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Solvent-free synthesis and oxidative aromatization of diethyl-2,6-dimethyl-4-(1-phenyl-3-aryl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylates using hypervalent iodine (III) reagents

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C H R O N I C L E	A B S T R A C T
	In this article, an efficient, environmentally benign, solvent-free synthesis of diethyl-2,6-dimethyl-4-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylates and their simple oxidative aromatization in presence of selected hypervalent iodine (III) reagents under solvent-free condition at room temperature is demonstrated. All reactions were carried out by grinding the reactant pyrazole substituted Hantzch-1,4-dihydropyridines and hypervalent iodine (III) reagent in a mortar with pestle. [Hydroxy(tosyloxy)iodo]benzene act as an more efficient oxidizing reagent in comparison to phenyliodine bistrifluoroacetate and iodobenzene diacetate in terms of reaction time and yields. The advantages of present protocol are the environment friendly, short reaction time, mild reaction conditions, and high yields of the products.

1. Introduction

The exploration of privileged structures in drug discovery is rapidly emerging theme in medicinal chemistry[1]. Pyrazoles and their derivatives are important class of compounds in organic and medicinal chemistry due to their biological properties [2] including anti-inflammatory, antimicrobial, analgesic, hypoglycaemic and non-nucleoside HIV-1 reverse transcriptase inhibitor properties. Pyridine and its derivatives are an important part of organic compounds that have significant place in medicinal chemistry[3]. Thus, the synthesis of highly substituted pyridines has attracted much attention, and a number of procedures have been developed[4]. Out of these trials, we selected the oxidative aromatization of 1,4-dihydropyridines (1,4-DHP's). The 1,4-DHP's and their oxidized derivatives belong to such immensely important class of heterocyclic systems, owing to their potent

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antihypertensive activity[5] and other biological utilities[6]. These compounds generally undergo oxidative metabolism in the liver by the action of cytochrome p-450 to form the corresponding pyridine derivatives[7]. Due to the relevance of this oxidative event to the biological NADH redox process[4-7], this transformation has attracted the attention of several research groups[7-42].

Out of these numerous oxidative protocols, we selected the aromatization of pyrazole substituted-1,4-DHP with hypervalent iodine (III) reagents under solvent-free condition. Recently hypervalent iodine (III) reagents have gained much importance as an oxidizing reagent due to their environmentally benign properties and replacing the use of toxic transition metals involved in such processes [43-46]. Hypervalent iodine (III) reagents are sparingly soluble in common organic solvents and therefore solvent free reactions are developed [47]. Solvent free reactions are of great importance in order to minimize pollution and toxic waste [48-50]. Literature survey shows that many exothermic reactions can be accomplished in high yields by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry' [51]. Reactions are initiated by grinding, with the transfer of very small amount of energy through friction. It is not only advantageous from the environmental point of view but also offers rate enhancement, less waste products and higher yields[51].

Encouraged by these observation and in continuation of our earlier studies on the oxidative aromatization of 1,4-DHP,s [39-42] and synthesis of biological active heterocyclic compounds [52-53], we report herein, solvent free aromatization of diethyl 2,6-dimethyl-4-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylates (**2a-g**) to diethyl 2,6-dimethyl-4-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarboxylates (**3a-g**) in presence of hypervalent iodine (III) reagents [iodobenzene diacetate (IBD) or phenyliodine bistrifluoroacetate (PIFA) or [hydroxy(tosyloxy)iodo]benzene (HTIB)] using grindstone chemistry (**Scheme 2**).

2. Results and Discussion

2.1 Synthesis of diethyl-2,6-dimethyl-4-(1-phenyl-3-aryl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylates (2a-g)

Compounds **2a-g** were synthesized by multi-components reactions of ammonium acetate, ethylacetoacetate, formyl pyrazole (**1a-g**) and silica without solvent at 90 ºC (**Scheme 1**). To optimize the reaction condition for the synthesis of 1,4-DHP,s (**2a-g**), 3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde **1b** (1 mmol), ethylacetoacetate (2.1 mmol), ammonium acetate (1.1 mmol), and silica (10 mole%) were heated at 90 ºC for 3 hrs afforded the corresponding 1,4-DHP **2b** in 85% yield. Then reaction was performed in ethanol at refluxed condition (**Table 1**) and it furnished **2b** in 75% yield. Without silica, time of reaction increased and yield of product decreased. Thus the reaction conditions were optimized (**Table 1**). Using optimized reaction condition, pyrazole substituted 1,4-DHP's were synthesized (80-90%). No electronic effect of substituents of formyl pyrazole was observed. Results are summarized in **Table 2**.

2.2. Oxidative aromatization of diethyl-2,6-dimethyl-4-(1-phenyl-3-aryl-1H-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylates (2a-g)

The high oxidizing power of hypervalent iodine (III) reagents led us to hypothesis that these reagents can act as efficient oxidizing reagents for this protocol. Initially diethyl 2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate **2b** has been used as a substrate to test the feasibility of hypervalent iodine (III) reagents as an oxidant (**Scheme 2**). To optimize the reaction condition, diethyl 2,6-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridine-3,5-dicarboxylate **2b** (1.0 mmol) and HTIB (1.1 mmol) were ground in a mortar by pestle. After 3 min the reaction mixture became wet and then we carried out grinding till completion of reaction (TLC). After usual workup, diethyl 2,6-dimethyl-4-(3-(4-nitrophenyl)-1-

phenyl-1*H*-pyrazol-4-yl)pyridine-3,5-dicarboxylate (**3a**) was obtained in excellent yield (88%). Then we performed the reaction of **2b** with IBD and PIFA. The oxidative efficiency of IBD or PIFA at room temperature was investigated, and it was observed that oxidation of pyrazole substituted 1,4-DHP,s did not proceed effectively at room temperature. A better activity of IBD and PIFA was obtained when the preheated 1,4-DHP **2b** was ground with these reagents. To optimize the reaction condition for IBD, hantzch-1,4-DHP was taken in mortar and kept in an oven at 80 ºC-90 ºC for 5 min, then it was removed from the oven, added IBD (1.1 mmol), and ground with pestle. After some time, exothermic reaction occurred with liberation of acetic acid and reaction mass was ground till the completion of reaction (TLC). Same procedure was adopted for the oxidative aromatization of **2b** with PIFA apart from the temperature of the oven. For PIFA mediated oxidative aromatization, compound **2b** was heated in oven at 50 ºC-60 ºC for 5 min and then it was ground with PIFA by pestle.
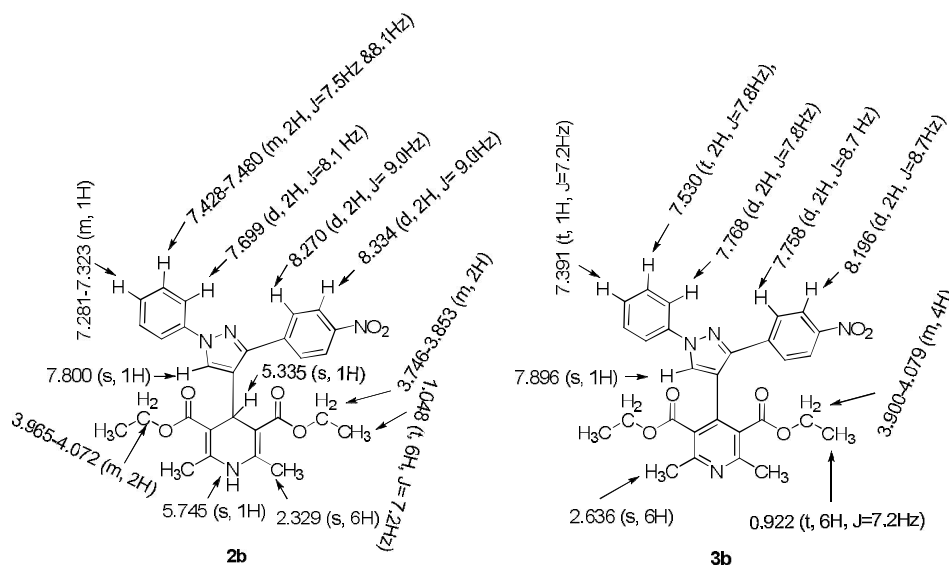

Fig.1. The hydrogen assignment in ¹H-NMR spectra of **2b** and **3b**

In ¹H-NMR spectra of **2b** the two separate multiplets appears at δ 3.746-3.853 and 3.965-4.072 for methylene protons but in ¹H-NMR spectra of **3b** these multiplets changes into a single multiplet at δ 3.900-4.079. Appearance of two multiplets in ¹H-NMR spectra of **2b** clearly indicates that both of the methylene groups are in different environment. This is further confirmed by finding most stable conformation of **2b** with ChemBio 3D ultra 11.0 (Chem Bio Office 2008) and by using MM2 force field method of energy minimization (**Fig. 2.**).
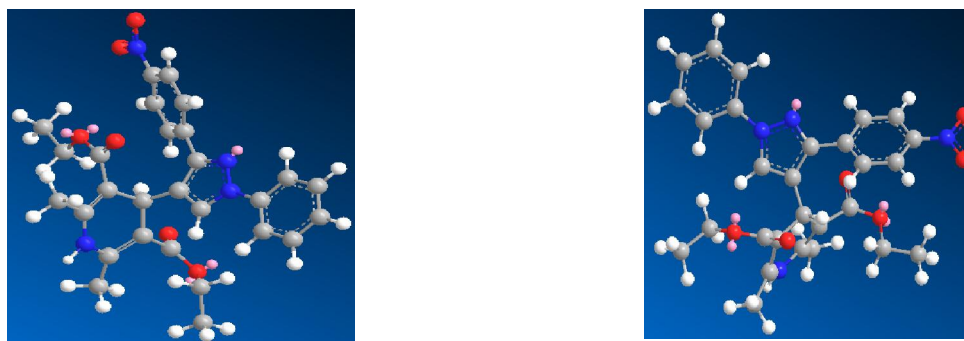

Fig. 2 Most stable conformation of **2b**

The total energy of the resulting conformation found for **2b** is 24.2179 kcal/mol. Appearance of one multiplet in ¹H-NMR spectra of **3b** shows that both of the methylene group are in similar

environment (**Fig. 3.**). In ^{1}H-NMR spectra of **3b**, the protons of methyl group, pyrazolyl proton, and aromatic proton of N-phenyl ring resonate at down field in comparison to **2b** which evidently prove the electron withdrawing effect of sp[2] hybridized nitrogen i.e. pyridine nitrogen. However, three types of proton (six protons of methyl group of ester, *ortho* and *meta* protons of *p*-nitrophenyl ring) resonate at high field.
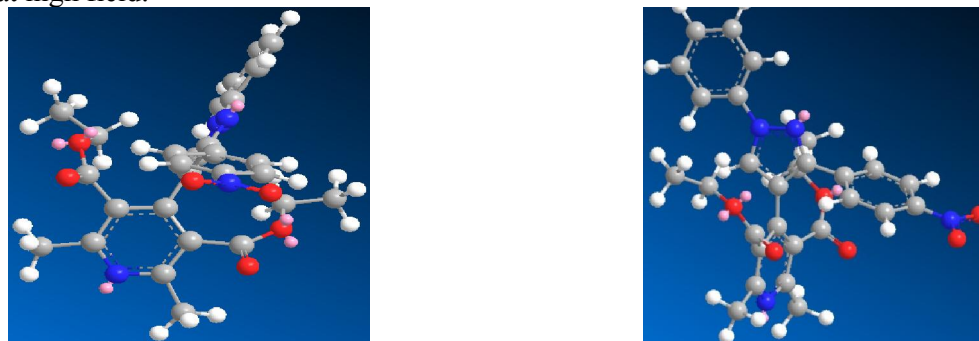

Fig. 3 Most stable conformation of **3b**

Under similar reaction conditions, various pyrazole substituted 1,4-dihydropyridines **2a-g** were efficiently aromatized to the pyridine derivatives **3a-g** and the results are given in **Table 1**. No electronic effect of 1,4-DHP's were observed.

Table 1. Silica-catalyzed synthesis of diethyl 4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**2a**) under different conditions.

S. No.	Solvent	Amount of silica, mol%	Reaction temperature, ℃	Yield, %
1	None	None	80	55
2	None	5	80	65
3	None	10	80	91
4	None	15	80	90
5	None	10	50	60
6	Ethanol	None	80	50
7	Ethanol	10	80	85

Table 2. Silica-catalyzed synthesis of diethyl 4-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (**2a-g**).

Entry	R	Time, h	Yield, %	m.p., ℃	Lit. m.p., ℃
2a	-H	3.0	90	167-169	169-171 [54]
2b	-NO2	3.5	85	123-125	124-126 [54]
2c	-OCH3	4.0	91	129-131	128-130 [54]
2d	-CH3	3.0	87	192-193	194-195 [54]
2e	-Br	4.0	92	181-182	174 [55]
2f	-Cl	4.0	90	166-168	167-168 [54]
2g	-F	4.0	90	176-177	175 [55]

Table 3. Solvent less oxidative aromatization of 4-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylates (**2a-g**).

Entry	R	Reaction with IBD		Reaction with PIFA		Reaction with HTIB		m.p., ℃	Lit m.p., ℃
		Time,[a] min	Yield, %	Time,[b] min	Yield, %	Time,[c] min	Yield, %		
3a	-H	20	70	15	77	10	90	114-116	111[55]
3b	-NO2	22	65	16	65	15	88	173-175	172[55]
3c	-OCH3	23	67	18	69	15	90	138-139	136[55]
3d	-CH3	20	70	15	70	13	92	110-112	105[55]
3e	-Br	25	72	18	70	14	87	116-118	115[55]
3f	-Cl	20	71	20	72	13	85	100-102	101-102[55]
3g	-F	20	73	18	74	15	90	125-126	121[55]

[a] 1,4-DHP's were heated in an oven for 5 min at 80-90 ℃. [b] 1,4-DHP's were heated in an oven for 5 min at 50-60 ℃.
[c] 1,4-DHP's were not heated, reaction was carried out at room temperature.
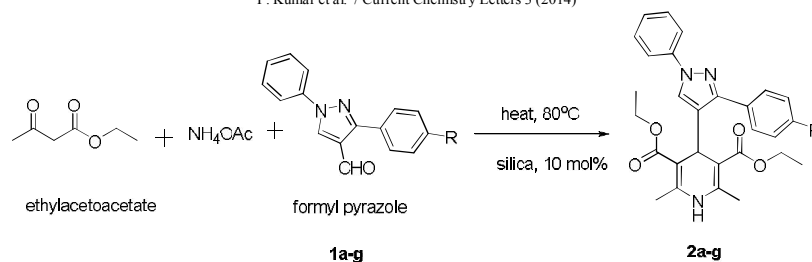
Scheme 1: Solvent-free synthesis of pyrazole substituted 1,4-DHP's
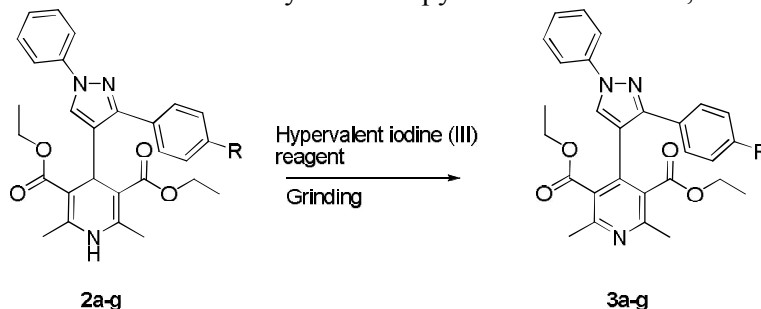
Scheme 2: Solvent-free oxidative aromatization of pyrazole substituted 1,4-DHP's.

3. Conclusions

In conclusion, in the present experiment, oxidation of 1,4-dihydropyridines with hypervalent iodine (III) reagents were performed efficiently. The hydroxy(tosyloxy)iodo]benzene (HTIB) was found more efficient reagent in comparison of IBD or PIFA. Literature survey[30] and our present protocol also illustrate that efficiency of hypervalent iodine (III) reagents in studied oxidative aromatization of 1,4-DHP's is rose following HTIB > PIFA> IBD.

Acknowledgements

4. Experimental

4.1. Materials and Methods

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 δ). IR spectra were taken on a Perkin Elmer FTIR spectrophotometer using KBr pellets and peaks are reported in cm^{-1}.

4.2.1. General procedure for the synthesis of 1,4-dihydropyridines 2a-g

A mixture of pyrazole aldehyde (5 mmol), ethyl acetoacetate (10 mmol), ammonium acetate (7.5 mmol) and silica (10 mol %) was heated at 90 °C for 3 hrs. Progress of reaction was monitored on TLC. After cooling, the reaction mixture was extracted with chloroform. Organic solvent was removed under vacuum. Then 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 (**2a-g**).

4.2.2. General procedure for the oxidation of 1,4-dihydropyridines (2a-g) with HTIB

A mixture of 1,4-dihydropyridine (**2a-g**) (2 mmol) and HTIB (2.2 mmol) was blended thoroughly in a mortar by pestle. The resulting homogeneous mixture was ground at room temperature for 5-10

min. The completion of reaction was indicated by wetting of the reaction mixture. Progress of reaction was monitored by TLC. After completion of reaction, saturated solution of aq. sodium bicarbonate (20 mL) was added to quench the reaction and filtered the product. The resulting crude product was purified by silica gel column chromatography (using different ratios of ethyl acetate and n-hexane as eluent according to different products).

4.2.3. General procedure for the oxidation of 1,4-dihydropyridines (2a-g) with IBD or PIFA

1,4-Dihdropydine was taken in mortar and heated in an oven by maintain the temperature of oven at 80-90°C. After heating, mortar was taken off from the oven and IBD was added to it. Then the reaction mass was blended with pestle till the completion of reaction. Progress of reaction was monitored on TLC. If starting compound was observed on TLC then again the reaction mass was kept in oven for 2-3 min. After completion of reaction, saturated solution of aq. sodium bicarbonate (20 mL) was added to quench the reaction and filtered the product. The resulting crude product was purified by silica gel column chromatography (using different ratios of ethyl acetate and n-hexane as eluent according to different products).

The same procedure was adopted for oxidative aromatization of 1,4-DHP with PIFA except the temperature of oven which was kept 50-60 ºC.

4.3.1. Spectral Data of diethyl-2,6-dimethyl-4-(3-aryl-1-phenyl-4-pyrazolyl)-1,4-dihydropyridine-3,5-dicarboxylates (2a-g)

2a: IR (KBr): 3355, 3035, 2986, 1697, 1689, 1602, 1465, 1213, 750.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.092 (t, J= 6.9Hz, 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, 2H), 7.353-7.377 (2H, d, J= 7.2Hz), 7.424-7.447 (2H, d, J= 6.9Hz) 7.760 (s, 1H), 7.681-7.706 (d, 2H, J= 7.5Hz); 7.844-7.868 (d, 2H, J=7.2Hz).

Anal. Calcd for C$_{28}$H$_{29}$N$_3$O$_4$. C, 71.32; H, 6.20; N, 8.91; Found: C, 71.45; H, 6.26; N 9.03.

2b: IR (KBr): 3385, 3077, 2991, 1696, 1681, 1623, 1543, 1467, 1338, 1235, 852, 720.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.048 (t, 6H, J= 7.2Hz), 2.329 (s, 6H), 3.746-3.853 (m, 2H), 3.965-4.072 (m, 2H), 5.335 (s, 1H), 5.745 (s, 1H), 7.281-7.323 (m, 1H), 7.428-7.480 (m, 2H, J=7.5Hz & 8.1Hz), 7.699 (d, 2H, J=8.1 Hz), 7.800 (s, 1H), 8.270 (d, 2H, J= 9.0Hz); 8.334 (d, 2H, J= 9.0Hz).

Anal. Calcd for C$_{28}$H$_{28}$N$_4$O$_6$. C, 65.11; H, 5.46; N, 10.85; Found: C, 65.29; H, 5.58; N 10.99.

2c: IR (KBr): 3322, 3033, 2981, 1696, 1683, 1621, 1451, 1220, 810.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.103 (t, 6H, J= 7.2Hz), 2.784 (s, 6H), 3.777-3.836 (m, 2H), 3.866 (s, 3H), 3.995-4.100 (m, 2H), 5.288 (s, 1H), 5.561 (s, 1H), 6.977 (d, 2H, J=8.7 Hz), 7.252 (t, 1H, J= 7.5 Hz), 7.388-7.440 (m, 2H, J=7.5Hz & J=7.8Hz), 7.683 (d, 2H, J= 7.8 Hz), 7.743 (s, 1H), 7.800 (d, 2H, J= 8.7 Hz).

Anal. Calcd for C$_{29}$H$_{31}$N$_3$O$_5$. C, 69.44; H, 6.23; N, 8.38; Found: C, 69.66; H, 6.39; N, 8.55.

2d: IR (KBr): 3347, 3066, 2992, 1695, 1685, 1610, 1597, 1442, 1211, 817, 720.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.087 (t, 6H, J= 7.2Hz), 2.223 (s, 6H), 2.403 (s, 3H), 3.753-3.827 (m, 2H), 3.952-4.072 (m, 2H), 5.311 (s, 1H), 5.724 (s, 1H), 7.175-7.201 (d, 2H, J=7.8 Hz), 7.211 (t, 1H, J= 7.5 Hz), 7.379-7.449 (m, 2H), 7.678 (d, 2H, J= 8.4 Hz), 7.761 (s, 1H), 7.832-7.858 (d, 2H, J= 7.8 Hz).

Anal. Calcd for C$_{29}$H$_{31}$N$_3$O$_4$. C, 71.73; H, 6.43; N, 8.65; Found: C, 71.98; H, 6.55; N 8.72.

2e: IR (KBr): 3399, 3063, 2981, 1695, 1683, 1612, 1466, 1208, 842.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.096 (t, 6H, J=7.2Hz), 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, 1H, J=7.2Hz), 7.400-7.451 (m, 2H, J= 7.5Hz & 7.8Hz); 7.575 (d, 2H, J=8.1 Hz), 7.678 (d, 2H, J= 7.8 Hz) 7.753 (s, 1H), 7.820 (d, 2H, J= 8.4 Hz).

Anal. Calcd for C$_{28}$H$_{28}$BrN$_3$O$_4$. C, 61.10; H, 5.13; N, 7.63; Found: C, 61.22; H, 5.27; N, 7.72.

2f: IR (KBr): 3344, 3074, 2979, 1697, 1682, 1603, 1470, 1222, 837.

^{1}H-NMR (CDCl$_3$, δ, ppm): 1.096 (t, 6H, J= 7.2Hz), 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, 1H, J=7.5Hz), 7.406-7.454 (m, 4H,) 7.668-7.75 (m, 2H, J=7.8 Hz & 6.9 Hz), 7.814 (s, 1H), 7.863-7.891 (d, 2H, J= 8.4 Hz).

Anal. Calcd for C$_{28}$H$_{28}$N$_3$O$_4$Cl. C, 66.47; H, 5.54; N, 8.31; Found: C, 66.47; H, 5.55; N, 8.31.

2g: IR (KBr): 3357, 3051, 2989, 1694, 1680, 1609, 1466, 1219, 831; ^{1}H-NMR (CDCl$_3$, δ, ppm): 1.040 (t, 6H, J=7.2Hz), 2.519 (s, 6H), 3.748-3.854 (m, 2H), 3.964-4.070 (m, 2H), 5.170 (s, 1H), 5.559 (s, 1H), 7.293 (d, 2H, J=7.5 Hz), 7.334-7.361 (m, 1H), 7.490-7.513 (m, 4H), 7.747 (d, 2H, J= 7.5 Hz), 7.920 (s, 1H).

Anal. Calcd for C$_{28}$H$_{28}$N$_3$O$_4$F. C, 68.70; H, 5.77; N, 8.58; Found: C, 68.88; H, 5.92; N 8.68.

4.3.2. Characterization data of dimethyl 2,6-dimethyl-4-pyrazolylpyridine-3,5-dicarboxylates (3a-g)

3a: IR (KBr): 3053, 3021, 2988, 1735, 1621, 1598, 1471, 1220, 745.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.943 (t, 6H, J=7.2), 2.621 (s, 6H), 3.912-4.081 (m, 4H), 7.108-7.309 (m, 4H), 7.816 (s, 1H), 7.582-7.689 (m, 6H).

 Anal. Calcd for C$_{28}$H$_{27}$N$_3$O$_4$: C, 71.62; H, 5.80; N, 8.95. Found: C, 71.84; H, 6.04; N 9.11.

3b: Yield- 68%; IR (KBr): 1728, 1234, 1034.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.922 (t, 6H, J=7.2Hz), 2.636 (s, 6H), 3.900-4.079 (m, 4H), 7.391 (t, 1H, J=7.2Hz), 7.530 (t, 2H, J=7.8Hz), 7.758 (d, 2H, J=8.4 Hz), 7.768 (d, 2H, J=7.8Hz), 7.896 (s, 1H), 8.196 (d, 2H, J=8.7Hz).

Anal. Calcd for C$_{28}$H$_{26}$N$_4$O$_6$: C, 65.36; H, 5.09; N, 10.89. Found: C, 65.55; H, 5.21; N 11.02.

3c: IR (KBr): 3051, 2994, 1737, 1611, 1588, 1452, 832.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.948 (t, 6H, J=7.2Hz), 2.784 (s, 6H), 3.832 (s, 3H), 3.917-4.049(m, 4H), 6.876 (d, 2H, J= 9.0 Hz), 7.350 (t, 1H, J=7.2Hz), 7.425 (d, 2H, J= 9.0 Hz); 7.475-7.528 (m, 2H, J=7.5Hz & 7.8 Hz); 7.755 (dd, 2H, J=2.4Hz & J= 7.5 Hz) 7.945 (s, 1H).

Anal. Calcd for C$_{29}$H$_{29}$N$_3$O$_5$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.86; H, 5.99; N 8.51.

3d: IR (KBr): 3067, 3008, 2991, 1741, 1617, 1590, 1445, 851, 719.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.937 (t, 6H, J= 7.2Hz), 2.389 (s, 3H), 2.531 (s, 6H), 3.921-4.070 (m, 4H), 7.256 (d, 2H, J=7.8 Hz), 7.323-7.449 (m, 3H), 7.715 (d, 2H, J= 8.2 Hz), 7.858 (d, 2H, J= 7.8 Hz), 7.931 (s, 1H).

 Anal. Calcd for C$_{29}$H$_{29}$N$_3$O$_4$: C, 72.03; H, 6.04; N, 8.69. Found: C, 71.91; H, 5.98; N 8.81.

3e: IR (KBr): 3036, 2982, 2899, 1745, 1601, 1559, 1502, 1441, 1379, 1339, 1296, 1238, 1205, 1091, 1039, 1007, 956, 863, 831, 754, 730, 691 cm^{-1}.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.938 (t, 6H, J=7.2Hz), 2.615 (s, 6H), 3.990-4.098 (m, 4H), 7.310-7.372 (m, 2H); 7.474-7.524 (m, 4H), 7.745 (d, 2H, J=7.8Hz), 7.922 (s, 1H).

Anal. Calcd for C$_{28}$H$_{26}$N$_3$O$_4$Br: C, 61.42; H, 4.75; N, 7.68. Found: C, 61.31; H 4.79; N 7.69

3f: IR(KBr): 3065, 2994, 2899, 1742, 1611, 1595, 1498, 1464, 1371, 1319, 1208, 1088, 1012, 957, 857, 833, 693 cm^{-1}.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.940 (t, 6H, J=7.2Hz), 2.620 (s, 6H), 3.898-4.118 (m, 4H), 7.310-7.370 (m, 2H); 7.487-7.513 (m, 4H), 7.746 (d, 2H, J=7.8Hz), 7.923 (s, 1H).

Anal. Calcd for C$_{28}$H$_{26}$ClN$_3$O$_4$: C, 66.73; H, 5.20; N, 8.34. Found: C, 61.88; H, 5.31; N 8.49.

3g: IR (KBr): 3072, 3018, 2987, 1742, 1615, 1581, 1461, 1212, 1021, 838, 720.

^{1}H-NMR (CDCl$_3$, δ, ppm): 0.947 (t, 6H, J=7.2Hz), 2.617 (s, 6H), 3.899-4.110 (m, 4H), 7.015 (t, 2H, J=8.4Hz), 7.341 (t, 1H, J= 7.2Hz), 7.472 (d, 2H, J= 7.8Hz), 7.537 (d, 2H, J= 8.4Hz), 7.746 (d, 2H, J=7.8 Hz), 7.924 (s, 1H).

Anal. Calcd for C$_{28}$H$_{26}$FN$_3$O$_4$: C, 68.98; H, 5.38; N, 8.62. Found: C, 69.08; H, 5.51; N 8.74.

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