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Experimental and computational insights for identification of dialkyl 5-oxo-5*H*-[1,3] thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylates

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ABSTRACT

The two-component reaction of 2-thiouracil and dialkyl acetylenedicarboxylate in solvent-free conditions occurred under thermal conditions and dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylate derivatives produced were formed. The reaction proceeded smoothly and cleanly under mild reaction conditions. The structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. We also used ethyl phenylacetylenecarboxylate and methyl acetylenecarboxylate in this reaction, but no reaction happened. Stability, dipole moment, and global reactivity parameters of the dimethyl 5-oxo-5*H*-[1,3]thiazolo[3, 2-*a*]pyrimidine-2,3-dicarboxylate molecule were calculated at the CAM-B3LYP/6-311G(d,p) level of theory.

1. Introduction

In the last several decades, pyrimidine derivatives are a group of heterocyclic compounds that have attracted considerable attention in medicinal chemistry because they have a diverse range of biological properties such as antihypertensive [1], anti-tumor [2], antimalarial [3], antioxidant [4], antimitotic [5], antileishmanial [6], and anti-HIV activities. A study of literature displayed that thiazolo [3,2-*a*]pyrimidine derivatives have received much regard during recent years because they are ulcerogenic [7], antifungal [8], antibacterial and antitubercular [9], cytotoxic [10], anti-inflammatory [11], antihypertensive [12], psychopharmacological [13], antinociceptive agents [14]. The current method for pyrimidine synthesis is the Biginelli reaction. Pyrimidines are prepared by condensation reactions between carbonyl compounds and amidines in the presence of catalyst sodium hydroxide or sodium ethoxide. Many synthetic methods of pyrimidines have been reported starting from thiobarbituric acid [15], chalcones [16], and thioureas [17]. No report has been presented for the synthesis dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3-dicarboxylats under solvent and catalyst-free conditions, in connection with our interest in the synthesis of heterocycles [18-20], we reported a two-component reaction of 2-thiouracil and dialkyl acetylenedicarboxylate in solvent-free and thermal conditions in good yields and mild reaction conditions. We also used ethyl phenyl acetylenecarboxylate and methyl acetylenecarboxylate instead of DMED and DEAD in this reaction, but no reaction happened.

2. Experimental

2.1. Chemical Methods

The starting materials and solvent were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The IR spectra were recorded on a Jasco FT-IR 6300 spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-250 Avance spectrometer at 250.0 and 62.9 MHz, respectively. The elemental analyses were realized using a Heraeus CHN-O-rapid analyzer.

2.2. General procedure

A mixture of 2-thiouracil (**1**, 1mmol) and dialkyl acetylenedicarboxylate **(2**, 1mmol**)** was stirred for the period indicated (TLC) (30-40 minutes) at 100^{o}C. After the reaction, the viscous residue was purified by a preparative layer chromatography (petroleum

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ether/ethyl acetate 2/1) on silica gel, and the products were obtained. The characterization data of compounds **3a** and **3b** are given below.

Dimethyl 5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidine-2,3-dicarboxylate (3a): Yellow oil, yield: 63%; Anal. Calcd. for $C_{10}H_8N_2O_5S$: C, 44.77; H, 3.01; N, 10.44. Found: C, 44.88; H, 2.98; N, 10.37; IR (KBr, cm^{-1}): 2983 (CH, aliphatic), 1752 (C=O), 1675 (C=O), 1625 (C=O), 1577, 1504, 1370, 1266, 1095, 1024, 754; ^{1}H-NMR (250.0 MHz, $CDCl_3$) δ: 3.94 and 4.05 (6H, 2*s*, $2OCH_3$), 6.31 (1H, *d*, $^3J_{HH}$ = 6.4 Hz, C*H*=CH-C=O) 7.97 (1H, *d*, $^3J_{HH}$ = 6.4 Hz, CH=C*H*-C=O); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 53.71 and 54.07 ($2OCH_3$), 107.40 (CH=*C*H-C=O), 117.11 and 132.89 (2C), 153.63 (*C*H=CH-C=O), 157.97 (C=N), 159.25, 159.39 and 161.84 (3C=O).

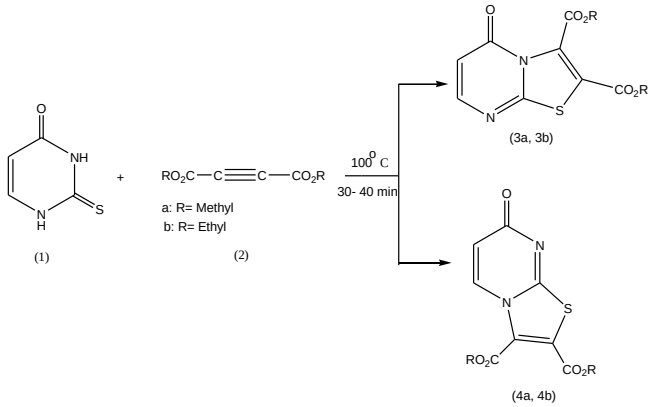
Diethyl 5-oxo-5H-[1,3]thiazolo[3,2-a]pyrimidine-2,3-dicarboxylate (3b): Yellow oil, yield: 56%; Anal. Calcd. for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.45. Found: C, 48.70; H, 4.03; N, 9.38; IR (KBr, cm^{-1}): 2957 (CH, aliphatic), 1756 (C=O), 1735 (C=O), 1687 (C=O), 1565, 1492, 1349, 1268, 1118, 1001, 794; ^{1}H-NMR (250.0 MHz, $CDCl_3$) δ: 1.19- 1.40 (6H, *m*, $2CH_3$), 4.17- 4.44 (4H, *m*, $2OCH_2$), 6.23 (1H, *d*, $^3J_{HH}$ = 6.6 Hz, C*H*=CH-C=O), 7.76 (1H, *d*, $^3J_{HH}$ = 6.6 Hz, CH=C*H*-C=O); ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 14.23 and 14.33 ($2CH_3$), 63.13 and 63.70 ($2OCH_2$), 105.82 (CH=*C*H-C=O), 111.71 and 128.25 (2C), 154.35 (*C*H=CH-C=O), 159.21 (C=N), 160.37, 162.53 and 162.73 (3C=O).

3. Computational Methods

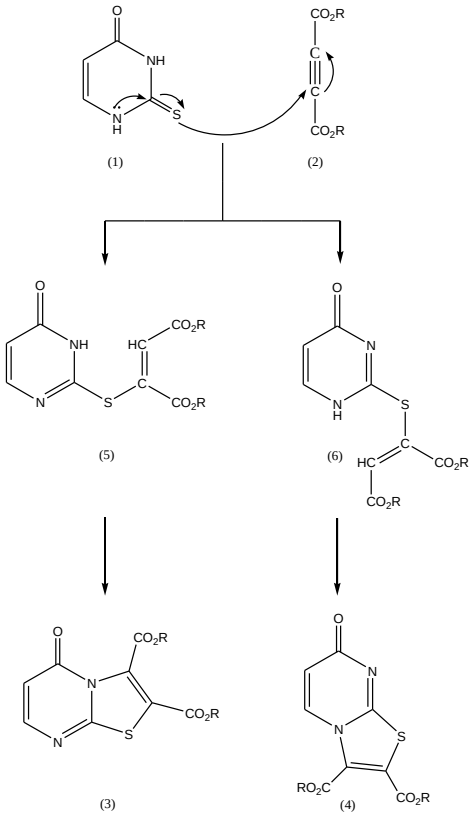
The quantum mechanics calculations were performed using the Gaussian 09 program [21]. The main group elements were described by standard 6-311G(d,p) basis set [22- 25]. The geometries of the compounds were optimized by the CAM-B3LYP functional. This function is Handy and coworkers' long-range corrected version of B3LYP using the Coulomb-attenuating method [26].

4. Results and Discussion

2-Thiouracil **(1)** and dialkyl acetylenedicarboxylate **(2)** react *via* a two-component reaction to give dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3 dicarboxylate derivatives **(3) (Scheme 1)**. The reaction proceeds smoothly and cleanly and affords the product. The substitution may occur at the sulfur atom and one of the cyclic nitrogen atoms, due to the position of hydrogen atoms in pyrimidine moieties. The intramolecular dehydration and cyclization can occur from tautomers (**5**) or (**6**) and the obtained compound may be described by one of the structures **(3)** or **(4)**. A mechanistic rationalization for this reaction is provided in **Scheme 2**. The structures of the products were deduced from their ^{1}H-NMR, ^{13}C-NMR, and IR spectra, and elemental analysis. For example, the ^{1}H-NMR spectrum of **3a** exhibited distinct signals arising from two OCH_3 groups (3.94 and 4.05 ppm, 2*s*), and two CH groups (6.31 and 7.97 ppm, 2*d*). The ^{13}C-NMR spectrum of **3a** showed 10 distinct resonances arising from two OCH_3 groups (53.71 and 54.07 ppm), two CH groups (107.40 and 153.63 ppm), two olefinic carbons (117.11 and 132.89 ppm), one C=N group (157.97 ppm), and three C=O groups (159.25, 159.39 and 161.84 ppm).



Scheme 1. The two-component reaction of 2-thiouracil and dialkyl acetylene dicarboxylate



Scheme 2. A proposed Mechanism for the Formation of (3, 4)

5. Energetic aspects

Possible isomers of the dimethyl 5-oxo-5H-[1,3]thiazolo[3, 2-a]pyrimidine-2,3-dicarboxylate molecule are depicted in Scheme 1. The absolute energy and relative energy values of conformers are gathered in Table 1. As can be seen, the **3**-isomer is more stable than the **4**-isomer.

Table 1. total energy (a.u), relative energy (**ΔE**, kcal/mol), and dipole moment (μ, Debye) of the two possible isomers of dimethyl 5-oxo-5*H*-[1,3]thiazolo[3, 2-*a*]pyrimidine-2,3-dicarboxylate molecule at the CAM-B3LYP/6-311G(d,p) level of theory.

	E	**ΔE**	**μ**
4	-1269.5601	8.44	8.17
3	-1269.5736	0.00	3.12

6. Dipole moment

The dipole moment values of the possible isomers of dimethyl 5-oxo-5*H*-[1,3]thiazolo[3, 2-*a*]pyrimidine-2,3-dicarboxylate molecule are listed in Table 1. Dipole moment values of polar **3**-isomer are smaller than **4**-isomer. The obtained result is consistent with smaller dipole moment values for more stable conformers [27].

7. Molecular orbital analysis

The frontier orbital energy and HOMO-LUMO gap values of the possible isomers of dimethyl 5-oxo-5*H*-[1,3] thiazolo [3, 2-*a*] pyrimidine -2,3- dicarboxylate molecule are calculated. It is also possible to find out that the larger HOMO-LUMO gap value in the **3**-isomer than in the **4**-isomer. This increase is compatible with the principles of minimum energy, and maximum hardness (MHP), that is, while a conformer changes from the most stable to the less stable species in most cases, the energy increases, and the hardness decreases [28-32].

The calculated electrophilicity (ω) values are listed in Table 2. It can be observed the smaller ω values in **3**-isomer in compared to **4**-isomer. This trend is compatible with the minimum electrophilicity principle (MEP) [33, 34] that is, while a conformer change from the most stable to another less stable species in most cases, the energy increases, and the electrophilicity increases.

MEP, MHP are used for comparison of thermodynamic stability of isomers. We have not discuss about of reactivity of molecules.

Table 2. Frontier orbital energy (eV), HOMO-LUMO gap energy (**ΔE**, eV), hardness (η, eV), chemical potential (μη, eV) , and electrophilicity (ω, eV) of the two possible isomers of dimethyl 5-oxo-5*H*-[1,3]thiazolo[3, 2-*a*]pyrimidine-2,3-dicarboxylate molecule at the CAM-B3LYP/6-311G(d,p) level of theory.

Isomer	**E (HOMO)**	**E (LUMO)**	**ΔE**	**η**	**μ**	**ω**
4	-7.90	-1.36	6.53	3.27	-4.63	3.28
3	-7.88	-1.13	6.75	3.38	-4.50	3.00

8. Conclusion

The reported method offers a mild, simple, and green chemistry route for the preparation of dialkyl 5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-2,3- dicarboxylate derivatives *v*ia a two-component reaction of 2-thiouracil and dialkyl acetylenedicarboxylate and solvent-free conditions. Computational investigations at the CAM-B3LYP/6-311G(d,p) level of theory revealed that the **3**-isomer is more stable than the **4**-isomer. This trend was compatible with the MEP, MHP, and MElP.

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References

[1] H. M. Marvaniya, P. K. Parikh and D. J. Sen, Synthesis and in-vitro screening of 3,4-dihydropyriidin-2(1H)-one derivative for antihypertensive and calcium channel blocking activity. *J. Appl. Pharm. Sci.*, 1 (2011) 109-113.

[2] S. A. Ahmed, O. M. Ahmed and A. O. Abdelhamid, Synthesis and anti- tumor activities of new [1,2,4]triazolo[1,5- a]pyrimidine derivatives. *Eur. J. Chem.*, 5 (2014) 334- 338.

[3] L.F. S.P. Azeredo, J. P. Coutinho, V. A. P. Jabor, P. R. Feliciano, M. C. Nonato, C. R. Kaiser, C. M. S. Menezes, A. S.O. Hammes, E. R. Caffarena, L. V.B. Hoelz, N. B. de Souza, G.A.N. Pereira, I. P. Ceravolo, A. U. Krettli and N. Boechat, Evaluation of 7-arylaminopyrazolo [1,5-a] pyrimidines as antiplasmodial falciparum, antimalarial, and Pf-dihydroorotate dehydrogenase inhibitors. *Eur. J. Med. Chem.*, 126 (2017) 72-83.

[4] H. A. Stefani, C. B. Oliveira, R. B. Almeida, C. M. P. Pereira, R. C. Braga, R. Cella, V. C. Borges, L. Savegnago and C. W. Nogueira, Dihydropyrimidin-(2H)-ones obtained by ultrasound irradiation: a new class of potential

antioxidant agents. *Eur. J. Med. Chem.*, 41 (2006) 513-518.

[5] R. Romagnoli, P. G. Baraldi, T. Sarkar, M. D. Carrion, C. Lopez Cara, O. C. Lopez, D. Preti, M. A. Tabrizi, M. Tolomeo, S. Grimaudo, C. Di Antonella, N. Zonta, J. Balzarini, A. Brancale, H.-P. Hsieh and E. Hamel, Synthesis and Biological Evaluation of 1-Methyl2-(3', 4', 5' -trimethoxybenzoyl)-3-aminoindoles as a New Class of Antimitotic Agents and Tubulin Inhibitors. *J. Med. Chem*., 51 (2008) 1464–1468.

[6] S. Pandey, S. N. Suryawanshi, S. Gupta and V. M. L. Srivastava, Synthesis and antileishmanial profile of some novel terphenyl pyrimidines. *Eur. J. Med. Chem*., 39 (2004) 969-973.

[7] H. N. Hafez and A. B. A. El-Gazzar, Design and synthesis of 3-pyrazolyl-thiophene, thieno [2, 3-d] pyrimidines as new bioactive and pharmacological activities. *Bioorg. Med. Chem. Lett*., 18 (2008) 5222-5227.

[8] M. Suresh, P. Lavanya, K. N. Raju, S. B. Jonnalagadda and C. V. Rao, Synthesis and biological studies of novel 2-(4-substitutedbenzylthio)-5-amino-6-(benzo[d]thiazol-2-yl)-7-(4- chlorophenyl)pyrido- [2,3-d]-pyrimidine-4(3H)-one derivatives. *Org. Commun*., 4 (2011) 33-41.

[9] D. Cai1, Z.-H. Zhang, Y. Chen, X.-J. Yan, S.-T. Zhang, L.-J. Zou, L.-H. Meng, F. Li and B.-J. Fu, Synthesis of some new thiazolo[3,2-a]pyrimidine derivatives and screening of their in vitro antibacterial and antitubercular activities. *Med. Chem. Res*., (2015).

[10] A. Khalilpour, S. Asghari and M. Pourshabb, Synthesis and Characterization of Novel Thiazolo[3,2-a]pyrimidine Derivatives and Evaluation of Antioxidant and Cytotoxic Activities. *Chem. Biodiversity*, 16 (2019).

[11] N. M. Khalifa, M. A. Al-Omar, A. E.-G. E. Amr, A. R. Baiuomy and R. F. Abdel-Rahman, Synthesis and biological evaluation of some novel fused thiazolo[3,2-a]pyrimidines as a potential analgesic and anti-inflammatory agents. *Russ. J. Bioorganic Chem.*, 41 (2015) 192-200.

[12] M. V. Laar, E. Volkerts and M. Verbaten, Subchronic effects of the GABA-agonist lorazepam and the 5-$HT_{2A/2C}$ antagonist ritanserin on driving performance, slow wave sleep and daytime sleepiness in healthy volunteers. *Psychopharmacology*, 154 (2001) 189-197.

[13] H. H. Sayed, A. H. Shamroukh and A. E. Rashad, Synthesis and biological evaluation of some pyrimidine, pyrimido[2,1-b][1,3]thiazine and thiazolo[3,2-a]pyrimidine derivatives*Acta Pharm.*, 56 (2006) 231-244.

[14] O. Alam, S. A. Khan, N. Siddiqui and W. Ahsan, Synthesis and pharmacological evaluation of newer thiazolo [3, 2-a] pyrimidines for anti-inflammatory and antinociceptive activity. *Med. Chem. Res*., 19 (2010) 1245-1258.

[15] V. K. Ahluwalia, H. R. Sharma, and R. Tyagi, A novel one-step synthesis of pyrano (2,3-d) pyrimidines. *Tetrahedron*, 42 (1986) 4045-4048.

[16] M.V. Jyothi, Y. Rajendra Prasad, P. Venkatesh and M. Sureshreddy, Synthesis, and Antimicrobial Activity of Some Novel Chalcones of 3-Acetyl Pyridine and their Pyrimidine Derivatives. *Chem. Sci .Trans.*, 1 (2012) 716-722.

[17] M. Kidwai, S. Saxena, R. Mohan, and R. Venkataramanan, A novel one-pot synthesis of nitrogen-containing heterocycles: an alternate methodology to the Biginelli and Hantzsch reactions. *J. Chem. Soc. Perkin Trans. I* (2002) 1845-1846.

[18] N. Shajari, R. Ghiasi, and A. Ramazani, One-pot synthesis of 2-acylaminobenzimidazoles from the reaction between trichloro acetyl isocyanate and 1,2-phenylenediamine derivatives and theoretical study of structure and properties of synthesized 2-acylaminobenzimidazoles. *J. Chil. Chem. Soc.,* 63 (2018) 3968-3973.

[19] F. Piryaei, N. Shajari and H. Yahyaei, Efficient ZrO(NO3)2.2H2O catalyzed synthesis of 1*H*-indazolo [1,2-*b*] phthalazine-1,6,11(13*H*)-triones and electronic properties analyses, vibrational frequencies, NMR chemical shift analysis, MEP: A DFT study *Heteroat. Chem.*, (2020).

[20] N. Shajari, A. R. Kazemizadeh and A. Ramazani, Synthesis of 5-aryl-N -(trichloroacetyl)-1,3,4-oxadiazole-2-carboxamide via three-component reaction of trichloroacetyl isocyanate,(N -isocyanimino)triphenylphosphorane, and benzoic acid derivatives *Turk. J. Chem.*, 39 (2015) 874-879.

[21] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria , M. A. Robb, J. R. Cheeseman, G.Scalman,V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox: Gaussian 09. Revision A.02 ed.; Gaussian, Inc.: Wallingford CT, (2009).

[22] P. J. Hay, Gaussian basis sets for molecular calculations. The representation of 3d orbitals in transition- metal atoms. *J. Chem. Phys.*, 66 (1977) 4377-4384.

[23] R. Krishnan, J. S. Binkley, R. Seege and J. A. Pople, Self- consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys*., 72 (1980) 650-654.

[24] A. D. McLean and G. S. Chandler, Contracted Gaussian basis sets for molecular calculations. I. Second row atoms, Z=11–18. *J. Chem. Phys.*, 72 (1980) 5639-5648.

[25] A. J. H. Wachters, Gaussian basis set for molecular wavefunctions containing third- row atoms. *J. Chem. Phys*., 52 (1970) 1033-1036.

[26] T. Yanai, D. Tew, and N. Handy, A new hybrid exchange-correlation functional using the Coulomb-attenuating method (CAM-B3LYP). *Chem. Phys. Lett*., 393 (2004) 51-57.

[27] C. L. Perrin, K .B. Armstrong, and M. A. Fabian, The origin of the anomeric effect: conformational analysis of 2-methoxy-1, 3-dimethylhexahydropyrimidine. *J. Am. Chem. Soc*., 116 (1994) 715–722.
[28] P.W. Ayers and R.G. Parr, Variational principles for describing chemical reactions: the Fukui function and chemical hardness revisited. *J. Am. Chem. Soc*., 122 (2000) 2010-2018.
[29] R. G. Parr and P. K. Chattaraj, Principle of maximum hardness. *J. Am. Chem. Soc*., 113 (1991) 1854-1855.
[30] R. G. Pearson, Recent advances in the concept of hard and soft acids and bases. *J. Chem. Educ*., 64 (1987) 561-567.
[31] R.G. Pearson, The principle of maximum hardness. *Acc. Chem. Res.*, 26 (1993) 250-255.
[32] R. G. Pearson, Maximum chemical and physical hardness. *J. Chem. Educ*., 76 (1999) 267-275.
[33] E. Chamorro, P. K. Chattaraj and P. Fuentealba, Variation of the electrophilicity index along the reaction path. *J. Phys. Chem. A*, 107 (2003) 7068-7072.
[34] R. Parthasarathi, M. Elango, V. Subramanian and P. K. Chattaraj, Variation of electrophilicity during molecular vibrations and internal rotations. *Theor. Chem. Acc*., 113 (2005) 257-266.