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One-pot synthesis of poly-substituted tetramic acids for the preparation of putative turn mimics

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ABSTRACT

A one-pot synthesis of poly-substituted tetramic acids and of their six-membered ring analogs have been obtained in one step by reaction of *N*-Boc dipeptides, activated as their *O*-succinimidyl esters (Boc-AA-AA-OSu), with the sodium anion of dibenzyl malonate. The adducts spontaneously cyclize to form five or six-member rings. To check whether this class of compounds may be used to promote reverse-turn conformations, one adduct was further derivatized. The formation of a hydrogen bond between the NH–Boc and the carbonyl at C2 of the heterocycle is highlighted, upon analysis of the product by IR, ^{1}H NMR, and MD techniques, thus suggesting that these compounds are good candidates to promote reverse-turn conformations or other secondary structures and may be used for the formation of new foldamers.

1. Introduction

Naturally occurring tetramic acids (pyrrolidin-2,4-dione) have attracted a great deal of interest because many natural compounds containing these heterocycles exhibit interesting biological activities,[1] such as dolastatin 15[2] and althiomycin.[3] HSAF (Fig. 1) was isolated from *Lysobacter enzymogenes*, a bacterium used in the biological control of fungal diseases of plants.[4] Furthermore the natural products tenuazonic acid,[5] melophlins,[6] and reutericyclin[7] are representative examples of the structurally diverse family of acyl-tetramic acids. Finally sintokamides A–E, 1,5-disubstituted tetramic acids, are the first natural products reported to selectively block transactivation of the N terminus of the androgen receptor in prostate cancer cells.[8]

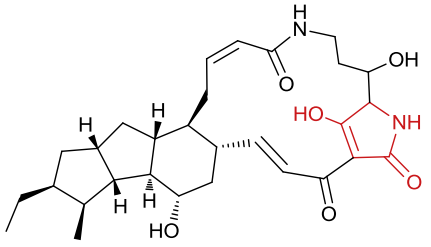

Fig. 1. Chemical structure of HSAF, the tetramic acid moiety is highlighted in red.

Tetramic acids are very polar and scarcely reactive and may be prepared with several methods. The most simple one is the activation of a Boc-protected amino acid with EDC, condensation with Meldrum's acid, and finally cyclization to give the Boc-protected pyrrolidine-2,4-diones. The following N-deprotection may be accomplished with TFA treatment giving the parent pyrrolidine-2,4-diones.[9] Another straightforward method is the condensation of methyl (*E*)-4-chloro-3-methoxy-2-butenoate with a 2-amino alcohol in the presence of triethylamine.[10]

The functionalization of these heterocycles is often a difficult task, due to their low reactivity and to the equilibrium between the ketonic and enolic form, although they may react with several classes of compounds. In many natural compounds, the tetramic acid moiety is present as a 3-acyl derivative or, less commonly, as a 4-*O*-alkyl ether derivative (Fig. 2).

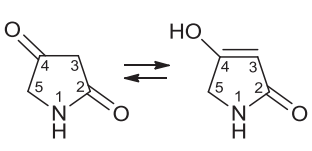

Fig. 2. Chemical structure of tetramic acid. The equilibrium between the two forms is shown.

Some synthetic methods have been reported. For instance the 3-acylation of tetramic acids was performed via O-acylation with

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carboxylic acids followed by acyl migration.[11] Another approach is the reaction of tetramic acids with the ylide Ph_3PCCO, that affords exclusively the corresponding 3-acylylidenetetramic acids. These were amenable to Wittig olefinations with aliphatic, aromatic, saturated and unsaturated aldehydes after deprotonation with KO^{t}Bu.[12] Very interesting are the studies reported by Tønder et al.[13] who have developed a straightforward strategy for the synthesis of *N*-acylates, *O*-alkylated pyrrolidin-2-ones by functionalization of tetramic acids, that leads to the formation of dipeptidomimetics comprising a pyrrolidinone and a protected amino acid. They have also reported an optimized two-step reductive amination procedure, which provides a small library of pyrrolidinone-containing dipeptide analogs. Another interesting approach to the synthesis of *N*-Boc 5-substituted tetramic acids is the cyclization of *N*-hydroxysuccinimide esters of Boc-protected α-amino acids.[14] The desired products have been obtained in two steps, by coupling of the α-amino acid derivatives with an alkyl malonate in the presence of NaH, with the formation of γ-amino-β-oxoalkanoates, that in turn cyclize under basic conditions to give the desired compounds.

We have become interested in the synthesis and in the derivatization of 1-acyl 3-carboxy tetramic acids, as they are constrained amino acid mimetics, contain an endocyclic carbonyl group and may be functionalized in several ways, thus they be may applied to the formation of pseudopeptide foldamers.[15] We have studied foldamers containing imide moieties, where the nitrogen atom is connected to an endocyclic and an exocyclic carbonyl, which tend to adopt always the trans conformation.[16] As a consequence of this locally constrained disposition effect, these imide-type oligomers are forced to fold in ordered conformations, such as PPII helixes,[17] β-band ribbon spirals,[18] β-sheets,[19] and β- or γ-turns.[20]

1-Acyl 3-carboxy tetramic acids are constrained β-amino acids, where the carbonyl unit is placed between the two functions, thus it forces the two carbonyls in the trans conformation, following the same effect that we have observed for the 4-carboxy-oxazolidin-2-ones (Fig. 3). As a consequence of this disposition, this scaffold may behave as a reverse-turn mimic, if it is introduced in the middle of a polypeptide chain, or it may promote the formation of new foldamers, if it is introduced in more complex structures. Although many examples of nonpeptidic reverse-turn surrogates have been reported, it is still challenging to find a new type of nonpeptidic scaffold that can adopt a highly populated reverse-turn conformation in solution[21] and that may be regarded as constrained pseudo-β-prolines.

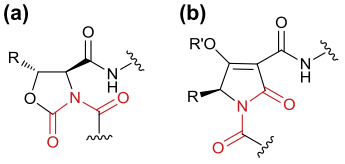
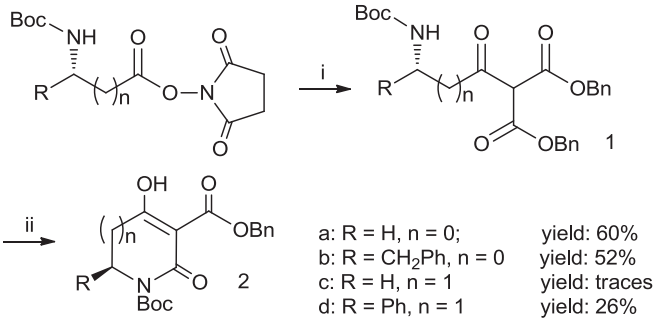


Fig. 3. (a) Preferential conformation of 4-carboxy-oxazolidin-2-ones and (b) possible preferential conformation of 1-acyl 3-carboxy tetramic acids.

2. Results and discussion

2.1. Synthesis of the heterocycles

We report here a one-pot synthesis of poly-substituted tetramic acids (4-hydroxy-2-oxo-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylates) and of the corresponding six-membered rings (4-hydroxy-2-oxo-5,6-dihydropyridine-1,3(2*H*)-dicarboxylates) starting from benzyl malonate and *N*-hydroxysuccinimide esters of Boc-protected amino acids (Scheme 1). As a first attempt, we utilized the protocol described by Igglessi-Markopoulou et al.[14a] that allows to obtain γ-amino β-oxo acids by reaction of *N*-hydroxysuccinimide esters of Boc-protected amino acids with alkyl malonate.



Scheme 1. Reagents and conditions: (i) $Na^{+\bullet-}CH(CO_2Bn)_2$ (1.5 equiv), dry THF, 30 min at 0 °C then 2h at rt; (ii) 2 M NaOH (166 equiv), BnOH, 2 h, rt.

As the final scope is the formation of a free carboxy unit, the reaction was performed with benzyl malonate, as the benzyl unit may be removed easily by hydrogenolysis. So benzyl malonate was treated with NaH in dry THF, followed by the *N*-hydroxysuccinimide esters, to afford the desired γ-amino β-oxo benzyl esters **1a**–**d** in high yield. This reaction allows to obtain the desired compound **1**, starting from both α- and β-amino acids (Scheme 1). The following cyclization was performed in benzyl alcohol and aqueous 2 M NaOH. While satisfactory yields were obtained for the synthesis of both 4-hydroxy-2-oxo-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylates **2a** and **2b** (60% and 52%, respectively), the synthesis of 4-hydroxy-2-oxo-5,6-dihydropyridine-1,3(2*H*)-dicarboxylates **2c** and **2d** afforded very unsatisfactory results, as **2c** was obtained only in traces from **1c** and **2d** in 26% yield from **1d**. No racemization occurred in the formation of **2b** (after analysis with HPLC equipped with a chiral column AD, *n*-hexane/*iso*-propanol 8:2, flow: 0.5 mL/min), probably due to the mild reaction conditions.

Then **2a** was deprotected from the Boc moiety by reaction with trifluoroacetic acid in dry dichloromethane, for further derivatizations. The desired product was obtained in high yield. Unfortunately, the following N-acylation reaction, performed with standard coupling conditions (HBTU or HATU, in the presence of tertiary amines) was totally unsuccessful, as the heterocyclic nitrogen of this compound is very unreactive. In effect, this reaction has been previously reported only in hard conditions,[13a] by reaction with a lithium base (*n*-BuLi or LiHMDS), followed by addition of an activated ester (Fmoc-AA-OPfp) at −50 °C.

To overcome this problem, we reversed the step order, making the coupling before the cyclization (Scheme 2). Thus four dipeptides were prepared containing both α- and β-amino acids, in both positions. Then the carboxy moieties were activated as the corresponding *N*-hydroxysuccinimide esters and treated with the sodium anion of the benzyl malonate to obtain the corresponding γ-amino β-oxo acids, as previously reported in Scheme 1. Much to our surprise, the expected products were not obtained, as the reaction proceeded directly to the formation of the heterocyclic rings. The reaction yield was further optimized with the addition of 2.5 equiv of base. No epimerization of **3b** was observed by ^{1}H NMR and HPLC analysis (chiral column AD, *n*-hexane/*iso*-propanol 8:2, flow: 0.5 mL/min).

The different behavior between Boc-AA-OSu and Boc-AA-AA-OSu may be ascribed to the secondary amide involved in the cyclization, that is, more acidic than the carbamate involved in the cyclization of Boc-AA-OSu. The heterocycles **3a**–**d** are obtained in good to high yield and can be further derivatized simply by removing the Boc or benzyl ester protecting groups.

Finally, the achiral **3d** was further derivatized to check if this new class of compounds may be utilized to promote the formation of reverse-turn mimics, as they may be considered as a mimic of the Gly-Pro moiety, that is, often present in the β-turn motifs.[22] Thus we replaced the OBn group with H-Ala-OMe that contains the small