Tetrahedron Letters,Vol.28,No.43,pp 5203-5204,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

FURANNULATION *via* RADICAL CYCLISATION

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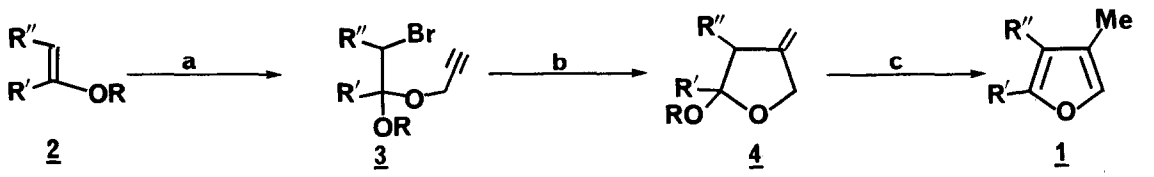
Abstract: A three step 4-methyl furan annulation sequence is described *via* the radical cyclisation of bromoacetal 3 to 2-alkoxy-4-methylene tetrahydrofuran 4

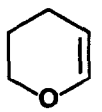
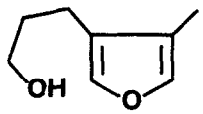
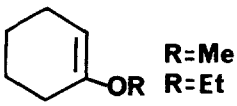
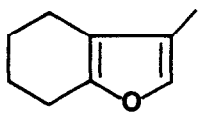
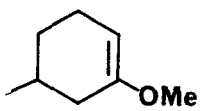
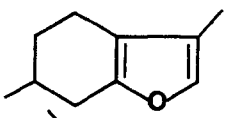
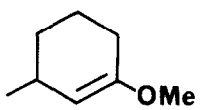
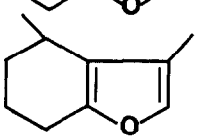
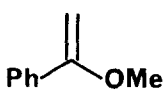
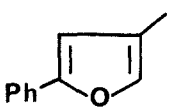
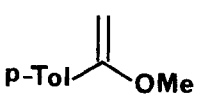
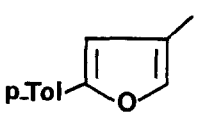
4-Methyl furans fused to a variety of carbon skeleta (1) are as commonly encountered as α-methylene-γ-butyrolactones in the field of terpenoids. Currently, radical cyclisation is widely accepted as a powerful tool in organic synthesis[1] and its utility in the synthesis of a variety of butyrolactones is well documented.[2,3] In continuation of our interest in this area,[3] we now wish to describe a three step strategy to 4-methyl furan annulation sequence starting from enol ether 2, using radical cyclisation as the key reaction.

The methodology is depicted in the Scheme 1; radical cyclisation of the bromoacetal 3 generates 2-alkoxy-4-methylene tetrahydrofuran 4, which on acid catalysed aromatisation leads to furan 1. The key radical precursors, bromoacetals 3, were obtained by low temperature (-40°C) bromination of enol ethers 2 using N-bromosuccinimide (NBS) in propargyl alcohol-methylene chloride medium in over 90% yield. The cyclisation of 3 to 4 can be carried out by refluxing a 0.02M solution in benzene with 1.1 equiv. of tri n-butyltinhydride (TBTH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), but was achieved more conveniently using TBTH generated *in situ* (n-Bu_3SnCl-$NaCNBH_3$-^{t}BuOH). The cyclised products were found to be too labile and were aromatised directly to furans 1,[4] without purification using a catalytic amount of p-toluenesulfonic acid in benzene at room temperature (30 min), except in the case of 4a which require 2 hr in refluxing benzene. The overall yields of furans 1 obtained from bromoacetals 3 are summarised in Table 1.



SCHEME 1: a. NBS (1.2 equiv.), HC≡C-CH_2OH, CH_2Cl_2, -40°C, 1.5 hr; b. n-Bu_3SnCl (0.15 equiv.), $NaCNBH_3$ (1.5 equiv.), AIBN (catalytic), t-BuOH, 80°C, 1.5 hr; c. p-TsOH (catalytic), benzene, R.T., 30 min.

Table 1: Furannulation via radical cyclisation.

entry	Enol ether 2	Furan 1	% Yield[a]
a.			51
b.	 R=Me R=Et		38 42
c.			45[b]
d.			45[b]
e.			57
f.			70

a. Yields refer to isolated and chromatographically pure furans based on bromoacetals 3.
b. Sequence was carried out using a 1:1 mixture of 2c and 2d.[5]

The generality of this methodology is exemplified by the synthesis of menthofuran (1c) along with its isomer 1d starting from 3-methyl cyclohexanone.[5]

References and notes:

1. a.Selectivity and synthetic application of radical cyclisation reactions, Tetrahedron symposia in print,ed.B.Giese,Tetrahedron, 41, 3887-4302 (1985); b. A. Srikrishna, Current Science, 56, 392 (1987).
2. Y. Ueno, O. Moriya, K. Chino, M. Watanabe and M. Okawara, J. Chem. Soc., Perkin Trans. I, 1351 (1986).
3. A. Srikrishna, J. Chem. Soc., Chem. Commun., 587 (1987).
4. Spectral data for 1a: IR (neat), 3400 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 6.93 (2H, br s), 3.47 (2H, t, J=6.5Hz), 2.31 (2H, t, J=7Hz), 1.87 (3H, d, J=1.5 Hz), 1.7 (2H,m); for 1f: IR (neat), 1615, 1540, 1490 cm^{-1}; ^1H NMR (60 MHz, CCl_4): δ 7.43 (2H, d, J=8Hz), 7.11 (1H, s), 7.0 (2H, d, J=8Hz), 6.33 (1h, s), 2.31 (3H, s), 2.03 (3H, d, J=1Hz). All other furans exhibited the spectral data identical to those reported in the literature.
5. For a regiospecific synthesis of 2c, see E. Wenkert, M.E. Alonso, B.L. Buckwalter and K.J. Chou, J. Am. Chem. Soc., 99, 4778 (1977).

(Received in UK 10 August 1987)