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Solid-Phase Organic Chemistry: Linkers and Functionalized Solid Supports

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Abstract. Since 1994, the quantity of papers published in the field of solid-phase organic chemistry has been growing almost exponentially. The scope of the existing peptide and oligonucleotide methodology has been greatly extended to accommodate those compound classes of interest to medicinal chemists. New polymer-bound linkers and functionalized resins have been developed to improve the versatility of the approach and to facilitate the preparation of molecules not accessible with existing technologies.

1. Introduction

From the pioneering efforts of *Merrifield* [1] and *Letsinger* [2] in the early sixties, solid-phase synthesis has developed to become the standard technique for the preparation of peptides and DNA. However, despite the work of scientists such as *Leznoff* [3], *Patchornik* [4], *Rapoport* [5] and *Frechet* [6] in the early seventies, this approach did not gain wide acceptance in the general arena of organic synthesis. This situation has changed dramatically over the last decade. With the introduction of high-throughput-screening methods, enormous pressure has been put on synthetic organic chemists to find ways of accelerating lead-compound production. This demand has led to an explosion of interest in combinatorial and parallel synthesis [7], which has in turn stimulated developments in solid phase organic chemistry [8] and allied analytical techniques [9], and in parallel chemoselective purification [10]. Nowadays, combinatorial and parallel-synthesis techniques are not only used in drug discovery but also in such diverse areas as material science, cosmetics, catalysis, and plant protection.

This interest in solid-phase organic synthesis has generated tremendous demands for new solid supports and linkers as chemists continually strive to broaden the range of molecule classes that can be produced by these techniques. In this paper, we give an overview of the commonly-used functionalized resins and solid-supported linkers and summarize how they can be used in organic chemistry to prepare a diverse range of compounds.

2. Solid-Phase Synthesis

For high-throughput chemical synthesis, the solid-phase approach has several attractions:

a) The technique is highly amenable to automation, enabling many compounds to be prepared simultaneously in parallel reactors [11].

b) Reactions can be driven to completion through the use of excess reagents. Soluble byproducts and excess reagents can be easily washed away by filtration of the resin [12][13].

c) The solid support can be used to monoprotect bifunctional symmetrical molecules in such a way that the compound of interest can be fished out of a complex mixture of reactants or from excess unreacted starting material [14]. This procedure, called the fishhook principle, can be exploited to allow selective modification of bifunctional molecules.

d) Reactions which exhibit poor chemoselectivity in solution can often be directed to give only the desired compound by attachment of the appropriate component to the solid support [15].

e) Reaction schemes can often be designed in such a way that the final step releases only the desired product from the support, with incorrectly assembled intermediates remaining attached to the resin [16].

f) By applying split-and-mix techniques [17] (also called portioning and mixing [18] or divide, couple and recombine [19]) libraries can be rapidly synthesized containing from tens to millions of individual components.

Many of these principles are illustrated by *Kurth*'s elegant solid-phase tetrahydrofuran synthesis [16] (see *Scheme 1*): the fish-hook principle was utilized to direct the [3+2] addition of the nitrile oxide to one of the two double bonds of the diene; since only the isoxazoline can be converted in the final cleavage step to the tetrahydrofuran, the side-products formed during the reaction sequence remain attached to the support.

Solid-phase synthesis does, however, have a number of limitations: heterogeneous reactions are difficult to perform; the kinetics of reactions on the solid phase are likely to be different from those in solution; reaction conditions optimized for solution synthesis often have to be adapted to solid-phase synthesis, due to restrictions in the use of certain solvents and reagents; solid-phase synthesis requires

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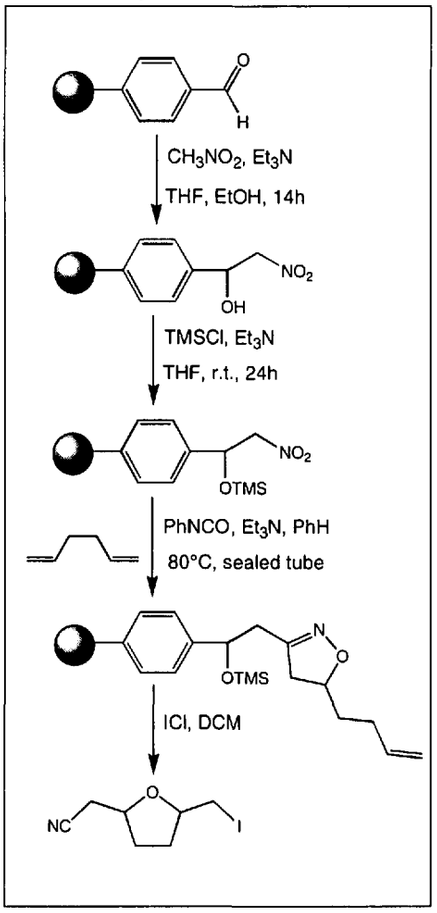
Scheme 1. *Solid-Phase Synthesis of 2,5-Disubstituted Tetrahydrofurans* [16]



the attachment of the starting material and release of the product from the solid support, which can sometimes add two extra steps.

3. Solid Supports

The solid matrices most frequently used in solid-phase synthesis are polystyrene (PS), crosslinked with 1 or 2% divinylbenzene, and PEG-PS (PEG: polyethyleneglycol) [20].

For routine synthesis, cross-linked 1%-DVB polystyrene is the preferred support, with the 2% cross-linked material generally being reserved for reactions involving high temperature and organometallic reagents. Polystyrene resins are less expensive and have a higher loading capacity than PEG-PS resins but do not swell in polar solvents such as methanol, water and acetonitrile, which somewhat limits their utility. The crosslinked PS resins are mechanically more stable than their PEG-PS counterparts.

There are three types of PEG-PS resins commercially available: *TentaGel* **1**, *NovaGel* **2**, and *ArgoGel* **3** (*Fig.*). These

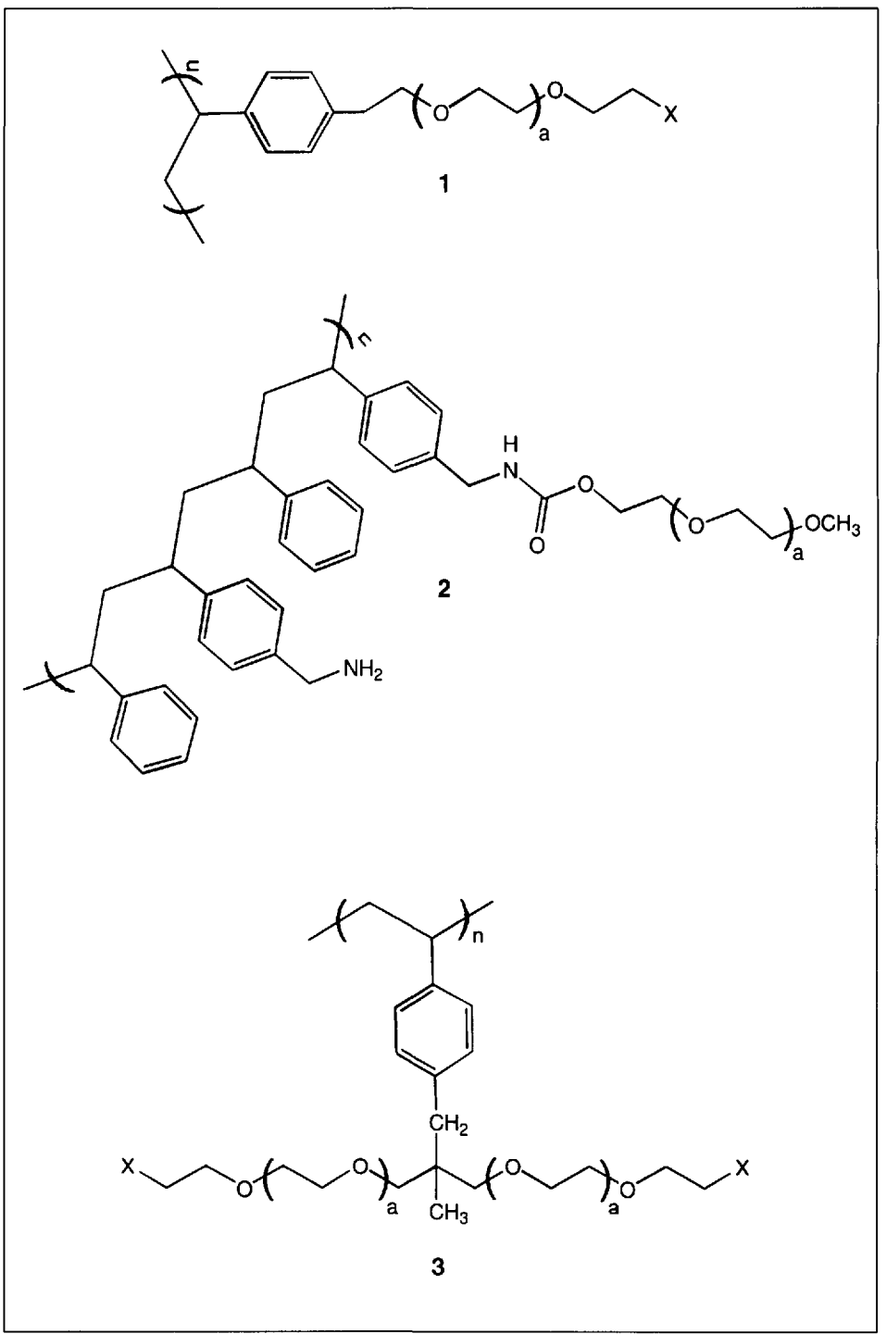


Figure. *PEG-PS copolymers: TentaGel* **1**, *NovaGel* **2**, *and ArgoGel* **3**; *X = functional group*, e.g., *$-NH_2$, –OH, or –Br*

Scheme 2. *Classification of Functionalized and Linker-Derivatized Resins in* A *(as protecting groups) and in* B *(as reagents)*

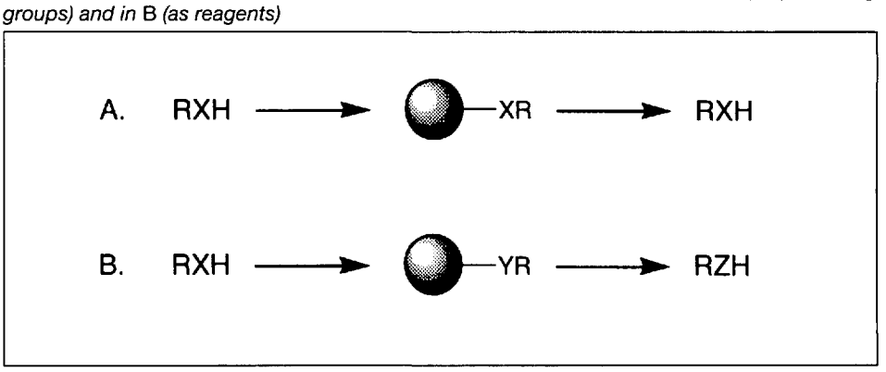
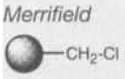
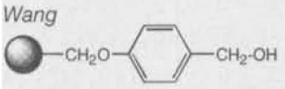
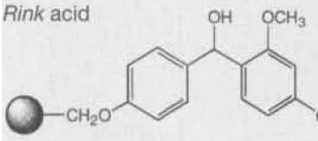
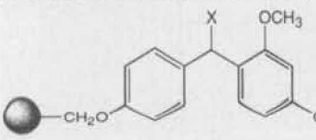
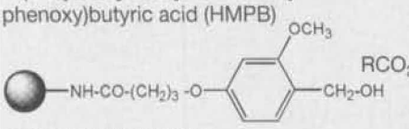
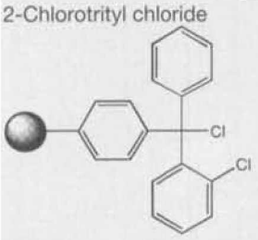
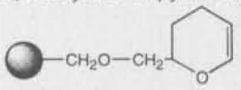
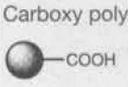
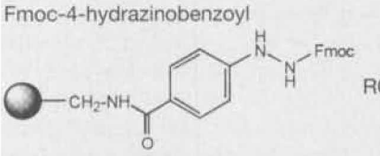
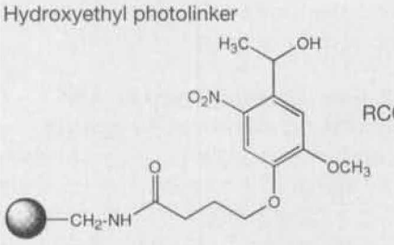
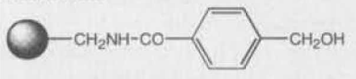
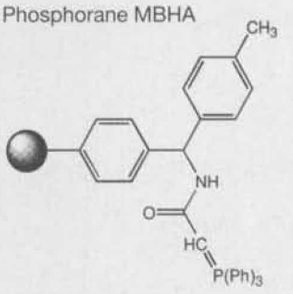
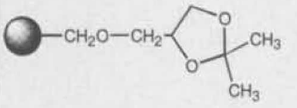
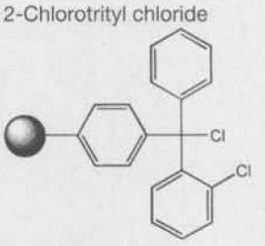
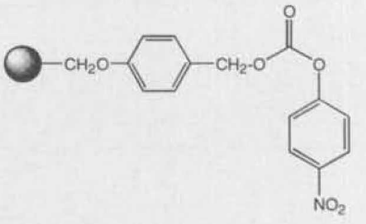
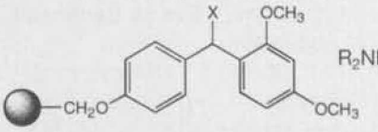
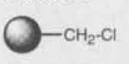
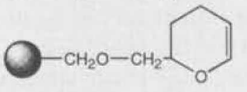
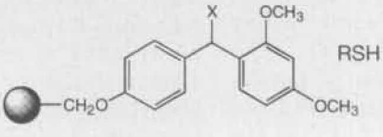


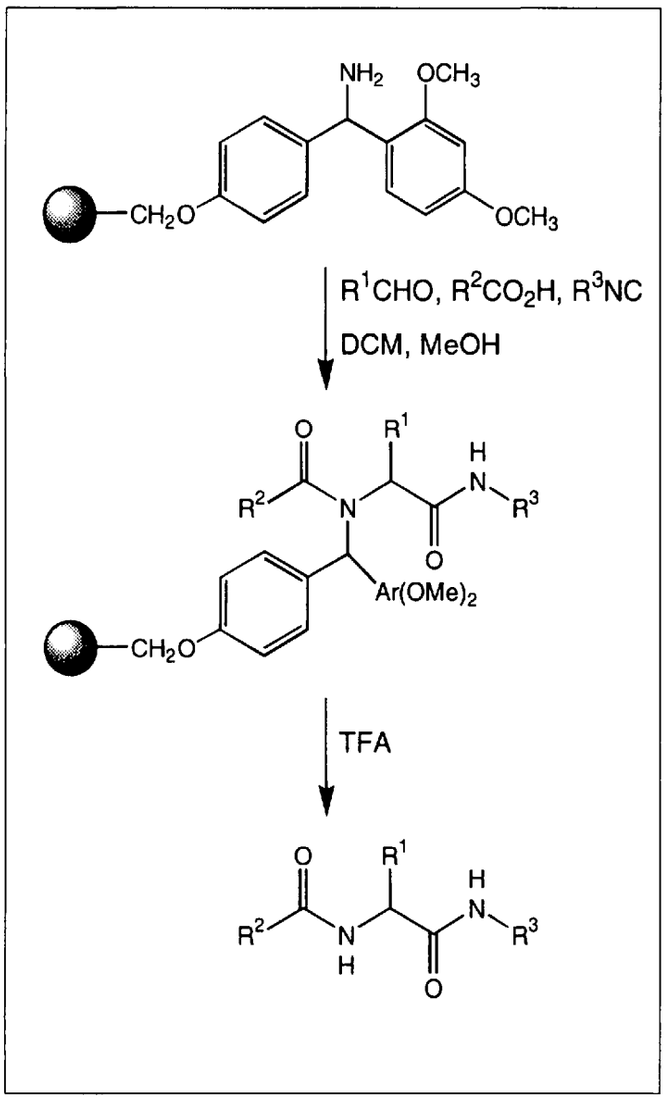
Table 1. *Functionalized and Linker-Derivatized Resins as Protecting Groups*

Functional Group/Linker	Attached Group = Leaving Group	Cleavage
Products: Carboxylic Acids/Alcohols		
Merrifield 	RCO_2H	TFMSA, HF, H_2/Pd [26]
Wang 	RCO_2H ROH	TFA [27] TFA [28]
Rink acid 	RCO_2H	10% AcOH in DCM [29]
Rink trifluoroacetate or *Rink* chloride 	ROH[a]	TFA [30–32]
4-(4-Hydroxymethyl-3-methoxy-phenoxy)butyric acid (HMPB) 	RCO_2H	1% TFA in DCM [33]
2-Chlorotrityl chloride 	ROH[a]	1–5%TFA in DCM [34]
3,4-Dihydro-2*H*-pyran-2-methoxymethyl (DHP) 	ROH	TFA/H_2O [35] TFA/DCM/EtOH [36]
Carboxy polystyrene 	ROH	K_2CO_3, 1:2 MeOH/THF [37][38] $(nBu)_4NOH$/THF [39] NaOMe, 4:1 THF/MeOH [38]
Fmoc-4-hydrazinobenzoyl 	RCO_2H	i. O_2, Cu (II) acetate ii. H_2O, DBU [40]
Hydroxyethyl photolinker 	RCO_2H	*hν* [41]
HMBA AM 	RCO_2H	aq. NaOH [12]

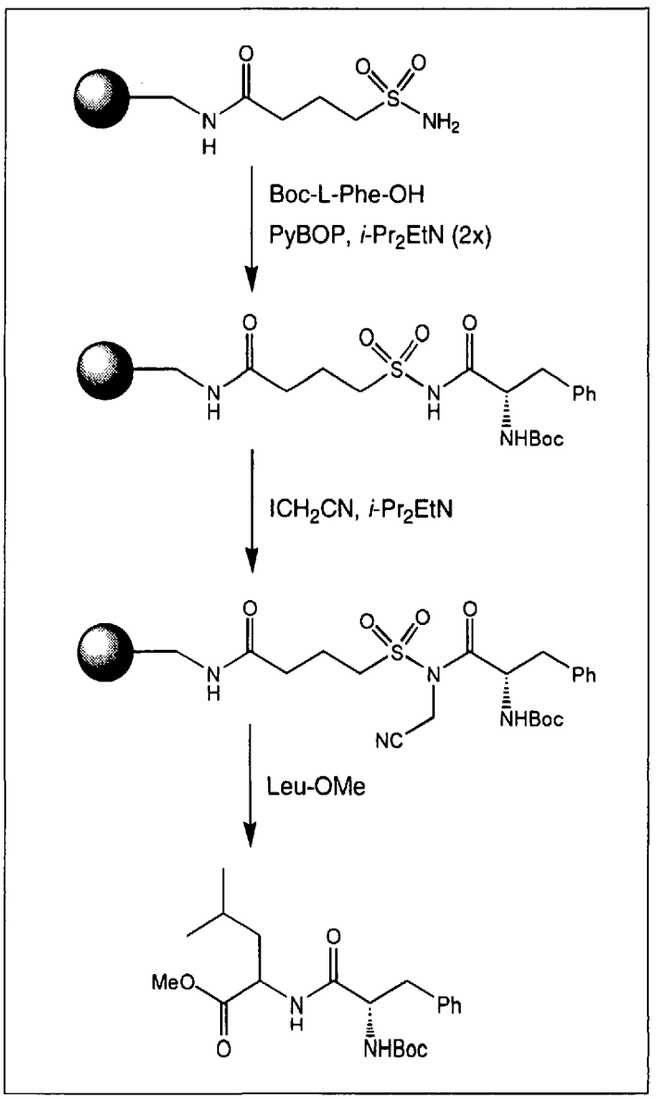
Functional Group/Linker	Attached Group = Leaving Group	Cleavage
Products: Aldehydes		
Phosphorane MBHA 	RCHO	O_3, DCM, −78° [42]
(±)-1-(2,3-Isopropylidene)glycerol 	RCHO	aq. HCl/dioxane [43][44]
Products: Amines/Hydrazides		
2-Chlorotrityl chloride 	RNH_2 $RCONHNH_2$	5–20% TFA in DCM [45][46]
p-Nitrophenyl carbonate *Wang* 	RNH_2	TFA [47][48]
Rink trifluoroacetate or *Rink* chloride 	R_2NH, RNH_2	TFA [30][32]
Merrifield 	R^1R^2NH	α-chloroethyl chloroformate (ACE-Cl) [49]
3,4-Dihydro-2*H*-pyran-2-methoxymethyl (DHP) 	Purine (R_2NH)	10% TFA in DCM [50]
Products: Thiols		
Rink trifluoroacetate or *Rink* chloride 	RSH	TFA [30][32]

[a]) ROH represents here also hydroxylamines.

Scheme 3. Rink *Amide Resin Used as Reagent* [23]



Scheme 4. *Solid-Phase Synthesis Using a Safety-Catch Linker* [24]



resins have a much broader spectrum of solvent compatibility than polystyrene supports, swelling in solvents ranging in polarity from toluene to water, and are most often used in applications requiring direct release of the target into aqueous media for screening purposes. Resins **1** and **3** are structurally quite similar, both having the reactive sites located at the ends of the PEG chains. They differ principally in the nature of the linkage between the PEG and the polystyrene matrix: in *ArgoGel*, there are two PEG chains joined through a quaternary carbon, whereas in *TentaGel*, a single PEG strand is grafted directly onto the polystyrene backbone. Resin **2** is prepared by partial derivatization of aminomethyl polystyrene with monomethylated PEG; functionality is provided by residual aminomethyl groups. The loading capacity of this support is approximately twice that of the other PEG-PS supports.

4. Linkers and Their Use in Solid-Phase Synthesis

There are many different ways of classifying linkers (discrete compounds which provide the link between the polymer matrix and the scaffold) and functionalized resins (polymers which have been chemically modified, or prepared by inclusion of functionalized monomers in the polymerization process, to contain reactive sites which can serve as anchor points) [22]. For this discussion, the classification has been made according to whether the linker or the functionalized resin functions simply as a protecting group or as an immobilized reagent (*Scheme 2*).

In the accompanying tables, ● represents the solid support. For functionalized resins, such as trityl, methylbenzhydrylamine (MBHA) or oxime resins, the phenyl ring of the polystyrene backbone is also shown.

4.1. *Functionalized and Linker-Derivatized Resins as Protecting Groups*

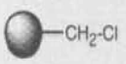
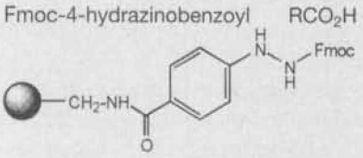
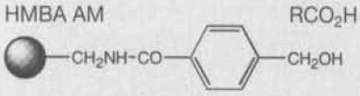
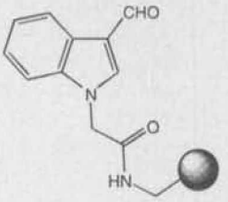
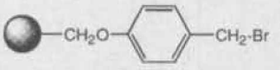
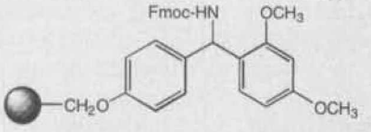
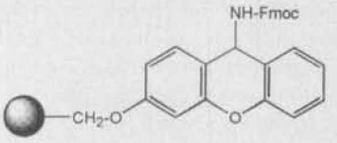
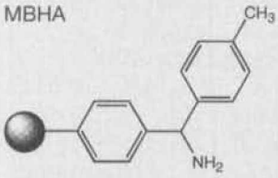
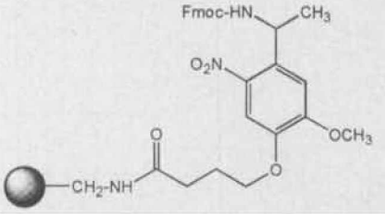
Resins in this class act essentially as insolubilizing protecting groups, *i.e.*, the functional group involved in bonding the starting material to the resin is regenerated upon release of the final product. Frequently used resins of this type are listed in *Table 1*, where they were grouped according to the nature of the functionality anchored to the support.

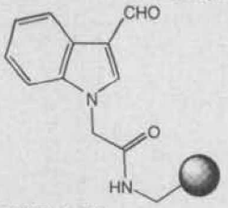
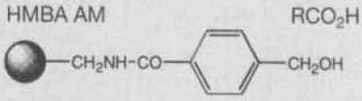
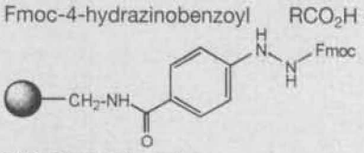
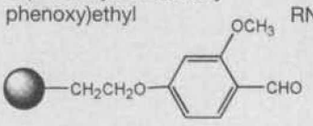
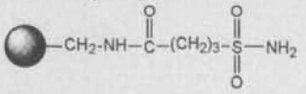
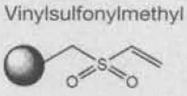
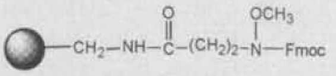
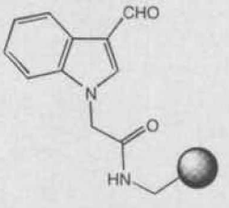
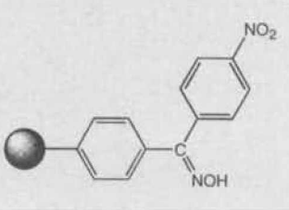
4.2. *Functionalized and Linker-Derivatized Resins as Reagents*

Resins in this class (*Table 2*) behave quite differently compared to those described above; when the bond linking the final product to the resin is cleaved, the functional group released is different from that of the starting resin.

The most commonly used resins of this type are the *Rink* amide resin and the

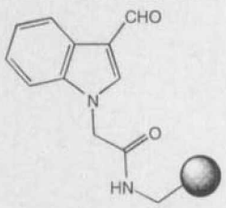
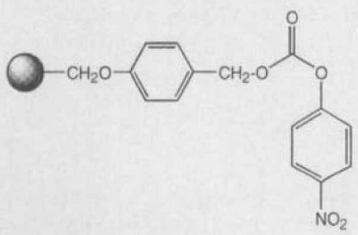
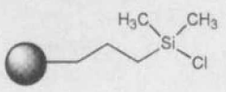
Table 2. *Functionalized and Linker-Derivatized Resins as Reagents*

Functional Group/Linker	Modification Attached Group RX → Leaving Group R^1Y (X,Y=Functional Groups)	Cleavage
Products: Alcohols		
Merrifield 	$RCO_2H \rightarrow R^1CH_2OH$	$LiBH_4$ [51] DIBAL [52]
Products: Esters		
Fmoc-4-hydrazinobenzoyl 	$RCO_2H \rightarrow R^1CO_2Me$	i. Cu (II) acetate [40] ii. MeOH, pyridine
HMBA AM 	$RCO_2H \rightarrow R^1CO_2Me$	MeOH [12][53]
Products: Sulfonamides		
Indole-3-carboxaldehyde 	$RNH_2 \rightarrow R^2SO_2NHR^1$	i. R^2SO_2Cl ii. TFA in DCM [54]
4-(Bromomethyl)phenoxymethyl 	$RNH_2 \rightarrow R^2SO_2NHR^1$	i. R^2SO_2Cl ii. TFA [55]
Products: Amides/Alkylamides		
Rink amide 	$RCO_2H \rightarrow R^1CONH_2$	TFA [29]
Sieber amide 	$RCO_2H \rightarrow R^1CONH_2$	1% TFA in DCM [56]
MBHA 	$RCO_2H \rightarrow R^1CONH_2$	HF, TFMSA [51]
Fmoc-aminoethyl-Photolinker 	$RCO_2H \rightarrow R^1CONH_2$	hν [41]

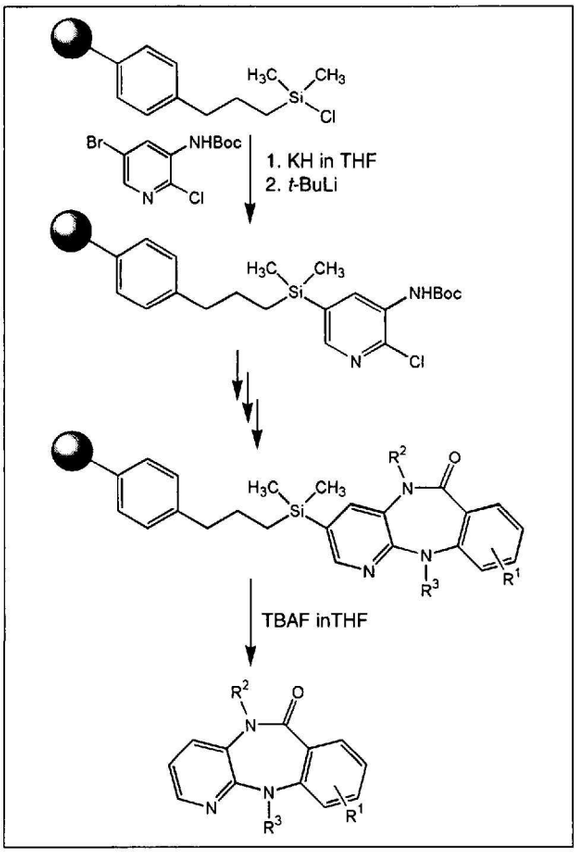
Functional Group/Linker	Modification Attached Group RX → Leaving Group R^1Y (X,Y=Functional Groups)	Cleavage
Products: Amides/Alkylamides		
Indole-3-carboxaldehyde 	$RNH_2 \rightarrow R^2CONHR^1$	i. R^2COA^a) ii. TFA in DCM [54]
HMBA AM 	$RCO_2H \rightarrow R^1CONHR^2$	R^2NH_2 [12]
Fmoc-4-hydrazinobenzoyl 	$RCO_2H \rightarrow R^1CO\ NHPr$	i. Cu (II) acetate ii. H_2NPr [40]
2-(4-Formyl-3-methoxy-phenoxy)ethyl 	$RNH_2 \rightarrow R^2CONHR^1$	i. R^2COA^a) ii. TFA [57] [58]
4-Sulfamylbutyryl 	$RCO_2H \rightarrow R^1CONHR^2$	i. ICH_2CN ii. R^2NH_2 [24]
Product: Substituted Amines		
Vinylsulfonylmethyl 	$R^1R^2NH \rightarrow R^1R^2R^3NH^+X^-$	i. R^3X ii. DIEA/DCM [59]
Product: Ketones		
Weinreb AM 	$RCO_2H \rightarrow R^1COR^2$	R^2MgX [60]
Product: Ureas		
Indole-3-carbaldehyde 	$RNH_2 \rightarrow R^2NHCONHR^1$	i. R^2NCO ii. TFA in DCM [54]
Oxime 	$RNCO \rightarrow R^2R^3NCONHR^1$	R^2R^3NH, toluene, 75° [61]

[a]) A represents an activating group.

Table 2 (Cont.). *Functionalized and Linker-Derivatized Resins as Reagents*

Functional Group/Linker	Modification Attached Group RX → Leaving Group R¹Y (X,Y=Functional Groups)	Cleavage
Product: Guanidines		
Indole-3-carbaldehyde 	RNH_2 → $R^1NHC{=}NH(NH_2)$	i. $(BocNH)_2CS$, DIC i. ii. TFA in DCM [54]
Product: Methylamines		
p-Nitrophenyl carbonate *Wang* 	$R^1R^2NH \rightarrow R^1R^2NCH_3$	$LiAlH_4$ [62]
Product: Substituted Arenes		
Chlorodimethylsilylpropyl 	ArLi → ArH	TBAF in THF [25]

Scheme 5. *Traceless Synthesis Using a Silyl Linker* [25]



MBHA resin. In *Scheme 3*, the *Rink* amide resin functions as an insoluble ammonia equivalent [23].

Other types of supports, such as those derivatized with safety-catch and traceless linkers, also fall into this category. A safety-catch linker is one which must be chemically activated in a separate reaction step before cleavage can take place. *Ellman*'s sulfamylbutyryl linker is a typical example (*Scheme 4*) [24]. The *N*-acylsulfonamide is not susceptible to nucleophilic attack unless activated by treatment with iodoacetonitrile.

The term traceless is used to describe any linker or resin which leaves no trace or artifact of its original point of attachment in the product. This principle is illustrated by the example given in *Scheme 5* [25].

Many supports can, of course, be placed in both categories, depending on the nature of the cleavage reaction. For instance, carboxylic acids attached to 4-(hydroxymethyl)benzoic acid aminomethyl (HMBA AM) resin can be released with aqueous NaOH (see *Table 1*), whereas treatment of the same resin with ammonia, hydrazine or a primary amine, generates the corresponding primary amide, hydrazide or *N*-alkylamide.

5. Conclusion

To date, the vast majority of solid-phase organic chemistry has been performed on linkers and functionalized resins related to those originally designed for use in peptide synthesis. A lot of effort is currently undertaken to broaden the range of linkers and functionalized resins bearing new scaffolds (*e.g.*, thiols, guanidines).

Emphasis will continue to be placed on the development of linkers that serve not only to immobilize the scaffold to the resin but also participate in functional-group transformation during the cleavage step. The range of mechanisms by which product release is achieved will broaden considerably. One can expect to see more examples of cleavage by reduction, oxidation, elimination, metathesis and nucleophilic displacement. Linkers that cleave under mild conditions releasing the product directly into aqueous solution are also likely to be the subject of future developments.

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