Chemistry of Heterocyclic Compounds, Vol. 45, No. 7, 2009

SYNTHESIS OF METHYL ESTERS OF 5-AROYL-6-ARYL-2-OXO-1,2,3,6-TETRAHYDROPYRIMIDINE-4-CARBOXYLIC ACIDS

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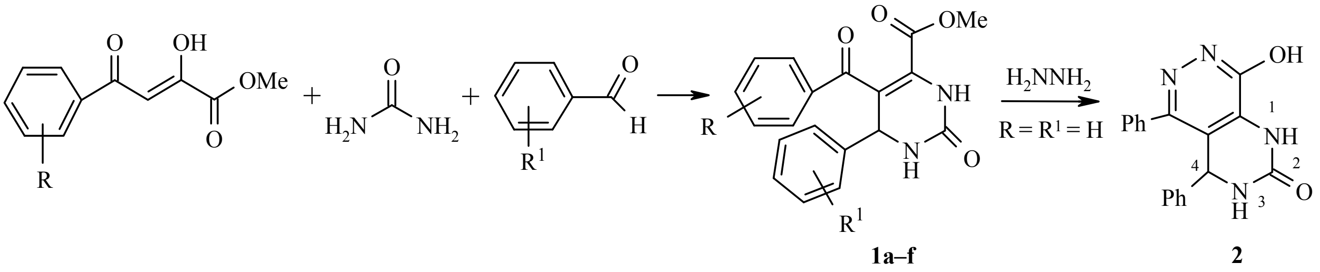
Methyl esters of 5-aroyl-6-aryl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acids were synthesized from three component mixtures of methyl esters of aroylpyruvic acids, urea, and substituted benzaldehydes. 8-Hydroxy-4,5-diphenyl-3,4-dihydropyrimido[4,5-d]pyridazin-2(1H)-one was synthesized by the reaction of 5-benzoyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidin-4-carboxylate with hydrazine hydrate.

Keywords: hydrazine hydrate, 8-hydroxy-4,5-diphenyl-3,4-dihydropyrimido[4,5-*d*]-pyridazin-2(1H)-one, substituted benzaldehydes, methyl esters of 5-aroyl-6-aryl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acids, urea, esters of aroylpyruvic acids.

The interaction of esters of acetylacetic acids with urea and substituted benzaldehydes led to the formation of tetrahydropyrimidin-2-ones [1]. However the reaction of esters of acylpyruvic acids with mixtures of urea and aromatic aldehydes was not studied.



1 a–d R = H, **a** R^1 = H, **b** R^1 = 3-MeO, **c** R^1 = 3,4-(MeO)$_2$, **d** R^1 = 3-MeO, 4-OH, **e**, **f** R = Cl, **e** R^1 = H, **f** R^1 = 3-MeO

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, 1046-1049, July, 2009. Original article submitted June 5, 2008.

Table 1. Characteristics of Methyl Esters of 5-Aroyl-6-aryl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic Acids **1a-f**

Compound	Empirical formula	Found, % Calculated, %			mp, °C (AcOH)	Yield, %
		C	N	H		
1a	$C_{19}H_{16}N_2O_4$	67.79 67.84	8.27 8.33	4.96 4.80	176-177	79
1b	$C_{20}H_{18}N_2O_5$	69.48 69.35	8.17 8.09	5.32 5.24	160-162	64
1c	$C_{21}H_{20}N_2O_6$	64.02 63.63	7.14 7.07	4.99 5.08	134-136	61
1d	$C_{20}H_{18}N_2O_6$	62.91 62.82	7.24 7.33	4.59 4.74	210-212	52
1e	$C_{19}H_{15}ClN_2O_4$	62.01 61.54	7.32 7.56	4.12 4.08	190-191	63
1f	$C_{20}H_{16}ClN_2O_5$	64.01 63.24	7.54 7.38	4.57 4.25	191-193	55

We have established that on fusing methyl esters of aroylpyruvic acids with a mixture of an aromatic aldehyde and urea at 130-150°C for 30 min methyl esters of 5-aroyl-6-aryl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic acids **1a-f** are formed.

The compounds obtained, **1a-f,** are colorless or yellow crystalline compounds, soluble in general organic solvents, but insoluble in water (Table 1).

The IR spectra of these compounds contain absorptions bands for ester carbonyl groups at 1720-1736, lactam carbonyl groups at 1688-1720, ketone carbonyl groups at 1640-1656, and N–H stretches of two amino groups in positions 1 and 3 of the pyrimidine ring at 3208-3240 and 3304-3376 cm^{-1} (Table 2).

In the ^1H NMR spectra of compounds **1a-f** signals of the methoxy group protons are observed in the 3.15-3.28 range, signals of aromatic protons in the 6.50-7.60 range, signals of the protons bonded to nitrogen atoms in the 7.70-7.93 and 9.00-9.20 ranges, signals of the methyne proton at positions 4 of the pyrimidine ring in the 5.22-5.35 range, and also signals of the methoxy group protons (for compounds **1b-d, f**) in the 3.60-3.70 range and of the OH group (for compound **1d**) at 8.80 ppm (Table 2).

The presence of the β-dicarbonyl systems in the methyl esters of 5-aroyl-6-aryl-1,2,3,6-tetrahydropyrimidine-4-carboxylic acids allows the discussion of compounds **1a-f** as suitable reagents for the synthesis of condensed heterocyclic systems.

In fact reaction of 5-benzoyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylate **1a** with hydrazine hydrate at 170-180°C gave 8-hydroxy-4,5-diphenyl-3,4-dihydropyrimido[4,5-*d*]pyridazin-2(1H)-one (**2**) as a colorless crystalline substance, soluble in common organic solvents, but insoluble in water. It gave a cherry color with ethanolic $FeCl_3$ solution.

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-20 instrument. ^1H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Fourier BS-567 A (100 MHz) instrument.

Methyl esters of 5-Aroyl-6-aryl-2-oxo-1,2,3,6-tetrhydropyrimidine-4-carboxylic Acids 1a-f (General Method). A mixture of a methyl ester of an aroylpyruvic acid (0.01 mol), urea (0.01 mol), and an aromatic aldehyde (0.01 mol) was fused at 135-150°C until evolution of the gas ceased. The reaction mixture was treated with ethanol, the precipitate was filtered off and recrystallized from conc. AcOH.

TABLE 2. Spectral Characteristics of Compounds **1a–f**

Com-pound	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm (*J*, Hz)				
	$COOCH_3$	CONH	C=O	NH	Ar, m	MeO, s	H-6, d	H-1, H-3, s	Other protons, s
1a	1720	1700	1640	3208, 3352	7.20-7.40 (10H, $2C_6H_5$)	3.17	5.34 (*J* = 2.7)	7.93, 9.32	
1b	1730	1690	1645	3240, 3376	6.58-7.59 (9H, C_6H_5, 3-$MeOC_6H_4$)	3.15	5.35 (*J* = 2.8)	7.80, 9.19	3.63 (3H, MeO)
1c	1735	1705	1650	3232, 3310	6.60-7.50 (8H, C_6H_5, 3,4-$(MeO)_2C_6H_3$)	3.18	5.28 (*J* = 2.7)	7.75, 9.11	3.60 (3H, MeO) 3.70 (3H, MeO)
1d	1736	1720	1656	3230, 3304	6.50-7.50 (8H, C_6H_5, 3-MeO-4-OHC_6H_3)	3.20	5.22 (*J* = 1.9)	7.70, 9.00	3.60 (3H, MeO) 8.80 (1H, OH)
1e	1728	1708	1640	3224, 3344	6.90-7.60 (9H, C_6H_5, 4-ClC_6H_4)	3.21	5.28 (*J* = 1.9)	7.80, 9.15	
1f	1730	1688	1644	3216, 3317	6.60-7.60 (8H, 4-ClC_6H_4, 3-$MeOC_6H_4$)	3.28	5.24 (*J* = 1.9)	7.78, 9.20	3.65 (3H, MeO)

8-Hydroxy-4,5-diphenyl-3,4-dihydropyrimido[4,5-*d*]pyridazin-2(1H)-one (2). A mixture of methyl 5-benzoyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylate (**1a**) (0.01 mol) and 98% hydrazine hydrate (0.01 mol) was heated at 170-180°C until evolution of gas ceased. The reaction mixture was treated with ethanol, the precipitate was filtered off and recrystallized from a mixture of conc. AcOH and DMF. Yield 1.81 g (57%); mp 295-297°C (mixture of AcOH–DMF). IR spectrum, ν, cm^{-1}: 1710 (CONH), 3210 (1-NH), 3358 (3-NH). ^{1}H NMR Spectrum, δ, ppm, (*J*, Hz): 5.30 and 5.31 (1H, d, *J* = 3.3, H-4); 7.05 (10H, m, arom); 7.83 (1H, s, H-1); 9.20 (1H, br. s, H-3); 13.20 (1H, s, OH). Found, %: C 67.95; 67.94; H 4.40; 4.33; N 17.69, 17.64. $C_{18}H_{14}N_4O_2$. Calculated, %: C 67.92; H 4.43; N 17.60.

REFERENCE

1. Ch. V. Reddy, M. Mahech, P. V. K. Raju, T. R. Babu, and V. V. N. Reddy, *Tetrahedron Lett.,* **43**, 2657 (2002).