# Efficient Synthesis of Fused 1,2,3-Triazolo-$\delta$-lactams Using Huisgen [3 + 2] Dipolar Cycloaddition "Click-chemistry" in Water

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A general approach for the quick synthesis of various 1,2,3-triazolo-$\delta$-lactams has been described, which involves the Huisgen [3 + 2] dipolar cycloaddition of azides derived from different amino acids with dimethyl acetylenedicarboxylate in water followed by cyclization.

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Small nitrogen heterocycles containing amine and amine-derived functionality are frequently found in a wide variety of natural and non-natural compounds of biological significance.[1] 1,3-Dipolar cycloaddition reaction between alkyne and azide developed by Huisgen[2] is the most popular reaction because the resulting five-membered substituted 1,2,3-triazole heterocyclic ring has a wide range of industrial applications such as dyes, photostabilizers, agrochemicals[3] as well as in the designing of new drugs.[4] This cycloaddition is typically carried out at higher temperature which usually gives a mixture of 1,4- and 1,5-substituted regioisomeric triazole products. The remarkable stability of triazole ring to the metabolic transformations like oxidation, reduction, both acidic and basic hydrolysis enhances its utility as a connecting group.[5] It is known that electron-withdrawing group on alkyne moiety enhances the rate of irreversible cycloaddition reaction and recently termed as "click chemistry."[6]

Medium sized ring lactams are important building blocks for the synthesis of bioactive molecules. Recently, a number of $\delta$-lactams (piperazone) **1** have been synthesized and evaluated as potent elastases inhibitors.[7] Similarly lactum based, both monocyclic and bicyclic piperazinone **2** building blocks as constrained peptidomimetics have been synthesized.[8] The synthesis of various 1,2,3-triazolo[1,5-*a*]quinoxaline compounds **3** and their binding to benzodiazepine and adenosine receptors have also been studied.[9] As a continuation of our interest in developing different strategies based on the amino acids as a chiral starting materials for the synthesis of bioactive compounds,[10] We report here the first general approach for the synthesis of fused 1,2,3-triazolo-$\delta$-lactams **4** using Huisgen [3 + 2] dipolar cycloaddition reaction between activated alkyne and azides derived from different amino acids in water as a "click-chemistry" reaction followed by cyclization. The retro synthetic analysis of our strategy is shown in Scheme 1. We established our methodology starting with various commercially available amino acids. As shown in Scheme 2, L-serine **5** was easily transformed into the corresponding alcohol **6** following a reported procedure.[11] The amino alcohol **6** was subjected to the tosyl protection with tosyl chloride/$Et_3N$ in dry DCM at 0 °C for 4 h, followed by nucleophilic substitution with $NaN_3$ in 1,4-dioxane/DMSO at

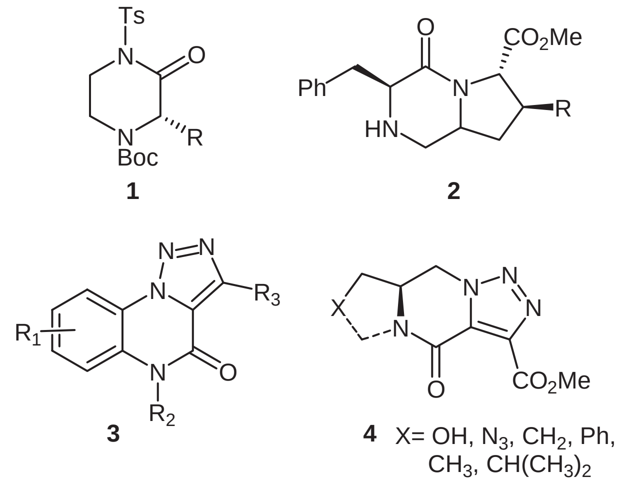
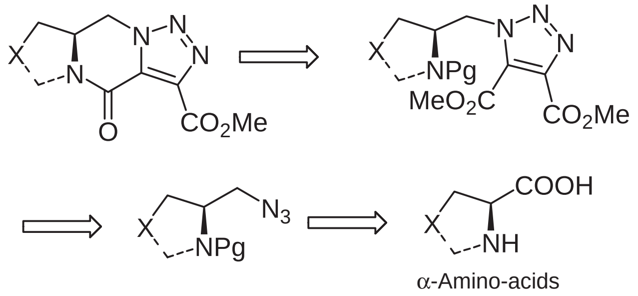
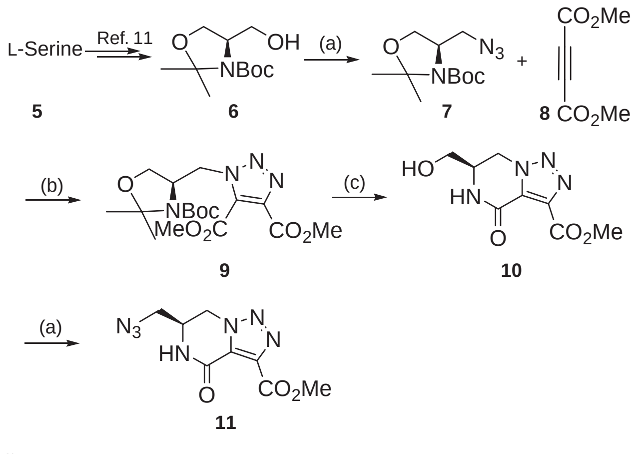


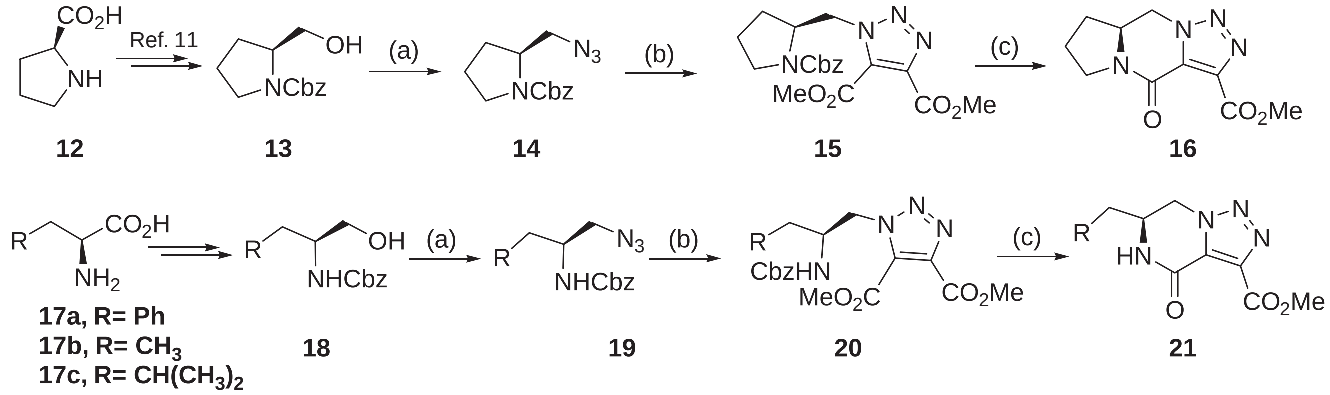
**Figure 1.**



**Scheme 1.** Reterosynthetic analysis of fused 1,2,3-triazolo-$\delta$-lactams.



**Scheme 2.** (a) (i) TsCl (1.1 equiv.), $Et_3N$ (1.2 equiv.), dry DCM, 0 °C, 4 h (ii) $NaN_3$ (2.2 equiv.), 1,4-Dioxane/DMSO (10:1), 65 °C, 6 h, 85% in two steps. (b) Dimethyl acetylenedicarboxylate **8** (1.1 equiv.), $H_2O$, 70 °C, 1 h, 95% yield (c) (i) TFA (2.5 equiv.), dry DCM, 6 h, (ii) MeOH/DMSO (5:1), reflux, 3.5 h, 78% in two steps.



**Scheme 3.** (a) (i) TsCl (1.1 equiv.), $Et_3N$ (1.2 equiv.), dry DCM, 0 °C, 4 h (ii) $NaN_3$ (2.2 equiv.), 1,4-Dioxane/DMSO (10:1), 65 °C, 6 h, 87% in two steps. (b) Dimethyl acetylenedicarboxylate **8** (1.1 equiv.), $H_2O$, 70 °C, 1 h, quantitative yield (c) (i) Pd/C (10 mol %), $H_2$ (1 atm), MeOH, rt, 2 h (ii) reflux, 4 h, yield mentioned in the text.

65 °C for 24 h to provide azido-derivative **7** with 85% yield in two steps. Our next aim was to carry out the Huisgen [3 + 2] dipolar cycloaddition of azido compound **7** with an activated alkyne in water. For this purpose, a mixture of **7** and dimethyl acetylenedicarboxylate **8** were heated in water at 70 °C for 1 h to provide cycloadduct **9** in 95% yield after passing through a small bed of silica gel. In order to achieve the synthesis of corresponding fused 1,2,3-triazolo-$\delta$-lactam **10**, the sequential deprotection of N-Boc and acetonide moiety followed by cyclization were successfully carried out in a single-pot two-step procedure using TFA/DCM at rt for 4 h followed by refluxing in MeOH/DMSO to provide bicyclic compound **10** with 78% yield after chromatographic purification. Further conversion of hybrid compound **10** into its corresponding azido derivative **11** was carried out with 88% yield in two steps, similar to the previous one as shown in Scheme 2.

Amino acid L-proline **12** containing pyrrolidine ring was transformed into its corresponding N-Cbz protected alcohol **13** following the standard procedure. The resulting alcohol was then transformed into its corresponding azido compound **14** using the sequence of tosyl protection/azide substitution by single-pot two-step procedures with excellent yield. The [3 + 2] dipolar cycloaddition reaction of compound **14** was carried out with 1.1 mol equiv. of **8** in water at 70 °C for 1 h to provide its corresponding cycloadduct **15** in almost quantitative yield.

In order to achieve the synthesis of its corresponding fused tricycilc triazolo-$\delta$-lactum **16**, the sequential deprotection of N-Cbz and further cyclization was successfully carried out with one-pot two-step procedure using Pd/C (10 mol %) in MeOH under hydrogen atmosphere at rt for 2 h followed by refluxing for 4 h to provide **16** with 80% yield. Similarly, the other amino acids like L-phenylalanine **17a**, L-valine **17b** and L-leucine **17c** were transformed into their corresponding azido derivatives **19**. The [3 + 2] dipolar cycloaddition of these azides with **8** in water under similar conditions, followed by intramolecular cyclization leads to the synthesis of different corresponding bicyclic triazolo-$\delta$-lactams **21** in excellent yields (Scheme 3). All the new compounds were fully characterized by spectroscopic means.[12]

In summery, we have developed an efficient and general route for the synthesis of new class of various triazolo-$\delta$-lactams in few steps from azides derived from amino acids. The main strength of this approach is that it allows the use of wide variety of existing amino acids as starting materials for the synthesis of various triazolo-$\delta$-lactams.

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