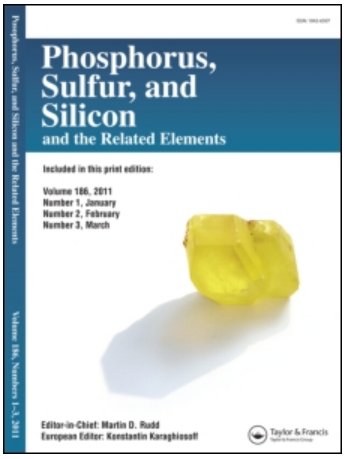

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CONVERSION OF 3-ARYL-5-PHENYL-2(3H)-FURANONES INTO 3(2H)-ISOTHIAZOLONE DERIVATIVES

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CONVERSION OF 3-ARYL-5-PHENYL-2(*3H*)-FURANONES INTO 3(*2H*)-ISOTHIAZOLONE DERIVATIVES

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Upon heating 3-aryl-5-phenyl-2(*3H*)-furanones (**1a-c**) with benzylamine at 100°C in the absence of solvents, ring opening occurred with the formation of the corresponding N-benzylamides (**3a-c**). When the latter compounds (**3a-c**) were allowed to react with thionyl chloride at room temperature, the corresponding isothiazolones (**4a-c**) were obtained.

Treatment of the isothiazolones (**4a-c**) with sodium hydroxide in benzene at room temperature affected debenzoylation to give the corresponding 2-benzyl-4-aryl-3(*2H*)-isothiazolones (**5a-c**).

Keywords: 2(*3H*)-Furanones; N-Benzylamides; Isomerization; 3(*2H*)-Isothiazolones; Debenzoylation

INTRODUCTION

There are several publications dealing with the use of 2(*3H*)-furanones as precursors of synthetically and biologically important heterocyclic compounds[1-10].

In this investigation, we wish to report the conversion of some 3-aryl-5-phenyl-2(*3H*)-furanones (**1a-c**) into the corresponding 3(*2H*)-isothiazalone derivatives.

RESULTS AND DISCUSSION

The starting materials (**1a-c**) were obtained by ring closure of α-aryl-β-benzoylpropionic acids using the procedure described previously

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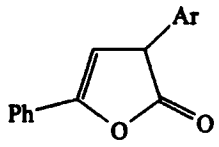
by one of us.[11] The infrared spectra of these furanones show absorption bands at 1760 cm^{-1} characteristic of a five-membered lactone ring and a strong stretching frequency at 1593 cm^{-1} attributable to a C=C double bond, (cf. Table I).



1a-c

a; Ar = C_6H_5
b; Ar = $C_6H_4OCH_3$(p)
c; Ar = C_6H_4Cl(p)

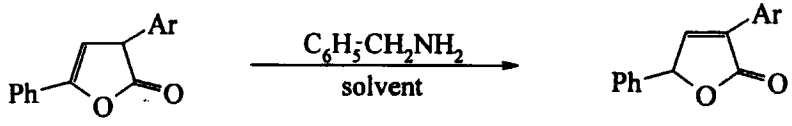
The ^{1}HNMR spectra of **1a-c** revealed doublet peaks in the range of δ 6.33 – 6.01 ppm characteristic of a saturated CH proton and other doublet peaks at 8.75–7.89 ppm attributable to an olefinic CH proton (cf. Table I). Furthermore, ^{13}C-NMR spectra exhibited signals at δ 150.36 and 160.55 ppm corresponding to carbonyl groups of both **1a** and **1b**, in addition to an absorption peak at 55.33 ppm referring to p-OCH_3 group situated in the phenyl moiety at position 3 in **1b**.

TABLE I Spectral data of 2(3*H*)-furanones (**1a-c**)

Compd.	*IR spectra* ν cm^{-1}		*^{1}HNMR spectra* δ *ppm*	*^{13}C-NMR spectra* δ *ppm*
	$\nu_{C=O}$	$\nu_{C=C}$		
1a	1761	1591	8.27–8.26 (d,1H, Olef. CH); 7.96–7.37 (m, 10H, ArH); 6.32–6.31 (d, 1H, Ar-CH)	150.36; 135.21; 129.41; 129.26; 129.09; 128.99; 128.65; 128.59; 127.29; 126.94; 126.84.;125.65; 81.21
1b	1759	1595	7.89–6.94 (m, 9H, Ar H); 7.51 (d, 1H, Olef. CH); 6.01 (d, 1H, Ar-CH); 3.85 (s, 3H, OCH_3)	160.55; 145.03, 137.07; 130.27; 129.19; 129.00; 128.56; 126.60; 121.80; 114.09; 81.48; 55.53.
1c	1760	1593	8.35 (d, 1H, Olef. CH); 8.01-7.35 (m, 9H, ArH); 6.33 (d, 1H, Ar-CH)	

Conversion of 2(3H)-furanones (1a-c) into 3(2H)-isothiazolones (4a-c)

It was of interest to the authors to try the conversion of 3-aryl-5-phenyl-2(3H)-furanones (**1a-c**) into the corresponding isothiazolones by allowing at first the furanones (**1a-c**) to react with benzylamine in ether under the same reported conditions[5] hoping to obtain the open-chain benzylamides which in turn could be used in the synthesis of the desired isothiazolones. Following the above methodology, the open-chain amides were not formed, but instead, the corresponding isomeric 2(5*H*)-furanones (**2a-c**) have been the only isolable products. On repeating the reaction using other solvents e.g. benzene, ethanol or ethyl acetate, only the latter isomeric products were again obtained even when the reaction was carried out at 0°C (Scheme 1). The formation of these products was confirmed by direct comparison of melting points and mixed melting points of authentic samples.[11]



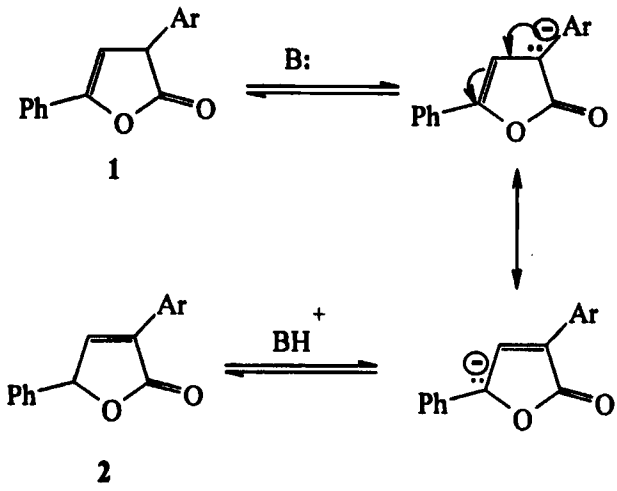
1 **2**

SCHEME 1 Solvent: Benzene, ethanol, ether or ethyl acetate

The foregoing result means that the process is merely an isomerization of these 2(*3H*)-furanones to the 2(*5H*)-isomers, a behaviour which was not observed[5] with the 2(*3H*)-furanones having no aryl groups at positions 3.

Now, it is proposed that the isomerization of **1** into **2** is controlled by either one of two factors. First, the stability of the carbanion intermediates and second the relative stabilities of these two ring systems. It is supposed that the former factor plays its role where the position-3 is either phenyl (**2a**)- or p-chlorophenyl (**2c**)-substituent which induces stabilization of the formed carbanion intermediate in a route leading to isomerization of **1a & c** to the more stable tautomers **2a & c** (Scheme 2).

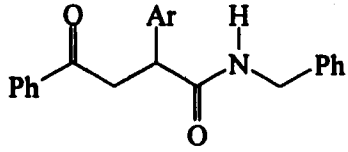
However, the second factor operates wherever the aryl group at position-3 is p-methoxyphenyl (**2b**)-substituent which cannot stabilize the carbanion intermediate and alternatively the thermodynamic stability governs



SCHEME 2

the isomerization of **1b** into **2b**, whose formation is in accordance with the reported studies on related furanone structures.[12,13]

In this point of view, it is evident that benzylamine was not capable of affecting ring opening of the 2(3H)-furanones (**1a-c**). Thus, the authors turned their attention to focus on another procedure involved heating of the furanones (**1**) with an excess of benzylamine (4 mol.) at 100°C, a methodology which successfully resulted in the formation of the corresponding open amides **3a-c**.



3a-c

a; Ar = C_6H_5
b; Ar = $C_6H_4OCH_3$(p)
c; Ar = C_6H_4Cl(p)

The structure of the amides **3a-c** was inferred from analytical data as well as the infrared spectra which showed two stretching frequencies at 1640 cm^{-1} and 1676 cm^{-1} characteristic of both the amide and ketonic carbonyl groups, in addition to another absorption band at 3304 cm^{-1} corresponding to the NH group. Moreover, the ^{1}HNMR spectrum of **3b** has shown a broad singlet at δ 5.95 ppm due to NH proton, two doublets of doublets at δ values 4.39 ppm and 4.14–4.02 ppm attributable to the two methylene protons linked to both benzoyl and phenyl groups. In addition, the two non-equivalent CH_2 protons adjacent to CH-Ar proton result in splitting of its signal to a doublet of doublets at δ 3.23–3.15 ppm (cf. Table II).

TABLE II

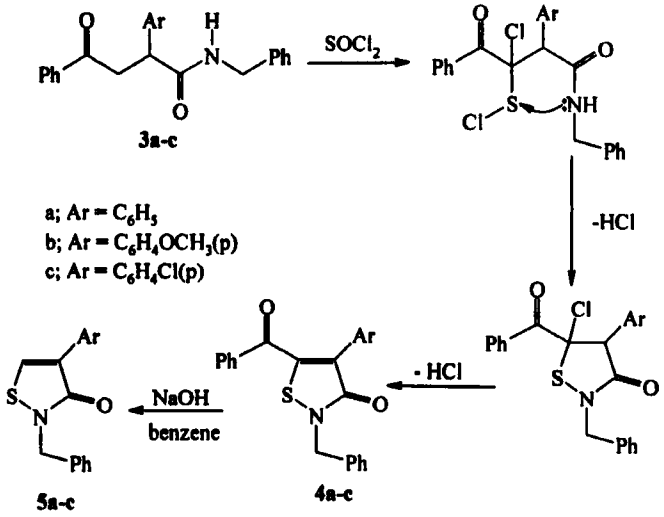
Comp	*IR spectra* ν cm^{-1}			^{1}*HNMR spectra* δ *ppm*
	$\nu_{C=O}$	$\nu_{C=O}$	ν_{NH}	
3a	1643	1670	3304	–
3b	1640	1676	3299	8.00–6.85 (m, 14H, ArH); 5.95 (s br, 1H, NH); 4.43–4.39 (dd, 2H, CH_2); 4.14 4.02 (dd, 2H, CH_2); 3.79 (s, 3H, OCH_3); 3.23–3.15 (dd, 1H, CH)
3c	1640	1676	3304	–
4c	1641	1691		8.71–7.21 (m, 14H, ArH); 5.40 (s, 2H, CH_2)
5c	1615			8.17 (s, 1H, Olef. CH); 7.89–7.36 (m, 9H, ArH); 5.02 (s, 2H, CH_2)

Having accomplished the preparation of these open-amides (**3a-c**), the authors focused their attention to the synthesis of the desired isothiazolones by treating **3a-c** with thionyl chloride at room temperature to afford the corresponding isothiazolones **4a-c**.

The structure assignment of these products was substantiated from (i) Analytical data. (ii) Their infrared spectra showing a cyclic amide $\nu_{C=O}$ group at 1634 cm^{-1} and a ketonic $\nu_{C=O}$ at 1691 cm^{-1}. (iii) Furthermore, the ^{1}HNMR spectrum of **4c** revealed a singlet peak at 5.08 ppm with integration of two protons attributable to benzyl CH_2-group, in addition to multiplet peaks in the region of δ 7.66–7.12 ppm with integration of fourteen protons corresponding to aromatic ones (cf. Table II).

The proposed structure (**4c**) was further supported by its mass spectrum revealing the fragmentation pattern m/e 405 (20.4%) as a parent peak, m/e 266 (20.4%) and 91 (100%) referring to the existence of fragments $M^{\ddagger}\bullet$-$PhCH_2$-N=S , H_2 and a tropylium ion.

Based on previous investigations[14] on the reactions of similar amides with thionyl chloride, the formation of isothiazolones (**4**) may be represented by the following scheme 3:



SCHEME 3

Upon treatment of the isothiazolones (4) with sodium hydroxide in benzene at room temperature, debenzoylation occurred with the formation of 2-benzyl-4-aryl-3(2H)-isothiazolones (5).

The infrared spectra of compounds **5** showed an absorption band at 1613 cm^{-1} characteristic of the carbonyl group of a cyclic amide while that of the ketonic group of **4** has disappeared. Comparing the ^{1}HNMR spectrum of **4c** with that of its corresponding isothiazolone **5c** revealed that the integration of aromatic protons in **5c** has been reduced to nine protons confirming the elimination of the benzoyl moiety. Furthermore, the mass spectrum of **5c** has shown the fragments m/e 301 (10.3%) and 91 (100%) corresponding to both the parent peak and tropylium ion.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out at the M-H-W laboratories, University of Minho, Braga, Portugal; and at the

microanalytical unit, Cairo University. The infrared spectra were performed on an Perkin Elmer 1600 FT.IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian plus 300 (300 MHz) and on a Varian Gemini (200 MHz) instrument, the ^{13}C-NMR spectra (with DEPT 135) on a Bruker WP80-XL 300 instrument. The mass spectra were determined using HP Model MS-5988 at electron energy 70 ev.

Preparation of 3-aryl-5-phenyl-2(3H)-furanones (1a-c)

A mixture of α-aryl-β-benzoylpropionic acid[15] (1 mol) and acetic anhydride (3 mol) was heated under reflux for 20 min. The reaction mixture was then cooled, poured onto ice, filtered off and the product was recrystallized from the suitable solvent to give **1a-c** as colorless crystals (cf. Table III).

TABLE III

Comp. No.	*Ar*	*M.p. °C Colour*	*Yield %*	*Solvent of Cryst.*	*Mol. Formula (M. Wt.)*	*Analysis*	
						C%	*H%*
1a	C_6H_5	108–109 colorless	59	Petroleum/ toluene 80–100	$C_{16}H_{12}O_2$ (236)	81.3 81.4	5.0 5.0
1b	$C_6H_4OCH_3$(p)	104–105 colorless	60.5	Petroleum/ toluene 80–100	$C_{17}H_{14}O_3$ (266)	76.6 76.5	5.2 5.3
1c	C_6H_4Cl(p)	126–128 colorless	60	Petroleum/ toluene 80–100	$C_{16}H_{11}O_2Cl$ (270.5)	70.9 70.5	4.0 4.2
2a	C_6H_5	286–288 colorless	71	–	$C_{16}H_{12}O_2$ (236)	81.3 80.8	5.0 5.3
2b	$C_6H_4OCH_3$(p)	300–301 colorless	70.5	–	$C_{17}H_{14}O_3$ (265)	76.6 76.2	5.2 5.3
2c	C_6H_4Cl(p)	291–293 colorless	73	–	$C_{16}H_{11}O_2Cl$ (270.5)	70.9 70.8	4.0 4.1

Preparation of authentic samples of 3-aryl-5-phenyl-2(5H)-furanones (2a-c)

A mixture of α-aryl-β-benzoylpropionic acids (1.0 mol), acetic anhydride (2 mol), acetic acid (2 mol) and few drops of conc. sulfuric acid was heated under reflux for 1h. The reaction mixture was then cooled, poured onto ice, filtered off and washed with ethanol to give colorless crystals of **2a-c** (cf. Table III).

Reactions of 3-aryl-5-phenyl-2(3H)-furanones (1) with benzylamine in different solvents

To a suspension of the furanone (**1**) (1.0 mol) in ethanol (20 ml), benzylamine (1.3 mol) was added. The reaction mixture was stirred at 100°C for one h. The product obtained was filtered off, washed with alcohol (cf. Table III).

The product obtained in each case was shown by direct comparison (m.p. & m.m.p.) to be the corresponding 2(5H)-furanone (**2**). When the reaction was repeated at room temperature, the same product (**2**) was obtained.

Also, the reaction was conducted at room temperature and then refluxed in a variety of solvents (diethyl ether, benzene, ethyl alcohol or ethyl acetate), and the product was shown in each case to be the 2(*5H*)-furanone.

Reactions of 3-aryl-5-phenyl-2(3H)-furanones (1) with benzylamine in the absence of solvent

A mixture of the 2(*3H*)-furanones **1** (1 mol) and benzylamine (4 mol) was heated at 100°C for 45 min. The reaction mixture was then cooled, poured on ice. The product obtained was filtered off and recrystallized from the suitable solvent (cf. Table IV).

Reaction of N-benzyl-α-aryl-β-benzoyl propionamides 3 with thionyl chloride. Formation of the isothiazolones 4

A mixture of **3** (0.001 mol) and thionyl chloride (20 ml) was stirred at 25°C for 24 h. The solution was then concentrated under vacuum. The solid obtained was recrystallized from the suitable solvent (cf. Table IV).

Debenzoylation of 4 into 2-benzyl-4-aryl-3(2H)-isothiazolones 5

A mixture of **4** (1.0 g) and solid NaOH (0.1 g) in 20 ml benzene was stirred at 25°C for 1h. When a fading of the initial yellowish colour was observed, the benzene layer was separated and concentrated under vacuum to give a solid residue which was recrystallized from the suitable solvent (cf. Table IV).

TABLE IV

Comp. No.	Ar	M.p. °C Colour	Yield %	Solvent of Cryst.	Mol. Formula (M. Wt.)	Analysis		
						C%	H%	N%
3a	C_6H_5	101–102 colorless	78	Petroleum /benzene 60–80	$C_{23}H_{21}O_2N$ (343)	80.40 80.22	6.10 6.30	4.10 4.40
3b	$C_6H_4OCH_3$(p)	115–117 colorless	71	Petroleum /benzene 60–80	$C_{24}H_{23}O_3N$ (373)	77.20 77.10	6.10 6.20	3.70 3.90
3c	C_6H_4Cl(p)	94–96 colorless	73	Petroleum /benzene 60–80	$C_{23}H_{20}O_2NCl$ (377.5)	73.1 72.8	5.2 5.1	3.7 3.4
4a	C_6H_5	48–50 Yellow	69	Petroleum 60–80	$C_{23}H_{17}O_2NS$ (371)	74.3 74.6	4.5 4.4	3.7 3.5
4b	$C_6H_4OCH_3$(p)	44–46 yellow	68	Petroleum 60–80	$C_{24}H_{19}O_3NS$ (401)	71.8 71.6	4.7 4.8	3.4 3.6
4c	C_6H_4Cl(p)	115–116 yellow	62	Ethanol	$C_{23}H_{16}O_2NSCl$ (405.5)	68.0 67.9	3.9 4.2	3.4 3.4
5a	C_6H_5	89–90 colorless	79	Petroleum /benzene 60–80	$C_{16}H_{13}ONS$ (267)	71.9 72.1	4.8 5.2	5.2 5.3
5b	$C_6H_4OCH_3$(p)	123–124 colorless	83	Petroleum /benzene 60–80	$C_{17}H_{15}O_2NS$ (297)	68.6 68.2	5.0 4.8	4.7 5.0
5c	C_6H_4Cl(p)	160–161 colorless	81	Petroleum /benzene 60–80	$C_{16}H_{12}ONSCl$ (301.5)	63.6 63.5	3.9 4.0	4.6 4.4

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