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

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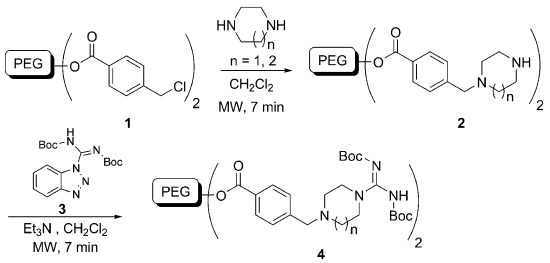
A novel intramolecular cyclization was discovered during the reaction of soluble polymer supported *bis*-*Boc*-guanidines with amines under microwave irradiation, leading to an oxadiazinone skeleton. The cyclized polymer conjugates have been further utilized to generate substituted 1,3,5-oxadiazinones 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.[4] The use of microwaves in solid supported organic synthesis has significantly contributed in the lead discovery and optimization processes of pharmaceutical companies.[5] 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.[9] 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*-cyanopiperazine/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 of conjugates **4**, which is absent in spectrum B. 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



Scheme 1 Synthesis of *bis*-*Boc*-guanidine conjugates.

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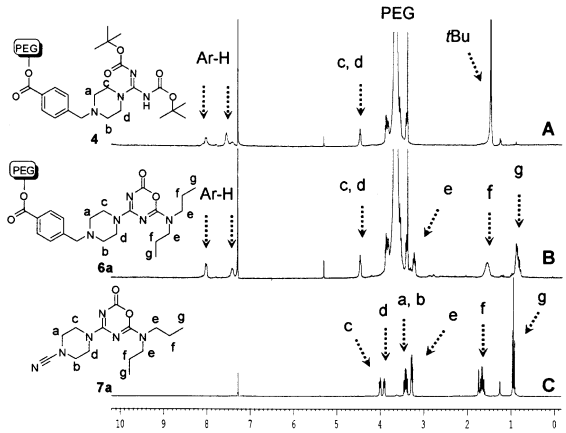
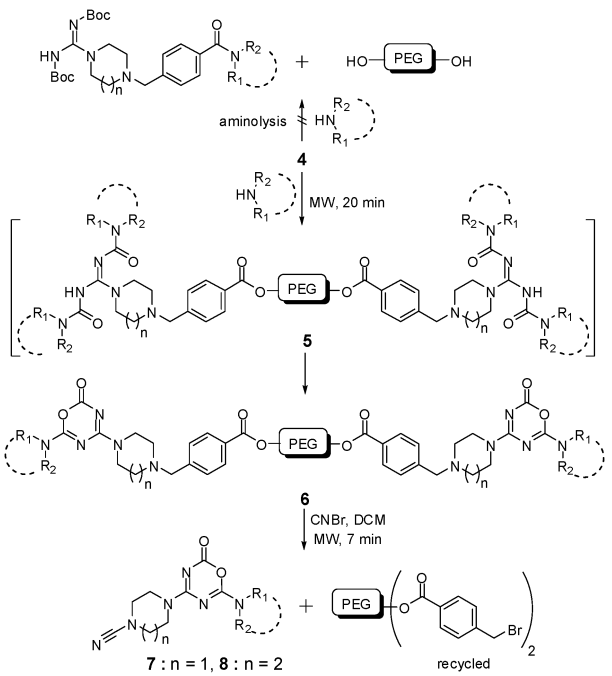


Fig. 1 Comparative NMR spectra of **4**, **6a** and **7a**.

identical. These observations, together with literature support,[13] 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.[14] Attempted cleavage of the polymer using CNBr in the presence of triethyl amine was achieved by von Braun cyanation conditions.[15] 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,[16] 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



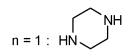
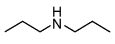
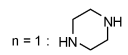
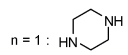
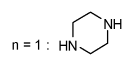
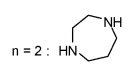
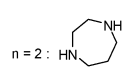
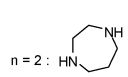
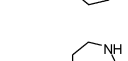
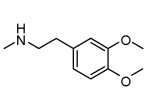
Scheme 2 Novel cyclization towards oxadiazinone.

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.[17] 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/diazepanyl oxadiazinones[a]

Entry	Piperazine/diazepane	NHR_1R_2	LRMS	Yield[b]
7a	n = 1 : 		306	84%
7b	n = 1 : 		276	92%
7c	n = 1 : 		305	83%
7d	n = 1 : 		304	88%
8a	n = 2 : 		306	80%
8b	n = 2 : 		304	91%
8c	n = 2 : 		306	90%
8d	n = 2 : 		414	83%

[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.

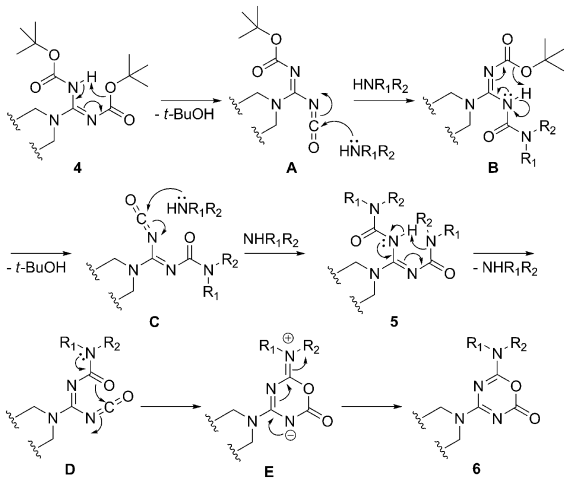
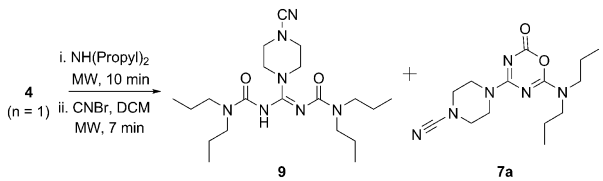


Fig. 2 Proposed mechanism for the formation of oxadiazinones.



Scheme 3 Trapping of intermediate **5a**.

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, 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 ^{1}H 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.

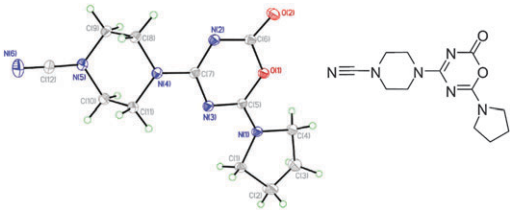


Fig. 3 ORTEP diagram of **7b**.

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

1 (*a*) S. L. Shreiber, *Science*, 2000, **287**, 1964; (*b*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74.
2 (*a*) P. H. Toy and K. D. Janda, *Acc. Chem. Res.*, 2000, **33**, 546; (*b*) C. M. Sun, in *Combinatorial Chemistry Methods and Protocols*, ed. L. Bellavance, The Humana Press Inc., NJ, 2002, p. 345.
3 P. Blaney, R. Grigg and V. Sridharan, *Chem. Rev.*, 2002, **102**, 2607.
4 (*a*) F. Al-Obeidi, R. E. Austin, J. F. Okonya and D. R. S. Bond, *Mini-Rev. Med. Chem.*, 2003, **3**, 459; (*b*) C. O. Kappe and D. Dallinger, *Nat. Rev. Drug Discovery*, 2006, **5**, 51.
5 (*a*) E. Suna and I. Mutule, *Top. Curr. Chem.*, 2006, **266**, 49; (*b*) C. O. Kappe and A. Stadler, in *Microwaves in Organic Synthesis*, Wiley-VCH, Wehingm, 2005.
6 (*a*) J. J. Lai, D. B. Salunke and C. M. Sun, *Org. Lett.*, 2010, **12**, 2174; (*b*) B. Maiti, K. Chanda and C. M. Sun, *Org. Lett.*, 2009, **11**, 4826; (*c*) V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629.
7 (*a*) R. A. Smits, M. Adami, E. P. Istyastono, O. P. Zuiderveld, C. M. E. van Dam, F. J. J. de Kanter, A. Jongejan, G. Coruzzi, R. Leurs and I. J. P. de Esch, *J. Med. Chem.*, 2010, **53**, 2390; (*b*) R. Bairwa, M. Kakwani, N. R. Tawari, J. Lalchandani, M. K. Ray, M. G. R. Rajan and M. S. Degani, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1623; (*c*) K. C. Ho and C. M. Sun, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1517.
8 (*a*) D. M. Casper, J. R. Burgeson, J. M. Esken, J. M. Ferrence and S. R. Hitchcock, *Org. Lett.*, 2002, **4**, 3739; (*b*) T. R. Hoover, J. A. Groeper, R. W. Parrott, S. P. Chandrashekar, J. M. Finefield, A. Dominguez and S. R. Hitchcock, *Tetrahedron: Asymmetry*, 2006, **17**, 1831.
9 S. F. Arisdorf and M. K. Pfeffingen, Oxadiazinones and pesticidal use, US Patent, 4742056, 1988.
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.
11 H. J. Musiol and L. Moroder, *Org. Lett.*, 2001, **3**, 3859.
12 (*a*) O. Guisado and J. Pastor, *Tetrahedron Lett.*, 1992, **33**, 6541; (*b*) A. Porcheddu, G. Giacomelli, A. Chighine and S. Masala, *Org. Lett.*, 2004, **6**, 4925.
13 (*a*) B. Drake, M. Patek and M. Lebl, *Synthesis*, 1994, 579; (*b*) R. Gompper and F. Towae, *Synthesis*, 1975, 522; (*c*) S. Guery, M. Schmitt and J. J. Bourguignon, *Synlett*, 2002, **12**, 2003.
14 T. Morgan, N. C. Ray and D. M. Parry, *Org. Lett.*, 2002, **4**, 597.
15 (*a*) J. von Braun, *Chem. Ber.*, 1900, **33**, 1438; (*b*) W. S. McCall, T. A. Grillo and D. L. Comins, *Org. Lett.*, 2008, **10**, 3255.
16 Preferentially benzylic nitrogen got quaternized, as the quaternization at oxadiazinones ring side nitrogen was less possible due to nitrogen lone pair in resonance with oxadiazinones ring.
17 H. Miel and S. Rault, *Tetrahedron Lett.*, 1998, **39**, 1565.

