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Synthesis of New 5-Aryl Pyrido [3′, 2′: 4, 5] Thieno [2, 3-*e*] [1, 2, 3, 4] Tetrazolo [1, 5-*c*] Pyrimidine Derivatives

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The synthesis of new 5-arylpyrido [3′, 2′: 4, 5] thieno [2, 3-*e*][1, 2, 3, 4] tetrazolo[1, 5-*c*] pyrimidine derivatives is described.

Key Words: Thienopyridine, thienopyridopyrimidine, sodium azide, phosphoryl chloride.

Few pyrido [3′, 2′: 4, 5] thieno [2, 3-*e*][1, 2, 3, 4] tetrazolo [1, 5-*c*] pyrimidines are known[1–4] but, to the best of our knowledge, none of their 5-aryl derivatives has been reported in the literature. The routes to these compounds are limited and start from suitably substituted pyridothienopyrimidines either through diazotization of their hydrazino derivative with sodium nitrite in acetic acid[1,4] or by the reaction of their chloro compound with sodium azide in ethanol or acetonitrile.[1,3,4] In connection with our interest in the chemistry of fused thienopyridines, we reported a convenient synthesis of pyrido [3′, 2′: 4, 5] thieno [3, 2-*d*] pyrimidine-4(3H)-ones from ethyl-3-amino [2, 3-*b*] pyridine-2 carboxylate through heterocyclization with aryl nitriles.[5] In continuation of this work and due to our interest in the synthesis of fused heterocycles[5–13] we report herein a facile one-step synthesis of new 5-arylpyridothieno tetrazolopyrimidine derivatives **(2a-f)**.

Results and Discussion

A number of 2-arylpyrido [3′, 2′: 4, 5] thieno [3, 2-*d*] pyrimidin-4(3H)-ones **(1a-f)** were prepared as reported previously.[5] These compounds were treated with phosphoryl chloride and sodium azide in boiling acetonitrile for a period of time as indicated in the Table similar to a procedure reported for the synthesis of 1-substituted cytosines by Golankiewicz et al.[14] The reaction was monitored by TLC ($CHCl_3$:MeOH, 95:5) and, after completion of the reaction, the solvent was evaporated in vacuo, the residue was dissolved in water

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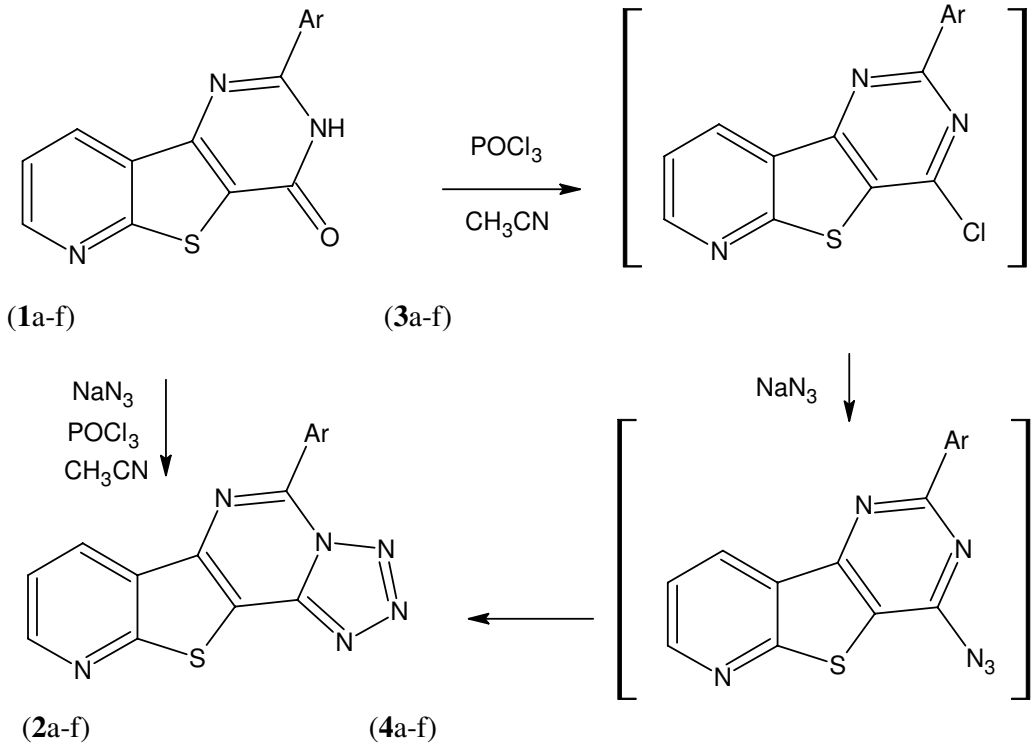
and subsequently neutralized with sodium bicarbonate, and the filtered precipitate was recrystallized from ethanol to afford the title tetracyclic compound in high yield (Table).

The structural elucidation of these compounds was based upon spectral and microanalytical data. For example, the IR spectrum of compound 2b was devoid of the absorption band at 1675 cm^{-1} due to an amide carbonyl group of the precursor. The ^{1}H-NMR of 2b showed only the presence of the characteristic signals for aromatic protons at δ7.2-9.1 and methyl group at δ2.45 and was devoid of the NH signal at δ13 ppm of the precursor. The MS of 2b showed a molecular ion peak at m/z 318 corresponding to the molecular formula $C_{16}H_{10}N_6S$ (Table).



a : Ar = 3-MeC_6H_4
b : Ar = 4-MeC_6H_4
c : Ar = 3-BrC_6H_4
d : Ar = 4-BrC_6H_4
e : Ar = 3-ClC_6H_4
f : Ar = 4-ClC_6H_4

Scheme

Table. Physical, spectral, and microanalytical data of 2-arylpyrido [3′, 2′:4, 5] thieno [2, 3-*e*] [1, 2, 3, 4] tetrazolo[1, 5-*c*] pyrimidines (2a-f) and key intermediates (3b and 4b).

Entry	Yield (%)	Time (hour)	mp (°C)	Spectral data
2a	74	9	388-390	^{1}H-NMR: δ(DMSO-d_6), 2.36 (s, 3H, CH_3), 7.3-9.0 (m,7H, Aromatic rings);^{13}C-NMR([$^2H_6$] DMSO, TMS) δ: 21.3, 121.2, 124.8, 127.3, 128.9, 129.4, 129.9, 131.5, 132.2, 139.7, 141.1, 144.7, 146.3, 151.2, 156.6, 159.3. MS m/z, M^+318; Anal. Calcd for $C_{16}H_{10}N_6S$: C, 60.36; H, 3.17; N, 26.40; S, 10.07. Found: C, 60.57; H, 3.33; N, 26.21; S, 10.16.
2b	79	7	391-393	^{1}H-NMR: δ($CDCl_3$), 2.45 (s, 3H, CH_3), 7.2-9.1 (m,7H, Aromatic rings); ^{13}C-NMR([$^2H_6$] $CDCl_3$, TMS) δ: 22.6, 121.8, 125.1, 128.2, 130.5, 131.2, 132.0, 139.4, 140.8, 143.2, 148.8, 154.7, 159.5, 161.1. MS m/z, M^+318; Anal. Calcd for $C_{16}H_{10}N_6S$: C, 60.36; H, 3.17; N, 26.40; S, 10.07. Found: C, 60.55; H, 3.28; N, 26.27; S, 10.01.
2c	78	10	364-366	^{1}H-NMR: δ(DMSO-d_6), 7.5-9.1 (m,7H, Aromatic rings);^{13}C-NMR([$^2H_6$] DMSO, TMS) δ: 122.1, 125.7, 126.6, 127.9, 128.3, 132.4, 132.8, 133.1, 135.2, 140.1, 145.4, 147.5, 153.3, 157.8, 159.3. MS m/z, M^+383 (M+2, 385); Anal. Calcd for $C_{15}H_7BrN_6S$: C, 47.01; H, 1.84; N, 21.93; S, 8.37. Found: C, 46.93; H, 1.96; N, 21.77; S, 8.28.
2d	81	8	368-370	^{1}H-NMR: δ(DMSO-d_6), 7.1-9.1 (m,7H, Aromatic rings); MS m/z, M^+383 (M+2, 385); Anal. Calcd for $C_{15}H_7BrN_6S$: C, 47.01; H, 1.84; N, 21.93; S, 8.37. Found: C, 47.12; H, 1.92; N, 21.81; S, 8.44.
2e	77	10	376-378	^{1}H-NMR: δ(DMSO-d_6), 7.6-9.1 (m,7H, Aromatic rings); MS m/z, M^+338 (M+2, 340); Anal. Calcd for $C_{15}H_7ClN_6S$: C, 53.18; H, 2.08; N, 24.81; S, 9.47. Found: C, 53.03; H, 2.15; N, 24.96; S, 9.39.
2f	74	8	380-382	^{1}H-NMR: δ(DMSO-d_6), 7.2-9.0 (m,7H, Aromatic rings); MS m/z, M^+338 (M+2, 340); Anal. Calcd for $C_{15}H_7ClN_6S$: C, 53.18; H, 2.08; N, 24.81; S, 9.47. Found: C, 53.09; H, 2.19; N, 24.69; S, 9.36.
3b	86	5	210-212	^{1}H-NMR: δ(DMSO-d_6), 2.42 (s, 3H, CH_3), 7.3-9.1 (m, 7H, Aromatic rings); MS m/z, M^+311 (M+2, 313); Anal. Calcd for $C_{16}H_{10}ClN_3S$: C, 61.63; H, 3.23; N, 13.48; S, 10.28. Found: C, 61.49; H, 3.31; N, 13.32; S, 10.22.
4b	73	8	184-186	^{1}H-NMR: δ($CDCl_3$), 2.43 (s, 3H, CH_3), 7.2-9.0 (m,7H, Aromatic rings); IR (KBr, disc), ν, N_3, 2220 cm^{-1}; MS m/z, M^+318; Anal. Calcd for $C_{16}H_{10}N_6S$: C, 60.36; H, 3.17; N, 26.40; S, 10.07. Found: C, 60.19; H, 3.31; N, 26.24; S, 10.11.

Based on the results shown in the Scheme, it appears that the formation of 2a-f occurs, firstly through the chlorination of the pyrimidine ring of the precursor, followed by nucleophilic substitution of the chlorine atom with sodium azide and finally heteroannulation of the pyrimidine ring to afford the tetracyclic compounds 2a-f. To study this multi-step synthesis, we heated 1b with phosphoryl chloride at reflux temperature and, after work-up, the reaction mixture 4-chloro derivative 3b was obtained and its structure was identified by spectral analysis. The treatment of the chloro derivative with sodium azide in water and acetonitrile at -5 °C gave the azide derivative 4b as the key intermediate. The characteristic strong absorption band at 2220 cm^{-1} in its IR spectrum clearly shows the azide moiety of this intermediate. When this compound was heated at reflux in acetonitrile for 3 h and, after work-up, the reaction mixture tetracyclic compound 2b was obtained in 84% yield. The spectral data of this compound completely resemble those of 2b that were obtained in one-step synthesis.

In summary, we have described a facile one-step synthesis of new 5-arylpyridothienotetrazolopyrimidine derivatives in high yield. This work can be extended to other heterocyclic systems.

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 ^{13}C-NMR (125 MHz) spectra were recorded on a Bruker AVANCE DRX-500 spectrometer. The MS were scanned on a Varian CH-7 instrument at 70 ev. Elemental analysis was performed on a Thermofinnigan Flash EA microanalyzer.

General procedure for the preparation of 2-arylpyrido [3′, 2′:4, 5] thieno [2, 3-*e*][1, 2, 3, 4] tetrazolo[1, 5-*c*] pyrimidines (2a-f).

A mixture of 2-arylpyrido [3′, 2′: 4, 5] thieno [3, 2-*d*] pyrimidin-4(3H)-ones **(1a-f)** (5 mmol), sodium azide (0.65 g), and phosphoryl chloride (5 mL) in acetonitrile (20 mL) was heated under reflux for 7.0 to 10.0 h. After the completion of the reaction, which was monitored by TLC ($CHCl_3$:MeOH, 95:5), the solvent was evaporated in vacuo, the residue was dissolved in water (15 mL) and subsequently neutralized by sodium bicarbonate. The precipitate was collected and recrystallized from ethanol to give compounds **2a-f** in high yield (Table).

Preparation of the 4-chloro-2-(4-methylphenyl)pyrido [3′, 2′:4, 5] thieno [3, 2-*d*] pyrimidine (3b).

A mixture of 2-(4-methylphenyl)pyrido [3′, 2′: 4, 5] thieno [3, 2-*d*] pyrimidin-4(3H)-one **(1b)** (5 mmol) and phosphoryl chloride (10 mL) was heated under reflux for 5.0 h. After the completion of the reaction, the mixture was poured onto crushed ice. Then, the precipitate was collected and washed with chloroform to give **3b** in 86% yield (Table).

Preparation of the 2-(4-methylphenyl)pyrido [3′, 2′:4, 5] thieno [3, 2-*d*] pyrimidin-4-yl azide (4b).

To a mixture of 4-chloro-2-(4-methylphenyl)pyrido [3′, 2′: 4, 5] thieno [3, 2-*d*] pyrimidine (3b) (2 mmol) and acetonitrile (15 mL) was added a solution of sodium azide (0.26 g) in water (7 mL). The mixture was stirred

at -5 °C for 8 h. After the completion of the reaction, the solvent was evaporated in vacuo, the residue was dissolved in water (15 mL), and the precipitate was collected and washed with chloroform to give 4b in 73% yield (Table).

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