, 5H), 7.745 (d, $J$ = 7.7 Hz, 2H), 7.920 (s, 1H).

Anal. Calcd. for $C_{28}H_{26}N_3O_4Br$: C, 61.42; H, 4.75; N, 7.68. Found: C, 61.55; H, 4.87; N, 7.86.

### 3.19. Diethyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-2,6-dimethylpyridine-3,5-dicarboxylate 2r

IR(KBr): 3055, 2989, 1747, 1620, 1597, 1461, 1322, 1087, 1002, 952, 850, 836, 698 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, $\delta$, ppm): 0.935 (t, $J$ = 7.2 Hz, 6H), 2.618 (s, 6H), 3.898–4.118 (m, 4H), 7.310–7.370 (m, 2H); 7.487–7.513 (m, 5H), 7.746 (d, $J$ = 7.8 Hz, 2H), 7.923 (s, 1H).

Anal. Calcd. for $C_{28}H_{26}ClN_3O_4$: C, 66.73; H, 5.20; N, 8.34. Found: C, 61.66; H, 5.29; N, 8.26.

### 3.20. Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate 3

IR (KBr): 2988, 1727, 1597, 1512, 1302, 1246, 1122, 1023, 776 $cm^{-1}$.

$^1H$ NMR (CDCl3, $\delta$, ppm): $\delta$ = 1.31 (t, $J$ = 7.12 Hz, 6H, $CH_3$), 2.75 (s, 6H, $CH_3$), 4.29 (q, $J$ = 7.12 Hz, 4H, $OCH_3$).

Anal. Calcd. for $C_{13}H_{17}NO_4$:C, 62.14; H, 6.82; N, 5.57. Found: C, 62.23; H, 7.01; N, 5.45.

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