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A Facile Strategy for the Construction of Cyclic Peptoids under Microwave Irradiation through a Simple Substitution Reaction

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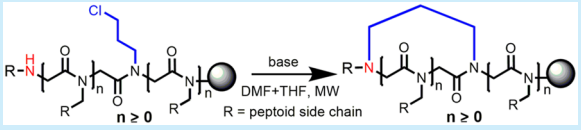
Supporting Information

ABSTRACT: We describe a fast and efficient side chain-to-tail cyclization of N-substituted glycine oligomers, peptoids, on a solid support and under microwave irradiation. We demonstrate that cyclic peptoids varied in their ring size and side chains can be synthesized by a bond formation between a chloropropyl group placed anywhere along the sequence and the secondary amine at the N-terminus. This S_N2 reaction leads to the formation of a new C−N bond using only one reagent (a base).



Peptoids,[1] oligomers of *N*-substituted glycines, have emerged during the past decade as an important class of peptide mimics due to their ease of synthesis,[2] their ability to fold into well-defined secondary structures,[3] and their utilization in various biological activities including metal binding,[4] catalysis,[5] and protein interaction.[1] Moreover, compared to peptides, peptoids exhibit improved cell permeability,[6] proteolytic resistance,[7] and tolerance toward high salt concentration, organic solvents, and various pH conditions. Thus, peptoids have been designed as biomimetic materials and used as antifouling and antimicrobial agents, lung surfactants, and more.[1] Similar to peptides, cyclization of peptoids was shown to be an effective strategy to rigidify their structures and increase their conformational order, aiming to enable tighter binding to protein targets.[8] In recent years, cyclic peptoids have gained much attention due to their structural ordering, biostability, and use as building blocks for the construction of unique supramolecular architectures, which enable defined biological activities. Cyclic peptoids have been exploited for various applications including metal binding[9] and cation transport[10] and have shown activity as selective antimicrobials,[11] potent antiproliferative agents,[12] and phase transfer catalysts.[13]

In general, cyclization of peptoids has been achieved by both solution-phase[14] and solid-phase methods.[15] Currently, the most practical cyclization approach is a solution-phase system, which was the first peptoid cyclization reaction reported in the literature.[14a] This is a head-to-tail cyclization method done in highly diluted solution after the cleavage and purification of the corresponding linear peptoids, under an inert atmosphere. Although this is an efficient and fast reaction (completes in 5 min) that takes place at rt, it is limited to only one type of cyclic peptoids (head-to-tail) as well as by the need to cleave and purify the linear products prior to cyclization. In contrast, there are currently four solid-phase methods for peptoid cyclization. The first one reported is a side chain-to-side chain method, which utilizes "click" chemistry.[16] Thus, it requires (i) initial incorporation of azide and alkyne groups in the linear peptoid sequence, (ii) a high excess of several reagents, such as CuI, ascorbic acid, and base, and (iii) an inert atmosphere. Other limitations of this method include a difficult workup aiming to remove residues of Cu binding to the peptoid products, and low efficiency due to intermolecular cyclization reactions. The second approach is a side chain-to-side chain method based on lactam formation.[17] This method also requires initial incorporation of specific functional groups in the linear peptoid sequence (namely carboxylic acid and amine) and a high excess of various reagents including a Pd catalyst. Moreover, the functional groups need to be protected and the peptoid needs to be acetylated at the C-terminus, procedures that add reagents and synthetic steps to the overall reaction. The third approach is a side chain-to-tail method based on triazine bridge formation.[18] Again, this method requires initial incorporation of specific functional groups in the linear peptoid sequence (this time thiol and cynuric chloride) as well as various reagents and protecting groups. The fourth approach is another side chain-to-tail method that utilizes the ring-closing metathesis reaction.[19] This method also requires the initial incorporation of specific functional groups, two alkene moieties, in the linear peptoid sequence and a protecting group. Moreover, most of the reported solid-phase cyclization methods require long reaction times (16−24 h) and lead to cyclic peptoid products that include undesired groups (e.g., triazole ring) in their sequence. Overall, the limitations of these methods inhibit their use in the generation of functional cyclic peptoids. Thus, there is a need for a simple, fast, and efficient solid-phase method for peptoid cyclization that involves a minimum amount of specific functional groups, reagents, and reaction steps. Herein we describe an effective and convenient solid-phase method for side chain-to-tail cyclization, which involves a simple substitution (S_N2) reaction, for the creation of cyclic peptoids in high yield and purity under microwave (MW) irradiation (Scheme 1).

Our design strategy was based on the fact that the secondary amine at the N-terminus of peptoid oligomers should be quite reactive toward an alkyl halide, providing there is an activating base in the reaction mixture. To test this hypothesis and to enable

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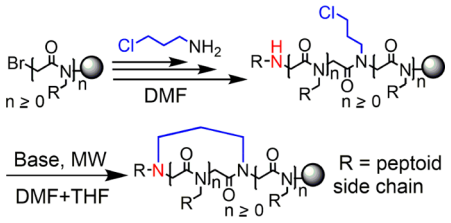
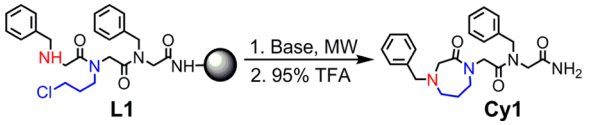
Scheme 1



side chain-to-tail cyclization, we have synthesized a peptoid trimer incorporating one chloropropyl group (Npl), which was introduced as a primary amine in the amine displacement step, and two benzyl groups (Npm) (**L1**, Table 1; L = linear). As mentioned above, cyclization of peptoids on a solid support requires long reaction times (18−24 h) and strong activating agents and/or metal catalysts to be completed at rt. Thus, **L1** was dissolved in a 1:1 mixture of THF/DMF and stirred with 10 equiv of NaH at rt for 24 h. Following this reaction, a sample of the peptoid was cleaved from the resin and analyzed by HPLC and electrospray mass spectrometry (ESI MS). These characterization methods reveal that only 49% of **L1** was converted into the desired cyclic peptoid product **Cy1** (Table 1, Cy = cyclic).

Table 1. Cyclic Peptoid Optimization Reactions[a]



entry	base	MW (watt)	time (h)	overall conversion (%)[b]	purity of **Cy1**[c] (%)
1	NaH[d]	none	24	59	83
2	NaH	300	1	73	78
3	K^{t}BuO	300	1	62	82
4	K^{t}BuO	200	1	92	76
5	K^{t}BuO	100	1	93	88
6	K^{t}BuO[e]	100	1	98	95
7	K^{t}BuO[e]	100	0.5	98	98
8	K^{t}BuO[f]	100	0.5	97	98
9	K^{t}BuO[g]	100	0.5	64	100
10	NaH[f]	100	0.5	100	75
11	NaH	none	0.5	10	100
12	no base	none	0.5	0	0
13	no base	100	0.5	0	0

[a]Reaction conditions: 10 mg of resin, 0.6 mL of 1:1 DMF/THF, 60 °C, 10 equiv of base. [b]Overall conversion was determined by HPLC analysis. [c]Purity was calculated by HPLC analysis as the amount of the desired product relative to the total amount of products. [d]Reaction was done at rt. [e]6 equiv of base were used. [f]5 equiv of base were used. [g]4 equiv of base were used.

To decrease the reaction time we have decided to develop a new solid-phase procedure for this cyclization reaction, which involves MW radiation. It is well-known that MW irradiation accelerates the rate of many chemical reactions,[20] including the solid-phase synthesis of peptoids.[21] We have recently described a fast and efficient incorporation of two metal-binding ligands with peptoid oligomers by the azide−alkyne cycloaddition (click) reaction in the solid phase using MW radiation.[22] In this example we have succeeded in reducing the reaction time from 4 days at rt to 30−35 min under MW irradiation at 60 °C on a solid support. We therefore decided to use the peptoid **L1** as a model to be tested in various radiation conditions. Initially we chose moderate settings in which the temperature will be below the boiling point of our solvents and will not decompose the peptoid. Thus, 10 mg of resin-bound peptoid were reacted with NaH by applying MW radiation of 300 W at 60 °C for 1 h. In these conditions, overall conversion of 73% was obtained as detected by HPLC (Table 1, entry 2; the overall conversion is defined as the conversion of the starting linear peptoid to both the desired cyclic product and undesired byproducts). From this products mixture, 57% were identified as **Cy1** (total of 78% purity), and 16% were unidentified products (probably polymeric or peptoid decomposition products).

Encouraged by these results we have decided to make some reaction optimizations including changing the base used in the reaction, the MW energy, and the reaction time, in order to increase the overall conversion and eliminate the generation of byproducts. The use of various milder bases than NaH, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, KOH, and NaOH, either fail to produce the cyclic product or were not at all reactive. In contrast, the use of K^{t}BuO resulted in 62% overall conversion, which included 51% **Cy1** and 11% byproducts (Table 1, entry 3). With this result showing higher purity of **Cy1** (82%) when K^{t}BuO is used rather than NaH, we decided to use K^{t}BuO as a base for additional reaction optimizations. To further improve the purity of the cyclic product, we decided to decrease the MW energy. Reducing the energy to 200 and 100 W at 60 °C for 1 h led to improved conversion (>90%) and the production of 76% and 88% **Cy1**, respectively, as detected by HPLC (entries 4 and 5 respectively). A further decrease in MW energy, with or without a temperature increase, did not lead to any additional improvements in conversion and purity.

Finally, we were able to improve the conversion to 98% and purity to 95% by reducing the amount of base from 10 to 6 equiv (Table 1, entry 6). Moreover, decreasing the reaction time to 30 min led to the best conversion (98%) with the highest purity to **Cy1** (96%). Running the reaction for 30 min, we were able to preserve the high conversion and purity even with 5 equiv of base; however, reducing this to 4 equiv resulted in decreased reactivity (entry 9). Notably, the use of NaH as a base instead of K^{t}BuO, under the same reaction conditions that produced 95% **Cy1** in 98% purity, resulted in 100% conversion albeit with only 75% purity of **Cy1** (entry 10). The use of NaH at 60 °C without MW irradiation produced only 10% of the cyclic product after 30 min (entry 10). Moreover, in the absence of base, the reaction did not occur at all (entries 12−13).

Overall, we achieved side chain-to-tail peptoid cyclization on a solid support with excellent conversion and very high purity, using 5−6 equiv of K^{t}BuO, MW radiation of 100 W, 60 °C, and a reaction time as short as 30 min. Crude HPLC traces of **L1** and **Cy1** prepared in these conditions are depicted in Figure 1.

Excited by these results we next studied the scope of this new cyclization method. Initially, we investigated whether scaling up our reaction and changing the position of propyl chloride in the peptoid sequence will effect the cyclization reaction. To this aim, we decided to apply our optimized reaction conditions to a set of three peptoid trimers bearing the propyl chloride group at different positions along the backbone (Figure 2). Thus, peptoids **L1**, having the propyl chloride side chain in the center of the oligomer, **L2**, having propyl chloride at the C-terminus, and **L3**, having propyl chloride at the N-terminus, were synthesized on 100 mg of resin in high purity (as determined by HPLC, Figures S1−S3), and their identity was verified by MS (Figures S28−S30). These three peptoids were subjected to our

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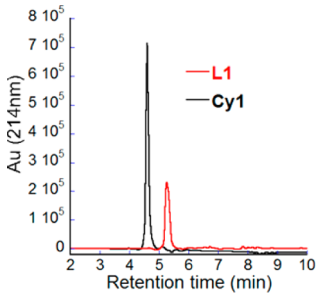

Figure 1. RP-HPLC chromatograms of crude peptoids **L1** (black) and **Cy1** (red). Cyclization conditions: 6 equiv of K^{t}BuO, 100 W, 60 °C, 30 min.

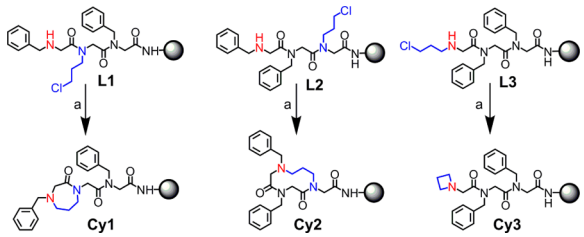

Figure 2. Synthesis of cyclic peptoids from trimers varied in the position of propyl chloride. (a) Reaction conditions: linear peptoids on 100 mg of resin, 6 equiv of K^{t}BuO, 2 mL of 1:1 DMF/THF, 60 °C, 100 W.

optimized cyclization conditions producing cyclic peptoids **Cy1**, **Cy2**, and **Cy3** with ring sizes of 7, 10, and 4, respectively (Figure 2 and Table 2, entries 1−3), in excellent purity as determined by HPLC and MS (Figures S12−S14 and S39−S41).

Table 2. Cyclic Peptoids with Various Sequences[a]

entry	cyclic peptoid	sequence of the linear peptoid	ring size	purity (%)[b]
1	**Cy1**	*N*pm-*N*pl-*N*pm	7	90
2	**Cy2**	*N*pm*N*pm*N*pl	10	96
3	**Cy3**	*N*pl-*N*pm-*N*pm	4	85
4	**Cy4**	*N*pm-*N*pm-*N*pm-*N*pl	13	95
5	**Cy5**	*N*pm-*N*pm-*N*pm-*N*pm-*N*pl	16	90
6	**Cy6**	*N*pm-*N*pm-*N*pm-*N*pm-*N*pm-*N*pl	19	90
7	**Cy7**	*N*pm-*N*pm-*N*pl-*N*pm-*N*pm	10	98
8	**Cy8**	*N*pm-*N*pl-*N*pm-*N*pm-*N*pm	7	95
9	**Cy9**	*N*me-*N*me-*N*me-*N*me-*N*me-*N*pl	19	96
10	**Cy10**	*N*spe-*N*spe-*N*spe-*N*spe- *N*spe-*N*pl	19	90
11	**Cy11**	*N*phen-*N*pm-*N*pl-*N*pm	10	90

[a]Reaction condition: 100 mg of resin, 2 mL of 1:1 DMF/THF, 60 °C, 100 W MW, and 6 equiv of base. [b]Purity was calculated by HPLC analysis as the amount of the desired product relative to the total amount of products (overall conversion). Overall conversion in all cases was 100%.

Next we studied the scope of our cyclization reaction. First, we prepared longer linear peptoids, the tetramer **L4**, the pentamer **L5**, and hexamer **L6**, bearing propyl chloride at the C-terminus and benzyl groups at the other positions. Using our optimized cyclization reaction conditions, cyclic peptoids **Cy4**, **Cy5**, and **Cy6** with ring sizes of 13, 16, and 19, respectively (Figure 3) were obtained in high purity (Table 2, entries 4−6) as determined by HPLC (Figures S15−S17). Their molecular weights were consistent with the expected masses (Figures S42−S44).

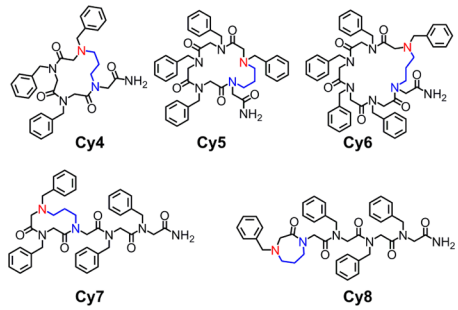

Figure 3. Structures of cyclic peptoids **Cy4**−**Cy6**, varied in oligomeric length (number of side chains), and **Cy7**−**Cy8**, varied in the position of the cyclic fragment.

Second, we prepared peptoids **L7** and **L8**, which are tetramers similar to **L4**, and changed the position of propyl chloride along the backbone. Our cyclization method is a side chain-to-tail approach, which enables generation of peptoids with two parts, cyclic and linear. Thus, applying our optimized cyclization conditions to **L7** and **L8** resulted in peptoids **Cy7** and **Cy8**, having linear parts (a dimer and trimer, respectively) and a cyclic part with ring sizes of 7 and 10, respectively (Figure 3). These peptoids were also obtained in excellent purity, as determined by HPLC and MS (Table 2, entries 7−8; Figures S18−19, S45−46).

We note here that in the presence of a strong non-nucleophilic base (KO^{t}Bu), polar aprotic solvents (a mixture of DMF and THF), and energy (heat plus MW irradiation) the chloropropyl group could undergo an elimination (E2) reaction. To prove the feasibility of our cyclization method, we prepared two new linear compounds: **L1′** and **L6′**, both identical to the sequences of **L1** and **L6** respectively, except they were synthesized using allyl amine instead of amino propyl chloride (see Supporting Information (SI)). HPLC analysis of mixtures containing both the linear (allylic) and cyclic peptoids, namely a mixture of **L1′** and **Cy1**, and a mixture of **L6′** and **Cy6**, revealed a different trace for each peptoid (Figures S25−S26). In addition, we performed MS/MS analysis of all four compounds. The results revealed that the fragmentation patterns of **Cy1** and **Cy6** are different from those of **L1′** and **L6′** respectively (Figures S54−S55). Such a difference in pattern was previously noted with other cyclic peptoids.[16a] Moreover, IR measurements of all four peptoids revealed an additional band at ∼935−960 cm^{-1}, characteristic of the C═C−H band only in the spectra of **L1′** and **L6′**, indicating that only these peptoids have allylic groups (Figures S57−S60). In addition, the stability of the resin under our MW-assisted cyclization reactions was verified by demonstrating that the solution mixture after the reaction does not contain any peptoid residues (see SI for details).

Finally, we wished to apply our methodology for the generation of functional cyclic peptoids, namely hydrophilic, chiral-helical, and metal-binding peptoids. To this aim, we synthesized three linear peptoids bearing propyl chloride groups: the hexamer **L9**, which contains hydrophilic methoxyethyl groups (Nme), the hexamer **L10**, having chiral bulky *S*-phenylethyl groups (Nspe), and the tetramer **L11**, which includes two benzyl groups and the transition-metal-binding ligand 1,10-phenanthroline (Nphen) as a pending group. From these oligomers, cyclic peptoids **Cy9**, **Cy10**, and **Cy11** were prepared according to our optimized cyclization reaction on a solid support (Figure 4). These three peptoids were obtained in an overall conversion of 100% and >90% purity (Table 2, entries 9−11) as determined by HPLC (Figures S20−S22), and their

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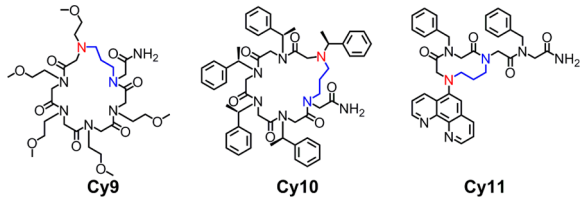

Figure 4. Structures of water-soluble cyclic peptoid **Cy9**, chiral helical cyclic peptoid **Cy10**, and cyclic metal binding peptoid **Cy11**.

molecular weights were consistent with the expected masses (Figures S47−S49). Peptoid **Cy10** was further characterized by circular dichroism (CD) spectroscopy in different solvents. It was previously shown that peptoids bearing chiral bulky side chains could form helices that resemble the polyproline helices[3] in solution, with a CD spectrum which typically resembles that of an α helix. Thus, **Cy10**, having five such groups, was expected to form a helical structure. CD measurements support these assumptions, showing spectra with characteristic double minima at about 202 and 220 nm for **Cy10** in both methanol and acetonitrile (Figure S56). Metal binding studies with **Cy11** are currently under investigation, toward the design and synthesis of functional cyclic peptoids for applications in catalysis.

In summary, we successfully developed a novel, simple, and efficient methodology for the preparation of cyclic peptoids using basic conditions under MW irradiation via an S_N2 reaction by introducing a chloropropyl group. Thus, a new C−N bond is formed between a chloropropyl side chain placed anywhere along the backbone and the N-terminus NH of the peptoid on resin. Our new methodology provides a particularly valuable tool for easy access to peptoids having both linear and cyclic fragments for further applications in selective metal binding, self-assembly, catalysis, and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

(i) Materials and methods, (ii) synthetic procedures, (iii) complementary HPLC, MS, IR, and CD data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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