Reactions of β-aroylacrylic acids with 2-aminophenols

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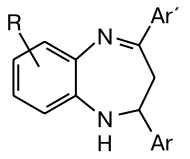
3,4-Dihydrobenzo-1,4-oxazin-2-ones were obtained from the corresponding β-aroylacrylic acids and 2-aminophenols. With 2-amino-4(5)-nitrophenols, stable intermediate α-amino adducts (4-aryl-4-oxobutyric acid derivatives) were isolated.

Key words: β-aroylacrylic acids, 2-aminophenols, 3,4-dihydrobenzo-1,4-oxazin-2-ones, cyclization, 4-aryl-4-oxobutyric acids.

Reactions of α,β-unsaturated carbonyl compounds with binucleophiles provide a convenient route to partially hydrogenated azaheterocycles. Earlier, we have found that reactions of chalcones with *o*-phenylenediamine[1] and 2-aminobenzenethiol[2,3] give 1,5-benzodiazepines **1** and 1,5-benzothiazepines **2**, respectively, while reactions with 2-aminophenol[4] yield phenoxazines **3**.



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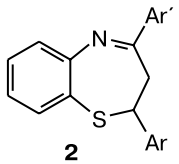

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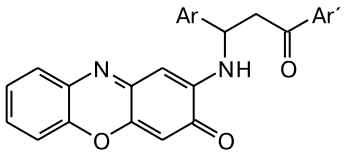

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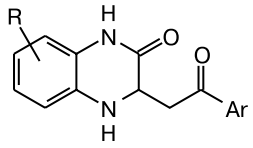
Our further investigations of the reactivities of enone systems deal with β-aroylacrylic acids. Although the chemistry of these acids has been studied for a sufficiently long time, data on their reactions with nitrogen-containing 1,4-binucleophiles remain limited. At the same time, β-aroylacrylic acid derivatives exhibit a broad spectrum of physiological (fungicidal, antitumor, hypotensive, hypolipedemic, *etc.*) activity,[4—10] which makes their reactions with 1,4-binucleophiles a subject of current interest for the synthesis of azaheterocycles.

Earlier, we have found that β-aroylacrylic acids undergo cyclocondensation in reactions with *o*-phenylenediamine[11] to give quinoxalin-2-ones **4** and with *o*-aminobenzenethiol[12] to give benzo-1,4-thiazin-3-ones **5** (not 1,5-benzothiazepines, as erroneously reported in Refs 13—17).



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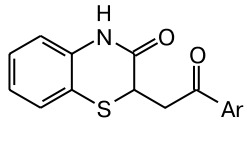

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Here, we studied the reactions of acids **6a—d** with 2-aminophenol (**7a**) and its substituted derivatives **7b—e** (Scheme 1).

Heating of 2-aminophenols **7a—c** with acids **6a—d** in boiling propan-2-ol or toluene gave 3-(2-aryl-2-oxoethyl)-3,4-dihydrobenzo-1,4-oxazin-2-ones **8a—f** in 33—48% yields.

Compound **8a** has been obtained earlier[18] (m.p. 180 °C) by reduction of the corresponding benzo-1,4-oxazin-2-one. Product **8a** we synthesized melts at 129—131 °C, which agrees better with both the melting points of compounds **8b—d** and the reported[18] melting points of 3,4-dihydrobenzo-1,4-oxazin-2-one derivatives.

Reactions of acids **6a—c** with 2-amino-4(5)-nitrophenols **7d,e** under the same conditions followed a different scheme. Yellow-orange crystalline solids **9a—d** isolated from the reaction mixture in 35—54% yields decompose on melting, are well soluble in polar solvents, give a positive test for the phenol OH group, and are soluble in alkaline solution.

Attempted cyclization of products **9a—d** by heating them in boiling ethanol, propan-2-ol, butanol, or toluene without and with addition of conc. HCl, as well as in

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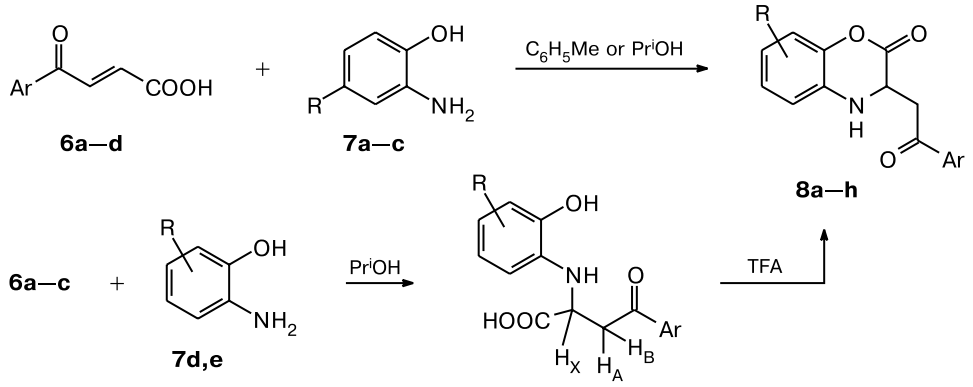
Scheme 1



6	Ar	7	R	8	Ar	R	8	Ar	R	9	Ar	R
a	Ph	**a**	H	**a**	Ph	H	**e**	4-BrC_6H_4	6-Me	**a**	Ph	5-NO_2
b	4-MeC_6H_4	**b**	Me	**b**	4-MeC_6H_4	H	**f**	4-BrC_6H_4	6-Cl	**b**	Ph	4-NO_2
c	4-ClC_6H_4	**c**	Cl	**c**	4-ClC_6H_4	H	**g**	Ph	7-NO_2	**c**	4-MeC_6H_4	4-NO_2
d	4-BrC_6H_4	**d**	4-NO_2	**d**	4-BrC_6H_4	H	**h**	4-MeC_6H_4	7-NO_2	**d**	4-ClC_6H_4	4-NO_2
		e	5-NO_2									

glacial acetic acid, failed: the starting reagents contaminated with resins were recovered from the reaction mixture. Yet the cyclization was successful for α-adducts **9b,c**: their heating in boiling trifluoroacetic acid afforded benzooxazines **8g** (43%) and **8h** (41%).

Interestingly, analogous reactions of aroylpyruvic acids and their esters with both 2-amino-4-nitrophenol[19] and 2-aminophenol[20—23] give exclusively cyclic products.

The observed different behavior of aminophenols **7a—e** is due to a considerable electron-withdrawing effect of the nitro group. As the result, the hydroxy group becomes substantially less nucleophilic, which hinders esterification and makes it possible to isolate α-adducts **9a—d**.

Experimental

The course of the reactions was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in toluene—MeCN (1 : 1) (spots were visualized in the iodine vapor). IR spectra were recorded on Impact-400 and Specord 75IR spectrometers (KBr pellets). ^{1}H NMR spectra were recorded on a Varian Mercury VX-200 instrument in DMSO-d_6 with Me_4Si as the internal standard. Elemental analysis was carried out on a LECO CHNS-900 analyzer. Melting points were measured on a Kofler instrument.

β-Aroylacrylic acids **6a—d** were prepared by the Friedel—Crafts acylation of the corresponding arenes with maleic anhydride; their physicochemical properties are in full agreement with the literature data.[24]

3-(2-Oxo-2-phenylethyl)-3,4-dihydrobenzo-1,4-oxazin-2-one (8a). A solution of acid **6a** (0.27 g, 1.5 mmol) and 2-aminophenol (**7a**) (0.16 g, 1.5 mmol) in toluene (6 mL) was refluxed for 3 h. The resulting precipitate was recrystallized from ethanol. The yield of compound **8a** was 0.17 g (42%), m.p. 129—131 °C. Found (%): C, 71.94; H, 4.91; N, 5.20. $C_{16}H_{13}NO_3$. Calculated (%): C, 71.94; H, 4.90; N, 5.24. IR, ν/cm^{-1}: 1698 (C(2)=O); 1668 (PhCO). ^{1}H NMR, δ: 3.65 (d, 2 H, CH_2, J = 5.4 Hz); 5.07 (t, 1 H, H(3), J = 5.4 Hz); 6.84—6.91 (m, 4 H, H arom.); 7.49—7.69 (m, 3 H, H arom.); 7.96—7.99 (m, 2 H, H arom.); 10.65 (s, 1 H, NH).

Compounds **8b—f** were obtained analogously but with propan-2-ol as a solvent.

3-(2-Oxo-2-*p*-tolylethyl)-3,4-dihydrobenzo-1,4-oxazin-2-one (8b). The yield was 0.16 g (38%), m.p. 164 °C (from ethanol). Found (%): C, 72.81; H, 5.35; N, 5.01. $C_{17}H_{15}NO_3$. Calculated (%): C, 72.85; H, 5.37; N, 4.98. IR, ν/cm^{-1}: 1692 (C(2)=O); 1662 (ArCO). ^{1}H NMR, δ: 2.37 (s, 3 H, Me); 3.62 (d, 2 H, CH_2, J = 5.0 Hz); 5.06 (t, 1 H, H(3), J = 5.0 Hz); 6.84—6.92 (m, 4 H, H arom.); 7.33, 7.88 (both d, 2 H each, H arom., J = 8.0 Hz); 10.70 (s, 1 H, NH).

3-[2-(4-Chlorophenyl)-2-oxoethyl]-3,4-dihydrobenzo-1,4-oxazin-2-one (8c). The yield was 0.15 g (33%), m.p. 140—141 °C (from ethanol). Found (%): C, 63.67; H, 4.03; N, 4.61. $C_{16}H_{12}ClNO_3$. Calculated (%): C, 63.69; H, 4.01; N, 4.64. IR, ν/cm^{-1}: 1692 (C(2)=O); 1662 (ArCO). ^{1}H NMR, δ: 3.68 (d, 2 H, CH_2, J = 5.4 Hz); 5.06 (t, 1 H, H(3), J = 5.4 Hz); 6.72—7.00 (m, 4 H, H arom.); 7.00, 7.60 (both d, 2 H each, H arom., J = 8.6 Hz); 10.73 (s, 1 H, NH).

3-[2-(4-Bromophenyl)-2-oxoethyl]-3,4-dihydrobenzo-1,4-oxazin-2-one (8d). The yield was 0.19 g (37%), m.p. 179—180 °C (from ethanol). Found (%): C, 55.52; H, 3.52; N, 4.07. $C_{16}H_{12}BrNO_3$. Calculated (%): C, 55.51; H, 3.49; N, 4.05. IR, ν/cm^{-1}: 1692 (C(2)=O); 1662 (ArCO). ^{1}H NMR, δ: 3.66 (d, 2 H, CH_2, J = 5.1 Hz); 5.06 (t, 1 H, H(3), J = 5.1 Hz); 6.84—6.91 (m, 4 H, H arom.); 7.74, 7.92 (both d, 2 H each, H arom., J = 8.3 Hz); 10.72 (s, 1 H, NH).

3-[2-(4-Bromophenyl)-2-oxoethyl]-6-methyl-3,4-dihydrobenzo-1,4-oxazin-2-one (8e). The yield was 0.25 g (48%), m.p. 192—194 °C (from methanol). Found (%): C, 56.66; H, 3.90; N, 3.86. $C_{17}H_{14}BrNO_3$. Calculated (%): C, 56.69; H, 3.92;

N, 3.89. IR, ν/cm^{-1}: 1695 (C(2)=O); 1663 (ArCO). ^{1}H NMR, δ: 2.20 (s, 3 H, Me); 3.64 (d, 2 H, CH_2, J = 5.2 Hz); 5.01 (t, 1 H, H(3), J = 5.2 Hz); 6.69 (m, 3 H, H arom.); 7.74, 7.93 (both d, 2 H each, H arom., J = 7.7 Hz); 10.68 (s, 1 H, NH).

3-[2-(4-Bromophenyl)-2-oxoethyl]-6-chloro-3,4-dihydrobenzo-1,4-oxazin-2-one (8f). The yield was 0.23 g (41%), m.p. 194—196 °C (from methanol). Found (%): C, 50.51; H, 2.94; N, 3.67. $C_{16}H_{11}BrClNO_3$. Calculated (%): C, 50.49; H, 2.91; N, 3.68. IR, ν/cm^{-1}: 1695 (C(2)=O); 1665 (ArCO). ^{1}H NMR, δ: 3.69 (d, 2 H, CH_2, J = 4.0 Hz); 5.12 (t, 1 H, H(3), J = 4.0 Hz); 6.89 (m, 3 H, H arom.); 7.74, 7.91 (both d, 2 H each, H arom., J = 8.0 Hz); 10.85 (s, 1 H, NH).

7-Nitro-3-(2-oxo-2-phenylethyl)-3,4-dihydrobenzo-1,4-oxazin-2-one (8g). A solution of compound **9b** (0.31 g, 1 mmol) in trifluoroacetic acid (5 mL) was refluxed for 5 h and then poured onto ice. The precipitate that formed was filtered off and recrystallized from methanol. The yield of product **8g** was 0.13 g (43%), m.p. 195 °C (from ethanol). Found (%): C, 61.51; H, 3.91; N, 8.94. $C_{16}H_{12}N_2O_5$. Calculated (%): C, 61.54; H, 3.87; N, 8.97. IR, ν/cm^{-1}: 1695 (C(2)=O); 1675 (ArCO); 1519, 1369 (NO_2). ^{1}H NMR, δ: 3.77 (d, 2 H, CH_2, J = 4.5 Hz); 5.28 (t, 1 H, H(3), J = 4.5 Hz); 7.06 (d, 2 H, H arom., J = 8.2 Hz); 7.49—7.70 (m, 4 H, H arom.); 7.89 (m, 1 H, H arom.); 7.99 (d, 2 H, H arom., J = 7.0 Hz); 11.35 (s, 1 H, NH).

Compound **8h** was obtained analogously from adduct **9c**.

7-Nitro-3-(2-oxo-2-*p*-tolylethyl)-3,4-dihydrobenzo-1,4-oxazin-2-one (8h). The yield was 0.13 g (41%), m.p. 189 °C (from ethanol). Found (%): C, 62.61; H, 4.29; N, 8.60. $C_{17}H_{14}N_2O_5$. Calculated (%): C, 62.58; H, 4.32; N, 8.58. IR, ν/cm^{-1}: 1692 (C(2)=O); 1673 (ArCO); 1518, 1369 (NO_2). ^{1}H NMR, δ: 2.32 (s, 3 H, Me); 3.75 (d, 2 H, CH_2, J = 4.6 Hz); 5.26 (t, 1 H, H(3), J = 4.6 Hz); 7.05 (d, 2 H, H arom., J = 8.1 Hz); 7.22, 7.74 (both d, 2 H each, H arom., J = 8.3 Hz); 7.96 (m, 2 H, H arom.); 11.31 (s, 1 H, NH).

2-[(2-Hydroxy-5-nitrophenyl)amino]-4-oxo-4-phenylbutyric acid (9a). A solution of acid **6a** (0.53 g, 3 mmol) and 2-aminophenol **7d** (0.46 g, 3 mmol) in propan-2-ol (15 mL) was refluxed for 3 h and then concentrated to dryness. The residue was washed with water (10×15 mL) and dried in air. The resulting semicrystalline substance was triturated with hexane and recrystallized from benzene—methanol (5 : 1). The yield of product **9a** was 0.41 g (41%), m.p. 170 °C. Found (%): C, 58.15; H, 4.29; N, 8.46. $C_{16}H_{14}N_2O_6$. Calculated (%): C, 58.18; H, 4.27; N, 8.48. IR, ν/cm^{-1}: 3423 (NH); 3313 (OH); 1725 (COOH); 1685 (PhCO); 1535, 1369 (NO_2). ^{1}H NMR, δ: 3.61 (dd, 1 H, H_A, ^2J = 16.0 Hz, ^3J = 6.0 Hz); 3.76 (dd, 1 H, H_B, ^2J = 16.0 Hz, ^3J = 4.0 Hz); 4.75 (dd, 1 H, H_X, ^3J = 6.0 Hz, ^3J = 4.0 Hz); 6.17 (d, 1 H, NH, J = 8.0 Hz); 6.70 (d, 1 H, H arom., J = 8.0 Hz); 7.48—7.98 (m, 7 H, H arom.); 10.30 (br.s, 1 H, OH); 12.30 (br.s, 1 H, COOH).

Compounds **9b—d** were obtained analogously.

2-[(2-Hydroxy-4-nitrophenyl)amino]-4-oxo-4-phenylbutyric acid (9b). The yield was 0.54 g (54%), m.p. 158 °C (from benzene—methanol (5 : 1)). Found (%): C, 58.14; H, 4.25; N, 8.50. $C_{16}H_{14}N_2O_6$. Calculated (%): C, 58.18; H, 4.27; N, 8.48. IR, ν/cm^{-1}: 3423 (NH); 3313 (OH); 1722 (COOH); 1675 (PhCO); 1532, 1369 (NO_2). ^{1}H NMR, δ: 3.60 (dd, 1 H, H_A, ^2J = 18.0 Hz, ^3J = 5.8 Hz); 3.77 (dd, 1 H, H_B, ^2J = 18.0 Hz, ^3J = 4.8 Hz); 4.73 (dd, 1 H, H_X, ^3J = 5.8 Hz, ^3J = 4.8 Hz); 6.23 (d, 1 H, NH, J = 8.0 Hz); 6.68 (d, 1 H, H arom., J = 8.0 Hz); 7.48—7.98 (m, 7 H, H arom.); 10.38 (br.s, 1 H, OH); 12.72 (br.s, 1 H, COOH).

2-[(2-Hydroxy-4-nitrophenyl)amino]-4-oxo-4-*p*-tolylbutyric acid (9c). The yield was 0.36 g (35%), m.p. 146 °C (from benzene—methanol (5 : 1)). Found (%): C, 59.34; H, 4.69; N, 8.14. $C_{17}H_{16}N_2O_6$. Calculated (%): C, 59.30; H, 4.68; N, 8.14. IR, ν/cm^{-1}: 3423 (NH); 3309 (OH); 1729 (COOH); 1682 (ArCO); 1535, 1362 (NO_2). ^{1}H NMR, δ: 2.36 (s, 3 H, Me); 3.57 (dd, 1 H, H_A, ^2J = 18.0 Hz, ^3J = 6.0 Hz); 3.73 (dd, 1 H, H_B, ^2J = 18.0 Hz, ^3J = 4.0 Hz); 4.73 (dd, 1 H, H_X, ^3J = 6.0 Hz, ^3J = 4.0 Hz); 6.18 (d, 1 H, NH, J = 8.0 Hz); 6.69 (d, 1 H, H arom., J = 8.0 Hz); 7.49—7.88 (m, 6 H, H arom.); 10.34 (br.s, 1 H, OH); 12.78 (br.s, 1 H, COOH).

4-(4-Chlorophenyl)-2-[(2-hydroxy-4-nitrophenyl)amino]-4-oxobutyric acid (9d). The yield was 0.52 g (48%), m.p. 107 °C (from benzene—methanol (5 : 1)). Found (%): C, 52.73; H, 3.57; N, 7.66. $C_{16}H_{13}ClN_2O_6$. Calculated (%): C, 52.69; H, 3.59; N, 7.68. IR, ν/cm^{-1}: 3403 (NH); 3310 (OH); 1702 (COOH); 1682 (PhCO); 1532, 1365 (NO_2). ^{1}H NMR, δ: 3.60 (dd, 1 H, H_A, ^2J = 18.0 Hz, ^3J = 6.0 Hz); 3.76 (dd, 1 H, H_B, ^2J = 18.0 Hz, ^3J = 4.0 Hz); 4.74 (dd, 1 H, H_X, ^3J = 6.0 Hz, ^3J = 4.0 Hz); 6.20 (d, 1 H, NH, J = 8.0 Hz); 6.69 (d, 1 H, H arom., J = 8.0 Hz); 7.49—7.99 (m, 6 H, H arom.); 10.31 (br.s, 1 H, OH); 12.69 (br.s, 1 H, COOH).

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