Functionalization and Cyclization Reactions of Various Acetanilides with 4-Benzoyl-5-phenyl-2,3-furandione. Experimental and Theroetical Investigations

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Received July 3, 1996

4-Benzoyl-5-phenyl-2,3-furandione (**1**) reacts with acetanilides **3a-c** under different conditions and gives the new open chained dibenzoylacetic acid derivatives **5a-c, 6** and a new heterocyclic compound such as oxazole derivative **7**. The electronic structures of the reactants, transitional states and final products of the reactions are investigated on the basis of AM1 method.

In recent papers many methods and reactions of cyclic oxalyl compounds have been reported to give substituted heterocyclic compounds [1]. 4-Benzoyl-5-phenyl-2,3-furandione (**1**) was obtained by the cyclocondensation reaction between dibenzoylmethane and oxalyl chloride [2]. The reactions of the substituted 2,3-furandione **1** with various nucleophiles or dienophiles at different solvents and temperatures have been studied [3]. Recent years have witnessed the development of a powerful new methodology for the synthesis of substituted aromatic systems and heterocyclic compounds, proceeding through putative ketene intermediates [4]. The thermal decomposition of furandione **1** leads to the formation of reactive dibenzoylketene intermediates [5]. A convenient method for the synthesis, the mechanism of the reactions and calculations on interactions of **1** with several semicarbazones, ureas and their thio-analogs have been reported recently [6].

This interest in ketene chemistry is also demonstrated by recent efforts to extend the MM2 and MM3 force fields to these types of molecules [7]. The general reactivity of ketenes has been reviewed recently, and a few *ab initio* calculations and semiempirical AM1 and PM3 calculations on a series of differently substituted α-oxoketenes, especially substituent effects on their stability as well as reactivity, have been published [8].

We synthesized the substituted amides **5a-c, 6** and perhydrooxazole derivative **7** (see Schemes 1 and 2) from **3** and **1** under different conditions and investigated their thermal decomposition and reactivity with anilides at high temperatures.

To study the mechanism of the reaction, all calculations were carried out by means of semiempirical AM1 and PM3 methods with full geometry optimization for reactants and products. Transitional states were approximately located by means of the reaction-coordinate method. The standard parameters [9] and the programs [10] were used in the AM1 calculations. The AM1 calculations were carried out by means of the MOPAC program package [10]. Model compounds with phenyl groups substituted by hydrogen atoms are used in the theoretical calculations.

The reactions between **1** and **3a-c** were performed in boiling benzene, toluene and xylene either (80-140°, see Experimental). Obviously (see Scheme 1), the corresponding dibenzoylacetic acid-*N*-arylamide **5a-c** formation goes through the CO disconnection under heating and results in the molecule of ketene **2**. Then the second molecule of **2** combines with the product and we get the final product **5** after CH_3CO_2H disconnection. The ketene formation under conditions mentioned was established in different papers [5].

The structure of **5** was confirmed by elemental analysis, ir, ^1H nmr and ^{13}C nmr spectroscopic data with **5a,b** taken as examples. The structural analogy of all compounds **5** is easily seen from the ir, ^1H and ^{13}C nmr spectra. In the ir spectra of compounds **5** the C=O absorption bands are found at about 1700, 1640 cm^{-1} (see details in Experimental, **5a**). Taking into account the ir and nmr spectral data on compounds **5a,b**, keto-enol tautomerism may be expected. For example, the ^1H nmr spectra are in the range of δ equal to 8.3-7.9 ppm and 3.34 ppm, and the ^{13}C spectra have peaks at δ = 148.2, 147.4 and 110.8, 104.3 ppm (C-3, C-3'). These weak peaks favour keto-enolic forms of the compounds **5a,b**.

As seen from the Table, containing selected structural data for the systems investigated, the molecule CO disconnection is realized through a transitional state (**TS1**) with the value of ΔH_f equal to -71.15 kcal/mol. The **TS1** is formed when the atom C2 moves to the distances of 1.95 Å and 1.89 Å from the atoms C3 and O1, respectively. The energy of the activation barrier comes up to 27.74 kcal/mol. The difference in the energy of the initial compound and the sum of the two final products is equal to 20.49 kcal/mol. The molecule CO full disconnection is observed with distances C2-C3 = 3.89 Å and O1-C2 = 3.50 Å. The transition for molecule **2** causes a bond angle increase for C4-C3-O8 equal to 179.84°, and the atom C3 conversion from the sp²-state to the linear sp-hybryd state. Molecule obtained **2** is planar, and the torsion angle C5-C4-C3-O8 is equal to 0.06°.

Scheme 1

5a-c

a: Ph, b: p-C₆H₄-NO₂, c: p-C₆H₄-Br
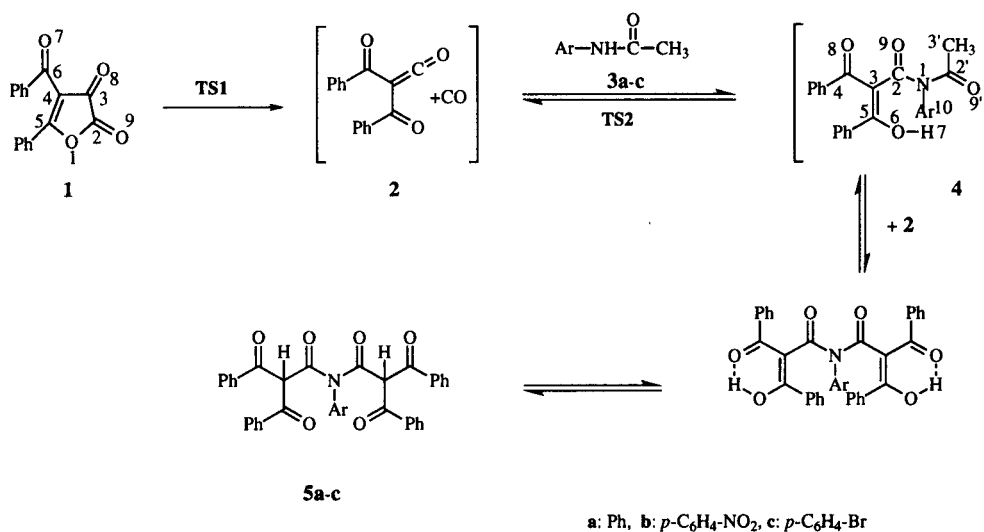
Scheme 2
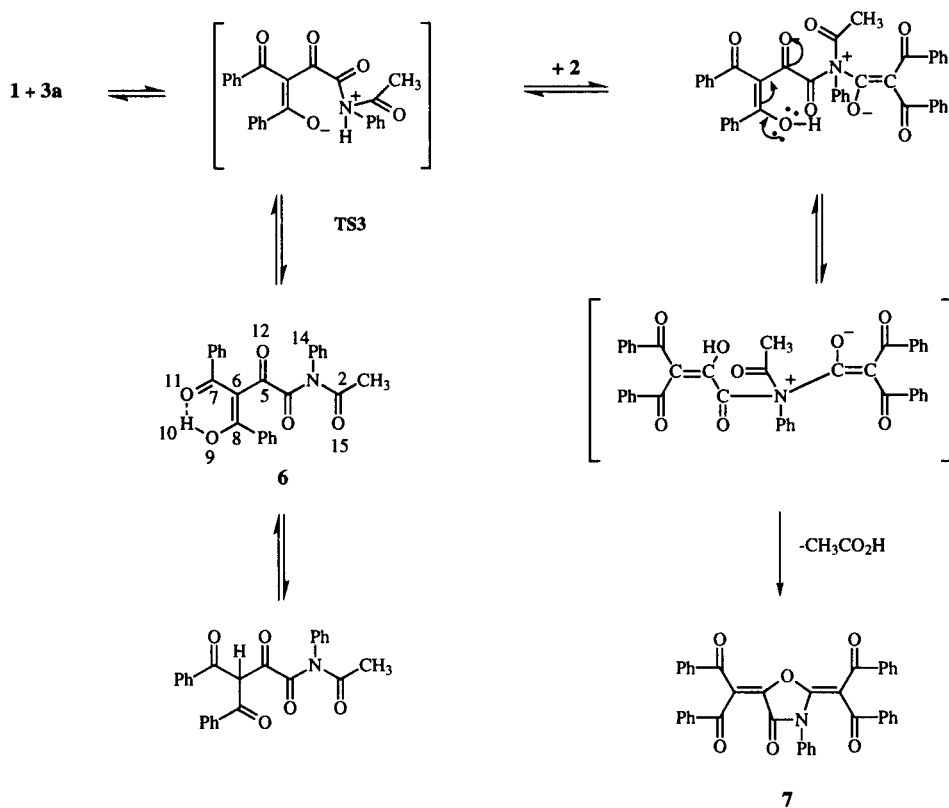
At the second stage a nucleophile is combined with a molecule of **2** and results in the transitional state (**TS2**). By this the atom N1 of the nucleophile attacks the atom C2 with new bond formation and old bond cleavage. As seen from the Table, the bonds N1-C2 and O6...H7 forma-

tion leads to bond-weakening of N1-H7 at the same time. **TS2** (ΔH_f = -112.50 kcal/mol) is characterized by the presence of the six-membered ring with bonds lengths substantially changed as compared with their initial values for the reagents. For **TS2** the distances N1-C2, N1-H7

Table

Structural Parameters of Starting Materials Transitions States and Final Products

Compounds	1	TS1	2		2 + 3	TS2	4		1 + 3a	TS3	6
Bond length											
O1-C5	1.383	1.263	1.235	O6-H7	2.611	1.849	0.971	N3-H10	0.992	1.547	3.965
O1-C2	1.427	1.892	3.500	O6-C5	1.233	1.251	1.351	O9-H10	2.350	1.144	0.975
C2-C3	1.529	1.952	3.890	N1-H7	0.987	1.036	2.656	C8-O9	1.385	1.334	1.347
C3-C4	1.477	1.371	1.339	N1-C2	4.038	1.577	1.398	N3-C4	2.730	1.451	1.386
C4-C5	1.371	1.453	1.460	N1-C2'	1.372	1.483	1.403	C5-C6	1.483	1.446	1.466
C4-C6	1.454	1.460	1.465	C2-C6	1.343	1.414	1.486	C6-C7	1.454	1.469	1.477
C6-O7	1.233	1.234	1.232	C2-O9	1.175	1.227	1.242	C4-C5	1.532	1.451	1.529
C3-O8	1.220	1.176	1.177	C2'-C3'	1.508	1.496	1.501	C4-O13	1.212	1.229	1.248
C2-O9	1.212	1.176	1.169	C3-C5	1.460	1.432	1.353	C2-N3	1.397	1.443	1.406
				C3-C4	1.460	1.459	1.471	C4-O9	1.431	2.555	3.265
Bond angles											
C2-O1-C5	107.77	105.20	121.64	O6-H7-N1	103.16	138.47	122.62	H10-N3-H14	114.09	96.95	107.21
O1-C2-C3	107.42	92.69	64.62	H7-N1-C2	102.04	107.14	69.93	N3-H10-O9	124.29	147.96	122.20
C2-C3-C4	105.31	100.59	102.01	N1-C2-C3	105.60	115.78	119.65	N3-C4-O13	85.86	120.98	118.62
C4-C3-O8	125.58	153.77	179.84	C3-C2-O9	179.26	135.53	121.90	C8-O9-H10	104.90	122.17	112.05
C3-C4-C6	120.11	119.53	120.19	H7-N1-H10	117.94	109.26	112.62	C6-C8-O9	113.40	128.59	128.53
				H7-N1-C2	121.84	106.68	103.71	C5-C6-C8	108.41	121.25	125.83
				C2-C3-C4	121.76	118.93	117.23	C2-N3-H14	115.10	116.43	117.54
Torsion angles											
C5-O1-C2-C3	-0.14	0.63	2.09	C2-N1-H7-O6	3.84	29.41	66.24	O9-H10-N3-H14	109.36	74.54	-123.91
C5-C4-C3-O8	0.23	0.15	0.06	C2-C3-C4-O8	0.67	8.15	24.59	C8-O9-H10-N3	-99.29	-15.18	-33.69
				H7-N1-C2'-O9'	176.64	-137.21	-109.52	C6-C8-O9-H10	80.94	14.46	-5.31
								C5-C6-C8-O9	0.62	11.67	1.50

and O6-H7 are, correspondingly, 1.58 Å, 1.04 Å and 1.85 Å. Further approach of the atoms N1 and C2 leads to the bonds N1-C2 and O6-H7 final formation and the bond N1-H7 breakage. The activation barrier for this reaction comes up to 13.94 kcal/mol, and the difference in the energies of the initial compound and the sum of two final products is equal to 8.74 kcal/mol. As the Table shows, the reaction results in the bonds and valent angles rearrangements in the reacting systems. The values of the valent angles of the atoms of carbon and nitrogen are close to the values of the angles for sp^2-hybryd bonds. The value of the torsion angle O2-N1-H7-O6 equal to 66.24° indicates that the atoms are not conplanar.

When changing the conditions of the reaction course, we have different final products. Unlike the previous reaction, under which the ketene is formed at the first stage, the attack of molecule 1 by the molecule of nucleophile 3a happens without preliminary disconnection of CO.

Besides the thermolysis reactions, compound 1 reacts also with numerous NH-nucleophiles [1a,3d,6a]. The subtituted amide derivative 6 is obtained from the nucleophilic addition reaction of 1 and acetanilide 3a with heating in benzene during 4 hours in 25% yield. By this, the NH-nucleophile attacks the atom C-2 of the furan ring by a Michael-addition type reaction (see Scheme 2). Struc-

ture elucidation of 6 is mainly based upon ^{13}C nmr spectroscopy: signals at 193.8 (d, C-7, C-8), 175.3 (d, C-4, C-5), 170.7 (s, C-2), 140.5 (s, C-6, in enol-form), 67.9 (s, C-6, in keto-form), 28.3 (s, C-1) could be assigned to the main chain-carbons of 6. For further details of the spectroscopic investigations see the Experimental.

The characteristic structural variations for the reacting molecules are given in the Table. The transition state TS3 is being formed with the seven-membered ring. By this, the distances N3-C4 and N3-H10 are 1.45 Å and 1.55 Å, correspondingly. The valent angle N3-H10-O9 comes to 147.96°, and the angle C6-C8-O9 is equal to 128.53°. The resting angles in the transitional seven-membered ring are close to 120°. The activation barrier is 22.90 kcal/mol. From a comparison of the energy of the reactants and 6 it follows that the reaction is exothermic ($\Delta H_f = 18.49$ kcal/mol). The approach of atom N3 to atom C4 causes a migration of proton H10 from N3 to O9. For the final product of the reaction the lengths of the bonds N3-C4 and O9-H10 are equal to 1.38 Å and 0.98 Å, respectively. Thus the value of the valence angle C8-O9-H10 is reduced to 112.05° and the torsion angle N3-H10-O9-C8 is increased to 33.69°.

In addition, the final product 7 was formed from 1 and 3a as a result of increased reaction time. As may be seen

in Scheme 2, diacylketene **2** is added to **TS3** in benzene medium and the stable oxazole ring is formed by disconnection molecule of acetic acid. The elemental analytical and spectroscopic data for **7** agree well with the proposed structure.

EXPERIMENTAL

Solvents were dried by refluxing with the appropriate drying agent and distilled before use. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyzer Model 1108. The ir spectra were obtained in as potassium bromide pellets using a Shimadzu Model 435 V-04 spectrometer. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian X4200 Gemini spectrophotometer using tetramethylsilane as an internal standard. All experiments were followed by tlc using DC Alufolien Kieselgel 60 F 254 Merck and with a Model Camag tlc lamp (254/366 nm).

N,N-Bis(dibenzoylacetic Acid)-N-phenylamide (5a).

4-Benzoyl-5-phenyl-2,3-furandione (**1**) (0.5 g) and 0.243 g of acetanilide (**3a**) (molar ratio 1:1) were refluxed in boiling xylene for one hour. Light yellow crystals were obtained and allowed to cool to room temperature, filtered and recrystallized from acetic acid to give 0.426 g (40%) of **5a**, mp 238°; ir (potassium bromide): ν = 3600-3200 (hydrogen bonded, OH), 3050 (CH aromatics superimposed upon OH stretch), 1700, 1640 (C=O, belonging to amide and other carbonyl groups), 1590, 1470 (C=C) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 8.00-7.90 ppm (q, 2H), 7.69-7.04 (m, 25H, aromatic), 3.34 (s, 2H, under the peak of H$_2$O in DMSO-d$_6$, probably); ^{13}C nmr (DMSO-d$_6$): δ 195.3 (s, C-4), 194.3 (s, C-4'), 175.9 (s, C-2), 174.9 (s, C-2'), 160.8 (s, C-5), 157.5 (s, C-5'), 148.2 (s, C-3, C-3', enol-form), 138.5, 137.9, 137.4, 136.2, 135.4 (m, N-Ph), 133.5-129.1 (m, C-Ph's), 110.8 (s, C-3, C-3', keto-form).

Anal. Calcd. for C$_{38}$H$_{27}$NO$_6$: C, 76.90; H, 4.55; N, 2.36. Found: C, 77.13; H, 4.42; N, 2.20.

N,N-Bis(dibenzoylacetic Acid)-N-p-nitrophenylamide (5b).

Compound **1** (0.5 g, 1.798 mmoles) and p-nitroacetanilide (**3b**) (0.26 g, 1.798 mmoles) were allowed to react in boiling toluene under reflux for 4 hours. The solvent was removed by evaporation and the oily residue was triturated with anhydrous ether to give a white coloured crude solid which was recrystallized from acetic acid yielding 0.459 g (40%) of pure **5b**, mp 328°; ir: ν 1680, 1640 (C=O), 1590, 1530, 1450 (C=C) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 8.30-8.25 ppm (d, 2H), 8.04-7.05 (m, 24H, aromatic), 3.34 (s, 2H, probably belonging to the O-H, under the water peak of DMSO-d$_6$); ^{13}C nmr (DMSO-d$_6$) δ 205.3 ppm (s, C-2, C-2'), 194.1 (s, C-4, C-4'), 160.7 (s, C-5, C-5'), 147.4 (s, C-3, C-3', enol-form), 142.9-123.5 (m, aromatic C), 104.3 (s, C-3, C-3', keto-form).

Anal. Calcd. for C$_{38}$H$_{26}$N$_2$O$_8$: C, 71.47; H, 4.07; N, 4.39. Found: C, 71.63; H, 4.02; N, 4.10.

N,N-Bis(dibenzoylacetic Acid)-N-p-bromophenylamide (5c).

The furandione **1** (0.5 g) and the corresponding p-bromoacetanilide (**3c**) (0.35 g) (molar ratio 1:1) were refluxed in boil-

ing benzene for 4 hours. After evaporation the oily residue was treated with dry ether. Then the precipitated crude red product was filtered and recrystallized from acetic acid to give 0.423 g (35%) of pure **5c**, mp 274°; ir (potassium bromide): ν 3050 (CH aromatic), 1700, 1660 (C=O), 1600, 1540, 1460 (C=C), 1320 (C-O).

Anal. Calcd. for C$_{38}$H$_{26}$NO$_6$Br: C, 67.85; H, 3.86; N, 2.08. Found: C, 68.23; H, 3.52; N, 2.05.

3,3-Dibenzoyl-2-oxopropanoic Acid-N-acetyl-N-phenylamide (6).

From 0.5 g (1.798 mmoles) of **1** and 0.243 g (1.798 mmoles) of **3a** after refluxing in boiling benzene for 4 hours, the solvent was removed by evaporation. The oily residue which formed was treated with dry ether. The precipitate was filtered and recrystallized from methanol, yielding 0.185 g (25%) of pure **6**, mp 155°; ir: 3050 and 2950 (CH, aromatic and aliphatic), 1710, 1670 (C=O), 1580, 1480, 1450 (C=C) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.94 (d, 1H), 7.90-7.27 (m, 15H aromatic), 2.05 (s, 3H); ^{13}C nmr (deuteriochloroform) δ 193.8 (d, C-7, C-8), 175.3 (d, C-4, C-5), 170.7 (s, C-2), 140.5 (s, C-6, enol-form), 138.1, 135.6 (q, N-Ph), 132.0-129.2 (m, C-Ph, aromatic C), 67.9 (s, C-6, keto-form), 28.3 (s, C-1).

Anal. Calcd. for C$_{25}$H$_{19}$NO$_5$: C, 72.63; H, 4.63; N, 3.39. Found: C, 72.81; H, 4.82, N, 3.54.

2,5-Bis(dibenzoylmethylene)-3-phenylperhydrooxazol-4-one (7).

By the same procedure as described for **5c** with a reaction time of 7-8 hours, **1** and **3a** (molar ratio 1:1) provided 0.379 g (35%) of **7** which was crystallized from acetic acid, mp 230°; ir (potassium bromide): 3050 (CH aromatic), 1710, 1640 (C=O), 1600-1450 (C=C), 1340, 1100 (C-N, C-O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.98-6.64 (m, aromatic H) ppm; ^{13}C nmr (deuteriochloroform): δ 194.6 (s, C-7, C-8), 177.9 (s, C-4), 164.3 (s, C-2), 162.9 (s, C-5), 138.7, 138.1, 136.7, 136.0, 135.7 (m, C-6, N-Ph, exchangeable), 133.6-128.1 (C-Ph, aromatic C).

Anal. Calcd. for C$_{39}$H$_{25}$NO$_6$: C, 77.66; H, 4.16; N, 2.32. Found: C, 77.96; H, 4.14; N, 2.22.

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