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PREPARATION OF CYCLIC ETHERS *VIA* OXIDATIVE CYCLISATION OF 2-(4-HYDROXYALKYL) AND 2-(5-HYDROXYALKYL)FURANS WITH DDQ.

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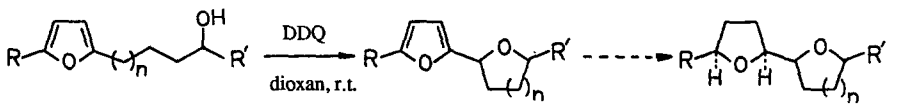
Summary: *Reaction of 2-(4- or 5-hydroxyalkyl)furans with DDQ leads to the smooth formation of cyclic ethers under neutral conditions, but aromatic analogues do not give useful yields of desired products.*

Much impetus for the development of novel means of constructing tetrahydrofurans and tetrahydropyrans[1] results from their fundamental constructional role in ionophore antibiotics[2], many of which contain linear arrays of contiguous cyclic ether units, as exemplified by lasolicid A[3], and monensin.[4] In this communication we report a mild oxidative cyclisation procedure which permits the construction of 2-(2-furanyl)tetrahydrofurans and tetrahydropyrans (Figure). Rhodium catalysed hydrogenation of 2,5-disubstituted furans has been used previously to prepare the corresponding *cis*-tetrahydrofurans[5] and this cyclisation procedure thus provides potential access to structures in which cyclic ether units are connected α- to the ring oxygen atoms.



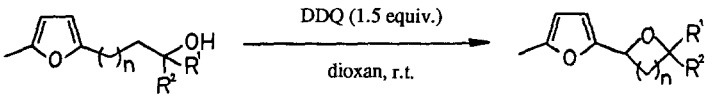
n = 1, 2

Figure

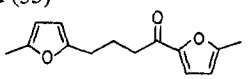
In a recently described procedure, β-(hydroxyalkyl)*p*-methoxystyrene derivatives have been shown to undergo oxidative cyclisation to the corresponding tetrahydrofurans and tetrahydropyrans in the presence of DDQ, albeit in moderate yield.[6] We have found that the furan derivatives (**1**), on treatment with 1.5 equivalents of DDQ in dioxan at room temperature, undergo smooth cyclisation to the corresponding ethers (**2**) over a period of 5-24 h (Table).[7] Whilst the 2,5-disubstituted tetrahydrofurans (**2c, d**) were formed as mixtures of *cis* and *trans* isomers, the 2,6-disubstituted tetrahydropyran (**2g**) was shown by nmr. to be > 95% the *cis* isomer.[8] Closure of alcohol (**1a**) to furnish an oxetane did not occur, but 4-(2-furanyl)butanoic acid (**1f**) was cyclised under identical conditions to furnish butyrolactone (**2f**). It is noteworthy that substrates (**1c, g**) undergo cyclisation rather than oxidation of the allylic alcohol moieties.[9] A study with substrate (**1d**), in which the hydroxyl group is at a furylic position, gave a mixture of cyclised and oxidised products permitting the isolation of the unstable tricycle (**2d**) in 35% yield together with the ketone (**3**) in 50% yield. The substrate (**1e**), on similar treatment was converted to a single product by tlc. analysis but attempted isolation always led to decomposition of the material.

Precursors possessing an aromatic group in place of the furan substituent proved to be inefficient substrates for cyclisation. The alcohol (**4a**) and the acid (**4b**) were unaffected by the conditions found to convert the corresponding furan derivatives (**1b, f**).[10] The presence of a more electron rich aromatic ring in 4-(*p*-methoxyphenyl)butanol (**4c**) did result in the desired tetrahydrofuran product (**5c**) being obtained in 10% yield but the major product (*circa* 60%) under all conditions investigated was the dimeric material (**6**).[11]

In summary, the oxidative cyclisation procedure described herein permits the preparation of novel 2-(2-furanyl)- cyclic ether systems, and the mild reaction conditions are compatible with the presence of oxidisable and acid labile moieties.

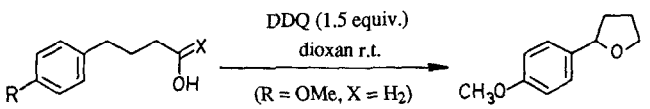


(1) (2)

(1)	Substrate n	R¹	R²	Time (h)	Product (isolated yield %)
a	1	H	H	24	No reaction
b	2	H	H	5	**2b** (35)[a]
c	2	H		16	**2c** (60)
d	2	H		16	**2d** (35)
					3  (50)
e	2	Me		16	No product isolable
f	2	=O		5	**2e** (79)
g	3	H		16	**2g** (67)

a Low isolated yield due to volatility of product and subsequent losses on work - up.

Table

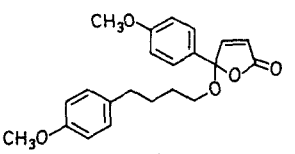


(4)

a R = H, X = H_2
b R = H, X = =O
c R = OMe, X = H_2

(5)

10%



(6)

60%

References

1. M. Bartok, "*Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues*", Vol. 2, 1980; See also I. Noda, K. Horita, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, 1986, 1917 and references cited therein.
2. W. Wierenga, "*Total Synthesis of Natural Products*", Vol. 4, 1981, Ed. J. ApSimon, Wiley - Interscience.
3. J. Berger, A. I. Rachlin, W. E. Scott, L. H. Steinbach, and M. W. Goldberg, *J. Amer. Chem. Soc.*, 1951, **73**, 5295.
4. A. Agtarap, J. W. Chamberlain, M. Pinkerton, and L. K. Steinrauf, *J. Amer. Chem. Soc.*, 1967, **89**, 5737.
5. H.Gerlach and H.Wetter, *Helv. Chim. Acta*, 1974, **57**, 2306.
6. Y. Oikawa, K. Horita, and O. Yonemitsu, *Heterocycles*, 1985, **23**, 553.
7. ***General Procedure:*** The substrate was stirred with DDQ (1.5 equiv.) at room temperature in dioxan until chromatography indicated complete disappearance of starting material (5 - 24 h.). The precipitated hydroquinone was filtered off and the excess DDQ removed by passing the reaction mixture through a plug of activated charcoal. After removal of solvent *in vacuo* the product was purified by chromatography or short path distillation, depending upon volatility of the product and its stability on silica.
8. All novel compounds isolated gave spectroscopic and microanalytical data in keeping with their assigned structures, except for (**1d**) and (**2c**) which were too unstable to permit elemental analysis.
9. For a review including DDQ mediated oxidations of allylic alcohols see: D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67**, 153.
10. Lactone formation *via* DDQ generated trityl cations has been reported: A. M. Creighton and L. M. Jackmann, *J. Chem. Soc.*, 1960, 3138.
11. The conversion of (**4c**) into (**5c**) in 5% yield has been reported using $Tl(TFA)_3$; E. C. Taylor, J. G. Andrade, G. J. H. Rall, I. J. Turchi, K. Stelion, G. E. Jagdmann, and A. McKillop, *J. Amer. Chem. Soc.*, 1975, **40**, 1454.

Spectroscopic data for (**6**): υ_{max} ($CHCl_3$) 3020, 1820, 1770 cm^{-1}; δH (300 MHz, $CDCl_3$) 1.65 (4H, m), 2.56 (2H, m), 3.51 (2H, m), 3.80 (3H, s), 3.84 (3H, s), 6.12 (1H, d, 6.3Hz), 6.83 (2H, d, 8.8Hz), 6.93 (2H, d, 8.8Hz) 7.08 (2H, d, 8.8Hz), 7.28 (2H, d, 6.3Hz), 7.41 (2H, d, 8.8Hz); δC (62.5 MHz) 27.9 (t), 29.1 (t), 34.6 (t), 55.2 (q), 55.3 (q), 64.5 (t), 109.2 (s), 113.8 (d), 114.2 (d), 121.3 (d), 127.3 (d), 127.9 (s), 129.3 (d), 134.3 (s), 157.8 (s), 160.5 (s), 170.8 (s).

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