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Review

N-Acyl-*N*-alkyl-sulfonamide anchors derived from Kenner's safety-catch linker: powerful tools in bioorganic and medicinal chemistry

Philipp Heidler and Andreas Link*

Faculty of Pharmacy, Philipps-University Marburg, Marbacher Weg 6, D-35032, Germany

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Abstract—In 1971 Kenner et al. introduced the safety-catch principle into solid phase peptide synthesis. Thus two contradicting needs were addressed. On the one hand, sufficient stability of the linker substrate bond to impede hydrolysis or similar side reactions, on the other hand mild chemical conditions allowing for unscathed liberation of the precious products. Over the years this linker type emerged in several different chemical disciplines and nowadays it presents a useful and broadly applicable tool. Recent advancements and applications based on Kenner's safety-catch linker are reviewed.

Contents

1. Introduction

When he invented dynamite, Alfred Nobel essentially managed to meet two contradicting needs. A successful explosive needs to be safe to store and handle but concurrently highly dynamic and utterly destructive when required. The legendary solution to this quandary could be compared to the ingenious development of a safety-catch linker by George W. Kenner in 1971.[1]

Since Merrifield introduced the term solid phase peptide synthesis (SPPS) in 1963,[2] the strategic integration of

* Corresponding author. Tel.: +49 06421 282 5900; fax: +49 06421 282 5901; e-mail: link@mailer.uni-marburg.de

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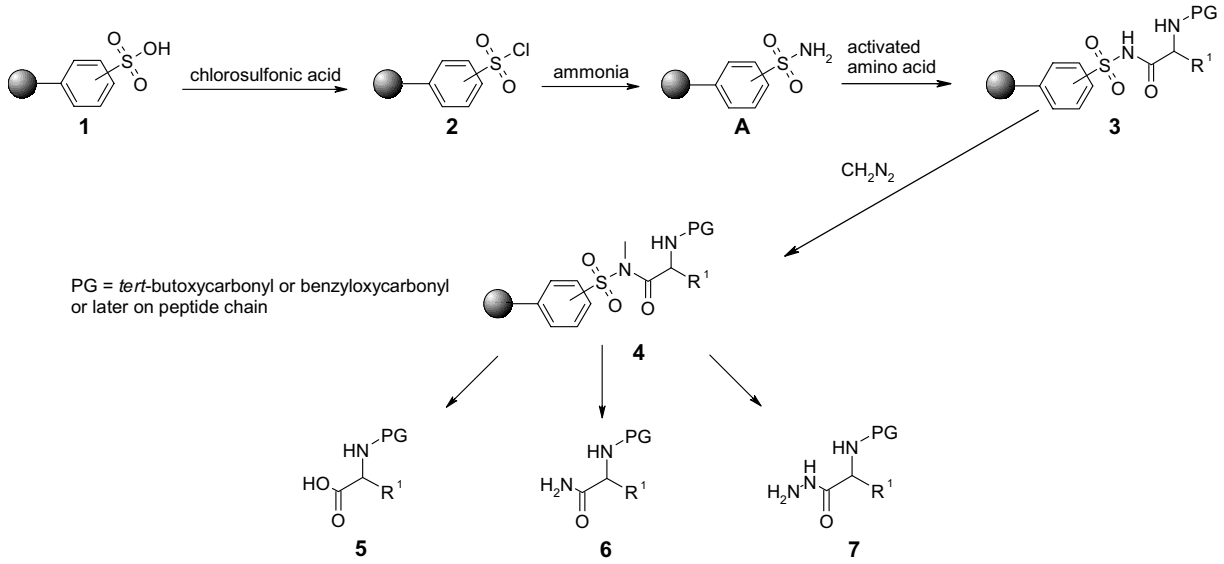
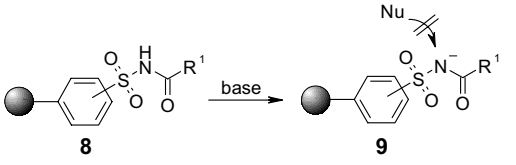


Scheme 1. Original preparation and use of the Kenner safety-catch linker **A**.

synthesis and purification is now widely recognized as a prominent advantage of the use of polymeric supports or other solubility-control auxiliaries in organic synthesis. Yet, the mild and selective removal of products from these temporarily attached solubility-modifying groups is an important prerequisite for the successful SPPS and solid phase organic synthesis (SPOS). Therefore, an anchor group in SPPS or SPOS should be stable under a wide range of reaction conditions and be able to withstand attack by nucleophiles or protons. Simultaneously, the linker must allow mild cleavage conditions at the end of a given synthetic sequence, to neither destroy product nor to lose material by incomplete removal from the support used. Due to the chemical discrepancy of the repeated acidic conditions necessary for protecting group removal of the amino acid building blocks, and the simultaneously demanded mild acidic conditions to cleave the final peptides from the solid support in the Merrifield solid phase peptide synthesis approach, a way out of this antagonism was highly demanded. Using *N*-acyl-*N*-alkyl-sulfonamides, Kenner solved this problem most elegantly by attaching the growing peptide chain to a sulfonamide anchor via an acyl sulfonamide functionality. In the beginning, Kenner et al. demonstrated the preparation of several small peptides on polystyrene beads (dipeptides to heptapeptides), being attached and assembled on polymer bound sulfonamides (Scheme 1). Cleavage with ammonia, hydrazine or hydroxide led to the corresponding amides, hydrazides or free carboxylic acids, respectively.

Starting with highly sulfonated polystyrene–2% divinylbenzene copolymer (**1**), a standard strongly acidic ion exchange resin, successive treatment with chlorosulfonic acid and aqueous ammonia led to the polymer bound sulfonamides **A**. In a next step, 2,4,5-trichlorophenyl activated amino acids were coupled onto the sulfonamide functionality yielding *N*-acyl-sulfonamides **3**. These are chemically resistant against alkaline hydrolysis, since basic attack ionizes the acidic NH-group (**9**),



Scheme 2. A 'safe' status of the *N*-acyl-sulfonamide.

and also against acidic attack with trifluoroacetic acid or hydrogen bromide in acetic acid (Scheme 2). The corresponding *N*-acyl-*N*-alkyl-sulfonamides (in the case of Kenner et al. *N*-methyl through alkylation with diazomethane) **4** lose the ability of ionization, the resulting stability in basic or acidic media is lost.

Thus, after N-alkylation, nucleophiles may displace the acyl moiety of the polymer bound *N*-acyl-*N*-alkyl-sulfonamides **4** through nucleophilic attack on the carbonyl carbon. This basic concept of Kenner's safety-catch linker is preserved till today, further modifications regarding the linker,[3–5] activation methods,[4,6] coupling conditions[7] etc. allow for a versatile and widespread use of this linker in both peptide and organic synthesis.

2. Use in classical peptide synthesis

2.1. Synthesis of peptides and peptide derived compounds

The originally intended use of the Kenner safety-catch linker **A** for the preparation of simple peptides never became a widespread application due to the striking disadvantages, such as for example poor loading efficiencies and low reactivity in comparison to other well-known standard linkers (e.g., Wang) in SPPS. Therefore the published applications of **A** in relation to peptide synthesis are scarce and served more or less only as proof of principle. Adding to the initially prepared peptides in 1971,[1] the group of Ellman published the

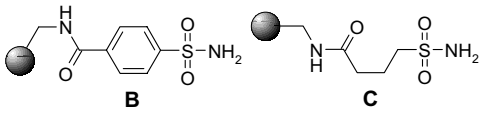


Figure 1. Modifications of the Kenner-linker developed by Ellman and co-workers.

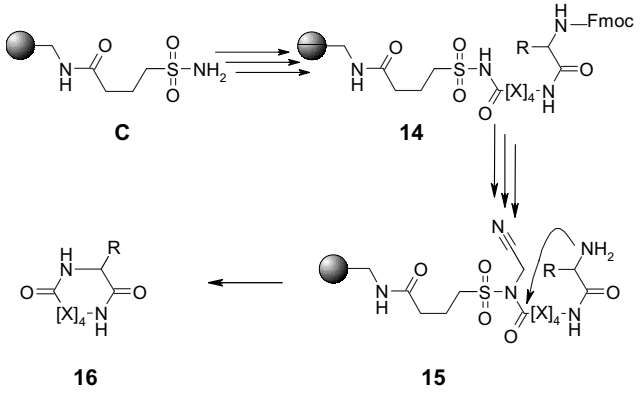
synthesis of a set of small peptides with the objective of pointing out a more detailed and carefully optimized procedure (see Section 4.2) in 1999 of preliminary results presented in 1996.[4] In addition to a new activation method with haloacetonitriles (bromo- and iodoaceto nitrile), two advanced options to obtain polymer bound sulfonamides (Fig. 1) **B** and **C** using aminomethylated polystyrene acylated with 4-sulfamoylbenzoic acid and 3-carboxypropane sulfonamide, respectively, were introduced.

Furthermore, coupling procedures for *N*-Boc as well as for *N*-Fmoc protected amino acids were presented by the same group. In the following years these coupling conditions and upgraded linkers many a time served for the preparation of cyclic peptides (compare Section 2.2), thioesters (compare Section 2.3) or peptide derived compounds. First mentioned in 1999 by Backes and Ellman[5] and a year later applied in somewhat greater extend by Sheppeck et al.[8] and Backes et al.,[9] fluorogenic peptide substrates were successfully prepared utilizing the Kenner safety-catch linker variant **C** (further discussed in Section 3.4). In the same year Overkleeft et al.[10] applied the modified Kenner linker for the preparation of peptide vinyl sulfones and peptide epoxyketones. Li et al.[11] successfully assembled some functionalized hexapeptides **13** (Scheme 3) and described limitations regarding the displacing nucleophile. Hindered amines such as dibenzylamine did not react in the desired direction. In 2001 Copeland and Miller[12] followed up an elegant concept to prepare a directed library of peptides with certain catalytical properties. Through co-functionalization of the beads with a permanent noncleavable linker in addition to the Kenner safety-catch linker, peptides could be released directly into multi-well plates and therefore allowed for single bead screening under homogeneous conditions. In 2002 Fattori et al.[13] prepared hairpin polyamide peptide conjugates using the modified Kenner safety-catch linker **C** and Tang and Ellman[14] synthesized β-peptides applying *tert*-butanesulfinyl protecting groups. One year later in 2003 Tamamura et al.[15] were able to prepare a set of C-terminal *N*-alkylamides.

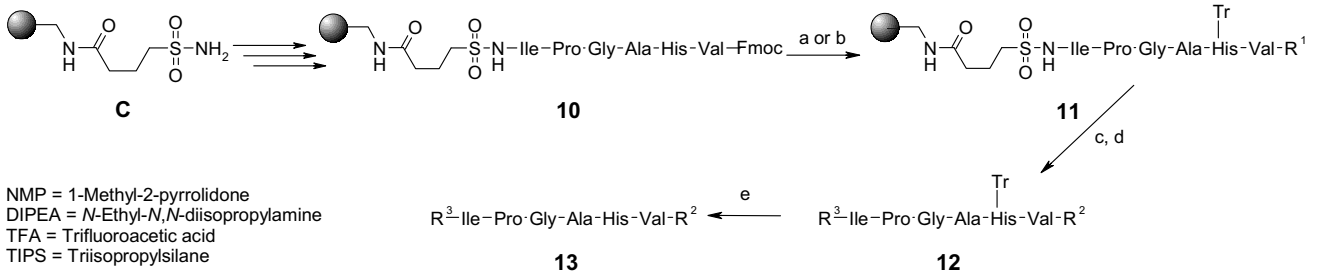
2.2. Cyclative cleavage yielding head-to-tail peptides

Cyclic peptides are important target molecules in peptide synthesis. In comparison to their linear counterparts, cyclic peptides demonstrate constrained conformations, in many cases inter alia increased receptor affinity/selectivity and metabolic stability. Yet the synthetic quandary for the preparation of cyclic peptides using Fmoc-protecting groups on solid phase originates in the need for stability of the linkage against the nucleophile piperidine, required for Fmoc removal, and lability against the amino function of the N-terminus at the end of the sequence at the same time. Until 1999 known methods afforded side chain anchorage, cyclization after cleavage or were not compatible with well established and optimized Fmoc-chemistry. Yang and Moriello[16] introduced a well-designed strategy for the preparation of head-to-tail peptides utilizing the Kenner safety-catch linker **C** (Scheme 4).

Combining the cleavage step with the cyclization of the amino acid chain in the last step of their synthesis, cyclic peptides could be synthesized in a comparably facile



Scheme 4. Cyclative cleavage yielding head-to-tail peptides according to Yang and Moriello.



Scheme 3. Synthesis of C-terminal N-substituted amide peptides according to Li et al. (R^1 = *N*-Boc, Tr = Trityl; (a) for R^2 = isovaleryl, acetyl or succinyl: 20% piperidine in NMP, isovaleryl chloride or acetyl chloride or succinic anhydride; DIPEA in NMP; for R^2 = H; (b) 20% piperidine in NMP, Boc_2O, DIPEA in NMP; (c) iodoacetonitrile, DIPEA in dry DMF, overnight; (d) R^3–NH_2 in THF, 4 h; (e) TFA/TIPS/DCM (5:5:90), 30 min).

fashion. After the assembly of the linear peptide **14** on solid phase through Fmoc chemistry, the N-terminal amino function was reprotected with a trityl group to ensure stability during the alkylation step with iodoacetonitrile. Consecutive activation and deprotection led to the primary amino function. The peptide could be displaced from the solid support through intramolecular nucleophilic attack of the N-terminal amino function yielding cyclic peptides **16** (in the referred case cyclo hexapeptides, e.g., seglitide).[16]

This approach represented a comparably convenient alternative for the preparation of cyclic peptides and was employed several times in the following years for the preparation of cyclic peptide antibiotics.[17–19]

2.3. Use for the preparation of thioesters for peptide ligation

Since the invention of peptide synthesis via native chemical ligation, the demand for possible amino acid thioester syntheses increased dramatically. Utilizing standard SPPS approaches, the high susceptibility of a direct thioester bond between the peptide fragment and the polymer to nucleophiles such as piperidine excluded the use of standard Fmoc synthesis protocols. At last in 1999 Ingenito et al.[7] constructed several peptides applying Fmoc protected amino acids using the aliphatic analogue **C** of the Kenner-linker and after activation with iodoacetonitrile the peptide fragment was successfully cleaved with catalytic amounts of strongly nucleophilic sodiumthiophenate. In situ transthioesterification with suitable thiols yielded the desired thioesters. Biancalana et al.[20] applied both linker variants **B** and **C**. Whereas activation with trimethylsilyldiazomethane led to poor yields of the desired thiobenzyl esters, activation with iodoacetonitrile failed completely in the hands of this group. Despite this negative result, this method proved to be a versatile and reliable approach to gain the highly desired thioesters for thio-ligation and enjoys great popularity until now. Pure peptide thioesters,[21–32] phosphopeptide-α-thioesters,[33] C-terminal diphenylphosphinomethanethioesters[34] and glycopeptide-α-thioesters[35–39] could successfully be prepared on solid support to date.

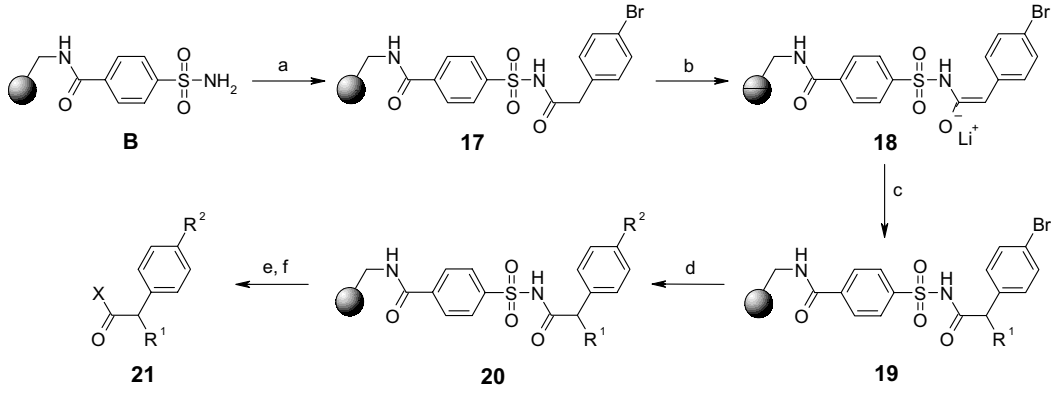
In 2001 Quaderer and Hilvert[40] improved the thioester cleavage reaction proposing the use of LiBr/THF instead of DMF in the cleavage step. It was suggested in this course, that this might aid solubilization and therefore facilitate the cleavage reactions.

3. Versatile use in natural product and diversity-oriented synthesis

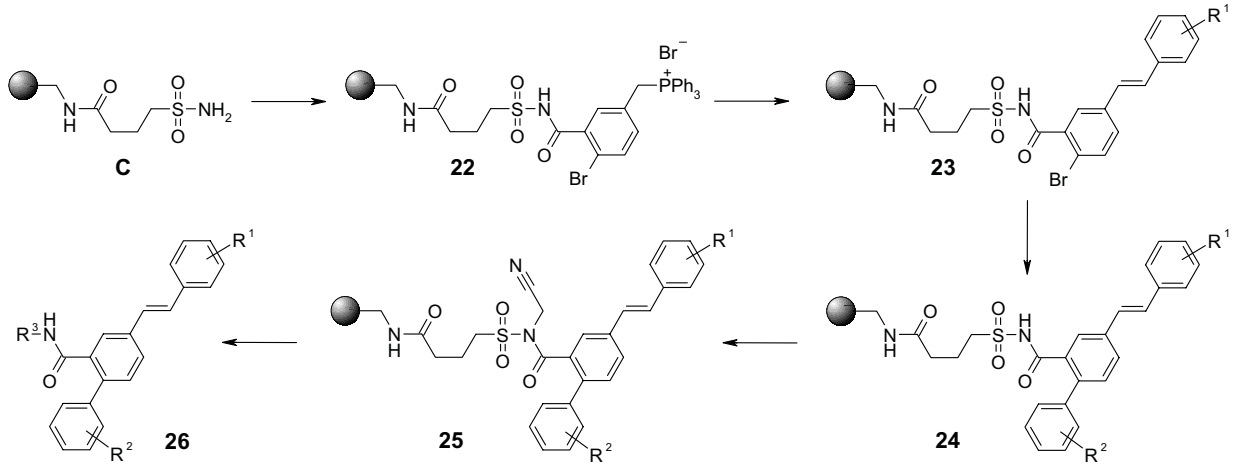
3.1. Application in solid phase organic synthesis

Besides the use of the Kenner-linker for the preparation of thioesters, its application in peptide synthesis is rather limited, as already mentioned. Quite to the contrary, the use of variants of the Kenner linker in SPOS became fairly accepted for the preparation of advanced acylating reagents as well as anchor for solid-phase synthesis of small organic molecules. In 1994 Backes and Ellman[3] successfully demonstrated the use of the Kenner-linker variant **B** in carbon–carbon bond-forming reactions (Scheme 5), such as enolate alkylations and Suzuki cross-coupling for the preparation of a set of cyclooxygenase inhibitors and thereby initiated the renaissance of the Kenner-linker.

Applying the activation methodology introduced by Kenner in 1971, methylation with diazomethane allowed for the use of water, benzylamine and piperidine as displacing nucleophile, whereas the poor nucleophile aniline fails to cleave the acyl-residue from the activated linker. Thus, to enable the application of a broad range of aromatic amines as disconnecting nucleophiles, the reactivity of the *N*-acyl-*N*-alkyl-sulfonamide had to be raised. In order to meet this challenge, Backes et al. pioneered the activation with haloacetonitriles in the following years. Due to the electron withdrawing effect of the cyanomethyl residue, a more activated intermediate could be obtained and paved the way for the use of anilines in the course of the disjointing reaction. In 1999



Scheme 5. A first use of a Kenner-linker (variant **B**) in solid-phase synthesis ((a) pentafluorophenyl 4-bromophenylacetate; DMAP; (b) LDA, THF, 0 °C; (c) alkyl halide, 0 °C; (d) alkyl-9-BBN or arylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, THF, 65 °C; (e) CH_2N_2; (f) HO^- or amine).



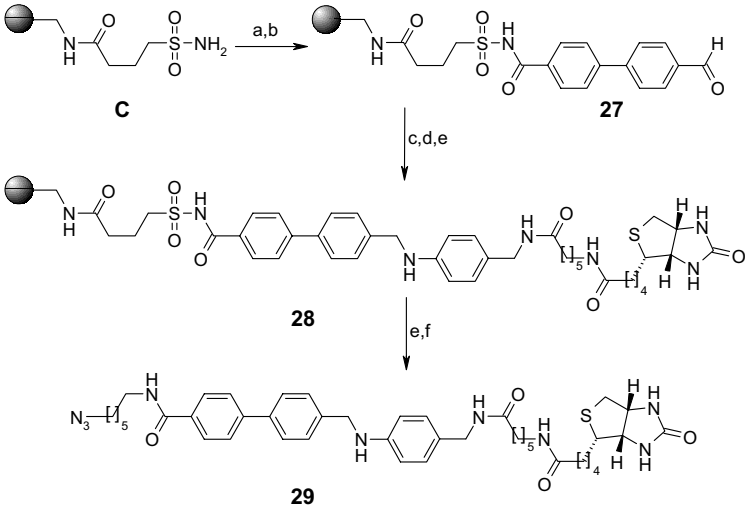
Scheme 6. Schematic outline of the synthetic protocol executed by Lew and Chamberlin.

Lew and Chamberlin[41] added the Wittig-coupling to the synthetic spectrum of the Kenner-linker. Through a succeeding Suzuki cross-coupling reaction, a library of phenylstilbene derivatives could be obtained (Scheme 6).

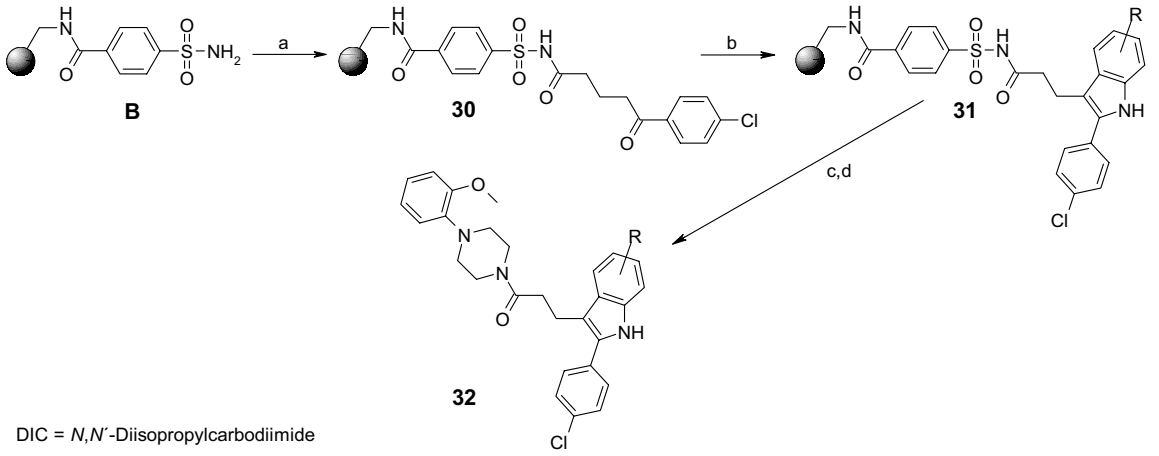
In the course of the preparation of azides **29** as Staudinger ligation substrates in 2003, Köhn et al.[42] performed besides the already described Suzuki cross-couplings, reductive alkylations on solid phase using the modified Kenner-linker **C** (Scheme 7).

Attempts to prepare arylindoles on solid phase using the modified version of the Kenner-linker **C** by Yang[43] failed and resulted in the formation of 2,6-diphenyl-4,5-dihydro-2*H*-pyridazin-3-ones. However in 2001 Cooper et al.[44] established a 2-arylindole synthesis protocol (in dependence on Hutchins and Chapman[45]). Fixation of 4-(4-chlorobenzoyl)butyric acid on **B** and subsequent treatment with substituted phenylhydrazines yielded the desired indoles **32** (Scheme 8). One year later in 2002 Willoughby et al.[6] applied a similar synthetic protocol to prepare several 2-arylindole-based libraries in a mixture format and introduced a novel activation protocol under Mitsunobu conditions using pentafluorobenzyl alcohol (details are described in Section 4.2). Through the use of 4-phenyl-pyrrolidine-3-carboxylic acid as a starting scaffold, Willoughby et al.[46] were able to form ureas (**33**), amides (**34**) and sulfonamides (**35**) on solid phase. After reaction with several piperidine and piperazine derivatives a set of bioactive compounds could be obtained. In 2002 Wei et al.[47] proceeded in a similar fashion to prepare *N*-sulfonyl and *N*-carbamoylprolyl/pipecolyl amides **36** and **37** (Fig. 2).

In 2003 Fattori et al.[48] described the formation of unsymmetrical di- and trisubstituted ureas upon treatment of the Kenner-linker with isocyanates. In the course of establishing optimized conditions, the



Scheme 7. Synthetic pathway executed by Köhn et al. ((a) 4-Iodobenzoic acid, benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), DIPEA, DMF 16 h; (b) 4-formylphenylboronic acid, $Pd(OAc)_2$, K_2CO_3, DIPEA, 16 h, 90 °C; (c) 4-(*N*-Boc-aminomethyl)aniline, $NaBH(OAc)_3$, Na_2SO_4, AcOH, dichloromethane, 12 h, ultrasonication; (d) TFA/dichloromethane (1:1); (e) trimethylsilyl diazomethane (TMS–CHN_2), hexane/dichloromethane (1:1), 3 h, room temperature (rt); (f) 6-azidohexanamine, DMF, 40 °C).



Scheme 8. 2-Arylindole synthesis presented by Cooper et al. ((a) 4-(4-Chlorobenzoyl)butyric acid, DIC, DMAP, dichloromethane, rt, 96 h; (b) R–$PhNHNH_2$·HCl, $ZnCl_2$, AcOH, 70 °C, 16 h; (c) bromoacetonitrile, DIPEA, NMP, rt, 16 h, (d) 1-(2-methoxy-phenyl)-piperazine).

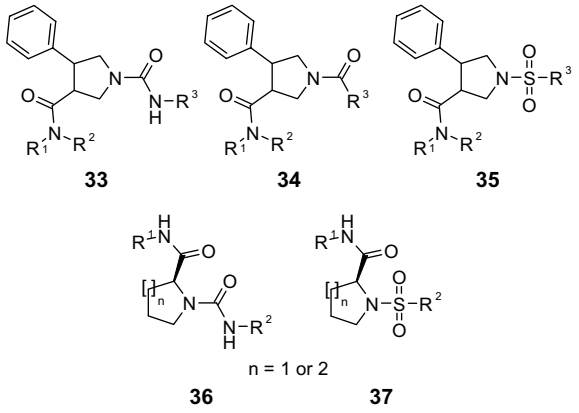
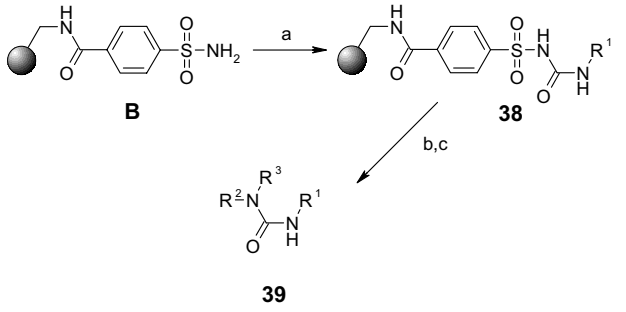


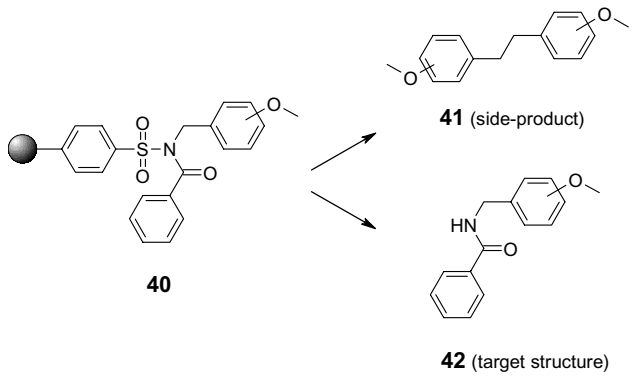
Figure 2. Core structures prepared by Willoughby et al. (**33**–**35**) and by Wei et al. (**36** and **37**) constructed on solid phase utilizing linker variant **B**.

aromatic linker variant **B** turned out to be superior to variant **C**, presumably caused by pronounced acidic properties (Scheme 9).

Interestingly, the activation with trimethylsilyldiazomethane in this case seemed to be by far superior to



Scheme 9. Synthesis of unsymmetrical ureas according to Fattori et al. ((a) THF/dichloromethane 1:1, isocyanate, DIPEA, rt, 12 h; (b) TMS–CH_2N_2 in THF; (c) amine, DMF, 60 °C, 3 h).



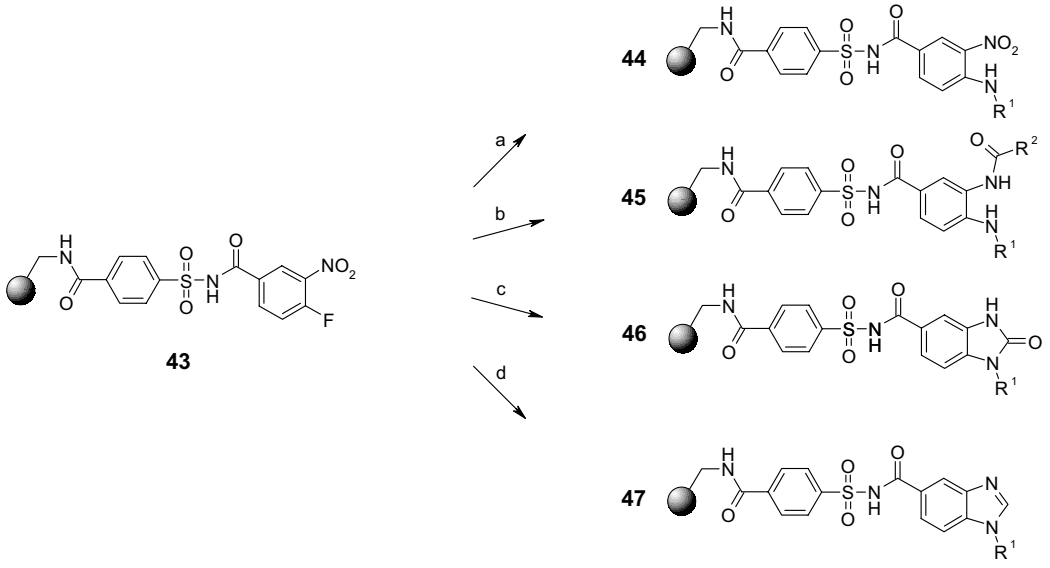
Scheme 10. Products observed after radical traceless cleavage according to Luo et al. ((a) $TiCl_4$, Zn, THF, reflux, 24 h; (b) 3% HCl).

the activation with haloacetonitriles. In addition to the already mentioned applications, Kanemitsu et al.[49] performed glycosylation reactions in 2002 to obtain tri- and tetrasaccharides.

In 2002 Luo and Huang[50] prepared secondary amides **42** and presented a new activation method. This approach featured the only reported case, in which the *N*-alkyl part of the *N*-acyl-*N*-alkyl-sulfonamide remains bound to the acyl moiety (Scheme 10).

Because the success of this method was strongly dependant on the substitution patterns of the regarding acyl moiety, a universal use seems unlikely.

Coupling of 4-fluoro-3-nitrobenzoic acid onto the Kenner-linker variant **B** allowed for the realization of a couple of subsequent reactions accomplished on solid phase. Besides nucleophilic substitutions of the fluoro atom with primary and secondary amines, treatment with reducing agents followed by addition of CDI and triethylorthoformiate, respectively, led to benzimidazolinone (**46**) and benzimidazole carboxylic acid equivalents (**47**) that were subsequently transferred onto amino scaffolds (Scheme 11).[51–54]



Scheme 11. Use of polymer bound 4-fluoro-3-nitro benzoic acid as starting scaffold for solid-phase synthesis.

3.2. N-selective acylation of natural product derived templates

Over the years the demand for chemoselective acylation reagents increased constantly.[55–57] The Kenner-linker was soon recognized to be able to transfer acyl residues selectively onto amino groups in the presence of hydroxy functions and aromatic amino groups yielding various substituted nucleoside derivatives intended for biological investigations (Fig. 3).

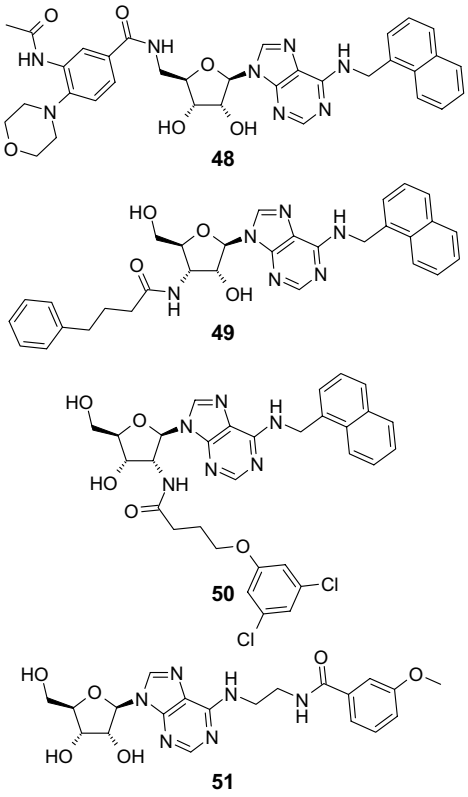
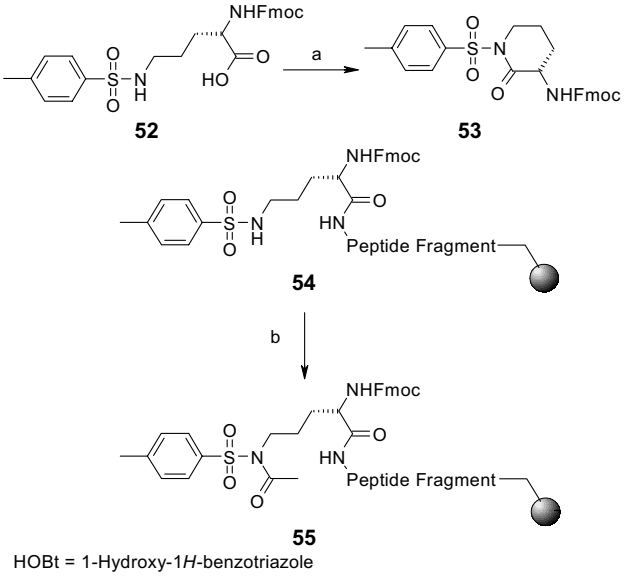


Figure 3. Products of N-selective acylations of adenosine derived scaffolds.

One rational for the investigation of the reactivity of *N*-alkyl-*N*-acyl-sulfonamides was the observation of side-reactions occurring during incorporation of sulfonyl-ornithines in SPPS described by Link et al.[58] in 1998. Similar to possible dimerization that occurs during construction of the Kenner-linker variant **C**, (Section 4.2) unwanted acylations of the sulfamoyl group of **52** by carboxylic acids results in intramolecular ring closure yielding **53**. At the same time, application of standard acetic acid anhydride capping in Fmoc-SPPS lead to the formation of *N*-acetyl-tosyl ornithine derivatives **55** (Scheme 12).



Scheme 12. Side reactions in SPPS due to improper activation of tosyl ornithine or capping procedures according to Link et al. ((a) THF/dichloromethane 1:1, HOBt, DIC, DMAP, DIPEA, rt, 4 h; (b) Ac_2O, pyridine, DMF, rt).

Exploitation of the former side reaction led to the development of polymer bound reagents that allowed for the straightforward preparation of nucleoside derivatives without the need for elaborate protecting group operations and time-consuming purification routines.[59] A small set of 2′-amido-2′-desoxyadenosines was prepared in high yields through acylation of the corresponding 2′-amino-2′-desoxyadenosines and no formation of possible *N*- or *O*-acylated side products could be observed.

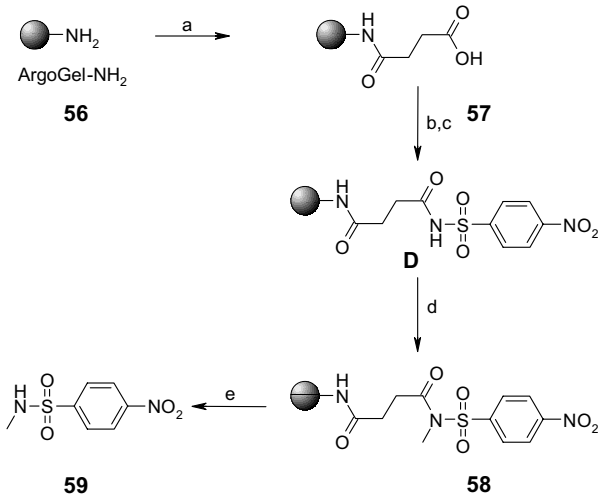
This synthetic approach logically combined the advantages of chemoselectivity with the striking benefits, such as quantitative conversion and no need for further work up steps, of polymer bound reagents. Consequently, several nucleoside related arrays of potentially bioactive compounds have been prepared in the following years with systematic variation of possible amido-deoxy-positions. On the one hand through the transfer of simple carboxylic acids (in 2′-position[60,61] 2′-position and 2′,5′-position,[62] in 3′-position[63,64]) and on the other hand through modifications, such as electrophilic substitution, reduction and acylation, on solid phase prior to amidation (in 2′-position,[51] 5′-position,[52] 3′,5′-position[54]). In addition to the above mentioned nucleoside analogues, the chemoselective preparation of 1,2,4-trisubstituted cyclopentane derivatives was presented by Guan et al.[65] in 2000 and Zohrabi-Kalantari et al. in 2004.[66] Besides the use of the Kenner-linker for simple chemoselective acylations, the group of Link[67] demonstrated the application of the modified Kenner-linker **B** as N-chemoselective biotinylation reagent in 2001, a circumstance that will be further discussed in Section 3.4.

3.3. Inverse use of the Kenner-linker

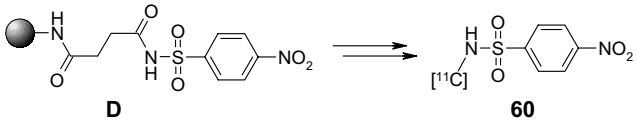
In 2001 Maclean et al.[68] developed a solid-phase synthesis for the preparation of *N*-alkyl-sulfonamides via the formation of *N*-acyl-*N*-alkyl-sulfonamides. Their synthetic approach followed closely the idea of Kenner, but in this case the acyl-moiety was polymer bound (succinic acid on ArgoGel-NH_2) and upon activation alkylated sulfonamides could be released from the solid support. The inverse Kenner-linker **D** could also be utilized in Suzuki couplings and thiazolidinone formation using benzaldehyde and mercaptosuccinic acid by the same group (Scheme 13).

Interestingly, activation was carried out differently from the standard protocols through alkylation with methyl-iodide. Only two years later in 2003 Maclean et al.[69] used the inverse Kenner-linker as an elegant possibility to synthesize 'PET-ready' (positron emission tomography) compounds. In comparison to a second approach using a REM-linker (regenerated Michael acceptor resin), Maclean et al. revealed the Kenner-linker to be slightly inferior and further investigations therefore focused on the REM-linker and the synthesis of triazines. But nonetheless this group established a simple and efficient route to prepare radiolabeled sulfonamides **60** (Scheme 14).

In addition to that, the structural element of *N*-acyl-*N*-alkyl-sulfonamides in solid phase chemistry independent



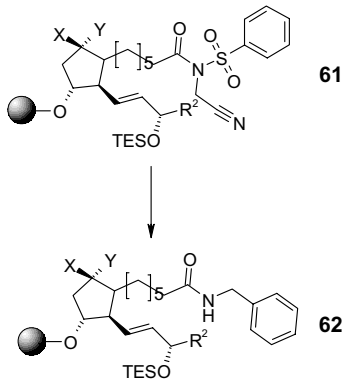
Scheme 13. Inverse use of the Kenner-linker according to Maclean et al. ((a) succinic anhydride, DIPEA, NMP, rt, 30 min; (b) pentafluorophenyl trifluoroacetate/pyridine/NMP (1:1:1), rt, 30 min; (c) *p*-nitrobenzenesulfonamide, DIPEA, DMAP, NMP, rt, 18 h; (d) MeI, DIPEA, DMF, rt, 2 h; (e) 2 M NH_3/MeOH, rt, 2 h).



Scheme 14. Preparation of PET-labeled *N*-alkyl-sulfonamides employing the inverse Kenner-linker.

from the concept of the Kenner-linker appeared in a few cases and may also be mentioned in this context. In 1998 Thompson et al.[70] used *N*-acyl-benzenesulfonamides as protecting groups for carboxylic acid functionalities in the solid-phase synthesis of prostaglandins (Scheme 15).

Deprotection was achieved through alkylation with bromoacetonitrile to the corresponding *N*-acyl-*N*-cyanomethyl-benzenesulfonamides. Addition of nucleophiles such as amines or alcohols in the presence of DMAP allowed for the displacement of *N*-alkyl-benz-



Scheme 15. Utilization of *N*-acyl-*N*-alkyl-sulfonamides as protecting group according to Thompson et al.

enesulfonamides and the desired carboxamides or esters remained on solid phase.

Finally in 2002 Xiong et al.[71] prepared acyl biarylsulfonamides using the 4-(4-hydroxymethyl-3-methoxyphenoxy)butyric acid (HMPB) linker. The synthetic protocol included the preparation of a urea moiety. Unfortunately, as anticipated by the authors, due to the presence of an alkylated sulfonamide functionality, the formation of an *N*-alkyl-*N*-aminoacyl-sulfonamide could be observed. Removal of this functionality could easily be achieved through addition of dimethylamine, comparable to the cleavage conditions suggested by Kenner et al. in 1971.[1] After acylation of the *N*-alkyl-sulfonamide functionality with a desired acyl moiety, Xiong et al. cleaved the desired *N*-acyl-sulfonamide through treatment with TFA owing to the HMPB-anchorage.

3.4. Labeling and monitoring techniques

Besides several evident advantages, restrictions in on-bead reaction control in solid phase still represent a profound drawback. Recently the term naked-eye reaction monitoring, denoting for example colour tests, gained more and more attention in the solid phase community (e.g.,[72–74]). Looking at the development of the Kenner-linker, already in 1994 Backes and Ellman[3] adopted the ninhydrin test for monitoring the coupling of the linker onto aminomethylated polystyrene. For monitoring subsequent loading steps, Backes and Ellman[3] at the same time proposed the use of the ninhydrin test for determination of unreacted sulfonamide groups, as well. Initially, the nonacylated sulfonamide was observed to show a pale red colour in contrast to the *N*-acyl-sulfonamide when treated with the Kaiser test solutions as described. Admittedly this preliminary report did not evolve into a reliable, regularly applied monitoring technique, later on.

In 1999 Backes and Ellman[5] introduced the use of Krchnák's bromophenol blue test[75] instead of the toxic Kaiser test solutions for the reaction control of the initial loading step. This fruitful suggestion consists of simple addition of a pH sensitive dye in the beginning of the reaction, which leads to dynamic visualization of the progress of the coupling reaction. Disappearance of free aminomethyl groups is indicated through a colour change of the pH indicator from deep blue to faint yellow (Fig. 4).

Looking at novel polymer backbone materials with basic properties (recently developed and published by Rademann and Barth[76]), the smart and straightforward use of pH indicators is not universally applicable. Alternatively, Heidler and Link[77] investigated the use of 4-(4-sulfamoyl-phenylazo)-benzoic acid as a further modification of the original Kenner-linker. Herein a coloured element was incorporated in the linker and the depth of colour of the polymer allowed for estimation of the loading level (Fig. 5).

Besides monitoring techniques assuring quantitative reactions on the Kenner-linker and its modifications, the use for the preparation of labeled compounds is another widespread application of the linker. At first suggested in 1999[5] and conducted more elaborate in 2000,[9] Backes et al. prepared a tetrapeptide positional-scanning synthetic combinatorial library **64** using the modified Kenner-linker **C**. The required fluorophor (here 7-amino-4-methylcoumarin), vital for the biological assay, was easily attached onto the previously built up tripeptides through a cleavage reaction, using C-terminal AMC-derivatized lysine or arginine **63** (Scheme 16).

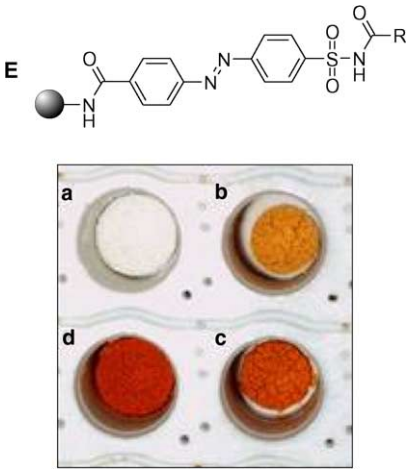


Figure 5. Coloured Kenner-linker analogue **E** ((a)–(d): increasing loading level from 0.0 mmol/g to 0.92 mmol/g).

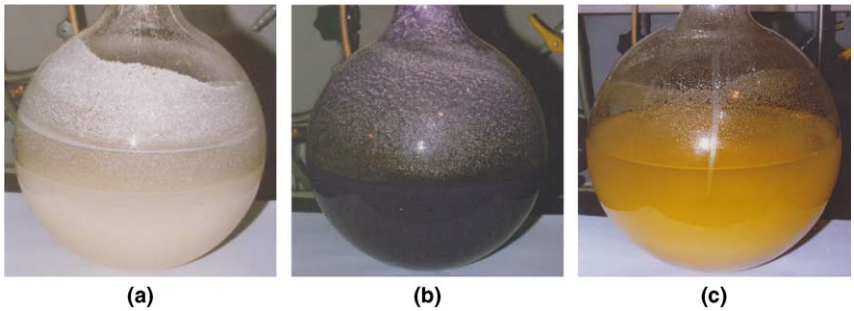
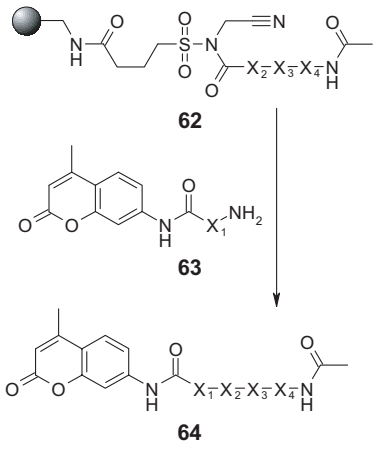


Figure 4. Visualization of reaction completion through addition of bromophenolblue: (a) aminomethylated polystyrene in THF; (b) after addition of bromophenolblue; (c) after 48 h of reaction time under standard coupling conditions.



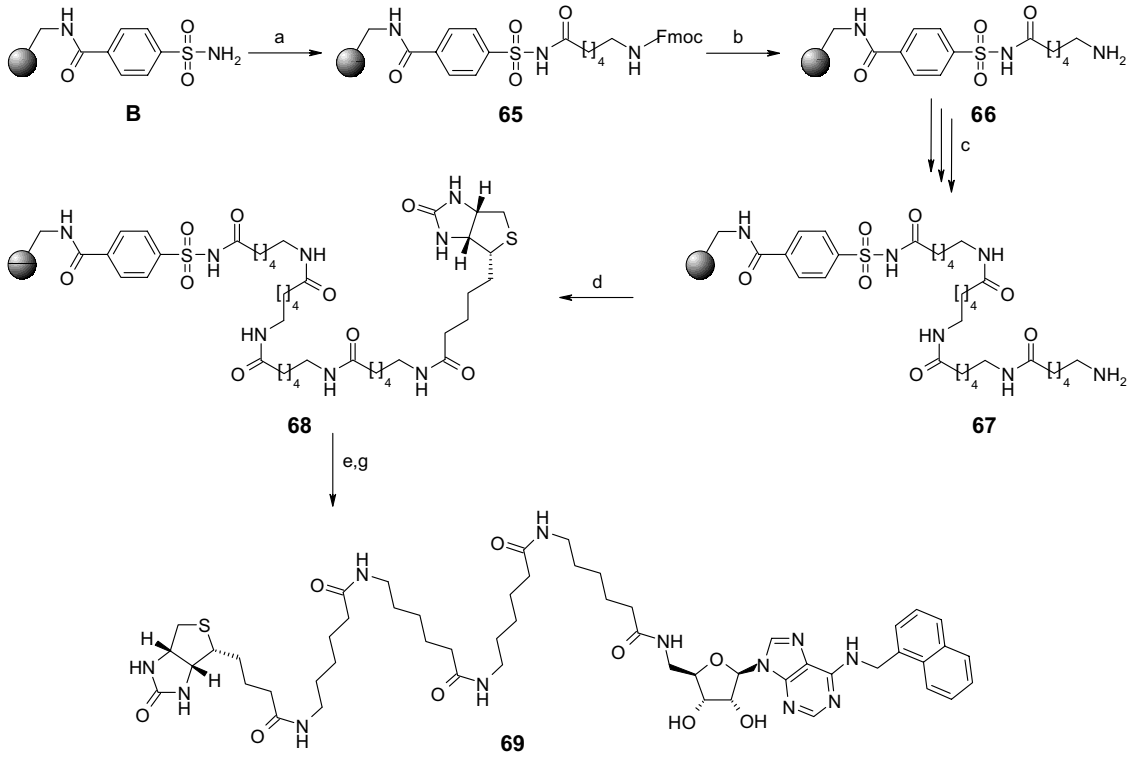
Scheme 16. PSC-library (X_1–X_4 representing the particular amino acid building blocks).

In the same year Sheppeck et al.[8] likewise proceeded to prepare a tripeptide library, in this case the amino acids designated at the P1-pocket of the target protease were varied to an even greater extent, emphasizing the versatility of this approach. Besides tagging peptides with fluorophores, in 2001 the group of Link et al.[67,78] was able to establish a convenient synthetic protocol to attach biotin onto the modified Kenner-linker **B** and successively transfer the biotin residue onto several amino templates. At that time different spacer elements had to be incorporated into the amino scaffold intended for biotinylation in solution prior to the labeling step. The versatility of this approach was improved later on through the construction of highly variable spacers on solid phase prior to anchorage of biotin.[79] The resulting spacer-biotin constructs could then successfully be transferred onto aminonucleoside templates making use of the advantageous N-chemoselective properties (Scheme 17).

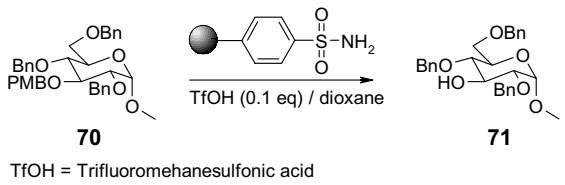
In 2002 Kanemutsi et al.[49] established a synthetic procedure for the preparation of oligosaccharides on solid phase, that allowed for the reaction control using gated decoupling ^{13}C NMR. Two ^{13}C enriched markers were incorporated in the synthetic sequence, on the one hand as part of the linker and on the other hand as part of a protecting group. To verify the synthetic sequence, a sialyl Lewis X branched tetrasaccharide was successfully built up. In 2003 Köhn et al.[42] focused on the preparation of azide functionalized small molecules that could be immobilized on glass surfaces via Staudinger ligation. After the preparation of biotin labeled prototypical compounds applying several solid-phase synthesis steps on the Kenner type linker, cleavage with 6-azidohexaneamine furnished the desired azide-labeled structures (compare Scheme 7 in Section 3.1).

3.5. Utilization in removal of protecting groups

In 2002 Hinklin and Kiessling[80] observed the quantitative removal of *para*-methoxybenzyl (PMB) ether protecting groups in the presence of sulfonamides and



Scheme 17. Assembly of spacer fragments, biotinylation and transfer onto amino nucleoside scaffold ((a) 6-(Fmoc-amino) hexanoic acid, DMF/dichloromethane, DIC, DMAP, rt, 6 h; (b) 20% piperidine in DMF, rt, 30 min; (c) repeat a/b three times; (d) biotin, DMF, DIC, HOBt, DIPEA, rt, 24 h; (e) bromoacetonitrile, NMP, DIPEA, rt, 12 h; (g) amino scaffold, NMP, 55 °C, 10 h).



Scheme 18. Use of the Kenner-linker as scavenger resin.

catalytic amounts of triflic acid, without affecting benzyl ether residues. Further investigations led to an easily applicable method for PMB protecting group removal to afford target alcohols. By the use of the Kenner-linker as polymer bound sulfonamide equivalent, the *para*-methoxybenzyl moiety could be scavenged in a convenient fashion (Scheme 18).

4. Practical considerations

4.1. Variations of the sulfonamide moiety

The prototype sulfonamide Kenner-linker **A** was built up on highly sulfonated polystyrene resins.[1] Incomplete reactions due to electrostatic effects of the resin matrix, such as ionization of the more acidic acylsulfonamide groups inhibiting ionization and hence acylation of the residual sulfonamides, were identified to be responsible for a narrowed loading level and eventually occurring side products from the beginning. Additionally the severe side reactions observed, such as racemization, transpeptidation and isomerization of ω-esters of aspartyl and glutamyl peptides, restricted a widespread use of the Kenner-linker **A**. But with the modifications **B** and **C** introduced by Backes and Ellman in 1994,[3] 1996[4] and 1999,[5] major improvements could be achieved. In 1994 the group of Ellman[3] started with the construction based upon aminomethylated polystyrene. Mild subsequent acylation of the latter with 4-sulfamoyl benzoic acid, *N*,*N*-diisopropylcarbodiimide and 1-hydroxybenzotriazole led to the required polymer bound sulfonamide function **B** in good to excellent yields, bearing even more reactive characteristics due to the electron withdrawing effects of the *para*-amido function. In the following years the in situ formation of symmetric anhydrides using DIC and subsequent acylation in the presence of DMAP, first mentioned in 1994[3] and further described in 1996,[4] became widely accepted (e.g.[6,46,78]).

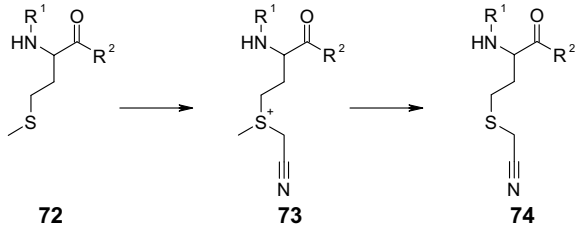
In 1996 Backes et al.[4] further contributed to the improvement of Kenner's safety-catch linker **A** through the introduction of an aliphatic analogue **C** based upon 3-carboxypropane sulfonamide. Because of the increased nucleophilicity and basicity, the aliphatic linker permits the cleavage of carboxylic acids even with α-electron withdrawing substitution, such as *N*-Boc-protected amino acids. In 1999 Backes and Ellman[5] optimized the coupling conditions as far as the occurrence of racemization during the loading step could be pushed back almost quantitatively. Recently the group of Link broadened the repertoire of Kenner-linker variants by addition of a coloured azo-benzene derived type **E**.

4.2. Loading and activation methods, fine-tuning of alkylation conditions

The group of Kenner[1] in 1971 originally prepared the necessary sulfamoyl moiety in such a way, that the linker was directly attached to the polystyrene core of the beads used. The other, newer variants are prepared by coupling a sulfamoyl-substituted carboxylic acid to mostly aminomethylated polymers using mild coupling conditions without affecting the unprotected sulfamoyl group. These reaction conditions are obviously crucial, because subsequently carboxylic acids have to be attached to the sulfamoyl group in high to quantitative yield. The most important tool for tuning the reactivity of the activated carboxylic acid is the formation of anhydrides in the absence of the strong acylation catalyst DMAP. Without the addition of DMAP and in the absence of a base like Hünig's base, carboxylic acid anhydrides or *O*-acyl ureas formed by the linker molecules **B**–**D** can be attached to amino groups without formation of acyl sulfonamides. In the case of variant **C**, the absence of unwanted dimerizations has been discussed controversially in a preliminary report, recently.[81]

For loading of carboxylic acids, Kenner's group used 2,4,5-trichlorophenyl esters of various *tert*-butoxycarbonyl-or benzyloxycarbonyl-amino acids for coupling amino acids onto the sulfonamide functionality. Applying two equivalents of activated amino acid in the presence of triethylamine led to poor conversion rates around 25%. Besides the insufficient coupling efficiencies, Kenner et al. observed comparably high racemization tendencies of the applied amino acids up to 4.5% (α-aspartylglycine β-isomer) and reported on side reactions when using ω-ester of aspartyl and glutamyl peptides. In 1996 Backes et al.[4] were able to raise the coupling yields by using the aliphatic analogue **C** on the on hand and applying a double coupling using PyBOP and Hünig's Base in DMF on the other hand (whereas the better coupling yields might probably also be due to the more efficient 3-carboxypropanesulfonamide linkage on aminomethylated polystyrene). After further profound optimization studies, in 1999 Backes and Ellman[5] were able to present coupling conditions for both *N*-Boc and *N*-Fmoc protected amino acids. These were prepared on the basis of the method proposed by Kim and Patel published in 1994[82] and only slightly modified for Fmoc applications through the use of chloroform instead of dichloromethane to improve the solubility of the Fmoc protected amino acids; this is of importance especially for Fmoc-Phe-OH, being one of the most insoluble Fmoc amino acids. Initial coupling proved to be at its best using three equivalents of the appropriate amino acid, PyBOP (three equivalents) and DIPEA (five equivalents) in chloroform at −20 °C with 8 h reaction time. Backes et al. pointed out the need for immediate filtration of the coupling mixture after expiration of the postulated reaction time of 8 h to avoid an increase in racemization. Reported contents of unwanted epimers were less than 1%. In 2002 Tang and Ellman even lowered the coupling temperature down to −40 °C (and minor other changes) to attach *N*-sulfinyl β-amino acids[14] onto the aliphatic modified Kenner-linker **C**. In

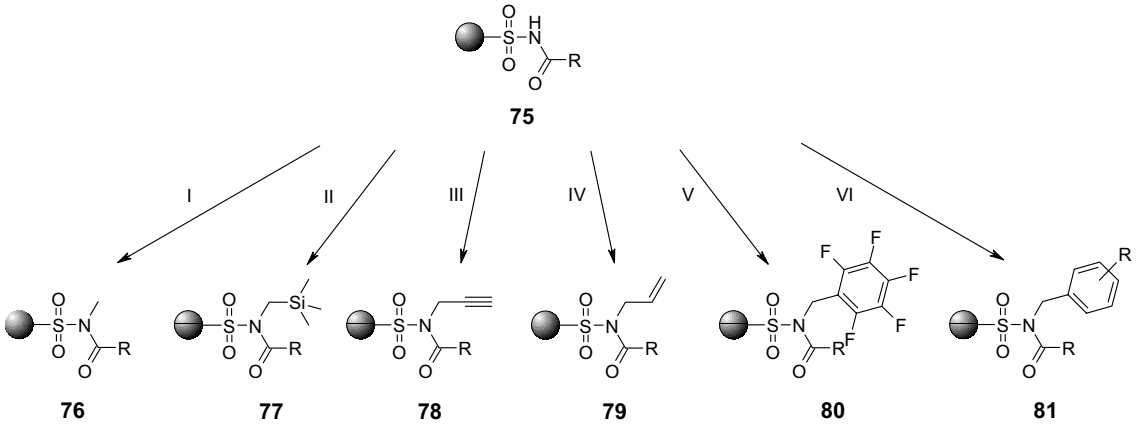
the same year Ingenito et al.[83] recommended the use of Fmoc amino acid fluorides as an efficient loading method for the sulfonamide linker **C**. Extensive exploration finally led to optimized conditions, using two equivalents of DIPEA included high coupling rates and small racemization tendencies. Besides the tender coupling conditions for amino acids to prevent epimerization of the chiral α-carbon, connection of non-α-chiral acid building blocks allows for much more rigorous coupling conditions. Within the first reports on the use of the Kenner safety-catch linker in solid-phase synthesis, Backes and Ellman[3] introduced another modification of the original linker **B** in the course of preparing drug-like small molecules. In this case, 4-bromophenyl acetic acid had to be coupled onto the polymer bound sulfonamide functionality. Besides the possibility of using symmetric anhydrides, easily accessible through reaction with carbodiimides, in the presence of DMAP as acylation catalyst, Backes and Ellman[3] additionally suggested the use of pentafluorophenyl activated esters. Furthermore in 1999 Lew and Chamberlin[41] reported the use of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) activated esters. Alternatively, use of acyl-chlorides or *O*-acyl-isoureas exhibits reliable coupling results. The choice of applied solvents such as DMF, dichloromethane or THF depended on the solubility of the relevant carboxylic acid derivatives. Prior to nucleophilic displacement of the acyl moiety (either amino acid or other carboxylic acid derivative), the *N*-acyl-sulfonamide had to be activated through alkylation of the imide nitrogen. In 1971 Kenner[1] originally used diazomethane (that was later on replaced by trimethylsilyldiazomethane due to easier handling) in ether-acetone to prepare the corresponding *N*-acyl-*N*-methyl-sulfonamides as active intermediates. It should be noted in this context that the question whether this activation protocol leads to the methyl-[7] or the trimethylsilyl[40]-derivative seems not to be explored and represents a contradictory case. When Backes and Ellman[3] adopted the proposed procedure in 1994, limitations were encountered using aniline derivatives as cleavage nucleophiles, even when employing forcing reaction conditions such as elevated temperatures or excess of displacing reagent, as mentioned in Section 3.1. of this review. To overcome these drawbacks, Backes et al.[4] hypothesized and experimentally testified in 1996 the use of an *N*-alkyl group with electron withdrawing properties enhancing the reactivity of the activated intermediate. After comparing several different substituents, the cyanomethyl group proved to be optimal. Backes et al. proposed the use of bromoacetonitrile or iodoacetonitrile in DMSO or NMP (NMP is employed rather than DMSO when using gel form resin to better solvate the resin) with Hünig's Base to catch the released acid equivalents. The emerging *N*-acyl-*N*-cyanomethyl-sulfonamide allowed for nucleophilic displacement even with limiting amounts of nucleophile. In addition to that, weak nucleophiles such as aniline were also acylated (admittedly, due to required heating, higher rates of competitive hydrolysis were reported) in contrast to the cleavage protocol reported in 1994. Nonetheless, extending the activation protocol to carboxylic acids that possess α-electronegative substituents such as *N*-Boc and *N*-Fmoc protected amino acids or benzoic acid proved to be problematic. Direct comparison to the activation applying diazomethane suggested incomplete alkylation of the *N*-acyl-sulfonamide functionality. Presumably, the electronegative α-protected amino function attenuated the nucleophilicity of the acylsulfonamide anion. As a possible solution Backes et al. suggested the use of an aliphatic sulfonamide linker **C**,[4,5] exhibiting increased basicity and enhanced nucleophilicity in combination with the activation using haloacetonitriles. Besides that, the aliphatic analogue was supposed to have a smaller racemization tendency, a putative property that was challenged in 2001 by Biancala et al.[20] Indeed, cleavage with aniline still required forcing conditions (90 °C in dioxane), 4-nitro-aniline and 7-amino-4-methylcoumarin (both relevant in enzymology as fluorogenic peptide substrates) did not react with the activated derivative. To widen the scope of possible applications, Backes et al. revealed the addition of lysine onto 7-amino-4-methylcoumarin to obtain an aliphatic amine with enhanced nucleophilicity bearing the desired fluorogenic residue. In 2000 Sheppeck et al.[8] as well as Backes et al.[9] demonstrated the versatility of this implementation. Besides insufficient alkylation, decomposition of Fmoc-His(Trt)-OH upon alkylation could be observed (proposed solution use of Fmoc-His(Boc)-OH). Interestingly the expected cyanomethylation of certain amino acid side chains, such as cystein(Trt) and methionine, did not occur in significant amounts, as reported in 1999 by Backes and Ellman.[5] However, in 2002 Flavell et al.[33] observed and elucidated a methionine ε-cyanomethylation resulting in a cyanilation, which was proved by several NMR-spectroscopic experiments (Scheme 19).



Scheme 19. Proposed mechanism of methionine ε-cyanilation (R^1 = Fmoc and R^2 = Gly-SBn).

An alternative to the alkylation methods previously described (namely, diazomethane,[1] trimethylsilyldiazomethane[7] and haloacetonitriles[4]) was presented in 2002 by Willoughby et al.[6] Alkylation of the *N*-acyl-sulfonamide was in this case achieved under Mitsunobu conditions, using triphenylphosphine, *N*,*N*-diisopropylazodicarboxylate and pentafluorobenzyl alcohol in THF (**80**).

In addition to that, He and Kiessling[84] presented a further alternative alkylation method intended to activate the *N*-acyl-sulfonamide residue. In this preliminary report, Pd(0)-catalyzed allylation of the *N*-acyl-sulfonamide nitrogen is claimed to result in the formation of *N*-acyl-*N*-alkyl-sulfonamides (Scheme 20). As desired,



Scheme 20. Summary of activation protocols used to date (I: diazomethane; II: trimethylsilyldiazomethane; III: haloacetonitriles; IV: Pd(0)-catalyzed; V: Mitsunobu conditions; VI: *O*-alkyl-isoureas).

the latter turned out to be highly labile against nucleophiles. This alternative activation protocol allows for alkylation under neutral and mild conditions, considerably broadening the possible applicability of the Kenner-linker and its derivatives towards alkaline sensitive compounds, particularly with regard to protected amino acids. In 2004, the group of Link used *O*-alkyl-isoureas as alkylating reagents for the activation of linker type **B** and **D**. This approach made the pentafluorobenzyl substituted *N*-acyl-*N*-alkyl-sulfonamides, as proposed by Willoughby, accessible under dissimilar conditions. According to preliminary, hitherto unpublished results, the use of the rather expensive pentafluorobenzyl alcohol to yield the novel *O*-alkyl-isourea reagent shown below, is not necessary, economically speaking. Easily accessible *O*-alkyl-isoureas based on cheaper alcohols such as 4-nitro benzyl alcohol lead to comparable or even superior performance in our hands.[85]

5. Conclusion

Since 1971 the Kenner-linker advanced from a revolutionary idea with narrowed applicability up to a standard technique in several diverse chemical disciplines. Developments regarding the linker, coupling conditions, activation methods, cleavage conditions and possible substrates established this linker and its modifications in modern chemistry and will without doubt be present in the future.

Similar to the sad end of Alfred Nobel, George W. Kenner did not live to see the fruitful impact his legacy exhibited on advanced bioorganic and medicinal chemistry. Among many significant achievements in total synthesis, the great chemist and pioneer of natural product chemistry left behind a robust and simultaneously scissile linker being implemented in several synthetic procedures, and provided the synthetic chemist with a powerful and reliable tool to access a capacious variety of chemical structures.

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Biographical sketch

Philipp Heidler was born in Hannover in 1975. He studied pharmacy at the Universität Hamburg and received his degree as pharmacist in 2001. He joined the research group of A. Link in 2001 and in his graduate studies he is concentrating on the development of techniques for the convergent polymer-assisted synthesis of bioactive molecules, in particular amides, which are relevant in studies of dopamine receptors, and enzymes of pathogenic protozoa.

Andreas Link was born in Flensburg in 1967. He studied pharmacy at the Universität Hamburg and received his Dr. rer. nat. in 1996 under the guidance of Detlef Geffken. After postdoctoral studies from 1996 to 1997 with Piet Herdewijn at the Rega Institute for Medical Research of the Universiteit Leuven he returned to the Universität Hamburg and received his habilitation in 2002. Since 2002 he is holding a professorship at the Philipps-Universität Marburg. Andreas Link has been the recipient of the Fachgruppen-Innovationspreis in Medicinal/Pharmaceutical Chemistry of the Gesellschaft Deutscher Chemiker and the Deutsche Pharmazeutische Gesellschaft 2001. His current research interests include bioorganic and medicinal chemistry, in particular the synthesis of nucleoside derived enzyme inhibitors and the parallel preparation of highly pure libraries of lead-structure analogues for the investigation of structure–activity relationships. In October 2004 he received a call to the Ernst Moritz Arndt-University Greifswald to take over the chair in pharmaceutical/medicinal chemistry.