Synthesis and Characterization of New α,β-Unsaturated γ-Lactones: Alkyl 3-Acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamates

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A convenient procedure for the preparation of carbamate derivatives of 5-oxo-2,5-dihydrofuran (**3**) was described. The method is based on the Michael type addition of three alkyl carbamates (**2**) with 4-acetyl-5-methyl-2,3-dihydro-2,3-furandione (**1**). According to ^{1}H nmr spectra of compounds show tautomeric forms (**3**,**4**,**5**) in $CDCl_3$. In the solid state the synthesized compounds are enol forms (**3**). The products were characterized with molecular spectroscopic methods.

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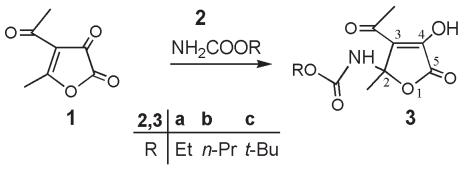
Many natural and bioactive compounds contain the 5-oxo-2,5-dihydrofuran (α,β-unsaturated γ-lactones) derivatives [1]. Structurally diverse 5-oxo-2,5-dihydrofurans, alkylated or acylated at position 2, 3 and 4, have been reported to possess considerable anti-fungal, anti-bacterial, anti-inflammatory, anti-tumor, cytotoxic and anti-oxidant activity [2-4]. On the other hand, 2,3-dihydro-2,3-furandiones in general are considered as convenient and versatile synthons in heterocyclic synthesis [5-10]. According to literature, nucleophilic addition some of H-active nucleophiles like hydrazines and carbazides to C-5 atoms of 2,3-dihydro-2,3-furandiones *via* Michael type addition gives the α,β-unsaturated γ-lactone intermediates [7,10]. Arrangements of these α,β-unsaturated γ-lactones, which are not isolated from the reaction medium, generate other heterocyclic compounds [7,10]. Due to the functional role in biological systems of 5-oxo-2,5-dihydrofurans, the purpose of this study is synthesize and characterize new 5-oxo-2,5-dihydrofurans. Thus, we set out to obtain 5-oxo-2,5-dihydrofurans *via* Michael type reactions of 2,3-dihydro-2,3-furandiones with H-active nucleophiles.

In this study, we synthesized only three alkyl 3-acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamate derivatives (**3a-c**) and characterized their structures by elemental analyses, IR, ^{1}H nmr, ^{13}C nmr, UV spectroscopic techniques and finally X-ray diffraction method for **3b**.

Alkyl 3-acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-yl carbamate derivatives were easily obtained in good yields (62-86%) *via* Michael addition of compound **2** to a solution of compound **1**. The reactions were performed with stirring at room temperature in dry benzene. The synthesis of **3a-c** outlined in Scheme 1.

Scheme 1



Earlier, Fabian *et al*. reported that 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione is generated by the reaction of various carbamates with some new oxazines and dibenzoylacetic acids in boiling benzene [16]. This report showed that 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione with carbamates did not undergo Michael type reactions. Instead, the thermal decomposition of 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione lead to the α-acylketene as intermediate which undergoes nucleophilic addition reactions with carbamates. However, in our study, the preparations of **3a-c** reveals that 2,3-furandiones, which are slightly sterically hindered, and carbamates may undergo Michael type reactions at room temperature.

Compounds (**3a-c**) consist of a γ-lactone ring in which the enol portion and the oxygen of the lactone moiety are conjugated to the carbonyl group of the ring. The lone electron pairs of the hydroxyl group attached to the C-4 is conjugated additionally to the ene-dione O=C-C=C-C=O system (π-*p* conjugation). The UV-spectra of the enone portions of 5-oxo-2,5-dihydrofuranes are characterized by an intense absorption band (K-band) in 215-250 nm region [4]. For compounds **3a**, **3b** and **3c** UV-bands with a bathochromic effect resulting from the conjugated carbonyl groups at the C-3 positions to enone systems are observed at 265, 267, 270 nm, resulting from the π-π* transition, respectively (Figure 1).

IR data of compounds (**3a-c**) and a tentative assignment of the some of the frequencies, which are made by comparison of related compounds described in literature [2,3,9,17], are listed in Table 1. The IR spectra of **3a**,**b**,**c** show N-H stretching bands at 3377, 3374, 3379 cm^{-1} and O-H stretching bands at 3146, 3161, 3170 cm^{-1} (broad), respectively.

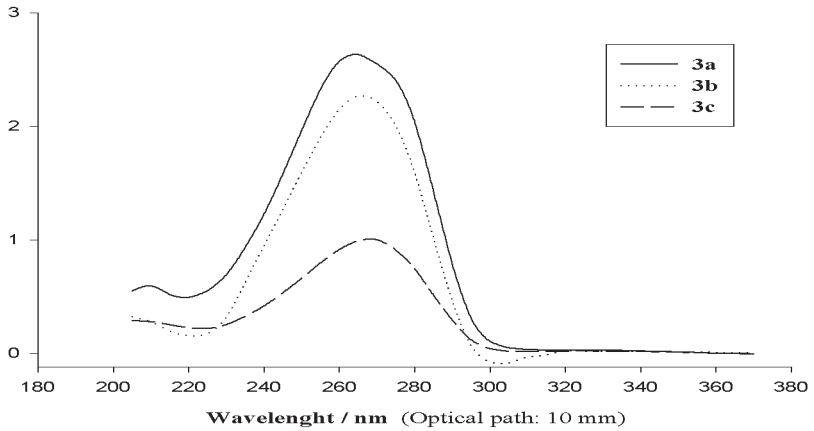


Figure 1. UV spectra of compound **3a**,**b**,**c** in diethyl ether.

The C=O absorptions of **3a**,**b**,**c** appear at 1761, 1762, 1759 cm^{-1} (ring), 1736, 1734, 1729 cm^{-1} (acetyl), 1643, 1643, 1647 cm^{-1} (carbamate), respectively. Furthermore, the carbonyl group, of the lactone rings, show second absorption bands at 1774-1776 cm^{-1}, approximately.

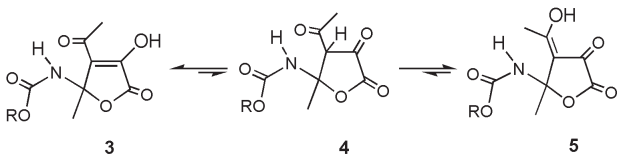
Table 1
Infrared Data for **3a**, **3b** and **3c**

3a	**3b**	**3c**	Assignments ν, δ
3377(s)	3374 (s)	3379 (s)	NH
3146(w)	3161 (w)	3170 (w)	OH (broad)
1761, 1774 (s)	1762, 1776 (s)	1759, 1776 (s)	C=O (lactone)
1736 (s)	1734 (s)	1729 (s)	C=O (acetyl)
1686(m)	1686 (m)	1685 (m)	C=C
1643 (s)	1643 (s)	1647 (s)	C=O (carbamate)
1534 (s)	1537 (s)	1528 (s)	NH
1442 (m)	1440 (m)	1441 (m)	CH
1309 (m)	1311 (m)	1312 (m)	C-N
1253 (s)	1250 (s)	1245 (s)	C-O-C (lactone)
1169 (m)	1168 (m)	1158 (m)	C-O-C (carbamate)
1092 (s)	1085 (s)	1087 (s)	C-OH

ν, stretch; δ, deformation.

The structures of **3a-c** were confirmed by nmr spectroscopic data that agree with those found for the similar compounds [2,3,9,17]. In the ^{1}H nmr spectra of **3a**, **3b** and **3c** the characteristic shifts of CH_3 protons adjacent to the ring at 1.86, 1.84, 1,84 ppm, CH_3C=O protons at 2.46, 2.49, 2.48 ppm, NH protons 7.27, 7.25, 7.29 were observed, respectively. While the corresponding deuterium oxide exchangeable OH proton signals (as highly broad peaks) of **3a** and **3c** at 9.44, 10.22 ppm were found, the OH proton signal of **3b** could not be detected. Because the keto-enol exchange rate of **3b** is relatively slow, as revealed by their ^{1}H nmr spectra registered in $CDCl_3$ solution, other broad OH proton signals at 5.6-5.7 ppm and in low intensity methine proton signals at 2.72-2.64 ppm show also that these γ-lactones have tautomeric forms (see Scheme 2). Among these tautomers, relative amount of forms **4**, in $CDCl_3$ solution, are very small (< 4 %). As well as, relative amount of forms **5**, in the solution, are found 10-17 %, approximately. The ORTEP representation of **3b** shows that the enol tautomer exists in the crystal form of compounds **3** (Figure 2). In the ^{13}C nmr of **3a**, characteristic signals related to the ring at 166.70 (C5=O), 150.10 (C4-OH), 123.75 (C3), 90.95 ppm (C2) were observed. Also, the ^{13}C nmr spectroscopic data of **3b**,**c** agree with the proposed 5-oxo-2,5-dihydrofuran skeleton (see Experimental).

Scheme 2



Tautomers of the compounds in $CDCl_3$.

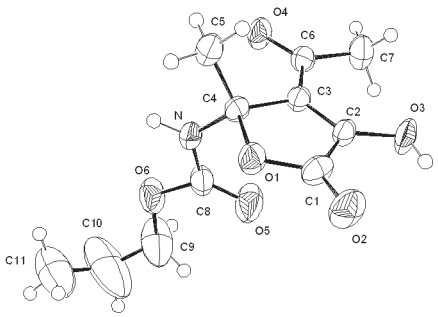


Figure 2. ORTEP drawing of the **3b** with the atomic numbering scheme. Displacement elipsoids are drawn at the 50 % probability level.

Table 2
Torsion Angles (°)

O2	C1	C2	C3	-178.4(6)	O6	C9	C10	C11	-18(3)
O1	C1	C2	O3	-178.5(5)	O5	C8	N	C4	-4.5(10)
C1	C2	C3	C6	179.5(5)	O6	C8	N	C4	175.4(5)
O3	C2	C3	C4	-179.1(5)	O1	C4	N	C8	-72.0(6)
C2	C3	C4	N	-120.1(5)	C3	C4	N	C8	43.1(7)
C6	C3	C4	N	61.4(7)	C5	C4	N	C8	173.4(5)
C6	C3	C4	O1	178.6(5)	O2	C1	O1	C4	176.5(5)
C2	C3	C4	C5	112.4(5)	N	C4	O1	C1	125.9(5)
C6	C3	C4	C5	-66.1(6)	C5	C4	O1	C1	-117.5(5)
C2	C3	C6	O4	-179.1(6)	N	C8	O6	C9	-176.4(7)
C4	C3	C6	C7	179.5(5)	C10	C9	O6	C8	156.1(12)

Table 3
Final atomic coordinates and equivalent anisotropic thermal parameters for non-hydrogen atoms.

Atom	x	y	z	Ueq*
N	0.8588(5)	0.0648(5)	1.0014(3)	0.0353(11)
O1	0.9806(4)	0.0363(4)	0.8485(3)	0.0413(11)
O2	0.9673(4)	0.0113(5)	0.6801(3)	0.0573(13)
O3	0.7885(4)	0.2480(5)	0.6825(3)	0.0497(11)
O4	0.7743(4)	0.3706(4)	0.9987(3)	0.0463(12)
O5	0.6644(5)	0.0113(5)	0.9145(4)	0.0763(17)
O6	0.7001(5)	-0.0639(5)	1.0722(3)	0.0587(14)
C1	0.9368(6)	0.0722(6)	0.7565(4)	0.0394(14)
C2	0.8488(6)	0.1928(5)	0.7645(4)	0.0331(13)
C3	0.8415(5)	0.2331(6)	0.8617(4)	0.0304(13)
C4	0.9298(6)	0.1383(5)	0.9240(4)	0.0323(13)
C5	1.0559(6)	0.2041(6)	0.9690(5)	0.0442(16)
C6	0.7685(6)	0.3476(6)	0.9072(4)	0.0354(14)
C7	0.6839(6)	0.4373(7)	0.8400(5)	0.0505(17)
C8	0.7351(6)	0.0053(6)	0.9890(5)	0.0429(15)
C9	0.5735(8)	-0.1410(11)	1.0689(8)	0.101(4)
C10	0.5693(11)	-0.2433(15)	1.1360(14)	0.191(9)
C11	0.6666(10)	-0.3136(10)	1.1878(10)	0.117(4)

*$U_{eq}=(p^2/3)S_iS_jU_{ij}a_i{}^*a_j{}^*\mathbf{a_i.a_j}$

Table 4
Bond lengths (Å)

C1	O2	1.207(7)	C4	C5	1.507(8)
C1	O1	1.331(7)	C6	O4	1.227(6)
C1	C2	1.460(8)	C6	C7	1.493(8)
C2	C3	1.342(8)	C8	O5	1.200(7)
C2	O3	1.343(7)	C8	O6	1.332(7)
C3	C6	1.454(8)	C8	N	1.347(7)
C3	C4	1.507(8)	C9	C10	1.335(13)
C4	N	1.425(7)	C9	O6	1.445(8)
C4	O1	1.492(6)	C10	C11	1.354(13)

Compound **3b** forms crystals in the orthorhombic system with space group $Pbc2_1$. The molecule has a non-planar configuration. The five different groups are connected to the furan ring A (C1-C4, O1). These groups are acetyl, hydroxyl, oxo, methyl and propylcarbamyl. The furan ring is planar with the acetyl, hydroxyl and oxo groups [The O1 atom is maximum deviation with 0.0305(4) Å of the A plane]. The propylcarbamyl group is not planar. The methyl group and propylcarbamyl group are out of the plane A. The dihedral angles between the A group and propylcarbamyl group are 90.84(2)°. The important torsion angles are tabulated in Table 2. There is not any van der Walls interaction in the molecule.

Table 5
Bond Angles (°)

O2	C1	O1	123.3(5)	O1	C4	C5	106.0(5)
O2	C1	C2	127.1(6)	C3	C4	C5	114.6(5)
O1	C1	C2	109.6(4)	O4	C6	C3	121.6(5)
C3	C2	O3	128.8(5)	O4	C6	C7	120.0(6)
C3	C2	C1	109.7(5)	C3	C6	C7	118.5(5)
O3	C2	C1	121.5(5)	O5	C8	O6	123.5(6)
C2	C3	C6	130.2(5)	O5	C8	N	126.1(6)
C2	C3	C4	108.0(5)	O6	C8	N	110.4(5)
C6	C3	C4	121.8(5)	C10	C9	O6	113.4(8)
N	C4	O1	107.5(4)	C9	C10	C11	133.8(10)
N	C4	C3	115.0(5)	C8	N	C4	124.4(5)
O1	C4	C3	103.7(4)	C1	O1	C4	108.9(4)
N	C4	C5	109.2(5)	C8	O6	C9	117.2(5)

EXPERIMENTAL

Solvents were purchased from Merck and dried by refluxing with the appropriate drying agent and distilled before use carbamates were purchased from Merck. Compound **1** was prepared according to published method [9]. The ^1H and ^{13}C nmr spectra were acquired from a Gemini-Varian 200(50) MHz spectrometer (in deuteriochloroform solution containing tetramethyl silane as the internal standart). Electronic spectra were measured on a Shimadzu UV-1208 spectrophotometer. Infrared absorption spectra were obtained from 4000 to 400 cm^{-1} in KBr pellet using a Jasco Plus Model 460 FT IR spectrometer. Elemental analyses were performed with a Carlo Erba Elemental Analyzer, 1108. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected.

Synthesis of Alkyl 3-Acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamates **3**.

General Procedure.

To 1.54 g (10 mmoles) of a solution of **1** in 30 ml of dry benzene, compound **2** (10 mmoles) were added, and the reaction mixture was stirred at room temperature for one week. The precipitates were collected by filtration and recrystallized from diethyl ether/benzene (1:2).

Ethyl 3-Acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamate (**3a**).

This compound was obtained in 62% yield, mp 132°, as colourless crystals; ^1H nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.86 (s, 3H, C2-CH_3), 2.46 (s, 3H, CH_3C=O), 4.06 (q, 2H, J = 7.2 Hz, CH_2CH_3) 7.27 (s, NH, 1H), 9.50 (s (br), OH, 1H was D_2O exchangeable); ^{13}C nmr (deuteriochloroform): δ 14.41 (CH_2-CH_3), 25.7 (C2-CH_3), 30.0 (CH_3C=O), 60.9 (CH_2), 90.9 (C2), 123.7 (C3), 150.1 (C4), 154.2 (N-CO), 166.7 (C5), 193.3 (Me-C=O).

Table 6
Crystal and Experimental Data

Formula	$C_{11}H_{15}NO_4$	*l* (Å)	0.71073
Molecular weight	257.24	Temperature (K)	293
Crystal system	Orthorombic	2*q* limits (°)	2.1 – 25
Space group	$Pbc2_1$	No. of measured reflections	1144
a(Å)	9.735(5)	No. of independent reclections	1143
b(Å)	9.770(5)	No. of reflections used	1143
c(Å)	13.169(5)	No. of parameters	164
V (Å^3)	1252.5(10)	Max. and min. D*r* (e-A^{-3})	0.246 – 0.225
Z	4	'Goodness of fit' S	1.04
D_c (g cm^{-3})	1.364	*R, Rw*	0.05, 0.111
F (0 0 0)	544		

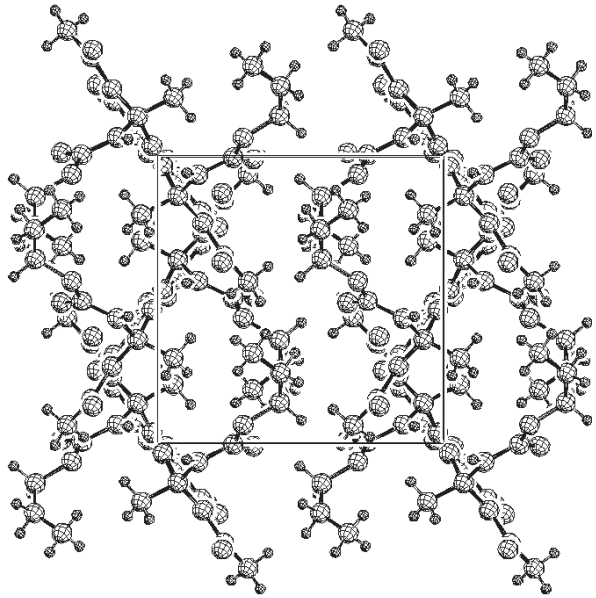


Figure 3. PLATON drawing of the unit cell.

Anal. Calcd. for $C_{10}H_{13}NO_6$ (243.2): C, 49.38; H, 5.39; N, 5.76. Found: C, 49.30; H, 5.38; N, 5.83.

n-Propyl 3-Acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamate (**3b**).

This compound was obtained in 80% yield, mp 142°, as colourless crystals; ^{1}H nmr (deuteriochloroform): δ 0.88 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.56 (sextuplet, 6H, OCH_2CH_2-CH_3), 1.85 (s, 3H, C2-CH_3), 2.49 (s, 3H, CH_3C=O), 3.90 (t, 2H, J = 6.7 Hz, $OCH_2CH_2CH_3$) 7.27 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 10.3 (CH_2CH_3), 22.3 ($CH_2CH_2CH_3$), 25.7 (C2-CH_3), 29.6 ($COCH_3$), 66.5 (OCH_2), 91.0 (C2), 122.9 (C3), 150.0 (C4), 154.3 (N-CO), 166.8 (C5), 193.1 (MeC=O).

Anal. Calcd. for $C_{11}H_{15}NO_6$ (257.2): C, 51.36; H, 5.88; N, 5.45. Found: C, 51.25; H, 5.75; N, 5.51.

tert-Butyl 3-Acetyl-4-hydroxy-2-methyl-5-oxo-2,5-dihydrofuran-2-ylcarbamate (**3c**).

This compound was obtained in 86% yield, mp 113°, as colourless crystals; ^{1}H nmr (deuteriochloroform): δ 1.39 (s, 9H, *tert*.-CH_3), 1.84 (s, 3H, C2-CH_3), 2.48 (s, 3H, CH_3C=O) 7.28 (s, 1H, NH), 10.22 (s (br), OH, 1H was D_2O exchangeable); ^{13}C nmr (deuteriochloroform): δ 25.7 (C2-CH_3), 28.0 (*tert*.-CH_3), 28.9 (CH_3C=O), 82.0 (CMe_3), 90.4 (C2), 123.7 (C3), 152.0 (C4), 153.2 (N-C=O), 166.0 (C5), 194.6 (Me-C=O).

Anal. Calcd. for $C_{12}H_{17}NO_6$ (271.3): C, 53.13; H, 6.32; N, 5.16. Found: C, 53.28; H, 6.29; N, 5.10.

Crystallography.

The intensity data were collected at room temperature using an Enraf-Nonius CAD 4 diffractometer [12] with MoK_α radiation using ω/2θ scan mode. The cell parameters were determined from least-squares of 25 centered reflections in the range of 2.1≤θ≤25. Three standard reflections for every 120 minutes were periodically measured during data collection and showed no significant intensity variations. The ranges of h,k,l are 0≤h≤11, -11≤k≤0, -15≤l≤0. The 1144 unique reflections were measured of which 1143 had I ≥2σ(I) for 164 parameters and were used for structure determination and refinement. Cell refinement and data reduction were carried out using SHELXL97 [13]. The structure was solved by direct methods using the solution program SHELXS97 [13] in the WinGX package [14]. All non-hydrogen atoms were refined isotropically and then anisotropically by full matrix least squares method. All the hydrogen atoms bonded to carbon atoms were placed geometrically. All hydrogen atoms were refined as riding with $U_{eq}(H)=1.2\ U_{iso}(C)$. The final cycle of the refinement included 164 variable parameters R(F)=0.05, wR(F)=0.111, Goodness of fit=1.04. The shortest and largest peak heights were found –0.225 and 0.246 eÅ^{-3}. The ORTEP drawing [15] of the molecule with 50% probability displacement thermal ellipsoids and atomic numbering scheme is shown in Fig. 2. The PLATON drawing [15] of the unit cell is shown in Figure 3. The crystal and experimental data are given in Table 6 and the final atomic parameters are presented in Table 3. Some of the important coordinative bonds, angles and torsions are given in Table 4, 5, 2, respectively.

Acknowledgments.

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