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A Simple Method for the Protection of Aryl Amines as their *t*-Butylcarbamoyl (Boc) Derivatives

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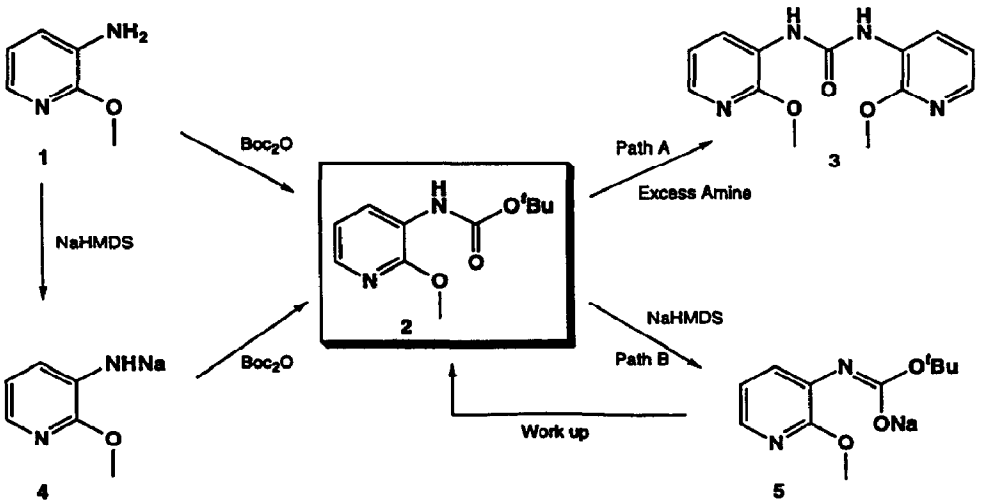
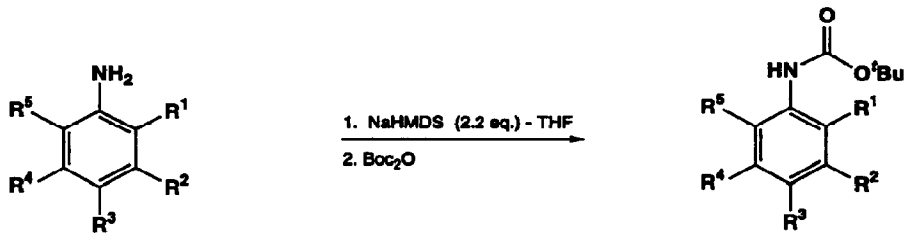
Abstract: It has been found that aryl amines can be directly protected as their Boc derivatives by treatment of the amine with two equivalents of NaHMDS in THF followed by one equivalent of di-*t*-butyldicarbonate. This procedure works on a wide variety of both electron-rich and electron-deficient aryl amines.

The *t*-butylcarbamoyl (Boc) group is one of the most useful derivatives for the protection of amines.[1] Its stability toward strong base also makes it an effective *ortho*-directing group for the lithiation and functionalization of aromatic rings.[2] Unfortunately, obtaining protected aryl amines is often more complicated than obtaining their aliphatic counterparts due largely to the decreased nucleophilicity of the aryl amine. In cases where the aryl amine does react, a number of side reactions can occur including bis-carbamoylation and/or urea formation. These problems often require that the carbamates be produced via Curtius rearrangements of the corresponding acyl azides followed by trapping of the intermediate isonitrile with *t*-butyl alcohol.[3] We report herein conditions for the direct conversion of aryl amines to their *t*-butyl carbamoyl derivatives in high yields.



During an attempt to protect the amino pyridine **1**[4] with di-*t*-butyldicarbonate (Boc_2O) and DMAP we isolated mainly the urea **3**. As this compound arises from attack of a second equivalent of the amine on the expected Boc-protected amine **2** (path a), we thought that deprotonation of **2** to give **5** (path b) would prevent its further reactivity. Furthermore, since the starting aryl amines are fairly acidic, problems associated with their low nucleophilicity might be overcome by formation of their alkali salts (**4**). This procedure would allow for the ***direct*** protection of both electron-rich and electron-deficient aryl amines and would complement routes that rely on the conversion of other functional groups. The tables below show the results obtained by treatment of aryl- and pyridyl- amines with two equivalents of NaHMDS followed by the addition of *t*-butyl-dicarbonate.

Table 1. Protection of Aryl Amines.

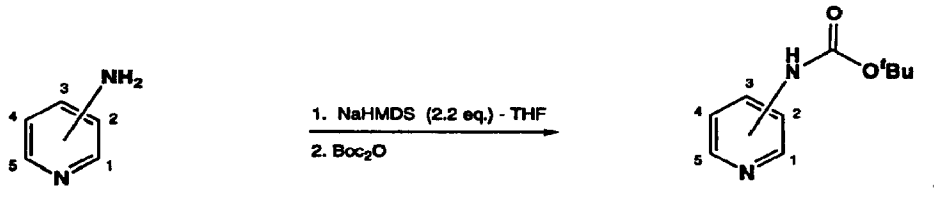


Product	R^1	R^2	R^3	R^4	R^5	Yield
6	H	OMe	H	H	H	88%
7	I	H	H	H	H	76%
8	Cl	Cl	Cl	H	H	91%
9	F	F	H	H	H	63%
10	H	F	H	F	H	88%
11	NO_2	H	H	H	H	92%
12	Me	H	Me	H	Me	0%
13	NO_2	H	H	H	NO_2	0%
14	H	NO_2	F	H	H	0%

The data shown in Table 1 demonstrate the scope and limitations of the reaction. Examples **6** through **11** show that the reaction does indeed work on both electron deficient and electron rich anilines. Previously, compounds **9** and **10** have only been synthesized via a Curtius rearrangement.[3] Examples **12** and **13** point to a steric limitation to the reaction when the amine is flanked by two substituents; in both of these cases only the starting aniline was recovered. Example **14** is interesting since no starting material was recovered from the reaction mixture. Most likely a polymerization reaction takes place wherein the anilide salt displaces a flourine on a second molecule of starting material. This activation of flourine as a leaving group in *ipso* substitution is well documented in cases where the flourine is *ortho* or *para* to an electron withdrawing group such as nitro.[5]

Table 2 shows results from the protection of a series of aminopyridines. High yields were obtained regardless of the position of the amino group on the ring (examples **16** - **18**).

Table 2. Protection of Aminopyridines.



Product	R^1	R^2	R^3	R^4	R^5	Yield
2	MeO	NHBoc	H	H	H	90%
15	MeO	NHBoc	H	H	MeO	94%
16	NHBoc	H	H	H	H	87%
17	H	NHBoc	H	H	H	72%
18	H	H	NHBoc	H	H	78%
19	NHBoc	Cl	H	Cl	H	77%
20	NHBoc	H	H	NO_2	H	61%

We have found that the most general procedure is to mix the amine with two equivalents of base and then to add the Boc_2O. This prevents side reactions in cases where the amine is nucleophilic enough to react with the Boc_2O without catalyst. If the amine itself does not react with the Boc_2O, it is possible to premix the amine and the Boc_2O and to effect the reaction by the rapid addition of base.

In conclusion we have developed a simple and efficient procedure for the direct protection of aryl amines as their Boc-derivatives. This method complements other established techniques to produce useful intermediates for *ortho*-directed lithiation chemistry.

General procedure:[6,7] Starting materials (except for **1**[4]) were obtained from commercial sources. To a solution of 2.2 mmol of the desired amine in 2 mL (slightly more if needed) of THF was added 4.4 mL (4.4 mmol) of a 1 M solution of NaHMDS in THF. After 15 min, a solution of di-*t*-butyldicarbonate (2 mmol) in THF was added and the reaction proceeded until complete by TLC (15 min to 3 hrs). Workup consisted of removal of the THF by rotary evaporation followed by partioning between 50 mL of 0.1 N HCl and 20 mL of EtOAc. A small amount of product may remain in the HCl layer at this point and can be removed by treatment of the HCl layer with 5 mL of a saturated $NaHCO_3$ solution followed by extraction into two 20-mL portions of EtOAc. The combined EtOAc layers are then dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel using EtOAc: Hexanes as the mobile phase.

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6. ^{1}H-NMR spectra were recorded on a Bruker WM 250 MHz spectrometer. CIMS were measured using methane gas by Oneida Labs (Whitesboro, NY).

7. **3-(*tert*-Butoxycarbonylamino)-2-methoxypyridine (2)** ^{1}H-NMR ($CDCl_3$): δ 1.52 (s, 9 H), 3.99 (s, 3 H), 6.85 (dd, J = 7.9 and 5.0 Hz, 1 H), 6.96 (broad s, 1 H), 7.76 (dd, J = 5.0 and 1.6 Hz, 1 H), 8.27 (broad d, J = 7.6 Hz, 1 H); CIMS: 225 (MH^+).
1-(*tert*-Butoxycarbonylamino)-3-methoxybenzene (6) ^{1}H-NMR ($CDCl_3$): δ 1.51 (s, 9 H), 3.77 (s, 3 H), 6.57 (ddd, J = 8.3, 2.4 and 0.7 Hz, 1 H), 6.68 (s, 1 H), 6.84 (dd, J = 8.0 and 1.3 Hz, 1 H), 7.10 - 7.19 (m, 2 H); CIMS: 224 (MH^+).
1-(*tert*-Butoxycarbonylamino)-2-iodobenzene (7) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 6.76 (dt, J = 7.6 and 1.5 Hz, 1 H), 6.81 (broad s, 1 H), 7.31 (dt, J = 7.8 and 1.4 Hz, 1 H), 7.74 (dd, J = 7.9 and 1.4 Hz, 1 H), 8.04 (dd, J = 8.3 and 1.4 Hz, 1 H); CIMS: 320 (MH^+).
1-(*tert*-Butoxycarbonylamino)-2,3,4-trichlorobenzene (8) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 7.04 (broad s, 1 H), 7.34 (d, J = 9.0 Hz, 1 H), 8.11 (d, J = 9.1 Hz, 1 H), ; CIMS: 296 (MH^+).
1-(*tert*-Butoxycarbonylamino)-2,3-difluorobenzene (9) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 6.76 (broad s, 1 H), 6.80 (apparent q, $J \approx 9$ Hz, 1 H), 7.01 (m, 1 H), 7.85 (broad t, J = 8.1 Hz, 1 H); CIMS: 230 (MH^+).
1-(*tert*-Butoxycarbonylamino)-3,5-difluorobenzene (10) ^{1}H-NMR ($CDCl_3$): δ 1.50 (s, 9 H), 6.45 (tt, J = 9.0 and 2.3 Hz, 1 H), 6.71 (broad s, 1 H), 6.95 (dd, J = 9.2 and 2.1 Hz, 2 H); CIMS: 230 (MH^+).
1-(*tert*-Butoxycarbonylamino)-2-nitrobenzene (11) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 7.08 (ddd, J = 8.5, 7.2 and 1.3 Hz, 1 H), 7.59 (ddd, J = 8.8, 7.4 and 1.7 Hz, 1 H), 8.17 (dd, J = 8.5 and 1.6 Hz, 1 H), 8.54 (dd, J = 8.6 and 1.2 Hz, 1 H), 9.65 (broad s, 1 H),; CIMS: 183 (MH^+ - $CH_2C(CH_3)_2$).
3-(*tert*-Butoxycarbonylamino)-2,6-dimethoxypyridine (15) ^{1}H-NMR ($CDCl_3$): δ 1.51 (s, 9 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 6.28 (d, J = 8.5 Hz, 1 H), 6.65 (broad s, 1 H), 8.18 (broad d, J = 7.2 Hz, 1 H); CIMS: 255 (MH^+).
2-(*tert*-Butoxycarbonylamino)-pyridine (16) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 6.91 (ddd, J = 7.3, 5.1 and 0.9 Hz, 1 H), 7.65 (ddd, J = 8.5, 7.3 and 1.8 Hz, 1 H), 7.99 (d, J = 8.5 Hz, 1 H), 8.34 (ddd, J = 5.0, 1.8 and 0.7 Hz, 1 H), 10.17 (s, 1 H); CIMS: 195 (MH^+).
3-(*tert*-Butoxycarbonylamino)-pyridine (17) ^{1}H-NMR ($CDCl_3$): δ 1.52 (s, 9 H), 6.01 (s, 1 H), 7.23 (broad dd, J = 8.2 and 4.4 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 1 H), 8.27 (d, J = 4.4 Hz, 1 H), 8.45 (s, 1 H); CIMS: 195 (MH^+).
4-(*tert*-Butoxycarbonylamino)-pyridine (18) ^{1}H-NMR ($CDCl_3$): δ 1.51 (s, 9 H), 7.12 (broad s, 1 H), 7.33 (dd, J = 4.9 and 1.5 Hz, 2 H), 8.42 (d, J = 6.1 Hz, 2 H); CIMS: 195 (MH^+).
2-(*tert*-Butoxycarbonylamino)-3,5-dichloropyridine (19) ^{1}H-NMR ($CDCl_3$): δ 1.53 (s, 9 H), 7.23 (broad s, 1 H), 7.68 (d, J = 2.3, 1 H), 8.32 (d, J = 2.3 Hz, 1 H); CIMS: 263 (MH^+).
2-(*tert*-Butoxycarbonylamino)-5-nitropyridine (20) ^{1}H-NMR ($CDCl_3$): δ 1.61 (s, 9 H), 8.26 (d, J = 9.3, 1 H), 8.48 (dd, J = 2.6 and 9.4 Hz, 1 H), 9.26 (d, J = 1.5 Hz, 1 H), 10.16 (s, 1 H),; CIMS: 240 (MH^+).

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