Tetrahedron Letters 53 (2012) 6025–6028

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new synthesis of 5-hydroxy-6-methyluracil

Stanislav A. Grabovskiy *, Yuri I. Murinov, Natalia N. Kabal'nova

Institution of the Russian Academy of Science, Institute of Organic Chemistry, Ufa Research Centre of the Russian Academy of Sciences, 71 prosp. Oktyabrya, 450054 Ufa, Russian Federation

ARTICLE INFO

Article history:
Received 24 June 2012
Revised 10 August 2012
Accepted 24 August 2012
Available online 5 September 2012

Keywords:
5-Hydroxy-6-methyluracil
Synthesis
Dihydro-5,6-dihydroxy-6-methyluracil
Dehydration
DFT

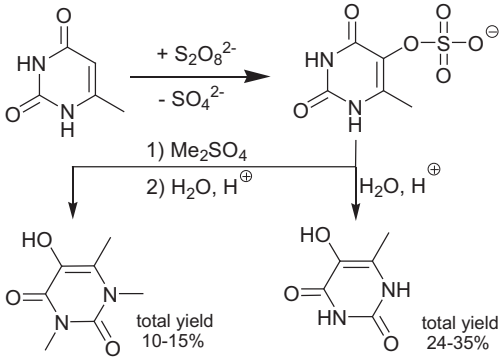
ABSTRACT

Dehydration of 5,6-dihydro-5,6-dihydroxy-6-methyl- and 5,6-dihydro-5,6-dihydroxy-1,3,6-trimethyluracil in 0.4 M aqueous sulfuric acid gives 5-hydroxy-6-methyl- and 5-hydroxy-1,3,6-trimethyluracil in quantitative yields. Two possible mechanisms have been examined using the mPW1k/6-311+G(2df,2pd)//mPW1k/6-31+G(d,p) method for the transformation of methylated and non-methylated 5,6-dihydro-5,6-dihydroxy-6-methyluracils into the corresponding 5-hydroxy-6-methyluracils. The first is a hydride C5–C6 shift occurring in concert with the loss of a water molecule and formation of the corresponding protonated 5,6-dihydro-5-oxo-6-methyluracils. The second is an acid-catalyzed dehydration reaction to yield 5-hydroxy-6-methyluracils. The calculations demonstrated that the second pathway was energetically most favorable.

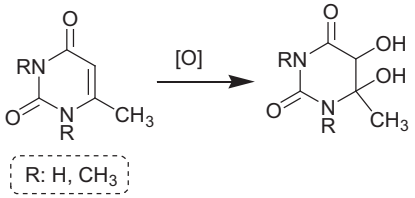
5-Hydroxy-6-methyluracil is a drug with a broad spectrum of action.[1] We have previously shown that it is a highly effective inhibitor of free radical oxidation.[2–4] Its analog, 5-hydroxy-1,3,6-trimethyluracil is soluble in organic solvents and can be regarded as a promising inhibitor in non-aqueous media.

The first report of the synthesis of 5-hydroxy-6-methyluracil was in 1902;[5] a yield of 15–25% was obtained via oxidation of 6-methyluracil with potassium permanganate in acetic acid. In 1958, a successful seven-step synthesis with an overall yield of 9% was described.[6] Subsequently, two stepwise syntheses[1,7,8] based on the oxidation of 6-methyluracil by peroxydisulfate in alkaline media followed by acid-catalyzed hydrolysis of the formed sulfate salt were reported (Scheme 1). 5-Hydroxy-1,3,6-trimethyluracil was synthesized by methylation of the formed sulfate salt of 6-methyluracil (Scheme 1).[1] The direct oxidation of 1,3,6-trimethyluracil by peroxydisulfate leads to 5,6-dihydro-6-hydroxy-1,3,6-trimethylpyrimidin-2,4,5-trione.[9] Interestingly, the formation of 5-hydroxy-1,3-dimethyluracil by refluxing 5,6-dihydro-5,6-dihydroxy-1,3-trimethyluracil with pyridine in CH_2Cl_2 was reported by Saladino et al.,[10] but the formation of 5-hydroxy derivatives of uracil from N(1)-non-substituted analogs was not observed.[10–12]

The formation of a double bond[5] from alcohols by dehydration using acid catalysis is classical methodology.[13] We applied this reaction for the synthesis of 5-hydroxy derivatives of uracil using 5,6-dihydro-5,6-diols as potential precursors. These diols are available compounds and can be obtained, easily in good yield, by oxidation of the double bond (Scheme 2) using potassium permanganate,[11,12] Ce(IV),[14] dimethyldioxirane,[15] or a catalytic system of methyltrioxorhenium.[10,16]



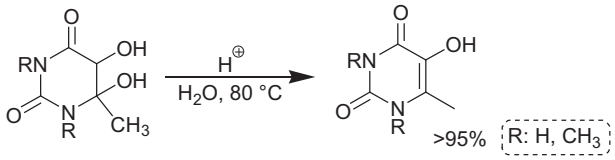
Scheme 1. Synthesis of 5-hydroxy-6-methyluracil and 5-hydroxy-1,3,6-trimethyluracil.



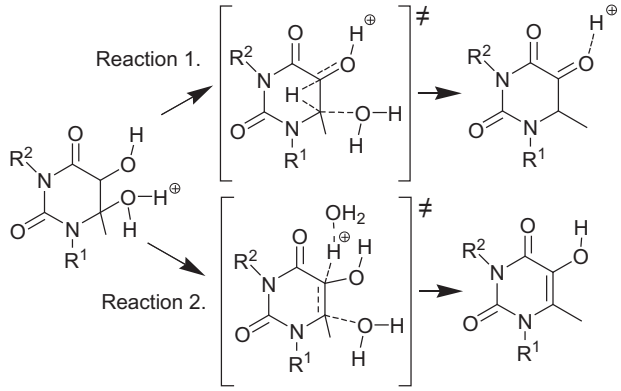
Scheme 2.

* Corresponding author. Tel.: +7 347 235 6011; fax: +7 347 235 6066.
E-mail address: stas_g@anrb.ru (S.A. Grabovskiy).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.133



Scheme 3. Synthesis of 5-hydroxy uracil derivatives.



Scheme 4. Two possible mechanisms of dehydration.

It was found that heating 5,6-dihydro-5,6-dihydroxy-6-methyluracil[17] or 5,6-dihydro-5,6-dihydroxy-1,3,6-trimethyluracil[17] at 80 °C in an aqueous solution of sulfuric acid (0.4 M) led to the formation of 5-hydroxy derivatives in high yields of 95% and 98%, respectively (Scheme 3).[18]

Previous studies employed milder dehydration conditions. Apparently, 5-hydroxy-derivatives of uracil from N(1) and N(3) non-substituted diols are not formed under those conditions.[12]

Earlier, the dehydration of diols was described in several papers[19–25] and two possible mechanisms were discussed. The first was a C5–C6 hydride shift occurring in concert with the loss of a water molecule (Scheme 4, reaction 1). The second was an acid-catalyzed dehydration proceeding via an E2 reaction (Scheme 4, reaction 2).

It is known that theoretical calculation at the mPW1k/6-31+G(d,p) level produces satisfactory results for ionic reactions.[26–28] Therefore, all calculations described in this work were performed using the mPW1k method by means of GAUSSIAN 09.[29] To avoid the hazards of basis set superposition error, final energies were obtained at the mPW1k/6-311+G(2df,2pd) level. The solvent effects of water were calculated using the polarized continuum model of Miertuš and Tomasi.[30] The solvent corrections for all structures were carried out as single point calculations at the mPW1k/6-311+G(2df,2pd) level based on the vacuum calculated structures.

The transition states (TS) for the dehydration processes (Scheme 4, reactions 1 and 2) were estimated and the thermodynamic parameters were calculated (Table 1). In the case of 5,6-dihydro-5,6-dihydroxy-uracil derivatives reaction 1 proceeds via a late TS, and reaction 2 goes via an early TS (Table 1, Fig. 1), compared to ethylene glycol.[25]

The calculated activation enthalpy of reaction 1 for substituted diols was larger than for reaction 2 by about 8 kcal/mol (Table 1, Fig. 2). The entropy of activation was more positive by approximately 2–7 cal/(mol·K) in the case of proton migration, which slightly reduces the difference between the pathways.

Gibbs free energy of activation in the gas phase reaction indicates a preference reaction 2. The effect of the solvent was to spread the difference of $\Delta G^{\neq}$ for the two mechanisms reinforcing the choice of the E2 process (reaction 2) over the C5–C6 hydride shift (reaction 1). It is clear from the calculations that reaction 2 (Scheme 4) is the significantly more favored pathway. According to values of $\Delta G^{\neq}$ (Table 1) the relative rate constant for the dehydration of **1d** and non-methylated **1a** is ~2800 to 1. Therefore, N-non-substituted derivatives require more stringent conditions or more time than their N-substituted counterparts.

In summary, a new synthesis of 5-hydroxy-6-methyluracil was developed through the acid-catalyzed dehydration of 5,6-dihydro-5,6-dihydroxy-6-methyluracil. Standard DFT calculations at the mPW1k/6-311+G(2df,2pd)//mPW1k/6-31+G(d,p) level have been applied to the question of whether the dehydration of 5,6-dihydro-5,6-diols of uracil derivatives occurred through a C5–C6 hydride shift with the loss of water to a protonated 5,6-dihydro-5-oxo-6-methyluracil derivative, or via an E2 reaction. The latter process was shown to proceed at a substantially lower activation enthalpy and Gibbs free energy than the route through concerted migration of a hydride.

Acknowledgments

This work was supported by the Program of Basic Research of the Division of Chemistry and Material Science of the Russian Academy of Sciences (program no.1).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.133.

Table 1
Enthalpies, entropies, and free energies in the gas phase and water of the reactions and transition states for the dehydrations calculated at the mPW1k/6-311+G(2df,2pd)//mPW1k/6-31+G(d,p) level of theory [ΔH and ΔG in kcal/mol; ΔS in cal/(mol·K)] and selected TS geometrical parameters (distances in Å)

Compound [a]	Reaction pathway [a]	$\Delta H^{\neq}_{298}$ [b]	$\Delta S^{\neq}_{298}$	$\Delta G^{\neq}_{298}$ [b]	$\Delta H^{\neq}_{298}(H_2O)$ [b]	ΔH_{298} [b]	ΔS_{298}	ΔG_{298} [b]	$\Delta G_{298}(H_2O)$ [b]	H···C5	H···C6	H···OH$_2$
1a	1	17.5	6.9	15.4	19.8	5.0	2.6	4.2	8.6	1.385	1.352	1.740
1b	1	16.4	9.4	13.6	17.5	4.3	2.9	3.4	7.8	1.381	1.351	1.768
1c	1	15.8	4.9	13.7	18.1	3.9	4.9	2.5	6.1	1.394	1.338	1.770
1d	1	15.0	7.3	12.8	16.6	3.5	2.2	2.8	6.3	1.388	1.339	1.794
1a	2	10.0	−3.4	11.0	12.2	−27.8	8.0	−30.2	−23.7	1.416		1.214
1b	2	6.9	−4.0	8.1	10.0	−20.8	8.7	−23.4	−17.9	1.420		1.210
1c	2	7.6	−2.6	8.3	9.5	−24.7	8.1	−27.1	−20.6	1.428		1.205
1d	2	7.0	0.2	7.0	7.5	−23.3	6.4	−25.2	−19.7	1.429		1.203

[a] See Scheme 4.
[b] Zero-point vibrational energies were obtained at the mPW1k/6-31+G(d,p) level of theory and were scaled by a factor of 0.9515.[27]

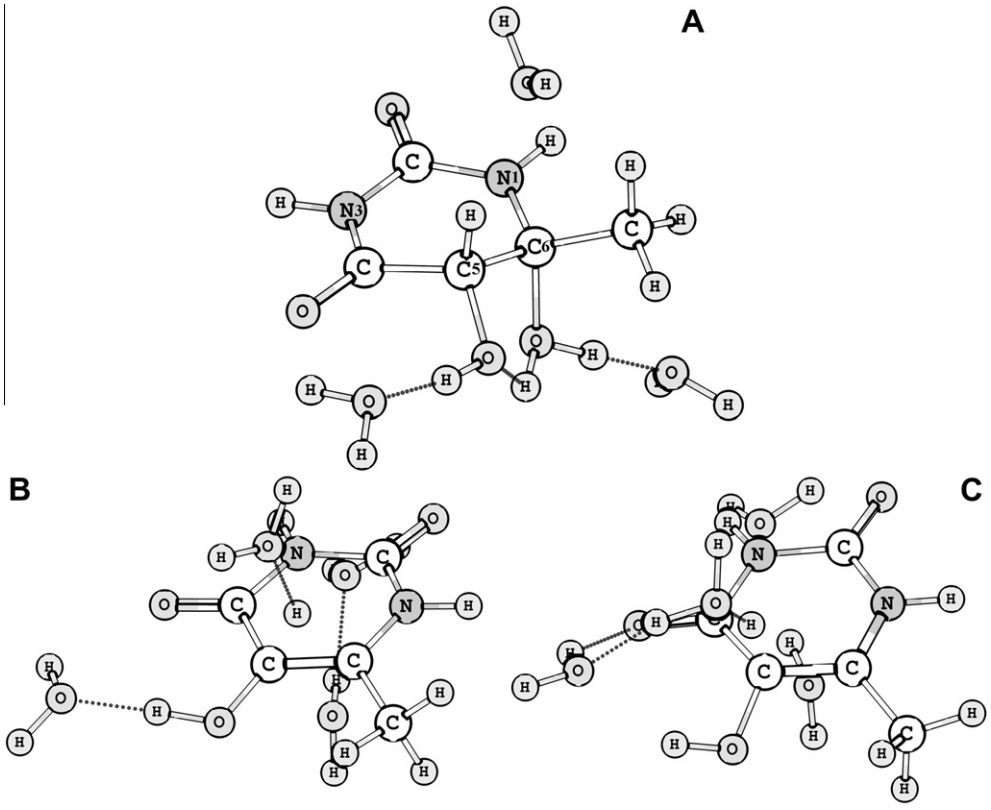


Figure 1. Optimized structures: protonated 5,6-dihydro-5,6-dihydroxy-6-methyluracil (*A*) and the transition states for a concerted hydride shift (*B*) and E2 process (*C*) at the mPW1k/6-31+G(d,p) level.

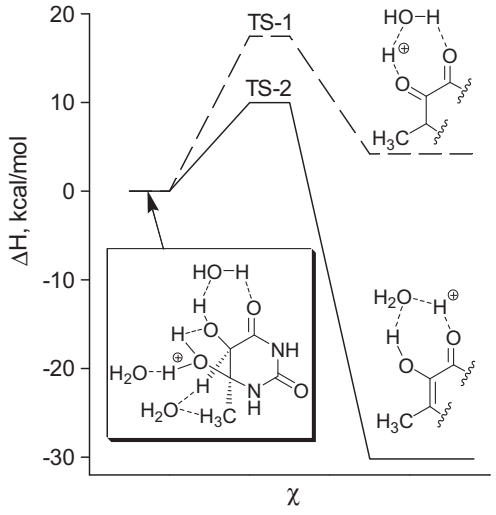


Figure 2. Reaction and activation enthalpies for the dehydration of 5,6-dihydro-5,6-dihydroxy-6-methyluracil.

References and notes

1. (a) Frivonogov, V. P.; Tolstikov, G. A.; Murinov, Yu. I.; Zarudii, F. S.; Lazareva, D. N.; Ismagilova, A. F.; Volkova, S. S.; Sahautdinova, G. M.; Spirihin, L. V.; Abdrahmanov, I. B.; Krivonogova, I. I. *Pharm. Chem. J.* **1993**, *27*, 112–120; (b) Lazareva, D. N.; Davydova, V. A. *Eksp. Klin. Farmakol.* **2005**, *68*, 53–55 (in Russian); (c) Dudkin, K. N.; Kruchinin, V. K.; Chueva, I. V. *Neurosci. Behav. Physiol.* **1994**, *24*, 329–340.
2. Kabal'nova, N. N.; Grabovskiy, S. A.; Nugumanov, T. R.; Ivanov, S. P.; Murinov, Yu. I. *Russ. Chem. Bull.* **2008**, *57*, 2241–2245.
3. Grabovskiy, S. A.; Abdrakhmanova, A. R.; Murinov, Yu. I.; Kabal'nova, N. N. *Curr. Org. Chem.* **2009**, *13*, 1733–1736.
4. Amorati, R.; Valgimigli, L.; Pedulli, G. F.; Grabovskiy, S. A.; Kabal'nova, N. N.; Chatgilialoglu, C. *Org. Lett.* **2010**, *12*, 4130–4133.
5. Behrung, R.; Grunewald, R. *Justus Liebigs Ann. Chem.* **1902**, *323*, 186–204.
6. Henze, H. R.; Kahlenberg, E. N. *J. Am. Chem. Soc.* **1958**, *80*, 1664–1666.
7. Hurst, D. T. *Aust. J. Chem.* **1983**, *36*, 1285–1289.
8. Gashev, S. B.; Gol'tsova, L. V.; Smirnov, L. D.; Lezina, V. P. *Chem. Heterocycl. Compd.* **1989**, *25*, 530–535.
9. Itahara, T.; Yoshitake, T.; Koga, S.; Nishino, A. *Bull. Chem. Soc. Jpn* **1994**, *67*, 2257–2264.
10. Saladino, R.; Bernini, R.; Crestini, C.; Mincione, E.; Bergamini, A.; Marini, S.; Palamara, A. T. *Tetrahedron* **1995**, *51*, 7561–7578.
11. Ducolomb, R.; Cadet, J.; Téoule, R. *Bull. Soc. Chim. Fr.* **1979**, 7–14.
12. Tremblay, S.; Wagner, J. R. *Nucleic Acids Res.* **2008**, *36*, 284–293.
13. Adkins, H.; Hartung, W. H. *Org. Synth. Colloid* **1926**, *1*, 15–17.
14. Lakshmi, S.; Renganathan, R. *Int. J. Chem. Kinet.* **1996**, *28*, 713–720.
15. Lupattelli, P.; Saladino, R.; Mincione, E. *Tetrahedron Lett.* **1993**, *34*, 6313–6316.
16. Saladino, R.; Carlucci, P.; Danti, M. C.; Crestini, C.; Mincione, E. *Tetrahedron* **2000**, *56*, 10031–10037.
17. Data for 5,6-dihydro-5,6-dihydroxy-6-methyluracil: Elemental Anal. Calcd for $C_5H_8N_2O_4$: C, 37.50; H, 5.04; N, 17.49. Found: C, 37.48; H, 5.07; N, 17.50. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.40 (s, 3H, CH_3), 4.04 (d, J = 6.4 Hz, 1H, OH), 5.42 (d, J = 6.4 Hz, 1H, OH), 5.71 (s, 1H, CH), 8.12 (s, 1H, NH), 10.09 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.22 (C-4), 153.66 (C-2), 81.44 (C-6), 73.66 (C-5), 25.53 (CH_3). Data for 5,6-dihydro-5,6-dihydroxy-1,3,6-trimethyluracil: Elemental Anal. Calcd for $C_7H_{12}N_2O_4$: C, 44.68; H, 6.43; N, 14.89. Found: C, 44.66; H, 6.45; N, 14.87. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.35 (s, 3H, CCH_3), 2.93 (s, 3H, N^1CH_3), 3.04 (s, 3H, N^3CH_3), 3.88 (d, 1H, J = 6 Hz, C–OH), 6.29 (d, 1H, J = 6 Hz, CH–O*H*), 6.35 (s, 1 H, C*H*OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.07 (CCH_3), 28.37 (N^1CH_3), 28.91 (N^3CH_3), 74.11 (C-5), 84.52 (C-6), 153.30 (C-2), 171.02 (C-4).
18. General procedure for the dehydration of 5,6-dihydro-5,6-dihydroxy-6-methyluracil and 5,6-dihydro-5,6-dihydroxy-1,3,6-trimethyluracil: Diol (3.1 mmol) and EDTA (10 mg, 0.03 mmol) were dissolved in a stirred aqueous solution of H_2SO_4 (4 ml, 0.4 M). The solution was heated for 1.5 h in a steam bath (80–90 °C). The reaction mixture was cooled in an ice bath and filtered. The filter cake was rinsed with cold H_2O (3 × 1.5 ml) and dried. The total yield was (3.0–2.9 mmol) 98–95%. The product was characterized by UV–Vis, IR, Raman, ^{1}H, and ^{13}C NMR spectroscopy. The data were found to be in accordance with the literature (see Supplementary data).
19. Fieser, L. F.; Fieser, M. *Advanced Organic Chemistry*; Reinhold: New York, 1961. p 287.
20. Ley, J. B.; Vernon, C. A. *J. Chem. Soc.* **1957**, 2987–2993.

21. Collins, C. J.; Rainey, W. T.; Smith, W. B.; Kay, I. A. *J. Am. Chem. Soc.* **1959**, *81*, 460–466.
22. Smith, W. B.; Bowman, R. E.; Kmet, T. J. *J. Am. Chem. Soc.* **1959**, *81*, 997–1003.
23. Nakamura, K.; Osamura, Y. *J. Phys. Org. Chem.* **1990**, *3*, 737–745.
24. Smith, W. B. *J. Phys. Org. Chem.* **1999**, *12*, 741–746.
25. Smith, W. B. *Tetrahedron* **2002**, *58*, 2091–2094.
26. Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811–4815.
27. Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2001**, *105*, 2936–2941.
28. Zhao, Y.; Lynch, B. J.; Truhlar, D. G.; Zhao, Y.; Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 2715–2719.
29. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H.P.; Izmaylov, A.F.; Bloino, J.; Zheng, G.; Sonnenberg, J.L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr. J.A.; Peralta, J.E.; Ogliaro, F.; Bearpark, M.; Heyd, J.J.; Brothers, E.; Kudin, K.N.; Staroverov, V.N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.C.; Iyengar, S.S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J.M.; Klene, M.; Knox, J.E.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Zakrzewski, V.G.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Dapprich, S.; Daniels, A.D.; Farkas, O.; Foresman, J.B.; Ortiz, J.V.; Cioslowski, J.; Fox D.J. GAUSSIAN 09, Revision C.01; GAUSSIAN, Inc.: Wallingford, CT, **2010**.
30. Miertuš, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239–245.