Cyclization of *N*-acetyl-*ortho*-cycloalkenylanilines on treatment with bromine and *N*-bromosuccinimide

R. R. Gataullin, I. S. Afon'kin, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov*

Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Russian Federation. Fax: +7 (347 2) 35 6066. E-mail: akhat@anrb.ru

The reaction of *N*-acetyl-2-(cyclohex-1-enyl)aniline with Br_2 or *N*-bromsuccinimide at 20 °C is accompanied by intramolecular cyclization to give brominated 3,1-benzoxazines or 4-acetyl-(3-bromo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole.

Key words: 2-(cyclohex-1′-enyl)aniline, *N*-acetyl-2-(cyclohex-1′-enyl)aniline, 2′-bromo-2-methylspiro[(4*H*-3,1-benzoxazine)-4,1′-cyclohexane], *N*-acetyl-2-(cyclopent-2′-en-1′-yl)-2-methylaniline, *N*-bromosuccinimide, intramolecular cyclization, 4-acetyl-(3-bromo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole).

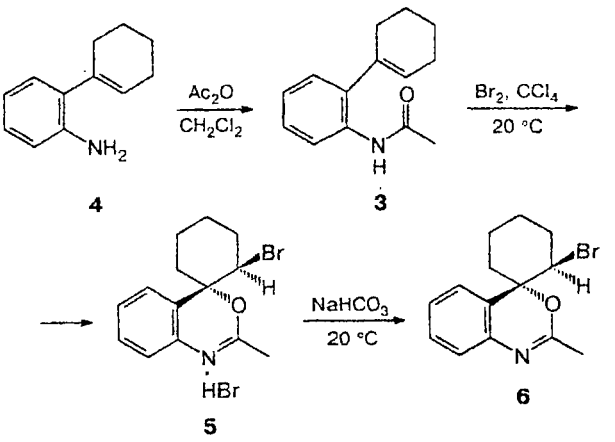
To continue our research[1,2] dealing with heterocyclization of *ortho*-alkenylarylamines, we studied the reaction of their acetyl derivatives with molecular bromine and *N*-bromosuccinimide. Previously, it has been reported[1] that 3,1-benzoxazine is formed on bubbling of gaseous HCl into a solution of *N*-acetyl-2-(cyclopent-1′-en-1′-yl)-6-methylaniline (**1**) in CH_2Cl_2 and that 2-(cyclopent-2′-en-1′-yl)-6-methylaniline hydrochloride (**2**) undergoes cyclization[2] at 200 °C to give 8-methylperhydrocyclopenta[*b*]indole. Both reactions afford compounds containing no functional groups in the side chains of the heterocycles.

In this study, we extended for the first time the known halocyclization reaction[3] to derivatives of *ortho*-alkenylarylamines,[4] in order to open a way to bromine-substituted benzoxazines and indolines. Thus, the addition of a CCl_4 solution of Br_2 at 20 °C to a CCl_4 solution of *N*-acetyl-2-(cyclohex-1′-enyl)aniline (**3**), prepared from amine **4** by a procedure described previously,[1] gives rise to 3,1-benzoxazine hydrobromide **5** (Scheme 1), whose treatment with a 10% solution of $NaHCO_3$ affords base **6** (yield 97%). It is known that halogenation of amido-derivatives of cyclohexene[5] and related six-membered rings[6,7] yields heterocycles with the *trans*-arrangement of the halogen and oxygen atoms. Apparently, in the benzoxazine that we prepared, these atoms are also arranged in this way.

Intramolecular cyclization of acetanilide **7** on treatment with NBS in CCl_4 gives indoline **8** in a high yield (Scheme 2), whereas the reaction of compound **7** with molecular bromine in CCl_4 affords isomeric dibromides **9** and **10** in 1 : 1 ratio (according to ^1H and ^{13}C NMR spectra).

In the ^1H NMR spectrum of indoline **8** recorded using the double resonance method, the H(3a) proton is exhibited at δ 4.92 as a doublet of doublets with

Scheme 1

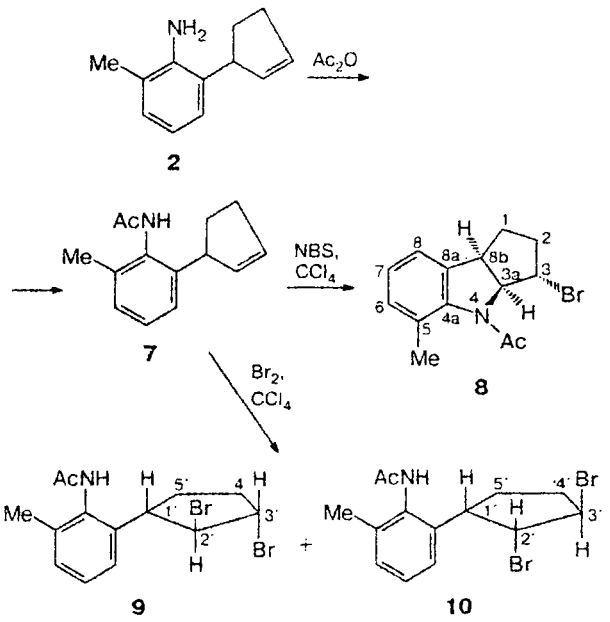


$J_{H(3a),H(8b)}$ = 7.99 Hz, pointing to the *cis*-arrangement of the H(3a) and H(8b) atoms; the low value of the vicinal constant, $J_{H(3a),H(3)}$ = 2.33 Hz, attests to the *trans*-orientation of the H(3a) and H(3) protons.[8] The substituents at the C(1′) and C(2′) atoms of the cyclopentyl fragment in molecule **9** occupy *trans*-positions; the conformation with the pseudoaxial orientation of substituents predominates, and the H(1′) and H(2′) protons are pseudoequatorial. This is indicated by the small spin—spin coupling constant of the H(2′) proton (a narrow multiplet at 4.74 ppm).[9,10] In addition, apparently, due to the *cis*-effect of the electron-withdrawing substituents on the H(1′) and H(2′) protons in compound **9**, the signals of these protons occur in a low field (4.02 and 4.74 ppm, respectively), whereas similar protons in compound **10** are manifested in a higher field (3.55 and 4.68 ppm, respectively). The substituents at

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 118—120, January, 2000.

1066-5285/00/4901-0122 $25.00

Scheme 2



the C(1′) and C(2′) atoms in molecule **10** are *cis*-arranged and the spin—spin coupling constants should be medium (4.5—6.5 Hz), which is actually observed for the H(2′) proton in the ^{1}H NMR spectra (6.08 Hz).[9,10]

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75 MHz, respectively). IR spectra were measured on a UR-20 instrument. Mass spectra were run on a MX 1320 mass spectrometer (EI, 70 eV). The purity of the reaction products was checked by TLC on Silufol UV-254 plates (in the CH_2Cl_2—MeOH system, 19 : 1).

2-(Cyclohex-1′-enyl)aniline (4). 2-(Cyclohex-2′-en-1′-yl)aniline (15.6 g, 3.03 mmol) was heated with 16 g of KOH for 50 min at 300 °C. The reaction mixture was cooled to 20 °C, decanted from solid KOH, and distilled *in vacuo*. Yield 14.8 g (95%), b.p. 120 °C (3 Torr). Found (%): C, 83.01; H, 8.42; N, 7.88. $C_{12}H_{15}N$. Calculated (%): C, 83.19; H, 8.73; N, 8.08. IR, ν/cm^{-1}: 3368; 3464 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 1.65—1.85 (m, 4 H, 2 CH_2); 2.15—2.30 (m, 4 H, 2 CH_2); 3.78 (s, 2 H, NH_2); 5.79 (m, 1 H, =CH); 7.10 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 22.08, 23.09, 25.24, 29.30 (C(3′), C(4′), C(5′), C(6′)); 115.29 (C(6)); 118.17 (C(4)); 126.71 (C(3)); 127.37 (C(2′)); 128.54 (C(5)); 130.36 (C(2)); 136.31 (C(1′)); 143.01 (C(1)).

***N*-Acetyl-2-(cyclohex-1′-enyl)aniline (3).** Yield 95%, m.p. 58—60 °C. Found (%): C, 78.10; H, 7.63; N, 6.34. $C_{14}H_{17}NO$. Calculated (%): C, 78.10; H, 7.96; N, 6.51. IR, ν/cm^{-1}: 3280 (NH). ^{1}H NMR ($CDCl_3$), δ: 2.07 (s, 3 H, Me); 1.66—2.37 (m, 8 H, 4 CH_2); 5.67 (m, 1 H, CH); 7.00—7.20 (m, 3 H, Ar); 7.68 (s, 1 H, NH); 8.05 (d, 1 H, H(2), J = 8.11 Hz). ^{13}C NMR ($CDCl_3$), δ: 21.62 (Me); 22.86, 24.39, 25.27, 29.67 (C(3′), C(4′), C(5′), C(6′)); 121.35 (C(6)); 123.91 (C(4)); 127.13 (C(3)); 128.11 (C(5)); 128.12 (C(2′)); 134.15 (C(2)); 134.92 (C(1′)); 135.76 (C(1)); 168.15 (C=O).

2′-Bromo-2-methylspiro[(4*H*-3,1-benzoxazine)-4,1′-cyclohexane] hydrobromide (5). A solution of Br_2 (0.1 mL, 1.9 mmol) in 5 mL of CCl_4 was added dropwise with stirring to a solution of compound **3** (0.4 g, 1.86 mmol) in 20 mL of dry CCl_4. The hydrobromide precipitate was filtered off and washed with 10 mL of CCl_4. Yield 0.65 g (94%), m.p. 165—167 °C. Found (%): C, 44.59; H, 4.31; Br, 42.40; N, 3.50. $C_{14}H_{17}Br_2NO$. Calculated (%): C, 44.83; H, 4.57; Br, 42.60; N, 3.73. ^{1}H NMR (DMSO-d_6), δ: 1.60—2.70 (m, 8 H, 4 CH_2); 2.51 (s, 3 H, Me); 4.86 (s, 1 H, H(2′)); 7.20—7.55 (m, 4 H, Ar); 8.35 (br.s, 1 H, HBr). ^{13}C NMR (DMSO-d_6), δ: 19.40 (C(3′)); 19.75 (C(6′)); 20.29 (Me); 29.79 (C(4′)); 30.11 (C(5′)); 54.19 (C(2′)); 79.31 (C(4)); 118.08 (C(5)); 123.86 (C(10)); 126.29 (C(7)); 127.56 (C(6)); 128.08 (C(8)); 129.80 (C(9)); 130.22 (C(7)); 168.43 (C(2)).

2′-Bromo-2-methylspiro[(4*H*-3,1-benzoxazine)-4,1′-cyclohexane] (6). Hydrobromide **5** (0.4 g, 1.7 mmol) was stirred with 20 mL of a 10% aqueous solution of $NaHCO_3$ for 5 min, the product was extracted with CH_2Cl_2 (2×20 mL) and dried with Na_2SO_4, and the solvent was evaporated at a reduced pressure. Yield 0.3 g (95%), m.p. 102—104 °C. Found (%): C, 57.10; H, 5.15; Br, 26.80; N, 4.64. $C_{14}H_{16}BrNO$. Calculated (%): C, 57.16; H, 5.48; Br, 27.16; N, 4.76. ^{1}H NMR ($CDCl_3$), δ: 1.60—2.65 (m, 8 H, 4 CH_2); 2.20 (s, 3 H, Me); 4.45 (br.s, 1 H, CH); 7.10—7.35 (m, 4 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 19.60 (C(3′)); 20.28 (C(6′)); 21.64 (Me); 29.54 (C(4′)); 29.98 (C(5′)); 53.93 (C(2′)); 78.91 (C(4)); 123.87 (C(6)); 125.66 (C(8)); 126.29 (C(7)); 126.95 (C(10)); 129.10 (C(5)); 138.22 (C(9)); 159.04 (C(2)).

***N*-Acetyl-2-(cyclopent-2′-en-1′-yl)-6-methylaniline (7).** Acetic anhydride (4.08 g, 40 mmol) was added to a solution of compound **2** (3.46 g, 20 mmol) in 10 mL of CH_2Cl_2 and the mixture was allowed to stand for 18 h, diluted with water, and extracted with 100 mL of CH_2Cl_2. The extract was washed with a 5% solution of $NaHCO_3$ until the evolution of CO_2 stopped and with water (20 mL) and dried with $MgSO_4$. The mixture was filtered and the solvent was evaporated to give 4.18 g (97.2%) of acetanilide **7**, R_f 0.68. IR, ν/cm^{-1}: 3280 (NH).

4-Acetyl-(3-bromo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole) (8). A mixture of anilide **7** (0.5 g, 2.3 mmol), NBS (0.45 g), and AIBN (10 mg) in 10 mL of CCl_4 was refluxed for 20 min, cooled, and filtered. The filtrate was washed with 20 mL of 10% $NaHCO_3$ and concentrated under reduced pressure. The residue was chromatographed on a short column with silica gel (2 g), using CH_2Cl_2 as the eluent, to give 0.61 g (91%) of indoline **8**, R_f 0.67. Found (%): C, 57.29; H, 5.51; Br, 27.13; N, 4.62. $C_{14}H_{16}BrNO$. Calculated (%): C, 57.16; H, 5.48; Br, 27.16; N, 4.76. ^{1}H NMR, δ: 1.70—2.30 (m, 4 H, 2 CH_2); 2.20 (s, 3 H, Me); 2.39 (s, 3 H, Me); 4.04 (t, 1 H, H(8′), J = 7.99 Hz); 4.27 (m, 1 H, H(3)); 4.92 (dd, 1 H, H(3a), $J_{H(3a),H(8b)}$ = 7.99 Hz, $J_{H(3a),H(3)}$ = 2.33 Hz); 6.95—7.30 (m, 3 H, Ar). ^{13}C NMR, δ: 20.94, 23.87 (Me); 30.89 (C(1)); 34.83 (C(2)); 45.39 (C(8b)); 55.50 (C(3)); 74.76 (C(3a)); 121.09, 125.71, 128.26, 130.33, 136.17, 140.50 (C arom.); 169.60 (C=O). MS, m/z: 294 $[M]^+$.

A mixture of (1′*RS*,2′*RS*,3′*RS*)- and (1′*RS*,2′*SR*,3′*SR*)-*N*-acetyl-2-(2′,3′-dibromocyclopent-1′-yl)-6-methylanilines (9 and 10). A solution of Br_2 (1.62 g, 11 mmol) in 15 mL of CCl_4 was added dropwise with stirring using a magnetic stirrer to a solution of anilide **7** (2.15 g, 10 mmol) in 50 mL of CCl_4. The mixture was stirred for an additional 1 h, diluted with 50 mL of CCl_4, washed with a 10% solution of $NaHCO_3$ and water, and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give 3.5 g (93%) of a mixture of isomers **9** and **10** as an oil. Found (%): C, 44.55; H, 4.39; Br, 42.29; N,

3.50. $C_{14}H_{17}Br_2NO$. Calculated (%): C, 44.80; H, 4.53; Br 42.67; N, 3.73. IR, ν/cm^{-1}: 3270 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.90—2.70 (m, 8 H, H(4′)$_a$, H(4′)$_b$, H(5′)$_a$, H(5′)$_b$); 2.05, 2.12, 2.14, 2.18 (all s, 12 H, 4 Me); 3.55 (q, 1 H, H(1′), J = 8.50 Hz); 4.02 (s, 1 H, H(1′)); 4.17 (m, 1 H, H(3′)); 4.39 (m, 1 H, H(3′)); 4.68 (d, 1 H, H(2′), J = 6.08 Hz); 4.74 (m, 1 H, H(2′)); 7.06—7.20 (m, 6 H, ArH); 7.31 (br.s, 1 H, NH); 7.43 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.44, 18.67, 23.03, 23.25 (Me); 26.06, 31.79 (C(5′)); 33.22, 35.28 (C(4′)); 42.87, 49.80 (C(1′)); 55.76, 56.25 (C(3′)); 63.49, 64.07 (C(2′)); 124.14, 124.28 (C(4)); 125.87, 127.24 (C(5)); 128.25, 129.54 (C(3)); 133.97, 134.40 (C(6)); 136.14, 136.69 (C(2)); 142.11, 43.12 (C(1)).

References

1. R. R. Gataullin, I. S. Afon'kin, I. V. Pavlova, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 398 [*Russ. Chem. Bull.*, 1999, **48**, 396 (Engl. Transl.)].
2. R. R. Gataullin, T. V. Kazhanova, L. T. Il'yasova, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 975 [*Russ. Chem. Bull.*, 1999, **48**, 967 (Engl. Transl.)].
3. C. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.
4. I. B. Abdrakhmanov, V. M. Sharafutdinov, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 2160 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
5. S. Knapp, M. J. Sebastian, and H. Ramanathan, *J. Org. Chem.*, 1983, **48**, 4786.
6. E. J. Corey, M. Shibasaki, and J. Knolle, *Tetrahedron Lett.*, 1977, **16**, 1625.
7. M. Georges and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1980, **102**, 3956.
8. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *YaMR-spektroskopiya v organicheskoi khimii* [*NMR Spectroscopy in Organic Chemistry*], Nauka, Leningrad, 1983, 170 (in Russian).
9. I. A. Korbukh, L. N. Abramova, and M. N. Preobrazhenskaya, *Zh. Org. Khim.*, 1977, **13**, 731 [*J. Org. Chem. USSR*, 1977, **13** (Engl. Transl.)].
10. A. G. Mustafin, M. A. Petrova, R. R. Gataullin, L. V. Spirikhin, A. A. Fatykhov, I. B. Abdrakhmanov, L. F. Chertanova, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1378 [*Russ. Chem. Bull.*, 1998, **47**, 1340 (Engl. Transl.)].

Received March 11, 1999;
in revised form July 12, 1999