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SHORT COMMUNICATIONS

Mild Reaction of Primary Alcohols with Ferulic Acid

L. A. Bakholdina[a], A. I. Khlebnikov[b], and V. P. Sevodin[a]

[a] *Biisk Institute of Technology (Branch), Polzunov Altai State Technical University, ul.Trofimova 27, Biisk, 659305, Altai Krai, 659305 Russia*
e-mail: ljuba27@mail.ru

[b] *Tomsk National Research Polytechnical University, pr. Lenina 30, Tomsk, 634050 Russia*

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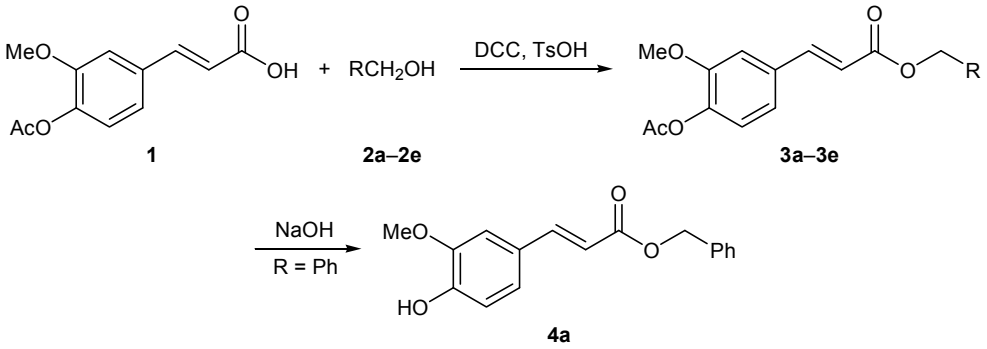
Until present, much data have been reported on the antioxidant activity of ferulic acid and its derivatives [1–11]; foods containing ferulic acid bound to glycerol [4], oligosaccharides [1], and sterols (γ-oryzanol) [10, 11] are used in the prophylactics of intestinal cancer. In the first two cases, substituents in the ferulic acid molecule are hydrophilic, and in the latter, hydrophobic. The mechanism of antioxidant action of ferulic acid is not completely clear, which may be related to difficult synthesis of its conjugates with mono- and oligosaccharides, as well as with sugar alcohols. Therefore, development of simple procedures for the preparation of ferulic acid derivatives under mild conditions is an important problem.

The most common approach is based on the acylation of alcohols with ferulic acid chlorides where the 4-hydroxy group is protected. A drawback of this approach is the necessity of protecting hydroxy groups in the substrates [12]. Acylation of alcohols and sugars with ferulic acid can be accomplished using *N*,*N*′-dicyclohexylcarbodiimide (DCC) as condensing agent. In this case, selective acylation is achieved, and there is no need of protecting hydroxy groups in polyols and sugars [13]. The presence of a catalytic amount of a strong acid considerably increases the yield [14].

We tried 4-*O*-acetylferulic acid (**1**) [15] as acylating agent toward various primary alcohols **2a**–**2e**. The reactions of alcohols **2a**–**2e** with acid **1** were carried out in pyridine in the presence of DCC and *p*-toluenesulfonic acid (TsOH). The esterification conditions were optimized using the reaction of **1** with benzyl alcohol (**2a**) (see table). The optimal ratio **1**–**2a**–DCC–pyridine was 0.01:0.011:0.012:49 (mol:mol:mol:mL). Benzyl alcohol was taken in slight excess (run no. 1), and further increase of the amount of **2a** did not affect the yield of ester **3a** to an appreciable extent (run no. 2). If acid **1** was taken in excess, the yield of **3a** decreased (run no. 3), and unreacted acid **1** was isolated together with target ester **3a**. Raising the amount of DCC above 20% also did not improve the yield (run no. 4).

The selected esterification procedure ensures easy isolation of the product by acidification of the mixture at 2–5°C and subsequent extraction with chloroform.



1 **2a–2e** **3a–3e** **4a**

R = Ph (**a**), $PhCH_2$ (**b**), CH_2=CH (**c**), 5-formylfuran-2-yl (**d**), oxolan-2-yl (**e**).

Reaction of 4-acetoxyferulic acid (**1**) with benzyl alcohol (**2a**) in the presence of DCC

Run no.	Amounts of reactants, mol			Yield of **3a**, %
	1	**2a**	DCC	
1	0.010	0.011	0.012	55±12
2	0.010	0.015	0.012	56±10
3	0.011	0.010	0.012	41±11
4	0.010	0.011	0.020	57±11

After recrystallization from 96% ethanol, esters **3a**–**3e** were isolated as white crystalline substances. Their structure was confirmed by IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of **3a**–**3e** contained signals from protons on the double-bonded carbon atoms as doublets at δ 6.76–6.81 and 7.29–7.32 ppm with a coupling constant ^3J of ~16 Hz, which is typical of *trans* configuration of the C=C double bond. The singlet from protons of the acetyl protecting group (δ 2.26 ppm) disappeared after deprotection, and a singlet at δ 9.68 ppm (OH) appeared instead. The IR spectrum of **4a** showed a medium-intensity absorption band at 3511 cm^{-1} due to O–H stretching vibrations. No signals assignable to carboxy groups were observed in the IR and NMR spectra of **3a**–**3e** and **4a**.

(*E*)-3-(4-Acetoxy-3-methoxyphenyl)prop-2-enoic acid (**1**) was synthesized from 4-acetoxyvanillin which was prepared in turn according to the procedure described in [16]. mp 196°C. UV spectrum, λ_{max}, nm: 278, 215. IR spectrum, ν, cm^{-1}: 3013 (OH), 2945 (C–H), 1763 (C=O) [15].

Esters 3a–3e (*general procedure*). Acid **1**, 0.01 mol, alcohol **2a**–**2e**, 0.011 mol, and *p*-toluenesulfonic acid, 0.09 g, were dissolved in 49 mL of pyridine, 0.012 mol of DCC was added, and the mixture was kept for 24 h at room temperature in the dark. Acetic acid, 0.01 mol, was then added, and the mixture was cooled to 4°C and left overnight. The mixture was filtered, the precipitate was washed with cold pyridine, 80 g of ice was added to the filtrate, and the mixture was acidified with 5 M aqueous HCl and extracted with chloroform (3×80 mL). The combined extracts were washed with water, aqueous sodium hydrogen carbonate, and water again, dried, and evaporated under reduced pressure, and the residue was recrystallized from ethanol.

Benzyl (2*E*)-3-(4-acetoxy-3-methoxyphenyl)-prop-2-enoate (3a). Yield 55%, mp 76–78°C, R_f 0.90. UV spectrum, λ_{max}, nm: 210, 233, 282. IR spectrum, ν, cm^{-1}: 2951 (C–H), 1756 and 1707 (C=O), 1634 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.26 s (3H, CH_3CO), 3.82 s (3H, CH_3O), 5.24 s (2H, CH_2), 6.80 d (1H, CH, J = 16.0 Hz), 7.13 d (1H, H_{arom}, J = 8.1 Hz), 7.30 d (1H, H_{arom}, J = 8.4 Hz), 7.37–7.43 m (5H, H_{arom}), 7.52 s (1H, H_{arom}), 7.71 d (1H, CH, J = 16.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.37, 38.69, 38.96, 39.24, 39.52, 39.79, 40.07, 40.35, 55.99, 65.72, 111.93, 118.14, 121.68, 123.22, 128.21, 128.49, 133.00, 136.17, 141.06, 144.28, 151.16, 166.10, 168.39.

2-Phenylethyl (2*E*)-3-(4-acetoxy-3-methoxyphenyl)prop-2-enoate (3b). Yield 45%, mp 108–110°C, R_f 0.88. UV spectrum, λ_{max}, nm: 210, 282. IR spectrum, ν, cm^{-1}: 2957 (C–H), 1759 and 1719 (C=O), 1639 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.26 s (3H, CH_3CO), 2.95 t (2H, CH_2, J = 13.5 Hz), 3.82 s (3H, CH_3O), 4.38 t (2H, OCH_2, J = 13.2 Hz), 6.69 d (1H, CH, J = 16.0 Hz), 7.12 d (1H, H_{arom}, J = 8.1 Hz), 7.27 d (1H, H_{arom}, J = 8.4 Hz), 7.30–7.22 m (5H, H_{arom}), 7.52 s (1H, H_{arom}), 7.64 d (1H, CH, J = 16.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.40, 34.44, 38.69, 38.97, 39.24, 39.52, 39.80, 40.08, 40.35, 56.03, 64.61, 111.89, 118.22, 121.71, 123.23, 126.43, 128.43, 128.88, 132.99, 137.99, 141.05, 144.07, 151.19, 166.22 168.41.

Prop-2-en-1-yl (2*E*)-3-(4-acetoxy-3-methoxyphenyl)prop-2-enoate (3c). Yield 42%, mp 60–62°C, R_f 0.89. UV spectrum, λ_{max}, nm: 233, 282. IR spectrum, ν, cm^{-1}: 2925 (C–H), 1764 and 1708 (C=O), 1633 and 1601 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.27 s (3H, CH_3CO), 3.45 s (3H, CH_3O), 4.69 d (2H, CH_2, J = 5.1 Hz), 5.25 d (1H, CH_2, J = 10.2 Hz), 5.37 d (1H, CH_2, J = 17.1 Hz), 5.99 m (1H, CH), 6.74 d (1H, CH, J = 16.2 Hz), 7.12 d (1H, H_{arom}, J = 8.1 Hz), 7.30 d (1H, H_{arom}, J = 8.1 Hz), 7.68 d (1H, CH, J = 16.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.38, 38.69, 38.96, 39.24, 39.51, 39.79, 40.06, 40.34, 56.00, 64.59, 111.96, 117.95, 118.07, 124.63, 123.23, 132.78, 133.00, 141.05, 144.20, 151.17, 165.88, 168.40.

(5-Formylfuran-2-yl)methyl (2*E*)-3-(4-acetoxy-3-methoxyphenyl)prop-2-enoate (3d). Yield 40%, mp 80–87°C, R_f 0.87. UV spectrum, λ_{max}, nm: 199, 216, 232, 281. IR spectrum, ν, cm^{-1}: 2945 (C–H), 1760 and 1711 (C=O), 1668 (C=C). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.26 s (3H, CH_3CO), 3.81 s (3H, CH_3O), 5.32 s (2H, CH_2), 6.78 d (1H, CH, J = 15.9 Hz), 7.12 d (1H, H_{arom}, J = 7.8 Hz), 7.31 d (1H, H_{arom}, J = 8.7 Hz), 7.54 s (2H, CH), 7.71 d (1H, CH, J = 15.9 Hz), 9.61 s (1H, CHO). ^{13}C NMR spectrum

($CDCl_3$), δ_C, ppm: 20.40, 38.69, 38.97, 39.24, 39.52, 39.80, 40.07, 40.35, 56.03, 57.71, 112.01, 113.18, 117.50, 121.89, 123.29, 123.90, 132.94, 141.24, 145.03, 151.22, 152.55, 155.46, 165.72, 168.48, 178.54.

(Oxolan-2-yl)methyl (2*E*)-3-(4-acetoxy-3-methoxyphenyl)prop-2-enoate (3e). Yield 45%, mp 106–108°C, R_f 0.9. UV spectrum, λ_{max}, nm: 214, 281. IR spectrum, ν, cm^{-1}: 2950 (C–H), 1760 and 1705 (C=O), 1633 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.92 m (4H, CH_2), 2.26 s (3H, CH_3CO), 3.66 t (2H, CH_2, J = 21.0 Hz), 3.83 s (3H, CH_3O), 4.13 m (3H, CH, CH_2, J = 26.7 Hz), 6.73 d (1H, CH, J = 16.0 Hz), 7.12 d (1H, H_{arom}, J = 8.1 Hz), 7.30 d (1H, H_{arom}, J = 8.1 Hz), 7.53 s (1H, H_{arom}), 7.65 d (1H, CH, J = 16.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.40, 25.23, 27.54, 38.70, 38.97, 39.25, 39.53, 39.80, 40.08, 40.35, 56.74, 66.06, 67.46, 75.93, 111.89, 118.18, 121.71, 123.23, 133.01, 141.04, 144.13, 151.17, 166.19, 168.41.

Benzyl (2*E*)-3-(4-hydroxy-3-methoxyphenyl)-prop-2-enoate (4a). Ester **3a**, 1 mmol, was dissolved in 50 mL of acetone, 50 mL of a 1 M solution of sodium hydroxide was added, and the mixture was stirred for 20 min at room temperature. The mixture was acidified with 2 M aqueous HCl and cooled in an ice bath, and the precipitate was filtered off, washed with water, and recrystallized. Yield 75%, mp 60–61°C, R_f 0.85. UV spectrum, λ_{max}, nm: 237, 331. IR spectrum, ν, cm^{-1}: 3510 (O–H), 2953 (C–H), 1695 (C=O), 1627 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.81 s (3H, CH_3O), 5.20 s (2H, CH_2), 6.55 d (1H, CH, J = 16.0 Hz), 6.84 d (1H, H_{arom}, J = 8.7 Hz), 7.13 d (1H, H_{arom}, J = 7.5 Hz), 7.37 m (5H, H_{arom}), 7.40 s (1H, H_{arom}), 7.61 d (1H, CH, J = 16.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.70, 38.98, 39.26, 39.53, 39.81, 40.09, 40.37, 55.76, 55.47, 111.23, 114.29, 115.58, 123.39, 125.64, 128.18, 128.57, 136.49, 145.55, 148.02, 149.51, 166.62.

The progress of the esterification reactions was monitored by TLC on Silicagel 60 F_{254} plates (Merck) using chloroform–ethanol (10 : 1) as eluent; spots were visualized under UV light. The UV spectra were measured in ethanol on a Shimadzu UV-1800 two-beam spectrophotometer. The IR spectra (500–4000 cm^{-1}) were recorded in KBr on an InfraLYuM FT-01 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AV 300 instrument at 300 and 75 MHz, respectively, using tetramethylsilane as internal standard.

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