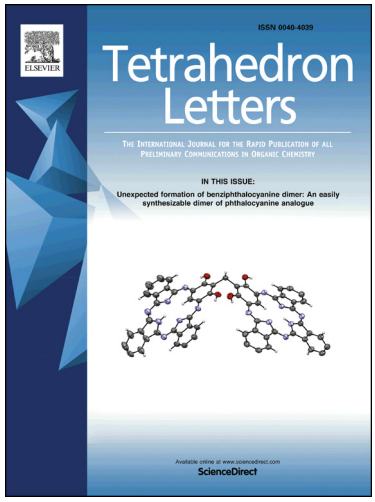

Enamines of 3-acyltetramic acids from β-enamino amides and amino acids

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Enamines of 3-acyltetramic acids from β-enamino amides and amino acids

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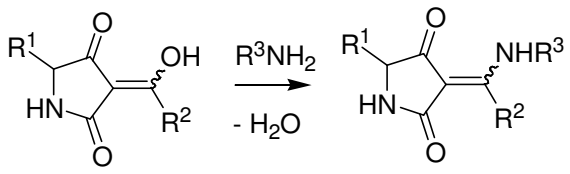
Abstract

A novel approach for the synthesis of enamine derivatives of *N*-protected 3-acyltetramic acids is described. The synthetic procedure relies on α-*C*-acylation of β-enamino amides with *N*-protected α-amino acids and subsequent cyclisation of the obtained intermediates in refluxing TFA. The tetramic derivatives are obtained with very good enantiopurity (e.r. ≥ 95:5). Ring-enlarged analogues (piperidine-2,4-diones) can also be obtained from β-amino acids.

Keywords: tetramic acids, amino acids, enamines, enaminones, *C*-acylation

Introduction

The pyrrolidine-2,4-dione ring system, commonly referred to as "tetramic acid", is a key structural motif in many natural products possessing antimicrobial, antifungal and antiviral properties.[1] The chemistry of tetramic acids has been extensively studied and several excellent reviews have been published in recent years.[2] The substitution pattern of the pyrrolidine-2,4-dione motif in natural products varies greatly, but most often these compounds bear an acyl substituent at position 3 of the ring system. Enamine derivatives of 3-acyltetramic acids are rarely found in nature and, with the notable exception of the synthetic inhibitor of microtubule assembly TN16,[3] have received little attention. There are scarce reports dealing with their synthesis, as well as antibacterial and herbicidal activity,[4, 3a] in all of which condensation between a preformed 3-acyltetramic acid and an amine is the synthetic method of choice.

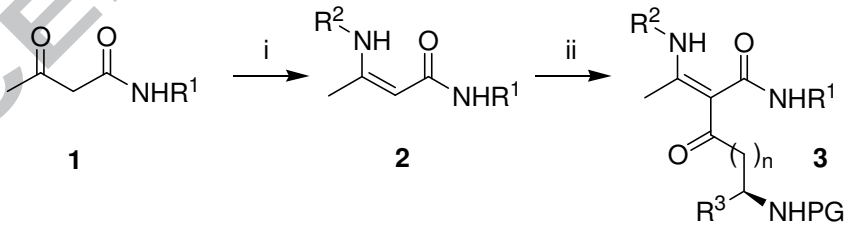


Scheme 1. *Traditional approach towards enamine derivatives of 3-acyltetramic acids.*

In the course of our studies regarding the chemistry of β-enamino amides,[5] a subclass of enaminones,[6] we have developed a novel approach towards enamine derivatives of *N*-protected 3-acyltetramic acids. In contrast to traditional methods, here the enamine moiety is introduced at the very beginning of the synthesis and the tetramic ring is constructed later by two consecutive reactions involving an amino acid.

Results and Discussion

β-enamino amides **2** are easily prepared by the condensation of β-ketoamides and amines.[5b] These compounds are nucleophilic at the α–position and we have previously made use of their reaction with acid chlorides to obtain α-*C*-acylated derivatives and subsequently turn them into unsymmetrical enaminoketones[5a] or β-ketoamides.[5b] Searching for an extension of this methodology, an attempt was made to acylate the β-enamino amides **2** with suitably activated amino acids instead of simple acid chlorides. The initial experiments with *N*-ethoxycarbonyl glycine and a range of activating reagents (DCC, DIC, T3P, alkyl chloroformates) gave promising results; regardless of the activation method, the reaction with enamino amide **2** gave the expected α-*C*-acylated product **3a** in good yield. For further experiments we chose the mixed carbonic anhydride method, using ethyl chloroformate as the activating reagent and a series of eight *N*-protected amino acids. The mixed carbonic anhydrides were prepared from *N*-methylmorpholine (NMM) salts of the corresponding *N*-protected amino acid in CH_2Cl_2 at 0 °C, and after addition of the β-enamino amide **2** and DMAP (0.2 equiv.) the reaction mixtures were stirred for 1 h at r.t. In all cases the α-*C*-acylated products **3** were obtained in high yields and, more importantly, with excellent retention of configuration when the reaction was carried out with chiral amino acids (Scheme 2, Table 1). To assess the stereochemical outcome of the acylation reaction, the experiments with alanine and phenylalanine were carried out using both racemic and enantiopure L-amino acids. The enantiomeric ratios were determined by chiral phase HPLC and were ≥99:1 for all chiral products **3d-j**.

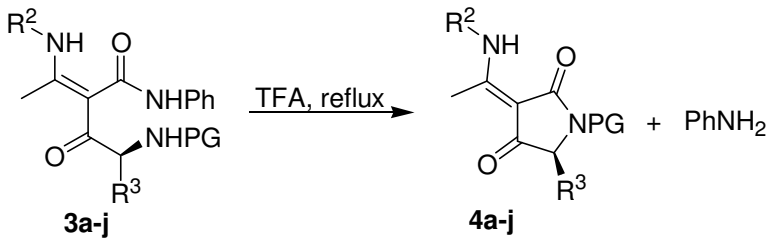


Scheme 2. *Preparation of α-C-acylated β-enaminoamides **3**. Reagents and conditions: (i) R^2NH_2 (1 equiv.), Na_2SO_4 (10 equiv.), CH_2Cl_2, 12 h, r.t.; (ii) Amino acid (1 equiv.), NMM (1 equiv.), EtOCOCl (1 equiv.), DMAP (0.2 equiv.), CH_2Cl_2, 1 h, 0 °C to r.t. See ESI for full experimental procedures.*

Table 1. *Yields of α-C-acylated compounds **3**, obtained according to Scheme 2.*

3	R^1	R^2	R^3	PG	n	Yield 3 (%)
a	Ph	Et	H	COOEt	0	91
b	Ph	Et	H	Troc	0	73
c	Ph	CH_2CH_2Ph	H	COOEt	0	92
d	Ph	Et	CH_3	COOEt	0	73
e	Ph	Et	CH_3	Troc	0	83
f	Ph	CH_2CH_2Ph	CH_3	COOEt	0	86
g	Ph	CH_2CH_2Ph	CH_3	Troc	0	68
h	Ph	Et	CH_2Ph	COOEt	0	69
i	Ph	Et	CH_2Ph	Troc	0	77
j	Ph	CH_2CH_2Ph	CH_2Ph	COOEt	0	70
k	H	CH_2CH_2Ph	H	COOEt	0	82
l	H	CH_2CH_2Ph	H	Troc	1	50
m	Ph	Et	H	Troc	1	79
n	Ph	Et	H	COOEt	1	85
o	Ph	CH_2CH_2Ph	H	COOEt	1	86
p	H	CH_2CH_2Ph	H	COOEt	1	55
q	Ph	CH_2CH_2Ph	H	Troc	1	83

Next, compounds **3** were heated in TFA at reflux– conditions known to cause *C-C* bond scission in simpler analogues.[5a] Here, however, no such reaction was observed. When R^1 in **3** was a phenyl group, heating at reflux in TFA for one hour led to clean formation of enaminotetramic derivatives **4** in nearly quantitative yield, accompanied by aniline as a co-product (Scheme 3). We were pleased to find that the enaminotetramic derivatives were obtained with very good enantiopurity, despite the harsh cyclisation conditions. Enantiomeric ratios of ≥ 95:5 were measured by chiral phase HPLC for all chiral products **4d-j**.



3a-j **4a-j**

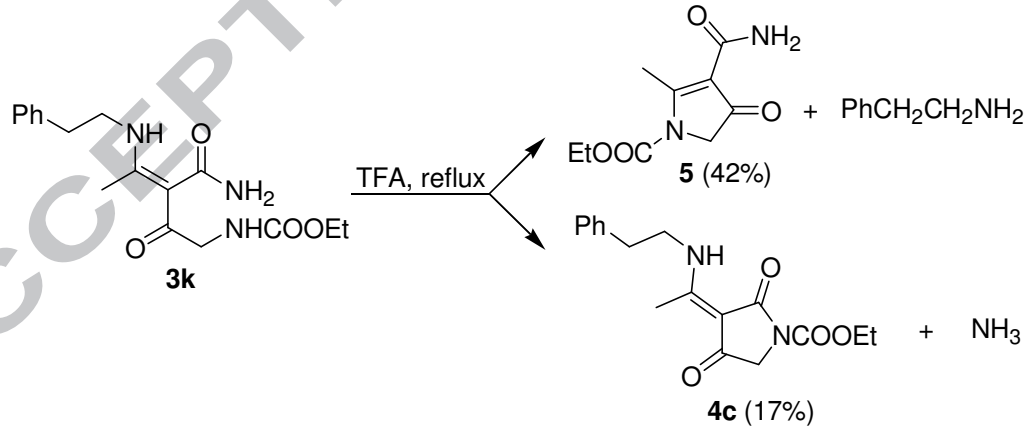
Scheme 3. *Cyclisation of **3a-j** to enamine derivatives of 3-acyltetramic acids **4.** Reagents and conditions: **3** in TFA (100mg/mL), reflux, 1 h.*

Table 2. *Yields and enantiomeric ratios of the enaminotetramic derivatives **4**, obtained according to Scheme 3.*

4	R^2	R^3	PG	Yield 4 (%)	e.r.[a]
a	Et	H	COOEt	93	-
b	Et	H	Troc	90	-
c	CH_2CH_2Ph	H	COOEt	78	-
d	Et	CH_3	COOEt	82	95 : 5
e	Et	CH_3	Troc	88	98 : 2
f	CH_2CH_2Ph	CH_3	COOEt	87	97 : 3
g	CH_2CH_2Ph	CH_3	Troc	89	97 : 3
h	Et	CH_2Ph	COOEt	95	96 : 4
i	Et	CH_2Ph	Troc	95	97 : 3
j	CH_2CH_2Ph	CH_2Ph	COOEt	90	96 : 4

[a] *Enantiomeric ratios are rounded to the nearest percent and were measured by HPLC, using Phenomenex Lux Amylose-1 or Lux Amylose-2 columns. See ESI for details.*

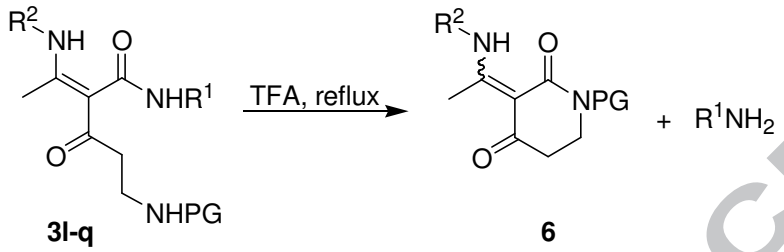
Attempts to achieve better atom economy by using the simpler starting material **3k** (R^1=H) were not successful. Two products, resulting from competing modes of cyclisation, were obtained – the expected tetramic derivative **4c** (17%) and pyrrolin-3-one **5** (42%) (Scheme 3).



Scheme 4. *Competing modes of cyclisation in compound **3k**.*

Similar cyclisation took place with chain-extended analogues **3l-q**, leading to piperidine-2,4-diones **6** (Scheme 5). Unlike the formation of 5-membered rings, the cyclisation mode here was not affected by

the R^1 substituent – the same product **6a** was obtained from both **3l** (R^1=H) and **3q** (R^1=Ph) in comparable yields. Likewise, **3o** (R^1=Ph) and **3p** (R^1=H) both gave product **6d**. Despite the better atom economy achieved with analogues in which R^1=H, the enamino anilides (**2**, R^1=Ph) are still preferable starting compounds with regard to the overall yield, because of their better performance in the acylation stage.



3l-q **6**

Scheme 5. *Cyclisation of chain-extended analogues **3l-o** to piperidine-2,4-diones **6**. Reagents and conditions: **3** in TFA (100mg/mL), reflux, 1 h.*

Table 3. *Yields of piperidine-2,4-diones **6**, obtained according to Scheme 5.*

3	6	R^1	R^2	PG	Yield 6 (%)
l	**a**	H	CH_2CH_2Ph	Troc	89
m	**b**	Ph	Et	Troc	70
n	**c**	Ph	Et	COOEt	92
o	**d**	Ph	CH_2CH_2Ph	COOEt	96
p	**d**	H	CH_2CH_2Ph	COOEt	80
q	**a**	Ph	CH_2CH_2Ph	Troc	92

As reported in earlier publications, the enamines of 3-acyltetramic acids equilibrate between the *Z*- and *E*-isomers in solution. The exchange is slow on the NMR time scale and in $CDCl_3$ at r.t. they are registered as a 1:1 mixture.[4,7] Indeed, all compounds of type **4** showed two broad NH signals in the 10.5 – 11.3 ppm region, integrating for 0.5H each. The rest of the signals were also affected in a similar way, but usually to a lesser extent and without clear separation. Compounds **6**, on the other hand, showed only one broad *NH* signal at about 13 ppm, with the rest of the signals being well resolved. This is likely an indication of faster *Z/E* exchange in the ring-enlarged analogues, rather than preference for any of the isomers, although VT NMR experiments would be necessary to clarify this.

Conclusion

In conclusion, we have successfully acylated β-enamino amides with *N*-protected amino acids and discovered a concise and operationally simple approach towards enamine derivatives of 3-acyltetramic acids and 3-acylpiperidine-2,4-diones. The method appears to be of broad scope and features very low racemisation.

Acknowledgements

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Highlights

- β-enamino amides are *C*-acylated with practically no racemisation.
- The *C*-acylated intermediates cyclise to enamines 3-acyltetramic acids.
- Ring-enlarged analogues are accessible.
- The enaminotetramic derivatives are obtained with e.r. ≥ 95:5.

Graphical Abstract

Enamines of 3-acyltetramic acids from β-enamino amides and amino acids

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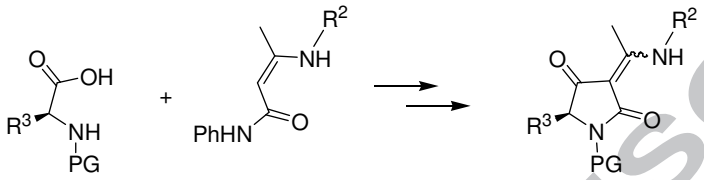

PG = Troc, COOEt; R^2 = Et, CH_2CH_2Ph; R^3 = H, CH_3, CH_2Ph

60 - 85% yield over two steps