Synthesis of quinolizin-2-one and pyrido[1,2-*a*]azepin-2-one derivatives from difluoroboron complexes of aroylacetones and *O*-methyllactims

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O-Methyllactims react at the methyl group of difluoroboron complexes of aroylacetones with the formation of condensation products, novel difluoroboron chelates of 1-aryl-4-(piperidin-2-ylidene)butane-1,3-diones and 1-aryl-4-(azepan-2-ylidene)butane-1,3-diones, which upon the action of concentrated HCl in ethanol are transformed into the corresponding quinolizin-2-one and pyrido[1,2-*a*]azepin-2-one derivatives.

Key words: *O*-methyllactims, difluoroboron chelates of aroylacetones, condensation, 1-aryl-4-(piperidin-2-ylidene)butane-1,3-diones, 1-aryl-4-(azepan-2-ylidene)butane-1,3-diones, quinolizin-2-ones, pyrido[1,2-*a*]azepin-2-ones.

In the present work, we report on a new approach to the synthesis of quinolizin-2-one and pyrido[1,2-*a*]azepin-2-one derivatives from difluoroboron chelates of aroylacetones and *O*-methyllactims.

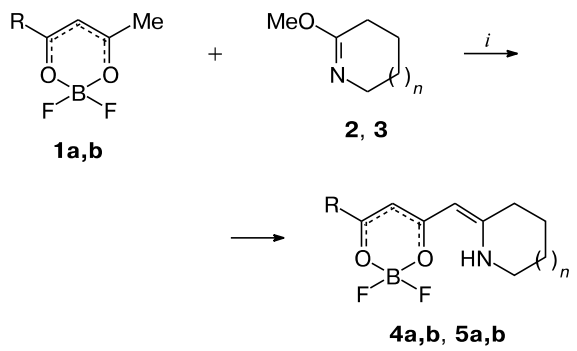
It is known that *O*-methyllactims, widely used in heterocyclic synthesis,[1—4] react with the methylene-active β-dicarbonyl compounds at the methylene group.[5,6]

However, chelation of β-dicarbonyl compounds with boron can dramatically change their reactivity and makes possible transformations uncharacteristic of the free ligands. Thus, in the framework of our studies on the application of boron-chelates of 1,3-diketones in the synthesis of nitrogen-containing heterocyclic compounds, we suggested new approaches towards pyrazoles[7], pyrazolo[1,5-*c*]pyrimidines,[8] and indazoles[9] based on the condensation of amide acetetals at the exocyclic methyl (methylene) group of the β-diketone difluoroboron chelates and subsequent heterocyclization of the thus obtained enaminodiketone complexes upon the action of the corresponding binucleophilic reactants (hydrazines, thiosemicarbazide, aminoguanidine). A convenient method for the preparation of pyridazin-4-one derivatives was also found,[10] which is based on the ability of the methyl group in the boron β-diketonates to undergo attacks by diazonium salts.

In continuation of these studies, in the present work we for the first time showed that *O*-methyllactims **2** and **3** react at the methyl groups of difluoroboron chelates of aroylacetones **1a**,**b** with the formation of chelate complexes **4a**,**b** and **5a**,**b** (Scheme 1).

The reaction was carried out in toluene in a sealed tube under microwave irradiation for 7 min. It should be noted that without irradiation, the reaction carried out in boiling toluene reached completion within 50—60 h.

Scheme 1



n = 1 (**2**, **4**), 2 (**3**, **5**)
R = Ph (**a**), 4-ClC_6H_4 (**b**)

i. PhMe, microwave irradiation, 7 min.

The mass spectra of the synthesized chelates are characterized by the presence of the peaks for the molecular ions $[M]^+$ and the fragment ions $[M - F]^+$. Their ^1H NMR spectra exhibit singlets for the protons of the CH group in both the ylidene fragment and the chelate ring at δ 4.8—4.9 and δ 5.9—6.0, respectively, as well as a broad singlet for the proton of the NH group at δ 9.7—9.8. The signal at δ 0.5—0.7 in the ^{11}B NMR spectra confirms the presence of the tetracoordinated B atom in the molecules of the compounds obtained.

It should be taken into account that an alternative structure of the type **6** with a competitive *N*,*O*-coordination of the B atom is possible for the compounds obtained.

Taken the product of condensation of chelate **1a** with lactim **2** as an example, we unambiguously established

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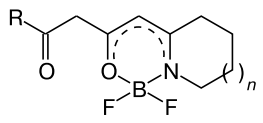


6

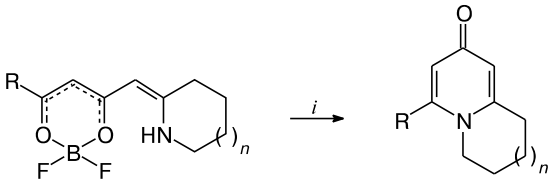
n = 1, 2

that it has the structure **4a** and, therefore, the *O*,*O*-coordination of the boron atom during reactions of difluoroboron-β-diketonates with *O*-methyllactims retained. Thus, in the ^{13}C NMR spectrum of the compound with the chelate site N—B—O (the structure **6a**, R = Ph) one could expect three triplet signals (C=O, C—N, CH_2—N) split due to the remote interaction with the fluorine nuclei. In this case, two of the signals (C=O, C—N) should be in the low field, whereas one of them (CH_2—N) should be in the high field. However, the ^{13}C NMR spectrum shows that only two C atoms interact with the fluorine atoms, which are characterized by the presence of two triplets at δ 175.3 and 168.4 with J = 1.5 Hz in the downfield region of the spectrum, whereas the upfield region exhibits the presence of four singlets for the carbon atoms, no one of which displays splitting due to the remote interaction with the fluorine nuclei.

The IR spectra of compounds **4a**,**b** and **5a**,**b** in KBr pellets contain a sharp absorption band in the region 3300 cm^{-1}, which does not disappear if the spectrum is recorded in a dilute solutions of THF, that indicates the presence of intramolecular hydrogen bond NH···O.

The boron-chelates **4** and **5** are orange crystalline substances soluble in dioxane, THF, benzene, poorly soluble in ethanol, ethyl acetate, diethyl ether, chloroform, and insoluble in hexane. The chelates are stable upon prolonged reflux in the solution of sodium acetate in EtOH. However, treatment of the latter with concentrated hydrochloric acid in boiling ethanol resulted in deboronation and subsequent heterocyclization of the free ligand to the derivatives of 6,7,8,9-tetrahydro-2*H*-quinolizin-2-one **7a**,**b** and 7,8,9,10-tetrahydro-6*H*-pyrido[1,2-*a*]azepin-2-one **8a**,**b**, respectively (Scheme 2).

Scheme 2



4a,b, **5a,b** **7a,b**, **8a,b**

n = 1 (**4**, **7**), 2 (**5**, **8**)
R = Ph (**a**), 4-ClC$_6$H$_4$ (**b**)

i. HCl, EtOH, reflux, 4 h.

Bicyclic compounds **7a**,**b** and **8a**,**b** are well soluble in ethanol, ethyl acetate, benzene, chloroform and virtually insoluble in diethyl ether and hexane. Their mass spectra exhibit peaks for the molecular ions $[M]^+$, whereas the ^{1}H NMR spectra in $CDCl_3$ are characterized by the presence of two signals for the protons of the pyridine fragment at δ 6.2 and 6.3. A characteristic absorption band at 1630 cm^{-1} is present in the IR spectra, which corresponds to the stretching vibrations of the carbonyl group of the pyridone fragment.

A bicyclic fragment with the bridging nitrogen atom is a part of many alkaloids exhibiting various biological activity.[11] Quinolizin-2-one derivatives are of special interest, since they were found to display hypoglycemic,[12,13] vasculo- and bronchodilating properties.[14]

It should be noted that the multi-step methods described in the literature for the synthesis of 4-methyl-6,7,8,9-tetrahydro-2-quinolizinone from diketene and 2-pyridylacetonitrile[15] or methyl 2-pyridylacetate[16] can be used for the preparation of neither compounds containing aryl substituents at position 4, nor pyrido[1,2-*a*]azepin-2-one derivatives.

In conclusion, the approach suggested by us opens a new efficient way for the construction of the indicated fused systems with the bridging N atom.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer (250 and 63 MHz, respectively) at 25 °C, ^{11}B NMR spectra, on a Bruker AC-200P spectrometer (64.21 MHz, $BF_3 \cdot OEt_2$ was an external standard, the low-field signals are given relatively to $BF_3 \cdot OEt_2$ with the "+" signs). IR spectra were recorded on a Specord M-82 spectrometer in KBr pellets. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV). Microwave irradiation was carried out in a Daewoo c.r.s. oven (concave reflectors, a double source of waves system, 480 W). Difluoroboron chelates of aroylacetones **1a,b** were obtained from the corresponding aroylacetones and boron trifluoride diethyl etherate in benzene according to the known procedure.[17] 6-Methoxy-2,3,4,5-tetrahydropyridine (**2**) was obtained according to the published method.[18] 7-Methoxy-3,4,5,6-tetrahydro-2*H*-azepine (**3**) commercially available from Aldrich was used without additional purification.

Reaction of aroylacetone difluoroboron chelates with *O*-methyllactims (general procedure). A mixture of chelate **1a,b** (2 mmol) and *O*-methyllactim **2** or **3** (3 mmol) in toluene (4 mL) was irradiated for 7 min in a sealed tube in a microwave oven (480 W). The solvent was evaporated on a rotary evaporator, ethanol (3 mL) was added to the residue. The crystals that formed were filtered off and recrystallized from ethyl acetate to obtain chelates **4a**,**b** or **5a**,**b** as orange crystals.

Difluoroboron chelate of 4-(piperidin-2-ylidene)-1-phenylbutane-1,3-dione (4a) was obtained from difluoroboron chelate of benzoylacetone (**1a**) and 6-methoxy-2,3,4,5-tetrahydropyridine (**2**). The yield was 41%, m.p. 209—210 °C. Found (%): C, 61.71; H, 5.68; N, 4.58. $C_{15}H_{16}BF_2NO_2$. Calculated (%): C, 61.89; H, 5.54; N, 4.81. MS, m/z (I_{rel} (%)): 291 $[M]^+$ (67), 271 $[M - F]^+$ (37), 225 (44). ^{1}H NMR ($CDCl_3$), δ: 1.82 (m, 4 H, 2 CH_2); 2.55, 3.50 (both m, 2 H each, 2 CH_2); 4.82, 5.95 (both s,

1 H each, 2 CH); 7.43, 7.86 (both m, total 5 H, Ar); 9.76 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 18.3, 21.0, 29.6, 42.4, 91.4, 94.0, 126.6, 128.3, 131.2, 133.9, 168.4 (C=O), 169.2 (C=O), 175.3. ^{11}B NMR ($CHCl_3$), δ: 0.67. IR, ν/cm^{-1}: 3316, 2960, 2876, 1552, 1448.

Difluoroboron chelate of 1-(4-chlorophenyl)-4-(piperidin-2-ylidene)butane-1,3-dione (4b) was obtained from difluoroboron chelate of 4-chlorobenzoylacetone (**1b**) and 6-methoxy-2,3,4,5-tetrahydropyridine (**2**). The yield was 41%, m.p. 215—216 °C. Found (%): C, 55.09; H, 4.80; N, 4.19. $C_{15}H_{15}BClF_2NO_2$. Calculated (%): C, 55.34; H, 4.64; N, 4.30. MS, *m/z* (I_{rel} (%)): 325 $[M]^+$ (4), 306 $[M - F]^+$ (2), 259 (6). ^{1}H NMR ($CDCl_3$), δ: 1.83 (m, 4 H, 2 CH_2); 2.55, 3.52 (both m, 2 H each, 2 CH_2); 4.82, 5.91 (both s, 1 H each, 2 CH); 7.36, 7.80 (both d, 2 H each, Ar, J = 8.8 Hz); 9.81 (br.s, 1 H, NH). ^{11}B NMR ($CHCl_3$), δ: 0.53. IR, ν/cm^{-1}: 3308, 2952, 2852, 1556, 1480.

Difluoroboron chelate of 4-(azepan-2-ylidene)-1-phenylbutane-1,3-dione (5a) was obtained from difluoroboron chelate of benzoylacetone (**1a**) and 7-methoxy-3,4,5,6-tetrahydro-2*H*-azepine (**3**). The yield was 43%, m.p. 189—190 °C. Found (%): C, 62.76; H, 6.10; N, 4.37. $C_{16}H_{18}BF_2NO_2$. Calculated (%): C, 62.95; H, 5.90; N, 4.59. MS, *m/z* (I_{rel} (%)): 305 $[M]^+$ (66), 285 $[M - F]^+$ (38), 239 (42). ^{1}H NMR ($CDCl_3$), δ: 1.70 (m, 6 H, 3 CH_2); 2.53, 3.53 (both m, 2 H each, 2 CH_2); 4.94, 6.00 (both s, 1 H each, 2 CH); 7.44, 7.88 (both m, total 5 H, Ar); 9.69 (br.s, 1 H, NH). ^{11}B NMR ($CHCl_3$), δ: 0.61. IR, ν/cm^{-1}: 3332, 2928, 2864, 1544, 1448.

Difluoroboron chelate of 4-(azepan-2-ylidene)-1-(4-chlorophenyl)butane-1,3-dione (5b) was obtained from difluoroboron chelate of 4-chlorobenzoylacetone (**1b**) and 6-methoxy-3,4,5,6-tetrahydro-2*H*-azepine (**3**). The yield was 46%, m.p. 213—214 °C. Found (%): C, 56.42; H, 5.13; N, 4.04. $C_{16}H_{17}BClF_2NO_2$. Calculated (%): C, 56.59; H, 5.05; N, 4.12. MS, *m/z* (I_{rel} (%)): 339 $[M]^+$ (65), 319 $[M - F]^+$ (9), 273 (18). ^{1}H NMR ($CDCl_3$), δ: 1.70 (m, 6 H, 3 CH_2); 2.50, 3.54 (both m, 2 H each, 2 CH_2); 4.94, 5.96 (both s, 1 H each, 2 CH); 7.38, 7.82 (both d, 2 H each, Ar, J = 8.8 Hz); 9.73 (br.s, 1 H, NH). ^{11}B NMR ($CHCl_3$), δ: 0.55. IR, ν/cm^{-1}: 3312, 2936, 2860, 1540, 1476.

Synthesis of 4-aryl-6,7,8,9-tetrahydro-2*H*-quinolizin-2-ones 7a,b and 4-aryl-7,8,9,10-tetrahydro-6*H*-pyrido[1,2-*a*]azepin-2-ones 8a,b (general procedure). Concentrated HCl (0.2 mL) was added to a suspension of chelate **4a**,**b** or **5a**,**b** (1 mmol) in ethanol (5 mL), and the reaction mixture was refluxed for 4 h, neutralized with 10% aqueous NaOH, and extracted with ethyl acetate. The ethyl acetate extract was dried, the solvent was evaporated, the residue was recrystallized from the corresponding solvent to obtain bicyclic compounds **7a**,**b**, **8a**,**b** as white crystals.

4-Phenyl-6,7,8,9-tetrahydro-2*H*-quinolizin-2-one (7a). The yield was 76%, m.p. 152—153 °C (hexane—benzene, 1 : 5). Found (%): C, 79.76; H, 6.83; N, 6.09. $C_{15}H_{15}NO$. Calculated (%): C, 79.97; H, 6.71; N, 6.22. MS, *m/z* (I_{rel} (%)): 225 $[M]^+$ (53), 198 (100), 169 (51). ^{1}H NMR ($CDCl_3$), δ: 1.83 (m, 4 H, 2 CH_2); 2.78, 3.63 (both m, 2 H each, 2 CH_2); 6.27, 6.29 (both m, 1 H each, 2 CH); 7.30, 7.50 (both m, total 5 H, Ar). IR, ν/cm^{-1}: 3044, 2924, 1624, 1536.

4-(4-Chlorophenyl)-6,7,8,9-tetrahydro-2*H*-quinolizin-2-one (7b). The yield was 79%, m.p. 183—184 °C (hexane—benzene, 1 : 5). Found (%): C, 69.25; H, 5.52; N, 5.25. $C_{15}H_{14}ClNO$. Calculated (%): C, 69.37; H, 5.43; N, 5.39. MS, *m/z* (I_{rel} (%)): 259 $[M]^+$ (70), 232 (100), 203 (49). ^{1}H NMR ($CDCl_3$), δ: 1.85 (m, 4 H, 2 CH_2); 2.80, 3.63 (both m, 2 H each, 2 CH_2); 6.27, 6.31 (both m, 1 H each, 2 CH); 7.27, 7.44 (both m, total 4 H, Ar). IR, ν/cm^{-1}: 3036, 2948, 1636, 1540.

4-Phenyl-7,8,9,10-tetrahydro-6*H*-pyrido[1,2-*a*]azepin-2-one (8a). The yield was 77%, m.p. 153—154 °C (hexane—benzene, 1 : 1). Found (%): C, 80.18; H, 7.30; N, 5.65. $C_{16}H_{17}NO$. Calculated (%): C, 80.30; H, 7.16; N, 5.85. MS, *m/z* (I_{rel} (%)): 239 $[M]^+$ (59), 211 (100), 182 (36). ^{1}H NMR ($CDCl_3$), δ: 1.64 (m, 6 H, 3 CH_2); 2.76, 3.78 (both m, 2 H each, 2 CH_2); 6.17, 6.28 (both m, 1 H each, 2 CH); 7.25, 7.40 (both m, total 5 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 26.2, 28.0, 28.1, 34.4, 50.0, 117.6, 118.4, 127.8, 128.3, 128.8, 134.9, 152.4, 154.3, 178.2. IR, ν/cm^{-1}: 3048, 2928, 1628, 1560.

4-(4-Chlorophenyl)-7,8,9,10-tetrahydro-6*H*-pyrido[1,2-*a*]azepin-2-one (8b). The yield was 81%, m.p. 207—208 °C (benzene). Found (%): C, 69.98; H, 6.00; N, 5.02. $C_{16}H_{16}ClNO$. Calculated (%): C, 70.20; H, 5.89; N, 5.12. MS, *m/z* (I_{rel} (%)): 273 $[M]^+$ (100), 245 (87), 216 (20). ^{1}H NMR ($CDCl_3$), δ: 1.64 (m, 6 H, 3 CH_2); 2.76, 3.78 (both m, 2 H each, 2 CH_2); 6.16, 6.30 (both m, 1 H each, 2 CH); 7.24, 7.40 (both m, total 4 H, Ar). IR, ν/cm^{-1}: 3056, 2924, 1628, 1560.

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