Chemistry of Heterocyclic Compounds, Vol. 41, No. 7, 2005

REACTION OF 5,5-DIMETHYL-2-OXOTETRAHYDROFURAN-4-YLACETO-HYDRAZIDE WITH ALDEHYDES AND KETONES

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The reaction of 5,5-dimethyl-2-oxotetrahydrofuran-4-ylacetohydrazide with a series of aldehydes and ketones led to the synthesis of systems which, according to the ^{1}H NMR spectra, exist exclusively in the linear form. According to the mass spectra, however, in the gas phase some of the compounds can also exist partly in the cyclic form.

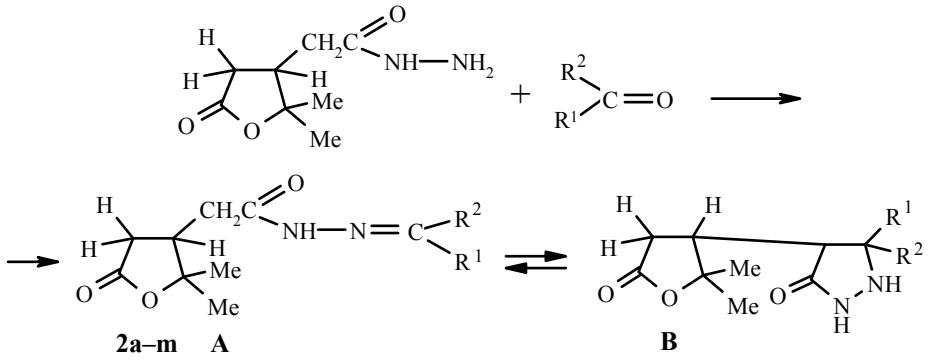
Keywords: 5,5-dimethyl-2-oxotetrahydrofuran-4-ylacetohydrazide.

In a continuation of previous investigations into the synthesis of substituted hydrazones [1-3] we have studied the reaction of 5,5-dimethyl-2-oxotetrahydrofuran-4-acetohydrazide (**1**) [4, 5] with certain aldehydes and ketones.

The reaction with aldehydes takes place when equimolar amounts of the initial compounds are boiled in absolute ethanol and in the presence of catalytic amounts of concentrated sulfuric acid except for acetaldehyde, the reaction of which takes place even at room temperature without the addition of acid.

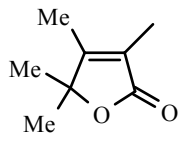
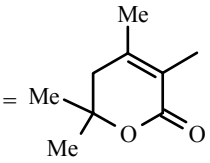
The required products **2a-e** were obtained with overall yields of 82-87% (Table 1).

Scheme 1



2a–m **A** **B**

2 a-e R^1 = H; **f-i, l, m** R^1 = Me; **a** R^2 = Me; **b, f** R^2 = Et; **c** R^2 = Pr; **d, i** R^2 = 2-HOC_6H_4; **e** R^2 = 4-O_2N–C_6H_4; **g** R^2 = *i*-Bu; **h** R^2 = Ph; **j** $R^1 + R^2 = (CH_2)_5$; **k** $R^1 + R^2 = (CH_2)_6$;

l R^2 =  ; **m** R^2 = 

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0009-3122/05/4107-0835

TABLE 1. The Physicochemical Characteristics of Compounds **2a-m**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f	Yield, %
		C	H	N	O			
2a	$C_{10}H_{16}N_2O_3$	56.63 / 56.60	7.52 / 7.56	13.24 / 13.20	22.62 / 22.64	144	0.60	86
2b	$C_{11}H_{18}N_2O_3$	58.44 / 58.41	7.93 / 7.96	12.42 / 12.39	21.21 / 21.24	127	0.58	85
2c	$C_{12}H_{20}N_2O_3$	60.12 / 60.00	8.39 / 8.33	11.61 / 11.67	19.88 / 20.00	167	0.56	84
2d	$C_{15}H_{18}N_2O_4$	62.05 / 62.07	6.25 / 6.21	9.58 / 9.66	22.12 / 22.06	168	0.51	82
2e	$C_{15}H_{17}N_2O_5$	56.47 / 56.43	5.31 / 5.33	13.24 / 13.17	25.08 / 25.07	280	0.55	87
2f	$C_{12}H_{20}N_2O_3$	60.12 / 60.00	8.39 / 8.33	11.61 / 11.67	19.88 / 20.00	95	0.56	82
2g	$C_{14}H_{24}N_2O_3$	62.73 / 62.69	8.87 / 8.95	10.49 / 10.45	17.92 / 17.91	87	0.54	86
2h	$C_{16}H_{20}N_2O_3$	66.61 / 66.67	6.97 / 6.94	9.78 / 9.72	16.64 / 16.67	162	0.53	86
2i	$C_{16}H_{20}N_2O_4$	63.22 / 63.16	6.55 / 6.58	9.24 / 9.21	20.98 / 21.05	158	0.53	82
2j	$C_{13}H_{20}N_2O_3$	61.82 / 61.90	7.57 / 7.94	11.35 / 11.11	19.46 / 19.05	110	0.54	84
2k	$C_{14}H_{22}N_2O_3$	63.21 / 63.16	8.24 / 8.27	10.56 / 10.53	18.01 / 18.04	155	0.54	83
2l	$C_{17}H_{24}N_2O_5$	60.73 / 60.71	7.11 / 7.14	8.36 / 8.33	23.79 / 23.80	150	0.51	82
2m	$C_{18}H_{26}N_2O_5$	61.74 / 61.71	7.44 / 7.43	8.03 / 8.00	22.78 / 22.86	173	0.51	81

The reaction with ketones takes place under analogous conditions with the only difference that the process requires longer heating (5-6 h). As a result the required products **2f-m** are also obtained with high overall yields (82-86%). Compounds **2l**,**m** are obtained without a catalyst and with even longer heating (8-10 h).

It is seen from Scheme 1 that compounds **2a-m** (Table 1) can in principle exist in both linear (hydrazone) form **A** and cyclic (pyrazolidone) form **B**.

The structure of the synthesized compounds was investigated by ^1H and ^{13}C NMR spectroscopy, and some of them were also submitted to mass spectral investigation.

Scheme 2

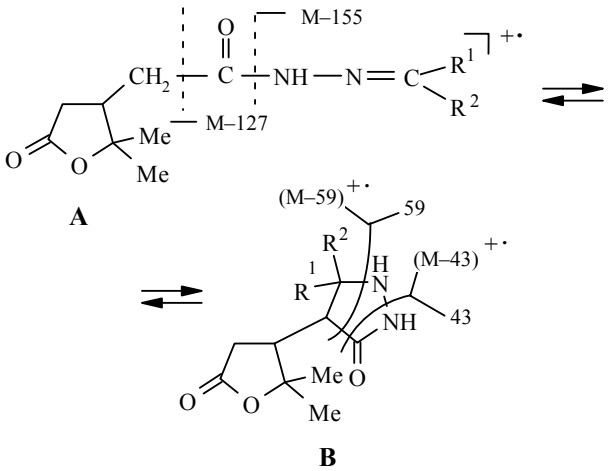


TABLE 2. The Spectral Characteristics of the Synthesized Compounds **2a-m**

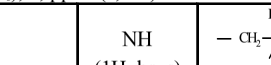
Com-pound	IR spectrum, ν, cm^{-1}					^1H NMR spectrum (DMSO-d_6), δ, ppm. (*J*, Hz)				
	C=N	C=O amide	C=O lactone	NH amide	NH amine	R^1	R^2	NH (1H, br. s)	 (5H, m)	$2CH_3$ (6H, s)
1	2	3	4	5	6	7	8	9	10	11
2a	1630	1670	1760	3180	3360	7.25 and 7.5 (1H, q, *J* = 5.6 and *J* = 5.4; HC=N)	1.86 and 1.90 (3H, d, *J* = 5.6 and *J* = 5.4; CH_3HC=N)	10.2 and 10.8	2.25-2.90	1.35 and 1.50
2b	1630	1670	1760	3180	3370	7.25 and 7.5 (1H, t, *J* = 5.4 and *J* = 4.8; HC=N)	1.13 and 1.18 (3H, t, *J* = 7.5 and *J* = 7.5; CH_2CH_3); 2.2 and 2.3 (2H, qd, *J* = 7.5; 5.4 and *J* = 7.5; 4.8; CH_2CH_3)	10.2 and 10.78	2.35-2.90	1.35 and 1.50
2c	1630	1670	1760	3180	3370	7.25 and 7.5 (1H, t, *J* = 5 4 and *J* = 4.8; HC=N)	0.93 and 0.98 (3H, t, *J* = 7.5 and *J* = 7.5 $CH_2CH_2CH_3$); 1.6-1.75 (2H, m, $CH_2CH_2CH_3$); 2.0 and 2.2 (2H, td, *J* = 7.5; 5.4 and *J* = 7.5; 4.8; $CH_2CH_2CH_3$)	10.2 and 10.8	2.30-2.95	1.35 and 1.50
2d	1630	1670	1760	3180	3370	8.22 and 8.3 (1H, s, HC=N)	6.7-7.5 (4H, m, Ar); 11.1 (1H, s, OH)	11.3 and 11.5	2.25-2.85	1.35 and 1.50
2e	1630	1670	1760	3200	3350	8.22 and 8.3 (1H, s, HC=N)	6.8-7.5 (4H, m, Ar)	10.2 and 10.78	2.30-2.85	1.35 and 1.50
2f	1630	1670	1760	3180	3360	2.0 and 2.2 (3H, s, CH_3C=N)	1.13 and 1.18 (3H, t, *J* = 7.5 and *J* = 7.5; CH_2CH_3); 1.8 and 1.96 (2H, q, *J* = 7.5 and *J* = 7.5; CH_2CH_3)	10.2 and 10.78	2.35-2.90	1.35 and 1.50

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
2g	1630	1670	1760	3180	3360	2.1 and 2.22 (3H, s, $\underline{CH_3}C{=}N$)	0.9 and 0.95 (6H, d, $J = 5.6$ and $J = 5.4$; $CH_2CH(\underline{CH_3})_2$); 1.55-1.65 (1H, m, $CH_2\underline{CH}(CH_3)_2$); 1.85 and 1.97 (2H, d, $J = 5.6$ and $J = 5.4$; $\underline{CH_2}CH(CH_3)_2$)	10.2 and 10.8	2.3-2.88	1.35 and 1.50
2h	1630	1670	1760	3180	3350	2.15 and 2.25 (3H, s, $\underline{CH_3}C{=}N$)	7.4-7.8 (5H, m, Ar)	10.25 and 10.5	2.35-3.0	1.35 and 1.50
2i	1630	1670	1760	3180	3350	2.15 and 2.25 (3H, s, $\underline{CH_3}C{=}N$)	7.4-7.8 (4H, m, Ar); 11.1 (1H, s, OH)	11.3 and 11.5	2.35-3.0	1.35 and 1.50
2j	1630	1670	1760	3180	3360		1.7-1.9 (4H, m, CH_2CH_2); 2.25 (4H, t, $J = 7.5$, 2 $NCCH_2$)	11.3 and 11.5	2.35-3.05	1.35 and 1.50
2k	1630	1670	1760	3180	3360		1.7-1.95 (6H, m, $CH_2CH_2CH_2$); 2.2 (4H, t, $J = 7.5$; 2 $NCCH_2$)	11.3 and 11.5	2.35-3.05	1.35 and 1.50
2l	1630	1670	1760	3200	3350	2.17 and 2.22 (3H, s, $\underline{CH_3}C{=}N$)	1.47 (6H, s, $2CH_3$); 2.15 (3H, s, $\underline{CH_3}C{=}C$)	10.33 and 10.56	2.32-2.84	1.28 and 1.44
2m	1630	1670	1760	3200	3350	2.19 and 2.22 (3H, s, $\underline{CH_3}C{=}N$)	1.45 and 1.5 (6H, s, $2CH_3$); 2.15 (3H, s, $\underline{CH_3}C{=}C$); 2.52 (2H, s, CH_2)	10.33 and 10.56	2.32-2.84	1.25 and 1.45

* In the spectra of all the compounds there were two singlets (3H each) for the $(CH_3)_2C$ group in the regions of 1.35 and 1.5 ppm, a multiplet for the . $-CH_2-\underset{|}{CH}-CH_2-CO$ fragment in the region of 2.25-2.95 ppm, and also two broad singlets for NH (1H) in the region of 10.2 and 10.8 ppm (for compounds **2d** and **2i**, 11.1 and 11.3 ppm, the effect of the *ortho*-OH group).

TABLE 3. The Mass Spectra* of Compounds **2a**,**d**,**f**,**h**

Compound	*m/z* (I_{rel}, %)
2a	212 (35), 197 (34), 169 (12), 156 (20), 153 (14), 127 (18), 126 (15), 112 (22), 111 (10), 86 (12), 85 (24), 84 (19), 83 (23), 69 (26), 68 (11), 58 (100), 57 (21), 55 (27), 43 (48), 42 (21), 41 (57), 39 (12)
2d	290 (100), 275 (13), 224 (14), 223 (42), 164 (15), 163 (12), 147 (30), 136 (20), 135 (19), 122 (10), 121 (53), 120 (33), 119 (18), 107 (11), 102 (19), 93 (15), 92 (12), 91 (10), 78 (10), 77 (15), 66 (16), 65 (17), 64 (11), 55 (10), 51 (14), 41 (18), 39 (12)
2f	240 (100), 225 (38), 211 (40), 197 (21), 181 (12), 154 (10), 114 (17), 113 (54), 109 (10), 99 (11), 87 (13), 86 (95), 85 (16), 83 (14), 71 (21), 70 (34), 69 (65), 68 (15), 57 (29), 56 (10), 55 (30), 54 (13), 43 (47), 42 (63), 41 (67), 39 (11)
2h	288 (71), 287 (33), 273 (19), 162 (25), 161 (19), 135 (13), 134 (100), 133 (46), 119 (19), 118 (29), 117 (14), 92 (11), 77 (29), 69 (12), 55 (12), 43 (18), 41 (23)

* The peaks of ions with I_{rel} > 10% are given.

According to the ^{1}H NMR spectra, recorded in DMSO-d_6 solution, the synthesized compounds exist in the linear form as a mixture of *syn* and *anti* isomers, since the spectra of compounds **2a-e** (R^1 = H) contain double signals for the protons of the CH=N group (in the region of 7.2-7.5 ppm for compounds **2a-c** and in the region of 8.2-8.3 ppm for **2d**,**e**) and also double signals for the CH_3–C=N group in the region of 2.1-2.2 ppm (compounds **2f-i**,**l**,**m**) (Table 2).

In the ^{13}C NMR spectrum of compound **2l** in the region of weak magnetic fields there are signals characteristic of the carbon atoms of the C=C and C=N groups (see the experimental section).

The mass spectra of compounds **2a**,**d**,**f**,**h** contain strong peaks for the molecular ions, and the main dissociation of the latter takes place predominantly with the formation of fragment ions $[M - 127]^+$ and $[M - 155]^{+\cdot}$ or rearrangement ions $[M - 126]^{+\cdot}$ and $[M - 154]^{+\cdot}$ (ketene dissociation), and the hydrogen atom is transferred from the acid part of the molecule onto the nitrogen-containing fragment.

The formation of such ions indicates the presence predominantly of the linear molecular form of the ion **A** in the gas phase (scheme 2).

However, in the mass spectra of the hydrazones of aliphatic carbonyl compounds **2a**,**f** in addition to the above-mentioned fragments there are also ions formed from the molecular ions with loss of 43 (HNCO) or 59 daltons (H_3N_2CO), also indicating the partial presence of the cyclic (pyrazolidinone) form of the molecular ion **B** in the gas phase. Such ions are not present in the mass spectra of the aryl-containing compounds **2d**,**h**.

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded in vaseline oil on a Specord IR-75 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 and 75 MHz respectively) and Tesla BS-497 (100 and 75 MHz respectively) spectrometers with HMDS (δ 0.05 ppm) as internal standard. The EI mass spectrum (direction injection) was obtained on an MX-1321A instrument at 50-70 eV. The purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates with 1:2 acetone–benzene as eluant and development in iodine vapor and in UV light.

The physicochemical and spectral characteristics are given in Tables 1-3.

The hydrazide (**1**) was synthesized by the method in [5].

Reaction of 5,5-Dimethyl-2-oxotetrahydrofuran-4-acetohydrazide (1) with Aldehydes. A. To a solution of the hydrazide **1** (0.5 g, 2.6 mmol) in absolute ethanol (5 ml) we added acetaldehyde (2 ml, 1.56 g, 35 mmol). The reaction mixture was stirred at room temperature for 2 h (monitored by TLC). After distillation

of the solvent the residue was cooled, and the white crystals that separated were filtered off, washed with cold ether, and dried in air. We obtained 0.45 g of compound **2a**.

B. To a solution of the hydrazide **1** (0.5 g, 2.6 mmol) in absolute ethanol (5 ml) we added the corresponding aldehyde (2.6 mmol) and 1-2 drops of concentrated sulfuric acid. The reaction mixture was refluxed for 2 h (monitored by TLC). The product was treated as in method A, and the products **2** were obtained in the form of crystals.

Reaction of the Hydrazide (1) with Ketones. A. To a solution of the hydrazide **1** (0.5 g, 2.6 mmol) in absolute ethanol (5 ml) we added the ketone (2.6 mmol) and 1-2 drops of concentrated sulfuric acid. The reaction mixture was refluxed for 5-6 h (monitored by TLC). The crystals of **2f-k** formed after distillation of the solvent were filtered off, washed with cold ether, and dried in air.

B. Reaction with 2-Acetyl-3,4,4-trimethyl-2-buten-4-olide. To a solution of the hydrazide **1** (0.5 g, 2.6 mmol) in absolute ethanol (10 ml) we added 2-acetyl-3,4,4-trimethyl-2-buten-4-olide (0.44 g, 2.6 mmol). The reaction mixture was refluxed for 8 h (monitored by TLC). The product was treated as in method A, and 0.74 g of **2l** was obtained. ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 21.94, 24.14, 24.14, 26.96 (CH_3); 14.54 (CH_3C=N); 12.41 (CH_3C=C); 32.66, 34.46 (CH_2); 40.29 (CH); 84.65, 85.05 (O–C); 123.01 (C=C); 168.40 (C=N); 169.15, 172.78, 174.01 (C=O).

C. Reaction with 3-Acetyl-4,6,6-trimethyl-5,6-dihydro-2-pyrone. To a solution of the hydrazide **1** (0.5 g, 2.6 mmol) in absolute ethanol (5 ml) we added 3-acetyl-4,6,6-trimethyl-5,6-dihydro-2-pyrone (0.47 g, 2.6 mmol). The reaction mixture was refluxed for 10 h (monitored by TLC). The product was treated as in method A, and 0.77 g of **2m** was obtained in the form of white crystals.

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