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A SIMPLE SYNTHESIS OF 2,3-DISUBSTITUTED FURANS

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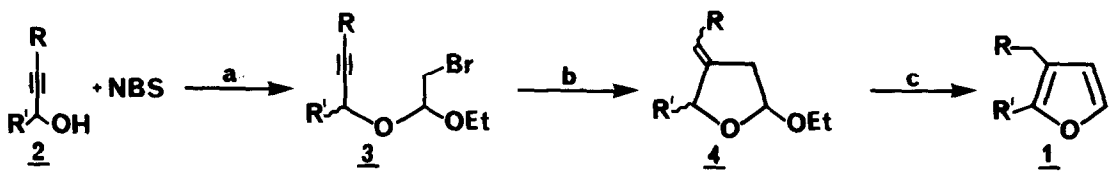
Abstract: A general, three step synthesis of 2,3-disubstituted furans via the radical cyclisation of bromoacetal 3 to 2-ethoxy-4-alkylidene tetrahydrofuran (4) is described.

In connection with an on going project towards the synthesis of furanoterpenoids, we searched for a mild and short synthesis of 2,3-disubstituted furans.[1] However, we were unable to find a methodology to these compounds which suits our conditions. This led us to develop a short, general and simple synthesis to 2,3-disubstituted furans (1) starting from propargyl alcohols 2, based on radical cyclisation reactions,[2] which is the subject of this communication.

The methodology is depicted in Scheme 1; radical cyclisation of the bromoacetal 3, obtained by bromination of ethyl vinyl ether in presence of propargyl alcohol 2, generates the 2-ethoxy-4-alkylidene tetrahydrofuran (4), which on acid catalysed aromatisation leads to furan 1. The requisite propargyl alcohols were obtained by the reaction of 1-lithio alkynes with appropriate aldehydes. The key radical precursors 3 were obtained, as a mixture of diastereomers in over 85% yield, by a slow addition of ethyl vinyl ether (1.2 eq., 1.5-2 hr) to a cold (-40°C) solution of propargyl alcohols 2 (1 eq.) and NBS (1.2 eq.) in methylene chloride. The radical cyclisation of 3 can be carried out by refluxing a 0.02M solution in benzene with 1.1 eq. of tri-n-butyl tin hydride (TBTH) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN), but was achieved more conveniently using catalytic TBTH generated in situ ($^{n}Bu_3SnCl$-$NaCNBH_3$) in refluxing $^{t}BuOH$ (1 hr).[3]



SCHEME-1: a:CH_2Cl_2, -40°C, CH_2=CH-OEt, 1.5-2 hr; b:$^{n}Bu_3SnCl$ (0.15 eq.), $NaCNBH_3$ (1.5 eq.), cat. AIBN, $^{t}BuOH$, 1-1.5 hr; c: pTSA, C_6H_6, RT, 5-8 hr.

Table 1: 2,3-disubstituted furans *via* radical cyclisation reactions.[a]

entry	R	R'	% Yield of 3[b]	4	1
a	n-C_4H_9	n-C_6H_{13}	71	80	62
b	n-C_4H_9	Phenyl	75	70	65
c	n-C_4H_9	p-Tolyl	66	82	70
d	n-C_4H_9	p-Anisyl	94	78	60
e	n-C_6H_{13}	Ethyl	65	89	63
f	n-C_6H_{13}	Phenyl	70	76	70
g	n-C_6H_{13}	p-Tolyl	70	70	74
h	n-C_6H_{13}	p-Anisyl	65	65	57

[a]Typically reactions were carried out on one mmole scale. All the compounds were purified over silicagel column and yields refer to isolated and chromatographically pure products.[4] [b]In addition varying amounts (5-25%) of starting propargyl alcohol 2 was also obtained.

Finally, the cylised products 4, obtained as a mixture of four stereoisomers, were transformed to 2,3-disubstituted furans (1) by treatment with a catalytic amount of toluene-p-sulphonic acid in benzene (5-8 hr) at room temperature. The yields of bromination, radical cyclisation and aromatisation are summarised in table 1.[4] Currently, this work is being extended to establish the flexbility of this methodology to multiply substituted furans available in nature.

References and notes:

1. For recent synthesis see J. Mann and H.J. Holland, Tetrahedron, 43, 2533 (1987); M. Ishiguro, N. Ikeda and H. Yamamoto, Chemistry Lett., 1029 (1982); H.J. Reich and R.E. Olson, J. Org. Chem., 52, 2315 (1987) and references cited therein.
2. Selectivity and synthetic application of radical cyclisation reactions, Tetrahedron symposia in print, ed. B. Giese, Tetrahedron, 41, 3887 - 4302 (1985); A. Srikrishna, Current Science, 56, 392 (1987).
3. A. Srikrishna, J. Chem. Soc., Chem. Commun, 587 (1987).
4. Spectral data for 2a: IR (neat), 3360 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ 4-4.4 (1H,m), 2.4 (1H,s), 2.15 (2H,m), 1.2-1.8 (14H,m), 0.7-1.2 (6H,m); 3a (1:1 mixture of diastereomers): IR (neat), 1130, 1040 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ 4.8 & 4.7 (1H,2t,O-CH-O), 4.2 (1H,m,≡C-CH-O), 3.6 (2H, m,OCH_2CH_3), 3.3 (2H,d,J=6Hz,CH_2Br), 2.2 (2H,m,≡C-CH_2), 0.7-1.9 (23H,m); 4a (mixture of four stereoisomers): IR (neat), 1460, 1050, 980 cm^{-1}; ^1H NMR (60 MHz, CCl_4), δ 4.8-5.4 (2H,m), 4.0-4.4 (1H,m), 3.0-3.8 (2H,m), 2.2-2.6 (2H,m), 1.7-2.2 (2H,m), 1.1-1.6 (14H,m), 0.6-1.0 (6H,m); 1a: IR (neat), 1510, 1380, 1150, 1050 cm^{-1}, ^1H NMR (60 MHz, CCl_4), δ 7.05 (1H,d, J=2Hz), 6.0 (1H,d,J=2Hz), 2.1-2.6 (4H,m), 1.1-1.8 (14H,m), 0.9 (6H,t). Similarly all the other compounds gave satisfactory spectral data.

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