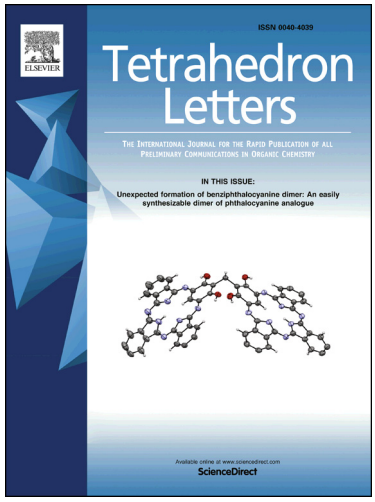

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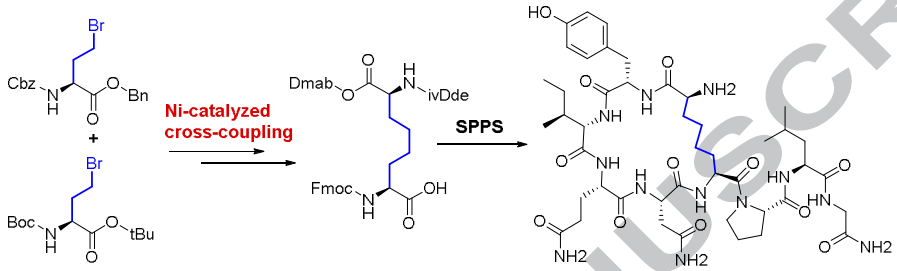

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Efficient synthesis of hydrocarbon-bridged diaminodiacids through nickel-catalyzed reductive cross-coupling

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ABSTRACT

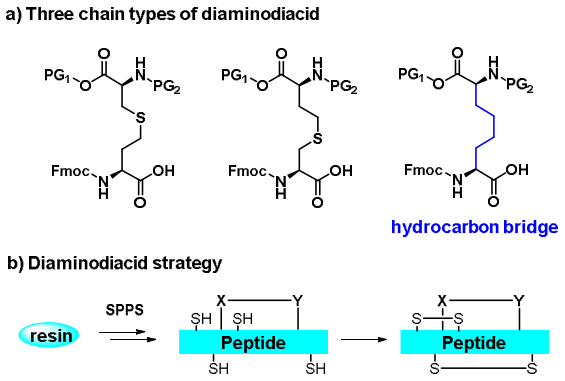
Solid-phase incorporation of pre-prepared diaminodiacids has been established as an efficient strategy for the chemical synthesis of peptide disulfide bond mimics. Hydrocarbon-bridged diaminodiacids represent one important category of diaminodiacids but they remain difficult to synthesize. In the present work, we reported the use of newly-developed nickel catalyzed reductive cross-coupling reaction to efficiently synthesize diaminodiacids with hydrocarbon bridges. Through optimization of the reaction conditions, the yield of the hydrocarbon bridge formation reached about 50%, even when the reaction was scaled up to the gram level. Subsequently, using our recently developed Dmab/ivDde protecting group system, we obtained a new hydrocarbon-bridged diaminodiacid that are suitable for metal-free deprotection conditions. We demonstrated the utility of this Dmab/ivDde protected hydrocarbon-bridged diaminodiacid in the synthesis of a disulfide surrogate of oxytocin.

1. Introduction

Conformationally rigidified peptidic macrocycles have been demonstrated to exhibit good metabolic stability, high bioactivity, and target selectivity in recent studies.[1] The favorable features enable these compounds to become highly promising molecules for diagnostic and therapeutic applications.[2] Many of such peptidic macrocycles contain one or multiple disulfide bridges, which are important to their thermal and metabolic stability, as well as conformational stability.[3] However, the disulfide bonds in these cyclic peptides are potentially unstable under reductive conditions or in the presence of disulfide isomerases.[4] Therefore, the development of stable peptide containing disulfide bond mimic has attracted considerable interest. Various strategies have been developed to stabilize peptide disulfide bond, using structures including thioether[5], lactam[6] as well as triazole bridges[7]. The different bridge types provide structural diversity of disulfide bond surrogates for tuning of bioactivity.

Unlike the post-chain-assembly side-chain cyclization approaches such as azide-alkyne cycloaddition, an alternative strategy is the use of diaminodiacids to replace disulfide bonds in cyclic peptides.[8] In this strategy, pre-prepared diaminodiacids are used to replace disulfide bonds during conventional 9-fluorenylmethoxycarbonyl-based solid phase peptide synthesis (Fmoc-SPPS). Since all the cyclization steps can be carried out by condensation of the amino group and the carboxylic acid in the polypeptide, it is possible to obtain a disulfide-substituted polypeptide directly on the resin. Till now, four pairs of orthogonal protecting group for diaminodiacids were developed, including allyl/allyloxycarbonyl (Alloc), p-nitrobenzyl (pNb) /pnitrobenzyloxycarbonyl (pNz), benzyl (Bn)/benzyloxycarbonyl (Cbz) and 4-(N-[1-(4,4-dimethyl-2,6-dioxocyclo-hexylidene)-3-methylbutyl]amino)benzyl (Dmab)/1-(4,4-dimethyl-2,6-dioxo-cyclohex-1-ylidene)-3-methylbutyl (ivDde) protecting group.[8d]

In previous reports, diaminodiacids were equipped with two types of thioether bridges and a hydrocarbon bridge (Scheme 1).[8a] The different chain types make a flexible synthetic route for generating disulfide bond surrogates with different structures. However, although the thioether-bridged diaminodiacids can be readily prepared, the synthesis of diaminodiacids with hydrocarbon bridges is rather challenging. This type of bridge was previously prepared by electrochemical oxidation decarboxylation of two glutamate segments using Kolbe electrolysis.[9] Unfortunately, this method suffered from relatively low yield (15%) of the bridge formation step, in addition to the need for specific operating conditions and technical equipment.[8a] Therefore, it is necessary to develop a more convenient and efficient strategy for the synthesis of hydrocarbon bridged diaminodiacids.

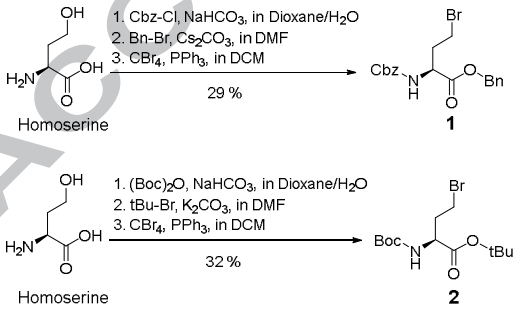


Scheme 1. a) Diaminodiacids with three chain types of bridge; b) General strategy for diaminodiacid-based SPPS.

In the present work, we report the use of nickel catalyzed reductive cross-coupling[10] to synthesize hydrocarbon-bridged diaminodiacids with high efficiency. After careful optimization of the reaction conditions, the yield for the construction of hydrocarbon bridges reached 52%. Even when the reaction was expanded to the gram level, the yield was still as high as 48%. The hydrocarbon-bridged diaminodiacid synthesized here is protected by the Dmab/ivDde pair, enabling the use of metal-free deprotection conditions. By using our new diaminodiacid as a building block in SPPS, we demonstrated that a hydrocarbon-bond-containing analogue of oxytocin could be synthesized in a facile and efficient manner.

2. Results and discussion

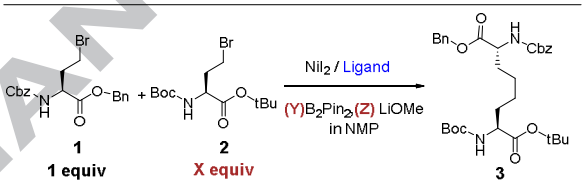
We design to synthesize the hydrocarbon bridge by linking benzyl (Bn)/Cbz protected homoserine bromides[11] and *tert*-butyl (tBu)/*tert*-butoxycarbonyl (Boc) protected homoserine bromides[12]. Thus our study began with the synthesis of two orthogonal protected homoserine bromides. According to the synthetic route shown in Scheme 2, we successfully obtained the Cbz/Bn protected homoserine bromide and Boc/tBu protected homoserine bromide in 29% and 32% yields respectively. With the two bromides in hands, we initially tested the nickel-catalyzed cross-coupling method using zinc powder as reductant, which was reported by Gong and co-workers in 2011.[13] Although we were able to obtain diaminodiacids **3** on 0.2 mmol scale with a 30% yield, the yield of product was reduced to 10% in a gram scale reaction which might due to the uncertain surface state of zinc powder as a heterogeneous reductant.



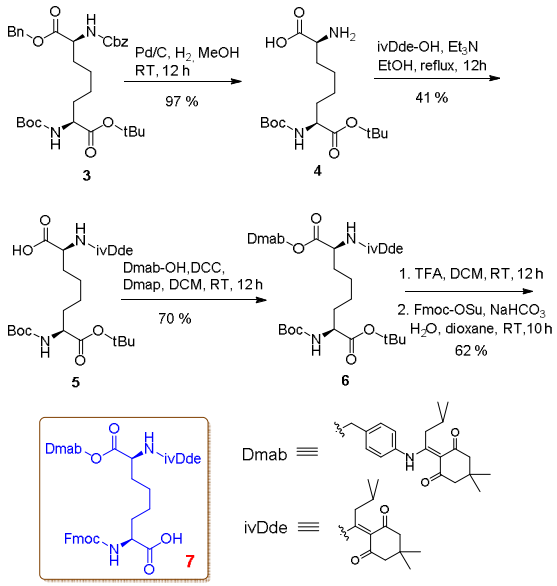
Scheme 2. The synthesis of homoserine bromides

To solve the problem, we turned to a recently developed method by Gong group in which bis(pinacolato)diboron ($B_2(Pin)_2$) was used as reductant regent.[10] This interesting reductant was reported to efficiently promote the nickel-catalyzed cross-coupling of inactive alkyl halides, especially for primary halides. Moreover, the feed ratio of two different alkyl halides was only 1:1.5, indicating good atomic economy of the reaction. Therefore, we set out to test whether this reaction system is suitable for cross-coupling of two ortho-protected homoserine bromides. We first tested this reaction according to the optimal conditions reported by Gong group (Table 1, Entry 2). Thin layer chromatography (TLC) monitoring indicated that the starting material **1** was completely consumed when reaction was carried out for about 4 hours. Then, the desired coupling product **3** was obtained in 41% yield. In order to save the starting material homoserine bromides, we next optimize the cross-coupling reaction to find a balance between the feed ratio and the reaction yield. Specifically, we first screened different ratios of Boc/tBu homoserine bromide, $B_2(Pin)_2$ and LiOMe and found that the highest yield (56%) was obtained by using 1.5 equivalents of bromide **2**, 2.2 equivalents of $B_2(Pin)_2$ and 2.5 equivalents of LiOMe (Table 1, Entry 3). To our delight, the reaction yield still reached 52% when only 1 equivalent of bromide **2** was used. Moreover, the yield of compound **3** was slightly reduced to 48% when the reaction was carried out on gram scale (6 mmol) (Table 1, Entry 6). Collectively, compared to the previous electrolytic approach, nickel-catalyzed cross-coupling enabled the production of hydrocarbon-bridged diaminodiacid with high efficiency and operational simplicity.

Table 1. Screening the reaction conditions

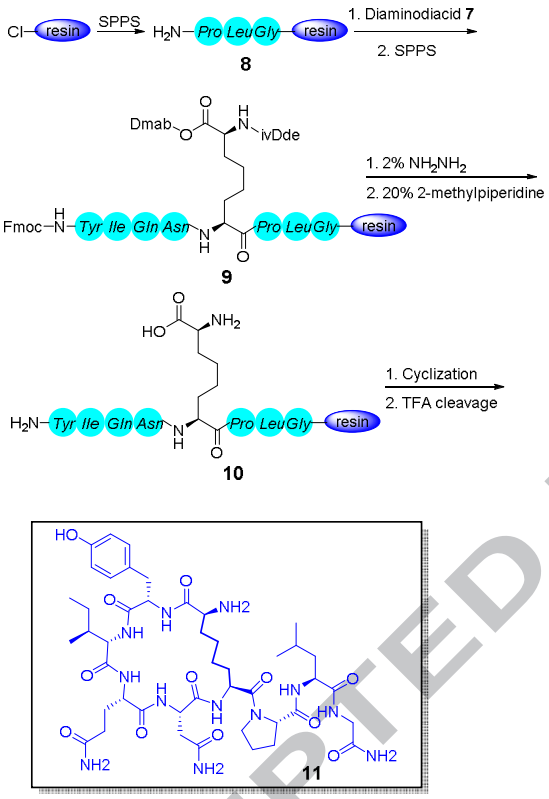


Entry	X	Y	Z	Yield	Time
1	1.2	2	2	36%	4 h
2	1.5	2	2.5	41%	4 h
3	1.5	2.2	2.5	56%	4 h
4	1.5	1.5	2	39%	4 h
5	1.5	2.5	2.5	42%	4 h
6	1	2.2	2.5	52%	4 h



Scheme 3. The synthetic route of Dmab/ivDde-protected carbon-bridged diaminodiacids

After the hydrocarbon bridge was successfully constructed, we next changed the protecting groups of diaminodiacid **3** to make it suitable for use in Fmoc-SPPS. Recently, we developed the Dmab/ivDde protecting group pair that can be easily removed by mild hydrazinolysis during solid-phase synthesis,[8d] we intended to obtain the first hydrocarbon-bridged diaminodiacid protected by Dmab/ivDde group (Scheme 3). To this end, the Cbz/Bn of **3** was cleaved with Pd/C in H_2 to yield compound **4**. The amino group of **4** was coupled with ivDde-OH to yield compound **5**. Then the esterification was carried out by using dicyclimide (DCC) as condensation reagent between the ivDde-protected amino acid **5** and Dmab-OH. After the Boc/tBu was cleaved with TFA, the product could be reacted with Fmoc-OSu to yield the final desired diaminodiacid **7** (17 % for overall yield).



Scheme 4. Synthetic route for oxytocin analogue **11** on solid support using diaminodiacid **7**

With hydrocarbon-bridged diaminodiacid **7** in hands, we next focused on determining the feasibility and efficiency of the diaminodiacid for the chemical synthesis of peptide containing disulfide bond mimic. The hypothalamic neuropeptide oxytocin was chosen as the synthetic target for this purpose. Oxytocin contains 9 amino acid residues and has a pair of intramolecular disulfide bond between the cysteine residues at positions 1 and 6.[14] It is a multifunctional peptide hormone and the *in vivo* receptor of oxytocin belongs to the G protein-coupled receptor family. Recently, oxytocin was found to play a crucial role in milk-ejection reflex and uterine contractility.[15] Some studies revealed that oxytocin receptor is important for many reproductive and social behaviors.[16] Nonetheless, most of oxytocin used in previous studies is in its natural form; thus we consider that it remain necessary to explore whether the use of disulfide bonds mimic analogues of oxytocin would have different effects. To this end, we have successfully synthesized oxytocin analogue by using the thioether-bridged diaminodiacids previously, whereas the analogue containing a hydrocarbon bridge has not been obtained. In this context, the disulfide-replaced analogue of oxytocin nonapeptide was synthesized by using Dmab/ivDde protected hydrocarbon-bridged diaminodiacid for the first time.

The synthesis of oxytocin analogue was carried out by using the rink amide AM resin. After the resin was swelled, a linear tripeptide was assembled onto the resin by using HCTU (5-chloro-1-[bis(dimethylamino)methylene]-1H benzotriazolium-oxide hexafluorophosphate) as the coupling reagent. Diamino-diacid **7** was coupled to the resin by using PyAop (3-hydroxy-3H-1,2,3-triazolo[pyridinato-O]tri-1-pyrrolidinyl-phosphonium heaxfluorophosphate) as condensation reagents.[17] Then, the other four amino acids (i.e. Aln, Gln, Ile, Tyr) were coupled to the resin by using HCTU. The Dmab-OH and ivDde-OH groups were removed through treatment with 2% NH_2NH_2 and the Fmoc protecting group of the peptide chain was also removed by 2-methylpiperidine (20% 2-methylpiperidine in DMF for 8-10 min). Next, the PyAop and NMM (N-methylmorpholine) were added to promote cyclization between the acid group of the diaminodiacid and the terminal amino group of the growing peptide chain.[18] Finally, the cleavage cocktail reagent, TFA/phenol/water/Tips (88:5:5:2 v/v/v/v) were subsequently added to react for 3 hours, and then the final product crude oxytocin analogue **11** was obtained by precipitation (Scheme 4).

The crude peptide **11** was analyzed by reverse-phase high performance liquid chromatography (HPLC) and mass spectrometry (MS). The results in Figure 1 indicate relative high purity and correct Molecular Weight (MW) of the product (Fig. 1a-b). We can obtain the purified oxytocin analogue **11** in a good yield after routine HPLC purification (Fig. 1a, overall yield = 20 %). In order to confirm the secondary structure of oxytocin analogue, we tested analogue **11** by circular dichroism spectrometer (CD). The CD spectrum showed a negative peak at 196 nm and a positive band at 220-230 nm (Fig. 1c). These observations were consistent with the structure of the reported native oxytocin, indicating correct folding of the synthetic analogue.[8d]

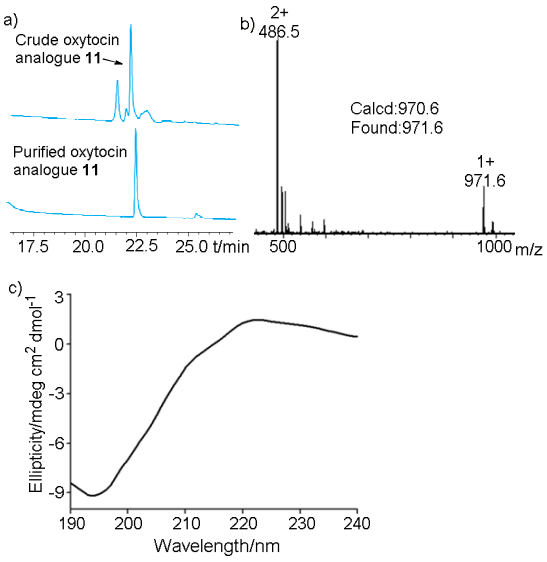


Fig 1. a) HPLC traces of crude and purified oxytocin analogue; b) ESI-QTOF-MS spectrum of oxytocin analogue **11**, Calcd: 970.6, Found: 971.6. c) CD spectra of oxytocin analogue in water.

3. Conclusions

In summary, we have developed a facile and efficient method

for the preparation of hydrocarbon-bridged diaminodiacid. Taking advantage of nickel-catalyzed reductive cross-coupling reaction, the hydrocarbon bridge could be synthesized smoothly with a 48% yield on gram scale, which presents advantages on the synthetic efficiency and operation simplicity over previous electrolysis method. By using our recently developed Dmab/ivDde protecting group system, we obtained a new hydrocarbon-bridged diaminodiacid with metal-free deprotection conditions. Subsequently, we also demonstrated that the oxytocin disulfide bond mimic **11** containing a hydrocarbon bridge can be obtained in good efficiency via the diaminodiacid-based strategy. We envisage that the Dmab/ivDde-protected hydrocarbon-bridged diaminodiacid would serve as a valuable complement to the growing arsenal of diamonodiacids, which provide a flexible approach for generating peptide disulfide bond mimics with structural diversity.

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Highlights

1. Hydrocarbon-bridged diaminodiacids have been developed via nickel catalyzed reductive cross-coupling reaction.
2. New diaminodiacids was protected by Dmab/ivDde protecting group.
3. a hydrocarbon-bond-containing analogue of oxytocin was synthesized.
4. newly-developed nickel catalyzed reductive cross-coupling reaction