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# Condensation of thiohydrazide analogues with 4-bromo-3, 6-dichloropyridazine: an efficient rout to pyridazino[4, 3-*e*][1, 3, 4] thiadiazines

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Abstract- Some new 3-(alkylsulfanyl)- 7-chloro-1-phenyl-1H-pyridazino [4,3-*e*][1,3,4]thiadiazine were synthesized by treatment of the alkyl-2-phenylhydrazinecarbodithioates with 4-bromo-3,6-dichloropyridazine in alkaline acetonitril. Orientation of the reaction has been determined by X-Ray crystallography technique. The chlorine atom on the number 7 position of these products was replaced by secondary amines in reflux condition.

**Keywords: 4-bromo-3, 6-dichloropyridazine, nucleophilic displacement, mass spectroscopy.**

## INTRODUCTION

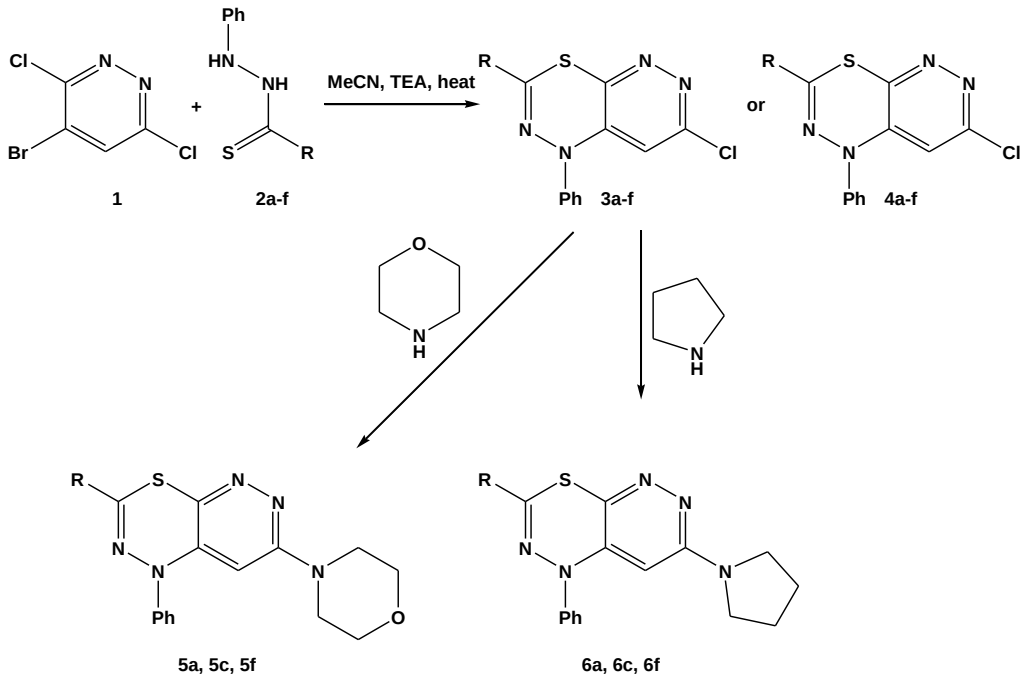
The diverse biological activities of pyridazino[1,3,4]thiadiazines persuaded us to search for newer and more efficient synthetic methods for this class of heterocyclic compounds. These compounds have been described as being potential inhibitors of cyclic nucleotide phosphodiesterase [1], dyestuff [2], and precursors of herbicides [3]. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported [4-9] and among those structural isomer, pyridazino[4,3-

*e*][1,3,4]thiadiazine (**3**) has been largely overlooked. The only undisputed example of this heterocyclic compound has been synthesized in two steps by Oda and his co-workers through cyclocondensation of 6-chloro-2-methyl-5-(1-methylhydrazino)-3(2H)-pyridazinone with benzyl isothiocyanate in the presence of sodium hydroxide [5].

Prompted by these findings and in continuing our synthetic studies on bioactive heterocycles [10–17] and fused [1,3,4]thiadiazines [18-20] we now exhibit a general and convenient procedure for the synthesis of a host of pyridazino[4,3-*e*][1,3,4] thiadiazines in a single step *via* heterocyclization of 4-bromo-3,6-dichloropyridazine with alkyl-2-phenylhydrazinecarbodithioates in the presence of triethylamine in boiling acetonitrile.

## RESULTS AND DISCUSSION

4-Bromo-3,6-dichloropyridazine **1** was recently exhibited as a suitable precursor for the multistep synthesis of pyridazino [4,3-e][1,3,4]thiadiazine derivatives [9]. In the present study we report the condensation of this compound with alkyl-2-phenylhydrazinecarbodithioates **2a-e** and dithizone **2f** in alkaline acetonitril as a convenient rout to the pyridazino [4,3-e][1,3,4]thiadiazine derivatives as shown in **Scheme I**.

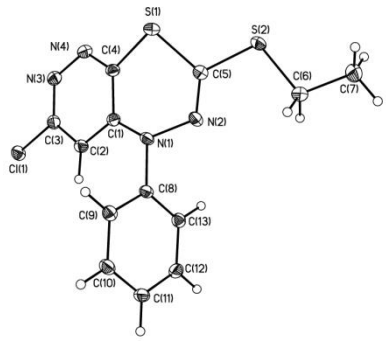



a: R= $CH_3$-S, b: R= $C_2H_5$-S, C: R= n-$C_3H_7$-S, d: R= n-$C_4H_9$-S, e: R= Ph-$CH_2$-S, f: R= Ph-NN-

**Scheme I**

Ring formation on this reaction was strongly confirmed by spectral and microanalytical data. The $^1$HNMR spectra of compounds **3a-f** were devoid of the signals at δ 6.0 and 9.0 ppm for NH groups of the precursors **2a-f** and showed further downfield shifts for aromatic protons plus a signal at 6.3 ppm for Aromatic CH moiety of precursor **1** indicating the construction of a thiadiazine ring around positions 3 and 4 of the pyridazine ring. Further proofs came from their IR spectra which lacked the N-H stretching frequencies of their precursors **2**. Mass spectra showed the expected molecular ion peak and fragmentation showed two peak on $m/z =$ (263 &

261) (1 to 3 ratio respectively) indicating lost of alkylthio groups for compounds **3a-e** and diazophenyl group for **3f** as expected. Microanalytical data of compounds **3** have no significant difference with the expected data. According to these results, there are two potential assignable structures for the products of the above reaction: pyridazino[4, 3-e][1,3,4]thiadiazines **3a-f** and pyridazino[4,3-e][1,3,4]thiadiazines **4a-f** as well as argued earlier [2]. For the determination of the reaction`s orientation, product of the reaction of **2b** with **1** was dissolved in ethanol and kept under crystallization condition. Single crystals appeared after two weeks and its structure was refined by X-Ray crystallography technique, which confirms the pyridazino[4,3-e][1,3,4]thiadiazine structure for the product of this reaction as shown in **Scheme II**.




Compounds **3a,c,f** have been treated with either boiling morpholine or pyrrolidine for 20 minutes and their chlorine atom was replaced by amines to afford **5a,c,f** and **6a,c,f** respectively. $^1$HNMR spectra of these compounds showed signals around δ 3.2-3.3 ppm belonging to $N(CH_2)_2$ moieties. Their mass spectra of these compounds showed the expected molecular ion peak and lacked the isotopic pattern due to their precursors, which strongly verified the replacement of chlorine atom by amines.

In conclusion the condensation of 4-bromo-3,6-dichloropyridazine with alkyl-2- phenylhydraz inecarbodithioates and further replacement with secondary amines exhibited as a convenient and general procedure for preparation of new pyridazino[4,3-*e*][1,3,4]thiadiazine derivatives.

## EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The $^1$HNMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. The purity of all new compounds synthesized was tested by TLC using chloroform as mobile phase.

**General procedure for preparation of (3a-e)**

A mixture of 4-bromo-3, 6-dichloropyridazine 1 (17 mmole, 4g), triethylamine (5 ml) and alkyl-2- phenylhydrazinecarbodithioates **2a-e** (17 mmole) in acetonitrile (20 ml) was heated under reflux condition for 4 hr. The solvent was removed under reduced pressure and the residue washed with water and crystallized from ethanol and washed with petroleum ether 40-60 after drying to give products **3a-e**.

**7-Chloro-3-(methylsulfanyl)-1-phenyl-1*H* -pyridazino[4,3-*e*][1,3,4]thiadiazine (3a)**

This compound was obtained as a yellow powder in 43% yield; m.p. 140-143 ºC; MS: m/z (%), 310 (35), 308 (100), 263, 261; IR( KBr): 3104, 3039, 2900 cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 2.5 (s, 3H, S-$CH_3$), 6.3 (s, 1H, $C_8H$), 7.4-7.7 (m, 5H, aromatic); *Anal.* Calcd. For $C_{12}H_9ClN_4S_2$: C, 46.67; H, 2.94; N, 18.14; S, 20.77. Found; C, 46.43; H, 3.04; N, 17.95; S, 20.58.

**7-Chloro-3-(ethylsulfanyl)-1-phenyl-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (3b)**

This compound was obtained as a yellow powder in 65% yield; m.p. 119-120 ºCMS: m/z (%), 324 (30), 322(100), 263, 261; IR( KBr): 3104, 3040, 2930, 2900, 2870cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.3 (t, 3H, $CH_3$), 3.1 (q, 2H, S-$CH_2$), 6.3 (s, 1H, $C_8H$), 7.3-7.7 (m, 5H, aromatic); *Anal.* Calcd. for $C_{13}H_{11}ClN_4S_2$: C, 48.36; H, 3.43; N, 17.35; S, 19.86. Found; C, 48.54; H, 3.53; N, 17.23; S, 19.64.

**7-Chloro-1-phenyl-3-(propylsulfanyl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (3c)**

This compound was obtained as a yellow powder in 61% yield; m.p. 97-98 ºC; MS: m/z (%), 338 (28), 336(100), 263, 261; IR( KBr): 3104, 3039, 2961, 2948, 2909, 2844cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.0 (t, 3H, $CH_3$), 1.7 (sext, 2H, $CH_2$), 3.1 (t, 2H, S-$CH_2$), 6.3 (s, 1H, $C_8H$), 7.4-7.7 (m, 5H, aromatic); *Anal.* Calcd. for $C_{14}H_{13}ClN_4S_2$: C, 49.92; H, 3.89; N, 16.63; S, 19.04. Found; C, 50.07; H, 3.95; N, 16.51; S, 18.95.

**3-(Butylsulfanyl)-7-chloro-1-phenyl-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (3d)**

This compound was obtained as a yellow powder in 65% yield; m.p. 95-96 ºC; MS: m/z (%), 352 (35), 350 (100), 263, 261; IR( KBr): 3100, 3040, 2950, 2830, cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 0.9 (t, 3H, $CH_3$), 1.3-1.9 (m, 4H, $2CH_2$), 3.1 (t, 2H, $CH_2$ -S), 6.3 (s, 1H, $C_8H$), 7.4-7.7 (m, 5H, aromatic); *Anal.* Calcd. for $C_{15}H_{15}ClN_4S_2$: C, 51.34; H, 4.31; N, 15.97; S, 18.28. Found; C, 51.48; H, 4.40; N, 15.69; S, 17.97.

**3-(Benzylsulfanyl)-7-chloro-1-phenyl-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (3e)**

This compound was obtained as a yellow powder in 53% yield; m.p. 120-121 ºC; MS: m/z (%) 386 (31), 384 (100), 263, 261; IR( KBr): 3115, 3050, 2900, 2865, cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 4.3 (s, 2H, S-$CH_2$), 6.3 (s, 1H, $C_8H$), 7.2-7.8 (m, 10H, aromatic); *Anal.* Calcd. for $C_{18}H_{13}ClN_4S_2$: C, 56.17; H, 3.40; N, 14.56; S, 16.66. Found; C, 56.29; H, 3.54; N, 14.32; S, 16.42.

**7-Chloro-1-phenyl-3-(phenyldiazenyl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (3f)**

A mixture of 4-bromo-3, 6-dichloropyridazine 1 (17 mmole, 4g), triethylamine (5 ml) and dithizone **2f** (0.44 gr, 17mmole) in acetonitrile (20 ml) was heated under reflux condition for 40 minutes. The reaction mixture was filtered after cooling and the filtrate washed with water and crystallized from ethanol to give product **3f**.

57% yield; m.p. 280-282 ºC; MS: m/z (%) 368 (31), 366 (100), 263, 261; IR( KBr): 3080, 2900 cm$^{-1}$; $^1$HNMR ($CDCl_3$): δ, 6.3 (s, 1H, $C_8H$), 7.4-7.9 (m, 10H, aromatic) ); *Anal.* Calcd. for $C_{17}H_{11}ClN_6S$: C, 55.66; H, 3.02; N, 22.91; S 8.74. Found; C, 55.75; H, 3.09; N, 22.67; S, 8.52.

**General procedure for preparation of (5a, 5c, 5f)**

Compounds **3a**, **3c**, or **3f** (0.54mmole) was dissolved in morpholine (5 ml) and heated under reflux condition for 20 minutes. The excess morpholine was removed under reduced pressure and the residue washed with water and crystallized from ethanol to give products **5a**, **5c**, **5f** respectively.

**3-(Methylsulfanyl)-7-(morpholin-4-yl)-1-phenyl-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (5a)**

This compound was obtained as a green powder in 58% yield; m.p. 223-224ºC; MS: m/z, 359, 312; IR( KBr): 3039, 2961, 2863, $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 2.3 (s, 3H, S-$CH_3$), 3.2 (t, 4H, N($CH_2$)$_2$), 3.6 (t, 4H, O($CH_2$)$_2$), 5.8 (s, 1H, $C_8$H), 7.3-7.4 (m, 5H, aromatic); *Anal.* Calcd. for $C_{16}H_{17}N_5OS_2$: C, 53.46; H, 4.77; N, 19.48; S, 17.84. Found; C, 53.69, H, 4.89; N, 19.25; S, 17.61.

**7-(Morpholin-4-yl)-1-phenyl-3-(propylsulfanyl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (5c)**

This compound was obtained as a green powder in 48% yield; m.p. 162 ºC; MS: m/z, (%) 387, 312; IR( KBr): 3039, 2974, 2850, $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.0 (t, 3H, $CH_3$), 1.7 (sextet, 2H, $CH_2$), 3.0 (t, 2H, $CH_2$- S), 3.4 (t, 4H, N($CH_2$)$_2$), 3.7 (t, 4H, O($CH_2$)$_2$), 5.9 (s, 1H, $C_8$H), 7.3-7.6 (m, 5H, aromatic); *Anal.* Calcd. for $C_{18}H_{21}N_5OS_2$: C, 55.79; H, 5.46; N, 18.07; S, 16.55. Found; C, 56.03; H, 5.72; N, 17.95; S, 16.34.

**7-(Morpholin-4-yl)-1-phenyl-3-(phenyldiazenyl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (5f)**

This compound was obtained as a violet powder in 40% yield; m.p. 209-210 ºC; MS: m/z, (%) 417, 312; IR( KBr): 3039, 2961, 2909, 2850 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 3.3 (t, 4H, N($CH_2$)$_2$), 3.7 (t, 4H, O($CH_2$)$_2$), 5.7(s, 1H, $C_8$H), 7.4-8.0 (m, 10H, aromatic); *Anal.* Calcd. for $C_{21}H_{19}N_7OS$: C, 60.42; H, 4.59; N, 23.49; S, 7.68. Found; C, 60.33; H, 4.63; N, 23.24; S, 7.44.

**General procedure for preparation of (6a, 6c, 6f)**

Compounds 3a, 3c, or 3f (0.54 mmole) was dissolved in pyrrolidine (5 ml) and heated under reflux condition for 20 minutes. The excess pyrrolidine was removed under reduced pressure and

the residue washed with water and crystallized from ethanol to give products **6a**, **6c**, **6f** respectively.

**3-(Methylsulfanyl)-1-phenyl-7-(pyrrolidin-1-yl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (6a)**

This compound was obtained as a green powder in 72% yield; m.p. 195-196 ºC; MS: m/z, 343, 296; IR (KBr): 3039, 2974, 2938, 2863 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.8 (t, 4H, $2CH_2CH_2N$), 2.3 (s, 3H, S-$CH_3$), 3.3 (t, 4H, $N(CH_2)_2$), 5.5 (s, 1H, $C_8H$), 7.3-7.4 (m, 5H, aromatic); *Anal.* Calcd for $C_{16}H_{17}N_5S_2$: C, 55.95; H, 4.99; N, 20.39; S, 18.67. Found; C, 56.04; H, 5.08; N, 20.16; S, 18.46.

**1-Phenyl-3-(propylsulfanyl)-7-(pyrrolidin-1-yl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (6c)**

This compound was obtained as a green powder in 43% yield; m.p. 98-99 ºC; MS: m/z, 371, 296; IR(KBr): 3039, 2961, 2863 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.0 (t, 3H, $CH_3$), 1.7-2 (m, 6H, $2CH_2CH_2N$ & $CH_2$), 3.0 (t, 2H, $CH_2$-S), 3.3 (t, 4H, $N(CH_2)_2$), 5.6 (s, 1H, $C_8H$), 7.4-7.7 (m, 5H, aromatic); *Anal.* Calcd. for $C_{18}H_{21}N_5S_2$: C, 58.19; H, 5.70; N, 18.85; S, 17.26. Found; C, 58.35; H, 5.83; N, 18.77; S, 16.95.

**1-Phenyl-3-(phenyldiazenyl)-7-(pyrrolidin-1-yl)-1*H*-pyridazino[4,3-*e*][1,3,4]thiadiazine (6f)**

This compound was obtained as a violet powder in 35% yield; m.p. 277-278 ºC; MS: m/z, 401, 296; IR( KBr): 3039, 2961, 2909, 2850 $cm^{-1}$; $^1$HNMR ($CDCl_3$): δ, 1.9 (t, 4H, $2CH_2CH_2N$), 3.3 (t, 4H, $N(CH_2)_2$), 5.4 (s, 1H, $C_8H$), 7.4-8.0 (m, 10H, aromatic); *Anal.* Calcd. for $C_{21}H_{19}N_7S$: C, 62.82; H, 4.77; N, 24.42; S, 7.99. Found; C, 62.73; H, 4.86; N, 24.23; S, 7.65.

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