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SYNTHESIS AND PROPERTIES OF 5-PHENYLETHYNYLFURAN-2-ALDEHDYE

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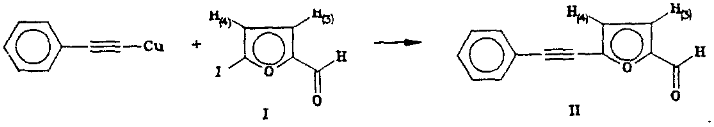
UDC 547.724'538.07

Phenylethynylation of 5-halofurfurals gives 5-phenylethynylfuran-2-aldehyde which can be converted into the corresponding acid and several of its derivatives with retention of the triple bond.

5-Phenylethynylfuran-2-aldehdye was prepared in 1966 [1, 2] in 64% yield by the reaction of 5-iodofurfural with copper phenylacetylide in boiling pyridine (4 h); there is however only one publication relating to its derivatives [3].

The object of the present work was to select conditions which would provide an increased yield of the aldehyde II and to study its reactions involving the aldehyde group and the triple bond.



I

II

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TABLE 1. Characteristics of Compounds Prepared

Compound	Empirical formula	M+	mp, °C	IR spectrum cm^{-1}	UV spectrum, λ_{max} nm (lg ε)*
II	$C_{13}H_8O_2$	196	91,5...92,5	1678, 2216	318 (4,43); 339 (4,39)
VI	$C_{13}H_9O_2N$	211	187...188	1653, 2228, 3217, 3442	206 (3,50); 224 (3,41); 296 (3,68); 305 (3,74); 310 (3,71); 325 (3,65)
VII	$C_{13}H_{10}O_2N_2$	226	163...164	1620, 2220, 3260, 3440	—
VIII	$C_{13}H_9O_2$	—	99...100	—	318 (4,64); 3,35 (4,52)
IX	$C_{19}H_{14}O_5$	—	159,5...160,5	1760, 1800, 2230	407
X	$C_{19}H_{16}O_5$	—	118...119	1760, 1800, 2230	316, 310, 296, 270, 268

TABLE 1. Continued

PMR spectrum δ, ppm (J, Hz)	Yield, %
6,62 (1H, d, 4-H); 7,17 (1H, d, 3-H); (3,7); 9,56 (2H, s, CHO); 7,25...7,62 (5H, m, C_6H_5)	85
6,62 (1H, d, 4-H); 7,17 (1H, d, 3-H); (3,7); 7,25...7,62 (5H, m, C_6H_5)	98
6,69 (1H, d, 4-H); 7,16 (1H, d, 3-H); (3,45); 7,83 (1H, s, NH); 3,97 (2H, c, NH_2); 7,28...7,57 (5H, m, C_6H_5)	98
6,66 (1H, d, 4-H); 7,21 (1H, d, 3-H); (3,7); 7,95 (1H, s, CH); 2,73 (1H, s, OH); 7,20...7,58 (5H, m, C_6H_5)	83
1,67 (6H, s, CH_3); 6,80 (1H, d, 4-H); 8,42 (1H, d, 3-H); (4,25); 8,22 (1H, s 1-H; $J_{13}=0,8$; $J_{14}=0,4$); 7,20...7,60 (5H, m, C_6H_5)	95
1,62 (3H, s, $CH_{3(a)}$); 1,70 (3H, s, $CH_{3(e)}$); 3,41 (2-H) and 3,88 (5-H) (AB system, $J_{15}=5$); 6,13 (1H, d, 4-H); 6,48 (1H, d, 3-H; $J_{34}=3,5$); 7,28 (5H, s, C_6H_5)	98

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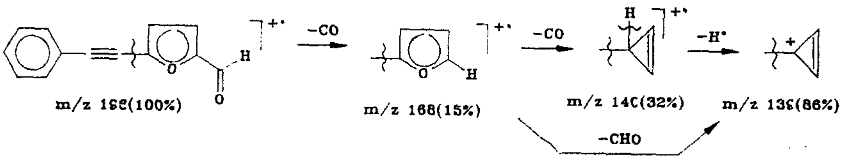
*For compounds II, VIII-X the solvent was heptane, for VI, ethanol

On repeating the synthesis of [1, 2] we established, using TLC, that at the end of the reaction the reaction mixture still contained some unreacted aldehyde I together with a small quanity of 1,4-diphenylbutadiene and an unidentified mixture of polymers.

With the object of improving the preparative conditions and increasing the yield of the product II, we carried out the reaction of the aldehyde I with copper phenylacetylide in a 1:1 mixture of pyridine and triethylamine at 85°C. Under these conditions the copper phenylacetylide had dissolved completely in 10-15 min whereas by the known method [1, 2] this required 3 to 3.5 h. The reaction was carried out in a current of nitrogen and was complete in 2 h. It is possible that the increase in the reaction rate and the increased yield of product on introducing triethylamine results from the polymeric copper phenylacetylide dissolving more readily under the action of the triethylamine salt of 5-iodofurfural [4]. An increase in the solubility of copper acetylides in triethyalmine-benzene mixtures on adding tetrabutylammonium bromide was noted in [5].

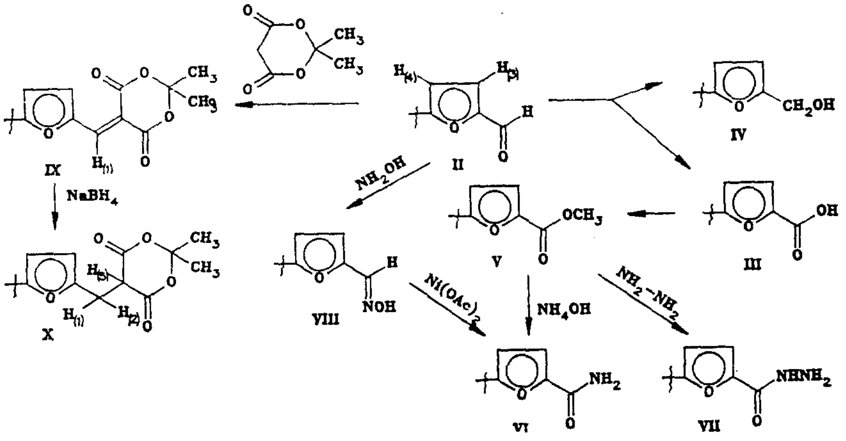
On treating the reaction mixture with sodium thiosulfate the initial 5-iodofurfural and possible secondary halogen compounds present as impurities are converted into the corresponding disulfides. Following such treatment and purification, the pure aldehyde II is obtained with mp 91.5-92.5°C, a value which differs considerably from that given in the literature – 79.5-81°C [1, 2]. In the electronic spectrum of the reaction product II in standard heptane there are two absorption bands in the region of 318 and 339 nm; from [1, 2] there is a single band at 324 nm. In the IR spectrum, absorption bands are present for the carbonyl group in the 1678 cm^{-1} region and for the triple bond at 2216 cm^{-1}. The PMR spectrum contains two doublets of protons of the furan ring at 6.62 (4-H) and 7.17 ppm (3-H) with J = 3.7 Hz, a singlet of the aldehyde proton at 9.56 ppm, and a multiplet of the phenyl ring protons in the region of 7.25-7.62 ppm.

In the mass spectrum of the aldehyde II there is an intense peak (100%) pertaining to the molecular ion with m/e 196. The main direction of the fragmentation of 5-phenylethynylfuran-2-aldehyde under electron bombardment (70 ev) can be depicted as follows:



In the method which we propose [6], copper phenylacetylide will also react with 5-bromofurfural although the reaction proceeds with more difficulty than when using 5-iodofurfural and the yield of the aldehyde II does not exceed 30%.

The next stage of our work was the conversion of the aldehyde II in reactions involving the aldehyde group and the triple bond. Oxidation was carried out using various oxidants ($KMnO_4$, $CrO_3 + H_2SO_4$, H_2O_2) in different media but in all cases the product was a mixture which it was difficult to separate. It is possible that reaction occurs simultaneously at the aldehyde group and at the triple bond and also at the furan ring. The aldehyde II readily enters into a dismutation reaction giving the acid III and 5-phenylethynylfurfuryl alcohol IV. The methyl ester V of the acid III was prepared by the usual methods and converted into the amide VI and the hydrazide VII of the acid III. The amide VI was also prepared by a Beckmann rearrangement of the oxime VIII.



In the reaction of the aldehyde II with Meldrum's acid under the conditions of the Knoevenagel reaction [7], compound IX is formed. By the reaction of compound IX with sodium borohydride in alcohol, compound X is obtained as a result of the reduction of the exocyclic double bond. We did not succeed in preparing acetals of 5-phenylethynylfuran-2-aldehyde although a large number of experiments were carried out using both mono- and difunctional alcohols. These reactions resulted in varying degrees of tar formation.

Experiments — hydration, and homogeneous and heterogeneous hydrogenation at room temperature — aimed at reactions at the double bond were also unsuccessful. Studies of the properties of 5-phenylethynylfuran-2-aldehyde and its derivatives indicated that reactions involving basic reagents proceed smoothly without complications; on the other hand, acidic reagents give rise to tar formation. The characteristics of the compounds prepared are set out in Table 1.

Biological tests on the prepared compounds showed a weak antistaphylococcal effect on the part of the compound IX and a weak membrane-stabilizing effect for the hydrazide VII.

EXPERIMENTAL

Infrared spectra were run on a Bruker spectrometer as KBr disks and the electronic spectra on a Specord UV-VIS in standard heptane and ethanol. PMR spectra were recorded on Tesla BS-467 (60 MHz) and Varian-80F instruments in $CDCl_3$ with HMDS as internal standard. Mass spectra were obtained on an LKB-2090 spectrometer with 20 and 70 eV ionization energy. Monitoring of the progress of the reactions, and of the purity of the individual substances, were effected by TLC on Silufol plates in 1:1 benzene-chloroform. The results of the elementary analyses for C, H, and N corresponded to those calculated.

5-Phenylethynylfuran-2-aldehyde (II). 5-Iodofurfural (22.2 g, 0.10 mole) and copper phenylacetylide (18.1 g, 0.11 mole) were heated in a current of nitrogen in a mixture of 50 ml pyridine and 50 ml triethylamine for 2 h in a boiling water bath. The solution was diluted with 500 ml ice water and filtered. The residue was washed with 100 ml water and dried and then heated at bp for 1 h in 150 ml 50% ethanol with the addition of 5 g sodium thiosulfate. This was cooled, diluted with 300 ml water, filtered, and the residue dried. 5-Phenylethynylfuran-2-aldehyde was isolated by two methods: A. Chromatography on a column of silica gel, elution with 1:1 benzene-chloroform, detection of the aldehyde II (light-blue luminescence) by means of an LPK-1 luminoscope; B. Distillation of the aldehyde out of the residue with superheated steam and subsequent recrystallization from petroleum ether. Methods A and B yielded 16.7 g (85%) aldehyde II with mp 91.5-92.5°C. The crystals of the aldehyde II were of a light yellow color; material purified by method B was more stable on storage than that from method A.

Amide of 5-Phenylethynylfuran-2-carboxylic Acid (VI). Ester V (11.3 g, 0.05 mole) was heated at bp with 100 ml 30% aqueous ammonia and 20 ml ethanol until the liquid on the bottom of the flask had disappeared. The crystals which deposited were filtered off and recrystallized from aqueous alcohol.

The oxime VIII of aldehyde II was prepared by the usual method.

Beckman Rearrangement of Oxime VIII. A mixture of 2.11 g (0.01 mole) oxime VIII, 0.2 g nickel acetate tetrahydrate and two drops piperidine in 50 ml xylene was heated 1 h at bp. It was then cooled and the product precipitated by adding 100 ml petroleum ether and the precipitate filtered off and recrystallized from aqueous alcohol. The yield of amide VI amounted to 1.95 g (92%).

Hydrazide of 5-Phenylethynylfuran-2-carboxylic Acid (VII). A suspension of 11.3 g (0.05 mole) ester V in 50 ml hydrazine hydrate was heated at bp until the liquid on the bottom of the flask had disappeared. The crystals were filtered off and reprecipitated from DMF with water.

2,2-Dimethyl-5-(5-phenylethynyl-2-furfurylidene)-1,3-dioxane-4,6-dione (IX). To a solution of 9.8 g (0.05 mole) aldehyde II and 9 g (0.05 mole) Meldrum's acid in 150 ml ethanol was added three drops triethylamine. After several minutes, golden yellow crystals appeared in the transparent solution. After 1 h they were filtered off, washed with water and recrystallized from aqueous alcohol.

2,2-Dimethyl-5-(6-phenylethynyl-2-furfuryl)-1,3-dioxane-4,6-dione (X). Compound IX (1.61 g, 5 mmole) was dissolved at bp in 60 ml ethanol and finely powdered $NaBH_4$ added in small portions to the solution until the yellow color had disappeared. It was then cooled, 20 g crushed ice and 20 ml cold water added and acidified with dilute (1:1) hydrochloric acid to pH ≈ 6. The colorless deposit which formed was filtered off, washed with 10 ml water, and dried. It was recrystallized from ethanol.

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