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New solid phase submonomer synthesis of arylopeptoid oligomers using reductive amination

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ABSTRACT

Herein, we describe a new methodology for the solid phase submonomer synthesis (SPSS) of arylopeptoids using a reductive amination reaction as the key step instead of a nucleophilic substitution reaction, which is generally used in conventional SPSS of peptoids. The new SPSS enables easy access to arylopeptoid oligomers in which phenyl side groups are directly attached to the aromatic main chain.

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Introduction

N-Substituted glycines (i.e., peptoids) have attracted growing attention as new synthetically accessible heteropolymers and 'foldamers'.[1,2] The submonomer approach for the synthesis of the peptoids reported by Zuckermann et al.[3] enables access to a diverse range of functionalized peptoids bearing a variety of side chains at modest cost and effort. The peptoids are mostly synthesized using the solid phase submonomer synthesis (SPSS) protocol based on a two-step cycle that includes a nucleophilic substitution reaction and a coupling reaction, without protection and deprotection of individual monomer molecules. Recently, arylopeptoids consisting of aromatic units as the repeating unit (main chain) in place of aliphatic units have also been described based on similar SPSS protocols (Fig. 1).[4,5] Since aromatic unit spacers can be longer and more rigid than conventional alkylpeptoids, the arylopeptoids could exhibit unique properties and functions. In fact, *N*-alkylated oligobenzamides with rather short lengths can act as α-helix mimetics to modulate protein–protein interactions.[6] Additionally, Nielsen et al. developed agonists toward peroxisome proliferator-activated receptors from a small library of arylopeptoids.[7] Very recently, it has been revealed that the peptide antibiotic albicidin is mainly composed of *p*-aminobenzoic acid.[8]

Herein we describe a new strategy for the SPSS of the arylopeptoids utilizing reductive amination as the key step instead of nucleophilic substitution.[9] We demonstrated that aromatic amines (typically, aniline derivatives) can be efficiently incorporated into arylopeptoids without using a large excess of the aromatic amine, which is generally required for the nucleophilic substitution reaction due to the low nucleophilicity of the aromatic amines (aromatic amine solutions required for conventional SPSS, 4 M, 20 equiv).[5b] In addition, it has been shown that the *N*-methylated aromatic anilide moieties in the backbone of the arylopeptoids generally prefer the *trans* conformation at the amide bond rather than the *cis* conformation. We thus believe that the newly developed SPSS using arylopeptoids could provide opportunities to access new functional foldamers.[10]

Results and discussion

Previous reports on the synthesis of arylopeptoid oligomers were based on the SPSS protocol, as shown in Figure 2A,[4,5] in which a two-step reaction (nucleophilic substitution reaction and coupling reaction) is repeated in order to generate the desired oligomer length, followed by cleavage from the resin to yield functionalized arylopeptoid oligomers. In contrast, this work

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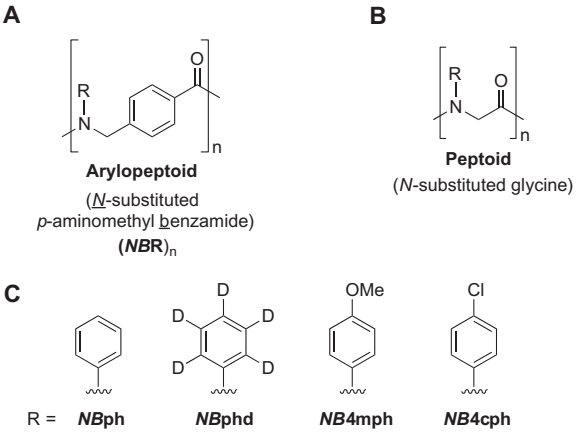

Figure 1. (A) Arylopeptoid and (B) generic peptoid structures. (C) Chemical structures of arylopeptoid side chains discussed in this study. Side chain abbreviations: ph = phenyl, phd = deuterated phenyl, 4mph = 4-methoxyphenyl, 4cph = 4-chlorophenyl.

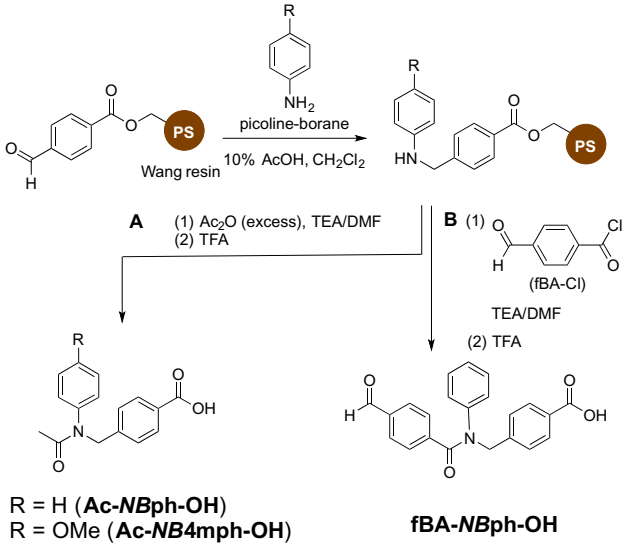

Figure 3. Scheme for the product analysis of (A) reductive amination and (B) coupling reactions.

describes an alternative SPSS for arylopeptoid oligomers using 4-formylbenzoic acid (fBA) (instead of 4-halomethylbenzoic acid) and aromatic amine derivatives in a reductive amination reaction (step (a)) and coupling reaction (step (b)), as shown in Figure 2B.

For the reductive amination step (step (a) in Fig. 2B), α-picoline-borane was used as the reducing agent because of its efficient and mild procedures, which are applicable to a wide variety of substrates, as well as its low explosive nature.[11] Based on the well-developed DIC/DMAP chemistry (DIC: *N*,*N*′-diisopropylcarbodiimide, DMAP: 4-dimethylaminopyridine),[4] fBA introduction to the Wang resin (typically, 100–200 mesh, 1% DVB (divinylbenzene)) was followed by the addition of aromatic amines and α-picoline-borane in 10% acetic acid/dichloromethane and the mixture was allowed to react at room temperature. The products were analyzed after acetyl capping using acetic acid anhydride, followed by subsequent cleavage from the resin using trifluoroacetic acid (TFA) (Fig. 3A) and purification by normal phase silica gel chromatography. As shown in Table 1 (entries 1–3), one equivalent of aniline at a concentration of 0.1 M was sufficient for this reaction, which is in sharp contrast to previous protocols (i.e., 20 equiv, 4 M).[5b] Aliphatic amines such as hexyl amine can be introduced under the same conditions (data not shown). In order to introduce functional groups to the aromatic side chains, an aromatic amine bearing ether functionality was investigated. We

Table 1
Reductive amination reaction using various aromatic amines (α-picoline-borane (10 equiv))

	Aromatic amine	Product	Yield[a] (%)
1	Aniline (1 equiv)	**Ac-*NB*ph-OH**	84
2	Aniline (2 equiv)	**Ac-*NB*ph-OH**	89
3	Aniline (5 equiv)	**Ac-*NB*ph-OH**	91
4	4-Methoxyaniline (2 equiv)	**Ac-*NB*4mph-OH**	84
5	4-Chloroaniline (2 equiv)	**Ac-*NB*4cph-OH**	72

[a] Isolated yield.

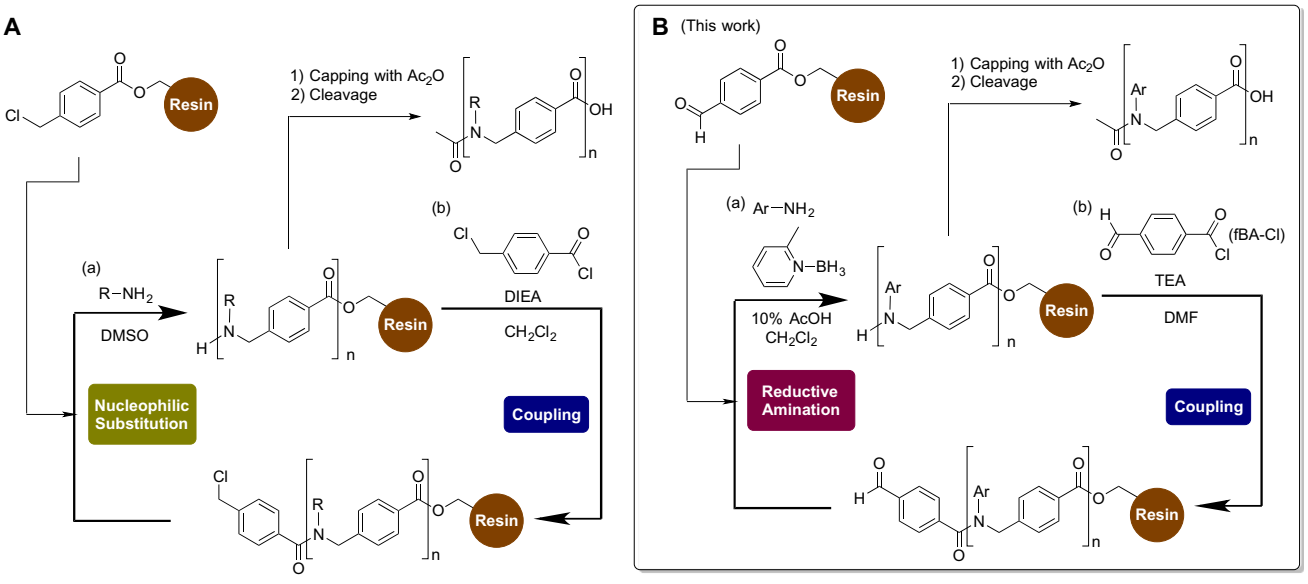

Figure 2. SPSS of arylopeptoids reported previously (A) and described in this study (B). (A) is based on nucleophilic substitution and coupling reactions and (B) is based on reductive amination and coupling reactions.

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