Chemistry of Heterocyclic Compounds, Vol. 38, No. 3, 2002

SYNTHESIS OF THE ETHYL ESTERS OF 4-(3-PYRIDYL)- AND 4-(4-PYRIDYL)-2-OXOBUTENOIC ACIDS

Dz. Sile, V. A. Slavinska, G. Rozental, J. Popelis, Yu. Balodis, and E. Lukevics

We have developed a method for the synthesis of ethyl 4-(3-pyridyl)- and 4-(4-pyridyl)-2-oxobutenoates by condensation of 3-pyridinecarbaldehyde and 4-pyridinecarbaldehyde monohydrate respectively with ethyl pyruvate, esterifiction of the target acids, and hydrolysis of the corresponding ethyl ester ketals in the presence of $FeCl_3 \cdot 6H_2O$.

Keywords: ketals, 3- and 4-pyridinecarbaldehydes, 2-oxobutenoate esters, ketal hydrolysis, aldehyde condensations.

Ethyl 4-substituted 2-oxobutenoates are used in the synthesis of antihypertensive substances [1].

The compounds referred to are a promising starting material for the preparation of the corresponding homo-α-amino acids, diamino acids, epoxides, and others [2].

The potassium salts of unsaturated α-keto acids are usually obtained by the condensation of aldehydes with pyruvic acid in basic medium [3]. A drawback to this procedure is the contamination of the target compound by the products of the reaction of pyruvic acid, which is of low stability upon storage and is difficult to purify [4-6].

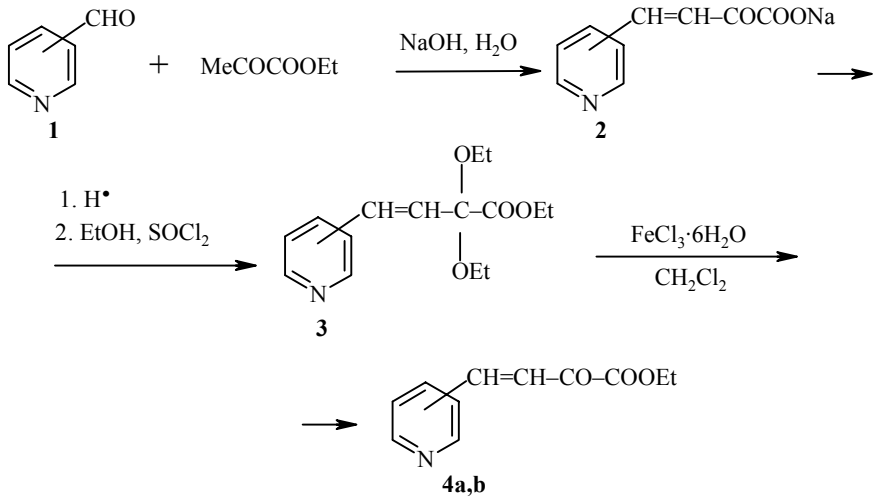
We have proposed a method for the preparation of the sodium salts of 4-substituted 2-oxobutenoic acids by condensation of ethyl pyruvate with aldehydes in basic medium [5-8]. Under these reaction conditions hydrolysis of the ester occurs and the pyruvic acid formed condenses with the aldehyde without undergoing conversion to side products. In addition, there is a possible reaction of the pyruvate ester with the aldehyde and subsequent hydrolysis of the ester of the corresponding butenoic acid. Using the proposed method we obtained the sodium salts of 4-phenyl-2-oxobutenoic acid, 4-(2-furyl)-2-oxobutenoic acid, and 4-(2-thienyl)-2-oxobutenoic acid in high yields and in high purity [5-8].

However, the condensation of 2-pyridinecarbaldehyde under the optimum conditions for the synthesis of the corresponding butenoic acid derivatives containing 2-furyl-, phenyl-, and 2-thienyl radicals does not give satisfactory results [5]. In these conditions, a strong tarring of the 2-pyridinecarbaldehyde occurs and it was not possible to separate the target product from the reaction mixture. For the condensation of 3-pyridinecarbaldehyde with ethyl pyruvate the yield of the sodium salt of the 4-(3-pyridyl)-2-oxobutenoic acid was also comparatively low (not greater than 33%) [5]. There are no reports in the literature of the synthesis of the sodium salt or other derivatives of 4-(4-pyridyl)-2-oxobutenoic acid.

In this work we propose a three stage method for the synthesis of ethyl 4-(3-pyridyl)- and 4-(4-pyridyl)-2-oxobutenoic acids according to the scheme:

Latvian Institute of Organic Synthesis, Riga LV-1006, Latvia; e-mail: dz.sile@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 321-325, March, 2002. Original article submitted September 27, 2000.

0009-3122/02/3803-0287$27.00



a 3-pyridyl, **b** 4-pyridyl

Bearing in mind the high solubility of the sodium salts of 4-(3-pyridyl)- (**2a**) and 4-(4-pyridyl)-2-oxobutenoic acids (**2b**) in polar solvents when compared with derivatives containing the phenyl, 2-furyl, or 2-thienyl radicals we suggest carrying out the condensation of 3- (**1a**) and 4-pyridinecarbaldehydes (**1b**) with ethyl pyruvate with a lower content of water in the reaction medium (molar ratio of ethyl pyruvate: 3-pyridinecarbaldehyde:NaOH; water equal to 1:2:0.9:13.9). Under these conditions the yield of the sodium salt **2a** reaches 40% with a 98% purity of the target product and the sodium salt of 4-(4-pyridyl)-2-oxobutenoic acid **2c** is obtained in 36% yield.

Esterification of 4-(3-pyridyl)-2-oxobutenoic acid by ethanol in the presence of p-toluenesulfonic acid or thionyl chloride occurs non selectively (see Table 1). A mixture of the ethyl ester and the full ketal of the indicated acid is obtained.

In the condition used, the yields of the ethyl ester and the other products are lower than the yield of the full ketal, that of the ethyl 4-(3-pyridyl)-2,2-diethoxybutenoate (**3a**) being 45%.

We have attempted to carry out the hydrolysis of the ketal **3a** using phosphoric acid in a mixture of water and acetonitrile [9] and $CuCl_2 \cdot H_2O$ [10]. However, under these conditions the hydrolysis occurs very unsuccessfully. Better results were obtained when carrying out the hydrolysis of ketal **3a** in the presence of $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2 solution [11]. Under optimum conditions, the yield of the ethyl 4-(3-pyridyl)-2-oxobutenoate (**4a**) after hydrolysis of the ketal was 62%.

EXPERIMENTAL

^{1}H NMR spectra were measured on Varian Mercury-200B (200 MHz) and Bruker WH-90 DS (90 MHz) instruments using $CDCl_3$ solvent and TMS or DSS (2,2-dimethyl-2-silapentane-5-sulfonic acid) as internal standard.

GLC Analysis was performed on an HP-5890 chromatograph with flame ionization detector and a quartz capillary column (0.53 mm × 25 m) with Permabond OV-1-DF-1.00 liquid phase, helium gas carrier, a temperature program of 50-270°C at 10°C/min, and vaporizer and detector temperature of 270°C. A normalized method of calculation was used.

Mass spectra were obtained on a Kratos MS-25 spectrometer with an ionization intensity of 70eV.

The starting materials were the ethyl pyruvate with a product purity not less than 97% (Fluka) and the 3-pyridinecarbaldehyde and 4-pyridinecarbaldehyde monohydrate with a purity of not less than 97%.

TABLE 1. Synthesis of the Ethyl Esters of 4-(3-Pyridyl)- and 4-(4-Pyridyl)-2-oxobutenoic Acids

Experiment	Starting material	Reagent or catalyst	Reaction conditions			Yield, molar %		Unreacted starting material, %
			Molar ratio of starting material to reagent	Reaction temperature, °C	Reaction time, h	ketals **3a,b**	target esters **4a,b**	
1	Sodium salt of 2-oxo-4-(3-pyridyl)butenoic acid **2a**	$SOCl_2$	1 : 3	20	25	36.5	6.2	—
2	– " –	$SOCl_2$	1 : 5	20	22	39.3	12.5*	—
3	– " –	$SOCl_2$	1 : 5	20	16	23.5	18.8	5.2
4	– " –	$SOCl_2$	1 : 5	20	6.5	21.8	26.9	6.0
5	– " –	$SOCl_2$	1 : 5	20	3.5	12.6	29.8	9.5
6	– " –	$SOCl_2$	1 : 5	20	23	45.8	19.4	—
7	– " –	*p*-toluenesulfonic acid	1 : 1.4	80	6	4.5	0.8	—
8	Sodium salt of 2-oxo-4-(4-pyridyl)butenoic acid **2b**	– " –	1 : 1.4	50	4			95.0
9	– " –	$SOCl_2$	1 : 5	20	48	39.4	2.1	—

* $NaHCO_3$ was used for the neutralization in the separation of the products.

Sodium Salt of 2-Oxo-4-(3-pyridyl)butenoic Acid (2a). A solution of NaOH (3.5 M, 30 ml) was added gradually over 0.5 h to a mixture of 3-pyridinecarbaldehyde (25.7 g, 0.24 mol) and ethyl pyruvate (14.9 g, 0.12 mol) cooled to 5°C. The product was stirred for 1 h at 5°C and then for 2 h at room temperature. Ethanol (70 ml) was added to the reaction mixture and it was left for 24 h at room temperature. The precipitated yellow salt **2a** was filtered off and washed on the filter (3 × 50 ml) with a mixture of ethanol and ether (1:1), then 2 × 50 ml of a mixture of ethanol, ether, and chloroform (1:0.5:0.5), and dried in air. The yield of the salt **2a** was 10 g (40%) with a purity of 98%. ^{1}H NMR spectrum (DMSO-d_6, TMS), δ, ppm, *J* (Hz): 6.93 and 7.49 (1H and 1H, dd, *J* = 16.5, CH=CH); 7.43 (1H, m, *J* = 7.8 and *J* = 4.8, 5-H_{Py}); 8.10 (1H, m, *J* = 7.8, 4-H_{Py}); 8.56 (1H, m, *J* = 4.8, *J* = 1.5, 6-H_{Py}); 8.79 (H, m, *J* < 2, 2-H_{Py}).

Sodium Salt of 2-Oxo-4-(4-pyridyl)butenoic Acid (2b). A solution of NaOH (3.5 M, 18 ml) was added gradually over 20 min to a mixture of 4-pyridinecarbaldehyde monohydrate (10.11 g, 80.8 mmol) and ethyl pyruvate (6.8 g, 58.6 mmol) cooled to 14°C with a solution pH of 9-10. The solution was stirred for 3 h at room temperature and the precipitated yellow salt **2b** was filtered off, washed with a small amount of ethanol, and dried in air to give a substance (4.38 g) which contained the salt **2b** (36%) with 97% purity. It was recrystallized from water. ^{1}H NMR Spectrum (D_2O, DSS), δ, ppm, *J* (Hz): 7.06 and 7.60 (2H, dd, CH=CH, *J* = 16.5); 7.55 (1H, d, *J* = 1.5, *J* = 5.4, 3-H_{Py}). 7.60 (1H, d, *J* = 1.5, *J* = 5.4, 5-H_{Py}); 8.53 (1H, d, *J* = 5.4, 2-H_{Py}); 8.55 (1H, d, *J* = 1.5, *J* = 5.4, 6-H_{Py}).

Ethyl 2,2-Diethoxy-4-(3-pyridyl)butenoate (3a). $SOCl_2$ (5.4 ml) was added dropwise to absolute ethanol (52 ml) cooled to -8°C followed by the salt **2a** (3 g, 15 mmol). The reaction mixture was stirred at room temperature for 23 h until the starting material had disappeared and then evaporated. The residue was dissolved in water (40 ml) and triethylamine (1 ml) was added to a solution pH of 5. The aqueous solution was extracted with ethyl acetate (8 × 25 ml). After each extraction the solution pH was corrected by the addition of triethylamine. The ethyl acetate extract was dried over anhydrous Na_2SO_4 and evaporated to give a dark oil (4.28 g) which contained compound **3a** (1.89 g, 45%). Mass spectrum, *m/z* (%): 250 (2) $[M\text{-}C_2H_5]^+$; 234 (8) $[M\text{-}OC_2H_5]^+$; 206 (77) $[M\text{-}COOC_2H_5]^+$; 150 (100) $[M\text{-}COOC_2H_5\text{-}2C_2H_4]^+$; 132 (64) $[Py–CH=CH–CO]^+$; 104 (30) $[M\text{-}C(OC_2H_5)_2\text{-}COOC_2H_5]^+$; 78 (13) $[Py]^+$; and 0.16 g (18%) of ethyl 2-oxo-4-(3-pyridyl)butenoate **4a** (mass spectrum, *m/z* (%): 205 (3) $[M]^+$; 177 (4) $[M\text{-}C_2H_4]^+$; 132 (100) $[M\text{-}COOC_2H_5]^+$; 104 (33) $[M\text{-}COCOOC_2H_5]^+$; 78 (14) $[Py]^+$).

Ethyl 2,2-Diethoxy-4-(4-pyridyl)butenoate (3b). $SOCl_2$ (1.08 ml) was added to absolute ethanol (10 ml) cooled to -8°C followed by the salt **2b** (0.6 g, 3 mmol). The reaction mixture was stirred at room temperature for 48 h until the starting material had disappeared and then evaporated. The residue was dissolved in water (20 ml) and triethylamine was added to a solution pH of 5-6. The product was extracted with ethyl acetate (5 × 10 ml), the extract dried over anhydrous Na_2SO_4, and evaporated to give a dark oil (0.52 g) which contained the ethyl ester **3b** (0.26 g, 31%) (the solution after extraction of ester **3b** contained a mixture of unidentified products. Mass spectrum, *m/z* (%): 250 (1) $[M\text{-}C_2H_5]^+$; 234 (8) $[M\text{-}OC_2H_5]^+$; 206 (72) $[M\text{-}COOC_2H_5]^+$; 178 (17) $[M\text{-}COOC_2H_5\text{-}C_2H_4]^+$; 150 (60) $[M\text{-}COOC_2H_5\text{-}(C_2H_4)_2]^+$; 132 (100) $[M\text{-}COOC_2H_5\text{-}(C_2H_5)_2]^+$; 104 (21) $[Py–CH=CH]^+$; 78 (16) $[Py]^+$.

Ethyl 2-oxo-4-(3-pyridyl)butenoate (4a). $FeCl_3\cdot 6H_2O$ (0.8 g) was added to a solution of 0.30 g of the mixture obtained in experiment 3 which contained the ketal **3a** (0.135 g) and the ester **4a** (0.093 g) in CH_2Cl_2 (5.5 ml), the product was refluxed for 20 min and a further 0.8 g of $FeCl_3\cdot 6H_2O$ was added and refluxed for a further 20 min. At the end of the reaction a saturated solution of $NaHCO_3$ (20 ml) was added and it was extracted with ethyl acetate (4 × 20 ml). The extract was washed with NaCl solution and dried over anhydrous Na_2SO_4. The ethyl acetate was evaporated to dryness and the residue of yellow material (0.180 g) was recrystallized from hexane to give the ethyl ester **4a** (0.121 g, 62.5% yield, 98% purity); mp 51-52°C. ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm, *J* (Hz): 1.46 (3H, t, CH_3); 4.46 (2H, q, CH_2); 7.47 (1H, dd, 5-H_{Py}); 7.91 and 7.49 (2H, d and d, *J* = 15.2, CH=CH); 8.05 (1H, dt, 4-H_{Py}); 8.73 (1H, dd, 6-H_{Py}); 8.91 (1H, d, 2-H_{Py}). Found, %: C 64.37; H 5.38; N 6.75. $C_{11}H_{11}NO_3$. Calculated, %: C 64.36; H 5.40; N 6.85.

Ethyl 2-oxo-4-(4-pyridyl)butenoate (4b). $FeCl_3 \cdot 6H_2O$ (0.6 g) was added with stirring to a solution of the crude mixture (0.26 g) from experiment 4 (which contained the ethyl ester **3b** (0.17 g)), in CH_2Cl_2 (5 ml) and then refluxed for 20 min. $FeCl_3 \cdot 6H_2O$ (0.6 g) was further added twice and after the addition of each new portion the solution was refluxed for 20 min. A saturated solution of $NaHCO_3$ (18 ml) was then added and the product was extracted with ethyl acetate (4 × 20 ml). The extract was dried over Na_2SO_4 and evaporated. The yellow residue (0.093 g) was recrystallized from hexane to give compound **4b** (0.066 g, 53% yield, 97% purity) with mp 53-54°C. ^{1}H NMR spectrum ($CDCl_3$, TMS), δ, ppm, *J* (Hz): 1.41 (3H, t, CH_3); 4.40 (2H, q, CH_2); 7.46 (2H, m, *J* = 6.0, 3,5-H_{Py}); 7.50 and 7.76 (2H, d and d, *J* = 16.2, CH=CH); 8.70 (2H, m, *J* = 6.0, 2,6-H_{Py}). Found, %: C 64.33; H 5.39; N 6.71. $C_{11}H_{11}NO_3$. Calculated, %: C 64.36; H 5.40; N 6.85.

This work was carried out with the financial support of the Latvian Council for Science (grant No. 696).

REFERENCES

1. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. E. Sile, E. Kh. Korchagova, and O. M. Galkin, *Structure and Activity of Zinc Containing Enzyme Inhibitors - Kinase II and Encephalinase* [in Russian], Riga, Zinatne (1990).
2. G. I. Chipens, V. A. Slavinskaya, A. K. Strautinya, D. E. Sile, D. R. Kreile, and A. Yu. Krikis, *Modified Amino Acids and Related Peptides* [in Russian], Riga, Zinatne (1987).
3. P. Cordier, *Pharm. Weekl.*, **93**, No. 2, 55 (1958).
4. A. J. Cooper, J. Z. Ginos, and A. Meister, *Chem. Rev.*, **83**, No. 3, 321 (1983).
5. M. Katkevics, E. Korchagova, Dz. Sile, V. D. Grigoryeva, and V. A. Slavinska, *Latv. J. Chem*, 220 (1993).
6. V. Slavinska, Dz. Sile, E. Korchagova, M. Katkevich, and E. Lukevics, *Synth. Commun.*, **26**, 2229 (1996).
7. V. Slavinska, Dz. Sile, E. Korchagova, N. Panchenko, I. Turovskis, and E. Lukevics, *Latv. J. Chem.*, No. 2, 87 (1998).
8. V. Slavinska, M. Katkevics, Dz. Sile, E. Korchagova, and R. Vegners, *Latv. J. Chem.*, 608 (1994).
9. M. Katkevics, E. Korchagova, Dz. Sile, V. Slavinska, V. Grigoryeva, and E. Lukevics, *Latv. J. Chem.*, No. 3-4, 108 (1996).
10. P. Saravanan, M. Chandrasekhar, R. Vijaya Anand, and Vinod K. Singh, *Tetrahedron Lett.*, **39**, 3091 (1998).
11. S. E. Sen, S. L. Roach, J. K. Boggs, G. J. Ewing, and J. Magrath, *J. Org. Chem.*, **62**, 6684 (1997).