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Microwave-Assisted Bohlmann–Rahtz Synthesis of Highly-Substituted 2-Aminonicotinates

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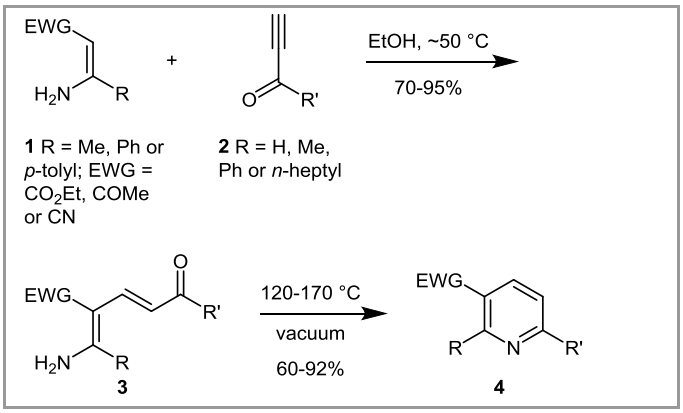
Abstract: Microwave irradiation of 2-carbethoxyacetamidine and an ethynyl ketone under acidic or basic conditions in ethanol at 150 °C for 1.5 h facilitated Bohlmann-Rahtz pyridine synthesis to give highly-substituted ethyl 2-aminonicotinates with total regio-control and in reasonable to excellent yield, following purification by immobilization upon an acidic resin.

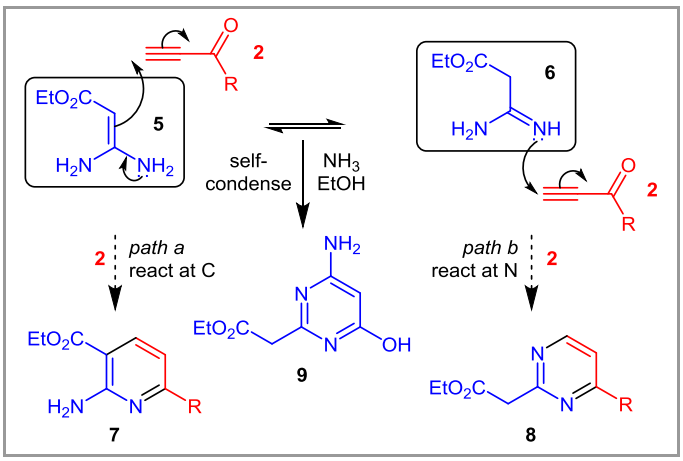
Key words: 2-aminopyridines, heterocycles, ethynyl ketones, microwave synthesis, catch-and-release

Bohlmann and Rahtz first reported the two-step synthesis of trisubstituted pyridines by the reaction of enamines **1** and ethynyl ketones or aldehydes, **2**, in 1957 (Scheme 1).[1] This cyclocondensation process is completely regioselective and proceeds by Michael addition, enamine *C*-functionalization giving a kinetically stable aminodiene intermediate **3** that can be isolated and purified, before heating at temperatures of 120–170 °C to promote *E/Z*-isomerization and spontaneous cyclodehydration to give 2,3,6-trisubstituted pyridines **4** in good overall yield.

Following its initial discovery, the Bohlmann–Rahtz pyridine synthesis received little attention for 40 years, after which it has seen many applications,[2-26] in particular for the synthesis of the 2,3,6-trisubstituted pyridine domain of thiopeptide antibiotics.[3-6] These studies have identified milder experimental procedures that are regio-, chemo- and even stereospecific, for potential application in natural product chemistry and target synthesis, and have provided alternative processing methods, such as the use of microwave dielectric heating, microwave flow reactors and continuous processing to enable the scale up of methodology.[2] Yet despite all of these advances, the Bohlmann-Rahtz pyridine synthesis is still frustrated by essentially the same limited substrate scope established in the original report[1] and so has only been used for the synthesis of alkyl-, aryl- or heteroaryl-substituted pyridines bearing electron-withdrawing groups. Indeed, the presence of an electron-withdrawing group, such as an ester, amide or nitrile, is essential for enamine **2** stabilization in this process. Some progress has been made towards the synthesis of 5-bromopyridines through capture of the aminodienone intermediate **3** with NBS,[27] but the synthesis of electron-rich pyridines by a Bohlmann-Rahtz approach was unrealized.



Scheme 1 Two-step pyridine synthesis, as reported by Bohlmann and Rahtz in 1957[1]

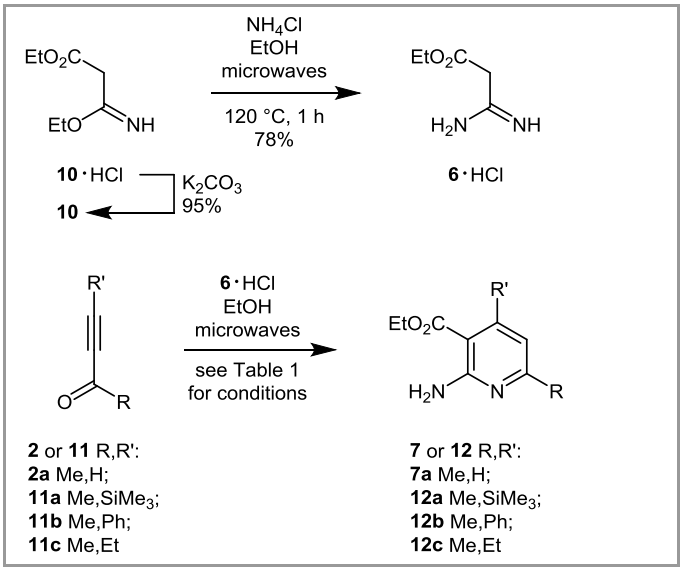


Scheme 2 Possible reaction pathways due to methylenediamine **5** -acetamidine **6** tautomerization

Herein, we describe a new rapid method for the synthesis of 2-aminopyridines using the Bohlmann-Rahtz reaction. Our disconnective scheme approached their synthesis using methylenediamine **5** in cyclocondensation with an ethynyl ketone (Scheme 2). 2-Aminonicotinates have been prepared before from precursor **5** by condensation with dicarbonyl compounds,[28] chromone derivatives,[29] chalcones using ethyl cyanoacetate and ammonium acetate adsorbed over neutral alumina,[30] β-aminovinyl ketones,[31] and β-methoxyvinyl ketones, or their corresponding sodio enolates in the presence of acetic acid, in the synthesis of naphthyridine-3-carboxamides as novel DNA ligase inhibitors.[32] Furthermore, related methylenediamines derived from phenyl cyanomethanesulfonate have been shown[33] to give 2-aminopyridines in Guareschi-Thorpe type reactions and so it was not unrea-

sonable that a similar profile of reactivity could be promoted for this bis-nucleophile in a Bohlmann-Rahtz process. However, diaminopropenoate **5** could be in dynamic equilibrium with the carbethoxyacetamidine tautomer (**6**) and it is known that amidines react readily with ethynyl ketones under both acidic and basic conditions to give pyrimidines,[34-36] so it was not at all obvious whether this approach was viable and would proceed through enamine *C*-functionalization (*path a*), to give aminopyridine **7**, or *N*-functionalization (*e.g. path b*), to give pyrimidine **8**, or whether a mixture of products would be obtained. It has long been known that carbethoxyacetamidine (**6**) undergoes self-condensation to give the pyrimidine derivative **9** under basic conditions,[37] routes to a number of 2-phenacylpyrimidine derivatives have been described by cyclocondensation of benzoylacetamidine,[38] and amidine **6** has been reported to give a mixture of pyridine- and pyrimidine-containing cyclocondensation products in a 2:3 ratio, which were difficult to separate, on reaction with a related prop-2-enylidine bis-electrophile.[39] Nonetheless, given our understanding of the Bohlmann-Rahtz reaction, as well as the precedent that the related hydroacetate salts of iminopropanoates[40] and a range of amidinoacetic esters[41] undergo *C*-alkylative Michael addition in the synthesis of Hantzsch dihydropyridines, the Bohlmann-Rahtz reaction of these derivatives seemed worthy of investigation.

Iminopropanoate hydrochloride **6**·HCl was prepared by a modification of a known route,[40,41] adopting microwave-assisted conditions and avoiding the use of anhydrous HCl gas, to dramatically shorten reaction times and simplify experimental procedures. To that end, ethyl imidate hydrochloride **10**·HCl was transformed to the free base **10** (observed, spectroscopically, as predominantly the enamine tautomer in $CHCl_3$) and reacted with ammonium chloride in EtOH under microwave irradiation at 120 °C for 1 h (Scheme 3) to give acetamidine hydrochloride **6**·HCl after a simple trituration. Reaction of amidine **6**·HCl with ethynyl ketone **2a**, or substituted derivatives (**11a-c**) thereof, using a range of different conditions (Table 1) indicated that Bohlmann-Rahtz cyclocondensation was indeed observed to some extent in all of these acid-mediated methods. Furthermore, only a single pyridine regioisomer was identified, proposed to be the product of Michael *C*-addition (Scheme 2, *path a*) with spontaneous *E*/*Z*-isomerization and cyclodehydration occurring under the reaction conditions. A number of trends were noted. High temperature conditions were required and the presence of additional acid (AcOH) appeared to facilitate the reaction of 4-(trimethylsilyl)butynone **11a** (entry 2 *vs*. 4; entry 5 *vs*. 6), presumably by accelerating protodesilylation in accordance with our previous observations on acid-catalyzed Bohlmann-Rahtz reactions.[20] Despite most procedures appearing to be effective, from spectroscopic analysis of the crude reaction mixtures, the isolated yields of either trisubstituted **7a** or tetrasubstituted pyridines **12b,c** were always moderate at best, after purification by column chromatography (entries 1-8), with small variation depending upon the substrate. Switching to an alternative isolation method and replacing chromatographic purification with immobilization upon a sulfonic acid resin, a related process which we have used before for isolating pyridine combinatorial libraries,[16] and eluting with alcoholic ammonia (entry 9) or alcoholic aqueous ammonia (entry 10), gave an immediate improvement in the isolated yield, even for highly unreactive substrates (**11c**) (entry 10). For butynone **2a**, irradiating the mixture at 150 °C for 1.5 h in the absence of acetic acid, followed by aqueous work up and immobilization on the resin, gave pyridine **7a** in excellent yield (entry 11), demonstrating that the Bohlmann-Rahtz synthesis of 2-aminonicotinates was viable and efficient.



Scheme 3 Synthesis of trisubstituted-**7** and tetrasubstituted 2-aminopyridines **12** using assorted Bohlmann-Rahtz methods

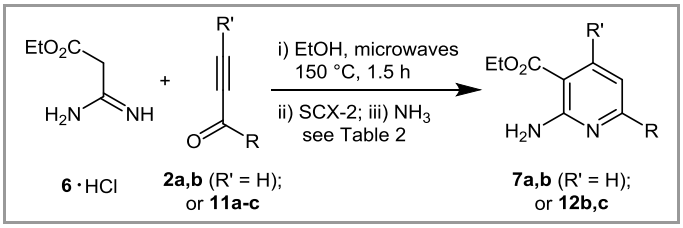
Table 1 Optimizing reaction conditions for the Bohlmann-Rahtz synthesis of 2-aminopyridines[a]

Entry	Substrate	Product	Acid[b]	Conditions[c]	Yield%
1	**2a**	**7a**	AcOH	140 °C, 1 h	38
2	**11a**	**7a**	AcOH	140 °C, 1 h	29
3	**11a**	**7a**	AcOH	150 °C, 1 h	33
4	**11a**	**7a**:**12a**	None	140 °C, 1 h	(7:5)[d]
5	**11a**	**7a**	AcOH	Reflux,[e] 24 h	34
6	**11a**	**7a**	None	Reflux,[e] 24 h	11
7	**11b**	**12b**	AcOH	140 °C, 1 h	25
8	**11c**	**12c**	AcOH	140 °C, 1 h	12
9	**11a**	**7a**	AcOH	140 °C, 1 h	60[f]
10	**11c**	**12c**	AcOH	150 °C, 1.5 h	29[f]
11	**2a**	**7a**	None	150 °C, 1.5 h	87[f]

[a] Isolated yields after reaction of amidine **6**·HCl (1 equiv.) with ethynyl ketone **2a** or **11** (1.1-1.7 equiv.) under the given conditions in EtOH, followed by purification by column chromatography on silica, unless stated otherwise.
[b] A Brønsted acid (AcOH) was added by carrying out the reaction in EtOH–AcOH (5:1 *v*/*v*) under the given conditions, followed by basic work up and purification by column chromatography on silica, unless stated otherwise.
[c] The reaction was carried out in a sealed Pyrex™ tube (10 mL) for the given time (hold-time) by microwave irradiation at the specified temperature using a single-mode microwave synthesizer (CEM Discover®) by moderation of the initial magnetron power (200 W).

[d] Isolated yield not determined as a mixture of trisubstituted-**7a** and tetrasubstituted pyridine **12a** was obtained (ratio given in parentheses, determined by ^{1}H NMR spectroscopic analysis).
[e] The reaction was carried out under traditional conductive heating in an open vessel.
[f] Isolated yield after basic work-up, followed by immobilization on a Biotage ISOLUTE SCX-2 column, eluting with methanolic ammonia (entry 9) or EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) (entries 10 and 11).

In order to progress towards a method suitable for the synthesis of pyridine arrays, the optimized microwave-assisted procedure was investigated, with or without the use of an aqueous work up prior to immobilization on SCX-2 resin (Table 2). A small range of ethynyl ketones was studied (Scheme 4), including the highly-reactive butynone **2a** and unreactive hexynone **11c**. In related acid-catalyzed Bohlmann-Rahtz methods, terminally-substituted alkynes retard the Michael addition and so commonly give lower yields of their respective pyridine products.[2,20] A similar trend was observed for this reaction (entry 1 *vs*. 3) and the process was still poorly efficient for the unreactive hexynone **11c** (entry 3). 4-(Trimethylsilyl)butynone **11a** was also not ideal as a substrate in this reaction as protodesilylation was incomplete under the chosen conditions (entry 4). However, for all of the other substrates, including 4-phenylbutynone **11b** (entries 5 and 6), the reaction was efficient. The use of an aqueous work-up made little difference to the isolated yield (entry 1 *vs*. 2; entry 5 *vs*. 6) and so, with simple immobilization upon an acidic resin, this experimental procedure[42] would appear to be highly amenable for array production. In all cases only a single pyridine regioisomer was isolated, in a reaction course that was consistent with the proposed Bohlmann-Rahtz mechanism,[2] proceeding by *C*-functionalization of diaminopropenoate tautomer **5** (Scheme 2, *path a*), followed by cyclodehydration.



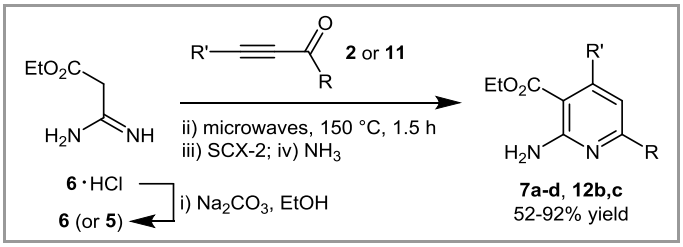
Scheme 4 Acid-mediated Bohlmann-Rahtz synthesis of 2-aminonicotinates **7a,b** and **12b,c**

Table 2 Isolated yields of 2-aminonicotinates **7a,b** and **12b,c** from the acid-mediated Bohlmann-Rahtz reaction of **6**·HCl and a range of ethynyl ketones[a]

Entry	**2**/**11**[b]	R	R′	**7**/**12**[c]	Work-up[d]	Yield%
1	**2a**	Me	H	**7a**	Yes	87
2	**2a**	Me	H	**7a**	No	82
3	**11c**	Me	Et	**12c**	Yes	29
4	**11a**	Me	$SiMe_3$	**7a**	No	n.d.[e]
5	**11b**	Me	Ph	**12b**	Yes	71
6	**11b**	Me	Ph	**12b**	No	71
7	**2b**	Ph	H	**7b**	No	73

n.d. denotes not determined.
[a] Isolated yield of 2-aminopyridine **7** or **12** after microwave irradiation of amidine **6**·HCl (1 equiv.) and ethynyl ketone **2a** or **11** (1.1 equiv.) in EtOH in a sealed Pyrex™ tube at 150 °C for 1.5 h (hold-time), by moderation of the initial magnetron power (200 W). After cooling, the solution was immobilized on a Biotage ISOLUTE SCX-2 column, eluting with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*).
[b] Ethynyl ketone **2** (R′ = H) or **11**, with substituents R and R′ as shown.
[c] Pyridine product, either trisubstituted **7** (R′ = H) or tetrasubstituted **11**, with substituents R and R′ as shown.
[d] Work-up indicates that, after cooling, the mixture was partitioned between aqueous $NaHCO_3$ solution and EtOAc. The organic extracts were combined, evaporated *in vacuo* and immobilized on a Biotage ISOLUTE SCX-2 column, eluting with EtOH–aq. NH_4OH (5:1 *v*/*v*).
[e] Incomplete protodesilylation occurred under the reaction conditions.

In order to understand the chemoselectivity of the process, and why it appeared that pyridines rather than pyrimidines were produced, conditions which one might expect would favour pyrimidine production[35] were investigated under microwave irradiation. Amidine hydrochloride **6**·HCl was transformed to the free base **6** (and/or tautomer **5**), by pre-treatment with Na_2CO_3 (Scheme 5), and reacted with six ethynyl ketones (**2a-d** and **11b,c**), of differing reactivity, in EtOH at 150 °C (Table 3). After cooling, the reaction mixture was immobilized directly, as before on a sulfonic acid resin, then eluted with ethanolic ammonia or aqueous ethanolic ammonia.[43] Surprisingly, the corresponding 2-aminopyridine product[44] was isolated in all cases and, for the most part, in comparable or improved yield (with the exception of entry 3). This demonstrated a clear reactivity profile: under microwave irradiation at high temperature, carbethoxyacetamidine (**6**) reacts with a range of ethynyl ketones in Bohlmann-Rahtz pyridine synthesis, under either acidic or basic conditions, to give highly-substituted 2-aminonicotinates in moderate to excellent yield.



Scheme 5 Base-mediated procedure for the Bohlmann-Rahtz synthesis of 2-aminonicotinates **7a-d** and **12b,c**

Table 3 Isolated yields of 2-aminonicotinates **7a-d** and **12b,c** from the base-mediated procedure[a]

Entry	Substrate	Product	R	R′	Yield%
1	**2a**	**7a**	Me	H	84
2	**2b**	**7b**	Ph	H	92
3	**11b**	**12b**	Me	Ph	52
4	**11c**	**12c**	Me	Et	54
5	**2c**	**7c**	*p*-C_6H_4Cl	H	72
6	**2d**	**7d**	*p*-anisyl	H	71

[a] The reaction was carried out using the amidine free-base **6** (and/or **5**), generated by pre-treatment of **6**·HCl with Na_2CO_3 (1 equiv.) in EtOH for 10 min prior to the addition of the ethynyl ketone. After irradiation at 150 °C for 1.5 h (hold-time), the mixture was immobilized on a Biotage ISOLUTE SCX-2 column, eluting with

ethanolic ammonia (2 M) (entries 1-4) or EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) (entries 5 and 6).

In conclusion, we have demonstrated that 2-carbethoxyacetamidine hydrochloride (**6**·HCl) may be easily and rapidly prepared under microwave-assisted conditions, simply by irradiating a mixture of the ethyl imidate free-base (**10**) and NH_4Cl in EtOH, and can be reacted with a range of ethynyl ketones by Bohlmann-Rahtz methods under both acidic and basic conditions upon microwave irradiation at 150 °C in EtOH for 1.5 h to give the corresponding highly-substituted 2-aminonicotinate in good yield and with total regiocontrol. Of the new processes that we have discovered, the base-mediated cyclocondensation would appear to be the most consistent. The method is amenable to high-throughput application and incorporates catch-and-release technology, using a sulfonic acid resin, to facilitate isolation of the products. Given the ready availability of automated technology for microwave-assisted chemistry, and our use of immobilization techniques for product purification, it is our hope that this new methodology can be applied in the synthesis of unique and highly-substituted 2-aminopyridine libraries for further derivatization or biological evaluation.

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(42) *Typical procedure for microwave-assisted synthesis of 2-aminonicotinates using hydrochloride salt **6**·HCl.* A solution of ethyl 3-amino-3-iminopropionate hydrochloride (**6**·HCl) (1 equiv.) and the ethynyl ketone (1.05 equiv.) in EtOH (3 mL) was irradiated at 150 °C for 1.5 h (hold-time) in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderation of the initial magnetron power (200 W). After cooling in a flow of com-

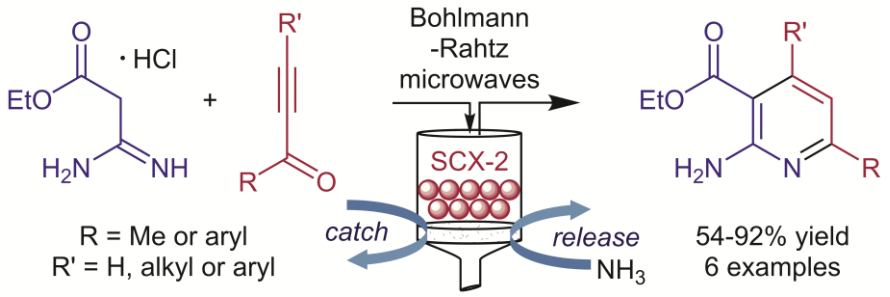
pressed air, the solution was immobilized on a Biotage ISOLUTE SCX-2 column and eluted with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) to give the title compound.

(43) *Typical procedure for microwave-assisted synthesis of 2-aminonicotinates using free base **6**.* An ethanolic solution of ethyl 3-amino-3-iminopropionate hydrochloride (**6**·HCl) (1 equiv.) was pre-treated with Na_2CO_3 (1 equiv.) for 10 min. After filtering, the ethynyl ketone (1.05 equiv.) was added and the mixture in EtOH (3.5 mL) was irradiated at 150 °C for 1.5 h (hold-time) in a pressure-rated glass tube (10 mL) using a CEM Discover microwave synthesizer by moderation of the initial magnetron power (200 W). After cooling in a flow of compressed air, the solution was immobilized on a Biotage ISOLUTE SCX-2 column and eluted with EtOH–NH_4OH (aq; 35%) (5:1 *v*/*v*) or ethanolic NH_3 (2 M) to give the title compound.

(44) See Supporting Information for detailed experimental procedures and characterization data for known compounds. *Ethyl 2-amino-6-methyl-4-phenylnicotinate* (**12b**) was prepared using the above procedure,[43] ethyl 3-amino-3-iminopropionate hydrochloride (**6**·HCl) (270 mg, 1.62 mmol), 4-phenyl-3-butyn-2-one (**11b**) (270 mg, 1.70 mmol) and Na_2CO_3 (270 mg, 1.62 mmol), in EtOH (3.5 mL), to give the title compound (216 mg, 52%) as a brown solid, mp 139 °C (Found MH^+, 257.1278. $C_{15}H_{17}N_2O_2$ [*MH*] requires 257.1285); ν_{max} (neat)/cm^{-1} 3443, 3272, 2977, 1682, 1606, 1582, 1241; δ_H (500 MHz; $CDCl_3$)/ppm 7.33-7.30 (3H, 3',4',5'-H), 7.20 (2H, m, 2',6'-H), 6.41 (1H, s, 5-H), 6.29 (2H, bs, NH_2), 3.88 (2H, q, J = 7.1 Hz, OCH_2), 2.37 (3H, s, Me), 0.69 (3H, t, J = 7.1 Hz); δ_C (125 MHz, $CDCl_3$)/ppm 168.5 (C), 160.3 (C), 158.7 (C), 153.8 (C), 141.5 (C), 127.9 (CH/CH), 127.4 (CH), 115.2 (CH), 104.7 (C), 60.4 (CH_2), 24.2 (Me), 13.1 (Me); *m/z* (EI) 256 ($M^{\bullet+}$). *Ethyl 2-amino-4-ethyl-6-methylnicotinate* (**12c**) was prepared using the above procedure,[43] ethyl 3-amino-3-iminopropionate hydrochloride (**6**·HCl) (200 mg, 1.26 mmol), 3-hexyn-2-one (128 mg, 1.32 mmol), and Na_2CO_3 (200 mg, 1.26 mmol) in EtOH (3.5 mL), to give the title compound (133 mg, 54%) as a brown solid, mp 141 °C (Found MH^+, 209.1282. $C_{11}H_{17}N_2O_2$ [*MH*] requires 209.1285); ν_{max} (neat)/cm^{-1} 3450, 3269, 3147, 2972, 1686, 1619, 1586; δ_H (500 MHz; $CDCl_3$)/ppm 6.33 (1H, s, 5-H), 6.19 (2H, bs, NH_2), 4.33 (2H, q, J = 7.0 Hz, OCH_2), 2.78 (2H, q, J = 7.0 Hz, 4-*CH*$_2$$CH_3$), 2.30 (3H, s, 6-Me), 1.36 (3H, t, J = 7.0 Hz, Me), 1.16 (3H, t, J = 7.0 Hz, 4-CH_2Me); δ_C (125 MHz, $CDCl_3$)/ppm 168.3 (C), 160.3 (C), 159.4 (C), 157.2 (C), 114.8 (CH), 104.6 (C), 60.7 (CH_2), 28.6 (CH_2), 23.9 (Me), 15.1 (Me), 14.0 (Me).

Short Title: Synthesis of Highly-Substituted 2-Aminonicotinates

Graphical Abstract:



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