A facile route for the synthesis of novel S-linked 1,3,5-triazine tethered peptidomimetics

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Abstract

An efficient one-pot synthesis of N<sup>a</sup>-protected S-linked 1,3,5-triazine tethered peptidomimetics is described. The protocol involves a three-component condensation reaction employing N<sup>a</sup>-protected amino alkyl isothiouronium salt, formaldehyde and amino acid ester or aryl amine as reactants. Various aryl amines with substitutions and amino acids with simple as well as bifunctional side chains were employed to obtain triazine tethered peptidomimetics in good yield.

Peptidomimetics have aroused great interest due to their wide utility in developing new therapeutic agents and in drug design. One of the useful approaches for the synthesis of such peptidomimetics involves the incorporation of heterocyclic units at one or more peptide bonds. In this context, triazoles, tetrazoles, thiazoles, oxazoles, oxadiazoles and many other biologically important heterocycles have been incorporated into the peptide backbone and their biological properties have been studied. 1,3,5-Triazine is an important heterocyclic unit that has found useful applications as antimicrobial and antitumor agents. It was also used as supramolecular agent, 4 and in the synthesis of dyes, as well as DNA cleavage reagent. Triazine derivatives also showed non-peptidic prokinecin antagonist 7 and analgesic properties. The S-linked 1,3,5-triazine derivatives also exhibit a wide range of pharmacological properties. Brown and co-workers described the synthesis of MAC13243, a new antibacterial compound which inhibits the activity of LolA protein, a crucial component of the lipoprotein targeting pathway in bacteria (Fig. 1). Belonging to the similar class, 5-chlorouracil-linked pyrazolo 1,3,5-triazines, serve as thymidine phosphorylase inhibitor. In an earlier report, Rabovsky et al., described the synthesis of triazinedione through two different methods. In the first method, commercially available sulfonic acid salt of 2-methyl isothiourea was treated with isocyanate in the presence of NaOH to form an intermediate which was then cyclized using methyl chloroformate and Et<sub>3</sub>N at –10 °C to rt to obtain the triazinediones. Parallely, commercially available thiourea was treated with CH<sub>3</sub>Cl in the presence of MeOH to prepare isothiourea as an intermediate which was then cyclized with N-chlorocarbonylisocyanate to yield triazinedione. Kong et al. reported the synthesis of S-linked 1,3,5-triazine-2,4-diones through cyclization of the intermediate obtained by the reaction of ethoxycarbonylisothiocyanate, methyl

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>THF</td>
<td>38</td>
</tr>
<tr>
<td>b</td>
<td>Acetonitrile</td>
<td>65</td>
</tr>
<tr>
<td>c</td>
<td>EtoH</td>
<td>40</td>
</tr>
<tr>
<td>d</td>
<td>1,4-Dioxane</td>
<td>89</td>
</tr>
<tr>
<td>e</td>
<td>Methanol</td>
<td>30</td>
</tr>
</tbody>
</table>

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amine and benzyl bromide in the presence of NaH in THF followed by treatment with isocyanate at 60 °C. Lam and co-workers described the preparation of S-linked triazines using Mukaiyama reagent in the presence of DMAP at about 60–110 °C. These methods inherit certain limitations wherein the isocyanates employed for the reaction are not commercially available and are moisture sensitive and toxic, which otherwise poses difficulty while handling. Also the methods described involve long reaction duration and harsh reaction conditions. Zhao et al. reported the synthesis of N^2-Cbz-amino acyl derived 3,5,6-trisubstituted 1,2,4-triazines using Cbz-protected amino acyl hydrazides and 1,2-diones in the presence of excess NH_4OAc at 180 °C.

Our group reported several new classes of peptidomimetics possessing heterocycles such as 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,3,4-thiadiazoles, triazoles, and tetrazoles. This list also includes Fmoc-protected amino alkyl S/Se-linked tetrazoles and Z/Boc-protected S-linked oxadiazole tethered peptidomimetics. Thus, with the continuing interest in designing heterocycle tethered peptidomimetics we envisaged the synthesis of the S-linked 1,3,5-triazine moiety incorporated into the peptide backbone.

The starting material, N^2-protected amino alkyl isothiourea salt required for the present study was prepared through the literature protocol as reported earlier by our group. The N^2-protected amino acid was subjected to reduction and then to Mitsunobu conditions to form iodo compound. Thus obtained iodo compound was then treated with thiourea in acetonitrile under argon atmosphere at reflux temperature for about 8–10 h to obtain corresponding isothiourea salt, which was used as such for the next step.

In an initial study, isothiourea salt derived from Fmoc-Phe-OH, that is, Fmoc-Phe-\(\psi\)[CH_2SC(NH)NH_2][H] \(4a\) was made to react with formaldehyde (37 wt % solution in water) and benzylamine as a test case in the presence of TEA in THF at rt. The product \(5a\) was obtained albeit in very low yield. The four solvents viz acetonitrile, EtOH, 1,4-dioxane and MeOH (Table 1) were screened in parallel reactions. An impressive yield of 89% of \(5a\) was isolated when the reaction was carried out using 1,4-dioxane as solvent, in the presence of 1.5 equiv of TEA, 2.0 equiv of HCHO, 1.5 equiv of amine and 1.0 equiv of isothiourea salt (Scheme 1).

With the optimized reaction conditions in hand, the generality of the present protocol was tested by using aryl amines which afforded the title molecules in good yield (Table 2). A plausible reaction mechanism was proposed for the formation of compound 5 (Scheme 2).
In the first step of the reaction, the amine was condensed with formaldehyde producing an imine intermediate $I$, which subsequently reacts with a molecule of N-protected amino alkyl isothiourrea, giving an intermediate $II$. This intermediate $II$ in the presence of formaldehyde undergoes dehydrocyclization to form N$^a$-protected S-linked 1,3,5-triazine tethered peptidomimetics. The formation of the desired product can also be explained through another possible pathway wherein deprotonated isothiouronium salt reacts with HCHO to give the corresponding imine-like diunsaturated intermediate. This will then react with the intermediate.


Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant 4</th>
<th>Products 7</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td><img src="image1" alt="Product Image" /></td>
<td>81</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td><img src="image2" alt="Product Image" /></td>
<td>80</td>
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<td>c</td>
<td></td>
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<tr>
<td>d</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>f</td>
<td></td>
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<td>76</td>
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<tr>
<td>g</td>
<td></td>
<td><img src="image7" alt="Product Image" /></td>
<td>72</td>
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<tr>
<td>h</td>
<td></td>
<td><img src="image8" alt="Product Image" /></td>
<td>79</td>
</tr>
<tr>
<td>i</td>
<td></td>
<td><img src="image9" alt="Product Image" /></td>
<td>75</td>
</tr>
</tbody>
</table>
and MeOH as eluent (95:5) to = 254 nm.)

1H NMR (400 MHz, CDCl3

and evaporated in vacuo

values, that is, at

(b) Whitesides, G. M.; Simanek, E. E.; Mathias, J. P.; Seto, C. T.; Chin, D.;

(2) In an aza-Diels Alder like process to afford the product

I) in an aza-Diels Alder like process to afford the product

The crude product was then purified through column chromatography using CHCl3 and MeOH as eluent (95:5) to afford the pure product in 85% yield (Scheme 3). The efficacy of this protocol was demonstrated by the synthesis of a series of compounds employing several N2-protected amino alkyl isothiouronium salts and amino acid methyl esters in moderate to good yields (Table 3). All the compounds were isolated as stable ones and characterized through mass, 1H and 13C NMR analyses.

The possibility of racemization, if any, during the synthesis of S-linked 1,3,5-triazine tethered peptidomimetics via the present protocol was assessed through RP-HPLC analysis of the intentionally made diastereomers, that is, \( \text{Fmoc-} \text{Phg-3Hg-(S)-PEA} \) and \( \text{Fmoc-} \text{Phg-3Hg-(S)-PEA} \). From these results it was found that the protocol was racemization-free and yielded optically pure products.

In the present Letter, we have demonstrated an application of N2-protected amino alkyl isothiouronium salts as precursor units for the preparation of S-linked 1,3,5-triazine tethered peptidomimetics in one pot. The synthetic protocol implemented was straightforward, mild and avoids the usage of isothiocyanates used in earlier reports, which were albeit toxic and hazardous and handling of such molecules is difficult. The products were obtained in good yields and characterized by mass, 1H and 13C analyses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.075.

References and notes


