HYDROXYMETHYLATION OF METHYL-SUBSTITUTED PYRROLE, THIOPHENE, AND FURAN IN THE PRESENCE OF H^+ CATION EXCHANGERS

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UDC 547.72:541.128.13

In the reaction of formalin with the 2,5-dimethyl derivatives of pyrrole, thiophene, and furan in the presence of the sulfo cation exchanger Amberlyst 15 electrophilic substitution takes place at various positions of the rings with the formation of 2,5-dimethyl-1-hydroxymethylpyrrole, 1,3-dioxacycloheptano[5,6-c]-2,5-dimethylthiophene (an intermediate in the formation of which is 2,5-dimethyl-3,4-dihydroxymethylthiophene), and 2,5-hexanedione respectively. Bis(5-methyl-2-thienyl)methane was obtained from 2-methylthiophene.

Recently [1-4] it was shown that the use of H^+ cation exchangers in electrophilic aromatic substitution of furan, thiophene, and pyrrole makes it possible to prevent resinification of these acidophobic heterocycles and to obtain a series of their difficultly obtainable derivatives with high preparative yields. In particular, furfuryl alcohol was obtained by the reaction of formaldehyde with furan in the presence of the strongly acidic sulfo cation exchanger Amberlyst 15, while the valuable synthon 5-methyl-2-hydroxymethylfuran was obtained from sylvane with the weakly acidic carboxylic cation exchanger Amberlite IRC-50 as catalyst. In order to investigate further the possibilities of using H^+ cation exchangers in the transformations of heterocyclic compounds and to determine the direction of reaction with electrophiles we studied the reaction of the 2,5-dimethyl derivatives of pyrrole, thiophene, and furan (I-III) and also 2-methylthiophene (IV) with formalin (a 35% aqueous solution of formaldehyde) in the presence of H^+ cation-exchange resins (Amberlyst 15 and Amberlite IRC-50). The reactions were conducted at room temperature with the substrate, CH_2O, and H^+ in ratios of 1:(0.5-10):(0.1-1). The dependence of the conversion and yield of the products on the time was determined by taking samples with a microsyringe during the reaction and analyzing them by GLC and chromato-mass spectrometry.

It is known that the acid-catalyzed processes in the reaction of unsubstituted furan, thiophene, and pyrrole with formalin take place through electrophilic aromatic substitution at position 2 of all these heterocycles [5-8]. In contrast to this the investigations conducted in the present work showed that the 2,5-dimethyl derivatives of the heterocycles (I-III) in reaction with formalin in the presence of Amberlyst 15 as catalyst react at various positions of the rings. Thus, with dimethylpyrrole (I) hydroxymethylation mostly takes place at the nitrogen atom of the ring with the formation of the corresponding alcohol, i.e., 2,5-dimethyl-1-hydroxymethylpyrrole (V). The reaction with dimethylthiophene (II) takes place at positions 3,4 of the ring with the formation of 1,3-dioxacycloheptano[5,6-c]-2,5-dimethylthiophene (VI) as the main product. The dimethylfuran (III) undergoes acid hydrolysis at the α-carbon atom of the ring with the formation of 2,5-hexanedione (VII). During the hydroxymethylation of 2-methylthiophene bis(5-methyl-2-thienyl)methane (VIII) was obtained with a high yield.

The weakly acidic cation exchanger Amberlite IRC-50 does not catalyze these reactions under the investigated conditions.

In the presence of the strongly acidic cation exchanger Amberlyst 15 reaction (1) with the pyrrole (I) as the most reactive among the investigated compounds takes place quickly, and after 10-15 min the degree of transformation amounts to

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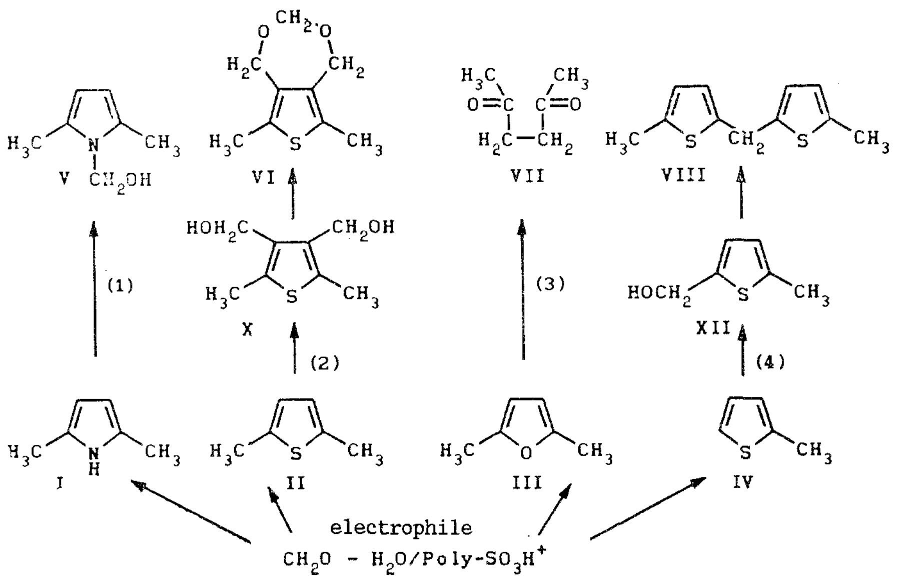
Institute of Organic Synthesis, Latvian Academy of Sciences, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1640-1643, December, 1991. Original article submitted April 19, 1991.

0009-3122/91/2712-1316$12.50 ©1992 Plenum Publishing Corporation

70-75%, while the yield of the alcohol (V) is approximately 60% (GLC), and polymerization of the reaction product (V) is then observed. In order to prevent the last process it is necessary at the end of the increase in the yield of compound (V) (GLC) to filter off the catalyst quickly, and the reaction then stops.



In the hydroxymethylation of compound (II), in addition to the main compound (VI) the following thiophene mono- and dialcohols were detected in the reaction products by chromato-mass spectrometry: 2,5-Dimethyl-3-hydroxymethylthiophene (IX). Mass spectrum, m/z (I_{rel}, %):* 142 (M^+, 100), 127 (22), 125 (48), 124 (70), 113 (20), 111 (22), 99 (21), 79 (10), 59 (13). 2,5-Dimethyl-3,4-dihydroxymethylthiophene (X). Mass spectrum, m/z (I_{rel}, %): 172 (M^+, 83), 154 (100), 139 (10), 124 (41), 111 (18), 77 (12), 59 (20). The intermolecular dehydration product bis(2,5-dimethyl-3-thienyl)methane (XI) was also detected. Mass spectrum, m/z (I_{rel}, %): 236 (M^+, 49), 221 (22), 161 (10), 124 (100), 59 (10). The previously unknown dialcohol (X) was isolated by preparative HPLC and identified by means of its PMR spectrum.

Hydroxymethylation was not observed in the reaction of formalin with dimethylfuran (III), but acid hydrolysis occurred [reaction (3)]. A test showed that the substrate (III) is hydrolyzed by water in the presence of the Amberlyst 15 resin with an almost quantitative yield of compound (VII).

During the hydroxymethylation of 2-methylthiophene, in addition to the main reaction product (VIII), a small amount of 5-methyl-2-hydroxymethylthiophene (XII) was also detected in the reaction mixture by chromato-mass spectrometry. Mass spectrum, m/z (I_{rel}, %): 128 (M^+, 100), 127 (31), 111 (65), 109 (43), 99 (47), 97 (20), 95 (28), 85 (21), 77 (10), 65 (20), 59 (32), 53 (33), 45 (38), 39 (30), 27 (15). This compound is an intermediate in the formation of the methane derivative (VIII). Attempts to increase the yield of the alcohol (XII) by varying the proportions of the reagents within the limits indicated above did not lead to positive results. The main reaction product under all the investigated conditions was the bisthienyl derivative (VIII). Compounds (V, VI, X) were obtained, isolated, and identified for the first time.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90/DS instrument in deuterochloroform with TMS as internal standard. The mass spectra were recorded on a Kratos MS-25 chromato-mass spectrometer at 70 eV. Gas-liquid chromatography was conducted on a Chrom 4 chromatograph with a flame-ionization detector (1.2 × 3 mm glass column, 10% of E-301 and 2.5% of Reoplex 400 on Chromosorb W/AW, grain size 60-80 mesh, helium, 60 ml/min). The column temperature was varied in the range of 100-200°C, depending on the composition of the reaction mixtures. The dialcohol (X) was isolated preparatively by HPLC on a Du Pont 880 Prep liquid chromatograph (Silasorb C18, 4.6 × 200 mm, 33% acetonitrile, 67% water, 2 mm/min, UV detector, $\lambda = 230$ nm). The retention time of the dialcohol (X) was 1.7 min.†

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*In the mass spectra the m/z values for peaks with $I_{rel} \geq 10\%$ are indicated.

†The analytical procedure was worked up by O. V. Sakhartova.

Cation exchangers Amberlyst 15 and Amberlite IRC-50 and the Fluka methyl derivatives of the heterocycles (I-IV) were used. The formalin was of analytical grade and the acetonitrile was of OP-3 special purity grade.

The elemental analysis for C, H, and N corresponded to the calculated compositions.

Hydroxymethylation of the Heterocyclic Compounds (General Procedure). A mixture of one of the compounds (I-IV), formalin, and the cation exchanger in specific ratios was stirred vigorously on a magnetic stirrer at ~20°C, while samples were taken periodically with a microsyringe and analyzed by GLC and chromato-mass spectrometry. At the end of the reaction the catalyst was filtered off, the filtrate was evaporated, and the product was submitted to fractional distillation under vacuum.

2,5-Dimethyl-1-hydroxymethylpyrrole (V) ($C_7H_{11}NO$). A mixture of 1 ml of compound (I), 1 ml of formalin, and 0.2 g of Amberlyst 15 resin was stirred for 15 min. The degree of conversion of the initial compound (I) amounted to 70%, while the yield of the main reaction product (V) was 60% (GLC). The reaction mixture was filtered, and the filtrate was evaporated under vacuum at 30°C and 14 mm Hg. The residue of the unreacted pyrrole (I) was distilled under vacuum at 50°C and 1 mm Hg. The alcohol (V) sublimed in the form of colorless transparent crystals; mp 85°C. Mass spectrum: 125 (M^+, 44), 108 (34), 95 (34), 94 (100), 93 (13), 80 (16), 67 (10), 53 (13), 42 (19), 29 (12). PMR spectrum: 2.19 (6H, s, CH_3); 2.35 (1H, bs, OH), 5.17 (2H, d, CH_2); 5.73 ppm (2H, s, H-3, H-4).

1,3-Dioxacycloheptano[5,6-c]-2,5-dimethylthiophene (VI) ($C_9H_{12}O_2S$) and 2,5-Dimethyl-3,4-di-hydroxymethylthiophene (X) ($C_8H_{12}O_2S$). A mixture of 1 ml of compound (II), 10 ml of formalin, and 1 g of Amberlyst 15 was stirred for 48 h until the initial thiophene (II) had been completely transformed. Here the yield of compound (VI) amounted to ~70% (GLC). The catalyst was filtered off, and the filtrate was evaporated under vacuum. Compound (VI) was obtained from the residue in the form of white crystals by vacuum sublimation at 100°C and 4 mm Hg; mp 128°C. Mass spectrum: 184 (M^+, 85), 153 (50), 138 (51), 125 (100), 111 (28), 91 (11), 59 (17). PMR spectrum: 2.28 (6H, s, CH_3); 4.64 (4H, s, CH_2); 5.08 ppm (2H, s, CH_2). The dialcohol (X) was isolated from the reaction mixture by preparative HPLC. PMR spectrum: 2.34 (6H, s, CH_3); 3.69 (2H, bs, OH), 4.50 ppm (4H, m, CH_2).

2,5-Hexanedione (VII). A mixture of 1 ml of compound (III), 3 ml of water, and 0.25 g of Amberlyst 15 was stirred for 72 h. The catalyst was filtered off, the filtrate was extracted with ether, and the extract was dried with magnesium sulfate. By fractional vacuum distillation we obtained 1.0 g of compound (VII). The yield was 93%; bp 80°C (15 mm Hg). Published data [9]: bp 78-79°C (15 mm Hg). The mass and PMR spectra of the obtained compound (VII) agreed with the spectra of an authentic sample.

Bis(5-methyl-2-thienyl)methane (VIII). A mixture of 1 ml of 2-methylthiophene (IV), 10 ml of formalin, and 1 g of Amberlyst 15 resin was stirred for 12 h until the initial compound (IV) had been completely transformed. The main reaction product was the methane derivative (VIII). The yield according to GLC was ~80%. The catalyst was filtered off, and the filtrate was evaporated under vacuum. Compound (VIII) was distilled from the residue under vacuum at 120-123°C (1 mm Hg) in the form of a light-yellow viscous liquid. Published data [5]: bp 116-117°C (0.8 mm Hg). Mass spectrum: 208 (M^+, 72), 207 (34), 193 (100), 111 (18), 97 (10), 59 (13), 45 (10). PMR spectrum: 2.38 (6H, s, CH_3); 4.13 (2H, s, CH_2), 6.55 ppm (4H, m, ring protons).

LITERATURE CITED

1. É. Ya. Lukevits, L. M. Ignatovich, Yu. Sh. Gol'dberg, and M. V. Shimanskaya, Khim. Geterotsikl. Soedin., No. 6, 853 (1986).
2. I. G. Iovel, Yu. Sh. Gol'dberg, M. V. Shimanskaya (Shymanska), and E. Lukevits (Lukevics), Synth. Commun., **18**, 1261 (1988).
3. I. G. Iovel, Yu. Sh. Gol'dberg, and M. V. Shimanskaya (Shymanska), J. Mol. Catal., **57**, 91 (1989).
4. I. G. Iovel', Yu. Sh. Gol'dberg, and M. V. Shimanskaya, Khim. Geterotsikl. Soedin., No. 6, 746 (1989).
5. T. L. Cairns, B. C. McKusick, and V. Weinmayr, J. Am. Chem. Soc., **73**, 1270 (1951).
6. W. H. Brown and H. Sawatzky, Can. J. Chem., **34**, 1147 (1966).
7. J. F. Walker, Formaldehyde, Third edition, Pergamon, New York (1964).
8. J. G. Berger and K. Schoen, J. Heterocyclic Chem., **9**, 419 (1972).
9. Syntheses of Organic Products [Russian translation], Vol. 2, IL, Moscow (1949).