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Reaction of 2-methyl-3,4-dihydro-β-carbolin-2-ium iodide with acylmethyl halides controlled by electronic effects: a new route to 1,2-dihydroazepino[4,5-*b*]indoles

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General methods

The starting compounds were provided by InterBioscreen Ltd. (Russia) and were used without additional purification. The solvents were purified using standard procedures. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 25 ^{o}C on Varian Unity-300 (300 MHz) and Bruker Avance 600 (600 MHz) spectrometers. The chemical shifts of ^{1}H and ^{13}C nuclei (δ) are reported relative to the residual signals of the deuterated solvent (δ = 2.49 for protons and 39.5 for carbon nuclei). The electron impact mass spectrum (70 eV) was obtained on a Finnigan MATINCOS 50 instrument with direct sample injection. Melting points were determined on a Fisher - Johns Melting Point Apparatus (Fisher Scientific, USA). The crystallographic data (except the structural factors) for structures **3a**, **4g** were deposited to the Cambridge Crystallographic Data Centre under the numbers: CCDC 1535545, 1535547. Elementary analysis was carried out by the classical microprobe analysis method. The course of the reactions and the purity of the compounds obtained were monitored by TLC (plates with Al_2O_3 of III activity grade, $CHCl_3$ as the eluent, visualization by iodine vapors in a humidity cabinet).

The following halo ketones were used as reagents: **2a –** phenacyl bromide; **2b –** 4-bromophenacyl bromide; **2c** – 4-nitrophenacyl bromide; **2d** – 4-methoxyphenacyl bromide; **2e –** 3,4-dimethoxyphenacyl bromide; **2f –** 3-chloroacetylindole; **2g** – 3-chloroacetyl-1,2-dimethylindole; **2h –** 5-methoxy-3-chloroacetyl-1,2-dimethylindole; 6-bromoacetyl-2,3-dihydrobenzo[*b*][1,4]dioxin.

Characteristics of compounds 3, 4:

*(3-Methyl-1,2-dihydroazepino[4,5-b]indol-4-yl)(phenyl)methanone (**3a**).*

Yield 82%. Orange crystals, m.p. 198-200 °C (EtOAc : MeCN 6 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.66 (s, 3H, Me), 3.07 (br. t, 2H, CH_2), 3.22 (br. t, 2H, CH_2), 6.26 (s, 1H, H-5), 6.95 (t, *J* 7.5 Hz, 1H, H-9), 7.02 (t, *J* 7.5 Hz, 1H, H-8), 7.22 (d, *J* 8.1 Hz, 1H, H-7), 7.43 (d, *J* 8.1 Hz, 1H, H-10), 7.46-7.58 (m, 3H, H-3′-5′), 7.82 (d, *J* 7.5 Hz, 2H, H-2′, 6′), 10.74 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 24.71, 41.10, 50.94, 108.22, 110.62, 115.15, 118.01, 188.63, 121.76, 128.36, 128.42, 129.13, 132.21, 132.29, 136.03, 138.45, 145.43, 193.74. Found (%): C, 79.16; H, 5.65; N, 9.01. Calculated for $C_{20}H_{18}N_2O$ (%): C, 79.44; H, 6.00; N 9.26. HRMS (ESI), m/z: 302 (calculated for $C_{20}H_{18}N_2O$, m/z: 302.14.

*(4-Bromophenyl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-4-yl)methanone (**3b**).*

Yield 80%. Red crystals, m.p. 195-198 °C (EtOAc). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.63 (s, 3H, Me), 3.06 (br.t, 2H, CH_2), 3.14 (br.t, 2H, CH_2), 6.35 (s, 1H, H-5), 6.96-6.99 (m, 1H, H-9), 7.06-7.09 (m, 1H, H-8), 7.26 (d, *J* 8.0 Hz, 1H, H-7), 7.50 (d, *J* 8.0 Hz, 1H, H-10), 7.42 (s, 4H, H-2′, 3′, 5′, 6′), 10.89 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 24.56, 41.02, 50.82, 109.00, 110.61, 115.51, 118.04, 118.62, 121.85, 126.07, 128.32, 131.05, 131.35, 132.02, 136.04, 137.50, 145.01, 192.65. Found (%): C, 62.91; H, 4.65; Br, 20.63; N, 7.02. Calculated for $C_{20}H_{17}BrN_2O$ (%): C, 63.00; H, 4.49; Br, 20.96; N 7.35.

*(3-Methyl-1,2-dihydroazepino[4,5-b]indol-4-yl)(4-nitrophenyl)methanone (**3c**).*

Yield 84%. Bright red crystals, m.p. 225-228 °C (CH_3CN). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.63 (s, 3H, Me), 3.06 (br.t, 2H, CH_2), 3.15 (br.t, 2H, CH_2), 6.35 (s, 1H, H-5), 6.99 (t, *J* 7.5 Hz, 1H, H-8), 7.09 (t, *J* 7.5 Hz, 1H, H-9), 7.27 (d, 1H, *J* 8.1 Hz, H-7), 7.52 (d, *J* 8.0 Hz, 1H, H-10), 7.99 (d, *J* 8.7 Hz, 2H, H-2′, 6′), 8.33 (d, *J* 8.7 Hz, 1H, H-3′,5′), 10.93 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 24.44, 40.98, 50.68, 110.73, 111.30, 116.47, 118.27, 118.74, 122.22, 123.35, 128.26, 130.24, 131.76, 136.23, 144.22, 144.60, 149.07, 192.23. Found (%): C, 69.28; H, 4.63; N, 12.00. Calculated for $C_{20}H_{17}N_3O_3$ (%): C, 69.15; H, 4.93; N 12.10. HRMS (ESI), m/z: 347 (calculated for $C_{20}H_{17}N_3O_3$, m/z: 347.37.

*(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-4-yl)-methanone (**3i**)*.

Obtained as a mixture with the 5-isomer (**4i**). Separation was performed on a column with Al_2O_3 in chloroform, yield 15%. Red crystals, m.p. 210-212 ºC (CH_3CN). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.60 (s, 3H, Me), 3.03 (d, *J* 5.4 Hz, 2H, CH_2), 3.18 (d, *J* 4.8 Hz, 2H, CH_2), 4.29-4.33 (m, 4H, $2CH_2$), 6.11 (s, 1H, H-5), 6.97-6.99 (m, 2H, H-8,9), 7.03-7.06 (m, 1H, H-8′), 7.25 (d, *J* 8.4 Hz, 1H, H-7′), 7.33 (d, *J* 2.4 Hz, 1H, H-5′), 7.39 (dd, *J* 2.4, 8.4 Hz, 1H, H-7), 7.48 (d, *J* 7.2 Hz, 1H, H-10), 10.83 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 24.74, 41.13, 51.00, 63.92, 64.48, 105.92, 110.47, 114.34, 116.87, 117.75, 118.10, 118.50, 121.41, 123.23, 128.41, 131.27, 132.35, 135.82, 142.87, 145.58, 147.43. Found (%): C, 73.01; H, 5.31; N, 7.92. Calculated for $C_{22}H_{20}N_2O_3$ (%): C, 73.22; H, 5.59; N 7.77.

(4-Methoxyphenyl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)methanone (***4d***).

Yield 70%. Dark beige crystals, m.p. 168-170 ºC (EtOAc : CH_3CN 10 : 1). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.08 (br. t, 2H, CH_2), 3.25 (s, 3H, Me), 3.55 (br. t, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.90-7.05 (m, 4H, H-7-10), 7.25 (s, 1H, H-4), 7.32-7.54 (m, 4H, 2′, 3′,5′, 6′-H), 11.20 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 24.80, 47.81, 53.19, 55.24, 102.04, 108.72, 111.09, 113.34, 116.25, 118.18, 119.84, 127.12, 130.65, 132.11, 133.84, 133.99, 155.08, 160.73, 193.62. Found (%): C, 75.49; H, 5.75; N, 8.65. Calculated for $C_{21}H_{20}N_2O_2$ (%): C, 75.88; H, 6.06; N 8.43. MS (ESI), m/z: 332 (calculated for $C_{21}H_{20}N_2O_2$, m/z: 332.15.

*(3,4-Dimethoxyphenyl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)methanone (**4e**)*.

Yield 68%, m.p. 192-196 ºC (EtOAc :CH_3CN 10 : 1). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.11 (br. t, 2H, CH_2), 3.15 (s, 3H, Me), 3.57-3.59 (m, 2H, CH_2), (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.91-6.98 (m, 2H, H-8,9), 7.00 (d, *J* 8.3 Hz, 1H, H-5′), 7.12 (dd, *J* 2.0, 8.2 Hz, 1H, H-6′), 7.15 (d, *J* 2.0 Hz, 1H, H-2′), 7.33 (s, 1H, H-4), 7.38 (d, 1H, *J* 7.5 Hz, H-7), 7.43 (d, *J* 8.1 Hz, 1H, H-10), 11.23 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 24.76, 47.75, 53.17, 55.51, 55.52, 101.87, 108.67, 110.59, 110.97, 112.23, 116.19, 118.11, 119.77, 122.13, 127.07, 132.11, 133.86, 133.92, 148.21, 150.45, 155.11, 193.48. Found (%): C, 72.59; H, 5.71; N, 7.42. Calculated for $C_{22}H_{22}N_2O_3$ (%): C, 72.91; H, 6.12; N 7.73

*(1H-Indol-3-yl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)methanone (**4f**)*.

Yield 62%. Beige crystals, m.p. 237-240 ºC (EtOAc : CH_3CN : H_2O 10 : 2 : 0.5). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.12-3.13 (m, 2H, CH_2), 3.17 (s, 3H, Me), 3.58 (t, *J* 4.4 Hz, 2H, CH_2), 6.91-6.96 (m, 2H, H-5′,6′), 7.14 (dt, *J* 0.8, 7.5 Hz, 1H, H-8), 7.19 (dt, *J* 1.2, 7.5 Hz, 1H, H-9), 7.37 (d, *J* 7.6, 1H, H-7′), 7.42 (d, *J* 7.3 Hz, 1H, H-7), 7.47 (d, *J* 8.0 Hz, 1H, H-10), 7.59 (s, 1H, H-4), 7.79 (s, 1H, H-2′), 8.04 (d, *J* 7.9 Hz, 1H, H-4′), 10.93 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 25.06, 47.02,52.91, 103.47, 108.27, 110.89, 11.86, 116.08, 116.87, 118.01, 119.59, 120.49,

121.06, 122.16, 126..83, 127.37, 131.29, 132.55, 133.93, 136.43, 152.77, 188.95. Found (%): C, 77.09; H, 5.88; N, 11.00. Calculated for $C_{22}H_{19}N_3O$ (%): C, 77.40; H, 5.61; N 12.31.

(1,2-Dimethyl-1H-indol-3-yl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)methanone ***(4g)***. Yield 60%. Light beige crystals, m.p. 234-237 ºC (EtOAc). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.58 (s, 3H, NCH_3), 2.96 (s, 3H, CH_3), 3.20 (br.t, 2H, CH_2), 3.17 (s, 3H, NMe), 3.66 (br.t, 2H, CH_2), 6.90-6.94 (m, 2H, H-5′,6′), 7.04-7.11 (m, 1H, H-8,9), 7.31-7.36 (m, 3H, H-7,10,7′), 7.40 (s, 1H, H-4), 7.58 (d, *J* 7.8 Hz, 1H, H-4′), 11.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.14, 25.00, 29.56, 47.31, 53.08, 103.73, 108.18, 109.70, 111.03, 113.96, 116.12, 118.13, 119.49, 119.65, 120.29, 121.09, 127.03, 127,27, 132.47, 133.90, 136.09, 140.46, 154.40, 189.75. Found (%): C, 77.81; H, 6.44; N, 11.06. Calculated for $C_{24}H_{23}N_3O$ (%): C, 78.02; H, 6.27; N 11.37. HRMS (ESI), m/z: 369.5 (calculated for $C_{22}H_{23}N_3O$, m/z: 369.46).

(5-Methoxy-1,2-dimethyl-1H-indol-3-yl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)-methanone ***(4h)***.

Yield 57%. Beige crystals, m.p. 203-206 ºC (EtOAc). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 2.51 (s, 3H, N-Me), 3.10 (s, 3H, C-Me), 3.13 (t, *J* 4.0 Hz, 2H, CH_2), 3.61 (br.t, 2H, CH_2), 3.70 (s, 3H, NCH_3), 3.72 (s, 3H, OCH_3), 6.78 (dd, *J* 2.4, 8.9 Hz, 1H, H-6′), 6.91-6.97 (m, 2H, H-8, 9), 7.14 (d, *J* 2.3 Hz, 1H, H-4′), 7.37-7.39 (m, 3H, 4, 7, H-7′), 7.44 (d, *J* 7.6 Hz, 1H, H-10), 11.38 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 12.22, 25.02, 29.64, 47.18, 53.04, 55.16, 101.53, 103.51, 108.09, 110.38, 110.84, 110.95, 113,78, 116.03, 118.05, 119.56, 127.25, 127.51, 131.20, 132.44, 133.87, 140.93, 154.10, 154.33, 189.69. Found (%): C, 74.89; H, 6.65; N, 10.14. Calculated for $C_{25}H_{25}N_3O_2$ (%): C, 75.16; H, 6.31; N 10.52.

(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)(3-methyl-1,2-dihydroazepino[4,5-b]indol-5-yl)-methanone ***(4i)***.

Obtained as a mixture with the 4-isomer. Separation was performed on a column with Al_2O_3 in chloroform. Yield 54%, beige crystals, m.p. 194-196 ºC (EtOAc). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 3.09-3.10 (m, 2H, CH_2), 3.15 (s, 3H, N-Me), 3.56-3.58 (m, 2H, CH_2), 4.27-4.30 (m, 4H, $2CH_2$), 6.91-7.06 (m, 5H, H-5′,7′,8′,8,9), 7.30 (s, 1H, H-4), 7.36-7.38 (m, 1H, H-7), 7.43-7.44 (m, 1H, H-10), 11.23 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 24.72, 47.79, 53.19,63.98, 64.22, 101.79, 108.67, 11.01, 116.18, 116.33, 117.60, 118.11, 119.77, 122.21, 127.03, 132.00, 133.92, 134.68, 142.82, 145.09, 155.17, 193.08. Found (%): C, 73.01; H, 5.31; N, 7.92. Calculated for $C_{22}H_{20}N_2O_3$ (%): C, 73.22; H, 5.59; N 7.77.