Synthesis of 4-Aroyl-4,5-dihydro-2(3H)-furanones and their Reactions with some Nucleophiles

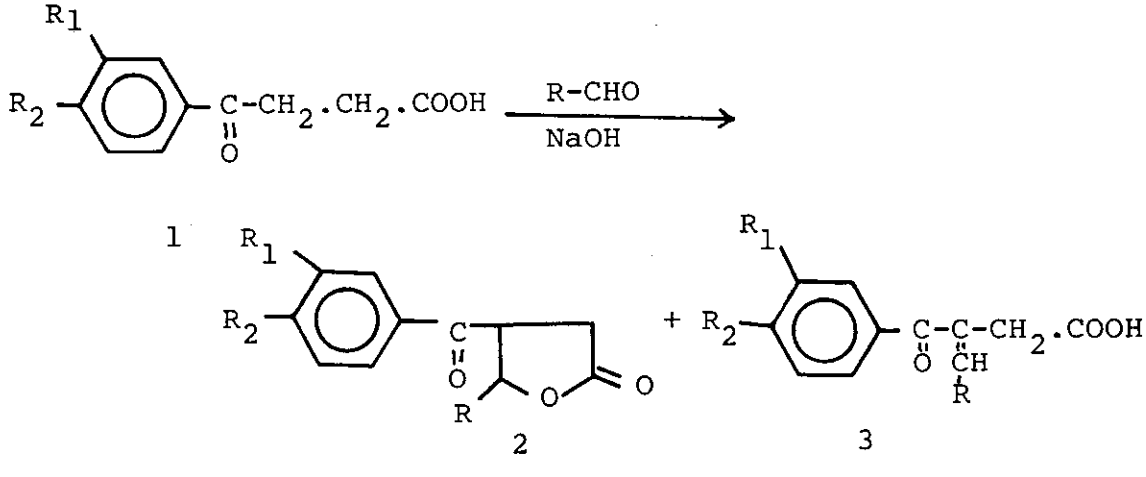
N.A.SHAMS, A.A.HAMED, S.G.DONIA AND S.A.SHAKER
Chemistry Department, Faculty of Science, Ain Shams University Cairo, Egypt.

(Received 27th April, 1985, Revised 23rd September,1985)

Summary: Hydroxyalkylation of 3-aroylpropanoic acids [1,2] (1a & b) using either formaldehyde or acetaldehyde in sodium hydroxide solution [3] gave two products, 4-aroyl-4,5-dihydro-2(3H)-furanones (2a-d), and butenoic or pentanoic acid derivatives (3a-d). Reaction of the title compounds with different molar ratio of hydrazine hydrate and with phenylmagnesium bromide was investigated.

The present investigation deals with the interaction of 3-(p-phenoxybenzoyl) (1a) [1] and 3-(3,4-dimethylbenzoyl (1b) [2] propanoic acids with formaldehyde or acetaldehyde in dilute sodium hydroxide solution [3] in a molar ratio 1:1.1:1.1, respectively, to give two products, in each case, 4-aroyl-4,5-dihydro-2(3H)-furanones (2a-d) [major product] and 3-aroyl-3-butenoic acids (3a & b) or 3-aroyl-3-pentenoic acids (3c & d) [minor product].

The structure of the products (2) and (3) was inferred from: (i) analytical data, (ii) the infrared spectra show absorption bands characteristic of $\nu C=O$ [aroyl and lactone for (2) and aroyl and carboxylic groups for (3)]. In addition the infrared spectra of (3) show $\nu C=C$ at ν 1640 cm^{-1} and (iii) the ^1H n.m.r. spectrum of (2b) shows signals at δ 4.73-4.0 (m, 3H, $CH,\cdot CH_2$); 3.24-2.82 (m, 2H, $CH_2.CO$) while the ^1H n.m.r.



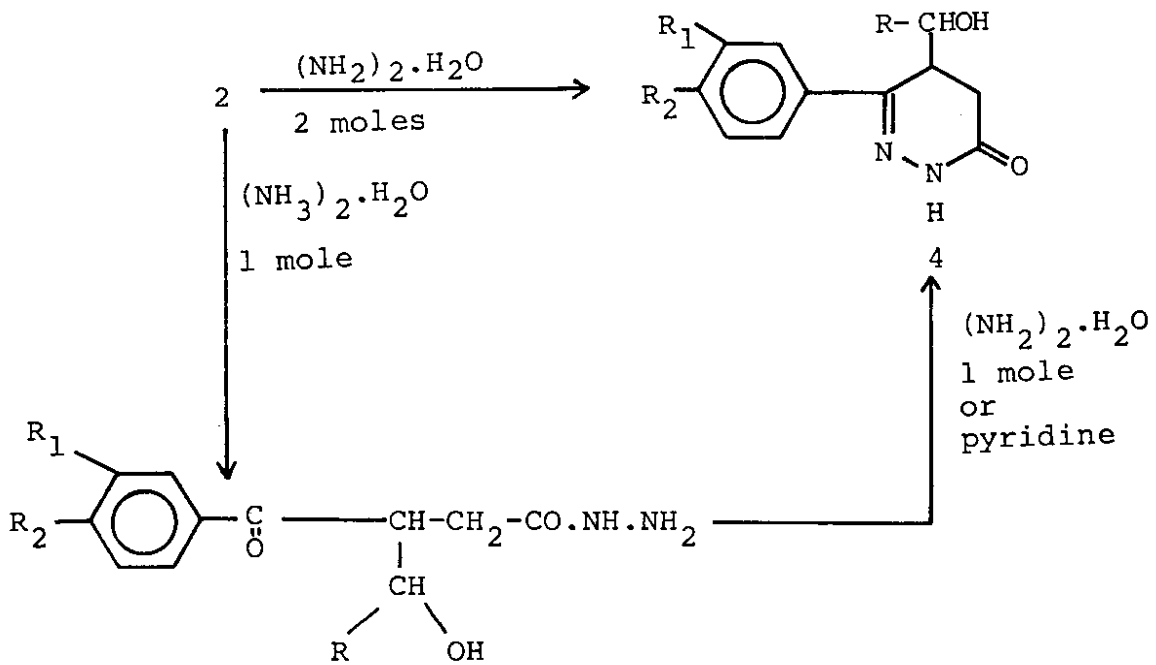
1,2,3a; $R=R_1=H$, $R_2=C_6H_5O-$
b; $R=H$, $R_1=R_2=CH_3$
c; $R=CH_3$, $R_1=H$, $R_2=C_6H_5O-$
d; $R=R_1=R_2=CH_3$

spectrum of (3b) shows signals at δ 9.68 (br. S, 1H, COOH); 6.22+5.79 (2 apparent S, 2H, $C=CH_2$); 3.58 (S, 2H, CH_2COOH).

The reaction of 4-aroyl (2a & b) and 4-aroyl-5-methyl (2c & d)-4,5-dihydro-2(3H)-furanones with hydrazine hydrate (98%) (1:2 molar ratio) at room temperature up to three hours, gave exclusively one product, in each case, to which structure (4) was assigned. The infrared spectra of the products indicate absorption due to C=O at 1650-1670 cm^{-1} and to NH at 2800-3600 cm^{-1}, very similar to the corresponding bands which appeared in the spectra of 4,5-dihydropyridazin-3(2H)-ones [4]. The electronic spectra shows maximum absorption at 285-298 nm (log $\varepsilon_{max}^{\lambda}$ 4.38-4.47) which is very similar to those of tetrahydropyridazinones [5]. This result confirms that the reaction (2a-d) with hydrazine hydrate in 1:2 molar ratio, irrespective of reaction time, affords the corresponding 6-aryl-4,5-dihydro-5-hydroxyalkyl-pyridazin-3(2H)-ones (4a-d).

However, when (2a) was allowed to react with hydrazine hydrate (1:1 molar ratio) at room temperature or even in boiling ethanol or n-butanol (as high boiling point solvent) up to three hours, it yielded 4-hydroxy-3-p-phenoxybenzoyl butanoic acid hydrazide (5) as a sole product in 92% yield.

The structure assigned to the product (5) was consistent with its infrared spectrum which displays absorption bands characteristic for the



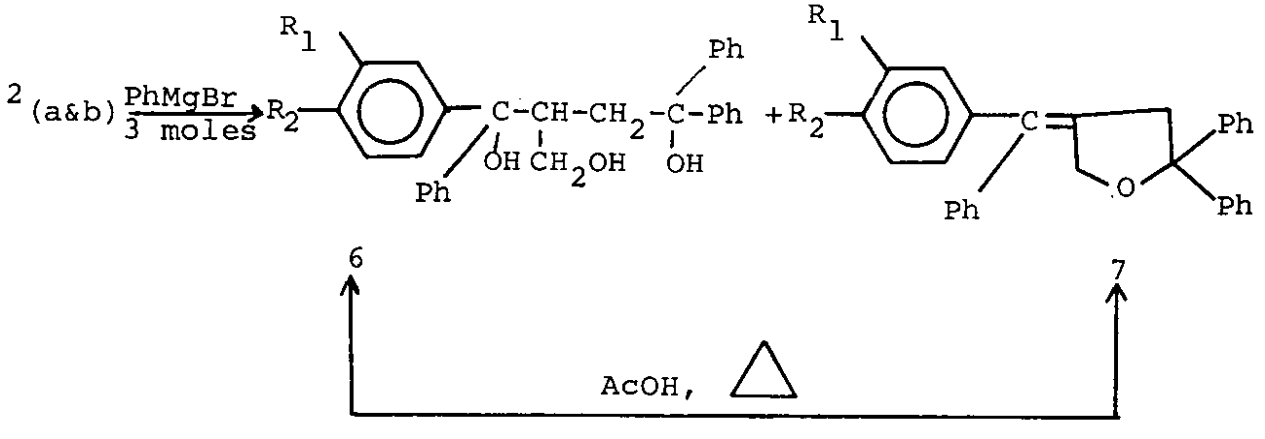
R=R_1=H, R_2=C_6H_5O-

2,4a; R=R_1=H, R_2=C_6H_5O-
b; R=H, R_1=R_2=CH_3
c; R=CH_3, R_1=H, R_2=C_6H_5O-
d; R=R_1=R_2=CH_3

stretching frequencies of C=O [both aroyl and hydrazide groups], NH and OH groups (table 1). This fact tempted us to investigate whether the nature of product controlled mainly by lactone/$(NH_2)_2$ hydrate molar or merely by the basicity of the medium. Thus, treatment of (5) with pyridine (1:1 molar ratio) in ethanol at room temperature for one hour yields exclusively the pyridazinone (4a), indicating that ring closure of (5) to (4a) was effected only by the basicity of the medium.

In continuation of our investigation on the ring opening reactions of 4-aroyl-4,5-dihydro-2(3H)furanones with some nucleophiles, we report that the reaction of (2a & b) with phenylmagnesium bromide (1:3 molar ratio) yielded two products in each case, 1-aryl-1,4,4-triphenyl-2-hydroxymethylbutane-1,4-diol (6a & b) and 2,2-diphenyl-4(aryl phenylmethylene)-tetrahydrofuran (7a & b).

The structural assignment for (6) was confirmed by elemental analysis and by their infrared spectra which show absorption bands in the 3, region characteristic of ν OH. In addition Zerewitinoff and Tschugaev's method [6 and 7] and by J.F. Lees and R.T. Lobeck modification [8] indicates that each product of structure (6) has 3 OH groups. On the other hand the infrared spectra of (7a & b) lack any band characteristic of OH and C=O stretching frequencies, but exhibit νC=C at about 1630 cm^{-1}, moreover the ^{1}H-n.m.r. spectrum of (7a) shows signals at δ 3.1; (S, $C\underline{H}$-C(Ph)(Ph)) and δ 3.6 (S, $-C\underline{H}_2O$), which indicate that the product derived from 1,2-addition to the aroyl group undergoes cleavage, under the influence of the nucleophile to give the corresponding acyclic ketone, which in turn reacts with another molecule of the reagent followed by elimination of two molecules of water. Structure (7) was rigidly established by the fact that: (i) their ethanolic solution decolourises potassium permengnate solution and (ii) (7a) is identical in all respects to the product obtained when (6a) was refluxed in glacial acetic acid for two hours.



6,7a; R_1=H; R_2=C_6H_5O-

b; R_1=R_2=CH_3

Table-1: Characterisation of Compounds (1-7).

Compound	Solvent	M.P. (°C)	Yield (%)	Formula (Mol.Wt.)	Analytical data Found/Required %			i.r. (cm^{-1})				Electronic Spectra	
					C	H	N	ν C=O	ν C=C	νNH	νOH	$\lambda_{(max)}$	$\log\varepsilon_{(max)}$
(2a)	B	101-2	82	$C_{17}H_{14}O_4$	72.66	5.21		1760,				262	4.05
				(282.3)	72.33	5.00		1675					
(b)	B	93-4	79	$C_{13}H_{14}O_3$	71.88	6.81		1780,				259	3.90
				(218.2)	71.54	6.47		1678					
(c)	T	107-8	76	$C_{18}H_{16}O_4$	72.73	5.64		1775,				266	4.10
				(296.3)	72.96	5.44		1670					
(d)	B	102-3	72	$C_{14}H_{16}O_3$	72.81	6.64		1778				264	4.20
				(232.3)	72.39	6.94		1675					
(3a)	L.P.	78-9	14	$C_{17}H_{14}O_4$	72.72	5.06		1700	1635				
				(282.3)	72.33	5.00		1678					
(b)	L.P.	71-2	17	$C_{13}H_{14}O_3$	72.01	6.77		1710,	1640				
				(218.2)	71.54	6.47		1678					
(c)	L.P	85-6	20	$C_{18}H_{16}O_4$	73.23	5.33		1708,	1640				
				(296.3)	72.96	5.44		1675					
(d)	L.P	98-9	22	$C_{14}H_{16}O_3$	72.12	7.23		1700,	1638				
				(232.3)	72.39	6.94		1670					
(4a)	B	153-4	78	$C_{17}H_{16}N_2O_3$	69.00	5.48	9.75	1670		3270,	2890(sh)	296	4.37
				(296.3)	68.90	5.44	9.45						
(b)	B	148-9	69	$C_{13}H_{16}N_2O_2$	67.64	7.02	12.43	1678		3086,	2900(sh)	285	4.38
				(232.3)	67.22	6.94	12.06						

Table-1: (Continued)

(4c)	B	160-1	70	$C_{18}H_{18}N_2O_3$	69.92	5.94	9.42	1663		3077	2874(sh)	298	4.47
				(310.3)	69.66	5.85	9.03						
(d)	B	172-3	74	$C_{14}H_{18}N_2O_2$	68.11	7.20	11.27	1672		3058	2970(sh)	289	4.45
				(246.3)	68.21	7.31	11.37						
(5)	L.P	141-2	81	$C_{17}H_{18}N_2O_4$	65.32	6.01	9.33	1645		3190	2920		
				(314.3)	64.95	5.77	8.91	1675					
(6a)	B	137-8	30	$C_{35}H_{32}O_4$	81.49	6.45				3115			
				(516.6)	81.37	6.24							
(b)	B	154-5	29	$C_{31}H_{32}O_3$	81.89	7.27				3110			
				(452.6)	82.27	7.13							
(7a)	L.P	168-9	55	$C_{35}H_{28}O_2$	87.88	5.89			1630				
				(480.6)	87.47	5.87							
(b)	L.P	182-3	57	$C_{31}H_{28}O$	88.94	7.03			1625				
				(416.5)	89.38	6.78							

B = Benzene, T = Toluene, L.P = Light petrol (b.p. 60-80°)

sh. = Sharp.

Experimental

Melting points are uncorrected. A Pye-Unicam SP 1200 infrared spectrophotometer was used to take infrared spectra using KBr wafer technique. Electronic spectra were recorded on a Perkin-Elmer Specord Model 4000 A spectrophotometer using ethanol as solvent, NMR spectra were measured on a Varian A-60 A spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Elemental analyses were carried out at the microanalytical units of Cairo University, and Drug Control, and Research Center, Cairo, Egypt.

Action of formaldehyde and acetaldehyde on 3-aroylpropanoic acids: Synthesis of (2a-d) and (3a-d):

37% Formaldehyde (8.91 gm. 1.1 mole) or acetaldehyde (4.8 gm, 1.1 mole) was added to a stirred solution of 3-p-phenoxybenzoylpropanoic acid (1a) (27 gm, 1 mole) or 3-(3,4-dimethyl))benzoylpropanoic acid (1b) (20.6 gm, 1 mole) in 0.5N sodium hydroxide (220 ml) [molar ratio of 1/aldehyde/NaOH=1:1.1:1.1]. After one hr. at room temperature, the mixture was acidified with concentrated hydrochloric acid (, 30 ml) and stirred for additional 12 hrs. The semi-solid product which separates, in each case, was triturated with ether 250 ml to give 4-aroyl (2a & b) or 4-aroyl-5-methyl (2c & d) 4,5-dihydro-2(3H)-furanones, respectively.

The ether-soluble fraction was chromatographed on silica gel, eluting with benzene/acetone (95:5), resulting in successive collection of (2a-d) in small yield and either 3-aroyl-3-butenoic acids (3a & b) or 3-aroyl-3-pentenoic acids (3c & d), respectively.

Action of hydrazine hydrate on 4-aroyl (2a & b) and 4-aroyl-5-methyl-4,5-dihydro-2(3H)-furanones:

After a mixture of 4-p-phenoxybenzoyl (2a) (28.2 gm, 1 mole), 4-(3,4-dimethyl)benzoyl (2b) (21.8 gm, 1 mole), 4-p-phenoxybenzoyl-5-methyl (2c) (29.6 gm,. 1 mole) or 4-(3,4-dimethyl)benzoyl-5-methyl (2d) (23.7 gm, 1 mole) 4,5-dihydro-2(3H)furanones in ethanol (100 ml) and hydrazine hydrate (98%, 10.012 gm, 2 moles) had stood at room temperature for two hours, the resulting solution was placed on a watch glass and allowed to evaporate to dryness in a current of air. The residue thus obtained was recrystallised from a suitable solvent to yield 6-aryl-4,5-dihydro-5-hydroxyalkylpyridazin-3 (2H)-ones (4a-d) as colourless crystals.

Synthesis of 4-hydroxy-3-p-phenoxybenzoylbutanoic acid hydrazide (5):

A solution of (2a) (2.82 gm, 0.01 mole) in ethanol or n-butanol (10 ml) was treated with hydrazine hydrate ((98%) 0.5 gm, 0.01 mole) at room temperature and under reflux up to 3 hrs. The mixture was treated as described in the fore-mentioned procedure. Filtration yielded 2.55 gm (81.2%) of crude (5), m.p. 132-136°C, and recrystallization from light petrol (b.p. 60-80°) afforded the pure compound as colourless needles, m.p. 141-2°C.

Synthesis of (4a) via cyclisation of (5):

Compound (5) (3.14 gm, 0.01 mole) in ethanol (25 ml) was treated with either hydrazine hydrate (0.5 gm, 0.01 mole) or pyridine (0.79 gm, 0.01 mole) and the reaction mixture was

left at room temperature for one hr. After concentration and cooling, the solid product obtained, in each case, was filtered off washed with water and crystallised from benzene to give 2.65 gm of 4,5-dihydro-5-hydroxymethyl-6-p-phenoxyphenyl pyridazin-3-(2H) -one, m.p. 153-4°C, yield 89.5%.

Action of phenylmagnesium bromide on 4-aryl-4,5-dihydro-2(3H)-furanones (2a & b):

To 3.6 gm of magnesium turnings (0.15 gm. atom) in 100 ml of dry ether was added dropwise 15.7 ml (23.55 gm, 0.15 mole) or bromobenzene. After the reaction had subsided, (2a) (8.46 gm, 0.03 mole) or (2b) (6.54 gm, 0.03 mole) dissolved in 100 ml dry benzene was added in portions over one hr. period. The mixture was heated under reflux for an additional 3 hrs. and then decomposed with saturated ammonium chloride solution (20 %). The ether-benzene layer was washed with water and dried over anhydrous sodium sulphate. Concentration of the ether-benzene mixture yielded a colourless solid, which on recrystallisation from benzene afforded 1-aryl-1,4,4-triphenyl-2-hydroxymethylbutane-1,4-diol (6a & b).

Evaporation of the filtrate recovered from (6) gave an oily residue. Trituration of the oil with light petrol (b.p. 40-60°) and concentration of the triturant yielded 2,2-diphenyl-4-(arylphenylmethylene)-tetrahydrofuran (7a & b).

Conversion of (6a) to (7a):

A mixture of (6a) (0.5 gm) and glacial acetic acid (10 ml) was heated on a steam bath for one hr. Pouring on ice cold water caused the precipitation of 0.3 gm of (7a), m.p. 158-163°C. Recrystallization from light petrol (60-80°) raised the m.p. to 168-9°C.

References

1. M.Huang, *J.Am.Chem.Soc.*, **68**, *2487 (1946).*
2. W.P.Campbell and M.D.Soffer, *J.Am.Chem.Soc.*, **64**, *417 (1942).*
3. G.Cignarella, G.Grella and M.M. Curzu, *Synthesis*, *825 (1980).*
4. F.G.Baddar, A.El-Habashi and A.K.Fateen, *J.Chem.Soc.*, *3342 (1965).*
5. A.K.Fateen and N.A.Shams, *J.Chem. U.A.R.*, **11(3)**, *301 (1968).*
6. T.Zerewitinoff, *Ber.*, **40**, *2023 (1907)*; *Ibid*, **41**, *2233 (1908).*
7. L.Tschugaeff, *Ber.*, **35**, *3912 (1902).*
8. J.F.Lees and R.T.Lobeck, *Analyst*, **88**, *782 (1963).*