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ACYLATION OF PYRROLIDINE-2,4-DIONES : BORON DIFLUORIDE COMPLEXES OF 3-ACYL TETRAMIC ACIDS

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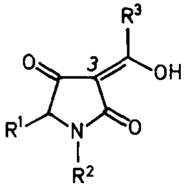
Summary Boron difluoride complexes of 3-acyl tetramic acids have been isolated from acylation of pyrrolidine-2,4-diones with acid chlorides and boron trifluoride-etherate, or prepared from 3-acyl tetramic acids. Their deprotonation has been studied.

For a number of years we have been involved in a programme of synthesis of the 3-acyl tetramic acids (1), a group of antibiotics and pigments from microorganisms. They display a range of biological activities; the 3-dienoyl derivative tirandamycin,[1] for example, is a potent inhibitor of bacterial DNA-directed RNA polymerase, and the 3-enoyl compound ikarugamycin[2] has specific antiprotozoal properties. Our strategy has centred on the acylation of pyrrolidine-2,4-diones (2) or their derivatives, and we have previously reported on the Lewis-acid promoted acylation of (2) with acid chlorides,[3] and the reactions of vinyl-lithiums (3) with aldehydes.[4] We now wish to report new findings based on the former method that have led to a revised protocol for acylations of (2) in the presence of boron trifluoride-etherate, isolation and identification of the boron difluoride complexes produced, and some further chemistry of these complexes.



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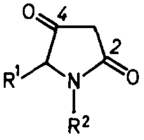

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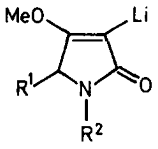


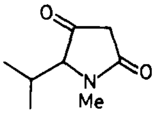
(3)

During studies directed towards the mould pigment erythroskyrine,[5] we investigated the Lewis-acid mediated acylation of dione (4), prepared from N-methyl-L-valine methyl ester.[4] When $TiCl_4$ was used as Lewis-acid in nitromethane, 3-C-acylation was observed with acid chlorides to give the 3-acyl tetramic acids (5b-d),[6] 31%, 60%, and 21%, respectively, using heptanoyl, (E)-2-butenoyl, and 3-methyl-2-butenoyl chlorides. If, however, boron trifluoride etherate was employed as Lewis-acid, and a basic aqueous work-up used to separate the acidic products (as had been the case in our earlier work[3]), then little or no 3-acyl tetramic acid was isolated except in the case of acetyl chloride, which gave (5a),[6] 45%.

We have found that a much improved procedure for these BF_3- mediated acylations involves isolation of the 3-acyl tetramic acids as their neutral boron difluoride complexes (6). Thus in a typical experiment the dione (4) in BF_3-etherate (50 ml/g) and the acid chloride (3-4 equiv.) were heated at 80°C until disappearance of the dione (t.l.c.). Addition of water and immediate extraction ($CHCl_3$ or EtOAc) gave material that did not give a positive ferric chloride test[7] and was chromatographed on silica to afford the boron difluoride complex (6). In this way complexes (6a-f)[6] were prepared (see Table) from acetyl, heptanoyl, (E)-2-butenoyl, 3-methyl-2-butenoyl, (E,E)-2,4-hexadienoyl, and benzoyl chlorides, respectively. Attempted hydrolysis of complexes (6a-f) with hot aqueous sodium acetate[8] led to extensive degradation, but they were smoothly converted into the corresponding 3-acyl tetramic acids (5a-f)[6] in good yield (see Table) simply on treatment with methanol (25-65°C as required, t.l.c. monitoring). We recommend this non-basic work-up followed by alcoholysis for BF_3-mediated acylations of other pyrrolidine-2,4-diones(2), including the 5-benzyl series reported previously[3] where the boron difluoride complexes are partially hydrolysed on aqueous work-up. The overall yields of C-acylation recorded here (see Table) are superior to almost all the previously reported examples of direct acylation of pyrrolidine-2,4-diones(2).[9]

The boron difluoride complexes (6), with the exception of sorbyl derivative (6e), are crystalline materials (see Table) that are useful for characterisation of the corresponding 3-acyl tetramic acids. The free acids may be converted to the complexes, as illustrated in the 3-benzoyl series where treatment of (5f) with BF_3-etherate (1 equiv., CH_2Cl_2, 25°C) gave (6f), 73%. Formulation of the boron difluoride complexes as derivatives (6) of the 3-exo-enol tautomer of the 3-acyl tetramic acids was made initially in accord with the predominance of this tautomer as determined in a number of cases in solution, and as found in the solid state.[10] This was confirmed by an X-ray analysis of the 3-acetyl compound (6a), illustrated in Fig.1.[11]

The 3-acetyl complex (6a) has possible synthetic applications to more complex 3-acyl tetramic acids. Deprotonation of (6a) ($LiNPr^i_2$, 1 equiv., THF, -80°C) and quenching with D_2O afforded mono-deuterated material (6g), whereas double deprotonation ($LiNPr^i_2$, $\gtrsim$ 2 equiv., THF, -80°C) and treatment with MeI (1 equiv.) gave the 5,5-disubstituted boron difluoride complex (7).[6] These reactions may be rationalised as involving a mono- and a di-anion represented as (8) and (9), respectively. This nucleophilic reactivity on the C-3 acetyl group has potential for chain extension and parallels the reactivity of recently reported 3-diethylphosphonoacetyl tetramic acids;[12] 3-acetyl tetramic acids are readily available.[13] We are actively exploring



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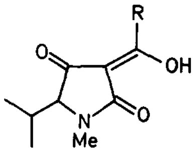

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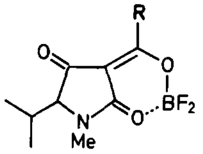


(6)

a; R = Me

b; R = $(CH_2)_5Me$

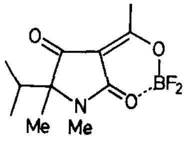
c; R = CH=CHMe

d; R = $CH=CMe_2$

e; R = $(CH=CH)_2Me$

f; R = Ph

g; R = CH_2D



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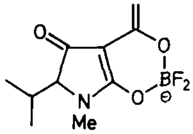

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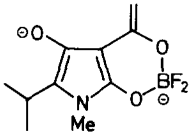

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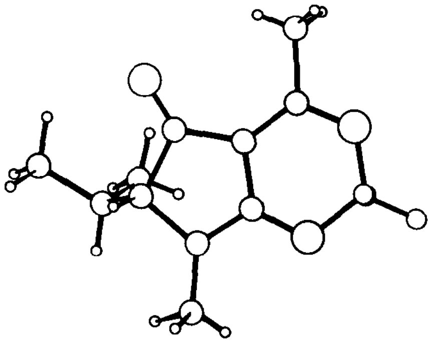

Fig. 1

TABLE : Acylation of Pyrrolidine-2,4-dione (4)

R	Boron Difluoride Complexes (6) Yield (%); M.p.	3-Acyl Tetramic Acids (5) Yield (%)
Me	71 ; 102 - 103°C	93
$(CH_2)_5Me$	71 ; 74 - 75°C	94
CH=CHMe	78 ; 123 - 124°C	86
$CH=CMe_2$	67 ; 137 - 138°C	92
$(CH=CH)_2Me$	51 ; -	80
Ph	50 ; 148 - 149°C	80

the reactions of the mono- and di-anions with various electrophiles.[14]

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References

1. D.J. Duchamp, A.R. Branfman, A.C. Button, and K.L. Rinehart, J.Am.Chem.Soc., 1973, 95, 4077.
2. S. Ito and Y. Hirata, Bull.Chem.Soc.Jpn., 1977, 50, 1813.
3. R.C.F. Jones and S. Sumaria, Tetrahedron Lett., 1978, 3173.
4. R.C.F. Jones and G.E. Peterson, Tetrahedron Lett., 1983, 24, accompanying Letter.
5. J. Shoji, S. Shibata, U. Sankawa, H. Taguchi, and Y. Shibanuma, Chem.Pharm.Bull., 1965, 13, 1240.
6. All new compounds gave spectra (IR, UV, NMR, MS) consistent with the assigned structure, and satisfactory combustion analysis or accurate mass measurement. Purity was also assessed by t.l.c. examination.
7. cf. K. Matsuo, I. Kitaguchi, Y. Takata, and K. Tanaka, Chem.Pharm.Bull., 1980, 28, 2494.
8. See, for example: C.R. Hauser, F.W. Swamer, and J.T. Adams, Org.React., 1954, 8, 59.
9. V.J. Lee, A.R. Branfman, T.R. Herrin, and K.L. Rinehart, J.Am.Chem.Soc., 1978, 100, 4225; S. Toda, S. Nakagawa, T. Naito, and H. Kawaguchi, J. Antibiotics, 1980, 33, 173; J.L. van der Baan, J.W.F.K. Barnick, and F. Bickelhaupt, Tetrahedron, 1978, 34, 223.
10. M.J. Nolte, P.S. Steyn, and P.L. Wessels, J.Chem.Soc., Perkin Trans.1, 1980, 1057.
11. This determination was kindly performed by Dr. M.J. Begley (Nottingham), and full details will be reported separately. Complex (6a), $C_{10}H_{14}NO_3BF_2$, crystallised in the triclinic system, space group $P\bar{1}$, dimensions $a = 7.814(1)$, $b = 7.840(1)$, $c = 10.025(1)$ Å, $\alpha = 93.96(1)$, $\beta = 96.60(1)$, $\gamma = 99.57(1)^\circ$. The structure was determined from 1556 observed reflections by direct methods using the MULTAN program and refined to R = 4.51%.
12. R.K. Boeckman and A.J. Thomas, J.Org.Chem., 1982, 47, 2823; P. DeShong, N.E. Lowmaster, and O. Baralt, ibid., 1983, 48, 1149. Acylation of dione (4) with diethylphosphonoacetyl chloride by our procedure led only to formation of the 4-*O*-ethyl enol ether of (4).
13. R.N. Lacey, J.Chem.Soc., 1954, 850.
14. Monoanion (8) has been found in a preliminary experiment to condense with benzaldehyde to afford a 3-cinnamoyl boron difluoride complex.

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