Novel cyclization of bis-Boc-guanidines: expeditive traceless synthesis of 1,3,5-oxadiazinones under microwave conditions†

Gorakh S. Yellol, Tsai-Wen Chung and Chung-Ming Sun*

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A novel intramolecular cyclization was discovered during the reaction of soluble polymer supported bis-Boc-guanidines with amines under microwave irradiation, leading to an oxadiazinone skeleton. The cyclized polymer conjugates have been further utilized to generate substituted 1,3,5-oxadiazinones by a traceless synthesis.

Diversity oriented organic syntheses have tremendous impact in effectively utilizing the chemical space for drug discovery.1 A large number of compounds needed for SAR studies have been excellently generated by adopting a macromolecular carrier in diversity oriented synthesis. The idea of having a macromolecular support possessing conventional solubility properties in organic solvents has been very well realized in the use of polyethylene glycol (PEG).2 Functionalization at PEG in many cases paves the way for traceless synthetic routes.3 Similarly, the application of microwave irradiation in synthesis remarkably reduces the reactions time, enhances the yields, and is thus greatly utilized for the development of novel chemistry.3 The use of microwaves in solid supported organic synthesis has significantly contributed in the lead discovery and optimization processes of pharmaceutical companies.3 Application of microwaves in multiple steps by using a properly functionalized support for a traceless synthesis has been successfully utilized to generate biologically important small heterocyclic libraries.6

We were intrigued to develop guanidine embedded heterocyclic skeletons due to their broad pharmaceutical applications.7 The guanidine derivatives, particularly oxadiazinone moieties, have been established as a chiral auxiliaries for asymmetric synthesis.8 Furthermore, 1,3,5-oxadiazinones were patented for their pesticidal activity.7 Here we disclose the unexpected on-support cyclization of bis-Boc-guanidines induced by secondary amines. The cyclized polymer conjugates were further utilized for the traceless synthesis of N-cyanopiperazone/diazepane oxadiazinones.

Piperazine and 1,4-diazepane were employed as nucleophiles to accomplish a kinetically controlled benzylic substitution of polymer conjugate 1.10 This C–N bond forming transformation needed 3 h under refluxing conditions in dichloromethane which was brought down to 7 min under open vessel microwave conditions leading to polymer conjugates 2 (Scheme 1). This creates the first point of structural diversity in the present synthetic strategy. Introduction of the guanidine moiety was performed by using bis-Boc-benzotriazole-carboxamidine 3.11 The highly reactive guanidinylating reagent 3 was prepared by reacting benzotriazole with bis-Boc-S-methylisothiourea in the presence of mercuric chloride and triethyl amine for 10 min under microwave conditions, which took 12 h using conventional reflux conditions. To the best of our knowledge, this is the first report to synthesize guanidinylating agent 3 under microwave conditions. The guanidine transfer from 3 to piperazine conjugates 2 was completed in 6 h at room temperature and in 2 h under refluxing conditions in dichloromethane. The same reaction in an open vessel microwave reactor needed only 7 min, showing a substantial improvement over earlier reports.12 Boc-protected guanidine conjugates 4 were purified by precipitation in cold ether and obtained in 92% yields.

The reaction with secondary amines was aimed at introducing the second point of structural diversity by aminolysis of the polymer ester bond to generate a variety of tert-benzamides. As a model reaction, polymer conjugate 4 was treated with di-isopropyl amine (3 eq.) under microwave in THF. To our surprise, the NMR spectrum of the product revealed an absence of the tert-butyl signal, indicating the removal of the Boc-group during the aminolysis. From a comparative proton NMR analysis of conjugates 4 and 6a as depicted in Fig. 1, it can be seen that spectrum A displays a strong singlet at 1.5 ppm due to the tert-butyl group. It is unlikely that the Boc-protection was cleaved in the presence of secondary amines since acidic conditions are typically needed for the cleavage of the Boc-group. One possibility was the formation of bis-urea derivative 5, but the product obtained after aminolysis indicated a fewer number of N-alkyl protons than is expected for 5. It is interesting to note the presence of the polymer support, which remains very much intact in this reaction. Both spectra A and B show the characteristic set of peaks at 4.45 ppm, corresponding to the PEG protons. In addition, the aromatic pattern in spectra A and B are also

† Laboratory of Combinatorial Drug Discovery, Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan. E-mail: cmsun@mail.nctu.edu.tw; Tel: +886 03 5131511
‡ Electronic supplementary information (ESI) available: Experimental procedures, full characterization data and copies of 1H and 13C NMR spectra for all the new compounds. CCDC 790233. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03519j
identical. These observations, together with literature support, lead us to believe that ring closure occurred. Consequently, the observed product was assigned and confirmed as cyclized structure 6, having an oxadiazinone ring with amine substitution at the 4-position and a PEG linked piperazinyl/diazepanyl moiety at the 6-position (Scheme 2).

Introduction of the cyano group at the ring nitrogen was planned in view of the electrophilicity of the nitrile and the reported high selectivity of N-cyano groups towards cysteine proteinases. Attempted cleavage of the polymer using CNBr in the presence of triethyl amine was achieved by von Braun cyanation conditions. The polymer cleavage with simultaneous N-cyanation was quite facile in dichloromethane and required 4 h at room temperature and 7 min under open vessel microwave conditions. A plausible reason for this reaction is the quaternization of the piperazinyl/diazepanyl ring nitrogen, which makes the benzylic carbon more prone for a nucleophilic attack by the bromide. The resulting N-cyanation was accompanied by benzylic C–N bond cleavage of the polymer conjugate 6, leading to a traceless synthesis of N-cyano-piperazinyl/diazepane oxadiazinones (Scheme 2). The reaction mixture was diluted with cold ether to precipitate out the PEG bound benzyl bromide, which could be recycled for further generation of conjugate 2. The polymer free oxadiazinones 7 or 8 were obtained in good (82–93%) yields. The traceless cleavage was confirmed by the NMR spectra of 7 and 8 which indicates the disappearance of the aromatic protons as well as the low field triplet at 4.45 ppm, characteristic of a PEG group (spectrum C, Fig. 1).

For the generalization of this unprecedented cyclization, various cyclic and acyclic secondary amines were employed. Gratifyingly, bis-Boc-guanidines underwent cyclization with all the amines and subsequent removal of polymer leading to the traceless synthesis of various piperazinyl/diazepanyl oxadiazinones. The results summarized in Table 1 show some representative examples to demonstrate the cyclization. The significance of the microwave conditions was proven by executing the present cyclization in classical heating conditions. The complete cyclized product was obtained (68%) after 48 h under refluxing conditions in THF.

Plausible steps involved in the ring closure of conjugates 4 to 6 are shown in Fig. 2. Stereoelectronic requirements for a facile expulsion of tert-butanol by electronic rearrangements through a six-membered transition state are easily met in the bis-Boc guanidine conjugate 4, leading to the generation of isocyanate A. A similar isocyanate has been invoked as an intermediate during the synthesis of Boc-amidino urea. Nucleophilic addition across the isocyanate leads to Boc-protected urea B. Repeated sequence of steps A and B, are expected to generate the bis-urea intermediate 5. Intermediate 5 can again expel a secondary amine to form isocyanate D. An

![Table 1 N-cyano-piperazinyl/diazepane oxadiazinones](#)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Piperazine/diazepane</th>
<th>NHR1R2</th>
<th>LRMS</th>
<th>Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>n = 1: HN</td>
<td>306</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>7b</td>
<td>n = 1: HN</td>
<td>276</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>7c</td>
<td>n = 1: HN</td>
<td>305</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>7d</td>
<td>n = 1: HN</td>
<td>304</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>n = 2: HN</td>
<td>306</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>n = 2: HN</td>
<td>304</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>8c</td>
<td>n = 2: HN</td>
<td>306</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>8d</td>
<td>n = 2: HN</td>
<td>414</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

a Only representative examples are shown in Table 1. A library of total 16 compounds is included in the ESI. b Yields were determined on the weight of purified samples.

![Scheme 2 Novel cyclization towards oxadiazinone.](#)

Fig. 1 Comparative NMR spectra of 4, 6a and 7a.

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intramolecular attack of the ureido oxygen on the isocyanate would lead to oxadiazinone conjugate 6.

Attempts have been made to isolate intermediate 5 to support the proposed mechanism. During the microwave assisted reaction of conjugates 4 with di-isopropyl amine, the reaction was stopped at the half time (10 min) and subsequently upon removal of the polymer by cyanation, two products, 7a and 9, were isolated and characterized. Compound 7a was the oxadiazinone, which was found to be the completely cyclized product, while compound 9 was characterized as the polymer free derivative of the mechanistically predicted intermediate 5a (Scheme 3). Its structure agreed with the mass spectrum (m/z 408, M+H) and the 1H NMR spectrum indicated the NH proton at 11.76 ppm in addition to other signals. This observation clearly revealed that the present cyclization proceeds through intermediate 5.

In addition to spectroscopic studies, the structure of the final compound was further confirmed by X-ray diffraction studies (CCDC 790233). The ORTEP diagram obtained by the analysis of a single crystal of 7b is shown in Fig. 3. The X-ray crystallographic data of compound 7b revealed that the piperazine ring exhibits the thermodynamically stable chair conformation. Both the cyano and the oxadiazinone ring occupy pseudo equatorial positions opposite to each other. The pyrrolidine is almost coplanar with oxadiazinone.

In summary, we have discovered a novel cyclization of bis-Boc-guanidines. Polymer supported piperazine and 1,4-diazepane based bis-Boc-guanidines underwent unprecedented intramolecular cyclization promoted by secondary amines leading to 1,3,5-oxadiazinone under microwave conditions.

![Fig. 2](https://example.com/fig2.png)  
**Fig. 2** Proposed mechanism for the formation of oxadiazinones.

![Scheme 3](https://example.com/scheme3.png)  
**Scheme 3** Trapping of intermediate 5a.

![Fig. 3](https://example.com/fig3.png)  
**Fig. 3** ORTEP diagram of 7b.

Removal of the support by van Braun cyanation constitutes a novel traceless synthesis of N-cyano-piperazinyl/diazepanyl oxadiazinones. The efficiency of parallel synthesis was greatly enhanced by combining the advantages of microwave synthesis and a soluble polymer support.

**Notes and references**

10. The polymer conjugate 1 was prepared by loading 4-chloromethyl benzoyl chloride on PEG (6000) under refluxing conditions for 48 h, the reaction time was brought down to 10 min by using open vessel microwave irradiation.
16. Preferentially benzyl dinitrogen got quaternized, as the quaternization at oxadiazinones ring side nitrogen was less possible due to nitrogen lone pair in resonance with oxadiazinones ring.