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[A0027]

Reaction of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine with benzaldehyde: experimental and theoretical investigation of the product

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Abstract

The cyclocondensation reaction of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine with benzaldehyde was found to result in the formation of 2-amino-4-phenyl-4,6-dihydro-1(3)(9)*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one. The reaction proceeded chemo- and regioselectively affording the 1,3,5-triazine ring closure at nitrogen atom adjacent to carbonyl group. The structure of 2-amino-4-phenyl-4,6-dihydro-1(3)(9)*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one was supported by ^{1}H,^{13}C NMR and 2D NOESY spectral data. From the experimental data, 3*H*- tautomeric form seemed to be predominant in DMSO-d_6 solution. The relative energies of the tautomers were estimated using calculations at different levels of theory (HF/6-311G**, B3LYP/6-311++G** and MP2/6-311++G**). Both the experimental and theoretical results excluded 6-hydroxy tautomer from the equilibrium. 2-Amino-4-phenyl-4,6-dihydro-1*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one was calculated to be the energetically preferred tautomeric form in gas phase.

Keywords: pyrimidines, guanidines, triazines, tautomerism, *ab initio* calculations.

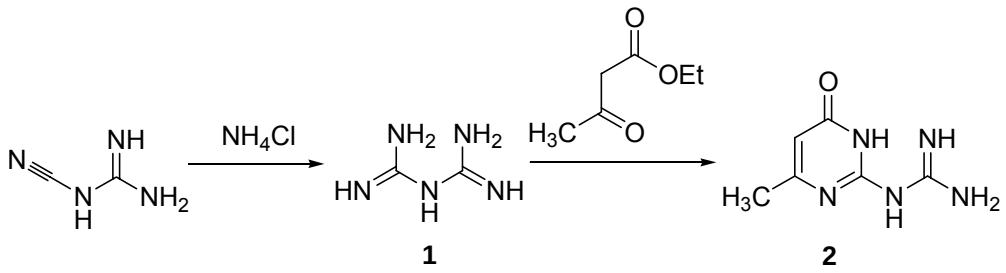
Introduction

Recently, we have shown that azaheterylguanidines are valuable synthons for the construction of potentially bioactive fused 1,3,5-triazines [1-9]. Using reactions of azaheterylguanidines with one-carbon inserting reagents, particularly aldehydes, various heterocyclic systems, namely 1,2,4-triazolo[1,5-*a*][1,3,5]triazines [1, 2], 1,3,5-triazino[1,2-*a*]benzimidazoles [3-6] and 1,3,5-triazino[2,1-*b*]quinazolines [7] have been prepared. Herein we report our attempt to extend this methodology to the synthesis of pyrimido[1,2-*a*][1,3,5]triazines using cyclocondensation of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine and benzaldehyde. The structure of the product was investigated using the experimental and theoretical approaches.

Results and discussion

Synthesis

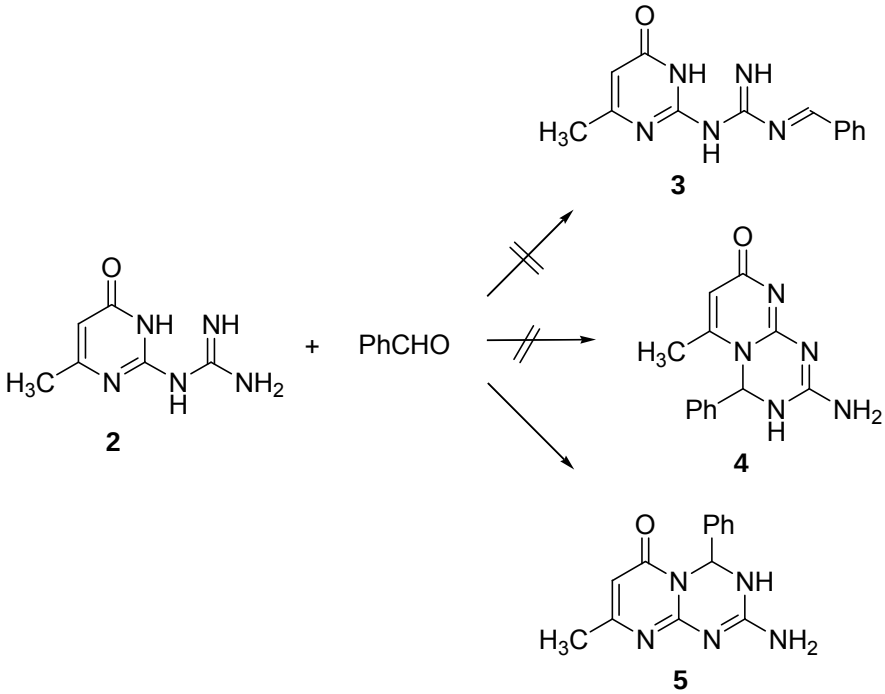
The starting material *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (**2**) [10] was synthesized using cyclocondensation of ethyl acetoacetate and biguanide (**1**), which was prepared by ammoniation of cyanoguanidine according to the reported method [11] (Scheme 1).



1 **2**

Scheme 1. Synthesis of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (**2**)

The reaction between *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (**2**) and benzaldehyde may proceed *via* three possible routes (Scheme 2).



Scheme 2. Reaction of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine with benzaldehyde

The structure of the product was established using data of NMR spectroscopy. The formation of the dihydro-1,3,5-triazine ring in the reaction was suggested by the signal at 59.8 ppm in the ^{13}C NMR spectrum of the product. This strong evidence of the sp^3 hybridization of C-4 ruled out the formation of the possible Schiff base-like compound **3** (Scheme 2). The absence of cross peaks between signals of protons located at sp^3 hybridized carbon and the methyl group in pyrimidine in 2D NOESY experiment excluded possible formation of structure **4**. Hence, the structure of 2-amino-4-phenyl-4,6-dihydro-1(3)(9)*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one (**5**) was assigned for the compound obtained.

Tautomerism study

Theoretically, pyrimido[1,2-*a*][1,3,5]triazine **3** may exist in four tautomeric forms: 1*H*- (**B**), 3*H*- (**A**), 9*H*- (**C**) and 6-hydroxy- (**D**) tautomers (Fig. 1). In 2D NOESY NMR experiments, the signal of migrating proton gave cross peaks with the singlet of H-4 and doublet of protons at *ortho*-position of phenyl ring thus suggesting 3*H*- form (**A**) to be predominant in DMSO solution. Cross peaks were observed neither between the migrating proton and methyl protons nor between the migrating proton and H-7 further excluding possibility of the existence of other forms.

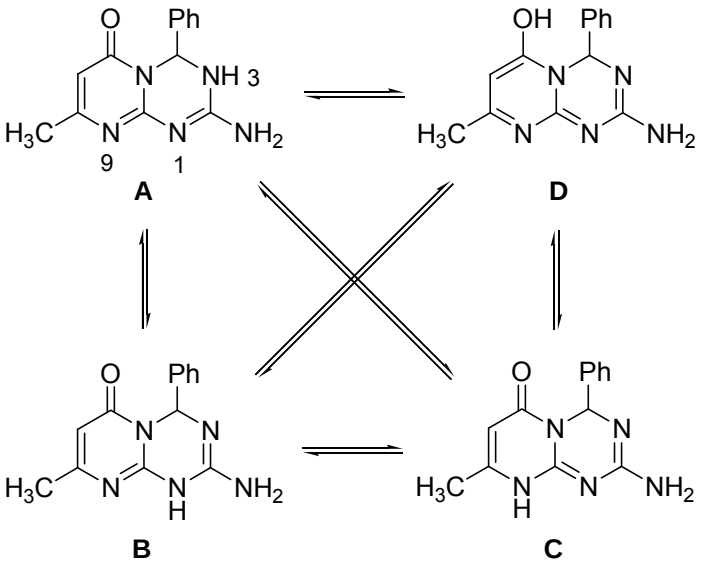


Figure 1. 2-Amino-4-phenyl-3,4-dihydro-pyrimido[1,2-*a*][1,3,5]triazin-6-one (**A**) and its possible tautomeric forms (**B-D**)

The structures of four tautomeric forms proposed were optimized with MP2/6-31G(d,p) basis set. Since, there was no imaginary frequency in the vibrational spectra, all the tautomers were confirmed to exist at stationary points corresponding to the local minima on the potential energy surface. Relative energies at

different levels of theory were calculated for tautomeric forms **A-D** (Table 1). Based on these results, tautomer **B** was determined to be the preferred form in the gas phase and the order of stability of the tautomeric forms was calculated to be **B** > **A** ≈ **C** > **D**. The 6-hydroxy form (**D**) was found to be significantly less energetically preferred. Even though form **B** appeared to possess lower energy in the calculations at all levels of theory applied, the energy difference between this form and tautomers **A** and **C** was found to be ≤5 kcal/mol.

Table 1. Relative energies for tautomers **A-D**

Method of calculation	Relative energies for tautomers, kcal/mol			
	NH forms			**D**
	A (3*H*-)	**B** (1*H*-)	**C** (9*H*-)	(OH form)
HF/6-311G**	2.88	0.00	3.45	28.28
B3LYP/6-311++G**	3.28	0.00	2.83	24.11
MP2/6-311++G**	5.02	0.00	4.15	23.37

Conclusion

A new method for the synthesis of pyrimido[1,2-*a*][1,3,5]triazine system was successfully developed using the reaction of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (**2**) with benzaldehyde. The structure of the product was studied using NMR spectroscopy and *ab initio* calculations.

Experimental

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO-d_6 as a solvent and TMS as an internal reference. IR spectra were performed on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer in potassium bromide pellets. Mass spectra were obtained on a Finnigan MAT LCQ LC-MS mass spectrometer using atmospheric pressure chemical ionization (APCI) mode. The course of the reactions was monitored by TLC on Silica gel 60 F_{254} plates (Merck, Germany).

Preparation of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (2).

Compound **2** was synthesized according to Curd et al. [10]. Sodium hydroxide solution (40%, 4.3 mL) was slowly added to the stirred suspension of biguanidinium sulfate (4.4 g, 20 mmol) in ethanol (6 mL) at 0°C. After stirring the mixture at room temperature for 15 min, ethyl acetoacetate (3.0 mL, 24 mmol) was added and the stirring was continued overnight. The white precipitate obtained was filtered, washed with ethanol and water and then dried. Yield

93%; mp >300 ºC; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (3H, s, Me), 5.58 (1H, s, H-5), 8.03 (4H, br. s, NHC(=NH)NH_2), 11.52 (1H, br. s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.2 (Me), 103.0 (CH), 158.5, 159.8, 163.0 (br. s), 166.9 (br. s). The prepared compound **2** was sufficiently pure and was used without further purification.

Reaction of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (2) with benzaldehyde.

A mixture of **2** (0.5 g, 2.5 mmol) and benzaldehyde (0.5 mL, 5.0 mmol) in acetic acid (5 mL) was heated under reflux for 5 h. The reaction mixture is allowed to cool to room temperature and water (10 mL) was added. The excess of aldehyde was removed by extraction with ethyl acetate (2 X 25 mL) and sodium carbonate solution (50%) was added to adjust pH of aqueous layer to ≈7. The precipitate formed was filtered and purified by column chromatography (dichloromethane / methanol - 8.5 / 1.5). Yield 61%; mp 264-265 ºC; LC-MS (APCI) *m/z* 256.3 (MH^+); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.05 (3H, s, Me), 5.72 (1H, s, H-7), 6.86 (1H, s, H-4), 7.00 (2H, br.s, NH_2), 7.23 (2H, d, J = 7.9 Hz, H-2' and H-6'), 7.31-7.39 (3H, m, H-3', H-4' and H-5'), 8.28 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.8 (Me), 59.8 (CH), 102.2 (CH), 125.2 (2CH), 128.4 (CH), 128.5 (2CH), 140.0, 154.1, 157.4, 160.5, 165.6; IR (KBr): NH 3342, CH 3057, C=O 1668, 1490, 1372, 1233, 1194, 1167, 1143, 853, 824, 792, 736, 694 cm^{-1}.

***Ab initio* calculations**

The geometry of the molecules has been optimized with MP2/6-31G(d,p) basis set using Gaussian 03 computational package. The single point calculations were performed at different levels of theory *viz.* HF/6-311G(d), B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) and the relative energies for the tautomers were calculated.

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