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2-AROYLHEXANONES IN THE SYNTHESIS OF AZOLES

A. G. Mikhailovskii[1]*, Z. G. Aliev[2], N. G. Bazina,

A. A. Pantyukhin[1], and M. I. Vakhrin[1]

2-Aroylcyclohexanones, obtained from piperidinocyclohexene, react with hydrazine, hydroxylamine, and o-phenylenediamine to give the corresponding derivatives of bicyclic heterocycles – indazole, 2,1-benzisoxazole, and 2-spiro-cyclohexylbenzimidazole. The structure of a derivative of benzyloxazole has been determined by X-ray crystallography.

Keywords: 3-aryl-4,5,6,7-tetrahydro-2,1-benzisoxazoles, 3-aryl-4,5,6,7-tetrahydroindazoles, 2-aroylcyclohexanones, hydrazine, hydroxylamine, piperidinocyclohexene, 2-*spiro*-(2-aroylcyclohexyl)benzimidazolidines, *o*-phenylenediamine, X-ray crystallography.

1,3-Diketones are well known as structural blocks used in the synthesis of heterocycles [1-3], in particular for the construction of natural and biologically active molecules. The 2-aroylcyclohexanones are the least well studied group of 1,3-diketones. In discussion of the properties of these compounds, it should be considered that the carbonyl group of the aroyl unit might be expected to be relatively inert in reactions with nucleophiles, leading to regio- and stereoselectivity of the process. The objective of the present study was to investigate the reactions of 2-aroylcyclohexanones with binucleophiles.

The starting diketones **2a-d** were obtained by the general method of alkylation of the enamine **1** with aroyl chlorides [4, 5]. The reaction was shown to proceed in good yield and was suitable for preparative purposes. The diketones obtained may be used in the synthesis of some five-membered heterocycles. For example, the diketones **2a**,**b** react with hydrazine hydrate to give the pyrazoles **3a**,**b**, the reaction of the diketones **2a**,**c** with hydroxylamine in any proportions gave the corresponding 4,5,6,7-tetrahydro-2,1-benzisoxazoles **4a**,**b**, and the reaction of the diketones **2a**,**b** with *o*-phenylenediamine in boiling glacial acetic acid gave the 2-*spiro*-cyclohexylimidazolines **5a**,**b**. The characteristics of the substances obtained are given in Table 1.

The signal of the proton of the CH group which is found between the two carbonyl groups in the ^{1}H NMR spectra, (4.17-4.34 ppm) appears as a broad triplet and is characteristic of the diketones **2a-d**. In the spectrum of the diketone **2c** this signal has an intensity corresponding to approximately 0.5H. In the spectrum of compound **2b** the signal of the CH group is not observed, but singlet corresponding to the OH group (16.45 ppm) is present, indicating the complete enolisation of the diketone **2b**.

* To whom correspondence should be addressed, e-mail: perm@pfa.ru.

[1]Perm State Pharmaceutical Academy, Perm 614990, Russia.
[2]Institute of the Problems of Chemical Physics, Russian Academy of Sciences, Chernogolovka 142432, Moscow Region, Russia; e-mail: aliev@icp.ac.ru.

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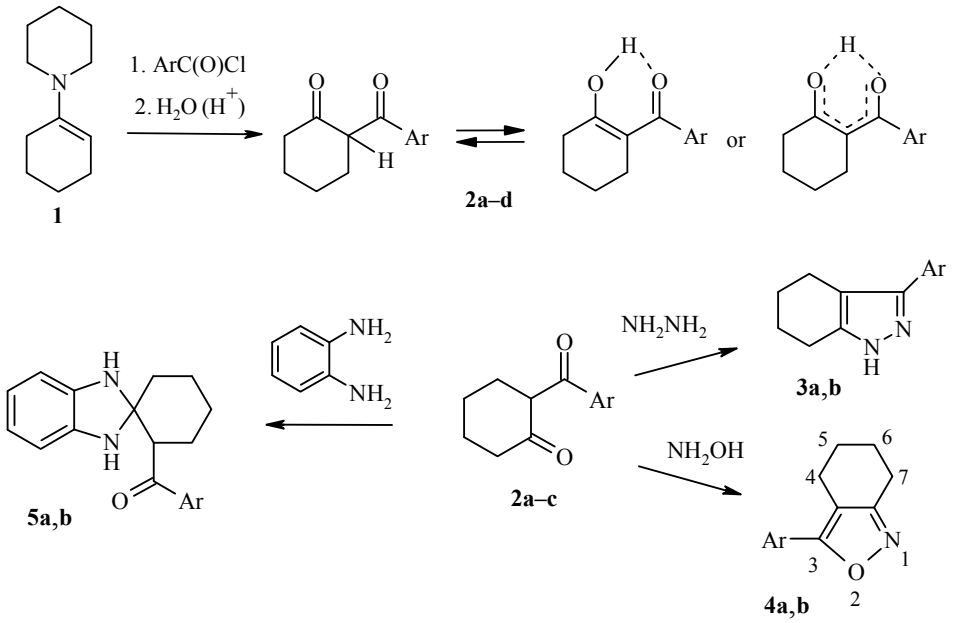


2a–5a Ar = *p*-MeC_6H_4; **2b**, **3b**, **5b** Ar = *p*-$NO_2C_6H_4$; **2c**, **4b** Ar = *p*-BrC_6H_4; **2d** Ar = 3,4-$(MeO)_2C_6H_3$

This fact is readily explained by the acceptor properties of the nitro group which increases the CH-acidity. The somewhat decrease in the integrated intensity of the signals of this CH group indicates the partial enolisation of the diketones **2a**,**d**. Ethanolic solutions of all four diketones **2a-d** gave a color with $FeCl_3$ solution which is a positive qualitative reaction for an enolic hydroxide.

In the ^1H NMR spectra of the pyrazoles **3a**,**b** singlets of the NH group are present (11.53 and 11.31 ppm respectively). In the case of the isoxazoles **4a**,**b** the singlets of the CH protons are absent which indicates the correctness of the structures. In the spectra of the benzimidazolines **5a**,**b** singlets of protons of two NH groups are present (11.06 and 11.05 ppm).

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	Br	N		
2a	$C_{14}H_{16}O_2$	77.7 / 77.8	7.4 / 7.5		—	92-93	84
2b	$C_{13}H_{13}NO_4$	63.1 / 63.2	5.3 / 5.3		5.8 / 5.7	72-73	32
2c	$C_{13}H_{13}BrO_2$	55.4 / 55.5	4.6 / 4.7	28.2 / 28.4	—	106-107	51
2d	$C_{15}H_{18}O_4$	68.6 / 68.7	6.8 / 6.9		—	108-110	47
3a	$C_{14}H_{16}N_2$	79.1 / 79.2	7.5 / 7.6		13.3 / 13.2	82-83	62
3b	$C_{13}H_{13}N_3O_2$	64.1 / 64.2	5.4 / 5.4		17.4 / 17.3	177-178	63
4a	$C_{14}H_{15}NO$	78.7 / 78.8	7.0 / 7.1		6.7 / 6.6	95-96	72
4b	$C_{13}H_{12}BrNO$	56.0 / 56.1	4.4 / 4.4	28.5 / 28.7	5.1 / 5.0	145-146	73
5a	$C_{20}H_{22}N_2O$	78.3 / 78.4	7.1 / 7.2		9.1 / 9.1	109-110	67
5b	$C_{19}H_{19}N_3O_3$	67.4 / 67.6	5.5 / 5.7		12.6 / 12.5	130-131	64

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	4,5-$(CH_2)_2$ (4H, m) cyclohexane	3-CH_2 (2H, m) и 6-CH_2 (2H, m) cyclohexane	2-CH (1H, br. t) cyclohexane	5,6-$(CH_2)_2$ (4H, m) heterocycle	4,7-$(CH_2)_2$ (4H, m), heterocycle	Aromatic protons	Remaining protons
2a	1.67-1.98	2.23-2.28, 2.46-2.63	4.34 (^{2}J = 10)	—	—	7.20-7.78 (4H, m)	2.39 (3H, s, CH_3)
2b	1.60-2.07	2.50-2.55, 2.47-2.60	—	—	—	7.33-8.86 (4H, m)	16.45 (s, OH)
2c	1.55-1.95	2.29-2.35, 2.35-2.50	4.20 (^{2}J = 10)	—	—	7.17-7.57 (4H, m)	16.43 (s, OH)
2d	1.60-2.10	2.20-2.43, 2.21-2.64	4.17 (^{2}J = 10)	—	—	6.83-7.25 (3H, m)	3.90 (3H, s, CH_3O), 3.91 (3H, s, CH_3O)
3a	—	—	—	1.75-1.81	2.60-2.64	7.19-7.50 (4H, m)	2.34 (3H, s, CH_3), 11.53 (s, NH)
3b	—	—	—	1.73-1.78	2.58-2.80	7.71-8.12 (4H, m)	11.31 (s, NH)
4a	—	—	—	1.80-1.82	2.73-2.81	7.26-7.63 (4H, m)	2.38 (3H, s, CH_3)
4b	—	—	—	1.79-1.87	2.73-2.79	7.36-7.86 (4H, m)	—
5a	1.43-2.05	2.83-3.05	3.30 (^{2}J = 8)	—	—	7.11-8.10 (8H, m)	2.37 (3H, s, CH_3), 11.06 (2H, s, 2NH)
5b	1.60-2.10	2.79-3.13	3.38 (^{2}J = 10)	—	—	7.13-8.32 (8H, m)	11.05 (2H, s, 2NH)

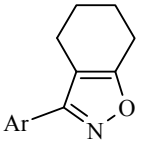
The ^{13}C NMR spectrum of compound **2a** was studied in order to investigate the tautomeric properties of the diketones. Analysis of the DEPT spectrum showed the presence of 8 methylene groups, which corresponds to a doubled set (21.28, 23.07, 23.59, 26.28, 27.35, 30.11, 32.77, and 42.77 ppm) and one CH group (58.24 ppm). These data indicate clearly the presence of two forms – ketonic and enolic.

In the IR spectra of the diketones **2a-d** (in $CHCl_3$) stretching vibrations of the C=O group were observed at 1700, 1675, and 1600 cm^{-1} corresponding to two ketonic carbonyls – free and chelated. A band at 3250 cm^{-1} in the spectra of compounds **3a**,**b** confirms the presence of the NH group of the pyrazole ring. The spectra of the imidazolines **5a**,**b** contain characteristic stretching bands of the C=O (1680) and NH (3400 cm^{-1}) groups.

Mass spectra confirmed the heterocyclic structures of compounds **3-5**. In the mass spectra of the tetrahydropyridazole **3b** and the isoxazole **4a** peaks are present of the molecular ions at 212* (80%) and 213 (53%) and peaks of fragment ions representing loss of the CH_3 group at 197 (5%) and 198 (3%) respectively.

In the mass spectrum of ketone **5a** the molecular ion peak is observed at 306 (12%) and more intense peak of the fragment ion, corresponding to the loss of the *p*-tolyl group 187 $[M - C(O)Ar]^+$ (56%), and also the 119 peak $[CH_3C_6H_4C(O)]^+$ (12%). The spectrum of ketone **5b** contains peaks of ions 337 $[M]^+$ (5%) and 187 $[M - C(O)Ar]^+$ (50%).

However the ^1H NMR, IR and mass spectral data do not permit a single possible structure for compounds **4a**,**b** which can be expressed by the formula



Therefore it was only possible to determine the structure in this case by X-ray crystallography. Monocrystals of compound **4a** for X-ray crystallography were obtained by crystallization from 2-propanol. The overall form of the molecule is shown in the Figure. All the bond lengths and valence angles (Tables 3 and 4) correspond well with values corresponding to atomic values. The independent part of the elementary lattice contains two molecules. The values given in the Tables are characteristic of both the first and second crystallographically independent molecules.

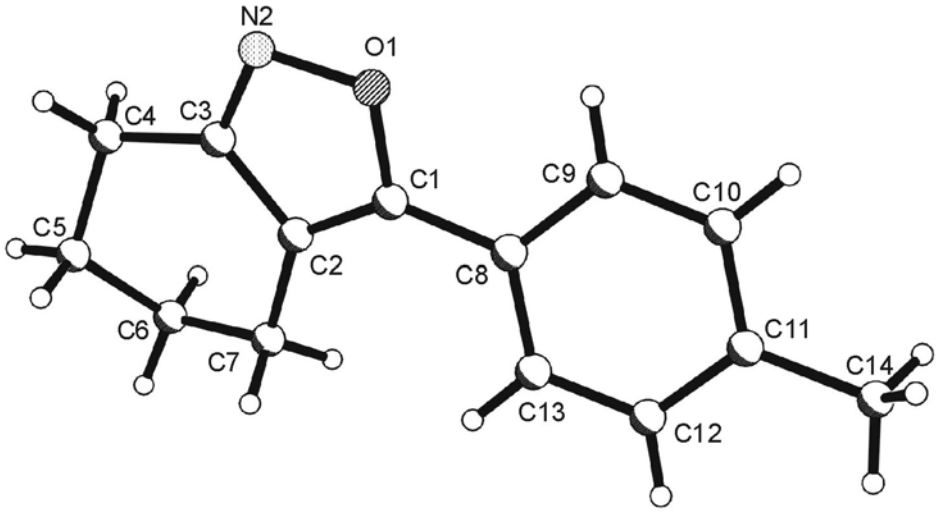


Fig. 1. Structure of the molecule of compound **4a** from X-ray diffraction.

* Here and below the values of the peaks are cited as m/z (I_{rel}).

Table 3. Basic Valence Angles (φ) in the Molecule of Compound **4a**

Angle	φ, deg	Angle	φ, deg
C(1)–O(1)–N(2)	108.5(2)	C(21)–N(21)–O(22)	108.8(2)
C(3)–N(2)–O(1)	104.9(2)	C(23)–N(22)–O(21)	104.2(2)
C(2)–C(1)–O(1)	109.3(2)	C(22)–C(21)–O(21)	109.3(2)
C(2)–C(1)–C(8)	135.4(3)	C(22)–N(21)–C(28)	134.0(3)
O(1)–C(1)–C(8)	115.2(2)	O(21)–C(21)–C(28)	116.6(2)
C(1)–C(2)–C(3)	104.3(2)	C(21)–C(22)–C(23)	104.6(3)
C(1)–C(2)–C(7)	133.4(3)	C(21)–C(22)–C(27)	132.7(3)
C(3)–C(2)–C(7)	122.2(3)	C(23)–C(22)–C(27)	122.7(3)
N(2)–C(3)–C(2)	112.9(3)	N(22)–C(23)–C(22)	113.1(3)
N(2)–C(3)–C(4)	122.7(3)	N(22)–C(23)–C(24)	122.4(3)
C(2)–C(3)–C(4)	124.4(3)	C(22)–C(23)–C(24)	124.4(3)
C(3)–C(4)–C(5)	109.9(3)	C(23)–C(24)–C(25)	110.0(3)
C(6)–C(5)–C(4)	112.5(3)	C(26)–C(25)–C(24)	114.9(3)
C(5)–C(6)–C(7)	112.9(3)	C(25)–C(26)–C(27)	115.9(3)
C(2)–C(7)–C(6)	110.6(3)	C(22)–C(27)–C(26)	109.3(3)
C(13)–C(8)–C(9)	117.2(3)	C(33)–C(28)–C(29)	117.8(3)
C(13)–C(8)–C(1)	112.9(3)	C(33)–C(28)–C(21)	121.0(3)
C(9)–C(8)–C(1)	120.2(3)	C(29)–C(28)–C(21)	121.1(3)
C(10)–C(9)–C(8)	120.9(3)	C(30)–C(29)–C(28)	120.1(3)
C(11)–C(10)–C(9)	121.9(3)	C(29)–C(30)–C(31)	122.3(3)
C(10)–C(11)–C(12)	117.2(3)	C(30)–C(31)–C(32)	116.7(3)
C(10)–C(11)–C(14)	120.9(3)	C(30)–C(31)–C(34)	121.6(3)
C(12)–C(11)–C(14)	121.9(3)	C(32)–C(31)–C(34)	121.7(3)
C(11)–C(12)–C(13)	121.8(3)	C(33)–C(32)–C(31)	121.9(3)
C(12)–C(13)–C(8)	120.9(3)	C(32)–C(33)–C(28)	121.1(3)

Table 4. Bond Lengths (*d)* in the Molecule of Compound **4a**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
O(1)–C(1)	1.366(3); 1.360(3)	C(2)–C(7)	1.491(4); 1.494(1)	C(8)–C(9)	1.386(4); 1.396(4)
O(1)–N(2)	1.421(3); 1.420(3)	C(3)–C(4)	1.490(4); 1.496(1)	C(9)–C(10)	1.378(4); 1.375(4)
N(2)–C(3)	1.302(4); 1.305(4)	C(4)–C(5)	1.516(4); 1.505(5)	C(10)–C(11)	1.374(4); 1.385(4)
C(1)–C(2)	1.356(4); 1.347(4)	C(5)–C(6)	1.503(4); 1.458(5)	C(11)–C(12)	1.374(4); 1.388(4)
C(1)–C(8)	1.463(4); 1.459(4)	C(6)–C(7)	1.540(4); 1.517(4)	C(11)–C(14)	1.512(4); 1.509(4)
C(2)–C(3)	1.417(4); 1.407(4)	C(8)–C(13)	1.386(4); 1.387(4)	C(12)–C(13)	1.380(4); 1.367(4)

The form of the molecule is close to planar, with atom C(5) displaced somewhat from the basic plane to give a *chair* conformation. There are no hydrogen bonds and no short intermolecular contacts in the crystal.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Bruker 300 (300 MHz) spectrometer in DMSO-d_6 for compound **5b** and in $CDCl_3$ for the other compounds, with HMDS (δ 0.05 ppm) as internal standard. IR spectra of

0.01 mol/l chloroform solutions were measured on a Specord M-80 spectrometer. Mass spectra were measured with Finigan MAT Incos 50 instrument (70 eV, EI). The purities of the substances prepared were determined by TLC on Silufol UV-254 plates with 1:3:6 acetone–ethanol–chloroform eluent, with development by UV light or bromine vapor.

The aroylcyclohexanones **2a-d** were prepared for the first time by a method described in [4]. All compounds were crystallized from 2-propanol.

X-ray Crystallographic Investigation of Compound 4a. Crystals $C_{14}H_{15}NO$ were monoclinic: a = 8.279(17), b = 11.382(2), c = 24.807(5) Å, β = 91.00(3)°, V = 2337.2(8) Å^3, M 213.27, d_{calc} = 1.212 g/cm^3, Z = 8, space group $P2_1/c$. Experimental reflections were measured with a KM-4 (KUMA DIFRACTION) automatic 4-circle diffractometer with X^{-4}, geometric method of ω/2θ scanning with monochromated Mo$K\alpha$ radiation (2θ ≤ 50). 4964 independent reflections were measured (R_{int} = 0.0276). Correction for adsorption was not carried out (μ = 0.076 mm^{-1}). The structure was determined by the direct method using the SIR 92 program [6] with subsequent calculations of electron density maps. All hydrogen atoms were placed geometrically. Full-matrix anisotropic (non-hydrogen atoms) calculations with least-squares analysis were carried out using the *SHELX 97* program [7] to R_1 = 0.0579 for 3661 reflections with $I \geq 2\sigma$ (I). *GOOF* = 1.005.

3-Aryl-4,5,6,7-tetrahydroindazoles 3a,b. A 70% solution of hydrazine hydrate (0.7 ml, 15 mmol) was added to a solution of ketone **2a** or **2b** (10 mmol) in boiling 2-propanol (10 ml). The mixture was boiled for 30 min, cooled to 20°C, diluted with ice water (50 ml), the precipitate was filtered off, dried, and recrystallized.

3-Aryl-4,5,6,7-tetrahydro-2,1-benzisoxazoles 4a,b. A solution of a mixture of hydroxylamine hydrochloride (1.40 g, 20 mmol) and NaOH (0.8 g 20 mmol) was added to a solution of ketone **2a** or **2c** (10 mmol) in boiling 2-propanol (10 ml). The reaction mixture was worked up as for compounds **3a**,**b**.

2-*spiro*-(2-Aroylcyclohexyl)-1,2-dihydrobenzimidazoles glacial 5a,b. A solution of ketone **2a** or **2b** (10 mmol) and *o*-phenylenediamine (1.08 g, 10 mmol) in glacial acetic acid (10 ml) was boiled for 30 min. The solution was cooled to 20°C, diluted with water (50 ml), the precipitate was filtered off, washed with a small amount of ammonia, then with water, dried, and recrystallized.

REFERENCES

1. J. Joule and K. Mills. *Chemistry of Heterocyclic Compounds* [Russian translation], Mir, Moscow (2004).
2. N. K. Hombrecher and G. Horter, *Synthesis*, 389 (1990).
3. H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.,* **90**, 942 (1958).
4. *Organicum* [Russian translation], Mir, Moscow, Vol. 2, p. 221 (2008).
5. S. Hunig and H. Hoch, *Fortshr. Chem. Forsch.,***14**, 235 (1970).
6. A. Altomare, G. Cascarano, C. Giacovazzo, and A. Gualardi. *J. Appl. Crystallogr.,* **26**, 343 (1993).
7. G. M. Sheldrick, *SHELX97*, *Programs for Crystal Structure Analysis*, Univ. of Göttingen, Germany, 2332 (1998).