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Microwave-assisted synthesis of 2-aminonicotinic acids by reacting 2-chloronicotinic acid with amines

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ABSTRACT

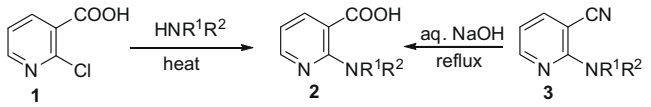
2-(Methylamino)nicotinic acid was readily prepared in high yield by reacting 2-chloronicotinic acid with 40% aq $MeNH_2$ under microwave irradiation either at 120 °C for 2 h or at 140 °C for 1.5 h. Subsequently, we found that a range of 2-aminonicotinic acids could be obtained under microwave heating. The optimal reaction conditions involved the use of 3 equiv of amine, water as the solvent and heating at 200 °C for 2 h in the presence of diisopropylethylamine (3 equiv).

2-Aminonicotinic acids are valuable intermediates for the preparation of compounds with potential as chemotherapeutic agents. For example, 2-(butylamino)nicotinic acid is an intermediate in the synthesis of the 1,8-naphthyridine ring for SMP-797, an acyl-CoA:cholesterol acyltransferase (ACAT) inhibitor with potential utility for the treatment of hypercholesterolemia and atherosclerosis.[1] Also, 2-aminonicotinic acids are intermediates in the synthesis of 1,8-naphthyridin-2(1*H*)-ones with potential as antiallergy agents,[2] 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridine-2-ones, possessing anti-inflammatory activity[3] and 2-amino-*N*-phenyl nicotinamides, which are reported as potent inhibitors of kinase insert-domain-containing receptor (Kdr).[4]

The nucleophilic aromatic substitution of 2-chloronicotinic acid with appropriate amines (Scheme 1) is a well-established method for the preparation of 2-aminonicotinic acids,[1,5,6] but harsh conditions involving prolonged heating are normally required. For example, 2-(butylamino)nicotinic acid was obtained by heating a mixture of 2-chloronicotinic acid and butylamine at reflux for 2 days.[1]

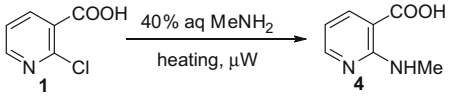
In an alternative approach, 2-(4-methylpiperazin-1-yl)nicotinic acid was obtained from 3-cyano-2-(4-methylpiperazin-1-yl)pyridine by alkaline hydrolysis (Scheme 1).[7] In connection with current work aimed at the production of a compound library directed against kinase anticancer targets, we were interested in the synthesis of 2-(methylamino)nicotinic acid (**4**). In literature reports, acid **4** was obtained from 2-chloronicotinic acid under the following conditions: (a) reaction with 40% aq $MeNH_2$ in a sealed tube at 120 °C for 15 h,[8] (b) reaction with 33% $MeNH_2$ in EtOH in a pressure vessel at 100 °C for 18 h,[9] and (c) reaction with $MeNH_2$·HCl in DMF at 100 °C for 18 h in the presence of K_2CO_3 and CuBr.[10]

Initially, we prepared **4** by the first of these methods. We then attempted to improve the reaction conditions for this nucleophilic



Scheme 1. Synthesis of 2-aminonicotinic acids.

Table 1
Synthesis of 2-(methylamino)nicotinic acid



Entry	40% $MeNH_2$ (equiv)	Temp (°C)	Reaction time (h)	Comments
1	15	120	0.17	Some product
2	15	120	1.0	Nearly to completion
3	7	120	1.5	Nearly to completion
4	7	140	1.5	Completion
5	7	120	2.0	Completion

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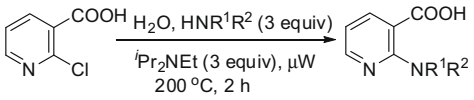
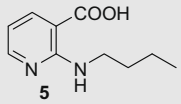
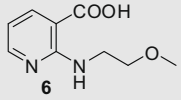
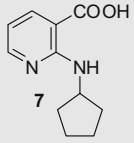
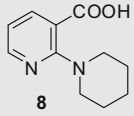
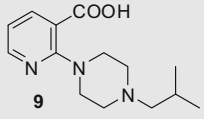
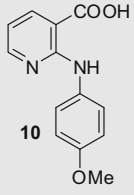
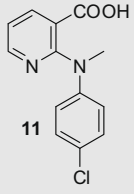
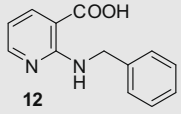
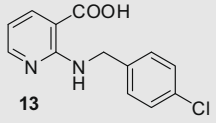
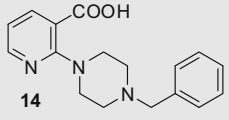
Table 2
Synthesis of 2-aminonicotinic acids by reaction of 2-chloronicotinic acid with amines



Entry	Product	Yield (%)
1	 **5**	70
2	 **6**	52
3	 **7**	75
4	 **8**	47
5	 **9**	74
6	 **10**	83
7	 **11**	63
8	 **12**	63
9	 **13**	80
10	 **14**	50

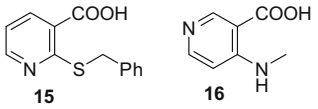


Figure 1.

aromatic substitution by exploring the use of microwave irradiation. A detailed investigation to identify the optimal conditions for this transformation gave the results that are summarised in Table 1.

In our hands, the optimal conditions for obtaining **4** under microwave irradiation involved the use of 7 equiv of 40% aq $MeNH_2$ and heating the reaction mixture either at 140 °C for 1.5 h or at 120 °C for 2 h (Table 1, entries 4 and 5).[11] Having established the optimal conditions for obtaining **4**, the scope of this reaction was investigated by reacting 2-chloronicotinic acid with a range of aliphatic amines, anilines and benzylamines. Again, water was used as the solvent but the reaction conditions were further optimised to accommodate the differences in amine reactivity. The temperature was raised to 200 °C, and the reaction time was set to 2 h in an effort to reduce the amount of amine required. Using *n*-butylamine, complete conversion of 2-chloronicotinic acid into **5** could be achieved with 3 equiv of the amine and 3 equiv of the tertiary amine base, diisopropylethylamine (Table 2).[11] Under these conditions, primary or secondary aliphatic amines, benzylamines and anilines gave the corresponding 2-aminonicotinic acids in moderate to high isolated yields (Table 2).

Subsequently, we briefly explored the reactivity of oxygen and sulfur-based nucleophiles with 2-chloronicotinic acid, under the conditions described in Table 2. Although, benzyl mercaptan gave the expected sulfide **15** (Fig. 1) in 45% yield, *n*-butanol failed to give any product as judged by LC–MS. It should be noted that 4-(methylamino)nicotinic acid (**16**) (Fig. 1) was also prepared from 4-chloronicotinic acid under microwave irradiation using conditions analogous to those described for the synthesis of **4**, though the reaction mixture was heated at 165 °C for 4 h. By following the work-up procedure described for **4**,[11] 4-(methylamino)nicotinic acid (**16**) was precipitated out during the final pH adjustment (i.e., pH 6.5), and subsequently was isolated by filtration in 83% yield.

In conclusion, 2-(methylamino)nicotinic acid was readily prepared in high yield by reacting 2-chloronicotinic acid with 40% aq $MeNH_2$ at 140 °C under microwave heating for 1.5 h. The 4-methylamino isomer was prepared similarly by heating at 165 °C for 4 h. 2-Chloronicotinic acid also reacted with primary or secondary aliphatic amines, benzylamines and anilines under microwave irradiation to provide a range of 2-aminonicotinic acids. The optimal reaction conditions involved the use of 3 equiv of amine, water as the solvent and heating at 200 °C for 2 h in the presence of diisopropylethylamine (3 equiv).

Acknowledgements

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References and notes

1. Ban, H.; Muraoka, M.; Ohashi, N. *Tetrahedron* **2005**, *61*, 10081.
2. Sherlock, M. H.; Kaminski, J. J.; Tom, W. C.; Lee, J. F.; Wong, S.-C.; Kreutner, W.; Bryant, R. W.; McPhail, A. T. *J. Med. Chem.* **1988**, *31*, 2108.
3. Ting, P. C.; Kaminski, J. J.; Sherlock, M. H.; Tom, W. C.; Lee, J. F.; Bryant, R. W.; Watnick, A. S.; McPhail, A. T. *J. Med. Chem.* **1990**, *33*, 2697.
4. Dominguez, C.; Smith, L.; Huang, Q.; Yuan, C.; Ouyang, X.; Cai, L.; Chen, P.; Kim, J.; Harvey, T.; Syed, R.; Kim, T.-S.; Tasker, A.; Wang, L.; Zhang, M.; Coxon, A.; Bready, J.; Starnes, C.; Chen, D.; Gan, Y.; Neervannan, S.; Kumar, G.; Polverino, A.; Kendall, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6003.
5. Kermack, W. O.; Weatherhead, A. P. *J. Chem. Soc.* **1942**, 726.
6. Ban, H.; Muraoka, M.; Ohashi, N. *Tetrahedron Lett.* **2003**, *44*, 6021.
7. Thunus, L.; Lapiere, C. L. *Eur. J. Med. Chem. Chim. Ther.* **1974**, *9*, 55.
8. Wozniak, M.; Buurman, D. J.; van der Plas, H. C. *J. Heterocycl. Chem.* **1985**, *22*, 765.
9. Gill, J. C.; Leslie, B. W. Patent WO95/30676, 1995; *Chem. Abstr.* **1996**, *124*, 202227.
10. Armour, D. R.; Bell, A. S.; Edwards, P. J.; Ellis, D.; Hepworth, D.; Lewis, M. L.; Smith, C. R. Patent WO2004020414 A1, 2004; *Chem. Abstr.* **2004**, *140*, 253449.
11. *Experimental procedures: A. 2-(Methylamino)nicotinic acid* (**4**): 2-Chloronicotinic acid (0.585 g, 3.7 mmol) was added to a solution of methylamine in H_2O (40%, 2.0 g, 26.0 mmol), and the reaction mixture was heated at 140 °C for 1.5 h under microwave conditions (Biotage Initiator™ Sixty, absorption level set to high; *Caution*: pressure may develop). After completion of the reaction, the solution was concentrated in vacuo, and the resultant viscous oily residue was treated with aqueous NaOH (1 M, 5 mL). The clear solution obtained was stirred at room temperature for 5 min, then concentrated in vacuo to afford a white solid which was dissolved in water (3.5 mL). The pH of the solution was adjusted to 6.5 with concd HCl; no precipitation of the product was observed. The water was removed under reduced pressure, and the resultant white solid was treated with warm MeOH (~50 mL). The insoluble material was removed, and the solution was concentrated under reduced pressure to afford the title compound as a white solid which was dried in vacuo over P_2O_5 (0.550 g, 98%). R_f 0.14 (EtOAc, neat); mp 256–258 °C (MeOH); δ_H (500 MHz; DMSO-d_6) 12.90 (1H, br s, exchangeable with D_2O, COOH), 8.25 (1H, dd, $J_1 = 4.7$, $J_2 = 1.8$, NC*H*CHCH), 8.03 (1H, dd, $J_1 = 7.7$, $J_2 = 1.8$, NCHCHC*H*), 7.92 (1H, br s, exchangeable with D_2O, N*H*Me), 6.56 (1H, dd, $J_1 = 7.6$, $J_2 = 4.8$, NCHC*H*CH), 2.93 (3H, s, NCH_3); δ_C (126 MHz; DMSO-d_6) 168.8, 158.8, 153.1, 139.9, 110.7, 106.2, 27.6; LC (3.5 min gradient: MeOH/0.1% formic acid)—MS (ESI, *m/z*): retention time = 0.60 min (99% purity)—153 [$(M+H)^+$, 100%].*B. Synthesis of 2-aminonicotinic acids* (Table 2)*-General procedure*: To a stirred suspension of 2-chloronicotinic acid and water (0.1 M) contained in a microwave vial was added diisopropylethylamine (3 equiv) followed by the amine (3 equiv). The reaction mixture was stirred at room temperature for 5–10 min, and then it was placed into a Biotage Initiator™ Sixty microwave apparatus and heated at 200 °C for 2 h (absorption level set to high; *Caution*: pressure may develop). Next, the solution was basified to pH 12 with 1 M NaOH solution and extracted with dichloromethane (3 × 20 mL). Finally, the pH of the aqueous layer was adjusted to 6.5. At this point, if a precipitate was obtained, it was collected by filtration, washed with Et_2O and dried. If a precipitate was not observed, the aqueous layer was extracted with ethyl acetate or was evaporated to dryness and the solid suspended in ethyl acetate (40 mL) and stirred for 15 min. The solid was then separated by filtration and the organics were collected and evaporated to give the desired products in 47–83% yields.