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SASRIN™, a Versatile Tool in Peptide Synthesis and Solid-Phase Organic Chemistry

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Sandmeyer Prize Winners 1998[a])

Abstract. The synthesis of the 4-(3-methoxy-4-(hydroxymethyl)phenoxymethyl) derivative of polystyrene-co-divinylbenzene (*SASRIN*™), its derivatives and its application in solid-phase peptide synthesis will be briefly reviewed in this paper. Solid-phase synthesis of fully protected peptide fragments may be the most important, but by far not the only application, as cleavage with nucleophiles or solid-phase synthesis on *SASRIN* derivatives will yield a range of useful *C*-terminally modified peptides, such as peptide hydrazides or *p*-nitroanilides.

1. Introduction

Synthetic bioactive peptides have found wide application in biology, biochemistry, medicine and related areas. Such compounds are made available by two principally different synthetic methods [1]; either by 'classical' convergent synthesis in solution, which is rather time-consuming, or by stepwise solid-phase peptide synthesis (SPPS) employing an insoluble carrier, a more recent development by *Merrifield* [2]. Even though peptides can be obtained far more rapidly by SPPS, the 'classical' solution synthesis still has its merits such as concomitant isolation, characterization and purification of intermediates, whereas in stepwise SPPS these operations are restricted to the final product. 'Convergent SPPS' [3] combines the advantages of both methods: fully protected peptide fragments obtained by SPPS on suitable resin derivatives followed by characterization and purification are coupled either to fragments in solution [4], or to resin-bound fragments [5]. Thus, crude products of better quality can be obtained, as usually side products stemming from incomplete fragment coupling are removed more easily than deletion sequences (*i.e.*, fragments lacking merely a single amino acid) accumulated during stepwise SPPS.

Fully protected peptide fragments can be obtained by SPPS only if the side-chain ('permanent') protecting groups are left intact during cleavage from the resin. Based on the work of *Sheppard et al.* [6], we at *BACHEM* developed and successfully marketed the Super Acid-Sensitive Resin (*SASRIN*™: 2-methoxy-4-alkoxybenzyl-alcohol resin **2**) [7][8]. The award of the *Sandmeyer* prize occasioned the writing of the present short and inevitably incomplete review of *SASRIN*'s manifold applications, including part of our recent work.

Initially, *SASRIN* was conceived for the synthesis of fully *tert*-butyl-type-protected fragments using temporary, base-labile N^{α}-[(9*H*-fluoren-9-yl)methoxy]-carbonyl (Fmoc) protection. Cleavage from *SASRIN* merely requires short repetitive treatments with 0.5 to 1% trifluoroacetic acid (TFA) in methylene chloride (DCM) [8][9]. *SASRIN* esters turned out to be sufficiently (but not excessively) acid-labile, so that the more acid-sensitive moieties Lys(Boc), Tyr(*t*Bu) and His(Trt) are left intact during cleavage, whereas Fmoc amino acids and hydroxybenzotriazole (HOBt) do not cause premature cleavage under normal coupling conditions. Naturally, *SASRIN* can be used in stepwise SPPS employing Fmoc/*t*Bu-protection as well. Even an additional advantage is gained: samples can be cleaved rapidly at any stage of the synthesis for monitoring purposes. By characterizing these samples an unambiguous batch-documentation system is obtained, which showed its value in solving synthetic problems and optimizing large-scale syntheses. The completed fully protected peptide obtained from *SASRIN* can be purified before cleaving the permanent protecting groups or, if

Abbreviations

Solvents/Reagents

DCM	dichloromethane, methylene chloride
TFA	trifluoroacetic acid
HFIP	hexafluoroisopropanol
DMF	dimethylformamide
DMA	dimethylacetamide
DIPEA	diisopropylethylamine
AcOH	acetic acid
THF	tetrahydrofuran

Protecting groups

Boc	(*tert*-butyloxy)carbonyl
*t*Bu	*tert*-butyl
Trt	trityl
Fmoc	[(9*H*-fluoren-9-yl)methoxy]carbonyl
Acm	acetamidomethyl
Mtt	4-methyltrityl
Pmc	2,2,5,7,8-pentamethylchroman-6-sulfonyl

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[a]) See *Chimia*, **1998**, *52*, 235.

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desired, be further modified in solution, *e.g.*, by iodine treatment to cleave Cys(Acm) and to form an S–S-bridge. Total deblocking of a *SASRIN*-bound peptide can be performed in two stages: *i*) cleavage from the resin with 0.5–1% TFA in DCM, and *ii*) removal of side-chain protecting groups in solution, thus facilitating the fine-tuning of cleavage conditions. A two-stage deprotection is recommended when cleaving acid-sensitive peptides such as *O*-sulfated peptides.

SASRIN and *SASRIN* derivatives have found many other applications including use in solid-phase organic synthesis since its development in 1986; some of them will be dealt with below.

2. Synthesis of *SASRIN*™ and Derivatives Thereof

As can be taken from *Scheme 1*, the *SASRIN* linker is obtained by *Vilsmeier* formylation of 3-methoxyphenol [6] followed by $NaBH_4$ reduction [7]. The Na-phenolate of the linker **1** is reacted with chloromethyl polystyrene. The conversion is nearly complete as only traces of chlorine can be found in the resulting polymer **2** [10].

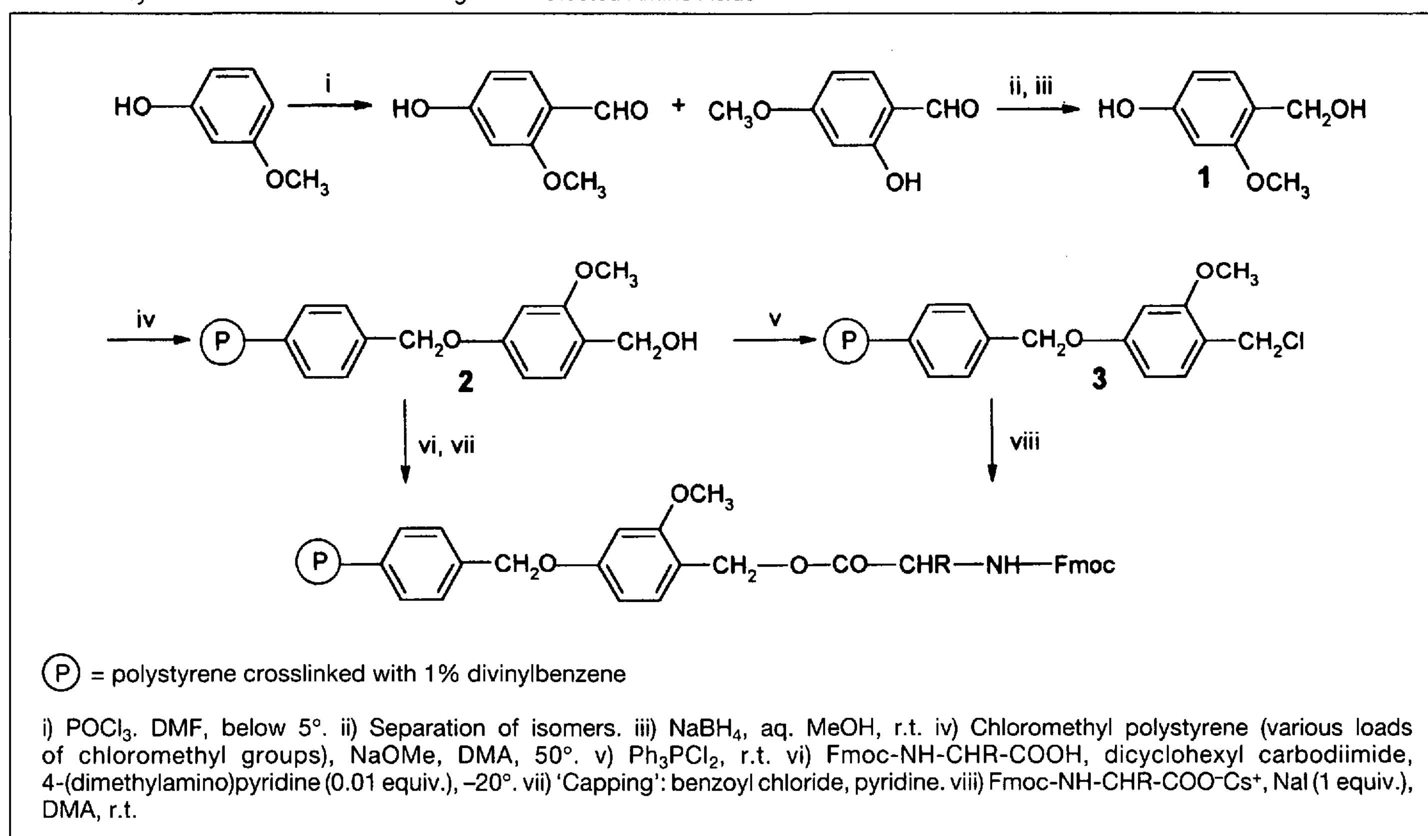
Resin **2** (*i.e.*, *SASRIN*) is loaded with a Fmoc/*t*Bu-protected amino acid. The conditions of esterification had to be optimized to get a high load whilst keeping concomitant racemization low [9] (*cf. Scheme 1*). But even then, several amino acid derivatives, especially derivatives of Cys and His, could only be esterified at the risk of considerable losses of optical purity, as these compounds racemize too rapidly upon activation. Hence, an alternative coupling method had to be found. Protected amino acids can be linked to *Merrifield* resin (*i.e.*, chloromethylated crosslinked polystyrene) *via* nucleophilic substitution, excellent results with virtually no concomitant racemization are obtained by employing their cesium salts [11]. Fortunately, *SASRIN* could be readily converted into the corresponding chloride **3** [12] by treatment with triphenylphosphine dichloride (generated *in situ* from triphenylphosphine and tetrachloromethane [13]). The chloride **3** reacts with the dry cesium salt of the desired Fmoc-amino acid and sodium iodide (which enhances nucleophilic displacement) to yield the *SASRIN* derivative. High conversions and, as expected, minimal racemization could be obtained [14]. Up to now, a broad range of Fmoc-amino acid derivatives of *SASRIN* could be made commercially available including side-chain linked Asp and Glu derivatives. The chloride **3** will also alkylate other nucleophiles, such as amines, leading to rather acid-labile derivatives [15].

3. Synthesis of Peptides Using *SASRIN*™

Except for the cleavage procedure, all synthetic protocols developed for *Wang* resin [16][17] can be applied to *SASRIN*, likewise the equipment for manual and automated SPPS. 'Maximum protection' is recommended, the following commonly used side-chain-protecting groups will be left intact during acidolytic cleavage from *SASRIN* (if properly performed): Trt, Mtt, (Asn, Gln); O*t*Bu (Asp, Glu); Pmc (Arg); Trt, Acm (Cys); Trt (His); Boc (Lys, Trp); *t*Bu (Ser, Thr, Tyr) and Boc or Fmoc for the *N*-terminus. When synthesizing peptides with a *C*-terminal Pro, the N^{α}-deblocking at the dipeptide stage will lead to rapid diketopiperazine (piperazine-2,5-dione) formation and concomitant cleavage, *i.e.*, loss of load, which can be circumvented by coupling a Fmoc dipeptide at the risk of racemization.

SASRIN lends itself especially to the synthesis of acid-sensitive peptide derivatives such as *O*-sulfated or *O*-glycosylated peptides. Under certain precautions, the hydroxy amino acids Tyr, Thr and Ser can be coupled without side-chain protection. Then, the following couplings must proceed unambiguously generating only amide bonds, otherwise selectively cleavable *O*-protecting groups such as trialkylsilyl or allyl have to be chosen. Allyl/

Scheme 1. *Synthesis of* SASRIN *and Loading with Protected Amino Acids*



(P) = polystyrene crosslinked with 1% divinylbenzene

i) $POCl_3$. DMF, below 5°. ii) Separation of isomers. iii) $NaBH_4$, aq. MeOH, r.t. iv) Chloromethyl polystyrene (various loads of chloromethyl groups), NaOMe, DMA, 50°. v) Ph_3PCl_2, r.t. vi) Fmoc-NH-CHR-COOH, dicyclohexyl carbodiimide, 4-(dimethylamino)pyridine (0.01 equiv.), –20°. vii) 'Capping': benzoyl chloride, pyridine. viii) Fmoc-NH-CHR-COO^-Cs^+, NaI (1 equiv.), DMA, r.t.

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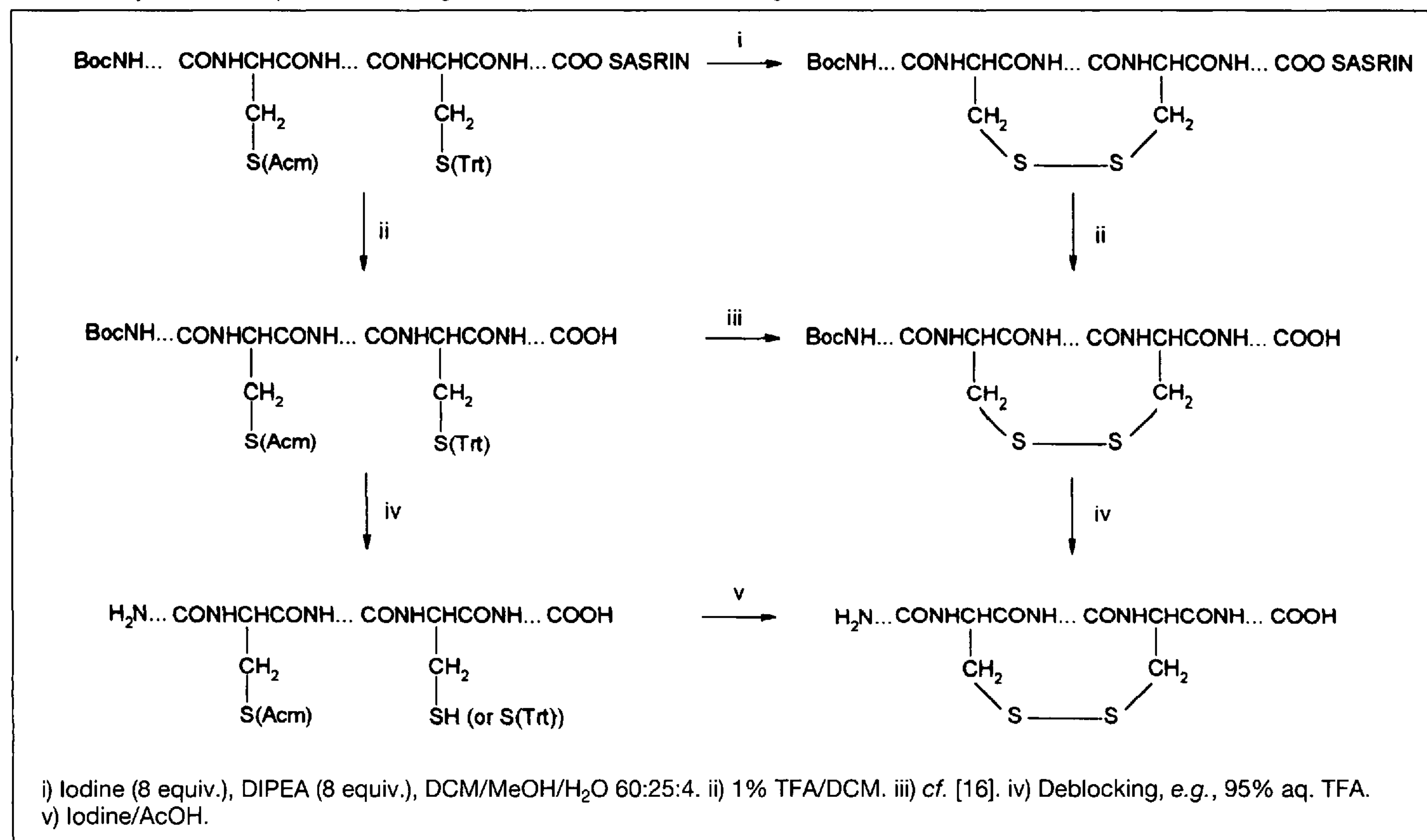
Scheme 2. *Synthesis of Peptides Containing an Intramolecular Disulfide Bridge*



i) Iodine (8 equiv.), DIPEA (8 equiv.), DCM/MeOH/H_2O 60:25:4. ii) 1% TFA/DCM. iii) *cf.* [16]. iv) Deblocking, *e.g.*, 95% aq. TFA. v) Iodine/AcOH.

allyloxycarbonyl side-chain-protecting groups could be cleaved as described in [18] leaving the peptide-resin bond intact.

For *O*-sulfation of Tyr, the otherwise fully protected resin-bound peptide is treated with a large excess of sulfur trioxide/pyridine complex in dry DMF/pyridine 2:1 followed by thorough washing which includes treatment with diluted aqueous sodium carbonate in DMF to obtain the less acid-labile sodium salt. The sulfation should be monitored by analyzing the cleavage products obtained from resin samples; sulfation may be repeated with fresh reagent in case of unsatisfactory conversion. If two or more amino acids have to be modified, better results may be obtained by coupling the corresponding amino-acid derivative (*e.g.*, Fmoc-Tyr(SO_3Na)OH) if available. This approach will equally benefit from the acid-lability of *SASRIN*.

Oxidation of resin-bound peptides containing cysteines leading to intramolecular disulfide-bond formation will only succeed if the bridge is also formed smoothly in solution. Moreover, proper swelling and reduced loads are essential prerequisites. When oxidizing with iodine (*e.g.*, 8 equiv. of iodine in DCM/MeOH/water 60:25:4 [19]), a base such as DIPEA has to be added to neutralize hydrogen iodide formed during the oxidation. *Scheme 2* summarizes various synthetic strategies for cystine-containing peptides employing *SASRIN*.

The analysis of samples taken, washed und cleaved turned out to be the only reliable method of monitoring the synthesis of Ψ-[CH_2NH] pseudopeptides, *i.e.*, peptides containing reduced peptide bonds, on *SASRIN*. The Ψ-[CH_2NH] bond is created *via* reductive alkylation [20], *i.e.*, the amino terminus is reacted with a Fmoc-aminoaldehyde to form the *Schiff* base which is reduced with $NaBH_3CN$ and a small amount of acetic acid. Then, chain elongation cannot be monitored unambiguously by the color tests applied in standard SPPS [16b][17] anymore. Albeit less reactive than the α-amino group, the Ψ-[CH_2NH] group can be acylated, thus precautions have to be taken.

4. Cleavage of Fully Protected Fragments

It cannot be overemphasized that all polar impurities have to be washed out carefully with methylene chloride before starting the cleavage procedure, which only then will proceed rapidly and smoothly. Treatments with 0.5–1% TFA/DCM should be kept short (2–5 min), with rapid filtration and immediate neutralization of the solution, *e.g.*, with pyridine, to follow [3b][8]. Upon first treatment with diluted TFA the donor groups of the peptide such as the amide bonds are protonated, consuming part of the TFA and solubilizing the protected fragment. Thus, additional TFA is needed for rapid cleavage whilst neutralization may suffice to precipitate the fragment. In the course of cleavage, the resin turns deeply violet. If Trp, Met, Cys are present, the color will change less dramatically, if at all, as the 'violet species' resulting from the cleavage will alkylate the indole and thioether moieties, respectively, and thus bind the peptide irreversibly. In this case cleavage yields can be improved by employing Trp(Boc) or adding a suitable cation scavenger, *e.g.*, ethane-1,2-dithiol [21]. Good yields have also been obtained by cleaving the peptide resin with mixtures of hexafluoroisopropanol (HFIP) and DCM [22]. Treatment with HFIP/DCM 1:4 (*v/v*) for 3 to 5 h or HFIP/DCM 3:7 (*v/v*) for less than 1 h leaves Tyr(tBu) and Lys(Boc) intact, whereas His(Trt) is partially cleaved. Side-chain alkylation, as described above, may occur as well. The cleavage rate slightly depends on the *C*-terminal amino acid; the highest rate has been observed with *C*-terminal Gly [23], the lowest with *C*-terminal His(Trt). This cleavage procedure is especially suitable for large-scale SPPS and for fragments to be coupled, as neither

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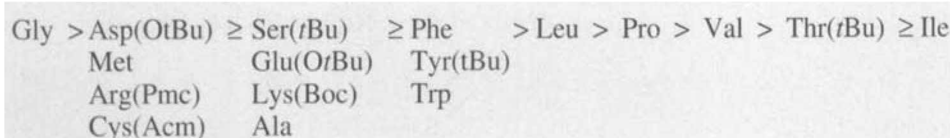
acids nor bases have to be added (and, in the course of work-up, thoroughly removed).

5. Cleavage with Nucleophiles

(Fully) protected short peptides with a modified *C*-terminus can be obtained from *SASRIN* by cleavage with nucleophiles. *Scheme 3* summarizes the options of this cleavage method. Cleavage rates are significantly influenced by steric hindrance (except for reductive cleavage), *i.e.*, by the type of α-substituent of the *C*-terminal amino acid as well as by the bulkiness of the attacking nucleophile.

The ease of cleavage decreases approximately in the order:



Gly > Asp(OtBu) ≥ Ser(*t*Bu) ≥ Phe > Leu > Pro > Val > Thr(*t*Bu) ≥ Ile
Met, Arg(Pmc), Cys(Acm) | Glu(O*t*Bu), Lys(Boc), Ala | Tyr(tBu), Trp

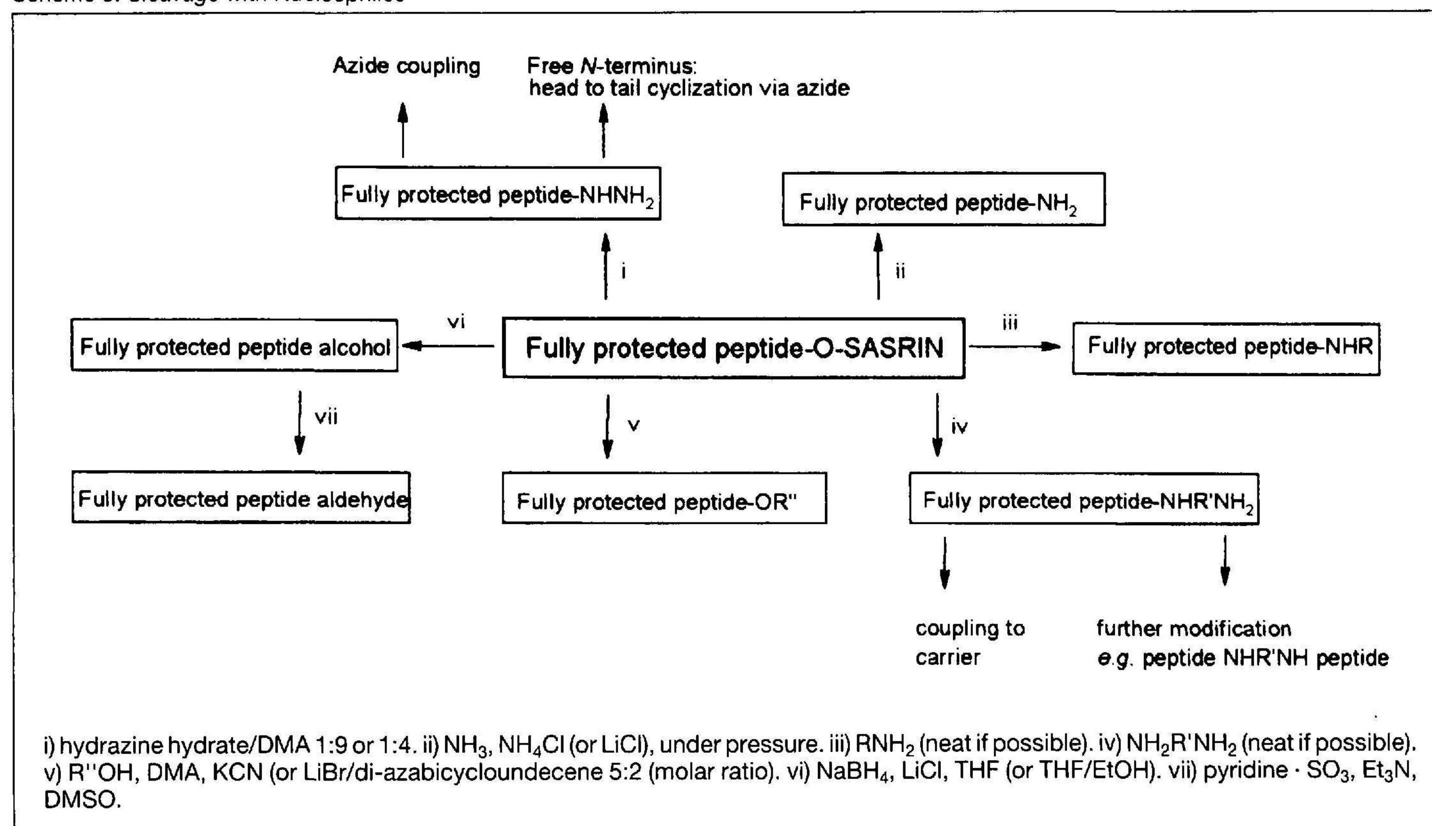
Good swelling facilitates the attack of the nucleophile. But if the cleavage rate is low, base-catalyzed *C*-terminal epimerization may become a problem, especially if the *C*-terminal amino acid is prone to racemization. So, peptides with a *C*-terminal Phe may epimerize considerably. Asp(O*t*Bu)-containing peptides are susceptible to side reactions, if treated with bases. Especially sequences such as -Asp(O*t*Bu)-Gly- will yield mixtures even under most carefully controlled conditions, whereas Glu(O*t*Bu) and Asn(Mtt) tend to be less sensitive. N^{α}-Fmoc is removed under most of the conditions applied, but the *N*-terminus need not be protected. An unambiguous correlation between the length of the fragment and cleavage yield has not been noted, but in some cases a decreasing rate with increasing length (up to ten amino acids) has been observed. The procedure can be repeated; repetitive shorter treatments with the nucleophile may be more effective than a prolonged cleavage.

The rate of *hydrazinolysis* with hydrazine hydrate [24] moderately depends on the nature of the solvent: *N,N'*-dimethylpropylidene urea > *N*-methylpyrrolidone ≥ *N,N*-dimethylacetamide > *N,N*-dimethylformamide > *N,N,N',N'*-tetramethyl urea. But except for DMA, these solvents slowly react with hydrazine hydrate. A higher rate, *e.g.*, at cleaving peptides with β-branched *C*-termini, can be achieved by using anhydrous hydrazine. A fully protected peptide azide is generated from the corresponding hydrazide, and this highly reactive species is coupled *in situ* to a suitable peptide fragment (or to its own deprotected *N*-terminus, *i.e.*, cyclization, *cf. Scheme 3*). Thus, as protected peptide hydrazides and protected 'free acids' can be obtained rapidly from the same batch of peptide resin, the most suitable activation/fragment-coupling method can be chosen without additional synthetic work.

Ammonolysis/aminolysis yielding the fully protected (*N*-alkyl)-amides [25] can be performed with neat primary *N*-alkylamine (under pressure in case of ammonia, methylamine, and ethylamine [26]). Fortunately, cleavage with secondary amines proceeds extremely slowly, so that standard Fmoc cleavage by repetitive short treatments with piperidine/DMF 1:4 will cause only negligible losses of load when synthesizing medium-sized peptides (up to 30 amino acids).

Base-catalyzed *transesterification* yields fully protected peptide esters [27]. Rate and yield can be increased considerably by adding a solvent for proper swelling such as DMA, as the peptide resin does not swell sufficiently in alcohols. Unfortunately, the concomitant racemization of the *C*-terminal amino acid will also be accelerated (Phe >> Ala > Val > Leu > Pro). Lithium bromide/1,8-diazabicyclo[5.4.0]-undec-7-ene [28] and potassium cyanide

Scheme 3. *Cleavage with Nucleophiles*



i) hydrazine hydrate/DMA 1:9 or 1:4. ii) NH_3, NH_4Cl (or LiCl), under pressure. iii) RNH_2 (neat if possible). iv) $NH_2R'NH_2$ (neat if possible). v) R''OH, DMA, KCN (or LiBr/di-azabicycloundecene 5:2 (molar ratio). vi) $NaBH_4$, LiCl, THF (or THF/EtOH). vii) pyridine · SO_3, Et_3N, DMSO.

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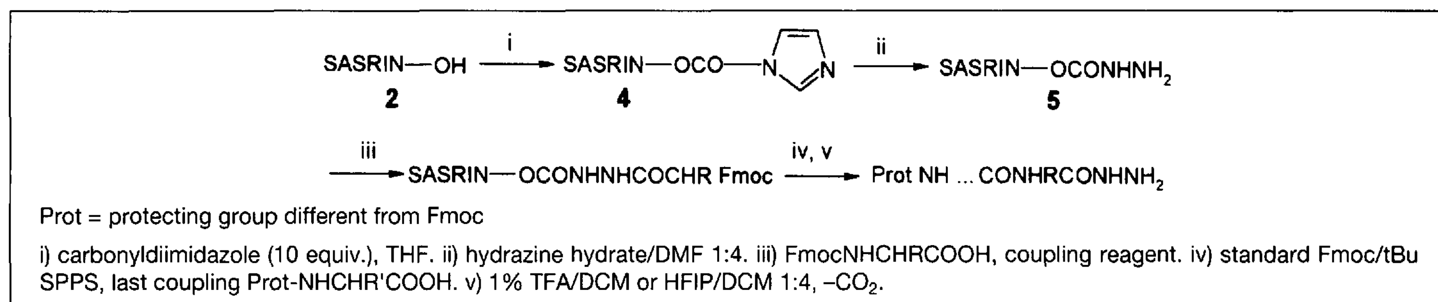
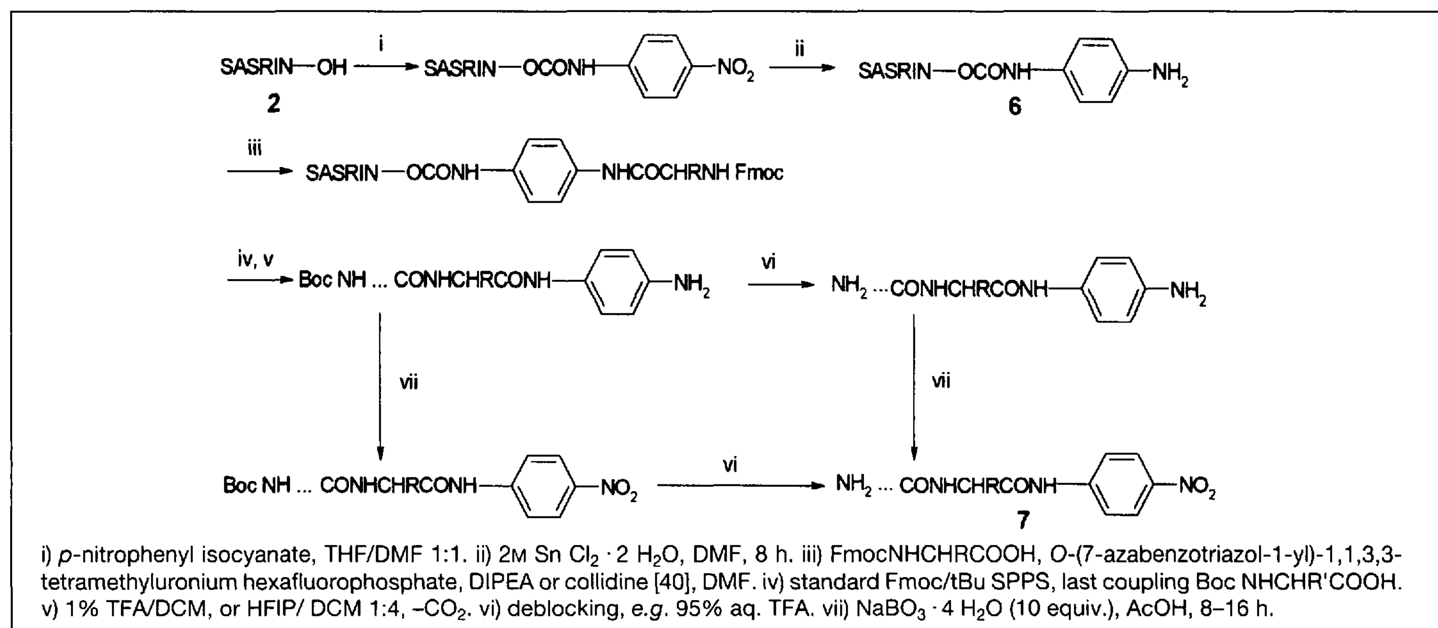
Scheme 4. *Synthesis of Fully Protected Peptide Hydrazides* via SASRIN *carbazate*



Prot = protecting group different from Fmoc

i) carbonyldiimidazole (10 equiv.), THF. ii) hydrazine hydrate/DMF 1:4. iii) FmocNHCHRCOOH, coupling reagent. iv) standard Fmoc/tBu SPPS, last coupling Prot-NHCHR'COOH. v) 1% TFA/DCM or HFIP/DCM 1:4, $-CO_2$.

Scheme 5. *Synthesis of Peptide* p-*Nitroanilides* **7**



i) *p*-nitrophenyl isocyanate, THF/DMF 1:1. ii) 2M Sn $Cl_2 \cdot 2\ H_2O$, DMF, 8 h. iii) FmocNHCHRCOOH, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, DIPEA or collidine [40], DMF. iv) standard Fmoc/tBu SPPS, last coupling Boc NHCHR'COOH. v) 1% TFA/DCM, or HFIP/ DCM 1:4, $-CO_2$. vi) deblocking, *e.g.* 95% aq. TFA. vii) $NaBO_3 \cdot 4\ H_2O$ (10 equiv.), AcOH, 8–16 h.

[29] proved to be the most effective catalysts of transesterification, thus, cleavage with the former catalysts proceeds more rapidly, whereas removal of the latter is more convenient.

The ease of *reductive cleavage* does not depend on the nature of the *C*-terminal amino acid, Ile reacts as smoothly as Gly [30]. The choice of the lithium salt (chloride, bromide) and the composition of the solvent, *i.e.*, the amount of ethanol added to the THF, determine the reactivity of the system, which has to be optimized to suppress side reactions. Special care has to be taken to avoid reductive cleavage of peptide bonds if the peptide contains Pro or *N*-alkylamino acids, as the tertiary amide bond is quite susceptible towards reduction. Asp(O*t*Bu) may be slowly reduced to yield homoserine, whereas Glu(O*t*Bu) is more resistant to reduction. Cleavage yields may decrease with increasing peptide length. Fully protected peptide alcohols can be oxidized to yield the corresponding aldehydes, *e.g.*, with sulfur trioxide/pyridine complex, dimethylsulfoxide and triethylamine (*Parikh-Doering* method), whereas the attempt to obtain these compounds directly by reductive cleavage with diisobutyl aluminum hydride at low temperature failed.

6. *SASRIN*™ Derivatives

The scope of applications of *SASRIN* can even be further extended by employing reactive derivatives such as **4** (see *Scheme 4*) [31]. The carbazate **5** (available from **4** and hydrazine hydrate) has been used for the synthesis of fully protected peptide hydrazides, as the cleavage conditions do not differ from those described in *Sect. 4*. *SASRIN* carbazate lends itself especially to the synthesis of protected hydrazides containing Asp(O*t*Bu), *C*-terminal Pro (no formation of diketopiperazine), or a *β*-branched *C*-terminus.

Peptide *p*-nitroanilides which have found wide application as chromogenic enzyme substrates can be rapidly obtained by SPPS on (*p*-aminophenyl) aminocarbonyl oxymethyl polystyrene followed by oxidation of the peptide *p*-aminoanilide cleaved from the resin [32]. But, as **4** reacted only sluggishly with weak bases such as 4-phenylenediamine, a different synthetic pathway had to be found to obtain the *p*-aminoanilide derivative of *SASRIN* **6** [33]. The analogous derivative of hydroxymethylated polystyrene has already been synthesized by a method not applicable to *SASRIN* [32]. The synthesis of **6** avoiding bifunctional reagents and its use is outlined in *Scheme 5*. Unexpectedly, the nitro derivative could be smoothly reduced with stannous chloride without premature cleavage from the resin.

Burdick's resin [32] and the *SASRIN* derivative have been employed for the synthesis of peptide *p*-aminoanilides to be oxidized in solution to yield the peptide *p*-nitroanilides **7**, compounds having gained importance as enzyme substrates. Again, the mild cleavage procedure (1% TFA/DCM works as well as HFIP/DCM) turns out to be an additional advantage, Trp(Boc)-containing, protected peptide *p*-nitroanilides could be obtained by perborate oxidation, whereas the unprotected indole moiety would have been attacked.

N-SASRIN-yl ethylamine can be obtained smoothly by treating **3** with ethylamine/DMF 1:2, Fmoc/*t*Bu SPPS, followed by cleavage with 95% aq. TFA, yields the deprotected peptide *N*-ethylamide [34], for the *N*-ethylamide derivative of *SASRIN* is considerably less acid-sensitive than the *SASRIN* esters (cleavage of *N*-unsubstituted amides from the corresponding *SASRIN* derivative proved even more difficult, only low yields of peptide amides were obtained, *e.g.*, with TFA/thioanisol 95:5 [35]).

The synthesis of acid-labile *SASRIN* ethers has not been tackled yet, whereas the less acid-sensitive *SASRIN* thioethers, *e.g.*, the derivative of *N*-Fmoc-cysteamine, can be rapidly obtained by reacting *SASRIN* chloride **3** with thiols and a tertiary amine.

7. Conclusions and Outlook

In this review we have demonstrated the versatility of *SASRIN* and several derivatives thereof. Besides its standard applications in solid-phase peptide synthesis, such as synthesis of fully protected peptide fragments, a broad range of peptide derivatives can be obtained either by variation of the cleavage method or by employing *SASRIN* derivatives such as *p*-(*SASRIN*-oxycarbonylamino)aniline **6**. *SASRIN* found further applications in combinatorial chemistry. So *SASRIN* was used as a carrier in solid-phase organic synthesis, *e.g.*, of *p*-substituted benzoic acids *via Suzuki* coupling on solid phase [36], of quinazoline-2,4-diones [37], and of *β*-lactams [38]; solid phase reactions were monitored by recording the FTIR and *Raman* spectra of a single bead [39]. The development of further *SASRIN* derivatives will be stimulated certainly not only by the needs of peptide synthesis but as well by the demands of combinatorial chemistry.

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