Russian Journal of Organic Chemistry, Vol. 40, No. 7, 2004, pp. 999–1002. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 7, 2004, pp. 1040–1043.

Synthesis of Alkyl 4-(1-Alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates and Their Reactions with Amines

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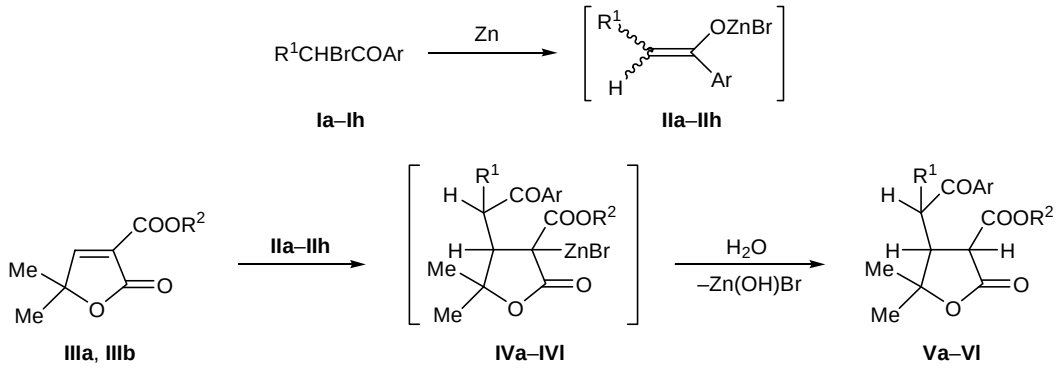
Received November 18, 2003

Abstract—Zinc enolates derived from 1-aryl-2-bromoalkanones react with alkyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylates to give alkyl 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates. Reactions of the latter with amines, such as *p*-toluidine, cyclohexylamine, and piperidine, lead to the corresponding carboxamides.

One of the main ways of modifying 2,5-dihydrofuran-2-one derivatives includes their reactions with nucleophiles [1–3]. With the aim of obtaining functional derivatives of these heterocyclic systems in the present work we examined reactions of alkyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylates **IIIa** and **IIIb** with zinc enolates **IIa**–**IIh** generated from 1-aryl-2-bromoalkanones **Ia**–**Ih**. Initial compounds **IIIa** and **IIIb** contain three electrophilic centers: the C^4 atom and carbonyl carbon atoms of the lactone and ester groups. The results showed that zinc enolates as nucleophiles attack exclusively the soft electrophilic center in the substrate, the C^4 atom with rupture of the double bond. The products were alkyl 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates **Va**–**Vl**.

The structure of compounds **Va**–**Vl** was confirmed by the IR and ^{1}H NMR spectra. The IR spectra contained absorption bands due to stretching vibrations of the ketone, ester, and lactone carbonyl groups at 1670–1690, 1725–1745, and 1765–1780 cm^{-1}, respectively. In the ^{1}H NMR spectra of **Va**–**Vj** characteristic signals at δ 1.39–1.43 (CH_3), 1.54–1.56 (CH_3), 2.81–2.97 (4-H), 3.80–3.89 (C**H**R^1), and 3.89–3.99 ppm (3-H) were present. The spectrum of ethyl 5,5-dimethyl-4-[1-(2,4,6-trimethylbenzoyl)propyl]-2-oxotetrahydrofuran-3-carboxylate (**Vk**) considerably differed from those of compounds **Va**–**Vj**. For example, the signal from the

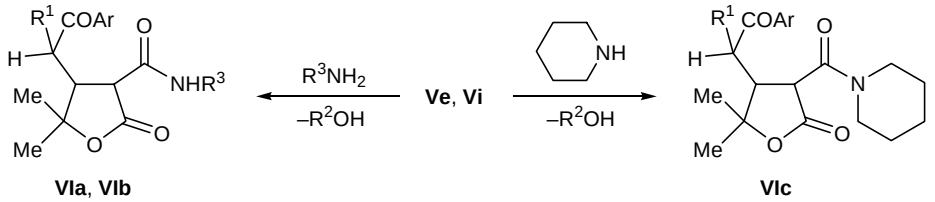
Scheme 1.



I, **II**, R^1 = Me, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**); R^1 = Et, Ar = Ph (**e**), 4-BrC_6H_4 (**f**), 2,4,6-$Me_3C_6H_2$ (**g**); R^1 = *i*-Pr, Ar = 4-BrC_6H_4 (**h**); **III**, R^2 = Me (**a**), Et (**b**); **V**, R^1 = R^2 = Me, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); R^1 = Me, R^2 = Et, Ar = Ph (**d**), 4-MeC_6H_4 (**e**), 4-BrC_6H_4 (**f**), 4-$MeOC_6H_4$ (**g**); R^1 = Et, R^2 = Me, Ar = Ph (**h**), 4-BrC_6H_4 (**i**); R^2 = Et, Ar = Ph (**j**), 2,4,6-$Me_3C_6H_2$ (**k**); R^1 = *i*-Pr, R^2 = Et, Ar = 4-BrC_6H_4 (**l**).

1070-4280/04/4007-0999

Scheme 2.



VIa, **VIb** **VIc**

VI, R^1 = Me, R^3 = 4-MeC_6H_4, Ar = 4-MeC_6H_4 (**a**), R^1 = Et, R^3 = *cyclo*-C_6H_{11}, Ar = 4-BrC_6H_4 (**b**), R^1 = Me, Ar = 4-MeC_6H_4 (**c**).

4-CH proton of **Vk** was a doublet displaced by about 1 ppm upfield. Presumably, this is the result of steric effect of the 2,4,6-trimethylphenyl group which restricts conformational freedom of the molecule. The ^{1}H NMR spectra of the products also indicated that the reaction was both regio- and stereoselective. Only one diastereoisomer ($J_{3,4}$ = 11 Hz) of the four possible was obtained. However, its steric structure was not determined rigorously.

With a view to obtain new nitrogen-containing compounds on the basis of furancarboxylates **V** we examined reactions of compounds **Ve** and **Vi** with N-nucleophiles, i.e., amines. The reaction with primary or secondary amines was charge-controlled: the attack by amine was directed at the ester carbonyl carbon atom to afford 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates **VIa**–**VIc** (Scheme 2). The yields of products **VIa** and **VIb** obtained by reactions with primary amines (both highly basic cyclohexylamine and weakly basic *p*-toluidine) were fairly high (74–85%). The reaction of **Ve** and **Vi** with piperidine (secondary amine) was characterized by a poor yield (35%), indicating a strong effect of steric factor on the process.

The structure of compounds **VIa**–**VIc** was proved by their elemental compositions and IR and ^{1}H NMR spectra. In the IR spectra of **VIa**–**VIc** we observed absorption bands belonging to the amide, lactone, and ester carbonyl groups at 1630–1640, 1670–1685, and 1755–1765 cm^{-1}, respectively; compound **VIb** showed in the spectrum NH absorption band at 3280 cm^{-1}; NH stretching vibrations of compound **VIa** gave rise to a broadened band in the region 3045–3220 cm^{-1}. The ^{1}H NMR spectra of amides **VIa**–**VIc** are given in Experimental.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra of **Va**–**Vl** and **VIa**–**VIc** were measured on a Bruker DRX spectrometer (500 MHz) from

Table 1. Yields, melting points, IR spectra, and elemental analyses of alkyl 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates **Va**–**Vl**

Comp. no.	Yield, %	mp, °C	IR spectrum, νC=O, cm^{-1}			Found, %		Formula	Calculated, %	
			lactone	ester	ketone	C	H		C	H
Va	91	148–150	1775	1735	1675	67.12	6.59	$C_{17}H_{20}O_5$	67.09	6.62
Vb	84	181–183	1775	1730	1680	67.88	6.96	$C_{18}H_{22}O_5$	67.91	6.97
Vc	81	159–161	1770	1725	1680	64.57	6.65	$C_{18}H_{22}O_6$	64.66	6.63
Vd	84	136–137	1770	1725	1680	67.90	6.99	$C_{18}H_{22}O_5$	67.91	6.97
Ve	91	124–125	1770	1735	1670	68.65	7.12	$C_{19}H_{24}O_5$	68.66	7.28
Vf	72	127–128	1765	1735	1675	54.42	5.31	$C_{18}H_{21}BrO_5$	54.42	5.33
Vg	92	115–117	1775	1735	1675	65.51	6.9	$C_{19}H_{24}O_6$	65.50	6.94
Vh	64	123–124	1775	1735	1675	67.85	7.02	$C_{18}H_{22}O_5$	67.91	6.97
Vi	71	124–127	1775	1730	1680	54.42	5.32	$C_{18}H_{21}BrO_5$	54.42	5.33
Vj	72	109–111	1775	1730	1680	68.60	7.25	$C_{19}H_{24}O_5$	68.66	7.28
Vk	71	123–124	1770	1725	1680	70.59	8.01	$C_{22}H_{30}O_5$	70.56	8.07
Vl	57	116–117	1775	1740	1670	56.41	5.99	$C_{20}H_{25}BrO_5$	56.48	5.92

Table 2. ^{1}H NMR spectra of alkyl 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates **Va**–**Vl**

Comp. no.	Chemical shifts δ, ppm
Va	1.17 d (3H, CH**Me**), 1.43 s and 1.56 s (6H, Me_2C), 2.96 d.d (1H, 4-H), 3.55 s (3H, OMe), 3.89 m (1H, C**H**Me), 3.95 d (1H, 3-H), 7.56–8.00 m (5H, Ph)
Vb	1.16 d (3H, CH**Me**), 1.43 s and 1.55 s (6H, Me_2C), 2.38 s (3H, 4-**Me**C_6H_4), 2.94 d.d (1H, 4-H), 3.54 s (3H, OMe), 3.85 m (1H, C**H**Me), 3.92 d (1H, 3-H), 7.36 d and 7.89 d (4H, 4-MeC_6**H**$_4$)
Vc	1.16 d (3H, CH**Me**), 1.42 s and 1.55 s (6H, Me_2C), 2.93 d.d (1H, 4-H), 3.53 s (3H, COOMe), 3.83 m (1H, C**H**Me), 3.87 s (3H, **Me**OC_6H_4), 3.91 d (1H, 3-H), 7.06 d and 7.97 d (4H, 4-$MeOC_6$**H**$_4$)
Vd	1.03 d.d (3H, CH_2**Me**), 1.17 d (3H, CH**Me**), 1.43 s and 1.55 s (6H, Me_2C), 2.95 d.d (1H, 4-H), 3.89 m (1H, C**H**Me), 3.93 d (1H, 3-H), 3.94 m and 4.03 m (2H, OCH_2), 7.56–8.00 m (5H, Ph)
Ve	1.03 d.d (3H, CH_2**Me**), 1.16 d (3H, CH**Me**), 1.43 s and 1.55 s (6H, Me_2C), 2.38 s (3H, 4-**Me**C_6H_4), 2.83 d.d (1H, 4-H), 3.84 m (1H, C**H**Me), 3.93 d (1H, 3-H), 3.94 m and 4.03 m (2H, OCH_2), 7.36 d and 7.89 d (4H, 4-MeC_6**H**$_4$)
Vf	1.05 d.d (3H, CH_2**Me**), 1.21 d (3H, CH**Me**), 1.43 s and 1.55 s (6H, Me_2C), 2.82 d.d (1H, 4-H), 3.80 m (1H, C**H**Me), 3.93 d (1H, 3-H), 3.94 m and 4.03 m (2H, OC**H**$_2$), 7.77 d and 7.95 d (4H, 4-BrC_6H_4)
Vg	1.03 d.d (3H, CH_2**Me**), 1.15 d (3H, CH**Me**), 1.42 s and 1.55 s (6H, Me_2C), 2.81 d.d (1H, 4-H), 3.83 m (1H, C**H**Me), 3.86 s (3H, OMe), 3.89 d (1H, 3-H), 3.93 m and 4.02 m (2H, OCH_2), 7.06 d and 7.97 d (4H, 4-$MeOC_6$**H**$_4$)
Vh	0.72 t (3H, $CHCH_2$**Me**), 1.39 s and 1.55 s (6H, Me_2C), 1.66 m (2H, CHC**H**$_2$Me), 2.95 d.d (1H, 4-H), 3.53 s (3H, OMe), 3.87 m (1H, C**H**Et), 3.99 d (1H, 3-H), 7.55–8.03 m (5H, Ph)
Vi	0.71 t (3H, CH_2**Me**), 1.39 s and 1.55 s (6H, Me_2C), 1.62 m (2H, C**H**$_2$Me), 2.97 d.d (1H, 4-H), 3.54 s (3H, OMe), 3.83 m (1H, C**H**Et), 3.93 d (1H, 3-H), 7.77 d and 7.96 d (4H, 4-BrC_6H_4)
Vj	0.72 t (3H, $CHCH_2$**Me**), 1.02 d.d (3H, OCH_2**Me**), 1.40 s and 1.56 s (6H, Me_2C), 1.67 m (2H, CHC**H**$_2$Me), 2.97 d.d (1H, 4-H), 3.86 m (1H, C**H**Et), 3.96 d (1H, 3-H), 3.92 m and 4.01 m (2H, OCH_2), 7.56–8.04 m (5H, Ph)
Vk	0.79 t (3H, $CHCH_2$**Me**), 1.22 s and 1.35 s (6H, Me_2C), 1.25 d.d (3H, OCH_2**Me**), 1.62 m and 1.69 m (2H, CHC**H**$_2$Me), 2.21 s and 2.24 s (9H, 2,4,6-**Me**$_3C_6H_2$), 2.92 d (1H, C**H**Et), 3.04 d (1H, 4-H), 4.05 d (1H, 3-H), 4.18 m and 4.20 m (2H, OC**H**$_2$), 6.91 s (2H, 2,4,6-Me_3C_6**H**$_2$)
Vl	0.81 d and 0.86 d (6H, CHCH**Me**$_2$), 1.06 d.d (3H, OCH_2**Me**), 1.27 s and 1.54 s (6H, Me_2C), 1.96 m (1H, CHC**H**Me_2), 3.12 d.d (1H, 4-H), 3.81 t (1H, C**H**$CHMe_2$), 3.98 d (1H, 3-H), 4.01 m and 4.07 m (2H, OCH_2), 7.75 d and 8.00 d (4H, 4-BrC_6H_4)

solutions in DMSO-d_6 using tetramethylsilane as internal reference.

Alkyl 4-(1-alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylates Va–Vl (*general procedure*). Alkyl 5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **IIIa** or **IIIb**, 0.011 mol, and 1-aryl-2-bromoalkanone **Ia**–**Ih**, 0.014 mol, were added to a mixture of 2 g of metallic zinc (prepared as fine turnings), 7 ml of diethyl ether, and 7 ml of ethyl acetate. The mixture was heated to initiate the reaction which then occurred spontaneously. When the reaction was complete, the mixture was heated for 15 min under reflux, cooled, treated with 10% hydrochloric acid, and extracted with diethyl ether. The organic phase was separated, washed with a 10% solution of sodium hydrogen carbonate until neutral reaction, dried over sodium sulfate, and evaporated. The products were purified by double recrystallization from methanol (Tables 1, 2).

4-(1-Alkyl-2-aryl-2-oxoethyl)-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxamides VIa–VIc (*general procedure*). *p*-Toluidine, cyclohexylamine, or piperidine, 0.0017 mol, was added to a solution of 0.0016 mol of compound **Ve** or **Vi** in 6 ml of *o*-xylene. The mixture was heated for 6 h, the solvent was distilled off, and the residue was recrystallized twice from methanol.

5,5-Dimethyl-4-[1-methyl-2-(4-methylphenyl)-2-oxoethyl]-2-oxo-*N*-(*p*-tolyl)tetrahydrofuran-3-carboxamide (VIa). Yield 85%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 1640 (C=O, amide), 1680 (C=O, ketone), 1765 (C=O, lactone), 3045–3250 (N–H).

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.18 d (CH**Me**); 1.32 s and 1.56 s (6H, Me_2C); 2.27 s and 2.38 s (6H, 4-**Me**C_6H_4); 3.07 d.d (1H, 4-H); 3.89 m (1H, C**H**Me); 4.02 d (1H, 3-H); 7.09 d, 7.29 d, 7.33 d, 7.86 d (8H, 4-MeC_6**H**$_4$); 9.82 s (1H, NH). Found, %: C 73.26; H 6.91. $C_{24}H_{27}NO_4$. Calculated, %: C 73.26; H 6.92.

4-[1-(4-Bromobenzoyl)propyl]-*N*-cyclohexyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxamide (VIb). Yield 74%, mp 212–213°C. IR spectrum, ν, cm^{-1}: 1635 (C=O, amide), 1685 (C=O, ketone), 1755 (C=O, lactone), 3280 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm 0.75 t (3H, $CHCH_2$**Me**), 0.8–1.27 m and ~1.50–1.70 m (10H, C_6H_{10}), ~1.63 m (CHC**H**$_2$Me), 1.22 s and 1.50 s (6H, Me_2C), 3.01 d.d (1H, 4-H), 3.42 m (NHC**H**), 3.72 m (1H, C**H**Et), 3.87 d (1H, 3-H), 7.74 d and 7.96 d (4H, 4-BrC_6H_4), 7.75 d (1H, NH). Found, %: C 59.48; H 6.54. $C_{23}H_{30}BrNO_4$. Calculated, %: C 59.49; H 6.51.

5,5-Dimethyl-4-[1-(4-methylbenzoyl)ethyl]-*N*,*N*-pentamethylene-2-oxotetrahydrofuran-3-carboxamide (VIc). Yield 35%, mp 137–139°C. IR spectrum, ν, cm^{-1}: 1630 (C=O, amide), 1670 (C=O, ketone), 1760 (C=O, lactone). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.12 d (3H, CH**Me**), 1.39 s and 1.50 s (6H, Me_2C), 1.10–1.55 m and 2.95–3.45 m (10H, $C_5H_{10}N$), 2.39 s (3H, 4-**Me**C_6H_4), 3.07 d.d (1H, 4-H), 3.80 m (1H, C**H**Me), 4.38 d (1H, 3-H), 7.35 d and 7.92 d (4H, 4-MeC_6**H**$_4$). Found, %: C 71.09; H 7.89. $C_{22}H_{29}NO_4$. Calculated, %: C 71.13; H 7.87.

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