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HIGHLY EFFECTIVE STEREOSELECTIVE SYNTHESIS OF VINYL ETHERS OF 5-ALKYL-2-(2-FURYL)-5-HYDROXYMETHYL-1,3-DIOXANES

B. A. Trofimov[1], L. A. Oparina[1], O. V. Vysotskaya[1], A. V. Stepanov[1], and N. K. Gusarova[1]*

The vinylation of cis-5-alkyl-5-hydroxymethyl-2-(2-furyl)-1,3-dioxanes in the KOH–DMSO system in acetylene at atmospheric or elevated pressures (85-100°C, 3 h) takes place stereoselectively and leads to the formation of cis-5-alkyl-2-(2-furyl)-5-vinyloxymethyl-1,3-dioxanes with yields of up to 93%.

Keywords: acetylene, vinyl ethers, triols, furfural, cycloacetals.

1,3-Dioxanes continue to attract the attention of research workers as a fundamental class of heterocyclic compounds widely used for the production of medicinal products [1-3], chemical means for the protection of plants [4-6], special solvents, fuel additives [7-9], etc. In recent years special attention has been paid to functionalized 1,3-dioxanes synthesized from renewable raw material. In this respect it is necessary to mention the furan hydroxyl-containing 1,3-dioxacyclanes, which can be obtained readily by the reaction of furfural (the product from hydrolysis of pentosans stock) with polyhydric alcohols [10-14]. This class of compound includes, for example, the product Krasnodar-1 (5-ethyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxane) [5], which has growth-regulating and fungicidal activity. Selective modification of hydroxyl-containing furan dioxacyclanes can substantially raise their synthetic and practical potential. Promising in this direction is their reaction with acetylene, which opens up a convenient approach to the synthesis of new derivatives of furan 1,3-dioxanes containing highly reactive vinyl groups.

The aim of the present investigation was to develop a simple and technically feasible method for the vinylation of 5-alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes with acetylene.

In the literature methods have been discribed for the synthesis of the initial 5-alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes by the condensation of tris(hydroxymethyl)alkanes and furfural at room temperature or with heat (80-120°C) in the presence of acidic catalysts (*p*-toluenesulfonic acid, sulfuric acid, benzoic acid, cation-exchange resins, $BF_3 \cdot Et_2O$). Under these conditions 5-alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes are formed with yields of up to 74% in the form of a mixture of *cis* and *trans* isomers (in relation the position of the furyl and hydroxymethyl groups at positions 2 and 5 of the dioxane ring) [10-12, 14].

* To whom correspondence should be addressed, e-mail: gusarovairk@rambler.ru.

[1]A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk 664033, Russia.

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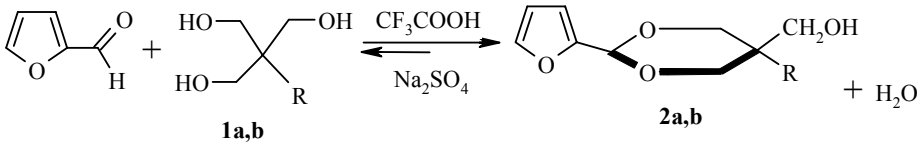
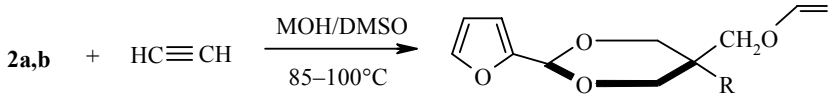
In the present work we improved the method, i.e., increased its effectiveness and stereoselectivity. This was achieved by reacting tris(hydroxymethyl)alkanes with furfural at room temperature (48 h, THF) in the presence of catalytic amounts (1 wt.%) of trifluoroacetic acid. In addition in order to shift the equilibrium of this reaction toward more complete conversion of the initial reagents (i.e., to suppress the reverse hydrolysis reaction) calcined Na_2SO_4 was added to combine with the released water. Under these conditions the condensation of 1,1,1-tris(hydroxymethyl)ethane (**1a**) and 1,1,1-tris(hydroxymethyl)propane (**1b**) with furfural leads to the stereoselective formation of the *cis* isomers of the corresponding 5-alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes **2a**,**b** with yields of up to 90%.



1a,b **2a,b**

1, 2 a R = Me, **b** R = Et

Experiments showed that the synthesized *cis* isomers of hydroxymethyl-1,3-dioxanes **2a**,**b** react with acetylene in the superbasic MOH (M = Na, K)–DMSO systems at atmospheric or elevated pressure at 85-100°C (3-11 h) to form the corresponding vinyl ethers **3a**,**b** with retention of the *cis* configuration of the initial alcohol (Table 1). This shows that reversible opening of the dioxane ring does not occur during vinylation.



3a,b

M = K, Na

TABLE 1. The Reaction of 5-Alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes with Acetylene*

Experiment	Alcohol **2**, 25 mmol	MOH, 50 mol%	Temperature, °C	Time, h	Conversion **2**, %	Vinyl ether **3**	Yield*[2], %
1	*cis*-**2a**	KOH	100	3	100	*cis*-**3a**	91
2	*cis*-**2b**	KOH	100	3	100	*cis*-**3b**	92
3	*cis*-**2a**	KOH	85-90	3	100	*cis*-**3a**	93
4	*cis*-**2b**	KOH	85-90	3	100	*cis*-**3b**	90
5	*cis*-**2a**	KOH	85	3	76	*cis*-**3a**	67
6	*cis*-**2b**	KOH	85	3	73	*cis*-**3b**	60
7	*cis*-**2b**	KOH	85	5	95	*cis*-**3b**	80
8	*cis*-**2b**	NaOH	85	11	15	*cis*-**3b**	9*[3]
9	*cis*-**2b**	NaOH	100	6	90	*cis*-**3b**	80

* Experiments 1, 2, and 5-9 were carried out at atmospheric pressure (acetylene delivery rate, ~1 l/min); experiments 3 and 4 were realized in an autoclave (initial acetylene pressure 14 atm); in all the experiments DMSO (25 ml) was used as solvent.

*[2] Preparative yield (calculated on the taken amount of the alcohol **2**).

*[3] The yield was calculated from data from the ^{1}H NMR spectrum.

Under the best conditions (the KOH–DMSO system, 100°C, 3 h, atmospheric pressure or the KOH–DMSO system, 85-90°C, 3 h, initial acetylene pressure 14 atm) the yield of compounds **3a**,**b** amounts to 90-93% with full conversion of the initial hydroxymethyl-1,3-dioxanes **2a**,**b** (Table 1, expts. 1-4).

The reaction was monitored by ^{13}C NMR. The formation of the vinyl ethers **3a**,**b** was observed from the increase of the signals for the β-carbon atom of the vinyloxy group (δ 86-87 ppm), and the conversion of the initial compounds was judged from the disappearance of the resonance signals of the carbon atoms attached to the hydroxyl groups (δ 60-65 ppm). One set of signals in the ^{1}H NMR spectra of the vinyl ethers **3a**,**b** indicates that these ethers are formed stereoselectively in the form of one (in this case *cis*) stereoisomer.

The synthesized vinyl ethers are colorless low-melting crystalline substances readily soluble in ether, alcohol, and acetone, less soluble in hydrocarbons, and insoluble in water. In the IR spectra of compounds **3a**,**b**, apart from the characteristic bands for the furan and dioxane rings, there absorption bands for the vinyloxy group at 1620-1640, 1320, 1200, and 830 cm^{-1} [15].

Thus, as a result of the investigation an effective and stereoselective method was developed for the synthesis of new functional 1,3-dioxanes containing furan heterocycles and vinyloxy groups capable of further modification [15-19].

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker DPX-400 instrument (400 and 100 MHz respectively) in $CDCl_3$; the δ values are given with reference to the residual signals of the deuterated solvent. The IR spectra were recorded in tablets with KBr on a Bruker JFS-25 spectrometer in the range of 400-4000 cm^{-1}. The melting points were determined on a Stuart SMP3 instrument (in a capillary).

Before use the furfural was purified by fractional distillation; all the other reagents and solvents were used without additional purification. 1,1,1-Tris(hydroxymethyl)ethane from Aldrich and 1,1,1-tris(hydroxymethyl)propane from BASF were used in the work.

Synthesis of 5-Alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes (2) (General Method). To a solution of furfural (4.8 g, 50 mmol) in THF (15 ml) we added the triol **1** (50 mmol), Na_2SO_4 (6.0 g), and CF_3COOH (0.10-0.12 g) (1 wt.% on the mixture of reagents). The suspension was stirred at room temperature for 48 h and filtered, and the THF was distilled from the filtrate at reduced pressure. The precipitate was washed with diethyl ether (~25-30 ml), and the ether extract was combined with the syrupy mass obtained after distillation of the THF. The precipitated unreacted triol **1** was filtered off, and the ether filtrate was concentrated on a rotary evaporator and then under vacuum until the final product crystallized spontaneously. The *cis* isomers of the dioxanes **2** were obtained by recrystallization from CCl_4. The spectral characteristics of the synthesized compounds **2a**,**b** were identical with the characteristics of the isomers described previously in [14, 20, 21]; their *cis* configuration was established in [22] by X-ray crystallographic analysis.

***cis*-2-(2-Furyl)-5-hydroxymethyl-5-methyl-1,3-dioxane (2a)**. The yield was 6.19 g (62%); mp 78°C (CCl_4) (mp 76-78°C [14], mp 67-68°C [20]).

***cis*-5-Ethyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxane (2b)**. The yield was 9.55 g (90%); mp 80-82°C (CCl_4) (mp 70°C [20, 21]).

Vinylation of 5-Alkyl-2-(2-furyl)-5-hydroxymethyl-1,3-dioxanes (General Method). A. In a 50-ml reaction flask fitted with an efficient reflux condenser, a thermometer, a magnetic stirrer, and a bubbler for the delivery of acetylene we placed DMSO (25 ml), alcohol **2** (25 mmol), and $KOH \cdot 0.5H_2O$ (0.82 g, 12.5 mmol). The mixture was heated to 100°C, and acetylene was passed into the flask at a rate of ~1 l/h until the signals of the initial compounds in the ^{13}C NMR spectrum of the reaction mixture had disappeared (3 h). At the end of the synthesis the reaction mixture was diluted with water (1:1) and extracted with diethyl ether (7×10 ml). The combined extracts were washed with water (2×10 ml) and dried with Na_2SO_4. After removal of the solvent the crude product was further purified by flash chromatography (basic Al_2O_3, hexane).

B. In an autoclave (V = 0.25 liter) with stirring we heated (85-90°C, 3 h) the alcohol (**2**) (25 mmol), $KOH \cdot 0.5H_2O$ (0.82 g, 12.5 mmol), and DMSO (25 ml) in the presence of acetylene (initial pressure 14 atm). The reaction mixture was treated similarly to method A.

***cis*-2-(2-Furyl)-5-methyl-5-vinyloxymethyl-1,3-dioxane (3a)**. The yield was 5.09 g (91%) (method A), 5.20 g (93%) (method B); white crystals, mp 50°C (hexane). IR spectrum, ν, cm^{-1}: 528 m, 559 m, 599 m, 632 m, 666 m, 740 s, 760 s, 803 m, 827 s, 845 m, 881 m, 916 s, 927 s, 947 s, 968 s, 1010 s, 1026 s, 1042 m, 1078 w, 1109 s, 1144 s, 1153 s, 1174 s, 1204 s, 1229 m, 1253 w, 1315 m, 1322 m, 1360 s, 1406 s, 1463 s, 1506 m, 1617 s, 1638 sh, 2793 w, 2836 m, 2869 m, 2920 m, 2937 m, 2965 m, 2980 m, 3050 w, 3126 m, 3148 w. ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.84 (3H, s, CH_3); 3.63 (2H, d, ^2J = 11.7, H-4*a*,6*a*); 3.92 (2H, s, OCH_2); 4.00 (1H, dd, ^3J = 6.8, ^2J = 1.8, =CH-*cis*); 4.07 (2H, d, ^2J = 11.7, H-4*e*,6*e*); 4.26 (1H, dd, ^3J = 14.3, ^2J = 1.8, =CH-*trans);* 5.52 (H, s, H-2); 6.37 (H, dd, ^3J = 2.9, ^3J = 1.6, H-4 of furan); 6.46 (1H, d, ^3J = 2.9, H-3 of furan); 6.53 (1H, dd, ^3J = 14.3, ^3J = 6.8, =CHO); 7.41 (1H, br. s, H-5 of furan). ^{13}C NMR spectrum, δ, ppm: 152.25 (OCH=); 150.81 (C-2 of furan); 142.61 (C-5 of furan); 110.28 (C-4 of furan); 107.55 (C-3 of furan); 96.40 (C-2, $^1J_{C,H}$ = 161.1); 86.66 (CH_2=); 73.31 (C-4,6); 70.20 (OCH_2); 34.36 (C-5); 17.35 (CH_3). Found, %: C 64.42; H 7.18. $C_{12}H_{16}O_4$. Calculated, %: C 64.27; H 7.19.

***cis*-5-Ethyl-2-(2-furyl)-5-vinyloxymethyl-1,3-dioxane (3b)**. The yield was 5.47 g (92%) (method A), 5.35 g (90%) (method B); white crystals, mp 41°C (hexane). IR spectrum, ν, cm^{-1}: 521 m, 590 m, 627 m, 661 m, 753 s, 776 m, 801 m, 815 s, 832 s, 849 m, 882 m, 894 m, 926 s, 940 s, 958 sh, 971 s, 994 m, 1013 s, 1030 s, 1059 s, 1103 s, 1148 s, 1157 s, 1200 s, 1217 sh, 1252 m, 1278 w, 1323 m, 1360 m, 1372 m, 1380 m, 1412 s, 1452 sh, 1470 s, 1506 m, 1601 sh, 1621 s, 2807 w, 2862 m, 2887 m, 2933 m, 2965 m, 2981 m, 3042 w, 3093 m, 3120 w. ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.84 (3H, t, ^3J = 7.6, CH_3); 1.29 (2H, q, ^3J = 7.6, CH_2); 3.63 (2H, d, ^2J = 11.7, H-4*a*,6*a*); 3.99 (2H, s, OCH_2); 4.01 (1H, dd, ^3J = 6.7, ^2J = 1.6, =CH-*cis*); 4.11 (2H, d, ^2J = 11.7, H-4*e*,6*e*); 4.27 (1H, dd, ^3J = 14.3, ^2J = 1.6, =CH-*trans*); 5.50 (1H, s, H-2); 6.37 (1H, dd, ^3J = 2.9, ^3J = 1.6, H-4 of furan; 6.45 (1H, d, ^3J = 2.9, H-3 of furan); 6.52 (1H, dd, ^3J = 14.3, ^3J = 6.7, =CHO); 7.40 (1H, br. s, H-5 of furan). ^{13}C NMR spectrum, δ, ppm: 152.14 (OCH=); 150.84 (C-2 of furan); 142.59 (C-5 of furan); 110.26 (C-4 of furan); 107.54 (C-3 of furan); 96.49 (C-2); 86.55 (CH_2=); 72.53 (C-4,6); 66.85 (OCH_2); 36.42 (C-5); 24.03 (CH_2); 6.80 (CH_3). Found, %: C 65.63; H 7.54. $C_{13}H_{18}O_4$. Calculated, %: C 65.53; H 7.61.

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