Review

Protecting Groups in Solid-Phase Organic Synthesis

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Reviews

Protecting Groups in Solid-Phase Organic Synthesis

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Introduction

Solid-phase chemistry was initially almost exclusively devoted to peptide synthesis. However, with the growing use of solid-phase and combinatorial methods for the preparation of more complex organic molecules,[1] more challenging chemistry is now being carried out routinely on the solid phase. The increasing degree of sophistication of the chemistry being performed means that increasing numbers of syntheses conducted on the solid phase require the use of protecting group strategies.

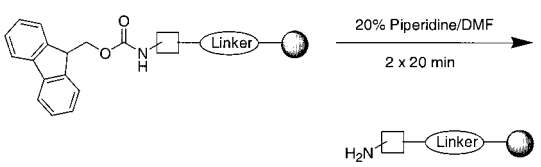
This article will review the protecting groups reported in the literature between March 1998 and June 2000; for earlier examples the reader is directed to the reviews by Hermkens.[2] The review is divided into six main sections according to the functional group that is protected. Each section is then further divided into subsections, where individual protecting groups are described in relation to the methods of removal.

Linkers used in solid-phase chemistry are generally derived from known protecting groups. This review aims to highlight the different methods by which protecting groups have been removed in the presence of various linkers. In addition, examples where specific protecting groups have been removed in the presence of other protecting groups are highlighted. The nature of the solid support may also influence the deprotection conditions, and so the examples described refer to the type of polymer support used and any variation from normal solution deprotection procedures reported. Table 1 at the end of the review summarizes this information and details for each example the resin, the linker, and the conditions used for the removal of the protecting group. To help the reader in finding the entry of interest, the examples in the table are listed in the order in which they appear in the text.

I. Amine Protecting Groups

Amines are the most widely used functional group in solid-phase organic chemistry. This is mainly due to the fact that *N*-protected amino acids are powerful and readily available building blocks. There are three major types of protecting group that are currently used: fluorenylmethoxycarbonyl (Fmoc), *tert*-butoxycarbonyl (Boc) and allyloxycarbonyl (Aloc). Nevertheless, other protecting groups have been used, and they are classified according to their removal method.

I.1. Base-Sensitive Amine Protecting Groups. I.1.1. *N*-Fluorenylmethoxycarbonyl (Fmoc). The Fmoc group is one of the most common protecting groups in solid-phase chemistry, with a large number of building blocks available containing this group. Loading levels can be readily determined,[3] its removal is very efficient, and a large range of linkers are compatible. Generally, the Fmoc group is removed by treating the resin with 20% piperidine in DMF (reaction 1.1).



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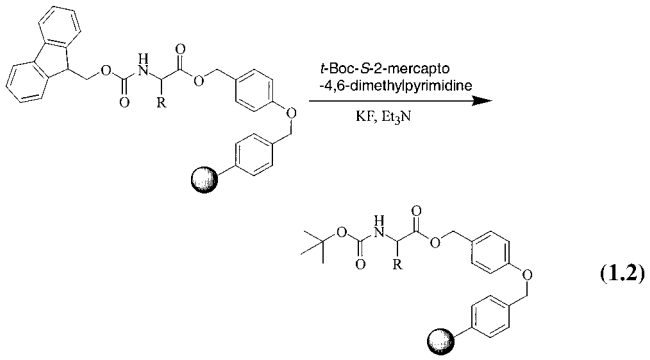
Solvents other than DMF can be used. During the synthesis of cyclic oligocarbamates on TentaGel resin with a base-sensitive alkyl ester linkage, Fmoc groups were removed with 20% piperidine in *N*-methyl-2-pyrrolidinone (1 × 5 min, 1 × 10 min)[4] while 20% piperidine in *N*,*N*-dimethylacetamide was used for the synthesis of a number of lipopeptides on polystyrene resin with a Wang linker.[5] The piperidine/DMF system has also been replaced by morpholine in a 1:1 mixture with DMF[6] or 1% DBU in DMA.[7]

Aimoto studied the role of the base during the preparation of peptide thioesters using a Fmoc/^{t}Bu solid-phase approach.[8] The authors were interested in finding a system to remove the Fmoc group without cleaving the thioesters by aminolysis, which is associated with 20% piperidine in DMF. The study was first conducted in solution on the model compound Fmoc-Phe-Leu-Ala-Cys(Acm)-His-Gly-$SCH_2CH_2CONH_2$ using a 25% solution of different amines in NMP for 20 min. With piperidine, cyclohexylamine, 4-aminomethylpiperidine, and morpholine, the Fmoc groups were quantitatively removed but the thioester was also completely cleaved. Hexamethylenimine and heptamethylenimine completely removed the Fmoc group, while 20−25% of the thioester moiety remained intact. Dicyclohexylamine, *cis*-2,6-dimethylpiperidine, and DIPEA did not cleave the thioester moiety but were not sufficient to remove the Fmoc group within 20 min. With 1-methylpyrrolidine, the thioester moiety was intact and the Fmoc groups were completely removed. Aminolysis could be suppressed by the addition of HOBt to the reaction mixture. Following this study, the synthesis of Vero-toxin(11−25)-$SC(CH_3)_2CH_2CONH_2$ was carried out on the solid phase using Fmoc chemistry. The best result was an overall yield of 24%, using a mixture of 25% 1-methylpyrrolidine, 2% hexamethylenimine, and 2% HOBt in NMP/DMSO (1:1) to cleave the Fmoc group.

In 1998 Mata published a technique to remove an Fmoc group and protect *in situ* the amine with a Boc group.[9] Two procedures were used: (a) potassium fluoride/triethylamine/*t*-Boc-*S*-mercapto-4,6-dimethylpyrimidine; (b) potassium fluoride/triethylamine/di-*tert*-butyl dicarbonate (reaction 1.2).



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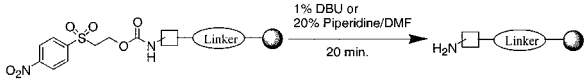
Both techniques gave good conversion with yields of 76−100% for method a and 71−100% for method b.

I.1.2. 2-(4-Nitrophenylsulfonyl)ethoxycarbonyl (Nsc) Group. Albericio[10] and Hruby[11] reported the Nsc group as a protecting group for amines in solid-phase chemistry. While this group is completely interchangeable with the Fmoc protecting group (it is removed with a mixture of 1% DBU or 20% piperidine in DMF for 20 min (reaction 1.3)), some



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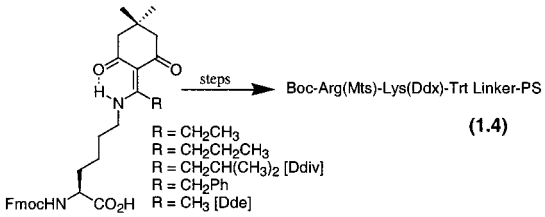
advantages were reported. Two studies compared the use of the Nsc group to the Fmoc group during peptide synthesis. In both studies, the Nsc group showed better performance than the Fmoc group in the synthesis of difficult peptides. The Nsc group also displayed a greater stability under neutral and weakly basic media than the Fmoc group and was also rapidly and selectively removed. Finally irreversible formation of a vinyl sulfone/piperidine adduct means that no alkylation of free amines is observed following deprotection.

I.1.3. 1-(4,4-Dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) Group and Derivatives. The primary amine protecting group *N*-1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) has become a very useful protecting group, particularly in the case of the lysine side chain. Although this group is relatively stable to TFA, small losses of Dde occur during each deprotection cycle of Fmoc groups with 20% piperidine in DMF, and *N*−*N*′ migration side reactions can also present a problem. For these reasons various Dde derivatives based on the model compound Boc-Arg(Mts)-Lys(DdX)-Trt-linker-PS were studied (reaction 1.4) with 20% piperidine in DMF.



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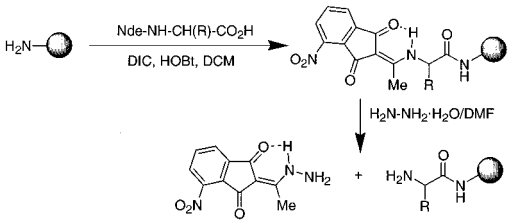
Samples were cleaved after 2, 4, and 36 h of treatment and showed no trace of deprotected material for any of the DdX derivatives. In contrast, the corresponding *N*-Dde-protected model dipeptide showed losses of 3% and 6.5% of the Dde group over 2 and 4 h, respectively. *N*−*N*′ migration was studied by treating Boc-Lys(Fmoc)-Pro-Lys(DdX)-Phe-Trt-PS with 50% piperidine in DMF. The best results were obtained for the protecting group *N*-Ddiv (R = $CH_2CH(CH_3)_2$) for which 94% and 84% of the desired peptide were obtained after 4 and 9 h, respectively; however, only 33% was obtained when the *N*-Dde group was used.[12] All the *N*-Ddx groups were removed smoothly and efficiently by treatment with 2% v/v hydrazine hydrate in DMF within 10 min.

Bycroft has published studies of a new derivative of the Dde group: *N*-1-(4-nitro-1,3-dioxoindan-2-ylidene)ethyl (*N*-Nde). The removal method is the same as for Dde: treatment with 2% hydrazine hydrate in DMF. However, the authors noticed that the removal of the Dde group took considerably longer than for the Nde group. In addition, removal of the Nde group could be followed visually and monitored at 290 nm (reaction 1.5). Although Nde-protected amines on solid phase are resistant to treatment with neat TFA for 24 h (loss of less than 0.5%), their lability to 20% piperidine in DMF under continuous flow was estimated at 6% and 13% loss after 3 and 6 h, respectively.[13] Although the Dde and Nde



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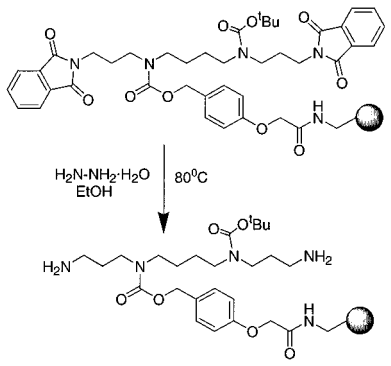
groups can be used with Rink, Sieber, and trityl linkages, less hindered ester linkages are potentially susceptible to hydrazinolysis during prolonged exposure. Nevertheless, the Dde group has been successfully removed with 2% hydrazine in DMF on a resin containing a Wang ester[14a,b] and a Wang "oxycarbonyl" linkage.[14c]

I.1.4. Phthalimide Group. The phthalimide group, like the Dde group, is sensitive to hydrazine, but its removal requires more forcing conditions. During the synthesis of spermine derivatives on a Wang "oxycarbonyl" linker, the phthalimide group was removed by treatment of the resin with 5 equiv of hydrazine monohydrate in absolute EtOH at 80 °C overnight (reaction 1.6).[15]



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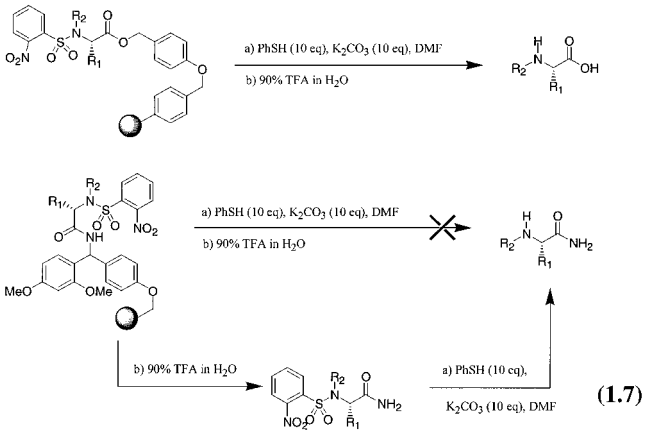
For the solid-phase synthesis of 1,3-diamino ketones, Subramanyam used a THP linker and a diamine scaffold containing a phthalimide and *o*-nitrobenzenesulfonamide protection.[16] The phthalimide protection was efficiently removed by treatment with hydrazine in a 3:1 DMF/THF mixture for 16 h, while under these conditions, the sulfonamide was stable. As previously mentioned, this type of protecting group is not compatible with ester linkages.[17]

I.1.5. Sulfonamide Group. The most widely used protecting sulfonamide in SPOS is that of Fukuyama, and it has been used as both an activating and a protecting group for amines. Miller[18] reported that both *o*- and *p*-nitrobenzenesulfonyl chlorides readily coupled to free amines of a support-bound peptide in 2 h in a DCM solution containing collidine. Quantitative removal was achieved with a solution of β-mercaptoethanol and DBU in DMF for 30 min. It was noticed that the *o*-Ns groups were removed more readily than *p*-Ns. β-Mercaptoethanol was later substituted by thiophenol because it removed sulfonamides more quickly and was less noxious. Deprotection could be followed easily via the formation of a bright-yellow color due presumably to the release of 2-(2-nitrophenylthio)ethanol. β-Mercaptoethanol and DBU were used in NMP for 20 h to remove the *o*-Ns protecting group by Subramanyam in the presence of *o*-phenoxy or alkylbenzenesulfonamides.[16]

Bycroft activated a primary amine using the *o*-Ns group while using a Dde linker. Introduction was achieved by treatment of the resin with 4 equiv of *o*-NsCl in the presence of 6 equiv of DIPEA in THF for 5 h. Its removal was accomplished by two 1 h treatments of a solution of 1 M NaSPh in DMF.[19] During the synthesis of α-keto amides on a chlorotrityl linker, deprotection of a *p*-Ns group was achieved with a mixture of thiophenol and potassium carbonate in DMF.[20] Under the same conditions, Nuss noticed that an *o*-Ns group could not be removed from a solid support containing a Rink linker but was cleaved when a Wang linker was used (reaction 1.7).[21]



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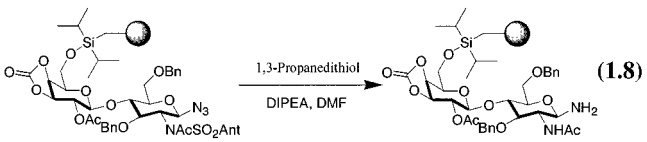
Miller was able to remove selectively an *o*-Ns group from a tertiary sulfonamide with sulfanylethanol and DBU, conditions that left an unalkylated secondary sulfonamide intact.[22] In the same study, the authors looked at the efficiency of the *o*-Ns group in comparison to the Fmoc group as a protecting group for the synthesis of a thrombin receptor agonist. The final peptide, after purification, was obtained in 50% and 62% yield for the *o*-Ns and Fmoc strategies, respectively.

Piscopio has reported the use of the 2,4-dinitrobenzenesulfonamide group as an amine protecting group. It was removed by treatment of the resin with *n*-butylamine (10 equiv in DCM) for 2 h.[23] The same group was used by Hone in the synthesis of modified polyamines,[14c] with the group being successfully introduced by treatment of the resin containing the free amino group with 2,4-dinitrobenzenesulfonyl chloride (4 equiv) and 2,6-lutidine (4 equiv) in DCM for 2 h. Its removal was achieved in 30 min with mercaptoacetic acid (10 equiv) and DIPEA (10 equiv) in DCM.

During the synthesis of glycopeptides on polystyrene resin with a silyl linker, Danishefsky used anthracenesulfonamide in an azasulfonamidation sequence. The sulfonamide was removed by a 6 h treatment with 1,3-propanedithiol and DIPEA in DMF. This step was concomitant with the reduction of the azide, providing one of the first examples of solid-phase azide reduction (reaction 1.8).[24]



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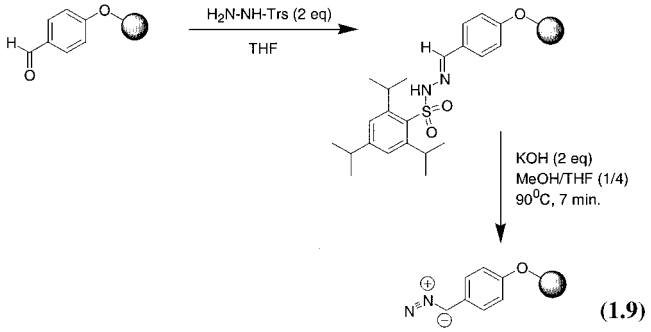
I.1.6. 2,4,6-Triisopropylsulfonamide (Trs) Group. Bhalay used a 2,4,6-triisopropylsulfonamide (Trs) protected hydrazine for the generation of an activated diazo linker. Polystyrene resin with a Wang aldehyde linker was treated with Trs-hydrazine to afford the Trs-protected immobilized hydrazone. This was then treated with potassium hydroxide (2 equiv) in MeOH/THF (1:4) at 90 °C for 7 min to remove the Trs group and to generate the activated diazo linker (reaction 1.9).[25]



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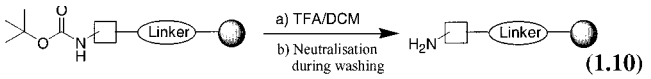
I.2. Acid-Sensitive Amine Protecting Groups. Although Boc/Bzl based peptide chemistry was once the stalwart of solid-phase peptide synthesis, acid-sensitive amine protecting groups are now used much less often than base-sensitive ones, since syntheses conducted on the solid phase at this moment in time use acid-sensitive linkers. Nevertheless, some acid-sensitive protecting groups continue to be used in cases where the cleavage of the linker requires either more drastic acidic conditions than removal of the protecting group or conditions such as light- or cyclization-mediated cleavage.

I.2.1. Boc and Bpoc Groups. The *tert*-butoxycarbonyl or Boc group is the most widely used acid-sensitive amine protecting group in SPOS. Introduction of the Boc group has been achieved most routinely by treatment of the resin with Boc_2O in the presence of DIPEA in DCM[17] or THF.[26] In most cases, removal of the Boc group is achievedwith a solution of TFA in DCM, affording the TFA salt (reaction 1.10).



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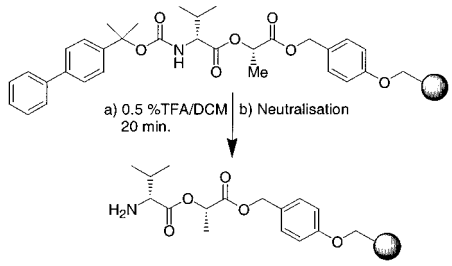
The amount of TFA and reaction time for removal is always dependent on the acid sensitivity of the linker. A solution of 50% TFA in DCM for several hours could be used for linkers that are only cleaved with a very strong acid such as an electron-poor benzhydryl linker[27] or when using a cyclative release ring-closing metathesis strategy.[23] A Boc group was removed by Kurth on a resin containing an alkyl ester linkage by treatment with 50% TFA in DCM at 0 °C for 2 h,[28] while the base-sensitive Kaiser linker on polystyrene resin was deprotected using a 33% TFA/DCM solution for 1.5 h[29] and 25% TFA in DCM for 30 min[30] or 2 h.[31]

On more acid-sensitive silyl linkers on polystyrene resin, Boc removal was achieved in 10 min with 50% TFA in DCM. The linker was cleaved using the same conditions for 24 h.[32] The Boc group was also removed from a resin containing an aminal linker by treatment with TFA and thioanisole in DCM (3:1:6) for 15−20 min.[33]

The Boc group has also been cleaved with conditions that do not use TFA. For example, Botta used a solution of methanesulfonic acid (1.5 mol equiv) in dioxane under reflux for 16 h to remove the Boc protection from an amidine.[34] When TFA was used to deprotect an *N*-Boc-protected aniline linked to the solid support via a silyl linker, the linker was found to be only partially stable. To overcome this problem, the Boc group was rapidly removed with *B*-chlorocatecholborane in DCM.[35] Boc groups have also been removed from the very acid-sensitive Rink amide linker with a mixture of trimethylsilyl triflate and 2,6-lutidine in DCM for 1 h.[36] Under these deprotection conditions methyltrityl, Fmoc, triisopropylsilyl, 2,4-dinitrophenyl, and formyl groups were tolerated.

For the synthesis of depsides and depsipeptides on a resin containing a Wang linker, Riguera used the 2-(4-biphenylyl)-2-propyloxycarbonyl or Bpoc group to protect amino acids.[37] Deprotection of the Bpoc group was achieved with a solution of 0.5% TFA in DCM for 20 min, conditions mild enough to be compatible with the Wang linker (reaction 1.11).



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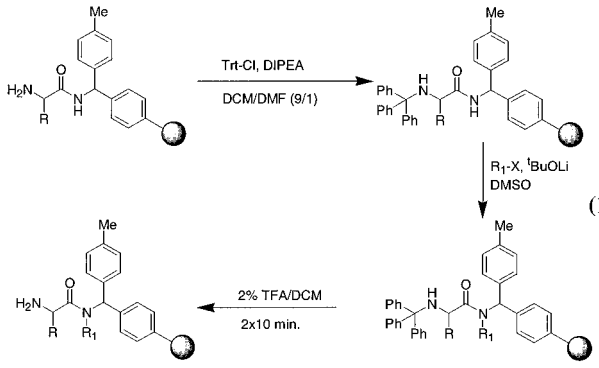
I.2.2. Trityl Group and Derivatives. The trityl group is more acid labile than the Boc group and so requires less harsh conditions for its removal. It is generally introduced by treating the resin with a solution of trityl chloride in DCM/DMF (9:1), in the presence of DIPEA. One advantage of this bulky group is its shielding effect (in an amino acid, the α proton experiences this effect). For example, alkylation of amides can be carried out without affecting the nitrogen bearing the trityl group (reaction 1.12). The trityl group has



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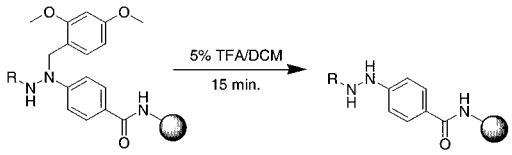
been removed by two treatments of the resin with a solution of 2% TFA in DCM for 10 min.[27,38]

More acid-sensitive protecting groups derived from the trityl group have been used. During the synthesis of cyclic

peptides on crowns using an acid-sensitive Rink linker, a lysine residue protected with 4-methyltrityl (Mtt) was used. Deprotection was achieved with a solution of 1% TFA in DCM with 5% TIPS as a scavenger.[39] However, Frank reported that the Mtt groups were not removed as readily as expected if syntheses were performed on hydrophilic supports such as TentaGel resin or cellulose.[40] More acid-labile monomethoxytrityl (Mmt) and dimethoxytrityl (Dmt) groups have been studied, with the *N*-Dmt derivatives showing slow decomposition in protic solvents, whereas the *N*-Mmt derivatives were stable. A model peptide was built on TentaGel resin with a base-labile linker, and lysine was incorporated, protected with Mmt or Mtt. The resins were treated with a mixture of acetic acid/trifluoroethanol/dichloromethane (1:2:7 v/v) for 15 min cycles until no yellow or red trityl cations were visible in the eluent. Under these conditions, the Mmt group was efficiently cleaved whereas the Mtt group was completely stable. The Mmt group was successfully cleaved with 4% dichloroacetic acid in dichloromethane[41] or 3% trichloroacetic acid in dichloroethane for 3 min on CPG.[42]

I.2.3. 2,4-Dimethoxybenzyl (DMB) Group. Recently, Ladlow developed a latent aryl hydrazine safety-catch linker based on the backbone amide linker (BAL).[43] The DMB group was used as the blocking group for the arylhydrazine. Its removal, which was achieved by 5% TFA in DCM for 15 min, activated the safety-catch linker (reaction 1.13).



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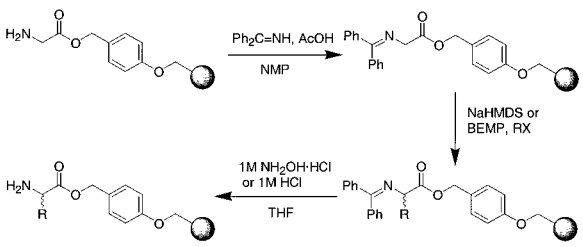
I.2.4. *N*-Diphenylmethyleneamine Group. Like the sulfonamide group, the diphenylmethyleneamine group can be regarded as an activating protecting group. This property has been used in the synthesis of unnatural peptides starting from glycine, using an approach developed in solution in the 1980s. Protection was accomplished by treatment of the resin with benzophenone imine, acetic acid, and NMP;[45] the resultant protected amine has an active methylene group that can be alkylated with different Michael acceptors[44] or alkyl halides (using BEMP[45] or NaHMDS[46] as bases). Deprotection can be carried out with a solution of 1 M hydroxylamine hydrochloride or 1 M HCl in THF (1:2) for 5 and 4 h, respectively (reaction 1.14).



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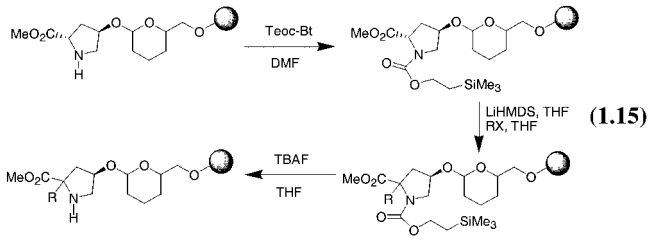
I.3. Miscellaneous Conditions. I.3.1. 2-(Trimethylsilyl)-ethoxycarbonyl (Teoc) Group. As for the diphenylmethylene group, *N*-Teoc-protected α-amino esters or amides allow α C-alkylation. The Teoc group is introduced by treatment of the resin with 3 equiv of 2-(trimethylsilyl)-ethoxycarbonylbenzotriazolyl ester (Teoc-Bt) in DMF for 24 h.[47] Deprotection was carried out with a solution of TBAF in THF. This protecting group has been successfully used with Wang,[48] chlorotrityl,[49] and THP linkers[47] (reaction 1.15).



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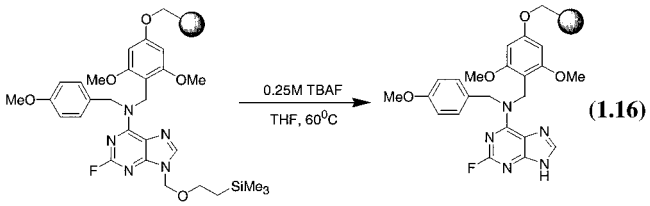
I.3.2. 2-Trimethylsilylethoxymethyl (SEM) Group. During the synthesis of 2,6,9-trisubstituted purine libraries, the SEM-protected purine scaffold was anchored onto a polystyrene resin via the acid-labile BAL linker.[50] Deprotection was carried out with a solution of 0.25 M TBAF in THF at 60 °C (reaction 1.16).



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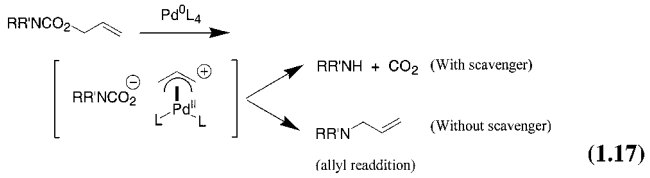
I.3.3. Allyloxycarbonyl (Aloc) Group. The Aloc group is sufficiently robust to withstand the basic conditions of the removal of Fmoc groups and the acidic conditions of Boc removal. Its removal on solid phase is typically achieved with tetrakis(triphenylphosphine)palladium(0); in the presence of a scavenger re-addition of the allyl unit onto the amine is prevented (reaction 1.17).



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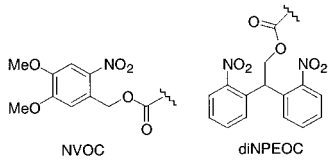
To remove an Aloc group, Rabe used a mixture of Pd(PPh$_3$)$_4$, *N*,*N*-dimethyltrimethylsilylamine, and trimethylsilyl trifluoroacetate in DCM for 6 h.[51] A mixture of Pd(PPh$_3$)$_4$, trimethylsilyl azide, and TBAF in DCM was used by Ellman[52] and Schwarz.[53] On an acid-sensitive aminal linker, the Aloc protection was removed from a benzamidine position with Pd(PPh$_3$)$_4$, 0.5 N HCl, and morpholine in THF, DMSO.[33] Kilburn used dimedone as a scavenger in DCM/THF to remove an Aloc protecting group.[54]

More recently, Albericio reviewed a variety of potential scavengers (NDMBA, TSA, Ph$_3$SiH) and in particular amine/borane complexes (NH$_3$·BH$_3$, Me$_2$NH·BH$_3$, Me$_3$N·BH$_3$, Py·BH$_3$).[55] Initially, a solution study of the Aloc deprotection of Aloc-Tyr(^{t}Bu)-OMe showed that all the scavengers were efficient and led exclusively to the deprotected nonallylated amine. However, in the case of Aloc-protected *N*-methylbenzylamine, some scavengers gave a mixture of allylated

and nonallylated amines. The best scavangers were NDMBA, TSA, $H_3N{\cdot}BH_3$, and $Me_2NH{\cdot}BH_3$. The two amino/borane complexes were used further for solid-phase studies because they were found to be the most efficient; these scavengers took less than 10 min for Aloc removal using $Pd(PPh_3)_4$. A pentapeptide was prepared on a PAL-PS resin with *N*-Aloc-protected amino acids. Removal of the *N*-Aloc groups was accomplished under an argon atmosphere with 10 mol % of $Pd(PPh_3)_4$ and 6 equiv of $H_3N{\cdot}BH_3$ or $Me_2NH{\cdot}BH_3$ in DCM. After cleavage, the crude peptide showed only one peak by HPLC, demonstrating the efficiency of the method. Most of the usual protecting groups used in peptide chemistry are compatible with this deprotection protocol except for the formyl protection of tryptophan derivatives, which was reduced.

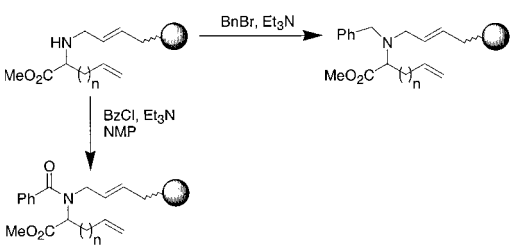
The Aloc group has been used as a protecting group in the solid-phase synthesis of Dynorphin A analogues.[56] To remove this group, the authors used a mixture of $Pd(PPh_3)_4$ (3 equiv) in DCM/AcOH/NMM (92.5:5:2.5) and compared the efficiency of this method using two different resins: PAL-PS and PAL-PEG-PS. For the PEG-PS resin, removal was complete after 3 h, instead of 24 h for the PS resin. However, better purity was observed for the PS resin.

I.3.4. NVOC and diNPEOC Groups. During the synthesis of oligonucleotides on the solid phase, Vasseur used two photocleavable groups: 6-nitroveratryloxycarbonyl (NVOC) and 2,2′-bis(2-nitrophenyl)ethoxycarbonyl (diNPEOC) (reaction 1.18).[57] The oligonucleotides were constructed using a UV-sensitive linker to allow the protecting groups to be cleaved at the same time as the compound. Lower coupling yields were observed compared to reactions using *N*-acyl-protected analogues. NVOC deprotection was dependent on the concentration of oligonucleotide, and completion was reached after 45 and 75 min for 0.05 and 0.1 mM concentrations, respectively. diNPEOC deprotection was achieved more quickly (15−20 min) with the concentration level showing little influence.



(1.18)

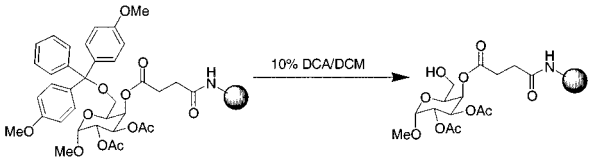
I.3.5. Benzoyl and Benzyl Groups. During the synthesis of *N*-heterocyles using ring-closing metathesis cleavage, secondary amines were protected with benzyl or benzoyl groups introduced via their chloride derivatives in the presence of triethylamine or NMP (reaction 1.19).[58] Lubell introduced a Cbz group by reaction of Cbz-Cl in the presence of DIPEA in DCM.[59]



(1.19)

II. Hydroxyl Protecting Groups

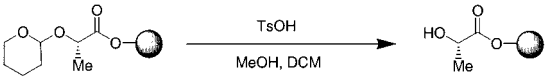
II.1. Acid-Sensitive Hydroxyl Protecting Groups. II.1.1. Trityl Derivatives. The trityl family of protecting groups is widely used for the protection of hydroxyl groups in SPOS. The most widely used of these is the dimethoxytrityl (Dmt) group. This has been used in the solid-phase synthesis of oligosaccharides, with the Dmt group being removed with 10% dichloroacetic acid (DCA) in DCM in the presence of base-labile ester linkages (reaction 2.1).[60]



(2.1)

Guzaev and Lönnberg observed that the trityl groups could not be removed from hydrophobic conjugates of oligonucleotides by 3% DCA or 2% TCA in DCM. Deprotection was achieved quantitatively through the use of 2% TFA in DCM in 40 s in the presence of a base-sensitive phosphate-based linker.[61] The Dmt group has also been removed from a Fmoc-L-threonine residue with 2.5% DCA in DCM for 10 min.[62] The trimethoxytrityl (Tmt) group has found use in the preparation of prostaglandins.[63] After selection of the dibutylsilyl linker as the best linker for the synthesis, it was found that the Tmt group had to be used in place of the less acid-labile Dmt group in order to minimize cleavage from the solid support during deprotection. Deprotection was accomplished with 1 M formic acid in DCM in 5 min with less than 5% cleavage observed. Deprotection was followed by spectroscopic quantitation of the released trimethoxytrityl cation.

II.1.2. Tetrahydropyran (THP) Group. The THP group is another common hydroxyl protecting group. While the major method of deprotection is treatment with *p*-TsOH, there is some choice over which solvent to use. Cleavage has been performed with a catalytic amount of *p*-TsOH in MeOH/DME (4:1) for 18 h at 50 °C in the presence of the acid-cleavable Wang linker[58] or by *p*-TsOH in 1-butanol/DCE (1:1) with a photocleavable linker.[64] The removal of the THP group has also been achieved with *p*-TsOH (5 mg/mL, 0.5 equiv) in DCM/MeOH (97:3) for 2 × 1 h in the solid-phase synthesis of depsides and depsipeptides using the Wang linker (reaction 2.2).[37] Solid-phase deprotection in MeOH did not work even though this was the solvent of choice during the solution-phase studies. This was attributed to the poor resin-swelling properties of MeOH.[37,65]



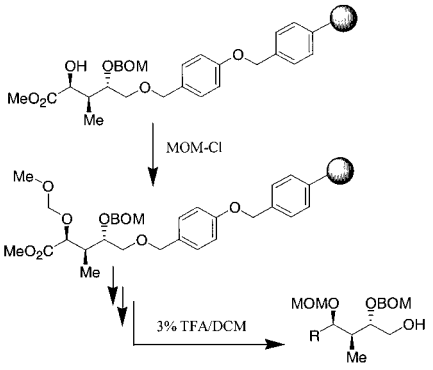
(2.2)

Deprotection of a THP group has been achieved with 0.5 equiv of *p*-TsOH in MeOH/DCM (3:1) over 17 h on a solid support containing an ester linkage.[66] Barrett has reported the deprotection of a THP-protected hydroxyl group by heating with CSA in THF/H_2O.[67]

II.1.3. Dimethoxybenzyl Group. The mild acid-labile dimethoxybenzyl group has been used to protect a phenolic OH group and was cleanly removed with 33% TFA/DCM with no cleavage of a thiobenzyl moiety observed (reaction 2.3).[68]

(2.3)

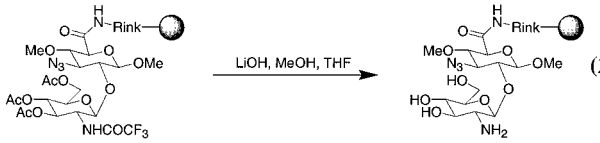
II.1.4. Monomethoxymethyl (MOM). The monomethoxymethyl group has been used to protect a secondary hydroxyl group on the solid phase. Protection was carried out using MOM-Cl (reaction 2.4).[69] The MOM group, which



(2.4)

is usually removed in solution synthesis under either harsh acidic conditions or Lewis acidic conditions, was stable to 3% TFA during the cleavage of the substrate from the Wang linker.

II.2. Base-Sensitive Hydroxyl Protecting Groups. II.2.1. Acetyl Group (Ac). By far the most common base-labile group used for the protection of hydroxyl groups is the acetyl group. The most usual method of deprotection is the use of NaOMe-promoted hydrolysis. In a synthesis of a library of Sarcodictyin analogues on polystyrene resin with a ketal linker, Nicolaou used NaOMe in MeOH to remove the acetyl group in 95% yield.[70] Removal of the acetyl groups from sugar moieties has also been accomplished using NaOMe in MeOH and water (2:1).[71] The acetyl groups on a disaccharide attached via a Rink linker to a solid support were removed by 0.5 M LiOH in THF/MeOH (1:1). The trifluoroacetyl-protected amine was also deprotected under these conditions (reaction 2.5).[72] In contrast 0.1 M LiOH·

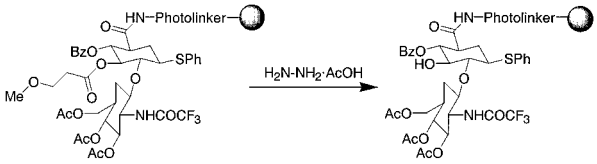


(2.5)

H_2O in THF/MeOH (4:1) for 1 h cleaved the acetyl groups of a disaccharide while reportedly leaving the trifluoroacetyl-protected amine intact.[73]

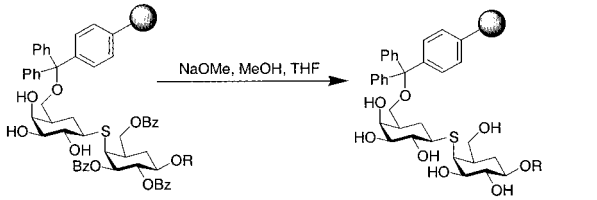
Hydrazine hydrate has also been used to cleave *O*-acetates. An acetyl-protected sugar moiety on polystyrene resin was deprotected in the presence of a Rink linker by hydrazine hydrate in MeOH (4:1) for 2 h.[74] In contrast, the acetyl groups in a disaccharide have been reported to survive treatment with hydrazine in acetic acid. Their removal was accomplished with a 1 M solution of hydrazine in THF from a solid support containing a photolinker.[73]

II.2.2. Levulinate (Lev). An *O*-levulinate-protected disaccharide attached to the resin via a photolinker was deprotected by treatment with hydrazine/acetic acid. The reaction conditions did not lead to the deprotection of other ester protecting groups present (reaction 2.6).[73]



(2.6)

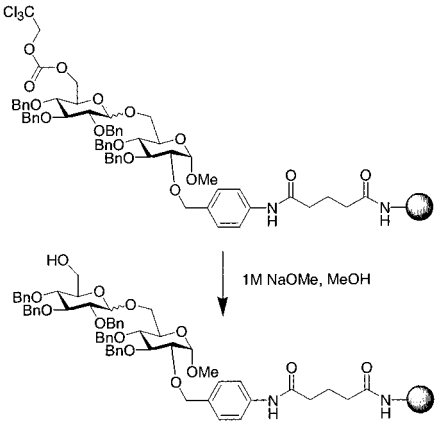
II.2.3. Benzoyl (Bz). In the synthesis of thiooligosaccharides, benzoyl groups were removed from a solid support using sodium methoxide in THF (reaction 2.7).[75] A



(2.7)

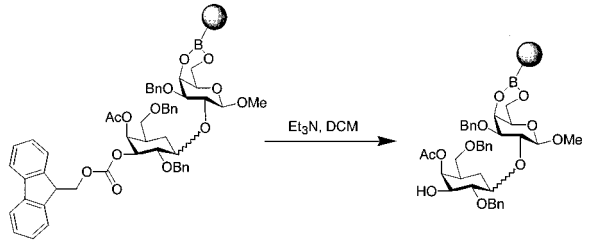
benzoyl-protected sugar moiety has been deprotected with 0.5 equiv of sodium methoxide in methanol/DCM (1:1) in 21 h.[76]

II.2.4. 2,2,2-Trichloroethoxycarbonyl (Troc). The Troc group has also been used in oligosaccharide synthesis. During a synthesis using the oxidatively cleaved *p*-acylaminobenzyl ether linker, a Troc group was removed using 1 M NaOMe in MeOH for 1 h (reaction 2.8).[77]



(2.8)

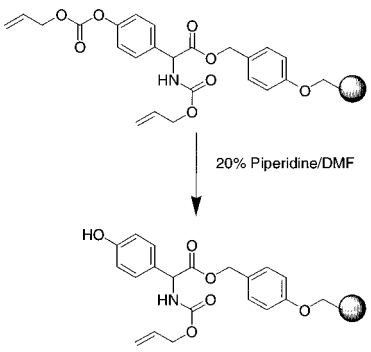
II.2.5. Fluorenylmethoxycarbonyl (Fmoc). An *O*-Fmoc group has been cleaved from a resin-bound oligosaccharide with triethylamine in DCM (reaction 2.9).[78] It was necessary



(2.9)

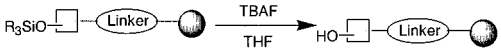
to use an organic base in an aprotic solvent in order to avoid cleavage of a boronic ester linkage.

II.2.6. Allyloxycarbonyl (Aloc). Tyrosine derivatives protected with the Aloc group on the phenol and amine positions were anchored onto a polystyrene resin with a Wang or Trityl linker via the carboxylic acid functionality.[79] The phenol Aloc protecting group could be selectively removed by treatment of the resin with a solution of 20% piperidine in DMF (reaction 2.10). The deprotection was accomplished in 90 min.



(2.10)

II.3. Silyl Protecting Groups. The silyl family of hydroxyl protecting groups has also found widespread use in solid-phase organic synthesis. While they are usually introduced as preprotected building blocks, there are examples of silyl protection being carried out on the solid phase. Cleavage is performed most commonly with TBAF, although the reaction conditions vary (reaction 2.11). The use of



(2.11)

hydrogen fluoride is reported, although this is usually confined to instances where the linker used is not acid-labile. A more detailed discussion of the individual silyl protecting groups follows.

II.3.1. *tert*-Butyldimethylsilyl (TBDMS). The most common silyl protecting group in solid-phase organic chemistry appears to be the TBDMS group. Protection of free hydroxyl groups has been carried out with 3 equiv of TBDMSCl and TEA and 0.1 equiv of DMAP in DCM.[80] Generally, deprotection is carried out with TBAF in THF. When acid-labile linkers have been employed, the TBDMS group has been removed using 1 M TBAF in THF.[80a,81] With a base-labile phosphonate linker, the deprotection conditions were 3 equiv of TBAF in THF for 12 h[82] while 10 equiv of TBAF for 13 h deprotected the TBDMS ether in the presence of a tin-based linker employed in a Stille coupling cyclorelease strategy.[83] Removal of a TBDMS group has also been carried out using 1 M TBAF in THF for 24 h on ArgoGel resin with an acid-sensitive methoxy benzaldehyde (AMEBA) linker for which cleavage from the resin was effected by TFA/TIS (95:5).[80b]

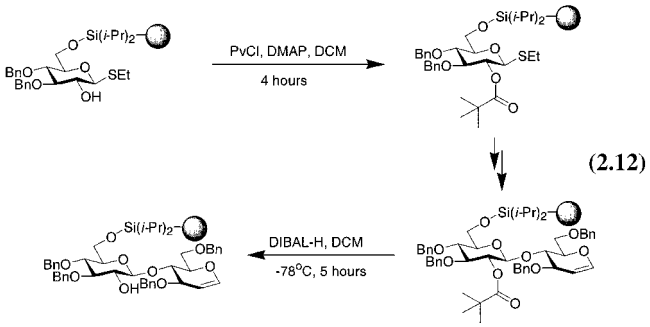
Another method used for the deprotection of TBDMS-protected hydroxyl groups on solid phase is the use of triethylamine trihydrofluoride (TREAT-HF). This reagent has been used to simultaneously remove both a TMS and a TBDMS group from a protected pivaloylglycol photocleavable linker.[84]

II.3.2. *tert*-Butyldiphenylsilyl (TBDPS). The TBDPS group has been removed by treatment with HF·py in THF for 15 h during an oligosaccharide synthesis using a photocleavable linker to attach a growing oligosaccharide chain to the support.[85] Its removal has also been achieved by treatment with 8 equiv of TBAF and 8 equiv of acetic acid in dioxane for 18 h when employing a base-labile linker[86] or 5 equiv of TBAF for 4 h with a resin bearing a Wang linker.[66]

II.3.3. Trimethylsilyl (TMS). The TMS group has been introduced using TMSCl and Et_3N in THF. The hydroxyl groups were then subsequently deprotected using TBAF in THF in the presence of a Rink linker.[87] Deprotection of a trimethylsilyl ether on a pivaloylglycol-based photolinker has been accomplished simultaneously with the removal of a TBDMS group by treatment with triethylamine trihydrofluoride in THF (1:4) for 24 h.[84]

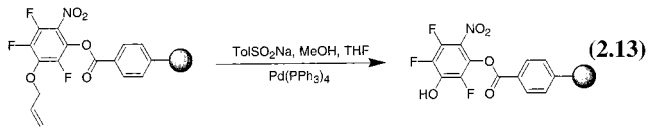
II.3.4. Triisopropylsilyl (TIPS). While making a library of Sarcodictyin analogues, Nicolaou used 10 equiv of TBAF in THF for 8 h to deprotect a TIPS-protected hydroxyl group in the presence of an acid-labile ketal linker.[70]

II.4 Miscellaneous Conditions. II.4.1. Pivaloyl (Pv). The pivaloyl group has found a use in the solid-phase synthesis of β-linked oligosaccharides. Danishefsky introduced the pivaloyl group to a thioethyl glycoside (linked to the polymer support via a diisopropylsilyl ether linker) using pivaloyl chloride with DMAP in DCM for 4 h. The resulting pivaloyl-protected glycoside was then deprotected using DIBAL in DCM at −78 °C for 5 h (reaction 2.12).[88]



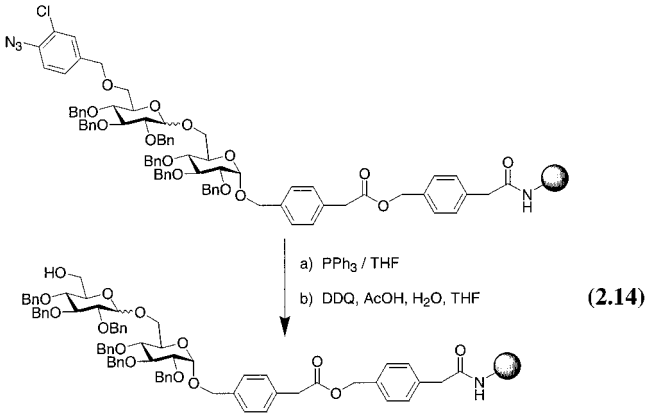
(2.12)

II.4.2. Allyl. A phenolic OH protected by an allyl group was deprotected with sodium *p*-toluene sulfinate and tetrakis-(triphenylphosphine)palladium(0) in MeOH/THF (reaction 2.13).[89]



(2.13)

II.4.3. 4-Azido-3-chlorobenzyl Group (ClAzb). The ClAzb group was used in a solid-phase oligosaccharide synthesis utilizing a base-labile ester linkage. The group was stable to the acidic conditions of glycosidations. Its removal was effected in two stages via a safety catch protocol. First, the azido moiety was converted to an iminophosphorane with triphenylphosphine in THF, followed by DDQ mediated oxidation deprotection in THF in the presence of acetic acid and water (reaction 2.14).[90]



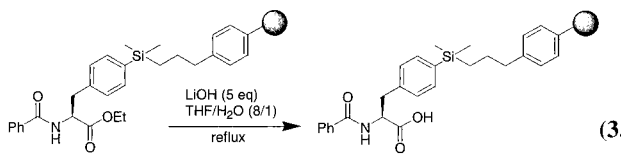
(2.14)

III. Carboxylic Acid Protecting Groups

The carboxylic acid functional group is widely used in solid-phase organic chemistry. Carboxylic acids are also often used when protected as esters, and the protecting groups have been classified as base-sensitive (methyl and ethyl esters), acid-sensitive (*tert*-butyl ester), and palladium-sensitive (allyl ester).

III.1. Base-Sensitive Carboxylic Acid Protecting Groups. The general protocol for removing methyl or ethyl esters on the solid phase is to add an aqueous solution of lithium, sodium, or potassium hydroxide with an organic solvent that allows swelling of the resin.

For the synthesis of 1,3,5-trisubstituted pyridin-2-ones on Chiron macrocrowns containing a Rink linker, methyl benzoic esters were removed with a solution of 1 M LiOH in H_2O/dioxane (1:1) for 4 h.[91] After the reaction, the resin was washed with a solution of 1 M HCl(aq)/THF (1:1) to provide the free carboxylic acid. A methylbenzoic ester was hydrolyzed from a polystyrene matrix via a Kaiser oxime linker, with LiOH (3 equiv) in a mixture of THF/MeOH/H_2O (3:1:1) for 12 h.[81] Bilodeau used 10 equiv of potassium hydroxide in a 3:1 mixture of dioxane/water for 12 h to hydrolyze an α-amino acid methyl ester on an ArgoGel resin loaded with an acid-sensitive MB-CHO linker.[92] The same type of ester was removed on polystyrene resin with a Wang urethane linkage by treatment with 5 equiv of lithium hydroxide in THF/H_2O (5:1) for only 1 h.[48] Sometimes hydrolysis requires stronger conditions. During the synthesis of 3,4,5-substituted 1,5-benzodiazepin-2-ones on a polystyrene resin with a Rink linker, hydrolysis of a methyl ester was achieved with a 1:1 mixture of 1 M NaOH and THF at 55 °C for 24 h.[93] Subsequent cleavage from the resin showed clean hydrolysis in almost quantitative yield. Silverman noticed that on a polystyrene resin loaded with a silyl linker, hydrolysis of an ethyl ester did not proceed at all with 5 equiv of LiOH in THF/H_2O (8:1) for 16 h,[32] although hydrolysis proceeded to completion when the same solution was heated to reflux for 1 h (reaction 3.1).

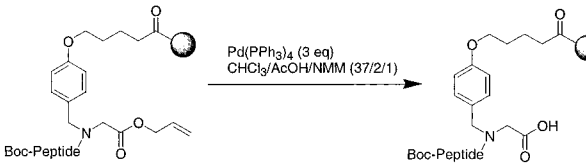


(3.1)

III.2. Acid-Sensitive Carboxylic Acid Protecting Groups. The *tert*-butyl ester protecting group is removed with high concentrations of TFA in DCM and therefore is not used with acid-labile linkers unless concomitant cleavage of the linker and *tert*-butyl group is desired. A *tert*-butyl ester side chain protecting group has been hydrolyzed with 95%[94] or 60%[27] TFA in DCM. During the solid-phase synthesis of *N*-heterocycles, *tert*-butyl ester hydrolysis was performed with a 20% solution of TFA in DCM for 2 h in the presence of an aryl ester linkage (reaction 3.2).[58]

(3.2)

III.3. Palladium Removable Carboxylic Acid Protecting Group. Like the Aloc group used for amine protection, removal of an allyl ester has been achieved with $Pd(PPh_3)_4$ using various solvent systems and scavengers. One of the most common protocols is the use of $Pd(PPh_3)_4$ in a mixture of $CHCl_3$/AcOH/NMM (37:2:1) for 3 h (reaction 3.3).[95]



(3.3)

Excess palladium can be removed by washing the resin with a 10% solution of diethyldithiocarbamic acid in DMF.

N-Methylaniline has been used successfully as a scavenger. Lee removed an allyl ester with $Pd(PPh_3)_4$ in 10% *N*-methylaniline/THF for 12 h, followed by extensive washing of the resin (pyridine, NMP, and DCM) to remove the catalyst.[96] The same scavenger has been used by Heerding in the synthesis of hexahydroisoindoles in DMSO/DMF (1:1) at 55 °C with 20% of the catalyst.[97] During the synthesis of a library of fucopeptides on a PEG-PS resin, Wong used a catalytic amount of $Pd(PPh_3)_4$ and dimedone as a scavenger in THF for 18 h.[98] A mixture of $Pd(PPh_3)_4$, HOBt, and PPh_3 in DMF/DCM has been used to remove an allyl ester by Metcalf.[7] In the synthesis of glycopeptides on polystyrene resin, Danishefsky used dimethylbarbituric acid (NDMBA) as the scavenger,[24] also used as a 0.25 M solution in DCM.[99]

IV. Sulfur Protecting Groups

IV.1. Trityl Acid-Sensitive Sulfur Protecting Group. The trityl protecting group is by far the most common protecting group reported in solid-phase synthesis for the protection of thiols. While its removal is accomplished with TFA (reaction 4.1), the concentration of the acid and choice of scavenger vary.

(4.1)

Houghten has removed the trityl group from S-protected cysteine residues loaded onto polystyrene resin with an MBHA linker with 5% TFA/5% triisobutylsilane in DCM[27,100] and has also reported the use of 10% TFA and 5% tri-

Table 1

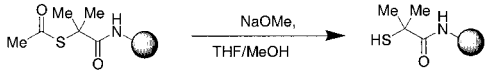
protecting group	resin-linker type	deprotection condtions	ref
		Amine Function	
Fmoc	TG-alkyl ester	20% piperidine in NMP	4
Fmoc	PS-Wang	20% piperidine in DMA	5
Fmoc	PS-HYCRON	50% morpholine in DMF	6
Fmoc	PS-Wang	1% DBU in DMA	7
Nsc	PS/PEG-AM, PS-Rink/Wang	1% DBU or 20% piperidine in DMF	10, 11
Dde	PS-Wang	2% hydrazine in DMF	14
N-DdX	PS-Trt	2% hydrazine in DMF	12
N-Nde	NovaSyn KR100	2% hydrazine in DMF	13
Pht	PS-Wang	H_2NNH_2, EtOH, 80 °C	15
Pht	PS-THP	H_2NNH_2, DMF/THF (3/1)	16
o/*p*-Ns	PS−Rink	β-mercaptoethanol, DBU, DMF	18, 22
o-Ns	PS-THP	β-mercaptoethanol, DBU, NMP	16
o-Ns	PS-Dde	1 M NaSPh in DMF	19
o-Ns	PS-Wang	PhSH, K_2CO_3, DMF	21
p-Ns	PS-Trt	PhSH, K_2CO_3, DMF	20
2,4-Ns	PS-RCM	*n*-$BuNH_2$, DCM	23
2,4-Ns	PS-Wang	mercaptoacetic acid, DIPEA, DCM	14
$AnthSO_2$	PS-silyl	propanedithiol, DIPEA, DMF	24
Boc	PS-MBHA	50% TFA in DCM	27
Boc	PS-RCM	50% TFA in DCM	23
Boc	PS-ester alkyl	50% TFA in DCM, 0 °C, 2 h	28
Boc	PS-Kaiser oxime	TFA/DCM (1/2), 1.5 h	29
Boc	PS-Kaiser oxime	25% TFA in DCM, 30 min	30
Boc	PS-Kaiser oxime	25% TFA in DCM, 2 h	31
Boc	PS-silyl	TFA/DCM (1/1), 10 min	32
Boc	PS-aminal	TFA/thioanisole/DCM (3/1/6), 15−20 min	33
Boc	PS-ester	MSA in dioxane, reflux	34
Boc	PS-silyl	*B*-chlorocatecholborane, DCM	35
Boc	PS-Rink	trimethylsilyl triflate, 2,6-lutidine, DCM	36
Bpoc	PS-Wang	0.5% TFA in DCM	37
Trt	PS-MBHA	2% TFA in DCM	38
Mtt	crown Rink	1% TFA in DCM	39
Mmt	TG-ester	acetic acid/trifluoroethanol/DCM (1/2/7)	40
Mmt	CPG-ester	4% dichloroacetic acid, DCM	41, 42
DMB	PS-hydrazine	5% TFA in DCM	43
Ph_2C═	PS-Wang	NH_2OH·HCl, THF/H_2O	44−46
Ph_2C═	PS-Wang	1N HCl in THF	45
Teoc	PS-Wang	TBAF, THF	48
Teoc	PS-THP	TBAF, THF	49
Teoc	PS-Trt-2-Cl	TBAF, THF	47
SEM	PS-BAL	0.25 M TBAF, THF	50
Aloc	PS-MBHA	$Pd(PPh_3)_4$, Me_2NSiMe_3, $CF_3CO_2SiMe_3$, DCM	51
Aloc	AG-carbazate	$Pd(PPh_3)_4$, Me_3SiN_3, TBAF, DCM	52
Aloc	PS-aminal	$Pd(PPh_3)_4$, 0.5 N HCl, morpholine, THF/DMSO	33
Aloc	PS-Rink	$Pd(PPh_3)_4$, dimedone, DCM/THF	54
Aloc	PS-PAL	$Pd(PPh_3)_4$, H_3N·BH_3 or Me_2NH·BH_3, DCM	55
Aloc	PS-PEG PAL or PS-PAL	$Pd(PPh_3)_4$, DCM/AcOH/NMM	56
		Hydroxy Function	
Dmt	PS,TG,CPG-succinimide	10% DCA in DCM	60
Dmt	CPG-ester	2% TFA in DCM	61
Dmt	CPG-Icaa	2.5% DCA in DCM	62
Tmt	PS-silyl	1 M formic acid in DCM	63
THP	PS-Wang	*p*-TsOH in MeOH/DME (4/1)	58
THP	PS-photolinker	*p*-TsOH, BuOH/DCE (1/)	64
THP	PS-Wang	*p*-TsOH, DCM/MeOH (97/3)	65, 37
THP	PS-ester	*p*-TsOH, DCM/MeOH (3/1)	66
THP	PS	CSA, THF/H_2O	67
DMB	PS-thioester	TFA/DCM (1/2)	68
Ac	PS-ketal	NaOMe/MeOH	70
Ac	PS−Rink	0.5 M LiOH, THF/MeOH (1/1)	72
Ac	PS-photolinker	0.1 M LiOH, THF/MeOH (4/1)	73
Ac	PS-Rink	H_2NNH_2·H_2O/MeOH (4/1)	74
Lev	PS-photolinker	hydrazine/acetic acid	73
Bzl	PS-Trt	NaOMe, THF	75
Bzl	PS-silyl	NaOMe, MeOH/DCM (2/1)	76
Troc	AG-acylamino benzyl ether	1 M NaOMe, MeOH	77
Fmoc	PS-borane	Et_3N in DCM	78
Aloc	PS-Trt	20% piperidine in DMF	79
TBDMS	AG-AMEBA	1 M TBAF, THF	80
TBDMS	PS-Kaiser	1 M TBAF, THF	81

Table 1 (Continued)

protecting group	resin-linker type	deprotection condtions	ref
		Hydroxy Function (Continued)	
TBDMS	PS-phosphonate	TBAF, THF	82
TBDMS	PS-tin	TBAF, THF	83
TBDMS	PS-photolinker	TREAT-HF, THF (1/4)	84
TBDMS	AG-MB-CHO	0.2 M TREAT-HF, THF	80
TBDPS	PS-photolinker	HF·Py, THF	85
TBDPS	PS-ester	TBAF, AcOH, dioxane	86
TBDPS	PS-Wang	TBAF, THF	66
TMS	PS-Rink	TBAF, THF	87
TMS	TG-photolinker	TREAT-HF/THF (1/4)	84
TIPS	PS-acetal	TBAF, THF	70
Pv	PS-silyl	DIBAL, DCM, −78 °C	88
allyl	PS-ester	$Pd(PPh_3)_4$, $TolSO_2Na$, MeOH/THF	89
ClAzb	PS-ester	(1) PPh_3, THF, (2) DDQ, THF, (3) AcOH, H_2O	90
		Carboxylic Acid Function	
Me	crown-Rink	1 M LiOH/doxane (1/1)	91
Me	PS-Kaiser	LiOH, THF/MeOH/H_2O (3/1/1)	81
Me	AG-MB-CHO	KOH, dioxane/H_2O (3/1)	92
Me	PS-Wang	LiOH, THF/H_2O (5/1)	48
Me	PS-Rink	1 N NaOH, THF, 55 °C	93
Et	PS-silyl	LiOH, THF/H_2O (8/1)	32
^{t}Bu	PS-MBHA	95% TFA in DCM	94
^{t}Bu	PS-MBHA	60% TFA in DCM	27
^{t}Bu	PS-RCM	20% TFA in DCM	58
allyl	PS-Wang	$Pd(PPh_3)_4$, CH_3Cl/AcOH/NMM	95
allyl	PS−Wang	$Pd(PPh_3)_4$, 10% methylaniline, THF	96
allyl	PS-Wang	$Pd(PPh_3)_4$, DMSO/THF (1/1) 10% methylaniline, 55 °C	97
allyl	PS-PEG-acetal	$Pd(PPh_3)_4$, dimedone, THF	98
allyl	PS-Wang	$Pd(PPh_3)_4$, HOBt, PPh_3, DMF/DCM	7
allyl	PS-silyl	$Pd(PPh_3)_4$, NDMBA, THF	24
allyl	TG-ester	$Pd(PPh_3)_4$, 0.25 M NDMBA in DCM	99
		Sulfur Function	
Trt	PS-MBHA	5% TFA, 5% ^{i}Bu$_3$SiH in DCM	27, 100
Trt	PS-MBHA	10% TFA, 5% ^{i}Bu$_3$SiH in DCM	101
Trt	PS-Rink	2% TFA, 2% Et_3SiH in DCM	102
Trt	PS-Sasrin	2% TFA, 2% Et_3SiH in DCM	4
Mmt	PS-MBHA	1% TFA in DCM/Et_3SiH (95/5)	103
Ac	PS-BAL	NaOMe in THF/MeOH (3/1)	104
EtS	PS-Trt	DTT in THF/MeOH/Et_3N (10/2/1)	75
^{t}BuS	TG-Rink	0.1 M DTT in DMF/0.2 M NH_4HCO_3 (2/1)	105
		Acetylene Function	
TMS	PS-Rink	1.0 M TBAF in THF	106a
TMS	PS-THP	1.0 M TBAF in THF	106b,c
		Aldehyde Function	
diethyl acetal	PS-RCM	*p*-TsOH(cat), NMP/acetone (2/1), 50 °C	58

isobutylsilane in DCM.[101] The removal of a trityl group has been achieved with 2% TFA and 2% triethylsilane in DCM for 2 × 10 min in the presence of the acid-sensitive Rink linker, which was later cleaved using 96% TFA, 2% thioanisole, and 2% water.[102] Conversely, for the synthesis of a library of oligocarbamates, Schultz reported that the Rink linker was cleaved under the conditions of trityl group deprotection (2% TFA and 2% triethylsilane in DCM in this case).[4] The PAL linker was also found to be unstable to the trityl deprotection reaction.[4] The lack of stability of these linkers was attributed to the acid-labile carbamate group that bound the oligocarbamate to the linker. The problem was overcome with the use of an MBHA linker modified with a 4-(4′-aminomethyl-3′-methoxyphenoxy)butyric acid handle. The trityl group was then cleaved with 2% TFA and 2% triethylsilane in DCM for 5 × 10 min. The monomethoxytrityl group has also been used to protect cysteine residues on polystyrene resin with an MBHA linker and was cleaved by 1% TFA in DCM/triethylsilane (95:5) in 30 min.[103]

IV.2. Acetyl Base-Sensitive Sulfur Protecting Group. Ellman has reported the deprotection of an *S*-acetyl group using methanolysis (reaction 4.2) with sodium methoxide in THF/MeOH (3:1).[104]

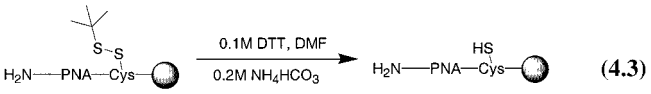


(4.2)

IV.3. Dithiothreitol (DTT) Sensitive Sulfur Protecting Groups. IV.3.1. *S*-Ethyl Group. The anomeric sulfur protected as a disulfide by an *S*-ethyl group in a sugar moiety bound to the support via a trityl linker was deprotected with DTT in THF, MeOH, and Et_3N (10:2:1) in 18 h at 20 °C.[75]

IV.3.2. *S-tert*-Butylmercapto Group. In a solid-phase PNA synthesis using the Rink linker, an *S-tert*-butylmercapto

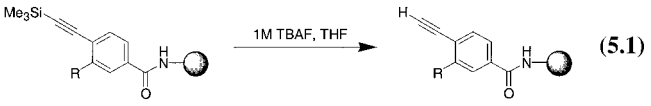
group was removed from a cysteine residue with 0.1 M DTT in DMF and 0.2 M NH_4HCO_3 (2:1 v/v) in 4 h (reaction 4.3).[105]



(4.3)

V. Acetylene Protecting Group (TMS Group)

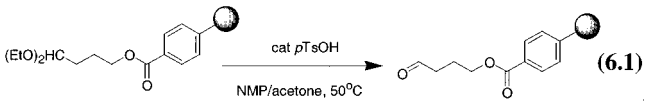
Reports on acetylenic protecting groups have been limited to the use of the trimethylsilyl group. The removal of the TMS group was accomplished with 1.0 M TBAF in THF when either a Rink linker or a THP linker was employed (reaction 5.1).[106]



(5.1)

VI. Aldehyde Protecting Groups (Diethyl Acetal)

The diethylacetal group has been used to protect an aldehyde group on the solid phase in the presence of a base-labile ester linkage. Deprotection was achieved by three successive treatments with a 0.1 equiv of *p*-TsOH in NMP/acetone (2:1) at 50 °C for 3 h (reaction 6.1).[58]



(6.1)

VII. Conclusion

As this review has shown, a wide variety of protecting groups are now being used in solid-phase organic chemistry. However, careful consideration needs to be given to the compatibility of the deprotection steps with both the linkers being used and any other protecting groups present. In addition, the nature of the solid support can influence the choice of the removal step, in some cases requiring modification to existing solution-phase strategies or allowing excesses of reagents to be used. It is hoped that the examples in this review illustrate these concerns. Table 1 summarizes all of the examples contained within this review.

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Abbreviations

Ac	acetyl
AG	ArgoGel
All	allyl
Aloc	allyloxycarbonyl
AMEBA	acid-sensitive methoxybenzaldehyde
BAL	backbone amide linker
BEMP	2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
BHA	benzhydrylamine
Boc	*tert*-butyloxycarbonyl
Bpoc	2-(*p*-biphenyl)-2-propyloxycarbonyl
Bt	benzotriazole
Bz	benzoyl
Choc	cyclohexylcarbonyl
Chx	cyclohexyl
ClAzb	4-azido-3-chlorobenzyl
CPG	control pore glass
CSA	camphor sulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCA	dichloroacetic acid
DCM	dichloromethane
Dde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL-H	diisobutylaluminum hydride
diNPEOC	2,2′-bis(2-nitrophenyl)ethoxycarbonyl
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-*N*,*N*-(dimethylamino)pyridine
DMB	2,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dmt	dimethoxytrityl
DNP	2,4-dinitrophenyl
DTT	dithiothreitol
Fmoc	9-fluorenylmethoxycarbonyl
For	formyl
HF	hydrogen fluoride
HOBt	*N*-hydroxybenzotriazole
HPLC	high-pressure liquid chromatography
Lev	levulinate
MBHA	methylbenzhydrylamine
Mmt	monomethoxytrityl
MOM	monomethoxymethyl
MSA	methanesulfonic acid
Mtt	methyltrityl
Nde	1-(4-nitro-1,3-dioxoindan-2-ylidene)ethyl
NDMBA	*N*,*N*′-dimethylbarbituric acid
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidone
Ns	nitrobenzenesulfonamide
Nsc	2-(4-nitrophenylsulfonyl)ethoxycarbonyl
NVOC	6-nitroveratryloxycarbonyl
PAL	peptide amide linker
PEG	poly(ethylene glycol)
PNA	peptide nucleic acid
PS	polystyrene
Pv	pivaloyl
RCM	ring-closing metathesis
rt	room temperature
SEM	2-trimethylsilylethoxymethyl
SPOS	solid-phase organic synthesis
SPPS	solid-phase peptide synthesis
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TCA	trichloroacetic acid
TEA	triethylamine
Teoc	2-trimethylsilylethyl carbamate
TES	triethylsilyl
TFA	trifluoroacetic acid
TFMSA	trifluoromethanesulfonic acid
TG	TentaGel
THF	tetrahydrofuran

THP	tetrahydropyran
TIPS	triisopropylsilane
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TREAT-HF	triethylamine trihydrofluoride
Troc	2,2,2-trichloroethoxycarbonyl
Trs	2,4,6-triisopropylsulfonamide
Trt	trityl
Ts	tosyl
TSA	thiosalicylic acid
Z	benzyloxycarbonyl

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