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Review

Recent progress of on-resin cyclization for the synthesis of clycopeptidomimetics

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ABSTRACT

Cyclopeptidomimetics are class of cyclopeptides with unnatural linkage. They usually displayed unique constrained structure, enhanced proteolytic stability, and other drug-like character; and have been widely used in medicinal chemistry. Therefore, development of efficient strategies for the synthesis of cyclopeptidomimetics has received many attentions. On-resin cyclization strategy is one of the effective approaches developed to overcome the competing side reaction such as oligomerization and cyclooligomers occurred in solution cyclization. This approach took advantage of the "*pseudo*-dilution" effect to avoid these undesired by-products and greatly simplified the downstream product purification process. This review summarized the recent on-resin peptide cyclization strategies for the synthesis of cyclopeptidomimetics.

1. Introduction

Cyclopeptidomimetics are analogs of natural occurring cyclopeptides, where original amide or disulfide bond was replaced with unnatural linker bridge. These kinds of compounds usually featured with unique restricted conformation, thereby making them to display enhanced metabolic stability and binding specificity to their molecular targets [1]. In addition, cyclization scaffold provides favorable benefits on other essential properties required for drugs, such as membrane permeability, bioavailability, and overall pharmacokinetics [2]. To date, cyclopeptidomimetics are dominantly used in treating infectious disease and oncology as well as in cardiovascular disease and immunology [3]. Therefore, many efforts have been made to explore efficient cyclization strategies for the synthesis of cyclopeptidomimetics.

Cyclopeptidomimetics usually prepared by solid phase peptide synthesis (SPPS) of linear precursors followed by in solution cyclization [1d,3b,4]. However, this cyclization step is still considered as a formidable challenge because intermolecular reaction proceeds much faster than intramolecular reaction, thus generating undesired linear oligomers and relevant cyclooligomers as by-products. As a result, time and cost consuming purification is needed to obtain high purity target compound for biological study. Using high dilution condition can only suppress this side reaction in limited success [5]. On the other hand, peptide on-resin cyclization strategy has emerged as a powerful approach for the synthesis of cyclopeptidomimetics, which perform the pivotal cyclization reaction while the linear peptide is still anchored on the resin. This strategy took advantage of the well-known "*pseudo*-dilution" effect by favoring intramolecular reaction over the intermolecular reaction [6]. And by-products could be easily separated by washing and filtration process. Moreover, on-resin cylcization can be utilized to construct combinatorial library by incorporation of multiple amino acids and perform post-cyclization modification for the hit-to-lead purpose in drug discovery. In this review, we focused on the recently developed on-resin peptide cyclization strategies for the efficient synthesis of cyclopeptidomimetics. The general methodologies of on-resin cylcization include: Cu (I)-catalyzed "click chemistry", thio-ene "click chemistry", ring-closing metathesis (RCM), intramolecular S_N2 or S_NAr nucleophilic substitute reaction and transition metal catalyzed intramolecular coupling reaction.

2. Syntheses of cyclopeptidomimetics

2.1. Cu(I)-catalyzed huisgen azide-alkyne cycloaddition (CuAAC)

Huisgen azide-alkyne cycloaddition (CuAAC), also defined as "click chemistry" by Barry Sharpless, is a cycloaddition reaction between an azide and an alkyne group under mild condition using

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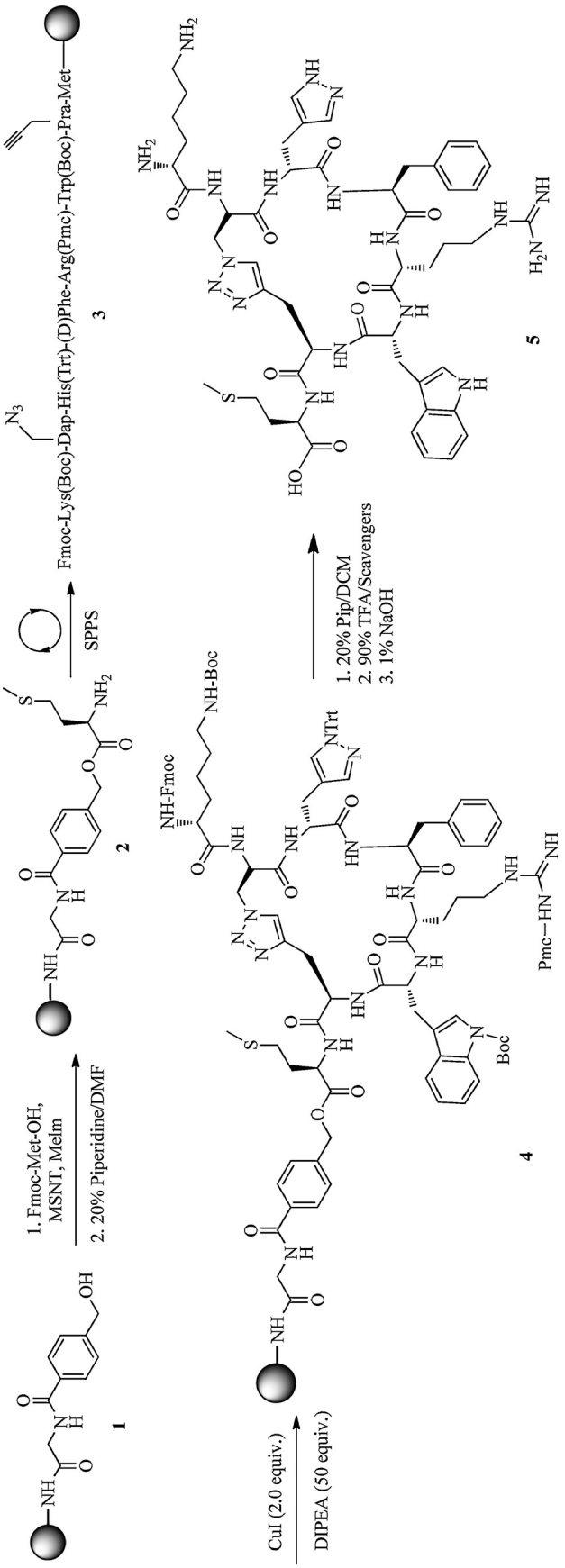
copper as catalyst [7]. This reaction joined two species together by formation a five-membered 1, 2, 3-triazole ring linkage, which is believed to have similar physicochemical profiles as the amide bond [8]. In addition, the triazole unit is resistant to enzymatic degradation, and display excellent stability toward hydrolysis and oxidation. Furthermore, replacing amide bond with triazole linkage could generate interesting structures with unique conformation when binding with biological target.

Meldal's group firstly reported on-resin CuAAC cyclization using PEGA (poly-(ethylene glycol)-poly(acrylamide)-copolymer) resin which have excellent swelling properties in various solvents [9]. PEGA amine resin was equipped with a base labile linker, HMBA (hydroxymethyl benzoic acid); then linear peptide Fmoc-Lys(Boc)-Dap(N_3)-His(Trt)-(D)Phe-Arg(Pmc)-Trp(Boc)-Pra-Met was assembled by standard Fmoc chemistry. Azide and alkyne modified amino acid, Fmoc-Dap(N_3)-OH and propargylglycine-OH, were incorporated into appropriate position, respectively, to give resin bound precursor **3** (Scheme 1). Linear peptide was detached from the resin using 0.1 mol/L NaOH and confirmed by HPLC. Both the side chain fully protected and deprotected peptide mimetics were used for the on-resin cyclization under typical click chemistry condition. On-resin cyclization proceeded smoothly in both cases to give cyclipeptidomimetics product **5** in 76% to 79% yield after work-up and purification by HPLC.

Finn's group described the Wang-resin based peptide head-to-tail CuAAC cyclization under copper catalyst [10]. In their studies, 11-mer and 19-mer peptide **6** and **7** containing Arg-Gly-Asp (RGD) sequence were synthesized by standard Fmoc chemistry or Boc chemistry. Amino acids containing clickable function group, such as L-propargylglycines and 5-azidopentanoic acid, were introduced at the second position of C-terminal and N-terminal, respectively. Under "click chemistry" condition and subsequent cleavage from the solid support, cyclodimerization products **8** and **9** were generated selectively in 10%–20% of yield without detection of linear product after purification by HPLC and characterized by MALDI-TOF MS. Subsequent detailed mechanism study demonstrated that this unexpected cyclodimerization is independent of peptide sequence, but sensitive to the distance of alkyne group to resin and solvents composition. Cyclodimerization prefer to form α- and β-peptides but not δ-peptides (Scheme 2) [11].

Similarly, Khan's group applied on-resin click chemistry to synthesize cyclic NGR and RGD peptides, which were further modified to give fluorescence labeled compound **14** [12]. The binding profile with aminopeptidase A, cell lysates from MCF-7 and SKOV-3 cancer cell lines was further investigated (Scheme 3). Recently, Zhang *et al.* utilized on-resin CuAAC strategy to synthesize two asymmetrical cyclopeptidomimetics CP1 and CP2, and further explored their self-assembly behavior in solution to better understand the mechanism of protein self-assembly [13].

Vidal and co-worker investigated the on-resin head-to-tail cyclization for the synthesis of vascular endothelial growth factor (VEGF) ligands using CuAAC reaction [14]. Based on the crystal structure data of protein, peptide mimics containing the essential amino acids are designed and synthesized by standard Fmoc chemistry on Rink amide MBHA resin. The L-propargylglycine was installed in the C-terminal and N-terminal azido glycine was introduced by either azido acid coupling or direct solid-phase diazo-transfer reaction using N-terminal amine group. The cyclization process was monitored by IR spectroscopy and modified Kaiser Test. Interestingly, cyclomonomeric products **17** are produced exclusively in their studies. Over all crude cyclization products are formed in a yield of around 50% and a purity of 70%. The structure was confirmed by ESI-mass and NMR spectroscopy after purification by RP-HPLC (Scheme 4). Later, Lokey's group developed this strategy as a macrocyclization tool to prepare cyclic tetra-, penta-, hexa-, and heptapeptides successfully [15]. Reaction



Scheme 1. CuAAC on PEGA resin for the synthesis of cyclopeptidomimetics.