Chelate synthesis of 8-diaminomethylene-5,6,7,8-tetrahydroquinazoline-7-one derivatives

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A scheme for synthesizing 5,6,7,8-tetrahydroquinazoline systems from ketene aminal **1** *via* its diphenylboron chelate **2** has been suggested. The interaction of *p*-toluamidine with the condensation product of the chelate with dimethylformamide dimethylacetal results in the formation of 8-(*N*-benzoyldiaminomethylene)-2-*p*-tolyl-5,6,7,8-tetrahydroquinazoline-7-one, which is easily debenzoylated by sodium ethoxide. 8-Diaminomethylene-5,6,7,8-tetrahydroquinazolinone derivatives can be used for the preparation of boron chelate complexes.

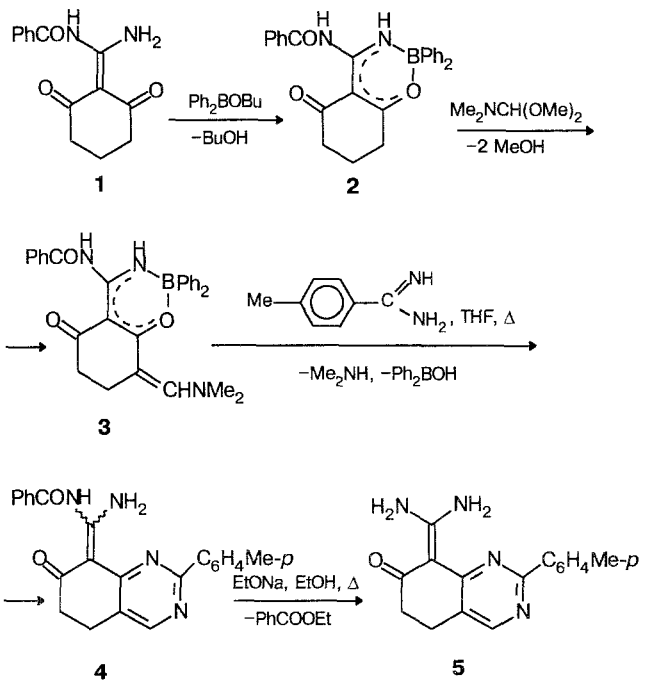
Key words: ketene aminals, boron chelates; dimethylformamide dimethylacetal; tetrahydroquinazolinones, debenzoylation.

Diacetyl ketene aminals (DKA) containing one or two NH_2 groups[1,2] are efficient reagents in heterocyclization.[3–5] The area of their synthetic application can be substantially enlarged due to the ability of DKA to form chelates, because coordination interaction considerably changes the chemical properties of ligands. For example, we successfully used boron chelates of DKA for the preparation of functionalized 4-pyridones.[6] It is also known that the easily available ketene aminal **1** (see Ref. 2) gives diphenylboron chelate **2**, which is condensed under mild conditions with dimethylformamide dimethylacetal[7] to form product **3*** (Scheme 1). Treatment of **3** with hydrazine hydrate is accompanied by the closing of the pyrazole cycle and results in the formation of 7-(*N*-benzoyldiaminomethylene)-4,5,6,7-tetrahydroindazole-6-one.

In the present work, we demonstrate that it is possible to create a quinazoline system based on chelate **3**. The use of amidines as dinucleophiles (similarly to hydrazine) results in the formation of the pyrimidine cycle. In particular, 8-(*N*-benzoyldiaminomethylene)-2-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-7-one (**4**) was obtained in good yield upon condensation of complex **3** with *p*-toluamidine (heating in THF).

An ethanolic solution of EtONa easily debenzoylates derivative **4** into compound **5** with both amino groups unsubstituted (see Scheme 1).

Scheme 1



The functionalized tetrahydroquinazolines **4** and **5** are colorless crystalline substances soluble in chloroform and benzene. Compound **4** is poorly soluble in EtOH, DMSO, and DMF, while the solubility of **5** is substantially higher. Intense molecular ion peaks are observed in the mass spectra of these compounds. The ^1H and ^{13}C NMR spectra correspond to structures **4** and **5**. The characteristic absorption band of the benzoyl group

* The structure of **3** was confirmed by the data of X-ray analysis (M. G. Kurella and L. G. Vorontsova, N. D. Zelinsky Institute of Organic Chemistry, RAS). The results of studies will be published elsewhere.

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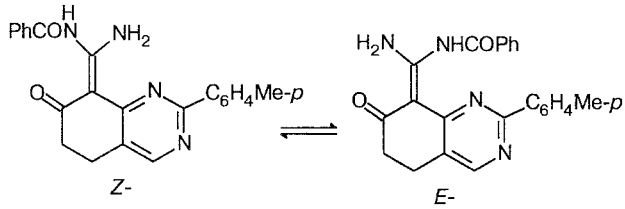
(1680 cm^{-1}) is observed in the IR spectrum of **4** (unlike that of **5**).

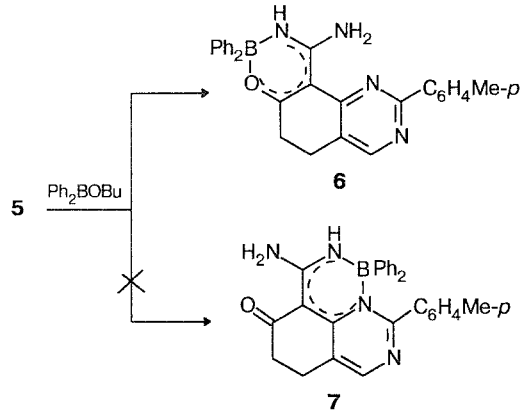
The ^1H NMR spectrum of compound **4** in $CDCl_3$ contains two sets of signals (in the ratio 9 : 1), which points to the existence of *Z,E*-isomers. The signals from both of the isomers are also observed in the ^{13}C NMR spectrum. This isomerism is observed, in particular, for asymmetric ketene aminals.[8]



The ^1H NMR spectra of compound **5** in $CDCl_3$ are characterized by one set of signals with a singlet CH characteristic of the pyrimidine cycle (δ 8.30). According to the data from ^1H NMR and IR spectroscopy, structure **5** contains intramolecular N—H...O and N—H...N bonds.

Ketene aminals **4** and **5** can be used as reagents in the synthesis of fused heterocyclic systems. Compounds **4** and **5**, like **1**, can form chelate complexes. Chelate **6** was obtained by the reaction of **5** with Ph_2BOBu (Scheme 2). Chelate **6** is structurally similar to complexes **2** and **3**. It should be mentioned that the coordination interaction of ligand **5** with boron might also be represented as occurring through the participation of the pyrimidine N atom (see chelate structure **7** with *N,N*-coordination).

Scheme 2



However, the parameters of the ^{13}C NMR spectra attest to the direct participation of the carbonyl group of **5** in the chelate formation (as in the case with **1** and **2**), *i.e.*, they favor structure **6**. The signals of the C atoms of the free carbonyl groups of **1** are characterized by the chemical shifts at 199.34 and 199.84 ppm, whereas in **2** the signal with δ 198.85 corresponds to the free C=O group, and that with 192.80 corresponds to the group involved in the coordination interaction. A signal with δ 195.99 (C atom of the free C=O group) is observed in the ^{13}C NMR spectrum of quinazoline **5**, and in **6**, the most low-field signal has δ 182.6 (C—O—B). The chelate complex **6** is easily soluble in benzene and chloroform, and is highly hydrolytically stable. It remains unchanged in air and even on boiling in pentanol.

Experimental

^1H NMR spectra were recorded on a Bruker WH-250 instrument, ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. IR spectra were registered on a UR-20 spectrometer. Mass spectra were obtained on a MAT-311A instrument (EI, 70 eV).

2-(*N*-Benzoyldiaminomethylene)cyclohexane-1,3-dione (1) was prepared by the known procedure,[2] and its **diphenylboron chelate (2)** was prepared according to Ref. 7. ^{13}C NMR of **1** ($CDCl_3$), δ: 19.19 (C(5)); 38.22, 38.41 (C(4), C(6)); 98.64 (C(2)); 127.92, 128.98, 131.90, 133.57 (C_6H_5); 162.65 (NCN); 169.59 (NCO); 199.34, 199.84 (C(1), C(3)). ^{13}C NMR of chelate **2** ($CDCl_3$), δ: 19.50 (C(5)); 33.57 (C(4)); 37.50 (C(6)); 100.64 (C(2)); 126.59, 127.55, 127.85, 129.26, 131.41, 131.75, 133.98 (3 C_6H_5); 156.57 (NCN); 169.49 (NCO); 192.80 (C—O—B); 198.95 (C(1)).

[2-(*N*-Benzoyldiaminomethylene)-4-dimethylaminomethylenecyclohexane-1,3-dionato-*O,N*]diphenylboron (3). A mixture of 3.03 g (7.20 mmol) of chelate **2** and 1.91 mL (14.40 mmol) of $Me_2NCH(OMe)_2$ in 5 mL of THF was stirred for ~48 h at 20 °C. The precipitated crystals of **3** were filtered off, an additional amount of **3** was isolated from the filtrate by column chromatography (SiO_2, $CHCl_3$ as the eluent); total yield was 2.62 g (65 %), m.p. 250—252 °C (from THF). Found (%): C, 73.20; H, 6.20; B, 2.55; N, 8.78. $C_{29}H_{28}BN_3O_3$. Calculated (%): C, 72.96; H, 5.91; B, 2.27; N, 8.85. IR (CH_2Cl_2), ν/cm^{-1}: 3300, 3150—2800 (NH, CH); 1685, 1640, 1627 (C=O, C=C). ^1H NMR ($CDCl_3$), δ: 2.55 (t, 2 H, CH_2); 2.95 (t, 2 H, CH_2); 3.23 (s, 6 H, 2 CH_3); 7.20—7.70 (m, 13 H, 3 C_6H_5); 7.88 (s, 1 H, CH); 8.10 (m, 2 H, C_6H_5); 10.40 (br.s, 1 H, NH); 14.32 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$, δ, *J*/Hz): 21.94 (t, C(5), ^1J = 137); 37.10 (t, C(6), ^1J = 129); 44.20 (q, $(CH_3)_2N$, ^1J = 137); 95.60 (s, C(2)); 97.30 (m, C(4)); 126.00, 127.30, 127.70, 129.12, 171.70, 132.50, 133.40 (3 C_6H_5); 151.60 (d, CH, ^1J = 167); 156.5 (NCN); 169.30 (m, NCO); 180.10 (m, C—O—B); 196.50 (m, C(1)). Mass spectrum: *m/z* 400 $[M-C_6H_5]^+$.

8-(*N*-Benzoyldiaminomethylene)-2-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-7-one (4). A mixture of 2.26 g (4.70 mmol) of compound **3** and 1.40 g (10.44 mmol) *p*-toluamidine in 20 mL of THF was refluxed for 8 h and kept overnight. The precipitate formed was filtered off and recrystallized from benzene to give 1.62 g (87 %) of ketene aminal **4**, m.p. 232—234 °C (from benzene). Found (%): C, 72.31; H, 5.25; N, 14.07. $C_{23}H_{20}N_4O_2$. Calculated (%): C, 71.86; H, 5.24; N, 14.58. IR (CH_2Cl_2), ν/cm^{-1}: 3345, 3110, 2850 (NH, CH); 1678, 1335, 1600, 1582, 1555 (C=O, C=N, C=C). ^1H NMR ($CDCl_3$, the first value refers to the predominant isomer), δ: 2.45/2.38 (s, 3 H, CH_3); 2.70/2.90 (m, 2 H, CH_2); 6.95—8.18 (9 H, C_6H_5, C_6H_4); 8.40/8.61 (s, 1 H, CH); 10.15/10.00, 12.40/11.90, 15.60/15.20 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$, the first value refers to the predominant isomer), δ: 21.31

(CH_3); 23.10/23.28 (C(5)); 38.49/38.52 (C(6)); 91.61 (C(8)); 121.74 (C(4a)); 127.63, 128.13, 128.36, 128.49, 128.68, 128.99, 129.09, 129.40, 132.80, 133.29, 135.48, 140.48 (C_6H_5, C_6H_4); 153.02/153.32 (C(4)); 160.64, 161.24, 162.79 (C(8a), NCN, C(2)); 169.89 (NCO); 196.43 (C(7)). Mass spectrum: *m/z* 384 $[M]^+$.

8-Diaminomethylene-2-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-7-one (5). Ketene aminal **4** (1.87 g, 4.74 mmol) was added to a solution of EtONa prepared from 0.11 g (4.80 mmol) of sodium and 20 mL of EtOH. The mixture was refluxed for 1 h. The solution was neutralized with acetic acid and filtered, and the filtrate was evaporated *in vacuo*. The oily residue was triturated with a 1 : 2 ether—hexane mixture until crystals were formed. The crystals were filtered off and recrystallized from the benzene—ethanol—hexane (20 : 1 : 2) mixture to give 0.78 g (59 %) of **5**, m.p. 214—215 °C (from benzene). Found (%): C, 68.61; H, 5.45; N, 21.02. $C_{16}H_{16}N_4O$. Calculated (%): C, 68.55; H, 5.75; N, 21.04. IR (CH_2Cl_2), ν/cm^{-1}: 3470, 2930, 2860 (NH, CH); 1605, 1588, 1569, 1539 (C=O, C=N, C=C). ^1H NMR ($CDCl_3$), δ: 2.41 (s, 3 H, CH_3); 2.60 (t, 2 H, CH_2); 2.81 (t, 2 H, CH_2); 5.20 (br.s, 2 H, NH_2); 7.28 (d, 2 H, C_6H_4); 8.05 (d, 2 H, C_6H_4); 8.29 (s, 1 H, CH); 11.20 (br.s, 2 H, NH_2). ^{13}C NMR (CD_3OD), δ: 21.60 (CH_3); 24.47 (C(5)); 37.37 (C(6)); 92.67 (C(8)); 122.83 (C(4a)); 128.81, 130.46, 137.12, 141.73 (C_6H_4); 152.58 (C(4)); 162.49, 165.58 (C(8a), NCN, C(2)); 195.9 (C(7)). Mass spectrum: *m/z* 280 $[M]^+$.

[8-Diaminomethylene-2-*p*-tolyl-5,6,7,8-tetrahydroquinazolin-7-onato-*O,N*]diphenylboron (6). A mixture of ketene aminal **5** (0.78 g, 2.79 mmol) and 1.54 mL (5.57 mmol) of Ph_2BOBu in 4 mL of toluene was refluxed for 4 h. The solvent was removed, the residue was washed with hexene and recrystallized from benzene to give 1.102 g (89 %) of chelate **6**, m.p. 284—286 °C (from benzene). Found: (%): C, 74.53; H, 6.08; B, 2.02; N, 12.98. $C_{28}H_{25}BN_4O$. Calculated (%): C, 75.68; H, 5.67; B, 2.43; N, 12.61. IR (CH_2Cl_2), ν/cm^{-1}: 3470, 3396 (NH, CH); 1633, 1585, 1555 (C=O, C=N, C=C). ^1H NMR ($CDCl_3$), δ: 2.45 (s, 3 H, CH_3); 2.71 (s, 4 H, 2 CH_2); 5.79 (s, 1 H, NH); 7.20—7.50 (12 H, 2 C_6H_5, C_6H_4); 7.02 (m, 2 H, C_6H_4); 8.21 (s, 1 H, CH). ^{13}C NMR (DMSO-d_6, δ, *J*/Hz): 21.00 (q, CH_3); 21.90 (t, C(5)); 30.10 (t, C(6); ^1J = 132); 95.20 (m, C(8)); 121.0 (m, C(4a)); 125.00, 126.60, 127.30, 129.30, 131.00, 134.60, 140.20 (2 C_6H_5, C_6H_4); 153.70 (d, C(4), ^1J = 178); 158.30 (d, C(8a), ^3J = 3); 160.20, 160.40 (C(2), NCN); 182.60 (t, C(7), ^2J = 6).

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