Cyclization of \(N\)-acetyl-\(ortho\)-cycloalkenylanilines on treatment with bromine and \(N\)-bromosuccinimide


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The reaction of \(N\)-acetyl-2-(cyclohex-1'-enyl)aniline with \(Br_2\) or \(N\)-bromosuccinimide 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[4H-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 into 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, 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 \(^1\)H and \(^13\)C NMR spectra).

In the \(^1\)H NMR spectrum of indoline 8 recorded using the double resonance method, the \(H(3a)\) proton is exhibited at \(\delta 4.92\) as a doublet of doublets with \(J_{H(3a),H(3)} = 7.99\) Hz, pointing to the \(cis\)-arrangement of the \(H(3a)\) and \(H(3b)\) 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 pseudooxial 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


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2'-Bromo-2-methylspiro[4H-3,1-benzoxazine]-4',1'-cyclohexane) hydrobromide (5). A solution of Br2 (0.1 mL, 1.9 mmol) in 5 mL of CC14 was added dropwise with stirring to a solution of compound 3 (0.4 g, 1.86 mmol) in 20 mL of dry CC14. The hydrobromide precipitate was filtered off and washed with 10 mL of CC14. Yield 0.65 g (94%), m.p. 165–167 °C. Found (%): C, 57.10; H, 5.15; Br, 26.80; N, 4.64. C14H16BrNO. Calculated (%): C, 57.16; H, 5.48; Br, 27.16; N, 4.76. 13C NMR (DMSO-d6, δ: 19.40 (C3′); 19.75 (C6′); 20.29 (Me); 29.79 (C4′); 30.11 (C5′); 54.19 (C2′); 79.31 (C4); 118.05 (C10); 123.86 (C10); 126.29 (C7); 126.29 (C6); 128.08 (C8); 129.80 (C9); 130.22 (C7); 168.43 (C2). 2'-Bromo-2-methylspiro[4H-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 NaHCO3 for 2 min. The product was extracted with CH2Cl2 (2×20 mL) and dried with Na2SO4, 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. C14H16BrNO. Calculated (%): C, 57.16; H, 5.48; Br, 27.16; N, 4.76. 13C NMR (DMSO-d6): δ: 1.60–2.65 (m, 8 H, 4 CH2); 2.20 (s, 3 H, Me); 4.45 (br.s, 1 H, CH); 7.10–7.35 (m, 4 H, Ar). 13C NMR (DMSO-d6, δ: 19.60 (C3′); 20.28 (C6′); 21.64 (Me); 29.54 (C4′); 29.98 (C5′); 53.93 (C2′); 78.91 (C4); 123.87 (C6); 125.66 (C8); 126.29 (C7); 126.95 (C10); 129.10 (C15); 136.22 (C9); 159.04 (C2). N-Acetyl-2-(cyclopent-l'-enyl)-6-methyl-anilines (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 CH2Cl2 and the mixture was allowed to stand for 18 h, diluted with water, and extracted with 100 mL of CH2Cl2. The extract was washed with 5% solution of NaHCO3 until the evolution of CO2 stopped and with water (20 mL) and dried with MgSO4. The mixture was filtered and the solvent was evaporated to give 4.18 g (97.2%) of anilinide 7, Rf 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 CC14 was refluxed for 20 min. The mixture was cooled in an ice bath, and the filtrate was washed with 20 mL of 10% NaHCO3 and concentrated under reduced pressure. The residue was chromatographed on a short column with silica gel (2 g), using CH2Cl2 as the eluent, to give 0.61 g (91%) of indoline 8, Rf 0.67. Found (%): C, 57.29; H, 5.51; Br, 27.13; N, 4.62. C14H16BrNO. Calculated (%): C, 57.16; H, 5.48; Br, 27.16; N, 4.76. 1H NMR, δ: 1.60–2.70 (m, 8 H, 4 CH2); 2.20 (s, 3 H, Me); 4.45 (br.s, 1 H, CH). 13C NMR (DMSO-d6, δ: 20.94, 22.08, 25.24, 30.30 (C3′), 34.83 (C4′), 51.79 (C5′), 118.17 (C4); 126.71 (C3); 127.37 (C2′); 128.34 (C5′); 130.36 (C2); 136.31 (C1′)); 142.01 (C1)). N-Acetyl-(cyclopent-l'-enyl)anilines (3). Yield 95%, m.p. 58–60 °C. Found (%): C, 78.10; H, 7.63; N, 6.34. C14H17NO. Calculated (%): C, 78.10; H, 7.66; N, 6.51. IR, ν/cm−1: 3280 (NH). 1H NMR (DMSO-d6): δ: 2.07 (s, 3 H, Me); 1.66–2.37 (m, 8 H, 4 CH2); 5.67 (1 H, CH); 7.00–7.20 (m, 3 H, Ar); 7.68 (s, 1 H, NH); 8.05 td, 1 H, H2); J = 8.11 Hz). 13C NMR (DMSO-d6, δ: 21.62 (Me); 22.86, 24.39, 25.27, 29.67 (C3′), 34′, 5′, 6′); 121.35 (C6); 123.91 (C4′); 127.13 (C3′); 128.11 (C5′); 128.12 (C2′); 134.15 (C2′); 134.92 (C1′); 135.76 (C1); 168.15 (C=O).