Chemistry of Heterocyclic Compounds, Vol. 47, No. 4, July 2011 (Russian original Vol. 47, No. 4, April, 2011)

SYNTHESIS OF 3,5-DIAROYLPYRIDINES

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Previously unknown 3,5-diaroylpyridines have been synthesized by the condensation of 1,3-diketones according to the Hantzsch reaction.

Keywords: 3,5-diaroylpyridines, 1,4-dihydropyridines, 1,3-diketones, Hantzsch pyridines.

The main method of synthesizing pyridines of symmetrical and unsymmetrical structure with various sets of acceptor substituents (nitro, alkanoyl, aroyl, ethoxycarbonyl, cyano, carbamoyl, etc.) in positions 3 and 5 of the pyridine nucleus is the two-stage synthesis of Hantzsch [1–6]. The stage of cyclization of 1,4-dihydropyridines, which have a broad spectrum of biological activity [7–10], is constantly being improved, and has several experimental modifications [11]. The stage of aromatization of the 1,4-dihydropyridines is carried out by chemical, electrochemical, and enzymatic oxidation [12, 13]. The chemical oxidation of 1,4-dihydropyridines has been well studied and a wide range of both organic and inorganic reagents have been used [14–18]. Progress in the investigation of the oxidation of dihydropyridines and the fundamental knowledge of establishing the mechanism of the cleavage of the hydride-mobile hydrogen from dihydropyridines, for the understanding of the most important biological processes involving nicotinamide-adenine dinucleotides and their phosphates, is considered systematically and fully in a review [19].

The aim of the present work was the synthesis of previously unknown symmetrical 3,5-diaroylpyridines.

Interest in the synthesis of new representatives of 3,5-diaroyl-1,4-dihydro-pyridines is caused by the recently discovered ability of certain 3,5-diacetyl- and 3,5-dibenzoyl-1,4-dihydropyridines to display the properties of effective inhibitors of P-glycoprotein. An increase in the expression of P-glycoprotein and other transmembrane transporters of medicinal preparations affects the emergence of drug resistance in various illnesses, including many forms of cancer. One of the means of suppressing medicinal resistance is the use of inhibitors of transport proteins, blocking the transport of medicinal substances from cells, and increasing their intracellular concentration [20–22].

Dedicated to bright memories of Professor Reva Safarovich Sagitullin

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 586–590, April, 2011. Original article submitted March 7, 2011.

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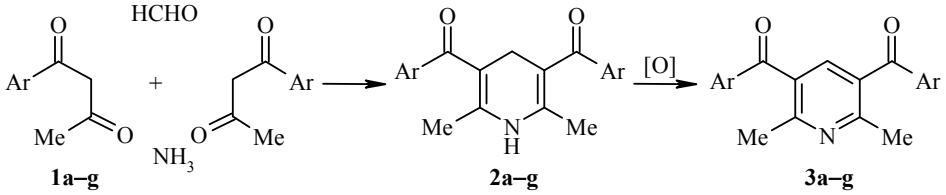
For the synthesis of 3,5-diaroyl-1,4-dihydropyridines **2a–g**, having no substituent in position 4, the simplest and most effective preparative method is the modified method of cyclocondensation of β-diketones **1a–g** according to Hantzsch. In place of formaldehyde and ammonia in the classical variant of the Hantzsch synthesis, hexamethylenetetramine and ammonium acetate are used [11]. Only 3,5-dibenzoyl-1,4-dihydropyridine **2a** of the 1,4-dihydropyridines **2a–g** synthesized by us by the procedure of [11], has been described previously [18].



1a–g **2a–g** **3a–g**

1–3 **a** Ar = Ph, **b** Ar = 4-ClC_6H_4, **c** Ar = 4-BrC_6H_4, **d** Ar = 4-$MeOC_6H_4$, **e** Ar = 3-$MeOC_6H_4$, **f** Ar = 1-naphthyl, **g** Ar = 2-naphthyl

TABLE 1. Characteristics of the Synthesized Dihydropyridines **2a–g** and Pyridines **3b–g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2a	$C_{21}H_{19}NO_2$	–	–	–	195–196 195–200 [18]	65
2b	$C_{21}H_{17}Cl_2NO_2$	65.38 65.30	4.46 4.44	3.70 3.63	192–193	52
2c	$C_{21}H_{17}Br_2NO_2$	52.98 53.08	3.62 3.61	2.90 2.95	202–203	84
2d	$C_{23}H_{23}NO_4$	73.26 73.19	6.18 6.14	3.79 3.71	181–182	41
2e	$C_{23}H_{23}NO_4$	73.15 73.19	6.05 6.14	3.67 3.71	138–139	50
2f	$C_{29}H_{23}NO_2$	83.37 83.43	5.48 5.55	3.39 3.35	252–253	80
2g	$C_{29}H_{23}NO_2$	83.40 83.43	5.56 5.55	3.32 3.35	229–230	71
3b	$C_{21}H_{15}Cl_2NO_2$	65.70 65.64	3.95 3.93	3.71 3.65	139–140	72
3c	$C_{21}H_{15}Br_2NO_2$	53.38 53.31	3.18 3.20	3.05 2.96	155–156	73
3d	$C_{23}H_{21}NO_4$	73.57 73.58	5.61 5.64	3.68 3.73	161–162	62
3e	$C_{23}H_{21}NO_4$	73.62 73.58	5.60 5.64	3.76 3.73	100–101	40
3f	$C_{29}H_{21}NO_2$	83.88 83.83	5.13 5.09	3.44 3.37	153–154	95
3g	$C_{29}H_{21}NO_2$	83.84 83.83	5.07 5.09	3.32 3.37	126–127	91

*Solvent: dioxane (compound **2a**), ethanol (compounds **2b–e**, **3f,g**), acetic acid (compounds **2f,g**), hexane (compounds **3b,c,e**), 2-propanol (compound **3d**).

TABLE 2. IR and ^{1}H NMR Spectra of Dihydropyridines **2a–g** and Pyridines **3a–g**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm (*J*, Hz)*				
	C=O	NH	NH (1H, br s)	4-CH_2 (2H, s)	4-CH (1H, s)	2,6-CH_3 (6H, s)	Other signals
2a	1667, 1627	3294	5.73	3.35	–	1.86	7.34–7.53 (10H, m, H Ar)
2b	1650	3312	5.76	3.31	–	1.86	7.34–7.40 (4H, m, AA'XX', J_{AX} = 8.3, H Ar); 7.56–7.62 (4H, m, AA'XX', J_{AX} = 8.3, H Ar)
2c	1661, 1629	3304	5.81	3.30	–	1.86	7.45–7.53 (4H, m, H Ar); 7.58–7.64 (4H, m, H Ar)
2d	1657	3323	5.68	3.36	–	1.84	3.83 (6H, s, 4',4"-OCH_3); 6.84–6.91 (4H, m, AA'XX', J_{AX} = 8.6, H Ar); 7.66–7.72 (4H, m, AA'XX', J_{AX} = 8.6, H Ar)
2e	1661	3308	5.90	3.34	–	1.84	3.81 (6H, s, 3',3"-OCH_3); 6.97–7.02 (2H, m, H Ar); 7.15–7.30 (6H, m, H Ar)
2f	1726, 1627	3305	8.83	3.24	–	1.60	7.40 (2H, dd, ^3J = 7.0, ^4J = 1.3, H-2',2"); 7.50 (2H, dd, ^3J = 7.0, ^3J = 8.3, H-3',3"); 7.53–7.56 (4H, m, H-6',7',6",7"); 7.81–7.85 (2H, m, H-5',5"); 7.94–7.98 (4H, m, -4',8',4",8")
2g	1668, 1625	3295	8.83	3.30	–	1.77	7.54–7.61 (4H, m, H-6',7',6",7"); 7.66 (2H, dd, ^3J = 8.4, ^4J = 1.7, H-3',3"); 7.93–7.95 (2H, m, H-5',5"); 7.96 (2H, d, ^3J = 8.4, H-4',4"); 8.04–8.06 (2H, m, H-8',8"); 8.18 (2H, m, H-1',1")
3a	1664	–	–	–	8.01	2.97	7.63–7.83 (10H, m, H Ar)
3b	1665	–	–	–	7.55	2.58	7.41–7.48 (4H, m, AA'XX', J_{AX} = 8.6, H Ar); 7.67–7.75 (4H, m, AA'XX', J_{AX} = 8.6, H Ar)
3c	1665	–	–	–	7.56	2.59	7.59–7.64 (8H, m, H Ar)
3d	1656	–	–	–	7.95	2.92	3.87 (6H, s, 4',4"-OCH_3); 6.91–7.00 (4H, m, H Ar); 7.67–7.82 (4H, m, H Ar)
3e	1660	–	–	–	7.57	2.57	3.81 (s, 6H, 3',3"-OCH_3); 7.10–7.35 (8H, m, H Ar)
3f	1661	–	–	–	7.69	2.71	7.37 (2H, dd, ^3J = 7.2, ^3J = 8.2, H-3',3"); 7.49–7.51 (2H, m, H-2',2"); 7.52–7.56 (2H, m, H-6',6"); 7.57–7.61 (2H, m, H-7',7"); 7.85–7.88 (2H, m, H-5',5"); 7.97 (2H, br d, ^3J = 8.2, H-8',8"); 8.53–8.56 (2H, m, H-4',4")
3g	1672, 1651	–	–	–	7.75	2.68	7.53 (2H, ddd, ^3J = 6.9, ^3J = 8.2, ^4J = 1.3, H-6',6"); 7.60 (2H, ddd, ^3J = 6.9, ^3J = 8.2, ^4J = 1.3, H-7',7"); 7.84–7.87 (2H, m, H-5',5"); 7.87–7.90 (2H, m, H-8',8"); 7.90 (2H, br d, ^3J = 8.6, H-4',4"); 7.96 (2H, dd, ^3J = 8.6, ^4J = 1.8, H-3',3"); 8.17–8.18 (2H, m, H-1',1")

*The ^{1}H NMR spectra were taken in $CDCl_3$ (compounds **2a–e** and **3a–g**) and DMSO-d_6 (compounds **2f,g**).

Under analogous conditions 3,5-diacetyl-1,4-dihydropyridine was formed from acetylacetone in 65% yield but the remaining members of the series of 3,5-dialkanoyl-1,4-dihydropyridines were obtained in yields from 20 to 48% [23]. Oxidative dehydrogenation of 3,5-dibenzoyldihydropyridine **2a** to the corresponding aromatic pyridine **3a** was carried out by heating it with chloranil in benzene, but dihydropyridines **2b–g** were oxidized to aromatic pyridines **3b–g** with sodium nitrite in acetic acid. It should be mentioned that pyridine **3a** was previously obtained by the reaction of 3,5-dicyano-2,6-dimethylpyridine with phenyl magnesium bromide, however its melting point, given in [24], differed significantly from the melting point of pyridine **3a**, obtained by us by the oxidation of 3,5-dibenzoyl-1,4-dihydropyridine **2a**. The structures of compounds **2b–g, 3b–g** synthesized for the first time, were confirmed by data of ^{1}H NMR and IR spectra, and by elemental analysis. The characteristics of compounds and the spectral data are given in Tables 1 and 2.

EXPERIMENTAL

The IR spectra were obtained on a Simex FT 801 instrument in the solid phase with an attachment for a single broken internal reflection. The ^{1}H NMR spectra were recorded on a Bruker Avance DRX-400 (400 MHz) in $CDCl_3$ and DMSO-d_6, internal standard was the residual protons of the solvent ($CDCl_3$ δ 7.25 and DMSO-d_6 δ 2.50 ppm). Elemental analysis was carried out on a Perkin-Elmer CHN Analyzer. A check on the progress of reactions and the purity of the obtained compounds was effected by TLC on Silufol UV-254 plates in the solvent system benzene-ethyl acetate, 9:1, visualization was with UV light.

1,3-Diketones **1a–g,** obtained by the procedures of [25–30] were used.

Synthesis of Dihydropyridines 2a–g (General Method). A mixture of the corresponding 1,3-diketone **1a–g** (120 mmol), hexamethylenetetramine (urotropin) (1.54 g, 11 mmol), and ammonium acetate (4.92 g, 60 mmol) in ethanol (60 ml) was boiled for 1 h. After cooling, the precipitated solid was filtered off.

3,5-Dibenzoyl-2,6-dimethylpyridine (3a). A mixture of 1,4-dihydropyridine **2a** (3.17 g, 10 mmol) and chloranil (3.98 g, 16 mmol) in benzene (100 ml) was boiled for 2 h, the mixture was cooled and the precipitated solid of tetrachlorohydroquinone was filtered off. Hydrochloric acid (15%, 20 ml) was added to the filtrate, the aqueous layer was separated, neutralized with aqueous ammonia, and the precipitated pyridine was filtered off. The yield of pyridine **3a** 2.74 g (87%); mp 145–146°C (benzene–hexane) (lit. mp 80–81°C [24]).

Preparation of Pyridines 3b–g (General Method). Sodium nitrite (0.69 g, 10 mmol) was added in portions at room temperature with stirring to a suspension of the corresponding dihydropyridine **2b–g** (5 mmol) in acetic acid (17 ml). After adding all the sodium nitrite the reaction mixture was stirred for 2 h at room temperature. The mixture was then poured onto ice, neutralized with ammonia, and the precipitated crystals of pyridines were filtered off, and washed with water.

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