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One-pot Synthesis and Characterization of 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione

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Abstract: 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione was successfully synthesized by the reaction of thiocyanic acid and 3-fluoroaniline in acetone. The proposed structure is in agreement with the elemental analysis, infrared and nuclear magnetic resonance spectroscopic data. X-ray investigation showed that the compound crystallized in orthorhombic system with space group *Pbca*, a = 8.8061(18) Å, b = 15.009(3) Å, c = 10.209(2) Å, Z=4 and V=1342.8(5) $Å^3$.The benzene and pyrimidine-thione rings are almost perpendicular with dihedral angle of 84.00(15)°.

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Introduction

Dihydropyrimidine-thione derivatives have been reported to possess pharmacological activities such as antibacterial [1], antitumor[2], antioxidative[3], analgesic and anti-inflammatory properties [4-5]. In addition, these compounds act as antihypertensive agents as well as calcium channel blockers and neuropeptide Y antagonists [6]. The synthesis of these compounds usually requires a long reflux time and involves several steps [7]. The yields are always low. A new series of 4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione was discovered by the formation of 4,4,6-Trimethyl-1-phenyl-3,4-dihydropyrimidine-2-(1H)-thione[8-9]. In this paper, another analog of1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione was obtained by a new one-pot reaction method. The X-ray structure is also described.

Experimental

All chemicals were Analar Grade and used without further purification. The solvents were distilled prior to usage. Perkin Elmer GX spectrophotometer (range 4000–400 cm^{-1}) was used to record the infrared spectrum of the sample in KBr pellet form. The Nuclear Magnetic Resonance (NMR) spectrum was recorded on a 400 MHz Joel Ltd ECP Spectrometer. Single X-ray Diffractometer from Bruker SMART APEX CCD with Molybdenum source Kα (λ=0.71073 Å) was used for crystallographic study.

Preparation of 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione

1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione was synthesized by adding 3-fluoroaniline (0.01 mol, 1.11 g) into a beaker containing ammonium thiocyanate (0.01 mol, 0.76 g) in acetone which was heated for half an hour at 50°C. The mixture was further heated for another 30 minutes. The solution was left to evaporate at room temperature. Some colourless crystals were obtained after 2 days. The yield 78%.M.p: 183.8-185.9 °C.

Results and Discussion

The microelemental analysis data is in agreement with the structure solved by X-ray study, experimental: C= 62.1 %, H= 6.2 %, N= 11.5 %, S= 12.6 %, calculated: C= 62.4 %, H= 6.0 %, N= 11.2 %, S= 12.8 %. The infrared spectrum shows an intense ν(C=S) peak at 1216.81 cm^{-1}, medium C-N peak at 1366 $cm^{-1}$and C=C benzene at 1427 cm^{-1}. The C-H methyl and N-H amine stretchings are at 2970 and 3178 cm^{-1}respectively. The^{1}H-NMR (d_6-DMSO) spectrum shows the chemical shift for the two methyl groups attached to carbon-4 at δ 1.28 ppm (6H, s) and the methyl attached to carbon-6 at δ 1.43 ppm (3H, s). The olefinic proton attached C-5 has a chemical shift at δ 4.97 ppm (1H, s). The chemical shift at δ 8.90 ppm (1H, s) is assigned to the amino N-3 proton. The multiple aromatic benzene protons are between δ 7.00-7.30 ppm. The ^{13}C-NMR (d_6-DMSO) spectrum shows the two methyl carbons attached to carbon-4 and one methyl attached to carbon-6 at 30.52 and 19.55 ppm respectively. The chemical shift for quarternary carbon-4 is at 51.74 ppm. The chemical shift at 109.68 and 131.14 ppm are for the olefinic carbon C-5 and C-6 respectively. The chemical shift for the thiono carbon-2 is at 176.26 ppm and the aromatic carbons are in the range of 129.88-118.01 ppm.

Table 1 : Crystal data and structure refinement for the title compound.

Empirical formula	C_{13} H_{15} F N_2 S
Formula weight	250.33
Wavelength	0.71073 A
Crystal system	Orthorhombic
Space group	*Pbca*
Unit cell dimensions	a = 8.8061(18) Å; b 15.009(3) Å; c = 10.209(2) Å
Volume	1342.8(5) A^3
Z, Calculated density	4, 1.238 Mg/m^3
Absorption coefficient	0.233 mm^{-1}
F(000)	528
Crystal size	0.50 x 0.38 x 0.22 mm
Theta range for data collection	2.32 to 25.00°
Limiting indices	-10<=h<=10, -17<=k<=17, -10<=l<=12
Reflections collected / unique	4456 / 1494 [R(int) = 0.0218]
Completeness to theta = 25.49	63.1 %
Max. and min. transmission	0.9506 and 0.8925
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1494 / 0 / 162
Goodness-of-fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1085
R indices (all data)	R1 = 0.0518, wR2 = 0.1142
Absolute structure parameter	0.011(3)
Largest diff. peak and hole	0.144 and -0.139 $e.A^{-3}$

The compound crystallized in orthorhombic system with space group *Pbca*a = 8.8061(18) Å, b = 15.009(3) Å, c = 10.209(2) Å, Z=4 and V=1342.8(5) $Å^3$. The crystal data and structure refinement are shown in Table 1. The crystal is a polymorph to the previously reported compound which crystallized in monoclinic system [10].

The molecular structure of 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione and numbering scheme are shown in Figure 1.

The benzene (C8-C13) and pyrimidine-thione (C1/N1/C2/C3/C4/N2) are each planar with maximum deviation of 0.092(3) for C4 atom from the least-squares plane. The dihedral angle between the two rings is 84.26(12)º. The bond lengths and angles are in normal ranges [11] with C1=S1, C1-N1, C1-N2 bond lengths of 1.690(2)Å, 1.319(3)Å, and 1.373(3) Å respectively. In the crystal structure, the molecules are linked by one intermolecular hydrogen bond N1—H1A·S1 (symmetry code as in Table 2) to form dimer and arranged parallel to *ab* face (Figure 2).

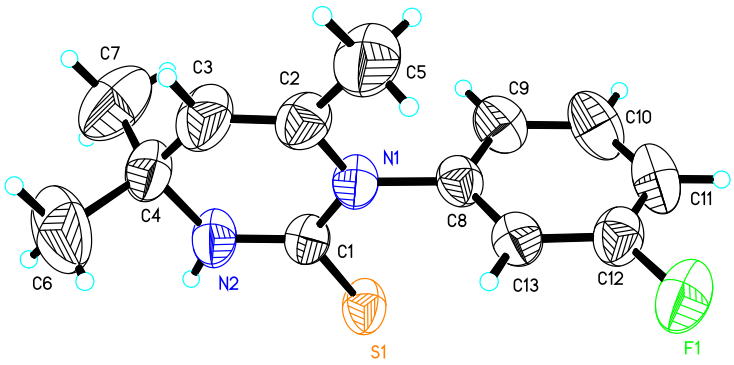


Figure 1 : Molecular structure of 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione drawn at 50% ellipsoid level.

Table 2 : Hydrogen-bond geometry (Å, º)

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···S1^{i}	0.86	2.57	3.400 (3)	162

Symmetry code: (i) −x+1, −y, −z+1.

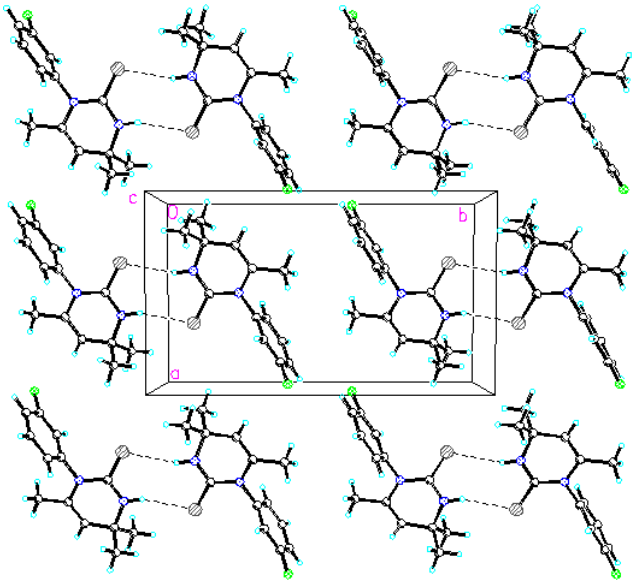
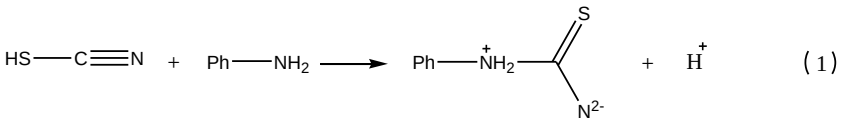
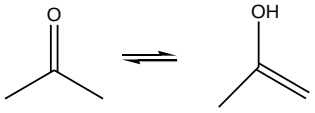


Figure 2 : A packing diagram viewed down the *c*- axis. Hydrogen bonds are shown by dashed lines.

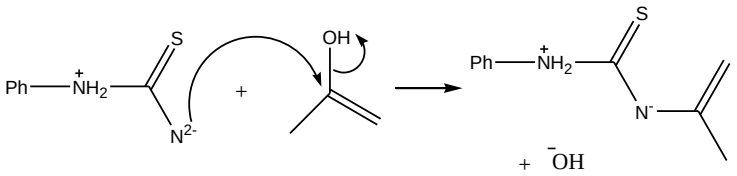
The compound is an unexpected product instead of N-halo phenylthiourea as predicted by the established mechanism for the thiourea formation [12]. Therefore, in this reaction the acetone plays an important role that lead to the formation of the product. The reaction mechanism involving tautomerism of acetone is proposed as shown in Figure 3.



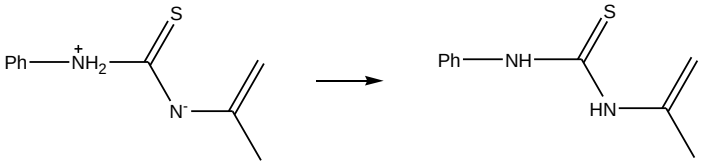
(1)



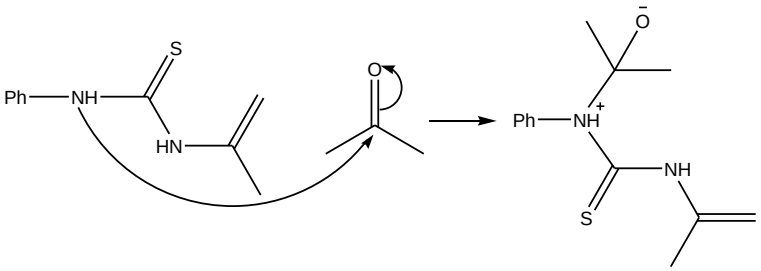
(2)



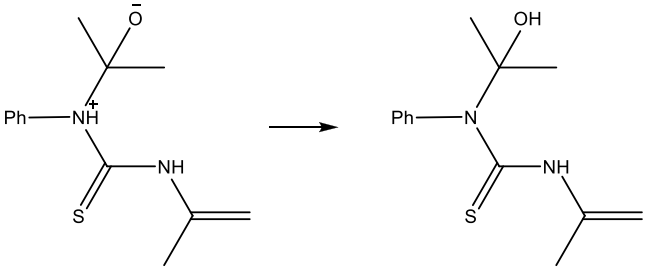
(3)



(4)



(5)



(6)

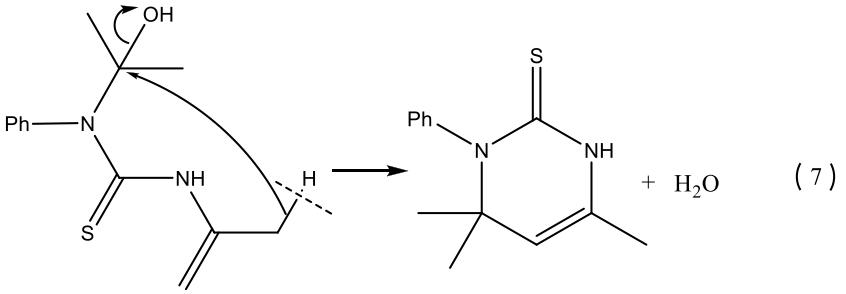


Figure 3 : Proposed reaction mechanism of 1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione formation.

Conclusion

1-(3-fluorophenyl)-4,4,6-trimethyl-3,4-dihydropyrimidine-2(1H)-thione has been successfully synthesized by a one-pot synthesis. The molecule is not planar due to the dihedral angle of 84.00(15)^{o} between the benzene and the pyrimidine ring. In the crystal structure, the molecule formed dimersbyN1—H1A···S1 intermolecular hydrogen bonds. The formation of the product can be explained by the mechanism involving tautomerism of the acetone solvent.

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References

1. Alam, O., Imran, M. & Khan, S. A. (2005) *Indian J. Heterocycl. Chem.*, **14**, 293–296.
2. Swamy, S. N., Basappa, Priya, B. S., Prabhuswamy, B., Doreswamy, B. H., Prasad, J. S. & Rangappa K. S. (2005) *Eur. J. Med. Chem.,* **41**, 531–538.
3. Sriram, D., Yogeeswari, P. & Devakaram, R. V. (2006) *Bioorg. Med. Chem.*, **14**, 3113–3118.
4. Leite, A. C. L., Lima, R. S., Moreira, D. R. M., Cardoso, M. V. O., Brito, A. C. G., Santos, L. M. F., Hernandes, M. Z., Kiperstok, A. C., Lima, R. S. & Soares, M. B. P. (2006) *Bioorg. Med. Chem.*, **14**, 3749–3757.
5. Kappe, C. O. (2000) *Acc. Chem. Res.*, **33**, 879–888.
6. Rovnyak, G. C., Kimball, S. D., Beyer, B., Cucinotta, G., DiMarco, J. D., Gougoutas, J., Hedberg, A., Malley, M., McCarthy, J. P., Zhang, R. &Moreland, S. (1995) *J. Med. Chem.*, **38**, 119–129.
7. Sarac, S., Zorkun, I. S., Celebi, S. and Erol, K. (2006) *Bioorg. Med. Chem.*, **14**, 8582–8589.
8. Ismail, N. L., Othman, E. & Yamin, B. M. (2007) *ActaCryst.*, **E63**, o2442– o2443.
9. Yamin, B. M., Kasim, N. A. M. & Hamzah, N. (2005) *ActaCryst.*, **E61**, o55–o57.
10. Yamin, B. M., Lawi, R. L., Salem, H. F. (2011) *ActaCryst.*, **E67**, o1810.
11. Sheldrick, G. M. (2008) *ActaCryst.*, **A64**, 112–122.
12. Yamin, B. M. & Saleem, H. F. (2010) *ActaCryst.*, **E66**, o789.

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