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Synthesis of Multi-Substituted 2-Iminopyridine by Conjugate Addition of Ethyl Cyanoacetate Derivatives to Alkynyl Imines

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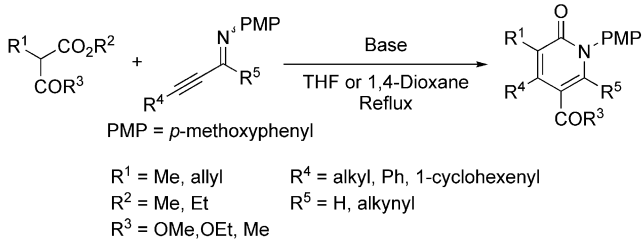
The synthesis of multi-substituted 2-iminopyridines by conjugate addition of ethyl cyanoacetate derivatives to alkynyl imines has been developed. The reaction of ethyl cyanoacetate derivatives with alkynyl imines provided multi-substituted 2-iminopyridines in good yields. Also described is the transformation of 2-iminopyridines into 2-aminopyridines by deprotection of the substituent on the nitrogen under acidic conditions.

Introduction

Biologically active compounds containing a 2-iminopyridine structure are less well known than those containing the 2-pyridone counterpart.[1] However, due to their strong biological activities, 2-iminopyridines are highly attractive compounds compared with members of the large group of biologically active 2-pyridones.[2,3] Several methods for the synthesis of 2-iminopyridines by condensation reactions of cyano derivatives have already been reported.[4] In addition, the synthesis of 2-iminopyridines by cobalt- or nickel-catalyzed cyclotrimerization of 2 equivalents of alkynes with carbodiimides has been developed.[5] Takahashi et al. reported a selective preparation of 2-iminopyridines from two different alkynes via azazirconacycles.[6] However, the former methods are not satisfactory from the point of view of synthesizing 2-iminopyridines possessing the desired substituents. Therefore, the development of alternative methods for the synthesis of multi-substituted 2-iminopyridines from readily available starting materials is highly desirable.

We previously developed a strategy for the synthesis of 2-pyridones by the conjugate addition of malonic esters or β-keto esters to alkynyl imines to give 5-alkoxycarbonyl- or 5-acetyl-2-pyridones, respectively (Scheme 1, R^5 = H).[7] Recently, we found that the reaction of dialkynyl imines with active methine compounds gave 3,4,5,6-tetrasubstituted 2-pyridones (Scheme 1, R^5 = alkynyl).[8] During these investigations into the synthesis of heterocycles using alkynyl imines we found that the reaction of ethyl cyanoacetate derivatives with alkynyl imines gave 2-iminopyridines. Herein, we report a synthesis of multi-substituted 2-iminopyridines by the conjugate addition of ethyl cyanoacetate derivatives to alkynyl imines (Scheme 2).



Scheme 1. Synthesis of multi-substituted 2-pyridones by the conjugate addition of malonic esters or β-keto esters to alkynyl imines.

Scheme 2. Synthesis of multi-substituted 2-iminopyridines by the conjugate addition of ethyl cyanoacetate derivatives to alkynyl imines.

Results and Discussion

Table 1 shows the effect of base on the model reaction of ethyl 2-cyanopropanoate (**1a**) with alkynyl imine **2a**, which was prepared from phenylpropynal and *p*-methoxyphenylmethylamine, in diethylene glycol dimethyl ether at 160 °C. When NaH was used as a base, the desired 2-iminopyridine **3a** was obtained in 27% yield (entry 1). Other sodium salt bases such as NaOEt and sodium hexamethyldisilazide (NaHMDS) gave the adduct **3a** in lower yields

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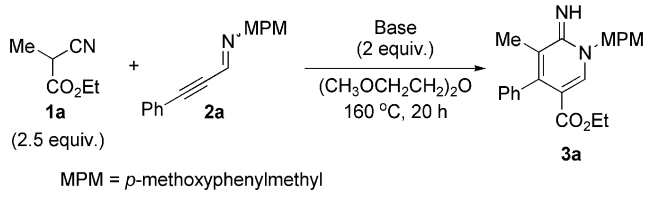
(entries 2 and 3). The use of potassium salt bases afforded the product **3a** in better yields because the potassium salt of the cyanoacetate derivative **1a** is more reactive. Among the potassium salt bases tested, potassium hexamethyldisilazide (KHMDS) was found to be the most effective (entry 6). To improve the product yield, the effects of different reaction conditions, such as solvents, reaction temperature and the amounts of KHMDS and **1a**, were investigated. When amounts of both KHMDS and **1a** were increased, 2-iminopyridine **3a** was obtained in 70% yield (entry 7).

Table 1. Effect of base on the reaction of 2-cyanopropanoate (**1a**) with alkynyl imine **2a**.



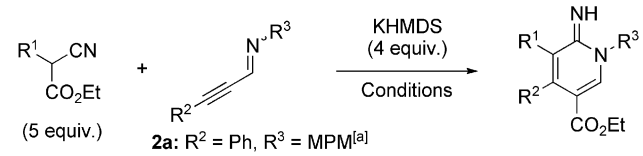
MPM = *p*-methoxyphenylmethyl

Entry	Base	% Yield[a]
1	NaH	27
2	NaOEt	2
3	NaHMDS[b]	11
4	KOEt	35
5	KO*t*Bu	33
6	KHMDS[c]	44
7	KHMDS[d]	70

[a] Isolated yield. [b] In $(CH_3OCH_2CH_2)_2O$/THF (8:1). [c] In $(CH_3OCH_2CH_2)_2O$/toluene (8.9:1). [d] KHMDS (4 equiv.) and **1a** (5 equiv.) were used in $(CH_3OCH_2CH_2)_2O$/toluene (3.1:1) at 160 °C for 3.0 h.

Table 2 summarizes the results. The reaction of alkynyl imine **2b** bearing a double bond gave the adduct **3b** in 57% yield (entry 1). The reaction of alkynyl imine **2c** possessing a butyl group gave the corresponding 2-iminopyridine **3c** in a moderate yield (entry 2). However, the use of ethyl 2-cyano-2-phenylacetate (**1b**) in diethylene glycol dimethyl ether at 160 °C (conditions A) did not give the desired 2-iminopyridine **3d**. Although alkynyl imine **2a** was not recovered due to decomposition, the cyanoacetate **1b** was recovered in 95% yield. When the reaction of **1b** with **2a** was carried out in 1,4-dioxane under reflux (conditions B), the desired 2-iminopyridine **3d** was obtained in 51% yield (entry 3). This result indicates that the cyanoacetate **1b** is less reactive than **1a** because the phenyl group is sterically more demanding and acts as an electron-withdrawing group. We next examined the use of the alkynyl imines prepared from alkynal and *p*-methoxyphenylamine. The reaction of the imines **2d** and **2e** proceeded in 1,4-dioxane/toluene under reflux (conditions C) to give 2-iminopyridines **3e** and **3f** in 81 and 84% yields, respectively (entries 4 and 5). The reaction of the imine **2f** gave 2-iminopyridine **3g** in a moderate yield (entry 6). Even with the use of the cyanoacetate **1b**, the reaction of **2d** proceeded smoothly to give 2-iminopyridine **3h** in a high yield (entry 7). The reactions of **1b** with the imines **2e** and **2f** also gave 2-iminopyridines **3i** and **3j** in moderate yields, respectively (entries 8 and 9). Furthermore, the reaction of the cyanoacetate **1c** bearing an allyl group, which could be transformed into other functional groups such as an aldehyde, carboxylic acid and hydroxy group, was carried out. The imines **2d** and **2e** afforded 2-iminopyridines **3k** and **3l** both in 66% yields (entries 10 and 11).

Table 2. Synthesis of 2-iminopyridines **3** by conjugate reaction of ethyl cyanoacetate derivatives **1** to alkynyl imine **2**.



1a: R^1 = Me
1b: R^1 = Ph
1c: R^1 = allyl

2a: R^2 = Ph, R^3 = MPM[a]
2b: R^2 = 1-cyclohexenyl, R^3 = MPM[a]
2c: R^2 = *n*Bu, R^3 = MPM[a]
2d: R^2 = Ph, R^3 = PMP[b]
2e: R^2 = 1-cyclohexenyl, R^3 = PMP[b]
2f: R^2 = *n*Bu, R^3 = PMP[b]

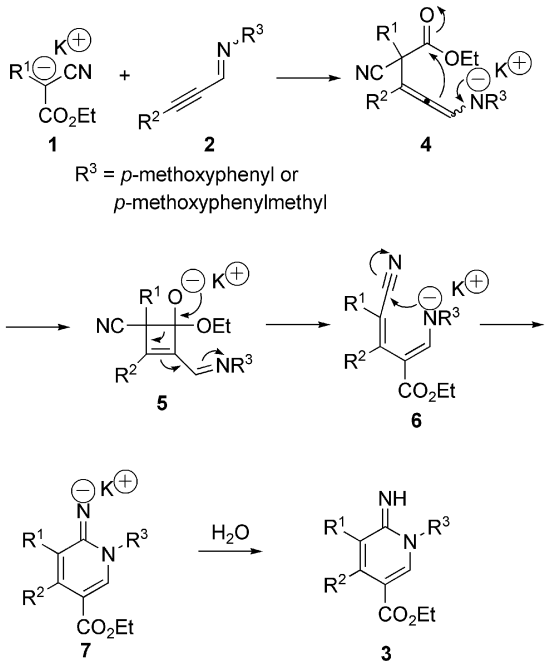
Entry	R^1	R^2	R^3[a][b]	Conditions	Time [h]	Product	% Yield[c]
1	Me	*c*Hex[d]	MPM	A[e]	3.5	**3b**	57
2	Me	*n*Bu	MPM	A[e]	3.5	**3c**	47
3	Ph	Ph	MPM	B[f]	45.0	**3d**	51
4	Me	Ph	PMP	C[g]	25.0	**3e**	81
5	Me	*c*Hex	PMP	C[g]	19.0	**3f**	84
6	Me	*n*Bu	PMP	C[g]	20.0	**3g**	48
7	Ph	Ph	PMP	B[f]	21.5	**3h**	84
8	Ph	*c*Hex	PMP	B[f]	20.0	**3i**	45
9	Ph	*n*Bu	PMP	B[f]	20.0	**3j**	50
10	Allyl	Ph	PMP	B[f]	16.0	**3k**	66
11	Allyl	*c*Hex	PMP	B[f]	16.0	**3l**	66

[a] MPM = *p*-methoxyphenylmethyl. [b] PMP = *p*-methoxyphenyl. [c] Isolated yield. [d] *c*Hex = 1-cyclohexenyl. [e] Conditions A: in $(CH_3OCH_2CH_2)_2O$/toluene (3.1:1) at 160 °C. [f] Conditions B: in 1,4-dioxane under reflux. [g] Conditions C: in 1,4-dioxane/toluene (2.4–3.1:1) under reflux.

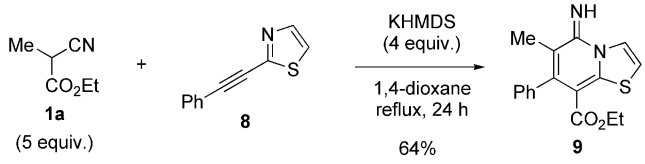
We have proposed a plausible mechanism for the conjugate addition reaction, as shown in Scheme 3. Metalloenamine **4** would be generated by conjugate addition of the potassium salt of the cyanoacetate derivative **1** to the alkynyl imine **2** and undergo a chemoselective intramolecular cyclization at the ethoxycarbonyl group to give the cyclobutene oxide intermediate **5**. The cyclobutene oxide **5** would collapse into metalloenamine **6** by ring-opening to release ring strain in the cyclobutene and subsequent cyclization gives 2-iminopyridine **3** after protonation of the 2-iminopyridine potassium salt **7** with water to quench the reaction.

The use of alkynylthiazole **8** instead of alkynyl imines **2** to synthesize a bicyclic compound containing a 2-iminopyridine structure was examined. The reaction of **8** with **1a** proceeded to give the corresponding product **9** in 64% yield (Scheme 4). We also investigated the synthesis of 3,4,5,6-tetrasubstituted 2-iminopyridine. The reaction of **10** with **1a** gave 2-iminopyridine **11** in 52% yield (Scheme 5).

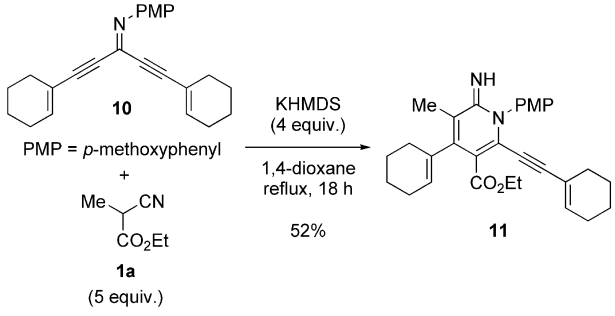
We next examined the transformation of 2-iminopyridine into 2-aminopyridine by deprotection of the substituent at the nitrogen.[9] 2-Aminopyridines are one of the most important heterocycles due to their biological activity.[4b,10] First, we attempted to deprotect the *p*-methoxyphenyl



Scheme 3. Plausible mechanism for the conjugate addition reaction.



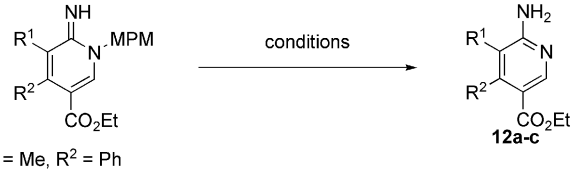
Scheme 4. Synthesis of bicyclic 2-iminopyridine **9**.



Scheme 5. Synthesis of 3,4,5,6-tetrasubstituted 2-iminopyridine **11**.

group of 2-iminopyridine **3e** by using ceric(IV) ammonium nitrate (CAN) as oxidant. However, the desired 2-aminopyridine was not obtained and instead 2-iminnopyridine **3e** was recovered in 79% yield. We next investigated the use of different conditions for the deprotection of the *p*-methoxyphenylmethyl group of 2-iminnopyridine **3a**. The results are summarized in Table 3. The deprotection of **3a** was carried out in trifluoroacetic acid (TFA) under reflux to give the desired 2-aminopyridine **12a** in 20% yield along with recovered **3a** in 76% yield (entry 1). The reaction of **3a** with CAN (4 equiv.) in CH_3CN/H_2O (1:1) at room temperature proceeded to give 2-aminopyridine **12a** in 57% yield without any recovered **3a** (entry 2). Because the yield was not yet satisfactory and 2-iminopyridine **3a** was not recovered by using CAN, other reaction conditions were examined (entries 3 and 4) but these did not give any 2-aminopyridine **12a**. Since the conversion yield of **12a** was good in entry 1, trifluoromethanesulfonic acid (TfOH), which is a stronger acid than TFA, was added to promote the deprotection of **3a**. Under these conditions, the reaction proceeded smoothly to give 2-aminopyridine **12a** in 70% yield (entry 5). The deprotection of 2-iminopyridines **3c** and **3d** was also carried out under acidic conditions to give the corresponding 2-aminopyridines **12b** and **12c** in moderate yields (entries 6–8).

Table 3. Synthesis of 2-aminopyridines **12** by deprotection of 2-iminopyridines **3**.



3a: R^1 = Me, R^2 = Ph
3c: R^1 = Me, R^2 = *n*Bu
3d: R^1 = R^2 = Ph

Entry	R^1	R^2	Conditions	Time [h]	Product	% Yield[a]
1	Me	Ph	TFA[b], reflux temp.	24.0	**12a**	20 (76)[c]
2	Me	Ph	CAN[d] (4.0)[e] in CH_3CN/H_2O (1:1) at r.t.	17.0	**12a**	57
3	Me	Ph	DDQ[f] (4.0)[e] in CH_3CN/H_2O (1:1) at r.t.	12.0	**12a**	0 (56)[c]
4	Me	Ph	$AlCl_3$ (4.0)[e] in anisole/MeOH (2:1) at 0 °C→r.t.	20.5	**12a**	0 (41)[c]
5	Me	Ph	TfOH[g] (1.0)[e] in TFA[b] reflux temp.	24.0	**12a**	70
6	Me	*n*Bu	TfOH[g] (1.3)[e] in TFA[b] reflux temp.	24.0	**12b**	47 (48)[c]
7	Me	*n*Bu	TfOH[g] (3.0)[e] in TFA[b] reflux temp.	24.0	**12b**	59
8	Ph	Ph	TfOH[g] (1.3)[e] in TFA[b] reflux temp.	24.0	**12c**	62

[a] Isolated yield. [b] TFA = trifluoroacetic acid. [c] Yield of the recovered reagents. [d] CAN = cerium(IV) ammonium nitrate. [e] Equivalent of reagents. [f] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. [g] TfOH = trifluoromethanesulfonic acid.

Conclusions

We have found an efficient method for the synthesis of multi-substituted 2-iminopyridines by conjugate addition of ethyl cyanoacetate derivatives to alkynyl imines and also the transformation of 2-iminopyridines into 2-aminopyridines by deprotection of the substituent on the nitrogen under acidic conditions. These methodologies are attractive because alkynyl imines and substituted ethyl cyanoacetate derivatives are readily available from alkynals, cyanoacetic esters and nitriles, respectively. Studies exploring the application of 2-imino- and 2-aminopyridines to the synthesis of biologically active compounds are now in progress.

Experimental Section

General: Infrared spectra were recorded with a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded with a JEOL EX-270 (270 MHz) or JNM α-500 spectrometer (500 MHz) with tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded with a JEOL EX-270 (67.8 MHz) or JNM α-500 spectrometer (126 MHz). Chemical sifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ = 77.0 ppm) as the internal reference. High-resolution mass spectra (EI) were recorded with a JEOL JMS-700D mass spectrometer. 1,4-Dioxane and diethylene glycol dimethyl ether were distilled from calcium hydride and stored over sodium. Products was purified by column chromatography on silica gel [Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)] and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). Potassium hexamethyldisilazide (KHMDS) toluene solution was purchased from Tokyo Chemical Industry Co., Ltd. (TCI) and used after titration. 95% Potassium hexamethyldisilazide (KHMDS) was purchased from Aldrich and used without further purification. Ethyl 2-cyanopropanoate (**1a**) is commercially available from TCI and was used after distillation. Ethyl cyanoacetate derivatives **1b**[11] and **1c**,[12] alkynyl imines **2d**,[7a] **2e**[7a] and **2f**[7a] and alkynylthiazole **8** were prepared according to the literature.[13] A solution of ammonia in dichloromethane was prepared by extracting ammonia from aqueous ammonia with dichloromethane and drying with sodium sulfate. All reactions were carried out under argon.

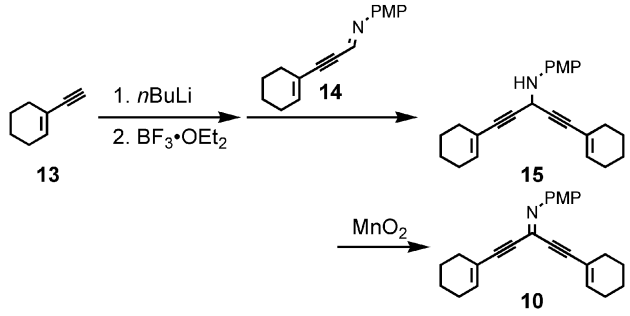
Synthesis of Alkynyl Imines 2a–2c: A solution of phenylpropynal (1.92 g, 15.3 mmol) in CH_2Cl_2 (4.9 mL) was added to a solution of *p*-methoxyphenylmethylamine (1.85 g, 15.0 mmol) in CH_2Cl_2 (7.7 mL) in the presence of 4-Å molecular sieves (6 g) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was filtered through a Celite pad to remove the molecular sieves. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 7:1) to give imine **2a** as a black oil (3.55 g, 93% yield).

2a: The ratio of geometrical mixtures of the C=N bond was 58:42. IR (neat): $\tilde{\nu}$ = 3058, 3033, 3000, 2933, 2905, 2834, 2206, 1607, 1511, 1444, 1364, 1335, 1300, 1247, 1175, 1109, 1034, 976, 920, 821, 758, 692, 589 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (t, J = 1.4 Hz, 0.42 H), 7.79 (t, J = 1.2 Hz, 0.58 H), 7.51–7.54 (m, 2 H), 7.21–7.45 (m, 5 H), 6.87–6.90 (m, 2 H), 4.88 (d, J = 1.4 Hz, 0.84 H), 4.71 (d, J = 1.2 Hz, 1.16 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 158.8, 158.6, 145.3, 143.0, 132.1, 132.1, 131.2, 130.0, 129.7, 129.7, 129.4, 129.2, 128.5, 128.3, 121.4, 121.2, 113.9, 113.8, 97.6, 91.5, 86.6, 82.0, 65.1, 59.5, 55.1 ppm. HRMS (EI): calcd. for $C_{17}H_{15}NO$: 249.1154 [M]$^+$; found 249.1168.

2b: The ratio of geometrical mixtures of the C=N bond was 50:50. Brown oil. IR (neat): $\tilde{\nu}$ = 3027, 2999, 2932, 2859, 2835, 2190, 1656, 1604, 1511, 1441, 1341, 1299, 1247, 1176, 1137, 1109, 1076, 1037, 959, 920, 819 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68 (t, J = 2.1 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.17–7.20 (m, 1 H), 6.85–6.89 (m, 2 H), 6.28–6.34 (m, 1 H), 4.76 (d, J = 2.1 Hz, 1 H), 4.64 (s 1 H), 3.79 (s, 1.5 H), 3.79 (s, 1.5 H), 2.10–2.21 (m, 4 H), 1.56–1.70 (m, 4 H) ppm. ^{13}CNMR (126 MHz, $CDCl_3$): δ = 158.7, 158.5, 145.6, 143.4, 139.2, 138.6, 131.5, 130.3, 129.3, 129.1, 119.7, 119.6, 113.9, 113.8, 99.9, 93.8, 84.5, 80.1, 65.0, 59.2, 55.1, 28.6, 28.5, 25.8, 25.8, 22.0, 22.0, 21.2, 21.1 ppm. HRMS (EI): calcd. for $C_{17}H_{19}NO$: 253.1467 [M]$^+$; found 253.1470.

2c: The ratio of geometrical mixtures of the C=N bond was 50:50. Brown oil. IR (neat): $\tilde{\nu}$ = 2955, 2867, 2216, 1608, 1512, 1459, 1300, 1248, 1174, 1108, 1035, 962, 823, 757 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 53–7.54 (m, 1 H), 7.23–7.26 (m, 1 H), 7.15–7.18 (m, 1 H), 6.82–6.87 (m, 2 H), 4.75 (d, J = 1.7 Hz, 1 H), 4.58 (s, 1 H), 3.75 (s, 1.5 H), 3.74 (s, 1.5 H), 2.30–2.43 (m, 2 H), 1.37–1.59 (m, 4 H), 0.87–0.96 (m, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.7, 158.5, 145.6, 143.5, 131.4, 130.3, 129.3, 129.1, 113.8, 113.8, 100.5, 94.0, 78.7, 74.7, 64.7, 64.3, 59.0, 55.1, 30.1, 30.0, 21.8, 18.9, 18.8, 13.4 ppm. HRMS (EI): calcd. for $C_{15}H_{19}NO$ 229.1467 [M]$^+$; found 229.1547.

Synthesis of Dialkynyl Imine 10 (Scheme 6): *n*BuLi (3.3 mL, 1.58 M in hexane, 5.21 mmol) was added to a solution of 1-ethynlcyclohexene (**13**) (541 mg, 5.10 mmol) in THF (20 mL) at –78 °C. After stirring for 30 min, BF_3·OEt_2 (0.65 mL, 5.27 mmol) was added to the solution and the mixture was stirred for 10 min. Alkynyl imine **14** (610 mg, 2.55 mmol) was then added and the reaction mixture was warmed to room temperature and stirred for 1 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL) and then dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 7:1) to give the (dialkynylmethyl)-amine **15** as a brown oil (821 mg, 93% yield).



Scheme 6.

15: IR (neat): $\tilde{\nu}$ = 3363, 3027, 2930, 2859, 2833, 2220, 2046, 1617, 1512, 1441, 1407, 1343, 1238, 1179, 1118, 1073, 1040, 977, 918, 821 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.74–6.81 (m, 4 H), 6.09–6.10 (m, 2 H), 5.10 (s, 1 H), 3.71–3.81 [m, 4 H, including a singlet of O*CH*$_3$ at δ = 3.75 (3 H)], 2.04–2.10 (m, 4 H), 1.53–1.62 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 153.4, 139.5, 135.5, 119.9, 116.9, 114.4, 84.4, 83.3, 55.5, 39.8, 28.9, 25.5, 22.1, 21.4 ppm. HRMS (EI): calcd. for $C_{24}H_{27}NO$ 345.2093 [M]$^+$; found 345.2032.

To a solution of the (dialkynylmethyl)amine **15** (821 mg, 2.38 mmol) in dichloromethane (25 mL) was added MnO_2 (6 g, 69 mmol) at room temperature. The reaction mixture was stirred for 13 h at room temperature. The reaction mixture was filtered through a Celite pad. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 7:1) to give the dialkynyl imine **10** as a brown solid (721 mg, 88% yield).

10: M.p. 126–127 °C. IR (KBr): $\tilde{\nu}$ = 3052, 2997, 2965, 2932, 2837, 2190, 1596, 1570, 1519, 1493, 1456, 1330, 1294, 1248, 1200, 1161, 1120, 1072, 1023, 955, 921, 837, 754, 690 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.31 (m, 2 H), 6.85–6.90 (m, 2 H), 6.37–6.39 (m, 1 H), 6.21–6.23 (m, 1 H), 3.81 (s, 3 H), 2.20–2.25 (m, 2 H), 2.05–2.18 (m 6 H), 1.54–1.69 (m 8 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.9, 143.0, 140.0, 139.0, 132.2, 123.6, 119.8, 113.5, 96.5, 91.3, 86.9, 82.9, 55.4, 28.5, 28.1, 25.9, 22.1, 21.9,

21.3, 21.1 ppm. HRMS (EI): calcd. for $C_{24}H_{25}NO$ 343.1936 $[M]^+$; found 343.1931.

Synthesis of 2-Iminopyridines 3a–c (Conditions A): A solution of ethyl 2-cyanopropanoate (**1a**) (131 mg, 1.0 mmol) in diethylene glycol dimethyl ether (2.0 mL) was added to KHMDS (1.3 mL, 0.62 M in toluene, 0.80 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 min and then to it was added a solution of alkynyl imine **2a** (49.9 mg, 0.20 mmol) in diethylene glycol dimethyl ether (2.0 mL). The resulting reaction mixture was stirred at 160 °C for 3.0 h and then cooled to room temperature. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (ammonia solution in dichloromethane/methanol, 20:1) to give 2-iminopyridine **3a** as a brown oil (50.8 mg, 70%).

3a: IR (neat): $\tilde{\nu}$ = 3348, 3058, 2983, 2837, 1695, 1624, 1566, 1513, 1445, 1369, 1294, 1250, 1177, 1109, 1032, 958, 916, 845, 772, 704 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.29–7.39 (m, 5 H), 7.05–7.07 (m, 2 H), 6.89–6.92 (m, 2 H), 5.19 (s, 2 H), 3.88 (q, J = 7.0 Hz, 2 H), 3.79 (s, 3 H), 1.74 (s, 3 H), 0.87 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 165.3, 159.7, 159.3, 142.9, 141.4, 139.7, 129.5, 127.9, 127.8, 127.8, 127.0, 123.6, 114.2, 107.5, 60.0, 55.2, 53.8, 15.3, 13.6 ppm. HRMS (EI): calcd. for $C_{23}H_{24}N_2O_3$ 376.1787 $[M]^+$; found 376.1786.

3b: Yellow oil. IR (neat): $\tilde{\nu}$ = 3352, 3020, 2936, 2858, 2838, 1710, 1626, 1560, 1513, 1442, 1371, 1293, 1249, 1218, 1181, 1107, 1034, 979, 919, 780, 765, 748, 735, 669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 1 H), 7.26–7.28 (m, 2 H), 6.88–7.05 (m, 2 H), 5.32–5.37 (m, 1 H), 5.16 (d, J = 14.5 Hz, 1 H), 5.11 (d, J = 14.5 Hz, 1 H), 4.14–4.21 (m, 2 H), 3.78 (s, 3 H), 2.19–2.26 (m, 1 H), 2.11–2.16 (m, 2 H), 1.97 (s, 3 H), 1.86–1.93 (m, 1 H), 1.72–1.78 (m, 3 H), 1.58–1.67 (m, 1 H), 1.26 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 165.0, 159.9, 159.2, 145.2, 141.6, 136.7, 129.4, 127.9, 123.7, 122.1, 114.2, 107.1, 60.1, 55.2, 53.7, 29.1, 25.0, 22.7, 21.9, 14.6, 14.4 ppm. HRMS (EI): calcd. for $C_{23}H_{28}N_2O_3$ 380.2100 $[M]^+$; found 380.2101.

3c: Brown oil. IR (neat): $\tilde{\nu}$ = 3352, 2956, 1705, 1627, 1560, 1512, 1444, 1378, 1287, 1251, 1211, 1165, 1076, 1031, 959, 918, 815, 773 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (s, 1 H), 7.23–7.26 (m, 2 H), 6.87–6.90 (m, 2 H), 5.13 (s, 2 H), 4.21 (q, J = 7.0 Hz, 2 H), 3.79 (s, 3 H), 2.83 (t, J = 7.6 Hz, 2 H), 2.01 (s, 3 H), 1.39–1.46 (m 4 H), 1.29 (t, J = 7.0 Hz, 3 H), 0.94 (t, J = 6.9 Hz, 3 H) ppm. ^{13}CNMR (126 MHz, $CDCl_3$): δ = 165.3, 159.4, 159.1, 143.6, 141.8, 129.1, 127.9, 122.3, 114.0, 106.7, 60.0, 55.1, 53.6, 31.7, 29.8, 22.9, 14.1, 13.8, 13.4 ppm. HRMS (EI): calcd. for $C_{21}H_{28}N_2O_3$ 356.2100 $[M]^+$; found 356.2063.

Synthesis of 2-Iminopyridines 3d, 3h–l, 9 and 11 (Conditions B): A solution of ethyl 2-cyano-2-phenylacetate (**1b**) (189 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added to solid 95% KHMDS (168 mg, 0.80 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 min and then a solution of the alkynyl imine **2a** (49.9 mg, 0.20 mmol) in 1,4-dioxane (2.0 mL) was added. The resulting reaction mixture was stirred under reflux for 45.0 h and then cooled to room temperature. A saturated aqueous $NaHCO_3$ solution (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (ammonia solution in dichloromethane/methanol, 20:1) to give 2-iminopyridine (**3d**) as a light brown solid (44.4 mg, 51%).

3d: M.p. 142–143 °C. IR (KBr): $\tilde{\nu}$ = 3316, 2947, 2832, 1718, 1624, 1553, 1511, 1438, 1388, 1360, 1302, 1244, 1208, 1173, 1120, 1077, 1031, 961, 874, 799, 762, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.38–7.42 (m, 2 H), 6.89–7.20 (m, 12 H), 5.19 (s, 2 H), 3.89 (q, J = 7.0 Hz, 2 H), 3.82 (s, 3 H), 0.85 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 165.3, 159.7, 159.4, 143.4, 142.9, 138.6, 135.4, 130.5, 130.2, 129.8, 128.4, 128.4, 127.7, 127.4, 127.0, 126.5, 114.3 107.7, 60.1, 55.2, 53.8, 13.6 ppm. HRMS (EI): calcd. for $C_{28}H_{26}N_2O_3$ 438.1943 $[M]^+$; found 438.1997.

3h: White solid; m.p. 118–119 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3444, 3061, 2970, 2842, 1694, 1619, 1562, 1510, 1447, 1372, 1303, 1229, 1143, 1081, 1021, 923, 836, 797, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.39–7.42 (m, 2 H), 7.17–7.20 (m, 2 H), 7.08–7.14 (m, 4 H), 7.00–7.05 (m, 4 H), 6.95–6.98 (m, 2 H), 3.94 (q, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 0.92 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.2, 159.5, 143.7, 138.5, 130.5, 128.4, 128.1, 127.4, 127.1, 126.6, 114.9, 108.0, 60.2, 55.5, 13.7 ppm. HRMS (EI): calcd. for $C_{27}H_{24}N_2O_3$ 424.1787 $[M]^+$; found 424.1797.

3i: Brown solid; m.p. 110–111 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 2930, 2838, 1719, 1622, 1559, 1511, 1442, 1368, 1308, 1256, 1201, 1080, 1128, 1074, 1024, 900, 837, 799, 766, 737, 704, 603 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.20–7.30 (m, 5 H), 7.06–7.10 (m, 2 H), 6.90–6.95 (m, 2 H), 5.18–5.22 (m, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.76 (s, 3 H), 1.05–2.15 [m, 11 H, including a triplet at δ = 1.20 (J = 7.2 Hz, 3 H)] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.8, 160.6, 159.4, 146.5, 143.7, 135.7, 135.5, 134.8, 129.5, 128.3, 128.0, 127.5, 126.0, 114.8, 107.8, 60.3, 55.5, 29.3, 24.8, 22.3, 21.5, 14.3 ppm. HRMS (EI): calcd. for $C_{27}H_{28}N_2O_3$ 428.2100 $[M]^+$; found 428.2127.

3j: Brown oil. IR (neat): $\tilde{\nu}$ = 3314, 2928, 1710, 1619, 1559, 1507, 1459, 1416, 1367, 1296, 1223, 1173, 1071, 1035, 833, 797, 736, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.44–7.47 (m, 2 H), 7.31–7.39 (m, 3 H), 7.18–7.22 (m, 2 H), 6.99–7.02 (m, 2 H), 4.25 (q, J = 7.2 Hz, 2 H), 3.83 (s, 3 H), 2.50–2.57 (m, 2 H), 1.33–1.40 (m, 2 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.14–1.21 (m, 2 H), 0.73 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.2, 160.5, 159.4, 145.5, 144.3, 135.9, 134.8, 130.1, 129.9, 129.1, 128.1, 128.0, 114.8, 107.0, 60.3, 55.5, 32.4 30.9, 22.8, 14.3, 13.6 ppm. HRMS (EI): calcd. for $C_{25}H_{28}N_2O_3$ 404.2100 $[M]^+$; found 404.2104.

3k: Brown solid; m.p. 113–114 °C. IR (KBr): $\tilde{\nu}$ = 3433, 3058, 2959, 1705, 1633, 1562, 1505, 1414, 1365, 1312, 1284, 1248, 1218, 1175, 1132, 1029, 903, 852, 767, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.92 (s, 1 H), 7.32–7.40 (m, 5 H), 7.15–7.20 (m, 2 H), 7.03–7.08 (m, 2 H), 5.74–5.88 (m, 1 H), 4.92–5.06 (m, 2 H), 3.91 (q, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 3.03 (d, J = 4.9 Hz, 2 H), 0.91 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, CDCl3): δ = 165.1, 159.7, 144.2, 142.3, 139.0, 134.7, 128.3, 127.7, 127.6, 127.1, 116.0, 115.1, 107.8, 60.1, 55.5, 33.5, 13.7 ppm. HRMS (EI): calcd. for $C_{24}H_{24}N_2O_3$ 388.1787 $[M]^+$; found 388.1789.

3l: Brown solid; m.p. 109–111 °C. IR (KBr): $\tilde{\nu}$ = 3304, 3074, 2930, 2837, 1715, 1629, 1564, 1510, 1414, 1366, 1286, 1247, 1170, 1122, 1030, 913, 838, 783, 734 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.26–7.29 (m, 2 H), 7.00–7.03 (m, 2 H), 5.83–5.93 (m, 1 H), 5.43–5.47 (m, 1 H), 5.10 (d, J = 17.1 Hz, 1 H), 5.05 (d, J = 10.1 Hz, 1 H), 4.15–4.24 (m, 2 H), 3.85 (s, 3 H), 3.34 (dd, J = 15.0, 5.6 Hz, 1 H), 3.24 (dd, J = 15.0, 5.8 Hz, 1 H), 2.25–2.32 (m, 1 H), 2.13–2.18 (m, 2 H), 1.94–2.01 (m, 1 H), 1.73–1.81 (m, 3 H), 1.60–

1.68 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.8, 159.6, 158.7, 146.5, 142.6, 136.1, 135.7, 134.1, 128.3, 125.3, 123.9, 115.9, 115.1, 107.2, 60.1, 55.5, 33.3, 29.4, 25.0, 22.7, 21.9, 14.4 ppm. HRMS (EI): calcd. for $C_{24}H_{28}N_2O_3$ 392.2100 $[M]^+$; found 392.2142.

9: Brown solid; m.p. 110–111 °C. IR (KBr): $\tilde{\nu}$ = 3451, 3048, 2977, 2925, 1650, 1587, 1490, 1442, 1397, 1372, 1305, 1265, 1214, 1148, 1036, 980, 908, 829, 768, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, J = 4.6 Hz, 1 H), 7.32–7.39 (m, 3 H), 7.07–7.10 (m, 3 H), 3.86–3.91 (m, 2 H), 1.81 (s, 3 H), 0.69–0.73 (m, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.2, 157.8, 152.9, 143.6, 140.8, 127.8, 127.7, 126.7, 124.8, 115.1, 113.9, 99.6, 60.0, 14.9, 13.3 ppm. HRMS (EI): calcd. for $C_{17}H_{16}N_2O_2S$ 312.0933 $[M]^+$; found 312.0932.

11: Yellow oil. IR (neat): $\tilde{\nu}$ = 3442, 2931, 2856, 2198, 1716, 1621, 1553, 1509, 1446, 1378, 1300, 1253, 1227, 1174, 1140, 1079, 1022, 919, 835, 783 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18–7.22 (m, 2 H), 7.02–7.06 (m, 2 H), 5.76–5.80 (m, 1 H), 5.56–5.60 (m, 1 H), 4.24–4.34 (m, 1 H), 4.12–4.22 (m, 1 H), 3.87 (s, 3 H), 2.61 (m, 1 H), 2.11 (s, 3 H), 2.09–2.01 (m, 3 H), 1.75–1.51 (m, 8 H), 1.49–1.47 (m, 4 H), 1.33 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 159.8, 159.0, 143.9, 137.8, 136.0, 132.2, 130.1, 128.0, 126.2, 125.6, 119.6, 117.4, 115.1, 103.3, 79.5, 74.7, 61.1, 55.6, 28.9, 27.9, 25.7, 25.0, 22.6, 21.8, 21.1, 15.3, 14.2 ppm. HRMS (EI): calcd. for $C_{30}H_{34}N_2O_3$ 470.2569 $[M]^+$; found 470.2510.

Synthesis of 2-Iminopyridines 3e–g (Conditions C): A solution of ethyl 2-cyanopropanoate (**1a**) (131 mg, 1.0 mmol) in 1,4-dioxane (2.0 mL) was added to KHMDS (1.3 mL, 0.45 M in toluene, 0.77 mmol) at room temperature. The reaction mixture was stirred at room temperature for 10 min, and then a solution of the alkynyl imine **2d** (47.1 mg, 0.20 mmol) in 1,4-dioxane (2.0 mL) was added. The resulting reaction mixture was stirred at 160 °C for 25.0 h and then cooled to room temperature. A saturated aqueous $NaHCO_3$ solution (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (ammonia solution in dichloromethane/methanol, 20:1) to give 2-iminopyridine **3e** as a yellow solid (58.6 mg, 81%).

3e: M.p. 123–124 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 3302, 3019, 2963, 2841, 1711, 1632, 1562, 1510, 1463, 1444, 1418, 1373, 1356, 1293, 1221, 1167, 1132, 1070, 1029, 960, 909, 882, 855, 835, 782, 764, 739, 704, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.38–7.42 (m, 2 H), 7.32–7.37 (m, 3 H), 7.13–7.17 (m, 2 H), 7.05–7.08 (m, 2 H), 3.92 (q, J = 7.0 Hz, 2 H), 3.88 (s, 3 H), 1.85 (s, 3 H), 0.92 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.2, 159.8, 143.2, 141.4, 139.5, 128.4, 127.9, 127.8, 127.0, 115.3, 108.1, 60.1, 55.5, 15.7, 13.7 ppm. HRMS (EI): calcd. for $C_{22}H_{22}N_2O_3$ 362.1630 $[M]^+$; found 362.1621.

3f: Brown oil. IR (neat): $\tilde{\nu}$ = 3301 3021, 1708, 1630, 1513, 1425, 1371, 1293, 1218, 1136, 1034, 927, 746, 673 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.26–7.29 (m, 2 H), 7.01–7.04 (m, 2 H), 5.40–5.42 (m, 1 H), 4.17–4.22 (m, 2 H), 3.86 (s, 3 H), 2.26–2.32 (m, 1 H), 2.14–2.18 (m, 2 H), 2.05 (s, 3 H), 1.95–2.01 (m, 1 H), 1.75–1.82 (m, 3 H), 1.63–1.70 (m, 1 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}CNMR (126 MHz, $CDCl_3$): δ = 165.1, 159.7, 145.5, 141.7, 136.7, 128.4, 123.8, 115.2, 107.6, 60.2, 55.6, 29.1 25.1, 22.7, 22.0, 14.9, 14.4 ppm. HRMS (EI): calcd. for $C_{22}H_{26}N_2O_3$ 366.1943 $[M]^+$; found 366.1918.

3g: Brown oil. IR (neat): $\tilde{\nu}$ = 3453, 2959, 2929, 1709, 1635, 1560, 1511, 1463, 1369, 1290, 1252, 1218, 1152, 1087, 1015, 962, 836, 775 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, 1 H), 7.24–7.27 (m, 2 H), 7.02–7.05 (m, 2 H), 4.22 (q, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 2.88 (t, J = 7.8 Hz, 2 H), 2.12 (t, 3 H), 1.43–1.52 (m, 4 H), 1.29 (t, J = 7.2 Hz, 3 H), 0.97 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.5, 159.8, 159.0, 144.1, 141.9, 133.8, 128.5, 124.5, 115.3, 107.6, 60.3, 55.6, 31.7, 29.9, 23.1, 14.3, 13.9.13.7 ppm. HRMS (EI): calcd. for $C_{20}H_{26}N_2O_3$ 342.1943 $[M]^+$; found 342.2008.

Synthesis of 2-Aminopyridines 12a–c: A solution of trifluoromethansulfonic acid (3.2 mL, 0.02 M in trifluoroacetic acid, 0.064 mmol) was added to iminopyridine **3a** (24.0 mg, 0.064 mmol) at room temperature. The reaction mixture was stirred under reflux for 24 h and then cooled to room temperature. A saturated aqueous $NaHCO_3$ solution (15 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried with sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (ammonia solution in dichloromethane/methanol, 50:1) to give 2-aminopyridine **12a** as a white oil (11.3 mg, 70%).

12a: M.p. 83–84 °C. IR (KBr): $\tilde{\nu}$ = 3415, 2987, 2935, 2873, 1702, 1606, 1583, 1547, 1472, 1428, 1371, 1328, 1294, 1270, 1211, 1180, 1153, 1094, 1028, 963, 861 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.34–7.42 (m, 3 H), 7.09–7.12 (m, 2 H), 4.98 (br. s, 2 H), 3.98 (q, J = 7.3 Hz, 2 H), 1.83 (s, 3 H), 0.96 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.6, 159.5, 150.7, 148.8, 139.1, 127.9, 127.2, 117.5, 114.2 60.2, 13.8, 13.7 ppm. HRMS (EI): calcd. for $C_{15}H_{16}N_2O_2$ 256.1212 $[M]^+$; found 256.1132.

12b: Yellow oil. IR (neat): $\tilde{\nu}$ = 3300, 3135, 2927, 2860, 1711, 1638, 1589, 1550, 1429, 1385, 1269, 1167, 1092, 1025, 969, 793 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1 H), 4.73 (br. s, 2 H), 4.31 (q, J = 7.0 Hz, 2 H), 2.96–2.99 (m, 2 H), 2.09 (s, 3 H), 1.41–1.52 (m, 4 H), 1.36 (t, J = 7.2 Hz, 3 H), 0.96 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 159.3, 152.0, 149.4, 117.0, 113.8, 60.3, 32.1, 29.4, 23.1, 14.3, 13.9, 12.2 ppm. HRMS (EI): calcd. for $C_{13}H_{20}N_2O_2$ 236.1525 $[M]^+$; found 236.1498.

12c: Brown solid; m.p. 130–131 °C. IR (KBr): $\tilde{\nu}$ = 3417, 3360, 3304, 3053, 2982, 1696, 1640, 1605, 1576, 1469, 1437, 1393, 1368, 1305, 1273, 1213, 1151, 1117, 1073, 1044, 1022, 910, 811, 759, 735, 700 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 7.16–7.27 (m, 3 H), 7.09–7.14 (m, 3 H), 7.02–7.05 (m, 2 H), 6.92–6.95 (m, 2 H), 4.84 (br. s, 2 H), 4.01 (q, J = 7.0 Hz, 2 H), 0.95 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.7, 158.7, 150.7, 150.5, 138.2, 135.2, 130.3, 128.7, 128.6, 127.5, 127.2, 126.8, 120.6, 117.5, 60.3, 13.7 ppm. HRMS (EI): calcd. for $C_{20}H_{18}N_2O_2$ 318.1368 $[M]^+$; found 318.1368.

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