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Reaction of 2-(2-Oxo-2-arylethylidene)-2,3-dihydropyrimidine-4(1*H*)-ones with Aldehydes

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Abstract—2-(2-Oxo-2-arylethylidene)-2,3-dihydropyrimidine-4(*1H*)-ones react with aromatic and heteroaromatic aldehydes to form the unsaturated ketones, whereas in the case of 3- and 4-benzaldehydes the corresponding *trans*-2-styrylpyrimidine-4(*3H*)-ones were obtained. A possible mechanism of hydrolytic cleavage of the product of condensation of 2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidine-4(*1H*)-one with paraformaldehyde under acid catalysis and mechanochemical activation has been discussed.

Keywords: pyrimidinone, pyrimidine, benzaldehyde, condensation

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Only a few pyrimidine derivatives have been considered CH nucleophiles in condensation with carbonyl compounds. Most of the studies reported so far have been devoted to synthesis of 5-ylidene and 5,5'-ylidenebishydroxypyrimidines from barbituric acids and their derivatives [1]. Nevertheless, recently efficient methods to prepare a series of styrylpyrimidines from benzaldehydes and methylpyrimidines have been developed [2–4] due to emerging interest towards investigation of photophysical and photochemical properties of heterocyclic analogs of stilbene [5].

In continuation of our studies on synthesis of 2-alkylidenepyrimidines [6–8], herein we discuss some features of interaction of 2-(2-oxo-2-arylethylidene)-pyrimidines **Ia** and **Ib** with aromatic and heteroaromatic aldehydes.

Addition of the corresponding aldehyde to the exocyclic double bond of **Ia**, **Ib** was accompanied with the subsequent dehydration. Structure of the reaction products was determined by nature of the substituent in the starting benzaldehyde.

In particular, reaction of pyrimidine **Ia** with benzaldehyde and 4-bromobenzaldehyde afforded arylideneketones **IIa** and **IIb**, respectively, whereas the reactions with 3- and 4-nitrobenzaldehydes under similar conditions (refluxing in acetic acid in the presence of catalytic amounts of *p*-toluenesulfonic acid monohydrate) resulted in *trans*-2-styrylpyrimidine-4(3*H*)-ones **IIIa** and **IIIb**, respectively (Scheme 1).

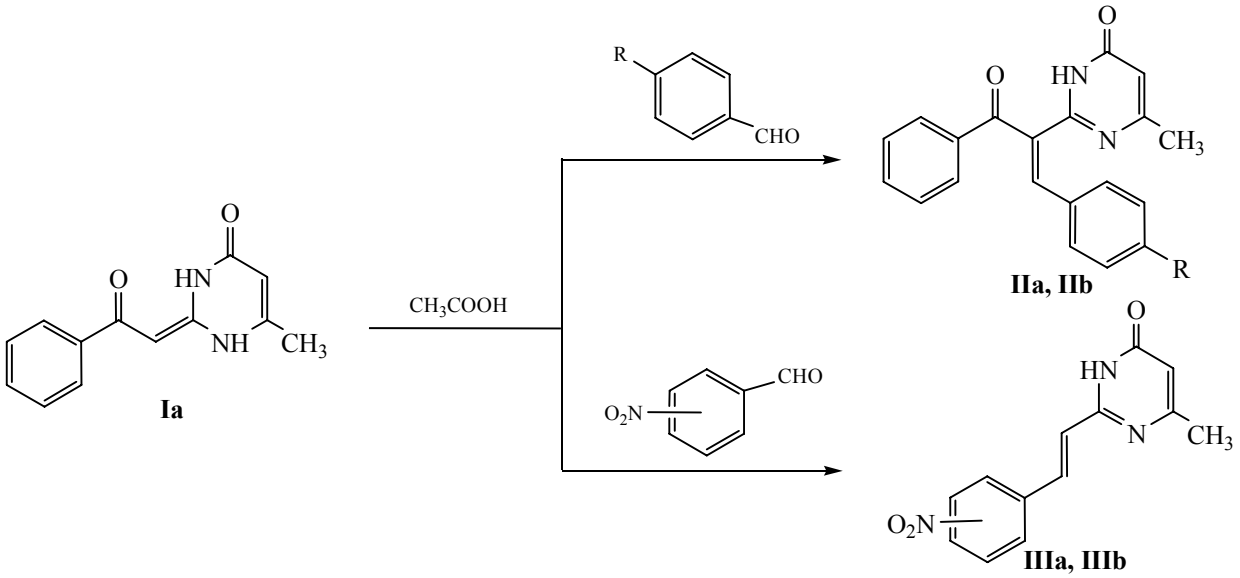
The high-boiling benzaldehyde, nicotinic aldehyde, and furfural could be used simultaneously as solvents in the reaction with pyrimidines **Ia**, **Ib**.

Short-run heating of compounds **Ia**, **Ib** with excess of the corresponding aldehydes at 160–170°C gave unsaturated ketones **IIa**, **IIc**–**IIf** with yields of 30–82% (Scheme 2).

Unlike aromatic aldehydes, paraformaldehyde could react with pyrimidine **Ia** in the solid phase in the presence of acid without heating. Mechanochemical activation of compound **Ia** mixed with paraformaldehyde in the presence of catalytic amount of *p*-toluenesulfonic acid monohydrate afforded the derivative **IV** with good yield.

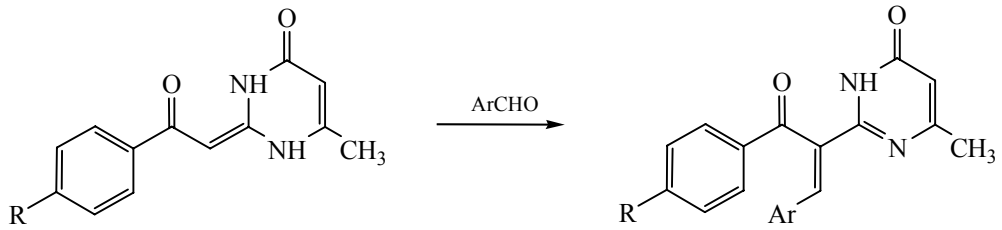
The optimal molar ratio compound **Ia** to *p*-toluenesulfonic acid monohydrate was of 4 : 1. Decreasing the acid content led to slowing down the reaction, or even to reaction stopping. When the amount of *p*-toluenesulfonic acid monohydrate was up to >20%, hydrolytic cleavage of compound **IV** occurred to give symmetrically substituted propane **V**.

Scheme 1.



R = H (**IIa**), Br (**IIb**), 3-NO_2 (**IIIa**), 4-NO_2 (**IIIb**).

Scheme 2.



Ia, Ib **IIa, IIc–IIf**

R = H (**Ia**), NO_2 (**Ib**); R = H, Ar = Ph (**IIa**); R = H, Ar = 3-Py (**IIc**); R = H, Ar = 2-Fur (**IId**); R = NO_2, Ar = Ph (**IIe**); R = NO_2, Ar = 2-Fur (**IIf**).

The latter could be preparatively obtained both in solution and in the solid phase under mechanical activation in the presence of equimolar amount of the acid (Scheme 3).

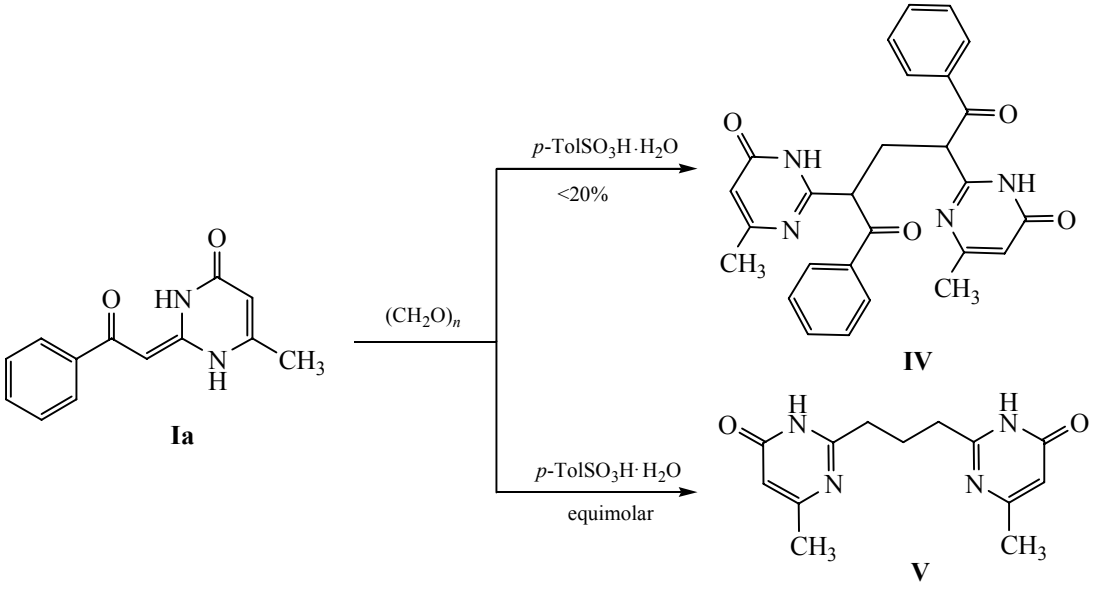
Examples of the carbon-carbon bond cleavage under mild conditions have been reported in the cases of certain β-dicarbonyl compounds [9], including the side reactions accompanying alkylation of 2-mercapto-3-ureidopyridines and 5-amino-6-mercaptopyrimidines halo-β-diketones [10, 11].

In the studied case, the ease of bispyrimidine **IV** transformation into compound **V** could be due to the acid catalysis (Scheme 4) of successive stages of intramolecular of heterocycle nitrogen atom to the benzoyl group. On the other hand, the strain in the six-membered tetrahedral intermediates **A** should have facilitated cleavage of the C–C bond to form *N*-benzoyl derivative **B** followed by hydrolysis yielding benzoic acid and, finally, compound **V** (X = H). We believe that in that reaction the pyrimidine ring acted as a peculiar agent promoting dissociation of the C–benzoyl bond (Scheme 4).

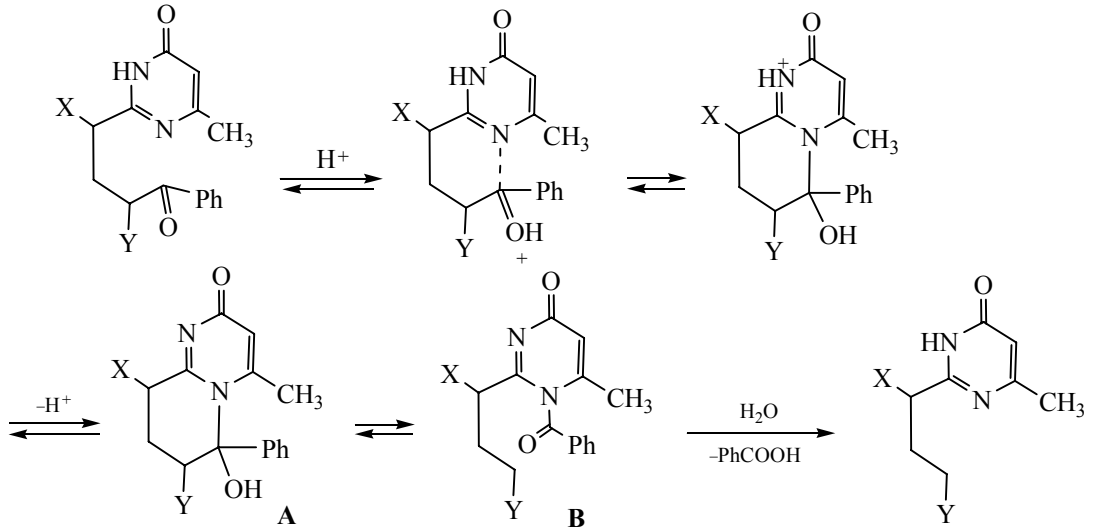
EXPERIMENTAL

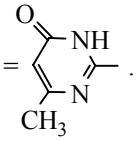
The solvents were purified by standard proceduress [12]. TLC analysis was performed with Silufol UV-254 plates, eluting with chloroform–acetonitrile–heptane (5 : 2 : 1) or chloroform–acetonitrile–methanol (5 : 2 : 1) mixture. Solid phase synthesis was performed in the electromechanical sealed vibrating mortar KM–1 (Germany). ^{1}H NMR spectra were

Scheme 3.



Scheme 4.



X = PhCO (**IV**), H (**V**), Y =  .

registered with the Varian WXP-300 spectrometer (299.9 MHz). Mass spectra were recorded using the MX 1321 mass spectrometer (70 eV, the ion source temperature 220°C). Mass spectrum (fast atom bombardment) of **IV** was obtained with the VG Analitycal 7070 ED instrument.

2-[1-Benzoyl-2-phenylvinyl]-6-methylpyrimidine-4(3*H*)-one (IIa). *a*. A mixture of 0.5 g of pyrimidine **Ia**, 0.5 g of freshly distilled benzaldehyde, and 0.08 g of *p*-$TolSO_3H·H_2O$ in 10 mL of acetic acid was refluxed during 8 h. After the solvent was distilled off, the solid residue was washed with small amount of

methanol and recrystallized from ethanol. Yield 0.3 g (43%), mp 235–237°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.58 br.s (1H, NH), 7.99 s (1H, CH_{olefin}), 7.88 d (2H, CH_{Ar}, *J* 7.5), 7.60 t (1H, CH_{Ar}, *J* 7.5), 7.48 t (2H, CH_{Ar}, *J* 7.5), 7.33–7.27 m (5H, CH_{Ar}), 6.22 s (1H, $CH_{pyrimidine}$), 2.06 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel},%): 316(30), 287(100), 259(6), 211 (86), 204(10), 178(7), 128(28), 110(6) 101(7), 84(38), 77(90). Found, %: C 75.86; H 5.14; N 8.86. $C_{20}H_{16}N_2O_2$. Calculated, %: C 75.93; H5.10; N 8.85.

b. A mixture of 1 g of pyrimidine **Ia** and 5 mL of freshly distilled benzaldehyde was heated during 1 h at 160–170°C. After cooling, the precipitate was filtered off, washed with benzene, and dried in air. Yield 0.5 g (36%), mp 235–237°C.

2-[1-Benzoyl-2-(4-bromophenyl)vinyl]-6-methylpyrimidine-4(3*H*)-one (IIb). A mixture of 0.2 g of **Ia**, 0.3 g of *p*-bromobenzaldehyde, and 0.03 g of *p*-$TolSO_3H{\cdot}H_2O$ in 10 mL of acetic acid was refluxed during 14 h. After the solvent was distilled off, the solid residue was washed with methanol and recrystallized from ethanol. Yield 0.1g (27%), mp 231–232°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.58 br.s (1H, NH), 7.95 s (1H, CH_{olefin}), 7.86 d (2H, CH_{Ar}, *J* 7.5), 7.61 t (1H, CH_{Ar}, *J* 7.5), 7.51 d (2H, CH_{Ar}, *J* 8.4), 7.48 t (2H, CH_{Ar}, *J* 7.5), 7.26 d (2H, CH_{Ar}, *J* 8.4), 6.22 s (1H, $CH_{pyrimidine}$), 2.06 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 394(20), 367(63), 291 (19), 287(12), 211(63), 206(10), 143(12), 127(14), 110 (7), 105(62), 100(8), 77(100). Found, %: C 60.69; H 3.87; N 7.05. $C_{20}H_{15}BrN_2O_2$. Calculated, %: C 60.78; H 3.83; N 7.09.

2-(1-Benzoyl-2-pyridin-3-yl-vinyl)-6-methylpyrimidine-4(3*H*)-one (IIc). A mixture of 0.4 g of **Ia** and 1.1 mL of nicotinic aldehyde was heated during 1 h at 160–170°C. After cooling, the reaction mixture was diluted with 4 mL of benzene, and then with 4 mL of heptane. The resulting precipitate was filtered off and washed with small amount of methanol. Yield 0.3 g (54%), mp 214–215°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.43 br.s (1H, NH), 8.54 s (1H, $CH_{pyridine}$), 8.45 d (1H, $CH_{pyridine}$, *J* 6.0), 8.02 s (1H, CH_{olefin}), 7.88 d (2H, CH_{Ar}, *J* 6.0), 7.66–7.58 m (2H, CH_{Ar}, $CH_{pyridine}$), 7.49 t (2H, CH_{Ar}, *J* 6.0), 7.31 d.d (1H, $CH_{pyridine}$, *J* 6.0, 3.0), 6.27 s (1H, $CH_{pyrimidine}$), 2.10 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 317 (32), 289(51), 288(55), 287(45), 211(48), 129(12), 105(62), 84(27), 77(100). Found, %: C 75.86; H 5.15; N 8.88. $C_{20}H_{16}N_2O_2$. Calculated, %: C 75.93; H 5.10; N 8.85.

2-[1-Benzoyl-2-(2-furyl)vinyl]-6-methylpyrimidine-4(3*H*)-one (IId). A mixture of 1 g of pyrimidine **Ia** and 5 mL of freshly distilled furfural was heated during 1 h. The precipitate was filtered off and washed with benzene on the filter. Yield 1.1 g (82%), mp 240–242°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.32 br.s (1H, NH), 7.87 d (2H, CH_{Ar}, *J* 6.0), 7.86 s (1H, CH_{olefin}), 7.63 d (1H, CH_{furyl}, *J* 1.5), 7.61 t (1H, CH_{Ar}, *J* 6.0), 7.49 t (2H, CH_{Ar}, *J* 6.0), 6.74 d (1H, CH_{furyl}, *J* 3.0), 6.54 d.d (1H, CH_{furyl}, *J* 3.0, 1.5), 6.20 s (1H, $CH_{pyrimidine}$), 2.07 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 306(57), 277(32), 251(26), 224(22), 201 (17), 198(13), 175(12), 118(13), 105(63), 84(23), 77 (100). Found, %: C 70.51; H 4.70; N 9.11. $C_{18}H_{14}N_2O_3$. Calculated, %: C 70.58; H 4.61; N 9.15.

2-[1-(4-Nitrobenzoyl)-2-phenylvinyl]-6-methylpyrimidine-4(3*H*)-one (IId). A mixture of 0.5 g of pyrimidine **Ib** and 3 mL of freshly distilled benzaldehyde was heated during 5 h. After cooling, the reaction mixture was diluted with 3 mL of benzene, and the reaction product was precipitated with heptane. The solvents were decanted. Gummy precipitate was triturated with methanol, and the crystals formed were filtered off and dried in air. Yield 0.2 g (30%), mp 170–180°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.80 br.s (1H, NH), 8.30 d (2H, CH_{Ar}, *J* 9.0), 8.12 d (2H, CH_{Ar}, *J* 9.0), 8.0 s (1H, CH_{olefin}), 7.36–7.26 m (5H, CH_{Ar}), 6.25 s (1H, $CH_{pyrimidine}$), 2.05 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 361(42), 333(100), 287(12), 273(7), 256(17), 211(38), 150(12), 128(24), 110(6), 104(24), 92(8), 84(50), 77(20). Found, %: C 66.41; H 4.22; N 11.59. $C_{20}H_{15}N_3O_4$. Calculated, %: C 66.48; H 4.18; N 11.63.

2-[1-(4-Nitrobenzoyl)-2-(2-furyl)vinyl]-6-methylpyrimidine-4(3*H*)-one (IIe). A mixture of 0.3 g of pyrimidine **Ib** and 4 mL of freshly distilled furfural was refluxed during 1.5 h. The precipitate was filtered off and washed with benzene on the filter. Yield 0.3 g (77%), mp 250–252°C. ^{1}H NMR spectrum, (DMSO-d_6), δ, ppm (*J*, Hz): 12.45 br.s (1H, NH), 8.33 d (2H, CH_{Ar}, *J* 9.0), 8.12 d (1H, CH_{Ar}, *J* 9.0), 7.95 s (1H, CH_{olefin}), 7.64 d (1H, CH_{furyl}, *J* 1.5), 6.85 d (1H, CH_{furyl}, *J* 3.0), 6.57 d.d (1H, CH_{furyl}, *J* 3.0, 1.5), 6.23 s (1H, $CH_{pyrimidine}$), 2.07 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 351 (100), 323(42), 310(7), 297(47), 280(12), 276(14), 269 (22), 201(33), 175(28), 150(37), 118(27), 104(47), 92 (17), 84(47), 77(46). Found, %: C61.48; H 3.77; N 11.99. $C_{18}H_{13}N_3O_5$. Calculated, %: C 61.54; H 3.73; N 11.96.

2-[2-(3-Nitrophenyl)vinyl]-6-methylpyrimidine-4(3*H*)-one (IIIa). A mixture of 1.0 g of pyrimidine **Ia**, 0.99 g of *m*-nitrobenzaldehyde, and 0.17 g of *p*-$TolSO_3H·H_2O$ was refluxed in 50 mL of acetic acid during 28 h. The resulting precipitate was filtered off, washed sequentially with methanol, water, and methanol. Yield 0.6 g (55%), mp 270–273°C. ^{1}H NMR spectrum, (DMSO-d_6), δ, ppm (*J*, Hz): 12.39 s (1H, NH), 8.43 s (1H, CH_{Ar}), 8.23 d (1H, CH_{Ar}, *J* 8.1), 8.08 d (1H, CH_{Ar}, *J* 8.1), 7.95 d (1H, CH_{olefin}, *J* 15.9), 7.74 t (1H, CH_{Ar}, *J* 8.1), 7.08 d (1H, CH_{olefin}, *J* 15.9), 6.13 s (1H, $CH_{pyrimidine}$), 2.24 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 257(100), 240(10), 210(75), 182(18), 128(40), 110 (10), 101(20), 91(7), 84(85). Found, %: C 60.61; H 4.36; N 16.38. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N 16.33.

2-[2-(4-Nitrophenyl)vinyl]-6-methylpyrimidine-4(3*H*)-one (IIIb) was prepared similarly, the reaction time was 20 h. Yield 60%, mp >300°C. ^{1}H NMR spectrum, (DMSO-d_6), δ, ppm (*J*, Hz): 12.46 s (1H, NH), 8.28 d (2H, CH_{Ar}, *J* 8.7), 7.93 d (1H, CH_{olefin}, *J* 15.9), 7.89 d (2H, CH_{Ar}, *J* 8.7), 7.09 d (1H, CH_{olefin}, *J* 15.9), 6.14 s (1H, $CH_{pyrimidine}$), 2.24 s (3H, CH_3). Mass spectrum, *m/e* (I_{rel}, %): 257 (100), 240(27), 210 (78), 182(8), 128(22), 110(8), 101(12), 91(5), 84(75). Found, %: C 60.59; H 4.38; N.32. $C_{13}H_{11}N_3O_3$. Calculated, %: C 60.70; H 4.31; N.33.

1,3-Bis(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1,3-dibenzoylpropane (IV). A mixture of 0.7 g of **Ia**, 0.18 g of paraformaldehyde, and 0.12 g of *p*-$TolSO_3H·H_2O$ was stirred in the vibration mortar during 17–20 h (reaction progress was monitored by TLC). The reaction mixture was transferred onto a glass filter, washed with water, and dried under water jet pump vacuum. The precipitate was mixed with 70 mL of methylene chloride, and the solid part was filtered off. The filtrate was diluted with 50 mL of hexane and incubated for precipitate formation. The precipitate was filtered off and dried on air. Yield 0.6 g (83%), mp 135–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.45 br.s (2H, 2NH), 8.08–7.47 m (10H, CH_{Ar}), 6.15 s (1.2H, $2CH_{pyrimidine}$), 5.99 s (0.8H, $2CH_{pyrimidine}$), 4.94–4.76 m (2H, 2CHCO), 2.63–2.59 m (1H, CH_2), 2.26 s (3.6H, $2CH_3$), 2.20–2.06 m (1H, CH_2), 1.97 s (2.4H, $2CH_3$). Mass spectrum (FAB): *m/e* 469 $[M + H]^+$. Found, %: C 69.17; H 5.21; N 11.99. $C_{27}H_{24}N_4O_4$. Calculated, %: C 69.22; H 5.16; N 11.96.

1,3-Bis(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propane (V). *a*. Synthesis was performed similarly to that of **IV** from 0.9 g of pyrimidine **Ia**, 0.25 g of paraformaldehyde, and 0.75 g of *p*-$TolSO_3H·H_2O$. The reaction product was dissolved in water and filtered. The filtrate was neutralized with sodium carbonate and evaporated on a rotary evaporator to dryness. The solid residue was extracted three times with chloroform–methanol mixture (1 : 1). The combined extracts were evaporated to dryness; the residue was washed with hot benzene and recrystallized from methanol–dioxane mixture (1 : 3). Yield 0.33 g (64%), mp 273–275°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 12.20 br.s (2H, 2NH), 5.99 s (2H, $2CH_{pyrimidine}$), 2.54 t (4H, $2CH_2$, *J* 7.2), 2.12 s (6H, $2CH_3$), 2.03 t (2H, CH_2, *J* 7.2). Mass spectrum, *m/e* (I_{rel}, %): 260(6), 137(100), 124(71), 105(7), 84(18). Found, %: C 59.89; H 6.25; N 21.57. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.99; H 6.20; N 21.52.

b. A mixture of 0.9 g of pyrimidine **Ia**, 0.25 g of paraformaldehyde, and 0.75 g of *p*-$TolSO_3H·H_2O$ was dissolved in minimal amount of boiling ethanol. The solution was heated during 15 h, and then the solvent was evaporated on a rotary evaporator. The residue was dissolved in water and filtered. The filtrate was neutralized with sodium carbonate and evaporated on a rotary evaporator to dryness. The solid residue was extracted three times with chloroform–methanol mixture (1 : 1). The combined extracts were evaporated to dryness, the residue was washed with hot benzene and recrystallized from methanol–dioxane mixture (1 : 3). Yield 0.3 g (59%), mp 273–275°C.

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