Preparation of 4-Alkyl-2-[*N*-(*tert*-butoxycarbonyl)amino]-pyridines by Alkylation, Nucleophilic Addition, and Acylation of 2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-picoline[1]

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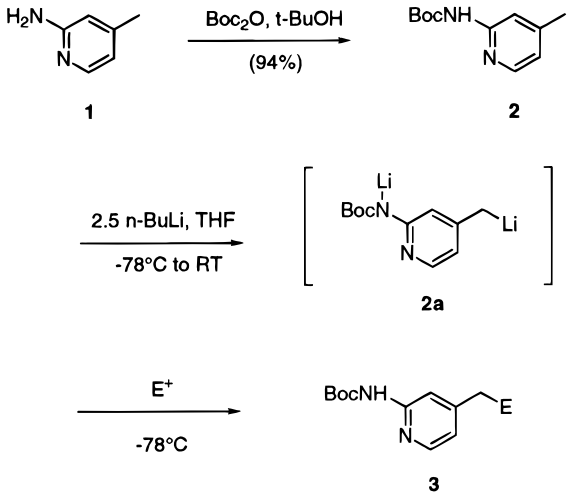
Received January 29, 1996

As part of an ongoing drug discovery project, we sought a mild and general method for the preparation of structurally diverse 4-alkyl-2-aminopyridines. While a number of simple 2-aminopyridines are commercially available, methods for preparation of 4-substituted derivatives are limited. The Chichibabin reaction, in which a pyridine is allowed to react with sodium amide, is conceptually simple, but the reaction conditions are harsh.[2] A milder approach relies on the nucleophilic displacement reaction between an amine and a 2-halopyridine,[3] but the preparations of 2-halopyridines typically involve multistep sequences. In this paper we report a new method for the preparation of 4-alkyl-2-aminopyridines by the alkylation, nucleophilic addition, and acylation of 2-[*N*-(*tert*-butoxycarbonyl)amino]-4-picoline (**2**).



Our approach is based on methodology reported for the preparation of 4-alkylpyridines that involves the alkylation of the 4-picolyllithium anion.[4] We sought to extend this technology to include 2-amino-4-picolyl anions. 2-Amino-4-picoline (**1**) serves as a convenient, commercially available starting material. To facilitate the anion chemistry, we introduced a protecting group on the amine nitrogen. The Boc-protected derivative **2** was found to be suitable in terms of its stability to anionic reaction conditions and ease of protecting group removal.[5]

Results and Discussion

The Boc protection of 2-aminopyridines requires unusual acylation conditions. Typically, in halogenated or ethereal solvents di-*tert*-butyl dicarbonate reacts to provide significant amounts of *N*,*N*′-di-2-pyridylureas.[6] These byproducts can be minimized by slow addition of the aminopyridine to a solution of di-*tert*-butyl dicarbonate or, more conveniently, by carrying out the reaction using *tert*-butyl alcohol as solvent. Under these conditions, **1** was cleanly protected to provide **2** in 94% yield.

A solution of **2** in THF at −78 °C was treated with 2.5 equiv of *n*-BuLi, and the resulting solution was allowed to warm to room temperature for 30 min. Quenching the reaction with D_2O resulted in clean regeneration of **2** with >95% incorporation of deuterium in the methyl group,[7] indicating successful formation of the presumed dianion **2a**. This dianion has limited solubility in THF (<0.1 M) and generally precipitates from the bright orange solution, even at room temperature. In spite of this low solubility, **2a** reacted readily at low temperature after the reaction flask was returned to a −78 °C bath. Addition of allyl bromide led to rapid discharge of the orange color and dissolution of the precipitate. After 5 min, the reaction was quenched and worked up, and product **3a** was isolated in 77% yield.

To explore the scope of this method, a variety of electrophiles were investigated (Table 1). In addition to allyl bromide, benzyl bromide reacted rapidly. In this case, the crude yield of **3b** was >90% by ^{1}H NMR, but separation from unreacted **2** was difficult. Recrystallization from hexanes/ethyl acetate provided pure **3b**, albeit in low yield. In addition to the activated halides, primary alkyl bromides (Table 1, entry 3) and even epoxides (Table 1, entry 4) will alkylate the dianion of **2**, although higher temperatures and/or longer reaction times were required. With the epoxide, no sign of the regioisomeric product was detected.

Carbonyl electrophiles will also react with **2a**. Benzaldehyde undergoes an addition reaction within 10 min, providing the alcohol **3e** in 63% yield. A clean, selective acylation was accomplished using a Weinreb amide as electrophile (Table 1, entry 6).[8] In this case, ketone **3f** was isolated and no polyacylation products were detected.

In each condensation reaction, NMR analysis of the crude product indicated the presence of 10−30% of **2**, along with the expected **3**. Because of the high efficiency of the deprotonation step, as indicated by the deuterium quench experiment, this suggests inappropriate protonation of **2a** prior to its reaction with the carbon electrophiles. The source of this undesirable quenching remains uncertain.

The anion chemistry of **2** provides a convenient approach for the construction of 4-alkyl-2-aminopyridines.

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(1) Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

(2) McGill, C. K.; Rappa, A. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1988; Vol. 44, pp 2−82. Cislak, F. E. U.S. Patent 2 807 619, 1957; *Chem. Abstr.* **1958**, *52*, 2932e. Case, F. H.; Butte, W. A. *J. Org. Chem.* **1961**, *26*, 4415.

(3) Vorbrüggen, H. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, 1990; Vol. 49, pp 118−193.

(4) Chung, J. Y. L.; Zhao, D.; Hughes, D. L.; Grabowski, E. J. J. *Tetrahedron* **1993**, *49*, 5767.

(5) A phthalimide-protected derivative decomposed under the deprotonation conditions. The Boc protecting group is easily removed by treatment with TFA or anhydrous HCl.

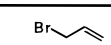
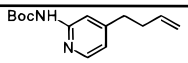
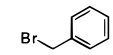
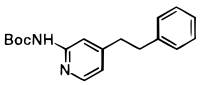
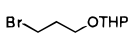
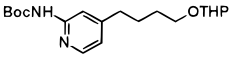
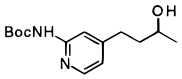
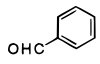
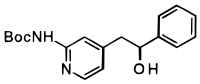
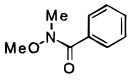
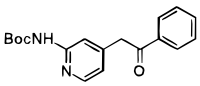
(6) Venuti, M. D.; Stephenson, R. A.; Alvarez, R.; Bruno, J. J.; Strosberg, A. M. *J. Med. Chem.* **1988**, *31*, 2136.

(7) Determined by integration of the methyl signal in the ^{1}H-NMR spectrum.

(8) For an example of acylation of the dianion of 2-[*N*-(*tert*-butoxycarbonyl)amino]-3-picoline by DMF, see: Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871.

S0022-3263(96)00184-3 CCC: $12.00

Table 1. Alkylation of 2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-methylpyridine (2)

Entry	Electrophile	Product	Reaction Time (min)	% Yield[a]
1		 **3a**	5	77
2		 **3b**	5	22[b]
3		 **3c**	90[c]	66
4		 **3d**	150	57
5		 **3e**	10	63
6		 **3f**	15	58[b]

[a] Isolated yield after chromatography. [b] Isolated yield after recrystallization. [c] This reaction was allowed to warm to −50 °C over a period of 90 min.

Alkylations can be carried out with activated or unactivated alkyl halides and epoxides. Addition to benzaldehyde and acylation by a Weinreb amide are also efficient. Advantages of this route over existing preparative methods include relatively mild conditions, high efficiency, and a minimal number of reaction steps. The application of this methodology in the preparation of new bioactive molecules will be described in due course.

Experimental Section

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-methylpyridine (2). A solution of 2-amino-4-methylpyridine (**1**, 5.01 g, 46.4 mmol) in 100 mL of melted *t*-BuOH was treated with di-*tert*-butyl dicarbonate (11.1 g, 51 mmol). After the solution was stirred overnight, the solvent was evaporated, and the residue was purified by flash filtration (50 × 150 mm silica, $CHCl_3$), providing **2** as a white crystalline material (8.85 g, 94%). Recrystallization from hot 10% EtOAc/hexanes provided analytically pure colorless needles: mp 118−119 °C; R_f 0.15 ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80−8.55 (br s, 1H), 8.16 (dd, J = 5, 1 Hz, 1H), 7.82 (s, 1H), 6.78 (d, J = 5 Hz, 1H), 2.34 (s, 3H), 1.54 (s, 9H). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.57; H, 7.69; N, 13.45.

Representative Procedure for Dianion Reaction: 2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(3-buten-1-yl)pyridine (3a). A solution of **2** (227 mg, 1.09 mmol) in 10 mL of THF was cooled in a −78 °C bath. *n*-BuLi (1.6 M in hexanes, 1.7 mL, 2.7 mmol) was added during 1 min, and then the cooling bath was removed. After 30 min at room temperature, the orange suspension was returned to the −78 °C bath. Allyl bromide (140 μL, 1.6 mmol) was added, and after 5 min, the reaction was quenched by the addition of HOAc in Et_2O. The mixture was warmed to rt, diluted with EtOAc, and then washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20 × 150 mm silica, 10% EtOAc/hexanes) provided **3a** (207 mg, 77%) as a white crystalline solid: mp 106−108.5 °C; R_f 0.21 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 5 Hz, 1H), 7.79 (s, 1H), 7.40 (br s, 1H), 6.80 (dd, J = 5, 1 Hz, 1H), 5.82 (ddt, J = 13, 10, 7 Hz, 1H), 5.08−4.97 (m, 2H), 2.70 (t, J = 7 Hz, 2H), 2.40 (m, 2H), 1.53 (s, 9H). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.76; H, 8.12; N, 11.28. Found: C, 67.72; H, 8.09; N, 11.37.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(2-phenylethyl)pyridine (3b). Following the general procedure, **2** (214 mg, 1.03 mmol) was alkylated with benzyl bromide (184 μL, 1.55 mmol) for 5 min at −78 °C. The product **3b** was inseparable from unreacted **2** by silica gel chromatography under several conditions, but recrystallization from hot 10% EtOAc/hexanes provided **3b** (67 mg, 22%) as colorless needles: mp 145−148 °C; R_f 0.40 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 5 Hz, 1H), 7.85 (s, 1H), 7.46 (s, 1H), 7.31−7.17 (m, 5H), 6.76 (dd, J = 5, 1 Hz, 1H), 2.92 (s, 4H), 1.54 (s, 9H). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.30; H, 7.49; N, 9.53.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-[4-(tetrahydropyran-2-yloxy)butyl]pyridine (3c). Following the general procedure, **2** (211 mg, 1.01 mmol) was alkylated with 1-bromo-3-(tetrahydropyranyloxy)propane (340 mg, 1.5 mmol) for 90 min at −78 to −50 °C. Flash chromatography (20 × 150 mm silica, 20% EtOAc/hexanes) provided **3c** (235 mg, 66%) as a white crystalline material: mp 80−81 °C; R_f 0.20 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 5 Hz, 1H), 7.78 (s, 1H), 7.33 (s, 1H), 6.79 (d, J = 5 Hz, 1H), 4.57 (m, 1H), 3.86 (m, 1H), 3.76 (dt, J = 10, 6 Hz, 1H), 3.50 (m, 1H), 3.40 (dt, J = 10, 7 Hz, 1H), 2.63 (t, J = 7 Hz, 2H), 1.90−1.50 (m, 10H), 1.53 (s, 9H). Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.39; H, 8.58; N, 7.99.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(3-hydroxybutyl)pyridine (3d). Following the general procedure, **2** (255 mg, 1.23 mmol) was alkylated with propylene oxide (130 μL, 1.8 mmol) for 150 min at −78 °C. Flash chromatography (20 × 150 mm silica, 50% EtOAc/hexanes) provided **3d** (187 mg, 57%) as a white solid: mp 123−125 °C; R_f 0.26 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.17 (d, J = 5 Hz, 1H), 7.85 (s, 1H), 6.81 (d, J = 5 Hz, 1H), 3.83 (m, 1H), 2.82−2.61 (m, 2H), 1.82−1.75 (m, 2H), 1.54 (s, 9H), 1.24 (d, J = 6 Hz, 3H). Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.33; N, 10.52. Found: C, 62.87; H, 8.24; N, 10.55.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(2-hydroxy-2-phenylethyl)pyridine (3e). Following the general procedure, **2** (222 mg, 1.07 mmol) was alkylated with benzaldehyde (163 μL, 1.6 mmol) for 10 min at −78 °C. Flash chromatography (10 × 150 mm silica, 30% EtOAc/hexanes) provided **3e** (213 mg, 63%) as a white solid: mp 124−126 °C; R_f 0.20 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 5 Hz, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 7.40−7.26 (m, 5H), 6.79 (dd, J = 5, 1 Hz, 1H), 4.97 (m, 1H), 3.02−2.99 (m, 2H), 1.99 (d, J = 3 Hz, 1H), 1.54 (s, 9H). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.90; H, 7.00; N, 8.90.

2-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(2-oxo-2-phenylethyl)pyridine (3f). Following the general procedure, **2** (212 mg, 1.02 mmol) was acylated with *N*-methoxy-*N*-methylbenzamide (0.23 mL, 1.5 mmol) for 15 min at −78 °C. Flash chromatography was not effective in separating product from excess acylating reagent, but recrystallization from 20% EtOAc/hexanes provided **3f** as colorless needles (186 mg, 58%): mp 163−165 °C; R_f 0.52 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.23 (d, J = 5 Hz, 1H), 8.00 (d, J = 7 Hz, 2H), 7.93 (s, 1H), 7.59 (t, J = 7 Hz, 1H), 7.48 (t, J = 8 Hz, 2H), 6.87 (dd, J = 5, 1 Hz, 1H), 4.29 (s, 2H), 1.53 (s, 9H). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.19; H, 6.47; N, 8.99.

Acknowledgment. The authors acknowledge Dr. Mark E. Duggan for helpful discussions, the West Point analytical chemistry group for combustion analyses, and Ms. J. Kaysen for assistance in the preparation of this manuscript.

JO960184T