

Novel 4-Aroyl-3-alkoxy-2(5H)-furanones as Precursors for the Preparation of Furo[3,4-b][1,4]-diazepine Ring System[‡]

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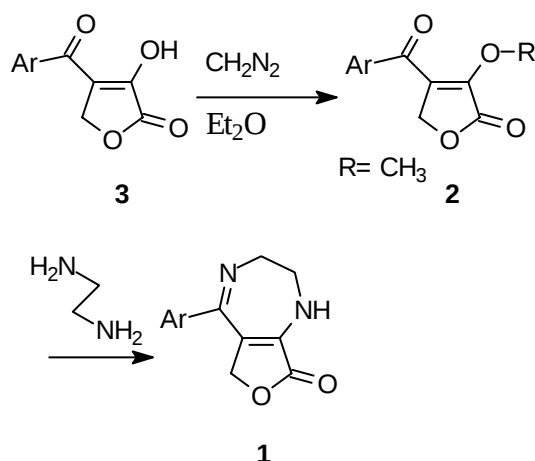
Abstract: A general synthesis of tetronic acid derivatives, namely 4-aroyl-3-alkoxy-2(5H)-furanones, is achieved *via* the treatment of an anhydrous dimethylformamide (DMF) solution of 4-aroyl-3-hydroxy-2(5H)-furanones with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base at -10-0°C, followed by the addition of alkyl iodide. Their structural assignments are based on spectroscopic data and confirmed by X-ray crystallography. These furanones were used as starting materials for the preparation of furodiazepines.

Keywords: 4-Aroyl-3-alkoxy-2(5H)-furanones, 7-aryl-4,5-dihydro-2-oxo-3H,8H-furo-[3,4-b][1,4]diazepines, X-ray structures.

Introduction

Benzodiazepines are an important class of psychotherapeutic compounds. In recent years some examples of heterocyclic rings fused to the seven member diazepine ring system have been synthesized which exhibit psychotropic activities [2-7]. Recently, we have reported on a facile synthesis of novel furodiazepines, namely 7-aryl-4,5-dihydro-2-oxo-3H,8H-furo[3,4-b][1,4]diazepines (**1**) using 4-aroyle-3-methoxy-2(5H)-furanones (**2**) [1,8]. This procedure was however limited since many 4-aroyle-3-hydroxy-2(5H)-furanones **3** [9,10] are insoluble in ether, the solvent needed for the transformation of **3** into the 3-methoxy analogs **2** ($R = \text{CH}_3$) (Scheme 1).

Scheme 1.



Results and Discussion

In this work we report the results based on our efforts to develop an extended, general O-alkylation procedure for compounds of type **3**. We found that treatment of a solution of **3** in anhydrous dimethylformamide (DMF) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base at $-10-0^\circ\text{C}$, followed by the addition of a primary alkyl iodide afforded type **2** compounds in moderate yields (Scheme 2). Our results are summarized in Table 1

Scheme 2

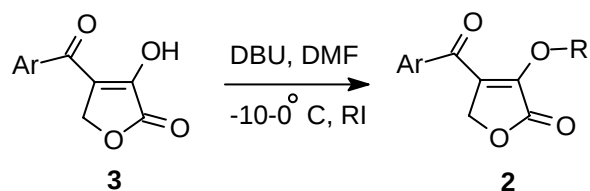
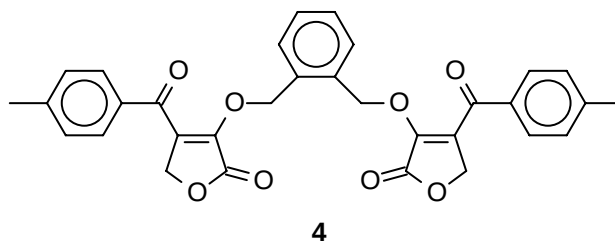


Table 1.

Entry	Ar	R	Yield (%)	Mp (°C)
2a	C ₆ H ₅	CH ₃ CH ₂ -	42	Oil
2b	C ₆ H ₅	CH ₂ =CHCH ₂ -	51	52
2c	<i>o</i> -Cl C ₆ H ₄	CH ₃ CH ₂ -	35	48
2d	<i>o</i> -Cl C ₆ H ₄	(CH ₃) ₂ CHCH ₂ -	41	Oil
2e	<i>m</i> -CNC ₆ H ₄	CH ₃ -	47	116
2f	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ -	31	Oil
2g	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ CH ₂ -	28	Oil
2h	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ (CH ₂) ₂ CH ₂ -	29	42
2i	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ (CH ₂) ₅ CH ₂ -	31	Oil
2j	<i>p</i> -CH ₃ C ₆ H ₄	C ₆ H ₅ CH ₂ -	42	84
2k	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ =CHCH ₂ -	48	70
2l	<i>p</i> -CH ₃ C ₆ H ₄	(CH ₃) ₂ CHCH ₂ -	17	55
2m	<i>p</i> -CH ₃ C ₆ H ₄	CH ₃ CH ₂ O ₂ CH ₂ -	53	84
2n	<i>p</i> -CH ₃ C ₆ H ₄	(CH ₃) ₂ CH-	23	73
2o	<i>p</i> -CH ₃ C ₆ H ₄	(CH ₂) ₄ CH-	25	80
2p	<i>p</i> -NO ₂ C ₆ H ₄	CH ₃ -	30	85
2q	5-CH ₃ -2-thienyl	CH ₃ -	33	Oil
4	<i>p</i> -CH ₃ C ₆ H ₄	<i>o</i> -C ₆ H ₄ (CH ₂) ₂	24	98

This O-alkylation could also be employed to synthesize bis-ethers. Thus, when one equivalent of 1,2-bis(iodomethyl)benzene was allowed to react with two equivalents of **3** (Ar= 4-CH₃C₆H₄), 4-(methylbenzoyl)-3-[2-(4-methylbenzoyl)-2-oxo(3-hydrofuryl-5-oxy)methylphenyl)methoxy]-(5H)-furan-2-one (**4**) was obtained in 24% yield.



Depending upon the reactivity of the alkyl iodide an excess ranging between one to five equivalents was used to favor the formation of the corresponding ether **2** in an S_N2-like reaction. Secondary alkyl iodide were also could be used in this reaction. Structural assignments of the ethers **2** are made on spectroscopic ground, which are summarized in Table 2. Definite proof of the ether

Experimental

General

Melting points were determined on a Melt-Temp apparatus and are uncorrected. TLC was conducted on plates prepared from E. Merck silica gel 60 F₂₅₄, 0.2 mm thickness. Silica gel from EM science in a column with 20 mm diameter was used for flash column chromatography pressured with compressed nitrogen. NMR spectra were acquired on a Bruker AC250 spectrometer with TMS as internal standard. A Hewlett-Packard 6890 Gas chromatograph/mass spectrometer was used to record MS data. For high resolution mass spectra a Kratos MS-801 DS-55 spectrometer was used. Elemental analysis were performed by M-H-W Laboratories, Phoenix, Arizona.

General Procedure: 4-Aroyl-3-alkoxy-2(5H)-furanones (2).

DBU (0.37 mL, 2.5 mmol) was added to a solution of **3** (2.5 mmol) in anhydrous DMF (35 mL) in a three-neck-round-bottom flask equipped with a thermometer and a magnetic stirring bar under an inert atmosphere. The solution was cooled to a temperature between -10-0°C and stirred for 10 min. Then an excess of alkyl iodide was added and the solution was stirred for 2 h. The resulting mixture was allowed to come to room temperature and stirring was continued for 24 h. The yellow-brown reaction mixture was poured into ice water (300 mL) and extracted with ether (3 x 25 mL). The organic layers were combined and dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was chilled overnight. Solids were recrystallized from ethanol, while oils were subjected to column chromatography on silica gel using methylene chloride as eluent. Spectroscopic and analytical data are given in Table 2.

General Procedure: 7-Aryl-4,5-dihydro-2-oxo-3H,8H-furo[3,4-b][1,4]diazepines (1).

To a solution of **2** (2.5 mmol) in chloroform (50 mL) was added 1,2-ethylenediamine (3 mmol) under an inert gas atmosphere. The mixture was stirred at room temperature for 24 h. The solvent was evaporated and the resulting residue was recrystallized from methanol or ethanol. Spectroscopic and analytical data are given in Table 3.

Table 2: ^1H - , ^{13}C -NMR, MS and analytical data of **2a-q** and **4**

Product	^1H NMR ^a δ (ppm)	^{13}C NMR ^a δ (ppm)	Molecular formula	MS	Analysis % Calc./Found C H
2a	1.17 (t, 3H), 4.32 (q, 2H), 5.01 (s, 2H), 7.50, 7.63, 7.86 (m, m, d, 5H)	14.85, 67.63, 67.85, 127.97, 128.18, 128.98, 133.58, 136.32, 142.79, 167.59, 189.49	$\text{C}_{13}\text{H}_{12}\text{O}_4$	232, 203, 188, 159, 143, 132, 105	67.24 5.01 67.30 5.21
2b	4.78(d, 2H), 5.04 (s, 2H), 5.07 (d, 1H), 5.10 (d, 1H), 5.76 (m, 1H), 7.50, 7.63, 7.85 (m, m, d, 5H)	67.72, 71.74, 118.97, 128.35, 129.15, 130.25, 131.60, 133.74, 136.36, 143.54, 167.67, 189.40	$\text{C}_{14}\text{H}_{12}\text{O}_4$	244, 172, 122, 105	68.85 4.95 68.68 5.03
2c	1.01 (t, 3H), 4.47 (q, 2H), 5.05 (s, 2H), 7.40 (m, 4H)	14.30, 66.28, 67.20, 126.32, 127.22, 127.89, 128.94, 130.03, 131.05, 138.10, 146.62, 166.95, 188.09	$\text{C}_{13}\text{H}_{11}\text{ClO}_4$	266, 231, 203, 166, 159, 139, 131	58.55 4.16 58.65 4.35
2d	0.62 (d, 6H), 1.58 (m, 1H), 4.22 (d, 2H), 5.06 (s, 2H), 7.39 (m, 4H)	18.19, 28.44, 66.79, 77.70, 126.87, 127.17, 128.34, 129.65, 130.88, 131.50, 138.89, 147.21, 167.54, 188.85	$\text{C}_{15}\text{H}_{15}\text{ClO}_4$	294, 239, 203, 159, 139, 131	61.13 5.13 61.19 5.27
2e	4.13 (s, 3H), 5.08 (s, 2H), 7.62, 7.88, 8.07 (3m, 4H)	59.03, 67.14, 112.65, 117.47, 126.59, 129.15, 132.53, 132.77, 136.07, 137.30, 145.31, 187.05	$\text{C}_{13}\text{H}_9\text{NO}_4$	243, 214, 168, 130, 102	64.20 3.73 64.40 3.90
2f	2.38 (s, 3H), 3.87 (s, 3H), 4.94 (s, 2H), 7.23 (d, 2H), 7.71 (d, 2H)	b	$\text{C}_{13}\text{H}_{12}\text{O}_4$	232, 189, 159, 119, 91	b
2g	1.11 (t, 3H), 2.35 (s, 3H), 4.21 (q, 2H), 4.91 (s, 2H), 7.21 (d, 2H), 7.70 (d, 2H)	15.02, 21.60, 67.84, 68.01, 128.51, 129.11, 129.36, 133.88, 143.37, 145.05, 167.79, 189.19	$\text{C}_{14}\text{H}_{14}\text{O}_4$	246, 231, 189, 159, 146, 119, 91	68.27 5.73 68.52 5.72
2h	0.80 (t, 3H), 1.19 (m, 2H), 1.51 (m, 2H), 2.45 (s, 3H), 4.27 (t, 2H), 5.03 (s, 2H), 7.29 (d, 2H), 7.77 (d, 2H)	13.46, 18.56, 21.77, 31.52, 67.97, 72.06, 128.60, 129.19, 129.49, 134.17, 143.91, 145.05, 167.96, 189.39	$\text{C}_{16}\text{H}_{18}\text{O}_4$	275 (M+1), 219, 119, 91	70.06 6.62 70.23 6.60

Table 2 (Cont.)

2i	0.85 (t, 3H), 1.21 (m, 8H), 1.52 (m, 2H), 2.44 (s, 3H), 4.27 (t, 2H), 5.03 (s, 2H), 7.29 (d, 2H), 7.67 (d, 2H)	13.87, 21.64, 22.36, 25.22, 28.60, 29.41, 31.47, 67.85, 72.19, 128.60, 129.06, 129.40, 134.08, 143.83, 144.85, 167.88, 189.26	C ₁₉ H ₂₄ O ₄	316, 301, 219, 146, 119, 91	72.11 7.65 72.20 7.62
2j	2.43 (s, 3H), 5.02 (s, 2H), 5.39 (s, 2H), 7.10 (m, 2H), 7.25 (m, 5H), 7.69 (d, 2H)	21.81, 68.01, 72.95, 127.88, 127.97, 128.43, 128.51, 129.23, 129.58, 130.58, 135.18, 143.29, 145.02, 168.05, 189.10	C ₁₉ H ₁₆ O ₄	308, 278, 225, 187, 144, 119, 91	74.00 5.23 74.06 5.33
2k	2.37 (s, 3H), 4.76 (d, 2H), 4.97 (s, 2H), 5.07 (bs, 1H), 5.12 (bs, 1H), 5.64 – 5.80 (m, 1H), 7.19 (d, 2H), 7.71 (d, 2H)	21.60, 67.80, 71.77, 118.98, 129.10, 129.40, 129.61, 131.68, 133.78, 142.94, 144.97, 167.72, 188.89	C ₁₅ H ₁₄ O ₄	258, 243, 146, 119, 91	69.74 5.47 69.92 5.52
2l	0.76 (d, 6H), 1.81 (m, 1H), 2.44 (s, 3H), 4.07 (d, 2H), 5.04 (s, 2H), 7.28 (d, 2H), 7.77 (d, 2H)	18.52, 21.81, 28.65, 67.97, 78.22, 128.77, 129.24, 129.52, 134.21, 144.17, 145.01, 168.05, 189.45	C ₁₆ H ₁₈ O ₄	274, 259, 219, 174, 146, 119, 91	67.83 ^c 6.76 ^c 67.59 6.34
2m	1.28 (t, 3H), 2.43 (s, 3H), 4.23 (q, 2H), 5.01 (s, 2H), 5.08 (s, 2H), 7.27 (d, 2H), 7.88 (d, 2H)	14.01, 21.73, 61.60, 65.90, 68.01, 129.15, 129.70, 133.79, 141.89, 144.93, 167.71, 168.26, 188.67	C ₁₆ H ₁₆ O ₆	305 (M+1), 277, 185, 123, 119	63.14 5.30 63.30 5.25
2n	1.16 (d, 6H), 2.45 (s, 3H), 5.05 (s, 2H), 5.25 (qu, 1H), 7.27 (d, 2H), 7.89 (d, 2H)	21.73, 22.45, 67.97, 74.93, 128.94, 129.61, 130.29, 133.88, 143.08, 144.85, 168.22, 189.28	C ₁₅ H ₁₆ O ₄	261 (M+1), 219, 147, 119, 91	69.20 6.20 68.94 6.10
2o	1.39 - 1.45 (m, 4H), 1.60 – 1.66 (m, 4H), 2.45 (s, 3H), 5.06 (s, 2H), 5.48 (t, 1H), 7.28 (d, 2H), 7.76 (d, 2H)	21.69, 23.12, 33.12, 67.93, 84.26, 128.85, 129.44, 130.04, 134.04, 143.07, 144.63, 168.14, 189.27	C ₁₇ H ₁₈ O ₄	286, 219, 119, 91	71.31 6.34 71.36 6.29
2p	4.13 (s, 3H), 5.09 (s, 2H), 7.27 (m, 2H), 8.34 (m, 2H)	59.13, 67.31, 123.41, 126.59, 129.95, 141.44, 145.78, 150.20, 167.14, 187.73	C ₁₂ H ₉ NO ₆	263, 146, 150, 104	54.76 3.45 54.77 3.21

Table 2 (Cont.)

2q	2.59 (s, 3H), 4.07 (s, 3H), 5.01 (s, 2H), 6.89 (d, 1H), 7.71 (d, 1H)	b	C ₁₁ H ₁₀ O ₄ S	238, 223, 140, 125, 112, 97	b
4	2.41 (s, 6H), 4.98 (s, 4H), 5.08 (s, 4H), 7.04 (m, 2H), 7.19 (d, 4H), 7.62 (m, 2H), 7.77 (d, 4H)	21.65, 67.88, 70.28, 128.79, 129.11, 129.28, 130.61, 133.79, 142.95, 145.02, 167.67	C ₃₂ H ₂₆ O ₈	539 (M+1), 321, 195, 119	71.37 4.87 71.47 4.97

a) in CDCl₃ as solvent, q= quartet, qu= quintet b) not determined c) calcd. for C₁₆H₁₈O₄ • 0.5 H₂O

Table 3: ¹H-NMR, MS and analytical data of **1c,e,f,p** and **q**

Product ^a	Yield (%)	Mp (°C)	¹ H NMR ^b δ (ppm)	Molecular formula	MS	Analysis % Calc./Found		
						C	H	N
1c	42	176	3.55 (bs, 2H), 3.94 (bs, 2H), 4.56 (bs, 2H), 6.39 (bs, 1H), 7.37 (m, 4H)	C ₁₃ H ₁₁ ClN ₂ O ₂	262, 227, 217, 183	59.44 4.22 10.66 59.54 4.27 10.82		
1e	48	172	3.62 (bs, 2H), 4.21 (bs, 2H), 4.76 (s, 2H), 5.68 (bs, 1H), 7.55, 7.74 (2m, 4H)	C ₁₄ H ₁₁ N ₃ O ₂	253, 252, 208, 181, 179, 142, 140, 102	66.40 4.38 16.59 66.60 4.60 16.68		
1f	39	178	2.38 (s, 3H), 3.61 (bs, 2H), 4.20 (bs, 2H), 4.78 (s, 2H), 5.31 (bs, 1H), 7.22 (m, 2H), 7.34 (m, 2H)	C ₁₄ H ₁₄ N ₂ O ₂	242, 227, 197, 183, 170, 128, 105, 91	69.41 5.82 69.22 5.90		
1p	51	198	3.57 (bs, 2H), 4.15 (bs, 2H), 4.64 (s, 2H), 5.51 (bs, 1H), 7.53 (d, 2H), 8.17 (d, 2H)	C ₁₃ H ₁₁ N ₃ O ₄	273, 256, 228, 182, 151	57.14 4.06 15.38 57.24 4.14 15.31		
1q	27	170	2.47 (s, 3H), 3.69 (bs, 2H), 4.13 (bs, 2H), 5.10 (s, 2H), 5.72 (bs, 1H), 6.71 (d, 1H), 7.29 (d, 1H)	C ₁₂ H ₁₂ N ₂ O ₂ S	248, 233, 215, 203, 176, 111	58.05 4.87 11.28 57.91 5.08 11.27		

a) Numbers are given so that Ar will match the ones in Table 1; b) in CDCl₃ as solvent

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11. Crystallographic data for the structures reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 146275-146279. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Sample Availability: Not Available

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