Chelate synthesis of pyrazolyl(ethoxycarbonyl)ketene aminals, the precursors of functionalized pyrazolo[1,5-*c*]pyrimidines

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A scheme for the preparation of novel synthetic reagents, pyrazolyl(ethoxycarbonyl)ketene aminals, from acetyl(ethoxycarbonyl)ketene (*N*-benzoyl)aminal *via* its difluoroboron chelate is suggested. The possibility of cyclization of the ketene aminals obtained into functionally substituted pyrazolo[1,5-*c*]pyrimidines is shown.

Key words: ketene aminals; pyrazoles; amide acetals; difluoroboron chelates; hydrazines; pyrazolo[1,5-*c*]pyrimidines; heterocyclization; *E*,*Z*-isomerism.

The conversion of functionally substituted β-diketones and enaminones into chelate-type complexes that can often undergo reactions that are not characteristic of the free ligands substantially extends the uses of these reagents in organic synthesis.

Recently we suggested novel schemes for building some heterocyclic systems, which involved the formation of difluoro- or diphenylboron chelates from α,α-dioxoketene aminals and their reactions with amide acetals.[1—4] In particular, we found that chelate complex (**2**) prepared from the *N*-benzoyl derivative of acetyl(ethoxycarbonyl)ketene aminal (**1**) reacts with dimethylformamide dimethyl acetal (**3**) to give the product of condensation at the methyl group (**5**) (Scheme 1), which then reacts with *p*-toluamidine with the closure of a pyrimidine ring to yield the corresponding derivative of pyrimidinylketene aminal.[4]

In the present work we used a similar approach to the synthesis of ketene aminals with pyrazole substituents at the C=C bond. We showed that chelate complexes **5** and **6** (the latter is prepared by condensation of difluoroboron chelate **2** with dimethylacetamide dimethyl acetal (**4**)) react with hydrazine hydrate and methylhydrazine to give pyrazoles. We used this pathway to prepare pyrazolyl(ethoxycarbonyl)ketene (*N*-benzoyl)aminals (**7—9**) in 55—74 % yields. It should be noted that the reaction of **5** with methylhydrazine occurs regioselectively yielding only one of the two possible isomers **9** and **10**, namely, compound **9** (see Scheme 1).

These transformations may be compared with the reactions described by us previously involving annelation of a pyrazole ring to 2-(*N*-benzoyl)diaminomethylene-1,3-cyclohexanedione.[2] Hydrazines act as dinucleophiles, like *p*-toluamidine in the synthesis of pyrimidinylketene aminals,[4] and the cyclization steps should have similar mechanisms in all of the above-mentioned cases.

Ketene aminals **7—9** are yellow crystalline solids, readily soluble in chloroform and benzene and slightly soluble in ethanol and THF. Their structures were confirmed by the data of mass spectrometry (the presence of the $[M]^{+\cdot}$ ion) and IR and ^1H and ^{13}C NMR spectroscopy. The location of the Me group in the pyrazole ring of **9** was determined from the ^{13}C NMR spectrum. It was found that the C(5) atom of the pyrazole moiety has a spin coupling constant of 2 Hz with the N(1)—Me protons, whereas in the case of structure **10**, the C(3) atom is too remote from NMe for this coupling to occur. In addition, according to the ^1H NMR spectra in $CDCl_3$, one of the hydrogen atoms of the NH groups of the compound synthesized does not participate in the formation of intramolecular hydrogen bonds (IHB), which is consistent with structure **9**, whereas in compounds **7** and **8**, all of the NH groups of the diaminomethylene fragment are involved in intramolecular interaction with the carbonyl group and the N(2) atom of the pyrazole ring (this would also be expected in the case of the ketene aminal having structure **10**). Thus, compounds **7** and **8** should be considered to be pyrazoles substituted in position 3, and the product of the reaction of compound **5** with methylhydrazine is the 5-substituted pyrazole (**9**).

Though α-oxoketene aminals, being push-pull systems, generally have[5] low barriers to rotation about the C=C bond, these barriers can be somewhat higher due to the formation of IHB.[6,7] In fact, the ^1H NMR spectra of ketene aminals **7** and **8** exhibit double sets of signals (in a 4 : 1 ratio in $CDCl_3$ and a 3 : 2 ratio in DMSO-d_6), which indicates that the solutions contain equilibrium mixtures of *Z* and *E* isomers. On the other

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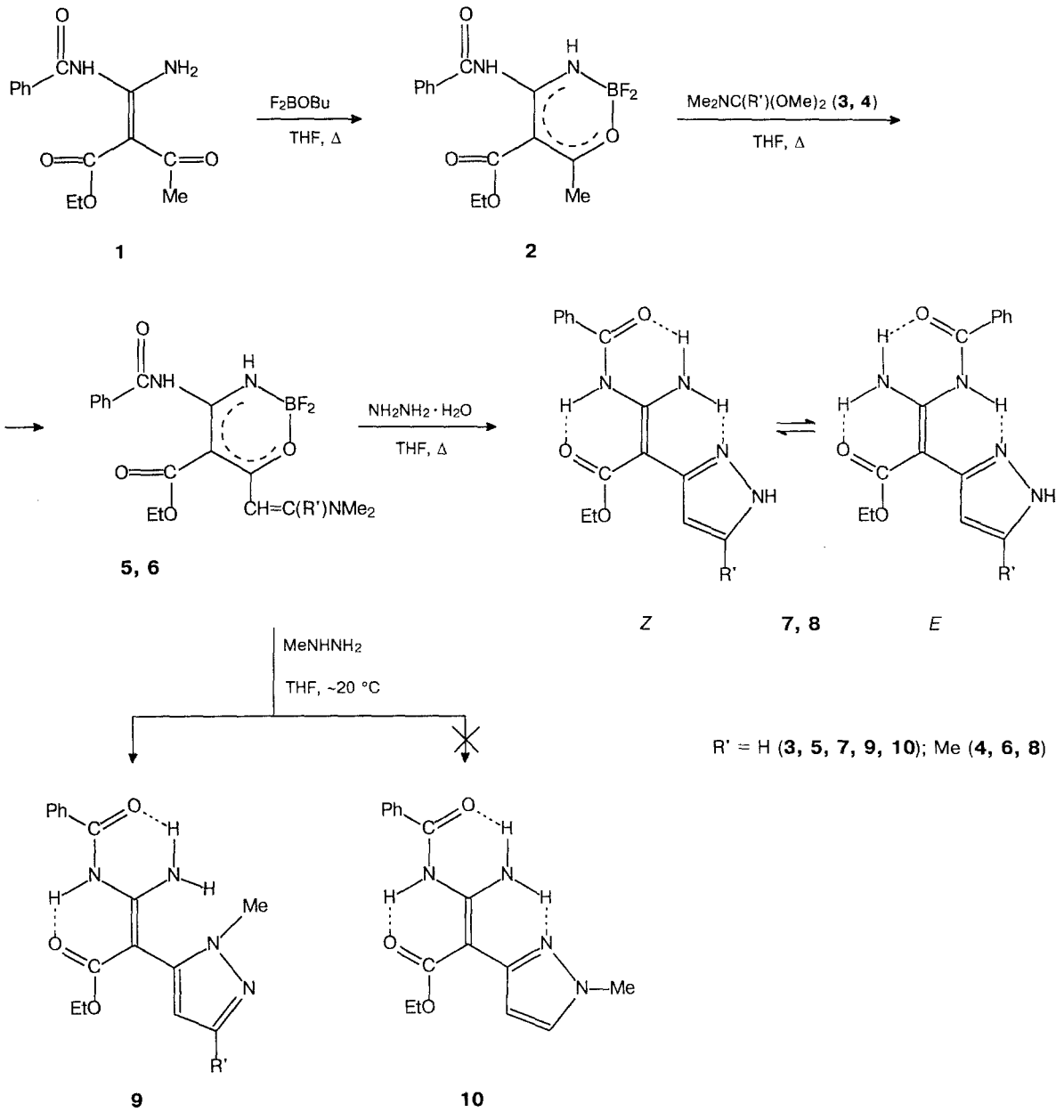
Scheme 1



1 **2** **5, 6** *Z* **7, 8** *E* **9** **10**

hand, the ^{1}H NMR spectrum (in $CDCl_3$) of compound **9**, which does not contain the N—H···N IHB, exhibits only one set of signals, which apparently correspond to the more thermodynamically favorable isomer.

Spectroscopic studies of α-monooxoketene *N*-benzoylaminals have shown that the NH signal located the furthest down-field in their ^{1}H NMR spectra corresponds to the amide proton involved in the formation of the IHB with the carbonyl group.[7] A comparison of the ^{1}H NMR spectra of compound **1** [6] and the *N*-unsubstituted ketene aminal resulting from debenzoylation of **1** [8] confirms these data. Therefore, the signal located the furthest down field in the spectrum of a solution of compound **9** in $CDCl_3$ at δ 13.60 can be assigned to PhCON—H···O, whereas the signal at δ 8.75 corresponds to the weak NH···O=CPh IHB. The second proton of the NH_2 group remains free (δ 5.20). Thus, in $CDCl_3$, ketene aminal **9** exists exclusively as the *Z*-form.

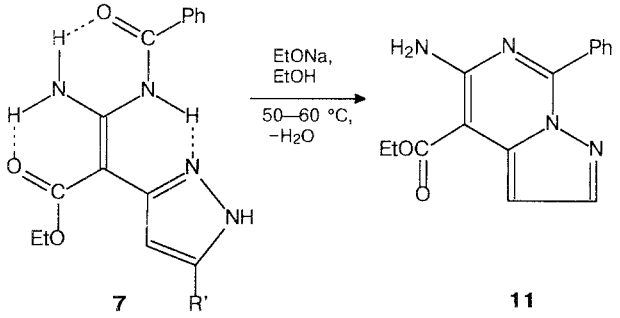
Based on the foregoing data, one may conclude that the *Z*-isomer prevails for compounds **7** and **8**, since the signal at δ ~14 (PhCON—H···O) in the ^{1}H NMR spectra

recorded in $CDCl_3$ is more intense than that at δ ~13 (PhCON—H···N). The other protons of the NH and NH_2 groups are manifested as considerably overlapping signals in the δ ~8.0—10 region.

The ketene aminals prepared are of interest as potential reagents for heterocyclic synthesis. In particular, for compounds **7** and **8**, annelation of a pyrimidine ring to the pyrazole ring is possible.

In fact, whereas treatment of ketene aminal **1** with MeONa in MeOH only results in its debenzoylation,[8] the reaction of compound **7** with a solution of EtONa in EtOH at 50—60 °C occurs as intramolecular cyclization (with abstraction of H_2O) involving the benzamide group and the NH group of the pyrazole ring (Scheme 2). The reaction yields 5-amino-4-ethoxycarbonyl-7-phenylpyrazolo[1,5-*c*]pyrimidine (**11**) as a yellow crystalline solid, readily soluble in acetone, chloroform, and benzene and slightly soluble in ethanol and hexane. The mass spectrum of compound **11** exhibits the molecular ion peak and its IR and ^1H and ^{13}C NMR spectra also correspond to structure **11**.

Scheme 2



Of the various types of pyrazolopyrimidines, it is perhaps the [1,5-*c*]-system that has been investigated the least (see Ref. 9). At the same time, some of its derivatives have been found to possess hypnotic and sedative properties.[10]

The use of pyrazolylketene aminals **7** and **8** as the precursors of pyrazolo[1,5-*c*]pyrimidines is of interest because it makes it possible to synthesize the representatives of this bicyclic series having functional groups in positions 4 and 5 that have been almost inaccessible.

Experimental

^1H NMR spectra were recorded on a Bruker WM-250 instrument, ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer; IR spectra were run on a UR-20 spectrophotometer. Mass spectra were obtained on a Varian MAT-311A mass spectrometer (EI, 70 eV).

[Ethyl-2-(*N*-benzoyl)diaminomethylene-acetylacetato-*N,O*]difluoroboron (**2**) and **[ethyl-2-(*N*-benzoyl)diaminomethylene-5-dimethylamino-3-oxo-4-pentenoato-*N,O*]difluoroboron** (**5**) were prepared according to the known procedure.[4]

^{13}C NMR spectrum of chelate **5** ($CDCl_3$), δ: 14.3 (q, Me, J = 127 Hz); 37.4 (q, MeN, J = 139 Hz); 45.6 (q, MeN, J = 139 Hz); 61.1 (t, CH_2, J = 149 Hz); 85.4 (s, CCOO); 93.3 (d, CH, J = 163 Hz); 127.7, 129.1, 132.6, 133.4 (Ph); 155.8 (d, CHN, J = 169 Hz), 160.2 (s, NCN); 168.8 (t, NCO or COO, ^2J = 4 Hz); 169.6 (s, NCO or COO); 176.9 (s, COB).

[Ethyl-2-(*N*-benzoyl)diaminomethylene-5-dimethylamino-3-oxo-4-hexenoato-*N,O*]difluoroboron (**6**). Chelate **6** was prepared from chelate **2** and acetal **4** similarly to compound **5**,[4] yield 62 %, m.p. 209—210 °C (benzene). Found (%): C, 54.85; H, 5.61; F, 9.12; N, 10.79. $C_{18}H_{22}BF_2N_3O_4$. Calculated (%): C, 54.98; H, 5.64; F, 9.66; N, 10.69. MS, *m/z*: 393 $[M]^{+\cdot}$. IR (KBr), ν/cm^{-1}: 3290, 3100—2820 (NH, CH); 1677, 1652 (CO); 1610. ^1H NMR ($CDCl_3$), δ: 1.40 (t, 3 H, CH_3CH_2); 2.58 (s, 3 H, Me); 3.15 (s, 6 H, Me_2N); 4.30 (q, 2 H, CH_2); 6.05 (s, 1 H, CH); 7.50—8.02 (m, 5 H, Ph); 10.20 (br.s, 1 H, NH); 13.58 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 14.5 (q, CH_3CH_2, J = 127 Hz); 18.8 (qd, Me, ^1J = 127 Hz, ^3J = 5 Hz); 41.3 (q, Me_2N, J = 142 Hz); 60.9 (tq, CH_2, ^1J = 148 Hz, ^2J = 5 Hz); 86.0 (s, CCOO); 94.7 (d, CH, ^1J = 155 Hz); 127.7, 129.0, 132.7, 133.3 (Ph); 160.2 (s, NCN); 167.1 (m, Me_2NC); 168.8 and 170.2 (NCO and COO); 176.4 (COB).

Ethyl 3,3-(*N*-benzoyl)diamino-2-(1*H*-pyrazol-3-yl)acrylate (**7**). A mixture of ether **3** (0.29 g, 0.76 mmol) and $N_2H_4 \cdot H_2O$ (0.05 mL, 1.00 mmol) in 12 mL of THF was stirred at 20 °C for 5 days. The solvent was evaporated, and the dry residue was recrystallized from benzene to give 0.15 g (66 %) of ester **7**, m.p. 213—214 °C. Found (%): C, 60.03; H, 5.29; N, 18.49. $C_{15}H_{16}N_4O_3$. Calculated (%): C, 59.99; H, 5.37; N, 18.66. MS, *m/z*: 300 $[M]^{+\cdot}$. IR (CH_2Cl_2), ν/cm^{-1}: 3468, 3380 br (NH); 3100—2800 (NH, CH); 1683 sh, 1668 sh, 1633, 1585, 1570; (KBr), ν/cm^{-1}: 3410, 3338, 3200—2800 (NH, CH); 1665, 1635, 1610, 1580. ^1H NMR ($CDCl_3$), δ, *Z*/*E*-isomers: 1.28/1.26 (t, 3 H, Me); 4.18/4.14 (q, 2 H, CH_2); 6.48/6.52 (d, 1 H, CH); 7.50—8.10 (m, 6 H, Ph, NCH); 9.00—9.60 (br.s, 2 H, NH_2); 12.70/12.90 (br.s, 1 H, NH); 14.10/13.90 (s, 1 H, NHCO). ^{13}C NMR (DMSO-d_6), δ, *Z*/*E*-isomers: 14.2/14.3 (q, Me); 59.2/58.6 (t, CH_2, J = 148 Hz), 77.0 (CCOO); 105.4/105.7 (dd, pyrazole C-4, ^1J = 178 Hz, ^2J = 9 Hz); 127.1, 127.4, 127.8, 128.5, 129.0, 129.1 (Ph); 132.9 (C-3); 147.4 (br.s, C-5); 155.8/155.6 (NCN); 167.1/167.5 and 168.9/170.3 (NCO and COO).

Ethyl 3,3-(*N*-benzoyl)diamino-2-(5-methyl-1*H*-pyrazol-3-yl)acrylate (**8**). Ester **8** was prepared from chelate **6** similarly to ester **7**, yield 55 %, m.p. 166—167 °C (benzene). Found (%): C, 61.15; H, 5.19; N, 17.62. $C_{16}H_{18}N_4O_3$. Calculated (%): C, 61.13; H, 5.77; N, 17.83. MS, *m/z*: 314 $[M]^{+\cdot}$. IR (KBr), ν/cm^{-1}: 3340, 3300 sh, 3210—2800 (NH, CH); 1664 (CO); 1608 sh, 1590. ^1H NMR ($CDCl_3$), δ, *Z*/*E*-isomers: 1.35/1.36 (t, 3 H, CH_3CH_2); 2.34 (s, 3 H, Me); 4.28 (m, 2 H, CH_2); 6.30/6.38 (s, 1 H, CH); 7.40—8.10 (m, 5 H, Ph); 8.20—10.00 (br.s, 3 H, NH_2, NH); 14.13/13.10 (s, 1 H, NHCO).

Ethyl 3,3-(*N*-benzoyl)diamino-2-(1-methylpyrazol-5-yl)acrylate (**9**). Ester **9** was prepared from chelate **5** and methylhydrazine similarly to **7**, yield 75 %, m.p. 139—140 °C (benzene). Found (%): C, 60.58; H, 5.65; N, 17.69. $C_{16}H_{18}N_4O_3$. Calculated (%): C, 61.13; H, 5.77; N, 17.83. MS, *m/z*: 314 $[M]^{+\cdot}$. IR (KBr), ν/cm^{-1}: 3360, 3280—2800 (NH, CH); 1675 sh, 1630 br (CO); 1580. ^1H NMR ($CDCl_3$), δ: 1.16 (t, 3 H, Me); 3.70 (s, 3 H, MeN); 4.01—4.32 (m, 2 H, CH_2); 5.20 (br.s, 1 H, NH_2); 6.17 (d, 1 H, CH); 7.50—8.10 (m, 5 H, Ph); 8.75 (br.s, 1 H, NH_2); 13.62 (s, 1 H, NHCO). ^{13}C NMR (DMSO-d_6), δ: 14.5 (q, Me, ^1J = 126 Hz); 35.9 (q,

MeN, ^1J = 140 Hz); 59.1 (t, CH_2, ^1J = 147 Hz); 72.0 (CCOO); 107.6 (dd, pyrazole C-4, ^1J = 174, ^2J = 10 Hz); 127.3, 129.3, 132.6, 133.4 (Ph); 134.9 (dqd, C-5, ^2J = 8 Hz, ^3J = 6 Hz, ^3J = 6 Hz, ^3J = 2 Hz); 137.8 (dd, C-3, ^1J = 183 Hz, ^2J = 5.8 Hz); 156.5 (NCN); 167.2 and 169.3 (NCO and COO).

5-Amino-4-ethoxycarbonyl-7-phenylpyrazolo[1,5-*c*]pyrimidine (11). A mixture of ester **7** (0.15 g, 0.50 mmol) and EtONa, prepared by dissolution of Na (0.012 g, 0.50 mmol) in 4 mL of EtOH, was stirred for 3 h at 50—60 °C, cooled to ~20 °C, and acidified with AcOH. The precipitate was filtered off and recrystallized from benzene to give 0.07 g (51 %) of pyrazolopyrimidine **11**, m.p. 193—195 °C. Found (%): C, 63.41; H, 4.94; N, 19.84. $C_{15}H_{14}N_4O_2$. Calculated (%): C, 63.82; H, 5.00; N, 19.85. MS, *m/z*: 282 $[M]^{\cdot+}$. IR (CH_2Cl_2), ν/cm^{-1}: 3502, 3362 (NH); 1675 (CO); 1618, 1590, 1522. ^1H NMR (DMSO-d_6), δ: 1.40 (t, 3 H, Me); 4.35 (q, 2 H, CH_2); 6.60 (d, 1 H, CH); 7.51—7.65 (m, 3 H, Ph); 8.02 (d, 1 H, NCH); 8.31 (m, 2 H, Ph); 9.95 (br.s, 2 H, NH_2). ^{13}C NMR (DMSO-d_6, δ: 14.7 (q, Me); 60.8 (t, CH_2); 87.9 (C-4); 98.3 (C-3); 128.2, 131.8, 132.0, 132.7 (Ph); 143.6 (C-3a); 146.4 (NCH); 152.2 and 156.9 (C-7 and C-5).

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