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2-Methoxy-5-Alkoxy-2,5-Dihydrofurans: New Useful Polyfunctionalized C_4 Building Blocks.

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Abstract: The first one step synthesis of 2-methoxy-5-alkoxy-2,5-dihydrofurans (**2a-i**) is reported by reacting the commercially available 2,5-dimethoxy derivative (**1**) with alcohols. Unexpectedly the use of thiophenol and of *cis*-2,4-but-2-enediol leads to 2-furyl phenyl thioether (**4**) and *cis*-2-propenal-1,3-dioxep-5-ene (**5**), respectively.

The widespread occurence of substituted dihydro and tetrahydrofuran rings as substructures in an unusually large number of natural products[1], has promoted considerable interest in the development of synthetic routes to these compound classes.

The commercially available 2,5-dimethoxy-2,5-dihydrofuran **1**, represents a useful[2] polyfunctionalised C_4 synthon that seems to be an interesting starting point for building these skeletons. In a previous paper we studied the possibility of substituting only one of the two methoxy groups present in **1** with a sulphonic moiety, thus obtaining a more important target molecule.[3]

In this paper we report a general new methodology to gain non-symmetric 2-methoxy-5-alkoxy-2,5-dihydrofurans (**2**), which are useful intermediates for further synthetic transformations.

In a general procedure 0.01 mol of the alcohol **3a-i** was reacted with a twofold excess of starting material **1**, in CH_2Cl_2 (300 ml), in the presence of a catalytic amount of toluene p.sulfonic acid. The reaction was conducted in refluxing CH_2Cl_2 in a Dean Stark apparatus to distil the azeotropic CH_2Cl_2 / MeOH mixture.

After removing the solvents (150 ml), the residue was quenched by the addition of anhydrous K_2CO_3 and after the usual workup, the crude **2** (*cis/trans* mixture) was obtained (See Table 1).

High yields were obtained when a non hindered alcohol is employed.

Surprisingly, when phenols or carboxylic acids are used instead of the alcoholic substrate, no reaction takes place. On the contrary, 2-furyl phenyl thioether (**4**) is quantitatively recovered (Scheme 1) employing thiophenol as a nucleophile. The use of *cis*-1,4-but-2-ene diol (**1** / **3** molar rate = 2:1), gives *cis*-2-propenal-1,3-dioxep-5-ene (**4**) (Scheme 1) in 50% overall yield.

Compound **4** is a monoprotected *trans*-unsaturated dialdehyde and is a useful C_4 building block, which has so far only been obtained with difficulty.

Compound **5**, to the best of our knowledge, is not available in only one step. The operational simplicity and the possible further synthetic transformations of compounds **2a-i** are noteworthy.

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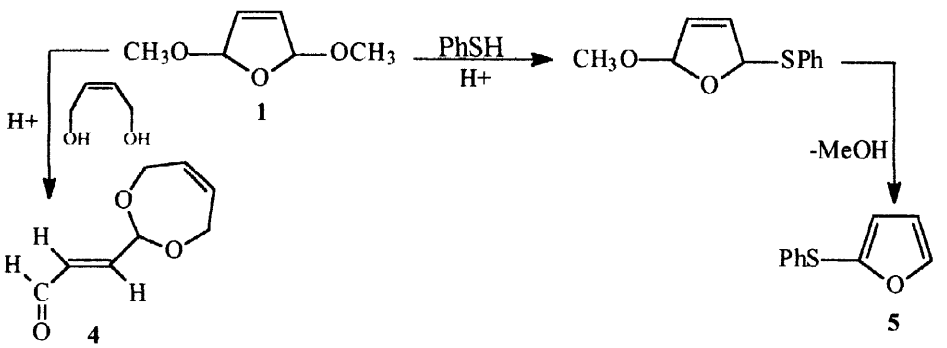
Table 1. Substitution of 1 with alcohols promoted by p.TsOH

Entry	Alcohol	(1) / (3)	MeO—(furan)—OR	Conversion [a,b]
1	$CH_3(CH_2)_7OH$ **3a**	2/1	$CH_3(CH_2)_7$ **2a**	100%
2	CH_3CH_2OH **3b**	2/1	CH_3CH_2 **2b**	100%
3	$CH_3CH{=}CHCH_2OH$ **3c**	2/1	$CH_3CH{=}CHCH_2$ **2c**	100%
4	$HC{\equiv}CCH_2CH_2OH$ **3d**	2/1	$HC{\equiv}CCH_2CH_2$ **2d**	100%
5	$ClCH_2CH_2OH$ **3e**	2/1	$ClCH_2CH_2$ **2e**	100%
6	$BrCH_2CH_2OH$ **3f**	2/1	$BrCH_2CH_2$ **2f**	100%
7	$ClCH_2CH_2CH_2OH$ **3g**	2/1	$ClCH_2CH_2CH_2$ **2g**	100%
8	$(CH_3)_3COH$ **3h**	2/1	$(CH_3)_3C$ **2h**	0%
9	$(CH_3)_2CHOH$ **3i**	2/1	$(CH_3)_2CH$ **2i**	20%

a) All compounds gave satisfactory ^1H, ^{13}C NMR, FT-IR and mass spectra; b) The excess of (1) employed can be easily recovered by distillation; the conversions are calculated on the distilled products and referred to the starting **3**.

Scheme1



Our efforts are currently devoted to employ these compounds in the synthesis of furofuranes and γ-lactons of biological interest.

References

1. a) Holzapfel C.W., Williams D.B.G., *Tetrahedron*, **1995**, 51, 8555-8564;
   b) Audin C., Lancelin J-M., Beau J-M., *Tetrahedron Lett.*, **1988**, 29, 3691-3694;
   c) Harrison T., Pattenden G., *Tetrahedron Lett.*, **1988**, 29, 3869-3872;
   d) Vader J., Koopmans R., De Groot A., *Tetrahedron*, **1988**, 44, 2663-2674;
   e) Ghosh A.K., Chen Y., *Tetrahedron Lett.*, **1995**, 36, 505-508;
   f) Perron F., Albizati K.F., *Chem.Rev.*, **1989**; 89, 1617-1661;
   g) Rao Y.S., *Chem.Rev.*, **1976**, 625-694;
   h) Rao Y.S., *Chem.Rev.*, **1964**, 353-388;
   i) Alvarez E., Coudenas M.L., Perez R., Ravelo J.L., Martin J.D., *Chem.Rev.*, **1995**, 95, 1950-1953.
2. a) Kaas N.C., Limborg F., Fakstorp J., *Acta Chem. Scand.*, **1948**, 2, 109-115;
   b) Kaas N.C., *Acta Chem. Scand.*, **1952**, 6, 569-571;
   c) Kaas N.C., Limborg F., Colens K., *Acta Chem. Scand.*, **1952**, 6, 531-534;
   d) Elming N., Kaas N.C., *Acta Chem. Scand.*, **1952**, 6, 535-544;
   e) D'annibale A., Scettri A., *Tetrahedron Lett.*, **1995**, 36, 4659-4660;
   f) Cecchini C., D'Onofrio F., Piancatelli G., *Tetrahedron Lett.*, **1983**, 34, 7957-7961;
   g) Cuny G.D., Buchwald S.L., *Organometallics*, **1991**, 10, 363-365;
   h) Baussanne I., Chiaroni A., Husson H.P., Royer C.R., *Tetrahedron Lett.*, **1994**, 35, 3931-3934;
   i) Fontaine H., Baussanne I., Royer J., *Synth. Commun.*, **1997**, 27, 2817-2824.
3. a) Malanga C., Aronica L. A., Lardicci L., *Synth. Commun.*, **1996**, 26, 2317-2327.