Chemistry of Heterocyclic Compounds, Vol. 42, No. 1, 2006

A NEW REACTION OF THE PHENYLHYDRAZONES OF 1,5-DIKETONES. SYNTHESIS OF DIHYDROPYRAN DERIVATIVES

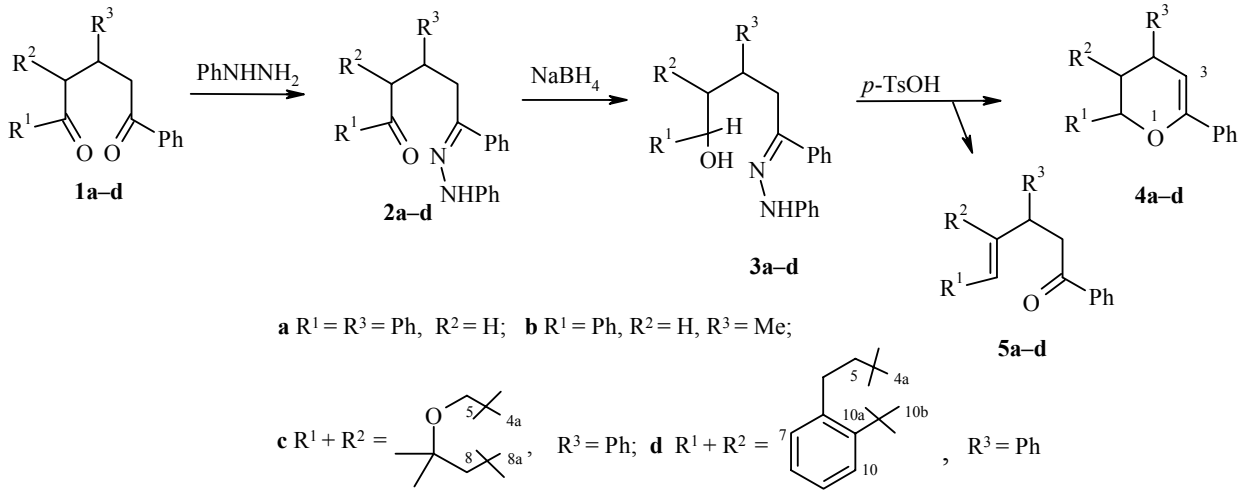
T. V. Moskovkina

It was shown that the monophenylhydrazones of 1,5-diketones are converted by reduction with borohydride followed by treatment of the obtained hydrazino alcohols with acidic agents into derivatives of dihydropyran with the elimination of phenylhydrazine as the respective salt. γ,δ-Unsaturated ketones were isolated as side products of this reaction. The ways in which these compounds are formed are discussed.

Keywords: dihydropyrans, 1,5-diketones, monophenylhydrazones, unsaturated ketones, borohydride reduction, cyclization.

1,5-Diketones and their derivatives are readily obtainable synthons for the synthesis of various heterocyclic systems. For example, pyridocarbazoles [1], indoloacridines [2], cinnolines [3], and indole derivatives [4] were obtained from the phenylhydrazones of 1,5-diketones, while a homolog of vibrindole (an antibiotic of the diindolylmethane series) was synthesized from the bisphenylhydrazone of heptane-2,6-dione [5].

In the present work it was shown that the monophenylhydrazones **2a-d**, obtained from the 1,5-diketones **1a-d**, are transformed into derivatives of dihydropyran **4a-d** during borohydride reduction followed by treatment of the reaction mixtures with acidic agents.

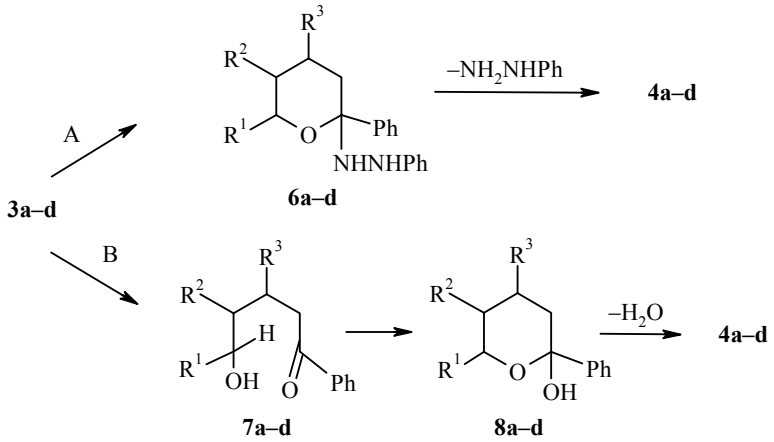


Far-East State University, Institute of Chemistry and Applied Ecology, Vladivostok, Russia; e-mail: innast@imb.dvo.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 26-31, January, 2006. Original article submitted April 26, 2004.

The monophenylhydrazones **2a-d** were obtained during the reaction with phenylhydrazine in alcohol with boiling in the presence of sodium acetate. Compounds **2a-c** had been known before [3, 4], while the hydrazone **2d** was obtained for the first time.

The production of the dihydropyrans **4a-d** from the phenylhydrazones **2a-d** can be realized in one or two stages, i.e., with or without isolation of the intermediate hydrazono alcohols **3a-d**. The latter are produced with good yields after borohydride reduction of the hydrazones **2a-d** in ethyl or isopropyl alcohols and give the derivatives **4a-d** and phenylhydrazine as the salt of the respective acid when treated with *p*-toluenesulfonic acid or with absolute alcohol saturated with hydrogen chloride. The yields of the target compounds **4a-d** amount to 30-50%.

Their formation can be represented as resulting from cyclization of the hydrazino alcohols followed by the elimination of phenylhydrazine (path A). We consider path B through hydrolysis of the hydrazone fragment, subsequent cyclization of the ketols **7a-d**, and dehydration of the hydroxytetrahydropyrans **8a-d** to be less likely. In actual fact, the hydrazone groups of the initial compounds **2a-d** were not hydrolyzed during the above-mentioned treatment with acid, as was established by TLC. It can be assumed that such hydrolysis also does not occur in the hydrazono alcohols **3a-d**.



The properties and spectral data of the obtained compounds are given in Table 1. It should be noted that the IR spectrum of the hydrazone **2c** contains an absorption band at 1700 cm^{-1}, confirming that the hydrazone ia formed at a carbonyl of the phenacyl type. Accordingly, in the IR spectra of the hydrazones **2c**,**b**,**d** the bands of the C=O stretching vibrations are at 1670-1678 cm^{-1}. For the hydrazone **2d** the choice in favor of the presented structure was made on the basis of its mass spectrum. In the electron-impact mass spectrum of the previously unknown hydrazone **2d** there is not only a molecular ion peak at 444* but there is also a peak for a fragment ion at 298, corresponding to removal of the side chain with cleavage of the C–C bond at the β position to the carbonyl group of the tetralone fragment of the molecule.

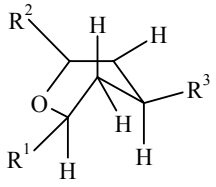
The hydrazono alcohols **3a-d** do not have bands for the stretching vibrations of the carbonyl group in the IR spectra, but there are bands for the hydroxyl group at 3580-3600 and also bands for the N–H bonds at 3296-3340 and the C=N bonds at 1602 cm^{-1}.

In addition to the data from the NMR spectra, given in Table 1, the structure of the dihydropyrans **4a-d** is also confirmed by the data from the IR, mass, and UV spectra. Thus, their IR spectra do not contain bands for the stretching vibrations of the C=O and O–H groups, but there are bands for the C=C bond at 1645-1652 cm^{-1}.

* Here and subsequently the *m*/*z* values for the ion peaks are given.

In the UV spectra (isopropyl alcohol–water) absorption maxima are observed at 270 nm. In the mass spectra of compounds **4a**,**b**,**d** there are molecular ion peaks at 312, 250, and 338, while in the chemical ionization mass spectrum of compound **4c** there is a peak for the $[M+H]^+$ ion at 321.

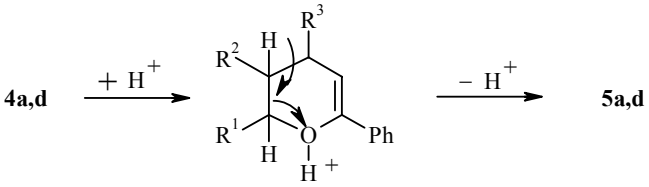
Features of the ^{1}H NMR spectra of compounds **4a**,**b** make it possible to put forward certain ideas about the stereochemistry of these compounds. Thus, in the spectra of **4a**,**b** the signals for the H-6 protons are observed in the form of a doublet of doublets at 5.06 ppm. The presence of spin–spin coupling constants of the axial–axial type (J = 10 Hz) demonstrates that this proton has the axial orientation. The vinyl proton H-3 gives a doublet of doublets at 5.59 and 5.42 ppm (J_1 = 4.6 and J_2 = 1.2 Hz in the spectrum of compound **4a**, and J_1 = 4.4 and J_2 = 1.0 Hz in the spectrum of **4b** respectively). The small constant probably results from so-called W interaction with one of the protons at position 5. Stereochemically these compounds then correspond to the formula **9**.



9

The unsaturated ketones **5a**,**d** were isolated in this reaction as side products. The structure of the ketones **5a**,**d** was demonstrated by data from the NMR, IR, and mass spectra. For compound **5d** it was also proved by 2D NMR spectroscopy, i.e., by ^{1}H, ^{1}H-COSY, and HMQC experiments, which made it possible to identify all the spin systems (Table 1). Their mass spectra have molecular ion peaks at the same m/z values as in the spectra of the corresponding dihydropyrans **4a**,**d**.

These compounds are presumably formed from the corresponding dihydropyrans according to the scheme given below. This was confirmed by an experiment on the transformation **4a** → **5a** during treatment with absolute alcohol saturated with HCl.



The main method for the production of dihydropyran derivatives is diene synthesis from α,β-unsaturated ketones and various compounds containing a double bond [6-9]. It was also possible to convert certain compounds containing carbonyl groups at positions 1 and 5 into such derivatives. Thus, the synthesis of dihydropyrans from ε-keto acids by the action of acetic anhydride is well known [10]. Oxopropylpyrazolones undergo cyclization during ionic hydrogenation with triethylsilane and trifluoroacetic acid in the presence of catalytic amounts of boron trifluoride etherate with the formation of substituted 5,6-dihydropyrano[3,2-*d*]-pyrazoles [11]. Although the synthesis of dihydropyrans from the 1,5-diketones themselves has not been described, various triketones of the oxo-1,5-diketone type were converted by ionic or catalytic hydrogenation over Raney nickel or by borohydride reduction into dihydropyran derivatives containing a keto group conjugated with the double bond of the dihydropyran ring [11]. At the same time during catalytic hydrogenation over Raney nickel at 150°C in acetic acid 2-(3-oxo-1,3-diphenylpropyl)tetral-1-one (**1d**) undergoes reduction of the carbonyl groups and heterocyclization, leading to the corresponding tetrahydropyran [11].

TABLE 1. The Properties of Dihydropyrans **4a-d** and Unsaturated Ketones **5a**,**d**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Mass spectrum, *m/z*	Yield, %
		C	H			
4a	$C_{23}H_{20}O$	88.56 / 88.46	6.27 / 6.41	120	312 $[M]^+$	66
4b	$C_{18}H_{18}O$	86.62 / 86.40	7.10 / 7.20	100-101	250 $[M]^+$	30
4c	$C_{23}H_{20}O$	86.00 / 86.25	6.10 / 6.25	88-90	320 $[M]^+$	40
4d	$C_{25}H_{22}O$	88.54 / 88.75	6.28 / 6.50	63-64	338 $[M]^+$	50
5a	$C_{23}H_{20}O$	88.42 / 88.46	6.30 / 6.41	78	312 $[M]^+$	30
5d	$C_{25}H_{22}O$	88.68 / 88.75	6.60 / 6.50	64	339 [M+H]	24

TABLE 2. The Spectra of Dihydropyrans **4a-d** and Unsaturated Ketones **5a**,**d**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
4a	1652 (C=C)	5.59 (1H, dd, J_1 = 4.6, J_2 = 1.2, H-3); 5.06 (1H, dd, J_1 = 10.0, J_2 = 2.7, H-6); 3.67 (1H, m, H-4); 2.38 (1H, ddd, J_1 = 6.3, J_2 = 10.0, J_3 = 13.7, H_a-5); 2.18 (1H,ddt, J_1 = 13.7, J_2 = 2.7, J_3 = 1.2, H_e-5)
4b	1650 (C=C)	5.42 (1H, d, J_1 = 1.0, J_2 = 4.4, H-3); 5.05 (1H, dd, J_1 = 2.7, J_2 = 9.5, H-6); 2.42 (1H, ddd, J_1 = 3.2, J_2 = 6.7, J_3 = 13.4, H-4); 2.10 (1H, ddd, J_1 = 6.1, J_2 = 9.5, J_3 = 13.7, H_a-5); 1.83 (1H, ddt, J_1 = 1.2, J_2 = 3.7, J_3 = 13.7, H_e-5); 1.17 (3H, d, J_1 = 4.9, CH_3)
4c	1650 (C=C)	5.38 (1H, d, *J* = 3.6, H-3); 4.51 (1H, m, H-8a); 3.71 (2H, m, H-5); 3.53 (1H, dd, J_1 = 3.6, J_2 = 6.1, H-4); 1.98 (1H, m, H-4a); 1.66 (1H, dd, J_1 = 4.1, J_2 = 13.7, H_e-8); 2.05 (1H, dd, J_1 = 8.0, J_2 = 13.7, H_a-8); 1.26 (3H, s, CH_3); 1.38 (3H, s, CH_3)
4d	1656 (C=C)	5.47 (1H, d, *J* = 2.8, H-3); 4.95 (1H, d, *J* = 2.8, H -10b); 3.45 (1H, dd, J_1 = 2.8, J_2 = 6.0, H-4); 1.88 (1H, m, H -4a); 3.0 (2H, m, H-6); 2.7 (2H, m, H-5)
5a	1648 (C=C), 1681(CO)	3.51 (2H, AB part of ABX system J_1 = 7.0, J_2 = 2.2, J_3 = 16.7, 2H-2); 4.31 (1H, m, H-3); 6.41 (1H, m, H-4)
5d	1652 (C=C), 1678 (CO)	3.46 (1H, dd, J_1 = 7.3, J_2 = 16.6, H-2); 3.64 (1H, dd, J_1 = 7.2, J_2 = 16.6, H-2); 4.24 (1H, t, *J* = 7.5, H-3); 6.35 (1H, br. d, *J* = 1.4, H-5); 2.17 (2H, m, 2H-6); 2.72 (2H, m, 2H-7)

The transformation of the monophenylhydrazones of 1,5-dicarbonyl compounds into dihydropyran derivatives was previously unknown. Thus, we have discovered a new direction for the transformations of these readily obtainable compounds.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in deuterochloroform on a Bruker WM-250 instrument (250 MHz) with TMS as internal standard. The IR spectra were recorded on a Spectrum BX-2 FT-IR System spectrometer (Perkin-Elmer). The mass spectra were obtained on an LKB 9000S instrument with direct injection into the ion

source at ionization potential 70 eV. HPLC-MS was conducted on an Agilent 1100 Series LC/MSD chromato-mass spectrometer (Hewlett Packard, USA) with an LiChrCART CN column (4 × 250 mm, sorbent grain size 5 μ) with thermostat temperature 40°C and linear gradient elution (30-70% aqueous acetonitrile) at 2 deg/min. The elution rate was 0.5 ml/min, detection was by the electron absorption spectra (200-300 nm), electrospray ionization at atmospheric pressure, positive ion recording, ionizer potential 70 eV, potential in ionization chamber 4 kV, drying gas (nitrogen) rate 6 l/min, spray gas (nitrogen) pressure 50 kg/cm^2. The range of recorded masses was *m*/*z* 150-700.

The melting points of the isolated compounds were determined on a Boetius bench. Silica gel L (Chemapol, former Czechoslovakia) or aluminum oxide was used for column chromatography. The reactions were monitored and the reaction mixtures were separated by TLC on Sorbfil plates with development in UV light or with iodine vapor.

Monophenylhydrazones of 1,5-Diketones 2a-d. These compounds were obtained as described in [4]. Compounds **2a-c** were previously known [3, 4]. The yield of the monophenylhydrazone **2d** was 90%; mp 131°C (alcohol). Found %: C 84.00; H 6.25; N 6.47. $C_{31}H_{28}N_2O$. Calculated %: C 83.78; H 6.30; N 6.30. IR spectrum (potassium bromide), ν, cm^{-1}: 1605 (C=N), 1671 (C=O), 3260 (N–H). Mass spectrum (electron impact), *m*/*z* (I_{rel}, %): 444 $[M]^+$ (20); 335 (7); 298 (70); 99 (90); 57 (100).

Reduction of Monophenylhydrazones 2a-d Followed by Heterocyclization. A. To a solution of the hydrazone **2a-d** (1 mmol) in isopropyl alcohol (20 ml) we added $NaBH_4$ (0.152 g, 4 mmol), and we boiled the mixture for 2 h. The solvent was removed by heating on a water bath, and water (30 ml) and ether (30 ml) were added to the residue. The ether layer was separated, washed to a neutral reaction with water, dried with magnesium sulfate, and evaporated. The residue was boiled with a 0.6% solution of *p*-toluenesulfonic acid in absolute benzene (10 ml) with a Dean–Stark trap. The solvent was distilled from the reaction mixture, and the residue was treated with water (20 ml) and ether (20 ml). The ether layer was separated, washed to a neutral reaction with water, dried with magnesium sulfate, and evaporated. The residue was chromatographed on a column of aluminum oxide in the 1:50 ethyl acetate–petroleum ether system. 2,4,6-Triphenyl-5,6-dihydropyran (**4a**), 4-methyl-2,6-diphenyl-5,6-dihydropyran (**4b**), 7,7-dimethyl-2,4-diphenyl-4a,7,8,8a-tetrahydro-4H,5H-pyrano[4,3-*b*]pyran (**4c**), 2,4-diphenyl-4a,5,6,10b-tetrahydro-4H-benzo[*h*]chromene (**4d**), and (as side products) the unsaturated ketones 1-oxo-1,3,5-triphenyl-4-pentene (**5a**) and 1-(1,2-dihydro-3-naphthyl)-1,3-diphenyl-3-propanone (**5d**) were obtained (Tables 1 and 2).

B. The reduction was conducted as described above. The hydrazono alcohols **3c**,**d** were crystallized from alcohol, while the hydrazono alcohols **3a**,**b** were purified by flash column chromatography on aluminum oxide with gradient elution with ethyl acetate and petroleum ether (1:50 → 1:1) as solvents. The yield of compound **3a** was 88% in the form of an oil. IR spectrum (potassium bromide), ν, cm^{-1}: 1602 (C=N), 3592 (OH), 3300 (NH). The yield of compound **3c** was 93%; mp 110-112°C (alcohol). IR spectrum (potassium bromide), ν, cm^{-1}: 1602 (C=N), 3578 (O–H), 3264 (N–H). Mass spectrum (electron impact), *m*/*z* (*I*, %): 429, $[M+H]^+$. The yield of compound **3d** was 73%; mp 176°C (from alcohol). IR spectrum (potassium bromide), ν, cm^{-1}: 1602 (C=N), 3591 (O–H), 3260 (N–H). Mass spectrum (electron impact), *m*/*z* (*I*, %): 446 $[M]^+$, 428 $[M^+ - H_2O]$, 298, 167.

The obtained hydrazono alcohols were cyclized as described above. The constants and analytical and spectral data of the products are given in Tables 1 and 2.

Preparation of the Unsaturated Ketone 5a from the Dihydropyran 4a. A solution of the dihydropyran **4a** (30 mg) in absolute ethanol (2 ml) saturated with HCl was heated for 1 h. The ethanol was distilled under vacuum, and water (5 ml) and ether (5 ml) were added to the residue. The ether layer was washed with water and dried with magnesium sulfate. The ether was distilled, and the residue was purified by flash column chromatography on aluminum oxide in the 1:50 ethyl acetate–petroleum ether system. We obtained 19 mg (65%) of the ketone **5a**.

REFERENCES

1. T. V. Moskovkina and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.*, 46 (1986).
2. T. V. Moskovkina and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.*, 822 (1983).
3. T. V. Moskovkina and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.*, 645 (1976).
4. T. V. Moskovkina, *Khim. Geterotsikl. Soedin.*, 1355 (2002).
5. T. V. Moskovkina, T. V. Pyanzin, and V. V. Isakov, *Khim. Geterotsikl. Soedin.*, 281 (2001).
6. A. Sera, M. Ohara, H. Yamada, E. Egashira, N. Ueda, and J. Setsune, *Bull. Chem. Soc. Jpn.*, **67**, 1912 (1994).
7. W. G. Dauben and H. O. Krabbenhoft, *J. Org. Chem.*, **42**, 282 (1977).
8. R. I. Longley, Jr. and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).
9. G. Dujardin, M. Maudet, and E. Brown, *Tetrahedron Lett.*, **35**, 8619 (1994).
10. M. Trolliet, R. Longegari, and J. Dreux, *Bull. Soc. Chim. France*, 1484 (1974).
11. V. G. Kharchenko, N. V. Pchelintseva, L. I. Markova, and O. V. Fedotova, *Khim. Geterotsikl. Soedin.*, 1155 (2000).