

2 Synthetic methods

Part (v) Protecting groups

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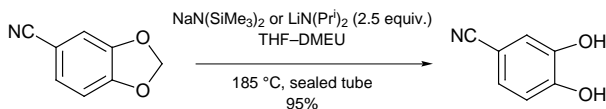
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Another excellent and comprehensive ‘update’ review of protecting group strategies in organic synthesis has appeared this year.¹

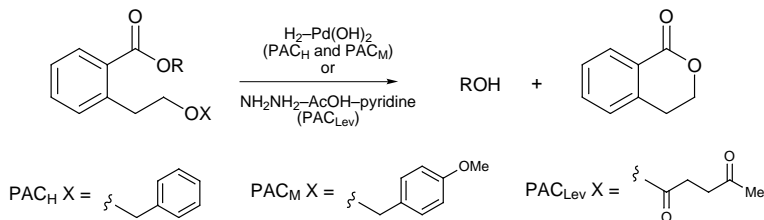
1 Hydroxy protecting groups

The use of allylic protection of alcohols in the context of complex synthesis (mainly of oligosaccharides) has been reviewed.² Sodium borohydride–iodine (THF at 0 °C) appears to be an attractive method for the reductive cleavage of both aryl and alkyl allyl ethers.³ An alternative reductive cleavage of allyl ethers employs naphthalene catalysed lithiation.⁴ This method uses an excess of lithium powder in the presence of catalytic naphthalene at low temperature and generally gives higher yields for the removal of benzyl ethers and is also effective for the de-sulfonylation of primary tosyl amides and tosyl or mesyl carboxamides. Deprotection of allyl ethers is also frequently achieved by a two step procedure involving base or transition metal complex mediated isomerisation to the corresponding vinyl ether followed by acid, mercury(II) chloride, or iodine assisted hydrolysis. Wacker type oxidation offers a mild alternative for this second step.⁵ Such oxidation is compatible with acid sensitive benzyldiene acetals and proceeds with retention of configuration for anomeric vinyl ethers. Benzyltriethylammonium tetrathiomolybdate in acetonitrile effects selective deprotection of propargyl ethers in the presence of allyl and benzyl ethers and other easily reducible functionalities such as nitro, aldehyde and keto groups, under essentially neutral conditions.⁶ Two very similar new methods for the selective removal of *p*-methoxybenzyl ethers are ethanethiol–aluminium trichloride [or tin(II) chloride] and dimethylsulfide–magnesium bromide.^{7,8} The former method employs 0.2 equiv. of Lewis acid at ambient temperature and is tolerant of methyl and benzyl ethers, *p*-nitrobenzoyl esters, *tert*-butyldiphenylsilyl ethers (TBDPS) and isopropylidene acetals, whilst the latter employs 3 equiv. of Lewis acid at ambient temperature and is tolerant of 1,3-dienes, *tert*-butyldimethylsilyl (TBDMS) and benzyl ethers, benzoyl esters and isopropylidene acetals.

Commercially available, and reusable, HSZ zeolites offer a useful and environmentally benign method for the large scale preparation of both alkyl and aryl tetrahydropyranyl ethers (THP) in neat dihydropyran (DHP).⁹ Selectivity for the former over the latter is also possible. The same zeolite catalyst can also be employed to effect



Scheme 1



Scheme 2

quantitative deprotection in methanol, as can anhydrous tin(II) chloride.¹⁰ An interesting method for the deprotection of methyl and benzyl aryl ethers in good to excellent yields employs sodium hexamethyldisilazide (NaHMDS) or lithium diisopropylamide (LDA) in THF–1,3-dimethyl-2-imidazolidinone (DMEU) at 185 °C in a sealed tube.¹¹ NaHMDS is slightly less reactive than LDA and this can be exploited for the mono deprotection of *o*-dimethoxybenzenes. Of particular note is that either base can also be employed for the almost quantitative deprotection of the methylenedioxy functionality (Scheme 1).

Partial resolution (39–97% ee) of the enantiomers of selected simple *cis*-diols has been achieved by acetal formation with a polymer-supported 7-keto-steroid followed by hydrolysis.¹²

In the area of ester protection of alcohols there has been exciting progress in the area of non-enzymatic kinetic resolution of secondary alcohols *via* acylation using a number of ‘synthetic’ chiral catalysts and this area has been briefly reviewed.¹³ The use of magnesium methoxide in methanol at ambient temperature has been advocated for the deprotection of alkyl acetates.¹⁴ Of note is the sensitivity of the procedure to steric hindrance thereby allowing the selective removal of primary acetates in the presence of secondary and tertiary acetates in complex substrates. Three 2-(2-oxyethyl)benzoate protecting groups, PAC_H, PAC_M and PAC_{Lev}, have been introduced and their utility demonstrated for the preparation of phosphorylated inositol derivatives.¹⁵ These esters are generally introduced using DCC–DMAP and have cleavage properties dependent on the 2-oxyethyl ether substituent: *e.g.* H₂–Pd(OH)₂ or H₂–PdCl₂ for the 2-benzyloxy-, and 2-(4-methoxybenzyloxy)ethylbenzoyl groups (PAC_H and PAC_M) and NH₂NH₂–AcOH–pyridine for the 2-(2-levulinoyloxy)ethylbenzoyl group (PAC_{Lev}). PAC is an abbreviation for ‘proximately assisted cleavable group’ as the ester hydrolysis is facilitated by 6-*exo*-trig lactonisation (Scheme 2).

A protecting group closely related to PAC_{Lev} is the 2-(levulinoyloxymethyl)nitrobenzoyl group (LMNBz) which has been employed successfully as a 5'-hydroxy protecting group which suppresses depurination [*cf.* dimethoxytrityl (DMTr)] during automated ribonucleoside and 2'-deoxyribonucleoside 3'-phosphoramidite synthesis.¹⁶ Cleavage is *via* 5-*exo*-trig lactonisation using 0.5 M imidazole in acetonitrile following ether cleavage using 0.5 M NH₂NH₂ in 1:4 AcOH–pyridine.

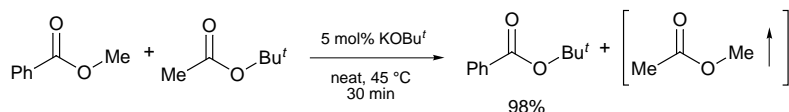
Two new carbonate type 5'-hydroxy protecting groups for ribonucleoside synthesis have been developed: the 2-(2-nitrophenyl)ethoxycarbonyl group (NPEoc) is removed by photolysis (365 nm) and displays a *ca.* 3-fold rate enhancement for cleavage relative to the 2-nitrobenzyloxycarbonyl group (NBoc).¹⁷ The (2-cyano-1-phenyl)ethoxycarbonyl group (CPEoc) is base labile (0.1 M DBU in acetonitrile) and works efficiently in conjunction with 4-ethoxytetrahydropyran-4-yl 2'-hydroxy protection.¹⁸ Carbonate protection of the phenol of tyrosine as a 2,4-dimethyl-3-pentyloxycarbonyl group (Doc) has been proposed as an alternative to the 2-bromobenzyloxycarbonyl group (2-BrZ) during *tert*-butoxycarbonyl (Boc) solid phase synthesis.¹⁹ However, although this group displays superior resistance to nucleophilic cleavage it is more acid sensitive and much less rapidly cleaved using 20% piperidine–DMF.

The tris(trimethylsilyl)silyl group (Sisyl) has been introduced as a new fluoride resistant, photolabile (medium pressure Hg lamp, MeOH, *ca.* 30 min) protecting group for primary and secondary alcohols.²⁰ These ethers are prepared from the corresponding chlorosilane using CH₂Cl₂–DMAP (1.2 equiv.). They are not stable towards certain nucleophiles (TBAF, BuLi, LiAlH₄) but are stable towards other fluoride sources (CsF, KF–18-crown-6), Grignard and Wittig reagents (MeMgBr, Ph₃P=CH₂), oxidation (Jones' reagent) and are more acid stable than TBDMS, TBDPS and triisopropylsilyl (TIPS) groups [*p*-TSA (1 equiv.), 0.2 M HCl–acetone (1:1)]. These latter silyl ethers are photostable under the conditions which remove the Sisyl group. Primary TBDMS ethers can be selectively removed in the presence of secondary TBDMS ethers using LiBr–18-crown-6 in acetone at elevated temperatures.²¹ Additionally, quinolinium fluorochromate has been shown to effect concomitant cleavage and oxidation of primary TBDMS ethers (including allyl and benzyl) to aldehydes in the presence of secondary TBDMS ethers (including allyl and benzyl). Primary methoxymethyl (MOM), THP and TBDPS ethers are stable to these conditions.²² The efficient one-pot deprotection–oxidation of primary and secondary trimethylsilyl ethers (TMS) using 3-carboxypyridinium chlorochromate in refluxing acetonitrile or dichloromethane to give aldehydes and ketones respectively has also been described.²³ THP ethers also undergo this oxidation but more slowly. The susceptibility to cleavage by LiAlH₄ of TBDMS ethers 1,3- or 1,4-disposed to an unprotected hydroxy group has been demonstrated and is proposed to result from intramolecular hydride delivery from the alcohol-derived alkoxyaluminium hydride.²⁴

2 Carboxy protecting groups

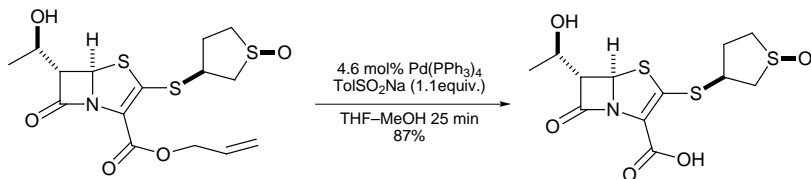
Just 5 mol% of potassium *tert*-butoxide, believed to form highly reactive caged tetramers, effects almost quantitative ester metathesis between methyl benzoate and *tert*-butyl acetate to give *tert*-butyl benzoate provided the volatile by-product (methyl acetate) is removed by application of an aspirator vacuum.²⁵ The full scope of this procedure has yet to be established (Scheme 3).

The π -acid tetracyanoethylene (TCNE) is an effective catalyst (20 mol%) for the esterification of lauric acid with a wide variety of alcohols (1°, 2°, benzyl, allyl, propargyl, 2-trimethylsilylethyl), for the esterification of α -hydroxy-, and *N*-benzyloxycarbonyl- (Cbz) or *N*-Boc- α -amino acids with methanol to give methyl esters and also for the transesterification of methyl laurate with a variety of alcohols (1°, 2°,



Scheme 3

benzyl, allyl, propargyl).²⁶ These reactions are driven towards products by using the appropriate alcohol as solvent. Magnesium bromide etherate has been previously shown to cleave β -(trimethylsilyl)ethoxymethyl esters (SEM) and this methodology has now been extended to amino acid and peptide derivatives in the presence of protecting groups typically encountered in peptide chemistry [Boc, Cbz, fluoren-9-ylmethoxycarbonyl (Fmoc) and 2,2,2-trichloroethoxycarbonyl (Troc) carbonates, and benzyl (Bn), Bu^t, TBDMS ethers].²⁷ Other fluoride sensitive protecting groups are stable to magnesium bromide. An extensive survey of allyl scavengers has been undertaken for the tetrakis(triphenylphosphine) catalysed deprotection of allyl esters.²⁸ Toluenesulfinic acid was identified as the most efficient scavenger (better than carboxylic acids, morpholine, dimedone, *etc.*) allowing efficient deprotection on sensitive penem substrates (Scheme 4).



Scheme 4

Salts of toluenesulfinic acid can also be employed and this allows the use of other palladium catalysts such as palladium acetate, dichlorobis(acetonitrile)palladium triethylphosphite although these reactions are substantially slower. 2-Chloroallyl, 2-methylallyl, crotyl and cinnamyl esters are similarly efficiently scavenged and the process can also be extended to the deprotection of allyl carbonates, allyl ethers, allylamines and *O*-allyl oximes.

3 Phosphate and sulfate protecting groups

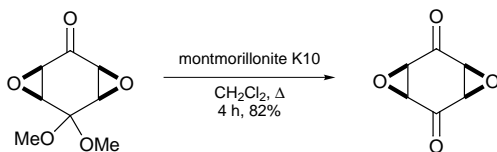
Non-hydrolytic deprotection of phosphite and phosphate alkyl esters is often accomplished using TMS iodide or TMS chloride. The reactive inorganic polymer, silica chloride, is an attractive alternative.²⁹ *tert*-Butyl and benzyl esters are cleaved almost quantitatively at ambient temperature in chlorinated hydrocarbon solvents (CCl₄, CHCl₃, CH₂Cl₂) in under an hour as are the corresponding sulfite esters. Isopropyl and phenyl esters, however, do not react and the reaction was shown to produce racemic 1-phenethyl chloride when using bis(*S*)-1-phenethylphosphite as substrate. The use of ammonia gas under pressure offers an efficient alternative to hot aqueous ammonium hydroxide for the deprotection and cleavage steps during the large scale synthesis of oligonucleotides, and their phosphorothioate (PS) analogues prepared using *N*-pent-4-enoyl (PNT) protected nucleoside phosphoramidites (*O*-2-cyanoethyl,

N,N-diisopropyl) and *H*-phosphonates.³⁰ Methylamine with or without added ammonium hydroxide has also been advocated for the same purpose when employing *N*-acetyl protected nucleoside phosphoramidites (*O*-2-cyanoethyl, *N,N*-diisopropyl) and *H*-phosphonates.³¹ Use of *N*⁴-acetyldeoxycytidine (dC^{Ac}) was noted to suppress transamination relative to use of dC^{Bz} during this procedure. *O*-4-Cyanobut-2-enyl protection (CB) has been reported as an alternative to the ubiquitous *O*-2-cyanoethyl phosphoramidite protecting group.³² Deprotection by δ -elimination is effected using aqueous ammonium hydroxide under identical conditions as the *O*-2-cyanoethyl analogues but the method is purported to be *ca.* 60% less costly on a kilogram scale. Eight new *S*-protecting groups have been investigated for the synthesis of dithymidine phosphorothioates by the solution phase phosphotriester method.³³ The best of these was the 4-chloro-2-nitrobenzyl group which allowed efficient coupling using 4-nitro-6-trifluoromethylbenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyFNOP, 96%, 15 min) and could be removed with a minimum of side reactions using thiophenolate.

The trifluoroethyl ester has been demonstrated to be a useful protecting group for sulfate monoesters in carbohydrates.³⁴ These esters are readily formed from the appropriate sulfate using trifluoroethyl diazoethane, are stable to TFA but cleaved with mineral acids (dil. H₂SO₄), stable to TBAF, sodium methoxide in methanol and hydrogenation but selectively cleaved using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol.

4 Carbonyl protecting groups

Monomorillonite K10 in dichloromethane at ambient temperature has been found to be an extremely convenient, mild and efficient method for the deprotection of acetals and ketals.³⁵ Its utility has been demonstrated in the first synthesis of *syn*-4,8-dioxatricyclo[5.1.0.0^{3,5}]octane-2,6-dione and is effective not only for dimethyl acetals but also 1,3-dioxolanes and 5,5-dimethyl-1,3-dioxanes (Scheme 5).

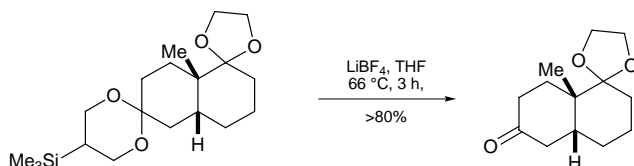


Scheme 5

Monomorillonite K10 in refluxing dichloromethane is also efficient for the deprotection of 1,1-diacetates.³⁶ Ferric chloride hexahydrate is a mild promoter of hydrolytic deprotection of acetals in dichloromethane at ambient temperature which appears to be more selective for this process (particularly with 1,3-dioxolanes) over interaction with other acid sensitive functionalities than alternative Lewis acids.³⁷ Hydrogenolytic deprotection of 4-phenyl-1,3-dioxolane protected ketones and aldehydes simply using Pd-C-H₂ has been shown to be a very clean and efficient alternative to electrolytic deprotection.³⁸ Cyclo-SEM has been introduced as a new

fluoride labile acetal protecting group for carbonyl groups.³⁹ Protection is accomplished at ambient temperature using a slight excess of 2-trimethylsilylpropane-1,3-diol in dry dichloromethane with activated powdered 3 or 4 Å MS and catalytic camphorsulfonic acid (0.25 equiv.) and deprotection using LiBF_4 in THF (conditions which do not affect 1,3-dioxolanes, Scheme 6).

A rapid and efficient deprotection of a series of simple aryl aldehyde 1,1-diacetates catalysed by 'expansive graphite' in refluxing dichloromethane or benzene has been reported, preceded by details of the synthesis of the catalyst.⁴⁰

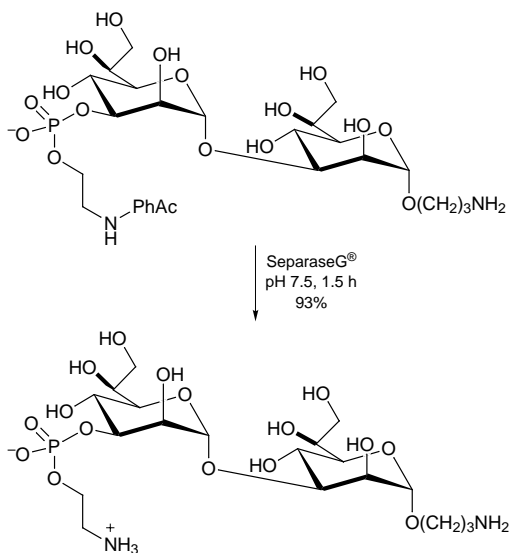


Scheme 6

5 Amine protecting groups

Amides are rarely used for amine protection in peptide synthesis due to their proclivity towards racemisation (*via* azalactones) and resistance to hydrolysis. The hydrolysis of *N*-trifluoroacetyl- α -amino acid *tert*-butyl esters to the corresponding *tert*-butyl ester hydrochlorides using liquid–liquid phase transfer catalysis [20% KOH, triethylbenzylammonium chloride (10 mol%) $\text{H}_2\text{O}-\text{CH}_2\text{Cl}_2$, 25–35 °C] followed by precipitation (HCl, Et_2O) has been reported but is accompanied by partial racemisation in the case of phenylalanine (23%) and complete racemisation for phenylglycine.⁴¹ The corresponding *N*-trifluoroacetyl- α -amino acids can be obtained using TFA (probably without racemisation although this was not verified). A more effective approach to amide deprotection employs enzymatic amide hydrolysis. The exquisite selectivity of *N*-phenylacetyl deprotection using immobilised penicillin G acylase (Separase®) under extremely mild, neutral conditions allowed cleavage of an *N*-phenylacetyl ethanolamine phosphate heptosyl disaccharide⁴² (Scheme 7).

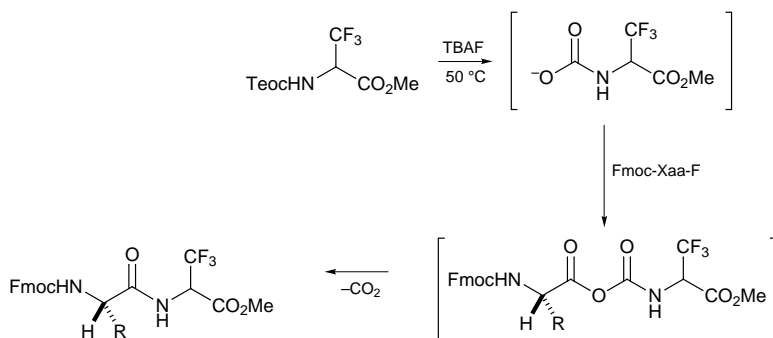
Soluble penicillin G acylase has also been found to be effective for the deprotection of a controlled pore glass (CPG) bound TGGGG-pentanucleotide containing *N*-phenylacetyl protected bases.⁴³ The synthetic scope of recombinant phthaloyl amidase for the mild unmasking of *N*-phthaloyl imides (Phth) following partial hydrolysis to their mono acids has also been further delineated.⁴⁴ A range of primary amines can be deprotected and the enzyme exhibits modest chiral selectivity between diastereomeric dipeptides. An alternative solution to mild phthalimide deprotection is to employ a tetrachlorophthalyl group (TCP).⁴⁵ Installation can be accomplished in two steps by treating the free base with commercially available TCP anhydride followed by ring closure with Ac_2O –pyridine and the group is stable under conditions ranging from mildly basic to harshly acidic. Cleavage is effected by 2–4 equiv. of ethylenediamine at 60 °C in MeCN–THF–EtOH (2: 1:), conditions under which glycopeptides containing standard *N*-Phth and ester groups retain their constitutional and stereochemical integrity. *trans*-2-Hydroxycinnamic acid has been investigated as a photolabile protecting group for amines.⁴⁶ Photolysis (low intensity 4 W lamp, 365 nm) of derived amides results in quantitative cleavage *via trans* to *cis* isomerisation and 6-*exo*-trig



Scheme 7

lactonisation. Secondary amides are cleaved more slowly than primary amides and in both cases the addition of a trace of acid to the organic solvent (*e.g.* MeOH–AcOH, 70:1) is essential to assist lactonisation. The free phenol present in this protecting group was noted as a limitation but presumably this could be orthogonally protected if necessary.

Allyl based protection strategies for the synthesis of peptides are attractive alternatives to Boc and Fmoc strategies for both solid and solution phase peptide synthesis, particularly of sensitive glyco-, nucleo-, and sulfopeptides, due to the extremely mild nature of the palladium catalysed deprotection conditions. This strategy has now been further refined for large-scale solution phase synthesis exploiting the chemoselective deprotection of *N*-allyloxycarbonyl-*O*-dimethylallyl- α -amino esters with a water soluble Pd⁰ catalyst generated *in situ* from Pd(OAc)₂ and triphenylphosphinotrisonate sodium salt (TPPS) with diethylamine as allyl scavenger.⁴⁷ Care however needs to be taken to avoid *N*-terminal diketopiperazine (DKP) formation. This problem has been addressed in the context of allyl based solid phase protection strategies by employing phenyltrihydrosilane (PhSiH₃) as a neutral, non-nucleophilic allyl scavenger.⁴⁸ The allyloxycarbonyl group (Alloc) has also been shown to be a useful orthogonal protection group for the indolic nitrogen of tryptophan (preventing oxidation during global phosphorylation) during Fmoc–Bu^t solid phase synthesis providing the Fmoc groups are removed using DBU.⁴⁹ C-terminal incorporation of α -trifluoromethyl substituted amino acids into Fmoc peptide acyl fluorides *via in situ* deprotection of *N*-(trimethylsilyl)ethoxycarbonyl (Teoc) derivatives using tetraethylammonium fluoride in acetonitrile at 50 °C has been described.⁵⁰ α -Trifluoromethyl amino acids are notoriously non-nucleophilic at the α -nitrogen and this coupling is proposed to proceed *via* the ‘mixed anhydride’ of the Fmoc protected peptide and the Teoc derived carbamic acid. This subsequently extrudes CO₂ (Scheme 8).



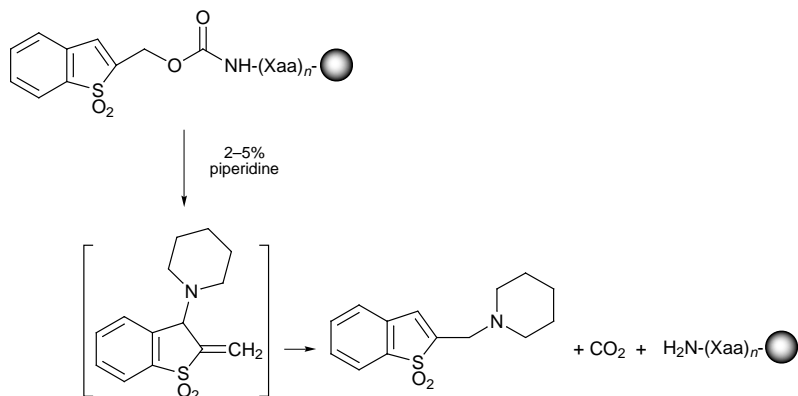
Scheme 8

Since all the α -trifluoromethyl amino acids used in this study were racemic the configurational integrity of the α -trifluoromethyl residue during coupling could not be ascertained. The *p*-nitrobenzyloxycarbonyl group (PNZ) has been utilised in syntheses of β -GlcNAc terminating glycosides as an efficient participating group in the stereoselective formation of the 2-amino- β -glucosidic linkage and as an *N*-protecting group which can be removed either by hydrogenolysis or by reaction with dithionite under neutral conditions.⁵¹ Lewis acid mediated deprotection of Boc groups is well established but improved methods for their clean removal using boron trifluoride etherate in dichloromethane and for the deprotection of *N,N'*-bis(*tert*-butoxycarbonyl) protected guanidino groups using tin(IV) chloride have been reported.^{52,53}

Interestingly, *N*-silylated carbamates (*e.g.* *N*-Boc-*N*-TMS aliphatic, benzyl and amino acids) are readily formed from the corresponding primary carbamates using silyl triflates, are generally stable to silica chromatography and provide a useful method for the temporary protection of the carbamate NH.⁵⁴ Base sensitive carbamates such as Fmoc owe their reactivity to facile β -elimination. The β -elimination side-product, dibenzofulvene, is usually trapped out but occasionally this proves problematic. A new type of urethane protecting group, the 1,1-dioxobenzo[*b*]thiophen-2-ylmethyloxycarbonyl group (Bsmoc) has been introduced as an alternative protecting group for solution and solid phase peptide segment synthesis which circumvents this limitation.⁵⁵ This group owes its base sensitivity to an ingenious Michael-type addition process whereby the deblocking event is simultaneously a scavenging event (Scheme 9).

A variety of nucleophiles were investigated: piperidine was preferred for solid phase synthesis, whilst tris(2-aminoethyl)amine (TAEA) gave a water soluble side product making this the nucleophile of choice for solution phase work. The Bsmoc group was compatible with acyl fluoride and *in situ* ammonium or phosphonium salt based coupling methods and being UV active allows for accurate tracking and quantitation. The Bsmoc group is more sensitive to piperidine than Fmoc, is stable to tertiary amines [pyridine, diisopropylethylamine (DIEA), hydroxybenzotriazole (HOBt)-DIEA], stable to neat TFA or saturated HCl in EtOAc (but not HBr in AcOH), but is rapidly cleaved by thiols.

Sulfonamide protection of amines has traditionally been plagued by their problematic deprotection in highly functionalised, sensitive substrates. However, in recent



Scheme 9

years a number of sulfonamide protecting groups which are amenable to mild deprotection have been developed. Samarium iodide (SmI_2) has become widely used for selective arylsulfonamide deprotection particularly of amino sugars.⁵⁶ 2,4-Dinitrobenzenesulfonamides are readily deprotected using excess *n*-propylamine (20 equiv.) in dichloromethane at ambient temperature or more conveniently using $\text{HSCH}_2\text{CO}_2\text{H}$ (1.3 equiv.) and triethylamine (2 equiv.) whereby the side-product, 2,4-dinitrophenylthioacetic acid can be easily removed by washing with aqueous NaHCO_3 .⁵⁷ This year a new sulfonamide analogue of the Boc group, *tert*-butylsulfonyl (Bus) has been introduced which is stable to strong metallation conditions but readily cleaved using 0.1 M triflic acid in dichloromethane.⁵⁸ Introduction of this group requires a two step procedure, employing *tert*-butylsulfinyl chloride followed by oxidation (*m*-CPBA or $\text{RuCl}_3\text{-NaIO}_4$) since *tert*-butylsulfonyl chloride is unreactive and unstable. The group is stable towards $\text{Bu}^\oplus\text{Li-TMEDA}$, 0.1 M HCl-MeOH , 0.1 M $\text{TFA-CH}_2\text{Cl}_2$ and pyrolysis neat at 180 °C for 3 h. Selective deprotection of Bus groups from secondary amines in the presence of primary amines (using triflic acid) is possible although the origin of this selectivity is unclear.

The vinyl group has been reported to be an efficient and economical group for the protection of azole nitrogens in simple heterocyclic systems (*e.g.* imidazole).⁵⁹ Protection is a one-pot, two step process involving heating first with 1,2-dibromoethane- Et_3N , then aqueous NaOH to effect elimination and removal involves treatment with ozone in MeOH at -78°C in the presence of dimethylsulfide. A methylene 'bridge' between the N-1 nitrogens of two 1,2,4-triazoles has also been advocated as a simple but effective protecting group during selective 4-alkylation.⁶⁰ The 2-adamantylloxymethyl group (2-Adom) has been utilised for imidazole protection of histidine during peptide synthesis.⁶¹ $\text{Boc-His(N}^\pi\text{-2-Adom)-OH}$ is prepared from $\text{Boc-His(N}^\pi\text{-2-Boc)-OMe}$ by treatment with 2-adamantylloxymethyl chloride followed by saponification (NaOH). The group is stable to TFA, 1 M NaOH , and 20% piperidine-DMF and easily removed by 1 M trifluoromethanesulfonic acid-thioanisole or anhydrous HF. The *o*-nitrobenzyl group has been shown to function as a reasonably efficient photocleavable protecting group for indoles, ben-

zimidazoles and 6-chlorouracil.⁶² The 1-thiophenylbenzyl group has been introduced as a β -lactam protecting group during the synthesis of *N*-unsubstituted β -lactams by [2 + 2] cycloaddition.⁶³ Deprotection is *via* oxidation using potassium persulfate. The monomethoxytrityl group (MMTr) is frequently employed for alcohol protection in nucleoside chemistry but its utility as an amino protecting group is often overlooked. A rare instance of this group's utility in this capacity is its application for the protection of a lysine side chain during the synthesis of complex cathespin B-sensitive maleimidocaproyl-Phe-Lys linked prodrugs. The favourable solubilising properties conferred by the lipophilic MMTr unit were noted.⁶⁴

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