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Solution-Phase Synthesis of Aminooxy Peptoids in the *C* to *N* and *N* to *C* Directions†

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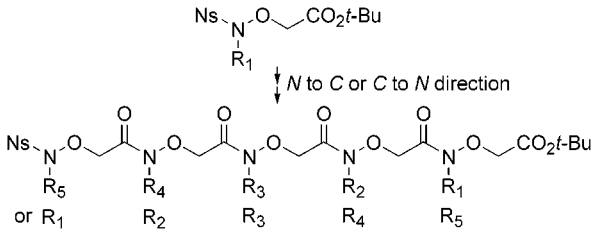
ABSTRACT



Aminooxy peptoids, which are potential peptidomimetics, were synthesized by a stepwise monomer assembly. Ns-protected *N*-substituted aminooxyacetate *tert*-butyl esters were used as a monomer in both the *C* to *N* and the *N* to *C* directions. Submonomer synthesis of aminooxy peptoids is also described.

Peptides are known to have severe limitations for use as therapeutic agents due to degradation by proteases and low membrane permeability.[1] To overcome these limitations and to improve bioavailability for therapeutic applications, a number of backbone-modified peptides (pseudopeptides) have been designed, synthesized, and characterized for over a decade.[1,2] Peptoids, which are one of the earliest pseudopeptides,[3] have been extensively studied for their biological functions[4] and structural features.[5] Recently, it was found that peptoids with aminoethyl side chains could transfer DNA into cells and thus potentially be employed as a novel type of a gene delivery vehicle.[6] Other peptoid analogues such as ureapeptoids,[7] retropeptoids,[8] oligomannopeptoids,[9] β-peptoids,[10] and hydrazinoazapeptoids[11] have been synthesized in order to provide more structural diversity and useful biological properties.

† **Abbreviations:** DIC, diisopropylcarbodiimide; EDC, 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide·HCl; HOAt, 1-hydroxy-7-azabenzotriazole; HBTU, *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOBt, *N*-hydroxybenzotriazole; PyBop, benzotriazole-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate; TFFH, tetramethylfluoroformamidinium hexafluorophosphate.

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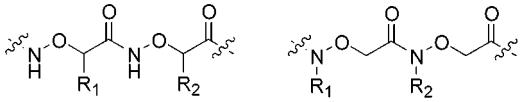
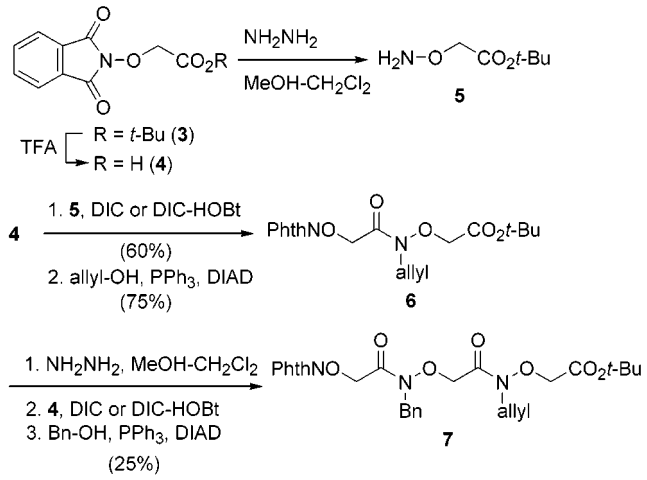
The α-aminooxy peptide (**1**), which is formed from α-aminooxy acid monomers, is another pseudopeptide.[12,13] Spectroscopic studies and computational analysis indicated that even short *β*-aminooxy peptides are capable of adopting eight-membered, hydrogen-bonded turns (N−O turns). As part of an effort to explore new peptoid analogues with potentially useful biological properties, we have synthesized aminooxy peptoids **2**, in which side chains are attached to the nitrogen atom of aminooxy acid monomer instead of the α-carbon atom of each monomer in α-aminooxy peptides. The synthesis was accomplished in both the *C* to *N* and the *N* to *C* directions.



Initially, we examined the submonomer synthesis of aminooxy peptoids using aminooxyacetate *tert*-butyl ester protected by the phthaloyl (**3**) or *o*-nitrobenzenesulfonyl group (**8**) at the *N*-terminus. Phthalimidooxyacetic acid (**4**),[12b] prepared from acid-promoted *tert*-butyl deprotection of **3**, was coupled to aminooxyacetate *tert*-butyl ester (**5**) under several coupling conditions (DIC, DIC−HOBt, HOBt−HBTU, PyBop−HOBt and EDC−DMAP) (Scheme 1). It was found that DIC or DIC−HOBt gave the desired dimer in a moderate yield (∼60%), but HOBt−HBTU gave low coupling yields (∼30%) and PyBop−HOBt or EDC−DMAP gave no desired product even after a prolonged coupling time. The resulting dimer was alkylated under Mitsunobu conditions with allyl alcohol, PPh_3, and DIAD to provide the *N*-allylated dimer **6** (45% overall yield).[14] The second chain elongation steps (deprotection, coupling, and *N*-alkylation) using benzyl alcohol gave the dialkylated trimer **7** in a low overall yield (25%). Since the yield for each cycle of chain elongation decreased abruptly as the length of aminooxy peptoids increased, oligo-aminooxy peptoids were barely synthesized.

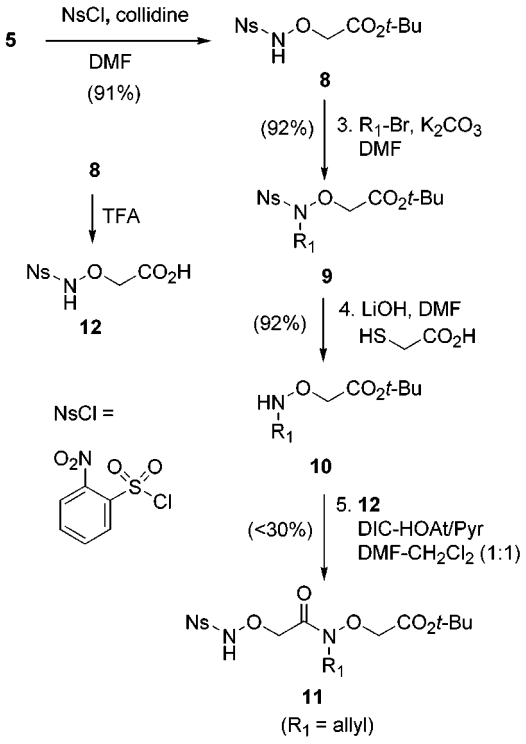
We, then, changed the phthaloyl protecting group of the *N*-terminus in **3** to an Ns (*o*-nitrobenzenesulfonyl) group for submonomer synthesis of aminooxy peptoids (Scheme 2). It was reported that the Ns protecting group of an amine functional group is suitable for solid- or solution-phase

Scheme 1



synthesis of *N*-alkylated peptides or ureapeptoids.[7a,15] The Ns-protected aminooxy ester **8** was obtained from reaction of **5** with *o*-nitrobenzenesulfonyl chloride (NsCl) in the presence of collidine as a base in DMF in 91% yield. It should be noted that the sulfonylation reaction is highly sensitive to the employed base and solvent. DIEA, which is a stronger base than collidine and the most widely used for the peptide synthesis, produced the bis-sulfonylated aminooxy ester ($Ns_2NOCH_2CO_2t$-Bu) as a major product, and CH_2Cl_2 as a solvent needed longer reaction time to complete the sulfonylation. The pK_a value of NH in **8** after monosulfonylation is significantly lowered and thus the partial

Scheme 2



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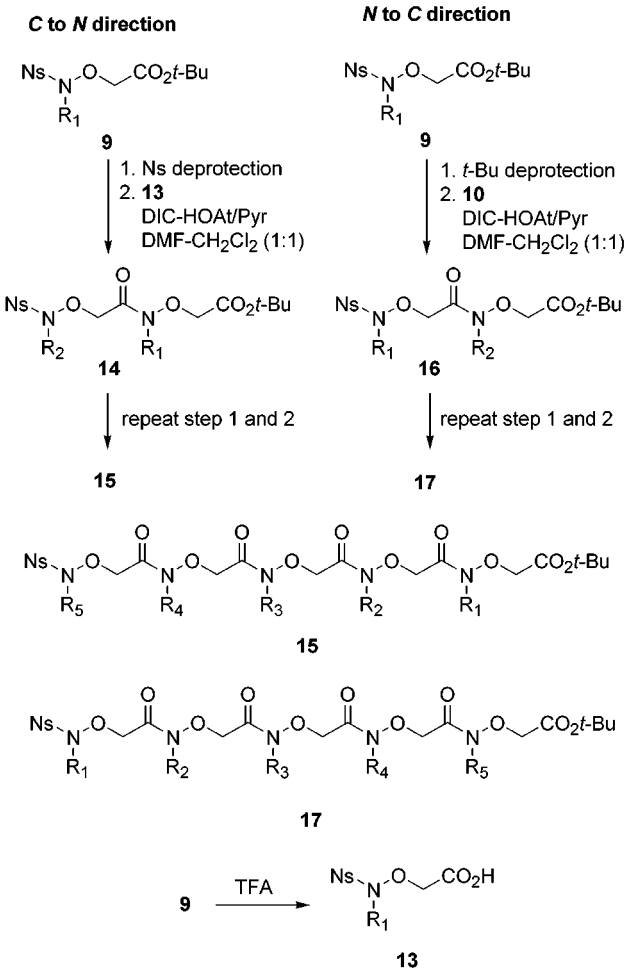
Scheme 3



deprotonation of NH in **8** by a stronger base DIEA may result in accelerating the formation of bis-sulfonylation of **8**. The *N*-allylation of sulfonamide **8** with allyl bromide and K_2CO_3 afforded the allylated monomer **9** in high yield (92%). Deprotection of the Ns group in **9** was examined under several conditions ($HSCH_2CO_2H-LiOH$, $HSCH_2CO_2H-K_2CO_3$, $HSCH_2CO_2H-DBU$, $PhSH-K_2CO_3$, $HSCH_2CH_2OH-DBU$, and $HSCH_2CH_2OH-KOtBu$).[15] We found that 2 equiv of $HSCH_2CO_2H$ and 10 equiv of LiOH gave the most efficient deprotection reaction and less than 10 equiv of LiOH did not give a complete deprotection of the Ns group. However, PhSH or $HSCH_2CH_2OH$, which is normally employed to remove the Ns group, was not suitable in this case. The byproduct of *o*-$O_2NC_6H_4SPh$ or *o*-$O_2NC_6H_4SCH_2CH_2OH$ formed by desulfonylation had to be removed by flash column chromatography causing partial decomposition of the product **10**, which was obtained in low yield. The conditions that use $HSCH_2CO_2H$ have an advantage over PhSH or $HSCH_2CH_2OH$ conditions in that the byproduct of *o*-$O_2NC_6H_4SCH_2CO_2H$ can be easily removed by a basic workup. The crude product obtained after the removal of

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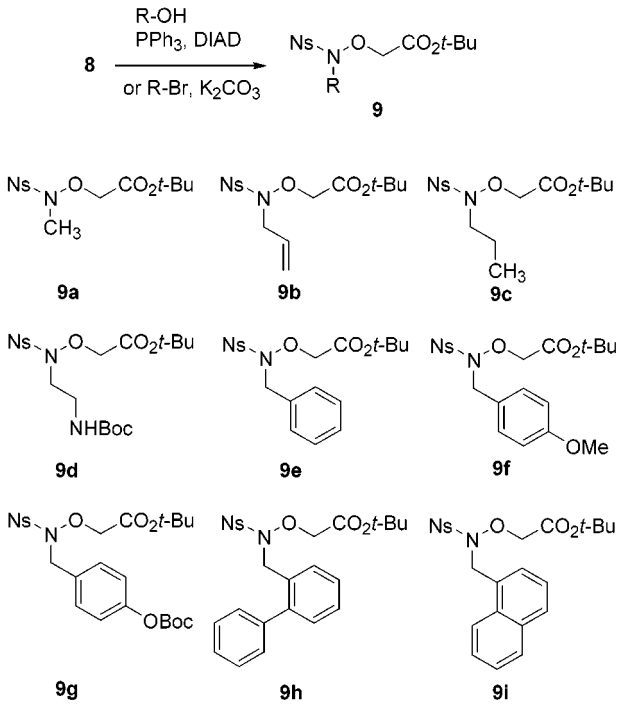
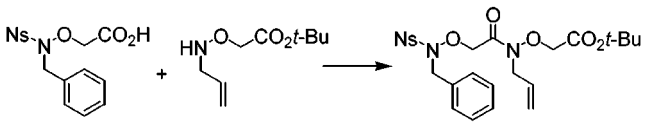


Figure 1.

the Ns group is pure enough to use for the next reaction without further purification.

We, then, examined the coupling of **10** to **12** with several coupling reagents to form the dimer **11**. Only DIC−HOAt−pyridine produced the product in low yield (<30%) while coupling with DIC−HOAt−DIEA, DIC−DMAP, DIC, EDC−DMAP, PyBop−HOBt, and HOBt−HBTU did not give any desired product. Presumably, the acidic proton of

Table 1.



coupling conditions	yield, %
PyBop−DIEA, CH_2Cl_2	*a*
PyBop−Pyr, CH_2Cl_2	55
TFFH−DIEA, CH_2Cl_2	51
TFFH−DIEA, DMF	*a*
TFFH−Pyr, CH_2Cl_2	*a*
TFFH−collidine, CH_2Cl_2	*a*
DIC, CH_2Cl_2	60
DIC−DIEA, CH_2Cl_2	40
DIC−HOBt, CH_2Cl_2	50
DIC−HOAt, Pyr, CH_2Cl_2	63
DIC−HOAt, DIEA, DMF−CH_2Cl_2 (1:1)	*a*
DIC−HOAt, NEM, DMF−CH_2Cl_2 (1:1)	*a*
DIC−HOAt, Pyr, DMF−CH_2Cl_2 (1:1)	93

[a] No product.

Table 2.

	R_1	R_2	R_3	R_4	R_5
15a	allyl	*p*-Bn-OMe (92%)[a]	Bn (72%)	Me (50%)	CH_2-1-Naph (<10%)
15b	allyl	Bn (93%)	Me (74%)	CH_2-1-biphenyl (83%)	$CH_2CH_2CH_3$ (20%)
15c	allyl	*p*-Bn-OMe (92%)	CH_2CH_2NHBoc (75%)	Bn (54%)	Me (32%)
17a	Bn	$CH_2CH_2CH_3$ (80%)	allyl (68%)	Me (86%)	CH_2CH_2NHBoc (51%)
17b	Bn	$CH_2CH_2CH_3$ (80%)	allyl (68%)	Me (86%)	*p*-Bn-O(Boc) (34%)
17c	CH_2-1-Naph	Me (95%)	Bn (78%)	*p*-Bn-OMe (50%)	allyl (46%)
17d	CH_2-1-Naph	Me (95%)	Bn (78%)	*p*-Bn-OMe (50%)	CH_2CH_2NHBoc (48%)

[a] Yield for both deprotection and coupling reactions.

NH in **12** might have some affect on the coupling reaction. To test this assumption, we attempted to couple an *N*-allylated monomer to a *N*-benzylated monomer with DIC−HOAt−pyridine (vide infra). As expected, the *N*-alkylated dimer was obtained in high yield (93%).

On the basis of the result of the high coupling yield between *N*-alkylated monomers, we decided to prepare oligo-aminooxy peptoids by stepwise monomer assembly using *N*-alkylated monomers **9**. Synthesis in both the *C* to *N* and the *N* to *C* directions was tested (Scheme 3). Several monomers shown in Figure 1 were prepared under Mitsunobu conditions or by conventional alkylation in high yield (>90%). For synthesis of aminooxy peptoids in the *C* to *N* direction, the Ns group in **9** was first removed by $HSCH_2CO_2H$−LiOH (2 equiv:10 equiv) in DMF as described above and then the resulting secondary amine without further purification was reacted with acid **13** to provide dimer **14**. We investigated the coupling reaction of Ns-protected *N*-benzyl aminooxy acid and *N*-allyl aminooxyacetate *tert*-butyl ester in more detail (Table 1). While PyBop and pyridine in CH_2Cl_2 gave the dimer in 55% yield, no product was observed in the presence of DIEA as the base. When PyBop as a coupling reagent was changed to TFFH, which was known to be very powerful coupling reagent,[16] only DIEA as a base in CH_2Cl_2 provided the product in moderate yield (51%). HOAt−DIC−pyridine conditions in DMF−CH_2Cl_2 (1:1) were found to be optimal to give the highest yield (93%) among the examined conditions.[17] Use of DIEA or *N*-ethylmorpholine (NEM) instead of pyridine resulted in side reactions mainly. Pure DMF or CH_2Cl_2 turned out to be inefficient for the coupling reaction. Dimer **14** was used in three consecutive Ns-deprotection/coupling cycles to prepare pentamers **15** shown in Table 2.

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Alternatively, several penta-aminooxy peptoids were synthesized in the *N* to *C* direction (Scheme 3). The *tert*-butyl group of monomer **9** was removed by TFA and then subsequent coupling to **10** with HOAt−DIC−pyridine in DMF:CH_2Cl_2 (1:1) afforded dimer **16** in high yield. The dimer was used in the next iteration of the sequence (*t*-Bu deprotection and coupling) to furnish pentamers **17** shown in Table 2.

It is worthwhile mentioning that, in both the *C* to *N* and the *N* to *C* directions, the coupling of the chain-extending peptoids containing bulky side chains at terminal positions to *N*- or *C*-deprotected monomers gave a relatively low yield due to steric effects. In addition, preparation of pentamers in the *N* to *C* direction was found to give, in general, a better overall yield than that in the *C* to *N* direction since as the chain length of aminooxy peptoids gets longer and longer, the deprotection of the Ns group in the extending aminooxy peptoids is problematic due to the poor recovered yield of Ns-deprotected products from the basic workup.

In summary, we have successfully synthesized in both the *C* to *N* and the *N* to *C* directions several penta-aminooxy peptoids by a stepwise monomer assembly using monomers. The screening for biological activities of the aminooxy peptoids is in progress and will be reported in due course.

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Supporting Information Available: Detailed descriptions of the experimental procedure to synthesize monomers, dimers, and pentamers and their analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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