BEHAVIOR OF 2(3*H*)- AND 2(5*H*)-FURANONES HAVING NO EXOCYCLIC DOUBLE BOND TOWARDS SOME NITROGEN NUCLEOPHILES

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Abstract

The behavior of 3-aryl-5-phenyl-2(3*H*)-furanones **1** and their 2(5*H*)-isomers **2** towards aniline, benzylamine, piperidine and ammonia was studied in an attempt to show the effect of position of the double bond on the reaction mode. It was found that either isomerization or amination occurred depending on the reaction conditions.

Introduction

2(3*H*)- in addition 2(5*H*)-furanones represent two important classes of heterocyclic compounds. The former is the precursors of a wide variety of other heterocycles.[1] The synthesis and properties of 2(5*H*)-furanones have recently attracted much attention owing to the unique carbon skeleton of this class, which is widely spread in a variety of biologically active natural products.[2,3,4]

Results and Discussion

In our earlier communications[5] we have discussed the conversion of 3-aryl-5-phenyl-2(3*H*)-furanones **1a-c** into 3(2*H*)-isothiazolones. We now report the successful studies of the reactions of 2(3*H*)-furanones **1a-c** and their 2(5*H*)-isomers **2a-c** with some primary and secondary amines such as ammonia, aniline, piperidine, and benzylamine under different conditions. 3-Aryl-5-phenyl-2(3*H*)-furanones **1a-c** and **2a-c** were obtained by ring closure of α–aryl-β-benzoylpropionic acids using the procedure we described previously.[6]

The reaction of 2(3*H*)-furanones **1a-c** with primary and secondary amines such as ammonia, aniline, benzylamine and piperidine was found to depend on the reaction conditions. Thus, when the reaction was conducted in the presence of polar and nonpolar solvents such as ethanol, diethyl ether and/or benzene, at different temperatures 0 $^{\circ}$C,

25°C and boiling point of solvents, isomerization occurred to give the corresponding 2(5*H*)-furanones **2a-c**. But, when the reaction was carried out in neat (without solvent), at the boiling point of amines, the corresponding 2(3*H*)-pyrrolones **3a-f** were obtained in 79-91% yields as shown in Table 2. Surprisingly, the same 2(3*H*)-pyrrolones **3d-f** was obtained from the reaction of 2(5*H*)-furanones **2a-c** with aniline or benzylamine in neat at boiling point of each amine as shown in Scheme 1.
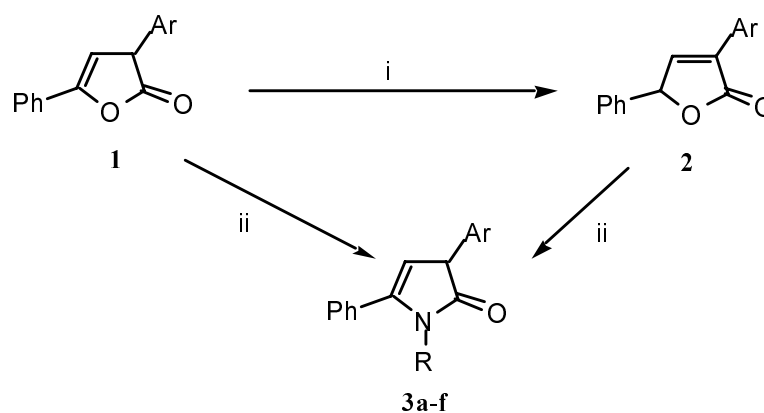

Ar = C$_6$H$_5$-, C$_6$H$_4$OCH$_3$(*p*-), C$_6$H$_4$Cl(*p*-); R= C$_6$H$_5$-, and C$_6$H$_4$CH

Reagent and condition   i) Ammonia, aniline, benzylamine, pepridine/benzene, ethanol and ether at 0 $^{\circ}$C, 25 $^{\circ}$C and at b.p. of solvents. ii) Aniline and/or benzylamine in neat at b.p.
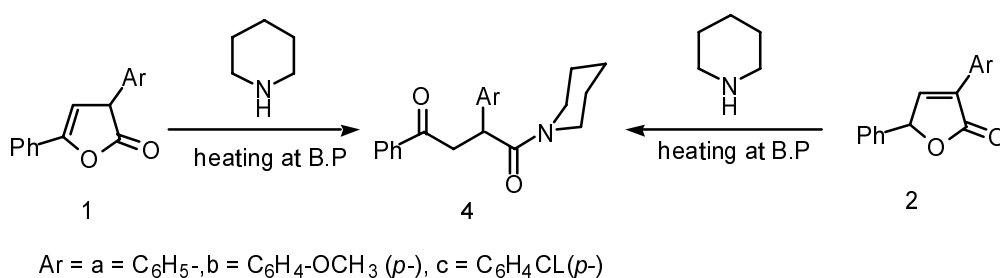
Scheme 1

The ^{1}H NMR spectrum of the 2(3*H*)-pyrrolones **3d-f** exhibits two unexpected doublet signals centered at δ 3.6 and δ 5.2 for the same larger coupling constant (*J* = 15.2-15.6 Hz) are associated with the two-methylene (-N-C$\underline{H}_2$-) protons. The split of the two-proton of C$\underline{H}_2$ into different resonance at δ 3.6 and δ 5.2 caused by electrical quadrupole moment effect on nitrogen and adjacent carbonyl.[7] It was possible to identify three spots characteristic of 2(5*H*)-furanone **2a-c**, 2(3*H*)-furanone **1a-c** and 2(3*H*)-pyrrolones **3a-f** were realized by performing TLC on an aliquot taken from the reaction mixture after 5 minutes. The isomerisation of 2(5*H*)-furanones **2a-c** into 2(3*H*)-isomers **1a-c** at boiling point of amines maybe represented by the following mechanistic pathway as shown in Scheme 2.
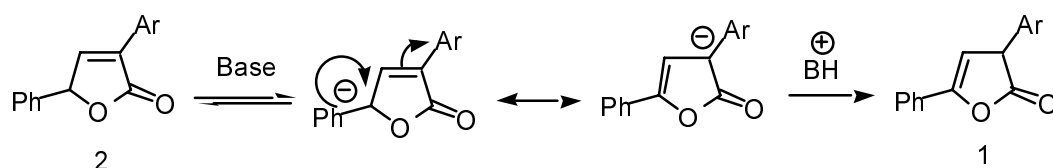
Scheme 2

The reaction of 2(3*H*)-furanones **1a-c** with piperidine was also studied at boiling point of piperidine in neat over 1-2 hours to give the α-aryl-β-benzoyl-piperidyl propionamides **4a-c** in 79-89% yields as illustrated in Table 2. The latter products **4a-c** were also obtained from the reaction of 2(5*H*)-furanones **2a-c** with piperidine at the same reaction condition. Piperidine firstly affects isomerisation of the 2(5*H*)-furanones into 2(3*H*)-isomers **1a-c**, which then undergo ring opening to give the amides **4a-c**, as illustrated as shown in Scheme 3.

Ar = a = C_6H_5-, b = C_6H_4-OCH_3 (*p*-), c = C_6H_4CL (*p*-)

Scheme 3

The ^{1}H NMR spectrum of α-aryl-β-benzoylpiperidyl propionamides **4a-c** exhibits two doublets of a doublet centered at δ 2.99- 3.05 and δ 3.89-4.10, attributed to the methylene protons (-C$\underline{H}_2$-). The methylene protons split the methine proton (-C$\underline{H}$-C_6H_5) absorption into a doublet of a doublet at 4.47-4.56 with the areas in the ratio of 1:2. This due to the highr order spectrum effect (ABX tending to an AMX type).

Experimental

^{1}H NMR spectra were recorded on Varian Plus 300 (300 MHz) or Bruker XL 300 (300 MHz) and on a Varian Gemini (200 MHz) instruments, the ^{13}C NMR spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument. Infrared spectra listed as recorded 'neat' refer to a thin film of material on NaCl disks, and were taken on a Perkin Elmer 1600 FT-IR spectrometer. Melting points were measured on an electrothermal digital melting point apparatus and are uncorrected. The R$_f$ values reported for TLC analyses

were determined on Macherey-Nagel 0.25 mm layer fluorescent UV_{254} plates with the indicated solvent system. M-H-W Laboratories (Phoenix, AZ) at University of Minho, Braga, Portugal and microanalysis unit at University of Cairo, Egypt, performed elemental analyses.

3-Aryl-5-phenyl-2(3*H*)-furanones (1a-c) were prepared following the literature[4] reports and our recent communications.[5] The structures of the products were confirmed by ^{1}H and ^{13}C NMR spectrum and the spectral data is listed in Tables 1, 2 and 3.

Table 1. Infrared (IR) and ^{1}H NMR (300 MHz) spectral data for compounds [(**1a-c**), (**2a-c**), (**3a-f**) and (**4a-c**)].

Cpd No.	Alkyl group (R)	Aryl group (Ar)	$(IR)\upsilon_{max}$ *(Nujol)/cm^{-1}* $\upsilon_{C=O}$ $\upsilon_{C=C}$	^1H *NMR (300 MHz, DMSO); δH*
1a		C_6H_5	1761(s), 1591(s)	δ = 6.32 (d, 1H, *J* = 2.1 Hz), 7.44 (m, 8H), 7.93 (d, 1H, *J* = 1.8 Hz), 7.95 (d, 1H, *J* = 1.8 Hz), 8.27 (d, 1H, *J* = 2.1 Hz) ppm.
1b		$C_6H_5OCH_3(p)$	1759(s), 1595(s)	δ = 3.85 (s, 3H, Ar-OC<u>H</u>$_3$), 6.01 (d, 1H, *J* = 2.1 Hz), 6.96 (d, 2H, *J* = 9 Hz, C$_6$<u>H</u>$_4$-OCH$_3$), 7.42-7.27 (m, 5H, -C$_6$<u>H</u>$_5$), 7.51 (d, 1H, *J* = 2.1 Hz, C$_6$<u>H</u>$_4$-OCH$_3$), 7.89 (d, 2H, *J* = 9 Hz, C$_6$<u>H</u>$_4$-OCH$_3$) ppm.
1c		-C$_6$H$_4$Cl	1760(s), 1593(s)	δ = 6.33 (d, 1H, *J* = 1.8 Hz), 7.43-7.35 (m, 5H, -C$_6$<u>H</u>$_5$), 7.54 (d, 2H, *J* = 9 Hz, C$_6$<u>H</u>$_4$-Cl), 7.99 (d, 2H, *J* = 9 Hz, C$_6$<u>H</u>$_4$-Cl), 8.35 (d, 1H, *J* = 1.8 Hz) ppm.
2a		C_6H_5	1749(s), 1594(s)	δ = 7.32-7.45 (m, 10H), 7.7 (d, 1H, *J* = 2.2 Hz), 8.97 (d, 1H, *J* = 2.2 Hz) ppm.
2b		$C_6H_4OCH_3(p)$	1748(s), 1599 (s)	δ = 3.8 (s, 3H, Ar-OC<u>H</u>$_3$ 7.3 (d, 2H, *J* = 8.7 Hz, C$_6$<u>H</u>$_4$-OCH$_3$), 7.4-7.6 (m, 5H, -C$_6$<u>H</u>$_5$), 7.89 (d, 2H, *J* = 8.7 Hz, C$_6$<u>H</u>$_4$-OCH$_3$), 8.5 (d, 1H, *J* = 2.2 Hz), 8.9 (d, 1H, *J* = 2.2 Hz) ppm.
2c		-C$_6$H$_4$Cl	1751(s), 1595(s)	δ = 7.3-7.5 (m, 5H, -C$_6$<u>H</u>$_5$), 7.6 (d, 2H, *J* = 8.9 Hz, C$_6$<u>H</u>$_4$-Cl), 8.1 (d, 2H, *J* = 9 Hz, C$_6$<u>H</u>$_4$-Cl), 8.4 (d, 1H, *J* = 2.1 Hz), 8.9 (d, 1H, *J* = 2.1 Hz) ppm.
3a	- C$_6$H$_5$	-C$_6$H$_5$	1664(s), 1596(s)	δ = 6.2 (d, 1H, *J* = 1.8 Hz, C<u>H</u>-Ar), 7.08-8.02 (m, 15H, 3C$_6$<u>H</u>$_5$-), 7.75 (d, 1H, *J* = 1.8 Hz, C=C<u>H</u>) ppm.

Table 1 Continued.

3b	- C_6H_5	$C_6H_4OCH_3(p)$	1681(s),	1595 (s)	δ = 3.77 (s, 3H, -OC$\underline{H}_3$), 5.1 (d, 1H, J = 2.1 Hz, -C$\underline{H}$-), 6.98 (d, 2H, J = 9 Hz, C$_6\underline{H}_4$OCH$_3$), 7.1-7.38 (m, 10H, 2C$_6\underline{H}_5$-), 7.47 (d, 1H, J = 2.1 Hz, C=C$\underline{H}$-), 8.00 (d, 2H, J = 9 Hz, C$_6\underline{H}_4$-OCH$_3$) ppm.
3c	- C_6H_5	-C_6H_4Cl (p-)	1672(s),	1594 (s)	δ = 5.7 (d, 1H, J = 2.4 Hz, C=C$\underline{H}$), 7.1-7.33 (m, 10H, 2C$_6\underline{H}_5$-), 7.41 (d, 2H, J = 8.6 Hz, C$_6\underline{H}_4$Cl), 7.58 (dd, 1H, J = 2.4 and 0.3 Hz, -C$\underline{H}$-Ar), 7.93 (d, 2H, J = 8.6 Hz, C$_6\underline{H}_4$Cl) ppm.
3d	$C_6H_4CH_2$-	- C_6H_5	1681(s),	1596 (s)	δ = 3.77 (d, 1H, J = 15.6 Hz, -NC$\underline{H}_2$-), 4.13 (d, 1H, J = 15.6 Hz, -NC$\underline{H}_2$-), 5.1 (d, 1H, J = 2.4 Hz, -C$\underline{H}$-C$_6$H$_5$), 7.1-7.41 (m, 13H), 7.6 (d, 1H, J = 2.4 Hz), 8.01 (d, 1H, J = 1.5 Hz), 8.04 (d, 1H, J = 1.5 Hz) ppm.
3e	$C_6H_4CH_2$-	$C_6H_4OCH_3(p)$	1681(s),	1490 (s)	δ = 3.82 (s, 3H, -OC$\underline{H}_3$), 3.7 (d, 1H, J = 15.2 Hz, -NC$\underline{H}_2$-), 4.86 (d, 1H, J = 2.0 Hz, -C$\underline{H}$-C$_6$H$_5$), 5.29 (d, 1H, J = 15.2 Hz, -N-C$\underline{H}_2$-), 6.90 (d, 2H, J = 8.6 Hz, C$_6\underline{H}_4$OCH$_3$), 7.03 (d, 1H, J = 2.0 Hz, C=C$\underline{H}$-), 7.1-7.37 (m, 10H, 2 C$_6\underline{H}_5$), 7.97 (d, 2H, J = 8.6 Hz, C$_6\underline{H}_4$-OCH$_3$) ppm.
3f	$C_6H_4CH_2$-	-C_6H_4Cl (p-)	1669(s),	1609(s)	δ = 3.77 (d, 1H, J = 15.3 Hz, -NC$\underline{H}_2$-), 4.98 (d, 1H, J = 15.3 Hz, -NC$\underline{H}_2$-), 5.15 (d, 1H, J = 2.1 Hz, -C$\underline{H}$-C$_6$H$_5$), 7.08-7.41 (m, 10H, 2 C$_6\underline{H}_5$), 7.49 (d, 2H, J = 8.4 Hz, C$_6\underline{H}_4$-Cl), 7.69 (d, 1H, J = 2.1 Hz, C=C$\underline{H}$-), 8.09 (d, 2H, J = 8.4 Hz, C$_6\underline{H}_4$-Cl) ppm.
4a		- C_6H_5	1631(s),	1686(s)	δ = 0.85-1.44 (m, 6H, pip.), 3.05 (dd, 1H, J = 3.3 and 17.7 Hz, -C$\underline{H}_2$-), 3.25-3.50 (m, 4H, pip.), 3.95 (dd, 1H, J = 10.8 and 17.7 Hz, -C$\underline{H}_2$-), 4.51 (dd, 1H, J = 3.3 and 10.8 Hz, -C$\underline{H}$-C$_6$H$_5$), 7.24-7.98 (m, 10H, 2 C$_6$H$_5$) ppm.
4b		$C_6H_4OCH_3(p)$	1629(s),	1680(s)	δ = 1.42-1.47 (m, 4H, pip.), 2.99 (dd, 1H, J = 3.3 and 17.7 Hz, -C$\underline{H}_2$-), 3.15-3.47 (m, 6H, pip.), 3.72 (s, 3H, -OCH$_3$), 3.89 (dd, 1H, J = 10.5 and 17.7 Hz, -C$\underline{H}_2$-), 4.47 (dd, 1H, J = 3.3 and 10.5 Hz, -C$\underline{H}$-C$_6$H$_5$), 6.90 (d, 2H, J = 8.7 Hz, -C$_6\underline{H}_4$-OCH$_3$) 7.26 (d, 2H, J = 8.7 Hz, -C$_6\underline{H}_4$-OCH$_3$), 7.46-7.63 (m, 3H, -C$_6\underline{H}_5$), 7.95 (d, 2H, J = 1.2 and 8.4 Hz, -C$_6\underline{H}_5$) ppm.
4c		-C_6H_4Cl (p-)	1634(s),	1683(s)	δ = 1.53 (m, 6H, pip.), 3.04 (dd, 1H, J = 4.0 and 17.6 Hz, -C$\underline{H}_2$-), 3.4-3.6 (m, 4H, pip.), 4.1 (dd, 1H, J = 9.6 and 17.6 Hz, -C$\underline{H}_2$-), 4.56 (dd, 1H, J = 4.0 and 9.6 Hz, -C$\underline{H}$-C$_6$H$_5$), 7.44 (d, 2H, J = 8.4 Hz, -C$_6\underline{H}_4$Cl) 7.24-7.7.55 (m, 3H, -C$_6\underline{H}_5$), 7.95 (d, 2H, J = 8.4 Hz, -C$_6\underline{H}_4$Cl) ppm.

3-Aryl-5-phenyl-2(5H)-furanones (2a-c); A mixture of α-aryl-β-benzoylpropionic acids (1 mole), acetic anhydride (2 mole), acetic acid (2 mole) and few drops of concentrated sulfuric acid were heated under reflux for 1 hour. The reaction mixture was cooled on ice, filtered off and finally washed with ethanol to produce products in 75-82% yields, as illustrated in Table 2.

3-Aryl-1,5-diphenyl-2(3H)-pyrrolones (3a-c): 3-Aryl-5-phenyl-2(3H)-furanones **1a-c** (1.0 mole) and aniline (1.3 equivalent) were mixed in neat. A mixture was stirred and heated at boiling point of aniline for 1-2 hours and then cooled to precipitate. The precipitate was collected by filtration and recrystallized from the suitable solvent to yield pyrrolones **3a-c** in 81-87% as shown in Table 2. These compounds were obtained also by starting from 3-aryl-5-phenyl-2(5H)-furanones **2a-c** instead of 3-aryl-5-phenyl-2(3H)-furanones **1a-c**, following the same procedure. The 3-aryl-1,5-diphenyl-2(3H)-pyrrolones **3a-c** showed by direct comparison of m.p., and mixed m.p., TLC, and some spectral data to be identical with the authentic sample in all aspects.

3-Aryl-1-benzyl-5-phenyl-2(3H)-pyrrolones (3d-f); 3-Aryl-5-phenyl-2(3H)-furanones **1a-c** (1.0 mole) and benzylamine (4 equivalent) were mixed in neat. Following the same method described above for preparing compound **3a-c**. The white precipitate was collected by filtration and recrystallized from the suitable solvent to yield 1-benzylpyrrolones **3d-f** in 79-91%, as illustrated in Table 2. These compounds were obtained also by reaction of 3-aryl-5-phenyl-2(5H)-furanones **2a-c** with benzylamine following the same procedure described above. 3-Aryl-1-benzyl-5-phenyl-2(3H)-pyrrolones **3d-f** showed by direct comparison of m.p., and mixed m.p., TLC, and some spectral data to be identical with the authentic sample in all aspects.

α-Aryl-β-benzoyl-piperidyl propionamides (4a-c): A suspension of 3-aryl-5-phenyl-2(3H)-furanones **1a-c** (1.0 mole) with piperidine (1.5 equivalent) in neat. The suspension mixture was stirred and heated at boiling point of piperidine for 2 hours. The reaction mixture was then cooled and poured on 5.0 g of ice with 1.0 *N* HCl (25 mL). The

precipitate was collected by filtration and recrystallized from the suitable solvent to yield propionamides **4a-c** in 79-89%, as illustrated in Table 2. These compounds were obtained also by reaction of 3-aryl-5-phenyl-2(5*H*)-furanones **2a-c**, following the same method described above. The α-aryl-β-benzoyl-piperidyl propionamides **4a-c** showed by direct comparison of m.p., and mixed m.p., TLC and some spectral data to be identical with the authentic sample in all aspects.

Table 2. Yields and physical data for compounds [(**1a-c**), (**2a-c**), (**3a-f**) and (**4a-c**)].

Cpd No.	Alkyl group	Aryl group	m.p °C	Yield	Recryst. Solv.	MF	Analysis [Calcd/found] C	H	N
1a		C_6H_5	110-112	45 %	Petrol.	$C_{16}H_{12}O_2$	81.34/81.38	5.11/5.03	
1b		$C_6H_4OCH_3$	133-135	32 %	ether/	$C_{17}H_{14}O_3$	76.68/76.55	5.29/5.35	
1c		C_6H_5Cl	125-127	31 %	toluene	$C_{16}H_{11}ClO_2$	70.99/70.98	4.09/4.23	
2a		C_6H_5	156-158	75 %		$C_{16}H_{12}O_2$	81.34/80.82	5.11/5.30	
2b		$C_6H_4OCH_3$	175-177	82 %		$C_{17}H_{14}O_3$	76.68/76.69	5.29/5.35	
2c		C_6H_5Cl	168-170	82 %		$C_{16}H_{11}ClO_2$	70.99/70.85	4.09/4.11	
3a	C_6H_5	C_6H_5	201-203	81%	EtOH	$C_{22}H_{17}NO$	84.86/84.82	5.50/6.24	4.49/3.91
3b	C_6H_5	$C_6H_4OCH_3$	136-138	87 %		$C_{23}H_{19}NO_2$	80.91/80.65	5.60/6.19	4.10/3.89
3c	C_6H_5	C_6H_5Cl	184-186	86 %		$C_{22}H_{16}ClNO$	76.40/76.46	4.66/4.51	4.05/4.40
3d	$C_6H_5CH_2-$	C_6H_5	147-148	79 %		$C_{23}H_{19}NO$	84.89/84.86	5.88/5.81	4.30/4.44
3e	$C_6H_5CH_2-$	$C_6H_4OCH_3$	157-158	81%		$C_{24}H_{21}NO_2$	81.10/81.13	5.95/5.98	3.94/4.01
3f	$C_6H_5CH_2-$	C_6H_4Cl	120-121	91%		$C_{23}H_{18}ClNO$	76.76/76.56	5.04/5.03	3.89/3.49
4a		C_6H_5	115-117	89%	Petrol. /	$C_{21}H_{23}NO_2$	78.47/78.67	7.21/7.34	4.36/4.32
4b		$C_6H_4OCH_3$	120-122	88%	EtOH	$C_{22}H_{25}NO_3$	75.18/75.25	7.16/7.13	3.98/4.10
4c		C_6H_4Cl	199-201	79%		$C_{21}H_{22}ClNO_2$	70.87/70.81	6.23/6.12	3.93/3.59

Table 3; ^{13}C Chemical shifts for **3-Aryl-5-phenyl-2(3*H*)-furanones (1a-b)**.
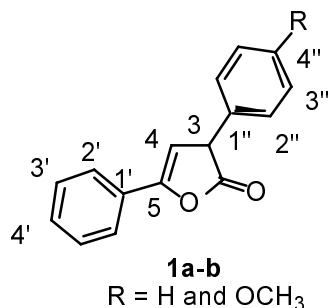
Cpd. No.	C-3	C–4	Ci–5	Ci-1'	C-2'	C-3'	C-4'
1a	81.2	125.2	135.2	129.4	126.9	128.6	128.6
1b	81.5	114.0	145.0	135.1	121.8	126.6	128.6

Cpd. No.	C=O	R	C-1''	C-2''	C-3''	C-4''
1a	150.4	---	129.3	126.9	129.1	129.0
1b	160.5	55	130.2	129.1	129.2	134.2

Table 3; ^{13}C Chemical shifts for ***N*^{1}-benzyl-3,5-diphenyl-2(3*H*)-pyrrolone (3d).**

3d
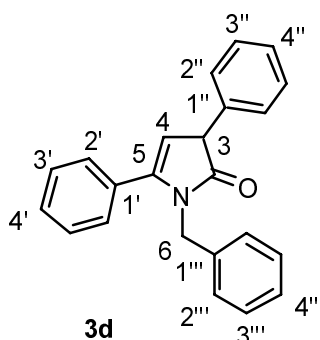
C-3	C–4	C–5	C-6	C=O	Ci-1'	C-2'	C-3'	C-4'	Ci-1''
90.5	126.6	148.1	43.1	166.6	137.7	126.2	128.9	128.3	136.5

C-2''	C-3''	C-4''	Ci-1'''	C-2'''	C-3'''	C-4'''
127.8	128.5	129.1	157.9	127.9	128.7	128.8

Conclusions

The reactions of 2(3*H*)-furanones **1a-c** with amines in solvent was conducted at 0 °C, 25 °C and also at refluxing temperature. It was not possible to obtain any amides or pyrrolones but instead isomerization occurred to give the corresponding 2(5*H*)-isomers **2a-c**, which was found to be unaffected under these conditions. It was realized that the amination occurred only in neat at boiling point of each amine.

References

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Povzetek
Raziskali smo reaktivnost 3-aril-5-fenil-2(3*H*)-furanonov **1** in 2(5*H*)-izomerov **2** z anilinom, benzilaminom, piperidinom in amoniakom z namenom, da bi ugotovili vpliv reakcijskih pogojev na strukturio produktov. Ugotovili smo, da v odvisnosti od reakcijksih pogojev poteče izomerizacija ali aminiranje.