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SYNTHESIS OF 5-SUBSTITUTED 4-O-METHYL TETRAMATES

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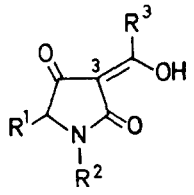
Summary: 4-Methoxy-Δ^3-pyrrolin-2-ones (4-O-methyl tetramates) are alkylated at C-5 via a lithio-derivative; an N-substituent may be introduced either during or after heterocycle formation.

As part of an on-going programme of synthesis directed towards the 3-acyltetramic acids (1), the heterocyclic nucleus common to family of natural metabolites found in microorganisms and having a range of biological properties,[1] we have previously reported the metallation of 4-methoxy-1-alkyl-Δ^3-pyrrolin-2-ones (4-O-methyl tetramates; 2) to form the vinyl-lithiums (3).[2] Reaction of (3) with aldehydes is the basis of an acylation sequence at C-3. In order to develop this chemistry we required a route to the methyl tetramates (2) with flexibility in the choice of substituent at N-1 and C-5, and this Letter outlines our studies towards this end.



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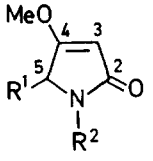
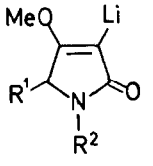


(2)



(3)

Our own approach,[2] and others recently reported,[3] are based on α-amino-acids and lack the requisite flexibility. In this context the route outlined recently[4] from acetoacetate esters was attractive. Indeed, the preparation of the 5-unsubstituted methyl tetramates (2a) and (2b)[5] proceeded smoothly from methyl acetoacetate (4a) by formation of methyl 4-bromo-3-methoxy-2-butenoate (5a) [$(MeO)_3CH$, H_2SO_4, 20°C; then N-bromosuccinimide, AIBN, CCl_4, reflux; 75% overall] and treatment of this with aqueous ammonia or methylamine, respectively (20°C, 12 h; 73% and 65%, respectively, after chromatography). However, when we attempted to prepare the 5-isopropyl compounds (2c) and (2d), of relevance to our interest in the mould pigment erythroskyrine,[6] we were unable to complete this route. Methyl 5-methyl-3-oxohexanoate (4b), prepared

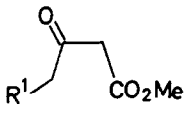
from the dianion of methyl acetoacetate and isopropyl iodide,[7] was smoothly converted into the enol ether[5] [$(MeO)_3CH$, H_2SO_4, 20°C; 93%] and thence into the 4-bromo derivative (5b)[5] (N-bromosuccinimide, AIBN, CCl_4, reflux; 76%). Bromoester (5b), on the other hand, failed to react with ammonia or methylamine to form the corresponding methoxypyrrolinones (2c) and (2d), even at elevated temperature in water or ethanol; presumably the cyclisation is sensitive to steric hindrance by substituents destined for C-5 of the heterocycle. Problems with this sequence may also be envisaged for potential C-5 substituents containing functionality incompatible with, for example, the bromination or aminolysis steps.

We thus developed an alternative approach to C-5 substitution of a preformed heterocycle, examined on the readily available 5-unsubstituted methyl tetramate (2b). Treatment with n-butyl-lithium (1,2 equiv., THF, -78°C) followed by quenching with D_2O led to deuterium incorporation at C-5 (90% by p.m.r. spectroscopy). Addition of an alkyl halide to the pale yellow solution of the metallated derivative at -78°C produced the desired 5-alkyl compounds; for example with methyl iodide the 5-methyl-4-methoxypyrrolinone (2e)[5] was obtained in 82% yield after column chromatography. Likewise, ethyl 2-bromopropionate afforded (2f)[5] (94%) and ethyl 3-bromopropionate produced the 5-(2-ethoxycarbonylethyl) compound (2g)[5] (90%). The 1-ethoxycarbonylethyl substituent in (2f) is a precursor to the C-5 side chain in the 3-dienoyltetramic acid metabolite streptolydigin,[8a] whilst (2g) is of interest in relation to the naturally occurring 5-(2-carboxyethyl)-3-acyltetramic acid antibiotics oleficin and lipomycin,[8b] The 5-isopropyl derivative (2d), elusive in our earlier efforts, was also prepared (50%) from lithiated (2b) and isopropyl iodide.

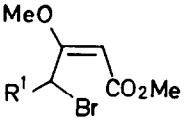
The presumed dienolate intermediate in this process could be trapped by treatment with chlorotrimethylsilane to produce the moisture-sensitive 2-trimethylsilyloxy-4-methoxypyrrole (6) (quantitative by p.m.r. spectroscopy); trapping with chloro-t-butyldimethylsilane was less efficient. Further treatment of (6) with n-butyl-lithium regenerated the dienolate.

Alkylation at C-5 of the N-unsubstituted 4-methoxypyrrolinone (2a) necessitated protection at N-1. The silyl derivatives (2h)[5] and (2i)[5] were thus prepared from (2a) using chloro-t-butyldimethylsilane or tri-isopropylsilyl trifluoromethanesulphonate (DBU, MeCN; 92% and 70% respectively). Deprotonation of (2h) ($LiNPr^i_2$, THF, -78°C) and addition of ethyl bromoacetate, followed by treatment with 40% aq. HF, afforded the 5-(ethoxycarbonylmethyl) compound (2j)[5] (46%); the 5-methylpyrrolinone (2k)[5] was similarly prepared from (2h) and methyl iodide.

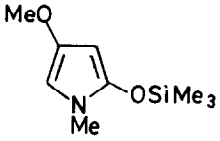
Substituents at N-1 can be approached in two ways. Use of the appropriate alkylamine (or ammonia) in reaction with the bromo-ester (5a) is illustrated by the synthesis of (2a) and (2b) above, but this method as



(4)a; R^1 = H
b; R^1 = $CHMe_2$



(5)a; R^1 = H
b; R^1 = $CHMe_2$



(6)

(2)

a; R^1=R^2=H
b; R^1=H, R^2=Me
c; R^1=$CHMe_2$, R^2=H
d; R^1=$CHMe_2$, R^2=Me
e; R^1=R^2=Me
f; R^1=$CHMeCO_2Et$, R^2=Me
g; R^1=$(CH_2)_2CO_2Et$, R^2=Me
h; R^1=H, R^2=$SiMe_2Bu^t$
i; R^1=H, R^2=$SiPr^i_3$
j; R^1=CH_2CO_2Et, R^2=H
k; R^1=Me, R^2=H
l; R^1=H, R^2=2,4-dimethoxybenzyl
m; R^1=H, R^2=CH_2Ph
n; R^1=H, R^2=$(CH_2)_7Me$

reported[4] uses a large excess of the amine component in aqueous solution; the bromo-ester is not soluble. In cases where the amine also has low water solubility, we observe no cyclisation; we also wished to be able to use the amine in stoichiometric amounts. We now report an improved procedure, namely treatment of (5a) with an amine (1 equiv.) in ethanol containing triethylamine (1 equiv.), as exemplified by the preparation of (2ℓ)[5] from the bromo-ester and 2,4-dimethoxybenzylamine[9] (20°C, 7 days; 60%). The N-(2,4-dimethoxybenzyl) group has been used as a protecting group in tetramic acid chemistry.[10] Likewise, benzylamine and octylamine afforded (2m) (40%) and (2n)[5] (45%), respectively. In another approach, alkylation of the NH-pyrrolinone (2a) at nitrogen was accomplished by two procedures;[11] for example, the 1-methyl compound (2b) was prepared from (2a) either by deprotonation (n-BuLi, 0°C) and addition of methyl iodide, or more conveniently by treatment with methyl iodide under conditions of solid-liquid phase-transfer (powdered KOH, Bu_4NHSO_4, THF, 25°C; 55%). Reactions of (2a) by the latter method with benzyl bromide afforded (2m) (60%), and with octyl iodide (at reflux) gave (2n) (43%).[12]

Investigation of the application of the variety of substrates accessible by these methods to 3-acyltetramic acid synthesis is continuing. We thank S.E.R.C. for a Studentship (A D.B.).

References and Notes

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5. All new compounds gave spectra (i.r., u.v., n.m.r., m.s.) consistent with the assigned structure, and satisfactory accurate mass measurement or combustion analysis. Purity was also assessed by t.l.c. examination.

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9. We thank Mr. Richard F. Jones for this experiment. The 2,4-dimethoxybenzylamine was prepared by reduction ($NaBH_4$, $BF_3.OEt_2$, THF, reflux; 66%) of 2,4-dimethoxybenzonitrile.

10. R.H. Schlessinger and G.R. Bebernitz, J.Org.Chem., 1985, 50, 1334; R.H. Schlessinger, G.R. Bebernitz, and P. Lin, J.Am.Chem.Soc., 1985, 107, 1777; P. DeShong, S. Ramesh, V. Elango, and J.J. Perez, ibid., p.5219.

11. N-Acylation of methyl tetramates has been reported; see ref. 3, also K. Inami and T. Shiba, Tetrahedron Lett., 1984, 25, 2009; G.D. James, G. Pattenden, and S D Mills, ibid., 1985, 26, 3617.

12. Also isolated as minor products from these phase-transfer alkylations were the 1,5-dialkyl-4-methoxypyrrolinones, i.e the 1,5-dimethyl compound (2e), the 1,5-dibenzyl or the 1,5-dioctyl derivative.

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