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Synthesis of pyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-one derivatives

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Abstract Some new pyrido[3′,2′:4,5]thieno[2,3-*e*]-[1,2,4]triazolo[4,3-*a*] pyrimidin-5(4*H*)-ones were prepared through heterocyclization of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate with phenyl or ethyl isothiocyanate followed by nucleophilic displacement with hydrazine, and finally cyclocondensation with orthoesters.

Keywords Pyridothienotriazolopyrimidine; Isothiocyanates; Hydrazine hydrate; Triethylorthoesters; Cyclocondensation.

Introduction

Among the various pyridothienotriazolopyrimidine ring systems [1–6], pyrido[3′,2′:4,5]thieno[2,3-*e*]-[1,2,4]triazolo[4,3-*a*]pyrimidines have found little attention so far and there is only one reference dealing with the synthesis and biological activities of this heterocyclic ring system [7]. In connection with our interest in the synthesis of new fused heterocyclic compounds with potential biological activities [8–14] we report herein the synthesis of some new pyrido-[3′,2′:4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-ones **4a**–**4e** that might be of pharmacological interest.

Results and discussion

Our synthesis started from ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **1** [1] which was converted to 2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]-pyrimidin-4(1*H*)-ones **2a** and **2b** when heated at reflux temperature with phenyl or ethyl isothiocyanate in the presence of potassium *tert*-butoxide in a mixture of *tert*-butanol and *N*,*N*-dimethylformamide. The construction of pyrimidine-2-thione through heterocyclization of properly functionalized precursors with isothiocyanates or carbon disulfide has already been reported in the Refs. [15–19]. The thione derivatives **2a** and **2b** were then refluxed with hydrazine hydrate in pyridine to give the hydrazino derivatives **3a** and **3b**. The latter compounds subsequently underwent cyclocondensation with triethyl orthoesters in ethanol on heating under reflux to give the desired tetracyclic products, pyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidin-5(4*H*)-ones **4a**–**4e** (Scheme 1).

The structural assignment of **2**–**4** was based upon spectral and microanalytical data. For example, the ^{1}H NMR spectrum of **4a** did not show the NH_2 and NH signals of the precursor **3a** at $\delta = 4.63$ and 8.77 ppm, but instead showed a sharp ^{1}H signal at $\delta = 9.85$ ppm belonging to the triazole ring indicating the formation of the tetracyclic **4a**. The IR spectrum was devoid of the NH_2 and NH absorption bands at $\bar{\nu} = 3390$, 3320, and 3246 cm^{-1} of the precursor. The MS of **4a** showed a molecular ion peak at $m/z = 319$ (M^+) corresponding to the molecular formula $C_{16}H_9N_5OS$.

In conclusion, we described the synthesis of new pyrido[3′,2′:4,5]thieno[2,3-*e*][1,2,4]triazolo[4,3-*a*]-pyrimidin-5(4*H*)-ones **4a**–**4e** through heterocyclization of hydrazino derivatives **3a** and **3b** with

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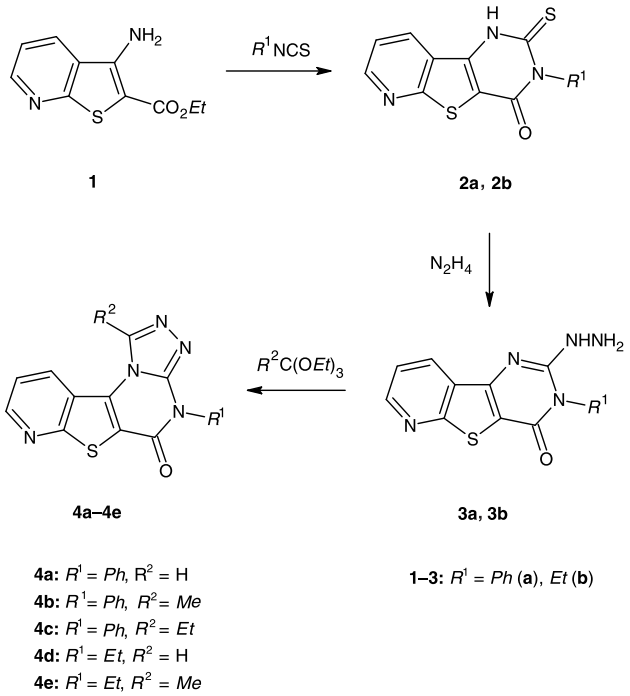

Scheme 1

triethylorthoesters in boiling ethanol in the presence of catalytic amounts of acetic acid.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (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 analyses were performed on a Thermo Finnigan Flash EA microanalyzer and the results were found to agree satisfactorily with the calculated values.

General procedure for the synthesis of 2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-ones ***2a***, ***2b***

A mixture of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate (**1**) (3 mmol), the appropriate isothiocyanate (3.5 mmol) in 25 cm^3 *DMF* and 5 mmol potassium *tert*-butoxide in 7 cm^3 *tert*-butanol was heated under reflux for 4.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the solvent was evaporated *in vacuo*, the residue was dissolved in 10 cm^3 water and subsequently neutralized with 1 *N* HCl. The crude product was collected and recrystallized from ethanol to give **2a** and **2b** as white crystals in 83 and 81% yields.

3-Phenyl-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (**2a**, $C_{15}H_9N_3OS_2$)

Mp 314–315°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 6.90$–7.85 (m, 6H, Phenyl, C8H), 8.60–8.90 (m, 2H, C7H, C9H), 12.80 (br, s, 1H, NH) ppm; IR (KBr): $\bar{\nu} = 3230$ (NH), 1672 (C=O) cm^{-1}; MS: m/z (%) = 311 [M$^+$] (2), 310 (4), 309 (26), 308 (76), 307 (96), 306 (100), 289 (26), 274 (90), 243 (98), 229 (90), 212 (40), 198 (94), 172 (92), 144 (94), 119 (52), 101 (93), 90 (88), 76 (92).

3-Ethyl-2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (**2b**, $C_{11}H_9N_3OS_2$)

Mp 340–342°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.18$ (t, 3H, $J = 6.8$ Hz, CH_3), 3.90 (q, 2H, $J = 6.8$ Hz, CH_2), 7.50–8.90 (m, 3H, C7H, C8H, C9H), 12.63 (br, s, 1H, NH) ppm; IR (KBr): $\bar{\nu} = 3242$ (NH), 1667 (C=O) cm^{-1}; MS: m/z (%) = 263 [M$^+$] (2), 261 (4), 260 (18), 259 (24), 243 (84), 215 (41), 199 (13), 172 (100), 145 (42), 119 (10), 102 (37), 76 (17).

General procedure for the synthesis of 2-hydrazinopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-ones ***3a***, ***3b***

A mixture of 2-thioxo-2,3-dihydropyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(1*H*)-ones **2a** and **2b** (3 mmol) and hydrazine hydrate (1 cm^3) in pyridine (15 cm^3) was heated under reflux for 8.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the mixture was cooled to room temperature and the precipitate was filtered off and recrystallized from ethanol to give compounds **3a** and **3b** as white crystals in 75 and 70% yields, respectively.

2-Hydrazino-3-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**3a**, $C_{15}H_{11}N_5OS$)

Mp 274–276°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 4.63$ (br, 2H, NH_2), 7.28–7.73 (m, 6H, Phenyl, C8H), 8.40–8.72 (m, 2H, C7H, C9H), 8.77 (br, s, 1H, NH) ppm; IR (KBr): $\bar{\nu}$ = 3390, 3320, 3246 (NH_2 and NH), 1660 (C=O Stretching and NH_2 Bending) cm^{-1}; MS: m/z (%) = 309 [M$^+$] (7), 308 (27), 307 (97), 306 (100), 289 (8), 275 (47), 246 (8), 213 (6), 185 (6), 173 (15), 144 (28), 130 (14), 101 (33), 90 (20), 76 (47).

3-Ethyl-2-hydrazinopyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**3b**, $C_{11}H_{11}N_5OS$)

Mp 264–267°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.21$ (t, 3H, $J = 6.8$ Hz, CH_3), 4.12 (q, 2H, $J = 6.8$ Hz, CH_2), 4.55 (br, 2H, NH_2), 7.50–8.85 (m, 3H, C7H, C8H, C9H), 8.95 (br, s, 1H, NH) ppm; IR (KBr): $\bar{\nu} = 3378$, 3324, 3252 (NH_2 and NH), 1662 (C=O Stretching and NH_2 Bending) cm^{-1}; MS: m/z (%) = 261 [M$^+$] (2), 260 (8), 259 (26), 258 (98), 257 (100), 241 (24), 228 (77), 225 (34), 214 (17), 198 (88), 185 (7), 172 (45), 158 (8), 144 (49), 128 (20), 120 (8), 101 (84), 76 (13).

General procedure for the synthesis of pyrido[3′,2′:4,5]-thieno[2,3-e][1,2,4]triazolo[4,3-a]pyrimidin-5(4H)-ones ***4a–4e***

To a solution of the 2-hydrazinopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **3a**, **3b** (3 mmol) in 20 cm^3 ethanol in the presence of 5 drops acetic acid as catalyst, the respective triethyl orthoester (5 mmol) was added. The reaction mixture was heated under reflux for 7.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 93:7), the mixture was cooled to room temperature. The crude product

was collected and recrystallized from 1,4-dioxane to give **4a**–**4e** as white crystals.

4-Phenylpyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]triazolo[4,3-a]-pyrimidin-5(4H)-one (**4a**, $C_{16}H_9N_5OS$)
Yield 83%; mp 308–309°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 7.55$–7.68 (m, 5H, Phenyl), 7.85 (dd, 1H, $^3J_1 = 8.7$ Hz, $^3J_2 = 4.5$ Hz, C9H), 8.87 (dd, 1H, $^3J_1 = 4.5$ Hz, $^4J_2 = 1.3$ Hz, C10H), 9.23 (dd, 1H, $^3J_1 = 8.7$ Hz, $^4J_2 = 1.3$ Hz, C8H), 9.85 (s, 1H, C1H) ppm; IR (KBr): $\bar{\nu} = 1668$ (C=O) cm^{-1}; MS: m/z (%) = 319 [M$^+$] (16), 318 (60), 317 (98), 316 (100), 289 (97), 275 (7), 254 (20), 198 (13), 184 (22), 170 (39), 158 (60), 144 (66), 131 (90), 101 (73), 76 (63).

1-Methyl-4-phenylpyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]tri-azolo[4,3-a]pyrimidin-5(4H)-one (**4b**, $C_{17}H_{11}N_5OS$)
Yield 75%; mp 288–290°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 3.11$ (s, 3H, *Me*), 7.45–7.64 (m, 5H, Phenyl), 7.73 (dd, 1H, $^3J_1 = 8.7$, $^3J_2 = 4.5$ Hz, C9H), 8.88 (dd, 1H, $^3J_1 = 4.5$, $^4J_2 = 1.3$ Hz, C10H), 9.12 (dd, 1H, $^3J_1 = 8.7$, $^4J_2 = 1.3$ Hz, C8H) ppm; IR (KBr): $\bar{\nu} = 1665$ (C=O) cm^{-1}; MS: m/z (%) = 333 [M$^+$] (8), 332 (33), 331 (100), 306 (63), 289 (36), 275 (33), 184 (7), 170 (11), 158 (7), 144 (21), 131 (9), 101 (23), 76 (28).

1-Ethyl-4-phenylpyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]tri-azolo[4,3-a]pyrimidin-5(4H)-one (**4c**, $C_{18}H_{13}N_5OS$)
Yield 69%; mp 264–266°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.20$ (t, 3H, $J = 7.0$ Hz, CH_3), 2.72 (q, 2H, $J = 7.0$ Hz, CH_2), 7.45–9.15 (m, 8H, Phenyl, C8H, C9H, C10H) ppm; IR (KBr): $\bar{\nu} = 1670$ (C=O) cm^{-1}; MS: m/z (%) = 347 [M$^+$] (11), 346 (44), 345 (100), 330 (4), 289 (28), 260 (4), 183 (13), 158 (7), 144 (15), 131 (8), 101 (20), 76 (28).

4-Ethylpyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]triazolo[4,3-a]-pyrimidin-5(4H)-one (**4d**, $C_{12}H_9N_5OS$)
Yield 70%; mp 343–345°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.30$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.28 (q, 2H, $J = 7.2$ Hz, CH_2), 7.76 (dd, 1H, $^3J_1 = 8.7$, $^3J_2 = 4.5$ Hz, C9H), 8.89 (dd, 1H, $^3J_1 = 4.5$, $^4J_2 = 1.3$ Hz, C10H), 9.13 (dd, 1H, $^3J_1 = 8.7$, $^4J_2 = 1.3$ Hz, C8H), 9.78 (s, 1H, C1H) ppm; IR (KBr): $\bar{\nu} = 1666$ (C=O) cm^{-1}; MS: m/z (%) = 271 [M$^+$] (2), 270 (5), 269 (14), 268 (73), 267 (76), 238 (100), 211 (11), 197 (9), 183 (10), 158 (14), 144 (25), 130 (29), 104 (10), 101 (30), 76 (7).

4-Ethyl-1-methylpyrido[3′,2′:4,5]thieno[2,3-e][1,2,4]tri-azolo[4,3-a]pyrimidin-5(4H)-one (**4e**, $C_{13}H_{11}N_5OS$)
Yield 80%; mp 327–330°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.31$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.25 (q, 2H, $J = 7.2$ Hz, CH_2), 7.68 (dd, 1H, $^3J_1 = 8.7$, $^3J_2 = 4.5$ Hz, C9H), 8.81 (dd, 1H, $^3J_1 = 4.5$, $^4J_2 = 1.3$ Hz, C10H), 9.05 (dd, 1H, $^3J_1 = 8.7$, $^4J_2 = 1.3$ Hz, C8H) ppm; IR (KBr): $\bar{\nu} = 1662$ (C=O) cm^{-1}; MS: m/z (%) = 285 [M$^+$] (2), 284 (6), 283 (30), 282 (39), 253 (87), 243 (100), 215 (86), 199 (63), 172 (98), 145 (87), 131 (13), 119 (40), 103 (87), 102 (88), 101 (84), 93 (18), 76 (65).

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