Solid-Supported *tert*-Alkoxycarbonylation Reagents for Anchoring of Amines during Solid Phase Organic Synthesis

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The preparation and characterization of a homologous series of solid phase synthesis resins for anchoring amines via a Boc-like linker are described. The scope and limitations of these resins are explored with respect to procedures for attachment and cleavage of a variety of primary amines, secondary amines, and α-amino esters.

Introduction

Most of the existing resin attachment strategies used in solid phase organic synthesis (SPOS) have been determined by those specialties such as peptide, oligosaccharide, and oligonucleotide synthesis which have had the longest history in successful utilization of SPOS. For example, there are many resin attachment strategies for carboxylic acids that are attributable to solid phase peptide synthesis.[1] Similarly, oligosaccharide chemistry has provided methods to attach alcohols to resins by forming an ether linkage.[2] Recently, solid phase methodology has been applied to the synthesis of a wide variety of nonoligomeric molecules,[3] but often the synthesis of such small organic molecules is restricted by the availability of linking strategies. A number of articles describing new resin linker strategies, including tetrahydropyranyl-,[4] silyl-,[5] sulfonyl-,[6] benzyloxycarbonyl-,[7] and ADCC-linked solid supports[8] have been published.

In the course of developing solid phase syntheses of a variety of heterocyclic molecules, we found the need for a resin linker to which amino groups may be anchored. Other desirable properties of the linker include stability to strongly basic conditions, temperatures as high as 100 °C, and strong nucleophiles. Lastly, the linker should be cleaved under reasonably mild conditions. The solid phase equivalent of a *t*-Boc protecting group would be predicted to fulfill these requirements. Resin bound tertiary alcohols have been prepared by two-step syntheses from polystyrene−divinylbenzene[9] and (chloromethyl)polystyrene−divinylbenzene (Merrifield resin).[10] These have been elaborated to a phenyl carbonate derivative and reacted with hydrazine to give a solid-supported (*tert*-alkoxycarbonyl)hydrazine which is used in the synthesis of C-terminal hydrazides of peptides. The use of these literature methods in the Boc-like anchoring of amines to solid supports has not been widely reported, presumably because of difficulties in achieving quantitative loading of amines via the *ter*t-alkyl phenyl carbonate moiety which is a relatively unreactive acylating agent.

Results and Discussion

We found that regiospecific monoalkylation of diols **2** by Merrifield resin is a simple, one-step approach to the synthesis of support bound tertiary alcohols that provides a range of carbon chain lengths between the linking functionality and the polymeric support (Scheme 1). Thus, 6-methyl-1,6-heptanediol (**2**, $n = 5$),[11] 5-methyl-1,5-hexanediol (**2**, $n = 4$),[12] and 4-methyl-1,4-pentanediol (**2**, $n = 3$)[13] are prepared by the addition of excess MeLi to the appropriate lactone (**1**, $n = 5$, 4, or 3), and 3-methyl-1,3-butanediol (**2**, $n = 2$) is obtained commercially. Treatment of each diol with an equimolar amount of potassium *tert*-butoxide generates the corresponding monoalkoxides which are alkylated by Merrifield resin (**3**) to yield a series homologous solid-supported *tert*-alkyl alcohols (**4**, $n = 5$, 4, 3, or 2). Loading was verified by elemental analysis which, within experimental error (±0.4% Cl), is consistent with nearly quantitative loss of Cl (Table 1). Attempted acetylation (Ac_2O/pyridine) of $\mathbf{4}_{(n=4)}$ affords a polymer which does not display a carbonyl stretch in its IR spectrum, providing strong evidence for regiospecific reaction of Merrifield resin with the primary alcohol. Significant resin crosslinking is not suspected with any of these diols on the basis of results with subsequent reactions.

Reaction of **4** with *N*,*N*′-carbonyldiimidazole (CDI) and 4-(dimethylamino)pyridine (DMAP) affords resin bound (*tert*-alkoxycarbonyl)imidazoles **5**, as verified by N analysis (Table 1) and the presence of a carbonyl absorption in the IR spectrum at 1750 cm^{-1}. Confirmation of the level of acylation was afforded by the amount of imidazolium trifluoroacetate obtained upon cleavage with 10% TFA/DCM. In general, the reaction with CDI is efficient but not quantitative. Repeating the reaction does not

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Scheme 1. Formation and Cleavage of Resin Bound *tert*-Alkyl Carbamates

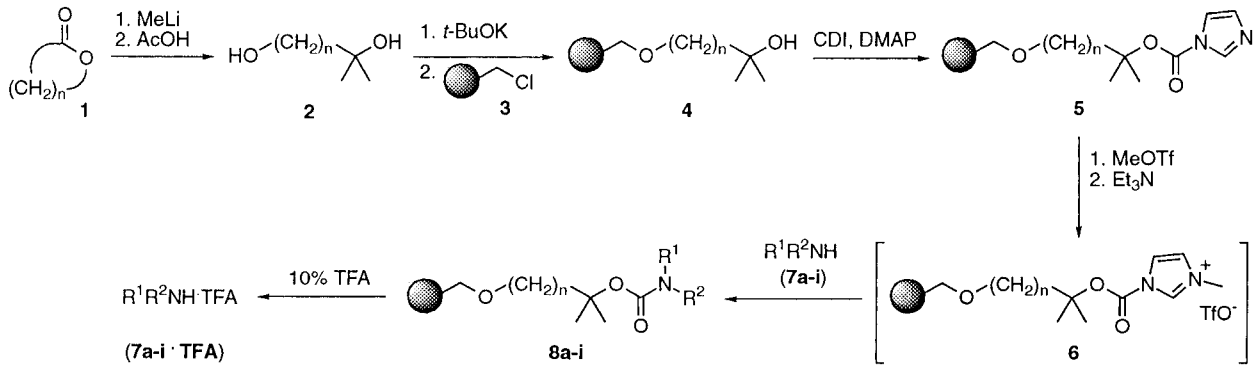

Table 1. Variables Depending on the Length of the Alkyl Chain, *n*

alkyl chain, *n*	**4** found %Cl[a]	**5** found %N	removal conditions for the linker fragments from **7d**·TFA
5	0.56	1.40	vacuum (2.5 mmHg), 15 h, a fragment remains
4	0.19	2.40	vacuum (2.5 mmHg), 15 h
3	0.29	1.62	vacuum (2.5 mmHg), 2 h
2	0.05	2.61	not required

[a] Merrifield resin **3**; %Cl, 4.78.

significantly enhance the N content of the resin or increase the amount of imidazolium trifluoroacetate recovered upon cleavage. We cannot conclusively discount the possibility that a small fraction of the tertiary alcohol groups remain free nor can we rule out a small amount of cross-linking, but given the difficulty of preparing *tert*-butyl carbonate in solution, it would seem unlikely that cross-linking occurs. The support bound (*tert*-alkoxycarbonyl)imidazoles **5** are stable polymers[14] but also are poor *tert*-alkoxycarbonylating reagents. For example, $\mathbf{5}_{(n=4)}$ does not acylate leucine methyl ester under a variety of conditions, including those reported for the preparation of resin bound benzyl carbamates (*N*-methylmorpholine, 60 °C, 4 h).[7b]

The N-alkylation of imidazolides is known to greatly enhance their reactivity as acyl transfer agents.[15] Existing literature recommends the use of methyl trifluoromethanesulfonate (MeOTf) as alkylating reagent and THF[15c] or $MeNO_2$[15b] as solvent. THF was initially our solvent of choice due to its better resin-swelling properties. Treatment of $\mathbf{5}_{(n=4)}$ with MeOTf (300 mol %) for 30 min at 10 °C generates the corresponding resin bound (*tert*-alkoxycarbonyl)-3-methylimidazolium triflate $\mathbf{6}_{(n=4)}$, which is reacted *in situ* with amines to produce resin bound *tert*-alkyl carbamates $\mathbf{8}_{(n=4)}$. Cleavage (10% TFA/DCM) of $\mathbf{8d}_{(n=4)}$ and removal of solvents *in vacuo* returned the starting amines as their TFA salts with no contamination by imidazolium trifluoroacetate. The amines are slightly contaminated, however, by a high-boiling material which displays ^{1}H NMR signals consistent with 1,4-butanediol, an impurity that presumably originates by reaction of MeOTf with THF.[16] The conclusive identity of this material and mechanism by which it is attached to and cleaved from the resin were not investigated in detail. Whereas this side reaction between THF and MeOTf does not seem to interfere in related solution chemistry, it represents a significant problem in this solid phase method. Replacement of THF with 1,2-dichloroethane (DCE) afforded a different problem, in the case of primary amines, which is also related to the use of excess MeOTf. *In situ* methylation gives rise to secondary amines, and the solid phase acylimidazolium salt is sufficiently reactive that it does not discriminate between primary and secondary amines. Thus both the expected amine and its *N*-methyl analog are observed upon cleavage, the ratio being dependent on the relative amounts of primary amine and MeOTf employed. This difficulty is alleviated by reducing the amount of MeOTf (to 170 mol %) and quenching the remaining excess with Et_3N (500 mol %) prior to addition of the primary amine (600 mol %). Therefore, sequential treatment of a suspension of **5** in DCE with MeOTf, followed by Et_3N, followed by an amine is the preferred method for preparation of **8**.

The length of the carbon chain between the benzylic ether and carbamate groups in **8** affects the ease of isolation of amine salt upon cleavage (Table 1). Treatment of a homologous series (n = 5, 4, 3, and 2) of **8d** with 10% TFA/DCM and concentration of the filtrate at reduced pressure gives crude **7d**·TFA. Examination of these crude products by ^{1}H NMR shows the presence of contaminating linker fragments with the higher three homologs (n = 5, 4, and 3) whereas pure **7d**·TFA is observed with the lowest homolog (n = 2). With the homologs where n = 4 and 3, these linker fragments are sufficiently volatile so as to be removed by more rigorous vacuum drying at room temperature. Similar conditions did not permit the ready removal of linker fragments with the highest homolog (n = 5). Identities of these linker fragments have not been conclusively established but ^{1}H NMR spectra of these crude product mixtures suggest that some of the extraneous signals can be accounted for by the presence of cyclic ethers resulting from the intramolecular participation of the benzylic oxygen atom in the cleavage. Interestingly, the hydroxy group of **7d** does not participate in the cleavage, since neither bicyclic urethane nor ether analogs of **7d** are observed by ^{1}H NMR.

The solid phase anchoring of a variety of amines and α-amino acid esters by reaction with $\mathbf{6}_{(n=2\text{or}4)}$ describes the scope and limitations of this strategy (Table 2). Primary and secondary amines **7a**−**d** react efficiently with $\mathbf{6}_{(n=2\text{or}4)}$, affording nearly quantitative conversion to **8a**−**d** in 3.5 h, regardless of the linker length. The efficiency of coupling was determined by the mass of amine salt recovered after TFA cleavage. It is notewor-

(14) Resins **5** were stored up to 6 months at room temperature with no effect on the subsequent loading of amines.

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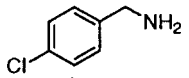
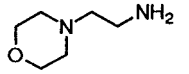
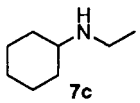
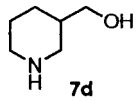
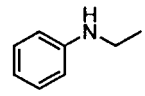
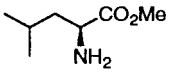
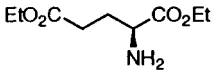
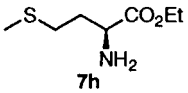
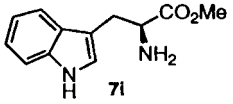
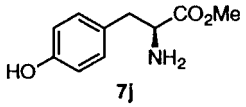
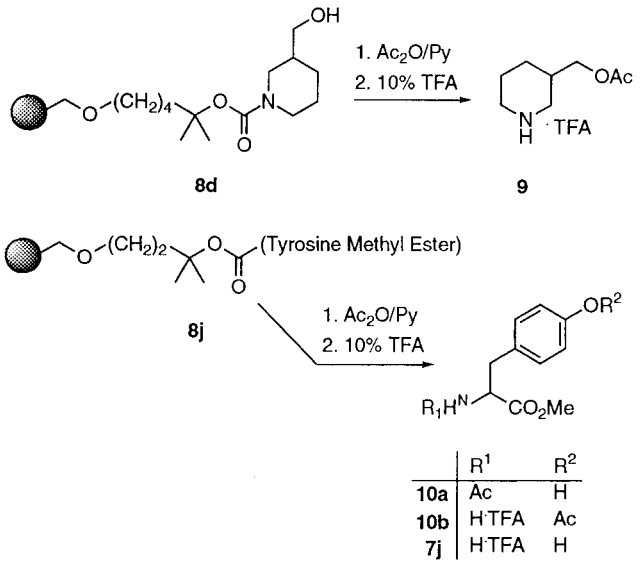
Table 2. *tert*-Alkoxycarbonylation of Amines 7

Amine 7	Alkyl Chain, n	8		
		%N	mmol N/g	mmol cleaved amine /g
 **7a**	4	0.79	0.56	0.59
	2	1.22	0.87	0.85
 **7b**	4	1.48	1.06	0.57
	2	2.19	1.56	0.76
 **7c**	4	1.01	0.68	0.68
	2	1.25	0.88	0.84
 **7d**	4	0.96	0.69	0.69
	2	1.19	0.85	0.89
 **7e**	4	0.56	0.40	0.29
	2	1.00	0.71	0.68
 **7f**	4	0.78	0.55	0.59
	2	1.11	0.79	0.86
 **7g**	4	0.89	0.63	0.51
	2	1.18	0.83	0.77
 **7h**	4	0.92	0.66	0.60
	2	1.12	0.80	0.76[a]
 **7i**	4	1.57	1.12	0.50
	2	2.07	1.48	0.69
 **7j**	2	0.92	0.66	0.60

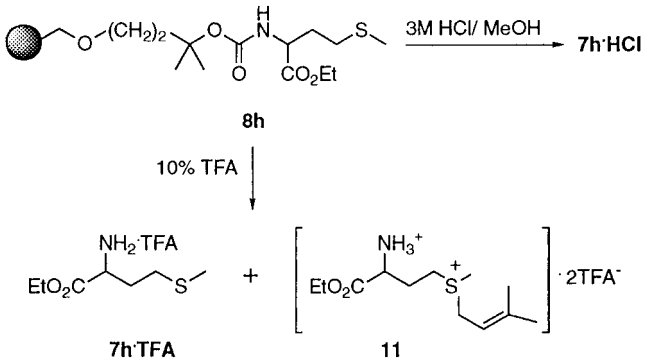
[a] Cleavage conditions: 3 M HCl/CH_2Cl_2, MeOH, MeOAc.

thy that the shortest linker ($n = 2$) consistently requires longer TFA treatment (4.5 h) than any of the longer homologs (≤3 h) to complete the cleavage reaction. The secondary aniline **7e**, being less nucleophilic and more sterically hindered, defines a limitation in the ability of **6** to anchor amines. In this case the shorter linker ($n = 2$) appears to afford superior anchoring of **7e** as compared to the longer linker ($n = 4$), a fact that may be related to increased stability of $\mathbf{6}_{(n=2)}$ as compared to $\mathbf{6}_{(n=4)}$ during the longer coupling time employed (≥7 h). An additional limiting case is indole which gave no coupling to the resin (data not shown). A variety of functional groups are tolerated by the coupling conditions, including ether, tertiary amine, ester, and hydroxyl groups. Free phenols were shown to be problematic (**7j**). In order to establish the N vs O regiospecificity of coupling for **7d** and **7j**, the support bound *tert*-alkyl carbamates $\mathbf{8d}_{(n=4)}$ and $\mathbf{8j}_{(n=2)}$ were acetylated (Scheme 2). Cleavage of $\mathbf{8d}_{(n=4)}$ provided **9**; therefore $\mathbf{6}_{(n=4)}$ preferentially reacts with an amino group in the presence of a hydroxy group. Cleavage of $\mathbf{8j}_{(n=2)}$ gave a mixture of **10a**, **10b**, and **7j**·TFA, which is

Scheme 2



Scheme 3



consistent with a combination of attachment at either the phenolic OH group, the NH_2 group, or both (cross-linking). Thus if tyrosine esters are to be coupled to the resin, the phenolic OH group must first be protected.

The HCl salts of **7f**−**i** were neutralized *in situ* with Et_3N prior to coupling with $\mathbf{6}_{(n=4\text{or}2)}$. An intermediate coupling time of 5.5 h gives excellent yields of amino esters as their TFA salts upon cleavage. Methionine ethyl ester (**7h**) gives a 4:1 mixture of **7h**·TFA and **11** (Scheme 3) upon cleavage of $\mathbf{8h}_{(n=2)}$ whereas only **7h** was obtained from the longer homolog, $\mathbf{8h}_{(n=4)}$. Acid-catalyzed cleavage of (3-methyl-2-butenoxy)methyl resin to generate an allylic carbocation, which is quenched by the thioether, is a likely explanation for the formation **11**. The lack of such a sulfonium impurity from $\mathbf{8h}_{(n=4)}$ is likely the result of the cyclic ether formation discussed previously. The use of a 3 M HCl solution that is prepared from acetyl chloride and DCM/MeOH (3:2) for cleavage eliminates the sulfonium byproduct, affording **7h**·HCl upon evaporation.

Experimental Section

General. Glassware was oven dried before use and cooled to room temperature under N_2. Dry solvents and MeOTf were purchased from Aldrich Chemical Co. 3-Methyl-1,3-butanediol was purchased from Fluka Chemical Corp. Merrifield resin (1.35 mmol of Cl/g) was purchased from Bachem. IR spectra were taken with samples prepared as KBr pellets (2−8 mg of resin was pulverized with 100 mg of KBr and pressed into a pellet in standard fashion). Elemental analyses were performed by Robertson Microlit, Inc., Madison, NJ. ^{1}H NMR

spectra were recorded in CD_3OD, and H coupling constants, *J*, are reported in hertz.

General Procedure for the Preparation of Diols $2_{(n=5)}$,[11] $2_{(n=4)}$,[12] and $2_{(n=3)}$.[13] A 1.4 M MeLi/ether solution (250 mol %) was added to a solution of lactone **1** (100 mol %) in dry THF (1.7 mL/mmol), cooled at −78 °C. The mixture was stirred for 30 min at −78 °C and for 6 h while being warmed to rt. AcOH (250 mol %) was added, and the suspension was stirred overnight at rt. After filtration, the filter cake was rinsed with THF and the filtrates were evaporated to give the crude diol **2** which was purified by vacuum distillation.

General Procedure for the Preparation of Resin Bound *tert*-Alkyl Alcohols 4. A 1 M *t*-BuOK/THF (300 mol %) solution was added to a solution of diol **2** (300 mol %) in dry THF (2.5 mL/mmol), cooled at 0 °C. The solution was stirred at 0 °C for 45 min and for 3 h while being warmed to rt. Merrifield resin (100 mol % of chlorine sites, $L = 1.35$ mmol/g) was added, and the suspension was shaken for 3.5 days at rt. After filtration, the resin bound *tert*-alkyl alcohol **4** was washed with THF (four times), 1/1 DMF/H_2O (two times), DMF (two times), 1/1 DMF/H_2O (two times), DMF (two times), THF (two times), and CH_2Cl_2 (two times), and dried.

Resin $4_{(n=5)}$. Found: C, 86.19; H; 8.13; N, 0.02; Cl, 0.56.

Resin $4_{(n=4)}$. Found: C, 86.88; H; 8.18; N, 0.07; Cl, 0.19.

Resin $4_{(n=3)}$. Found: C, 87.35; H; 8.35; N, 0.02; Cl, 0.29.

Resin $4_{(n=2)}$. Found: C, 86.95; H; 8.43; N, 0.02; Cl, 0.05.

General Procedure for the Preparation of Resin Bound (*tert*-Alkoxycarbonyl)imidazoles 5. DMAP (50 mol %) and CDI (400 mol %) were added to a suspension of the resin **4** (100 mol % of *tert*-alkyl alcohol sites)[17] in dry DMF (4.5 mL/mmol). The mixture was shaken for 24 h at rt and filtered. The resin bound (*tert*-alkoxycarbonyl)imidazole **5** was washed with CH_2Cl_2 (three times), THF (three times), CH_2Cl_2 (three times) and dried.

Resin $5_{(n=5)}$: IR 1754 cm^{-1}. Anal. Found: C, 85.50; H, 7.58; N, 1.40.

Resin $5_{(n=4)}$: IR 1751 cm^{-1}. Anal. Found: C, 84.20; H, 7.75; N, 2.40.

Resin $5_{(n=3)}$: IR 1750 cm^{-1}. Anal. Found: C, 85.90; H, 7.95; N, 1.62.

Resin $5_{(n=2)}$: IR 1747 cm^{-1}. Anal. Found: C, 83.44; H, 7.33; N, 2.61.

General Procedure for the Preparation of Resin Bound *(tert*-Alkoxycarbonyl)-3-methylimidazolium Triflates 6. Methyl triflate (170 mol %) was added to a suspension of the resin **5** (100 mol % of carbonylimidazole sites) in dry 1,2-DCE (16 mL/mmol), cooled at 10 °C. The mixture was stirred for 15 min at this temperature and for 5−10 min while being warmed to rt. After addition of Et_3N (500 mol %), stirring was continued for an additional 5 min and then the suspension used directly as the *tert*-alkoxycarbonylating/anchoring reagent.

General Procedure for the Preparation of Resin Bound *tert*-Alkyl Carbamates $8_{(n=4)}$ and $8_{(n=2)}$ from Amines. The amine **7** (600 mol %) was added, neat or as a solution in CH_2Cl_2 (**7d**) or DMF (**7j**), to a stirred suspension at rt of the resin bound (*tert*-alkylcarbonyl)-3-methylimidazolium triflate **6** (100 mol %) prepared as above. The mixture was shaken for 3.5 h (**7a**−**e**) or 5.5 h (**7j**) at rt and filtered. The resin bound *tert*-alkyl carbamate **8** was washed with THF (three times), 1/1 THF/MeOH (three times), THF (three times), and CH_2Cl_2 (three times) and dried.

Resin $8a_{(n=4)}$: IR 1717 cm^{-1}. Anal. Found: C, 84.01; H, 7.46; N, 0.79.

Resin $8a_{(n=2)}$: IR 1716 cm^{-1}. Anal. Found: C, 82.54; H, 7.63; N, 1.22.

Resin $8b_{(n=4)}$: IR 1714 cm^{-1}. Anal. Found: C, 83.62; H, 8.17; N, 1.48.

Resin $8b_{(n=2)}$: IR 1713 cm^{-1}. Anal. Found: C, 82.92; H, 7.86; N, 2.19.

Resin $8c_{(n=4)}$: IR 1688 cm^{-1}. Anal. Found: C, 86.03; H, 8.57; N, 1.01.

Resin $8c_{(n=2)}$: IR 1680 cm^{-1}. Anal. Found: C, 84.55; H, 8.36; N, 1.25.

Resin $8d_{(n=4)}$: IR 1670, 1655 cm^{-1}. Anal. Found: C, 84.92; H, 8.19; N, 0.96.

Resin $8d_{(n=2)}$: IR 1696, 1663 cm^{-1}. Anal. Found: C, 83.78; H, 8.10; N, 1.19.

Resin $8e_{(n=4)}$: IR 1698 cm^{-1}. Anal. Found: C, 87.24; H, 8.00; N, 0.56.

Resin $8e_{(n=2)}$: IR 1698 cm^{-1}. Anal. Found: C, 85.67; H, 7.91; N, 1.00.

Resin $8j_{(n=2)}$: IR 1750, 1717 cm^{-1}. Anal. Found: C, 80.82; H, 7.39; N, 0.92.

General Procedure for the Preparation of Resin Bound *tert*-Alkyl Carbamates $8_{(n=4)}$ and $8_{(n=4)}$ from Amino Esters·HCl. Et_3N (600 mol %) was added to a solution/suspension of the amino ester·HCl **7**·HCl (600 mol %) in CH_2Cl_2 (9 mL/mmol) and the resulting suspension filtered. The amino ester solution was transferred *via* syringe to a stirred suspension at rt of the resin bound (*tert*-alkoxycarbonyl)-3-methylimidazolium triflate **6** (100 mol %) prepared as above. The mixture was shaken for 5.5 h at rt and filtered. The resin bound *tert*-alkyl carbamate **8** was washed with THF (three times), 1/1 THF/MeOH (three times), THF (three times), and CH_2Cl_2 (three times) and dried.

Resin $8f_{(n=4)}$: IR 1717 (broad) cm^{-1}. Anal. Found: C, 84.03; H, 8.21; N, 0.78.

Resin $8f_{(n=2)}$: IR 1744, 1720 cm-1. Anal. Found: C, 83.56; H, 8.08; N, 1.11.

Resin $8g_{(n=4)}$: IR 1734, 1717 cm^{-1}. Anal. Found: C, 82.93; H, 8.11; N, 0.89.

Resin $8g_{(n=2)}$: IR 1734 (broad) cm^{-1}. Anal. Found: C, 81.93; H, 7.58; N, 1.18.

Resin $8h_{(n=4)}$: IR 1733, 1716 cm^{-1}. Anal. Found: C, 82.98; H, 7.78; N, 0.92.

Resin $8h_{(n=2)}$: IR 1733, 1717 cm^{-1}. Anal. Found: C, 81.99; H, 7.84; N, 1.12.

Resin $8i_{(n=4)}$: IR 1734, 1716 cm^{-1}. Anal. Found: C, 83.52; H, 7.96; N, 1.57.

Resin $8i_{(n=2)}$: IR 1732 (broad) cm^{-1}. Anal. Found: C, 82.26; H, 7.28; N, 2.07.

General Procedure for Cleavage of Resin Bound *tert*-Alkyl Carbamates $8_{(n=4)}$ and $8_{(n=2)}$. Resin bound *tert*-alkyl carbamates $\mathbf{8}_{(n=4)}$ and $\mathbf{8}_{(n=2)}$ were treated with 10% TFA/CH_2Cl_2 (2.5 mL/100 mg of resin) for 3 and 4.5 h, respectively, and filtered. For both types of resin, the resin was rinsed with CH_2Cl_2 (three times) and MeOH (two times) and the filtrates were evaporated and dried (vacuum, overnight) to give back amine **7**, as its TFA salt. The ^1H NMR spectra of the cleaved amines showed them to be identical to those obtained from authentic samples of ammonium trifluoroacetates **7**·TFA.

Cleavage of Resin Bound *tert*-Alkyl Carbamate $8h_{(n=2)}$. Acetyl chloride (10.2 mL, 0.14 mol) was added to a 3/2 CH_2Cl_2/MeOH (40 mL) solution, cooled at 0 °C. The resin $\mathbf{8h}_{(n=2)}$ (36 mg) was treated with the HCl solution (2.5 mL) for 4.5 h and filtered. The resin was rinsed with CH_2Cl_2 (four times), and the filtrates were evaporated and dried (vacuum, overnight) to give back methionine ethyl ester (**7h**), as its HCl salt (6 mg). A ^1H NMR spectrum of the cleaved ammonium hydrochloride **7h**·HCl showed it to be identical to the one obtained from an authentic sample of methionine ethyl ester·HCl.

3-(Acetoxymethyl)piperidinium Trifluoroacetate (9·TFA).[18] Ac_2O (0.2 mL, 2.12 mmol) was added to a suspension of the resin $\mathbf{8d}_{(n=4)}$ (171 mg, $L = 0.69$ mmol/g) in pyridine (1.6 mL), and the mixture was shaken at rt for 24 h. After filtration, the resin was washed with CH_2Cl_2 (three times), THF (three times), 1/1 THF/MeOH (three times), THF (three times), and CH_2Cl_2 (three times) and dried: weight of resin, 175 mg; IR 1740, 1645 cm^{-1}. Anal. Found: C, 84.14; H, 7.87; N, 0.98.

(17) The theoretical loading of *tert*-alkyl alcohol was calculated on the basis of the Cl content of the starting Merrifield resin, assuming the observed Cl displacement is due to exclusive monoalkylation by 1°-alcohol.

(18) Ackerman, J.; Banner, D.; Gubernator, K.; Hadvary, P.; Hilpert, K.; Mueller, K.; Labler, L.; Schmid, G.; Tschopp, T.; et al. European Patent Application, EP 468231 A2, 1992.

A portion of the resin (59 mg) was treated with 10% TFA/CH_2Cl_2 (2.5 mL) for 3 h and filtered. The resin was rinsed with CH_2Cl_2 (three times) and MeOH (two times), and the filtrates were evaporated and dried (vacuum, overnight) to give **9**·TFA (9.3 mg); ^{1}H NMR δ 4.07 (dd, J = 11.3, 5.2, 1H), 3.96 (dd, J = 11.2, 7.2, 1H), 3.37 (2d J = 14.5, 14.1, 2H), 2.91 (dt, J = 2.9, 12.7, 1H), 2.77 (t, J = 12.2, 1H), 2.13 (m, 1H), 2.05 (s, 3H),1.99−1.67 (m, 3H), 1.36 (m, 1H); IR 1737, 1677 cm^{-1}.

Mixture of *N*-Acetyltyrosine Methyl Ester, *O*-Acetyltyrosine Methyl Ester·TFA, and Tyrosine Methyl Ester·TFA (10a, 10b, 7j·TFA). Resin **8j**$_{(n=2)}$ was acetylated and cleaved as above to afford a mixture of **10a**, **10b**·TFA, and **7j**·TFA (~4:3:2 ratio): ^{1}H NMR δ {7.29 (d), 7.12 (d), 7.05 (d), 7.00 (d), 6.78 (d), 6.68 (d)} (4H); {4.58 (dd), 4.33 (dd), 4.22 (dd)} (1H); {3.83 (s), 3.81(s), 3.66 (s)} (3H); 3.34−2.80 (m, 2H); {2.26 (s), 1.90 (s)} (2.3H).

Summary

In summary, a homologous series of novel resins (**5**, n = 5, 4, 3, and 2) for anchoring of amines by *tert*-alkoxycarbonylation has been developed. These resins are conveniently prepared in two steps from Merrifield resin and are stable to long term storage. *In situ* activation by stepwise treatment with MeOTf and Et_3N allows for anchoring of a wide variety of amines to a polymeric support for further solid phase synthesis. Cleavage of the amines is readily accomplished under acidic conditions which are reasonably mild. The slightly different behavior of each homolog could make more convenient the use of one or another depending on the nature of the loading amine and the synthetic sequence involved. The commercial availability of 3-methyl-1,3-butanediol (**2**, n = 2) and relative ease of removal of linker fragments after cleavage generally make **5**$_{(n=2)}$ the preferred resin within the series.

Supporting Information Available: IR spectra of resins **5**$_{(n=2)}$, **8a**$_{(n=2)}$, and **8f**$_{(n=2)}$ (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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