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PSEUDOESTERS AND DERIVATIVES. XXX[1]. SYNTHESIS OF 5-SUBSTITUTED FURAN-2(5*H*)-ONES BY THE REGIOSPECIFIC REACTION OF ANIONS OF ENAMINOFURANONES WITH ELECTROPHILES

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Abstract - Reactions of lithium enolates **2a,b** derived from 5-methoxy(or 5-ethylthio)-4-(pyrrolidin-1-yl)-furan-2(5*H*)-ones (**1a,b**) with various electrophiles, such as alkylating agents, aldehydes, phenyl isocyanate, acyl chlorides, and trimethylsilyl chloride, occur regiospecifically to give the corresponding 5-substituted derivatives in synthetically useful yields.

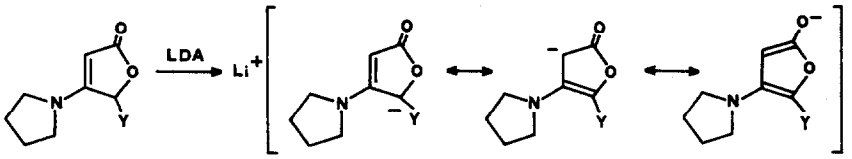
INTRODUCTION

In recent years much interest has been focused on furan-2(5*H*)-ones because of their wide occurrence in a variety of biologically active natural products[2] and their utility as valuable synthetic intermediates[3]. For these reasons, considerable effort has been made in the development of generally applicable synthetic routes for the construction of this class of compounds[4].

A convenient approach to substituted furan-2(5*H*)-ones is the reaction with electrophiles of enolate anions generated from simple furanone derivatives. However, only few examples of the direct introduction of substituents in the furanone ring have been reported. Thus, anions from furan-2(5*H*)-ones react with alkyl halides to afford the corresponding C-3-alkylation product[5,6] or mixtures of the C-3- and C-5-alkylated derivatives[7], while Michael acceptors react exclusively at the C-5 position[5]. Moreover, the reaction of anions from furan-2(5*H*)-ones with aldehydes allows the formation of mixtures of C-3 and C-5 hydroxyalkyl derivatives[8], although the presence of electron-releasing substituents at 4-position favours the exclusive formation of the C-5-substituted derivatives[4g,9,10]. We have recently shown[1] that 5-(ethylthio)furan-2(5*H*)-one is readily deprotonated to its anion and this species reacts with various electrophiles and, depending on its nature, affords the C-3-, C-5- or *O*-substituted derivative in a regiospecific manner. In contrast, attempts to react this anion with alkylating agents failed due to the competitive Michael addition with another molecule of furanone to afford the self-condensation product. Recently, however, examples of C-5-alkylation of 5-phenylsulphonylfuran-2(5*H*)-one have also been reported[11].

The above results indicate that it is difficult to predict the regioselectivity of the reactions of furanone anions with electrophiles that seems to be dependent upon such factors as (a) substitution on the substrate, (b) nature of the electrophile, (c) type of metal counter-ion, and (d) experimental conditions (solvent, temperature, time).

The observation that the anions of cyclic enaminoketones undergo alkylation at the γ-position[12,13] and recent reports on C-5-alkylation of some enaminofuranones[9,14] prompted us to investigate the behaviour of 5-methoxy-(and 5-ethylthio)-4-pyrrolidin-1-ylfuran-2(5*H*)-one anions **2a,b** towards electrophiles. The furanones **1a,b** are readily available[15] and the presence of the pyrrolidino group at C-4 is desirable for the avoidance of self-condensation processes. In this paper we have studied the generation of anions from 5-methoxy(and 5-ethylthio)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones **1a,b** by deprotonation with an appropriate base and their reactions with various electrophiles. We now report that the alkylation of these anions with alkyl halides, the acylation with acyl chlorides and the reactions with other electrophiles, such as aldehydes, occur exclusively at the 5-position.

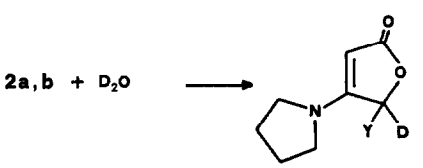


1a,b **2a,b**

a: Y = OMe
b: Y = SEt

RESULTS AND DISCUSSION

Lithium enolates from 5-methoxy- or 5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones are readily generated by treatment of **1a,b** with lithium diisopropylamide (LDA) in THF at -70 °C. for 15 min.[17] Although the anions of **2a** and **2b** can act as tridentate anions, as indicated in the scheme, immediate quenching of **2a,b** with D_2O produced only the 5-deuterio derivatives **3a** and **3b** in 55% and 75% yields, respectively, along with recovered starting furanone **1a** and **1b**, respectively. No product arising from C-3-substitution was detected.

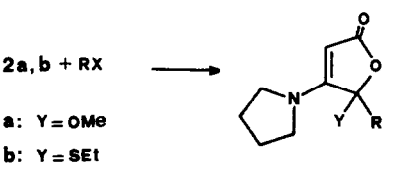


a: Y = OMe
b: Y = SEt

3a,b

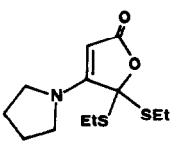
Reaction with alkylating agents

We have now found that the lithium enolates **2a,b** react with a variety of alkylating agents to afford the product of exclusive C-5-alkylation (Table 1). Thus, the alkylation with either methyl iodide or allyl bromide occurs cleanly and furnishes the corresponding C-5-alkylated furanones[18] **4a,b** and **5a,b** in good yields.



4a,b: R = Me
5a,b: R = $CH_2CH=CH_2$
6a,b: R = CH_2Ph
7a,b: R = CH_2CO_2Me

In contrast, the reaction of the lithium enolates **2a** and **2b** with benzyl chloride proceeds rather slowly and provides only moderate to low yields of the 5-benzyl furanones **6a** and **6b**, respectively. In the latter case substantial amounts of the starting furanone **1b** are recovered and the reaction mixture also contains small quantities of a minor component (4%) identifiable as compound **8**. The latter is presumably derived from the attack of **2b** onto the sulphur atom of the furanone molecule.



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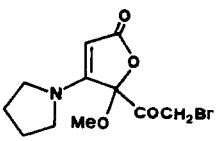

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Methyl bromoacetate also reacts with the lithium derivative **2b** to give exclusively the C-5-alkylation product **7b** in 75% yield. However, when this reaction is conducted with **2a** a substantial amount of the starting enaminofuranone **1a** is recovered and the product is a ca. 1:1 mixture of the expected C-5-alkylated furanone **7a** and the furanone **9**, originated from the attack of the anion **2a** to the carbonyl group of the bromoester. The last result has no precedence in previous reactions of related enaminoketone anions with bromoesters, which afford exclusively the alkylation product[9]. The different behaviour of **2a** may be attributed to the presence of the OMe group, which enhances significantly the hardness of the anion.

The formation of C-5-alkylation products is in accord with previous results reported in the literature for related systems.[9,14] In the present case, the presence of the pyrrolidin-1-yl group at C-4 favours the exclusive alkylation of the furanones on the carbon bearing the OMe or SEt groups.

Table 1: Reactions of lithium enolates 2a,b with electrophiles

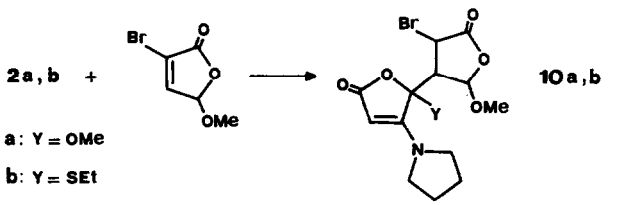
Enolate	Electrophile	Equiv	Temp., °C	Time	Products (% yield)[a]
2a	MeI	1.2	-70	1 h	**4a** (69)
2b	MeI	1.3	-70→-20	3 h	**4b** (75)
2a	CH_2=$CHCH_2Br$	1.2	-18	36 h	**5a** (80)
2b	CH_2=$CHCH_2Br$	1.2	-18	24 h	**5b** (80)
2a	$PhCH_2Cl$	1.0	-18	16 h	**6a** (43)
2b	$PhCH_2Cl$	1.0	-18	16 h	**6b** (22), **1b** (50), **8** (4)
2a	$BrCH_2CO_2Me$	1.0	-18	12 h	**7a** (18), **9** (17), **1a** (20)
2b	$BrCH_2CO_2Me$	1.0	-18	16 h	**7b** (75)
2a		1.0	-70	1 h	**10a+10a'** (60)[b]
2b		1.0	-70	1.5 h	**10b** (75)
2a	EtCHO	1.2	-70	5 min	**11a+11a'** (60)[c], **1a** (5)
2b	EtCHO	1.2	-70	4 min	**11b** (72)
2b	EtCHO	1.2	-70	2 h	**11b+1b**[d]
2a	PhCHO	1.2	-70	5 min	**12a** (64), **12a'** (5)
2a	PhCHO	1.0	-70	1 h	**12a+12a'** (50), **1b** (25)
2b	PhCHO	1.0	-70	3 min	**12b** (66), **12b'** (5),**1b** (4)
2b	PhCHO	1.0	-60	1 h	**12b+12b'+1b**[e]
2a	PhNCO	1.0	-70	1 h	**13a** (35)
2b	PhNCO	1.0	-18	24 h	**13b** (50), **1b** (27)
2a	MeCOCl	1.0	-70	2 h	**14a** (26), **19** (13), **1a** (20)
2a	MeCOCl	2.0	-40	1 h	**14a** (57), **1a** (18)
2b	MeCOCl	1.3	-70	4 h	**14b** (71)
2a	PhCOCl	1.1	-70	5 min	**15a** (59), **18** (13)
2b	PhCOCl	1.0	-70	3 h	**15b** (70)
2a	EtOCOCl	1.0	-70	4 h	**16a** (65)
2b	MeOCOCl	1.0	-70	4 h	**17b** (71)
2a	Me_3SiCl	1.1	-70→+15	6 h	**20** (22), **1a** (28)

[a] Isolated yield, non optimized. [b] Diastereomers ratio: 75:25 (determined by ^{1}H-NMR). [c] Diastereomers ratio: 80:20 (determined by ^{1}H-NMR). [d] Products ratio: 71:29 (determined by ^{1}H-NMR). [e] Product ratio (12b+12b'):1b is 58:42 (determined by ^{1}H-NMR.

Reaction with Michael acceptors

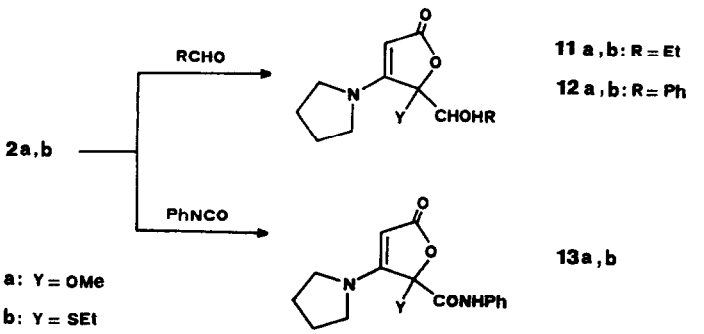
Attempts to react the lithium derivative **2a** with acrylonitrile or methyl acrylate, under different conditions, afford only recovered starting furanone **1a** and no traces of the Michael adduct. Moreover, the reaction of **2b** with methyl acrylate is not complete and leads to a mixture of compounds one component of which appears to be the expected Michael adduct. Presumably in the present case the hardness of the nucleophilic center in **2a,b** is increased, when compared with that in 5-(ethylthio)furan-2(5*H*)-one[1] anion, and therefore the conjugate addition is disfavoured, the main reaction being the polymerisation.

In contrast to the above results, when lithium enolates **2a** and **2b** are reacted with a good Michael acceptor, such as 3-bromo-5-methoxyfuran-2(5*H*)-one, afford the expected adducts **10a** and **10b** in good yields, in the first case as a 75:25 mixture of diastereoisomers (Table 1).



Reactions with aldehydes and phenyl isocyanate

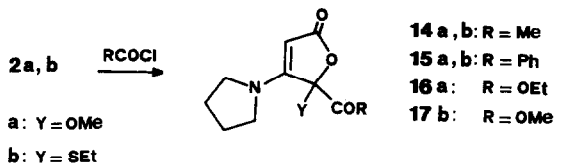
Lithium enolates **2a** and **2b** react with a slight excess of propionaldehyde or benzaldehyde at -70 °C to give the corresponding 5-hydroxyalkyl derivatives **11a,b** and **12a,b**. In most cases the products appear as mixtures of *erythro* and *threo* isomers, which can be separated by chromatography or detected by spectral analysis of the mixture. The reversion of the reaction is observed even at very low temperatures (-70 °C.). However, when the reaction is conducted for a short time (3-5 min), acceptable yields of the hydroxyalkylation products are obtained (Table 1).



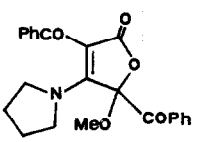
In a similar manner, treatment of **1a,b** with LDA followed by quenching of **2a,b** with phenyl isocyanate affords the amides **13a,b** in moderate yields.

Reaction with acyl chlorides

Treatment of the lithium enolate **2b** with 1 molar equiv. of acetyl chloride or benzoyl chloride affords the products of the exclusive C-5-acylation **14b** and **15b**, respectively, in marked contrast with the *O*-acylation observed previuously by us in the case of 5-(ethylthio)furan-2(5*H*)-one anion[1].



The major components obtained from the reaction of enolate **2a** with acetyl chloride or benzoyl chloride are also the C-5-acylation products **14a** and **15a**, respectively. In this case, however, the reaction with benzoyl chloride also affords the 3,5-diacylation product **18** as a minor component. Moreover, in order to obtain acceptable yields of **14a**, the enolate **2a** must be reacted with 2 molar equiv. of acetyl chloride at -40 °C. ; the use of equimolar quantities of the reagents at -70 °C. also produces **19** as a minor component, originated by the addition of enolate **2a** to the carbonyl group of the acylation product **14a** initially formed. The last reaction also produces substantial amounts of recovered **1a**.



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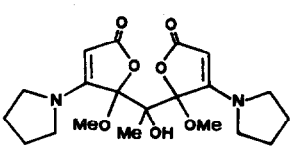

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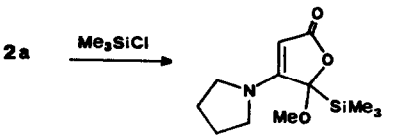
Finally, the reaction of the enolates **2a,b** with alkyl chloroformates affords the corresponding C-5-substituted alkoxycarbonyl furanones **16a** and **17b**, respectively.

Reaction with trimethylsilyl chloride

The reaction of the enolate **2a** with trimethylsilyl chloride affords the 5-trimethylsilyl furanone **20** in low yield, along with considerable amounts of recovered starting furanone **1a**. This result contrast with the previously reported reactions of furanone anions with this electrophile, which afforded the corresponding 2-trimethylsilyloxyfuran[4g,19]. Therefore, in the present case the course of the reaction is



2o

determined by the presence of the pirrolidin-1-yl group at C-4. Attempts to effect a similar reaction with the lithium enolate **2b** were unsuccessful.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on either a Philips PV-9716, a Perkin-Elmer model 257 or a model 681 grating spectrometers, ν values in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker WP-200-SY instrument. Chemical shifts are reported in ppm (δ) downfield from Me_4Si for $CDCl_3$ solutions. Mass spectra were recorded in a Hewlett-Packard 5985 spectrometer at 70 eV. Microanalyses were performed with a Heraeus analyzer. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column chromatography and analytical tlc, respectively.

5-Ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (1b)

A solution of 5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (**1a**[16], 1 mmol), ethanethiol (1.2 mmol), and boron trifluoride-diethyl ether (2 ml) was refluxed for 16 h and water was added to the reaction mixture. The organic layer was washed successively with 10% K_2CO_3 solution and water and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was recrystallized from diethyl ether to yield **1b** (87%). M.p. 45-46 °C. IR (Nujol) 1720, 1605. ^{1}H-NMR 5.84 (s, 1H), 4.58 (s, 1H), 3.9 (m, 1H), 3.28 (m, 3H), 2.68 (m, 2H), 2.02 (m, 4H), 1.29 (t, 3H, J=7.5 Hz). MS *m/z* (relative intensity) 213 (M^+, 10), 152 (100), 124 (31), 70 (14). Analysis Calcd. for $C_{10}H_{15}O_2NS$: C, 56.34; H, 7.04; N, 6.57; S, 15.02. Found: C, 56.44; H, 7.05; N, 6.60; S, 14.80.

Generation of 2a and 2b and Reaction with Electrophiles. General Procedure

A solution of lithium diisopropylamide was prepared by addition at -70 °C, under an argon atmosphere, of a solution of *n*-butyllithium (1.65 mmol) to a solution of diisopropylamine (1.8 mmol) in tetrahydrofuran (1 ml). A solution of furanone **1a** or **1b** (1.5 mmol) in dry tetrahydrofuran (8.5 ml) was added and the mixture was stirred for 15 min at -70 °C. A solution of the electrophile in tetrahydrofuran was then added, and the reaction mixture was kept under the conditions indicated in each case (Table 1). The solution was poured into saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were dried (Mg_2SO_4) filtered and concentrated under reduced pressure. The crude isolated products were purified by column chromatography on silica gel or crystallization.

5-Methoxy-5-methyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (4a)

Purified by column chromatography (5:5:3 hexane-dichloromethane-ethyl acetate). M.p. 85-88 °C (from cyclohexane-carbon tetrachloride). IR (Nujol) 1740, 1615. ^{1}H-NMR 4.25 (s, 1H), 3.57 (m, 1H), 3.26 (m, 1H), 3.05 (m, 2H), 3.01 (s, 3H), 1.83 (m, 4H), 1.50 (s, 3H). MS *m/z* (relative intensity) 197 (M^+, 16), 182 (3), 154 (6), 95 (100), 70 (9). Analysis Calcd. for $C_{10}H_{15}O_3N$: C, 60.91; H, 7.61; N, 7.11. Found: C, 61.06; H, 7.69; N, 7.40.

5-Ethylthio-5-methyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (4b)

Purified by column chromatography (2:1 ethyl acetate-hexane). IR (neat) 1740, 1605. ^{1}H-NMR 4.50 (s, 1H), 4.33 (m, 1H), 3.30 (m, 3H), 2.50 (m, 2H), 2.01 (m, 4H), 1.84 (s, 3H), 1.19 (t, 3H, J=7.5). MS *m/z* (relative intensity) 227 (M^+, 8), 166 (100), 70 (26). Analysis Calcd. for $C_{11}H_{17}O_2NS$: C, 58.15; H, 7.49; N, 6.17; S, 14.10. Found: C, 58.00; H, 7.78; N, 6.18; S, 13.77.

5-Allyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (5a)

Purified by column chromatography (10:2 toluene-acetone). M.p. 57-60 °C. (from carbon

Table 2: ^{13}C-NMR data for 5-substituted 4-(pyrrolidin-1-yl)furan-2(5H)-ones

	C-2[a]	C-3	C-4[a]	C-5	SCH_2 CH_3 (OCH_3)	NCH_2		CH_2						
1a	172.2	81.1	162.6	98.5	(54.8)	49.2	47.5	25.5	24.3					
1b	172.5	81.1*	165.1	80.0*	22.9 14.3	49.4	47.9	25.4	24.1					
4a	170.3	81.6	164.1	103.4	(49.8)	49.3	46.6	25.5	23.4	22.6				
4b	171.5	82.1	168.0	88.3	22.8 14.1	50.8	47.6	26.3	24.2	24.2				
5a	171.0	83.6	163.1	105.4	(50.3)	49.7	47.1	26.1	23.9	129.8	119.2	40.1		
5b	171.4	83.4	166.2	90.4	22.3 14.1	50.3	47.3	25.9	24.0	129.8	119.3	40.6		
6a	170.7	84.7	162.8	106.0	(50.7)	49.7	47.5	26.4	24.1	133.4	130.0	127.9	126.9	42.0
6b	171.5	84.6	166.0	91.1	22.8 14.3	50.5	47.7	26.5	24.1	133.3	129.9	128.1	127.3	42.4
7a	170.6	84.0	162.6	103.2	(50.4)	50.1	48.3	26.2	24.2	167.8	52.0	41.8		
7b	171.0	82.9	166.0	87.7	22.4 13.9	50.6	47.3	25.9	24.0	167.2	51.9	41.4		
9	169.7	83.8	160.9	103.2	(51.3)	50.3	48.2	26.1	24.4	192.3	30.7			
10a	169.3*	84.8	160.9	104.0	(51.1)	50.4	47.8	26.3	24.1	169.5*	104.4	57.9	56.5	36.7
10b	170.2*	84.1	164.2	88.5	22.5 13.9	51.0	47.8	26.2	23.8	168.7*	104.6	58.0	56.1	36.7
11a	171.0	84.1	162.8	106.5	(50.4)	50.0	48.0	26.1	24.0	74.6	23.7	9.9		
11a'	171.9	86.8	163.2	107.1	(50.0)	50.0	48.0	26.1	24.0	73.8	23.9	10.2		
11b	171.7	83.7	165.9	95.1	22.1 14.2	49.6		25.0		75.1	24.4	10.0		
12a	170.6	85.6	161.9	106.5	(51.3)	50.0	48.2	26.4	24.1	136.6	128.4	127.9	127.1	75.6
12b	171.5	84.7	165.3	94.6	22.9 14.4	51.0	47.6	26.5	24.3	137.0	128.7	128.1	126.8	75.9
12b'	172.0	84.8	166.1	94.2	23.1 14.2	-[b]	-[b]	-[b]	-[b]	137.6	128.9	128.2	128.1	76.1
13a	170.8	83.7	162.4*	101.6	(51.5)	50.2	47.8	26.1	24.4	161.5*	136.5	129.1	125.1	119.9
13b	170.8	81.6	164.5*	90.6	23.0 14.0	51.4	49.6	26.2	24.1	162.9*	136.6	128.8	125.0	120.3
14a	170.7	83.6	161.5	103.7	(51.1)	50.0	47.9	26.0	24.3	199.1	24.5			
14b	171.5	82.6	163.7	94.5	22.1 14.0	50.9	47.9	26.1	24.0	198.9	24.5			
15a	170.6	83.2	162.3	104.7	(50.8)	50.0	48.2	26.0	24.3	189.9	133.8	132.8	130.6	128.1
15b	171.0	82.4	164.8	94.4	23.2 13.8	50.7	48.4	26.0	24.0	189.4	133.7	133.5	130.0	128.0
16a	170.8	82.6	161.6*	100.4	(51.3)	49.9	47.4	25.8	24.1	164.8*	62.6	13.7		
17b	171.1	82.3	163.9*	89.7	22.4 13.8	50.4	47.8	25.9	24.1	165.5*	53.6			
19	170.6	84.7	163.8	107.3	(50.3)	50.8	49.6	26.6	23.9	81.4	19.6			
20	172.2	84.6	166.0	106.6	(50.5)	49.7	48.0	26.3	24.0	-3.2				

[a] C-2, C-4 not conclusively assigned. [b] Signals not observed. * Values with an asterisk may be interchanged within the same row.

tetrachloride). IR (neat) 1750, 1620. ^{1}H-NMR 5.65 (m,1H), 5.07 (m, 2H), 4.44 (s, 1H), 3.77 (m, 1H), 3.41 (m, 1H), 3.20 (m, 2H), 3.18 (s, 3H), 2.79 (dd, 1H, J=14.4, J=6.6), 2.58 (dd, 1H, J=14.4, J=7.7), 1.95 (m, 4H). MS m/z (relative intensity) 223 (M^+, 26), 195 (27), 182 (67), 154 (100), 95 (83), 70 (15). Analysis Calcd. for $C_{12}H_{17}O_3N$: C, 64.57; H, 7.62; N, 6.28. Found: C, 64.68; H, 7.56; N, 5.89.

5-Allyl-5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (5b)

Purified by column chromatography (4:3 ethyl acetate-hexane). M.p. 63-65 °C. (from cyclohexane). IR (Nujol) 1740, 1605. ^{1}H-NMR 5.70 (m, 1H), 5.15 (m, 2H), 4.52 (s, 1H), 4.33 (m, 1H), 3.30 (m, 3H), 2,92 (dd, 1H, J=14.7, J=6.6), 2.74 (dd, 1H, J=14.7, J=7.7), 2.50 (m, 2H), 2.00 (m, 4H), 1.19 (t, 3H, J=7.4). MS m/z (relative intensity) 253 (M^+, 30), 212 (6), 192 (100), 70 (17). Analysis Calcd. for $C_{13}H_{19}O_2NS$: C, 61.66; H, 7.51; N, 5.53. Found: C, 62.03; H, 7.87; N, 5.80.

5-Benzyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (6a)

Purified by column chromatography (5:4:2 hexane-dichloromethane-ethyl acetate). M.p. 125-126 °C. (from carbon tetrachloride). IR (Nujol) 1735, 1615. ^{1}H-NMR 7.21 (m, 5H), 4.27 (s, 1H), 3.87 (m, 1H), 3.62 (m, 1H), 3.34 (d, 1H, J=14.0), 3.26 (s, 3H), 3.17 (d, 1H, J=14.0), 3.08 (m, 2H), 2.03 (m, 4H). MS m/z (relative intensity) 273 (M^+, 16), 242 (10), 182 (75), 154 (100), 91 (45), 70 (3). Analysis Calcd. for $C_{16}H_{19}O_3N$: C, 70.33; H, 6.96; N, 5.13. Found: C, 70.33; H, 7.01; N, 5.20.

5-Benzyl-5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (6b)

Purified by column chromatography (1:1 ethyl acetate-hexane). M.p. 92-94 °C. (from cyclohexane). IR (KBr) 1740, 1610, 1600. ^{1}H-NMR 7.23 (m, 5H), 4.45 (m, 1H), 4.30 (s, 1H), 3.63 (m, 1H), 3.45 (d, 1H, J=14.2), 3.26 (d, 1H, J=14.2), 3.12 (m, 2H), 2.54 (m, 2H), 2.02 (m, 4H), 1.20 (t, 3H, J=7.5). MS m/z (relative intensity) 303 (M^+, 6), 242 (100), 212 (16), 91 (14), 70 (7). Analysis Calcd. for $C_{17}H_{21}O_2NS$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.18; H, 7.10; N, 4.80.

5,5-Di(ethylthio)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (8)

Purified by column chromatography (1:1 ethyl acetate-hexane). IR (neat) 1750, 1610. ^{1}H-NMR 4.58 (s, 1H), 4.00 (m, 2H), 3.30 (m, 2H), 2.72 (q, 4H, J=7.5), 1.98 (m, 4H), 1.25 (t, 6H, J=7.5). MS m/z (relative intensity) 273 (M^+, 4), 212 (100), 184 (43), 70 (9).

5-Methoxy-5-(methoxycarbonylmethyl)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (7a)

Purified by column chromatography (1:1 benzene-acetone). IR (neat) 1760, 1745, 1620. ^{1}H-NMR 4.55 (s, 1H), 3.69 (m, 1H), 3.67 (s, 3H), 3.27 (m, 3H), 3.25 (s, 3H), 3.17 (d, 1H, J=14.4), 2.96 (d, 1H, J=14.4), 2.04 (m, 4H). MS m/z (relative intensity) 255 (M^+, 33), 223 (48), 182 (29), 154 (33), 95 (100), 70 (6).

5-Bromoacetyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (9)

Purified by column chromatography (1:1 benzene-acetone). M.p. 132-134 °C. (from carbon tetrachloride). IR (Nujol) 1765, 1750, 1620. ^{1}H-NMR 4.64 (s, 1H), 4.48 (d, 1H, J=15.3), 4.36 (d, 1H, J=15.3), 3.50 (m, 1H), 3.39 (s, 3H), 3.30 (m, 3H), 1.98 (m, 4H). MS m/z (relative intensity) 305, 303 (M^+, 4), 274, 272 (2), 182 (100), 154 (79), 70 (3). Analysis Calcd. for $C_{11}H_{14}O_4BrN$: C, 43.42; H, 4.61; Br, 26.31; N, 4.61. Found: C, 43.58; H, 4.57; Br, 25.79; N, 4.90.

5-Ethylthio-5-(methoxycarbonylmethyl)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (7b)

Recrystallized from carbon tetrachloride. M.p. 76-78 °C. IR (Nujol) 1750, 1735, 1600. ^{1}H-NMR 4.57 (s, 1H), 3.66 (s, 3H), 3.64 (m, 1H), 3.32 (m, 3H), 3.27 (d, 1H, J=14.9), 3.05 (d, 1H, J=14.9), 2.57 (m, 2H), 2.00 (m, 4H), 1.21 (t, 3H, J=7.5). MS m/z (relative intensity) 285 (M^+, 8), 224 (100), 154 (15), 70 (28). Analysis Calcd. for $C_{13}H_{19}O_4NS$: C, 54.74; H, 6.67; N, 4.91; S, 11.23. Found: C, 54.40; H, 6.84; N, 4.85; S, 10.93.

5-(3'-Bromo-5'-methoxy-2'-oxotetrahydrofuran-4'-yl)-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (10a + 10a')

The crude product was a 75:25 mixture of two main diastereosiomers **10a** and **10a'** (determined by ^{1}H-NMR).

10a was separated by column chromatography (5:5:3 hexane-dichloromethane-ethyl acetate). A sample still containing some impurities of **10a'** showed m.p. 156-158 °C. (from carbon tetrachloride). IR (Nujol) 1795, 1755, 1625. ^{1}H-NMR 5.65 (d, 1H, J=4.0), 4.67 (s, 1H), 4.20 (d, 1H, J=7.7), 3.82 (m, 1H), 3.61 (s, 3H), 3.49 (m, 1H), 3.33 (s, 3H), 3.32 (m, 2H), 3.25 (dd, 1H, J=4.0, J=7.7), 2.08 (m, 4H). MS m/z (relative intensity) 377, 375 (M^+, 4), 296 (6), 182 (47), 155 (100), 154 (59), 95 (40), 70 (2). Analysis Calcd. for $C_{14}H_{18}O_6BrN$: C, 44.68; H, 4.79; Br, 21.28; N, 3.72. Found: C, 44.57; H, 4.76; N, 3.92; Br, 20.94.

10a': ^{1}H-NMR 5.06 (d, 1H, J=4.5), 4.84 (d, 1H, J=6.7), 4.66 (s, 1H), 3.82 (m, 1H), 3.49 (m, 1H), 3.48 (s, 3H), 3.32 (m, 2H), 3.30 (s, 3H), ≃3.25 (m, 1H), ≃2.0 (m, 4H).

5-(3'-Bromo-5'-methoxy-2'-oxotetrahydrofuran-4'-yl)-5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (10b)

The presence of diastereoisomers was not detected by NMR. Recrystallized from carbon tetrachloride. M.p. 153-155 °C. IR (Nujol) 1795, 1745, 1605. ^{1}H-NMR 5.67 (d, 1H, J=4.6), 4.67 (s, 1H), 4.38 (m, 1H), 4.30 (d, 1H, J=8.3), 3.65 (s, 3H), 3.48 (m, 1H), 3.32 (m, 2H), 3.23 (dd, 1H, J=8.3, J=4.6), 2.55 (m, 2H), 2.03 (m, 4H), 1.24 (t, 3H, J=7.4). MS *m/z* (relative intensity) 346, 344 (M^+-61, 52), 286, 284 (78), 258, 256 (50), 205 (65), 95 (100), 70 (44). Analysis Calcd. for $C_{15}H_{20}O_5BrNS$: C, 44.33; H, 4.93; Br, 19.70; N, 3.45; S, 7.86. Found: C, 44.76; H, 5.22; Br, 19.34; N, 3.42, S, 8.13.

5-(1-Hydroxyprop-1-yl)-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (11a+11a')

The crude product was a 80:20 mixture of *erythro*- and *threo*-isomers (determined by ^{1}H-NMR).

11a was separated by column chromatography (5:1 ethyl acetate-hexane) to afford a sample still containing some impurities of **11a'**. M.p. 128-132 °C (from carbon tetrachloride). IR (KBr) 3390, 1720, 1610. ^{1}H-NMR 4.58 (s, 1H), 3.84 (m, 2H), 3.31 (m, 3H), 3.30 (s, 3H), 2.02 (m, 4H), 1.47 (m, 2H), 1.01 (t, 3H, J=7.4). MS *m/z* (relative intensity) 241 (M^+, 9), 210 (3), 182 (100), 154 (66), 70 (6), 59 (5). Analysis Calcd. for $C_{12}H_{19}O_4N$: C, 59.75; H, 7.88; N, 5.81. Found: C, 59.63; H, 7.94; N, 6.05.

11a': ^{1}H-NMR 4.60 (s, 1H), 3.84 (m, 2H), 3.31 (m, 3H), 3.26 (s, 3H), 2.02 (m, 4H), 1.47 (m, 2H), 1.04 (t, 3H, J=7.3).

5-Ethylthio-5-(1-hydroxyprop-1-yl)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (11b)

The presence of the *erythro*- and *threo*-isomers was not detected by ^{1}H-NMR. The crude product was recrystallized from carbon tetrachloride. M.p. 144-146 °C. IR (Nujol) 3350, 1720, 1610. ^{1}H-NMR 4.58 (s, 1H), 4.42 (m, 1H), 3.89 (dd, 1H, J=9.3, J=4.0), 3.24 (m, 3H), 2.50 (m, 2H), 2.29 (br, 1H), 2.03 (m, 4H), 1.43 (m, 2H), 1.21 (t, 3H, J=7.5), 1.01 (t, 3H, J=7.3). MS *m/z* (relative intensity) 271 (M^+, 9), 212 (47), 210 (59), 184 (39), 154 (25), 75 (100), 70 (43). Analysis Calcd. for $C_{13}H_{21}O_3NS$: C, 57.56; H, 7.75; N, 5.17; S, 11.81. Found: C, 57.86; H, 7.72; N, 5.20, S, 11.93.

5-Hydroxybenzyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (12a+12a')

The crude product was a mixture of *erythro*- and *threo*-isomers. The isomers **12a** (64% yield) and **12a'** (4% yield) were isolated by column chromatography (4:1 ethyl acetate-hexane).

12a: M.p. 166-168 °C (from acetone). IR (Nujol) 3330, 1720, 1615. ^{1}H-NMR 7.31 (m, 5H), 5.09 (s, 1H), 4.23 (s, 1H), 3.81 (m, 1H), 3.53 (m, 1H), 3.36 (s, 3H), 3.09 (m, 2H), 2.90 (br, 1H), 2.02 (m, 4H). MS *m/z* (relative intensity) 289 (M^+, 2), 182 (96), 154 (100), 122 (40), 77 (62), 70 (6). Analysis Calcd. for $C_{16}H_{19}O_4N$: C, 66.44; H, 6.57; N, 4.84. Found: C, 66.55; H, 6.75; N, 4.90.

12a': ^{1}H-NMR 7.41 (m, 2H), 7.32 (m, 3H), 5.06 (s, 1H), 4.43 (s, 1H), 3.79 (m, 2H), 3.28 (s, 3H), 3.26 (m, 2H), 1.99 (m, 4H). MS *m/z* (relative intensity) 289 (M^+, 3), 182 (100), 154 (60), 122 (12), 77 (9), 70 (4).

5-Ethylthio-5-hydroxybenzyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (12b+12b')

The crude product was a mixture of *erythro*- and *threo*-isomers. The isomers **12b** (66% yield) and **12b'** (5% yield) were isolated by column chromatography (4:1 ethyl acetate-hexane).

12b: M.p. 204-205 °C (from chloroform). IR (Nujol) 3270, 1710, 1600. ^{1}H-NMR 7.28 (m, 5H), 5.08 (s, 1H), 4.40 (m, 1H), 4.18 (s, 1H), 3.60 (m, 1H), 3.04 (m, 2H), 2.80 (br, 1H), 2.55 (m, 2H), 2.02 (m, 4H), 1.24 (t, 3H, J=7.5). MS *m/z* (relative intensity) 258 (M^+-61, 5), 212 (100), 184 (61), 152 (61), 77 (42), 70 (23). Analysis Calcd. for $C_{17}H_{21}O_3NS$: C, 63.95; H, 6.58; N, 4.39; S, 10.03. Found: C, 63.75; H, 6.80; N, 4.65; S, 9.80.

12b': M.p. 143-145 °C. IR (Nujol) 3300, 1710, 1595. ^{1}H-NMR 7.48(m, 2H), 7.34 (m, 3H), 5.08 (s, 1H), 4.54 (s, 1H), 3.35 (m, 4H), 2.45 (m,2H), 1.98 (m, 4H), 1.14 (t, 3H, J=7.5). MS *m/z* (relative intensity) 319 (M^+, 2), 258 (2), 212 (100), 184 (48), 152 (21), 77 (22), 70 (16).

5-Methoxy-5-phenylcarbamoyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (13a)

Purified by column chromatography (2:2:1 chloroform-ethyl acetate-hexane). M.p. 188-190 °C (from ethanol). IR (Nujol) 3315, 1735, 1705, 1700, 1620, 1600. ^{1}H-NMR 8.54 (br, 1H), 7.59 (m, 2H), 7.35 m, 2H), 7.19 (m, 1H), 4.69 (s, 1H), 3.59 (m, 1H), 3.44 (s, 3H), 3.37 (m, 3H), 1.97 (m, 4H). MS *m/z* (relative intensity) 302 (M^+, 9), 182 (100), 154 (53), 120 (2), 92 (3), 77 (6), 70 (2). Analysis Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.58; H, 5.96; N, 9.27. Found: C, 63.30; H, 5.88; N, 9.30.

5-Ethylthio-5-phenylcarbamoyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (13b)
Purified by column chromatography (2:1 ethyl acetate-hexane). IR (neat) 3290, 1745, 1695, 1605. ^{1}H-NMR 8.83 (br, 1H), 7.59 (m, 2H), 7.31 (m, 2H), 7.14 (m, 1H), 4.58 (s, 1H), 4.32 (m, 1H), 3.92 (m, 1H), 3.26 (m, 2H), 2.63 (m, 2H), 1.96 (m, 4H), 1.24 (t, 3H, J=7.5). MS *m/z* (relative intensity) 271 (M^+-61, 6), 212 (12), 184 (10), 120 (7), 92 (20), 77 (36), 70 (25), 55 (100).

5-Acetyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (14a)
Purified by column chromatography (2:2:1 ethyl acetate-dichloromethane-hexane). M.p. 96-98 °C (from cyclohexane). IR (Nujol) 1755, 1735, 1635, 1615. ^{1}H-NMR 4.60 (s, 1H), 3.52 (m, 1H), 3.34 (s, 3H), 3.25 (m, 3H), 2.32 (s, 3H), 1.95 (m, 4H). MS *m/z* (relative intensity) 225 (M^+, 8), 182 (69), 154 (100), 122 (31), 70 (4). Analysis Calcd. for $C_{11}H_{15}O_4N$: C, 58.67; H, 6.67; N, 6.62. Found: C, 58.46; H, 6.62; N, 6.50.

5,5'-(1-Hydroxyethane-1,1-diyl)di[5-methoxy- 4-(pyrrolidin-1-yl)furan-2(5*H*)-one] (19)
Purified by column chromatography (10:4 benzene-acetone). M.p. 78-80 °C (from ethanol). IR (neat) 3450, 1740, 1610. ^{1}H-NMR 4.58 (s, 2H), 3.75 (m, 2H), 3.54 (m, 2H), 3.28 (m, 4H), 3.21 (s, 6H), 2.02 (m, 8H), 1.39 (s, 3H). MS *m/z* (relative intensity) 408 (M^+, 2), 268 (6), 226 (14), 182 (100), 154 (86), 70 (10). Analysis Calcd. for $C_{20}H_{28}O_7N_2$: C, 58.82; H, 6.86; N, 6.86. Found: C, 58.75; H, 6.98; N, 6.66.

5-Acetyl-5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (14b)
Purified by column chromatography (2:1 ethyl acetate-hexane). IR (neat) 1755, 1725, 1605. ^{1}H-NMR 4.65 (s, 1H), 4.07 (m, 1H), 3.27 (m, 3H), 2.53 (m, 2H), 2.32 (s, 3H), 1.98 (m, 4H), 1.23 (t, 3H, J=7.5). MS *m/z* (relative intensity) 255 (M^+, 6), 212 (100), 194 (13), 184 (72), 122 (28), 95 (86), 70 (62). Analysis Calcd. for $C_{12}H_{17}O_3NS$: C, 56.47; H, 6.67; N, 5.49; S, 12.55. Found: C, 56.75; H, 6.61; N, 5.72; S, 12.25.

5-Benzoyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (15a)
Purified by column chromatography (2:1 ethyl acetate-hexane). M.p. 133-135 °C (from cyclohexane-acetone) IR (Nujol) 1755, 1700, 1625. ^{1}H-NMR 8.16 (m, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 4.66 (s, 1H), 3.45 (s, 3H), 3.44 m, 4H), 1.95 (m,4H). MS *m/z* (relative intensity) 287 (M^+, 2), 182 (100), 154 (57), 105 (10), 77 (17), 70 (2). Analysis Calcd. for $C_{16}H_{17}O_4N$: C, 66.89; H, 5.92; N, 4.88. Found: C, 67.10; H, 5.77; N, 5.20.

3,5-Dibenzoyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (18)
Purified by column chromatography (2:1 ethyl acetate-hexane). M.p. 62-65 °C. IR (KBr) 1760, 1690, 1640, 1600, 1590. ^{1}H-NMR 8.19 (m, 2H), 7.91 (m, 2H), 7.55 (m, 6H), 3.68 (m, 2H), 3.55 (s, 3H), 3.45 (m, 1H), 3.16 (m, 1H), 1.97 (m, 4H). MS *m/z* (relative intensity) 391 (M^+, 2), 286 (84), 217 (27), 105 (100), 77 (44), 70 (3).

5-Benzoyl-5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (15b)
Purified by column chromatography (2:1 ethyl acetate-hexane). M.p. 63-65 °C. IR (neat) 1755, 1685, 1610. ^{1}H-NMR 8.16 (m, 2H), 7.59 (m, 1H), 7.44 (m, 2H), 4.67 (s, 1H), 4.01 (m, 1H), 3.31 (m, 3H), 2.60 (m, 2H), 1.93 (m, 4H), 1.25 (t, 3H, J=7.5). MS *m/z* (relative intensity) 317 (M^+, 11), 256 (24), 212 (100), 184 (30), 105 (28), 77 (21), 70 (15). Analysis Calcd. for $C_{17}H_{19}O_3NS$: C, 64.35; H, 5.99; N, 4.42; S, 10.09. Found: C, 64.21; H, 6.20; N, 4.59; S, 9.72.

5-Ethoxycarbonyl-5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (16a)
Purified by column chromatography (8:2 benzene-acetone). M.p. 84-87 °C (from cyclohexane). IR (neat) 1765, 1700, 1625. ^{1}H-NMR 4.61 (s, 1H), 4.31 (q, 2H, J=7.2), 3.64 (m, 1H), 3.41 (s,3H), 3.30 (m, 3H), 2.00 (m, 4H), 1.31 (t, 3H, J=7.1). MS *m/z* (relative intensity) 255 (M^+, 17), 224 (4), 182 (100), 154 (70), 70 (4).

5-Ethylthio-5-methoxycarbonyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (17b)
Purified by column chromatography (2:1 ethyl acetate-hexane). M.p. 95-98 °C (from cyclohexane). IR (Nujol) 1750, 1735, 1605. ^{1}H-NMR 4.63 (s, 1H), 4.09 (m, 1H), 3.84 (s, 3H), 3.26 (m, 3H), 2.60 (m, 4H), 1.98 (m, 4H), 1.24 (t, 3H, J=7.5). MS *m/z* (relative intensity) 271 (M^+, 13), 212 (16), 210 (100), 154 (44), 70 (21), 59 (30). Analysis Calcd. for $C_{12}H_{17}O_4NS$: C, 53.14; H, 6.27; N, 5.17. Found: C, 52.96; H, 6.44; N, 5.33.

5-Methoxy-5-trimethylsilyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (20)
Purified by column chromatography (4:1 ethyl acetate-hexane). IR (KBr) 1725, 1620, 1600. ^{1}H-NMR 4.55 (s, 1H), 3.84 (m, 2H), 3.54 (m, 2H), 3.18 (s, 3H), 1.95 (m, 4H), 0.14 (s, 9H). MS *m/z*

(relative intensity) 255 (M^+, 6), 240 (96), 227 (17), 212 (100), 182 (67), 154 (67), 95 (62), 73 (97), 70 (14).

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15. 5-Methoxy-4(pyrrolidin-1-yl)furan-2(5*H*)-one (**1a**) is readily prepared from a 4-halogenated furan-2(5*H*)one by reaction with pyrrolidine[16]. The 5-ethylthio derivative **1b** is obtained from **1a** by acid-catalysed treatment with EtSH (see Experimental Section).
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17. All attempts to generate the anions of **2a,b** by potassium carbonate in a solid-liquid two-phase system in the presence of a phase-transfer catalyst were unsuccessful. This failure contrasts with previous results obtained by us with the unsubstituted 5(ethylthio)furan-2(5*H*)-one, which is converted into such anionic species under the above mentioned conditions[1].
18. The regiochemical assignments of the new 5,5-disubstituted furanones were based on the spectral data obtained for each compound. Thus, the ^{1}H-NMR spectra of these compounds lacked resonances corresponding to the acetal-type protons at C-5, but exhibited signals assignable to the olefinic proton at 3-position. Furthermore, the ^{13}C-NMR spectra (Table 2) displayed signals assignable to C-5 quaternary carbons that show differences in chemical shifts in accord with the nature of the new substituent introduced. IR and MS data corroborated the proposed structures.
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