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HETEROCYCLIZATION OF AMIDO-PHENACYLATION PRODUCTS OF URACIL

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When uracil is reacted with benzoylamino(chloro)acetophenone, we obtain two amidophenacylation products depending on the condensation conditions. The first product contains an amidophenacyl moiety at the N^1 center, and in the second product two such moieties are located at the N^1 and N^3 centers of the uracil. Treatment of these accessible uracil derivatives with phosphorus oxychloride, thionyl chloride, or phosphorus pentasulfide leads to cyclization of the amidophenacyl side group, which is used to synthesize a number of modified pyrimidine bases with 2,5-diphenyloxazole or 2,5-diphenylthiazole residues.

Keywords: oxazole, thiazole, uracil, amidophenacylation, heterocyclization.

Reaction of uracil (**1**) with benzoylamino(chloro)acetophenone (**2**) at 0°C in the presence of sodium hydroxide leads to formation of the N^1-amidophenacylation product **3** [1]. Furthermore, at 20°C for a 1:2:2 mole ratio of the indicated reagents, we obtain the N^1,N^3-di(amidophenacylation) product **4** in high yield. As we see from the scheme, both these accessible uracil derivatives **3, 4** could be used to obtain a series of novel modified pyrimidine bases **5-9** containing substituted azolyl moieties in the 1 position or in the 1 and 3 positions.

Thus when substrate **3** is treated with phosphorus oxychloride in DMF, the Vilsmeier reaction does not occur but rather intermediate **5** is formed, which after hydrolysis is converted to 1-(2,5-diphenyloxazol-4-yl)-uracil (**6**). The latter is not formed when we try to carry out heterocyclization in excess thionyl chloride; we note that $SOCl_2$ in the presence of $POCl_3$ displays not only a condensing effect but also a chlorinating effect, converting uracil **3** to a mixture of compounds **5** and **6** [2]. Furthermore, the reaction of substrate **4** with thionyl chloride occurs without complications and leads to 1,3-bis(2,5-diphenyloxazol-4-yl)uracil (**7**).

The conversions **3** → **5** and **4** → **7** are special cases of the Robinson–Gabriel synthesis of substituted oxazoles [3]. The occurrence of these cyclocondensations is supported by ^{1}H NMR spectra, which allow us to follow the disappearance of the resonance signals from the =CH–NH– moiety after treatment of substrates **3** and **4** with condensing agents.

Reactions of nucleophilic substitution of the chlorine atom in compound **5** are described below. The halogen in the 4 position of compound **5** is rather mobile, as shown by the example of reactions with amines of different basicity (**5** → **8** conversions). It is quite possible that substrate **5** could also be used in condensations with O- and S-nucleophiles.

And finally, we have shown that it is possible to obtain 1,3-bis(2,5-diphenylthiazol-4'-yl)-4-thiouracil (**9**) when substrate **4** is reacted with phosphorus pentasulfide. Thionation is directed toward the 4 position, as is supported by the shift of the signal from the (5-H) proton in compound **9** compared with compound **4**. Thionation does not occur at the 2 position of the ring, which is probably connected with steric factors.

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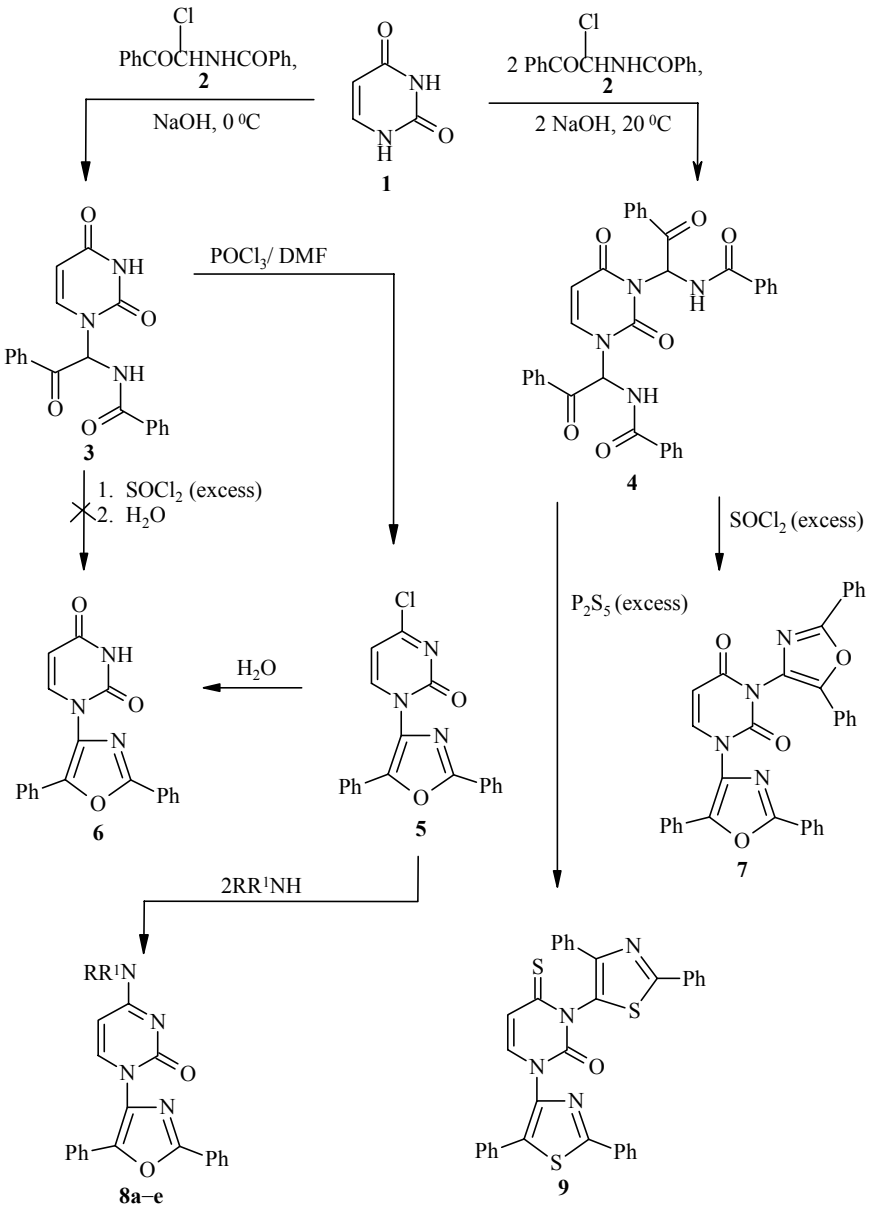
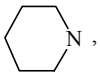


a RR^1N = MeNH, **b** $RR^1N = Et_2N$, **c** RR^1N = PhNH,

d RR^1N =  , **e** RR^1N = 

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WP-200 spectrometer (200 MHz) in DMSO-d_6 solutions, internal standard TMS.

TABLE 1. Characteristics of Synthesized Compounds **4-9**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, %
		C	H	N	S	Cl		
4	$C_{34}H_{26}N_4O_6$	69.87 / 69.62	4.38 / 4.47	9.48 / 9.55	—	—	196-197	79
5	$C_{19}H_{12}ClN_3O_2$	65.08 / 65.24	3.54 / 3.46	11.97 / 12.01	—	9.91 / 10.15	249-252	58
6	$C_{19}H_{13}N_3O_3$	68.99 / 68.88	4.02 / 3.95	12.36 / 12.68	—	—	304-306	97
7	$C_{34}H_{22}N_4O_4$	74.08 / 74.17	4.09 / 4.03	10.23 / 10.18	—	—	293-295	61
8a	$C_{20}H_{16}N_4O_2$	70.04 / 69.75	4.78 / 4.68	15.93 / 16.27	—	—	262-263	41
8b	$C_{23}H_{22}N_4O_2$	71.42 / 71.48	5.61 / 5.74	14.01 / 14.49	—	—	241-243	38
8c	$C_{25}H_{18}N_4O_2$	73.61 / 73.88	4.84 / 4.46	13.90 / 13.79	—	—	265-268	83
8d	$C_{24}H_{22}N_4O_2$	72.12 / 72.34	5.64 / 5.57	13.94 / 14.06	—	—	228-229	67
8e	$C_{23}H_{20}N_4O_3$	68.96 / 68.99	4.96 / 5.03	14.03 / 13.99	—	—	239-240	81
9	$C_{34}H_{22}N_4OS_3$	68.09 / 68.20	3.70 / 3.70	9.25 / 9.36	16.10 / 16.06	—	236-237	83

TABLE 2. Parameters of ^{1}H NMR Spectra of Compounds **4-9**

Compound	Chemical shifts, δ, ppm (*J*, Hz)			
	5-H (d, *J*, Hz)	6-H (d, *J*, Hz)	C_6H_5 (m)	Other signals
4	6.25 (8.3)	8.18 (8.3)	7.57-7.92 (20H, $4C_6H_5$ + 2 CH–NH)	9.96 (1H, d, NH–CH, *J* = 10.2); 10.13 (1H, d, NH–CN, *J* = 10.2)
5	5.85 (8.3)	7.86 (8.3)	7.47-8.12 (10H, $2C_6H_5$)	11.80 (1H, NH-uracil)
6	5.86 (8.3)	7.83 (8.3)	7.45-8.12 (10H, $2C_6H_5$)	
7	6.25 (8.3)	8.22 (8.3)	7.60-8.12 (20H, $4C_6H_5$)	
8a	6.14 (8.3)	7.89 (8.3)	7.47-8.10 (10H, $2C_6H_5$)	3.14 (3H, d, CH_3–NH, *J* = 7.0); 8.00 (1H, m, NH–CH_3)
8b	6.21 (8.3)	7.81 (8.3)	7.46-8.08 (10H, $2C_6H_5$)	1.15 (6H, t, CH_3–CH_2); 3.49 (4H, m, CH_2–CH_3)
8c	6.21 (8.3)	7.93 (8.3)	7.33-8.26 (15H, $3C_6H_5$)	10.12 (1H, s, NH–Ph)
8d	6.41 (8.2)	7.56 (8.2)	7.46-7.91 (10H, $2C_6H_5$)	1.75 (6H, m, $C(CH_2)_3C$); 3.60 (4H, m, CH_2NCH_2)
8e	6.43 (8.2)	7.95 (8.2)	7.60-8.11 (10H, $2C_6H_5$)	3.68 (4H, m, CH_2NCH_2); 3.83 (4H, m, CH_2OCH_2)
9	6.40 (8.3)	8.32 (8.3)	7.47-7.98 (20H, $4C_6H_5$)	

1,3-Di[(benzoylamino)phenacyl]uracil (4). Uracil (1.12 g, 10 mmol) was added to a solution of sodium hydroxide (0.8 g, 20 mmol) in water (10 ml). Then after the uracil had dissolved, a solution of reagent **2** (5.48 g, 20 mmol) in dioxane (20 ml) was added at 20°C. The mixture was stirred for 2 h. The precipitate of uracil **4** was washed with water (50 ml), dried in air, and recrystallized from acetonitrile (Table 1).

1-(2,5-Diphenyloxazol-4-yl)-4-chloropyrimidin-2(1H)-one (5). DMF (3 ml) was added dropwise at 10°C with stirring to $POCl_3$ (10 ml). The mixture was stirred at that temperature for 0.5 h, and then compound **3** (3.5 g, 10 mmol) was added in small portions. The reaction mass was refluxed for 7 h; the solution was

evaporated down under a vacuum created by a water-jet pump, and absolute acetonitrile (3 ml) was added to the oily residue. The precipitate of compound **5** was washed with absolute acetonitrile, dried in a vacuum desiccator over P_2O_5, and recrystallized from absolute acetonitrile.

1-(2,5-Diphenyloxazol-4-yl)uracil (6). The reaction was carried out according to the procedure described above. After refluxing for 7 h, the solution was cooled and poured over ice. The precipitate of uracil **6** was washed with water, dried in air, and recrystallized from dioxane.

1,3-Bis(2,5-diphenyloxazol-4-yl)uracil (7). A mixture of compound **4** (3 g, 5 mmol) and thionyl chloride (20 ml, 250 mmol) was refluxed for 2 h. The solution was evaporated under a vacuum created by a water-jet pump, the residue was triturated with acetonitrile (10 ml), the precipitate of uracil **7** formed was washed with water, dried in air, and recrystallized from dioxane.

1-(2,5-Diphenyloxazol-4-yl)-4-RR'N-pyrimidin-2(1H)-ones (8a-e). A solution of the corresponding amine (3.6 mmol) in absolute benzene (2 ml) was added dropwise to a solution of compound **5** (0.5 g, 1.2 mmol) in absolute benzene (5 ml). The reaction mixture was stirred for 48 h at 20°C; the precipitate was filtered out, washed with water, and dried in air. Compounds **8a,b** were recrystallized from acetone; compound **8c** was recrystallized from dioxane; and compounds **8d,e** were recrystallized from benzene.

1,3-Bis(2,5-diphenylthiazol-4-yl)-4-thiouracil (9). A mixture of compound **4** (3 g, 5 mmol), P_2S_5 (4.5 g, 20 mmol), and absolute dioxane (25 ml) was refluxed for 3 h. The hot solution was decanted from the precipitate, the dioxane was evaporated under a vacuum created by a water-jet pump down to a volume of 2-3 ml, and 2-propanol (2-3 ml) was added. The mixture was heated to boiling, and after cooling a bright yellow precipitate of thiouracil **9** was obtained which was filtered off, dried, and recrystallized from benzene.

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