

Desymmetrizing Hantzsch pyridines via promoter-free benzylic C-H functionalization

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Dedicated to Xiyan Lu on the occasion of his 91st birthday

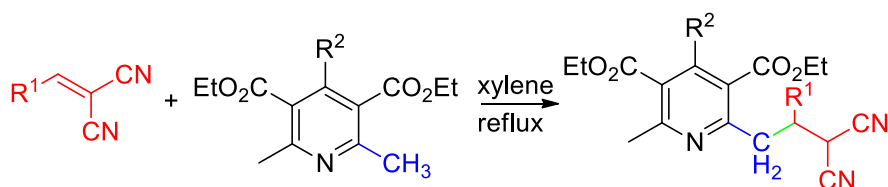
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Abstract

1,4-Dihydropyridines are an important class of calcium channel blockers. However, difficulties in the preparation of nonsymmetric Hantzsch esters impede further development in this area. Benzylic C-H functionalization of Hantzsch pyridines is an efficient approach to nonsymmetric Hantzsch pyridines. We herein report a promoter-free benzylic C-H functionalization of pyridines, which allows preparation of a variety of pyridines unsymmetrically substituted in the 2/6-positions. A plausible mechanism is proposed for this reaction. This work provides a new way to prepare unsymmetrical pyridines and enriches the scope of C-H functionalization of aza-arenes.



- No additive required
- 12 Examples
- Yield up to 97%

Keywords: Hantzsch pyridines, benzylic C-H functionalization, azaarenes, malononitriles

Introduction

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are important pharmaceuticals, which are well-known as dipines (calcium channel blockers) (Figure 1).¹⁻³ Interestingly, most are nonsymmetric 1,4-DHPs except for a few (*e.g.*, Nifedipine, which is symmetrical). The Hantzsch reaction⁴⁻⁷ is an efficient way to produce symmetric 1,4-DHPs. However, nonsymmetric 1,4-DHPs are not easy to be obtained via Hantzsch reaction directly, as an enamine has to be prepared beforehand.^{8,9} As it has been reported that polysubstituted pyridines can be reduced directly to the corresponding 1,4-dihydropyridines,¹⁰⁻¹² this gives rise to new approaches to nonsymmetric 1,4-dihydropyridines.

Recently, two research groups^{13,14} have reported that the direct benzylic C-H bond functionalization of azaarenes leads to nonsymmetric pyridines bearing cyano groups (CN), which have the potential to act as a chemical handle. We are very interested in applying these methods by direct benzylic C-H bond functionalization of Hantzsch pyridines to construct a variety of asymmetric Hantzsch pyridine derivatives, which, by themselves or after reduction to asymmetric 1,4-DHPs, might show antianginal, antiarrhythmic, or antihypertensive bioactivity.

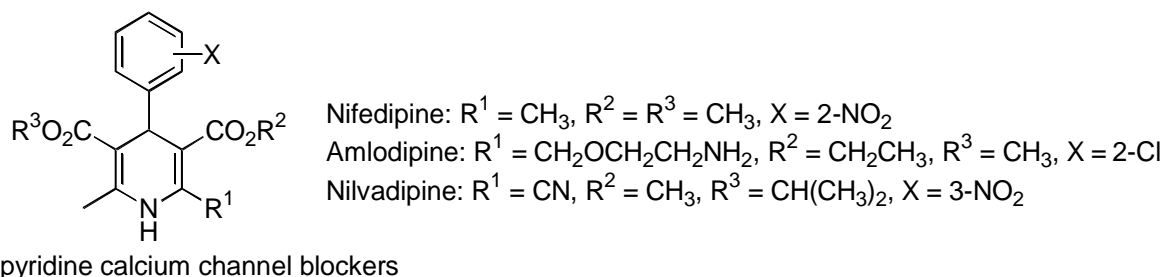
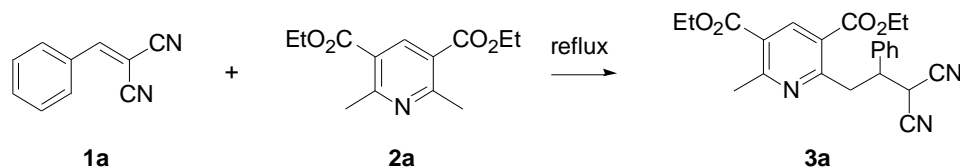


Figure 1. Representative 1,4-dihydropyridines as calcium channel blockers.

Results and Discussion

Initially, **1a** (2-benzylidenemalononitrile) and **2a** (Hantzsch pyridine) were both dissolved in PEG-400 and heated to 100 °C for 24 hr.¹⁴ However, no product was detected (Table 1, entry 1). Then if the mixture was suspended in H₂O and heated at 100 °C for 10 hr,¹³ the desired product **3a** could be obtained in 50 % yield (entry 2). To further optimize the reaction conditions, we carried out further trials. Under the condition of Pd/C (5 mol%) + TsOH (10 %) in MeOH under reflux for 20 hr, 59 % of the desired product was achieved (entry 3). When TsOH (10 %) was employed as acidic catalyst and toluene was used as solvent, **3a** was obtained in 60 % yield (entry 4). Interestingly, promoter-free conditions gave a slightly higher yield (entry 5). Therefore it seems that the promoter does not contribute much to the reaction; the reaction temperature is the important factor. Under promoter-free conditions we tried three different solvents at reflux. It turned out that refluxing in xylene for 10 hr gave the best results (88 % in 10 hr). See Table 1.

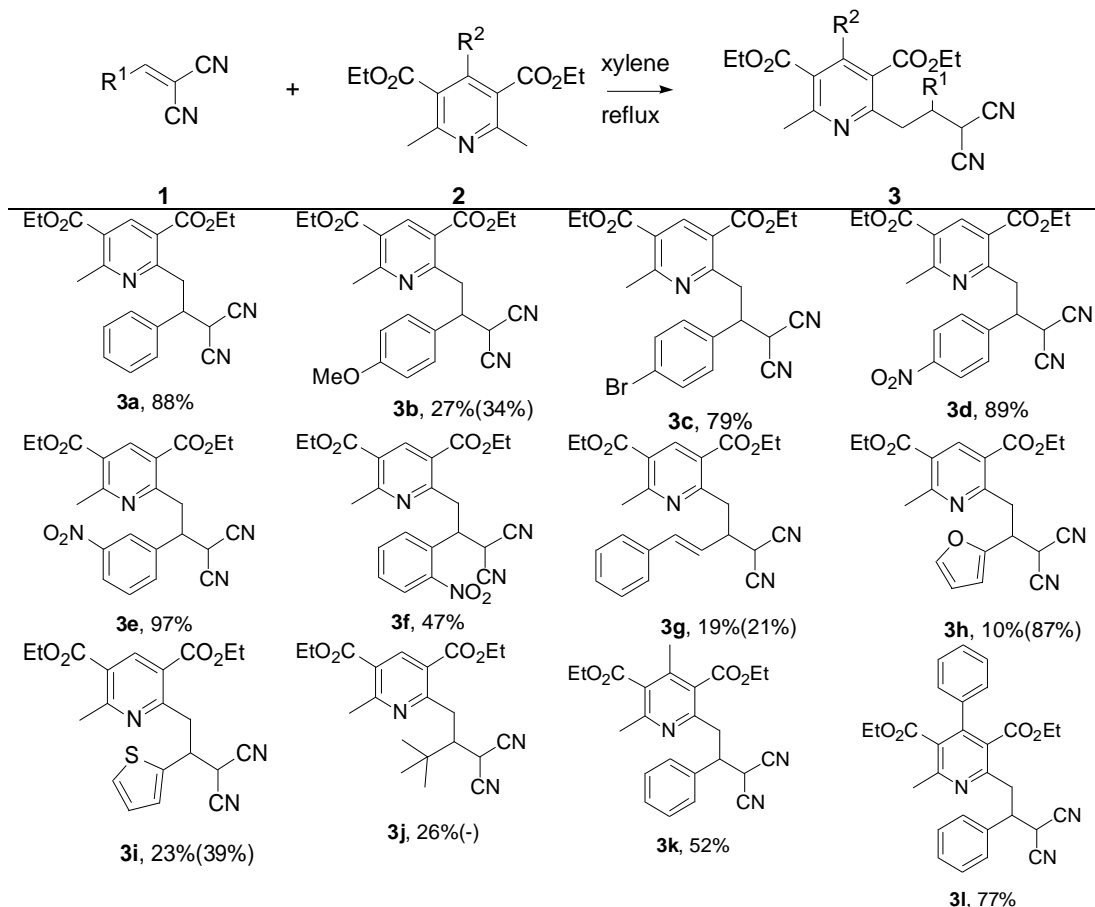
With the optimal conditions in hand, we were eager to know whether this reaction could tolerate different functional groups. Reactions of alkenes with different functional groups and pyridines bearing electron-withdrawing groups were carried out, and the results are listed in Table 2.

Table 1. Screening of benzylic C-H functionalization of Hantzsch pyridine **2a** with electron deficient alkene **1a**^a

Entry	Additive	Solvent	Time/h	Yield/% ^b
1	None	PEG-400	24	-
2	None	H ₂ O	10	50
3	Pd/C (5mol%) + TsOH (10 %)	MeOH	20	59
4	TsOH (10 %)	Toluene	20	60
5	None	Toluene	20	63
6	None	MeOH	20	55
7	None	xylene	10	88
8	None	DCM	24	-

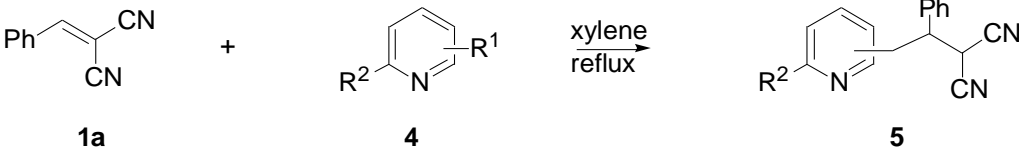
^a Solvent (2 mL) was added into a reaction vessel charged with compound **1a** (1.0 mmol), **2a** (1.2 mmol) and additives, the vessel was purged with nitrogen and then heated under reflux over the indicated period. ^b Isolated yield.

Refluxing in xylene, all of the alkenes reacted smoothly with Hantzsch pyridines **2**, although the yields of the products were variable. For alkenes with a 3-aryl group, the electronic nature of the functional group at the *para* position affects the reaction yield. When it is an electron-donating group, the yield decreases markedly (see **3b**). However, an electron withdrawing group does not affect the yield much (see **3c** and **3d**). Interestingly, when alkenes with nitro group on different position of the aryl group are tested, it is found that *meta*-nitro substitution gives higher yield than *para*-nitro substitution, while a nitro group in the *ortho* position makes the yield drop (see **3d**, **3e** and **3f**). In terms of electron-deficient alkenes with heteroaryl group, electron donating furyl and thienyl both gave poor yields (see **3h** and **3i**). We were curious to know whether an alkyl group on the alkene would retard this reaction because of its electron donating capability. *t*-Butyl was chosen as an example of alkyl group to avert any C-H bond on the α -position of the alkene being cleaved and generating undesired side products.¹⁵⁻¹⁸ The reaction did occur although the yield is, not surprisingly, unsatisfactory. (see **3j**) When a Hantzsch pyridine bearing a 4-phenyl group was used as the nucleophile, the addition product was isolated in reasonable yield (see **3l**). Furthermore, microwave irradiation was tried on reactions with poor yields (see **3b**, **3g-j**), and yields were improved somewhat except for that of **3j**. It is also interesting to find that a 2-methyl is preferred to a 4-methyl for the C-H functionalization of a Hantzsch pyridine (see **3k**). With the weak electron-donating group, phenyl, on the 4-position of the Hantzsch pyridine, the outcome of the reaction is much better than that of the 4-methyl Hantzsch pyridine (see **3k** and **3l**).

Table 2. Benzylic C-H functionalization of Hantzsch pyridines **2** with methylenemalononitriles **1**^a

^aSolvent (2mL) was added into reaction vessel charged with compound **1** (1.0 mmol) and **2** (1.2 mmol), the vessel was purged with nitrogen and then heated under reflux for 10 hours. ^bIsolated yield, the yield in parenthesis is that obtained under microwave irradiation for 10 hours.

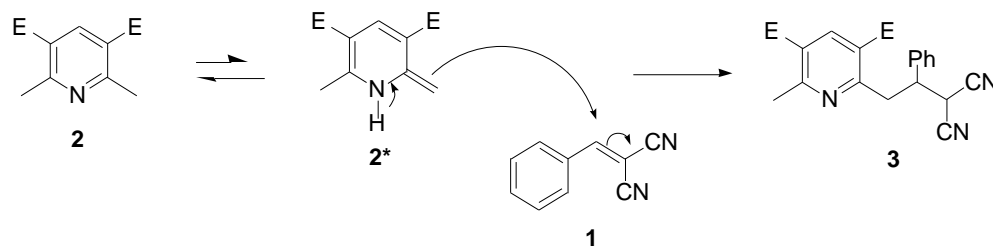
To understand the mechanism of this promoter-free C-H functionalization reaction, several easily accessible methylpyridines were subjected to these reaction conditions and the results are listed in Table 3. As observed above, a methyl in the 2-position reacts more readily than one at the 4-position, while a methyl in a 3-position does not participate in the reaction at all.

Table 3. Benzylic C-H functionalization of methyl pyridines **4** with 2-benzylidenemalononitrile **1a**^a


2	R¹	R²	Product	Time/h	Yield/%^b
1	2-CH ₃	CH ₃	5a	4.5	62
2	4-CH ₃	H	5b	29	12
3	3-CH ₃	H		40	- ^c

^a Solvent (2 mL) was added into reaction vessel charged with compounds **1a** (1.0 mmol) and **4** (1.2 mmol), the vessel was purged with nitrogen and then heated under reflux over the indicated period. ^b Isolated yield. ^c No desired product isolated.

From the above findings, the reaction mechanism could be postulated as shown in Scheme 1. There is an equilibrium between compound **2** and its enamine tautomer **2***, which is the Michael donor in the reaction but much less stable than ground state compound **2**. Intermediate **2*** adds to electron-deficient compound **1** to give product **3** via nucleophilic conjugate addition.

**Scheme 1.** A plausible mechanism of benzylic C-H functionalization on Hantzsch pyridine with electron-deficient alkenes.

Conclusions

A promoter-free benzylic C-H functionalization on substituted pyridine with electron deficient alkene is found, which can tolerate a variety of pyridine substrates. Fourteen compounds have been prepared by this method, might be applied to a series of bioassay to find out interesting pharmaceutical activities. This promoter-free benzylic C-H functionalization could be an effective tool to prepare nonsymmetric pyridine derivatives.

Experimental Section

General. The solvents used were analytical reagent purchased from Sinopharm Chemical Reagent Co, Ltd. The starting materials used were prepared in-house from chemicals purchased from Sinopharm. The reactions described in this manuscript were performed in standard laboratory glassware. Melting points were recorded on a WRS-1B digital melting point recorder from Shanghai Precision Scientific Instrument Corporation. Infrared

spectra were recorded on a Nicolet Avatar 370 DTGS machine. ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker AV400 equipment. MS data were recorded on a Shimadzu LCMS-2010EV mass spectrometer or an Agilent 5973N GC/MS. The HRMS were run using an Agilent 6224 TOF LC/MS or a Thermo LXQ Linear Ion Trap Mass Spectrometer.

General procedure (Method A) for preparation of unsymmetrical Hantzsch pyridines

Xylene (2 mL) was added into reaction vessel charged with compound **1** (1.0 mmol) and **2** (1.2 mmol), the vessel was purged with nitrogen and then heated under reflux for 10 hr. The reaction mixture was then subjected to flash chromatography to give the required product.

Alternative procedure (Method B)

Xylene (2 mL) was added into reaction vessel charged with compound **1** (1.0 mmol) and **2** (1.2 mmol), the vessel was irradiated with microwave at 250W for 10 hr. The reaction mixture was then subjected to flash chromatography to give the product.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-phenylbutyronitrile (3a). Light yellow oil (361 mg, 0.89 mmol), yield 88 %. $R_f = 0.36$ (PE-EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.75 (s, 1H, Py-H-4'), 7.46-7.32 (m, 5H, Ph-H), 4.81 (d, J 5.2 Hz, 1H, H-2), 4.42 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.39 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.07 (dt, J 8.8, 5.6 Hz, 1H, H-3), 3.99-3.88 (m, 2H, H-4), 2.92 (s, 3H, Py- CH_3 -2'), 1.42 (t, J 7.2 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.39 (t, J 7.2 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 165.3, 162.4, 160.2, 141.4, 137.2, 129.0, 128.8, 128.2, 124.0, 123.5, 112.5, 112.0, 61.9, 61.7, 44.5, 37.8, 28.9, 25.1, 14.3, 14.2. IR (KBr) ν_{max} 2983, 2254, 1720, 1595 cm^{-1} . MS (EI, 70eV) m/z (%) = 405 (M^+ , 31), 251 (100). HRMS-TOF: calcd for $\text{C}_{23}\text{H}_{24}\text{N}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 406.1761, found: 406.1759.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(4-methoxyphenyl)butyronitrile (3b). Light yellow oil, 27 % (120 mg, 0.28 mmol); 34 % (157 mg, 0.36 mmol) by Method B. $R_f = 0.30$ (PE-EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H, Py-H-4'), 7.37 (d, J 8.8 Hz, 2H, Ph-H-3' & Ph-H-5'), 6.92 (d, J 8.8 Hz, 2H, Ph-H-2' & Ph-H-6'), 4.71 (d, J 5.2 Hz, 1H, H-2), 4.41 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.39 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.03 (dt, J 9.2, 5.2 Hz, 1H, H-3), 3.91 (dd, J 16.0, 5.2 Hz, 1H, H-4), 3.83 (dd, J 15.6, 9.6 Hz, 1H, H-4), 3.81 (s, 3H, OCH_3), 2.89 (s, 3H, Py- CH_3 -6'), 1.42 (t, J 7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J 7.2 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 165.5, 165.3, 162.4, 160.3, 159.8, 141.4, 129.3, 129.2, 124.0, 123.6, 114.4, 112.6, 112.1, 61.9, 61.7, 55.3, 43.9, 37.9, 29.2, 25.1, 14.3, 14.2. IR (KBr) ν_{max} 2983, 2254, 1717, 1612, 1595, 1552 cm^{-1} . HRMS-TOF: calcd for $\text{C}_{24}\text{H}_{26}\text{N}_3\text{O}_5$ [$\text{M} + \text{H}$] $^+$ 436.1867, found: 436.1868.

3-(4-Bromophenyl)-2-cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]butyronitrile (3c). Yellow oil, 79 % (328 mg, 0.68 mmol). $R_f = 0.35$ (PE-EtOAc, 4:1). ^1H NMR (400 MHz, CDCl_3) δ 8.72 (s, 1H, Py-H-4'), 7.54 (d, J 8.4 Hz, 2H, Ph-H-3' & Ph-H-5'), 7.34 (d, J 8.4 Hz, 2H, Ph-H-2' & Ph-H-6'), 4.73 (d, J 5.2 Hz, 1H, H-2), 4.42 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.39 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.06 (dt, J 9.2, 5.6 Hz, 1H, H-3), 3.91 (dd, J 16.0, 5.6 Hz, 1H, H-4), 3.82 (dd, J 16.0, 9.2 Hz, 1H, H-4), 2.88 (s, 3H, Py- CH_3 -6'), 1.43 (t, J 7.2 Hz, 3H, OCH_2CH_3), 1.40 (t, J 7.2 Hz, 3H, OCH_2CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 165.3, 165.0, 162.3, 159.7, 141.3, 136.1, 132.0, 129.8, 123.9, 123.3, 122.7, 112.2, 111.7, 61.8, 61.6, 43.8, 37.4, 28.6, 24.9, 14.1, 14.1. IR (KBr) ν_{max} 2983, 2905, 2255, 1719, 1594, 1552 cm^{-1} . HRMS-TOF: calcd for $\text{C}_{23}\text{H}_{23}\text{BrN}_3\text{O}_4$ [$\text{M} + \text{H}$] $^+$ 484.0866, found: 484.0864.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(4-nitrophenyl)butyronitrile (3d). Light brown oil, 89 % (448 mg, 0.99 mmol). $R_f = 0.35$ (PE-EtOAc, 3:1). ^1H NMR (400 MHz, CDCl_3) δ 8.78 (s, 1H, Py-H-4'), 8.29 (d, J 8.8 Hz, 2H, Ph-H-3' & Ph-H-5'), 7.69 (d, J 8.8 Hz, 2H, Ph-H-2' & Ph-H-6'), 4.88 (d, J 5.2 Hz, 1H, H-2), 4.43 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.41 (q, J 7.2 Hz, 2H, OCH_2CH_3), 4.25 (dt, J 8.8, 5.6 Hz, 1H, H-3), 3.99 (dd, J 16.0, 5.6 Hz, 1H,

H-4), 3.93 (dd, *J* 16.4, 9.2 Hz, 1H, H-4), 2.91 (s, 3H, Py-CH₃-6'), 1.43 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.42 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.3, 165.0, 162.4, 159.2, 147.9, 144.4, 141.4, 129.4, 124.2, 124.0, 123.3, 112.0, 111.5, 61.8, 61.7, 43.9, 37.3, 28.4, 24.9, 14.11, 14.10. IR (KBr) ν_{\max} 3082, 2984, 2907, 2256, 1721, 1596, 1525 cm⁻¹. HRMS-TOF: calcd for C₂₃H₂₃N₄O₆ [M + H]⁺ 451.1612, found: 451.1611.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(3-nitrophenyl)butyronitrile (3e). Off-white solid, 97 % (471 mg, 1.05 mmol). M.p. 109.4-111.2 °C; *R_f* = 0.32 (PE-EtOAc, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H, Py-4'-H), 8.35 (t, *J* 1.6 Hz, 1H, Ph-H-2'), 8.25 (dd, *J* 8.0, 1.2 Hz, 1H, Ph-H-4'), 7.87 (d, *J* 8.0 Hz, 1H, Ph-H-6'), 7.63 (t, *J* 8.0 Hz, 1H, Ph-H-5'), 4.82 (d, *J* 5.6 Hz, 1H, H-2), 4.421 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.415 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.27 (dt, *J* 8.8, 5.6 Hz, 1H, H-3), 4.00 (dd, *J* 16.0, 5.6 Hz, 1H, H-4), 3.92 (dd, *J* 16.0, 7.2 Hz, 1H, H-4), 2.88 (s, 3H, Py-CH₃-6'), 1.43 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.42 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 165.2, 162.7, 159.3, 148.5, 141.7, 139.2, 134.5, 130.3, 124.4, 123.9, 123.6, 123.5, 112.0, 111.5, 62.1, 61.9, 44.1, 37.6, 28.7, 25.1, 14.31, 14.29. IR (KBr) ν_{\max} 3089, 2984, 2907, 2256, 1716, 1595, 1533 cm⁻¹. HRMS-TOF: calcd for C₂₃H₂₃N₄O₆ [M + H]⁺ 451.1612, found: 451.1611.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(2-nitrophenyl)butyronitrile (3f). Yellow oil, 47 % (237 mg, 0.53 mmol). *R_f* = 0.31 (PE-EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃) δ 8.67 (s, 1H, Py-H-4'), 7.89 (dd, *J* 8.0, 1.2 Hz, 1H, Ph-H-3'), 7.74 (d, *J* 7.2 Hz, 1H, Ph-H-6'), 7.60 (td, *J* 7.6, 1.2 Hz, 1H, Ph-H-4'), 7.48-7.44 (m, 1H, Ph-H-5'), 4.93 (dt, *J* 8.8, 5.6 Hz, 1H, H-3), 4.73 (d, *J* 4.8 Hz, 1H, H-2), 4.43 (qd, *J* 7.2, 1.6 Hz, 2H, OCH₂CH₃), 4.37 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.28 (dd, *J* 16.8, 9.6 Hz, 1H, H-4), 3.92 (dd, *J* 16.8, 5.6 Hz, 1H, H-4), 2.68 (s, 3H, Py-CH₃-6'), 1.44 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.39 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 165.1, 162.4, 158.8, 150.3, 141.2, 133.4, 132.1, 129.3, 128.4, 124.0, 123.9, 123.0, 112.0, 111.7, 61.8, 61.6, 37.8, 36.7, 28.4, 24.4, 14.2, 14.1. IR (KBr) ν_{\max} 2984, 2908, 2257, 1716, 1596, 1532 cm⁻¹. HRMS-TOF: calcd for C₂₃H₂₃N₄O₆ [M + H]⁺ 451.1612, found: 451.1607.

2-Cyano-3-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]methyl-5-phenyl-4-pentenitrile (3g). Yellow oil, 19 % (102 mg, 0.24 mmol); 21 % (113 mg, 0.26 mmol) by Method B. *R_f* = 0.39 (PE-EtOAc, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H, Py-H-4'), 7.40-7.27 (m, 5H, Ph-H), 6.68 (d, *J* 15.6 Hz, 1H, H-5), 6.27 (dd, *J* 15.6, 9.2 Hz, 1H, H-4), 4.58 (d, *J* 4.4 Hz, 1H, H-2), 4.42 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.40 (qd, *J* 7.2, 0.4 Hz, 2H, OCH₂CH₃), 3.77-3.74 (m, 1H, H-3), 3.63-3.55 (m, 2H, Py-H-2'), 2.90 (s, 3H, Py-CH₃-6'), 1.42 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.41 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 165.3, 162.5, 160.2, 141.5, 135.8, 128.7, 128.5, 126.8, 124.5, 124.2, 123.7, 112.5, 111.8, 62.0, 61.8, 43.4, 37.9, 28.0, 25.2, 14.3. IR (KBr) ν_{\max} 2983, 2909, 2254, 1721, 1595, 1552 cm⁻¹. HRMS-TOF: calcd for C₂₅H₂₆N₃O₄ [M + H]⁺ 432.1918, found: 432.1917.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(2-furanyl)butyronitrile (3h). Yellow oil, 10 % (39 mg, 0.10 mmol); 87 % (330 mg, 0.83 mmol) by Method B. *R_f* = 0.43 (PE-EtOAc, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H, Py-H-4'), 7.43 (dd, *J* 2.0, 0.8 Hz, 1H, Furan-H-5'), 6.40 (d, *J* 3.2 Hz, 1H, Furan-H-3'), 6.36 (dd, *J* 3.2, 2.0 Hz, 1H, Furan-H-4'), 4.70 (d, *J* 5.2 Hz, 1H, H-2), 4.42 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.41 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.30 (dt, *J* 8.4, 5.6 Hz, 1H, H-3), 3.95 (dd, *J* 16.0, 6.0 Hz, 1H, H-4), 3.80 (dd, *J* 16.0, 8.8 Hz, 1H, H-4), 2.88 (s, 3H, Py-Me-6'), 1.43 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.42 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.4, 165.2, 162.4, 159.4, 150.3, 143.0, 141.4, 124.17, 123.5, 112.1, 111.6, 110.6, 108.8, 61.9, 61.6, 38.7, 36.4, 27.2, 25.0, 14.19, 14.15. IR (KBr) ν_{\max} 2984, 2908, 2256, 1721, 1595, 1553 cm⁻¹. HRMS-TOF: calcd for C₂₁H₂₂N₃O₅ [M + H]⁺ 396.1554, found: 396.1553.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]-3-(2-thienyl)butyronitrile (3i). Off-white oil, 23 % (88 mg, 0.21 mmol); 39 % (210 mg, 0.51 mmol) by Method B. *R_f* = 0.37 (petroleum ether-EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H, Py-H-4'), 7.30 (dd, *J* 4.8, 1.2 Hz, 1H, Thiophene-H-5'), 7.22 (d, *J* 3.2 Hz, 1H, Thiophene-H-3'), 7.03 (dd, *J* 4.8, 3.6 Hz, 1H, Thiophene-H-4'), 4.80 (d, *J* 5.2 Hz, 1H, H-2), 4.47-4.38 (m, 1H, H-3),

4.42 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.41 (q, *J* 7.2 Hz, 2H, OCH₂CH₃), 4.02 (dd, *J* 16.4, 5.2 Hz, 1H, H-4), 3.89 (dd, *J* 16.4, 9.2 Hz, 1H, H-4), 2.91 (s, 3H, Py-Me-6'), 1.43 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.42 (t, *J* 7.2 Hz, 3H, OCH₂CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 165.2, 162.5, 159.4, 141.5, 139.4, 127.2, 126.8, 125.7, 124.1, 123.6, 112.3, 111.7, 61.9, 61.7, 40.1, 39.0, 29.6, 25.1, 14.3, 14.2. IR (KBr) ν_{\max} 3110, 2984, 2906, 2256, 2227, 1716, 1595, 1553 cm⁻¹. HRMS-TOF: calcd for C₂₁H₂₂N₃O₄S [M + H]⁺ 412.1326, found: 412.1322.

2-Cyano-3-[2-(3,5-diethoxycarbonyl-6-methyl)pyridyl]methyl-4,4-dimethylvaleronitrile (3j). Colorless liquid, 26 % (107 mg, 0.28 mmol). *R_f* = 0.49 (petroleum ether-EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃) δ 8.75 (s, 1H, Py-H-4'), 4.44-4.39 (m, 4H, OCH₂CH₃), 4.32 (d, *J* 2.4 Hz, 1H, H-2), 3.78 (dd, *J* 16.0, 2.8 Hz, 1H, H-4), 3.38 (dd, *J* 16.0, 11.2 Hz, 1H, H-4), 2.92 (s, 3H, Py-Me-6'), 2.84 (dt, *J* 10.8, 2.8 Hz, 1H, H-3), 1.429 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.425 (t, *J* 7.2 Hz, 3H, OCH₂CH₃), 1.18 (s, 9H, *t*-Bu). ¹³C NMR (100 MHz, CDCl₃) δ 165.7, 165.4, 162.6, 161.5, 141.6, 123.9, 123.4, 113.5, 61.7, 61.6, 48.5, 34.7, 34.5, 27.9, 25.0, 22.9, 14.3. IR (KBr) ν_{\max} 2971, 2252, 1723, 1596, 1552 cm⁻¹. HRMS-TOF: calcd for C₂₁H₂₈N₃O₄ [M + H]⁺ 386.2074, found: 386.2070.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-4,6-dimethyl)pyridyl]-3-phenylbutyronitrile (3k). Brown oil, 52 % (142 mg, 0.34 mmol). *R_f* = 0.30 (petroleum ether-EtOAc, 4:1). ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.38 (m, 5H, Ph-H), 4.74 (d, *J* 4.4 Hz, 1H, H-2), 4.44 (q, *J* 7.2 Hz, 2H, Py-CO₂CH₂CH₃-5'), 4.39 (q, *J* 7.2 Hz, 2H, Py-CO₂CH₂CH₃-3'), 3.96 (dt, *J* 10.0, 4.4 Hz, 1H, H-3), 3.45 (dd, *J* 15.6, 10.0 Hz, 1H, H-4), 3.27 (dd, *J* 15.6, 4.4 Hz, 1H, H-4), 2.55 (s, 3H, Py-CH₃-6'), 2.28 (s, 3H, Py-CH₃-4'), 1.41 (t, *J* 7.2 Hz, 3H, Py-CO₂CH₂CH₃-5'), 1.34 (t, *J* 7.2 Hz, 3H, Py-CO₂CH₂CH₃-3'). ¹³C NMR (100 MHz, CDCl₃) δ 167.9, 167.6, 155.5, 153.5, 143.0, 137.0, 129.1, 128.9, 128.8, 128.2, 128.1, 112.5, 111.8, 62.1, 61.9, 44.6, 36.9, 28.7, 23.0, 17.2, 14.2, 14.1. IR (KBr) ν_{\max} 2983, 2255, 1735, 1561 cm⁻¹. HRMS-TOF calcd for C₂₄H₂₆N₃O₄ [M + H]⁺ 420.1918, found: 420.1914.

2-Cyano-4-[2-(3,5-diethoxycarbonyl-6-methyl-4-phenyl)pyridyl]-3-phenylbutyronitrile (3l). Off-white oil, 77 % (223 mg, 0.46 mmol). *R_f* = 0.44 (petroleum ether-EtOAc, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.36 (m, 8H, Ph-H), 7.24-7.22 (m, 2H, Ph-H), 4.77 (d, *J* 4.8 Hz, 1H, H-2), 4.06-4.00 (m, 1H, H-3), 4.02 (q, *J* 7.2 Hz, 2H, Py-CO₂CH₂CH₃-5'), 3.96 (q, *J* 7.2 Hz, 2H, Py-CO₂CH₂CH₃-3'), 3.54 (dd, *J* 16.0, 10.0 Hz, 1H, H-4), 3.38 (dd, *J* 16.0, 4.4 Hz, 1H, H-4), 2.64 (s, 3H, Py-CH₃-6'), 0.91 (t, *J* 7.2 Hz, 3H, Py-CO₂CH₂CH₃-5'), 0.81 (t, *J* 7.2 Hz, 3H, Py-CO₂CH₂CH₃-3'). ¹³C NMR (100 MHz, CDCl₃) δ 167.5, 167.3, 156.1, 154.1, 147.1, 137.1, 136.2, 129.2, 129.0, 128.8, 128.3, 128.2, 128.1, 127.7, 112.5, 111.9, 61.9, 61.7, 44.8, 37.1, 28.8, 23.2, 13.6, 13.5. IR (KBr) ν_{\max} 2982, 2254, 1724, 1557 cm⁻¹. ESI-MS *m/z* 504.6 [M + Na]⁺. HRMS-ESI calcd for C₂₉H₂₈N₃O₄ [M + H]⁺ 482.2074, found: 482.2076.

2-Cyano-4-[2-(6-methyl)pyridyl]-3-phenylbutyronitrile (5a).¹⁴ Green oil, 62 % (229 mg, 0.88 mmol). *R_f* = 0.36 (PE-EtOAc, 3:1). ¹H NMR (400 MHz, CDCl₃) δ 7.51 (t, *J* 7.6 Hz, 1H, Py-H-4'), 7.44-7.36 (m, 5H, Ph-H), 7.05 (d, *J* 7.6 Hz, 1H, Py-H-5'), 6.95 (d, *J* 7.6 Hz, 1H, Py-H-3'), 4.83 (d, *J* 5.2 Hz, 1H, H-2),¹¹ 3.91 (dt, *J* 9.6, 5.2 Hz, 1H, H-3), 3.45 (dd, *J* 15.2, 10.0 Hz, 1H, H-4),¹¹ 3.29 (dd, *J* 15.2, 4.8 Hz, 1H, H-4),¹¹ 2.56 (s, 3H, Py-CH₃-6'). ¹³C NMR (100 MHz, CDCl₃) δ 158.4, 156.1, 137.1, 137.1, 129.0, 128.7, 128.0, 121.8, 120.9, 112.5, 112.0, 45.1, 39.3, 28.6, 24.4. IR (KBr) ν_{\max} 2903, 2255, 2205, 1967, 1883, 1652, 1594, 1576 cm⁻¹. ESI-MS *m/z* 284.2 ([M + Na]⁺), 196.1 ([M - CH₂(CN)₂ + H]⁺). HRMS-TOF calcd for C₁₇H₁₆N₃ [M + H]⁺ 262.1339, found: 262.1336.

2-Cyano-3-phenyl-4-(4-pyridyl)butyronitrile (5b). Pale yellow oil, 12 % (33 mg, 0.13 mmol). *R_f* = 0.59 (EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 8.48 (d, *J* 6.0 Hz, 2H, Py-H-2'&Py-H-6'), 7.42-7.37 (m, 3H, Ph-H-3', Ph-H-4'&Ph-H-5'), 7.32-7.30 (m, 2H, Py-H-2'&Py-H-6'), 7.04 (d, *J* 6.0 Hz, 2H, Py-H-3'&Py-H-5'), 3.98 (d, *J* 5.6 Hz, 1H, H-2), 3.52 (dt, *J* 8.8, 6.4 Hz, 1H, H-3), 3.33 (dd, *J* 14.0, 6.8 Hz, 1H, H-4), 3.25 (dd, *J* 14.0, 8.8 Hz, 1H, H-4). ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 145.7, 135.4, 129.5, 129.5, 127.9, 124.3, 111.7, 111.5, 47.3, 37.8, 29.4. IR (KBr) ν_{\max} 3070, 3034, 2929, 2803, 2251, 2216, 1603, 1559 cm⁻¹. HRMS-TOF calcd for C₁₆H₁₄N₃ ([M + H]⁺) 248.1182, found: 248.1181.

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Supplementary Material

¹H NMR and ¹³C NMR data.

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