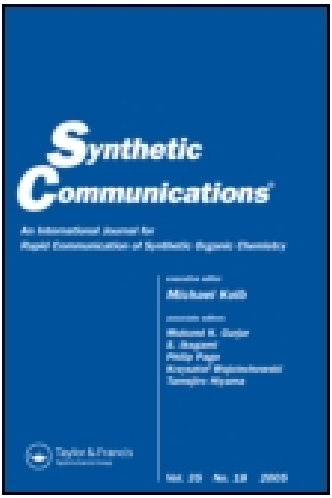

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HIGHLY EFFICIENT SYNTHESIS OF 2-AMINO-3-PYRIDINECARBOXALDEHYDE

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ABSTRACT

2-Amino-3-pyridinecarboxaldehyde is synthesized in a highly efficient process via *ortho*-lithiation of 2-(pivaloylamino)pyridine and reaction with DMF, followed by acid hydrolysis. Major impurities were identified and were cleanly eliminated through careful choice of base and solvent.

1,8-Naphthyridines are key components of several pharmaceutically active compounds, including ones having antifungal and antibiotic activity.[1,2] Friedländer condensation between 2-amino-3-pyridinecarboxaldehyde **4** and ketones and/or other active methylene compounds has been one of the most general methods for the preparation of variety of 1,8-naphthyridines.[3,4] To provide material to support a combinatorial approach to 1,8-naphthyridines, and to supply drug development needs on lead compounds, an efficient preparation of aldehyde **4** was required. Despite its synthetic use, an efficient route to this intermediate has not been

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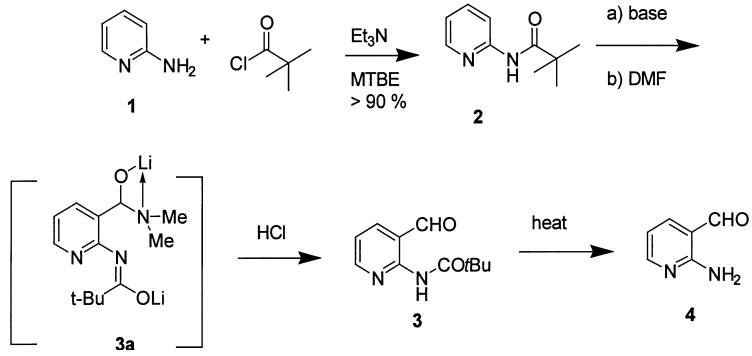
well developed. Several methods have been reported, including dibromination of phthalimide protected 2-amino-3-picoline, followed by hydrolysis;[5] and hydrolysis of 2-(3-pyridyl)pyrido[2,3-d]pyrimidine[6] (52% and 50% isolated yields, respectively). In 1983, Turner reported the preparation of aldehyde **3** in 54% yield via *ortho*-directed lithiation of 2-(pivaloylamino)-pyridine **2**, followed by addition of DMF.[7] The low yield of the formylation product was surprising, given the fact that quenching the dianion with TMSCl or D_2O provided the corresponding products in 86% and 87% isolated yields, respectively. Herein, we report further studies on this reaction that have led to a highly efficient and simple method for the preparation of aldehyde **4**, as shown in Scheme 1.



Scheme 1.

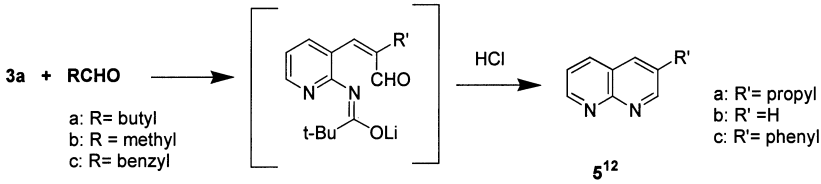
The starting material pivalamide **2** was prepared in high yield by pivaloylation of 2-aminopyridine using triethylamine in MTBE.[8] Formylation of **2** was carried out using the original conditions reported by Turner (2.3 equiv. *n*-BuLi in THF, followed by addition of DMF).[7] Two major impurities were isolated from the reaction and identified as 3-propyl-1,8-naphthyridine **5a** and 1,8-naphthyridine **5b**. Although aldehyde **4** is crystalline, the presence of these impurities prevented crystallization, resulting only in oiling out, which made purification by direct crystallization impractical.[12] The mechanism for formation of these impurities and conditions developed to control them are discussed below. The results of these formylation studies on pivalamide **2** are summarized in Table 1.

We reasoned that the 3-propyl impurity **5a** was generated from the Friedländer condensation between formyl pivalamide intermediate **3a** and pentanal, generated from *n*-BuLi and DMF (Scheme 2). As expected, increasing the amount of *n*-BuLi to 3 equiv. increased the amount of **5a**

Table 1. Formylation of Pivalamide **2**

			Yields (%)[a]				
			Before Hydrolysis		After Hydrolysis		
Entry	Base (equiv.)	Solvent	3[b]	2[b]	4[c]	5a[c]	5b[c]
1	*n*-BuLi (2.0)	THF	84	8	80	0.3	2.5
2	*n*-BuLi (2.1)	THF	80	1.7	75	4.5	3.3
3	*n*-BuLi (2.2)	THF	73	0	63	3.7	2.4
4	*n*-BuLi (3.0)	THF	56	0	46	7.9	3.3
5	*t*-BuLi (2.3)	THF	80	1.5	81	0	18
6	*t*-BuLi (2.3)	THP	90	5.0	84	0	0
7	*t*-BuLi (2.3)	Toluene[d]	67	1.5	—	[e]	—
8	*t*-BuLi (2.3)	*t*-Butylbenzene[d]	84	1.6	82	0	0
9	*t*-BuLi (2.1)	Butylether	67	8.0	67	0	0

[a]assay yields are reported based on starting material **2**;
[b]assay yield after HCl extraction, prior to hydrolysis;
[c]assay yield after HCl hydrolysis;
[d]5 eq of THP ligand was added;
[e]compound **5c** was obtained as Friedländer product (10.2%).



Scheme 2.

(entry 4). Avedano et al.[9] reported a one-pot synthesis of substituted quinolines from *N*-pivaloylanilines. They found that the deprotection of the pivaloyl group happened spontaneously, allowing for cyclization of the quinoline ring. In our case, however, the propyl impurity **5a** was not observed until after HCl hydrolysis. Unfortunately, washing the HCl layer with *t*-BuOMe (MTBE) prior to hydrolysis, hoping to remove pentanal from the aqueous layer, did not prevent the formation of **5a**.

In an attempt to avoid aldol condensation leading to 3-substituted naphthyridines, we chose *t*-BuLi as base, which should generate the non-enolizable *t*-BuCHO byproduct upon reaction with DMF. In doing so, the formation of propyl impurity **5a** was avoided. However, the other impurity, 1,8-naphthyridine **5b**, was generated in 18% yield (entry 5).

The formation of naphthyridine **5b** could be attributed to the Friedländer condensation between 2-amino-3-pyridinecarboxaldehyde **4** and acetaldehyde, presumably generated from the degradation of THF solvent in the presence of the stronger base *t*-BuLi.[10] As proof, when THF-d_8 was used as solvent, the naphthyridine byproduct **5b** was deuterated at 2 and 3 positions (94% and 54%, respectively), as determined by NMR. As a result, we tested other solvents that would be suitable for this reaction and should not generate any aldehydes in the presence of a strong base. Although using butyl ether as solvent (entry 9) did not produce the naphthyridine byproduct **5b**, the yield was low, and other minor impurities were formed. Best results were obtained when tetrahydropyran (THP) was used as a solvent, giving an overall assay yield of 84% of 2-amino-3-pyridinecarboxaldehyde **4** from pivalamide **2**. We have found that toluene could also be used as a solvent in the presence of 5 equiv. of THP as a ligand. The formylation step afforded 90% crude assay yield of the formyl pivalamide **3**. Upon quenching with 3 N HCl, however, the yield dropped to 67% and a new byproduct was generated. The byproduct was identified as 3-phenyl-1,8-naphthyridine **5c**, generated from benzyl lithium and DMF and amino aldehyde **4**. This problem could be circumvented by replacing toluene with *t*-butylbenzene as a solvent (entry 8).

In conclusion, we have developed an efficient process for the preparation of 2-amino-3-pyridinecarboxaldehyde **4**[11] starting from cheap and readily available starting materials. With careful choice of solvent and base used, major impurities could be avoided. Results show that optimal yield was obtained when using *t*-BuLi and THP during the lithiation process. Using these conditions, 2-amino-3-pyridinecarboxaldehyde could be obtained in 78% isolated yield.

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8. Synthesis of 2-(pivaloylamino)pyridine **2**. To a 3-L, 3-neck flask charged with 100 g (1.06 mol) 2-aminopyridine **1** in MTBE (1100 mL) was added 160 mL (1.17 mol) triethylamine. The solution was then cooled to 0°C, whereupon 136 mL (1.13 mol) pivaloyl chloride was added dropwise such that the internal temperature was less than 20°C. The solution was stirred for 2 h at r.t. and a white precipitate was observed. After the reaction was complete, cooled H_2O (1×300 mL) was added. The layers were separated and the organic layer was washed with H_2O (1×300 mL), sat. $NaHCO_3$ (1×300 mL), then brine solution (1×300 mL). The organic layer was dried over Na_2SO_4. Sodium sulfate was filtered off and MTBE was distilled under reduced pressure and replaced with THF (other solvents may be used, see text). The crude material was used in the formylation step without further purification. Typical assay yield is 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (m, 2H, H-3, H-6), 8.04 (br, 1H, N-H), 7.70 (m, 1H, H-4), 7.03 (m, 1H, H-5), 1.32 (s, 9H, *t*-butyl). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.0, 151.6, 147.6, 138.4, 119.7, 113.9, 39.8, 27.5. m.p. 69°–71°C (lit.[6] m.p. 71°–73°C).
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11. Typical synthesis of 2-amino-3-pyridinecarboxaldehyde **4**. To a 100-mL flask was charged 2.5 g (14 mmol) of 2-(pivaloylamino)pyridine **2** and 30 mL of THP. This solution was cooled to −20°C, whereupon *t*-BuLi (1.6 M in pentane, 2.3 equiv.) was added over a 30-min period such that the internal temperature was below −5°C. The solution was then aged for 2.5 h at 0°C, after which 2.2 mL DMF (28 mmol) was added such that the internal temperature was less than 5°C. The solution was aged at 0°C for 1 h, then allowed to warm slowly to r.t. After the reaction was complete, the solution was cooled to −10°C and quenched with 3 N HCl (77 mmol), keeping the temperature below 0°C. The

aqueous layer was separated and excess THP was distilled in vacuo. The aqueous layer was heated overnight at 100°C. The reaction mixture was cooled to room temperature, then washed with MTBE (2 × 10 mL). The aqueous layer was cooled to 0°C after the addition of 15 mL of isopropyl acetate (IPAC) and 5 g NaCl. To the mixture was added 5 N NaOH at a rate such that the internal temperature was less than 15°C until pH 10.3. The organic layer was separated. The aqueous layer was re-extracted with IPAC (2 × 15 mL). The combined organic layers were concentrated under reduced pressure to give 1.59 g crude material consisting mainly of product and traces of starting material. The desired 2-amino-3-pyridinecarboxal-dehyde was easily purified by SiO_2 column chromatography, eluting first with 2:1 hexane:EtOAc then with 1:1 hexane:EtOAc after pivalamide staring material had eluted completely. Fractions containing desired compound were concentrated under vacuum to give 1.33 g yellow crystals (78% isolated yield based on pivalamide **2** starting material). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (s, 1H, CHO), 8.22 (m, 1H, H-6), 7.76 (m, 1H, H-4), 7.04 (br, 2H, N-H), 6.69 (m, 1H, H-5). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.6, 158.4, 154.6, 144.2, 113.8, 112.8. m.p. 97°–99°C (lit.[6] m.p. 98°–99°C).

12. On large-scale synthesis (0.49 mol of **2**, nBuLi and THF conditions), the IPAc solution containing crude **4** was passed through a silica-gel pad (2:1 wt/wt silica : crude wt. of **4**). The filtered solution was concentrated under reduced pressure to give 46.0 g of **4** in 96 wt% purity. This material was heated to 70°C in EtOAc (75 mL), then gradually cooled to 50°C and seeded. After 30 min stirring at 50°C, methylcyclohexane (295 mL) was added (50 mL/h) and allowed to cool overnight. The crystals were filtered and washed with 4:1 methylcyclohexane, then dried to give 37.5 g of **4** (97.9 wt% purity by HPLC method based on analytical standard, 58% overall yield from **1**).
13. Analytical data: **5a**:^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (dd, J = 2.0, 4.3 Hz, 1H), 8.94 (d, J = 2.5 Hz, 1H), 8.05 (dd, J = 2.0, 8.1 Hz, 1H), 7.89 (d, J = 2.5 Hz, 1H), 7.42 (dd, J = 4.3, 8.1 Hz, 1H), 2.76 (t, J = 7.6 Hz, 2H), 1.70 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.2, 155.0, 152.5, 136.6, 136.4, 134.9, 122.5, 122.0, 34.9, 24.1, 13.6. HRMS *m/z* calc. for $C_{11}H_{12}N$ (M+H) 173.1073, found 173.1077. **5b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (m, 2H), 8.15 (m, 2H), 7.42 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 156.1, 153.6, 137.1, 122.8, 122.1. m.p. 91°–93°C. **5c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.44 (d, J = 2.4 Hz, 1H), 9.14 (d, J = 3.9 Hz, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.73 (m, 2H), 7.50 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 155.5, 153.4, 153.1, 137.2, 137.0,

135.0, 133.9, 129.3, 128.5, 127.5, 122.6, 122.5. Anal. calc. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.24; H, 4.74; N, 13.60. m.p. 128.5°–129.5°C.

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