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Synthesizing Betulin Vinyl Ethers *via* Direct Vinylation by Acetylene in Superbasic KOH/DMSO Medium

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Abstract

Basing on betulin vinylation by acetylene in superbasic medium KOH/DMSO, mono- and divinyl esters of betulin, valuable monomers and intermediates for the synthesis of polymers and biologically active compounds were obtained.

Key words: betulin, acetylene, vinyl esters, superbasic medium

INTRODUCTION

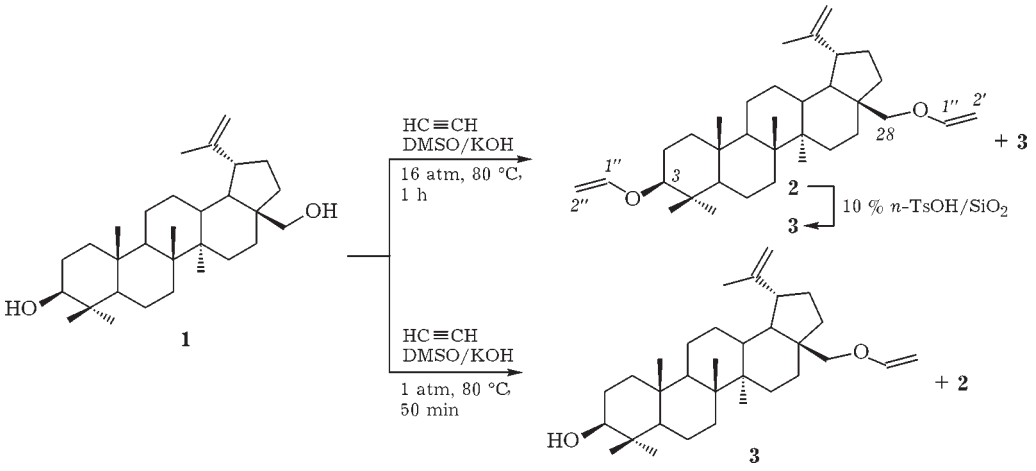
Vinyl ethers are widely used as monomers in polymer chemistry and intermediates in the synthesis of biologically active compounds [1–10]. Among the existing methods for producing O-vinyl ethers [11, 12] there is a method considered to be the most available that consists in the direct vinylation of alcohols by acetylene in superbasic media MOR/DMSO (M = K, Na; R = H, *t*-Bu) [13, 14]. In recent years, there are reports appeared in the literature concerning successful applying this method to the synthesis of the vinyl esters of hydroxyl-containing natural compounds such as sugars [15, 16], steroids [17, 18] and alkaloids [19].

Higher pentacyclic triterpenoids those represent, as a rule, high oxygenated compounds could be used as promising substrates for this reaction. The transformation of hydroxyl functions into the oxyvinyl ones allows significantly expanding the synthetic potential of this class of compounds. One of the promising applications of triterpene oxyvinyl derivatives could be presented by the synthesis of biologically active homo- and copolymers.

The purpose of this work consisted in developing a method for direct vinylation of betulin **1** (the most accessible representative of pentacyclic triterpenoids from lupane series) by acetylene in superbasic media.

RESULTS AND DISCUSSION

Initially, the interaction of betulin **1** with acetylene in superbasic media KOH/DMSO was carried out in an autoclave at a pressure of 16–19 atm at 80 °C during 1 h. The reaction proceeded with the formation of product of complete vinylation such as divinyl ether **2**, a small amount of monovinyl ether **3** and by unidentified polymerization products. Ethers **2** and 3 were isolated by means of column chromatography on SiO_2 impregnated with Et_3N, with the yields equal to 58 and 4 %, respectively. An increase either in the reaction time or in the temperature up to 100 °C resulted in an increase in the percentage of polymerization products, whereas a decrease in the duration of the process leads to increasing the content of monovinyl ether **3** in the mixture (Scheme 1).



Scheme 1.

It should be noted that the secondary vinyloxy group of the ether **2** very readily undergo hydrolysis in the course of chromatographing on silica gel, not treated by Et_3N, which made difficult to isolate divinyl ether **2**. In the case of prolonged contact time of compounds **2** and **3** with the sorbent, both vinyloxy groups underwent the hydrolysis. The selective hydrolysis of the secondary vinyloxy group of diether **2** could be realized under the action *n*-TsOH/SiO_2 in a benzene solution for three weeks.

It is known that the vinylation of a primary hydroxyl group in some sugars [17, 18] and alkaloid lupinine [19] by acetylene takes place at atmospheric pressure in superbasic media KOH/DMSO or *t*-BuOK/DMSO. In the case of betulin **1** the selective vinylation primary 28-OH group occurred at an atmospheric pressure in superbasic medium KOH/DMSO at 80 °C.

The ^{1}H NMR spectrum of divinyl ether **2** contained the entire set of signals inherent in the protons of the vinyloxy group: two-single proton doublets at 6.35 and 6.55 ppm (J 14.4 and 6.8 Hz), located in the α-position with respect to the oxygen atom, and four one-proton doublets at 3.94 ppm (H_A-2′, J = 6.8 and 1.8 Hz), 4.17 ppm (H_B-2′, J = 14.4 and 1.8 Hz), 3.97 ppm (H_A-2″, J = 6.8 and 1.3 Hz), 4.27 ppm (H_B-2″, J = 14.4 and 1.3 Hz) related to β-protons. In the spectrum of monovinyl ether **3**, there was one set of similar signals: two doublets at 6.55 ppm (J = 14.4 and 6.8 Hz) as well as two doublets at 3.95 ppm (J = 6.8 and 1.8 Hz) and 4.17 ppm (J = 14.4 and 1.8 Hz). The ^{13}C NMR spectra of ethers **2** and **3** were completely consistent with the proposed structure.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were registered at a room temperature using a Bruker AM-300 spectrometer with the operating frequency of 300 and 75 MHz as well as $CDCl_3$ as a solvent with no standard. The chemical shift values are presented with respect to the signal of solvent: δ_H = 7.27 ppm and δ_C = 77.1 ppm, the multiplicity of ^{13}C signals was found from carbon spectra with the modulation of C–H interactions. The assignment of the ^{13}C NMR spectral signals was performed using a JMOD mode and heteronuclear correlation. The angles of rotation were determined using a PerkinElmer 141 polarimeter. The column chromatography was carried out on SiO_2 (L grade, 100/160 mesh, Russia). For the TLC we used Sorbfil plates (Sorbpolymer Co., Krasnodar, Russia). Melting point values were determined with the help of a Kofler bench. Betulin was isolated from birch bark by means of the method described in [20]. DMSO was held above KOH and distilled then above CaH_2 under vacuum, in argon atmosphere [21].

Vinylation of betulin ***1***

Method A. A mixture of 2.0 g (4.52 mmol) of betulin **1**, 0.88 g (13.55 mmol) of

$KOH \cdot 0.5H_2O$ and 50 mL of DMSO was placed into a rotating steel autoclave with a capacity of 300 mL, saturated with acetylene (initial pressure of 16 atm) and stirred during 1 h at 80 °C. After cooling the reaction mixture was diluted with MTBE, ice water was added, the organic layer was separated, the aqueous layer was extracted with MTBE (3×50 mL); the organic extracts were joined together, washed with water, dried with K_2CO_3; the solvent was evaporated. To the residue obtained we added hexane. A fraction insoluble in hexane was filtered, the filtrate was evaporated and chromatographed SiO_2, impregnated with Et_3N (benzene). We obtained 1.2 g (54 %) of divinyl ether **2** and 0.08 g (4 %) monovinyl ether **3**.

3β,28-Divinyloxylup-20(29)-en 2. M. p. 176–178 °C (colourless needles, pentane). [α] +1.1° (s 0.69, $CHCl_3$). ^{1}H NMR spectrum: 0.7 d (1H, H-5, J = 8.7 Hz), 0.84 s (3H, CH_3-24), 0.87 s (3H, CH_3-26), 0.93 s (3H, CH_3-23), 0.99 s (3H, CH_3-27), 1.10 s (3H, CH_3-25), 1.72 s (3H, CH_3-30), 2.41 dd (1H, H-19, J = 15.1, 9.5 Hz), 3.27 dd (1H, H-3, J = 12.6, 4.0 Hz), 3.35 d (1H, H_A-28, J = 9.5 Hz), 3.78 d (1H, H_B-28, J = 9.5 Hz), 3.94 dd (1H, vinyl, H_A-2′, J = 6.8, 1.8 Hz), 3.97 dd (1H, vinyl, H_A-2″, J = 6.8, 1.3 Hz), 4.17 dd (1H, vinyl, H_B-2′, J = 14.4, 1.8 Hz), 4.27 dd (1H, vinyl, H_B-2″, J = 14.4, 1.3 Hz), 4.60 s (1H, H_A-29), 4.70 s (1H, H_B-29), 6.35 dd (1H, vinyl, H-1″, J = 14.4, 6.8 Hz), 6.55 dd (1H, vinyl, H-1′, J = 14.4, 6.8 Hz). ^{13}C NMR spectrum: 14.82 (C-27), 16.01 (C-24), 16.15 (C-25), 16.38 (C-26), 18.17 (C-6), 19.15 (C-30), 20.88 (C-11), 23.61 (C-12), 25.22 (C-15), 27.14 (C-2), 27.99 (C-23), 29.82 (C-16), 29.82 (C-21), 34.20 (C-7), 34.61 (C-22), 37.18 (C-10), 37.62 (C-13), 38.50 (C-4), 38.69 (C-1), 40.96 (C-8), 42.72 (C-14), 46.74 (C-17), 47.95 (C-19), 48.82 (C-18), 50.40 (C-9), 55.74 (C-5), 66.12 (C-28), 85.57 (vinyl, C-1′), 87.38 (C-3), 87.18 (vinyl, C-1″), 109.79 (C-29), 152.31 (vinyl, C-2″), 152.83 (vinyl, C-2′), 150.40 (C-20). Found, %: C 82.61, H 11.67. $C_{34}H_{54}O_2$. Calculated, %: C 82.53, H 11.00.

28-Vinyloxylup-20(29)-en-3β-ol 3. M. p. 106–107 °C. [α] + 3.1° (c 0.33, $CHCl_3$), [α] + 6.4° (s 2.16, toluene). ^{1}H NMR spectrum: 0.7 d (1H, H-5, J = 8.7 Hz), 0.75 s (3H, CH_3-24), 0.82 s (3H, CH_3-26), 0.96 s (3H, CH_3-23), 0.97 s (3H, CH_3-27), 1.02 s (3H, CH_3-25), 1.68 s (1H, H-30), 3.15 dd (1H, H-3, J = 10.5, 5.0 Hz), 2.40 dd (1H, H-19, J = 10.5, 5.0 Hz), 3.35 d (1H, H_A-28, J = 9.7 Hz), 3.80 d (1H, H_B-28, J = 9.5 Hz), 3.95 dd (1H, vinyl, H_A-2′, J = 6.8, 1.8 Hz), 4.17 dd (1H, vinyl, H_B-2′, J = 14.4, 1.8 Hz), 4.58 s (1H, H_A-29), 4.68 s (1H, H_B-29), 6.55 dd (1H, vinyl, H-1′, J = 14.4, 6.8 Hz). ^{13}C NMR spectrum: 14.80 (C-27), 15.37 (C-24), 15.96 (C-25), 16.09 (C-26), 18.29 (C-6), 19.10 (C-30), 20.81 (C-11), 25.21 (C-21), 27.39 (C-2), 27.10 (C-15), 27.99 (C-23), 29.79 (C-21), 29.79 (C-16), 34.19 (C-7), 34.58 (C-22), 37.61 (C-13), 37.15 (C-10), 38.85 (C-1), 38.71 (C-4), 40.90 (C-8), 42.70 (C-14), 46.71 (C-17), 47.93 (C-19), 48.80 (C-18), 50.38 (C-9), 55.29 (C-5), 66.18 (C-28), 78.96 (C-3), 85.54 (vinyl, C-1′), 109.71 (C-29), 150.41 (C-20), 152.83 (vinyl, C-2′). Found, %: C 81.87, H 11.58. $C_{32}H_{52}O_2$. Calculated, %: C 81.99, H 11.18.

Method B. A flow of acetylene was passed through a mixture of 0.5 g (1.13 mmol) of betulin and 0.38 g (1.387 mmol) $KOH \cdot 0.5H_2O$ in 23 mL of DMSO at atmospheric pressure and 80 °C during 50 min (until complete consumption of the initial betulin amount). The reaction mixture was cooled, diluted with ice water (50 mL), extracted with MTBE (5 × 30 mL). The organic extract were joined together, washed with water, dried with K_2CO_3; the solvent was evaporated, and the residue was chromatographed on SiO_2 impregnated with Et_3N (hexane/ethyl acetate = 5 : 1). We obtained 0.01 g (2 %) of divinyl ether **2**, 0.4 g (75 %) of monovinyl ester **3** and 0.07 g of compound **1**.

Hydrolysis of 3β,28-divinyloxylup-20(29)-ene 2. A solution of 50 mg (0.101 mmol) of divinyl ether **2** in 4 mL of benzene was stirred with 5 mg 10 % *p*-TsOH/SiO_2 for three weeks. The catalyst was filtered, the solvent was evaporated and the residue was then chromatographed on SiO_2/Et_3N (hexane/EtOAc = 5 : 1). We obtained 37 mg (79 %) of **3**, 9 mg of **2** and trace amounts of betulin **1**.

CONCLUSION

Thus, by the example of betulin it was first demonstrated that it is possible to perform the direct O-vinylation of triterpene alcohols belonging to the lupane series by means of acetylene in superbasic KOH/DMSO media.

Methods are developed for synthesizing the comprehensive and selective vinylation prod-

ucts of betulin hydroxy functional groups such as di- and monovinyl ethers, promising intermediates and monomers for the synthesis of biologically active compounds and polymers.

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