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Development of a practical solid-phase synthesis approach to 1,3,5-triazepan-2,6-diones

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ABSTRACT

1,3,5-Triazepan-2,6-diones are a class of conformationally restricted heterocycles derived from dipeptides. With the aim to develop a general and practical method useful for library production, three polymer-assisted syntheses, all based on a catch and release approach, have been evaluated and compared. The method involving a Hofmann rearrangement of *N*-Boc dipeptide carboxamides and subsequent trapping of the isocyanate on polymer-supported *N*-hydroxysuccinimide (PS-HOSu) was found to be the most reliable and versatile, allowing rapid access to the 1,3,5-triazepan-2,6-dione skeleton.

1. Introduction

Compounds with triazepine skeletons have attracted much attention as a result of their interesting biological properties.[1] Triazepandiones represent a particular subset, of which a number of functional isomers have been synthesized.[2–4] In the search for novel heterocyclic scaffolds derived from peptides, we became interested by the 1,3,5-triazepan-2,6-dione skeleton **1** (Scheme 1) whose main features are: (i) a short reaction sequence with *N*-protected dipeptides as starting materials; (ii) a densely functionalized core with up to 5 points of diversity; (iii) possibilities for further functionalization at urea nitrogens by post-cyclization reactions (e.g., mono- and di-alkylation, mono-acylation); (iv) three dominant ring conformations depending on the substitution patterns.[5–7] The 1,3,5-triazepan-2,6-dione system whose ring structure shows overall similarity with that of 2,5-diketopiperazine (DKP) may thus be seen as a rigid peptide mimetic scaffold. In addition, the ring conformation of 4,5-fused 1,2,5-triazepane-3,6-diones, originally developed as constrained *cis*-peptidyl prolinamide mimetics[3] and 1,7-fused-1,3,5-triazepan-2,6-diones match perfectly,[5] thus suggesting that 1,3,5-triazepan-2,6-diones could also be used as mimics of native *cis*-peptidyl conformations.

We have started to explore the potential applications of 1,3,5-triazepan-2,6-diones in biology. Biological screening of a small pilot library led to the identification of compounds with some activity against the malaria liver stage.[5] Concurrently, a collection of 2150 druggable active sites from the Protein Data Bank was screened by high-throughput docking to identify putative targets for a small set of representative 1,3,5-triazepan-2,6-diones. This led to the discovery of inhibitors of human group V (hgV) and human group X (hGX) secreted phospholipases A2 (sPLA2).[8]

In previous work, 1,3,5-triazepan-2,6-diones have been prepared in solution from *N*-Boc dipeptides in four steps. The dipeptide was first converted to its acyl azide derivative. The isocyanate generated in situ upon *Curtius* rearrangement of the corresponding dipeptidyl azide was trapped by *N*-hydroxysuccinimide to give the corresponding activated succinimidyl carbamate.[5,9] Following Boc removal, cyclization of the resulting salt was performed in the presence of a tertiary amine base. Efficient ring formation requires the *cis*-conformation around the amide bond to be populated (i.e., $R^3 \neq H$). Although this solution synthesis approach is robust, a faster access to the 1,3,5-triazepan-2,6-dione skeleton is needed to generate librairies and fully address the potential of this scaffold in biological applications. A general polymer-assisted solution-phase synthesis approach involving cyclative cleavage and employing polymer bound carbamate **B** as a key intermediate is outlined in Scheme 1. Previously, *route A*, which parallels the solution phase synthesis has been positively evaluated for two heterocycles starting from purified *N*-Boc dipeptides (i.e., Boc–Phe–Sar–OH and

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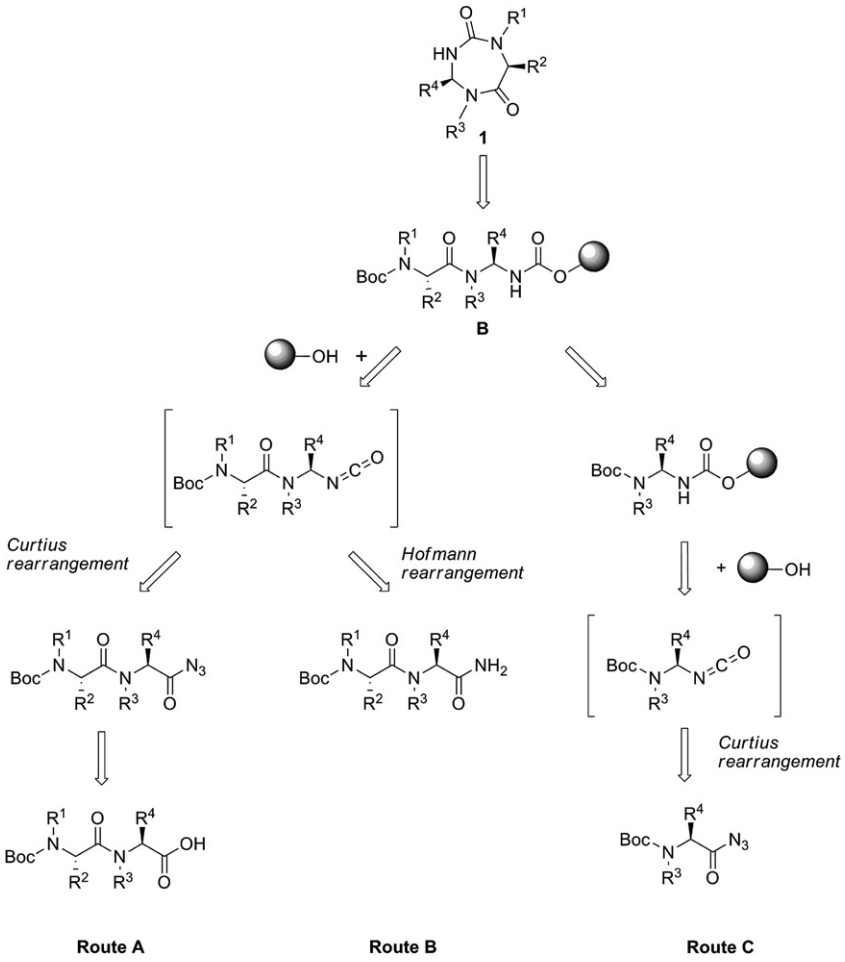


Scheme 1. Polymer-assisted synthesis approaches to 1,3,5-triazepan-2,6-diones evaluated in this study.

Boc–Phe–*N*MePhe–OH synthesized in solution). However, to be practically useful for the preparation of compounds in a library format, the synthesis needs to work with crude dipeptide arrays accessible by parallel solid-phase techniques.

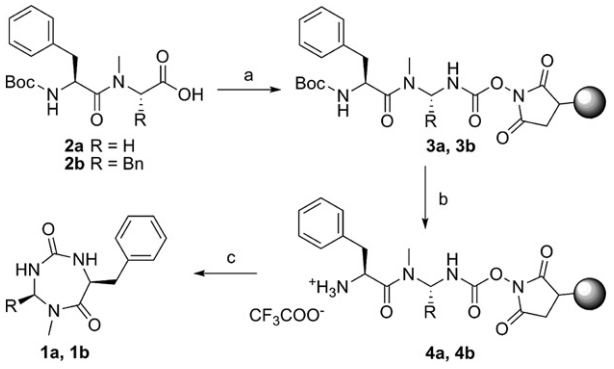
To meet these specifications, we have now decided to re-evaluate *route A* in comparison with two new alternative routes involving either the Hofmann rearrangement of *N*-Boc dipeptide carboxamides (Scheme 1, *route B*) or trapping of *N*-protected α-amino isocyanates derived from commercially available *N*-protected α-amino acids (Scheme 1, *route C*).

2. Results and discussion

All reaction sequences corresponding to *routes A–C* have been evaluated using a compact multiparallel synthesizer Miniblock™ Bodhan® from Mettler Toledo filled with 4 mL polypropylene reaction tubes and have been optimized independently. In all cases, the formation of the key polymer bound carbamate intermediates **B** was monitored by FTIR spectroscopy.

2.1. Synthesis via *Curtius* rearrangement of dipeptidylacyl azides (*route A*)

We selected *cyclo*(Phe–*g*Sar–CO) (**1a**) and *cyclo*(-Phe–*gN*MePhe–CO) (**1b**)[10] as reference 1,3,5-triazepan-2,6-diones to evaluate this *route*. The experimental procedure previously set up[5] to access **1a** and **1b** by *route A* needed first to be slightly refined because of the limited airtightness of the system, resulting in uncontrolled evaporation of the solvent (THF) during the *Curtius* rearrangement (T=70 °C). Substituting DMF for THF gave consistently better results, triazepan-2,6-diones **1a** and **1b** being obtained in good yield (>75%) and purity (>81% based on C_{18} RP-HPLC) when starting from purified *N*-Boc–dipeptides (Scheme 2). We



Scheme 2. Reagents and conditions. (a) (i) DPPA (1.1 equiv), TEA (1.1 equiv), DMF, rt, 30 min; (ii) 70 °C, 1.5 h; (iii) PS-SuOH 1.54 mmol/g (0.3 equiv), 70 °C, 40 min; (b) TFA/CH_2Cl_2 (1:3, *v*/*v*), 2×25 min, rt; (c) DIPEA (1.2 equiv), CH_2Cl_2, 40 °C 1 h.

found however, that the timing to dispense the polystyrene polymer-supported *N*-hydroxysuccinimide (PS-HOSu)[11] in the reaction mixture with respect to isocyanate formation was critical. If the resin was added prior to *Curtius* rearrangement, a fraction of dipeptidyl acyl azide was trapped by PS-HOSu to form the