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Synthesis of 1,5-Benzothiazepine Dipeptide Mimetics via Two CuI-Catalyzed Cross Coupling Reactions

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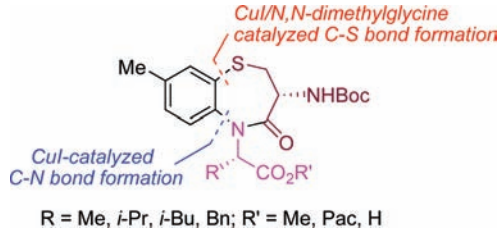
ABSTRACT



R = Me, *i*-Pr, *i*-Bu, Bn; R' = Me, Pac, H

CuI-catalyzed coupling of 4-methylphenyl bromide with amino acids gives N-aryl amino acids, which are converted into linear dipeptides via iodination and condensation with L-cysteine derived acyl chloride. Cyclization is achieved via a CuI/*N*,*N*-dimethylglycine catalyzed intramolecular coupling of aryl iodides with the liberated thiol to afford 1,5-benzothiazepine dipeptide mimetics.

Since it was introduced by Slade and co-workers for the assembly of designed angiotensin converting enzyme inhibitors in 1985,[1] 1,5-benzothiazepine **1** (Figure 1), a bridging dipeptide analog, has been frequently employed as a scaffold for the development of peptidomimetics.[2−7] These efforts have led to the discovery of a considerable number of pharmaceutically interesting molecules. Recent examples include CGRP receptor antagonist **3**,[3] compound **4** that could be used for treatment of hyperproliferation diseases,[4] IAP (inhibitors of apoptosis proteins) antagonist **5**,[5] interleukin-1 converting enzyme inhibitor **6**,[6] as well as selective bradykinin agonist JMV1116 (**7**).[7]

One problem for 1,5-benzothiazepine **1** as a dipeptide analog is the lack of substituents at the α-position of its ester moiety, which limits its potential in drug discovery, because it cannot fully mimic the most dipeptide backbones. Considering known synthetic protocols, it looks difficult to introduce some suitable substituents at this position to generate substituted 1,5-benzothiazepines **2**, particularly in an enantioselective manner.[1] Therefore, an alternative route is highly required to solve this problem.

Recently, great progress has been made in the development of ligand-promoted Ullmann-type coupling reactions, which has delivered many mild conditions for C−N, C−O, C−S

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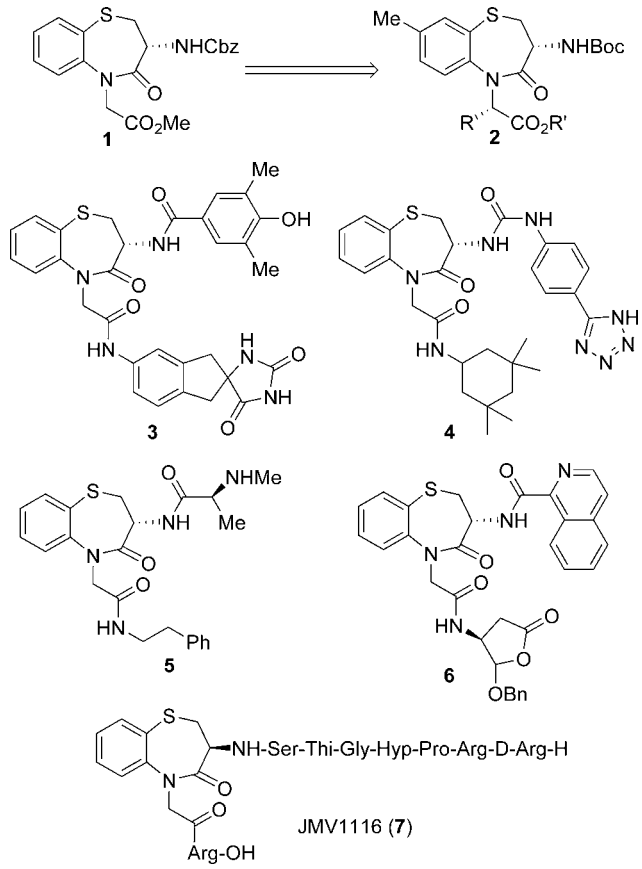


Figure 1. Structures of substituted 1,5-benzothiazepine derivatives.

and C−C bond formation starting from aryl halides.[8] These new methods have opened new routes for construction of bioactive compounds and their analogues.[8c,d] Taking this advantage, we developed a facile approach to assemble substituted 1,5-benzothiazepines **2**. As depicted in Figure 2,

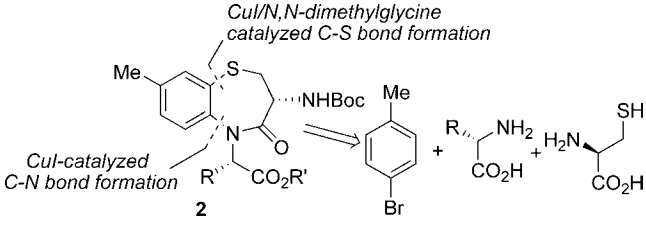
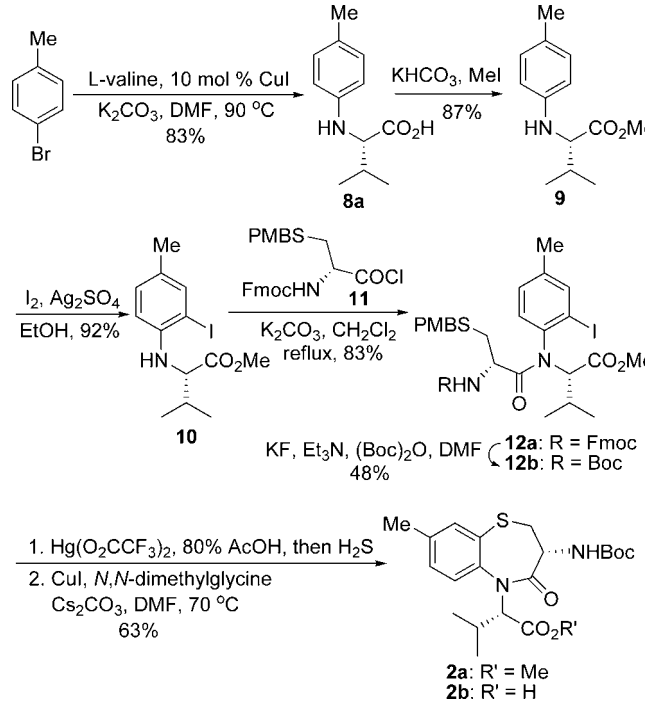


Figure 2. Assembly of substituted 1,5-benzothiazepine derivatives **2** via two CuI-catalyzed coupling reactions.

the key elements of this route include a CuI-catalyzed N-arylation of amino acids,[9] and a CuI/*N*,*N*-dimethylglycine catalyzed intramolecular S-arylation.[10] Herein, we wish to disclose our investigations.

As shown in Scheme 1, we started our synthesis by coupling 4-methylphenyl bromide with L-valine. This CuI-catalyzed reaction worked well in DMF to give N-toluyl

Scheme 1



L-valine **8a** in 83% yield,[9a] which was treated with methyl iodide and $KHCO_3$ to afford methyl ester **9**. Iodination of **9** with iodine and Ag_2SO_4 gave **10**. Next, we planned to introduce the required cysteine part into amine **10** via an amide bond formation. This operation was proven challenging because of the poor reactivity of the sterically hindered amine. For example, amine **10** was inert toward EDCI and HATU-mediated condensation with Boc-L-Cys(Bn)−OH, as well as toward direct condensation with some L-cysteine derived mixed anhydrides. Accordingly, we moved our attention to use the more reactive acyl chloride **11** as a coupling partner. After having failed in a Et_3N-mediated coupling, we were pleased to find that using K_2CO_3 as a base the reaction gave the desired dipeptide **12a** in 83% yield. Changing the N-protecting group in **12a** by treatment with $KF/Et_3N/(Boc)_2O$[11] afforded **12b**, which was reacted with $Hg(O_2CCF_3)_2$ to remove the PMB protecting group.[12] The liberated thiol was then subjected to a CuI/*N*,*N*-dimethylg-

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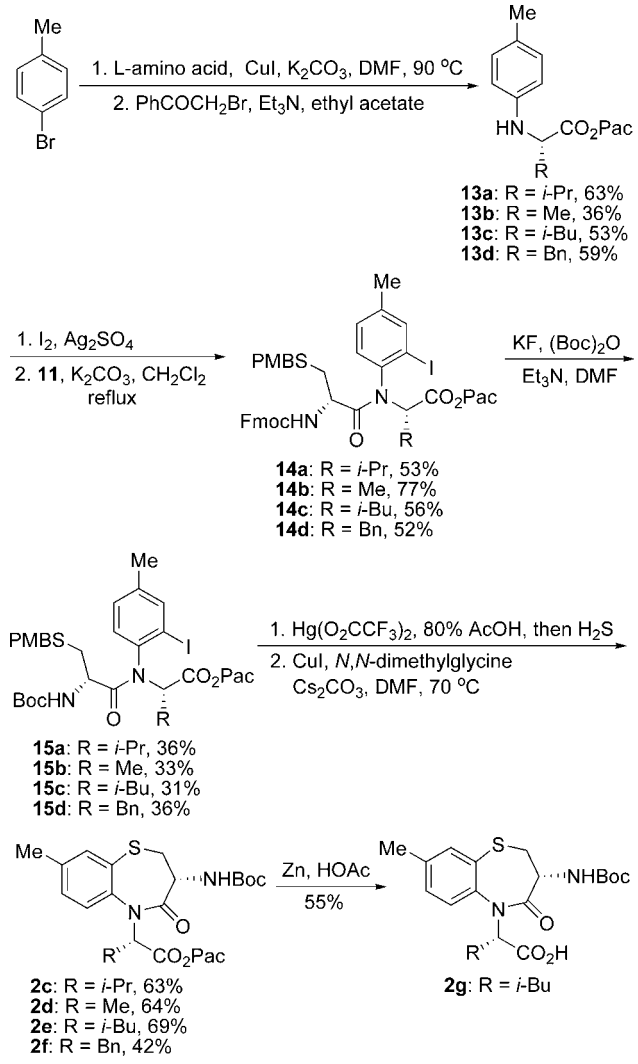
lycine catalyzed intramolecular coupling reaction to furnish 1,5-benzothiazepine **2a** in 63% yield.[10a] With **2a** in hand, we now tried to cleave the methyl ester group to obtain acid **2b**. Disappointingly, this transformation was rather difficult under various reaction conditions (such as NaOH/MeOH/THF/H_2O and *n*-PrSNa/HMPA). The problem might result from the steric hindrance of the ester group and makes the elongation of the side chain at this site impossible, thereby limiting further applications of 1,5-benzothiazepine **2a**.

Scheme 2



To solve the above problem, we decided to change the ester protecting group to phenacyl (Pac),[13] because it could be cleaved via reducing its ketone part. Therefore, it would allow to avoid attack of the sterically hindered ester moiety. Accordingly, after coupling of 4-methylphenyl bromide with four amino acids respectively, resultant N-aryl amino acids were treated with phenacyl bromide and Et_3N in EtOAc to afford Pac esters **13** in 36−63% yields. Exposure of **13** to iodine and Ag_2SO_4 provided the aryl iodides, which were condensed with acyl chloride **11** to deliver dipeptides **14**. For carrying out the copper-catalyzed intramolecular coupling, the base-sensitive Fmoc was changed to Boc to provide **15**. After removal of the PMB protecting group in **15**, intramolecular coupling effected by CuI/*N*,*N*-dimethylglycine produced the cyclization products **2c**−**2f**. Now this is the stage for the cleavage of the Pac protecting group. We were pleased to find that treatment of **2e** with zinc and 90% acetic acid at room temperature furnished the desired acid **2g** in 55% yield. This result demonstrated that the ester protecting group in **2c**−**2f** could be removed for the development of peptidomimetics.

In conclusion, we have developed a novel protocol to assemble 1,5-benzothiazepines based on applying two copper-catalyzed coupling reactions. The most important feature of this method is that it allows for the introduction of various N-substituents by changing the amino acid coupling partners. This will enable the development of more diverse peptidomimetics for biological investigations. The application of the presented building blocks in discovery of new enzyme inhibitors is actively pursued in our group, and the results will be disclosed in due course.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectrum for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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