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Simple and efficient synthesis of 2,6-dialkyl-3,5-dialkoxycarbonyl-4-(3-aryl-1-phenyl-pyrazol-4-yl)pyridines using TPAP/NMO as a catalyst under mild conditions

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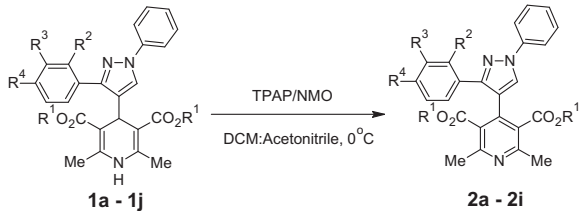
ABSTRACT

Biologically important pyrazolylpyridines were synthesized in excellent yield by the oxidation of pyrazolyl 1,4-dihydropyridines (pyrazolyl 1,4-DHPs) using tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) under mild conditions at 0 °C.

1. Introduction

Pyrazoles form an integral part of many natural products of therapeutic importance and possess potentially reactive sites for a variety of chemical reactions to generate molecular diversity. (*S*)-3-Pyrazolylalanine,[1] lonazolac,[2] difenamizole,[3] mepirizole,[4] metamizol,[5] phenidone,[6] pyrazomycine, fezolamin, 4,5-dihydro-3-phenyl-6*H*-pyrrolo[1,2-*b*]pyrazole are some of the examples of biologically active compounds endowed with antimicrobial,[7] anti-inflammatory,[8] analgesic,[9] hypoglycaemic,[10] and non nucleoside HIV-1 reverse transcriptase inhibitor properties.[11] Pyrazolyl 1,4-DHPs have pronounced pharmacological applications as anti-inflammatory agents, and also possess calcium channel activity,[12] including control of arthropod pests,[13] and also pyrazolylpyridine ligands exhibit efficient lanthanide sensors.[14]

Oxidation of 1,4-DHP has received considerable attention because DHP based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P450 in the liver.[15] Efforts on the synthesis of heteroaryl DHP chemistry mimicking NADH coenzyme is recently expanding to explore the mechanisms and utilizing them for a variety of synthetic reactions. Therefore, the synthesis of these moieties has become of interest to synthetic chemists and biologists. This manuscript describes our efforts on the synthesis of pyrazolylpyridines from pyrazolyl 1,4-DHPs. We report the rapid and efficient catalytic oxidation of pyrazolyl 1,4-DHP derivatives at 0 °C in DCM/acetonitrile (Scheme 1). Several groups have reported the oxidation of 1,4-DHPs with metal based catalysts,[16] I_2/UHP,[17] *N*-nitroso-2-aryl-1,3-oxazolidines,[18] magtrone™,[19] 9-phenyl-10-methylacridinium/O_2,[20] IBX,[21] NO gas,[22] claycop,[23] *S*-nitrosoglutathione,[24] 4-phenyl-1,2,4-triazol-3,5-dione,[25] electrochemical,[26] and photooxidation,[27] and chloranil[28] promote these type of reactions including ones at room temperature. Although some of these reactions are performed under mild conditions, most of them require a long period for completion, high temperature, freshly prepared reagents, tedious work-up, include the formation of side products, and give only modest yields of the products. Therefore, development and introduction of a convenient, milder and efficient method for the oxidation of heterocyclic 1,4-DHPs to the corresponding pyridines is of practical importance and is still in demand.



Scheme 1. TPAP/NMO catalyzed synthesis of pyrazolylpyridines **2a**–**i**.

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Recently, the TPAP/NMO combination has received considerable attention as a mild catalyst for oxidation reactions at lower temperature.[29] Here, TPAP/NMO is introduced as a mild and highly efficient catalyst for the preparation of pyrazolylpyridine derivatives under mild conditions.

2. Results and discussion

The experimental procedure is simple and clean. 1,4-DHPs were prepared using the appropriate aldehyde, ammonium acetate, and alkyl acetoacetate under reflux conditions using reported literature.[30] Pyrazolylpyridines have been synthesized by TPAP/NMO catalyzed oxidation of pyrazolyl 1,4-DHPs under mild conditions. In our method, including $RuCl_3$, MnO_2, and TPAP/NMO were screened initially for catalytic activity and the compared studies results are summarized in Table 1.

Table 1
Screening of oxidants for the conversion of **3c** to **4c**[a]

Entry	Catalyst	Amount	Conditions	Time	Yield (%)
a	$Fe(ClO_4)_3$	2 mol %	AcOH, rt	1.5 h	91[16d]
b	$VOCl_3$	2.1 equiv	DCM, rt	60 h	97[16u]
c	V_2O_5	2.1 equiv	AcOH, rt	168 h	84[16u]
d	I_2	50 mol %	UHP (2 equiv), AcOEt, rt	25 min	89[17]
e	$RuCl_3$	5 mol %	O_2, AcOH, rt	53 h	55[16y]
f	N–NO Oxazolidine	10 mol %	DCM, rt	6 h	96[29]
g	MnO_2	5 equiv	DCM, rt	30 min	87[16g]
h	$Mn(OAc)_3$	2 equiv	AcOH, rt	35 min	98[16h]
i	$BiCl_3$	30 mol %	$PhCH_2Ph_3PHSO_5$, acetonitrile, rt	2 h	89[16p]
i	TPAP	5 mol %	NMO (0.1 equiv), DCM/acetonitrile, 0 °C	30 min	97

[a] Isolated yields.

The oxidation of **1a** using TPAP/NMO as a catalyst was chosen as a model for optimization of the solvent. Initially, the reaction of pyrazolyl 1,4-DHP **1a** was carried out in the presence of TPAP/NMO in different solvents at 0 °C. The catalytic activity of TPAP/NMO is found to vary with different solvents (Fig. 1). Dichloromethane/acetonitrile were found to give maximum yield followed by acetonitrile alone. The catalyst was found to be only mildly effective in toluene.

The effect of an ionic liquid on the TPAP/NMO catalyzed reaction was also examined. The method reported is favorable and gave good yields (89–94%).

We decided to find out the optimal amount of catalyst (TPAP) to reach complete conversion at 0 °C. The results are presented in Fig. 2. The incremental amount of catalyst drastically accelerates the reaction with the same level of selectivity. From the results outlined in Fig. 2 and 5 mol % of catalyst was chosen for further experiments. The simple methyl and phenyl substituted 1,4-DHPs also worked well without the formation of side products (Table 2).

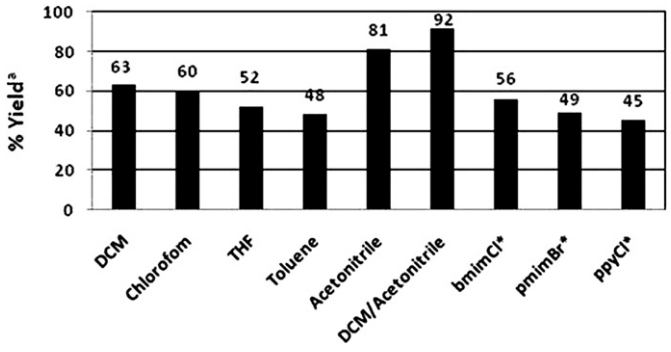


Fig. 1. Effect of solvent on the conversion of **1d** to **2d**. Reaction conditions: pyrazolyl 1,4-DHP (1 equiv), TPAP/NMO (5 mol%:0.1 equiv), Solvent (10 mL), 0 °C. *Ionic liquids (3 mL), rt. [a]Isolated yields.

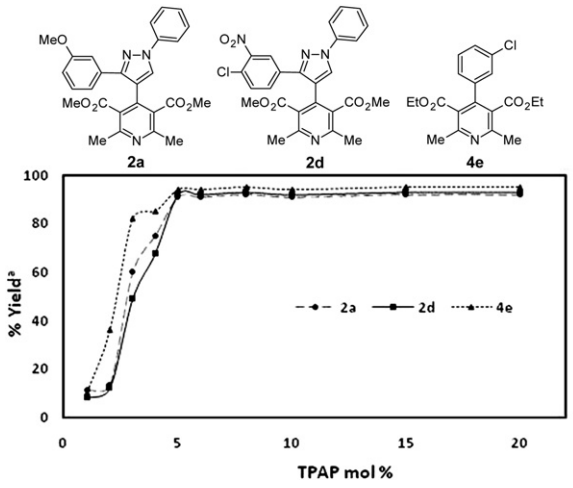
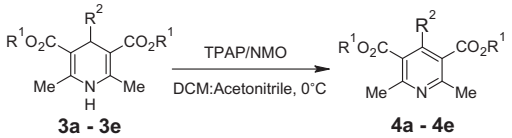
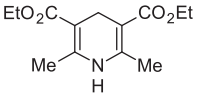
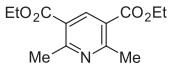
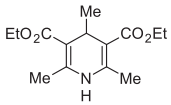
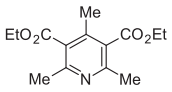
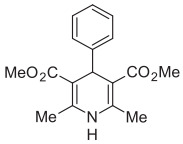
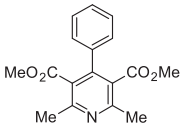
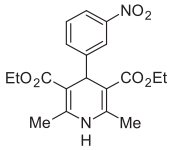
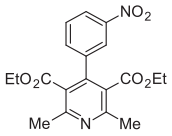
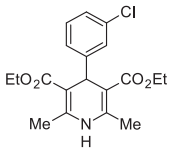
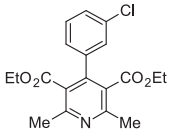


Fig. 2. Effect of catalyst loading on the synthesis of pyridines **2a**, **2d**, and **4e**. Reaction conditions: 1,4-DHP (1 equiv), NMO (0.1 equiv), solvent (10 mL), 0 °C. [a]Isolated yields.

Table 2
Synthesis of pyridines **4a**–**e**[a]

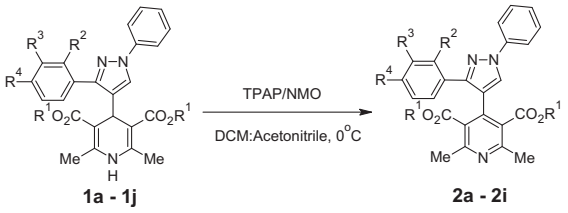


Entry	Reactant	Product	Time (min)	Yield[b] (%)
a	 **3a**	 **4a**	30	91
b	 **3b**	 **4b**	30	90
c	 **3c**	 **4c**	30	97
d	 **3d**	 **4d**	30	94
e	 **3e**	 **4e**	30	94

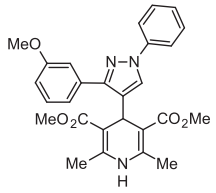
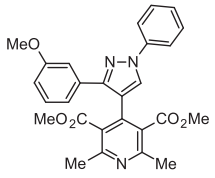
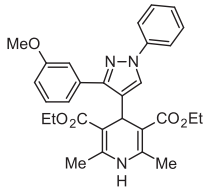
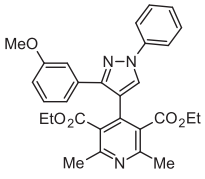
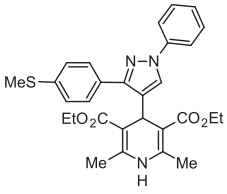
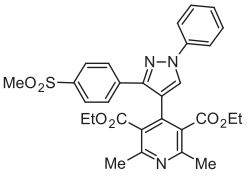
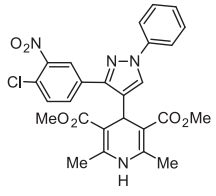
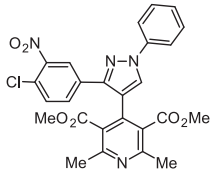
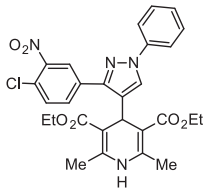
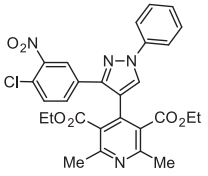
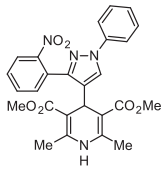
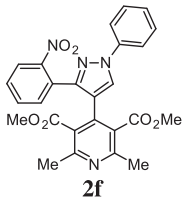
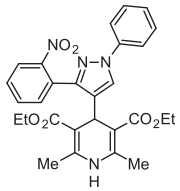
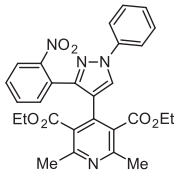
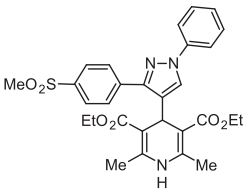
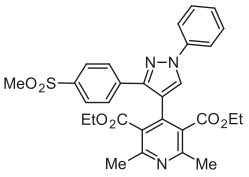
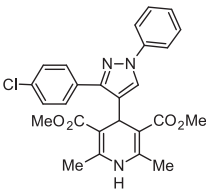
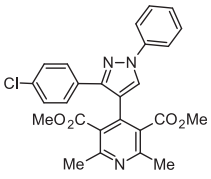
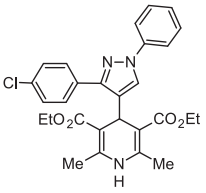
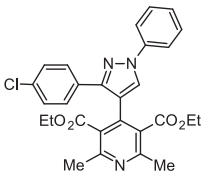
[a] Reaction conditions: 1,4-DHP (1 equiv), TPAP/NMO (5 mol%:0.1 equiv), DCM/acetonitrile (5 mL), 0 °C.
[b] Isolated yields.

Pyrazolyl 1,4-DHP **1e** reacted in the presence of TPAP/NMO to give **2e** in good yield (89%; Scheme 1). The reaction did not proceed to good extent in the presence of TPAP alone in DCM/acetonitrile (1:1). This result confirmed the need for a catalytic amount of NMO. We found that TPAP/NMO promoted reactions were clean and afforded higher yields of product. For an illustrative example, **1a** in DCM/acetonitrile mixture was stirred at ambient temperature under N_2 at 0 °C. To the stirring reaction mixture was added 5 mol% of TPAP, 0.1 equiv of NMO and the total consumption of **1a** after 30 min as monitored by TLC was an indication of completion of the reaction (Scheme 1). However, the reaction when conducted without the addition of TPAP/NMO did not afford any appreciable amount of **2a**. Furthermore, no aqueous work-up was required after completion of the reaction. The reaction mixture was directly charged into a column after removing the solvent under vacuum. The maximum yield observed was 94% for **2f**. All the pyrazolyl 1,4-DHPs oxidized to give pyrazolylpyridines **2a**–**i** in high yields (Scheme 1). The results are summarized in Table 3. In the case of **1c**, both DHP and 4-substituted methylsufanyl groups are get oxidized under the identical reaction conditions, yielding **2c** with good yield (Table 1, entry c). Pyrazolyl 1,4-DHPs **1c** and **1i**, in both cases the product was found to be pyrazolylpyridine **2c** (Scheme 2).

Table 3
Synthesis of pyrazolylpyridines **2a**–**i**[a]



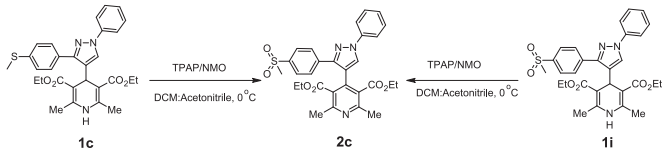
1a - 1j **2a - 2i**

Entry	Reactant	Product	Time (min)	Yield[b] (%)
a	 **1a**	 **2a**	30	91
b	 **1b**	 **2b**	30	90
c	 **1c**	 **2c**	30	90
d	 **1d**	 **2d**	30	92
e	 **1e**	 **2e**	30	90
f	 **1f**	 **2f**	30	94
g	 **1g**	 **2g**	45	92
h	 **1h**	 **2c**	30	89
i	 **1i**	 **2h**	45	90
j	 **1j**	 **2i**	45	93

[a] Reaction conditions: pyrazolyl 1,4-DHP (1 equiv), TPAP (5 mol %), NMO (0.1 equiv), DCM/acetonitrile [1:1] (10 mL), 0 °C.
[b] Isolated yields, and all the compounds were characterized by spectroscopic techniques.

3. Conclusions

In summary, we have found TPAP/NMO to be a valuable addition to the existing methods available for the oxidation of pyrazolyl 1,4-DHPs with the added advantage of mild reaction conditions, operational



Scheme 2. TPAP/NMO catalyzed synthesis of pyrazolylpyridines **2c**.

simplicity, fast, and cleaner reaction profiles, and high yields all of which make it an attractive strategy for the preparation of pyrazolylpyridines. Furthermore, the range of usefulness of TPAP/NMO in organic synthetic application has also been extended. This simple experimental procedure, offers an alternative route to synthesis of biologically active pyrazole derivatives.

4. Experimental section

4.1. General

Melting points were recorded on a Concord melting point apparatus and are uncorrected. Analytical TLC was performed on precoated sheets of silica gel G of 0.25 mm thickness containing PF_{254} indicator (Merck, Darmstadt). Catalyst was purchased from Aldrich and used as such. All the Hantzsch 1,4-DHPs needed for oxidation were using a reported procedure[30] and purified by column chromatography before subjecting to dehydrogenation. Known pyridine derivatives were analyzed by spectroscopic techniques and compared with reported methods. Column chromatography was performed with silica gel (100–200 mesh, Merck). Elemental analyses were done in VarioMicro analyzer. The Fourier-transform infrared (FT-IR) spectra of the products were recorded on a Thermo NICOLET AVATAR 360 spectrometer. NMR spectra were obtained on a JEOL 300 and 400 MHz spectrometer. NMR was recorded in $CDCl_3$, DMSO-d_6, and the chemical shifts are given in δ.

4.2. General procedure for the synthesis of pyrazolylpyridines 2a–i

To a solution of pyrazolyl 1,4-DHPs (**1a**, 200 mg, 0.422 mmol, 1 equiv) in DCM/acetonitrile [1:1] (10 mL), TPAP (8 mg, 0.021 mmol), and NMO (5 mg, 0.04 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C for the time indicated in Table 1. After complete conversion, as indicated by TLC, the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (30% EtOAc/hexane) gave the *title compound* **2a**. All the products were characterized by spectroscopic techniques.

*4.2.1. 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3-(3-methoxy phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2a**).* (181 mg, 91%) as a white solid; mp 129–130 °C; [found: C, 68.70; H, 5.29; N, 8.97. $C_{27}H_{25}N_3O_5$ requires C, 68.78; H, 5.34; N, 8.91%]; *m*/*z* 472.2 (M); ν_{max} (neat) 2997, 2945, 2843, 1728, 1614, 1554, 1503, 1463, 1435, 1341, 1283, 1236, 1198, 1104, 1070, 1032, 957, 857, 793, 748, 721, 680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.94 (1H, s, pyrazole C=C*H*), 7.77 (2H, d, *J* 7.9 Hz, Ph), 7.49 (2H, t, *J* 8.0 Hz, Ph), 7.34 (1H, d, *J* 7.3 Hz, Ph), 7.22–7.20 (1H, m, Ph), 7.08–7.06 (2H, m, Ph), 6.88 (1H, t, *J* 6.0 Hz, Ph), 3.72 (3H, s, PhO*Me*), 3.51 (6H, s, CO_2*Me*), 2.58 (6H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 167.9, 159.4, 155.7, 150.5, 139.4, 138.2, 133.3, 129.4, 129.3, 127.5, 126.7, 120.0, 118.8, 115.6, 112.4, 55.0, 52.2, 23.1.

*4.2.2. 2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-(3-methoxy phenyl) 1-phenyl-pyrazol-4-yl)pyridine (**2b**).* Yield (179 mg, 90%) as a white solid; mp 98–99 °C; [found: C, 69.76; H, 5.79; N, 8.48. $C_{29}H_{29}N_3O_5$ requires C, 69.72; H, 5.85; N, 8.41%]; *m*/*z* 500.2 (M); ν_{max} (neat) 2975, 2926, 1722, 1613, 1572, 1503, 1463, 1437, 1375, 1341, 1284, 1227, 1206, 1100, 1035, 955, 893, 859, 789, 754, 731, 692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.92 (1H, s, pyrazole C=C*H*), 7.58 (2H, d, *J* 7.34 Hz, Ph), 7.48 (2H, t, *J* 8.1 Hz, Ph), 7.34 (1H, d, *J* 7.5 Hz, Ph), 7.20 (1H, d, *J* 7.8 Hz, Ph), 7.12–7.08 (2H, m, Ph), 6.89 (1H, d, *J* 7.5 Hz, Ph), 4.07–3.92 (4H, m, CO_2CH_2Me), 3.71 (3H, s, PhO*Me*), 2.60 (6H, s, *Me*), 0.93 (6H, t, *J* 7.1 Hz, CO_2CH_2*Me*); δ_C (75 MHz, $CDCl_3$) 167.3, 159.4, 155.6, 150.4, 139.5, 138.1, 133.3, 129.4, 129.3, 127.9, 127.8, 126.7, 119.9, 115.8, 114.3, 112.2, 61.4, 55.0, 23.0, 13.4.

*4.2.3. 2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-(4-methyl sulfonyl phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2c**).* Yield (190 mg, 90%) as a off white solid; mp 158–159 °C; [found: C, 63.52; H, 5.40; N, 7.74; S, 5.82. $C_{29}H_{29}N_3O_6S$ requires C, 63.60; H, 5.34; N, 7.67; S, 5.86%] *m*/*z* 548.2 (M); ν_{max} (neat) 2983, 2922, 2852, 1722, 1596, 1561, 1500, 1442, 1406, 1379, 1340, 1306, 1235, 1206, 1146, 1111, 1089, 1067, 1035, 1006, 958, 906, 854, 777, 755, 730, 687, 656, 625, 559 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.94 (1H, s, pyrazole C=C*H*), 7.89 (2H, d, *J* 8.5 Hz, Ph), 7.76–7.74 (4H, m, Ph), 7.51 (2H, t, *J* 8.3 Hz, Ph), 7.37 (1H, t, *J* 7.5 Hz, Ph), 4.07–3.91 (4H, m, CO_2CH_2Me), 2.93 (3H, s, O_2S*Me*), 2.62 (6H, s, *Me*), 0.91 (6H, t, *J* 7.1 Hz, CO_2CH_2*Me*); δ_C (100 MHz, $CDCl_3$) 167.1, 155.9, 148.5, 139.6, 137.8, 137.3, 129.6, 128.4, 127.9, 127.8, 127.4, 127.2, 119.0, 116.3, 61.4, 44.4, 23.0, 13.5.

*4.2.4. 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3-(4-chloro-3-nitro-phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2d**).* Yield (183 mg, 92%) as a white solid; mp 150–151 °C; [found: C, 59.98; H, 4.15; N, 10.62. $C_{26}H_{21}ClN_4O_6$ requires 59.95; H, 4.06; N, 10.76%]; *m*/*z* 521.2 (M); ν_{max} (neat) 2923, 1731, 1597, 1540, 1500, 1435, 1361, 1278, 1232, 1204, 1105, 1034, 960, 909, 859, 830, 800, 747, 688, 549 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.20 (1H, d, *J* 1.7 Hz, Ph), 7.94 (1H, s, pyrazole C=C*H*), 7.76 (2H, d, *J* 8.2 Hz, Ph), 7.52 (3H, t, *J* 8.1 Hz, Ph), 7.45 (1H, d, *J* 8.4 Hz, Ph), 7.40–7.38 (1H, m, Ph), 3.55 (6H, s, CO_2*Me*), 2.61 (6H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 167.6, 156.1, 147.9, 147.3, 139.0, 136.9, 132.5, 131.7, 131.3, 129.6, 128.0, 127.6, 127.3, 126.0, 123.9, 118.9, 115.6, 52.3, 23.0.

*4.2.5. 2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-(4-chloro-3-nitro phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2e**).* Yield (179 mg, 90%) as a off white solid; mp 126–128 °C; [found: C, 61.18; H, 4.54; N, 10.27. $C_{28}H_{25}ClN_4O_6$ requires C, 61.26; H, 4.59; N, 10.21%]; *m*/*z* 549.2 (M); ν_{max} (neat) 2977, 2929, 1737, 1716, 1596, 1579, 1540, 1500, 1463, 1435, 1409, 1369, 1347, 1276, 1227, 1100, 1035, 960, 908, 860, 838, 752, 723, 687, 600 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, d, *J* 2.4 Hz, Ph), 7.94 (1H, s, pyrazole C=C*H*), 7.53 (2H, d, *J* 7.8 Hz, Ph), 7.57–7.49 (3H, m, Ph), 7.46 (1H, d, *J* 8.4 Hz, Ph), 7.38 (1H, t, *J* 7.3 Hz, Ph), 4.08–3.98 (4H, m, CO_2CH_2Me), 2.62 (6H, s, *Me*), 0.94 (6H, t, *J* 7.1 Hz, CO_2CH_2*Me*); δ_C (100 MHz, $CDCl_3$) 167.1, 156.1, 148.1, 147.3, 139.2, 136.8, 132.6, 131.7, 131.2, 129.6, 128.4, 127.9, 127.4, 126.1, 123.9, 119.1, 116.0, 61.5, 23.0, 13.5.

*4.2.6. 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3-(2-nitro phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2f**).* Yield (187 mg, 94%) as a white solid; mp 159–160 °C; [found: C, 64.17; H, 4.50; N, 11.57. $C_{26}H_{22}N_4O_6$ requires C, 64.19; H, 4.56; N, 11.52%]; *m*/*z* 487.2 (M); ν_{max} (neat) 2971, 2932, 2897, 2855, 1724, 1628, 1558, 1496, 1449, 1427, 1369, 1321, 1296, 1223, 1172, 1134, 1099, 1038, 1013, 988, 877, 831, 741, 702, 602 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.70 (1H, s, Ph), 7.93 (1H, s, pyrazole C=C*H*), 7.79 (2H, d, *J* 8.4 Hz, Ph), 7.58–7.52 (4H, m, Ph), 7.37 (1H, t, *J* 6.88 Hz, Ph), 7.17–7.16 (1H, m, Ph), 3.55 (6H, s, CO_2*Me*), 2.46 (6H, s, *Me*); δ_C (100 MHz, DMSO-d_6) 148.6, 145.6, 139.0, 136.4, 132.2, 129.8, 129.7, 129.5, 128.7, 127.6, 127.1, 124.6, 124.1, 118.1, 116.2, 52.4, 22.6.

*4.2.7. 2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-(2-nitrophenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2g**).* Yield (183 mg, 92%) as an off white solid; mp 127–128 °C; [found: C, 65.29; H, 5.01; N, 10.94. $C_{28}H_{26}N_4O_6$ requires C, 65.36; H, 5.09; N, 10.89%]; *m*/*z* 515.2 (M); ν_{max} (neat) 3076, 2947, 1730, 1598, 1559, 1503, 1455, 1432, 1396, 1306, 1277, 1227, 1103, 1067, 1035, 966, 958, 934, 892, 810, 749, 682,

575 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 7.98 (1H, s, pyrazole C=C*H*), 7.78 (1H, d, *J* 15.0 Hz, Ph), 7.63 (2H, d, *J* 5.8 Hz, Ph), 7.52–7.40 (4H, m, Ph), 7.39–7.28 (2H, m, Ph), 4.25–4.01 (4H, m, CO_2CH_2Me), 2.58 (6H, s, *Me*), 1.01 (6H, t, *J* 7.1 Hz, CO_2CH_2Me); δ_C (75 MHz, $CDCl_3$) 167.5, 149.2, 147.0, 144.0, 139.7, 132.8, 131.8, 129.6, 129.1, 128.4, 127.8, 126.5, 126.1, 123.8, 118.7, 102.7, 50.8, 29.7, 19.3.

*4.2.8. 2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(3-(4-chloro phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2h**).* Yield (179 mg, 90%) as a white solid; [found: C, 65.68; H, 4.61; N, 8.87. $C_{26}H_{22}ClN_3O_4$ requires C, 65.62; H, 4.66; N, 8.83; mp 144–145 °C; ν_{max} (neat) 2950, 2924, 2851, 1730, 1598, 1579, 1558, 1498, 1435, 1402, 1371, 1336, 1278, 1229, 1104, 1064, 1036, 958, 862, 833, 753, 730, 686 cm^{-1}; *m*/*z* 476.2 [M]; δ_H (300 MHz, $CDCl_3$) 7.92 (1H, s, pyrazole C=C*H*), 7.75 (2H, d, *J* 7.8 Hz, Ph), 7.47–7.44 (4H, m, Ph), 7.29–7.27 (3H, m, Ph), 3.51 (6H, s, CO_2Me), 2.59 (6H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 167.8, 155.8, 149.5, 139.3, 137.8, 134.0, 130.7, 129.5, 129.4, 128.6, 128.5, 127.7, 126.8, 118.8, 115.5, 52.2, 23.1.

*4.2.9. 2,6-Dimethyl-3,5-diethoxycarbonyl-4-(3-(4-chloro phenyl)-1-phenyl-pyrazol-4-yl)pyridine (**2i**).* Yield (185 mg, 93%) as a white solid; mp 101–102 °C; [found: C, 66.67; H, 5.25; N, 8.27. $C_{28}H_{26}ClN_3O_4$ requires C, 66.73; H, 5.20; N, 8.34%]; *m*/*z* 504.2 (M); ν_{max} (neat) 2982, 2899, 2361, 1716, 1559, 1502, 1441, 1413, 1379, 1339, 1296, 1238, 1205, 1091, 1039, 1007, 956, 863, 831, 754, 730, 691 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 8.63 (1H, s, pyrazole C=C*H*), 7.90 (2H, d, *J* 7.9 Hz, Ph), 7.52 (2H, t, *J* 7.9 Hz, Ph), 7.44–7.41 (4H, m, Ph), 7.35 (1H, t, *J* 7.2 Hz, Ph), 3.97–3.87 (4H, m, CO_2CH_2Me), 2.49 (6H, s, *Me*), 0.80 (6H, t, *J* 7.0 Hz, CO_2CH_2Me); δ_C (75 MHz, DMSO-d_6) 166.9, 155.6, 148.9, 139.4, 138.1, 133.3, 131.3, 130.1, 129.0, 128.9, 128.0, 127.2, 118.6, 115.8, 61.6, 23.1, 13.6.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.040.

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