CHEMISTRY LETTERS, pp. 371-372, 1988.

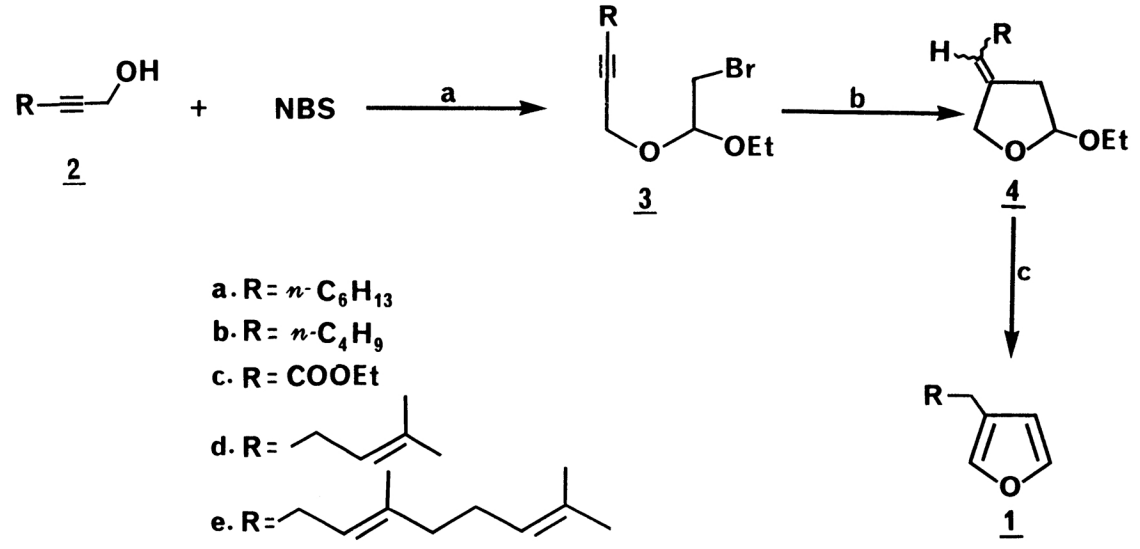
A Radical Cyclisation Route to 3-Alkyl Furans. Synthesis of Perillene and Dendrolasin

Adusumilli SRIKRISHNA* and Gajendran SUNDERBABU
Department of Organic Chemistry, Indian Institute of Science,
Bangalore - 560 012, India

A general three step synthesis of 3-alkyl furans, including Perillene and Dendrolasin, from alk-2-ynyl alcohols is described *via* radical cyclisation of 2-bromo-1-ethoxyethyl alk-2-ynyl ethers to 2-ethoxy-4-alkylidene tetrahydrofurans.

Currently radical cyclisation is widely accepted as a powerful tool in organic synthesis.[1] Its use in the synthesis of variety of butyrolactones is well documented.[2,3] 3-Alkyl furan (1) is an important functional moiety frequently encountered in variety of terpenoids, however, there are not many general useful synthetic methodologies to this important functional moiety.[4] We now wish to describe a general strategy to the synthesis of 3-alkyl furans (1) from alk-2-ynyl alcohols using radical cyclisation as the key step. This, incidentally establishes that a mixture of propargyl alcohol and ethyl vinyl ether can serve as an isoprene equivalent.

The methodology is depicted in Scheme 1; radical cyclisation of bromoacetal 3, obtained by bromination of ethyl vinyl ether in the presence of alk-2-ynyl alcohol 2, generates the 2-ethoxy-4-alkylidene tetrahydrofuran (4), which on acid catalysed aromatisation leads to 3-alkyl furan (1). The requisite alk-2-ynols (2) were obtained either by condensing formaldehyde with 1-lithioalkynes(for 2a,b) or by alkylating lithium salt of prop-2-ynol THP ether with alkyl halide followed



Scheme 1. a. CH_2Cl_2, -40 °C, CH_2=CH-OEt, 1.5-2 h; b. n-Bu_3SnCl (0.15 equiv.)/ $NaCNBH_3$ (1.5 equiv.)/cat.AIBN/t-BuOH; c. PTSA/benzene/RT.

Table 1. Synthesis of 3-alkyl furans via radical cyclisation[a)]

Entry	% yield of 3	4[b)]	1
a	98	97	89
b	98	76	67
c	96	55	65
d	80	75	67
e	80	72	75

a) All the compounds were purified by silicagel column chromatography and yields refer to the isolated and chromatographically pure products.
b) Mixture of stereoisomers (≈ 1:1).

by pyridinium p-toluenesulfonate catalysed hydrolysis (for 2c-e). The key radical precursors 3# were obtained in over 80% yield (Table 1) by a slow addition of ethyl vinyl ether (1.2 equiv., 1.5-2 h) to a cold (-40 °C) solution of alcohol 2 (1 equiv.) and NBS (1.2 equiv.) in methylene chloride. The radical cyclisation (3→4) was best achieved by *in situ* generated catalytic tri-n-butyltinhydride (n-$Bu_3SnCl/NaCNBH_3$) in refluxing t-BuOH (1 to 3 h) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN). The cyclised product (4)# was obtained as a mixture of stereoisomers (≈ 1:1) as evidenced by NMR and the mixture was used as such in the next aromatisation step. Finally, the cyclised products 4 were transformed to 3-alkyl furans (1)# by treatment with a catalytic amount of p-toluenesulfonic acid in benzene (5—8 h) at room temperature. The yields of bromination, cyclisation and aromatisation are summarised in Table 1.

The generality of this methodology is exemplified by the synthesis of two naturally occuring terpenoids Perillene (1d)[4,5)] and Dendrolasin (1e)[4,6)] starting from readily available dimethylallyl bromide and geranyl bromide (Table 1, entries d and e).[7)] Currently, this work is being extended to establish the flexibility of this methodology to multiply substituted furans available in nature.

Spectral data for 3a: IR (neat), 2300, 2240, 1120, and 1050 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ 4.75(1H,t,J=6 Hz), 4.15(2H,t,J=2 Hz), 3.60(2H,m), 3.3(2H,d,J=6 Hz), 2.15 (2H,m), 1.2-1.8(8H,m), 1.2(3H,t,J=7 Hz), 0.9(3H,t,J=6 Hz); 4a IR (neat), 1190, 1130, 1100, 1050, 1030, 1000, 930 cm^{-1}; ^1H NMR (60 MHz, CCl_4),δ5.1-5.4(1H,m,olefinic), 5.1(1H, m,H-2), 4.15-4.35(2H,m,H-5), 3.2-3.9(2H,m,-OCH_2CH_3), 2.25-2.6(2H,m,H-3), 1.7-2.2(2H,m,allylic), 0.8-1.6(14H,m); 1a IR (neat), 1500, 1460, 1030, 780, 730 cm^{-1}; ^1H NMR (60 MHz, CCl_4), 7.25(1H,t,J=1.5 Hz),δ 7.15(1H,br s), 6.2(1H,br s), 2.4(2H,br t,J=7 Hz,), 1.25(10H,m) 0.85(3H,t). Similarly, all other compounds gave satisfactory spectral data. Perillene (1d) and Dendrolasin (1e) exhibited spectral data identical to those reported in literature.

References

1) Selectivity and synthetic application of radical cyclisation reactions, Tetrahedron Symposia in Print, ed byB. Giese, Tetrahedron, 41, 3887-4302 (1985); A. Srikrishna, Current Science, 56, 392 (1987).
2) Y.Ueno, O. Moriya, K. Chino, M. Watanabe, and M. Okawara, J. Chem. Soc., Perkin Trans. 1, 1986, 1351.
3) A. Srikrishna, J. Chem. Soc., Chem. Commun., 1987, 587.
4) T.Mandai, M.Takeshita, K.Mori, M. Kawada, and J. Otera, Chem. Lett., 1983, 1909 and references cited therein.
5) R. Bernardi, C. Cardani, D. Ghiringhelli, A. Selva, A. Baggini, and M. Pavan, Tetrahedron Lett., 1967, 3893.
6) A. Quilico, F. Piozzi, and M. Pavan, Tetrahedron, 1, 177 (1957); Y. Hirose, M. Abu, and Y. Sekiya, Nippon Kagaku Zasshi, 82, 725 (1961).
7) For a similar methodology using haloacetal route for 3-alkyl furans see G. Stork, and R. Mook, J. Am. Chem. Soc., 105, 3720 (1983).

(Received August 17, 1987)