Reactions of *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids with active methylene compounds. Synthesis of 3-substituted tetramic acids

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The *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids react with active methylene compounds (cyanoacetic esters, malonic and acyl acetic esters), under basic conditions, to produce 3-substituted *N*-alkoxycarbonyl tetramic acids; in the case of the *N*-hydroxysuccinimide esters derived from L-aminoacids, the corresponding optically active tetramic acids are obtained.

The 3-acyltetramic acids, 3-substituted pyrrolidine-2,4-diones, form a structurally diverse family of biologically active natural products; therefore they have always been a popular target for synthetic investigation. The common feature of all these natural products is the five-membered heterocyclic ring, a pyrrolidine-2,4-dione, acylated at position 3 (Fig. 1). In the present work we report a synthetic approach for the construction of the *N*-alkoxycarbonylpyrrolidine-2,4-dione system carrying a substituent at position 3.

The first synthetic method for the 3-acetyltetramic acids was reported by Lacey.[1] This method has been used for the synthesis of 5-substituted 3-alkoxycarbonyl tetramic acids[2] and has been extended to the synthesis of 3-polyenoyltetramic acids.[3] A new strategy for the synthesis of 3-acyltetramic acids was developed by Jones and co-workers using pyrones,[4a] and more recently isoxazole-4-carboxylic esters[4b] as precursors. Moreover, De Shong *et al.* have synthesized 3-acyltetramic acid derivatives starting from 2,5-disubstituted isoxazolium salts.[5] Significant studies in the area of tetramic acids have been made by Ley and co-workers,[6] providing a series of β-keto amides as suitable precursors for the preparation of 3-acyltetramic acids.

A strategy for the construction of the 3-substituted pyrrolidine-2,4 dione system through an acylation reaction of an active methylene compound with the *p*-nitrophenyl ester of *N*-benzoyl and *N*-acetyl glycine followed by cyclization of the *C*-acylation compounds, has been developed in our laboratory.[7] Because of the problems associated with this method, we have attempted to develop a new methodology, using the *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-aminoacids as precursors.

Our new methodology (Scheme 1) involves the *C*-acylation reaction of an active methylene compound with the *N*-hydroxysuccinimide esters of *N*-Boc- and *N*-Z-α-amino acids (glycine, L- alanine) and *N*-Boc-L-phenylalanine (Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl). The *C*-acylation intermediate **3a** (not isolated) undergoes an *in situ* cyclization reaction to 3-substituted *N*-alkoxycarbonyl tetramic acid **4**, through an intramolecular condensation mechanism.

In a typical *C*-acylation–cyclization reaction, 3 equiv. of the active methylene compound **2** were treated with 3 equiv. of sodium hydride in anhydrous benzene, or 2 equiv. of potassium *tert*-butoxide in *tert*-butyl alcohol. The 3-substituted *N*-alkoxycarbonyltetramic acids **4** were isolated either as crystalline products or in an oil form (yield 40–70%, Table 1). In the case of cyanoacetic esters **2** (Y = CN), the *C*-acylation compounds **3** were isolated in their enolic form (yield 60–80%, Table 2),† without further cyclization.

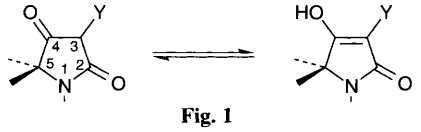
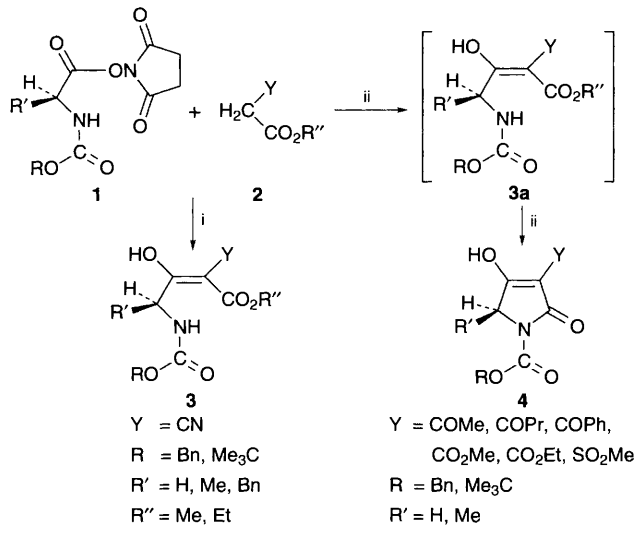


Fig. 1

An important feature of this route is the use of *N*-hydroxysuccinimide esters of *N*-alkoxycarbonyl-α-amino acids as acylating agents. The *N*-hydroxysuccinimide formed as a byproduct is soluble in water, and therefore easily removed from the reaction mixture. In addition, the chiral *N*-hydroxysuccinimide esters of *N*-Boc- and *N*-Z-L-amino acids, useful precursors for the synthesis of optically active tetramic acids,



Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, Bu^{t}OH, room temp.; ii, NaH, anhydrous benzene, room temp.

Table 1 Yields for the *C*-acylation–cyclization reactions (**1** → **4**)

Y	R	R′	Yield %
COMe	Bn	H	70
COPr	Bn	H	45
COPh	Bn	H	42
CO_2Me	Bn	H	54
CO_2Et	Bn	H	60
SO_2Me	Bn	H	40
COMe	Me_3C	H	62
COPr	Me_3C	H	55
COPh	Me_3C	H	40
CO_2Me	Me_3C	H	70
CO_2Et	Me_3C	H	45
COMe	Bn	Me	45
CO_2Et	Bn	Me	55
COMe	Me_2C	Me	40
COEt	Me_2C	Me	38

can be easily prepared.[8] Moreover, the *N*-protective groups, Boc and Z, have proved to be very stable under the basic reaction conditions.

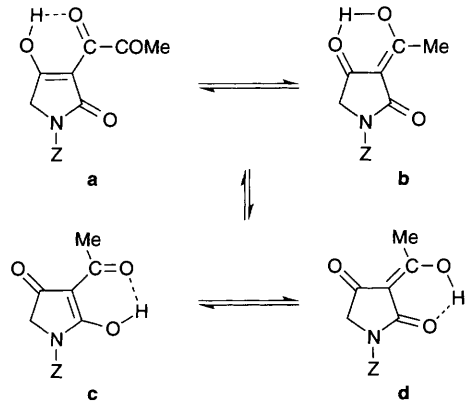
The structure of the newly obtained compounds, 3-substituted *N*-alkoxycarbonyltetramic acids **4** was confirmed by elemental analysis and ^{1}H NMR spectral data. Only one set of signals was observed for all protons in [$^2H_6$]Me_2SO solution (polar solvent). In $CDCl_3$ solution, two sets of signals were observed for certain protons, indicating the presence of the 'external' tautomers **ab** and **cd** (Scheme 2). For the *N*-benzyloxycarbonyl-3-acetyltetramic acid **4** (Y = COMe, R = Bn, R′ = H) the signal of 5-position protons was split into two parts, δ 4.12 (**cd**) and 4.29 (**ab**), with an intensity ratio of **cd**/**ab** = 1.4, showing that the dominant form should be the 'external' tautomer **cd**.‡

These data are fully in accord with the observations of Steyn *et al.*[9] that **cd** is the predominant tautomer of 3-acetyltetramic acid, as determined from the ^{1}H and ^{13}C NMR results ($CDCl_3$ solution). Semiempirical quantum mechanics calculations on the tautomerism of 3-acetyltetramic acid predict structure **d** to be thermodynamically favoured over **a**, **b** and **c**.[10a,b]

The application of the proposed methodology to the construction of chiral tetramic acids, with a stereogenic centre at the 5-carbon, derived from *N*-Boc-L-alanine, *N*-Z-L- alanine and *N*-Boc-L-phenylalanine is under investigation in our laboratory. Preliminary experiments have revealed that the reaction of active methylene compounds **2** (Y = COMe, CO_2Me, CO_2Et,) with the optically active *N*- hydroxysuccinimide esters of *N*-Z-L-alanine and *N*-Boc-L-alanine,[8] leads to *N*-Z-3-acetyltetramic acid **4** (Y = COMe, R = Bn, R′ = Me), *N*-Z-3-ethoxycarbonyltetramic acid **4** (Y = CO_2Et, R = Bn, R′ = Me), *N*-Boc-3-methoxycarbonyltetramic acid **4** (Y = CO_2Me, R = Me_3C, R′ = Me) and *N*-Boc-3-ethoxycarbonyl tetramic acid **4** (Y = CO_2Et, R = Me_3C, R′ = Me) (Scheme 1), which were found to have optical rotations of $[\alpha]_D^{21}$ −21.9 (*c* 0.8, CH_2Cl_2), $[\alpha]_D^{22}$ +39.1 (*c* 1.12, CH_2Cl_2), $[\alpha]_D^{30}$ −21.2 (*c* 0.87, CH_2Cl_2) and $[\alpha]_D^{28}$ +7.5 (*c* 1.07, CH_2Cl_2), respectively.

Table 2 Yields for the *C*-acylation reactions (**1** → **3**)

Y	R	R′	R″	Yield (%)
CN	Bn	H	Me	80
CN	Bn	H	Et	70
CN	Bn	Me	Me	65
CN	Me_3C	H	Me	70
CN	Me_3C	H	Et	85
CN	Me_3C	Bn	Me	64
CN	Me_3C	Bn	Et	55



Scheme 2

On the other hand, condensation of methyl and ethyl cyanoacetate with the optically active *N*-hydroxysuccinimide ester of *N*-Z-L-alanine and *N*-Boc-L-phenylalanine yielded the *C*-acylation compounds, methyl 4-(benzyloxycarbonyl)amino-2-cyano-3-hydroxypent-2-enoate **3** (Y = CN, R = Bn, R′ = Me, R″ = Me), ethyl 4-(*tert*-butoxycarbonyl)amino-2-cyano-3-hydroxy-5-phenylpent-2-enoate **3** (Y = CN, R = Me_3C, R′ = Bn, R″ = Et) and methyl 4-(*tert*-butoxycarbonyl)amino-2-cyano-3-hydroxy-5-phenylpent-2-enoate **3** (Y = CN, R = Me_3C, R′ = Bn, R″ = Me) (Scheme 1). These compounds were found to have optical rotations of $[\alpha]_D^{29}$ +43.4 (*c* 0.58, CH_2Cl_2), $[\alpha]_D^{22}$ +13.02 (*c* 3.84, MeOH) and $[\alpha]_D^{19}$ +80.3 (*c* 1.04, MeOH), respectively. The latter compound has been reported in the literature with an optical rotation $[\alpha]_D^{23}$ +77.9 (*c* 1.04, MeOH).[11]

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Footnotes

† *Spectral data* for **3** (Y = CN, R = Bn, R′ = H, R″ = Me): ^{1}H NMR ($CDCl_3$, 60 MHz): δ 3.8 (s, 3 H, CO_2CH_3), 4.3 (d, *J* 6 Hz, 2 H, $NHCH_2$), 5.1 (s, 2 H, $PhCH_2$), 5.5 (br s, 1 H, NH), 7.3 (s, 5 H, aromatic protons); ν_{max}(Nujol)/cm^{-1} 3410, 3310, 2220, 1690, 1660, 1610, 1530.

‡ *Physical and spectral data* for **4** (Y = $COCH_3$, R = Bn, R′ = H): mp 92–95 °C (Found: C, 61.1; H, 4.8; N, 5.25. Calc. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09%); ^{1} H NMR ($CDCl_3$, 250 MHz): δ 2.54 and 2.56 (two s, 3 H, $COCH_3$), 4.12 (**cd**) and 4.29 (**ab**) (two s, 2 H, CH_2-ring), 5.33 (s, 2 H, $PhCH_2$), 7.36–7.46 (m, 5 H, aromatic protons); ν_{max}(Nujol)/cm^{-1} 3320, 1740, 1715, 1645, 1610.

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