Chemistry of Heterocyclic Compounds, Vol. 41, No. 12, 2005

CARBONYL-CONTAINING SPIRO-DIHYDROFURANS IN REACTIONS WITH AMMONIUM ACETATE AND HYDRAZINE HYDRATE

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It has been shown that 2-spiro(3-R-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran)-2'-(5',5'-dimethylcyclohexane-1',3'-diones) undergo conversions in reactions with ammonium acetate and hydrazine hydrate into substituted dihydropyridin-2-ones and tetrahydro-1,2-diazepin-7-ones respectively as a result of ring-opening of the spirodimedonyl fragment through the corresponding amides and hydrazides of δ-keto acids.

Keywords: dihydropyridone, spirodihydrofuran, tetrahydrodiazepinone.

We previously reported that under Chichibabin reaction conditions ($AcONH_4$, AcOH) 2-spiro(3-R-6,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran)-2'-(5',5'-dimethylcyclohexane-1',3'-diones **1a,b** undergo conversion into 6-(3'-R-6',6'-dimethyl-4'-oxo-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl)-4,4-dimethyl-3,4-dihydropyridin-2-ones **2a,b,** accessible with difficulty under other conditions [1]. A probable mechanism was proposed for their formation through amides of δ-keto acids with subsequent N-heterocyclization.

Confirmation has been obtained in the present work that the ring-opening of the dimedone alicycle in the condensed spirodihydrofurans **1** in weakly acidic and basic media has a general character and takes place not only under the action of ammonium acetate in acetic acid on the latter, but also of hydrazine hydrate.

In fact spirodihydrofuran **1c** in the Chichibabin reaction, like its analogs **1a,b**, forms 6-[6',6'-dimethyl-3'-(4-methoxyphenyl)-4'-oxo-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl]-4,4-dimethyl-3,4-dihydropyridin-2-one (**2c**), existing in the lactam form.

By the action of hydrazine hydrate in isopropyl alcohol on spirane **1a** 3-(4'-hydrazono-6',6'-dimethyl-2',3',4',5',6',7'-hexahydrobenzofuran-2'-yl)-4,5,6,7-tetrahydro-1,2-diazepin-7-one (**3a**) is formed in 55% yield after 3 h.

Due to the absence of a substituent at the $C_{(3)}$ atom of the heterocyclic fragment not only does ring-opening of the spiroalicycle with subsequent azacyclization to a tetrahydro[1,2]-diazepin-7-one become possible, but also nucleophilic attack of hydrazine hydrate at the conjugated sterically unhindered carbonyl group with the formation of a hydrazone can occur.

Under the very same conditions, probably due to the steric factor, the carbonyl function at the $C_{(4)}$ atom of the hydrobenzofuran ring in substrate **1b** remains unaffected, when the general character of the reaction is retained.

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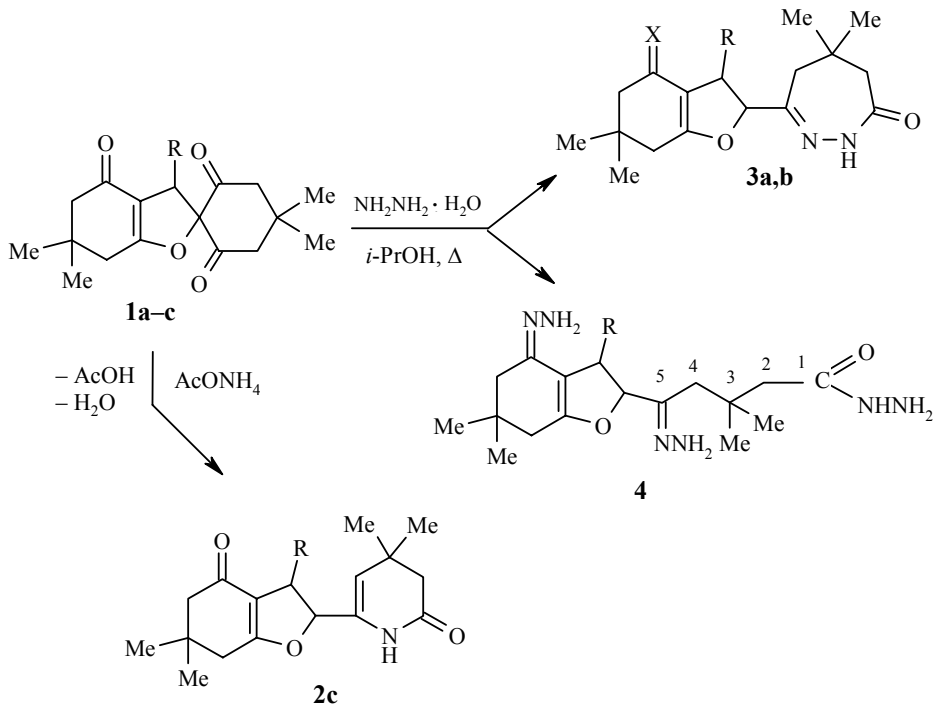

1,3 a R = H, **b** R = Ph; **1c**, **2c, 4** R = 4-MeOC$_6$H$_4$; **3 a** X = NNH$_2$, **b** X = O

Unlike spirodihydrofurans **1a,b** spirane **1c** undergoes a change only after 30 h on maintaining all the other parameters of the reaction (a check on the progress of the reaction was effected by TLC). The reaction product (97% yield) was the hydrazide of 5-[4'-hydrazono-6',6'-dimethyl-3'-(4-methoxyphenyl)-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl]-5-hydrazono-3,3-dimethylpentanoic acid (**4**).

The presence, apparently, of a bulky substituent adjacent in space and of two methyl groups at the $C_{(3)}$ atom of the aliphatic chain of the substituted δ-keto acid hinders heterocyclization, while not excluding functionalization under the action of hydrazine hydrate.

The formation of hydrazide **4** confirms the hypothesis, introduced by us when considering the reaction of spirodihydrofurans with ammonium acetate, on the participation of a δ-keto acid amide as an intermediate in the synthesis of substituted 3,4-dihydropyridin-2-ones [1]. The mechanism of forming tetrahydrodiazepinones **3a,b** is compatible with the proposed scheme and is in agreement with the known ability of spirodihydrofuran **1a**, under the action of sodium hydroxide, to give the corresponding δ-keto acid [2]. An analogous character of the conversions of the spirodimedone fragment was noted for 3-spiro(6,6-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-3-yl)-2'-(5',5'-dimethylcyclohexan-1',3'-dione) in the presence of sodium ethylate [3].

Absorption bands were present in the IR spectrum of dihydropyridin-2-one **2c** (Table 1) for the NH bond at 3208 and for carbonyl groups at 1664 cm^{-1} (br). There was a signal in the ^{1}H NMR spectrum of compound **2c** for an amide group proton at 1.77 ppm, which disappears on deuterium exchange, as in the 3-phenyl-substituted analog [1]. The vinylic proton resonates at 4.8 ppm (Table 2).

Bands were observed in the IR spectra of tetrahydrodiazepin-7-ones **3a,b** and product **4** for the stretching vibrations of the amide groups at 3100-3400 cm^{-1}, the conjugated carbonyl group, and the amide I band for product **3b** at 1636 cm^{-1} (broad band). For the unsubstituted compound **3a** the $\nu_{C=O}$ (amide I) band appears at 1630 cm^{-1}. The amide II bands (δ_{NH} and δ_{C-N}) for compounds **3a,b** and **4** are found at 1572-1580 cm^{-1}.

The ^{1}H NMR spectra of compounds **3a,b** (Table 2) contained four singlet signals for the protons of the methyl groups at 0.6-1.2 ppm. The protons of the methylene groups resonate at 1.92-2.12 (2.12-2.31) ppm respectively. The signals of the –NH$_2$ and =NH group protons at 1.40 and 1.68 ppm in the spectrum of

TABLE 1. Physicochemical Characteristics of Compounds **2c**, **3a,b,** and **4**

Compound	Empirical formula	Found, % / Calculated, %			IR spectrum, ν, cm^{-1}	mp, °C*	Yield, %
		C	H	N			
2c	$C_{23}H_{29}O_4N$	72.59 / 72.06	7.16 / 7.57	3.61 / 3.65	3208 (NH), 1664 (C=O, br.)	230-232	40
3a	$C_{17}H_{26}O_2N_4$	64.34 / 64.15	8.68 / 8.18	17.86 / 17.61	3415-3100 (NH, NH_2), 1630 ("Amide I"), 1572 ("Amide II")	114 (with dec.)	55
3b	$C_{23}H_{28}O_3N_2$	72.32 / 72.63	7.59 / 7.37	7.03 / 7.37	3250-3150, 3304 (NH, NH_2), 1636 (C=O), 1636 ("Amide I"), 1580 ("Amide II")	125 (with dec.)	52
4	$C_{24}H_{36}O_3N_6$	63.57 / 63.16	7.54 / 7.89	18.34 / 18.42	3500-3100 (NH, NH_2), 1612 ("Amide I"), 1572 ("Amide II")	130 (with dec.)	97

*Recrystallized from ethanol (compound **2c**) and hexane (compounds **3a,b** and **4**).

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)			
	NH; NH_2	OCH_3	Ar–H	other signals
2c	1.77* (1H, br. s)	3.69 (3H, s)	6.72–7.28 (4H, m)	0.66 (3H, s, CH_3); 0.85 (3H, s, CH_3); 1.01 (3H, s, CH_3); 1.15 (3H, s, CH_3); 1.94 (1H, d, *J* = 2, H-2'); 2.08 (5H, m, H-3',3,5'); 2.37 (2H, s, H-7'); 4.80 (1H, s, H-5)
3a	1.68 (1H, br. s); 1.40 (2H, br. s)	—	—	0.96 (12H, m, $4CH_3$); 1.92-2.12 (10H, m, H-3',5',7',4,6); 2.60 (1H, m, H-2')
3b	2.60 (1H, br. s)	—	7.12 (5H, m)	1.09 (12H, m, $4CH_3$); 2.12-2.31 (8H, m, H-4,6,5',7'); 4.40 (1H, d, *J* = 3, H-2'); 3.52 (1H, d, *J* = 3, H-3')
4	1.76 (1H, s); 1.60 (6H, m)	3.73 (3H, s)	6.80-7.04 (4H, m)	1.04 (12H, m, $4CH_3$); 2.10-2.52 (8H, m, H-2,4,5',7'); 4.32 (1H, d, *J* = 3, H-2'); 3.16 (1H, d, *J* = 3, H-3')

* Resonate in one region with the methylene group protons.

tetrahydrodiazepinone **3a** disappear on deuterium exchange, like the signal of the amide proton of product **3b** at 2.60 ppm. The H-2' protons of **3a** are displayed as a multiplet at 2.60 ppm, and the H-2',3' (**3b**) protons as doublets at 4.40 and 3.52 ppm respectively.

A singlet was observed in the ^{1}H NMR spectrum of hydrazide **4** for the protons of the methoxyl group at 3.73 ppm, and a multiplet for the aromatic protons at 6.80-7.04 ppm. Deuterium exchange was accompanied by disappearance of the signals at 1.76 and 1.60 ppm, which belong to the protons of the hydrazide and hydrazone functions. The H-2,4,5',7'-methylenic protons resonate as a multiplet at 2.10-2.52 ppm.

The presence in the molecules of the substances synthesized by us of two types of heterocycle opens new prospects for the chemistry of these complexly constructed compounds. The special features in the

behavior of the spirodihydrofurans made apparent under the conditions of the Chichibabin reaction, and the available literature information on acid–base catalysis of the ring-opening of dimedone, enable the process of their directed transformation to the corresponding azaheterocycles to be put into effect.

EXPERIMENTAL

The IR spectra were recorded on a Specord M 80 spectrometer in nujol and hexachlorobutadiene, and the ^{1}H NMR spectra on a Varian FT 80A (80 MHz) instrument, solvent was $CDCl_3$, internal standard was TMS.

6-[3'-(4-Methoxyphenyl)-6',6'-dimethyl-4'-oxo-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl]-4,4-dimethyl-3,4-dihydropyridin-2-one (2c). A solution of spirodihydrofuran **1c** (1 g, 3.4 mmol) and ammonium acetate (1.33 g, 18 mmol) in acetic acid (20 ml) was boiled under reflux for 12-16 h. The reaction mixture was washed with saturated sodium carbonate solution, extracted with chloroform, the extract was dried over $MgSO_4$, and evaporated. The residue, an oil, was rubbed in acetone and crystallized from isopropyl alcohol. Yield 0.4 g.

3-(4'-Hydrazono-6',6'-dimethyl-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl)-4,5,6,7-tetrahydro-1,2-diazepin-7-one (3a). A solution of spirodihydrofuran **1a** (0.5 g, 1.72 mmol) and hydrazine hydrate (0.43 g, 8.6 mmol) in isopropyl alcohol (15 ml) was boiled under reflux for 3 h, and evaporated. The residue, an oil, was rubbed under hexane, and crystallized from hexane. Yield 0.3 g.

2-(4'-Hydrazono-6',6'-dimethyl-3'-phenyl-2',3',4',5',6',7'-hexahydrobenzofur-2'-yl)-4,5,6,7-tetrahydro-1,2-diazepin-7-one (3b) was obtained analogously to compound **3a** from spirodihydrofuran **1b** (1 g, 2.7 mmol) and hydrazine hydrate (0.7 g, 13.6 mmol) in isopropyl alcohol (40 ml). Yield 0.56 g.

Hydrazide of 5-[4'-Hydrazono-3'-(4-methoxyphenyl)-6',6'-dimethyl-2',3',4',5',6',7'-hexahydro-benzofur-2'-yl]-5-hydrazono-3,3-dimethylpentanoic Acid (4) was obtained analogously to compound **3a** from spirodihydrofuran **1c** (0.37 g, 0.9 mmol) and hydrazine hydrate (0.63 g, 4.6 mmol) in isopropyl alcohol (30 ml) (boiling for 30 h). Yield 0.42 g.

The work was carried out with the support of grant RFFI 03-03-33026a.

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