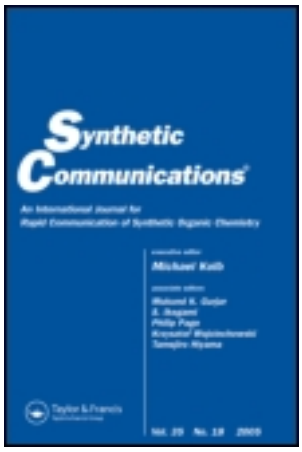

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AN IMPROVED SYNTHESIS OF N-BOC PROTECTED ARYL AMINES

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AN IMPROVED SYNTHESIS OF *N*-BOC PROTECTED ARYL AMINES

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ABSTRACT

There are several known methods of protecting amines as their Boc derivatives. For less nucleophilic amines such as aryl amines these methods often give poor yields and are generally not satisfactory. Here, Boc aryl amines are obtained by first introducing two Boc groups followed by selective removal of one of them. This procedure works well for a number highly sterically hindered substrates as well as electron deficient and electron rich aryl amines.

The Boc group has been used extensively for the protection of amines due to its ease of formation, stability under basic conditions and ease of removal.[1] Boc-protected aryl amines are important intermediates in organic

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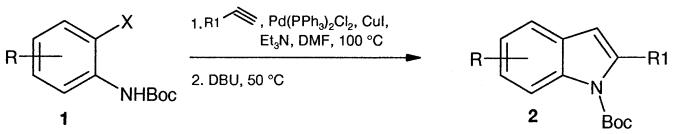
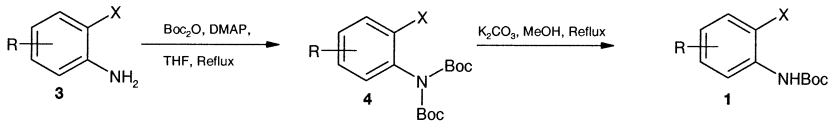


Figure 1.

synthesis and have been used for the directed lithiation of aromatic rings[2] and the preparation of unsymmetrical ureas[3] amongst others. Our interest in mono-Boc protected anilines arose from our desire to prepare a series of 2-halo-*N*-Boc-anilines as substrates in the well-documented Pd-mediated coupling/cyclization with terminal alkynes.[4]

Aryl amines are particularly difficult to protect with the Boc-group because of the reduced nucleophilicity of the nitrogen atom when compared to primary of secondary aliphatic amines. Thus, their synthesis often requires the Curtius rearrangement of acyl azides followed by trapping with *t*-butyl alcohol.[5] However, recent reports have demonstrated that the reaction of aryl amines with one equivalent of di-*t*-butyldicarbonate (Boc_2O) using extended reaction times,[6] elevated temperatures,[7] or the addition of a base (DMAP,[8] aq. NaOH[9] or pyridine[10]) can be successful in certain cases. In addition, Kelly and McNeil published a general method for the mono-*N*-Boc-protection of aryl amine derivatives using Boc_2O and sodium hexamethyldisilazide (NaHMDS).[11] This new procedure addressed many of the problems associated with mono-*N*-Boc-protection of aryl amines but was limited by steric effects, especially when the amine was flanked by two *ortho*-substituents.

Since our aryl amines all contained a halogen in the *ortho*-position and several were highly sterically hindered, they appeared to be very reluctant to undergo direct mono-Boc protection using one equivalent of Boc_2O. Using all of the conditions described above, including the NaHMDS method, the reactions proceeded in all cases to afford only di-Boc product (**4**) and recovered starting material (**3**, Scheme 1). It is thought that mono-Boc protection of these derivatives is very slow but once the first Boc group is incorporated, the carbamate NH is then sufficiently acidic to allow deprotonation and



Scheme 1.

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fast incorporation of a second Boc-group. We anticipated that one might exploit this phenomenon by purposefully exhaustively protecting the aryl amines and then performing a selective deprotection to afford the required mono-Boc-derivatives (Scheme 1).

Treatment of each *ortho*-halo aryl amine with a 3-fold excess of Boc_2O in the presence of a catalytic amount of DMAP in refluxing THF rapidly formed the di-Boc derivatives (**4**) in quantitative yield. The selective removal of one Boc-group is not well-precedented in the literature although isolated reports using TFA have appeared.[12,13] The deprotection of different carbamate groups in the presence of a Boc-group under basic conditions, is however, well-documented.[14,15] These conditions have been applied, again in isolated examples, to the selective deprotection of di-Boc amines.[16,17] We therefore chose to use potassium carbonate in methanol at reflux as the conditions to selectively remove one Boc-group and provide the required derivatives (**1**). The reactions were generally complete in 2–12 h and provided 70–90% yields of the required products after purification by flash silica gel chromatography. This method was successfully applied to a number of highly electron-deficient and sterically hindered substrates (Table 1).

As can be seen in Table 1, entries 4–11 show that this method is applicable to *ortho*-halo substituted aryl amines containing both activating and deactivating functional groups in the aromatic ring. Entries 12–15 clearly demonstrate that unprecedented sterically hindered amines where the amine is flanked by two substituents are also accessible using this method. Entries 16–21 are examples which were made to test whether this method is limited to *ortho*-halo substituted aryl amines. Entry 17 is of particular interest since this highly sterically hindered compound could not be synthesized using the NaHMDS method yet was obtained in good yield using this route. Entry 18 showed a limitation to the method in that upon subjecting the di-Boc derivative to the deprotection conditions, both Boc-groups were removed and only the starting aniline was recovered. However, if the deprotection was performed at ambient temperature, the required mono-Boc derivative was successfully obtained. Entry 20 demonstrates that the acid functionality is not stable to the reaction conditions. The reaction proceeded to afford some of the required product plus the corresponding methyl ester. This problem could be countered by using the methyl ester derivative (Entry 21) which was stable to the reaction conditions with no hydrolysis of the ester being observed.

In an attempt to convert this method into a one-pot synthesis, it was found that by concentrating the THF after the first reaction and using the material directly in the next reaction, good yields could be obtained. This led us to merely add potassium carbonate and methanol to the THF solution

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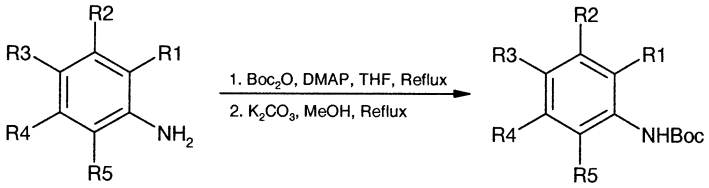
Table 1.



Product	R1	R2	R3	R4	R5	Yield (%)
4	I	H	H	H	H	76
5	Br	H	Cl	H	H	88
6	Br	H	H	Cl	H	88
7	Br	H	F	H	H	86
8	Br	H	H	NO_2	H	85
9	Br	H	NO_2	H	H	75
10	Br	H	H	CF_3	H	69
11	Br	H	t-Butyl	H	H	74
12	Br	H	F	H	F	82
13	Br	H	F	F	F	72
14	Br	H	Cl	H	Cl	73
15	Br	H	NO_2	H	Cl	81
16	H	H	H	Cl	H	83
17	NO_2	H	H	H	NO_2	78/97[a]
18	H	MeO	NO_2	H	MeO	0[b]
19	H	MeO	H	MeO	H	79
20	H	H	CO_2H	H	H	29[c]
21	H	H	CO_2Me	H	H	72

[a]Second yield reflects results from one-pot reaction procedure; [b]Complete removal of both Boc groups observed to afford only starting material. Mono-Boc deprotection successful if reaction performed at ambient temperature; [c]Reaction complicated by esterification of the acid functionality during Boc-deprotection step.

after completion of Boc-protection and proceed with the reaction. This method also worked well and even provided improved yields in one case (Entry 17).

In conclusion we have presented an improved general method to prepare inaccessible Boc-protected aryl amines using a simple two-step exhaustive Boc-protection/selective deprotection procedure which can also be used as a one-pot procedure. The method works well on several different

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substrates and is of particular use when highly sterically hindered aryl amines are employed.

General Procedure: To a solution of the aryl amine (9.69 mmol) in anhydrous THF (100 mL) was added Boc_2O (29 mmol) followed by DMAP (0.97 mmol). The solution was stirred at reflux for 2–12 h then concentrated to dryness and partitioned between 0.5 N HCl (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2×50 mL) and the combined organic phases were washed with brine (50 mL), dried over $NaSO_4$, filtered and concentrated to afford the crude di-Boc product usually as a solid.

The crude material was dissolved in methanol (100 mL), treated with potassium carbonate (29 mmol) and stirred at reflux for 2–12 h. The mixture was concentrated to dryness and partitioned between 0.5 N HCl (100 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (2×50 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to afford the crude product. This was purified by flash silica gel column chromatography eluting with hexane/EtOAc mixtures to afford the products as white solids or colourless oils in 70–90% overall yield.

(2-Iodo-phenyl)-carbamic acid *tert*-butyl ester (4): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.73 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.27 (m, 1H), 6.80 (br. s, 1H), 6.75 (m, 1H), 1.56 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 320 $(M + H)^+$.

(2-Bromo-4-chloro-phenyl)-carbamic acid *tert*-butyl ester (5): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, $J = 8.9$ Hz, 1H), 7.49 (d, $J = 2.4$ Hz, 1H), 7.24 (dd, $J = 8.9$, 2.4 Hz, 1H), 6.94 (br. s, 1H), 1.52 (s, 9H) ppm. Mass Spectrum: (EI) m/z 307 (M^+).

(2-Bromo-5-chloro-phenyl)-carbamic acid *tert*-butyl ester (6): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J = 2.4$ Hz, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 6.99 (br. s, 1H), 6.87 (dd, $J = 8.5$, 2.5 Hz, 1H), 1.55 (s, 9H) ppm. Mass Spectrum: (EI) m/z 307 (M^+).

(2-Bromo-4-fluoro-phenyl)-carbamic acid *tert*-butyl ester (7): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, $J = 9.1$, 5.5 Hz, 1H), 7.23 (m, 1H), 6.97 (m, 1H), 6.83 (br. s, 1H), 1.55 (s, 9H) ppm. Mass Spectrum: (EI) m/z 290 $(M + H)^+$.

(2-Bromo-5-nitro-phenyl)-carbamic acid *tert*-butyl ester (8): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, $J = 2.6$ Hz, 1H), 7.75 (dd, $J = 8.7$, 2.6 Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.15 (br. s, 1H), 1.55 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 319 $(M + H)^+$.

(2-Bromo-4-nitro-phenyl)-carbamic acid *tert*-butyl ester (9): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, $J = 2.6$ Hz, 1H), 7.75 (dd, $J = 8.7$, 2.6 Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.15 (br. s, 1H), 1.55 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 319 $(M + H)^+$.

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(2-Bromo-5-trifluoromethyl-phenyl)-carbamic acid *tert*-butyl ester (10): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.13 (dd, $J = 8.4$, 1.9 Hz, 1H), 7.09 (br. s, 1H), 1.54 (s, 9H) ppm. Mass Spectrum: (EI) m/z 340 $(M + H)^+$.

(2-Bromo-4-*tert*-butyl-phenyl)-carbamic acid *tert*-butyl ester (11): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, $J = 8.7$ Hz, 1H), 7.48 (d, $J = 2.2$ Hz, 1H), 7.28 (d, $J = 8.7$, 2.2 Hz, 1H), 6.88 (br. s, 1H), 1.59 (s, 9H), 1.33 (s, 9H) ppm. Mass Spectrum: (EI) m/z 327 $(M)^+$.

(2-Bromo-4,6-difluoro-phenyl)-carbamic acid *tert*-butyl ester (12): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 6.86 (m, 1H), 5.09 (br. s, 1H), 1.56 (s, 9H) ppm. Mass Spectrum: (EI) m/z 307 $(M)^+$.

(2-Bromo-4,5,6-trifluoro-phenyl)-carbamic acid *tert*-butyl ester (13): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 1H), 6.02 (br. s, 1H), 1.59 (s, 9H) ppm. Mass Spectrum: (EI) m/z 326 $(M + H)^+$.

(2-Bromo-4,6-dichloro-phenyl)-carbamic acid *tert*-butyl ester (14): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, $J = 2.3$ Hz, 1H), 7.41 (d, $J = 2.3$ Hz, 1H), 6.08 (br. s, 1H), 1.50 (s, 9H) ppm. Mass Spectrum: (EI) m/z 341 $(M)^+$.

(2-Bromo-6-chloro-4-nitro-phenyl)-carbamic acid *tert*-butyl ester (15): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, $J = 2.5$ Hz, 1H), 8.27 (d, $J = 2.5$ Hz, 1H), 6.38 (br. s, 1H), 1.39 (s, 9H) ppm. Mass Spectrum: (EI) m/z 350 $(M + H)^+$.

(5-Chloro-phenyl)-carbamic acid *tert*-butyl ester (16): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.20 (m, 2H), 6.96 (m, 1H), 6.45 (br. s, 1H), 1.50 (s, 9H) ppm. Mass Spectrum: (EI) m/z 227 $(M)^+$.

(2,6-Dinitro-phenyl)-carbamic acid *tert*-butyl ester (17): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (br. s, 1H), 8.25 (d, $J = 8.2$ Hz, 2H), 7.35 (t, $J = 8.2$ Hz, 1H), 1.54 (s, 9H) ppm. Mass Spectrum: (EI) m/z 283 $(M)^+$.

(2,5-Dimethoxy-4-nitro-phenyl)-carbamic acid *tert*-butyl ester (18): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.85 (s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 147 (s, 9H) ppm. Mass Spectrum: (EI) m/z 298 $(M)^+$.

(3,5-Dimethoxy-phenyl)-carbamic acid *tert*-butyl ester (19): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (d, $J = 2.1$ Hz, 2H), 6.45 (br. s, 1H), 6.15 (m, 1H), 3.76 (s, 6H), 1.42 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 254 $(M + H)^+$.

4-*tert*-Butoxycarbonylamino-benzoic acid (20): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.7$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 6.75 (br. s, 1H), 1.59 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 252 $(M + H)^+$.

4-*tert*-Butoxycarbonylamino-benzoic acid methyl ester (21): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.7$ Hz, 2H), 7.42 (d, $J = 8.7$ Hz, 2H), 6.63 (br. s, 1H), 3.88 (s, 3H), 1.54 (s, 9H) ppm. Mass Spectrum: (ESI) m/z 252 $(M + H)^+$.

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One-Pot Procedure: To a solution of 2,6-dinitroaniline (100 mg, 0.55 mmol) in anhydrous THF (5 mL) was added Boc_2O (358 mg, 1.64 mmol) followed by DMAP (6.8 mg, 0.054 mmol). The mixture was stirred at reflux for 3 h then cooled to ambient temperature. Potassium carbonate (228 mg, 1.64 mmol) and methanol (5 mL) were added and the mixture was stirred at reflux for 3 h. The mixture was cooled to ambient temperature, concentrated and the residue purified by flash silica gel column chromatography (hexane : EtOAc, 4:1), to afford 150 mg (97%) of (2,6-dinitrophenyl)-carbamic acid *tert*-butyl ester (**17**) as a white solid with identical MS and NMR to a sample prepared by the general two-step procedure.

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