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Research Article

Convenient synthesis of tetrazolo[1,5-b]pyridazine derivatives

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ABSTRACT

Reaction of 3,6-dichloropyridazine with hydrazine gave 1-(6-chloropyridazin-3-yl) hydrazine in high yield in ethanol at room temperature. Diazotization of the latter compound converted it to 6-chlorotetrazolo[1,5-b]pyridazine quantitatively in ice bath. 6-Chlorotetrazolo[1,5-b]pyridazine underwent a chlorine substitution is ethanol with amines at room temperature. The reaction mechanism and spectral data is discussed.

Keywords: 3,6-dichloropyridazine; diazotization; tetrazolo[1,5-b]pyridazine; hydrazine.

1. Introduction

The diverse biological activities of fused pyridazin 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, tetrazolo[1,5-b]pyridazine has been largely overlooked. In the present study, we present a new rout for the preparation of these compounds, which mainly utilizes water as solvent.

2. 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 (300MHz) spectra were recorded on a Bruker AC 300 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.

1-(6-Chloropyridazin-3-yl) hydrazine 2:

To a solution of 3,6- dichloro-pyridazine (7.4 gr, 0.05 mol) in ethanol (30 ml), hydrazine hydrate (5 ml) was added and stirred overnight at room temperature. The precipitant was filtered and washed with water and the dried by air.

Yield 6.5 g (90%), green powder, mp 75 °C. IR spectrum, ν, cm^{-1}: 3220, 3350. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 3.7 (2H, broad, NH_2), 6.4 (2H, broad, NH), 7.12 (1H, d, J=7.2, C_4H), 7.21 (1H, d, J= 7.2, C_5H). Mass spectrum, m/z: 144 $[M]^+$ (59%), 146 $[M+2]^+$ (20%). Anal. Calcd. for $C_4H_5ClN_4$: C, 33.23; H, 3.49; N, 38.76. Found: C, 33.42; H, 3.57; N, 38.53.

6-Chlorotetrazolo[1,5-*b*] pyridazine 3:

A solution of 1-(6-Chloropyridazin-3-yl) hydrazine (1.46 gr, 0.01 mol) in concentrated hydrochloric acid (2 ml) and water (4 ml) stirred in an ice bath to 0-5 °C. A solution of sodium nitrit (1 gr, 0.015 mol) in water (5 ml) was added and stirred for 15 minutes. The precipitant was filtered and then recrystallized from ethanol.

Yield 1.48 g (95%), brown powder, mp 62 °C. IR spectrum, ν, cm^{-1}: 850. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 7.53 (1H, d, J=7.2, C_5H), 8.34 (1H, d, J=7.2, C_4H). Mass spectrum, m/z: 155 $[M]^+$ (47%), 157 $[M+2]^+$ (16%). Anal. Calcd. for $C_4H_2ClN_5$: C, 30.89; H, 1.30; Cl, 22.79; N, 45.02. Found: C, 30.97; H, 1.34; N, 44.93.

General procedure for the reaction of amines with 6-chlorotetrazolo[1,5-*b*] pyridazine:

6-Chlorotetrazolo[1,5-*b*] pyridazine (0.31 gr, 0.002 mol) added to an appropriate amine (piperidine, morpholine, pyrrolidine and 1- methyl piperazine) (1ml) and stirred to a clear solution and continued for 30 minutes. Water (5 ml) was added and the precipitant was filtered and then recrystallized from ethanol to achieve products **4a-d**.

6-(Piperidin-1-yl)tetrazolo[1,5-b]pyridazine 4a:

Yield 0.34 g (84%), red powder, mp 112 °C. IR spectrum, ν, cm^{-1}: 2930, 2980. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 1.66 (m, 6H, ((CH_2)–CH_2N)), 3.61 (t, 4H, 2(CH_2N)), 7.27 (1H, d, J=7.2, C_5H), 7.98 (1H, d, J= 7.2, C_4H). Mass spectrum, m/z: 204 $[M]^+$. Anal. Calcd. for $C_9H_{12}N_6$: C, 52.93; H, 5.92; N, 41.15. Found: C, 53.11; H, 6.04; N, 40.94.

6-(Pyrrolidin-1-yl)tetrazolo[1,5-b]pyridazine 4b:

Yield 0.27 g (71%), red powder, mp 123 °C. IR spectrum, ν, cm^{-1}: 2930, 2980. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 2.06 (t, 4H, 2 ((CH_2)–CH_2N)), 3.52 (t, 4H, 2(CH_2N)), 7.01 (1H, d, J=7.2, C_5H), 7.95 (1H, d, J= 7.2, C_4H). Mass spectrum, m/z: 190 $[M]^+$. Anal. Calcd. for $C_8H_{10}N_6$: C, 50.52; H, 5.30; N, 44.18. Found: C, 50.69; H, 5.51; N, 44.03.

6-(Morpholin-4-yl)tetrazolo[1,5-b]pyridazine 4c:

Yield 0.33 g (79%), red powder, mp 129 °C. IR spectrum, ν, cm^{-1}: 2930, 2980. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 3.71 (t, 4H, $(CH_2)_2N$), 3.89 (t, 4H, $(CH_2)_2O$)), 7.28 (1H, d, J=7.2, C_5H), 8.15 (1H, d, J= 7.2, C_4H). Mass spectrum, m/z: 206 $[M]^+$. Anal. Calcd. for $C_8H_{10}N_6O$: C, 46.60; H, 4.89; N, 40.76. Found: C, 46.69; H, 5.02; N, 40.63.

6-(4-Methylpiperazin-1-yl)tetrazolo[1,5-b]pyridazine 4d:

Yield 0.33 g (75%), red powder, mp 92 °C. IR spectrum, ν, cm^{-1}: 2930, 2980. ^{1}HNMR spectrum, ($CDCl_3$), δ, ppm (J, Hz): 2.30 (s, 3H, $(CH_2)_2N\mathbf{CH_3}$), 2.49 (t, 4H, $(\mathbf{CH_2})_2NCH_3$), 3.68 (t, 4H, $(CH_2)_2N$)), 7.25 (1H, d, J=7.2, C_5H), 8.01 (1H, d, J= 7.2, C_4H). Mass spectrum,

m/z: 219 $[M]^+$. Anal. Calcd. for $C_9H_{13}N_7$: C, 49.30; H, 5.98; N, 44.72. Found: C, 49.51; H, 6.11; N, 44.63.

3. Results and discussion

In a previous communication [10], we reported the preparation of new fused tetrazoles by sequential treatment of 7-chloro--1*H*-pyrimido[4,5-*e*] [1,3,4] thiadiazines with hydrazine and aqueous sodium nitrit $NaNO_2$ as shown in Figure 1.

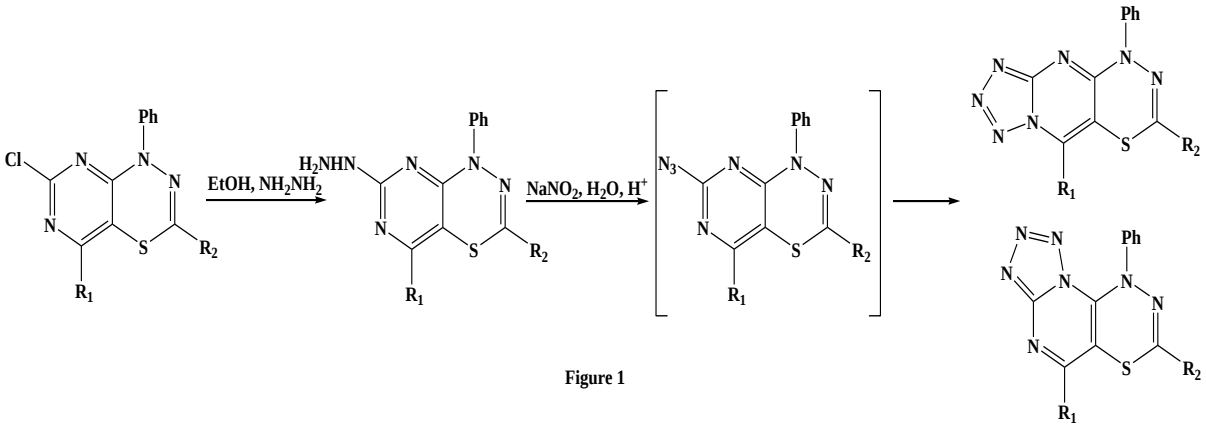
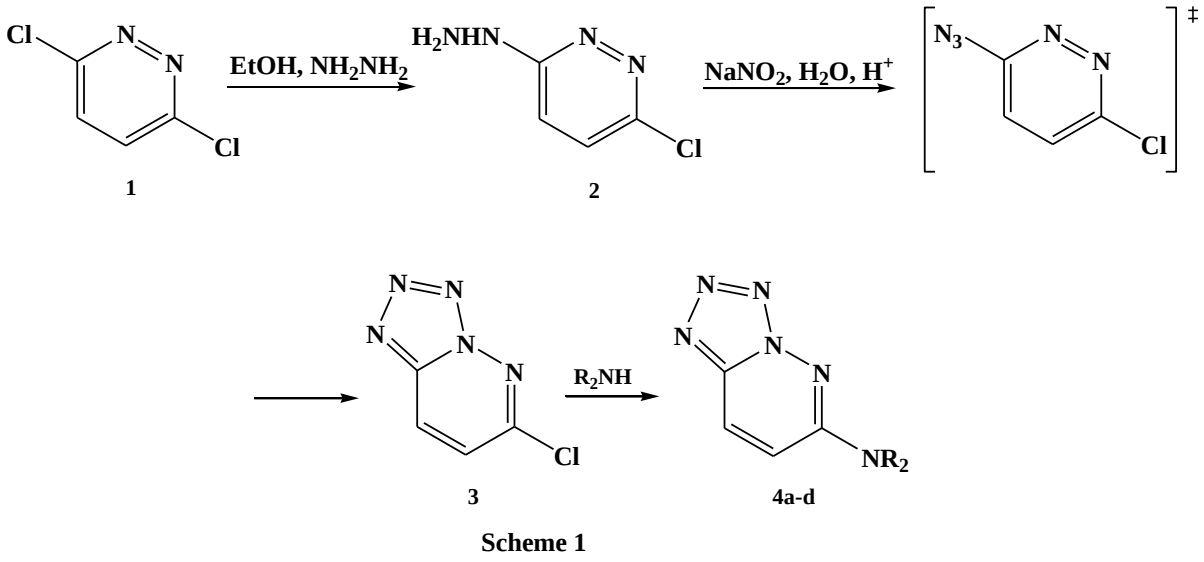


Fig.1. Route for synthesis of tetrazolo pyrimido[4,5-e] [1,3,4]thiadiazine

To extend the scope of this strategy, we explored chloro heterocycles that could successfully undergo similar reaction. For this propose, we started the synthesis from 3,6-dichloro-pyridazine **1**, which have easily converted to 1-(6-chloropyridazin-3-yl) hydrazine **2**. The latter compound was dissolved in HCl solution and rapidly converted to 6-chlorotetrazolo[1,5-*b*] pyridazine **3** by addition of sodium nitrit solution in an ice bath as shown in Scheme 1. 6-Chlorotetrazolo[1,5-*b*]pyridazine **3** is is a very active substance which underwent a fast nucleophilic substitution with amines at room temperature.



Scheme 1

Scheme 1. Route for synthesis of tetrazolo [1,5-b]pyridazine derivatives

The structures of novel compounds were strongly confirmed by their spectral and microanalytical data. The ^{1}HNMR spectrum of compound **2** showed broad signals at δ 3.7 & 6.4 ppm belonging to NH_2 and NH protons respectively. ^{1}HNMR spectrum of 6-chlorotetrazolo[1,5-*b*] pyridazine **3** lacked of the NH_2 and NH protons and showed a new signal at δ 8.34 ppm assignable to C_4H which was deshielded by anisotropic effect of tetrazole ring. We found that 6-chlorotetrazolo[1,5-*b*] pyridazine **3** could easily dissolve in amines and underwent a fast and exothermic displacement at room temperature to achieve products **4a-d**. ^{1}HNMR spectrum of compounds **4a-d** showed expected signals around δ 1,5-3.7 ppm concerning to CH_3 & CH_2 moieties plus δ 7.3 and 8.3 assignable to C_5H and C_4H respectively. More proofs came from IR spectra. IR spectrum of compound **2** show the stretching vibration bands at 3450 and 3300 cm^{-1} (broad, NH_2) which was disappeared on the IR spectrum of compound **3**, confirming the formation of tetrazole ring. Mass spectrum of compounds **2 & 3** showed the isotopic effect of a chlorin atom on the molecular ion region but it was completely lacked on the cases of compounds **4a-d**, confirming its replacement by amines. Microanalytical data of all synthesized compounds have no significant difference with their calculated values.

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