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Stereo- and regio-selective one-pot synthesis of triazole-based unnatural amino acids and β-amino triazoles†

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Synthesis of triazole based unnatural amino acids and β-amino triazoles has been described *via* a stereo and regioselective one-pot multi-component reaction of sulfamidates, sodium azide, and alkynes under MW conditions. The developed method is applicable to a broad substrate scope and has significant potential for the synthesis of unnatural amino acids with a triazole side chain.

The Huisgen 1,3-dipolar cycloaddition of azides and alkynes resulting in 1,2,3-triazoles is one of the most powerful click reactions.[1] After the pivotal discovery by Sharpless *et al.*[2] that Cu(I) catalyzes the formation of triazoles in a 1,4-substituted fashion, the chemistry of triazoles was brought from oblivion to renaissance. Triazole chemistry has seen exponential growth over the years and enormous gain in popularity in diverse areas of chemistry such as organic, material[3] and medicinal chemistry.[4] The 1,2,3-triazole moiety is present in many compounds exhibiting different biological properties such as antibacterial[5] (cefatrizine, Fig. 1), anti-HIV,[6] antiallergic,[7] and inhibitory[8] (tazobactam, Fig. 1) properties. Triazolobenzodiazepines[9] have shown a high affinity toward benzodiazepine receptors. The triazole chemistry has evolved to a great extent in recent years.[3–9] A comprehensive synthesis of triazole-modified unnatural amino acids was demonstrated by Mariusz *et al.* (Scheme 1).[10]

Almost all the papers reported in the literature followed the same synthetic strategy for the synthesis of triazole-based unnatural amino acid derivatives.[11] This method involves the Mitsunobu reaction, which requires the highly toxic and explosive dry hydrogen azide for the synthesis of azide intermediate along with other expensive and toxic reagents. Under these conditions,

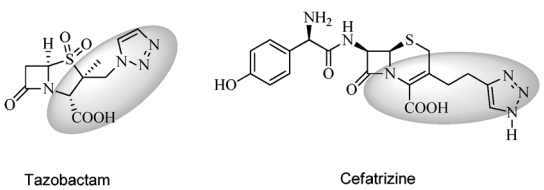

Fig. 1 Triazole-based antibiotics.

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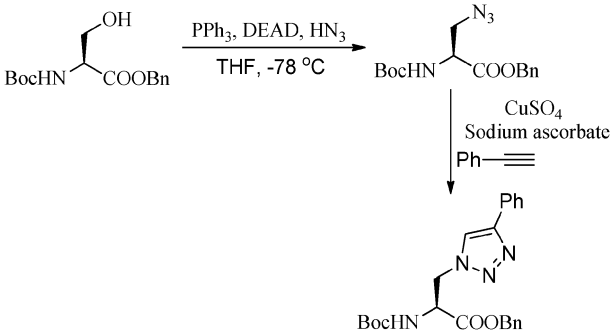


Scheme 1 Reported method for the synthesis of triazole-modified unnatural amino acid.

3-alkyl derivatives of serine (*e.g.* threonine) afford dehydroamino acids instead of the corresponding azide (ESI†, Scheme 1) which limits its scope thereby restricting its use to only serine-derived triazole-based unnatural amino acids.

To promote the development of green methods for the synthesis of biologically active molecules, a general method for the synthesis of triazole modified unnatural amino acids was developed. These amino acids could be very useful to modify biologically active peptide molecules as they are stable to metabolic degradation. 1,2,3-Triazoles are capable of hydrogen bonding which can be favorable in the binding of biomolecular targets and improving the solubility.[12] To eliminate the use of toxic hydrogen azide, we envisage aziridines or sulfamidates as important intermediates.

Sulfamidates are emerging as important chiral intermediates in organic synthesis.[13–15] Although they are the synthetic equivalents of aziridines, sulfamidates have added advantages over aziridines in terms of reactivity and selectivity,[13a] *i.e.* because the regio-selectivity problem could occur when aziridine intermediates are used (Fig. 2). The tedious separation of regio isomers and loss of up to 50% of the starting material (aziridine intermediate) would be another issue. Consequently, sulfamidates appear to be a better choice as intermediate for the development of an eco-friendly one-pot multi-step method for the synthesis of triazole-based unnatural amino acids and β-amino triazoles. In continuation of previous work on expeditious microwave (MW)-assisted chemistry,[16] a reaction scheme that involves the *in situ* generation of an azide intermediate followed by the cycloaddition to yield the corresponding triazole-unnatural amino acid and β-amino triazole has been designed.

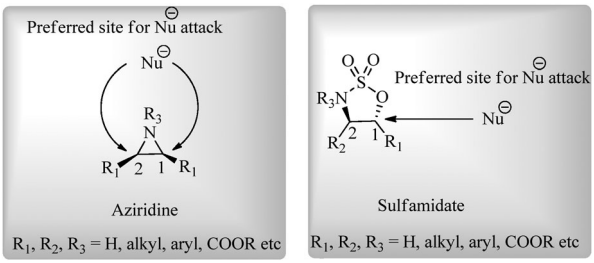
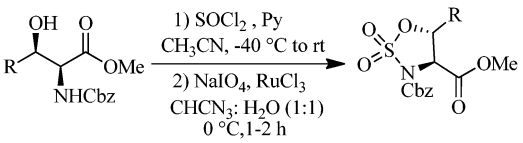


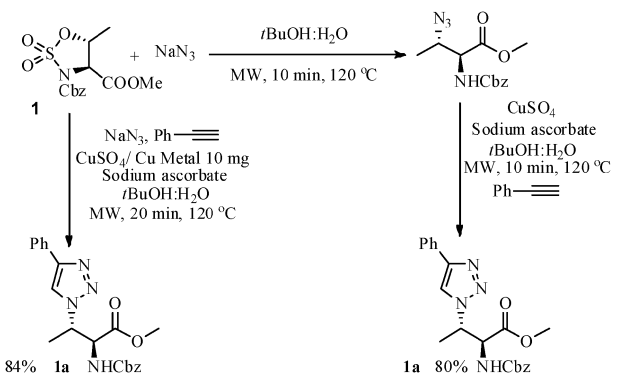
Fig. 2 Competitive nucleophilic attack on aziridine and sulfamidate.



Scheme 2 Synthesis of sulfamidates.

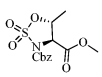
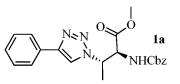
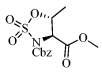
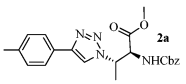
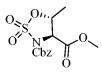
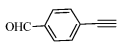
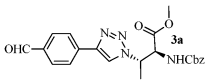
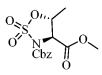
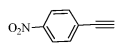
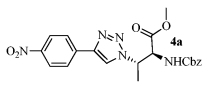
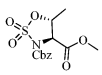
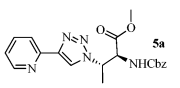
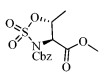
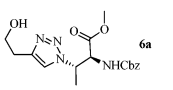
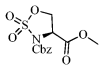
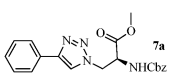
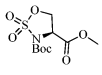
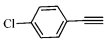
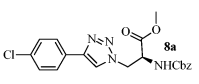
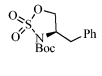
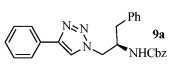
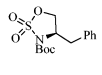
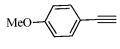
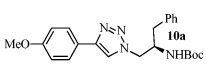
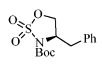
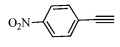
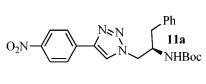
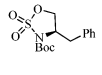
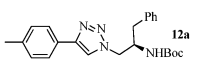
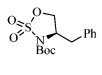
At the outset, sulfamidate carboxylate **1** from threonine was synthesized using a reported method (Scheme 2)[13] and treated with sodium azide [1.2 mmol, *t*-BuOH : H_2O (1 : 1)] under MW irradiation conditions (120 °C, 100 watts, 10 min). After isolation and confirmation of the azide intermediate using IR spectroscopy, the intermediate was subjected to the azide–alkyne cycloaddition (120 °C, 100 watts, 10 min) in a *t*-BuOH : H_2O mixture which led to the diastereoselective formation of the corresponding triazole amino acid **1a** (Scheme 3).

Subsequently, a one-pot strategy was envisioned which entails treating sulfamidate **1** with NaN_3 and alkyne in a *t*-BuOH–water mixture using $CuSO_4$/sodium ascorbate or $CuSO_4$/Cu(metal).[17] However, the best results were obtained when the reaction was performed using $CuSO_4$/sodium ascorbate and Cu-metal (Scheme 2). After successful optimization of the reaction conditions, the efficacy and scope of the reaction were examined using various substrates. The reaction of sulfamidate carboxylate (Table 1, entries 1–8) and sulfamidate (Table 1, entries 9–16) with a variety of alkynes afforded the corresponding triazole amino acids and β-amino triazoles, **1a–16a**, using a general method successful in all the cases (Table 1). The reactions proceeded smoothly to completion within 20–30 min and the products were isolated in good yields. In almost all the cases the reaction attained completion within 20 min except where the alkyne counterpart was *p*-nitrophenyl acetylene and homopropargyl alcohol which required 25 and 30 min respectively (Table 1, entries 4, 6, 11, 16).



Scheme 3 Synthesis of triazole modified unnatural amino acid.

Table 1 Synthesis of side chain modified unnatural amino acids

Entry	Sulfamidate	Alkyne	Time/min	Product	Yield[a] (%)
1			20		84
2			20		85
3			20		81
4			25		76
5			20		79
6			30		86
7			20		85
8			20		83
9			20		84
10			20		85
11			25		71
12			20		85
13			25		79[b]
14			20		85
15			20		86
16			25		72

[a] Reaction conditions: (i) 1.0 mmol of sulfamidate, 1.2 mmol of NaN_3, 1.2 mmol of alkyne, 5 mol% of $CuSO_4$, 10 mol% of sodium ascorbate, 10 mg of Cu metal, MW, 120 °C, power 100 watts; (ii) saturated citric acid solution, 5 min at rt. [b] Reaction conditions: (i) 1.0 mmol of sulfamidate, 1.2 mmol of NaN_3, 120 °C, power 100 watts, 10 min; (ii) 1.2 mmol of alkyne, 5 mol% of $CuSO_4$, 10 mol% of sodium ascorbate, 10 mg of Cu metal, MW, 70 °C, power 100 watts, 15 min; (iii) saturated citric acid solution, 5 min at rt.

The presence of various functional groups (–CHO, –Cl, –NO_2, –OH, –OMe *etc*.), heterocyclic ring system and different protecting groups present in sulfamidate did not have any significant effect on the product formation in the one-pot treatment of sulfamidate, alkyne, sodium azide and the catalyst with the exception of ethyl propionate (Table 1, entry 13), which formed a mixture of products. To minimize the formation of undesirable byproducts, we further modified the procedure. First, sulfamidate (1.0 equiv.) was treated with NaN_3 (1.2 equiv.) in *t*-BuOH : H_2O (1 : 1) and irradiated with microwaves (120 °C, 100 watts, 10 min). Subsequently, ethyl propionate (1.2 equiv.) and the catalyst were added and subjected to further MW irradiation (70 °C, 100 watts) for 15 min. The reaction proceeded cleanly and furnished the corresponding β-amino triazole **13a** in 79% yield (Table 1).

A very efficient and safe procedure for the synthesis of triazole-based unnatural amino acids and β-amino triazoles has been developed using a one-pot multi-component reaction of sulfamidates under MW irradiation conditions. To the best of our knowledge, this is an unprecedented example for the synthesis of triazole-modified unnatural amino acids. This newer protocol eliminates the use of highly toxic and explosive HN_3 and DEAD (diethylazodicarboxylate) reagents required for the synthesis of azide intermediates[10] under dry conditions. An additional green attribute is that the reaction can be performed in aqueous media.

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