Synthesis of New Tetracyclic Fused Imidazole Derivatives

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Abstract

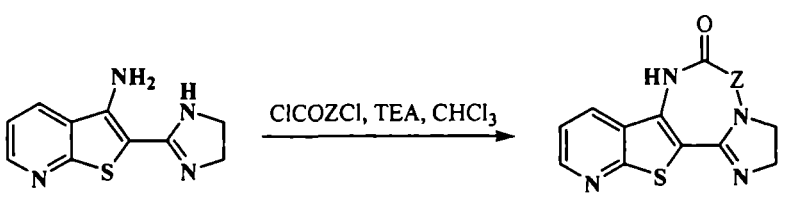
Reaction of 2- (4,5- dihydro- 1H- imidazol- 2- yl)thieno[2, 3- *b*]pyridine- 3- amine with monofunctional and bifunctional electrophilic reagents gave new imidazo[1, 2- *c*]pyrido[3`, 2` ,4, 5]thieno[2, 3- *e*]pyrimidine derivatives and derivatives of the novel heterocyclic ring system, imidazo[1, 2- *d*]pyrido[3`, 2` ,4, 5]thieno[2, 3- *f*][1, 4]diazepine respectively.

Introduction

Imidazole is a privileged structure that occurs in a number of pharmacologically significant molecules. Analogues have shown utility as GABA brain receptor ligands (1), antiallergy(2), gastric H^+, K^+ ATPase inhibitor (3), TNF- *a* production inhibitor (4), antimicrobial and fungicidal (5), carcinoma cells growth inhibitor(6), PAF receptor antagonists (7), immunosuppressive agents (8) and benzodiazepine receptor ligands (9). In view of these facts and due to our interest in the synthesis of fused heterocyclic compounds of biological significance, it seemes worthwhile to synthesize new tetracyclic fused imidazo derivatives with eventful perspectives for examination of their possible biological performance.

Results and Discussion

Our synthesis started from 2- (4,5- dihydro- 1H- imidazo- 2- yl)thieno[2, 3- *b*]pyridine- 3- amine **1**, which was prepared according to a published method (10). Reaction of this compound with chloroacetylchloride and oxalyl chloride gave 2,7- Dihydro- 3H- imidazo[1,2-*d*]pyrido[3`,2`:4,5]thieno[2,3-*f*][1,4]diazepin-6(5H)-one **2a** and 2,7- Dihydro- 3H- imidazo[1,2-*d*]pyrido[3`,2`:4,5]thieno[2,3-*f*][1,4]diazepin-5,6-dione **2b** respectively as shown in **Scheme 1**.



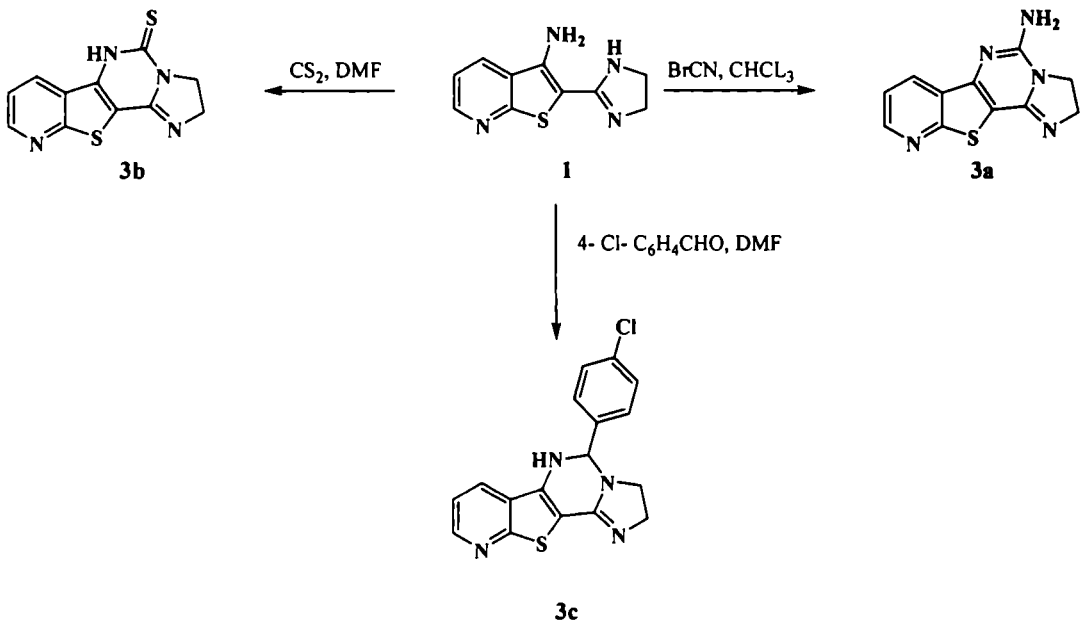
1

2a, Z= CH_2
2b, Z= CO

Scheme 1.

The IR spectra exhibit the stretching vibration bands at 1600&3200 cm^{-1} due to C=O and NH absorption. More proofs came from ^{1}HNMR spectra, which show a signal at

δ, 8.05 and 10 ppm for compounds **2a,b** due their NH moiety and methylene group of compound **2a** observed as a singlet on δ, 3.5 ppm. Condensation of precursor with cyanogenbromide, carbondisulfide and 4- chlorobenzaldehyde gave the imidazo[1, 2-*c*]pyrido[3`, 2` ,4, 5]thieno[2, 3- *e*]pyrimidine derivatives **3a-c** repectively as shown in **Scheme 2**.



Scheme 2.

The IR spectra exhibit the stretching vibration bands at 3300&3400 cm^{-1} due to NH_2 absorption for compound **3a** and a band around 3200 cm^{-1} for NH moiety of compounds **3b,c**. ^{1}HNMR spectra of compounds **3a-c** showed the shift of two methylene groups of imizoline ring to downfield in comparison with their precursor and confirmed the formation of pyrimidine nucleus. Mass spectra of all the above compounds truly showed their molecular ions. For example the molecular ions of 3c (M: M+2) was observed at 340 (35%), 342 (11%) corresponding to the molecular formula $C_{17}H_{13}ClN_4S$.

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.

2,7- Dihydro- 3H- imidazo[1,2-*d*]pyrido[3`,2`:4,5]thieno[2,3-*f*][1,4]diazepin-6(5H)-one (2a)

Chloroacetylchloride (0.25ml) was dropwisely added to 2- (4,5- dihydro- 1H-imidazol- 2- yl)thieno[2, 3- *b*]pyridine- 3- amine (1) (0.646 gr, 3mmol) in chloroform (15ml) and stirred for 12 hours. The precipitate was filtered off and crystallized from chloroform as orange powder (85% yield, mp 218 ^{0}C).

IR: 3200 cm^{-1} (NH), 1550 cm^{-1} (C=O), ^{1}HNMR: (d^6-DMSO) δ, 2.8-3.3 (m, 4H, $2CH_2$), 3.5 (s, 2H, CH_2), 7.45 (dd, 1H, CH), 8.05 (br, 1H, NH), 8.5 (dd, 1H, CH), 8.63

(dd, 1H, CH); ms: m/z, 258. *Anal.* Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found : C, 60.07; H, 3.65; N, 21.52; S, 12.20.

2,7- Dihydro- 3H- imidazo[1,2-*d*]pyrido[3`,2`:4,5]thieno[2,3-*f*][1,4]diazepin-5,6-dione (2b)

Oxalylchloride (0.25ml) was dropwisely added to 2- (4,5- dihydro- 1H- imidazol- 2-yl)thieno[2, 3- *b*]pyridine- 3- amine (1) (0.646 gr, 3mmol) in chloroform (15ml) and stirred for 12 hours. The precipitate was filtered off and crystallized from ethanole as orange powder (55% yield, mp 253 ^{0}C).

IR: 3280 cm^{-1} (NH), 1600 cm^{-1} (C=O), ^{1}HNMR: (d^6-DMSO) δ, 2.8-3.3 (m, 4H, $2CH_2$), 7.3 (dd, 1H, CH), 7.95 (dd, 1H, CH), 8.65 (dd, 1H, CH), 10 (br, 1H, NH); ms: m/z, 272. *Anal.* Calcd. for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.58; S, 11.78. Found : C, 53.12; H, 3.05; N, 20.39; S, 11.50.

2,3- Dihydroimidazo[1,2-*c*]pyrido[3`,2`:4,5]thieno[2,3-*e*]pyrimidin-5-amine (3a)

Cyanogenbromide (0.30gr) was added to 2- (4,5- dihydro- 1H- imidazol- 2-yl)thieno[2, 3- *b*]pyridine- 3- amine (1) (0.646 gr, 3mmol) in chloroform (15ml) and stirred for 24 hours. The precipitate was filtered off and crystallized from chloroform as brown powder (81% yield, mp 283 ^{0}C).

IR: 3300 and 3400 cm^{-1} (NH_2), ^{1}HNMR: (d^6-DMSO) δ, 3.3-3.6 (m, 4H, $2CH_2$), 6.5 (br, 2H, NH_2), 7.3 (dd, 1H, CH), 8.15 (dd, 1H, CH), 8.45 (dd, 1H, CH); ms: m/z, 243. *Anal.* Calcd. for $C_{11}H_9N_5S$: C, 54.31; H, 3.73; N, 28.79; S, 13.18. Found : C, 54.50; H, 3.65; N, 28.52; S, 12.96.

2,6-Dihydroimidazo[1,2-*c*]pyrido[3`,2`:4,5]thieno[2,3-*e*]pyrimidin-5(3H)-thione (3b)

Carbondisulfide (2ml) was added to 2- (4,5- dihydro- 1H- imidazol- 2- yl)thieno[2, 3-*b*]pyridine- 3- amine (1) (0.646 gr, 3mmol) in dimethylformamide (10ml) and refluxed for 12 hours. The reaction mixture was added to water (10ml) and then precipitate was filtered off and crystallized from ethanole as orange powder (61% yield, mp 220 ^{0}C).

IR: 3200 cm^{-1} (NH), ^{1}HNMR: (d^6-DMSO) δ, 4 (m, 4H, $2CH_2$), 7.65 (dd, 1H, CH), 8.8 (dd, 1H, CH), 9 (dd, 1H, CH)), 14 (br, 1H, NH); ms: m/z, 260. *Anal.* Calcd. for $C_{11}H_8N_4S_2$: C, 50.75; H, 3.10; N, 21.52; S, 24.63. Found : C, 50.52; H, 3.22; N, 21.72; S, 24.41.

5-(4-Chlorophenyl-2,3,5,6- tetrahydroimidazo[1,2-*c*]pyrido[3`,2`:4,5]thieno[2,3-*e*]pyrimidine (3c)

4- Chlorobenzaldehyde (0.42gr) was added to 2- (4,5- dihydro- 1H- imidazol- 2-yl)thieno[2, 3- *b*]pyridine- 3- amine (1) (0.646 gr, 3mmol) in dimethylformamide (10ml) and refluxed for 12 hours. The reaction mixture was added to water (10ml) and then precipitate was filtered off and crystallized from ethanole as yellow powder (78% yield, mp 335 ^{0}C).

IR: 3250 cm^{-1} (NH), ^{1}HNMR: (d^6-DMSO) δ, 3.2 (br, 1H, NH), 3.6 (m, 4H, $2CH_2$), 7.5-8.7 (m, 8H, aromatic and benzylic); ms: m/z, 340, 342. *Anal.* Calcd. for $C_{17}H_{13}ClN_4S$: C, 59.91; H, 3.84; N, 16.44; S, 9.41. Found : C, 59.72; H, 3.97; N, 16.25; S, 9.17.

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