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Synthesis of biaryl-linked cyclic peptoids

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ABSTRACT

Peptoids, a class of peptidomimetic, have gained considerable attention as potential therapeutic agents due to properties such as biocompatibility and resistance to enzymatic degradation. In linear peptoids, conformational heterogeneity can arise due to *cis/trans* isomerization around the backbone tertiary amide bond which has led to an increasing interest in cyclic peptoids. Biaryl linkages appear as a common structural motif in many synthetic and naturally occurring cyclic peptides but they are yet to be utilized in the formation of cyclic peptoids. Herein, we describe the application of a solid-phase Suzuki cross-coupling strategy as a means to prepare of a series of biaryl-linked cyclic peptoids. The methodology presented allows access to a range of novel biaryl containing cyclic peptoids with varying ring sizes.

Introduction

Peptoids (*N*-substituted glycines) belong to a class of synthetic molecules known as peptidomimetics, so named because of their similarity in structure to peptides (Fig. 1).[1,2] Like peptides, peptoids are oligomeric in nature and they contain side-chains (R) which may comprise of a wide variety of functional groups. However, a peptoid's backbone is devolved entirely of tertiary amide bonds, and, this in turn gives them a range of different physical and biological properties to peptides.

For example, peptoids are highly resistant to enzymatic degradation,[3] making then desirable molecules for a range of biological applications including imaging probes,[4] antimicrobials,[5–7] antifungal[8] and anticancer[4] agents. In addition the lack of an amide NH within the backbone means that there is no capacity to use hydrogen bonding to stabilize the formation of discreetly folded secondary structures. Peptoids thus display an increased conformational flexibility over peptides, and controlling the *cis–trans* isomer profile in the backbone can be challenging.[9]

This lack of a defined (or inherent) secondary structure in many peptoids presents an obstacle to their use as therapeutics due to the fact that good selectivity and binding affinity for a particular target often requires conformational rigidity.[10,11] Cyclization offers a well-established process to modulate conformational flexibility in peptides[12,13] and leading on from this various strategies have been developed to cyclise peptoids. These include solution phase head-to-tail condensation,[14–17] side-chain "stapling" *via* Grubbs metathesis,[18] halide substitution[19] and copper-catalysed azide-alkyne cycloaddition (CuAAC).[20,21]

Within our laboratory we are interested in the development of new building blocks and approaches that can be used to access biaryl containing cyclic peptides.[22] The biaryl motif is commonly found in a range of important naturally occurring peptides including Vancomycin and the Biphenomycins as well as synthetic Arylomycin A2.[23,24] The biaryl motif has also received considerable attention from the pharmaceutical industry and it appears commonly in many compounds that have activity as anti-fungal, anti-tumour, anti-hypertensive and anti-inflammatory agents.[25–27] Given the attention directed towards biaryl motifs in peptide chemistry[28–30] it is surprising that within the field of peptoid chemistry little work in this area has been reported.[31] Elegant recent work by Nam and Seo demonstrated the application of a Suzuki-Miyaura cross-coupling strategy as a means to access linear peptoids containing novel biaryl monomers.[32] The aforementioned work utilized an intermolecular Suzuki cross-coupling process (i.e. arylboronic acid added to an aryl-halide monomer on resin) and to the best of our knowledge the corresponding intramolecular reaction has not yet been exploited to access biaryl containing cyclic peptoids.

Herein, we report the preparation of a series of novel cyclic peptoids scaffolds that contain a biaryl linkage. Preparation of a range of ring sizes are demonstrated and ring closure has been achieved using on resin Suzuki cross-coupling strategy.

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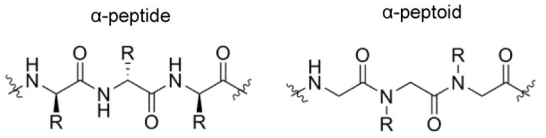
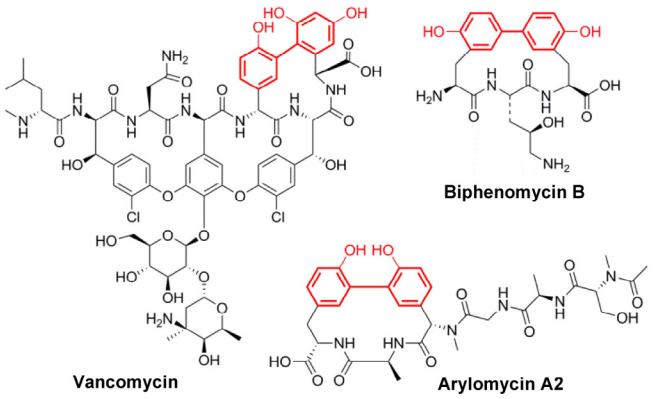


Fig. 1. Comparison of α-peptide and α-peptoid structures.



Results and discussion

In order to access cyclic peptoids *via* a Suzuki cross-coupling approach the linear parent peptoid has to contain both an aromatic halide (e.g. bromide or iodide) and an aromatic boronic acid. The established sub-monomer peptoid synthesis strategy[1] was used to build up the linear peptoid on Rink Amide resin and incorporation of the required aromatic halide was achieved using commercially available, 3-iodobenzylamine (**1**) (Scheme 1).

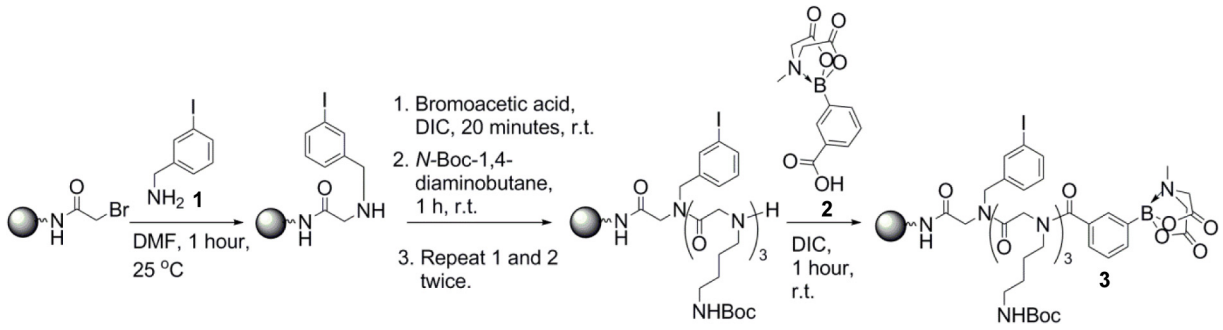
Incorporation of the aromatic boronic acid component was achieved using commercially available 3-carboxyphenyl boronic acid MIDA ester (**2**) with diisopropylcarbodiimide (DIC, Scheme 1). The boronic acid (**2**) is protected with *N*-methyliminodiacetic acid (MIDA), deprotection of which is afforded by treatment in aqueous base at room temperature.[33] MIDA boronates have been shown to be highly air stable, resistant to a wide variety of synthetic conditions[34] and previous work within the group in which MIDA boronate-containing peptides were synthesized, confirms their stability towards amide bond coupling conditions.[22]

The sequence of the first linear peptoid (**3**) chosen for cyclisation was designed to allow a relatively unstrained ring system to be accessed. We also incorporated Boc-protected amino butane monomers (Boc-*N*Lys) to aid solubility upon peptoid cleavage from the resin. We wanted to carry out the cyclisation/Suzuki cross-coupling whilst the parent linear peptoid (**3**) was still on resin. The advantages of carrying out the cross-coupling reaction whilst on resin are twofold: firstly, there is no need to cleave and purify the linear parent peptoid which is not only time consuming, but can often result in loss of overall yield. Secondly, after the Suzuki cross-coupling reaction has been carried out, any unreacted reagents (e.g. metals) and side-products can simply be removed by washing the resin, making purification of the final cyclic product easier. For the Suzuki cross-coupling we selected reaction conditions based on the previously reported work of Nam and Seo[32] and our own experiences of working with MIDA-protected amino acids.[22]

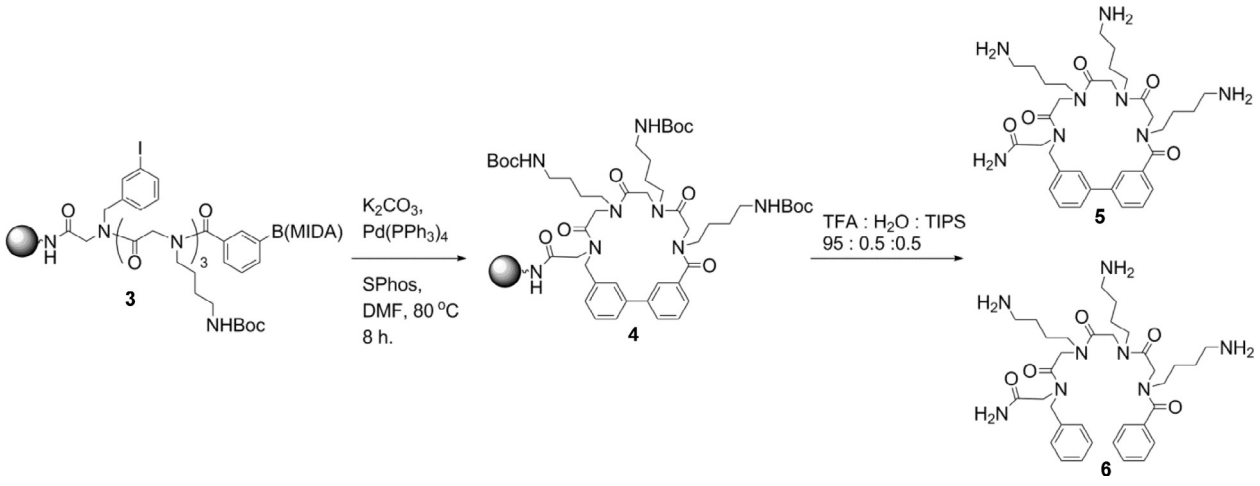
The cyclisation of the on resin linear peptoid (**3**) was therefore attempted using tetrakis palladium (5 mol%), Buchwald's ligand, and K_2CO_3 in DMF at 80 °C for 8 h. It should be noted that as the reaction procedure used K_2CO_3 in excess we did not carry out a separate deprotection step for the MIDA-protected boronate ester prior to carrying out the on resin Suzuki cross-coupling reaction. Following cleavage from the resin (TFA/DCM) cyclic peptoid **5** was isolated in a 15% yield as a water soluble white solid after reverse phase semi-preparative HPLC purification. While not isolated it is worth noting that the un-cyclised peptoid by-product (**6**) was observed in the LCMS of the crude reaction mixture (see Scheme 2).

Next, we wanted to probe the effects of flexibility and overall sequence length of the linear peptoid chain on the cyclisation reaction. To test this, we replaced one of the *N*Lys residues with a glycine monomer (increase in flexibility) and the synthesis of the linear parent peptoid (**7**) was completed by addition of 3-carboxyphenylboronic acid to the *N*-terminus as shown in Scheme 3. Suzuki cross-coupling, cleavage from the resin and subsequent HPLC purification gave the biaryl-containing cyclic peptoid **9** in 9% yield (Scheme 3). It should be noted that ESI LCMS analysis of the crude reaction mixture prior to HPLC purification again showed that the corresponding dehalogenation/deboronated product (**10**) was present.

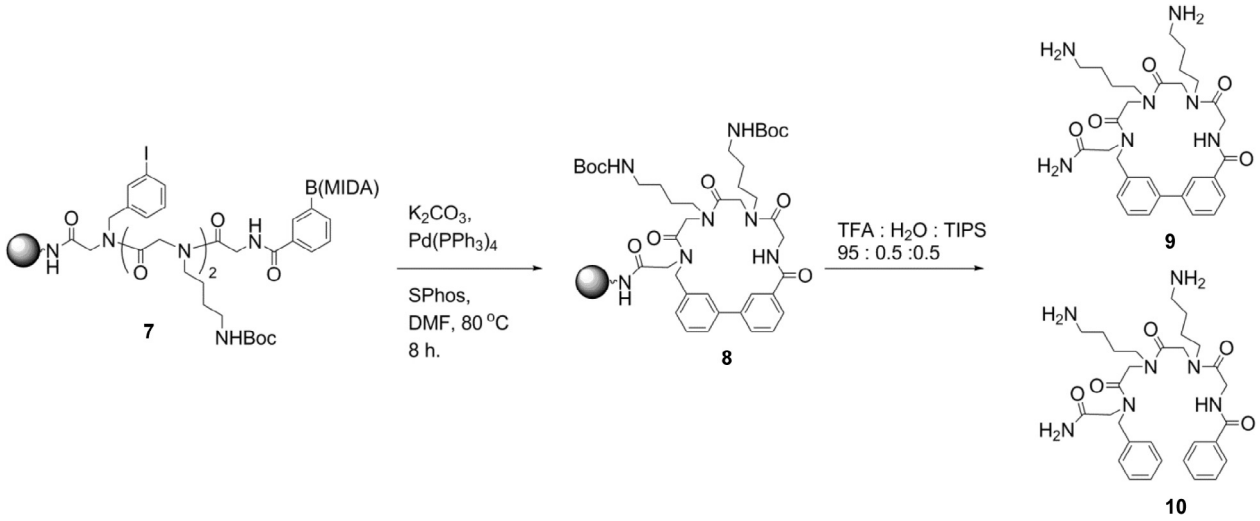
Having successfully isolated biaryl-containing cyclic peptoids **5** and **9**, we then proceeded to synthesise a small library of linear peptoids containing both an aromatic iodide and regio-isomeric MIDA-protected boronates (Table 1, 11–16). We carried out the Suzuki cross-couplings on each linear peptoid using the same reaction conditions in order to enable a simple comparison regarding the ease of ring formation (Table 1). Biaryl-containing cyclic peptoids were isolated from all of the linear sequences investigated, however, the isolated yields varied. Perhaps predictably, the longer sequences (**13**–**16**) appeared to be more difficult to cyclise, presumably due to a larger entropic penalty associated with constraining more flexible chains. With the exception of cyclic peptoids **9** and **20**, in each case, the yield of the cyclic peptoid recovered was lower as the sequence increased in length. For the shorter linear peptoids containing the 3-MIDA boronate building



Scheme 1. Incorporation of 3-iodobenzylamine (**1**) and 3-carboxyphenylboronic acid MIDA ester (**2**) into a linear peptoid (**3**).



Scheme 2. Solid phase cyclisation of parent linear peptoid (**3**) into resin bound cyclic peptoid (**4**) *via* Suzuki cross-coupling, followed by cleavage from the resin to give the free cyclic peptoid (**5**).



Scheme 3. Solid phase cyclisation of parent linear peptoid (**7**) into resin bound cyclic peptoid (**8**) *via* Suzuki cross-coupling, followed by cleavage from the resin to give the free cyclic peptoid (**9**).

block (i.e. compare **3** and **7**) incorporation of a less hindered glycine monomer into the sequence (**7**) reduced the yield of the cyclic peptoid obtained (i.e. compare **5** and **9**). This may indicate that the *N*Lys monomer confers some level of secondary structure in the linear peptoid (**3**) that makes the cross-coupling cyclisation reaction more favourable, whereas the extra flexibility conferred by the glycine monomer in **7** results in a greater entropic penalty having to be paid. Interestingly, the opposite is seen for the longer peptoids (i.e. **21** and **22**) with the glycine-containing linear peptoid (**16**) cyclising more readily than the *N*Lys-containing counterpart (**15**).

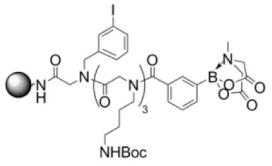
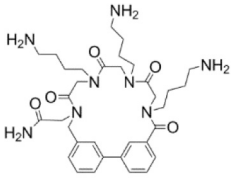
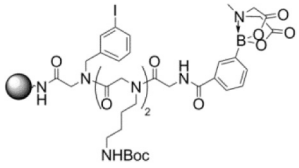
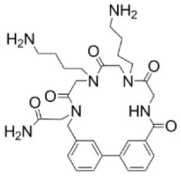
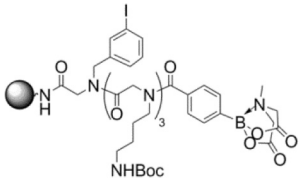
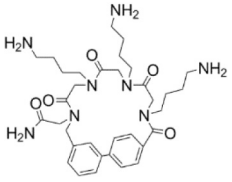
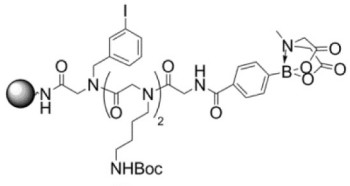
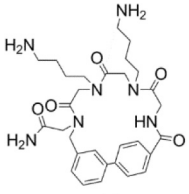
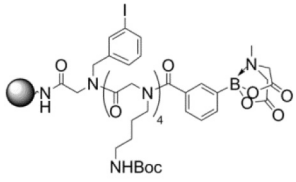
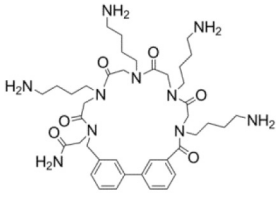
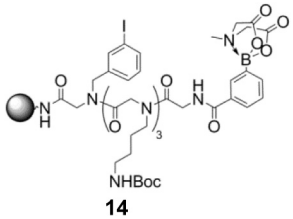
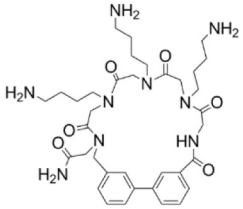
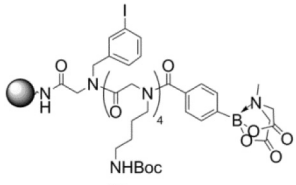
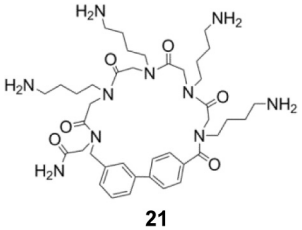
For the shorter linear peptoids containing the 4-MIDA boronate building block (**11** and **12**), the presence of the *N*Lys side-chain versus the glycine monomer appeared to make little difference to the efficiency of cyclisation, however, both resulting cyclic peptoids (**17** and **18**) were isolated in higher yields than the cyclic peptoids (**5** and **9**) formed from the corresponding shorter 3-MIDA boronate containing linear peptoids (**3** and **7**). This perhaps suggests that the formation of 3,4-biaryl-linked cyclic peptoids (**17** and **18**) is favored over the formation of the corresponding 3,3-biaryl-linked cyclic peptoids (**5** and **9**). The same trend is also seen as peptoid sequence length is increased, i.e. 3,4-biaryl-linked cyclic peptoid **22** was isolated in a higher yield than the corresponding 3,3-biaryl-linked cyclic peptoid **20**. However, given that the isolated yields in all of the aforementioned cases were not significantly different, it is difficult to draw any definitive conclusions from the data obtained. To gain more accurate information would require the linear peptoids to be cleaved and purified prior to Suzuki cross-coupling, but as discussed earlier the on-resin cyclisation confers many advantages in the overall synthetic strategy.

Conclusions

The primary aim of this study was to prepare a series of linear peptoids with suitable functionality that could be cyclised *via* an on-resin Suzuki cross-coupling in order to obtain novel biaryl-linked cyclic peptoids. This was achieved and a small library of cyclic peptoids with varying ring sizes and differing biaryl connectivity (i.e. 3,3- and 3,4-biaryl linkages) were prepared and isolated.

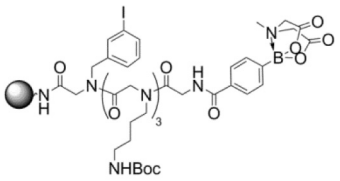
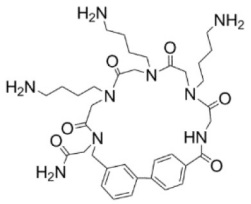
With the initial concept established, optimization of the on-resin cyclisation reaction is now ongoing and the formation of bi-cyclic biaryl-containing peptoids *via* application of novel MIDA-protected monomers is being explored. The biaryl-linked cyclic peptoids prepared are also undergoing biological evaluation and the results will be reported in due course.

Table 1
Library of linear and cyclic peptoids.

Linear peptoid	Cyclic peptoid[a]	Yield[b] (%)
 **3**	 **5**	15
 **7**	 **9**	9
 **11**	 **17**	23
 **12**	 **18**	22
 **13**	 **19**	14
 **14**	 **20**	13
 **15**	 **21**	3

(*continued on next page*)

Table 1 (*continued*)

Linear peptoid	Cyclic peptoid[a]	Yield[b] (%)
 **16**	 **22**	17

[a] Cyclic peptoids synthesized from linear parent peptoids under the conditions shown in Schemes 3 and 4.
[b] Isolated yields are calculated assuming that parent linear peptoids were synthesized with full conversion.

Acknowledgments

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A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.01.097. In addition underlying research data for this paper is available in accordance with EPSRC open data policy from http://dx.doi.org/10.15128/r2h128nd70n.

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