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New 1,3,5-triazine derivatives as templates for the homogeneous phase synthesis of chemical libraries

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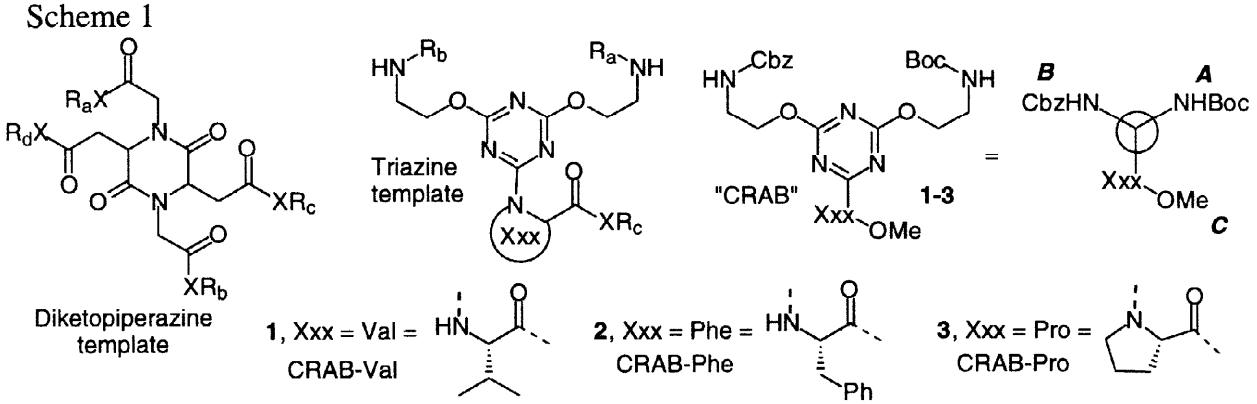
Abstract

The synthesis of tri-functionalized orthogonally protected CRAB templates based on the triazine skeleton are described together with some protocols for the preparation of families of diversomers using a parallel synthesis approach.

Keywords: Combinatorial chemistry, Triazines, Amides, Amino acids and derivatives

Chemical libraries are currently employed in modern drug discovery processes [1]. Very recently, solution-phase parallel and combinatorial syntheses [2] have been considered as practical alternatives to solid-phase protocols [3]. Several authors have proposed the strategy of creating a rigid core molecule carrying different functional groups, with well defined stereochemistry and stereo-orientation, that could be subsequently functionalized with different building blocks to generate a library of molecular diversomers [4]. On this idea, in this research group a diketopiperazine template fourfold functionalized with carboxyl groups, was recently designed and employed in a solution-phase parallel synthesis protocol (Scheme 1) [5].

Scheme 1



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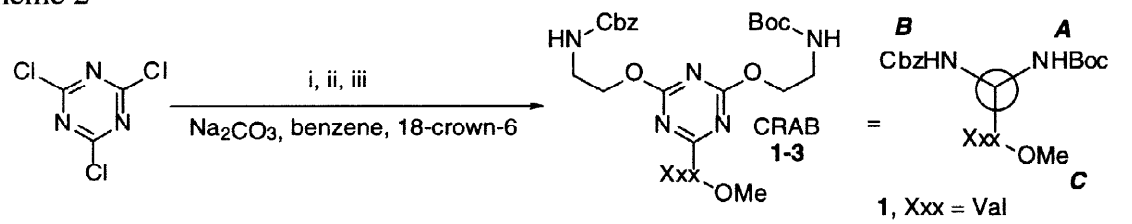
Triazine derivatives are widely employed in many bio-medical research fields: cancer chemotherapeutic agents, [6] multidrug resistance modulators [7] and trifunctional scaffolds in bundle protein preparation [8]. As a consequence, new methods for the preparation of substituted triazines have been studied [9]. Recently, Gustafson described the solution-phase parallel synthesis of a triazine-based library [10]. Stimulated by this paper, we report here our results on the synthesis of trifunctionalized triazine templates (CRAB)[11] and their use in the preparation of libraries of small and medium sized organic molecules using the parallel or the *split & recombine* strategy in homogeneous solution.

For the syntheses of CRAB **1-3** we found it convenient to apply an one-pot procedure [12]. Samples of 2,4,6-trichloro-1,3,5-triazine (cyanuric chloride) were treated with equimolar amounts of *N*-Boc-ethanolamine using Na_2CO_3 as base in refluxing benzene in the presence of 18-crown-6 as catalyst. After 24 h, equimolar amounts of *N*-Cbz-ethanolamine were added to the mixtures and heating was prolonged for further 24 h. Finally, a suitable amino acid methyl ester hydrochloride was added at r.t.. After 4 days at r.t., water was added and the reaction mixtures were extracted with CH_2Cl_2. The organic phase was washed (5% HCl, 10% $NaHCO_3$), dried and concentrated to give crude **1-3** that were purified by flash chromatograpy (EtOAc/petroleum ether 8/2). Pure CRAB **1-3** were obtained in 31-35% overall yields. They were fully characterized by ^1H and ^{13}C NMR analysis and were shown to be enantiomerically pure (^1H NMR analysis, 300 MHz in the presence of $Eufod_3$).

Scheme 2



i) *N*-Boc-ethanolamine, 24 h, 80°C. ii) *N*-Cbz-ethanolamine, 24 h, 80°C.
iii) HCl·H-Val-OMe or HCl·H-Phe-OMe or HCl·H-Pro-OMe, 4 days, rt.

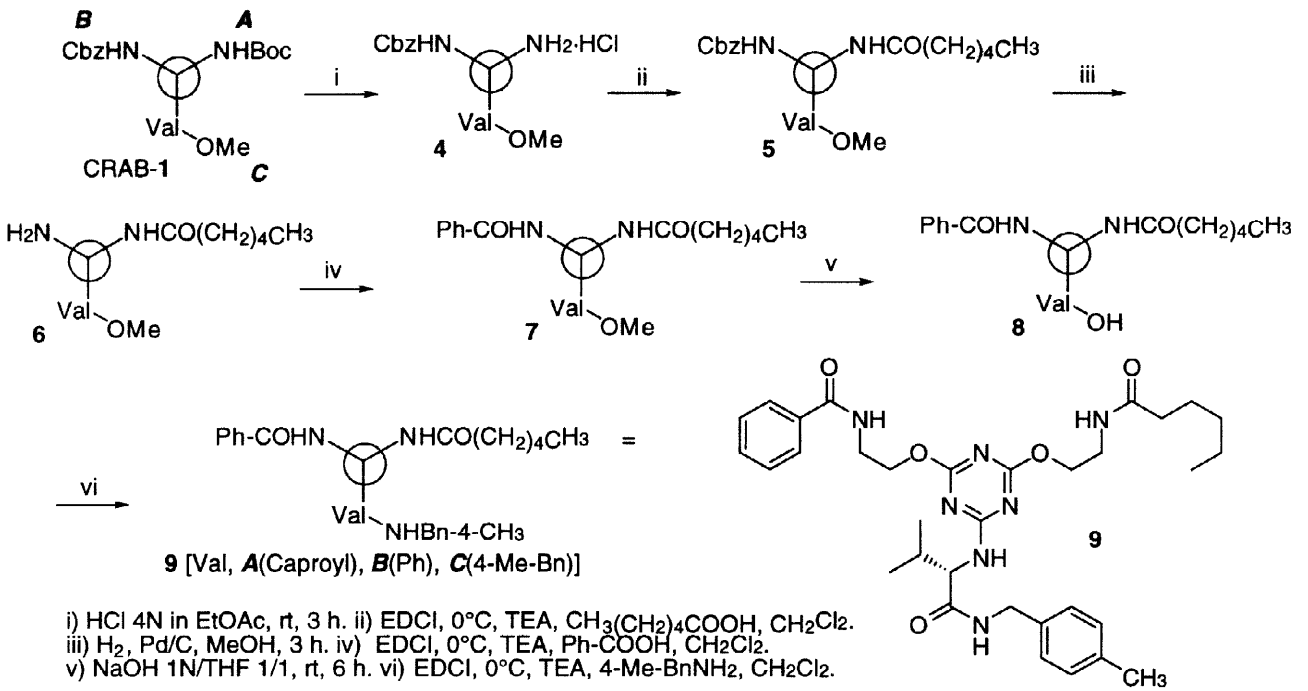
1, Xxx = Val
2, Xxx = Phe
3, Xxx = Pro

Different procedures can be employed to obtain families of diversomers starting from CRAB compounds **1-3**. By using compound CRAB-Val (**1**) we demonstrated the complete orthogonality of the protecting groups employed. In fact, position ***A***, ***B*** or ***C*** can be deprotected independently and in any order. For a more convenient handling procedure the best order of events was: deprotection at ***A***, coupling with acids, deprotection at ***B***, coupling with a second set of acids then deprotection at ***C*** and coupling with various amines. The problems arose from finding the best reaction conditions to realise a high throughput organic synthesis.

A model diversomer synthesis was carried out starting from the CRAB template **1** as described in scheme 3. The hydrochloride **4** was obtained in high purity and yield removing the Boc group of product **1** by using 4N HCl in EtOAc and filtering the solid residue (Scheme 3). Compound **4** was reacted with an excess (1.5 eq) of caproic acid in CH_2Cl_2 in the presence of triethylamine (TEA) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

(EDCI) at 0°C giving the amide **5** which was purified from reaction by-products by subsequent washing with acidic (5% HCl) and basic (5% NaOH) solutions. The removal of the Cbz group of the amide **5** was carried out in MeOH with 10% Pd/C in the presence of H_2 affording amine **6** that was employed without any purification. The treatment of **6** with benzoic acid (1.5 eq) in the presence of TEA/EDCI as described above afforded diamide **7** in good yield. The saponification of methyl ester **7** and the following treatment with 4-methylbenzylamine (1.5 eq) using the TEA/EDCI protocol afforded the pure CRAB-diversomer **9** (^1H and ^{13}C NMR, 300 MHz) in good overall yield.

Scheme 3

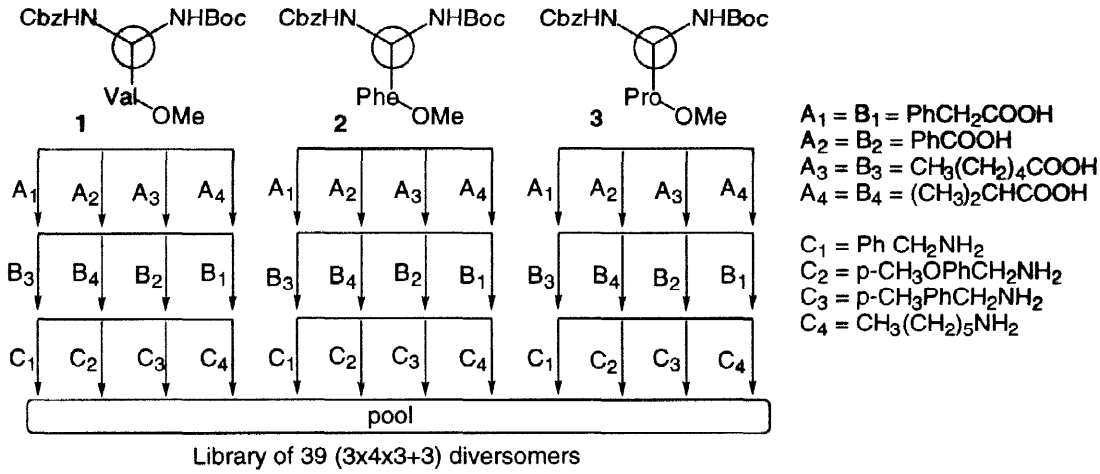


This synthetic protocol was optimized for a robot-like procedure. For the amide bond formation we selected the EDCI protocol: after each coupling step the amide formed could be purified from reaction by-products by simple washing with acidic and basic solutions.

We applied this procedure to a simple parallel synthesis as depicted in scheme 4. Starting from the CRAB products **1-3** and using four acids (A_1-A_4) in the first and second steps (B_1-B_4), and four amines (C_1-C_4) in the third coupling we obtained an array of 39 diversomers.

With this protocol we have prepared a class of simple polyfunctionalized scaffolds for liquid phase synthesis of libraries of small (and medium size) organic molecules in 1 g and larger scale, employing simple starting materials, cheap reagents and very simple procedures of manipulation that can be automated. Although not illustrated here, this approach can also be applied to a *split & recombine* strategy to increase the level of diversity. Studies directed to find a validation method for a mixing approach for the use of these scaffolds in the synthesis of dendrimer-like structures are currently underway in our laboratory.

Scheme 4



Library of 39 (3x4x3+3) diversomers

Acknowledgements

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