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A convenient synthesis of Carbocyclic fused Thieno [2,3-b] Pyridines and Carbocyclic fused 1H-Pyrazolo [3,4-b] Pyridines

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طريقة ملائمة لتخليق ثايينو (٢,٣ ب) بيريدينات ملتحمة الكربوكسيليك ومركبات 1H - بيرازولو (٢,٣ ب) بيريدينات ملتحمة الكربوكسيليك

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تم تحضير المركبات المذكورة اعلاه باستخدام 2(1H) بيريدين ثايون ملتحم الكربوكسيليك كمادة أولية، كذلك تم تعيين وتأكيد التركيب البنائي للنواتج عن طريق تحليل العناصر وبياناتها الطيفية.

Key Words: Synthesis of carbocyclic - Thieno (2,3,6) pyridines..

ABSTRACT

A synthesis of carbocyclic fused thieno [2,3-b] pyridines and carbocyclic fused 1H- pyrazolo [3,4-b] pyridines utilizing carbocyclic fused 2(1h)-pyridinethiones as starting components is described. The structures of the products were assigned and confirmed on the basis of their elemental analysis and spectral data.

We have described several noval synthesis of 2 (1H)-pyridinethiones [1-5]. These compounds are considered important an intermediates for the synthesis of the biologically active deazafolic acid and deazaaminopterine ring systems[6]. One of these papers has described the novel reaction of cyanothioacetamid **1** with sodium salts of 2-(hydroxymethylene)-1-cycloalkanones **2** producing the carbocyclic fused 2(1H)-pyridinethiones **3**[6]. In conjunction with this work we report in this paper a novel synthesis of fused 1H-pyrazolo [3,4-b] pyridines and fused thieno [2,3-b] pyridines utilizing the fused 2(1H)-pyridinethiones **3** as starting material. Moreover, the results of our work aimed to define the scope and limitation of our rocedures for the synthesis of fused pyridine derivatives. Thus, it has been found that compounds **3** reacted with etyl iodide in sodium ethoxide or CH_2Cl_2-NaOH to afford the corresponding S-alkyl derivative **4**. When **3** were subjected to the reaction of phenacyl bromide as alkylating agent, the S-alkylated derivative could not be isolated, but cyclize to the cycloalkane ring fused hthieno [2,3-b]-pyridine derivatives **5**. The structure of copounds 5 was established and confirmed on the basis of elemental analysis and spectral data (IR,MS,^{1}H NMR). THus, the IR spectrum of **5a** revealed the absence of a CN band, the mass spectrum was compatible with the molecular formla $C_{17}H_{14}N_2SO$ (M^+ = 294), and ^{1}H NMR contained a broad band at δ 7.20 ppm assignable to an amino function. A 2-chloro derivative **6** corresponding to the compound **3** could be prepared by treating the 2(1H)-pyridinethiones **3** with chlorine gas in chloroform at room temperature. Structures **6** was established based on elemental analysis and spectral data (IR, MS, ^{1}H NMR). The IR spectra of compound **6a** showed absence of a NH band. Compound **6** reacted with hydrazine hydrate in refluxing ethanol containing catalytic amounts of piperidine for 3 h to give the corresponding cycloalkane ring fused 1H-pyrazolo [3,4-b]-pyridine derivatives **7**. Compounds **7** could also be prepared by the reaction of 4 with hydrazine hydrate under the same conditions. The structure of compounds **7** was established on the basis of their elemental analysis and spectral data (IR, MS, ^{1}H NMR). Thus, the IR spectra of **7a** showed absence of a CN band and its ^{1}H NMR spectra showed a band at d 5.28 ppm assigned to an amino function and broad band at d 11.82 ppm assignable to NH group. The results indicate that the fused 2(^{1}H)-pyridinethiones **3** can be utilized as an excellent starting material for the preparation of other interesting fused heterocycles which are not readily accessible.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000 or on a Shimadzu IR 200 instrument 1HNMR spectra were measured on a Wilmad 270 MHz spectrometer for solutions in $(CD_3)_2SO$ using $SiMe_4$ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

Compounds 3a-d were prepared according to our literature procedure[6].

Cycloalkane ring fused 3-cyano 2-(ethylthio) pyridines (4a-d):

A mixture of 3 (0.01 mol), NaOH (0.02 mol), and EtI (0.015 mol) in dry dichloromethane (50 ml) was stirred at room temperature for 24 h and then diulted with cold water (100 ml). The dichloromethane layer was washed several times with water, dried and then evaporated. The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

4a: Yield (55%); m.p. 113°C; IR (KBr) ν 2220 (CN); ^{1}H NMR (DMSO) δ 1.10 (t, 3H CH_3), 1.92 (m, 2H, CH_2), 2.55-2.90 (m, 4H, $2CH_2$); 4.10 (q, 2H, CH_2), 7.56 (s, H, pyridine H); (Calcd for $C_{11}H_{13}N_2S$; C,64.4; H. 6.5; N, 13.6. Found: C,64.5; H, 6.5; N, 13.8%).

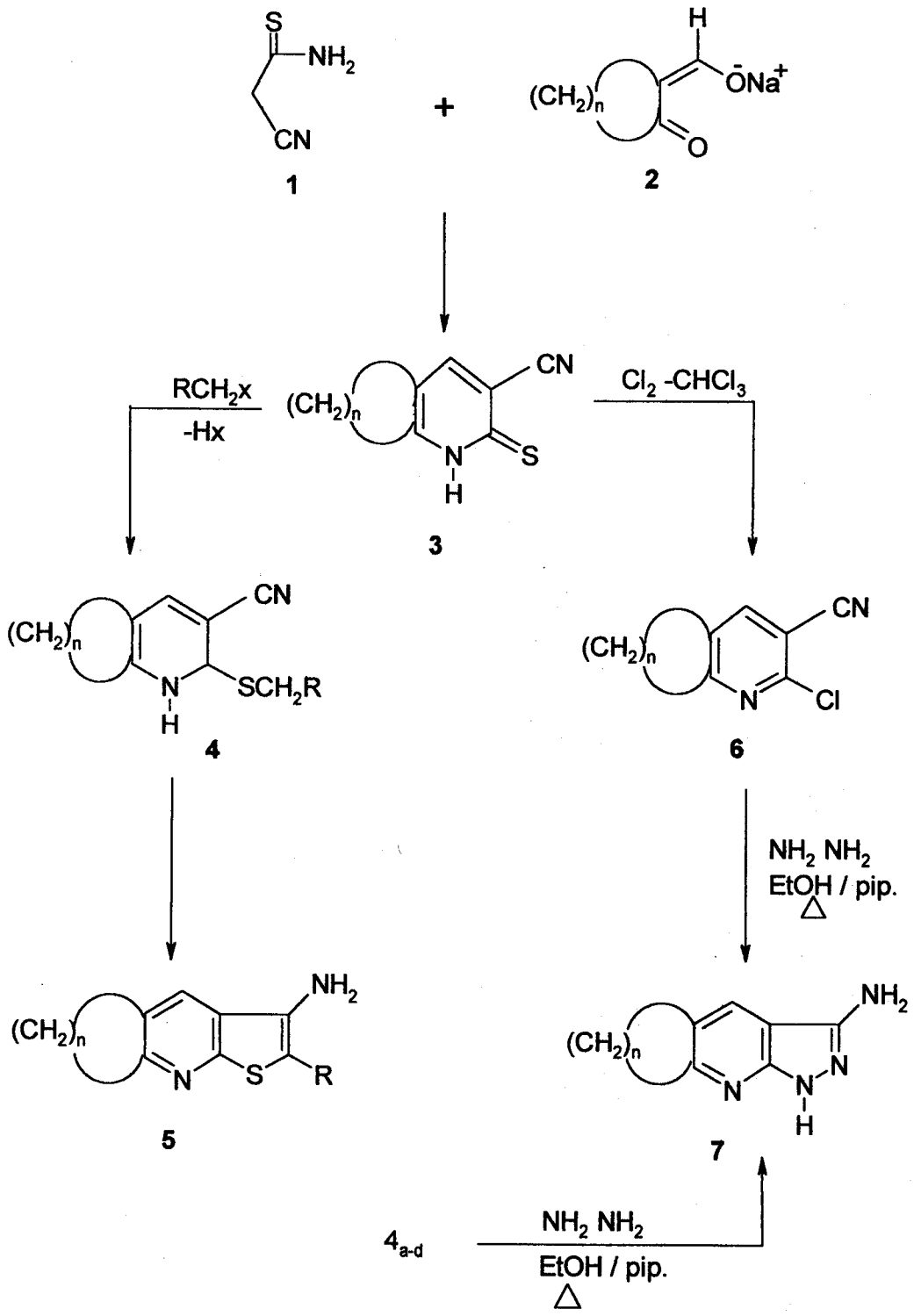
4b: Yield (40%); m.p. 89°C; IR (KBr) ν 2222 (CN); ^{1}H NMR (DMSO) δ 1.02 (t, 3H CH_3), 1.52 - 1.75 (m, 6H, $3CH_2$), 2.50-2.77 (m, 2H, $2CH_2$); 400 (q, 2H, CH_2), 7.58 (s, 1H, pyridine H-4); MS, m/e 218; (Calcd for $C_{12}H_{15}N_2S$; C,65.7; H. 6.8; N, 13.7. Found: C,66.0; H, 6.5; N, 13.3%).

4c: Yield (33%); m.p. 92°C; IR (KBr) ν 2218 (CN); ^{1}H NMR (DMSO) δ 1.11 (t, 3H CH_3), 1.38 - 1.77 (m, 6H, $3CH_2$), 2.40-2.75 (m, 2H, $2CH_2$); 2.80 - 2.95 (q, 2H, CH_2), 3.99 (q, 2H, CH_2), 7.88 (s, 1H, pyridine H-4); (Calcd for $C_{13}H_{17}N_2S$; C,67.0; H. 7.3; N, 12.0. Found: C,67.0; H, 7.0; N, 12.0%).

4d: Yield (30%); m.p. 105°C; IR (KBr) ν 2228 (CN); ^{1}H NMR (DMSO) δ 1.08 (t, 3H CH_3), 1.28 (m, 4H, $2CH_2$), 1.51 (s, 2H, $2CH_2$); 2.85 (m, 2H, CH_2), 3.95 (q, 2H, CH_2), 7.85 (s, 1H, pyridine H-4); (Calcd for $C_{14}H_{19}N_2S$; C,68.0; H. 7.7; N, 11.5. Found: C, 68.0; H, 7.5; N, 11.4%).

Cycloalkane ring-fused 3-amino-2-benzoylthieno [2,3-b]-pyridines (5a-d):

A mixture of 3 (0.01 mol), C_2H_5ONa (0.02 mol), and phenacyl bromide (0.01 mol) ind ray EtOH (50 ml) was



4	n	R	5	n	R	3,6,7	n
a,	3	CH_3	a,	3	COPh	a,	3
b,	4	CH_3	b,	4	COPh	b,	4
c,	5	CH_3	c,	5	COPh	c,	5
d,	6	CH_3	d,	6	COPh	d,	6

stirred at 50-60°C for 3h and then diluted with cold water (50ml). The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

5a: Yield (70%); m.p. 214-216°C; IR (KBr) ν 3577, 3285 (NH_2); ^{1}H NMR (DMSO) δ 1.90 (m, 2H CH_3), 2.57-2.88 (m, 4H, $2CH_2$), 7.20 (s, br, 2H, NH_2); 7.32-7.82 (m, 5H, C_6H_5), 7.95 (s, H, pyridine H-4); MS, m/e 294; (Calcd for $C_{17}H_{14}N_2S$; C, 69.4; H, 4.8; N, 9.5. Found: C, 69.0; H, 5.1; N, 9.3%).

5b: Yield (80%); m.p. 202-03°C; IR (KBr) ν 3520, 3440 (NH_2); ^{1}H NMR (DMSO) δ 1.50-1.80 (m, 2H CH_2), 2.50-2.77 (m,2H, $2CH_2$), 7.21 (s, br, 2H, NH_2); 7.32-7.89 (s, 5H, C_6H_5), 7-8.4 (s, 1H, pyridine H-4); MS, m/e 308; (Calcd for $C_{18}H_{16}N_2S$; C, 70.1; H, 5.2; N, 9.1. Found: C, 70.0; H, 5.2; N, 8.8%).

5c: Yield (70%); m.p. 103-104°C; IR (KBr) ν 3480, 3400 (NH_2); ^{1}H NMR (DMSO) δ 1.40-1.78 (m, 6H $3CH_2$), 2.42-2.78 (m, 2H, $2CH_2$), 2.79-3.01 (m, 2H, CH_2); 7.15 (s, br, 2H, NH_2), 7.28-7.68 (m,5H, C_6H_5), 7.91 (s, 1H, pyridine H-4); Calcd for $C_{19}H_{18}N_2SO$: C, 70.8, H, 5.6; N, 8.7. F Found: C, 70.0; H, 5.2; N, 8.8%).

5d: Yield (60%); m.p. 120-21°C; IR (KBr) ν 3450, 3400 (NH_2); ^{1}H NMR (DMSO) δ 1.30 (m, 4H $2CH_2$), 1.60 (s, 2H, CH_2), 2.40 (m, 2H, CH_2); 2.60 (s, 2H, CH_2), 2.91 (m, 2H, CH_5), 7.20 (s, br, 2H, NH_2), 7.28 - 7.80 (m, 5H, C_6H_5), 7.88 (s, 1H, pyridine H-4); Calcd for $C_{20}H_{20}N_2SO$: C, 71.4, H, 6.0; N, 8.3. Found: C, 71.0; H, 5.7; N, 8.0%).

Cycloalkane ring fused 2-chloro-3-cyanopyridines (6a-d):

A solution of 3 (0.01 mol) in choloroform (50ml) was stirred under a stream of dry chlorine gas for 2h, and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

6a: Yield (55%); m.p. 167°C; IR (KBr) ν 2220 (CN); ^{1}H NMR (DMSO) δ 1.88 (m, 2H, CH_2), 2.55-2.80 (m, 4H, $2CH_2$), 7.55 (s, 1H, pyridine H-4); MS m/e 178; (calcd for $C_9H_7ClN_2$; c, 60.5; H, 3.9, N, 15.7. Found: C, 60.1; H, 4.2; N, 15.5%).

6b: Yield (50%); m.p. 144°C; IR (KBr) ν 2218 (CN); ^{1}H NMR (DMSO) δ 1.65 (m, 2H, CH_2), 1.80-1.89 (m, 4H, $2CH_2$), 2.55-2.70 (m, 2H, CH_2), 7.8 (s, 1H, pyridine H-4); MS m/e 192; (calcd for $C_{10}H_9ClN_2$; c, 62.3; H, 4.7, N, 14.6. Found: C, 62.0; H, 5.0; N, 14.5%).

6c: Yield (60%); m.p. 112°C; IR (KBr) ν 2230 (CN); ^{1}H NMR (DMSO) δ 1.38-1.75 (m, 6H, $3CH_2$), 2.40-2.71 (m, 2H, CH_2), 2.72-3.0 (m, 2H, CH_2), 7.77 (s, 1H, pyridine H-4); (calcd for $C_{11}H_{11}ClN_2$; c, 63.9; H, 5.3, N, 13.6. Found: C, 64.0; H, 5.5; N, 13.5%).

6d: Yield (45%); m.p. 175°C; IR (KBr) ν 2220 (CN); ^{1}H NMR (DMSO) δ 1.28 (m, 4H, $2CH_2$), 1.62 (m, 2H, CH_2), 238 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 7.80 (s, 1H, pyridine H-4); (calcd for $C_{12}H_{13}ClN_2$; c, 65.3; H, 5.9, N, 12.7. Found: C, 65.5; H, 5.6; N, 12.5%).

Cycloalkane ring fused 3-amino-1H-pyrazolo [3,4-b]-pyridines (7a-d):

To a mixture of 4 or 6 (0.01 mol) and hyrazine hydrate (0.01 mol) in ethanol (50 ml), triethylamine (0.5 ml) was added. The mixture was heated under reflux for 3 h, and then allowed to stand overnight. The resultant precipitate was isolated by suction and crystallized from the appropriate solvent.

7a: Yield (40%), m.p. 250-252°C; IR (KBr) ν 3570, 3380 (NH, NH_2); ^{1}H NMR (DMOS) δ 1.85 (m, 2H, CH_2); 2.50-2.82 (m, 4h, $2CH_2$), 5.28 (s, br, 2H, NH_2), 7.80 (s, 1H, pyridine H-4); 11.82 (s, br, 1H, NH); MS, m/e 174; (calcd for $C_9H_{10}N_4$; C, 62.1; H, 5.7, N, 32.2. Found: C, 62.0; H 5.5; N, 32.0%).

7b: Yield (56%), m.p. 201-203°C; IR (KBr) ν 3435, 3279 (NH, NH_2); ^{1}H NMR (DMOS) δ 1.43-1.80 (m, 6H, CH_2); 2.50-2.72 (m, 2H, CH_2), 5.21 (s, br, 2H, NH_2), 7.56 (s, 1H, pyridine H-4); 11.88 (s, br, 1H, NH); MS, m/e 188; (calcd for $C_{10}H_{12}N_4$; C, 63.8; H, 6.4, N, 29.8. Found: C, 63.6; H 6.1; N, 29.5%).

7c: Yield (60%), m.p. 156°C; IR (KBr) ν 3480, 3450, 3300 (NH, NH_2); ^{1}H NMR (DMOS) δ 1.48-1.73 (m, 6H, $3CH_2$); 2.45-2.70 (m, 2H, CH_2), 2.70-2.92 (m, 2H, CH_2), 5.13 (s, br, 2H, NH_2), 7.81 (s, 1H, pyridine H-4); 12.23 (s, br, 1H, NH); (calcd for $C_{11}H_{14}N_4$; C, 65.3; H, 6.9, N, 27.7. Found: C, 65.0; H 6.5; N, 27.5%).

7d: Yield (50%), m.p. 198-200°C; IR (KBr) ν 3520, 3450, 3380 (NH, NH_2); ^{1}H NMR (DMOS) δ 1.32 (m, 4H, $2CH_2$); 1.58 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 2.88 (m, 2H, cH_2), 5.12 (s, br, 2H, NH_2); 7.80 (s, 1H, pyridine H-4); 11.98 (2, br, 1H, NH); (calcd for $C_{12}H_{16}N_4$; C, 66.7; H, 7.4, N, 25.9. Found: C, 66.6; H 7.1; N, 25.5%).

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