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ORIGINAL PAPER

Synthesis and Crystal Structure Analysis of Thiourea-Pendant Pyridines

Chomchai Suksai · Chaveng Pakawatchai · Thawatchai Tuntulani

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Abstract The crystal structures of pyridine containing thiourea moieties as substituents, (**1**) and (**2**), have been determined. The *ortho*-substituted pyridine (**1**) crystallized in monoclinic space group $P2_1/c$ with $a = 16.091(3)$ Å, $b = 11.368(2)$ Å, $c = 7.4364(14)$ Å, $\beta = 100.489(4)^\circ$, $V = 1337.5(4)$ Å^3, $z = 4$. In this structure an intramolecular N–H···N hydrogen bond forms a pseudo-seven-membered ring. The *meta*-substituted pyridine (**2**) crystallized in monoclinic space group $P2_1/c$ with $a = 14.5408(15)$ Å, $b = 8.8508(9)$ Å, $c = 10.7959(11)$ Å, $\beta = 106.435(2)^\circ$, $V = 1332.6(2)$ Å^3, $z = 4$. Crystal packing revealed that compounds (**1**) and (**2**) can form dimeric structures via intermolecular H-bonding using N–H···S and N–H···N interactions, respectively.

Keywords Pseudo-seven-membered ring · Heterocyclic thiourea

Introduction

Thioureas are of importance in medicinal chemistry due to their biological activity [1] as anti-bacteria and anti-microbial infection [2], as fungicides, herbicides, and rodenticides [3, 4] and in connection with biomimetic models [5]. Thiourea is well known as a good hydrogen bond donor and has been used as anion recognition sites for anion sensing using hydrogen bonding interactions [6, 7]. Furthermore, thiourea functionalities can form diverse hydrogen-bonded networks, making them a powerful building block for crystal engineering [8, 9].

In this work we present the synthesis and structural X-ray analysis of two thiourea-pendant pyridines. The influence of the position of the substituents on the pyridine ring regarding intra- and intermolecular hydrogen bonding interactions between molecules in crystals has been discussed.

Experimental

General

All reagents were of reagent grade and were used without further purification unless stated otherwise. ^{1}H-NMR, ^{13}C-NMR spectra were record in DMSO-d_6 on a BRUKER AVANCE 400 NMR spectrometer. Elemental analyses for C, H and N were performed on a Perkin-Elmer 2400 CHN elemental analyzer.

Synthesis

Scheme 1

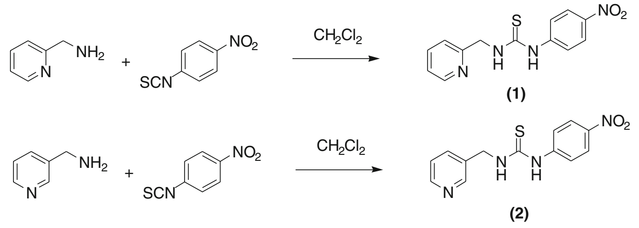
*1-(4-Nitrophenyl)-2-pyridin-2-ylmethylthiourea (**1**)*

To a well stirred solution of 2-picolylamine (0.16 mL, 1.64 mmole) in dry CH_2Cl_2 (10 mL) was slowly added a solution of 4-nitrophenylisothiocyanate (0.44 g, 2.46 mmole)

C. Suksai (✉)
Department of Chemistry, Faculty of Science, Burapha University, Chonburi 20131, Thailand
e-mail: jomjai@buu.ac.th

C. Pakawatchai
Department of Chemistry, Faculty of Science, Prince of Songkla University, Songkhla 90112, Thailand

T. Tuntulani
Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand



Scheme 1 Preparation of *1-(4-Nitrophenyl)-2-pyridin-2-ylmethylthiourea* (1) and *1-(4-Nitrophenyl)-3-pyridin-3-ylmethylthiourea* (2)

in dry CH_2Cl_2 (10 mL). The mixture was stirred for 3 days under N_2 leading to formation of a precipitate. The pale yellow product was isolated by filtration, washed with dichloromethane and dried in vacuo (0.31 g, 66%). m.p.: 159–160°C. ^1H NMR (400 MHz, DMSO-d_6) δ;10.537 (s, 1H, –N*H*–), 8.790 (s, 1H, –N*H*–), 8.570 (s, 1H, Ar*H*), 8.202 (d, $J = 7.2$ Hz, 2H, Ar*H*), 7.940 (d, $J = 7.6$ Hz, 2H, Ar*H*), 7.805 (m, 1H, Ar*H*), 7.410 (m, 1H, Ar*H*), 7.318 (m, 1H, Ar*H*), 4.860 (s, 2H, –C*H_2*–). ^{13}C NMR (100 MHz, DMSO-d_6) δ; 180.76, 157.22, 149.30, 146.83, 142.41, 137.30, 124.97, 122.89, 122.15, 120.99, 49.29. Anal. Calcd. for $C_{13}H_{12}N_4O_2S$ C, 54.15; H, 4.20; N, 19.43. Found: C, 54.17; H, 4.18; N, 19.48.

1-(4-Nitrophenyl)-3-pyridin-3-ylmethylthiourea (**2**)

To a well stirred solution of 3-picolylamine (0.16 mL, 1.64 mmol) in dry CH_2Cl_2 (10 mL) was slowly added a solution of 4-nitrophenylisothiocyanate (0.44 g, 2.46 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred for 3 days under N_2 leading to formation of a precipitate. The pale yellow product was isolated by filtration, washed with dichloromethane and dried in vacuo (0.33 g, 70%). m.p.: 184–185°C. ^1H NMR (400 MHz, DMSO-d_6) δ; 10.356 (s, 1H, –N*H*–), 8.790 (s, 1H, –N*H*–), 8.674 (s, 1H, Ar*H*), 8.597 (m, 1H, Ar*H*), 8.188, (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.859 (d, $J = 8.4$ Hz, 2H, Ar*H*), 7.786 (d, $J = 7.2$ Hz, 1H, Ar*H*), 7.380 (m, 1H, Ar*H*), 3.488 (s, 2H, –C*H_2*–).^{13}C NMR (100 MHz, DMSO-d_6) δ; 181.09, 149.40, 148.67, 146.67, 142.49, 135.89, 134.46, 124.93, 123.94, 121.29, 45.22. Anal. Calcd. for $C_{13}H_{12}N_4O_2S$ C, 54.15; H, 4.20; N, 19.43. Found: C, 54.10; H, 4.24; N, 19.45.

Crystal Structure Determination of (**1**) and (**2**)

X-ray quality crystals were obtained by slow evaporation of acetonitrile solutions of (**1**) and (**2**). Crystallographic data was collected on a BRUKER APEX CCD diffractrometer (graphite-monochromated Mo-Kα radiation with $\lambda = 0.71073$ Å). The structures were solved by direct methods using the program SHELXS-97 and refined by full-matrix least squares techniques against F^2 using the SHELXL-97 [10] on WinGX package [11]. All non-hydrogen atoms were refined with anisotropic thermal parameters in the latter stage of refinement. All hydrogen atoms (except H14 and H15) placed in geometrically idealized positions and refined as riding atoms. Packing diagrams were produced using Mercury [12]. The detailed crystallographic data and structure refinement parameters of (**1**) and (**2**) are summarized in Table 1.

Table 1 Crystallographic data and final refinement of (**1**) and (**2**)

	(**1**)	(**2**)
CCDC Number	665445	665446
Formula	$C_{13}H_{12}N_4O_2S$	$C_{13}H_{12}N_4O_2S$
Formula weight	288.33	288.33
Temperature	293(2) K	293(2) K
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a (Å)	16.091(3)	14.5408(15)
b (Å)	11.368(2)	8.8508(9)
c (Å)	7.4364(14)	10.7959(11)
β (°)	100.489(4)	106.435(2)
Color	Colourless	Colourless
Size (mm)	0.222 × 0.18 × 0.088	0.254 × 0.13 × 0.111
Volume (Å^3)	1337.5(4)	1332.6(2)
Z	4	4
ρ_{calc} (g cm^{-3})	1.432	1.437
Absorption coefficient (mm^{-1})	0.249	0.250
T_{min}, T_{max}	0.962, 0.973	0.947, 0.978
F(000)	600	600
Theta range for data collection	1.29 to 28.06°	1.46 to 28.05°
Index ranges	$-21 \leq h \leq 21$	$-18 \leq h \leq 19$
	$-14 \leq k \leq 15$	$-11 \leq k \leq 11$
	$-9 \leq l \leq 9$	$-14 \leq l \leq 14$
Reflections collected	15,600	15,544
Independent reflections	3,212 [R(int) = 0.0335]	3,237 [R(int) = 0.0394]
Absorption correction	None	None
Data/restraints/parameters	3,212/0/189	3,237/0/189
Goodness-of-fit on F^2	1.095	1.129
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0481$	$R1 = 0.0523$
	$wR2 = 0.1118$	$wR2 = 0.1142$
R indices (all data)	$R1 = 0.0618$	$R1 = 0.0689$
	$wR2 = 0.118/8$	$wR2 = 0.1216$
Largest diff. peak and hole (e. Å^{-3})	0.232 and −0.231	0.286 and −0.157

Results and Discussion

The reactions of 2- and 3-picolylamine with phenylisothiocyanate gave the corresponding heterocyclic thiourea derivatives (**1**) and (**2**), respectively. Bond distances and angles of compounds (**1**) and (**2**) are given in Table 2.

Table 2 Selected bond distances (Å) and angles (°) of (**1**) and (**2**)

Bond distances			
(**1**)			
C(1)–C(2)	1.374(2)	C(8)–C(9)	1.508(3)
C(1)–C(6)	1.382(2)	C(9)–N(4)	1.339(2)
C(1)–N(1)	1.461(2)	C(9)–C(10)	1.380(3)
C(2)–C(3)	1.378(2)	C(10)–C(11)	1.381(3)
C(4)–N(2)	1.411(2)	C(11)–C(12)	1.367(3)
C(5)–C(6)	1.375(2)	C(12)–C(13)	1.371(3)
C(7)–N(3)	1.336(2)	C(13)–N(4)	1.335(2)
C(7)–N(2)	1.352(2)	N(1)–O(2)	1.215(2)
C(7)–S(1)	1.6917(17)	N(1)–O(1)	1.216(2)
C(8)–N(3)	1.463(2)		
(**2**)			
C(1)–C(6)	1.370(3)	C(8)–N(3)	1.452(2)
C(1)–C(2)	1.379(3)	C(8)–C(9)	1.507(3)
C(1)–N(1)	1.458(3)	C(9)–C(10)	1.382(3)
C(2)–C(3)	1.372(3)	C(9)–C(13)	1.383(3)
C(3)–C(4)	1.389(3)	C(10)–C(11)	1.374(3)
C(4)–C(5)	1.396(3)	C(11)–C(12)	1.374(3)
C(4)–N(2)	1.401(2)	C(12)–N(4)	1.333(3)
C(5)–C(6)	1.374(3)	C(13)–N(4)	1.330(3)
C(7)–N(3)	1.340(2)	N(1)–O(1)	1.218(3)
C(7)–N(2)	1.360(2)	N(1)–O(2)	1.222(3)
C(7)–S(1)	1.6758(18)		
Bond angles			
(**1**)			
C(2)–C(1)–C(6)	122.22(15)	N(4)–C(9)–C(10)	121.70(18)
C(2)–C(1)–N(1)	119.42(15)	N(4)–C(9)–C(8)	115.30(16)
C(6)–C(1)–N(1)	118.36(16)	C(10)–C(9)–C(8)	122.99(17)
C(1)–C(2)–C(3)	118.50(15)	C(9)–C(10)–C(11)	118.81(19)
C(2)–C(3)–C(4)	120.32(16)	C(12)–C(11)–C(10)	119.60(19)
C(3)–C(4)–C(5)	120.22(15)	C(11)–C(12)–C(13)	118.3(2)
C(3)–C(4)–N(2)	117.67(15)	N(4)–C(13)–C(12)	123.10(19)
C(5)–C(4)–N(2)	121.95(14)	O(2)–N(1)–O(1)	123.01(18)
C(6)–C(5)–C(4)	119.75(15)	O(2)–N(1)–C(1)	118.26(17)
C(5)–C(6)–C(1)	118.98(16)	O(1)–N(1)–C(1)	118.73(18)
N(3)–C(7)–N(2)	115.50(15)	C(7)–N(2)–C(4)	127.21(15)
N(3)–C(7)–S(1)	120.54(12)	C(7)–N(3)–C(8)	127.16(15)
N(2)–C(7)–S(1)	123.89(13)	C(13)–N(4)–C(9)	118.44(16)
N(3)–C(8)–C(9)	115.27(16)		
(**2**)			
C(6)–C(1)–C(2)	121.38(19)	C(10)–C(9)–C(13)	116.44(18)
C(6)–C(1)–N(1)	119.4(2)	C(10)–C(9)–C(8)	123.17(17)
C(2)–C(1)–N(1)	119.2(2)	C(13)–C(9)–C(8)	120.39(17)
C(3)–C(2)–C(1)	118.8(2)	C(11)–C(10)–C(9)	119.89(18)
C(2)–C(3)–C(4)	120.91(19)	C(12)–C(11)–C(10)	118.97(19)
C(3)–C(4)–C(5)	119.19(18)	N(4)–C(12)–C(11)	122.8(2)
C(3)–C(4)–N(2)	117.21(17)	N(4)–C(13)–C(9)	124.79(19)
C(5)–C(4)–N(2)	123.48(18)	O(1)–N(1)–O(2)	123.1(2)
C(6)–C(5)–C(4)	119.68(19)	O(1)–N(1)–C(1)	118.2(2)
C(1)–C(6)–C(5)	120.03(19)	O(2)–N(1)–C(1)	118.7(2)
N(3)–C(7)–N(2)	112.55(16)	C(7)–N(2)–C(4)	129.43(16)
N(3)–C(7)–S(1)	122.46(14)	C(7)–N(3)–C(8)	125.52(16)
N(2)–C(7)–S(1)	124.93(14)	C(13)–N(4)–C(12)	117.13(18)
N(3)–C(8)–C(9)	112.67(16)		

Table 3 Hydrogen bonds distances (Å) and angles (°) for (**1**) and (**2**)

D–H···A	D–H	H···A	D···A	D–H···A
(**1**)				
N(2)–H(14)…N(4)	0.85(2)	1.98(2)	2.793(2)	162.2(19)
N(3)–H(15)…S(1)^{i}	0.80(2)	2.58(2)	3.3459(17)	160.3(19)
(**2**)				
N(2)–H(14)…N(4)^{ii}	0.89(2)	2.02(2)	2.902(2)	171(2)
N(3)–H(15)…N(4)^{ii}	0.80(2)	2.69(2)	3.309(3)	135(2)
N(3)–H(15)…S(1)^{iii}	0.80(2)	2.84(2)	3.4429(17)	134(2)

Symmetry transformations used to generate equivalent atoms: (i) −x, −y, −z, (ii) −x, −y + 2, −z, (iii) x, −y + 5/2, z−1/2

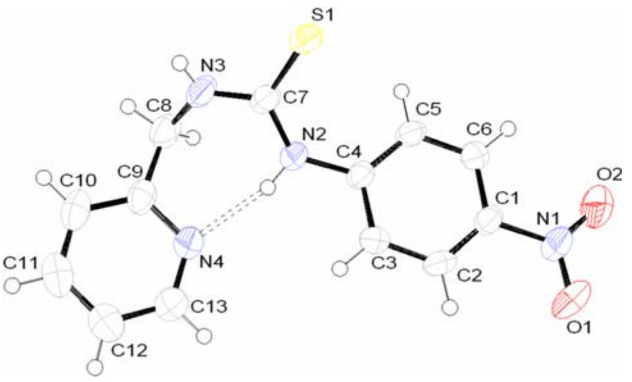


Fig. 1 Molecular structure of (**1**). Thermal ellipsoids shown at 50% possibility

Hydrogen bond distances and angles of those two compounds are presented in Table 3. Compound (**1**) crystallized in the monoclinic space group $P2_1/c$. A molecular diagram of the H-bonded dimeric structure is shown in Fig. 2. It should be noted that the compound (**1**) possesses an intramolecular N–H···N hydrogen bond (H(14)···N(4) = 1.98(2) Å and N(2)–H(14)···N(4) = 162.2(19)°) forming a pseudo-seven-membered ring, thus locking the molecular conformation and eliminating conformational flexibility (Fig. 1). The crystal structure of (**1**) also shows intermolecular interactions of the N–H···S bonds (H(15)···S(1)^{i} = 2.58(2) Å and N(3)–H(15)···S(1)^{i} = 160.3(19)°) generating a dimeric structure along the crystallographic 'a'-axis (Fig. 2).

Compound (**2**) also crystallized in monoclinic space group $P2_1/c$, Fig. 3. However, there is no intramolecular hydrogen bonding in the structure. The structure of (**2**) had a different intermolecular hydrogen bonding pattern when compared to (**1**). There are pairs of intramolecular hydrogen bond between the nitrogen pyridine and NH thioureas (H(14)···N(4)^{ii} = 2.02(2) Å and N(2)–H(14)···N(4)^{ii} = 171(2)° and H(15)···N(4)^{ii} = 2.69 Å and N(3)–H(15)···N(4)^{ii} = 135(2)°), Fig. 4.

The packing is not only stabilized by hydrogen bonding, but also by π–π packing interactions in the distance of 3.683 Å (Phenyl···Phenyl) and 3.718 Å (Pyridine···Pyridine) responsible for the crystal packing of (**1**). It should be mentioned that the relatively long N···S distances encountered for both compounds are facilitated by resonance lengthening of C=S [13] and are similar to those of previously determined thiourea dimers [14–16]. Moreover, the torsion angles of N2–C7–N3–C8 are −11.8(3)° and 175.51(18)° for (**1**) and (**2**), respectively. This is due to the formation of a pseudo-seven-membered ring in compound (**1**).

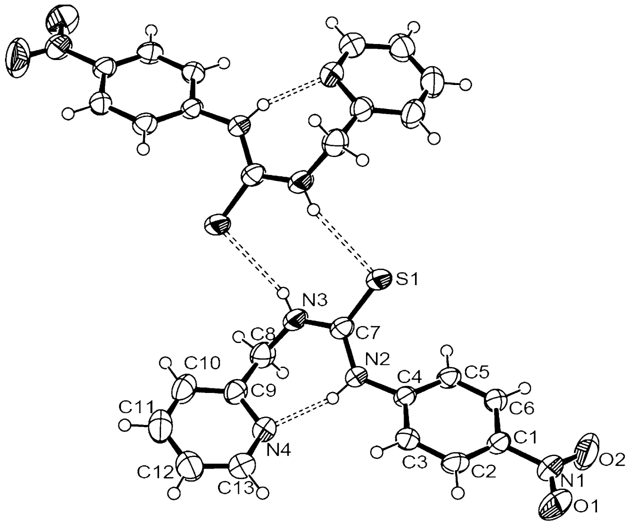


Fig. 2 The N–H···S intramolecular hydrogen bonding in the dimeric structure of (**1**)

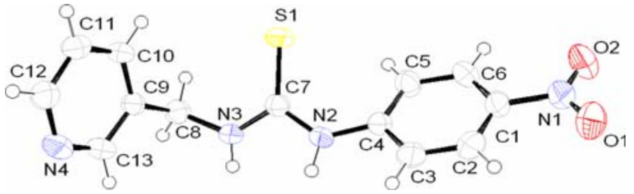


Fig. 3 Molecular structure of (**2**). Thermal ellipsoids shown at 50% possibility

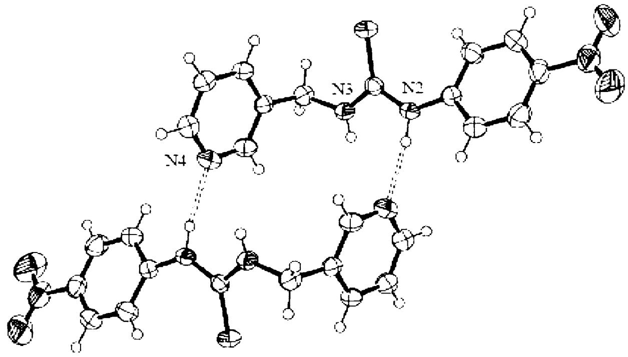


Fig. 4 The N–H···N intramolecular hydrogen bonding in the dimeric structure of (**2**)

From the structural features described above it is clear that the intramolecular hydrogen bonding has been found in the *ortho*-pyridine substituted thiourea derivatives. In addition, the supramolecular aggregation in both structures are due to N–H···N, N–H···S and π···π intermolecular interactions.

Supplementary Material

Supplementary crystal data are available from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk) on request, quoting the deposition numbers: CCDC 665445 and 665446 for compounds (**1**) and (**2**), respectively.

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References

1. Walpole C, Ko SY, Brown M, Beattie D, Campbell E, Dickerson F, Ewan S, Hughes GA, Lemaire M, Lerpiniere J, Partel S, Urban L (1998) J Med Chem 41:3159. doi:10.1021/jm970499g
2. Mallams AK, Moron JB, Reichert P (1981) J Chem Soc, Perkin Trans 1:2186. doi:10.1039/p19810002186
3. Schroeder DC (1955) Chem Rev 55:181. doi:10.1021/cr50001a005
4. Sarkis GY, Faisal ED (1985) J Heterocycl Chem 22:137
5. Tobe Y, Sasaki S, Hirose K, Naemura K (1997) Tetrahedron Lett 38:4791. doi:10.1016/S0040-4039(97)01034-4
6. Nie L, Li Z, Han J, Zhang X, Yang R, Liu W-X, Wu F-Y, Xie J-W, Zhao Y-F, Jiang Y-B (2004) J Org Chem 69:6449. doi:10.1021/jo049088f
7. Pfeffer FM, Gunnlaugsson T, Jensen P, Kruger PE (2005) Org Lett 7:5357. doi:10.1021/ol051497q

8. McBride MT, Luo T-JM, Palmore GTR (2001) Cryst Growth Des 1:39. doi:10.1021/cg0000060
9. Succaw GL, Weakley TJR, Han F, Doxsee KM (2005) Cryst Growth Des 5:2288. doi:10.1021/cg050162c
10. Sheldrick GM (1997) Shelxl97, Program for crystal structure determination. University of Göttingen, Germany
11. Farrugia LJ (1999) J Appl Cryst 32:837. doi:10.1107/S0021889899006020
12. Mercury 1.4.2 (2007) Cambridge Crystallographic Data Centre. Cambridge, UK
13. Allen FH, Bird CM, Rowland RS, Raithby PR (1997) Acta Crystallogr B 53:680. doi:10.1107/S0108768197002656
14. Valdes-Martines J, Hernandez-Ortega S, West DX, Ackerman LJ, Swearingen JK, Hermetet AK (1999) J Mol Struct 478:219. doi:10.1016/S0022-2860(98)00746-7
15. Kaminsky W, Goldberg KI, Wesr DX (2002) J Mol Struct 605:9. doi:10.1016/S0022-2860(01)00655-X
16. Venkatachalam TK, Sudbeck E, Uckun FM (2004) J Mol Struct 687:45. doi:10.1016/j.molstruc.2003.08.022