A Pyrone Strategy for the Synthesis of 3-Acyltetramic Acids

J. Chem. Research (S), 1999, 250–251
J. Chem. Research (M), 1999, 1201–1220

Raymond C. F. Jones,*[a] Gurdip Bhalay,[b] Jacqueline M. Patience[b] and Pravin Patel[a]

[a] *Department of Chemistry, The Open University, Walton Hall, Milton Keynes MK7 6AA, UK*
[b] *Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK*

The potential of pyrones as precursors to 3-acyltetramic acids is demonstrated by the conversion of 5-ethoxycarbonyl-4-methoxy-6-methyl-2-pyrone into a 3-acyltetramic acid.

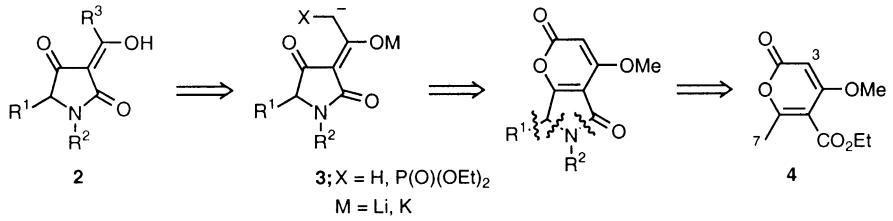
Introduction

Whilst developing new synthetic strategies for assembly of the heterocyclic trione moiety found in the biologically active 3-acylpyrrolidine-2,4-dione metabolites (3-acyltetramic acids; **2**),[1†] one of our approaches has been to generate the nitrogen heterocycle late in a synthetic sequence,[2] alleviating problems with manipulation and purification of the highly polar enolic moiety.[3] Our desire for non-polar building blocks as masked tricarbonyl systems was combined with (i) the strategy for elaboration of the 3-(poly)enoyl substituents often present in metabolites **2**, of generating a nucleophilic site at a 3-acetyl group either directly,[4] or with activation as in **3** ($X \neq H$),[5] and (ii) the preparation of methyl tetramates from acetoacetate esters,[6] in an analysis that identified pyrone **4** as a potential precursor (Scheme 1). Here X (of **3**) is an ester moiety, locked onto the C-4 carbonyl oxygen atom to form the pyrone ring.[7]

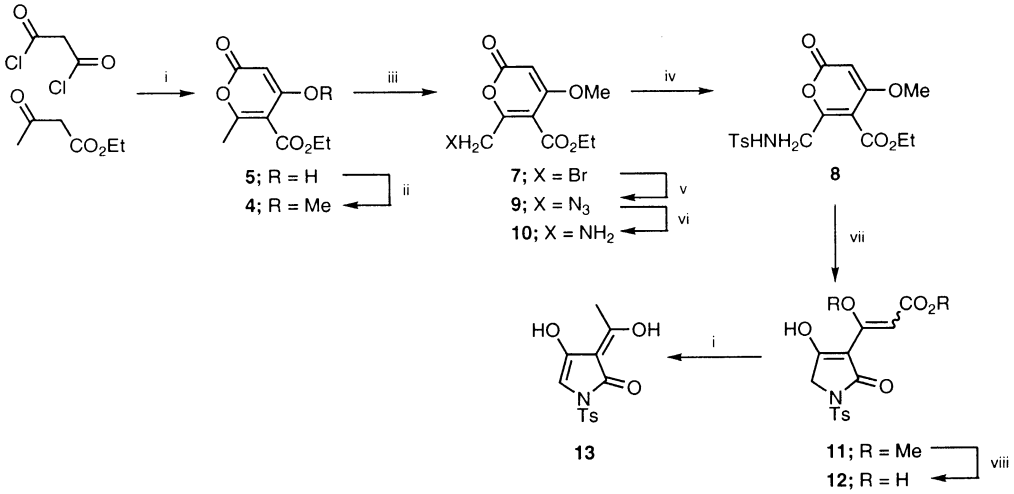
Results and discussion

5-Ethoxycarbonyl-4-hydroxy-6-methyl-2-pyrone **5** was prepared (64%) by treatment of ethyl acetoacetate with malonyl dichloride in toluene at reflux (Scheme 2);[8] any 5-ethoxycarbonyl-4,6-dimethyl-2-pyrone, from self-condensation of ethyl acetoacetate, was separated by base extraction of the acidic 4-hydroxypyrone **5** and acidification, and excess ethyl acetoacetate was separated by distillation. Several attempts were made to optimise the pyrone preparation, without any improvement.

Methylation of 4-hydroxy-2-pyrone **5** with dimethyl sulfate (K_2CO_3, acetone; 76%) afforded the building block **4** (Scheme 2). Regiospecific bromination of **4** was accomplished either by a radical protocol using *N*-bromosuccinimide (AIBN, CCl_4 at reflux), or by deprotonation ($LiNPr^i_2$, THF, −78 °C; inverse addition to Br_2) to give the 6-bromomethyl pyrone **7** (97 or 70%, respectively). Separation of bromide **7** from starting material **4** was problematic, so the radical protocol was the preferred procedure. Introduction of a nitrogen atom was accomplished by two methods. Treatment of bromide **7** with sodium

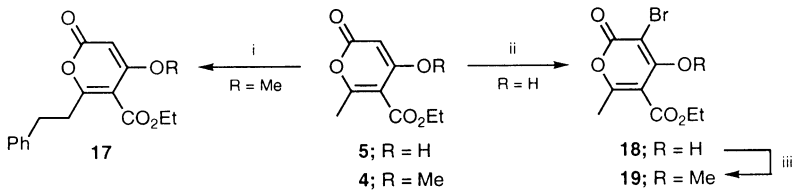


Scheme 1



Scheme 2 *Reagents and conditions*: i, toluene, reflux; ii, Me_2SO_4, K_2CO_3, acetone; iii, NBS, AIBN, CCl_4, reflux: or $LiNPr^i_2$, THF, −78 °C, Br_2; iv, NaNHTs, THF, 20 °C; v, NaN_3, DMF, 20 °C; vi, H_2, Pd–C, MeOH; vii, NaOMe, MeOH, reflux; viii, aq. NaOH, 25 °C

* To receive any correspondence.
† The acyltetramic acids are known to exist fully enolised. We illustrate a 3-*exo*-enol tautomer, the major enol observed in the solid state and in solution in non-polar solvents, see ref. 1 (*a*) and references therein.



Scheme 5 *Reagents and conditions*: i, $LiNPr^i_2$, THF, −78 °C, $PhCH_2Br$; ii, NBS, AIBN, CCl_4, reflux; iii, Me_2SO_4, K_2CO_3, acetone

toluene-*p*-sulfonamide (THF, 20 °C) efficiently afforded the sulfonamide **8** (92%); alternatively, reaction of bromide **6** with sodium azide (DMF, 20 °C) led to an azidomethylpyrone **9** (95%) that could be easily reduced to an unstable aminomethylpyrone **10** by hydrogenation (H_2, 1 atm, Pd–C, MeOH; 81%). Both amide **8** and amine **10** failed to cyclise directly onto the ester function to give the pyrano[2,3-*c*]pyrrole ring system under a variety of conditions including thermolysis. Treatment of bromo-ester **7** with excess aqueous methylamine[6] also failed to generate the required bicycle. Presumably this lack of cyclization is due in part to the strain involved in trying to close a fused five-membered ring that would contain three sp^2 centres and the amide function, and is consistent with our findings in related systems.[2b]

On the other hand, treatment of sulfonamide **8** with sodium methoxide (MeOH at reflux) afforded an acidic product that, on acidification, was shown to have undergone fission of the pyrone ring with concomitant ring closure of the nitrogen heterocycle to furnish the 3-substituted tetramic acid derivative **11** (80%).‡ Presumably pyrone ring opening removes any steric constraints to closure of the pyrrolidone ring. This easily manipulated compound has potential as an activated derivative for nucleophilic elaboration of the 3-acyl side chain, and demonstrates the synthetic equivalence of the pyrone C-2 function, and the ester moiety of **11**, to the activating group X of Scheme 1. Removal of the methoxycarbonyl group was cleanly accomplished by a two-step sequence. Treatment of **11** with aqueous sodium hydroxide afforded an intermediate carboxylic acid **12** (82%);‡ the enol ether was hydrolysed in the same process.[9] Decarboxylation of the *β*-ketoacid **12** was readily achieved by heating in toluene at reflux, to give the 3-acetyltetramic acid **13** (97%). Formation of the acyltetramic acid **13** was occasionally observed during the hydrolysis to form acid **12**. The NMR spectroscopic data for **13** indicate that, unusually, it exists in solution in $CDCl_3$–$(CD_3)_2SO$ as a dienolic tautomer such as that illustrated. Removal of the *N*-toluene-*p*-sulfonyl substituent was not attempted.

Elaboration of the pyrone **4** at C-7 and C-3 would provide substituents at C-5 and C-3(acetyl) of a tetramic acid, and we have demonstrated both reactivities in principle (Scheme 5). Alkylation at C-7 with benzyl bromide ($LiNPr^i_2$, THF, −78 °C) afforded 6-phenethylpyrone **17** (72%). Functionalisation at C-3 was shown by radical bromination of 4-hydroxypyrone **5** with *N*-bromosuccinimide (AIBN, CCl_4, reflux; 96%) to afford bromide **18**,§ and subsequent *O*-methylation with dimethyl sulfate (K_2CO_3, acetone; 71%) to give the 3-bromopyrone **19**. Lithium–halogen exchange (BuLi, THF, −78 °C) on bromide **19** was successful, as demonstrated by aqueous work-up to regenerate the pyrone **4**. The potential for reaction of the 3-lithiopyrone with *C*-electrophiles, or for Pd-catalysed couplings using the 3-bromo compound **19** remain to be explored.

We have thus demonstrated the viability of pyrones as precursors to 3-acyltetramic acids.

We thank the SERC for CASE studentships (G.B., J.M.P.), Roussel Laboratories (J.M.P.) and Shell Research (G.B.) for financial support, and Drs. P. Kennewell, J. Golec and P. A. Carter for helpful discussions.

Techniques used: IR, ^1H and ^{13}C NMR, MS, GC

Schemes: 5

References: 9

Received (by the RSC, Cambridge), 26th October 1998
Transferred to J. Chem. Research, 22nd December 1998
Accepted, 22nd December 1998
Paper E/8/09957J

‡ We have no definitive information on the tautomeric behaviour of ester **11** and acid **12**. Spectroscopic data suggest that both are mono-enolic in solution, and we illustrate a tautomer of **11** that highlights its relationship to the precursor pyrone **8**. The tautomer shown for acid **12** is selected by analogy with ester **11**.

§ It is assumed that this reaction is a radical process, since bromination does not occur under these conditions in the absence of AIBN.

Rererences cited in this synopsis

1 For leading references, see: (*a*) R. C. F. Jones, M. J. Begley, G. E. Peterson and S. Sumaria, *J. Chem. Soc., Perkin Trans. 1,* 1990, 1959; (*b*) B. J. L. Royles, *Chem Rev*., 1995, **95**, 1981.
2 See also: (*a*) R. C. F. Jones, G. Bhalay, P. A. Carter, K. A. M. Duller and S. I. E. Vulto, *Synlett*, 1995, 149; (*b*) R. C. F. Jones, G. Bhalay, P. A. Carter, K. A. M. Duller and S. I. E. Vulto, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2513.
3 *Cf*. R. K. Boeckman and R. B. Perni, *J. Org. Chem.*, 1986, **51**, 5486, footnote 21.
4 R. C. F. Jones and A. D. Bates, *Tetrahedron Lett*., 1987, **28**, 1565.
5 R. K. Boeckman, J. E. Starrett, D. G. Nickell and P.-E. Sum, *J. Am. Chem. Soc*., 1986, **108**, 5549; R. K. Boeckman, J. C. Potenza and E. J. Enholm, *J. Org. Chem*., 1987, **52**, 472; R. H. Schlessinger, G. R. Bebernitz, P. Lin and A. J. Poss, *J. Am. Chem. Soc*., 1985, **107**, 1777; R. H. Schlessinger and D. D. Graves, *Tetrahedron Lett*., 1987, **28**, 4385; S. J. Shimstock, R. E. Waltermire and P. DeShong, *J. Am. Chem. Soc*., 1991, **113**, 8791; T. Rosen, P. B. Fernandes, M. A. Marovich, L. Shen, J. Mao and A. G. Pernet, *J. Med. Chem*., 1989, **32**, 1062.
6 R. C. F. Jones and A. D. Bates, *Tetrahedron Lett*., 1986, **27**, 5285; R. C. F. Jones and J. M. Patience, *J. Chem. Soc., Perkin Trans. 1,* 1990, 2350; K. S. Kochhar, H. J. Carson and K. A. Clouser, *Tetrahedron Lett.,* 1984, **25**, 1871; K. S. Kochhar and H. W. Pinnick, *J. Org. Chem*., 1984, **49**, 3222; G. D. James, G. Pattenden and S. D. Mills, *Tetrahedron Lett*., 1985, **26**, 3617.
7 For a preliminary report of part of this work, see: R. C. F. Jones and J. M. Patience, *Tetrahedron Lett*., 1989, **30**, 3217.
8 *Cf. Chem. Abstr*., 1981, **94**, 15568.
9 *Cf*. R. C. F. Jones and G. E. Peterson, *Tetrahedron Lett*., 1983, **27**, 4751.