Heterocyclization of *N*-[2-(cyclopent-1-enyl)phenyl]acetamides and ethyl *N*-[2-(cyclopent-1-enyl)phenyl]carbamates under the action of hydrogen peroxide

Rail R. Gataullin,* Marat F. Nasyrov, Ol'ga V. Shitikova, Leonid V. Spirikhin and Il'dus B. Abdrakhmanov

Institute of Organic Chemistry, Ufa Scientific Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 3472 35 6066; e-mail: chemorg@anrb.ru

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The oxidation of *N*-[2-(cyclopent-1-enyl)phenyl]acetamides and ethyl *N*-[6-methyl-2-(cyclopent-1-enyl)phenyl]carbamate with hydrogen peroxide in methanolic NaOH gave spiro[4*H*-3,1-benzoxazine-4,1′-cyclopentanes]. On the other hand, ethyl [2-(cyclopent-1-enyl)phenyl]carbamate reacted with hydrogen peroxide in the presence of acetonitrile and NaOH to give ethyl 3a-hydroxy-2,3,3a,8b-tetrahydrocyclopenta[*b*]indole-4(1*H*)-carboxylate, which was dehydrated with polyphosphoric acid to ethyl 2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate.

Benzoxazine derivatives exhibit considerable activity in the inhibition[1] of chymase or reverse transcriptase of HIV-1.[2] Recently, we have reported a convenient synthesis of 3,1-benzoxazines from *ortho*-(alk-1-enyl)anilides under the action of hydrogen chloride or bromine.[3,4] At present, the cyclization of these anilides under the effect of oxidising agents as hydrogen peroxide has not been studied. In order to search for new methods of controllable heterocyclization of *ortho*-alkenylanilines, the effect of hydrogen peroxide on acetamides **1a**,**b** and carbamates **1c**,**d**† has been studied. Therefore, the reaction of **1a**[3] or **1c** with hydrogen peroxide in the presence of sodium hydroxide in acetonitrile and methanol as solvents gave 8-methylspiro[4*H*-3,1-benzoxazine-4,1′-cyclopentanes] **2a** or **2c**.‡ Under the same reaction conditions, carbamate **1d** gave ethyl 3a-hydroxy-2,3,3a,8b-tetrahydrocyclopenta[*b*]indole-4(1*H*)-carboxylate **4**, the effect of polyphosphoric acid on which caused dehydration and gave ethyl 2,3-dihydrocyclopenta[*b*]indole-4(1*H*)-carboxylate **5**.§ Compounds **1a**–**d** were found to be sensitive to oxidation conditions. The interaction of **1d** with H_2O_2 in the presence of Na_2WO_4 and H_3PO_4 resulted in 3,1-benzoxazinone **3**. Under these conditions, amide **1b** gives benzoxazine **2b** in 85% yield.¶ Under the same conditions, anilides **1a** and **1c** did not react.

To clarify the mechanism of the formation of **4**, the well-known reaction of aryl(cycloalk-1-enes) bearing no amine moiety with hydrogen peroxide, which leads to arylcycloalkylketones should be taken into account.[5] Probably, **4** is formed by the intramolecular cyclization of intermediate **A** (Scheme 1), which was not detected in the reaction mixture most probably because of its high reactivity under alkaline conditions.

The structure of compounds **1b**–**d**, **2a**–**c**, **3**–**5** was determined using spectral methods and elemental analyses.

† *General methods*. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz (with Me_4Si as an internal standard). IR spectra were recorded on a Specord M-80 spectrophotometer. The purity of initial compounds and reaction products was controlled with a Chrom 5 instrument and Silufol UV 25 plates. Mass spectra were recorded using an MH 1320 spectrometer (70 eV).

Acetamide **1b** was obtained according to the published method[3] by the reaction of *ortho*-(cyclopent-1-enyl)aniline[6] with acetic anhydride.

General procedure for the synthesis of carbamates **1c** *and* **1d**. Ethyl chloroformate (1.3 g, 12 mmol) was added dropwise to a vigorously stirred mixture of *ortho*-(cyclopent-1-enyl)aniline[6] or 2-methyl-6-(cyclopent-1-enyl)aniline[3] (10 mmol) and potassium carbonate (2.76 g, 20 mmol) in dichloromethane (20 ml) at 20 °C. After 1 h, water (2 ml) was added, the mixture was stirred, the precipitate was filtered off, and the filtrate was washed with water and dried ($MgSO_4$). The solvent was evaporated in a vacuum, the products were isolated as a yellowish oil.

1c: yield 95%, mp 51–53 °C. ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, Me, *J* 7.31 Hz), 1.90–2.70 (m, 6H, $3CH_2$), 2.30 (s, 3H, Me), 4.15 (m, 2H, CH_2), 5.90 (s, 1H, CH), 6.35 (s, 1H, NH), 7.10 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$) δ: 14.65 (Me), 18.34 (Me), 23.66 [C(4′)], 33.51 [C(3′)], 35.91 [C(5′)], 61.14 (OCH_2), 126.14 [C(5)], 126.73 [C(4)], 129.24 [C(2)], 130.91 [C(3)], 133.80 [C(6)], 136.37 [C(2′)], 138.35 [C(1)], 141.33 [C(1′)], 154.60 (C=O). Found (%): C, 73.19; H, 7.15; N, 5.43. Calc. for $C_{15}H_{19}NO_2$ (%): C, 73.47; H, 7.76; N, 5.71.

1d: yield 95%, R_f 0.6 (hexane–EtOAc, 4:1). ^{1}H NMR ($CDCl_3$) δ: 1.3 (t, 3H, Me, *J* 7.3 Hz), 2.0 (quint, 2H, CH_2, *J* 7.8 Hz), 2.6 (br. s, 2H, CH_2), 2.7 (br. s, 2H, CH_2), 4.2 (q, 2H, CH_2O, *J* 7.2 Hz), 5.9 (br. s, 1H, =CH), 7.0 (m, 1H, ArH), 7.1 (br. s, 1H, NH), 7.1–7.3 (m, 2H, ArH), 8.1 (d, 1H, ArH, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.3 (Me), 23.0, 33.5, 36.4 ($3CH_2$), 61.0 (CH_2O), 119.5 [C(6)], 122.7 [C(2′)], 127.3 [C(4)], 127.5 [C(3)], 127.6 [C(2)], 129.9 [C(5)], 134.6 [C(1′)], 140.3 [C(1)], 153.4 (C=O). Found (%): C, 72.68; H, 7.45; N, 5.99. Calc. for $C_{14}H_{17}NO_2$ (%): C, 72.70; H, 7.41; N, 6.06.

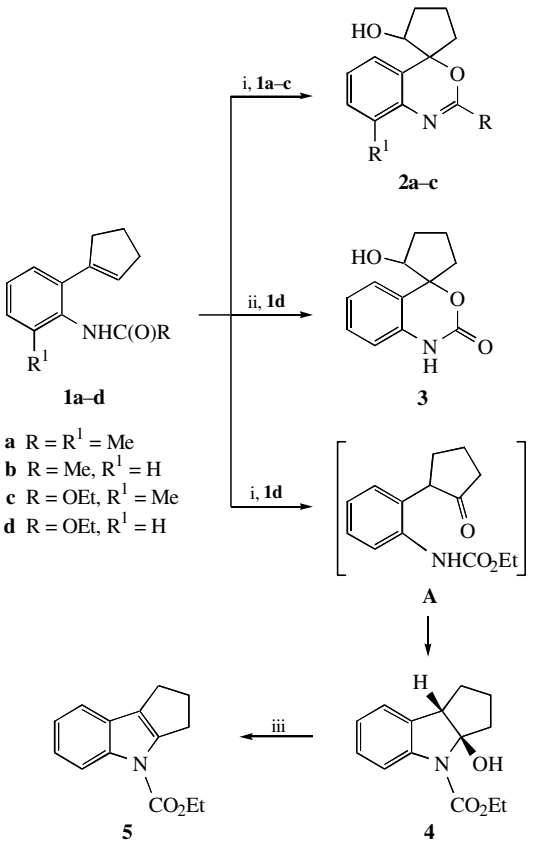
‡ *General procedure for the synthesis of spirobenzoxazinecyclopentanes* **2a** *and* **2c** *and tetrahydrocyclopentaindole* **4**. Acetamide **1a** or carbamate **1c** or **1d** was added to a stirred solution of sodium hydroxide (0.2 g) in methanol (5 ml) and acetonitrile (5 ml). To the resulting mixture, an excess of a 50% hydrogen peroxide solution (1 g, 29.4 mmol) was added dropwise. Evolution of oxygen and an increase of the reaction temperature were observed upon standing for 2 h. A saturated sodium thiosulfate solution (10 ml) was added, extracted with dichloromethane and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the yellowish oily residue was purified by column chromatography using silica gel (5 g, eluent: hexane–EtOAc, 2:1) to give spirobenzoxazinecyclopentane **2a**, which was recrystallised from ethyl acetate or spirobenzoxazinecyclopentane **2c**, which crystallised upon standing or tetrahydrocyclopentaindole **4**, which was obtained as an amorphous substance.

2a: yield 80%, mp 103 °C. ^{1}H NMR ($CDCl_3$) δ: 1.7–2.0 (m, 2H, CH_2), 2.1 (s, 3H, Me), 2.1–2.2 (m, 2H, CH_2), 2.3 (s, 3H, Me), 2.4–2.5 (m, 2H, CH_2), 2.9 (br. s, 1H, OH), 4.0 (d, 1H, CH, *J* 5.9 Hz), 7.0–7.3 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ: 17.3, 21.8 (2Me), 20.6, 31.5, 34.4 ($3CH_2$), 75.5 (CHOH), 90.2 [C(4)], 122.6 [C(6)], 123.5 [C(4a)], 125.4 [C(5)], 130.8 [C(7)], 132.4 [C(8)], 137.5 [C(8a)], 159.6 (C=N). MS, *m*/*z*: 231 (M^+). Found (%): C, 72.45; H, 7.42; N, 6.30. Calc. for $C_{14}H_{17}NO_2$ (%): C, 72.70; H, 7.41; N, 6.06.

2c: yield 63%, mp 105 °C. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t, 1H, Me, *J* 7.2 Hz), 1.7–2.2 (m, 6H, $3CH_2$), 2.3 (s, 3H, Me), 4.1 (br. s, 1H, CH–O), 4.4 (m, 2H, CH_2), 5.0 (br. s, 1H, OH), 6.9–7.0 (m, 2H, ArH), 7.1 (d, 1H, ArH, *J* 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.2, 17.0 (2Me), 20.6, 31.4, 34.2 ($3CH_2$), 64.3 (OCH_2), 75.4 (CHOH), 93.5 [C(4)], 122.3 [C(4a)], 122.6 [C(6)], 123.2 [C(5)], 130.7 [C(7)], 131.7 [C(8)], 140.0 [C(8a)], 154.8 (C=O). Found (%): C, 68.42; H, 7.21; N, 5.40. Calc. for $C_{15}H_{19}NO_3$ (%): C, 68.94; H, 7.33; N, 5.36.

4: yield 70%. ^{1}H NMR ($CDCl_3$) δ: 1.3 (t, 3H, Me, *J* 7.6 Hz), 1.5–1.7 (m, 2H, CH_2), 1.7–1.9 (m, 2H, CH_2), 2.2–2.4 (m, 2H, CH_2), 3.5–3.6 (m, 1H, CH), 4.3 (q, 2H, CH_2, *J* 6.9 Hz), 7.0 (t, 1H, ArH, *J* 7.4 Hz), 7.1–7.3 (m, 3H, ArH), 7.6 (br. s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 14.6 (Me), 25.4 [C(2)], 34.0 [C(1)], 42.2 [C(3)], 53.2 [C(8b)], 61.9 (OCH_2), 103.6 [C(3a)], 114.4 [C(5)], 123.2 [C(7)], 124.4 [C(8)], 129.0 [C(6)], 132.7 [C(8a)], 141.5 [C(4a)], 153.5 (C=O). Found (%): C, 67.83; H, 6.71; N, 5.78. Calc. for $C_{14}H_{17}NO_3$ (%): C, 68.00; H, 6.93; N, 5.66.

§ *Synthesis of tetrahydrocyclopentaindole* **5**. A mixture of tetrahydrocyclopentaindoline **4** (0.5 g, 2.02 mmol), phosphoric acid (85%) (3 g) and phosphorus pentoxide (2 g) was vigorously stirred and then left to stand for 10 h. The acid solution was neutralised with aqueous sodium hydroxide, extracted with benzene, and the organic extract was dried (NaOH). The solvent was evaporated to give crystalline tetrahydrocyclopentaindole **5**. Yield 97%, mp 67 °C. ^{1}H NMR ($CDCl_3$) δ: 1.4 (t, 3H, Me, *J* 6.2 Hz), 2.4 (q, 2H, CH_2, *J* 7.0 Hz), 2.7 (t, 2H, CH_2, *J* 6.8 Hz), 3.0 (t, 2H, CH_2, *J* 6.6 Hz), 4.4 (q, 2H, CH_2), 7.1–7.3 (m, 2H, ArH), 7.3 (d, 1H, *J* 7.4 Hz, H-8), 8.1 (d, 1H, H-5, *J* 6.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.5 (Me), 24.2, 27.5, 29.0 ($3CH_2$), 62.8 (OCH_2), 115.9 [C(5)], 118.7 [C(8)], 124.8 [C(6)], 125.1 [C(7)], 127.0 [C(8a)], 128.0 [C(8b)], 140.3 [C(3a)], 144.0 [C(4a)], 151.5 (C=O). Found (%): C, 74.01; H, 6.67; N, 6.00. Calc. for $C_{14}H_{15}NO_2$ (%): C, 73.34; H, 6.59; N, 6.11.



Scheme 1 *Reagents and conditions*: i, H_2O_2, NaOH, MeCN+MeOH (1:1); ii, H_2O_2, Na_2WO_4, H_3PO_4; iii, PPA, 20 °C.

¶ *General procedure for the synthesis of spirobenzoxazinecyclopentane* **2b** *and* **3**. A solution of sodium tungstate (50 mg, 0.17 mmol) in water (0.2 ml), one drop of conc. phosphoric acid and a solution of 50% of hydrogen peroxide (0.34 g, 4.98 mmol) were added to a solution of acetamide **1b** or carbamate **1d** (2.48 mmol) in methanol (5 ml). The reaction mixture was allowed to stand for 48 h at 30 °C, and then dichloromethane (50 ml) was added, washed with a saturated sodium thiosulfate solution followed by water and then the organic extracts were dried ($MgSO_4$). The solvent was evaporated *in vacuo* to give an oil of spirobenzoxazinecyclopentanes **2b** or **3**, which crystallised on standing.

2b: yield 80%, mp 143 °C. ^{1}H NMR ($CDCl_3$) δ: 1.7–2.0 (m, 2H, CH_2), 2.0 (s, 3H, Me), 2.1–2.2 (m, 2H, CH_2), 2.4–2.5 (m, 2H, CH_2), 2.7 (br. s, 1H, OH), 4.1 (d, 1H, CH, *J* 4.62 Hz), 7.0 (d, 1H, *J* 7.59 Hz), 7.1–7.3 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$) δ: 21.5 (Me), 20.5, 31.6, 34.7 ($3CH_2$), 75.9 (CHOH), 90.0 [C(4)], 123.5 [C(4a)], 123.6 [C(6)], 125.1 [C(7)], 125.8 [C(8)], 129.1 [C(5)], 139.1 [C(8a)], 160.3 (C=N). Found (%): C, 71.03; H, 6.82; N, 6.76. Calc. for $C_{13}H_{15}NO_2$ (%): C, 71.87; H, 6.96; N, 6.45.

3: yield 85%, mp 216 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.6–2.4 (m, 6H, $3CH_2$), 4.0 (m, 1H, CH–O), 4.9 (br. s, 1H, OH), 6.9 (d, 1H, H-5, *J* 8.2 Hz), 7.0 (t, 1H, ArH, *J* 7.6 Hz), 7.2 (t, 2H, ArH, *J* 7.4 Hz), 10.1 (s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 19.5, 32.1, 33.2 ($3CH_2$), 74.6 (CHOH), 92.8 [C(4)], 113.5 [C(8)], 120.7 [C(4a)], 121.7 [C(6)], 126.5 [C(5)], 128.6 [C(7)], 136.0 [C(8a)], 150.7 (C=O). Found (%): C, 65.30; H, 6.02; N, 6.36. Calc. for $C_{12}H_{13}NO_3$ (%): C, 65.74; H, 5.98; N, 6.39.

Finally, it must be concluded that the structure of products obtained (benzoxazine or indoline type) is dependent on the nature of protecting group and the type of catalysts used (tungstate–phosphoric acid or acetonitrile–alkali) despite that both of these systems are epoxydising.

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