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A new protocol to synthesize 1,4-dihydropyridines by using 3,4,5-trifluorobenzeneboronic acid as a catalyst in ionic liquid: synthesis of novel 4-(3-carboxyl-1*H*-pyrazol-4-yl)-1,4-dihydropyridines

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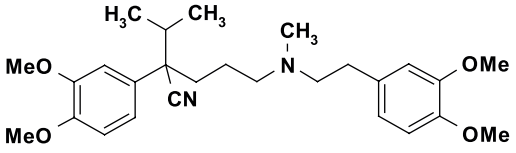
Abstract—3,4,5-Trifluorobenzeneboronic acid catalysed, ionic liquid mediated facile synthesis of 4-pyrazolyl 1,4-dihydropyridines at room temperature by the cyclocondensation of ethyl 3-aminocrotonate, pyrazole aldehyde and a β-keto ester is reported. The procedure adopted was found to be eco-benign, facile at room temperature and better than the conventional, [bmim]Cl mediated and $InCl_3$ catalysed, [bmim]Cl mediated 1,4-dihydropyridine syntheses.

1. Introduction

4-Aryl-l,4-dihydropyridines form a major class of drugs used in the management of cardiovascular diseases.[1,2] Baraldi et al. have explored the less common hetero aryl dihydropyridines for the calcium channel activity.[3,4]

Development of drug resistance, both intrinsic drug resistance and acquired drug resistance, remains a clinical obstacle in the chemotherapy of many cancers.[5,6] Among the possible resistance modifiers, the dihydropyridines (DHPs), calcium antagonists, have been studied extensively as the analogue of verapamil (VP) **1**.[7] The finding that the enantiomer of verapamil and nigludipine lacks calcium antagonistic activity but still has MDR reversal activity indicated that the MDR reversal activity is independent of the calcium antagonistic activity.[8,9] It was proposed by Tanabe et al. that NIK-250, **2** which possess a heterocyclic ring at the 4-postion can overcome MDR and has moderate calcium antagonistic activity in vitro without optical resolution.[10–14] Further, it was observed that imidazothiazole derivatives could potentiate the MDR reversal activity without significant side effects observed for 1,4-dihydropyridine derivatives.[15] Baraldi et al. during their exploration on the calcium antagonist activity revealed that pyrazolyl and imidazolyl 1,4-dihydropyridines exhibit weak calcium antagonist activity.[16] Manfredini et al.[17] have shown pyrazole nucleosides as potential analogues of ribavirin[18] in antitumor activity.



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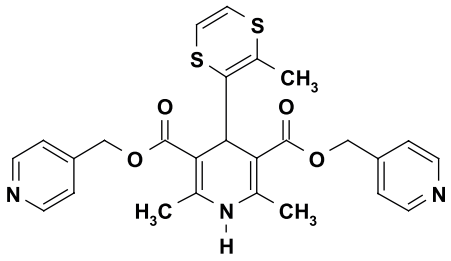

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Our interest was to synthesize 4-[3-ethoxycarbonyl-1*H*-pyrazol-4-yl]-1,4-dihydro-pyridine dicarboxylates in which the pyrazole-3-ester moiety mimic the one in pyrazole nucleoside reported by Manfredini et al. We expect these compounds to show weak calcium antagonist but high MDR

Keywords: 1,4-Dihydropyridines; 3,4,5-Trifluorobenzeneboronic acid; Ionic liquid; 4-(3-Carboxyl-1H-pyrazol-4-yl)-1,4-dihydropyridines; Vilsmeier reagent.
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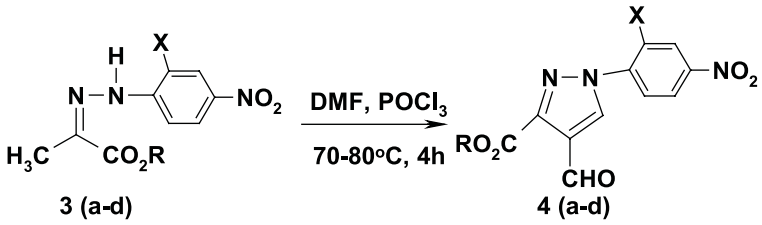


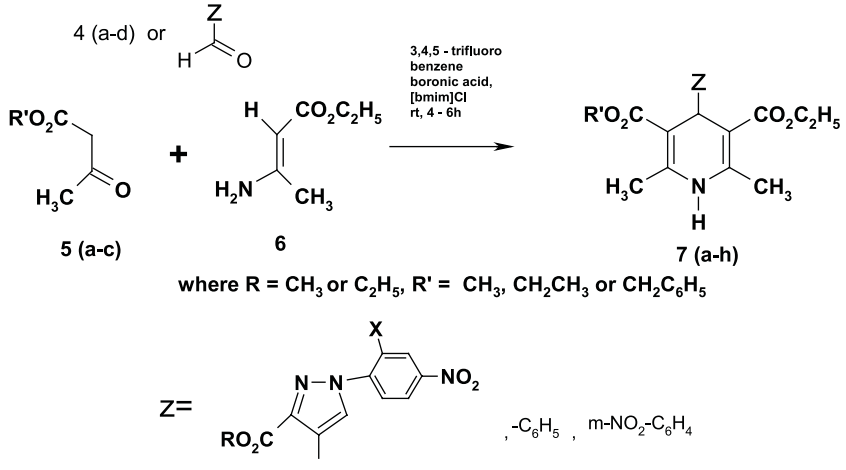
Scheme 1. Synthesis of alkyl-1(2,4-dinitrophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate.

Table 1. Synthesis of 1*H*-pyrazole-3-carboxylic acid esters

Entry	X	R	Time (h)	Yield (%)
4a	H	CH_3	4	85
4b	NO_2	CH_3	4	79
4c	H	C_2H_5	4	88
4d	NO_2	C_2H_5	4	80

reversal activity. The original Hantzsch[19] dihydropyridine synthesis consisted of the reaction of ethyl acetoacetate (2 equiv) with an aldehyde and ammonia. This method has been widely used for the preparation of the 1,4-dihydropyridine where the substitution at the fourth position is an aliphatic,[20] aromatic[21] or heterocyclic[22] residue. Enamines could replace ethyl acetoacetate and could serve as an ammonia source paving way to a series of 1,4-dihydropyridines of medicinal interest.[23] Microwave-assisted synthesis of dihydropyridines[24] was reported advantageous since it accelerates the reaction rate. A solid-phase synthesis of dihydropyridines was also demonstrated.[25] Conventional Hantzsch dihydropyridine syntheses generally involve organic solvents like methanol and acetic acid. Ionic liquid because of its polarity, negligible vapor pressure, recyclability, high thermal stability and immiscibility with a number of organic solvents has attracted much interest from synthetic chemists.[26] In continuation of our work on the synthesis of 1*H*-Pyrazole-4-carboxylates[27] using Vilsmeier methodology, we synthesized 4-formyl-1*H*-pyrazole-3-carboxylates[17b] **4**(**a**–**d**) (Scheme 1) from alkyl pyruvate 4-nitro or 2,4-dinitro phenyl hydrazones **3**(**a**–**d**) upon treatment with 8 equiv of DMF/$POCl_3$ (Table 1).

We have attempted the pyrazolyl dihydropyridines synthesis by using ionic liquid medium at room temperature. During the earlier attempts[28] to synthesise dihydropyridines by condensing an aldehyde, β-ketoester and methyl 3-aminocrotonate using [bmim]PF_6 and [bmim]BF_4 as the reaction media, it was observed that [bmim]Cl was unsuccessful. When we attempted the synthesis of 4-[3-ethoxycarbonyl-1H-pyrazol-4-yl]-1,4-dihydro-pyridine dicarboxylates in [bmim]Cl the reaction was facile with ethyl 3-aminocrotonate, pyrazole aldehydes and a β-keto ester. The reason may be attributed to the substrate effect that can contribute to the formation of the product dihydropyridine in moderate to good yields. The remaining ionic liquid was thoroughly washed with ethyl acetate after completion of the reaction (monitored by TLC) and recycled in subsequent reactions. Second and third reactions using recovered ionic liquid afforded similar yields to those obtained in the first run. In the fourth and fifth runs, the yields steadily decreased. That is in the case of pyrazole aldehyde **4d**, ethyl acetoacetate and ethyl 3-aminocrotonate in [bmim]Cl, the yields of **7e** obtained were 51, 50, 50, 48, 47 in five successive runs. However, the activity of ionic liquid was consistent and no decrease in yield was observed when the recycled ionic liquid was activated at 80 °C under vacuum in each cycle. In order to increase the yield of the dihydropyridine obtained through [bmim]Cl mediated synthesis we added 5 mol% of $InCl_3$ or 5 mol% of 3,4,5-trifluorobenzeneboronic acid (Scheme 2) to the reaction



Scheme 2. Synthesis of pyrazolyl dihydropyridines.

Table 2. Ionic liquid mediated synthesis of symmetrical and unsymmetrical dihydropyridines catalysed by 3,4,5-trifluorobenzene boronic acid

Entry	Aldehyde (Z-CHO)	Ester (R′)	Product	Time (h)	Yield (%)
1	**4a**	$-CH_3$	**7a**	6	92
2	**4a**	$-CH_2\ CH_3$	**7b**[31]	5	86
3	**4c**	$-CH_3$	**7c**	4	87
4	**4c**	$-CH_2\ CH_3$	**7d**	4	91
5	**4d**	$-CH_2\ CH_3$	**7e**	5	85
6	**4c**	$-CH_2\ C_6H_5$	**7f**	4	87
7	Benzaldehyde	$-CH_2\ CH_3$	**7g**	4	90
8	*m*-Nitro-benzaldehyde	$-CH_2\ CH_3$	**7h**	5	93

The compounds gave satisfactory spectral and elemental analysis value. Furthermore the structure of compound **7b** was confirmed by X-ray crystallographic study (Fig. 1).[31]

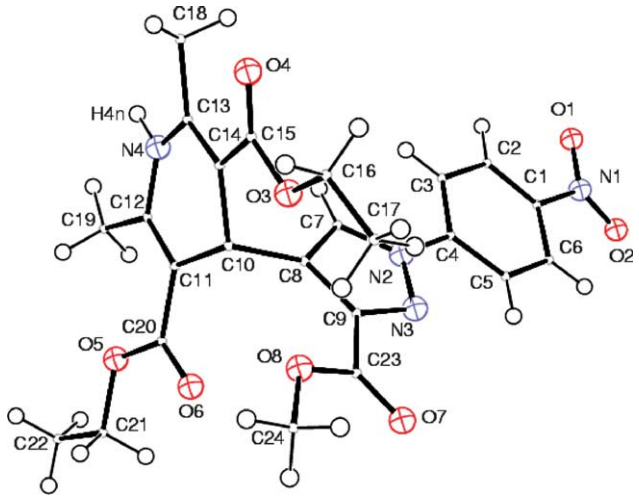


Figure 1. The ORTEP[31] view of 4-[3-methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, **7b** showing 30% probability displacement ellipsoids and the atom numbering scheme.

mixture and found that the yield obtained increased considerably (Table 2).

The stability of boronic acids to air and moisture and their relatively low toxicity (benzeneboronic acid:[29] LD_{50}, oral-rat = 740 mg/kg), have enthused us to employ 3,4,5-trifluorobenzeneboronic acid[30] as a catalyst in dihydropyridine synthesis.

The increase in yield might be due to increase in the acidity of the reaction mixture, which contributes to the product yield. Both the catalyst and [bmim]Cl recovered after the reaction are recyclable. The yield decreases during successive runs with the recovered ionic liquid-catalyst mixture but further addition of 5 mol% of catalyst to the reaction mixture ensures excellent yield of the product. Further we found that the formation of dihydropyridine in exceptional yields was feasible with other aromatic aldehydes also. The following comparison (Table 3) clearly indicates the versatility of 3,4,5-trifluorobenzeneboronic acid catalysed [bmim]Cl mediated synthesis over the other methods adopted for the synthesis of dihydropyridines.

Table 3. Comparison of dihydropyridine syntheses (synthesis of 7e)

Reaction condition	Time (h)	Yield (%)
Reflux in ethanol (Δ)	8	48
[bmim]Cl (rt)	6	51
[bmim]Cl + boronic acid	5	85
[bmim]Cl + $InCl_3$	6	80

In summary, we have developed a mild, simple and environmentally benign protocol for the synthesis of dihydropyridines in ionic liquid media using 3,4,5-trifluorobenzeneboronic acid as catalyst. We hope the pyrazolyl dihydropyidines we have synthesized to show MDR reversal activity, exploration of which would be our ultimate goal.

2. Experimental

2.1. General procedure for the preparation 1*H*-pyrazole-3-carboxylates

1.4 g of $POCl_3$ (0.008 mol) was added drop wise to an ice-cold stirred solution of ethyl pyruvate 2,4-dinitrophenyl hydrazone (0.001 mol) in 10 mL dry DMF. The reaction mixture was allowed to attain room temperature and then refluxed at 70–80 °C for about 4 h. The resulting mixture was poured onto crushed ice, neutralized with sodium acetate and left standing overnight. The pale yellow precipitate obtained was purified by silica gel (60–120 mesh) column chromatography with ethyl acetate–petroleum ether mixture (15:85) to yield the product.

2.1.1. Methyl-1(4-nitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4a. Yellow crystals (15% ethyl acetate: petroleum ether); mp 214 °C; IR (KBr) cm^{-1}: 3123, 2919, 2882, 1716, 1677, 1595, 1529, 1340, 1262, 857; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.46 (s, 1H, formyl –CH), 8.62 (s, 1H Pyrazole –CH), 8.40–8.42 (d, J = 9.2 Hz, 2H), 7.99–8.01 (d, J = 9.2 Hz, 2H), 4.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.2, 161.5, 147.4, 145.1, 142.8, 130.5, 126.6, 125.6, 120.6, 53.1; MS (*m*/*z*): 275 (M^+); Anal. Calcd for $C_{12}H_9N_3O_5$: C, 52.37; H, 3.30; N, 15.27; Found: C, 52.42; H, 3.28; N, 15.38.

2.1.2. Methyl-1(2,4-dinitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4b. Yellow crystals (15% ethyl acetate: petroleum ether); mp 138 °C; IR (KBr) cm^{-1}: 3120, 2958, 2888, 1727, 1684, 1611, 1541, 1348, 1257, 836, 743; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.43 (s, 1H, formyl –CH), 8.87–8.88 (d, J_1 = 2.3 Hz, 1H), 8.61–8.63 (dd, J_1 = 2.3 Hz, J_2 = 8.6 Hz, 1H), 8.39 (s, 1H, Pyrazole –CH), 7.92–7.93 (d, J_2 = 8.6 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 185.9, 161.1, 144.3, 147.8, 145.7, 136.5, 134.1,

128.7, 128.4, 126.5, 121.6, 53.1; MS (*m/z*): 320 (M^+); Anal. Calcd for $C_{12}H_8N_4O_7$: C, 45.01; H, 2.52; N, 17.50; Found: C, 44.92; H, 2.58; N, 17.56.

2.1.3. Ethyl-1(4-nitrophenyl)-4-formyl-1H-pyrazole-3-carboxylate, 4c. Yellow crystals (15% ethyl acetate: petroleum ether); mp 148 °C; IR (KBr) cm^{-1}: 3130, 2992, 2889, 1714, 1681, 1596, 1528, 1342, 1258, 856, 750; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.45 (s, 1H, formyl –CH), 8.62 (s, 1H, Pyrazole –CH), 8.39–8.41 (d, $J=9.2$ Hz, 2H), 8.00–8.01 (d, $J=9.2$ Hz, 2H), 4.51–4.55 (q, $J=7.5$ Hz, 2H), 1.46–1.49 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.3, 161.1, 147.3, 145.5, 142.8, 130.5, 126.5, 125.6, 120.6, 62.4, 14.4; MS (*m/z*): 289 (M^+); Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53; Found: C, 53.92; H, 3.81; N, 14.64.

2.1.4. Ethyl-1(2,4-dinitrophenyl)-4-formyl-1*H*-pyrazole-3-carboxylate, 4d. Yellow crystals (15% ethyl acetate: petroleum ether); mp 130 °C; IR (KBr) cm^{-1}: 3330, 3122, 3079, 2999, 2890, 1734, 1686, 1610, 1551, 1351, 1268, 1242, 1109, 742, 629; ^1H NMR (500 MHz, $CDCl_3$) δ: 10.45 (s, 1H, formyl –CH), 8.87–8.88 (d, $J_1=2.3$ Hz, 1H), 8.61–8.63 (dd, $J_1=2.3$ Hz, $J_2=8.6$ Hz, 1H), 8.36 (s, 1H Pyrazole –CH), 7.91–7.93 (d, $J_2=8.6$ Hz, 1H), 4.47–4.51 (q, $J=7.5$ Hz, 2H), 1.42–1.45 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 186.0, 160.6, 147.7, 146.1, 144.3, 136.6, 134.0, 128.7, 128.3, 126.5, 121.6, 62.6, 14.3; MS (*m/z*): 334 (M^+); Anal. Calcd for $C_{13}H_{10}N_4O_7$: C, 46.70; H, 3.02; N, 16.77; Found: C, 46.75; H, 3.06; N, 16.58.

2.2. General procedure for $InCl_3$ or 3,4,5-trifluorobenzeneboronic acid catalyzed synthesis of symmetrical and unsymmetrical dihydropyridines in ionic liquid at room temperature

0.72 g (2.5 mmol, 1 equiv) of pyrazole aldehyde **4c**, 0.33 g (2.5 mmol, 1 equiv) of ethyl acetoacetate, 0.32 g (2.5 mmol, 1 equiv) of ethyl 3-aminocrotonate were mixed with 2 grams of bmimCl and stirred after adding 5 mol% of $InCl_3$ or 5 mol% 3,4,5-trifluorobenzeneboronic acid for about six hours. Then the mixture was extracted with ethyl acetate and column chromatographed with 15% ethyl acetate–petroleum ether (bp. 60–80 °C) mixture to get pure yellow colored 4-[3-ethoxycarbonyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester **7d** in excellent yield. The remaining ionic liquid-catalyst mix was thoroughly washed with ethyl acetate and recycled for subsequent reactions.

2.2.1. 4-[3-Methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester, 7a. Yellow crystals (15% ethyl acetate:petroleum ether); mp 228 °C; IR (KBr) cm^{-1}: 3318, 2986, 1707, 1650, 1494, 1340, 1221, 855, 749; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.28–8.30 (d, $J=9.2$ Hz, 2H), 7.86–7.87 (d, $J=9.2$ Hz, 2H), 7.83 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.58 (s, 1H), 4.03–4.09 (m, 2H), 3.98 (s, 3H), 3.59 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 1.16–1.19 (t, $J=8.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.9, 167.5, 162.6, 146.1, 144.0, 143.9, 143.8, 143.3, 135.2, 128.6, 125.3, 119.5, 104.3, 104.1, 60.1, 52.1, 51.1, 29.7, 19.7, 19.6, 14.3; MS (*m/z*): 484 (M^+); Anal. Calcd for $C_{23}H_{24}N_4O_8$: C, 57.02; H, 4.99; N, 11.56; Found: C, 57.12; H, 5.04; N, 11.58.

2.2.2. 4-[3-Methoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7b. Yellow crystals (15% ethyl acetate:petroleum ether); mp 212 °C; IR (KBr) cm^{-1}: 3338, 3093, 2982, 1728, 1689, 1494, 1339, 1216, 1099, 854, 750; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.27–8.29 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.86 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.61 (s, 1H), 4.03–4.09 (m, 4H), 3.97 (s, 3H), 2.31 (s, 6H), 1.16–1.19 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.5, 162.5, 146.0, 143.9, 143.8, 143.3, 135.3, 128.7, 125.3, 119.4, 104.3, 60.0, 52.1, 29.7, 19.7, 14.3; MS (*m/z*): 498 (M^+); Anal. Calcd for $C_{24}H_{26}N_4O_8$: C, 57.83; H, 5.26; N, 11.24; Found: C, 57.94; H, 5.31; N, 11.13.

2.2.3. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-ethyl ester 5-methyl ester, 7c. Yellow crystals (15% ethyl acetate:petroleum ether); mp 202 °C; IR (KBr) cm^{-1}: 3336, 3094, 2982, 1720, 1690, 1495, 1339, 1217, 1098, 855, 750; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.27–8.29 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.82 (s, 1H, pyrazole –CH), 5.79 (brs, 1H), 5.59 (s, 1H), 4.44–4.48 (q, $J=7.5$ Hz, 2H), 4.05–4.09 (q, $J=7.5$ Hz, 2H), 3.59 (s, 3H), 2.32 (s, 3H), 2.30 (s, 3H), 1.44–1.47 (t, $J=7.5$ Hz, 3H), 1.15–1.18 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.9, 167.5, 162.3, 146.0, 144.0, 143.8, 143.7, 143.6, 135.1, 128.5, 125.3, 119.4, 104.4, 104.2, 61.2, 60.0, 51.1, 29.7, 19.7, 19.6, 14.5, 14.4; MS (*m/z*): 498 (M^+); Anal. Calcd for $C_{24}H_{26}N_4O_8$: C, 57.83; H, 5.26; N, 11.24; Found: C, 57.88; H, 5.11; N, 11.29.

2.2.4. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7d. Yellow crystals (15% ethyl acetate:petroleum ether); mp 224 °C; IR (KBr) cm^{-1}: 3334, 3090, 2990, 1722, 1693, 1492; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26–8.28 (d, $J=9.2$ Hz, 2H), 7.86–7.88 (d, $J=9.2$ Hz, 2H), 7.85 (s, 1H, pyrazole –CH), 5.83 (brs, 1H), 5.61 (s, 1H), 4.42–4.47 (q, $J=7.5$ Hz, 2H), 4.04–4.09 (q, $J=7.5$ Hz, 4H), 2.30 (s, 6H), 1.43–1.46 (t, $J=7.5$ Hz, 3H), 1.15–1.18 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.6, 162.2, 146.0, 143.9, 143.7, 143.7, 135.2, 128.6, 125.3, 119.4, 104.3, 61.1, 60.0, 29.7, 19.7, 14.4, 14.4; MS (*m/z*): 513 (M^+); Anal. Calcd for $C_{25}H_{28}N_4O_8$: C, 58.59; H, 5.51; N, 10.93; Found: C, 58.54; H, 5.48; N, 11.02.

2.2.5. 4-[3-Ethoxycarbonyl-1-(2,4-dinitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester, 7e. Yellow crystals (15% ethyl acetate:petroleum ether); mp 88 °C; IR (KBr) cm^{-1}: 3344, 3092, 2984, 1726, 1690, 1545, 1348, 1216, 1098, 912, 739; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.63–8.64 (d, $J_1=2.3$ Hz, 1H), 8.43–8.45 (dd, $J_1=2.3$ Hz, $J_2=8.6$ Hz, 1H), 7.86–7.88 (d, $J_2=8.6$ Hz, 1H), 7.60 (s, 1H, pyrazole –CH), 6.32 (brs, 1H), 5.49 (s, 1H), 4.35–4.39 (q, $J=7.5$ Hz, 2H), 3.98–4.09 (m, 4H), 2.22 (s, 6H), 1.36–1.39 (t, $J=7.5$ Hz, 3H), 1.12–1.15 (t, $J=7.5$ Hz, 6H); ^{13}C NMR (125 MHz,

$CDCl_3$, ppm): δ 167.6, 161.9, 146.1, 144.7, 144.3, 143.4, 137.2, 135.5, 131.3, 127.6, 127.1, 121.1, 103.7, 61.2, 59.9, 29.7, 19.3, 18.4, 14.3; MS (*m*/*z*): 558 (M^+); Anal. Calcd for $C_{25}H_{27}N_5O_{10}$: C, 53.86; H, 4.88; N, 12.56; Found: C, 53.80; H, 4.92; N, 12.62.

2.2.6. 4-[3-Ethoxycarbonyl-1-(4-nitrophenyl)-1*H*-pyrazol-4-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid 3-benzyl ester 5-ethyl ester, 7f. Yellow crystals (15% ethyl acetate:petroleum ether); mp 138 °C; IR (KBr) cm^{-1}: 3337, 3093, 2981, 1725, 1694, 1494, 1216, 1113, 855, 749; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.26–8.28 (d, $J=9.2$ Hz, 2H), 7.77–7.79 (d, $J=9.2$ Hz, 2H), 7.74 (s, 1H, pyrazole –CH), 7.21–7.27 (m, 5H), 5.80 (brs, 1H), 5.60 (s, 1H), 5.02–5.11 (q, $J=16.0$ Hz, 2H), 4.35–4.26 (m, 2H), 4.03–4.07 (q, $J=7.5$ Hz, 2H), 2.30 (s, 3H), 2.29 (s, 3H), 1.33–1.36 (t, $J=7.5$ Hz, 3H), 1.14–1.17 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.5, 167.3, 162.2, 146.0, 144.6, 143.9, 143.6, 136.7, 134.3, 128.7, 128.5, 128.1, 127.9, 125.2, 119.4, 104.0, 103.3, 65.7, 61.1, 60.0, 30.2, 19.9, 19.8, 14.4; MS (*m*/*z*): 575 (M^+); Anal. Calcd for $C_{30}H_{30}N_4O_8$: C, 62.71; H, 5.26; N, 9.75; Found: C, 62.63; H, 5.32; N, 9.65.

2.2.7. 2,6-Dimethyl-3,5-dicarboethoxy-4-phenyl-1,4-dihydropyridine,[32] 7g. Yellow crystals (15% ethyl acetate: petroleum ether); mp 158 °C (lit. mp 158–159)[32b]; IR (KBr) cm^{-1}: 3322, 1676, 1633, 1595, 1529, 1102, 851; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 7.01–7.26 (m, 5H), 6.00 (brs, 1H), 4.98 (s, 1H), 4.08 (q, $J=8.2$ Hz, 4H), 2.29 (s, 6H), 1.21 (t, $J=7.7$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 168.2, 152.2, 148.3, 144.9, 128.6, 126.2, 103.8, 59.6, 39.5, 19.3, 14.3; MS (*m*/*z*): 329 (M^+); Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; Found: C, 69.21; H, 7.07; N, 4.31.

2.2.8. 2,6-Dimethyl-3,5-dicarboethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine,[32] 7h. Yellow crystals (15% ethyl acetate:petroleum ether); mp 164 °C (lit. mp 162–163);[32b] IR (KBr) cm^{-1}: 3328, 1674, 1633, 1590, 1529, 1105, 857; ^1H NMR (500 MHz, $CDCl_3$, ppm): δ 8.13 (s, 1H), 8.02 (d, $J=7.5$ Hz, 1H), 7.66 (d, $J=7.5$ Hz, 1H), 7.38 (d, $J=8.6$ Hz, 1H), 6.16 (brs, 1H), 5.10 (s, 1H), 4.10 (q, $J=7.8$ Hz, 4H), 2.36 (s, 6H), 1.24 (t, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 167.2, 150.0, 148.1, 145.0, 134.5, 128.6, 123.1, 121.3, 103.2, 60.0, 40.0, 19.5, 14.2; MS (*m*/*z*): 374 (M^+); Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48; Found: C, 60.81; H, 5.88; N, 7.62.

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