Directed Lithiation of 3-[(*tert*-Butoxycarbonyl)amino]-2-methoxypyridines: Synthetic Route to Nevirapine and Its 4-Substituted Derivatives†

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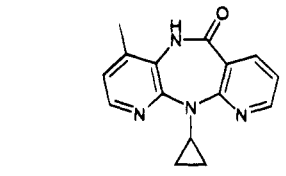
The antiviral agent nevirapine (**1**)[1] is a non-nucleoside inhibitor of HIV-1 reverse transcriptase (RT) and is currently undergoing clinical trials for the treatment of HIV infection and AIDS. A consequence of efforts to produce second generation derivatives that possess broader activity against mutant RT enzymes is the need for a number of 4-substituted 3-amino-2-methoxypyridines (**2**). An efficient route to these compounds would allow the structure–activity relationships about the 4-position of the dipyridodiazepinone ring system to be explored.



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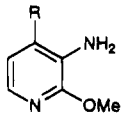

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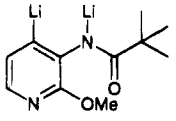

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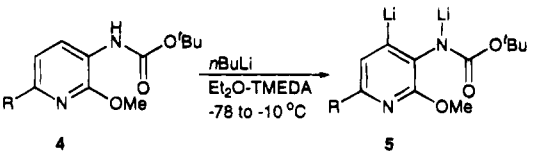
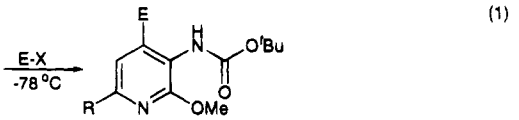
A powerful tool for the functionalization of aryl systems is *ortho*-directed lithiation chemistry.[2] Indeed, it has been shown that 3-amino-2-methoxypyridines protected as their pivaloyl amides can be efficiently lithiated at the 4-position by generation of their dianion with *n*-butyllithium (**3**).[3] Unfortunately, a number of the derivatives we sought to make would be unstable to the conditions required for the removal of the pivaloyl group. The *tert*-butyl carbamate (BOC) group is also known to be a strong *ortho*-directing group and has the advantage of being cleaved readily by acid.[4,5] The one previous drawback to using the BOC group has been the often encountered difficulty with the protection of arylamines by traditional BOC reagents.[6] This problem has been circumvented by treatment of an isocyanate (derived from the Curtius rearrangement of an acyl azide)[6] with *tert*-butyl alcohol or, more directly, by treatment of the sodium salt of the arylamine with di-*tert*-butyl dicarbonate (BOC anhydride) in the presence of a second equivalent of base.[7] With this information at our disposal, we decided to explore directed lithiation as a route to 4-substituted-3-[(*tert*-butoxycarbonyl)amino]-2-methoxypyridines (**6**).

Treatment of the desired 3-[(*tert*-butoxycarbonyl)-amino]-2-methoxypyridine (**4**)[7] with 2 equiv of *n*BuLi at −78 °C in an ether–TMEDA mixture produced the monoanion which underwent a second deprotonation upon warming to −10 °C generating intermediate **5**. Subsequent recooling to −78 °C and addition of the desired electrophile produced the 4-substituted derivatives **6** in good yields (Table 1).



4 **5**



6 (1)

A few comments on the reaction are in order. Firstly, it is possible to add the electrophile at −10 °C, but the yields are often significantly diminished. Secondly, the yields of the two iodonation reactions are lower than for the other electrophiles for unknown reasons. Iodonation at the 5- or 6-position of the pyridine ring has been ruled out since the only observed side products are unchanged starting materials. Attempts to increase the efficiency of these reactions by using other sources of electrophilic iodine were unsuccesful.

The results in Table 1 demonstrate the utility of this method for the generation of a variety of 4-substituted-3-[(*tert*-butoxycarbonyl)amino]-2-methoxypyridines. The use of these compounds in the synthesis of their corresponding dipyridodiazepinones is demonstrated in Scheme 1 with the synthesis of nevirapine.

Compound **6a** was treated with 4 M HCl in EtOAc to remove the BOC group and produce **7**. The free amine of this material was then coupled to 2-chloronicotinoyl chloride (**8**) to form the amide of the B-ring. Heating **9** in cyclopropylamine gave compound **10** which cyclized cleanly in the presence of 2.2 equiv of NaHMDS in pyridine at 90 °C to close the B-ring and produce nevirapine (**1**) in 91% yield.

We have demonstrated that a variety of 4-substituted 3-[(*tert*-butoxycarbonyl)amino]pyridines can be generated through the use of *ortho*-metalation chemistry. Furthermore, the conversion of these compounds to a series of dipyridodiazepinones has been demonstrated with the synthesis of the antiviral nevirapine.

† Dedicated to the memory of Dr. Simon J. Coutts, 1962–1994.

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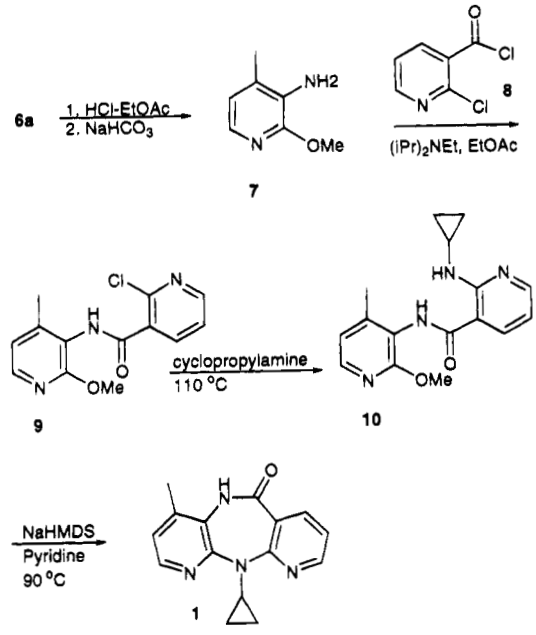
Table 1. Synthesis of 4-Substituted-3-[(*tert*-butoxycarbonyl)amino]-2-methoxypyridines

compound	R	E-*X*	% yield
6a	H	Me-*I*	84
6b	H	$PhCH_2$-*Br*	67
6c	H	Bu_3Sn-*Cl*	86
6d	H	I-*I*	59
6e	H	$BnOCH_2$-*Cl*	73
6f	H	CHO-NMe_2	91
6g	OMe	Me-*I*	77
6h	OMe	$PhCH_2$-*Br*	63
6i	OMe	Bu_3Sn-*Cl*	82
6j	OMe	I-*I*	47
6k	OMe	$BnOCH_2$-*Cl*	80
6l	OMe	CHO-NMe_2	89

Scheme 1



Experimental Section[8]

General Procedure for the Directed Lithiation. To a stirred solution of 5 mmol of the starting 3-*tert*-butoxycarbonylamino-2-methoxypyridine (**4**)[7] in 25 mL of dry ether containing 1.8 mL (12 mmol) of TMEDA at −78 °C under an argon atmosphere was added 4.8 mL (12 mmol) of a 2.5 M solution of *n*BuLi in hexanes. The mixture was then warmed to −10 °C for 2 h followed by recooling to −78 °C. The desired electrophile (7 mmol) was added, and the mixture was allowed to warm to room temperature for 3 h. After quenching with H_2O, the mixture was washed with 0.1 N HCl, dried over $MgSO_4$, and concentrated and the product purified by flash chromatography (silica gel, 9:1 hexanes:EtOAc). Analytical samples were recrystallized from heptane.

2-Methoxy-4-methyl-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6a): ^{1}H-NMR ($CDCl_3$) δ 1.49 (s, 9 H), 2.26 (s, 3 H), 3.94 (s, 3 H), 6.07 (bs, 1 H), 6.74 (d, J = 5.2 Hz, 1 H), 7.85 (d, J = 5.2 Hz, 1 H); CIMS 239 (MH^+); mp 93−5 °C. Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.39; H, 7.63; N, 11.66.

2-Methoxy-4-(phenylmethyl)-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6b): ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9 H), 3.95 (s, 3 H), 4.00 (s, 2 H), 6.02 (bs, 1 H), 6.60 (d, J = 5.2 Hz, 1 H), 7.14−7.32 (m, 5 H), 7.88 (d, J = 5.2 Hz, 1 H); CIMS 315 (MH^+); mp 92−3 °C. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.90; H, 7.16; N, 9.00.

2-Methoxy-4-(tri-*n*-butylstannyl)-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6c): ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 9 H), 1.07 (m, 6 H), 1.24−1.73 (m, 21 H), 3.94 (s, 3 H), 6.46 (bs, 1 H), 6.95 (d, J = 4.9 Hz, 1 H), 7.87 (d, J = 4.9 Hz, 1 H); CIMS 515 (MH^+); mp, oil; HRMS m/z calcd for $C_{23}H_{43}N_2O_3Sn$ 515.22957, found 515.22906.

4-Iodo-2-methoxy-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6d) (note: I_2 was added as a THF solution): ^{1}H-NMR ($CDCl_3$) δ 1.48 (s, 9 H), 3.94 (s, 3 H), 6.03 (bs, 1 H), 7.33 (d, J = 5.4 Hz, 1H), 7.64 (d, J = 5.4 Hz, 1H); CIMS 351 (MH^+); mp 109−11 °C. Anal. Calcd for $C_{11}H_{15}IN_2O_3$: C, 37.73; H, 4.32; N, 8.00. Found: C, 37.86; H, 4.38; N, 8.04.

4-(Benzyloxymethyl)-2-methoxy-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6e): ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 9 H), 3.97 (s, 3 H), 4.54 (s, 2 H), 4.57 (s, 2 H), 6.24 (bs, 1 H), 7.13 (d, J = 5.3 Hz, 1 H), 7.31−7.37 (m, 5 H), 7.99 (d, J = 5.3 Hz, 1 H); CIMS 345 (MH^+); mp, oil; HRMS m/z calcd for $C_{19}H_{25}N_2O_4$ 345.18143, found 345.18223.

4-Formyl-2-methoxy-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6f): ^{1}H-NMR ($CDCl_3$) δ 1.51 (s, 9 H), 4.05 (s, 3 H), 6.81 (bs, 1 H), 7.27 (d, J = 5.3 Hz, 1 H), 8.03 (d, J = 5.3 Hz, 1 H), 10.02 (s, 1 H); CIMS: 253 (MH^+); mp 109−11 °C. Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.21; H, 6.45; N, 11.10.

2,6-Dimethoxy-4-methyl-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6g): ^{1}H-NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.22 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 5.80 (bs, 1 H), 6.16 (s, 1 H); CIMS: 269 (MH^+); mp 95−7 °C. Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.11; H, 7.55; N, 10.34.

2,6-Dimethoxy-4-(phenylmethyl)-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6h): ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9 H), 3.85 (s, 3 H), 3.90−3.95 (m, 5 H), 5.72 (bs, 1 H), 6.08 (s, 1 H), 7.09−7.31 (m, 5 H); CIMS 345 (MH^+); mp 94−6 °C. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.03; H, 6.97; N, 8.15.

2,6-Dimethoxy-4-(tri-*n*-butylstannyl)-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6i): ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 9 H), 1.06 (m, 6 H), 1.24−1.73 (m, 21 H), 3.88 (s, 3 H), 3.92 (s, 3 H), 5.95 (bs, 1 H), 6.38 (s, 1 H); CIMS 545 (MH^+); mp 54−6 °C; HRMS m/z calcd for $C_{24}H_{45}N_2O_4Sn$ 545.24013, found 545.24260.

2,6-Dimethoxy-4-iodo-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6j) (note: I_2 was added as a THF solution): ^{1}H-NMR ($CDCl_3$) δ 1.50 (s, 9 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 5.77 (bs, 1 H), 6.81 (s, 1 H); CIMS: 381 (MH^+); mp 120−2 °C. Anal. Calcd for $C_{12}H_{17}IN_2O_4$: C, 37.91, H, 4.51, N, 7.37. Found: C, 38.30; H, 4.66; N, 7.39.

4-[(Benzyloxy)methyl]-2,6-dimethoxy-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6k): ^{1}H-NMR ($CDCl_3$) δ 1.46 (s, 9 H), 3.90 (s, 3 H), 3.95 (s, 3 H), 4.54 (s, 2 H), 4.56 (s, 2 H), 5.92 (bs, 1 H), 6.54 (s, 1 H), 7.26−7.37 (m, 5 H); CIMS: 375 (MH^+); mp 89−90 °C. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.16; H, 7.00; N, 7.48. Found: C, 64.19; H, 7.01; N, 7.39.

2,6-Dimethoxy-4-formyl-3-pyridinecarbamic acid, 1,1-dimethylethyl ester (6l): ^{1}H-NMR ($CDCl_3$) δ 1.49 (s, 9 H), 3.91 (s, 3 H), 4.01 (s, 3 H), 6.39 (bs, 1 H), 6.69 (s, 1 H), 10.02 (s, 1 H); CIMS: 283 (MH^+); mp 107−9 °C. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.26; H, 6.50; N, 9.89.

3-Amino-2-methoxy-4-methylpyridine (7). 2-Methoxy-4-methyl-3-pyridinecarbamic acid, 1,1-dimethylethyl ester **(6a)** (0.7 g, 2.9 mmol), was treated with 25 mL of 4 M HCl in EtOAC at room temperature overnight. The resulting suspension was carefully washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 0.4 g of the free amine as an oil (100%): ^{1}H-NMR ($CDCl_3$) δ 2.15 (s, 3 H), 3.98 (s, 3 H), 6.62 (d, J = 5.0 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H); CIMS 139 (MH^+); mp (MsOH salt, recrystallized from isopropyl alcohol) 199 °C dec. Anal. Calcd for $C_7H_{10}N_2O$. MsOH: C, 41.02; H, 6.02; N, 11.96. Found: C, 41.11; H, 5.98; N, 11.95.

2-Chloro-*N*-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide (9). To a solution of 0.4 g (2.9 mmol) of 3-amino-2-methoxy-4-methylpyridine **(7)** and 0.5 g (2.9 mmol) of 2-chloronicotinoyl chloride **(8)** in EtOAc at 0 °C was added 0.4 g (3.0 mmol) of diisopropylethylamine. Stirring was continued for 10 h at which point the mixture was washed with 0.1 N HCl, dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (1:1 EtOAc:hexanes) to yield 0.7 g (88%) of the desired material. Recrystallized from ethyl acetate. ^{1}H-NMR ($CDCl_3$) δ 2.35 (s, 3 H), 3.97 (s, 3 H), 6.84 (d, J = 4.8 Hz, 1 H), 7.41 (dd, J = 4.8, 7.7 Hz, 1 H), 7.82 (bs, 1 H), 7.98 (d, J =

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5.2 Hz, 1 H), 8.20 (dd, J = 1.9, 7.7 Hz, 1 H), 8.52 (dd, J = 1.9, 4.7 Hz, 1 H); CIMS: 278 (MH^+); mp 145–6 °C. Anal. Calcd for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 56.23; H, 4.40; N, 15.13.

2-(Cyclopropylamino)-*N*-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide (10). 2-Chloro-*N*-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide **(9)** (0.55 g, 2 mmol) was placed in a sealed tube containing cyclopropylamine (0.5 mL, 7 mmol) and heated to 110 °C overnight. Removal of the cyclopropylamine by rotary evaporation followed by flash chromatography of the residue on silica gel (1:1 EtOAc:hexanes) gave the desired compound in 86% yield (0.51 g). Recrystallized from heptane. ^{1}H-NMR ($CDCl_3$) δ 0.50–0.56 (m, 2 H), 0.79–0.85 (m, 2 H), 2.26 (s, 3 H), 2.86–2.90 (m, 1 H), 3.94 (s, 3 H), 6.63 (dd, J = 4.9, 7.7 Hz, 1 H), 6.82 (d, J = 5.2 Hz, 1 H), 7.40 (bs, 1 H), 7.85 (dd, J = 1.7, 7.7 Hz, 1 H), 7.94 (d, J = 5.2 Hz, 1 H), 8.13 (bs, 1 H), 8.39 (dd, J = 1.7, 4.9 Hz, 1 H); CIMS 299 (MH^+); mp 151–2 °C. Anal. Calcd for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.07; H, 6.07; N, 18.48.

Nevirapine (1). A solution of 2-(cyclopropylamino)-*N*-(2-methoxy-4-methyl-3-pyridinyl)-3-pyridinecarboxamide **(10)** (0.3 g, 1 mmol) in 2 mL of dry pyridine under an argon atmosphere was treated with 2.2 mL of a 1.0 M solution of NaHMDS. The solution was then warmed to 90 °C for 6 h. Upon cooling, the mixture was partitioned between EtOAc and 0.5 N HCl. The EtOAc layer was then washed further with 0.5 N HCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel (1:1 EtOAc:hexanes) to give nevirapine[1b] in 91% yield (0.24g).

Acknowledgment. We thank Walter Davidson for performing the high resolution mass spectrometry and John Proudfoot for helpful discussions.

Supplementary Material Available: Copies of ^{1}H-NMR spectra of **6c**, **6e**, and **6i** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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