Reactions of alkyl 3-amino-5-aryl-2-benzoyl-5-oxopent-2-enoates with hydrazine

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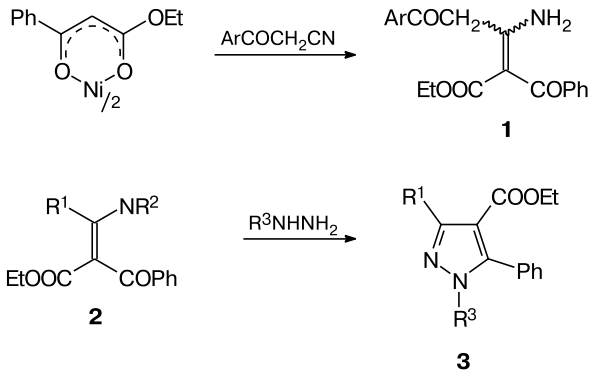
Reactions of alkyl 3-amino-5-aryl-2-benzoyl-2-oxopent-2-enoates with hydrazine were accompanied by debenzoylation and isomerization to give 3-amino-5-aryl-5-oxopent-3-enohydrazides, which underwent cyclization in the presence of an excess of hydrazine into 5(3)-arylpyrazol-3(5)-ylacetohydrazides.

Key words: hydrazine, 3-amino-5-aryl-5-oxopent-3-enohydrazides, pyrazol-3(5)-ylacetohydrazides, diphenylboron chelate, pyrazoles, heterocyclization.

Earlier,[1] we have developed a method for the synthesis of alkyl 3-amino-5-aryl-2-benzoyl-5-oxopent-2-enoates (**1**), which exist in solutions as an equilibrium mixture of the *E*- and *Z*-isomers[1] (Scheme 1). Compounds **1** can be used as reagents for heterocyclic synthesis: when refluxed in xylene, they transform into 4-amino-6-aryl-3-benzoylpyran-2-ones; on heating with ammonium acetate in AcOH, they undergo cyclization into alkyl 4-amino-6-aryl-2-phenylpyridine-3-carboxylates.[1]

Here we studied reactions of esters **1** with hydrazine. It is known[2—4] that aminomethylidene derivatives of ethyl benzoylacetate (**2**) react with hydrazines to give substituted ethyl pyrazole-4-carboxylates **3** (see Scheme 1). The formation of the pyrazole ring of products **3** involves the enaminone fragment of compounds **2**. Cyclization of compounds **1** with hydrazine could be expected to occur analogously, with correction for possible participation of the carbonyl group of the aroylmethyl fragment in this transformation.

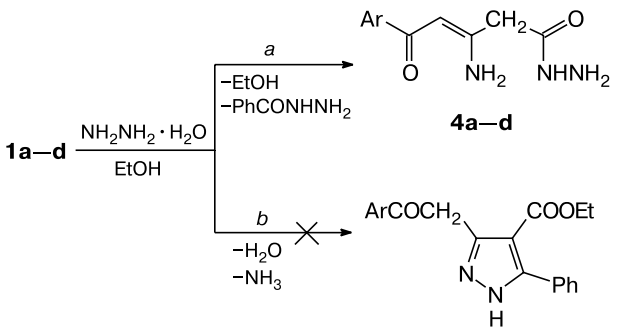
Scheme 1



R^1, R^2, R^3 = H, Me

Unexpectedly, treatment of alcoholic solutions of compounds **1a—d** with an excess of hydrazine hydrate at 20 °C for 30 min gave 3-amino-5-aryl-5-oxopent-3-enohydrazides **4a—d** in 73—83% yields (Scheme 2, pathway *a*), while cyclization into pyrazolecarboxylic acids of the type **2** (pathway *b*) as with compounds **2** did not occur. Nor were other by-products detected.

Scheme 2



Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**)

Reaction conditions: 30 min, 20 °C.

Thus, hydrazinolysis of esters **1a—d** is accompanied by debenzoylation and a migration of the double bond.

Compounds **4a—d** are white crystalline solids which are poorly soluble in most organic solvents (*e.g.*, in dioxane and chloroform). Their structures were confirmed

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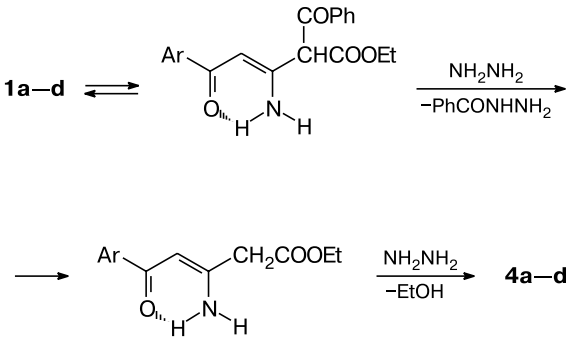
by spectroscopic data. For instance, the mass spectra of compounds **4a—d** contain molecular ion peaks $[M]^+$. The ^1H NMR spectra of hydrazides **4a—d** show singlets at δ 3.05—3.06 for the methylene protons, singlets at δ 5.70—5.75 for the HC= proton, and signals for five NH protons. The position of the double bond was derived from NOE and $^1H—^{13}C$ heteronuclear correlation experiments for compound **4a**. For instance, irradiation of the CH_2 protons at δ 3.05 caused NOE only with the proton HC(4) (δ 5.75). In contrast, irradiation of the proton at δ 5.75 (HC(4)) caused NOE with both the CH_2 protons (δ 3.05) and the *ortho*-protons of the phenyl substituent (δ 7.84—7.78), which matches structure **4** but excludes the isomeric pent-2-ene structure $ArC(O)CH_2C(NH_2)=CHC(O)NHNH_2$.

Therefore, the reactions of hydrazine with esters **1a—d** and related esters **2** yield essentially different products. Apparently, this is due to initial isomerization of compounds **1** in the presence of such a strong base as hydrazine (Scheme 3) into an intermediate containing an aminovinyl carbonyl fragment probably stabilized by an intramolecular hydrogen bond N—H...O. Obviously, this will significantly lower the probability of replacement of the NH_2 group but favor deacylation (*cf.* the deacylation of ethyl 2-benzoylacetoacetate in the presence of hydrazine[5]). Ultimately, debenzoylated ester transforms into hydrazide **4**.

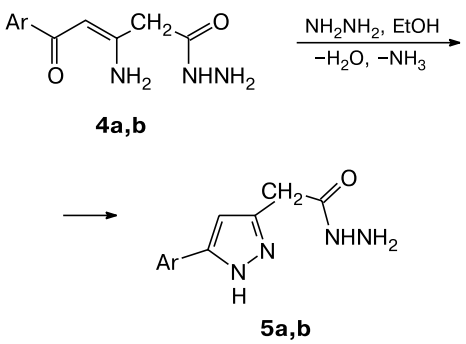
Scheme 3



Substantially longer treatment of esters **1a,b** with an excess of hydrazine hydrate at room temperature gave 5(3)-arylpyrazol-3(5)-ylacetohydrazides **5a,b** as cyclization products from compounds **4** (Scheme 4). The best route to pyrazoles **5** proved to be treatment of hydrazides **4** with an excess of hydrazine hydrate at room temperature for 72 h. Attempted acceleration of the reaction by heating failed because of resinification at elevated temperatures.

Compounds **5a,b** are colorless crystalline solids which are moderately soluble in ethanol and benzene. The mass spectra of these compounds contain molecular ion

Scheme 4



Ar = Ph (**a**), 4-ClC_6H_4 (**b**)

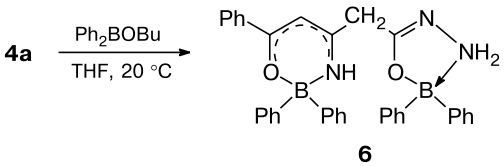
Reaction conditions: 72 h, 20 °C.

peaks $[M]^+$. Their ^1H NMR spectra (DMSO-d_6) show characteristic signals for the HC(4) protons of the pyrazole ring at δ 6.50 and for the CH_2 protons at δ ~3.50. The ^1H NMR data for pyrazole **5a** agree with previously reported[6] data for this compound obtained from methyl 3-hydroxy-5-phenylthiophene-2-carboxylate and hydrazine.

The presence of the enaminone fragment and the functional $NHNH_2$ group in compounds **4** makes them promising synthetic reagents and tetradentate ligands. Earlier,[1] with esters **1** as starting material, we have obtained diphenylboron chelates with the B atom coordinated through the N and O atoms of the enamino carbonyl fragment.

A reaction of hydrazide **4a** with an excess of butoxy(diphenyl)borane under analogous conditions gave a binuclear boron chelate formulated as structure **6** (Scheme 5). With one equivalent of the borylating reagent, we isolated the same complex **6** and unreacted hydrazide **4a**.

Scheme 5



Chelate **6** is a yellow crystalline solid which is well soluble in most organic solvents and stable when stored in air and in solutions. Data from physicochemical methods (including mass spectrometry and ^1H and ^{11}B NMR spectroscopy) are consistent with structure **6**. Its mass spectrum show characteristic features of mass spectra of four-coordinate boron chelates: the peak $[M]^+$ is absent and the highest-mass peak corresponds to the $[M - Ph]^+$

ion. The ^{1}H NMR spectrum (in DMSO-d_6) of chelate **6** contains broadened singlets for the NH protons at δ 10.18 and for the NH_2 protons at δ 8.65 (*cf.* the chemical shift of the amino group in the starting hydrazide **4a** (δ 4.30)) and singlets at δ 6.10 (HC(4)) and 3.75 (CH_2).

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-250 instrument (250.13 and 62.9 MHz, respectively) with Me_4Si as the internal standard. ^{11}B NMR spectra were recorded on a Bruker AC-200P instrument (64.21 MHz) with $BF_3 \cdot Et_2O$ as the internal standard. IR spectra were recorded on a Specord M-82 instrument. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV, ionization chamber temperature 250 °C, direct inlet probe). Elemental analysis was carried out at the laboratory for microanalysis of the N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

Ethyl 3-amino-5-aryl-2-benzoyl-5-oxopent-2-enoates **1a—d** were prepared as described earlier.[1]

3-Amino-5-oxo-5-phenylpent-3-enohydrazide (4a). Hydrazine hydrate (5.00 g, 80 mmol) was added to a solution of ester **1a** (3.40 g, 10 mmol) in ethanol (10 mL). After 30 min, the solution was triturated with a glass rod. The resulting precipitate was filtered off, washed with ethanol (2×3 mL), and dried *in vacuo*. The yield of hydrazide **4a** was 1.70 g (78%), m.p. 153—155 °C (decomp.). Found (%): C, 59.98; H, 6.08; N, 19.20. $C_{11}H_{13}N_3O_2$. Calculated (%): C, 60.26, H, 5.98; N, 19.17. MS, *m/z*: 219 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 3.05 (s, 2 H, CH_2); 4.30 (br.s, 2 H, H_2N—N); 5.75 (s, 1 H, HC=); 7.30—7.50 (m, 3 H, 3 H arom.); 7.66 (br.s, 1 H, NH); 7.78—7.84 (m, 2 H, 2 H arom.); 9.23 (br.s, 1 H, NH); 10.00 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 40.88 (C(2)); 90.56 (HC(4)); 126.69, 128.33, 130.76, 140.01 (Ph); 161.73 (C(3)); 166.92 (C(1)); 187.13 (C(5)). The signals were assigned from HMBC and HMQC data obtained according to Bruker standard procedures.

3-Amino-5-(4-chlorophenyl)-5-oxopent-3-enohydrazide (4b) was obtained analogously from ester **1b**. The yield was 83%, m.p. 160—161 °C (decomp.). Found (%): C, 52.16; H, 4.66; Cl, 14.02; N, 16.62. $C_{11}H_{12}ClN_3O_2$. Calculated (%): C, 52.08; H, 4.77; Cl, 13.97; N, 16.56. MS, *m/z*: 254 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 3.06 (s, 2 H, CH_2); 4.30 (br.s, 2 H, H_2N—N); 5.71 (s, 1 H, HC=); 7.87 (br.s, 1 H, NH); 7.47, 7.83 (both d, 2 H each, C_6H_4, J = 8.6 Hz); 9.22 (br.s, 1 H, NH); 9.99 (br.s, 1 H, NH).

3-Amino-5-(4-methylphenyl)-5-oxopent-3-enohydrazide (4c) was obtained analogously from ester **1c**. The yield was 76%, m.p. 155—156 °C (decomp.). Found (%): C, 61.58; H, 6.27; N, 17.93. $C_{12}H_{15}N_3O_2$. Calculated (%): C, 61.79; H, 6.48; N, 18.01. MS, *m/z*: 233 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 2.33 (s, 3 H, Me); 3.05 (s, 2 H, CH_2); 4.30 (br.s, 2 H, H_2N—N); 5.72 (s, 1 H, HC=); 7.64 (br.s, 1 H, NH); 7.23, 7.71 (both d, 2 H each, C_6H_4, J = 8.0 Hz); 9.21 (br.s, 1 H, NH); 9.94 (br.s, 1 H, NH).

3-Amino-5-(4-methoxyphenyl)-5-oxopent-3-enohydrazide (4d) was obtained analogously from ester **1d**. The yield was 76%, m.p. 145—146 °C (decomp.). Found (%): C, 57.96; H, 6.26; N, 16.62. $C_{12}H_{15}N_3O_3$. Calculated (%): C, 57.82; H, 6.07; N, 16.86. MS, *m/z*: 249 $[M]^+$. ^{1}H NMR (DMSO-d_6), δ: 3.04 (s, 3 H, CH_2); 3.81 (s, 3 H, MeO); 4.33 (br.s, 2 H, H_2N—N); 5.70 (s, 1 H, HC=); 7.57 (br.s, 1 H, NH); 6.97, 7.79 (both d, 2 H each, C_6H_4, J = 8.5 Hz); 9.22 (br.s, 1 H, NH); 9.89 (br.s, 1 H, NH).

5(3)-Phenylpyrazol-3(5)-ylacetohydrazide (5a). Hydrazine hydrate (1.5 g, 24 mmol) was added to a suspension of hydrazide **4a** (0.44 g, 2 mmol) in ethanol (5 mL). The reaction mixture was kept at 20 °C for 72 h. The solvent and the excess hydrazine were removed *in vacuo* and the residue was recrystallized from ethanol (4 mL). The yield of pyrazole derivative **5a** was 0.28 g (65%), m.p. 164—165 °C.* Found (%): C, 60.98; H, 5.57; N, 25.94. $C_{11}H_{12}N_4O$. Calculated (%): C, 61.10; H, 5.59; N, 25.91. MS, *m/z*: 216 $[M]^+$. IR (KBr), ν/cm^{-1}: 3320, 3230 br, 3130 (NH), 3040—2800 (NH, CH), 1650, 1624, 1532 (C=O, C=N, C=C). ^{1}H NMR (DMSO-d_6), δ: 3.40 (s, 2 H, CH_2); 4.20 (br.s, 2 H, H_2N—N); 6.50 (s, 1 H, HC(4)); 7.20—7.80 (m, 5 H, Ph); 9.20 (br.s, 1 H, NH); 12.90 (br.s, 1 H, NH).

5(3)-(4-Chlorophenyl)pyrazol-3(5)-ylacetohydrazide (5b) was obtained analogously from hydrazide **4b**. The yield was 70%, m.p. 170—171 °C. Found (%): C, 52.63; H, 4.50; Cl, 14.25; N, 22.37; $C_{11}H_{11}ClN_4O$. Calculated (%): C, 52.70; H, 4.42; Cl, 14.14; N, 22.35. MS, *m/z*: 251 $[M]^+$. IR (KBr), ν/cm^{-1}: 3312, 3245, 3136 (NH), 3040—2800 (NH, CH), 1656, 1628, 1536 (C=O, C=N, C=C). ^{1}H NMR (DMSO-d_6), δ**: 3.50 (br.s, 2 H, CH_2); 4.25 (br.s, 2 H, H_2N—N); 6.50 (br.s, 1 H, HC(4)); 7.40, 7.80 (both br.d, 2 H each, C_6H_4); 9.20 (br.s, 1 H, NH); 12.80, 13.10 (both br.s, 1 H each, NH).

Bis(diphenylboron) chelate of 3-amino-5-oxo-5-phenylpent-3-enohydrazide (6). Butoxy(diphenyl)borane (1.43 g, 6 mmol) was added to a suspension of hydrazide **4a** (0.44 g, 2 mmol) in THF (5 mL). The reaction mixture was refluxed to complete dissolution of the hydrazide (15 min) and then kept at 20 °C for 24 h. The solvent was removed *in vacuo* and the residue was crystallized from a mixture of benzene (4 mL) and hexane (2 mL). The crystals were filtered off, washed with benzene—hexane (2 : 1) and hexane (4 mL), and dried *in vacuo*. The yield of chelate **6** (in the form of **6**$\cdot C_6H_6$) was 0.83 g (66%), m.p. 223—225 °C. Found (%): C, 78.56; H, 6.14; B, 3.69; N, 6.62. $C_{35}H_{31}B_2N_3O_2 \cdot C_6H_6$. Calculated (%):C, 78.74; H, 5.96; B, 3.46; N, 6.72. MS, *m/z*: 470 $[M - Ph]^+$. IR (KBr), ν/cm^{-1}: 3236, 3204 (NH), 3050—2800 (NH, CH), 1644, 1616, 1568, 1532 vs (C=C, C=N, C=O). ^{1}H NMR (DMSO-d_6), δ: 3.75 (s, 2 H, CH_2); 6.10 (s, 1 H, HC=); 3.75 (s, 2 H, CH_2); 7.90—7.00 (m, 31 H, 5 Ph, PhH); 8.65 (br.s, 2 H, NH_2); 10.18 (br.s, 1 H, NH). ^{11}B NMR, δ: 3.83.

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* For pyrazole **5a**, m.p. 193—194 °C has been reported;[6] however, elemental analysis data for that material are unsatisfactory.

** All the signals are broadened because of the tautomeric transformations of pyrazole **5b**.

thesis and Preparation of Compounds with Valuable Practical Properties").

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