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RADICAL CYCLISATIONS OF PROPARGYL BROMOAMIDES AND PROPARGYL BROMOESTERS. NEW ROUTES TO TETRAMIC ACIDS, PYRROLINONES, TETRONIC ACIDS AND BUTENOLIDES.

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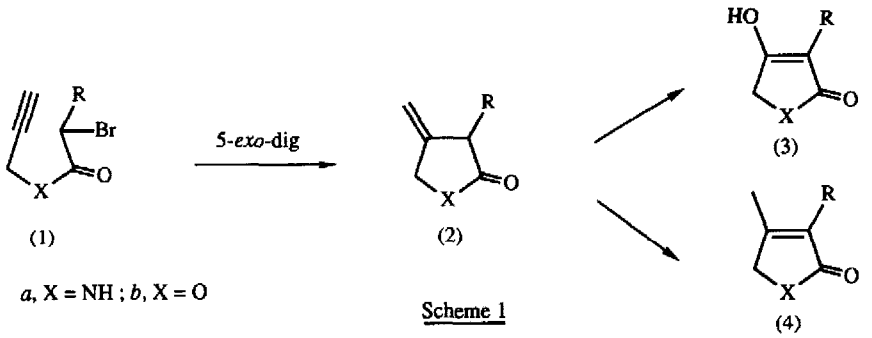
Summary: Radical cyclisations of the propargyl bromoamides (5) and (9), and the propargyl bromoesters (17) and (21a-e), produce precursors viz (6), (10), (18) and (22), to the tetramic acids (8) and (12), the pyrrolinones (7) and (11), the tetronic acids (20) and (23), and the butenolides (19) and 24), in high overall yields (Scheme 1).

Tetramic acids and 3-pyrrolin-2-ones, together with their oxygen analogues i.e. tetronic acids and but-2-enolides respectively, represent a diverse and profoundly important family of biologically active secondary metabolites, many of which have potential use in both medicine and agriculture.[1] Synthetic interest in this class of compound has been intense, particularly in the past decade.[2] Recently we reported the synthesis of various unsaturated lactones and lactams using a strategy based on oxidative free radical cyclisations of bromoacetals and carbamyl chlorides respectively in the presence of cobalt(I) salophen complexes.[3] We have now examined the scope for 5-exo-dig cyclisations of both propargyl bromoamides (1a) and propargyl bromoesters (1b) in the elaboration of 4-ylidenepyrrolidin-2-ones (2a) and 4-ylidenebutyrolactones (2b) as a new synthetic entry to tetramic and tetronic acids [(3), by oxidative cleavage], and to 3-unsaturated γ-lactams and γ-lactones [(4), by positional isomerisation] respectively (Scheme 1).



(1)

a, X = NH ; *b*, X = O

(2)

(3)

(4)

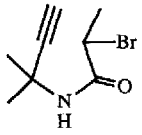
Scheme 1

Treatment of a solution of the bromoamide (5)[4] in toluene under reflux with a solution of tri-n-butyltin hydride (Bu_3SnH) in toluene containing azoisobutyronitrile (AIBN) over 14-24h (syringe pump) produced the crystalline lactam (6), m.p. 95-6°C, in 95% yield.[5] When a solution of (6) in ethyl acetate was kept at room temperature overnight, chromatography separated the conjugated lactam [(7), 90%]. In addition, when a solution of the lactam (6) in methanol at -78°C was treated with ozone for 10-15 min, work-up with triphenylphosphine followed by chromatography led to the corresponding tetramic acid (8) in 55-60% yield. In a similar manner, the bromoamide (9) was converted into the corresponding spiro-lactam [(11), 85%] and the spiro- tetramic acid [(12), 52%] *via* the intermediate pyrrolidin-2-one [(10), 91% from (9)]. Interestingly, when the bromoamide (13) lacking substitution at the propargylic methylene carbon was treated under the same conditions with Bu_3SnH-AIBN the only product isolated was the corresponding vinylstannane (14) resulting from simultaneous reduction (of C→Br) and hydrostannation (of C≡C) of (13).

In contemporary studies, both Stork[6] and Ikeda[7] and their respective collaborators, have investigated the corresponding radical cyclisations of allyl acetamides as a route to saturated γ-lactams.[8] These cyclisations were only realised when the nitrogen centres in the starting materials were appropriately substituted *e.g.* $COCF_3$, CH_2Ph or Ph; nitrogen-unsubstituted allyl acetamides gave instead predominantly the products of reduction. Stork has reasoned that the ineffectiveness of these cyclisations with N-substituted allyl acetamides is associated with the preferred *syn*-conformation (15) of the initially generated radical intermediate; by placing a sufficiently large group on nitrogen the *syn*-*anti* equilibrium is shifted in favour of the *anti*- conformation (16), thereby favouring cyclisation (Scheme 2). In the case of our propargyl N-unsubstituted amides (5) and (9) we ascribe the relative effectiveness of their cyclisations to the faster radical acceptor properties of the C→C triple bond over the C→C double bond. This property, no doubt is associated with the linear orientation (greater steric accessibility) and higher energy (two π-orbitals, large electron density) of the C≡C bond interacting strongly with the electrophilic radical centre.

In contrast to the results obtained with the amide (13), reaction between the silyl-protected bromoester (17) and Bu_3SnH-AIBN in benzene led to a good yield (∿80%) of the ylidenebutyrolactone (18) which could be isomerised to the corresponding allylsilane (19). Furthermore, oxidative cleavage of (18), using ozone-triphenylphosphine, produced the known tetronic acid [(20), 56%] m.p. 185-6°C. Using similar reaction sequences to those already described the analogous propargyl bromoesters (21a-e) were likewise converted in excellent overall yields into the corresponding tetronic acids (23) and but-2-enolides (24), *via* (22).[9]

It is likely that the straightforward and convergent syntheses of 5-ring nitrogen and oxygen heterocycles (3) and (4) (Scheme 1) described here will find useful applications in the synthesis of a range of bio-active products. These studies are now underway in our laboratory.



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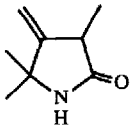

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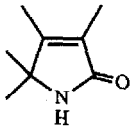

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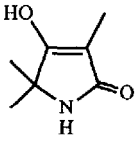

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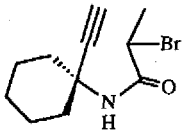

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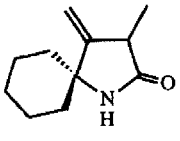

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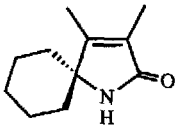

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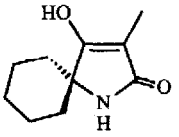

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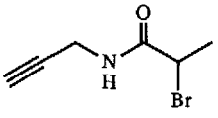

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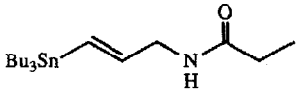

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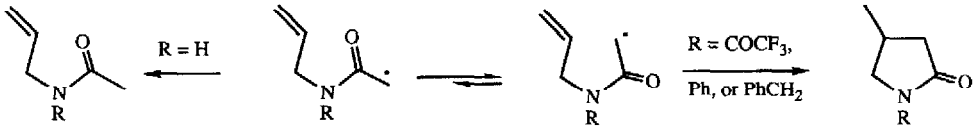
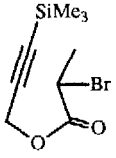


(15) (16)

Scheme 2



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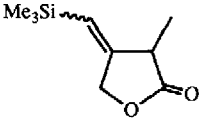

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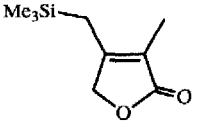

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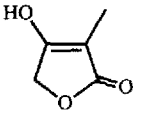

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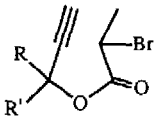

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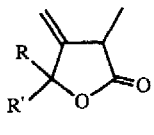

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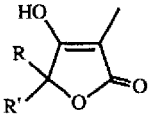

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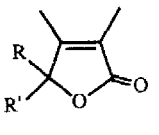

(24)

a, R = R' = Me ; *b*, R = R' = $(CH_2)_3$; *c*, R = Me, R' = ^{i}Bu ; *d*, R = Me, R' = C_5H_{11} ; *e*, R = Me, R' = Ph

References

1 See: "Microbial Products", CRC Handbook of Microbiology, 2nd Edition, Volume V, Edit. A.I. Laskin and H.A. Lechevalier, CRC Press, Inc., 1984, and references therein.

2 See for example: G. Pattenden, 'Natural 4-Ylidenebutenolides and 4-Ylidenetetronic Acids', Progress in the Chemistry of Organic Natural Products, 1978, 35, 133; R. Ramage, G.J. Griffiths, F.E. Shutt and J.N.A. Sweeney, J.Chem.Soc., Perkin Trans.I, 1984, 1539; J.R. Anderson, R.L. Edwards and A.J.S. Whalley, ibid., 1982, 215; R.N. Lacey, J.Chem.Soc., 1954, 850; D.J. Cram, O. Theander, H. Jager and M.K. Stanfield, J.Am.Chem.Soc., 1963, 85, 1430; D. Cartwright, V.J. Lee and K.L. Rinehart, Jnr., J.Am.Chem.Soc., 1978, 100, 4237; R.K. Boeckman, C.H. Weidner, R.B. Perni and J.J. Napier, J.Am.Chem.Soc., 1989, 111, 8036; L.A. Paquette, D. MacDonald, L.G. Anderson and J. Wright, ibid., 1989, 111, 8037; and references cited therein.

3 See: (a) H. Bhandal, G. Pattenden and J.J. Russell, Tetrahedron Lett., 1986, 27, 2299; (b) M.J. Begley, M. Ladlow and G. Pattenden, J.Chem.Soc., Perkin Trans., 1988, 1095; (c) G.B. Gill, G. Pattenden and S.J. Reynolds, Tetrahedron Lett., 1989, 30, 3229.

4 Prepared by reaction between the propargylamine (or propargyl alcohol) and α-bromoacetyl chloride (C_6H_5Me, C_5H_5N, 0°C, 3-5h), followed by evaporation and crystallisation.

5 All new compounds showed satisfactory spectroscopic data together with microanalytical and/or mass spectrometry data.

6 G. Stork and R. Mah, Heterocycles, 1989, 28, 723.

7 T. Sato, Y. Wada, M. Nishimoto, H. Ishibashi and M. Ikeda, J.Chem.Soc., Perkin Trans.I, 1989, 879.

8 For some other studies of the synthesis of pyrrolidinones via radical intermediates see: H. Nagashima, K. Ara, H. Wakamatsu and K. Itoh, J.Chem.Soc., Chem.Commum., 1985, 518; M. Mori, N. Kanda, I. Oda and Y. Ban, Tetrahedron, 1985, 41, 5465; C.K. Tseng, E.G. Teach and R.W. Simons, Synth.Commun., 1984, 14, 1027; M.D. Bachi, F. Frolow and C. Hoornaert, J.Org.Chem., 1983, 48, 1841; J-K. Choi and D.J. Hart, Tetrahedron, 1985, 41, 3959; A. Padwa, H. Nimmesgern and G.S.K. Wong, J.Org.Chem., 1985, 50, 5620; Tetrahedron Lett., 1985, 25, 957; J.E. Baldwin and C-S Li, J.Chem.Soc., Chem.Commun., 1987, 166; S.J. Danishefsky and J.S. Panek, J.Am.Chem.Soc., 1987, 109, 917; J. Cossy and C. Leblanc, Tetrahedron Lett., 1989, 30, 4531.

9 For a recent example of radical cyclisation of an allyl bromoester see: J.L. Belletire and N.O. Mahmoodi, Tetrahedron Lett., 1989, 30, 4363. For some alternative radical mediated syntheses of butyrolactones see under ref. 3(b).

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