Synthesis of acetonylmalonaldehyde and its interaction with aminoazoles

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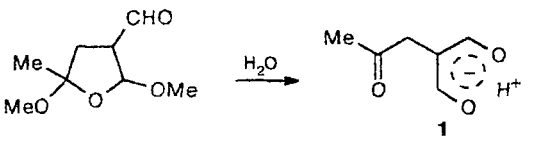
Acetonylmalonaldehyde (**1**) was obtained for the first time by hydrolysis of 2,5-dimethoxy-5-methyltetrahydrofuran-3-carbaldehyde. The interaction of **1** with 3-amino-5-methylpyrazole, 3-amino-1,2,4-triazole, 2-aminobenzimidazole, and 5-aminotetrazole results in the formation of functionally substituted azolopyrimidines.

Key words: tetrahydrofurans, hydrolysis; acetonylmalonaldehyde, aminoazoles, reaction.

The synthesis and properties of aldehydes of the tetrahydrofuran series, α-substituted β-formyl-2,5-dimethoxytetrahydrofurans, have been previously reported.[1,2] In a continuation of our studies, we found that 2,5-dimethoxy-5-methyltetrahydrofuran-3-carbaldehyde is hydrolyzed at room temperature to give novel acetonylmalonaldehyde (**1**) in quantitative yield (Scheme 1).

Scheme 1



1

The ^{1}H NMR spectrum shows that compound **1** exists in the enol form. The aldehyde protons are chemically equivalent and are detected as a singlet at δ 8.35, which is approximately equal to the average of the values of the characteristic chemical shifts (CS) of the protons at the C=C bond and the proton of the formyl group. Similar CS values were found for the aldehyde protons of malon- and methylmalonaldehyde.[3]

Intense absorption bands at 1715, 1645, and 1610 cm^{-1} as well as a broad band with a maximum at 3000 cm^{-1} are present in the IR spectrum of acetonylmalonaldehyde.

Acetonylmalonaldehyde **1** participates in cyclocondensation with aminoazoles containing amidine fragments in their molecules. Acetonylazolopyrimidines **2**—**5** were synthesized in high yields by boiling equimolar amounts of **1** and the pertinent aminoazole in dioxane (Scheme 2).

Taking into account that the structure of acetonylmalonaldehyde contains fragments of 1,3- and 1,4-dicarbonyl compounds, one could also expect that (4+1) type cyclocondensation would proceed with the formation of the corresponding pyrrols. However, this reaction does not proceed under the conditions used.

The ^{1}H NMR spectra of the heterocycles obtained contain signals in the δ 8.7—9.6 and δ 8.3—9.0 regions that belong to the protons of the pyrimidine ring. They are split into doublets with ^4J = 2.3 Hz. In the spectrum of tetrazolo[1,5-*a*]pyrimidine **5** an additional singlet with low intensity is detected at δ 8.53. This signal is due to partial isomerization of compound **5** into 2-azido-5-acetonylpyrimidine in DMSO (the ring-chain isomerism characteristic of tetrazoles). High-field singlets corresponding to the methylene and methyl groups of the substituent are found in the spectra of compounds **2**—**5**.

Experimental

NMR spectra were recorded on a Bruker AC-200P spectrometer (at frequencies of 200.13 MHz and 50.32 MHz for ^{1}H and ^{13}C nuclei, respectively) using $SiMe_4$ as the internal standard. IR spectra were recorded on an UR-20 instrument (as a thin layer). Mass spectra were recorded on a Finnigan MAT INCOS-50 spectrometer (70 eV).

Acetonylmalonaldehyde (1). 2,5-Dimethoxy-5-methyltetrahydrofuran-3-carbaldehyde[2] (1.8 g, 10 mmol) was dissolved in water (20 mL) and stirred with a magnetic stirrer for 15 min until it disappeared according to TLC. The mixture was evaporated to dryness *in vacuo* at 28—30 °C to give

† Deceased.

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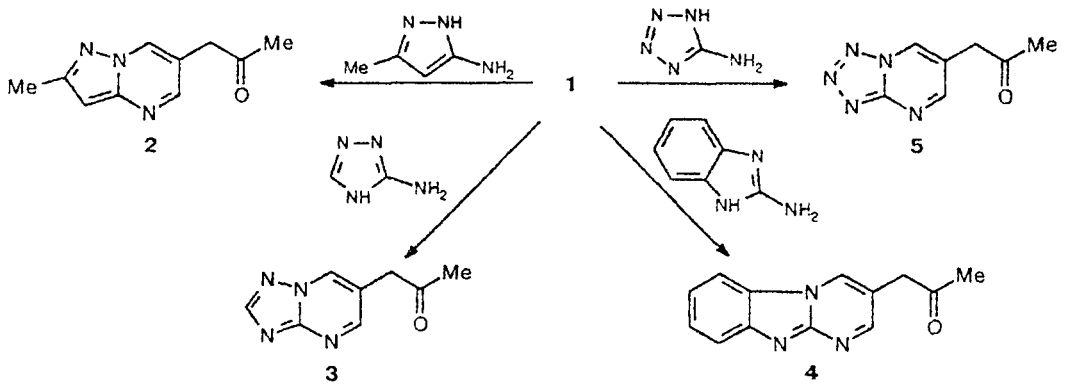
Scheme 2



aldehyde **1** (1.3 g, 98%) as a yellowish oil, b.p. 98—99 °C (2 Torr), n_D^{20} 1.4235. Found (%): C, 56.21; H, 6.32. $C_6H_8O_3$. Calculated (%): C, 56.25; H, 6.29. IR, ν/cm^{-1}: 3000, 1715, 1645, 1610. ^1H NMR ($CDCl_3$), δ: 8.80 (br. s, 1 H, OH); 8.35 (s, 2 H, CHO); 3.45 (s, 2 H, CH_2); 2.25 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 209.0 (CO); 180.7 (CHO); 115.7 (C^t); 36.6 (CH_2); 29.8 (CH_3). MS, *m/z* (I_{rel}(%)): 128 $[M]^+$(3), 100 (3), 43 (100), 39 (19).

6-Acetonyl-2-methyl-pyrazolo[1,5-*a*]pyrimidine (2). Aldehyde **1** (0.6 g, 4.7 mmol) and 3-amino-5-methylpyrazole (0.46 g, 4.7 mmol) were stirred in dioxane (10 mL) for 3 h at 50—60 °C, evaporated to dryness *in vacuo*, and the residue was recrystallized from Pr^iOH to give compound **2** (0.53 g, 60%), m.p. 117 °C. IR, ν/cm^{-1}: 1725, 1640, 1500—1550. ^1H NMR (DMSO-d_6), δ: 8.76 (d, 1 H, C(5)H, *J* = 2.3 Hz); 8.29 (d, 1 H, C(7)H, *J* = 2.3 Hz); 6.45 (s, 1 H, C(3)H); 3.90 (s, 2 H, CH_2); 2.42 (s, 3 H, Ar—CH_3); 2.25 (s, 3 H, CO—CH_3). ^{13}C NMR (DMSO-d_6), δ: 205.07 (CO); 153.835 (C(2)); 151.54 (C(5)); 147.58 (C(3a)); 134.15 (C(7)); 114.69 (C(6)); 94.76 (C(3)); 42.73 (Ar—$\underline{C}H_2$); 29.48 (CO$\underline{C}H_3$); 14.06 (Ar—$\underline{C}H_3$). MS, *m/z* (I_{rel}(%)): 189 $[M]^+$(26), 146 (85), 119 (15), 97 (45), 40 (100). Found (%): C, 63.50; H, 5.90; N, 22.29. $C_{10}H_{11}N_3O$. Calculated (%): C, 63.48; H, 5.86; N, 22.21.

6-Acetonyl-1,2,4-triazolo[1,5-*a*]pyrimidine (3). Aldehyde **1** (0.5 g, 3.9 mmol) and 3-amino-1,2,4-triazole (0.33 g, 3.9 mmol) were boiled in dioxane (7 mL) for 2 h, evaporated to dryness *in vacuo*, and the residue was recrystallized from ethanol to give compound **3** (0.52 g, 78%), m.p. 124—125 °C. Found (%): C, 54.50; H, 4.61; N, 31.79. $C_8H_8N_4O$. Calculated (%): C, 54.54; H, 4.58; N, 31.80. Spectral data coincide with those reported in Ref. 2.

3-Acetonylbenzmidazo[1,2-*a*]pyrimidine (4) was obtained analogously to compound **2** from aldehyde **1** and 2-aminobenzimidazole in 80% yield, m.p. 219—220 °C (from MeOH). IR, ν/cm^{-1}: 1720, 1630, 1500—1550. ^1H NMR (DMSO-d_6), δ: 9.32 (d, 1 H, C(4)H, *J* = 2.3 Hz); 8.67 (d, 1 H, C(2)H, *J* = 2.3 Hz); 8.25 (d, 1 H, C(9)H, *J* = 10 Hz); 7.85 (d, 1 H, C(6)H, *J* = 10 Hz); 7.55 (t, 1 H, C(8)H, *J* = 10 Hz); 7.45 (t, 1 H, C(7)H, *J* = 10 Hz); 4.00 (s, 2 H, CH_2); 2.27 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 205.43 (CO); 158.83 (C(2)); 149.58 (C(10a)); 143.67 (C(4)); 134.58 (C(9a)); 126.80 (C(5a)); 126.06 (C(8)); 121.49 (C(7)); 119.32 (C(9)); 114.11 (C(3)); 112.36 (C(6)); 43.02 (CH_2); 29.75 (CH_3). MS, *m/z* (I_{rel}(%)): 225 $[M]^+$(85), 183 (43), 182 (100). Found (%): C, 69.35; H, 4.95; N, 18.61. $C_{13}H_{11}N_3O$. Calculated (%): C, 69.32; H, 4.92; N, 18.65.

6-Acetonyltetrazolo[1,5-*a*]pyrimidine (5) was obtained analogously to compound **3** from aldehyde **1** and 5-aminotetrazole hydrate in 86% yield, m.p. 91—92 °C (from EtOH). IR, ν/cm^{-1}: 1720, 1640, 1500. ^1H NMR (DMSO-d_6), δ: 9.55 (d, 1 H, C(7)H, *J* = 2.3 Hz); 9.03 (d, 1 H, C(5)H, *J* = 2.3 Hz); 8.53 (s, 2 H, C(4)H, C(6)H in the azido form); 4.03 (s, 2 H, CH_2); 2.28 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 204.43 (CO); 162.23 (C(5)); 153.73 (C(3a)); 133.54 (C(7)); 121.24 (C(6)); 42.59 (CH_2); 29.83 (CH_3). MS, *m/z* (I_{rel} (%)): 177 $[M]^+$(9), 135 (15), 107 (16), 52 (28), 43 (100). Found (%): C, 47.47; H, 4.01; N, 39.52. $C_7H_7N_5O$. Calculated (%): C, 47.46; H, 3.98; N, 39.53.

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