A Cycloaddition Approach to 3-Acyltetramic and 3-Acyltetronic Acids

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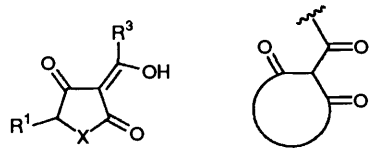
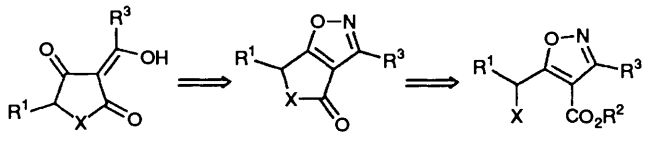
1,3-Dipolar cycloaddition of nitrile oxides to enamines formed from protected γ-amino- or γ-hydroxy-β-keto esters affords isoxazolecarboxylic esters that can be converted into 3-acyltetramic acids *via* dihydropyrroloisoxazol-4-ones, or into 3-acyltetronic acids.

The 3-acyltetramic **1a** and 3-acyltetronic acids **1b**† are part of a group of metabolites containing the (enolised) tricarbonyl motif **2**.[1,2] Problems associated with handling this highly polar moiety[3] have led us to search for new synthetic approaches in which the polar functionality is masked until a late stage in any synthetic sequence.[4] We were thus attracted to the use of isoxazole-4-carboxylic esters as latent tricarbonyl units, according to the strategy of Scheme 1.[5] Herein we report our studies that demonstrate the viability of such a strategy.



1a; X = NR^2
b; X = O

2

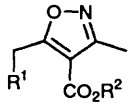


Scheme 1

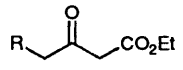
Ethyl 3,5-dimethylisoxazole-4-carboxylate **3a** was prepared (63%) as reported[6] by 1,3-dipolar cycloaddition of the pyrrolidine enamine of ethyl acetoacetate (benzene, reflux; 100%) to acetonitrile oxide prepared *in situ* ($EtNO_2$, $POCl_3$, Et_3N, $CHCl_3$, 0→25 °C). Functionalisation at the C-5 substituent was achieved by radical bromination (*N*-bromosuccinimide, CCl_4, reflux) with photolytic initiation to give the sensitive 5-bromomethyl derivative **3b**‡ (90% after distillation).[7] Reaction of the crude bromide with potassium phthalimide (DMF, 25 °C) afforded the 5-phthalimidomethylisoxazole **3c** (42%) which was deprotected efficiently (H_2NNH_2, MeOH, reflux; 84%) to yield the 5-aminomethyl compound **3d**. An alternative preparation of the amine **3d** which subsequently became our method of choice, began with an *N*-protected glycine. Thus *N*-phthaloyl- and *N*-benzyloxycarbonyl-glycine were converted into the corresponding β-keto esters **4a** and **4b** (99 and 97%, respectively) by activation (1,1'-carbonyldiimidazole, THF, 25 °C) and reaction (THF, 0 °C) with the magnesio derivative from ethyl hydrogen malonate (isopropylmagnesium bromide, 0→40 °C) followed by acidic work-up (0.3 mol dm^{-3} H_3PO_4 aq.).[8] Preparation of the pyrrolidine enamines (toluene, reflux) and the cycloaddition protocol as before ($EtNO_2$, $POCl_3$, Et_3N, $CHCl_3$, 0→25 °C) afforded the protected aminomethylisoxazoles **3c** and **3e** (43 and 85%, respectively). Deprotection of **3c** as above, and of **3e** (HBr–acetic acid, 33% w/v; 86%; then $NaHCO_3$ aq.; 72%) gave the amine **3d**. Cyclisation of the amino ester **3d** to the pyrroloisoxazolone **5a**, however, could not be accomplished under a variety of conditions.§

Since the ester at C-4 can be viewed as a vinylogous carbonate, in order to further activate the carboxy group, the 5-benzyloxycarbonylaminomethyl derivative **3e** was converted into the acid **3f** (NaOH aq., reflux; 75%) and thence into a mixed anhydride (Et_3N, EtO_2CCl, THF, 0→25 °C). Removal of the N-protecting group (HBr–acetic acid, 33% w/v, 25 °C) afforded the desired bicycle 3-methyl-5,6-dihydro-4*H*-pyrrolo-[3,4-*d*]isoxazol-4-one **5a**, a potential non-polar building block for the 3-acyltetramic acids, as its hydrobromide salt (77%). The remaining part of the strategy, to unmask the tricarbonyl moiety, was efficiently performed by hydrogenolysis (H_2, 1 atm, Pd–C, EtOH) followed by basic hydrolysis of the intermediate enamino ketone (2 mol dm^{-3} NaOH aq., 25 °C)[9,10] to generate 3-acetyltetramic acid **6a** (91%).

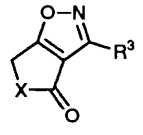
In preliminary investigations of this approach to the 3-acyltetronic acid system, the *tert*-butoxy- and benzyloxy-β-keto



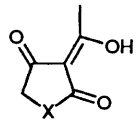
3a; R^1 = H, R^2 = Et
b; R^1 = Br, R^2 = Et
c; R^1 = PhtN, R^2 = Et
d; R^1 = NH_2, R^2 = Et
e; R^1 = ZNH, R^2 = Et
f; R^1 = ZNH, R^2 = H
g; R^1 = Bu^tO, R^2 = Et
h; R^1 = $PhCH_2O$, R^2 = Et
i; R^1 = Bu^tO, R^2 = H
j; R^1 = $PhCH_2O$, R^2 = H
k; R^1 = HO, R^2 = Et



4a; R = PhtN
b; R = ZNH
c; R = Bu^tO
d; R = $PhCH_2O$



5a; X = NH
b; X = O



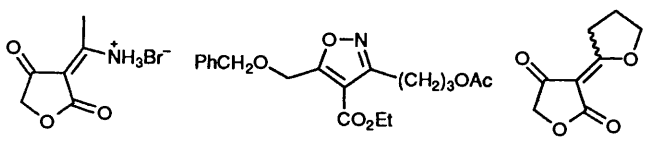
6a; X = NH
b; X = O

(Pht = N-phthaloyl; Z = benzyloxycarbonyl)

† The tautomer illustrated for structure **1** is the major enol observed for 3-acyltetramic acids in solution and in the solid phase, and a major contributor to 3-acyltetronic acids (refs. 1, 2).

‡ All new compounds gave spectral data (IR UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

§ Thermal, acid-mediated and base-mediated protocols were attempted.



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esters **4c** and **4d** were prepared from ethyl acetoacetate *via* the 4-bromo derivative.[11] Cycloaddition ($EtNO_2$, $POCl_3$, Et_3N, as above) to the corresponding enamines (pyrrolidine, toluene, reflux) furnished the 5-alkoxymethylisoxazoles **3g** (63%) and **3h** (88%). Saponification of these esters (NaOH aq., reflux) gave acids **3i** (94%) and **3j** (85%) that were activated as the mixed anhydrides (Et_3N, EtO_2CCl, THF, 0→25 °C). Interestingly, treatment of either of these mixed anhydrides with HBr–acetic acid (33% w/v, 1 mol equiv., 25 °C, 16 h) did not lead to the furoisoxazolone **5b** but instead afforded the enamine salt **7**, albeit in low yields (35 and 19%, respectively), which could be smoothly transformed into 3-acetyltetronic acid **6b** (2 mol dm^{-3} NaOH aq., 25 °C). We are currently optimising this novel N–O cleavage.*

The 5-*tert*-butoxymethylisoxazole **3g** was deprotected (trifluoroacetic acid, 25 °C; 46%). The hydroxy ester **3k** produced could again not be cyclised to the furoisoxazolone **5b**, but was converted into 3-acetyltetronic acid **6b** (42%) by the hydrogenolysis–base hydrolysis sequence used above to prepare **6a** from **5a**. 3-Methyl-4,6-dihydrofuro[3,4-*d*]isoxazol-4-one **5b** could be prepared by treatment of 5-*tert*-butoxymethyl acid **3i** with trifluoroacetic acid–trifluoroacetic anhydride (25 °C, 2 h).

Cycloaddition of the pyrrolidine enamine of the benzyloxy-β-keto ester **4d** with the nitrile oxide formed under the usual conditions ($POCl_3$, Et_3N) from 4-nitrobutyl acetate, itself prepared from 4-bromobutyl acetate ($NaNO_2$, DMSO, 25 °C), led to the 3-(3-acetoxypropyl)-5-benzyloxymethylisoxazole **8** as an inseparable mixture with unchanged nitro compound. The crude product was subjected to the hydrogenolysis–base hydrolysis protocol (see above) to afford the 3-(tetrahydrofuran-2-ylidene)tetrahydrofuran-2,4-dione geometric isomers **9** (45%, 5:4 *Z*:*E*), the 3-demethyl analogue of natural carolic acid.[12]

We have thus demonstrated the viability of our isoxazole strategy for heterocyclic tricarbonyl systems.

Experimental

Typical Procedures: Ethyl 5-Benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylate **3e** *and 5-Benzyloxycarbonylaminomethyl-3-methylisoxazole-4-carboxylic Acid* **3f**.—Ethyl 4-benzyloxycarbonylamino-3-oxobutanoate **4b** (14.70 g, 52.63 mmol) and pyrrolidine (4.12 g, 58.03 mmol) were heated together in dry toluene (150 cm^3) under reflux with a Dean–Stark trap. After 2 h water had separated (1.00 cm^3, 52.63 mmol) and the solvent was evaporated under reduced pressure. Triethylamine (16.00 g, 157.90 mmol) and nitroethane (4.34 g, 57.90 mmol) in chloroform (100 cm^3) were added to the residue and the solution was cooled to 0 °C. To this was added phosphorus oxychloride (8.90 g, 57.90 mmol) in chloroform (50 cm^3) dropwise over 1.5 h, and the mixture stirred at 25 °C for a further 2 h. The dark mixture was poured into water (200 cm^3) and the organic phase separated and washed successively with hydrochloric acid (6 mol dm^{-3}; 100 cm^3), aqueous sodium hydroxide (5% w/v, 100 cm^3), and saturated brine (100 cm^3). The organic solution was dried ($MgSO_4$), filtered and evaporated under reduced pressure to leave a dark brown oil which was purified by chromatography on silica gel, using hexane–ethyl acetate (1:1, v/v) as eluent to yield the *title compound* **3e** as a white solid, m.p. 66–68 °C (14.29 g, 85%) (Found: C, 60.3; H, 5.8; N, 8.8%; M^+, 318.1440. $C_{16}H_{18}N_2O_5$ requires C, 60.37; H, 5.70; N, 8.80%; *M*, 318.1261); λ_{max}/nm 209 (ε/dm^3 mol^{-1} cm^{-1} 10 440); $\nu_{max}(CHCl_3)$/cm^{-1} 3619, 3014, 2400, 1722, 1611, 1503, 1455, 1301 and 1108; $\delta_H(CDCl_3)$ 1.35 (3 H, t, *J* 7,† OCH_2CH_3), 2.50 (3 H, s, 3-CH_3), 4.35 (2 H, q, *J* 7, OCH_2CH_3), 4.80 (2 H, d, *J* 5, CH_2NH), 5.15 (2 H, s, $PhCH_2$), 5.70 (1 H, br s, NH) and 7.40 (5 H, s, Ph); $\delta_C(CDCl_3)$ 11.5 and 14.0 (Me), 37.4 (CH_2N), 60.9 and 67.0 (CH_2O), 109.0 (C), 127.9, 128.2 and 128.4 (CH), 136.0, 156.0, 159.8, 161.8 and 173.7 (C); *m*/*z* 318 (M^+), 211, 183, 165, 100 and 91 (100%). To the foregoing ester **3e** (14.36 g, 45.11 mmol) was added sodium hydroxide (2.00 g, 45.14 mmol) in water (100 cm^3) and the mixture heated at reflux for 4 h. After cooling, the solution was washed with chloroform (100 cm^3), filtered and the aqueous layer acidified to pH 3 using conc. hydrochloric acid. The resultant white precipitate was filtered off, taken up in chloroform, and the solution dried ($MgSO_4$), filtered and evaporated under reduced pressure, to afford the *title compound* **3f** as a white solid (9.31 g, 75%), m.p.168–169 °C (Found: $M^+ - Z - CO_2H$, 109.0521. $C_{14}H_{14}N_2O_5$ requires: $M - Z - CO_2H$, 109.0640); λ_{max}/nm 211 (ε/dm^3 mol^{-1} cm^{-1} 11 120); ν_{max}(KBr)/cm^{-1} 3300, 3025, 2975, 1695, 1600, 1440 and 1100; $\delta_H[(CD_3)_2SO]$ 2.45 (3 H, s, CH_3), 4.70 (2 H, d, *J* 5, CH_2NH), 5.15 (2 H, s, $PhCH_2$), 7.45 (5 H, s, Ph), 8.10 (1 H, br s, NH) and 13.40 (1 H, br s, CO_2H); $\delta_C[(CD_3)_2SO]$ 11.2 (CH_3), 37.1 (CH_2N), 65.7 (CH_2O), 108.8 (C), 127.8, 127.9 and 128.4 (CH), 136.8, 156.3, 159.7, 162.9 and 174.1 (C); *m*/*z* 151, 109 ($M^+ - Z - CO_2H$), 131, 100 (100%) and 79.

3-Methyl-5,6-dihydro-4H-pyrrolo[3,4-d]*isoxazole* **5a**.—To a solution of the foregoing acid **3f** (2.30 g, 8.40 mmol) in dry THF (50 cm^3) was added triethylamine (0.85 g, 8.40 mmol) at 0 °C and the mixture stirred for 10 min, after which time ethyl chloroformate (0.91 g, 8.40 mmol) was added dropwise to it and the suspension stirred at 25 °C for 12 h. The mixture was then filtered and evaporated under reduced pressure to yield the mixed anhydride; $\delta_H(CDCl_3)$ 1.40 (3 H, t, *J* 7, $CO_2CH_2CH_3$), 2.45 (3 H, s, 3-CH_3), 4.40 (2 H, q, *J* 7, $CO_2CH_2CH_3$), 4.65 (2 H, d, *J* 5, CH_2NH), 5.10 (2 H, s, $PhCH_2$), 5.50 (1 H, br s, NH) and 7.40 (5 H, s, Ph). To the crude mixed anhydride was added hydrogen bromide in glacial acetic acid (33% w/v; 0.70 g, 8.40 mmol) and the mixture stirred for 16 h. Dry ether (30 cm^3) was then added to the mixture and the precipitated solid was filtered and washed with dry ether (3 × 30 cm^3) to give the *title compound* **5a** as its hydrobromide salt, an off-white solid (1.40 g, 77%), m.p. 270–272 °C (Found: M^+ – HBr, 138.0422. $C_6H_6N_2O_2$ requires *M* – HBr, 138.0519); λ_{max}/nm 213 (ε/dm^3 mol^{-1} cm^{-1} 3930); ν_{max}(Nujol)/cm^{-1} 2923, 1742, 1603, 1513, 1286, 1175, 1111 and 743; $\delta_H[(CD_3)_2SO]$ 2.45 (3 H, s, CH_3), 4.60 (2 H, s, CH_2NH) and 8.80 (2 H, br s, NH and NH^+Br^-); $\delta_C[(CD_3)_2SO]$ 12.1 (CH_3), 39.5 (CH_2N), 111.6, 160.6, 163.1 and 170.2 (C); *m*/*z* 138 (M^+ – HBr), 128, 110, 80 (100%), 79 and 52.

3-Acetylpyrrolidine-2,4-dione **6a**.—The bicyclic salt **5a** (170 mg, 0.776 mmol) and palladium-on-charcoal (10%; 0.50 mg) were stirred together in ethanol (30 cm^3) at 25 °C under hydrogen (1 atm) until hydrogen uptake stopped (18.63 cm^3, 0.776 mmol). After this the mixture was filtered through Kieselguhr and the filtrate evaporated under reduced pressure to yield an off-white solid. To this was added aqueous sodium

* For a list of reagents for N–O cleavage, see ref. 5*c*, p. 12.

† *J* Values in Hz.

hydroxide (2 mol dm^{-3}; 10 cm^3) and the mixture stirred at 25 °C for 3 h; it was then carefully acidified using conc. hydrochloric acid. The precipitated solid was filtered off to afford the *title compound* **6a** as a white solid (46 mg, 97%), m.p. 174–176 °C (Found: M^+, 155.0548. $C_7H_9NO_3$ requires *M*, 155.0582); λ_{max}/nm 272 (ε/dm^3 mol^{-1} cm^{-1} 5000); ν_{max}(Nujol)/cm^{-1} 3170, 1660, 1628, 1331, 1248, 1039 and 720; δ_H(CF_3CO_2D–$CDCl_3$) 2.55 (3 H, s, CH_3CO), 2.90 (2 H, br s, CH_2CO) and 3.70 (2 H, br s, CH_2NH); δ_C[$(CD_3)_2SO$] 25.1 (CH_3), 35.0 and 36.9 (CH_2), 100.8, 171.5, 191.0 and 192.5 (C); *m*/*z* 155 (M^+, 100%), 140, 85 and 55.

Acknowledgements

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