The reactions of aroylpyruvic acids and their derivatives with *o*-aminophenyldiphenylmethanol

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Aroylpyruvic acids and their methyl esters react with *o*-aminophenyldiphenylmethanol to form 4-aryl-2-[2-(1-hydroxydiphenylmethyl)phenylamino]-4-oxobut-2-enoic acids and their esters. The α-enamino acids obtained undergo intramolecular heterocyclization in the presence of Ac_2O to afford substituted 4,5-dihydrobenzo[*e*][1,4]oxazepin-3(1*H*)-ones. The reaction of 5-arylfuran-2,3-diones with *o*-aminophenyldiphenylmethanol leads to products of decyclization, 2-(1-hydroxydiphenylmethyl)phenylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid, which upon heating in AcOH or Ac_2O yield 3-aroylacetyl-1,1-diphenyl-1*H*-benzo[*d*][1,3]oxazines.

Key words: aroylpyruvic acids; methyl aroylpyruvates, 5-arylfuran-2,3-diones, reactions with *o*-aminophenyldiphenylmethanol; amides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acid; 4,5-dihydrobenzo[*e*][1,4]oxazepin-3(1*H*)-ones, 1,1-diphenyl-1*H*-benzo[*d*][1,3]oxazines.

5-Arylfuran-2,3-diones (**1**), which are lactones of the γ-enolic form of aroylpyruvic acids (**2**, R = H), are known to react readily with 1,2-hydroxyamines, whose amino group opens the cycle of furan-2,3-diones forming hydroxyamides of aroylpyruvic acids.[1,2] Various products of recyclization, derivatives of 2*H*-1,4-benzoxazin-2-one[1–3] or substituted 1,2,4-oxadiazoles, are formed under somewhat more drastic conditions due to the high electrophilicity of the C(2) atom in derivatives of aroylpyruvic acids and in the absence of steric hindrances for closing of the cycle in reactions of 1,2-hydroxylamines.[1,4]

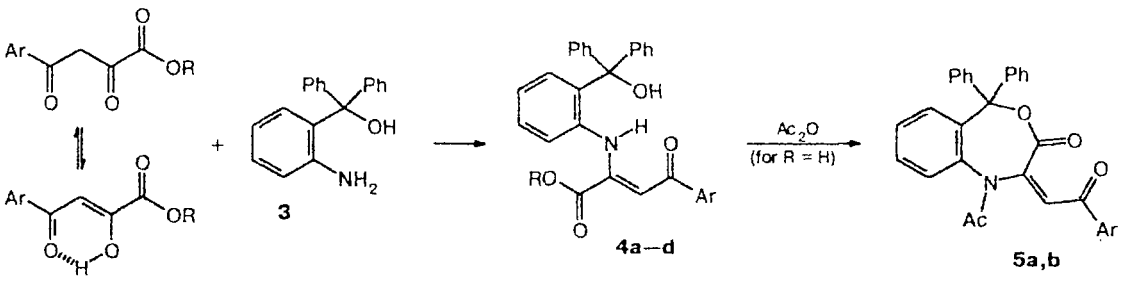
Reactions of 5-arylfuran-2,3-diones (**1**) with some 1,3-diamines resulting, depending on the nucleophilicity and spatial arrangement of amino groups, in the formation of various heterocyclization products or opening of the cycle of furan-2,3-diones involving both amino groups are also known.[1,5]

We studied for the first time the reactions of aroylpyruvic acids and their derivatives with 1,3-hydroxyamines and searched for biologically active compounds among the transformation products (see preliminary report[6]).

We chose accessible *o*-aminophenyldiphenylmethanol (**3**) as the 1,3-O,N-binucleophilic reagents, and aroylpyruvic acids (**2**, R = H), their methyl esters (**2**, R = Me), and cyclic derivatives 5-arylfuran-2,3-diones (**1**) were used as the substrates.

Both acids and their methyl esters (**2a—d**), which exist in solutions predominantly in the enolic form of derivatives of 4-aryl-2-hydroxy-4-oxobut-2-enolic acids[1] (according to the ^1H NMR spectroscopic data, 75—100% enol in a DMSO-d_6 solution), under mild conditions react readily with aminocarbinol **3** to form 4-aryl-2-[2-(1-hydroxydiphenylmethyl)phenylamino]-4-oxobut-2-enoic acids and their esters (**4a—d**) (Scheme 1).

Scheme 1



Ar = Ph (**2a**, **4a**, **5a**), 4-MeC_6H_4 (**2b**, **2c**, **4b**, **4c**, **5b**), 4-ClC_6H_4 (**2d**, **4d**); R = H (**2a,b,d**, **4a,b,d**), Me (**2c**, **4c**)

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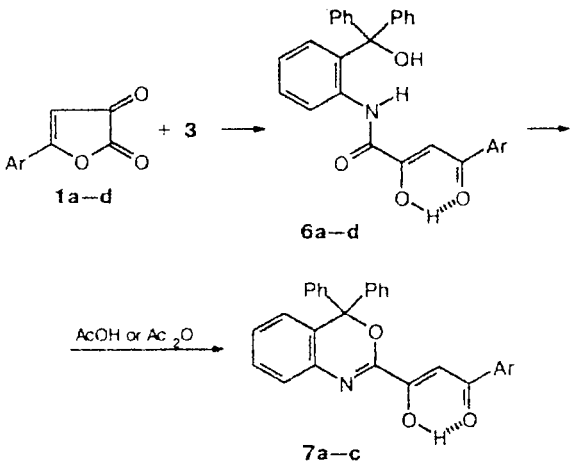
Under thermolysis in the presence of acetic anhydride, α-enamino acids **4a,b** are involved in intramolecular heterocyclization due to alcoholic hydroxyl and carboxyl groups. The heterocyclization is accompanied by *N*-acylation of enamine with an excess of acetic anhydride. As a result, 4-aroylmethylene-5-acetyl-1,1-diphenyl-4,5-dihydrobenzo[*e*][1,4]oxazepin-3(1*H*)-ones (**5a,b**) were obtained (see Scheme 1).

The presence of intense bands at 1820 and 1824 cm^{-1}, which are due to stretching vibrations of the lactonic carbonyl group in the IR spectra of compounds **5a,b**, relatively upfield signals of the CH methine group of the aroylmethylene fragment at 5.53 and 5.51 ppm in the ^1H NMR spectra, and signals of the characteristic fragmentation ions *m/z* 445 $[M - CO]^+$ and *m/z* 431 $[M - CH_2CO]^+$ in the mass spectrum of compound **5a** favor the structure ascribed to these compounds.

The reactions of 1,3-aminoalcohol **3** with 5-arylfuran-2,3-diones (**1a—d**) result in decyclization of the latter due to the nucleophilic attack of the amino group of the reagent to the lactonic carbonyl group of furan-2,3-diones to form substituted aroylpyruvoylamides, 2-(1-hydroxydiphenylmethyl)phenylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids (**6a—d**) (Scheme 2), which are enolized, as would be expected,[1] at the aroylacetyl fragment.

Scheme 2



We obtained 3-aroylacetyl-1,1-diphenyl-1*H*-benzo[*d*][1,3]oxazines (**7a—c**) also enolized at the β-dicarbonyl fragment (see Scheme 2) by the cyclization of amides **6a—c** upon heating in AcOH or Ac_2O.

The aroylacetyl group in compounds **6** and products of their heterocyclization, 1*H*-benzo[*d*][1,3]oxazines (**7**), exists as the *H*-chelate cycle with the aroylic carbonyl group involved in the intramolecular hydrogen bond of the >C=O...H—O—C= type. This is indicated, in particular, by a low-frequency broad absorption band of carbonyl groups in the IR spectra (1572—1590 cm^{-1}) and the absence of signals of the CH_2 methylene group in the ^1H NMR spectra. The structure suggested for compounds **7** is also indicated by the presence of the characteristic peak of the fragmentation ion *m/z* 284 $[M - PhCOCH_2CO]^+$ in the mass spectrum of compound **7a**.

Some compounds **4—7** synthesized exhibit a considerable antimicrobic activity.[6]

Experimental

IR spectra of the compounds synthesized were obtained on UR-20 and Specord M-80 spectrometers in Nujol. ^1H NMR spectra were recorded on RYa-2310 (60 MHz) and Bruker WP-200 (200 MHz) instruments in solutions of $CDCl_3$ (compound **4a**) and DMSO-d_6 (compounds **4b—d**, **6**, **7**) using HMDS as the internal standard. Mass spectra (EI) were recorded on a Varian MAT-311A spectrometer in the regime of direct introduction of the sample into the ion source, the emission current was 100 μA, and the energy of ionizing electrons was 70 eV. The reaction course and purity of compounds were monitored by TLC on Silufol UV-254 plates in a benzene—ether—acetone (10 : 9 : 1) mixture, and the plates were developed by iodine.

Starting 5-arylfuran-2,3-diones (**1**) were obtained according to the method described previously.[7]

4-Aryl-2-[2-(1-hydroxydiphenylmethyl)phenylamino]-4-oxobut-2-enoic acids and their methyl esters (4a—d). A mixture of aroylpyruvic acids **2a,b,d** (10 mmol) or methyl ester of *p*-toluylpyruvic acid **2c** (2.20 g, 10 mmol) and *o*-aminophenyldiphenylmethanol (**3**) (2.75 g, 10 mmol) was heated until dissolution in benzene (100 mL) and refluxed for 30—40 min (TLC monitoring). The residue that formed was filtered off and recrystallized from a benzene—MeCN (1 : 1) mixture.

Acid 4a (Ar = Ph, R = H). Yield 3.32 g (74%), m.p. 149—150 °C (decomp.). IR, ν/cm^{-1}: 1610 br (C=O of chelate, Ar); 1665 (COOH); 3160 (NH); 3320 (OH). ^1H NMR ($CDCl_3$), δ: 6.05 (s, 1 H, CH); 6.81—7.55 (m, 19 H, 3 Ph, C_6H_4). Found (%): C, 77.38; H, 5.16; N, 3.20. $C_{29}H_{23}NO_4$. Calculated (%): C, 77.51; H, 5.12; N, 3.12.

Acid 4b (Ar = 4-MeC_6H_4, R = H). Yield 3.89 g (84%), m.p. 172—173 °C (decomp.). IR, ν/cm^{-1}: 1610 br (C=O of chelate, Ar); 1660 (COOH); 3165 (NH); 3370 (OH). ^1H NMR (DMSO-d_6), δ: 2.28 (s, 3 H, Me); 6.05 (s, 1 H, CH); 6.75—7.83 (m, 18 H, 2 Ph, 2 C_6H_4). Found (%): C, 77.68; H, 5.55; N, 3.02. $C_{30}H_{25}NO_4$. Calculated (%): C, 77.75; H, 5.40; N, 3.03.

Ester 4c (Ar = 4-MeC_6H_4, R = Me). Yield 3.95 g (83%), m.p. 76—78 °C (decomp.). IR, ν/cm^{-1}: 1600 br (C=O chelate, Ar); 1728 (COOMe); 3120 (NH); 3380 (OH). ^1H NMR (DMSO-d_6), δ: 2.23 (s, 3 H, Me); 3.83 (s, 3 H, OMe); 6.22 (s, 1 H, CH); 6.68—8.13 (m, 18 H, 2 Ph, 2 C_6H_4). Found (%): C, 78.31; H, 5.60; N, 3.01. $C_{31}H_{27}NO_4$. Calculated (%): C, 78.15; H, 5.67; N, 2.94.

Acid 4d (Ar = 4-ClC_6H_4, R = H). Yield 2.41 g (50%), m.p. 168—169 °C (decomp.). IR, ν/cm^{-1}: 1604 br (C=O of chelate, Ar); 1656 (COOH); 3180 (NH); 3368 (OH). ^1H NMR (DMSO-d_6), δ: 6.18—7.97 (m, 19 H, CH, 2 Ph, 2 C_6H_4). Found (%): C, 71.83; H, 4.52; Cl, 7.45; N, 2.87. $C_{29}H_{22}ClNO_4$. Calculated (%): C, 71.98; H, 4.55; Cl, 7.33; N, 2.90.

4-Aroylmethylene-5-acetylene-1,1-diphenyl-4,5-dihydrobenzo[*e*][1,4]oxazepin-3(1*H*)-ones (5a,b). Compounds **4a** (5 mmol) and **4b** (5 mmol) were boiled in Ac_2O (50 mL) for 1—1.5 h (TLC monitoring). After cooling the residue that formed was filtered off and recrystallized from AcOH.

Compound 5a (Ar = Ph). Yield 1.80 g (76%), m.p. 182—184 °C (decomp.). IR, ν/cm^{-1}: 1648 (CO—Ph); 1660 (Me—CO—N<); 1820 (CO of lactone). ^1H NMR (DMSO-d_6), δ: 2.03 (s, 3 H, Me); 5.53 (s, 1 H, CH); 6.58—7.95 (m, 19 H, 3 Ph, C_6H_4). MS, *m/z* (*I* (%)), peaks with *I* > 5% are given: 473 (15) $[M]^+$, 445 (13) $[M - CO]^+$, 431 (5) $[M - CH_2CO]^+$, 403 (16) $[M - CH_2CO - CO]^+$, 368 (20) $[M - C_6H_5CO]^+$, 326 (7) $[M - C_6H_5CO - CH_2CO]^+$, 299 (56) $[MH - C_6H_5CO - CH_2CO - CO]^+$, 298 (16) $[M - C_6H_5CO - CH_2CO - CO]^+$, 284 (9) $[MH - C_6H_5CO - CH_2CO - CO - CH_3]^+$, 256 (100) $[PhN{=}CPh_2 - H]^+$, 255 (15) $[PhN{=}CPh_2 - 2H]^+$, 221 (14), 179 (19), 105 (56) $[C_6H_5 - CO]^+$, 77 (26) $[C_6H_5]^+$, 60 (23) $[CH_3COOH]^+$, 43 (32) $[CH_3CO]^+$. Found (%): C, 78.70; H, 4.71; N, 2.89. $C_{31}H_{23}NO_4$. Calculated (%): C, 78.65; H, 4.86; N, 2.95.

Compound 5b (Ar = 4-MeC_6H_4). Yield 1.30 g (53%), m.p. 217—218 °C (decomp.). IR, ν/cm^{-1}: 1644 (CO—Ar); 1674 (Me—CO—N<); 1824 (CO of lactone). ^1H NMR (DMSO-d_6), δ: 1.95 (s, 3 H, Me); 2.25 (s, 3 H, Me); 5.51 (s, 1 H, CH); 6.55—7.85 (m, 18 H, 2 Ph, 2 C_6H_4). Found (%): C, 78.53; H, 5.42; N, 2.61. $C_{32}H_{25}NO_4$. Calculated (%): C, 78.85; H, 5.73; N, 2.87.

2-(1-Hydroxydiphenylmethyl)phenylamides of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids (6a—d). A mixture of 5-arylfuran-2,3-diones **1a—d** (10 mmol) and *o*-aminophenyldiphenylmethanol (**3**) (2.75 g, 10 mmol) was heated until dissolution in benzene (100—150 mL) and refluxed for 10—15 min (TLC monitoring). After cooling the residue that formed was filtered off and recrystallized from benzene.

Amide 6a (Ar = Ph). Yield 4.04 g (90%), m.p. 211—212 °C (decomp.). IR, ν/cm^{-1}: 1580 br (C=O of chelate, Ar); 1650 (CO—NH); 3280 (CO—NH); 3412 (Ph_2C—OH). ^1H NMR (DMSO-d_6), δ: 6.85—8.38 (m, 20 H, 3 Ph, C_6H_4, CH); 11.11 (br.s, 1 H, NH). Found (%): C, 77.32; H, 5.41; N, 3.24. $C_{29}H_{23}NO_4$. Calculated (%): C, 77.51; H, 5.12; N, 3.12.

Amide 6b (Ar = 4-MeC_6H_4). Yield 4.26 g (92%), m.p. 225—227 °C (decomp.). IR, ν/cm^{-1}: 1572 br (C=O of chelate, Ar); 1650 (CO—NH); 3265 (CO—NH); 3414 (Ph_2C—OH). ^1H NMR (DMSO-d_6), δ: 2.35 (s, 3 H, Me); 6.85—8.38 (m, 19 H, 2 Ph, 2 C_6H_4, CH); 11.18 (br.s, 1 H, NH). Found (%): C, 77.62; H, 5.24; N, 2.77. $C_{30}H_{25}NO_4$. Calculated (%): C, 77.75; H, 5.40; N, 3.03.

Amide 6c (Ar = 4-$MeOC_6H_4$). Yield 3.98 g (83%), m.p. 230—231 °C (decomp.). IR, ν/cm^{-1}: 1580 br (C=O of chelate, Ar); 1651 (CO—NH); 3280 (CO—NH); 3420 (Ph_2C—OH). ^1H NMR (DMSO-d_6), δ: 3.84 (s, 3 H, OMe); 6.28—8.23 (m, 19 H, 2 Ph, 2 C_6H_4, CH); 11.05 (br.s, 1 H, NH). MS, *m/z* (*I* (%)), peaks with *I* > 5% are given: 479 (15) $[M]^+$, 285 (17) $[M - 4\text{-}MeOC_6H_4CO - CH_2CO - OH]^+$, 284 (22) $[M - 4\text{-}MeOC_6H_4CO - CH_2CO - H_2O]^+$, 256 (24) $[PhN{=}CPh_2 - H]^+$, 180 (8), 178 (14), 177 (100) $[4\text{-}MeOC_6H_4COCH_2CO]^+$, 150 (6), 135 (24) $[4\text{-}MeOC_6H_4CO]^+$, 109 (9), 105 (8) $[C_6H_5CO]^+$, 77 (15) $[C_6H_5]^+$, 69 (23) $[OCCH{=}C{=}O]^+$. Found (%): C, 75.36; H, 5.26; N, 2.84. $C_{30}H_{25}NO_5$. Calculated (%): C, 75.08; H, 5.02; N, 2.92.

Amide 6d (Ar = 4-ClC_6H_4). Yield 4.59 g (95%), m.p. 232—233 °C (decomp.). IR, ν/cm^{-1}: 1580 br (C=O of chelate, Ar); 1659 (CO—NH); 3270 (CO—NH); 3412 (Ph_2C—OH). ^1H NMR (DMSO-d_6), δ: 6.85—8.38 (m, 19 H, 2 Ph, 2 C_6H_4, CH); 11.10 (br.s, 1 H, NH). Found (%): C, 71.61; H, 4.28; N, 2.76. $C_{29}H_{22}ClNO_4$. Calculated (%): C, 71.98; H, 4.55; N, 2.90.

3-Aroylacetyl-1,1-diphenyl-1*H*-benzo[*d*][1,3]oxazines (7a—c). 3-Aroylpyruvoylamides **6a—c** (5 mmol) in AcOH or Ac_2O (30—50 mL) were refluxed for 1.5—2 h. After cooling the residue that formed was filtered off and recrystallized from a toluene—MeCN (1 : 1) mixture.

Compound 7a (Ar = Ph). Yield 0.64 g (30%), m.p. 226—228 °C (decomp.). IR, ν/cm^{-1}: 1590 br (C=O of chelate, Ar). ^1H NMR (DMSO-d_6), δ: 6.85—8.38 (m, 20 H, CH, 3 Ph, C_6H_4). MS, *m/z* (*I* (%)), peaks with *I* > 5% are given: 431 (5) $[M]^+$, 286 (14) $[MH - C_6H_5COCH{=}CO]^+$, 285 (55) $[M - C_6H_5COCH{=}CO]^+$, 284 (52) $[M - C_6H_5COCH{=}CO]^+$, 256 (23) $[PhN{=}CPh_2 - H]^+$, 239 (5), 207(8), 206(8), 165(16) $[C_6H_5COCH_2COOH_2]^+$, 147 (100) $[C_6H_5COCH_2CO]^+$, 120 (9) $[C_6H_5COCH_3]^+$, 105 (25) $[C_6H_5CO]^+$, 91(5), 77 (17) $[C_6H_5]^+$. Found (%): C, 80.56; H, 4.62; N, 3.41. $C_{29}H_{21}NO_3$. Calculated (%): C, 80.74; H, 4.87; N, 3.24.

Compound 7b (Ar = 4-MeC_6H_4). Yield 0.58 g (26%), m.p. 226—228 °C (decomp.). IR, ν/cm^{-1}: 1590 br (C=O of chelate, Ar). ^1H NMR (DMSO-d_6), δ: 2.38 (s, 3 H, Me); 6.91—7.97 (m, 19 H, CH, 2 Ph, 2 C_6H_4). Found (%): C, 80.83; H, 5.38; N, 3.02. $C_{30}H_{23}NO_3$. Calculated (%): C, 80.90; H, 5.17; N, 3.15.

Compound 7c (Ar = 4-$MeOC_6H_4$). Yield 0.62 g (27%), m.p. 229—230 °C (decomp.). IR, ν/cm^{-1}: 1590 br (C=O of chelate, Ar). ^1H NMR (DMSO-d_6), δ: 3.88 (s, 3 H, OMe); 6.85—8.05 (m, 19 H, CH, 2 Ph, 2 C_6H_4). Found (%): C, 78.22; H, 4.78; N, 3.03. $C_{30}H_{23}NO_4$. Calculated (%): C, 78.09; H, 4.99; N, 3.04.

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