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Investigation into the regioisomeric composition of some fused pyrimidines: ^{1}H NMR and theoretical studies

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The reaction of 6-methyl-2-thiouracil with bromodiethyl malonate gave a mixture of both regioisomers in different ratios. The same reaction with bromomalononitrile and 2-(bromomethyl)benzonitrile gave a single regioisomer in high yield. The results of these studies compared with those derived computationally using DFT and AIM methods at the B3LYP level of theory with 6-31G** as the basis set for the estimation of the major regioisomer.

Keywords: regioisomer; fused pyrimidines; thiouracil; heterocyclization; AIM; DFT

1. Introduction

We report here a dual investigation, experimental as well as theoretical, into the regioisomeric compositions of some fused pyrimidines derived from 6-methyl-2-thiouracil with bifunctional electrophilic reagents. Two motives have prompted us to carry out such a study; first, our recent interest in the synthesis of fused pyrimidines (*1–3*) including thiazolopyrimidines (*4*) and exploration of their synthetic pathways and second, contradictory reports cited in the literature pertaining to regioselectivity in cyclization of substituted or unsubstituted 2-thiouracils with dielectrophilic reagents to obtain 5H-thiazolo[3,2-*a*]pyrimidine-5-ones or their regioisomers, 7H-thiazolo[3,2-*a*]pyrimidine-7-ones (Scheme 1). A typical example includes a report by Andrew and his co-worker who prepared 5H-thiazolo[3,2-*a*]pyrimidine-5-one by *S*-alkylation of 6-methyl-2-thiouracil with 2-bromoketones followed by cyclization in sulfuric acid. 2-Thiouracil under the same condition gave the 7H-thiazolo[3,2-*a*]pyrimidine-7-one (*5*).

The regioselective synthesis of the 7H-regioisomer from 6-phenyl-2-thiouracil was reported by other workers (*6*) when they subjected the *S*-alkylated derivatives to acid catalyzed heterocyclization to get a single regioisomer. It is interesting to note that with 6-methyl-2-thiouracil the regioselective intramolecular cyclization at N3 is preferred over N1, while with 2-thiouracil or its 6-phenyl derivative the preference is with N1. An examination of the literature disclosed that

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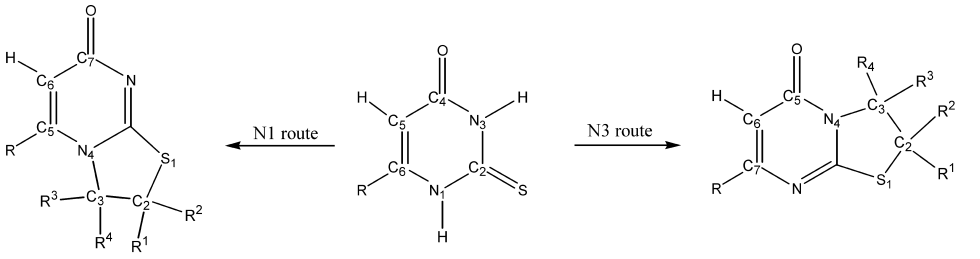


Scheme 1.

N3 of the 2-thiouracils is the prime position for the regioselective cyclization in acidic or basic media and the 5H-regioisomer is the more favored isomer (*7–20*) except for the product obtained from the Pd catalyzed heterocyclization of 2-propargylthio-6-methyl-4-oxopyrimidine for which the N1 regioselective cyclization has been reported (*21*). For the reasons described earlier and in light of these findings, in this paper, we wish to report the results of our investigation concerning orientation of heterocyclization of 6-methyl-2-thiouracil with dielectrophiles and the outcome of quantum chemical calculations performed on these compounds.

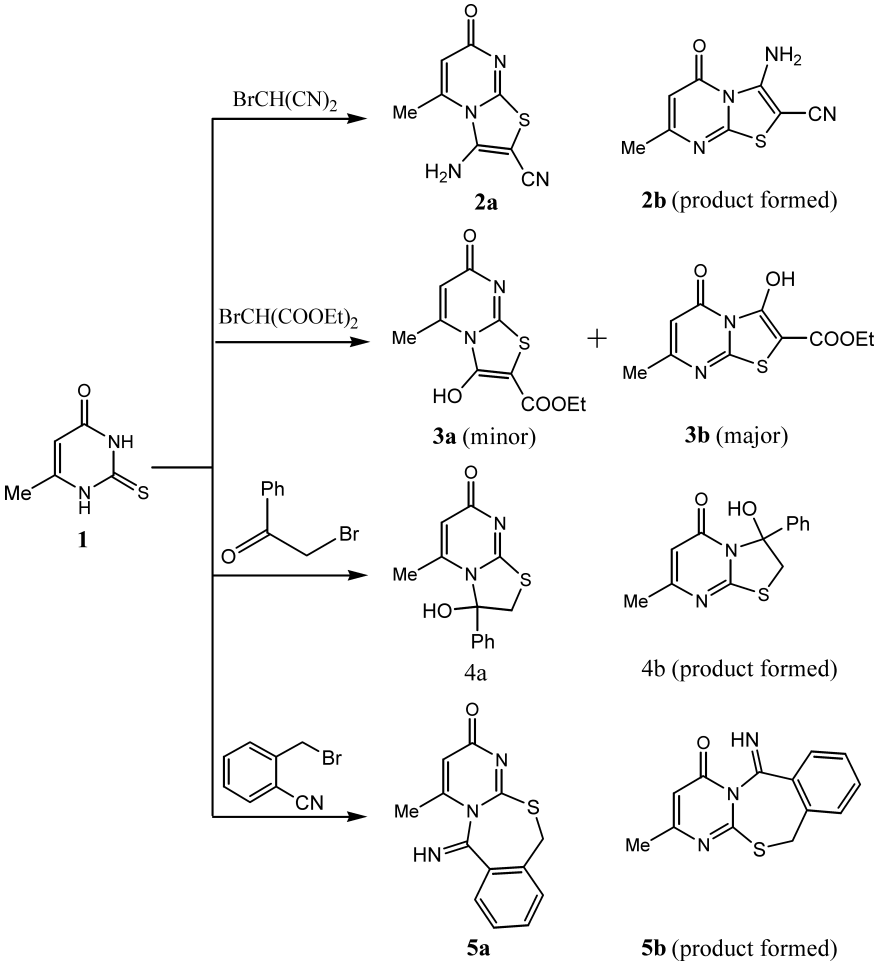
2. Computational methodology

All the computation in the present study was performed by using GAUSSIAN 03 series of programs (*22*). The geometry optimizations were carried out at HF and B3LYP method with 6-31G** basis set. Harmonic vibrational frequencies were evaluated at the same levels in order to confirm the nature of the stationary points found, and to account for the zero point vibrational energy (ZPVE) correction.

The nature of the bonds has been studied by using the atoms in molecules (AIM) theory of Bader (*23*) by means of AIM2000 (*24*) software and NBO analysis, with NBO 3.1 program implemented in GAUSSIAN 03.

3. Results and discussion

Treatment of 6-methyl-2-thiouracil **1** with bromomalononitrile in the presence of potassium hydroxide in ethanol at room temperature followed by refluxing the reaction mixture for six hours gave a product that was identified as a single regioisomer of either structure, 3-amino-5-methyl-7-oxo-7H-thiazolo [3,2-*a*]pyrimidine-2-carbonitrile **2a** or 3-amino-7-methyl-5-oxo-5H-thiazolo[3,2-*a*]pyrimidine-2-carbonitrile **2b** (Scheme 2). The ^{1}H NMR spectrum of the product in d_6-DMSO exhibited a singlet at δ 2.2 ppm attributed to methyl protons along with a singlet at δ 6.1 ppm, which was assigned to the pyrimidine ring proton. The broad peak at δ 3.9 ppm resembling an NH_2 group was removed on deuteration. The IR spectrum showed stretching vibration bands at 3300 and 3500 (NH_2), 2240 (CN), and 1640 cm^{-1} (C=O). It is noteworthy that a similar reaction of the substituted-2-thiouracils with bromomalononitrile has been reported as a regioselective cyclization with a single regioisomer (*25*, *26*). Repeating the reaction of **1** with bromodiethyl malonate lead to both regioisomers, **3a** and **3b**, as proved by its ^{1}H NMR and mass spectral analysis. The ^{1}H NMR spectrum of the product had a pair of three-proton singlets centered at δ 2.0 and 2.2 ppm due to the methyl groups and two one-proton singlets at δ 5.6 and 5.8 ppm (ring proton at position 6) in a 3:1 ratio plus two proton singlets at δ 12.6 and 13.2 ppm



Scheme 2.

belonging to two different OH groups, which were removed on deuteration. The latter signals clearly indicated that both regioisomers predominantly exist in their enolic forms. The mass spectrum showed the expected molecular weight ($M^{+\cdot} = 254$), which confirms the loss of a molecule of EtOH during cyclization.

Under the same condition the reaction of **1** with phenacyl bromide was repeated in our laboratory (Scheme 1) and in agreement with the earlier work (5), we also found that this reaction did not reach completion and gave a mixture of cyclized and uncyclized products, as indicated by its ^{1}H NMR spectrum.

Interestingly, the reaction of **1** with 2-(bromomethyl)benzonitrile gave a single regioisomer in 90% yield. This product had either structure **5a** or **5b** (Scheme 2). The structure of the cyclized product was confirmed by IR and ^{1}H NMR spectra and elemental analyzis. It showed absorption bands at 3450 and 1640 cm^{-1} assignable to NH and C=O stretching vibrations in the IR spectrum. The ^{1}H NMR spectrum exhibited signals assignable to the protons of a methyl group at δ 2.2 and the proton of the pyrimidine ring at δ 6.0 ppm as singlets, the protons of the phenyl ring at δ 7.3–8.0 as a multiplet and the proton of the NH group at δ 12.0 ppm as a broad signal, which was removed on deuteration. An unequivocal decision between these two structures and also the major regioisomer of each pair (see Scheme 2) was possible with the help of theoretical computations.

Theoretical computations on each pair of regioisomers were performed for the purpose of gaining some insight as to the stability of each regioisomer. These calculations reveal that the regioisomers resulting from the N3 intramolecular cyclization are more stable and form the major regioisomer (Table 1). The basis for these comparisons is: (a) the single and double bond lengths in the pyrimidine ring (Table 2), and (b) the value of electron densities in bond critical points (ρ_{BCP}) (Table 3). It can be seen that comparatively there is more effective resonance in pyrimidine ring of the regioisomers resulted from N3 intramolecular cyclization than from N1. Intramolecular interactions are also important in the stability of each regioisomer and can be assessed on the basis of AIM. Here, we compare each pair of regioisomers separately. As a first example, the most important interactions in regioisomers **2a** and **2b** are C−H…N and N−H…O intramolecular hydrogen bonds, respectively. Since the value of p_{BCP} in critical points of H…N and H…O contacts are 0.0125^{au} and 0.0329^{au}, respectively, N−H…O hydrogen bond is stronger than C−H…N hydrogen bond. Therefore, more effective resonance and stronger intramolecular hydrogen bonding exist in regioisomer **2b** and make it more stable relative to **2a**. There is a strong hydrogen bonding of H−O…H type in both regioisomers **3a** and **3b**. The ρ_{BCP} values in critical points of these contacts (0.0509^{au} and 0.0572^{au}, respectively) clearly show that hydrogen bonding in **3b** is stronger than in **3a**. In addition, there is a repulsive interaction of C…O type ($\rho_{BCP} = 0.0131^{au}$) in regioisomer **3a**, which makes it less stable than **3b**. In the case of regioisomers **4a** and **4b**,

Table 1. The energy differences (in kcal/mol) between regioisomers resulted from route N1 and route N3 (after zero point vibrational energy (ZPVE) correction) at HF and B3LYP methods using the 6-31G** basis set.

	E_{2a}-E_{2b}	E_{3a}-E_{3b}	E_{4a}-E_{4b}	E_{5a}-E_{5b}
HF	21.7	9.4	20.0	14.7
B3LYP	21.3	9.7	18.9	13.1

Table 2. Some of the bond lengths (in A°) and dihedral angels (in degree), calculated at B3LYP/6-31G** level of theory.

	N1C2	C2N3	N3C4	C4O	C4C5	C5C6	C6N1	C2N1C6C5	C2N3C4O	C6C5C4O
2a	1.414	1.280	1.410	1.220	1.469	1.351	1.416	–	177.64	−177.36
2b	1.299	1.390	1.444	1.231	1.431	1.375	1.371	−0.05	–	−179.93
3a	1.414	1.280	1.412	1.220	1.471	1.351	1.413	–	−179.99	−179.95
3b	1.304	1.383	1.426	1.244	1.423	1.382	1.367	−0.03	–	−179.96
4a	1.397	1.281	1.413	1.221	1.466	1.354	1.408	–	−177.15	176.33
4b	1.299	1.364	1.416	1.235	1.438	1.371	1.379	1.07	–	179.67
5a	1.397	1.286	1.409	1.221	1.463	1.351	1.414	–	177.48	−177.05
5b	1.297	1.373	1.446	1.220	1.444	1.364	1.382	3.83	–	−177.61

Table 3. Value of eletron densities in bond critical points (ρ_{BCP}) of pyrimidine ring.

	C2N1	C2N3	N3C4	C4O7	C4C5	C5C6	N1C6
2a	0.2916	0.3909	0.2990	0.4074	0.2797	0.3378	0.2790
2b	0.3795	0.3057	0.2682	0.3978	0.2977	0.3249	0.3215
3a	0.2913	0.3912	0.2975	0.4069	0.2788	0.3384	0.2795
3b	0.3759	0.3086	0.2796	0.3884	0.3017	0.3211	0.3244
4a	0.3028	0.3898	0.2983	0.4063	0.2813	0.3364	0.2879
4b	0.3795	0.3219	0.2870	0.3950	0.2944	0.3272	0.3180
5a	0.2980	0.3864	0.2991	0.4065	0.2832	0.3379	0.2833
5b	0.3786	0.3136	0.2696	0.4078	0.2913	0.3317	0.3165

there are two intramolecular interactions in regioisomer **4a,** one of the H…H repulsive type and the other one of the C−H…C attractive type, while in regioisomer **4b**, the hydrogen bonding is of H−O…H. Considering the value of ρ_{BCP} in the critical points of contact (H…H, H…C and H…O are 0.0085^{au}, 0.0100^{au} and 0.0313^{au}, respectively), it seems likely that regioisomer **4b** is more stable than **4a**. In regioisomer **5a**, there is a repulsive interaction of H…H type, while such an interaction is absent in isomer **5b**, which makes the latter a more stable isomer.

4. Experimental section

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. ^{1}H NMR spectra were recorded on Bruker-500 and Bruker AC 100 instruments. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The mass spectra were scanned on a Varian. Mat CH-7 at 70 EV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

4.1. *General procedure for the synthesis of fused pyrimidines (2−5)*

To a mixture of 6-methyl-2-thiouracil **1** (3.0 mmol; 0.426 g), powdered KOH (3.0 mmol, 0.168 g) in absolute ethanol (35 mL), the electrophilic reagent (3.0 mmol) was added slowly on stirring. The stirring continued for three hours and then the mixture was refluxed for six hours. After cooling of the reaction mixture to room temperature, the precipitate was collected by filtration, and then boiled in distilled water and filtered while hot. The residue was collected without further purification and dried in the oven to get the product.

4.2. *3-Amino-7-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2-carbonitrile* (*2b*)

Compound **2b** was obtained as brown powder, yield (90%), mp 230–233 °C; ^{1}H NMR (100 MHz, d_6-DMSO) δ 2.17 (s, 3H, CH_3), 3.94 (broad, 2H, NH_2), 6.07 (s, 1H, CH); IR (KBr disc) υ (cm^{-1}): 1640 cm^{-1} (CO), 3300, 3500 (NH_2), 2240 cm^{-1} (CN). MS, m/z: 206 (M^+).

4.3. *Ethyl 3-hydroxy-5-methyl-7-oxo-7H-thiazolo[3,2-a]pyrimidine-2-carboxylate* (*3a*)

Compound **3a** was obtained as a white powder, combined yield (82%), mp 125–127 °C; ^{1}H NMR (100 MHz, d_6-DMSO) δ 1.21 (t, 3H, CH_3, $J = 8.1$ Hz), 2.24 (s, 3H, CH_3), 4.18 (q, 2H, CH_2, $J = 8.1$ Hz), 5.85 (s, 1H, CH), 13.36 (broad, 1H, OH); IR (KBr disc) υ (cm^{-1}): 3480 (OH), 1640 and 1670 cm^{-1} (two CO, s). MS, m/z: 254 (M^+).

4.4. *Ethyl 3-hydroxy-7-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2-carboxylate* (*3b*)

Compound **3b** was obtained as a white powder, combined yield (82%), mp 125–127 °C; ^{1}H NMR (100 MHz, d_6-DMSO) δ 1.05 (t, 3H, CH_3, $J = 8.1$ Hz), 2.07 (s, 3H, CH_3), 4.04 (q, 2H, CH_2, $J = 8.1$ Hz), 5.72 (s, 1H, CH), 12.62 (broad, 1H, OH); IR (KBr disc) υ (cm^{-1}): 3480 (OH), 1640 and 1670 cm^{-1} (two CO, s), MS, m/z: 254 (M^+).

4.5. *3-Hydroxy-7-methyl-3-phenyl-2,3-dihydro-thiazolo[3,2-a]pyrimidin-5-one* (*4b*)

Compound **4b** was obtained as a brown powder, overall yield (80%), mp 154–158°C; ^{1}H NMR (100 MHz, $CDCl_3$) δ 2.34 (s, 3H, CH_3), 3.42 (d, 1H, S-CH, $J = 11.5$ Hz), 3.93 (d, 1H, S-CH, $J = 11.5$ Hz), 6.05 (s, 1H, CH), 6.34 (broad, 1H, OH), 7.37–7.94 (m, 5H, aromatic); IR (KBr disc) υ (cm^{-1}): 3400 (OH), 1650 (CO). MS, m/z: 260 (M^+).

4.6. *6-Imino-2-methyl-6,11-dihydro-4H-pyrimido[2,1-c][2,4]benzo thiazepin-4-one* (*5b*)

Compound **5b** was obtained as a white powder, yield (90%), mp 204 °C; ^{1}H NMR (100 MHz, d_6-DMSO) δ 2.17 (s, 3H, CH_3), 4.49 (s, 2H, S-CH_2), 5.98 (s, 1H, CH), 7.33–7.89 (m, 4H, aromatic), 12.52 (broad, 1H, NH); IR (KBr disc) υ (cm^{-1}): 3450 (NH), 1630 cm^{-1} (CO). MS, m/z: 257 (M^+). *Anal. Calc.* For $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46; Found: C, 60.49; H, 4.21; N, 16.02; S, 12.17.

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