Simultaneous Deprotection and Purification of BOC-amines Based on Ionic Resin Capture

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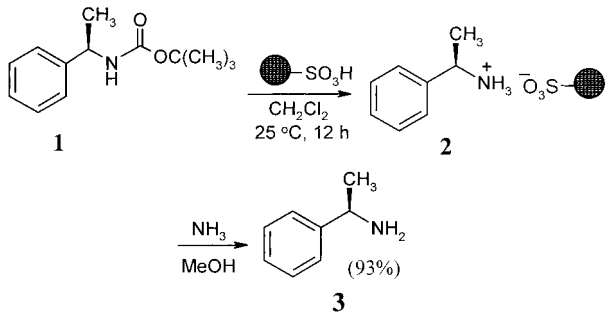
Combinatorial chemistry and the synthesis of chemical libraries has resulted in a need to develop new strategies to rapidly and simply purify, isolate, and manipulate library members during each synthetic step. Two major strategies have been used. The first uses cross-linked polymers such as those used in Merrifield's solid-phase peptide synthesis.[1,2] The second strategy uses soluble polymer supports or biphasic syntheses.[3,4] The recent development of polymer-supported quenching reagents as a rapid purification tool in solution-phase parallel synthesis is an outgrowth of the former strategy.[5] This chemistry typically relies on molecular reactivity and/or molecular recognition (often acid−base chemistry) as the means by which excess reagents or byproducts are sequestered and isolated. On the other hand, the "resin capture" idea has also recently been introduced as an alternative solution-phase library methodology.[6] This method uses functionalized resins to trap selectively (via a covalent bond linkage) the desired products away from solution-phase reagents or byproducts. The products are then released from the resin through an appropriate cleavage step. Herein, we disclose a new and simple ionic equivalent of this resin capture technique as demonstrated by the deprotection and purification of solution-phase BOC-protected amines through the use of a strongly acidic macroreticular ion-exchange resin, Amberlyst 15.

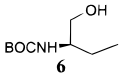
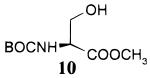
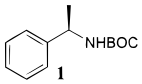
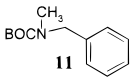
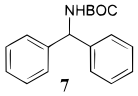
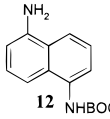
The *tert*-butyloxycarbonyl (BOC) group is widely used in organic synthesis as an amine protecting group. Deprotection of BOC-protected amines is usually achieved by using an acid like CF_3COOH or HCl.[7] Recently, ion-exchange chromatography was used to expedite purification of libraries of amines or amine derivatives.[8] We reasoned that a strongly acidic ion-exchange resin should be able to both deprotect BOC-protected amines and to also isolate the resulting amine products. This expectation has been successfully realized.

Scheme 1



1 2 3

Table 1. Deprotection/Purification of Various BOC-Amines Using Amberlyst 15[a]

entry	substrate	time(h)	yield(%)[b]	entry	substrate	time(h)	yield(%)[b]
a	BOCNHCH$_2$COOH **4**	5	92	f	BOCNHCH$_2$CH$_2$OH **8**	4	94
b	BOCNH(CH$_2$)$_5$COOH **5**	5	93	g[c]	BOCNH(CH$_2$)$_{17}$CH$_3$ **9**	14	96
c	 **6**	6	80	h	 **10**	10	91
d	 **1**	12	93	i	 **11**	8	87
e	 **7**	29	99	j	 **12**	4 days	92

[a] All reactions were carried out on 100 mg scale except entry g. [b] Isolated yields. [c] 1 g of the substrate was used.

In a typical procedure, *N*-BOC-(*R*)-α-methylbenzylamine (**1**) was treated with cleaned Amberlyst 15 by gentle agitation at 25 °C in CH_2Cl_2. All the BOC-amine **1** was deprotected in 12 h (Scheme 1). The reaction was readily monitored by TLC or HPLC. Complete disappearance of the BOC derivative by these methods served to indicate when complete deprotection of the BOC-amine had occurred. The pure (*R*)-α-methylbenzylamine (**3**) was then isolated in 93% yield in a second step by gently shaking the amine bound resin **2** with excess ammonia in methanol for 50 min. No additional purification steps were required. Various other BOC-protected amines were also deprotected satisfactorily as shown in Table 1. The deprotection/immobilization process took place smoothly in dichloromethane, THF, or chloroform but was very slow in methanol.

We found that both primary and secondary BOC-protected aliphatic amines can be deprotected efficiently

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with reaction times that ranged from 4 to 29 h at ambient temperature. Other functional groups such as alcohols, esters, and carboxylic acids (Table 1, entries a−c,f,h) do not interfere with the deprotection process. However, BOC-protected aromatic amines react slowly. For example, it took 4 days to deprotect mono-BOC-protected 1,5-diaminonaphthalene (Table 1, entry j). We also found that the deprotection of BOC-aniline was not complete even after 5 days in the presence of excess resin.

This procedure is synthetically useful on both small and large scales. We showed that 1 g of BOC-octadecylamine can be easily deprotected and purified by this method in high yield (Table 1, entry g). In addition, this technique is useful for the deprotection and purification of a BOC-protected amine in a mixture of compounds as was demonstrated in the following experiment. A mixture of (*R*)-*N*-BOC-methylbenzylamine (**1**) with methyl benzoate, *N*-phenylisopropylurethane, *N*-(1-phenylethyl)-*p*-toluenesulfonamide, benzyl alcohol, and *p*-nitrophenol in CH_2Cl_2 was treated with excess Amberlyst 15 at ambient temperature. The disappearance of *N*-BOC-methylbenzylamine was monitored by HPLC analysis of aliquots (Figure 1). Before addition of Amberlyst 15, there are six peaks on the HPLC chromatogram corresponding to each of these compounds (Figure 1A). Twelve hours later, after addition of the resin, the peak corresponding to BOC-methylbenzylamine (**1**) was completely absent (Figure 1B). More importantly, the relative ratios of the other components did not change significantly, indicating selectivity in reaction of the BOC-amine and in absorption of the amine. Slight decreases in peak areas for benzyl alcohol and *p*-nitrophenol were ascribed to physisorption of these components on the resin. Separate experiments showed that the physisorbed *p*-nitrophenol and benzyl alcohol could both be completely recovered by soaking the resin in a fresh polar solvent like methanol prior to release of the pure amine. A small extra peak at 2.53 min present in the HPLC (a, Figure 1B) reflected an impurity occasionally seen if the resin was not thoroughly washed before reaction.[9] The amine-bound resin was then filtered, rinsed with methanol, and treated with NH_3/MeOH to afford the free amine in 93% yield. RP-HPLC analysis (Figure 1C) showed the purity of the deprotected amine to be ~97%. The extra peak at 4.2 min (b, Figure 1C) was identified as an UV-active impurity in the solvent.

To further demonstrate the utility of this chemistry, we carried out two reactions that mimic a solution-phase, parallel synthesis. In the first example, *N*-BOC-ethanolamine **8** was treated with excess phenyl isocyanate in the presence of a catalytic amount of triethylamine in CH_2Cl_2 at 25 °C for 8 h (Scheme 2). Any unreacted isocyanate was then quenched with methanol. The mixture, which presumably consisted of two urethane compounds **13** and **14**, was treated with Amberlyst 15 in CH_2Cl_2 for 8 h at ambient temperature, and the amine-bound resin was collected and rinsed with THF and MeOH in order to remove any physically absorbed urethane **14**. Pure *N*-phenyl-2-aminoethylurethane (**15**) was isolated in 83% yield after the resin was treated with 4 M ammonia in methanol (Scheme 2).

In the second case, we obtained an 89% yield of N-phenyl-N′-[4-(aminomethyl)phenyl]urea (**19**) when we carried out this same chemistry in the presence of excess diamine (Scheme 3). Thus, 2 mmol of 4-(BOC-aminomethyl)aniline (**16**) and 1 mmol of 4-aminobenzylamine were allowed to react with 5 mmol of phenyl isocyanate

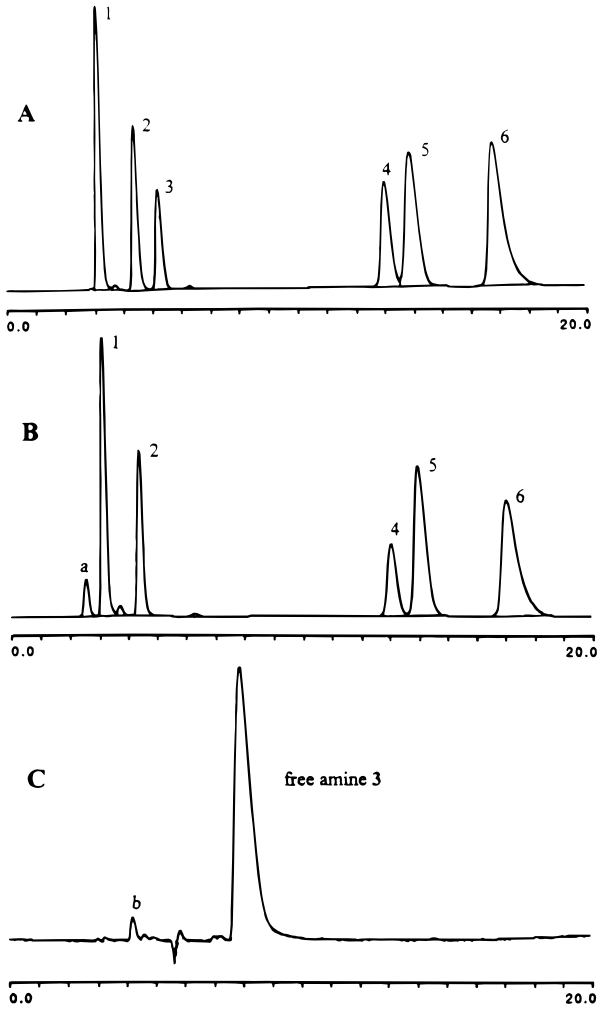
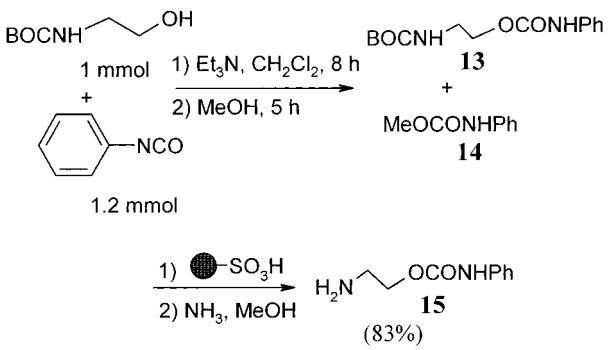


Figure 1. HPLC traces of an Amberlyst 15-promoted deprotection of a BOC-amine in a mixture of compounds with diverse functionality. (A) HPLC trace (MICROSRB-MV column, 5 μm SiO_2, 100 Å, 10:90 ethyl acetate/hexane) of reaction mixture before addition of the resin: (1) methylbenzoate; (2) *N*-phenylisopropylurethane; (3) *N*-BOC-α-methylbenzylamine; (4) benzyl alcohol; (5) *N*-(phenylethyl)-*p*-toluenesulfonamide; (6) *p*-nitrophenol. (B) Twelve hours after resin was added, BOC-amine **1** had been deprotected and absorbed while other components remained in solution. Peak *a* is an impurity from the resin. (C) HPLC trace (reversed-phase C_{18}-SiO_2, 80:20 MeOH/H_2O) of the free amine **3** isolated by washing the resin with NH_3/MeOH. Peak *b* is an impurity from the solvent.

Scheme 2



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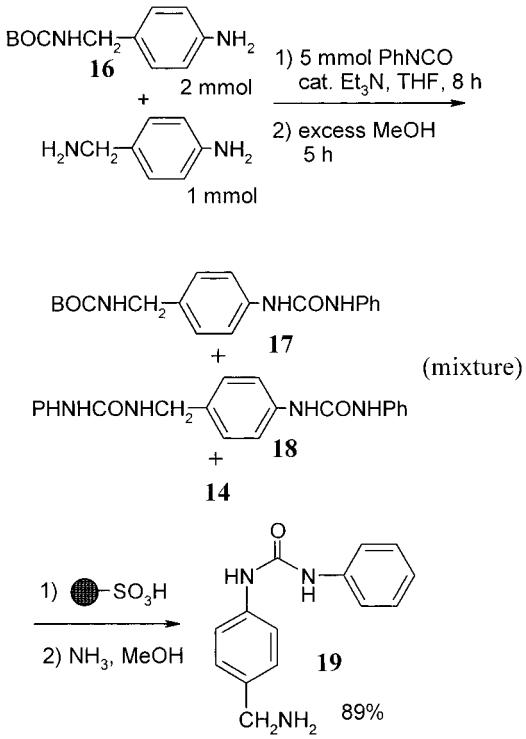
Scheme 3



in THF for 8 h. The unreacted isocyanate was then quenched with MeOH. The reaction mixture at this point presumably has three compounds (BOC-containing urea **17**, diurea **18**, and urethane **14**). Among these three compounds, only BOC-containing urea **17** is sequestrable with Amberlyst 15. Thus, using similar conditions described above, the free amine-containing urea **19** was easily obtained in high purity as confirmed by ^{1}H NMR analysis. In these two examples, the products were successfully deprotected and purified in a very simple manner that reverse differentiated the functional group's nucleophilicity.

In summary, the strongly acidic ion-exchange resin, Amberlyst 15, effectively deprotects, purifies, and isolates BOC-protected amine containing compounds. This method tolerates a variety of substrates and can be used for solution-phase parallel synthesis, which is widely employed in combinatorial chemistry.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 200 or 300 MHz with TMS as the internal reference. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ or DMSO-d_6 as the internal reference. THF was distilled from sodium−benzophenone ketyl, and CH_2Cl_2 was distilled from calcium hydride. All other reagents and solvents used were reagent grade. HPLC was performed using a Ranin SD-200 HPLC system equipped with a Dynamax UV-C detector (at 250 nm). Either a MICROSORB-MV column (5 μm SiO_2, 100 Å) or a MICROSORB-MV C18 column (5 μm, 100 Å) was used.

Cleaning of Amberlyst 15 Resin. Amberlyst 15 was obtained from Aldrich and was cleaned by the following procedure. It was first soaked in MeOH for 24 h, washed with MeOH, and then neutralized with 4 M ammonia in MeOH. The neutralized resin was acidified with 3 M HCl in 50% MeOH and rinsed with MeOH, THF, and CH_2Cl_2 successively. The acidic capacity of the resin was determined to be 3.5 mequiv/g by titration. BOC-protected amines **1**,[10d] **4**,[10a] **5**,[10b] **6**,[10c] **7**,[10e] **8**,[10f] **9**, **10**,[10g] **11**,[10h] and **12** were prepared according to the literature method from di-*tert*-butyl carbonate using triethylamine or sodium carbonate as the base.[7]

General Procedure for Deprotection/Purification with Amberlyst 15 As Described for *N*-(*tert*-Butyloxycarbonyl)-octadecylamine (9). A 1.0 g portion of *N*-*tert*-(butyloxycarbonyl)octadecylamine was dissolved in 20 mL of dichloromethane at ambient temperature. Then 2.5 g of cleaned resin was added, and the mixture was gently shaken. After 14 h, TLC (hexane) showed the complete disappearance of BOC-octadecylamine. The resin was then separated by filtration and washed with hexane, THF, and MeOH successively. This amine-bound resin was transferred to 10 mL of 4 M ammonia methanolic solution and was gently shaken for 50 min. To this mixture was added 20 mL of THF in order to dissolve all of the deprotected octadecylamine. The resin was then removed by filtration, and the solution was evaporated, yielding 0.70 g (96%) of octadecylamine that was identical (^{1}H NMR, ^{13}C NMR) with authentic octadecylamine.

***N*-(*tert*-Butyloxycarbonyl)octadecylamine (9):** colorless crystals; mp 56−58 °C (EtOAc); IR (KBr) 3382, 2935, 2866, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.27 (m, 30H), 1.44 (m, 11H), 3.10 (dd, 2H), 4.50 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.115, 22.680, 26.793, 28.402, 29.290, 29.350, 29.551, 29.677, 30.045, 31.907, 40.613, 78.950, 155.936. A satisfactory high-resolution mass spectrum of the parent ion could not be obtained for this compound.

1-[*N*-(*tert*-Butyloxycarbonyl)amino]-5-aminonaphthalene (12): white solid; IR (KBr) 3304, 3042, 1662 cm^{-1}; ^{1}H NMR (CDCl3) δ 1.55 (s, 9H), 3.90−4.35 (broad, 2H), 6.71−6.81 (m, 1H), 6.81−6.96 (broad, 1H), 7.28−7.63 (m, 4H), 7.92 (d, 1H); ^{13}C NMR($CDCl_3$) δ 28.4, 80.6, 80.8, 109.8, 110.9, 116.5, 116.8, 118.3, 118.5, 124.1, 124.7, 125.9, 126.5, 127.2, 133.4, 133.6, 142.8, 153.4; exact mass (M^+) 258.1368 (calcd for $C_{15}H_{18}N_2O_2$ 258.1381).

4-[[(*tert*-Butyloxycarbonyl)amino]methyl]aniline (16): colorless crystal; mp 87−88 °C (EtOAc/hexane 1:3); IR (KBr) 3359, 3011, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.444 (s, 9H), 1.503 (s, 1H), 4.175 (d, 2H), 4.70 (s, 1H), 6.635 (d, 2H), 7.064 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 28.396, 44.312, 79.237, 115.122, 128.856, 145.647, 155.795; exact mass (M + H) 223.1446 (calcd for $C_{12}H_{19}N_2O_2$ 223.1436).

***N*-Phenyl-(2-aminoethyl)urethane (15):** colorless liquid; IR (KBr) 3444, 3010, 2940, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.449 (s, 2H), 2.978 (t, 2H), 4.186 (t, 2H), 7.074 (m, 1H), 7.257−7.391 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 41.141, 67.232, 118.614, 123.368, 128.983, 137.862, 153.572; exact mass (M^+) 180.0899 (calcd for $C_9H_{12}N_2O_2$ 180.0907).

***N*-phenyl-*N*′-[4-(aminomethyl)phenyl]urea (19):** IR (KBr) 3428, 3012, 1647, 1607 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.650 (s, 2H), 6.948 (m, 1H), 7.207−7.464 (m, 7H), 8.752 (d, 2H); ^{13}C NMR (DMSO-d_6) δ 45.135, 118.144, 121.696, 127.518, 128.780, 137.280, 138.014, 139.877, 152.656; exact mass (M + H) 242.1293 (calcd for $C_{14}H_{16}N_3O$ 242.1292).

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Supporting Information Available: The ^{1}H NMR (200 or 300 MHz) spectra of the BOC-amines employed in these studies (5 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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