Brief Communications

Synthesis of 2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentan)-2(1*H*)-one and 2-amino-2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentane) from 6-(cyclopent-1-enyl)-2-methylaniline

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The reaction of 6-(cyclopent-1-enyl)-*N*-ethoxycarbonyl-2-methylaniline with Br_2 or its reaction with NH_3 followed by the reaction with Br_2 afforded 2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentan)-2(1*H*)-one and 2-amino-2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentane), respectively.

Key words: alkenylanilines, ureas, halocyclization, 3,1-benzooxazines.

Some compounds of the 3,1-benzooxazine series exhibit high activities in inhibition of chymase[1] or HIV-1 reverse transcriptase.[2] As a continuation of our studies on the synthesis of 3,1-benzooxazines,[3—5] we examined the reactions of Br_2 with *N*-substituted urethane (**1**) and urea (**2**) with the aim of preparing their 2-oxo and 2-amino analogs.

Results and Discussion

The reaction of amine **3**[3] with ethyl chloroformate in CH_2Cl_2 in the presence of K_2CO_3 afforded urethane **1** in 95% yield (Scheme 1). Heating of the latter in a methanolic solution of ammonia in an autoclave at 100 °C gave rise to arylurea **2** in 65% yield. The reaction of compound **1** with Br_2 in CCl_4 produced benzooxazinone **4** in high yield. The reaction of urea **2** with Br_2 in MeOH at 20 °C afforded hydrobromide **5**, which yielded aminobenzooxazine **6** upon treatment with Na_2CO_3.

The structures of the resulting compounds were established based on the data from spectroscopy and elemental analysis. The ^{13}C NMR spectra of benzooxazines **4—6** have a signal of the spiro-C(4) atom at δ 91—97, which is virtually identical with the values obtained by us previously for analogous structures.[3—5]

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz for ^1H; 75.47 MHz for ^{13}C; Me_4Si as the internal standard). The IR spectra were measured on a UR-20 spectrometer (Nujol mulls). The purities of the products were monitored by chromatography on Silufol UV-254 plates (CH_2Cl_2 as the eluent).

6-(Cyclopent-1-enyl)-*N*-ethoxycarbonyl-2-methylaniline (1). Potassium carbonate (10 g) was added to a solution of amine **3** (1.75 g, 10 mmol) in CH_2Cl_2 (20 mL). Then a solution of $EtCO_2Cl$ (1.6 g, 15 mmol) in CH_2Cl_2 (15 mL) was added dropwise with stirring at 20 °C. The reaction mixture was stirred for 2 h and kept at 20 °C for 18 h. The inorganic precipitate that formed was filtered off and washed with CH_2Cl_2 (2×10 mL). The filtrate was successively washed with a 10% aqueous solution of $NaHCO_3$ until liberation of CO_2 ceased and then with water and dried with $MgSO_4$. The solvent was evaporated and the residue was extracted with hot hexane.

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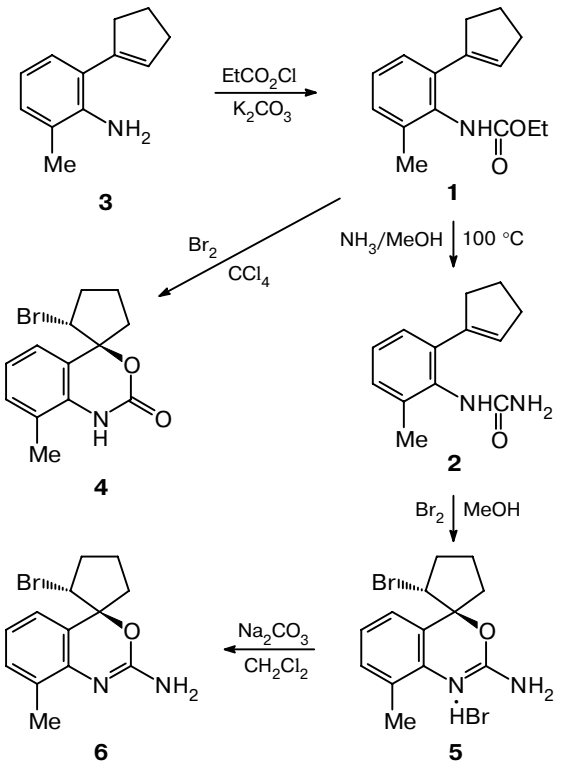
Scheme 1



After evaporation of the hexane, carbamate **1** was obtained in a yield of 2.34 g (95%), m.p. 51—53 °C. Found (%): C, 73.19; H, 7.15; N, 5.43. $C_{15}H_{19}NO_2$. Calculated (%): C, 73.47; H, 7.76; N, 5.71. IR, ν/cm^{-1}: 3290 (NH). ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 3 H, CH_3, J = 7.31 Hz); 1.90—2.70 (m, 6 H, 3 CH_2); 2.30 (s, 3 H, CH_3); 4.15 (m, 2 H, CH_2); 5.90 (s, 1 H, CH); 6.35 (s, 1 H, NH); 7.10 (m, 3 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 14.7 (Me); 18.3 (Me); 23.7 (C(4′)); 33.5 (C(3′)); 35.9 (C(5′)); 61.1 ((OCH$_2$); 126.1 (C(5)); 126.7 ((C(4)); 129.2 (C(2)); 130.9 (C(3)); 133.8 ((C(6)); 136.4 (C(2′)); 138.4 (C(1)); 141.3 (C(1′)); 154.6 (C=O).

***N*-[6-(Cyclopent-1-enyl)-2-methylphenyl]urea (2).** A solution of urethane **1** (2.4 g, 10 mmol) in a saturated methanolic solution of ammonia (17 mL) was heated in a metallic autoclave at 100 °C for 25 h. Then the reaction mixture was cooled and the precipitate that formed was filtered off, washed with a methanolic solution of ammonia (3 mL), and dried *in vacuo*. Urea **2** was obtained in a yield of 1.37 g (65%), m.p. 218 °C (MeOH/NH_3). Found (%): C, 72.07; H, 7.15; N, 12.85. $C_{13}H_{16}N_2O$. Calculated (%): C, 72.22; H, 7.41; N, 12.96. IR, ν/cm^{-1}: 3392, 3440 (NH, NH_2). ^{1}H NMR (DMSO-d_6), δ: 1.90—2.70 (m, 6 H, 3 CH_2); 2.20 (s, 3 H, Me); 5.70 (br.s, 2 H, NH_2); 5.90 (s, 1 H, CH); 7.10 (m, 3 H, Ar); 8.50 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 18.4 (Me); 23.3, 33.2, 35.3 (C(3′), C(4′), C(5′)); 125.8 (C(5)); 125.9 (C(4)); 128.8 (C(2)); 129.0 (C(3)); 134.6 (C(6)); 135.9 (C(2′)); 137.1 (C(1)); 141.8 (C(1′)); 157.0 (C=O).

2′-Bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentan)-2(1*H*)-one (4). A solution of Br_2 (0.5 g, 3.12 mmol) in CCl_4 (3 mL) was added dropwise with stirring to a solution of urethane **1** (0.4 g, 1.63 mmol) in CCl_4 (10 mL). The reaction mixture was kept at 20 °C for 1 h, the solvent was evaporated, and the residue was recrystallized from hexane. Benzooxazinone **4** was obtained in a yield of 0.42 g (87%), m.p. 171—173 °C. Found (%): C, 52.38; H, 4.41; Br, 26.54; N, 4.32. $C_{13}H_{14}BrNO_2$. Calculated (%): C, 52.72; H, 4.77; Br, 26.98; N, 4.73. ^{1}H NMR ($CDCl_3$), δ: 1.10—2.90 (m, 6 H, 3 CH_2); 2.30 (s, 3 H, CH_3); 4.60 (s, 1 H, H(2′)); 6.90—7.40 (m, 3 H, Ar); 9.10 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 16.9 (CH_3); 20.0 (C(4′)); 33.0 (C(5′)); 34.4 (C(3′)); 55.8 (C(2′)); 93.9 (C(4)); 120.2 (C(7)); 122.2 (C(8)); 122.7 (C(5)); 124.1 (C(6)); 131.1 (C(8a)); 133.0 (C(4a)); 152.3 (C(2)).

2-Amino-2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentane) hydrobromide (5). A solution of Br_2 (0.05 mL, 1 mmol) in MeOH (1 mL) was added dropwise with stirring to a solution of urea **2** (0.22 g, 1 mmol) in MeOH (5 mL) at 20 °C. The solvent was evaporated *in vacuo*. Hydrobromide **5** was obtained in a yield of 0.37 g (100%), m.p. 113—115 °C (CH_2Cl_2). Found (%): C, 41.28; H, 4.11; Br, 42.04; N, 7.02. $C_{13}H_{16}Br_2N_2O$. Calculated (%): C, 41.51; H, 4.30; Br, 42.49; N, 7.44. ^{1}H NMR ($CDCl_3$), δ: 1.10—2.90 (m, 6 H, 3 CH_2); 2.40 (s, 3 H, CH_3); 4.50 (s, 1 H, H(2′)); 6.90—7.30 (m, 3 H, Ar); 9.00 (br.s, 2 H, NH_2); 11.00 (s, 1 H, HBr). ^{13}C NMR ($CDCl_3$), δ: 18.4 (CH_3); 20.3 (C(4′)); 33.5 (C(5′)); 34.7 (C(3′)); 54.7 (C(2′)); 97.2 (C(4)); 120.3 (C(4a); 124.6 (C(5)); 125.1 (C(8)); 125.2 (C(6)); 128.6 (C(7)); 132.3 (C(8a)); 157.3 (C(2)).

2-Amino-2′-bromo-8-methylspiro(4*H*-3,1-benzooxazine-4,1′-cyclopentane) (6). A solution of compound **5** (0.38 g, 1 mmol) in CH_2Cl_2 (10 mL) was stirred with a 10% aqueous solution of Na_2CO_3 (10 mL) at 20 °C for 30 min. The organic phase was separated, washed with water (5 mL), dried with $MgSO_4$, and filtered. The solvent was evaporated *in vacuo*. Benzooxazine **6** was obtained as an amorphous compound in a yield of 0.27 g (93%), R_f 0.4 (CH_2Cl_2). Found (%): C, 52.58; H, 4.81; Br, 26.64; N, 9.12. $C_{13}H_{15}BrN_2O$. Calculated (%): C, 52.89; H, 5.13; Br, 27.07; N, 9.49. ^{1}H NMR ($CDCl_3$), δ: 1.10—2.90 (m, 6 H, 3 CH_2); 2.20 (s, 3 H, CH_3); 4.50 (s, 1 H, H(2′)); 5.00 (br.s, 2 H, NH_2); 6.90—7.30 (m, 3 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 17.9 (CH_3); 20.2 (C(4′)); 33.0 (C(5′)); 34.5 (C(3′)); 55.7 (C(2′)); 91.7 (C(4)); 121.4 (C(6)); 122.7 (C(8)); 123.5 (C(7)); 129.3 (C(4a)); 130.7 (C(7)); 140.1 (C(8a)); 153.8 (C(2)).

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