Chemistry of Heterocyclic Compounds, Vol. 34, No. 10, 1998

HYDROGENATION OF DERIVATIVES OF 2-OXO-4-(2-THIENYL)BUTENOIC ACID AT PALLADIUM AND NICKEL CATALYSTS

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The hydrogenation of sodium and ethyl 2-oxo-4-(2-thienyl)butenoate at Raney nickel and palladium black was investigated. With Raney nickel the reaction products were the corresponding derivatives of 2-oxo-4-(2-thienyl)butyric acid and 2-hydroxy-4-(2-thienyl)butyric acid and the products from bimolecular condensation. If palladium black is used, the reaction can be directed toward the selective formation of the corresponding derivative of 2-oxo-4-(2-thienyl)butyric acid. The hydrogenation of the salts is more selective than that of the esters. During the hydrogenation of ethyl 2-oxo-4-(2-thienyl)butenoate at palladium black in solution in anhydrous ethanol the ethyl esters of 2-oxo-4-(2-thienyl)butyric and 2-oxo-4-(2-tetrahydrothienyl)butyric acids and the corresponding ketals are formed. The mechanism of the hydrogenation of 4-substituted 2-oxobutenoic acids is discussed.

The derivatives of 4-substituted 2-oxobutyric acids are important synthons for the production of antihypertensive products [1], homoamino acids, hydroxamic acids, and other compounds [2]. In order to obtain these synthons we investigated the hydrogenation of derivatives of the 2-oxo-4-phenylbutenoic acid series at nickel and palladium catalysts [2-4]. During the hydrogenation of sodium 2-oxo-4-phenylbutenoate at nickel catalysts the corresponding salt of 2-hydroxy-4-phenylbutyric acid is obtained with yields of up to 94% [3]. At palladium catalysts a mixture of the salts of 2-hydroxy-4-phenylbutyric and 2-oxo-4-phenylbutyric acids is formed [4, 5]. Under strictly defined conditions the process can be directed toward the selective formation of sodium 2-oxo-4-phenylbutyrate. The 2-oxo-4-phenylbutenoic esters are hydrogenated at a higher rate but less selectively with respect to the formation of the corresponding saturated oxo compound than the corresponding sodium salt.

During the hydrogenation of sodium 2-oxo-4-phenyl-(2-furyl)butenoate at Raney nickel catalyst the corresponding salts of 2-oxo-4-(2-furyl)butyric and 2-hydroxy-4-(2-furyl)butyric acids and aliphatic compounds from the hydrogenolysis of the initial compound are formed [5]. Sodium 2-hydroxy-4-(tetrahydrofuryl)butyrate and a condensation product [a derivative of 3-(2-furylmethyl)-4-(2-furyl)-2-oxo-3,4-didehydroglutaric acid] were also detected in the products.

Comparison of the hydrogenation of the derivatives of 4-substituted furyl- and phenylbutenoic acids at Raney nickel catalysts indicates that the formation of sodium 2-oxo-4-(2-furyl)butyrate (yield 66%) is highly selective compared with the hydrogenation of the corresponding phenyl derivative, with which sodium 2-hydroxy-4-phenylbutyrate is mainly formed. The increased selectivity for the formation of the salt of the α-keto acids of the furan series is probably due to complexation between the compound and the nickel.

In the present communication we present data on the hydrogenation of sodium and ethyl 2-oxo-4-(2-thienyl)butenoate at Raney nickel and palladium black. There is no information in the literature on the hydrogenation of these compounds. The hydrogenation was carried out at 17-80°C with the compound at an initial concentration of 0.18-0.21 M in water–alcohol solution and a compound–Raney nickel (wet) ratio 1:1 and a compound—palladium black (wet) ratio 1:0.86 (Table 1). The hydrogenation products contained sodium 2-oxo-4-(2-thienyl)butyrate and 2-hydroxy-4-(2-thienyl)butyrate and condensation products. In the esterification products by chromato-mass spectrometry, apart from the ethyl esters of the above-mentioned acids, we found ethyl 3-(2-thienylmethyl)-4-(2-thienylethyl)-2-oxo-3,4-didehydroglutarate and the ketals of the corresponding

Latvian Institute of Organic Synthesis, Riga, Latvia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1329-1334, October, 1998. Original article submitted April 8, 1998.

0009-3122/98/3410-1127$20.00

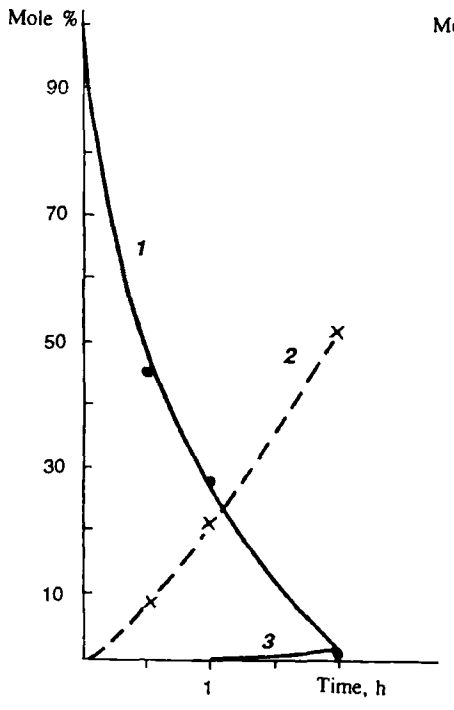


Fig. 1

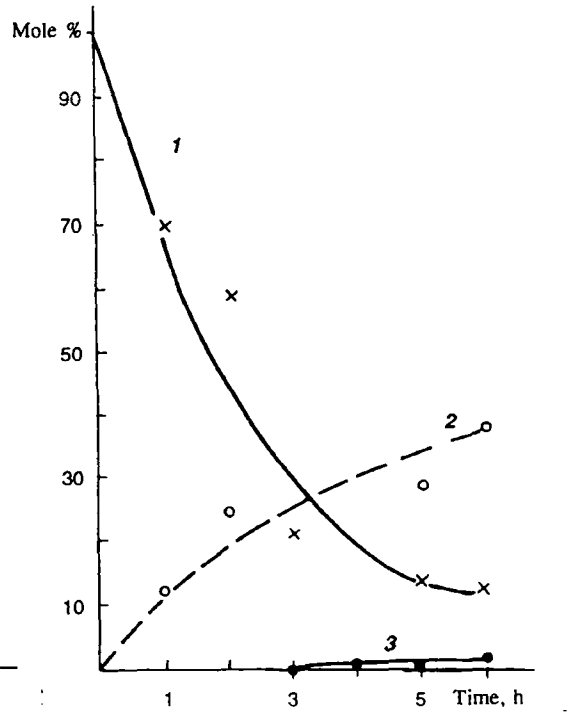
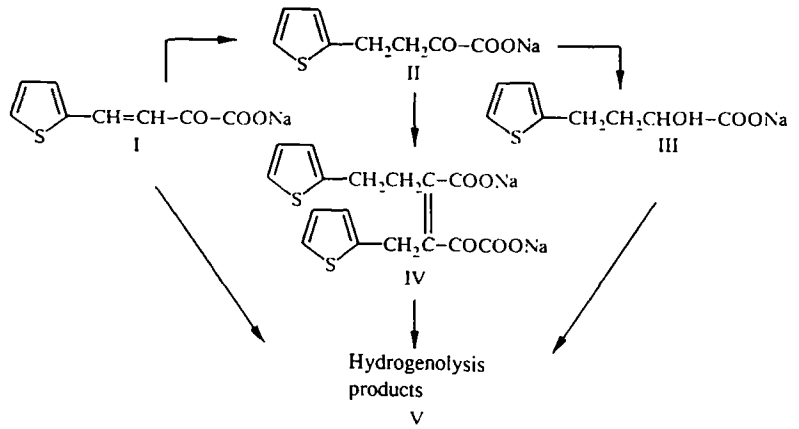


Fig. 2

Fig. 1. Dependence of the conversion of the initial compound and the accumulation of the hydrogenation products on the reaction time at Raney nickel (60-66°C, initial compound—catalyst ratio 1:1, initial concentration of raw material 0.204 M): 1) Unreacted initial compound; 2) sodium 2-oxo-4-(2-thienyl)butyrate; 3) sodium salt.

Fig. 2. Dependence of the conversion of the initial compound and the accumulation of the hydrogenation products on the reaction time for hydrogenation at palladium black (17°C, initial compound—catalyst ratio 1:0.86, initial concentration of raw material 0.205 M): 1) Unreacted initial compound; 2) sodium 2-oxo-4-(2-thienyl)butyrate; 3) sodium 2-hydroxy-4-(2-thienyl)butyrate.

butyric acids, which were formed under the conditions of esterification by ethanol in the presence of thionyl chloride. During the hydrogenation of sodium 2-oxo-4-(2-thienyl)butenoate the process takes place mainly according to the scheme:



The first stage of the hydrogenation of sodium 2-oxo-4-(2-thienyl)butenoate (I) at Raney nickel is saturation of the double bond with the formation of the corresponding salt of 2-oxo-4-(2-thienyl)butyric acid (II), which is subsequently converted

TABLE 1. Hydrogenation of Sodium 2-Oxo-4-(2-thienyl)butenoate at Raney Nickel Catalyst and Palladium Black (Initial compound—Raney nickel ratio 1:1, initial compound—palladium black ratio 1:0.86)

No.	Catalyst (wet)	Initial concentration of raw material, M	T,°C	Reaction time, h	Yield, mole %		Unreacted raw material, %†
					sodium 2-oxo-4-(2-thienyl) butyrate	sodium 2-hydroxy-4-(2-thienyl) butyrate	
1.	Raney Ni	0,204	80	1,0	56,9	2,1	7,5
2.	Raney Ni	0,204	80	1,5	66,6	2,8	0,2
3.	Raney Ni	0,204	80	2,5	63,8	8,1	0,1
4.	Raney Ni	0,205	40	1,5	58,4	6,8	0,2
5.	Raney Ni	0,205	40	2,5	54,4	10,3	0,1
6.	Raney Ni	0,205	40	4,5	56,8	18,3	0,1
7*.	Raney Ni	0,183	67	5,5	3,6	41,5	0,1
8.	Pd black	0,208	40	2,0	43,1	1,5	4,5
9.	Pd black	0,208	40	3,0	44,7	1,6	3,3
10.	Pd black	0,208	40	4,0	53,1	3,1	1,2
11.	Pd black	0,208	40	5,0	62,2	4,3	0,6
12.	Pd black	0,198	40	1,0	55,3	1,8	6,1
13.	Pd black	0,198	50	2,0	68,4	2,2	1,9
14.	Pd black	0,198	55	3,0	70,6	1,9	0,2

*During the reaction fresh portions of the catalyst were added each hour. (The overall ratio of the initial compound and the catalyst was 1:2.)

†The dehydrogenation products also contain aliphatic hydrogenolysis products.

into sodium 2-hydroxy-4-(2-thienyl)butyrate (III). Since compound (III) is formed with a small degree of conversion of the raw material, it can be supposed that it may also be produced from the initial substance by a parallel path, but the role of this process is insignificant (Figs. 1 and 2). With complete conversion of the raw material the condensation (IV) and hydrogenolysis (V) products are formed in the subsequent transformations of the target product (II). It is therefore recommended that the hydrogenation is conducted with high dilutions of the reaction mixture, which reduces the possibility of formation of the bimolecular condensation products (IV). At higher temperatures and longer reaction times the hydrogenolysis products may be formed as a result of desulfurization of the thienyl fragment.

In contrast to the hydrogenation of sodium 2-oxo-4-(phenyl)butenoate, compound (III) is formed with low selectivity. Whereas the yield of sodium 2-hydroxy-4-phenylbutyrate during the hydrogenation of the phenyl derivative amounts to 94%, the yield of compound (III) during the hydrogenation of sodium 2-oxo-4-(2-thienyl)butenoate does not exceed 41% (Table 1).

We suppose that the initial compound is adsorbed on the surface of the catalyst through the double bond in the side chain and the thienyl fragment, which lies flat on the surface of the catalyst, and these structural elements undergo catalytic transformation. The keto group of the initial molecule is comparatively stable under the conditions of hydrogenation. It is possible that the sulfur-containing thienyl fragment is adsorbed at the active centers responsible for the hydrogenation of the keto group or that these centers are poisoned by sulfur.

The stability of the keto group is seen particularly clearly during the hydrogenation of sodium 2-oxo-4-(2-thienyl)-butenoate at palladium black. In this case the main reaction product is the target product — sodium 2-oxo-4-(2-thienyl)-butyrate, which makes it possible to create a selective catalytic method for the production of this compound (yield 71%). The corresponding hydroxy compound is only formed in small amounts (0.4-4.0%). The hydroxy compounds are easily freed from impurities by recrystallization from water.

The reactivity varies according to the selectivity of the formation of the sodium salts of the 4-substituted 2-oxobutyric acids during hydrogenation at Raney nickel in the following order: 2-oxo-4-(2-thienyl)butyric acid (sodium salt) > 2-oxo-4-(2-furyl)butyric acid (sodium salt) > 2-oxo-4-phenylbutyric acid (sodium salt) [3, 5]. As far as the hydrogenation of ethyl 2-oxo-4-(2-thienyl)butenoate is concerned, by analogy with the hydrogenation of the corresponding esters of the phenyl and furyl derivatives the selectivity of the formation of ethyl 2-oxo-4-(2-thienyl)butyrate is significantly lower than the selectivity

of the formation of the sodium salt of this compound. During hydrogenation of the esters the formation of the condensation product (IV) and the side products is intensified. By analogy with the hydrogenation of ethyl 2-oxo-4-(2-furyl)butenoate the previously unknown ethyl 2-oxo-4-(2-tetrahydrothienyl)butyrate is formed during the hydrogenation of ethyl 2-oxo-4-(2-thienyl)butenoate at palladium black.

Thus, a preparative method for the preparation of the respective salt of 2-oxo-4-(2-thienyl)butyric acid with a high yield was developed on the basis of the hydrogenation of sodium 2-oxo-4-(2-thienyl)butenoate.

EXPERIMENTAL

The starting material — sodium 2-oxo-4-(2-thienyl)butenoate — was obtained by the method that we developed for the condensation of 2-thiophenecarbaldehyde with ethyl pyruvate. The content of the main product was 95.4%. The initial substance and the reaction products [sodium 2-oxo-4-(2-thienyl)butyrate, 2-hydroxy-4-(2-thienyl)butyrate, and 2-oxo-3-(thienylmethyl)-4-(2-thienylethyl)-3,4-didehydroglutarate were determined by HPLC on a Rainin chromatograph; Dynamax analytical column (4.6 × 250 mm), inverted phase C_8 at λ = 232 nm, eluant 15% acetonitrile in 0.25 N triethylammonium phosphate, pH 6.0 [6]. The amount of sodium 2-oxo-4-(2-thienyl)butenoate in the reaction mixture was determined at λ = 337 nm.

The sodium 2-hydroxy-4-(2-thienyl)butyrate was purified on a medium-pressure Buchi chromatograph; Kontes column, 25 × 600 mm, Silasorb C_{18} (particle size 30 μm), eluant 5-20% gradient acetonitrile in 0.1 M ammonium acetate, pH 5.0.

The PMR spectra were recorded on a Bruker WH-90 DS spectrometer in solution in DMSO with HMDSO as internal standard. The mass spectra were obtained on a Hewlett Packard HP-6890 mass spectrometer at 70 eV.

Synthesis of Sodium 2-Oxo-4-(2-thienyl)butenoate. To a mixture of 45 g (0.4 mole) of 2-thiophenecarbaldehyde and 23.22 g (0.2 mole) of ethyl pyruvate, cooled to +4°C, we added gradually over 1 h 100 ml of a 2.6 M solution of sodium hydroxide. The mixture was stirred at room temperature for 3.5 h. The yellow precipitate was filtered off and washed with ethanol. We obtained 36.8 g (86%) of sodium 2-oxo-4-(2-thienyl)butenoate. According to HPLC, the purity of the product was 96%. The free acid was obtained from the sodium salt by the method in [7]. PMR spectrum, DMSO-d_6, HMDSO (δ, ppm): 6.98 (1H, d, α-CH, J = 17.0 Hz); 7.17 (1H, dd, 4-H thiophene, J = 6.0 and 5.0 Hz); 7.66 (1H, d, 3-H thiophene, J = 5.0 Hz); 7.77 (1H, d, 5-H, J = 6.0 Hz); 7.88 (1H, d, β-CH, J = 17.0 Hz); 8.22 (1H, bs, COOH).

Hydrogenation of Sodium 2-Oxo-4-(2-thienyl)butenoate at Raney Nickel. In a two-necked flask, provided with a magnetic stirrer, a reflux condenser, and a tube for the delivery of hydrogen, we placed 1.0 g (4.9 mmole) of sodium 2-oxo-4-(2-thienyl)butenoate, 1 g of wet Raney nickel catalyst, 9 ml of ethanol, and 15 ml of water. The mixture was hydrogenated at 80°C for 1.5 h. The catalyst was filtered off and washed with water (3 × 20 ml), and the solution was evaporated. We obtained 0.98 g of a substance which contained 0.69 g of sodium 2-oxo-4-(2-thienyl)butyrate (yield 66.6%), 0.03 g of sodium 2-hydroxy-4-(2-thienyl)butyrate, and 0.002 g of the unreacted initial compound. The sodium 2-oxo-4-(2-thienyl)butyrate was isolated, and the raw material was washed with ethanol (4 × 20 ml). The undissolved residue was dried and recrystallized from water, and 0.5 g of sodium 2-oxo-4-(2-thienyl)butyrate was obtained (purity 99%). Found %: C 46.2; H 3.50; S 15. $C_8H_7O_3SNa$. Calculated %: C 46.60; H 3.42; S 15.55. PMR spectrum, DMSO-d_6, HMDSO (δ, ppm): 2.91 (4H, m, CH_2CH_2); 6.85 (2H, m, 3-H thiophene + 4-H thiophene); 7.25 (1H, dd, 5-H thiophene, J = 5.08, 2.0 Hz). From the ethanol solution obtained after washing the sodium salt of the respective α-keto acid by evaporation we obtained sodium 2-hydroxy-4-(2-thienyl)butyrate. for analysis it was isolated on a preparative chromatograph. PMR spectrum, DMSO-d_6, HMDSO (δ, ppm): 1.86 (2H, m, β-CH_2); 2.83 (2H, t, α-CH_2, J = 7.0 Hz); 3.91 (1H, dd, CH, J = 7.08, 5.0 Hz); 6.85 (2H, m, 3-H thiophene + 4-H thiophene); 7.27 (1H, dd, 5-H thiophene, J = 5.08, 2.0 Hz).

We dissolved 0.22 g of the raw material obtained in a parallel experiment under the conditions described above [sodium 2-oxo-4-(2-thienyl)butyrate and other reaction products] in 2.75 ml of DMFA and added 0.44 ml of ethyl iodide. The mixture was stirred at room temperature in the dark for 24 h. At the end of the reaction the solution was evaporated. The residue was dissolved in 15 ml of water, and the aqueous solution was extracted with a 1:1 mixture of hexane and ethyl acetate. The obtained solution was dried over anhydrous sodium sulfate. The solution was evaporated, and 0.2 g of a dark oil was obtained. It was determined by chromato-mass spectrometry that the oil contained ethyl 2-oxo-4-(2-thienyl)butyrate. Mass spectrum, % (m/z): 212(6), $M^{+\cdot}$; 194(10), $[M-H_2O]^{+\cdot}$; 139(19), $[M-COOC_2H_5]^+$; 110(10), $[M-COCOOC_2H_5]^{+\cdot}$; 97(100), $[M-CH_2CO-COOC_2H_5]^+$. Ethyl 2-hydroxy-4-(2-thienyl)butyrate. Mass spectrum,% (m/z): 214(6), $M^{+\cdot}$; 196(3),

$[M-H_2O]^{+\cdot}$; 141(5), $[M-COOC_2H_5]^+$; 111(21), $[M-CHOHCOOC_2H_5]^+$; 97(100), $[M-CH_2CH(OH)COOC_2H_5]^+$; 84(11), $[C_4H_4S]^{+\cdot}$. Ethyl 3-(2-thienylmethyl)-4-(2-thienylethyl)-2-oxo-3,4-didehydroglutarate. Mass spectrum, % (m/z): 406(8), $M^{+\cdot}$; 309(4), $[M-C_4H_3SCH_2]^+$; 263(7); 235(15); 97(100), $[C_4H_3SCH_2]^+$.

Hydrogenation of Sodium 2-Oxo-4-(2-thienyl)butenoate in the Presence of Palladium Black. In a flask fitted with a magnetic stirrer, a reflux condenser, and a tube for the delivery of hydrogen we placed 1.02 g (5 mmole) of sodium 2-oxo-4-(2-thienyl)butenoate, 9 ml of ethanol, 15 ml of water, and 0.93 g of wet palladium black. The mixture was hydrogenated with molecular hydrogen at +40°C for 5 h. At the end of the reaction the catalyst was filtered off and washed with water (5 × 15 ml). The filtrate was evaporated, and 1.02 g of a precipitate was obtained. It contained 0.64 g of sodium 2-oxo-4-(2-thienyl)butyrate (yield 62.2%), 0.04 g of sodium 2-hydroxy-4-(2-thienyl)butyrate (yield 4.3%), and 0.006 g of unreacted initial compound.

Hydrogenation of Ethyl 2-Oxo-4-(2-thienyl)butenoate. In a flask fitted with a magnetic stirrer and a tube for the delivery of hydrogen we placed 0.34 g (1.65 mmole) of ethyl 2-oxo-4-(2-thienyl)butenoate dissolved in 11 ml of anhydrous ethanol. The mixture was hydrogenated with molecular hydrogen in the presence of palladium black at room temperature, and fresh portions of the catalyst were added every 5 h. At the end of the reaction the catalyst was filtered off and washed with anhydrous ethanol (3 × 15 ml), and the filtrate was evaporated. We obtained 0.30 g of a dark oil, which contained 0.09 g of ethyl 2-oxo-4-(2-thienyl)butyrate (yield 27%) and 0.14 g of ethyl 2-oxo-4-(2-tetrahydrothienyl)butyrate (yield 41%). Mass spectrum, % (m/z): 216(5), $M^{+\cdot}$; 143(100), $[M-COOC_2H_5]^+$; 115(30), $[M-COCOOC_2H_5]^+$; 100(87), $[M-CH_3CO-COOC_2H_5]^{+\cdot}$; 87(64), $[C_4H_8S]^+$.

The work was financed by the Latvian Council for Science (Grant No. 696).

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