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Preparation of *N*-Substituted *N*-Arylsulfonylglycines and Their Use in Peptoid Synthesis

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Supporting Information

ABSTRACT: To increase the chemical diversity accessible with peptoids and peptide−peptoid hybrids, *N*-alkylated arylsulfonamides were used to prepare side chain protected *N*-substituted glycines compatible with solid-phase synthesis. The described procedures give access to peptoid monomers bearing a wide variety of functional groups from commercially available amines in four straightforward steps. The prepared *N*-substituted *N*-arylsulfonylglycines were used as monomers in solid-phase synthesis to introduce relevant functionalized side chains into peptoid oligomers and peptide−peptoid hybrids.

Peptides are useful tools in chemical biology and drug discovery, but their application as therapeutic agents has been hampered by poor bioavailability and degradation by proteases. Among the oligomeric peptidomimetics developed to overcome these drawbacks,[1] peptoids showed very attractive structural and biological properties.[2] Peptoids are oligomers of *N*-substituted glycines (NSG), and the simple migration of the side chains to the backbone nitrogens significantly improves relevant pharmacological properties. Compared to peptides, peptoids are immune to proteolytic degradation[3] and the removal of highly hydrated N−H bonds improves the cell permeability and bioavailability of these compounds.[4] On the other hand, the *N*-alkylation of one or several amino acid residues or their substitution by NSG residues in bioactive peptides was also shown to improve pharmacokinetic properties such as resistance to proteases and bioavailability.[5]

The synthesis of peptoid oligomers is straightforward, and two general routes have been developed: the monomer and submonomer approaches. The submonomer method introduced by Zuckermann et al.[6] is the most frequently used and involves iterative acylation and amination reactions on solid support to build up peptoid residues and generate oligomers after multiple rounds. In comparison, the monomer approach has a direct analogy with solid-phase peptide synthesis where *N*-Fmoc NSG monomers are sequentially coupled to the solid support to create oligomers.[2a,5c,d] A practical advantage of this approach is the use of essentially the same synthesis protocol as peptides, facilitating its implementation on automated peptide synthesizers to prepare peptoids and peptomers (peptide-peptoid hydrids) or perform a peptoid scan on a bioactive peptide. While the submonomer method requires a large excess of reagents, the monomer approach uses fewer equivalents, which is more economical when expensive side chain functionalized peptoid residues need to be incorporated in the sequence.

Typically, NSG derivatives are prepared in solution from their corresponding amine by *N*-alkylation with a bromoacetate alkyl ester followed by ester cleavage and *N*-Fmoc protection.[5c,d,7] Compared to NSG bearing neutral hydrophobic side chains, the number of commercially available amines to prepare side chain protected monomers is very limited. As protection of functionalized side chains is recommended to avoid side reactions during NSG synthesis and oligomerization, different routes have been developed to prepare side chain protected amines and their corresponding NSG monomers. Depending on the functional group needing protection, the synthesis of side chain protected NSG usually requires around 6 steps and they are often recovered in low yields (15−37%).[5c,d,8] In most cases, their preparation involves a sequence of (1) amine protection; (2) side chain protection; (3) amine deprotection; (4) *N*-alkylation with a bromoacetate ester; (5) ester cleavage; and (6) amine reprotection with an Fmoc group. In an effort to increase the chemical diversity accessible with the monomer approach and introduce interesting reactive or polar functionalities into peptoids and peptomers, we decided to develop a simple and affordable approach to prepare functionalized NSG derivatives bearing protected side chains and to use them in solid-phase synthesis. Herein we report our results concerning the use of *N*-alkylated 2-nitrobenzenesulfonamides to prepare *N*-substituted glycine building blocks for peptoid and peptomer synthesis.

Based on our previous work with *N*-substituted arylsulfonamides as alternative building blocks to prepare peptoids,[9] our

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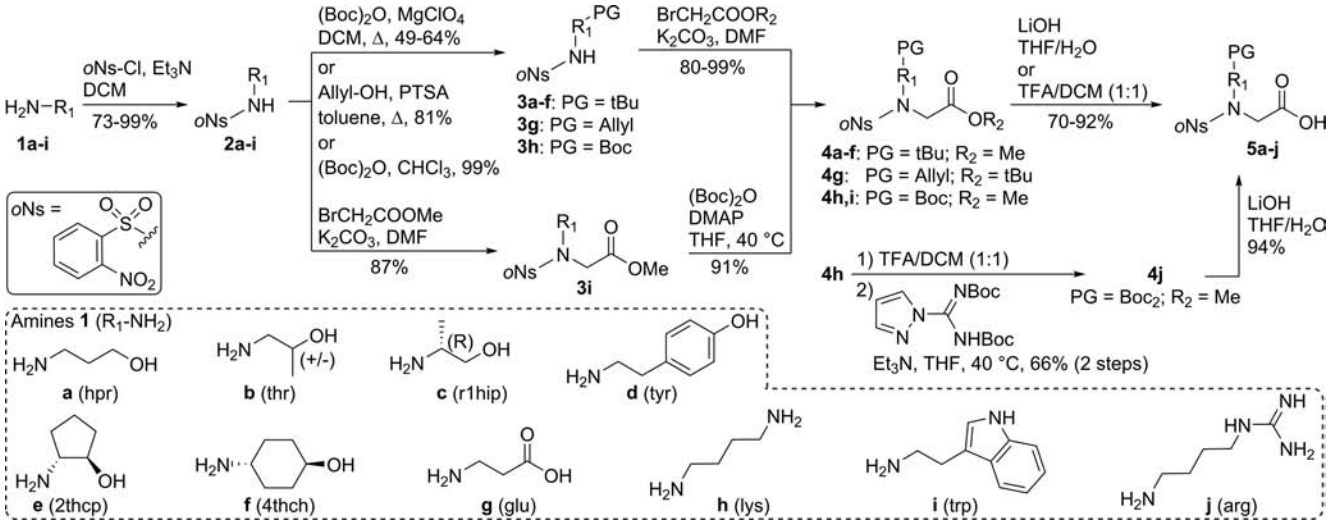
Scheme 1. Synthesis of Side Chain Protected *N*-Substituted *N*-Arylsulfonylglycines



strategy to obtain side chain protected NSG monomers was to use commercially available amines as starting material and protect/activate the amine with a 2-nitrobenzenesulfonyl group (*o*Ns) followed by side chain protection giving fully protected submonomers that could be directly *N*-alkylated with methyl bromoacetate and saponified (Scheme 1). This approach offers the opportunity to obtain protected NSG monomers in 4 steps by avoiding the amine deprotection/reprotection with Fmoc steps and to increase yields by using larger amounts of bromoacetate during the *N*-alkylation step to reach completion since bis-alkylation of the amine is not possible. The *o*Ns group was selected based on its compatibility with most standard protecting groups used in peptide and peptoid solid-phase synthesis. Initially described by Fukuyama et al.,[10] the *o*Ns protecting group activates the amino function to generate a nucleophilic anion that can be selectively alkylated under mild conditions with alkyl halides or a Mitsonobu reaction. The *o*Ns was found to be very useful to prepare *N*-methylated peptides.[11] During oligomerization, the *o*Ns group can be efficiently removed with thiophenol or *β*-mercaptoethanol in the presence of a base and the released chromophore is visible to the naked eye. Moreover, it is compatible with different reaction conditions used in functional group protection such as esterification, amide formation, and *O*-*tert*-butylation. Finally, *o*Ns-protected derivatives have a high propensity to form solid powders, which are significantly more convenient to handle and use as feedstock.[12]

The protected NSG monomers **5a**−**i** were prepared by a straightforward four-step synthesis from different commercially available amines **1a**−**i** (Scheme 1). First, the *o*Ns protected amines **2a**−**i** were prepared from *o*Ns-Cl and the corresponding amine under standard conditions. Due to a lack of selectivity between the primary amine and the phenolic hydroxyl of tyramine **1d**, a more selective procedure described by Penso et al.[13] with *o*Ns-Cl in a THF/DMF (8:1) mixture in the presence of lyophilized solid sodium carbonate as base was used to prepare *N*-*o*Ns-tyramine **2d** in good yields. For the second step, appropriate protection was performed on the functionalized side chains. First, *O*-*tert*-butylation of compounds **2a**−**f** was achieved with magnesium perchlorate and di-*tert*-butylcarbonate in refluxing DCM as described by Bartoli et al.[14] and gave the corresponding *tert*-butyl ethers **3a**−**f** (Table 1). With yields

Table 1. Isolated Yields for Protected NSG Monomers 5a−j

		overall yields[a] (%)	
amine **1**	residue	submonomer **3**	monomer **5**
a	*N*hpr(tBu)	49	44
b	*N*thr(tBu)	48	37
c	*N*1hipr(tBu)	44	36
d	*N*tyr(tBu)	42	39
e	*N*2thcp(tBu)	55	38
f	*N*4thch(tBu)	38	27
g	*N*glu(allyl)	70	56
h	*N*lys(Boc)	94	86
i	*N*trp(Boc)	–	57
j	*N*arg(Boc)$_2$	–	54

[a]Isolated yield after purification calculated from starting amines.

between 49% and 64%, the *O*-*tert*-butylation reaction is clearly the limiting step for the synthesis of **3a**−**f**. Improvement of this reaction would significantly increase the overall yields for submonomers **3a**−**f** and their respective monomers **5a**−**f**. The *o*Ns-*β*-Ala-Oallyl ester **3g** was obtained by esterification of **2g** with allyl alcohol and a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene. The allyl ester protected side chain is very useful to prepare a cyclic oligomer on solid support. Protection of the free amine of **2h** with a Boc group was conducted under standard conditions to give submonomer **3h** in good yields. Interestingly, compounds **3a**−**h** can be directly used as building blocks in peptoid synthesis by the submonomer approach using the appropriate bromine displacement conditions. Finally, because protection of **2i** with the Boc group occurred on both sulfonamide and indole nitrogens, a selective *N*-alkylation on the sulfonamide of **2i** was first performed with methyl bromoacetate to generate **3i** followed by protection of the indole with a Boc group to afford **4i** in 80% yields. *N*-Alkylation of submonomers **3a**−**f** and **3h** was achieved with methyl bromoacetate in the presence of K_2CO_3 to yield compounds **4a**−**f** and **4h**. Submonomer **3g** was alkylated with *tert*-butyl bromoacetate to avoid allyl ester hydrolysis with LiOH, and treatment of the fully protected NSG **4g** with a TFA solution afforded monomer **5g**. On the other hand, the methyl ester of compounds **4a**−**f**, **4h**, and **4i** was cleaved with LiOH to give side chain protected NSG **5a**−**f**,

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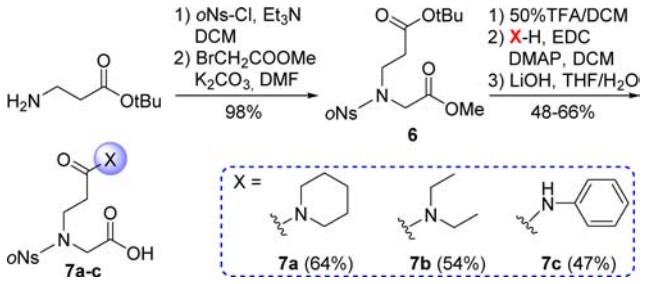
5h, and **5i** in good yields (70−91% for 2 steps). Finally, NSG **5j** bearing a guanyl moiety to mimic arginine was prepared from fully protected NSG **4h** by Boc-deprotection with a TFA solution and guanylation with *N*,*N*′-bis-Boc-1-guanylpyrazole followed by treatment with LiOH (Scheme 1). Overall, NSG monomers **5a−j** were obtained in moderate to good yields, and besides **5j**, their synthesis required 4 straightforward steps. The *o*Ns protection and *N*-alkylation reactions were the most efficient steps with 78−99% and 80−99% yields, respectively. Besides the O-*tert*-butylation reaction, side chain protection on amino and carboxyl groups was very efficient. Compared to the reported peptoid monomers synthesis of *homo*threonine (Fmoc-*N*thr(tBu)-OH, 6 steps, 15% yield),[5c] lysine (Fmoc-*N*lys(Boc)-OH, 4 steps, 20−38% yield),[8c,d] and *homo*tyrosine Fmoc-*N*tyr(tBu)−OH, 6 steps, 33−37%),[5d,8a,b] our approach allows a faster access to side chain protected NSG and in many cases with 2−3-fold increased yields.

Peptoid residues bearing amides can be useful to increase the molecular diversity of a library and explore a binding site in a compound optimization process. Amidated side chains have also been used to induce a particular folding and promote secondary or tertiary structures via hydrogen bonding.[15] To expend our approach to monomers with amidated side chains, NSG **7a−c** were prepared from commercially available *β*-alanine *tert*-butyl ester by a five-step synthesis (Scheme 2).

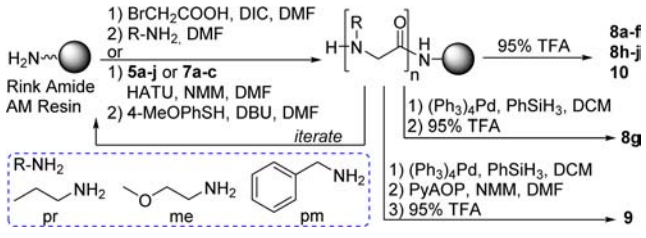
Scheme 2. Synthesis of Monomers with Amide Side Chains



First, the fully protected NSG **6** was obtained after amine protection with an *o*Ns group and *N*-alkylation as described above. After *tert*-butyl ester removal on **6**, different amines were coupled to the side chain followed by methyl ester cleavage to give monomers **7a−c** in 47−64% overall yields.

To demonstrate the compatibility of NSG monomers **5a−j** and **7a−c** with solid-phase synthesis, a series of peptoids were prepared on solid support (Scheme 3). The synthesis was performed on 50 mg of Rink amide resin using both submonomer and monomer approaches. For the submonomer method, peptoid residues were built up by an acylation step with bromoacetic acid and DIC (40 equiv) in DMF for 40 min followed by amination with a primary amine (30 equiv) in DMF for 40 min. For the monomer method, protected NSG

Scheme 3. Synthesis of Peptoid Oligomers



5a−j and **7a−c** were incorporated using HATU and HOAt with NMM as a base for 3 h and the *o*Ns group was cleaved with a solution of *p*-methoxybenzenethiol and DBU in DMF for 2 × 10 min (Scheme 3). In this case, *β*-mercaptoethanol was replaced by *p*-methoxybenzenethiol to avoid incomplete *o*Ns removal as described by different groups for poly-*N*-alkylated peptides and peptoids.[9,16] Cyclic peptoid **9** was obtained after allyl ester removal on peptoid **8g** with a catalytic amount of $Pd(PPh_3)_4$ in the presence of phenylsilane and macrocyclization on solid support with PyAOP. Peptoid **10** was prepared exclusively by the monomer method with *N*-substituted *N*-*o*Ns-glycines. Following side chain deprotection and cleavage from the resin with a TFA solution, the crude purity of the oligomers was evaluated by HPLC (Table 2). Excellent purities were obtained for most oligomers showing that *N*-substituted *N*-*o*Ns-glycines can be efficiently used as monomers in peptoid synthesis.

Table 2. Crude Purities and Isolated Yields for Oligomers Containing Monomers 5a−j and 7a−c

oligomer	sequence	purity[a] (%)	yield[b] (%)
8a	*N*pr-*N***1a**-*N*pr-*N*pm-*N*lys	91	67
8b	*N*pr-*N***1b**-*N*pr-*N*pm-*N*lys	84	73
8c	*N*pr-*N***1c**-*N*pr-*N*pm-*N*lys	93	67
8d	*N*pr-*N***1d**-*N*pr-*N*pm-*N*lys	89	71
8e	*N*pr-*N***1e**-*N*pr-*N*pm-*N*lys	67	55
8f	*N*pr-*N***1f**-*N*pr-*N*pm-*N*lys	75	74
8g	*N***1h**-*N*me-*N*pm-*N*pr-*N***1g**	91	78
8h	*N*pr-*N***1h**-*N*pr-*N*pm-*N*lys	92	95
8i	*N*pr-*N***1i**-*N*pr-*N*pm-*N*lys	95	75
8j	*N*pr-*N***1j**-*N*pr-*N*pm-*N*lys	87	70
8k	*N*pr-**7a**-*N*pr-*N*pm-*N*lys	93	82
8l	*N*pr-**7b**-*N*pr-*N*pm-*N*lys	95	75
8m	*N*pr-**7c**-*N*pr-*N*pm-*N*lys	98	55
9	c[*N***1h**-*N*me-*N*pm-*N*pr-*N***1g**]-NH_2	96[c]	69[c]
10	*N***1i**-**7b**-*N***1h**-*N***1d**-**7a**	70	41
11	**7b**-Ala-*N***1i**-Lys-*N***1d**	89	58

[a]Crude purities were determined by HPLC. [b]Isolated yield after purification by preparative HPLC. Based on initial loading of Rink Amide AM resin (0.56 mmol/g). [c]Three peaks containing only the expected cyclic compound were observed on the HPLC chromatogram. The reported crude purity and yield for **9** include all the peaks containing exclusively the expected compound.

As expected, oligomers **8e** and **8f** bearing hindered side chains were obtained in lower purities of 67% and 75%, respectively. Nevertheless the approach with monomers **5e** and **5f** showed an important improvement compared to purities of 39% for **8e** and 50% for **8f** obtained by the submonomer approach at room temperature.[9] These results suggest that the monomer approach could be more appropriate for hindered *α*-disubstituted amines. A previous study with submonomers **3e** and **3f** in solid-phase peptoid synthesis showed that the bromine displacement on solid support was the limiting step. In the monomer approach, this step is performed in solution and could be more efficient since a greater quantity of alkylating reagent can be used. This strategy offers, for more hindered residues, significant building block economy and the opportunity to increase oligomer purities and isolated yields. Moderate purities were observed for cyclic peptoid **9**, but LC-MS analysis confirmed the absence of the linear precursor and showed the presence of only one molecular ion

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corresponding to the expected mass for the cyclic product in each peak (Supporting Information, Figure S3). Such behavior has also been observed for cyclic peptoids by Kwon et al.[17] and, due to the absence of chirality, could be explained by the presence of different conformations. A peptomer containing three NSG and two amino acids was prepared by standard solid-phase peptide synthesis with HATU as a coupling reagent and a piperidine solution to remove the Fmoc group from the amino acid residues while the *o*Ns group from the NSG was cleaved with the solution described above. Peptomer **11** was obtained in good purities and yields showing that *N*-substituted *N*-*o*Ns-glycines can also be used as monomers in the synthesis of peptide−peptoid hybrids.

In conclusion, a convenient four-step synthesis was developed to prepare *N*-substituted *N*-*o*Ns-glycines from readily available amines. The described approach eliminates the amine deprotection/Fmoc reprotection steps commonly observed in the synthesis of side chain protected NSG and allows the synthesis of peptoid monomers bearing a wide variety of functional groups. The results obtained in this work demonstrate that these *N*-substituted *N*-*o*Ns-glycines can be used as buildings blocks in peptoid and peptomer synthesis to introduce interesting reactive or polar side chains. Moreover, the conditions used in this work allow a substantial building block economy compared to standard submonomer method conditions. Simple and affordable, the described procedures represent a complementary and interesting alternative approach to introduce relevant functionalities into peptoids and peptide−peptoid hybrids, increasing the chemical diversity accessible with the monomer method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02862.

Detailed experimental procedures, analytical and characterization data for all compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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