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LETTERS TO THE EDITOR

INTERACTION OF 2-PIPERAZINOBENZ-ALDEHYDE WITH CYANOACET(THIO)AMIDE: STEREOSELECTIVE CYCLIZATION BY THE "*tert*-AMINO EFFECT" MECHANISM

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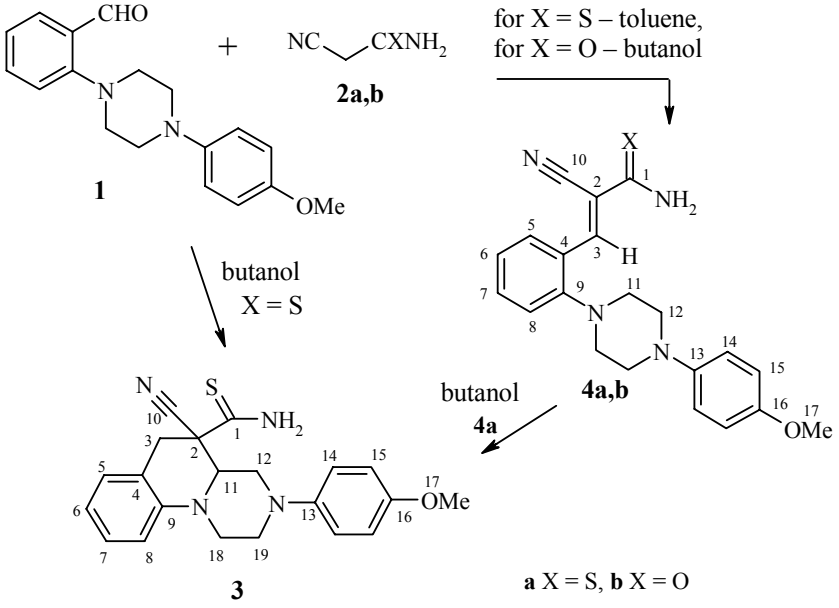
In continuing our research on the interaction of 2-dialkylaminobenzaldehydes with unsymmetrical CH-active compounds we have carried out the reaction of 2-piperazinobenzaldehyde **1** with cyanothioacetamide **2a** and cyanoacetamide **2b**. It was shown that the reaction of 2-piperazinobenzaldehyde **1** with cyanothioacetamide **2a** in butanol for 2 h the product of tandem reactions [2], the Knoevenagel condensation and cyclization by the "*tert*-amino effect" mechanism [3-6], 2,3,4,41,5,6-hexahydro-1H-pyrazin[1,2-*a*]quinoline **3** was formed, while reaction of benzaldehyde **1** with cyanoacetamide **2b** stopped at the stage of formation of the Knoevenagel



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condensation product **4b** which did not cyclize on prolonged heating. When the reaction of 2-piperazinobenzaldehyde **1** with cyanothioacetamide **2a** was carried out in toluene the vinyl derivative **4a** was isolated, which on heating in butanol cyclized to the pyrazinoquinoline **3**. The starting materials were recovered when the benzaldehyde **1** was boiled with cyanoacetamide **2b** in toluene.

It should be noted that compound **4a** contains two asymmetric centers, consequently it is possible to form two diastereoisomers. It was shown that the reaction occurs stereospecifically and leads predominantly to a single diastereomer in 95-98% yield. The proton in position 11 (see scheme) is axial, which is confirmed by its coupling constant in the ^{1}H NMR spectrum (J =14.5 Hz). In the ^{13}C NMR spectrum the signal of the carbon atom of the thiocarbamide group occurs at 199.88 ppm in the form of a triplet (J ~ 7.7 Hz, coupling with two axial protons), which indicates its axial position.

Thus we have shown that cyclization of the thioamide **4a** leads selectively to the (4*aR*,5R**)-isomer **3,** whereas under analogous conditions the amide **4b** does not cyclize at all: a Lewis acid catalyst [7] is necessary for cyclization.

^{1}H and ^{13}C NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker DRX instrument (400 and 100 MHz respectively).

(4aR*,5R*)-5-Cyano-3-(4-methoxyphenyl)-2,3,4,4*a*,5,6-hexahydro-1H-pyrazin[1,2-*a*]quinoline-5-carbothioamide (3). Yield 69%; mp 193°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (1H, s, NH); 9.39 (1H, s, NH); 7.17 (1H, dd, *J* = 8.2, 8.3, ArH); 7.11 (1H, d, *J* = 8.3, ArH); 7.08 (1H, d, *J* = 7.8, ArH); 6.91 and 6.88 (4H, AB, *J* = 9.2, C_6H_4); 6.78 (1H, dd, *J* = 7.8, *J* = 8.2, ArH); 4.09 (1H, ddd, *J* = 11.2, *J* = 2.6, *J* = 2.1, H-18*e*); 3.71 (1H, d, *J* = 16.4, H-3*e*); 3.70 (3H, s, CH_3); 3.69 (1H, dd, *J* = 11.0, *J* = 3.0, H-12*e*); 3.64 (1H, dd, *J* = 10.8, *J* = 3.0, H-11*a*); 3.54 (1H, ddd, *J* = 11.8, *J* = 3.0, *J* = 2.1, H-19*e*); 3.20 (1H, d, *J* =16.4, H-3*a*); 2.91 (1H, ddd, *J* = 11.9, *J* = 11.5, *J* = 3.0, H-18*a*); 2.80 (1H, ddd, *J* = 11.9, *J* = 11.8, *J* = 2.6, H-19*a*); 2.64 (1H, dd, *J* =11.0, *J* = 10.8, H-12*a*). ^{13}C NMR spectrum, δ, ppm: 199-88 (C-1); 153.77 (C-16); 144.55 (C-13); 144.04 (C-9); 129.15 (C-7); 127.85 (C-9); 119.04 (C-6); 118.68 (C-10); 118.26 (C-15); 117.98 (C-4); 114.51 (C-14); 113.44 (C-8); 58.44 (C-11); 55.20 (C-16); 53.90 (C-2); 52.00 (C-18); 50.13 (C-12); 46.12 (C-19); 38.54 (C-3). Found, %: C 66.81; H 5.92; N 14.99. $C_{21}H_{22}N_4OS$. Calculated, %: C 66.64; H 5.86; N 14.80.

2-Cyano-3-(2-(4-(4-methoxyphenyl)piperazin-1-yl)phenyl)thioacrylamide (4a). Yield 81%; mp 186°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.12 (1H, s, NH); 9.49 (1H, s, NH); 8.49 (1H, s, CH=); 7.93 (1H, dd, *J* = 7.6, *J* =1.5, ArH); 7.57 (1H, ddd, *J* = 8.5, *J* = 8.3, *J* = 1.5, ArH); 7.24 (1H, d, *J* = 8.3, ArH); 7.21 (1H, dd, *J* =7.6, *J* = 6.5, ArH); 6.95 (2H, d, *J* = 9.1, C_6H_4); 6.85 (2H, d, *J* = 9.1, C_6H_4); 3.70 (3H, s, CH_3); 3.20-3.25 (4H, m, $2NCH_2$); 3.06-3.10 (4H, m, $2NCH_2$). ^{13}C NMR spectrum, δ, ppm: 191.93 (C-1); 153.44 (C-16); 153.06 (C-9); 147.89 (C-3); 145.11 (C-13); 133.13 (C-5); 128.99 (C-7); 125.26 (C-4); 122.53 (C-6); 118.90 (C-8); 117.43 (C-15); 116.14 (C-10); 114.29 (C-14); 111.58 (C-2); 55.17 (C-17); 52.88 (C-11); 49.84 (C-12). Found, %: C 76.21; H 8.03; N 7.55. $C_{12}H_{15}NO$. Calculated, %: C 76.16; H 7.99; N 7.40.

2-Cyano-3-(2-(4-(4-methoxyphenyl)piperazin-1-yl)phenyl)acrylamide (4b). Yield 86%; mp 210°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.35 (1H,s, CH=); 7.91 (1H, dd, *J* = 7.9, *J* = 1.3, ArH); 7.90 (1H, s, NH); 7.72 (1H, s, NH), 7.56 ddd, *J* = 8.5, *J* = 7.5, *J* = 1.3, ArH), 7.25 (1H, d, *J* = 7.5, ArH), 7.22 (1H, dd, *J* = 7.3, *J* = 8.5, ArH); 6.95 (2H, d, *J* = 9.1, C_6H_4); 6.84 (2H, d, *J* = 9.1, C_6H_4); 3.70 (3H, s, CH_3); 3.18-3.22 (4H, m, $2NCH_2$); 3.05-3.10 (4H, m, $2NCH_2$). Found, %: C 76.21; H 8.03; N 7.55. $C_{12}H_{15}NO$. Calculated, %: C 76.16; H 7.99; N 7.40.

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