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REACTION OF 6-METHYL-2-(2-OXO-2-PHENYL-ETHYLIDENE)-2,3-DIHYDROPYRIMIDIN-4(1*H*)-ONE WITH HYDRAZINE AND HYDROXYLAMINE

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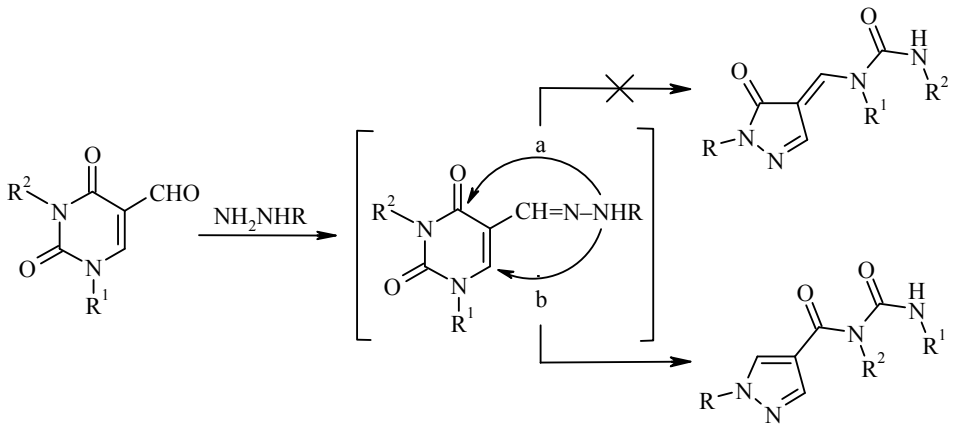
The reaction of 6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1H)-one and of its nitrosation product with hydroxylamine stops at the stage of forming the corresponding oximes. The reaction of 6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1H)-one with hydrazine yields a mixture of 3-amino-5-phenylpyrazole and 3-methyl-2-pyrazolin-5-one in 71 and 62% yields, respectively. The ketoxime is used in the synthesis of a series of imidazole N(3)-oxides substituted at the 1, 4, and 5 positions of the imidazole ring.

Keywords: hydrazine, hydroxylamine, imidazole *N*-oxides, pyrazoles, pyrimidine oximes, pyrimidines, pyrimidine ring transformation.

It is known that the interaction of hydrazines with pyrimidines depending on the structure of the reagents and the reaction conditions can be a convenient method for preparing 2-, 4(6)-hydrazinopyrimidines [1-3]. It can also lead to transformation of a pyrimidine ring to a pyrazole cyclic system [4-8].



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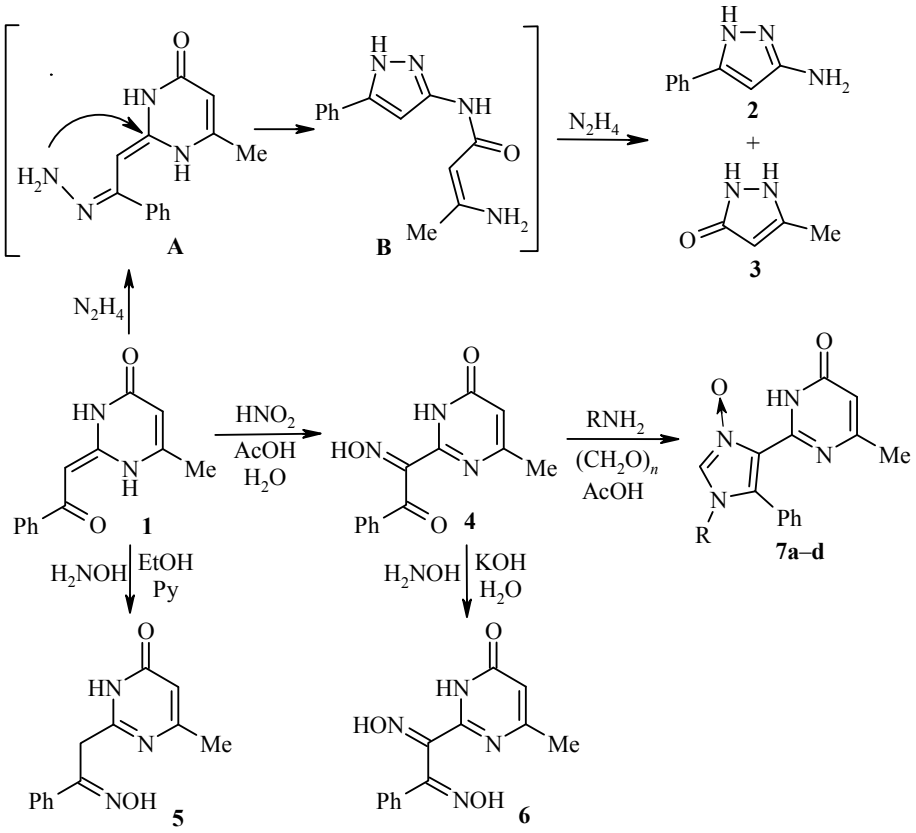
The usual mechanism for conversion of pyrimidines to pyrazoles involves nucleophilic attack of a hydrazine molecule at the C-4 and C-6 atoms of the pyrimidine followed by loss of the N(1)–C(2)–N(3) fragment [4, 5]. The presence of a substituent containing a carbonyl group in the pyrimidine ring can change the reaction course. Thus, 5-formyluracils react with hydrazines to give pyrazole-4-carboxylic acid ureides [8] which implies the intermediate formation of a formylhydrazone with subsequent intramolecular attack by the terminal amino group on the C-6 atom of the pyrimidine (route b). Formation of pyrazolin-5-one derivatives (route a) through reaction of 5-formyluracil with hydrazine was not observed.

Continuing studies of the reaction of pyrimidines with nitrogen-containing nucleophiles [2, 3, 9-11] we have examined the interaction of 6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (**1**) with hydrazine and with hydroxylamine.



7 a R = Me, **b** R = $(CH_2)_2OH$, **c** R = CH_2COOH, **d** R = $(CH_2)_2COOH$

We have found that reaction of pyrimidine **1** with an excess of hydrazine in refluxing ethanol gives a mixture of 3-amino-5-phenylpyrazole (**2**) [12] and 3-methyl-2-pyrazolin-5-one (**3**) [13, 14].

The formation of pyrazoles **2**, **3** from pyrimidine **1** containing a β-oxoethylidene fragment at the position 2 is theoretically possible through several routes. However, in our view, the most likely of these is the formation of hydrazone **A** with subsequent addition of its NH_2 fragment at the pyrimidine ring C-2 atom and opening of the six-membered ring. Then hydrazinolysis occurs, followed by cyclization of the 3-amino-5-phenylpyrazole derivative **B** to the pyrazoles **2** and **3**.

Treatment of pyrimidine **1** and its nitrosation product **4** with excess hydroxylamine in either neutral or basic medium stops at the stage of formation of the monooxime **5** or the dioxime **6**, respectively.

The ketoxime **4** was used by us for the preparation of a series of imidazole *N*(3)-oxides **7a-d** which are substituted at the positions 1, 4, and 5 of the imidazole ring. The transformation of oxime **4** to imidazole **7** was achieved using a mixture of paraformaldehyde and the corresponding monosubstituted amine (methylamine,

ethanolamine, glycine, or β-alanine). Condensation was carried out by short heating of the components in acetic acid. It was not possible to achieve this reaction using α-alanine, serine, and a series of other natural amino acids. Hence it should be noted that formation of the imidazole *N*-oxides from ketoxime **4** demands more forcing conditions when compared with similar reactions of 1,2-dialkyl- and 1,2-diphenylketoximes [15]. The influence of steric factors also proved significant in our case.

The structure of the synthesized compounds was established using mass spectrometry and ^{1}H NMR spectroscopy.

Hence it has been shown that the basic route, how 6-methylpyrimidin-4-one containing a β-oxoethylidene fragment at the position 2 interacts with hydroxylamine and hydrazine, is a substitution of the carbonyl oxygen (in the case of hydrazine, the reaction proceeds with subsequent destruction of the pyrimidine fragment). Simple methods are proposed for modification of the β-oxoethylidene fragment, to give the corresponding oxime, dioxime, and ketoxime which can serve as promising starting compounds in the synthesis of a series of noncondensed biheterocyclic systems.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian WPX-300 spectrometer (300 MHz) using DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on an MX 1321 instrument using direct introduction of the sample at an electron impact ionization energy of 70 eV and ion source temperature of 220°C. Melting points were determined on a PTP (TU 25-11-1144-76) apparatus in sealed and open capillaries at a heating rate of 4-6°C/min and 1-2°C/min near the melting point. The purity of the synthesized compounds was monitored by TLC on Silufol UV-254-VIS plates with MeOH–MeCN–$CHCl_3$ (1:3:7) as eluent.

The starting 6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4-(1*H*)-one (**1**) was synthesized by method [16].

3-Amino-5-phenylpyrazole (2) and 3-Methyl-2-pyrazolin-5-one (3). Compound **1** (1.00 g, 4.4 mmol) was dissolved in a minimal amount of refluxing EtOH (90-100 ml), and hydrazine hydrate (20 ml, 400 mmol) was added. The mixture was refluxed for 7 h and filtered. The filtrate was evaporated on a rotary evaporator. The oily residue was extracted with boiling benzene (4×20 ml). The crystals of compound **2** precipitated from the benzene were filtered off and dried *in vacuo*. Yield 0.50 g (71%). Colorless crystals; mp 124-127°C (mp 127°C (C_6H_6) [12]). ^{1}H NMR spectrum, δ, ppm: 11.77 (1H, s, NH); 7.66-7.26 (5H, m, H Ph); 5.76 (1H, s, H-4); 4.80 (2H, s, NH_2). Mass spectrum, *m/z* (I_{rel}, %): 159 $[M]^+$ (100), 130 (16), 102 (10), 77 (17). Found, %: C 68.00; H 5.74; N 26.46. $C_9H_9N_3$. Calculated, %: C 67.91; H 5.70; N 26.40. The residue insoluble in benzene was extracted with refluxing MeCN (6×20 ml), and the extract was evaporated to the start of crystallization. The precipitated pyrazolone **3** was filtered off and dried. Yield 0.25 g (62%). White powder; mp 215-218°C (mp 223-224°C (EtOH-Et_2O, 1:9) [14]). The ^{1}H NMR and mass spectrometry data corresponded to that given in [14].

2-(1-Hydroxyimino-2-oxo-2-phenylethyl)-6-methylpyrimidin-4(3*H*)-one (4). Compound **1** (1.0 g, 4.4 mmol) was dissolved in a minimal amount of AcOH (40-45 ml) at 80°C, and a saturated aqueous solution of $NaNO_2$ (0.9 g, 13.2 mmol) was added portionwise with stirring. The reaction mixture was left in a fume hood until the major part of the solvent had evaporated. The residue was filtered off, washed on the filter with cold water, dried, and recrystallized from EtOH. Yield 0.9 g (80%). White powder; mp > 215°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 12.76 (1H, s, NOH); 12.44 (1H, s, NH); 7.84-7.56 (5H, m, H Ph); 6.26 (1H, s, H-5); 2.06 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 257 $[M]^+$ (34), 213 (16), 152 (95), 136 (31), 122 (10), 105 (100), 94 (9), 77 (76). Found, %: C 60.85; H 4.37; N 16.30. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

2-(2-Hydroxyimino-2-phenylethyl)-6-methylpyrimidin-4(3*H*)-one (5). $NH_2OH{\cdot}HCl$ (1.5 g, 22 mmol) and pyridine (0.2 ml) were added to a saturated solution of compound **1** (0.5 g, 2.2 mmol) in refluxing EtOH (45-50 ml) and refluxed for 8 h. The solvent was evaporated *in vacuo*, and the residue was treated with water

(20 ml) and neutralized using AcOH. The precipitate formed was filtered off, dried in air and crystallized from MeCN. Yield 0.25 g (46%). Colorless crystals; mp 235-236°C. ^{1}H NMR spectrum, δ, ppm: 12.42 (1H, s, NH); 11.49 (1H, s, NOH); 7.72-7.36 (5H, m, H Ph); 6.00 (1H, s, H-5); 3.99 (2H, s, CH_2); 2.02 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 243 $[M]^+$ (33), 226 (18), 124 (100), 103 (13), 84 (15), 77 (15). Found, %: C 64.30; H 5.55; N 17.30. $C_{13}H_{13}N_3O_2$. Calculated, %: C 64.19; H 5.39; N 17.27.

2-(1,2-Dihydroxyimino-2-phenylethyl)-6-methylpyrimidin-4(3*H*)-one (6). Compound **4** (0.5 g, 2.0 mmol) and KOH (2.3 g, 40 mmol) were dissolved in water (10 ml). $NH_2OH·HCl$ (1.4 g, 20 mmol) was added, and the product was heated on a boiling water bath for 1.5 h. The reaction mixture was cooled and neutralized with AcOH. The precipitate was filtered off, dried in air, and crystallized from MeCN. Yield 0.3 g (57%). Colorless crystals; mp > 282°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 12.51 (1H, s, 1'-NOH); 12.19 (1H, s, NH); 11.56 (1H, s, 2'-NOH); 7.47-7.31 (5H, m, H Ph); 6.21 (1H, s, H-5); 2.07 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 272 $[M]^+$ (18), 255 (47), 254 (100), 237 (47), 224 (23), 210 (28), 209 (25), 177 (20), 152 (18), 136 (23), 128 (15), 119 (20), 110 (22), 103 (42), 91 (16), 84 (37), 77 (64). Found, %: C 57.40; H 4.50; N 20.50. $C_{13}H_{12}N_4O_3$. Calculated, %: C 57.35; H 4.44; N 20.58.

6-Methyl-2-(1-methyl-3-oxy-5-phenyl-1*H*-imidazol-4-yl)pyrimidin-4(3*H*)-one (7a). A mixture of compound **4** (0.18 g, 0.7 mmol), paraformaldehyde (0.04 g, 1.4 mmol), and $MeNH_2·HCl$ (0.09 g, 1.4 mmol) was refluxed in AcOH (5 ml) for 10 min. Solvent was evaporated *in vacuo*, and the residue was treated with an equal volume of MeOH and allowed to crystallize. The crystals were filtered off and dried in air. Yield 0.10 g (51%). Light-yellow crystals; mp > 250°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 15.12 (1H, br. s, NH); 8.90 (1H, s, H-2'); 7.56-7.46 (5H, m, H Ph); 6.01 (1H, s, H-5); 3.49 (3H, s, 1'-CH_3); 2.07 (3H, s, 6-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 282 $[M]^+$ (25), 266 (45), 265 (100), 184 (14), 118 (17), 84 (10), 77 (10). Found, %: C 63.90; H 5.00; N 19.75. $C_{15}H_{14}N_4O_2$. Calculated, %: C 63.82; H 5.00; N 19.85.

2-[1-(2-Hydroxyethyl)-3-oxy-5-phenyl-1*H*-imidazol-4-yl]-6-methylpyrimidin-4(3*H*)-one (7b). A mixture of compound **4** (0.30 g, 1.17 mmol), paraformaldehyde (0.07 g, 2.40 mmol) and ethanolamine (0.15 ml, 2.40 mmol) was refluxed in AcOH (10 ml) for 15 min. Solvent was evaporated *in vacuo*, and the oily residue was treated with an equal volume of $CHCl_3$ and allowed to crystallize. The precipitate was filtered off, washed with hot benzene, and crystallized from MeCN. Yield 0.10 g (30%). Light-yellow crystals; mp 228-230°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.10 (1H, br. s, NH); 8.89 (1H, s, H-2'); 7.55-7.46 (5H, m, H Ph); 5.99 (1H, s, H-5); 5.07 (1H, t, *J* = 6.0, OH); 3.88 (2H, t, *J* = 5.4, $NC\underline{H}_2CH_2OH$); 3.57 (2H, q, *J* = 5.4, $NCH_2C\underline{H}_2OH$); 1.81 (3H, s, 6-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 312 $[M]^+$ (66), 296 (67), 295 (100), 279 (93), 268 (38), 253 (20), 252 (60), 251 (64), 182 (13), 170 (23), 128 (17), 116 (14), 104 (36), 84 (41), 77 (27). Found, %: C 61.67; H 5.20; N 17.90. $C_{16}H_{16}N_4O_3$. Calculated, %: C 61.53; H 5.16; N 17.94.

2-[4-(4-Methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-3-oxy-5-phenyl-1*H*-imidazol-1-yl]acetic Acid (7c). A mixture of compound **4** (0.30 g, 1.17 mmol), paraformaldehyde (0.07 g, 2.40 mmol) and glycine (0.18 g, 2.40 mmol) was refluxed in AcOH (10 ml) for 15 min. Solvent was evaporated *in vacuo*, and the residue was treated with an equal volume of MeOH and allowed to crystallize. The crystals were filtered off and dried in air. Yield 0.20 g (55%). White powder; mp 238-242°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 15.02 (1H, br. s, NH); 12.67 (1H, br. s, CO_2H); 8.90 (1H, s, H-2); 7.54-7.38 (5H, m, H Ph); 6.03 (1H, s, H-5'); 4.64 (2H, s, $NC\underline{H}_2CO_2H$); 1.82 (3H, s, 6'-CH_3). Mass spectrum, *m/z* (I_{rel}, %): 326 $[M]^+$ (18), 320 (10), 310 (51), 309 (74), 282 (15), 265 (14), 251 (16), 182 (11), 128 (51), 104 (12), 84 (15), 77 (10), 44 (100). Found, %: C 59.00; H 4.35; N 17.22. $C_{16}H_{14}N_4O_4$. Calculated, %: C 58.89; H 4.32; N 17.17.

2-[4-(4-Methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-3-oxy-5-phenyl-1*H*-imidazol-1-yl]propionic Acid (7d). Obtained similarly to compound **7c** from compound **4** (0.30 g, 1.17 mmol), paraformaldehyde (0.07 g, 2.40 mmol), and β-alanine (0.20 g, 2.40 mmol). Yield 0.30 g (75%). White powder; mp 236-238°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.06 (1H, br. s, NH); 12.58 (1H, br. s, CO_2H); 8.95 (1H, s, H-2); 7.56-7.47 (5H, m, H Ph); 6.00 (1H, s, H-5'); 4.04 (2H, t, *J* = 6.9, $NC\underline{H}_2CH_2COOH$); 2.68 (2H, t, *J* = 6.9, $NCH_2C\underline{H}_2COOH$); 1.81 (3H, s, 6'-$CH_3$). Mass spectrum, *m/z* (I_{rel}, %): 340 $[M]^+$ (16), 324 (18), 323 (22), 279 (26), 268 (100), 252 (32),

251 (97), 224 (10), 208 (15), 185 (12), 168 (34), 136 (23), 128 (16), 116 (10), 110 (16), 104 (26), 89 (14), 84 (29), 77 (26). Found, %: C 60.10; H 4.77; N 16.50. $C_{17}H_{16}N_4O_4$. Calculated, %: C 60.00; H 4.74; N 16.46.

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