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A FACILE AND EFFICIENT SYNTHESIS OF 3-AMINO-5-BROMOPYRIDINE DERIVATIVES USING MICROWAVE IRRADIATION

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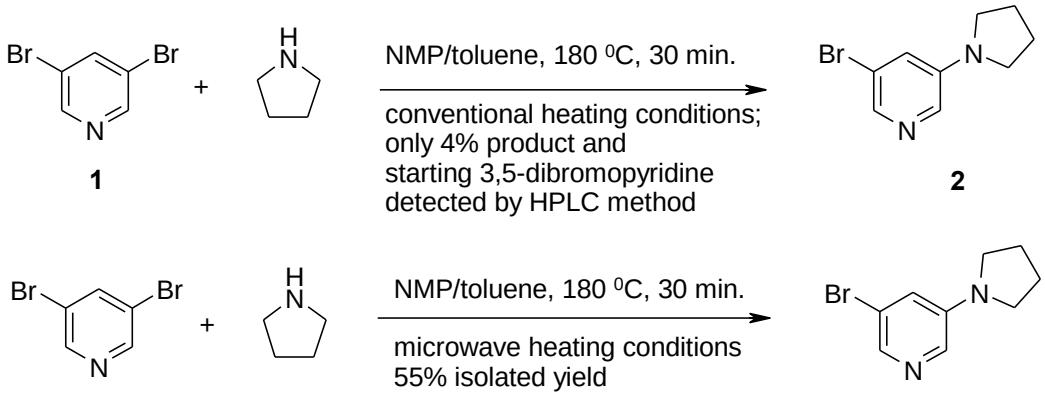
Abstract – A facile and general synthetic strategy was developed to synthesize 3-amino-5-bromopyridine derivatives under microwave heating conditions. The strategy involved reacting 3,5-dibromopyridine with an excess of an aliphatic amine using microwave heating, without the need to use either metal-mediated, base-promoted or harsh long thermal reaction times. The microwave approach enabled the rapid synthesis of 3-amino-5-bromopyridine derivatives in multi-gram quantities from commercially available starting materials.

Pyridine derivatives are highly useful and important building blocks in natural products and pharmaceuticals, therefore the development of efficient methods are important for the synthesis of highly functionalized intermediates.[1] For a medicinal chemistry lead optimization program we required a scalable approach to produce quantities of 3-amino-5-bromopyridine derivatives in high yield and purity. A review of the literature showed a paucity of general methods to synthesize such intermediates. The published methods to 3-dialkylamino-5-bromopyridines from 3,5-dibromopyridine and a secondary amine used either metal-catalyzed, base-promoted, or long harsh thermal reaction times.[2-5] In our work we found that extended thermal heating led to the formation of mixtures and multiple impurities that made purification difficult. In addition, in recent years a move to adopt "green chemistry" and minimize hazardous waste production and materials led us away from improving on the palladium mediated chemistry. Microwave heating conditions[6] has attracted a great deal of attention because of its simplicity, enhanced reaction times, and higher purity and yields compared to conventional thermal heating. In this paper we report optimization of the microwave conditions to synthesize 3-amino-5-bromopyridine derivatives starting from 3,5-dibromopyridine.

The synthesis of 5-bromo-3-diethylaminopyridine **3**[5a,b] was recently reported by two approaches starting with 3-amino-5-bromopyridine, however yields were not reported. The first method using 3-amino-5-bromopyridine, iodoethane and potassium bis(trimethylsilyl)amide as base reportedly produced a mixture of mono and bis-alkylated products. In the second method **3** was synthesized using reductive amination with acetaldehyde and sodium triacetoxyborohydride. 5-Bromo-3-diisopropylaminopyridine was synthesized in 30% yield from 3,5-dibromopyridine and diisopropylamine using strong base promoted (*t*-BuONa/$NaNH_2$) conditions.[5c] The desired product was produced along with a mixture of two by-products that caused purification issues. The 3-morpholinopyridine **5** was reportedly formed in 40% yield along with two additional by-products using the *t*-BuONa/$NaNH_2$ conditions.[5e,d] Furthermore, the synthesis of compound **5** was recently reported using $Pd_2(dba)_3$/rac-BINAP[5e] and a mixture of magnesium-zinc-copper reagents[5f] in 71% yield. Similarly, the reaction of 3,5-dibromopyridine and dimethylamine using *t*-BuONa/$NaNH_2$ led to a 1:1 mixture of 5-bromo-3-dimethylaminopyridine and 5-bromo-4-dimethylaminopyridine.[5g] 5-Bromo-3-dimethylaminopyridine was also reportedly synthesized in 23% yield from 3-amino-5-bromopyridine using aqueous formaldehyde, AcOH and $NaBH(OAc)_3$.[5h] Copper catalyzed (CuI/K_3PO_4) conditions were employed to synthesize 5-bromo-3-(pyrrolidin-1-yl)pyridine **2** (85 ºC, 60 h, 49% yield) using 3-bromo-5-iodopyridine and pyrrolidine.[5i] The reaction of 3,5-dibromopyridine with *N*-lithiopiperidine produced an intractable mixture of four products, none of which were the desired 5-bromo-3-(piperidin-1-yl)pyridine (**4**).[2b] Compound **4** was ultimately synthesized in 40% yield using copper sulfate and excess piperidine and pyridine mixture.[2b] The coupling reaction of 3,5-dibromopyridine with piperidine derivatives was also reported using Buchwald conditions ($Pd_2(dba)_3$/BINAP/*t*-BuONa).[2a,3a] The 3-piperazine derivative was also synthesized in low yield under thermal (130 ºC), but it required very long reaction times (100 h).[4] A basic piperazin-1-yl-pyridine analog, such as **6**, has not been previously described in the literature. In view of these multiple synthetic issues, we believe a more general synthetic method was necessary to synthesize 3-amino-5-bromopyridine derivatives. Therefore, we investigated the synthesis of such derivatives under microwave heating conditions.

The reaction of 3,5-dibromopyridine **1** and pyrrolidine was chosen for comparison of conventional heating versus microwave heating conditions (**Scheme 1**). The reaction of 3,5-dibromopyridine **1** and pyrrolidine (10 equiv.) in 1-methyl-2-pyrrolidinone (NMP) and toluene at 180 ºC for 30 min using microwave heating conditions produced 5-bromo-3-(pyrrolidin-1-yl)pyridine **2** in 55% isolated yield. Employing the identical experimental conditions under conventional heating conditions, produced the desired product **2** in only 4% yield and unreacted 3,5-dibromopyridine. The reaction using 1 equiv. of 3,5-dibromopyridine and pyrrolidine each under identical microwave heating conditions gave **2** in 22% yield with 78% unreacted

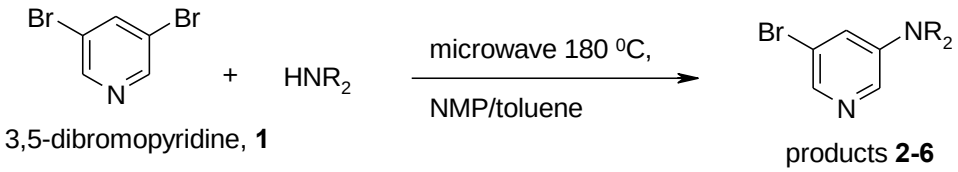
3,5-dibromopyridine (HPLC analysis). It was observed that using an excess of amine improved the yield of the desired mono-alkylated product with no bis-aminated by-product observed. The reactivity of the pyridine following the addition of the first electron-donating amino group was sufficiently reduced for S_NAr substitution, preventing the formation of bis-aminated derivative under these conditions. The synthesis of **2** using microwave heating conditions not only improved the yield but also shorten the reaction time compared to the conventional heating conditions.



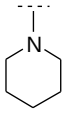
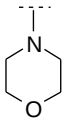
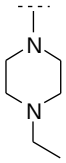
Scheme 1

The microwave heating conditions were applied to synthesize a focused set of 3-amino-5-bromopyridine derivatives as shown in **Table 1**. The results illustrate the general microwave heating conditions reacting 3,5-dibromopyridine and an excess amine in NMP and toluene. Simple amines, such as diethylamine, pyrrolidine, piperidine, morpholine and *N*-ethylpiperazine proceeded smoothly and gave moderate to good yields. The crude products were purified by silica gel flash column chromatography followed by crystallization to obtain analytically pure products. The acyclic diethylamine analog **3** was obtained in lower yields compared to the cyclic amine examples (entries **2**, **4**, **5**, and **6**). The synthesis of **2** (55%, 0.5 h reaction time) using this method was improved slightly based on yield, at significantly reduced the reaction times, compared to the literature method.[5i] As discussed earlier the synthesis of the acyclic diethylaminopyridine **3** was reported, but the yields were not reported, however, under microwave conditions it was produced 20% yield after 8 h. The yield of the 3-piperidinopyridine **4** (77%) was significantly improved, whereas the yield of 3-morpholinopyridine **5** (63%) was slightly less to the literature methods, without the unwanted by-products. Furthermore, 3-piperazinopyridine **6** was synthesized in moderate yield in < 1 h, compared with the long reaction times described in the literature.[4]

Table 1. Reaction of 3,5-dibromopyridine and amines



3,5-dibromopyridine, **1** products **2-6**

Entry	HNR_2	Reaction Time (h)	Yield (%)	mp (°C)
3		8.0	20	oil
2		0.5	55	90-91
4		0.5	77	34-35
5		1.1	63	84-85
6		0.7	43	oil

In summary, this paper communicates a general and rapid synthesis of 3-amino-5-bromopyridine derivatives under microwave heating conditions starting with commercially available 3,5-dibromopyridine and various aliphatic amines. The derivatives were synthesized using short reaction times (~1 h) except for the diethylaminopyridine **3**, which required 8 h of heating. This general method should be compatible with many simple and complex amines for rapid synthesis of numerous 3-amino-5-bromopyridine intermediates for use in organic synthesis.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 400 MHz in the solvent indicated with tetramethylsilane as an internal standard. Column chromatography was performed on silica gel flash chromatography. Quantitative Technologies, Inc. performed elemental analysis. All reagents were purchased from commercial sources and used as received. The microwave reactions were conducted in CEM discover microwave instrument.

General procedure

A solution of 3,5-dibromopyridine (5.14 g, 21.7 mmol) and pyrrolidine (14.97 g, 210.9 mmol) in a mixture of toluene (8.2 mL) and 1-methyl-2-pyrrolidinone (4.1 mL) in 80 mL microwave reaction vessel was irradiated (microwave power 300 watts) in a CEM discover microwave instrument at 180 ºC for a period of time as indicated. The crude product was purified by silica gel flash chromatography and then crystallized in the solvent indicated to produce pure compound.

5-Bromo-3-(diethylamino)pyridine(3).

1.01 g, 20% yield, Isolated as an oil; ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 6H, *J* = 7.09 Hz), 3.34 (q, 4H, *J* = 7.12 Hz), 7.02 (t, 1H, *J* = 2.00 Hz), 7.91 (d, 1H, *J* = 1.72 Hz), 7.98 (d, 1H, *J* = 2.64 Hz); MS: *m/z* 231 (M + 1). Anal. Calcd for $C_9H_{13}N_2Br$: C, 47.18; H, 5.72; N, 12.23. Found: C, 47.23; H, 5.74; N, 12.00.

5-Bromo-3-(pyrrolidin-1-yl)pyridine (2).

2.72 g, 55% yield, mp 90-91 °C (EtOAc), lit.,[5i] mp not reported; ^{1}H NMR ($CDCl_3$): δ 2.02-2.05 (m, 4H), 3.27-3.30 (m, 4H), 6.93 (brs, 1H), 7.87 (d, *J* = 2.48 Hz), 7.94 (brs, 1H); MS: *m/z* 229 (M + 1). Anal. Calcd for $C_9H_{11}N_2Br$: C, 47.60; H, 4.88; N, 12.33. Found: C, 47.43; H, 4.87; N, 12.01.

5-Bromo-3-(piperidin-1-yl)pyridine (4).

3.85 g, 77% yield, mp 34-35 °C (EtOAc), lit.,[2b] mp 36-37 ºC; ^{1}H NMR ($CDCl_3$): δ 1.61-1.68 (m, 2H), 1,70-1.72 (m, 4H), 3.19-3.22 (m, 4H), 7.27 (t, 1H, *J* = 2.04 Hz), 8.05 (d, 1H, *J* = 1.80 Hz), 8.19 (d, 1H, *J* = 2.56 Hz); MS: *m/z* 242 (M + 1). Anal. Calcd for $C_{10}H_{13}N_2Br$: C, 49.81; H, 5.43; N, 11.62. Found: C, 49.62; H, 5.39; N, 11.27.

5-Bromo-3-(morpholin-4-yl)pyridine (5).

3.31 g, 63% yield, mp 84-85 °C (EtOAc), lit.,[5c] mp 77 ºC (EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$): δ 3.19 (t, 4H, *J* = 4.88 Hz), 3.86 (t, 4H, *J* = 4.77 Hz), 7.28 (t, 1H, *J* = 1.96 Hz), 8.15 (d, 1H, *J* = 1.76 Hz), 8.20 (d, 1H, *J* = 2.56 Hz); MS: *m/z* 244 (M + 1). Anal. Calcd for $C_9H_{11}N_2BrO$: C, 44.47; H, 4.56; N, 11.52. Found: C, 44.23; H, 4.58; N, 11.43.

5-Bromo-3-(4-ethylpiperazin-1-yl)pyridine (6).

2.44 g, 43% yield, isolated as an oil, ^{1}H NMR ($CDCl_3$): δ 1.14 (t, 3H, *J* = 7.20Hz), 2.49 (q, 2H, *J* = 7.20 Hz), 2.61 (t, 4H, *J* = 5.17 Hz), 3.27 (t, 4H, *J* = 5.08 Hz), 7.30 (t, 1H, *J* = 2.32 Hz), 8.12 (d, 1H, *J* = 1.85 Hz), 8.21 (d, 1H, *J* = 2.56 Hz); MS: *m/z* 272 (M + 1). Anal. Calcd for $C_{11}H_{16}N_3Br$: C, 48.90; H, 5.97; N, 15.55.

Found: C, 48.72; H, 5.97; N, 15.35.

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