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UNUSUALLY FACILE PYRROLIZATION OF 2-ACETYLCOUMARONE OXIME WITH ACETYLENE

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The oxime of 2-acetylcoumarone reacts with acetylene under pressure in the system KOH–DMSO unusually readily forming 2-(2-pyrrolyl)coumarone and the corresponding O-vinyl oxime. Under more rigid conditions 2-(1-vinyl-2-pyrrolyl)coumarone is formed. The possibility of a two-stage transformation of 2-acylcoumarones into 2-pyrrolylcoumarones has therefore been demonstrated for the first time.

Keywords: acetylene, O-vinyl oxime, 1-vinylpyrrole, 2-acetylcoumarone oxime, pyrrole.

The benzo[*b*]furan (coumarone) system enters into the molecular structure of many important natural products (euparin, usnic acid, and peicedanine [1], other furocoumarins, aflatoxins, furochromones, rotenoids [2]). Among them substances are known possessing high physiological activity (for example, spasmolytics, phytoalexins, insecticides, coronary vasodilators, etc. [2]), antimicrobial and antioxidant [3], and also antihemorrhagic [4] properties. Addition as a substituent to the benzofuran system of a pyrrole ring, which is a fragment of many molecules providing the active life of organisms (chlorophyll, hemoglobin, etc.), seemed of interest both for the chemistry of benzofuran and pyrrole, and for the purpose-directed search for new biologically active compounds.

Addition of the pyrrole ring to terpenoids [5] and steroids [6,7] has been effected by the Trofimov reaction. In the present work the possibility has been studied of using this reaction for the synthesis of previously unknown 2-pyrrolylbenzo[*b*]furans starting from the oxime of 2-acetylcoumarone (**1**).

A close structural analog of compound **1**, the oxime of 2-acetylfuran, reacts with acetylene (70-78°C, 6 h, 14 atm, KOH) in aqueous DMSO forming 2-(2-furyl)pyrrole in low yield (11%), but gives mainly the product of vinylation, the O-vinyl oxime (38%) [8]. From oxime **1** and acetylene under pressure in anhydrous KOH–DMSO even after 5 min at 70°C the intermediate O-vinyl oxime **2** and the desired pyrrole **3** were obtained in low yield, 22 and 24% respectively. The vinylation of oximes of dialkyl and alkyl aryl ketones [9] and also diaryl and aryl hetaryl ketones [10] under similar conditions is a known fact, and the rapid rearrangement of **2** → **3** after so short a time is unexpected (Scheme 1).

The more ready pyrrolization of O-vinyl ketoxime **2** in comparison with the O-vinyl oxime of 2-acetylfuran is evidently caused by the formation of a thermodynamically more stable conjugation system due to the participation in it of the benzene ring annelated with the furan ring and including the resulting pyrrole

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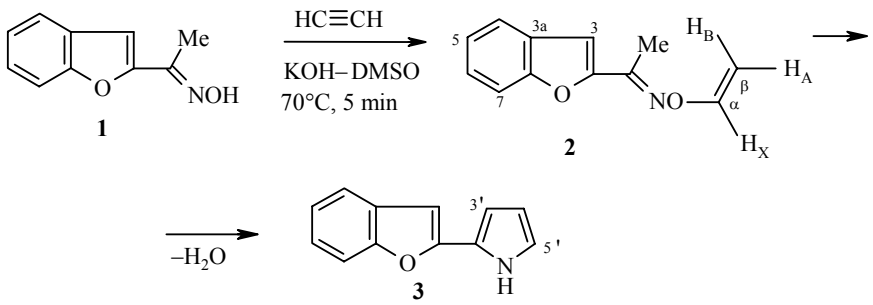
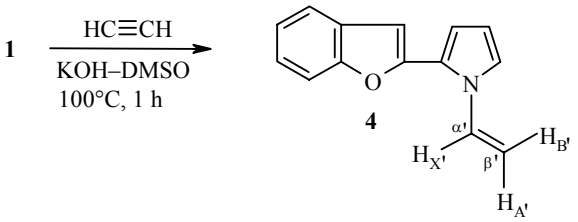
Scheme 1



ring. This also explains the ready transformation of 2-acetylnaphthalene oxime into the corresponding pyrrole (KOH–DMSO, acetylene, 60°C, 3 h) [11, 12] compared with its nonannelated analog, the oxime of acetophenone (75°C, 3 h) [8, 13].

At higher temperatures (100°C) and increasing the reaction time to 1 h N-vinylpyrrole **4** (yield 46%) is formed as the sole product from oxime **1** and acetylene. A similar conversion occurs in the case of oximes of alkyl furyl ketones. Under closely similar conditions (100-130°C, 2.5-3 h, initial pressure 16 atm) N-vinyl-2-furylpyrroles were obtained in 50-85% yield [13].



The structures of the synthesized products **2**-**4** were confirmed by IR (by comparison with the previously obtained data of [14, 15]), ^{1}H and ^{13}C NMR spectroscopy (Tables 1 and 2) and the compositions by elemental analysis.

Procedures of homonuclear ^{1}H-^{1}H 2D spectroscopy (COSY and NOESY) and heteronuclear ^{1}H-^{13}C 2D spectroscopy (HSQC and HMBC) were used to assign signals in the ^{1}H and ^{13}C spectra. Unidimensional sections of HSQC spectra at appropriate frequencies were also considered to refine the position of the signals of aromatic protons.

The signal of the H-3 proton in the ^{1}H NMR spectrum of the *Z*-isomer of O-vinyl oxime **2** was displaced significantly towards low field in comparison with the analogous signal in the spectrum of the *E*-isomer (Table 1), which is caused by the spatial proximity of this proton to the oxime oxygen atom [16]. The position of the signal of the NH group proton in the spectrum of pyrrole **3** was almost no different from the position of the analogous signal in the spectrum of 2-phenylpyrrole. The same applies to the frequency of the stretching vibrations of the N–H bond of both compounds (3480 cm^{-1}) [17]. The data given show the absence, as in the case of 2-(2-furyl)pyrrole [18], of an intramolecular N–H···O bond in pyrrole **3**. The signal of the $H_{X'}$ proton in the spectrum of N-vinylpyrrole **4** is displaced towards low field by 0.2 ppm in comparison with the corresponding signal for N-vinyl-2-(2-furyl)pyrrole [19]. This displacement is probably caused by the anisotropic effect of the condensed benzene ring. No intramolecular C–H···O hydrogen bonds are formed in either of the indicated compounds.

TABLE 1. ^{1}H NMR Spectra of Compounds **2-4**

Compound	Proton signals, δ, ppm (coupling constants, *J*, Hz)											
	CH_3/NH	H-3	H-4, m	H-5, m	H-6, m	H-7	H_A/$H_{A'}$, dd	H_B/$H_{B'}$, dd	H_X/$H_{X'}$, dd	H-3'	H-4'	H-5'
(*E*)-**2**	2.33	7.07 (d, J = 1.0)	7.54	7.23	7.34	7.58 (m)	4.23 (J_{AB} = –1.8)	4.71 (J_{BX} = 14.2)	7.12 (J_{AX} = 6.6)	—	–	—
(*Z*)-**2**	2.40	7.76 (d, J = 1.0)	7.50	7.26	7.38	7.66 (m)	4.25 (J_{AB} = –1.8)	4.77 (J_{BX} = 14.2)	7.02 (J_{AX} = 6.6)	—	—	—
3	8.74	6.69 (s)	7.51	7.18	7.22	7.48(d, J = 8.2)	—	—	—	6.65 (m)	6.31 (m)	6.89 (m)
4	—	6.70 (s)	7.54	7.21	7.27	7.48 (d, J = 8.2)	4.85 ($J_{A'B'}$ = -1.1)	5.25 ($J_{B'X'}$ = 15.5)	7.32 ($J_{A'X'}$ = 8.6)	6.64 (dd, $J_{3'5'}$ = 1.6)	6.32 (dd, $J_{3'4'}$ = 3.6)	7.14 (dd, $J_{4'5'}$ = 2.6)

TABLE 2. ^{13}C NMR Spectra of Compounds **2-4**

Compound	Signals of ^{13}C nuclei, δ, ppm													
	$C_{(2)}$	$C_{(3)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(7a)}$	C=N/$C_{(2')}$	Me/$C_{(3')}$	$C_{(4')}$	$C_{(5')}$	C_{α}/$C_{\alpha'}$	C_{β}/$C_{\beta'}$
(*E*)-**2**	149.51	107.99	127.77	121.56	123.34	126.03	111.78	155.34	150.95	12.57	—	—	152.90	89.09
(*Z*)-**2**	146.05	114.61	128.23	121.52	122.21	126.59	111.59	153.65	146.49	17.66	—	—	152.73	88.89
3	150.06	98.16	129.46	120.46	123.06	123.48	110.76	154.02	123.35	110.34	107.73	119.44	—	—
4	148.96	103.28	128.91	120.73	123.05	124.13	111.11	154.55	124.13	112.16	110.69	120.23	132.12	100.87

As a result of the carried out investigation it has been shown possible in principle to synthesize previously unknown 2-pyrrolylcoumarones from available 2-acyl derivatives of benzofuran by the Trofimov reaction. After optimizing the reaction conditions, as the attempt to develop it indicates (see for example [11]), the yields of pyrroles may be considerably higher. The presence of a reactive N-vinyl group in the synthesized pyrroles raises additional possibilities for synthesizing polymers, medicinal preparations of prolonged action, and also ligands for the design of complexed metal catalysts.

EXPERIMENTAL

The ^{1}H (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded on a Bruker-400DPX spectrometer in $CDCl_3$, internal standard was HMDS (0.055 ppm for ^{1}H and 2.00 ppm for ^{13}C). The IR spectra were taken on a Bruker ISF 25 instrument.

2-Acetylcoumarone Oxime (1). Finely powdered NaOH (14.44 g, 361.1 mmol) was slowly added in small portions with shaking to a mixture of 2-acetylcoumarone (10.80 g, 67.4 mmol), $NH_2OH{\cdot}HCl$ (7.32 g, 105.3 mmol), 95% EtOH (40 ml), and H_2O (5 ml), then H_2O (10 ml) was poured in. The mixture obtained was stirred for 1 h at room temperature and poured into a cold solution of conc. hydrochloric acid (36 ml) in H_2O (250 ml). The solid was filtered off, washed carefully with cold water, and after drying in the air, oxime **1** (11.36 g, 96%) was obtained as a white powder; mp 110-114°C (ethanol). Found, %: C 68.71; H 5.23; N 7.88. $C_{12}H_9NO$. Calculated, %: C 68.56; H 5.18; N 8.00.

2-Acetylcoumarone O-Vinyl Oxime (2) and 2-(2-Pyrrolyl)coumarone (3). A mixture of ketoxime **1** (2.00 g, 11.4 mmol) and finely powdered $KOH{\cdot}0.5H_2O$ (1.48 g, 22.8 mmol) in DMSO (50 ml) was saturated with acetylene in an autoclave (initial pressure 14 atm) at room temperature, then heated rapidly to 70°C, and maintained at this temperature for 5 min. After cooling, water (100 ml) was added to the reaction mixture, and the mixture was extracted with ether (4 × 40 ml). The total ether extract was washed with water (3 × 30 ml), and dried over K_2CO_3. After removing the ether, the residue obtained was chromatographed on a column [basic Al_2O_3, hexane–ether (gradient from 1:0 to 1:1)] and product **2** (0.51 g) and product **3** (0.5 g) were isolated.

O-Vinyl Oxime 2. Yield 22%, transparent colorless liquid, n_D^{22} 1.6025. IR spectrum (film), ν, cm^{-1}: 3126 (CH_2=), 3066 (HC=), 3039 (HC=), 2926 (asCH_3), 2853 (sCH_3), 1637 (C=N), 1607 (C=C-O), 1560 (skeletal ring vibrations), 1473 ($\delta_{as}CH_3$), 1451 ($\delta_{as}CH_3$), 1381 (δ_sCH_3), 1353 (δ_sCH_3), 1307, 1259 (C–C), 1219, 1180 (C–O), 1165 (C–O), 1146 (C–O), 1111 (C–C skeletal vibrations of the benzofuran frame), 1081, 1014 (–O–CH=CH_2), 979 (N–O), 948, 934, 883 (γCH), 839 (δCH_2=), 810 (δCH_2=), 751 (4 adjacent hydrogen atoms in an aromatic ring), 738 (γCH), 714, 697, 664, 614, 576, 565, 515, 482, 431. Found, %: C 71.79; H 5.62; N 7.05. $C_{12}H_{11}NO_2$. Calculated, %: C 71.63; H 5.51; N 6.96.

Coumarone 3. Yield 24%, fine white needle-like crystals; mp 128-132°C (ether). IR spectrum (KBr), ν, cm^{-1}: 3427 (N–H), 3107 (CH=), 3047 (CH=), 3022 (CH=), 1624, 1611, 1555, 1532, and 1520 (skeletal ring vibrations), 1472, 1456, 1410, 1351, 1305, 1289, 1255 (C–C), 1212, 1169, 1145 (C–O), 1121, 1099 (C–C skeletal vibrations of the benzofuran frame), 1043, 1029, 1006, 949, 932, 880, 792, 750 (4 adjacent hydrogen atoms in an aromatic ring), 720 (γCH), 633, 545, 533, 513, 441. Found, %: C 78.65; H 4.96; N 7.08. $C_{12}H_9NO$. Calculated, %: C 78.67; H 4.95; N 7.65.

2-(1-Vinyl-2-pyrrolyl)coumarone (4). Using the procedure for the synthesis of compounds **2** and **3** a mixture of ketoxime **1** (1.47 g, 8.4 mmol) and finely powdered $KOH{\cdot}0.5H_2O$ (1.09 g, 16.8 mmol) in DMSO (50 ml) was saturated with acetylene, then heated for 30 min to 100°C, and maintained at this temperature for 1 h. After working up and removal of the ether, product **4** (0.81 g) was isolated from the residue by column chromatography (basic Al_2O_3, hexane). Yield 46%, transparent bright-yellow liquid, n_D^{23} 1.6535. IR spectrum (film), ν, cm^{-1}: 3108 (H_2C=), 3063 (HC=), 3045 (HC=), 1643 (C=C), 1611, 1599 and 1513, 1462 (stretching vibrations of the hetero ring), 1442, 1420 (δ-CH=CH_2), 1346, 1320 (δ-CH=CH_2), 1305, 1290, 1260, 1227

(C–O), 1212, 1174, 1160, 1145, 1108, 1076, 1062, 1034, 1008, 993, 963 (γ-CH=CH_2), 914, 874, 791, 749 (4 adjacent hydrogen atoms), 720 (γH–C=), 678, 613, 591, 461, 436. Found, %: C 80.17; H 5.10; N 6.74. $C_{14}H_{11}NO$. Calculated, %: C 80.36; H 5.30; N 6.69.

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REFERENCES

1. A. R. Katritzky and J. M. Lagowski, *Heterocyclic Chemistry,* John Wiley & Sons, New York (1960), 274 pp.
2. D. H. R. Barton and W. D. Ollis (editors), *Comprehensive Organic Chemistry*, Pergamon, Oxford (1979); [Russian translation], Khimiya, Moscow (1985), pp. 167, 178, 188, 196, 202.
3. S. Demizu, K. Kajiyama, K. Takahashi, Y. Hiraga, S. Yamamoto, Y. Tamura, K. Okada, and T. Kinoshita, *Chem. Pharm. Bull.*, **36**, 3474 (1988).
4. T. Kosuge. H. Ishida, and T. Satoh, *Chem. Pharm. Bull.*, **33**, 202 (1985).
5. B. A. Trofimov, A. M. Vasil'tsov, E. Yu. Schmidt, O. V. Petrova, and A. I. Mikhaleva, *Zh. Org. Khim.*, **30**, 576 (1994).
6. A. M. Vasil'tsov, E. Yu. Schmidt, A. I. Mikhaleva, A. V. Afonin, and A. B. Zaitsev, *Khim. Geterotsikl. Soedin.*, 1641 (2001).
7. A. M. Vasil'tsov, A. B. Zaitsev, A. I. Mikhaleva, E. Yu. Schmidt, and A. V. Afonin, *Khim. Geterotsikl. Soedin.*, 66 (2002).
8. O. A. Tarasova, S. E. Korostova, A. I. Mikhaleva, L. N. Sobenina, R. N. Nesterenko, S. G. Shevchenko, and B. A. Trofimov, *Zh. Org. Khim.*, **30**, 810 (1994).
9. B. A. Trofimov, A. I. Mikhaleva, A. M. Vasil'tsov, E. Yu. Schmidt, O. A. Tarasova, L. V. Morozova, L. N. Sobenina, T. Preiss, and J. Henkelmann, *Synthesis*, 1125 (2000).
10. A. B. Zaitsev, A. M. Vasil'tsov, E. Yu. Schmidt, A. I. Mikhaleva, L. V. Morozova, A. V. Afonin, I. A. Ushakov, and B. A. Trofimov, *Tetrahedron*, **58**, 10043 (2002).
11. B. A. Trofimov and A. I. Mikhaleva, *N-Vinylpyrroles* [in Russian], Nauka, Novosibirsk (1984).
12. S. E. Korostova, B. A. Trofimov, L. N. Sobenina, A. I. Mikhaleva, and M. V. Sigalov, *Khim. Geterotsikl. Soedin.*, 1351 (1982).
13. B. A. Trofimov, A. I. Mikhaleva, R. I. Polovnikova, S. E. Korostova, R. N. Nesterenko, N. I. Golovanova, and V. K. Voronov, *Khim. Geterotsikl. Soedin.*, 1058 (1981).
14. B. A. Trofimov, *Heteroatomic Derivatives of Acetylene. New Polyfunctional Reagents, Monomers, and Intermediates* [in Russian], Nauka, Moscow (1981).
15. V. A. Koptyug (editor), *Atlas of Spectra of Aromatic and Heterocyclic Compounds, Part 21. Absorption Spectra of Pyrrole and 1-Vinylpyrrole in Infrared, Ultraviolet, and Visible Regions* [in Russian], Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk (1981).
16. A. V. Afonin, I. A. Ushakov, S. V. Zinchenko, O. A. Tarasova, and B. A. Trofimov, *Magn. Res. Chem.*, **38**, 994 (2000).
17. A. V. Afonin, I. A. Ushakov, O. V. Petrova, L. N. Sobenina, A. I. Mikhaleva, V. K. Voronov, and B. A. Trofimov, *Zh. Org. Khim.*, **36**, 1074 (2000).
18. A. V. Afonin, S. Yu. Kuznetsova, I. A. Ushakov, V. K. Voronov, A. I. Mikhaleva, and E. Yu. Schmidt, *Zh. Org. Khim.*, **38**, 1712 (2002).
19. A. V. Afonin, I. A. Ushakov, S. Yu. Kuznetsova, O. V. Petrova, E. Yu. Schmidt, and A. I. Mikhaleva, *Magn. Res. Chem.*, **40**, 114 (2002).