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RESEARCH ARTICLE

A general synthesis of pyridazino[4,3-*e*][1,3,4]thiadiazines

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A straightforward synthesis of pyridazino[4,3-*e*][1,3,4] thiadiazines **3**(**a**–**j**) from cyclocondensation of 3,6-dichloro-4-(1-methylhydrazino) pyridazine (**2**) with various isothiocyanates is described.

Keywords: Arylisothiocyanates; Pyridazino thiadiazines; Trihalopyridazines; Heterocyclization

1. Introduction

In continuation of our interest in the chemistry of fused heterocycles of pharmacological importance and exploration of their synthetic pathways, in a previous investigation we studied the reaction of 5-bromo-2-chloro-6-methylpyrimidin-4-amine with isothiocyanates in the presence of sodamide in DMF which led to thiazolo[4,5-*d*]pyrimidine derivatives [1]. In order to further study heterocyclization of isothiocyanates with other suitably polyhalogenated heterocycles to obtain biologically active compounds, we decided to synthesize pyridazinothiadiazines which are of interest as potential inhibitors of cyclic nucleotide phosphodiesterase [2], dyestuff [3], and precursors of herbicides [4]. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported [5–9] and among those the 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 [6] (scheme 1). Prompted by these findings and in continuing our synthetic studies on bioactive heterocycles [10–15] we have now extended this synthetic strategy as a general and convenient procedure for the synthesis of a host of

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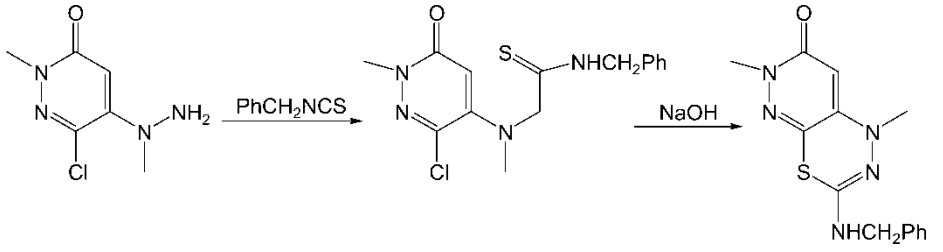


SCHEME 1

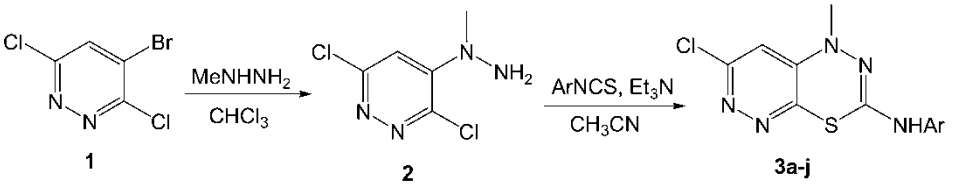
pyridazino[4,3-*e*][1,3,4] thiadiazines in a single step *via* heterocyclization of 3,6-dichloro-4-(1-methylhydrazino)pyridazine with arylisothiocyanates in the presence of triethylamine in boiling acetonitrile.

2. Results and discussion

The starting material used in this synthesis was 4-bromo-3,6-dichloropyridazine (**1**), and it was quantitatively prepared by a published method [16]. Treatment of 4-bromo-3,6-dichloro-pyridazine (**1**) with methyl hydrazine in chloroform at room temperature yielded 3,6-dichloro-4-(1-methylhydrazino) pyridazine (**2**) exclusively; only the 4-bromo substituent has been replaced by the methylhydrazino substituent.

The position of the hydrazino substituent was confirmed on the basis of an earlier report pertaining the selective displacement of halogenosubstituents from 3,4,6-trihalogenopyridazine with ammonia and methylhydrazine [6, 16]. The mass spectrum and micro analytical data are also supporting the proposed structure and clearly showed the presence of two chlorine atoms in the molecule. Treatment of compound (**2**) with various arylisothiocyanates in the presence of triethylamine and acetonitrile under an atmosphere of nitrogen at reflux afforded the pyridazino[4,3-*e*][1,3,4]thiadiazine 3(a–j) as yellow needles (scheme 2).

The structures of new compounds **3a–j** were confirmed by their spectral and micro analytical data. For example, the IR spectrum of **3a** did not exhibit the stretching vibration band at 3445 and 3275 cm^{-1} due to NH_2 functionality of the precursor **2** but exhibits vibration band at 3340 cm^{-1} due to NH moiety. The ^{1}H-NMR spectrum of **3a** was also devoid of the broad NH_2 signal at δ 4.02 ppm but showed a signal at δ 9.5 ppm assignable to NH proton which exchanged with D_2O. The molecular ion of **3a** (M: $M + 2$) was observed at 291 and 293 (100%:38%) corresponding to the molecular formula $C_{12}H_{10}ClN_5S$.



1 **2** **3a-j**

a: Ar=Ph, **b**: Ar = 3-CH_3-C_6H_4,
c: Ar =4-CH_3-C_6H_4, **d**: Ar = 4-F-C_6H_4,
e: Ar = 3-Cl-C_6H_4, **f**: Ar = 4-Cl-C_6H_4,
g: Ar = 2-Br-C_6H_4, **h**: Ar = 3-Br-C_6H_4,
i: Ar = 4-Br-C_6H_4, **j**: Ar = 4-NO_2-C_6H_4

SCHEME 2

Table 1. Physical, spectral and micro analytical data of pyridazino[4,3-*e*][1,3,4]thiadiazines **3a–j**.

Entry	Yield (%)	m.p. (°C)	Spectral data[†]	Molecular formula	C% (calcd)	H% (calcd)	N% (calcd)	S% (calcd)
3a	60	234–235	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.0–7.5 (m, 5H, ph), 9.4 (s, 1H, NH, D_2O exchangeable). IR: ν 3340, 3245, 1636, 1596, 746 cm^{-1}, m/z 291 (M^+, 100), 292(15.6), 293 (37.9).	$C_{12}H_{10}ClN_5S$	49.31 (49.40)	3.48 (3.45)	24.09 (24.00)	10.80 (10.99)
3b	52	252	^{1}H NMR: δ 2.2(s, H, $CH_3-C_6H_4$), 3.2(s, 3H, CH_3-N), 6.8(s, 1H, pyridazine), 6.9–7.4 (m, 4H, aromatic), 9.3(s, 1H, NH,D_2O exchangeable). IR: ν 3340, 3216, 2950, 1605, 1524, 690 cm^{-1}, m/z 305 (M^+, 100%), 306 (13.9%), 307(35%).	$C_{13}H_{12}ClN_5S$	51.00 (51.05)	3.86 (3.96)	22.70 (22.90)	10.37 (10.48)
3c	68	253–254	^{1}H NMR: δ 2.2(s, H, $CH_3-C_6H_4$), 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.1–7.5 (dd, $J = 8$ Hz, 4H, Ph), 9.3(s, 1H, NH, D_2O exchangeable). IR: ν 3300, 3251, 3037, 1591, 1529, 1509, 815 cm^{-1}, m/z 305 (M^+, 100%), 306 (14.5%), 307 (36.9%).	$C_{13}H_{12}ClN_5S$	51.03 (51.05)	3.93 (3.96)	22.89 (22.90)	10.40 (10.48)
3d	63	242–243	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.1–7.6 (m, 4H, Ph), 9.5(s, 1H, NH, D_2O exchangeable). IR: ν 3310, 3224, 3003, 1569, 1529, 1506, 699, 513 cm^{-1}, m/z 309 (M^+, 100%), 310 (15.4%), 311 (37.3%).	$C_{12}H_9ClFN_5S$	46.48 (46.53)	2.86 (2.93)	22.50 (22.61)	10.10 (10.35)
3e	53	259	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.1–7.6 (m, 4H, Ph), 9.6(s, 1H, NH, D_2O exchangeable). IR: ν 3434, 2922, 1590,1524, 1480, 678 cm^{-1}, m/z 325 (M^+, 100%), 326 (15.4%), 327 (68.9%).	$C_{12}H_9Cl_2N_5S$	44.03 (44.18)	2.73 (2.78)	21.43 (21.47)	9.71 (9.83)
3f	47	247–248	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.3–7.6 (dd, $J = 8$ Hz, 4H, Ph), 9.5(s, 1H, NH, D_2O exchangeable). IR: ν 3343, 3253, 2988, 1609, 1553, 704 cm^{-1}, m/z 325 (M^+, 100%), 326 (15.3%), 327 (70.0%).	$C_{12}H_9Cl_2N_5S$	44.08 (44.18)	2.79 (2.78)	21.50 (21.47)	9.17 (9.83)
3g	55	267–268	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.2–7.8 (m, 4H, Ph), 9.5(s, 1H, NH, D_2O exchangeable). IR: ν 3378, 2990, 1594, 1529, 839, 770 cm^{-1}, m/z 369 (M^+, 74.0%), 371 (100%), 373 (28.0%).	$C_{12}H_9BrClN_5S$	38.80 (38.89)	2.46 (2.45)	18.81 (18.89)	8.25 (8.65)
3h	55	267–268	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.2–7.8 (m, 4H, Ph), 9.6(s, 1H, NH, D_2O exchangeable). IR: ν 3380, 2923, 1585, 1522, 861, 770 cm^{-1}, m/z 369 (M^+, 72.3%), 371 (100%), 373 (27.6%).	$C_{12}H_9BrClN_5S$	38.79 (38.89)	2.43 (2.45)	18.81 (18.89)	8.41 (8.65)
3i	60	266–267	^{1}H NMR: δ 3.2(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.2–7.7 (m, 4H, Ph), 9.6(s, 1H, NH, D_2O exchangeable). IR: ν 3349, 3100, 2983, 1608, 1550, 1529, 819, 702 cm^{-1}, m/z 369 (M^+, 73.4%), 371 (100%), 373 (25.9%).	$C_{12}H_9BrClN_5S$	38.84 (38.89)	2.43 (2.45)	18.86 (18.89)	8.71 (8.65)
3j	70	309	^{1}H NMR: δ 3.3(s, 3H, CH_3-N), 6.9(s, 1H, pyridazine), 7.6–8.2 (m, 4H, Ph), 10.1(s, 1H, NH, D_2O exchangeable). IR: ν 3324, 2922, 1594, 1575, 1413, 1331, 750 cm^{-1}, m/z 336 (M^+, 100%), 337 (15.9%), 338 (37.8%).	$C_{12}H_9O_2ClN_6S$	42.61 (42.80)	2.59 (2.69)	24.69 (24.96)	9.23 (9.52)

[†]The solvent for ^{1}H NMR is DMSO-d_6 and the chemical shifts are in ppm.

In summary we have described a general and convenient one step synthesis of pyridazino[4,3-*e*][1,3,4] thiadiazines *via* heterocyclization of 3,6-dichloro-4-(1-methylhydrazino)pyridazine with arylisothiocyanates.

3. Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are not corrected. The IR spectra were obtained on a 4300 Shimadzu spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC l00 spectrometer. The mass spectra were obtained on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA micro analyzer.

3.1 *3,6-Dichloro-4-(1-methylhydrazino)pyridazine*

A solution of methyl hydrazine (0.02 mol, 0.92 g) in chloroform (10 ml) was added at once to a stirred solution of 4-bromo-3,6-dichloro-pyridazine (**1**) (0.02 mol, 4.56 g) and triethylamine (0.02 mol) in chloroform (10 ml). The stirring was continued for 3 h at room temperature. The solvent was evaporated and the residue was recrystallized from ethanol as white plates. Yield = 69%, m.p.: 82–83 °C; MS: m/z 193 (M^+). ^{1}H-NMR ($CDCl_3$) δ 3.4 ppm (s, 3H, CH_3), 4.0 ppm (s, 2H, NH_2 exchanged with D_2O. IR: ν 3445, 3275, 3178, 1644, 1552 cm^{-1}. Anal. Calcd. for $C_5H_6Cl_2N_4$; C 31.11, H 3.13, N 29.02. Found; C 31.10, H 3.09, N 29.10.

3.2 *General procedure for the preparation of pyridazino[4,3-e][1,3,4] thiadiazines 3(a–j)*

To a solution of 3,6-dichloro-4-(1-methylhydrazino)pyridazine (**2**) (0.001 mol, 0.193 g) in dry acetonitrile (10 ml), triethylamine (0.001 mol) and the appropriate isothiocyanate (0.001 mol) was added at once. The solution was then heated at reflux for 3–4 h before it was cooled to room temperature. The resulting solid was filtered off and recrystallized from ethanol as yellow needles (data in table 1).

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