First Synthesis of Methyl 2-Amino-6-Methoxynicotinate Using a Combination of Microwave and Flow Reaction Technologies

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Abstract: The synthesis of methyl 2-amino-6-methoxynicotinate, a valuable building block for the preparation of fused 2-pyridones, is reported. The optimized synthesis includes sequential microwave-induced regioselective 6-methoxylation, esterification, followed by microwave-induced reaction with *p*-methoxybenzylamine, and final deprotection under flow reaction hydrogenation conditions. Two key steps in the reported synthesis are a microwave-induced methoxylation and a microfluidic hydrogenation that afford improved regioselectivity and purity profile of the reaction products.

Key words: 2-pyridone, microwave, microfluidic reaction, cyclization, hydrogenation

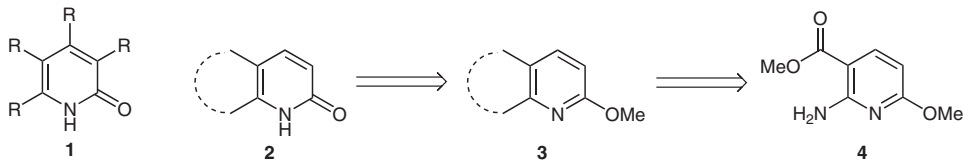
2-Pyridone **1** (Scheme 1) is a valuable structural motif in a variety of biologically relevant molecules. Both substituted and fused 2-pyridone core motifs are known as a promising class of inhibitors of HIV-1 non-nucleoside reverse transcriptase,[2] DNA gyrase,[3,4] and bacterial topoisomerase,[5] as noncompetitive inhibitors of MAPK kinase,[6] as ligands for the benzodiazepine binding site of the $GABA_A$ receptor,[7] and as 5-HT1A/5-HT2A receptor ligands.[8] The importance of pyridones in natural products and ring-construction methodologies has been reviewed recently.[9]

Fused pyridones **2** are of particular interest in our quest for new medicinally important building blocks, and retrosynthetically they can be derived from 2-amino-6-methoxynicotinate (**4**) through methoxy pyridine derivatives **3** (Scheme 1). We envisaged that the *ortho*-aminocarboxypyridine fragment can be further elaborated into a variety of heterocyclic systems[10] fused to the 2-pyridone ring. While being fascinated with the broad synthetic potential of compound **4**, we were surprised to discover that it is unknown in the literature and is not commercially available.[11]

We herein report the synthesis of methyl 2-amino-6-methoxynicotinate (**4**), a valuable building block for the synthesis of medicinally relevant compounds, starting from commercially available 2,6-dichloronicotinic acid (**5**).

The synthesis of 2-amino-6-methoxynicotinate starts from the preparation of 2-chloro-6-methoxynicotinic acid (**6**) by direct methoxylation of commercial 2,6-dichloronicotinic acid (**5**, Scheme 2). Our preliminary experiments as well as reports found in the literature revealed poor regioselectivity of the process.[12–15] In our hands the typical reaction mixture obtained from the reaction of **5** with sodium methoxide in methanol consisted of 2-chloro-6-methoxynicotinic acid (**6**), 6-chloro-2-methoxynicotinic acid (**7**), and 2,6-dimethoxynicotinic acid (**8**), with the predominant product being the undesired regioisomer **7**. Hirokawa and co-workers[12] previously reported similar results for the reaction of methyl 2,6-dichloronicotinate with sodium ethoxide in nonpolar media, although in alcoholic and polar aprotic medium (DMF) the reverse regioselectivity was observed. The regioisomer formation (1:1) was previously reported for 2-substituted derivatives of benzyl alcohol,[13] while in the case of {2,2-dimethyl-6-(9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}-methanol[14] predominant formation of the 2-isomer was observed. Switching to the use of potassium methoxide, formed in situ from potassium *tert*-butoxide in methanol, results in improved predominant formation of the 6-methoxy derivative **6**,[11] but requires extremely long reaction times.[15]

In our hands, similar results were obtained for the reaction between acid **5** and potassium methoxide, but, when the



Scheme 1 Retrosynthetic route of 2-pyridones

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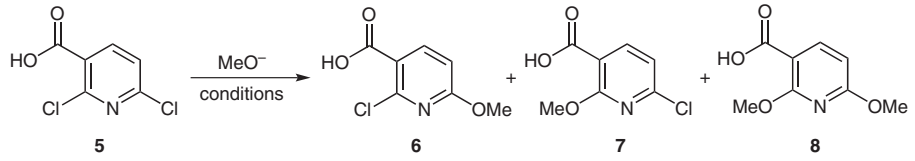


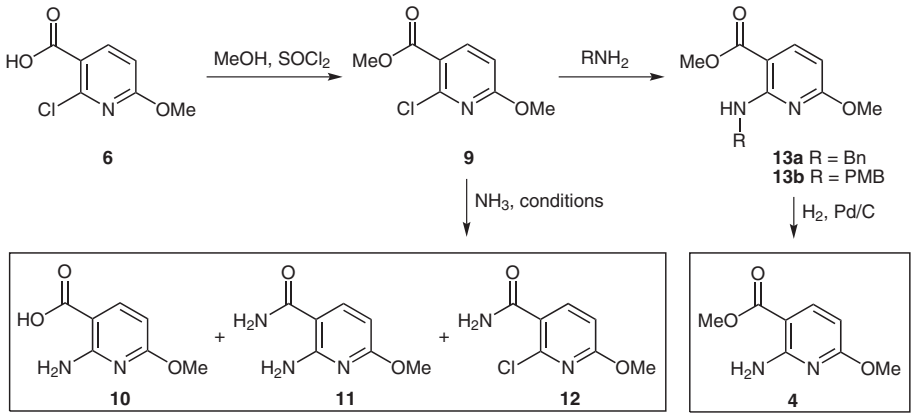
Scheme 2 Direct methoxylation of 2,6-dichloronicotinic acid

reaction was microwave irradiated at 300 W, a significant enhancement in both overall yield (ca. 90% yields of the crude mixture of **6**, **7**, and **8**) as well as regiochemistry was observed, giving **6** in 85–90% (^{1}H NMR analysis). Although neither this mixture nor the corresponding mixture of esters produced in 92–95% yields after simple esterification with $SOCl_2$/MeOH (Scheme 3, structures of esters derived from **7** and **8** omitted for clarity purposes) are separable under chromatography conditions, the crude product **9** was sufficiently pure to be used directly in the amination step (see Supporting Information for a typical LC-MS trace of the mixture).

Contrary to known amination chemistry using methylamine[14] and *p*-trifluoromethylbenzylamine,[16] our initial approach involving the reaction of crude chloro-intermediate **9** with ammonia proved to be problematic. Thus, reactions with ammonia in EtOH at reflux at atmospheric pressure or in an autoclave at 4 bar did not result in the formation of the 2-aminopyridine product; only starting material **9** was recovered.

Microwave conditions (ammonium hydroxide, EtOH, microwave at 300 W, 100 °C, 5 h) resulted in 60–70% conversion of the starting material, but the product was identified as a mixture of **10**, **11**, and **12** (26%, 60%, and 14%, respectively, based on HPLC-MS result). Therefore we set out to develop an alternate synthetic route. Upon reaction of crude **9** with benzylamine or *p*-methoxybenzylamine (10 equiv of amine, 1,4-dioxane, microwave at 300 W, 170 °C, 2 h) the corresponding derivatives **13a**,**b** were obtained in moderate to good isolated yields (45% and 67%, respectively) with excellent (>97% LC-MS and NMR) purities after purification by column chromatography. Similar reactions under conventional heating provided insufficient 17–25% conversion of **9** after 24 hours reflux (10 equiv of amine, 1,4-dioxane).

We further examined the deprotection of compounds **13a**,**b** to obtain the final product **4**. The first attempt was performed in EtOH in an autoclave under hydrogen pressure (3 bar) in the presence of 10% of Pd/C. In the case of benzyl derivative **13a** these reaction conditions were insufficient for the required deprotection; only trace amounts of product **4** were detected (HPLC-MS analysis) after 2 days at either ambient temperature or 70 °C. Nevertheless, these reaction conditions were successfully employed for the deprotection of **13b**, affording 85% isolated yield of the product after 48 hours (25 °C) to 30 hours (70 °C) reaction time. Implementation of H-Cube® technology for the deprotection of either **13a** or **13b** under flow-reaction hydrogenation conditions[18] was explored to optimize the reaction conditions.[18] Conducting the reaction in 'controlled mode'[17d] at 40 °C resulted in no product formation for debenzylation of **13a**. Similarly, the PMB deprotection resulted in only 9% of **4** being observed by LC-MS analysis. Switching to 'full hydrogenation mode'[17d] yielded 9%, 34%, and 87% conversion of the PMB derivative **13b** at 25 °C, 40 °C, and 70 °C, respectively, whereas a mediocre 41% conversion of **13a** to **4** was obtained at 70 °C under similar hydrogenation conditions. Based on our experimental observations, the use of the PMB-protected aniline **13b** was chosen as the preferred intermediate in this synthesis due to its ease of removal of protecting group compared to the analogous benzyl group **13a**. The optimized reaction conditions for the preparation of **4** involved the hydrogenolysis of **13b** (H-Cube®, full hydrogenation mode at 70 °C), which afforded 87–90% isolated yields in repeated syntheses of the target compound.



Scheme 3 Preparation of methyl 2-amino-6-methoxynicotinate on alternate synthetic route

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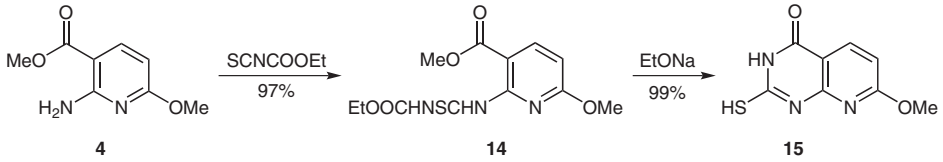

Scheme 4 Synthesis of the fused 2-pyridone system

In an additional proof of concept experiment, **4** was transformed into 7-methoxy-2-mercaptopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**15**, Scheme 4),[19] thus demonstrating the utility of 2-amino-6-methoxynicotinate in the synthesis of the fused 2-pyridone systems. The synthetic sequence involved reaction with ethoxycarbonyl isothiocyanate,[20] followed by cyclization of the intermediate thiourea **14** into 7-methoxy derivative **15**.[21]

In summary, we report herein the first synthesis of methyl 2-amino-6-methoxynicotinate (**4**) and proved its utility in the synthesis of fused 2-pyridone systems. The key features of the four-step process are microwave-induced regioselective 6-methoxylation, esterification, and sequential microwave-induced reaction with *p*-methoxybenzylamine followed by deprotection under flow-reaction hydrogenation conditions. The microwave-induced and microfluidic steps are advantageous and time-saving while maintaining the desired regioselectivity and improving the purity profile of the product. Further preparations of fused heterocyclic systems based on **4** are in progress and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **Experimental Procedures for the Preparation of Methyl 2-Amino-6-methoxynicotinate (4) and Fused Pyrimidines 14 and 15**

Procedures and analytical data for 2-chloro-6-methoxynicotinic acid (**6**) and methyl 2-chloro-6-methoxynicotinate (**9**), as well as methyl 2-[3-(ethoxycarbonyl)thioureido]-6-methoxynicotinate (**14**) and 7-methoxy-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4 (1*H*)-one (**15**) can be found in the Supporting Information.

Methyl 6-Methoxy-2-(benzylamino)nicotinates 13a,b

A 100 mL Milestone microwave reaction vessel was charged with crude methyl 2-chloro-6-methoxynicotinate (**9**, 6.50 g, 32.2 mmol), 1,4-dioxane (128 mL), and benzylamine or 4-methoxybenzylamine (0.32 mol, 10 equiv). The vessel was capped and the reaction mixture was microwave irradiated at 170 °C for 2 h using a Milestone MicroSYNTH T640 Microwave instrument. The vessel was cooled to r.t. and the reaction mixture concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography on silica with hexanes–EtOAc eluent by gradient method from 4:1 to 1:1. The fractions were concentrated under reduced pressure and the residue was triturated with diethyl ether to afford compounds **13a**,**b**.

Methyl 6-Methoxy-2-(benzylamino)nicotinate (13a)

Yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br s, 1 H), 7.99 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 5.95 (d, *J* = 8.5 Hz, 1 H), 4.73 (d, *J* = 5.8 Hz, 2 H), 3.85 (s, 3 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.5, 158.8, 142.3, 139.9, 128.4, 127.4, 126.9, 98.0, 97.8, 53.4, 51.3, 44.8. ESI-HRMS: *m/z* calcd for $C_{15}H_{16}N_2O_3$ $[M + H]^+$: 273.1234; found: 273.1234. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.40; H, 5.98; N, 10.14.

Methyl 6-Methoxy-2-(4-methoxybenzylamino)-nicotinates (13b)

Yield 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.43 (br s, 1 H), 7.98 (d, *J* = 8.5 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.95 (d, *J* = 8.5 Hz, 1 H), 4.66 (d, *J* = 5.7 Hz, 2 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.5, 158.7, 158.6, 142.3, 131.9, 128.7, 113.9, 97.9, 97.7, 55.3, 53.4, 51.3, 44.3. ESI-HRMS: *m/z* calcd for $C_{16}H_{18}N_2O_4$ $[M + H]^+$: 303.1340; found: 303.1339. Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.85; H, 6.02; N, 9.37.

Methyl 2-Amino-6-methoxynicotinate (4)

A solution of methyl 6-methoxy-2-(4-methoxybenzylamino) nicotinate (4.0 g, 13.23 mmol) in EtOH (25 mL) was hydrogenated in an H-Cube instrument over a 70 mm 10% Pd/C CatCart column under full hydrogenation mode (ref. 18) and column temperature 70 °C. The solvent was removed under reduced pressure to afford 2.3 g (95%) of the title compound. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.93 (d, *J* = 8.5 Hz, 1 H), 7.27 (br s, 2 H), 6.01 (d, *J* = 8.5 Hz, 1 H), 3.82 (s, 3 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.6, 166.6, 159.7, 142.2, 99.7, 98.3, 53.5, 51.4. ESI-HRMS: *m/z* calcd for $C_8H_{10}N_2O_3$ $[M + H]^+$: 183.0764; found: 183.0764.

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