SYNTHESIS OF NEW PYRIDO [3',2':4,5]THIENO[2, 3-*e*]PYRROLO[1,2-*a*]PYRAZINES

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Abstract :

The aim of the present paper is to describe the synthesis of several unknown polyfused heterocycles containing the pyrazine ring. Novel pyrido[3',2':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazines derivatives have been synthesized starting from methyl 3-amino thieno[2,3-b] pyridines carboxylates via a Curtius rearrangement.

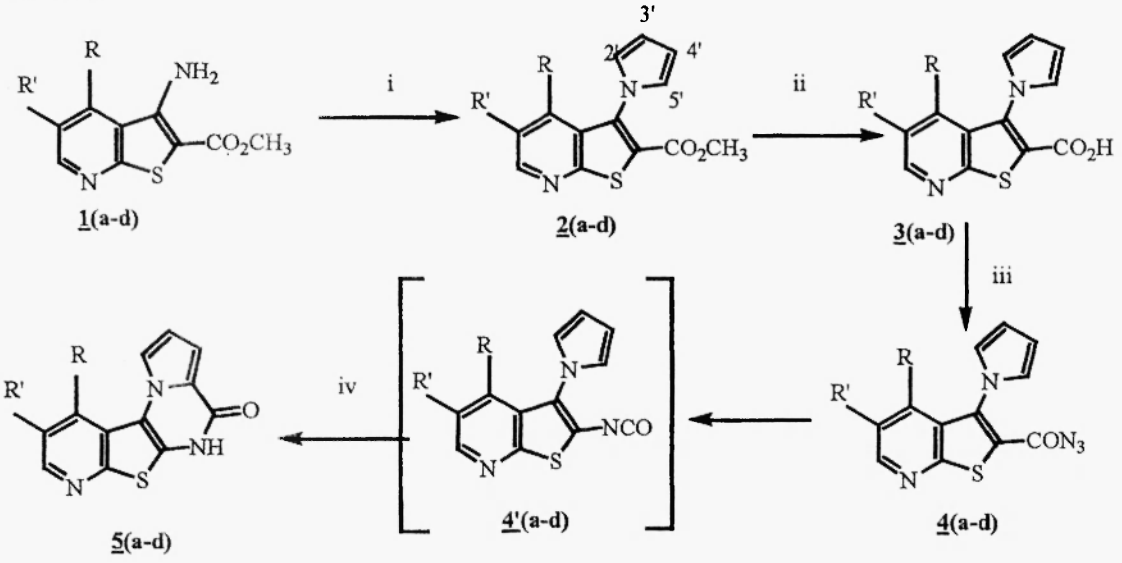
Introduction :

Some pyrrolo-thieno-pyrazines described in the literature are known for their antineoplastic activity[1-6]. In continuation of our program for exploring the synthetic applications of methyl 3-aminothieno[2,3-b]pyridine carboxylates, a number of heterotetracyclic compounds have been synthesized and during the course of this investigation, novel pyrido[3',2':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazines have been obtained.

Results and discussion :

We describe a new tetraheterocyclic system, namely pyrido[3',2':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazine derivatives. Thus pyrido [3',2':4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazine derivatives were obtained in a four step pathway starting from methyl 3-aminothieno[2,3-b]pyridine–2–carboxylate **1(a-d)**, prepared from α-methylene ketone using the procedure published earlier[7]. Treatment of **1(a-d)** with 2,5-dimethoxytetrahydrofuran in boiling acetic acid gave the corresponding methyl–3-(pyrrol-1-yl)thieno[2,3-b]pyridine–2–carboxylate **2(a-d)**. Saponification of **2(a-d)** with KOH-aqueous ethanol lead to the acid **3(a-d)** which is transformed into the carbonylazide **4(a-d)** by treatment with ethyl chloroformate and sodium azide in dry THF. When **4(a-d)** was heated in boiling orthodichlorobenzene at 180°C, a Curtius rearrangement occurs with subsequent cyclisation to give the pyrido [3',2':4,5]thieno[2, 3-e]pyrrolo[1,2-a]pyrazines **5(a-d)**.

Scheme 1:



Reagents and Conditions:

i:2,5-dimethoxy-THF, AcOH
ii:KOH , C_2H_5OH
iii: $(C_2H_5)_3N$, H_2O,Acetone/$ClCO_2C_2H_5$/ NaN_3
iv: o-dichlorobenzene 180°C

R, R': alkyl, aryl, cycloalkyl

The structure of **1(a-d)**, **2(a-d)** and **3(a-d)** was confirmed by spectral data. Presence of a signal at around 11,5 ppm for **5(a-d)** seems to indicate that the structure is a lactame instead of the lactimewhich is consistent with the numerous literature on tautomerism spectroscopy.
The synthetic pathway used allows the access to the new compound in good yield as every step has itself yield between 85 and 95 %.

Experimental :

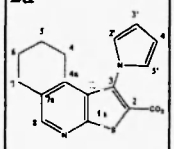
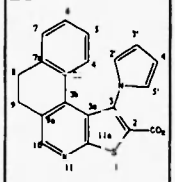
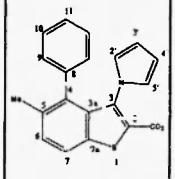
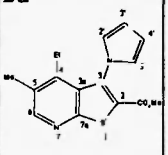
All melting points were measured in open capillary tubes. NMR spectra were recorded on a Bruker AC 250 (250 MHZ) spectrometer in deuterochloroform $CDCl_3$ or hexadeuterodimethylsulfoxide DMSO-d_6.

Preparation of methyl-3-aminothieno[2,3-b]pyridine-2-carboxylate **1(a-d)** :

This compound was synthesized according to a know procedure[7].

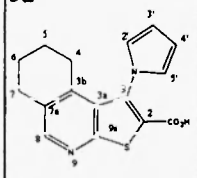
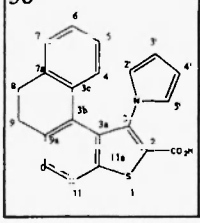
Preparation of methyl-3-(pyrrol-1-yl)thieno[2,3-b]pyridine-2-carboxylate **2(a-d)** ; General Procedure :

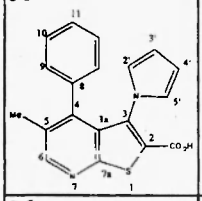
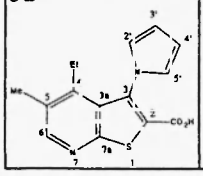
A mixture of methyl-3-amino thieno[2,3-b]pyridine-2-carboxylate **1(a-d** (0,02 mol), 2,5-dimethoxytetrahydrofuran (0,02 mol), and glacial acetic acid (60 ml) is heated at reflux temperature for 1 h. The solvent is distilled under reduced pressure and the residual crude product is triturated with water. The solid residue is collected by suction, washed with water, and dried .

Products	Yields (%)	mp(°C)	^{1}H NMR (δ en ppm)	^{13}C NMR (δ en ppm)
2a 	96	229 (EtOH)	1,63-177(m,4H); 2,36 (m,2H); 2,83(m,2H);3,78(s,3H); 6,36(t,2H,J=1,78 Hz,H3',H4'); 6,72(t,2H,J=1,78 Hz,H2',H5'); 6,39(s,1H pyridine).	C4 (21,80); C6 (21,93); C5 (21,99), C7 (26,80); C methyl (52,45); C2 (96,43), C3' (109,48); C4' (109,48); C3a (128,11); C2' (128,35); C5' (128,35); C3b (130,23); C3 (134,23); C7a (139,54); C8 (151,76); C9b (153,21); C=O (164,56).
2b 	82	214 (EtOH)	2,83(m,4H);3,83(s,3H,CH_3); 6,02-6,67(t,2H, J=1,22 Hz, H3',H4'); 6,73-6,78(t,2H,J=1,22Hz,H2',H5'); 7,09-7,38(m,4HAr); 8,59 (s, 1H pyridine).	C8 (26,80); C9 (27,56); C methyl (52,60), C2 (101,43); C3' (108,35); C4' (108,35); C2' (109,47) ; C5' (109,47) ;C6(114,01); C3a(125,35); C5(125,41); C3b(133,24);C7(133,28); C4(135,22); C3(136,23) ;C9a(140,05); C7a(146,34) ;C3c(147,45); C10(150,76); C11a(153,11);C=O(160,56).
2c 	84	218 (EtOH)	2,08(s,3H);3,75(s,3H,CO_2Me); 5,78(t,2H, J=1,85 Hz,H3',H4'); 6,22 (t,2H, J=1,85 Hz,H2',H5'); 6,86-7,15(m,5Har); 8,63(s, 1H pyridine 6).	C methyl (17,01); C methyl ester (52,48); C2(96,13); C3' (108,74); C4' (108,74);C11 (126,84)); C2' (127,27); C5' (127,27); C10(127,40); C9 (129,54); C3a (129,56); C3 (130,24); C4(134,24); C5 (134,95); C6 (146,70); C7a (146,75); C8 (151,72); C=O(160,94).
2d 	93	202 (Ethyl-acetate)	0,61-0,67(t,3H, J=7 Hz); 1,84-1,87(q,2H, J=7 Hz); 2,07(s,3H);3,46(s,3H,CO_2Me); 6,04(t,2H, J=1,83 Hz,H3',H4'); 6,45 (t,2H, J=1,83 Hz,H2',H5'); 8,16(s, 1H pyridine).	H_3C ethyl (14,77); H_3C methyl (15,20); H_2C ethyl (19,71); H_3C ester (62,20); C3' (107,70); C4' (107,70); C2' (108,67);C5' (108,67);C2 (128,59); C3a (128,66); C5 (135,25); C3 (140,01) ; C4 (148,86); C6 (151,01); C7a (156,99); CO (161,95)

Preparation of 3-(pyrrol-1-yl)thieno[2,3-b]pyridine-2-carboxylic acids **3(a-d)** ; General Procedure :

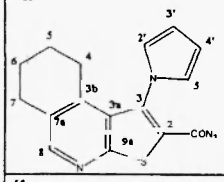
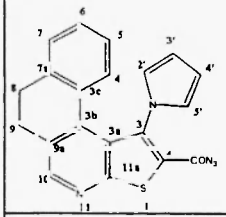
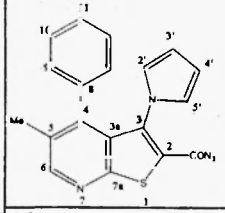
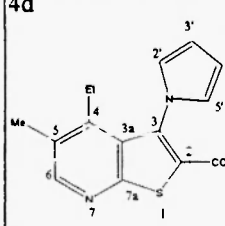
To a solution of compound **2(a-d)** (4 g) in ethanol (40 ml) is added a solution of potassium hydroxide solution (4 g) in H_2O (40 ml). The resulting mixture is heated to reflux for 1,5 h. The hydrolysate is evaporated to ½ of its volume, cooled, and acidified with dilute hydrochloric acid. The precipitate is isolated by suction, washed with water, and dried.

Products	Yields (%)	mp (°C)	^{1}H NMR (δ en ppm)	^{13}C NMR (δ en ppm)
3a 	98	258 (EtOH)	1,39-1,58(m,4H); 2,11(m,2H); 2,62(m,2H); 5,11(s broad,1H(OH)); 6,09(t,2H, J=1,74 Hz, H3',H4'); 6,52 (t,2H, J=1,74 Hz, H2',H5'); 8,16(s,1H pyridine)	C4 (19,89); C6 (20,03); C5 (21,10), C7 (21,31); C2 (92,75); C3' (108,58); C4' (108,58); C3a (127,94),C2' (129,33); C5' (129,33);C3b (134,93); C7a (137,61); C3 (143,43),C8 (150,55); C9a(155,34); C=O (161,80).
3b 	98	260 (EtOH)	2,69(m,4H);4,7(s broad ,1H(OH); 5,81(t,2H, J=1,22 Hz, H3',H4'); 6,43 (t,2H, J=1,22 Hz, H2',H5'); 6,54-7,26(m,4HAr); 8,44(s, 1H pyridine)	C8 (25,17); C9 (28,76); C2 (107,19); C3' (107,65); C4' (107,65); C2'(109,41); C5'(109,41); C6 (113,49); C3a (125,50); C5(128,23);C7(129,31); C4 (131,28); C3b (133,23); C3 (136,30);C9a (141,55); C10 (146,56); C11a (147,30);C3c (149,01); C7a (153,10); C=O (161,30).

3c 	92	208 (EtOH)	2,05(s,3H) 4,46(s broad,1H(OH)) 6,02(t,2H, J=1,80 Hz, H3',H4') 6,56 (t,2H, J=1,80 Hz, H2',H5') 6,76-7,26(m,5HAr) 8,49(s, 1H pyridine)	C methyl (17,02); C2 (96,23); C3' (108,17); C4' (108,17);C10 (126,87); C2' (127,25); C5' (127,25); C11 (127,53); C3a (128,58); C8 (129,54) ; C3 (129,56);C4 (130,13); C5 (134,17);C7a (146,38); C9 (146,41); C6 (151,70); C=O (165,21)
3d 	83	249 (Ethyl-acetate)	0,62-0,65(t,3H, J=7 Hz); 1,83-1,85 (q,2H J=7 Hz); 2,05(s,3H); 4,78(s broad,1H(OH)) 6,03(t,2H, J=1,85 Hz, H3',H4') 6,47 (t,2H, J=1,85 Hz,H2',H5') 8,15(s, 1H pyridine)	H_3C ethyl (14,66); H_3C methyl (15,11); H_2C ethyl (19,60);C3' (108,57); C4' (108,57); C2' (109,13); C5' (109,13); C2 (120,11);C3a (127,66); C5 (128,59); C4 (134,72); C3 (138,61); C6 (150,92); C7a (156,89); CO (161,86)

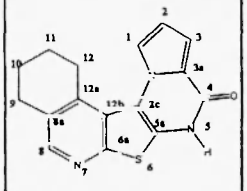
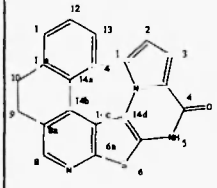
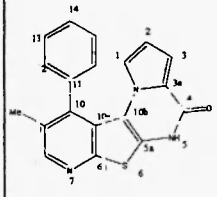
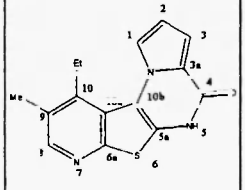
Preparation of 2-azidocarbonyl –3-(pyrrol-1-yl)thieno[2,3-b]pyridine **4** (**a-d**); General Procedure :

To a stirred, cold (-10°C) solution of compound **3**(**a-d**) (5,33 mmol) in dry THF 25 ml is added a solution of triethylamine (11,47 mmol) and a solution of ethyl chloroformate (8,37 mmol). Stirring is continued for 1 h (-10°C), a solution of sodium azide (0,93 g) in water 7 ml and the stirring again continued for 1 h (-10 °C). The solvent is removed under reduced pressure and the residual crude product is triturated with water. The solid residue is collected by suction, washed with water, and dried .

Products	Yields (%)	mp(°C)	^{1}H NMR (δ en ppm)	^{13}C NMR (δ en ppm)
4a 	92	277 (EtOH)	1,5-1,7(m,4H); 2,29 (m,2H);2,78(m,2H); 6,18(t,2H, J=1,90 Hz, H3',H4'); 6,71 (t,2H, J=1,90 Hz, H2',H5'); 8,22 (s, 1H pyridine)	C4 (21,51); C6 (21,77); C5 (22,92); C7 (26,61);C2 (92,71), C3' (107,84); C4' (107,84); C3a (127,45); C2' (128,88); C5' (128,88); C3b(130,33); C7a (138,80); C3 (142,23); C8 (149,21); C9a (155,51); CO (165,51).
4b 	97	148 (EtOH)	2,84(m,4H); 6,03(t,2H,J=1,45 Hz H3',H4'); 6,56 (t,2H, J=1,45 Hz H2',H5'); 6,68-7,20 (m,4Har); 8,62(s, 1H pyridine).	C8 (23,37); C9 (26,26); C2 (107,23); C3'(107,70); C4'(107,70); C2'(109,37); C5'(109,37) C6 (112,85; C3a (125,52); C5 (126,73); C7 (127,56); C4 (129,15); C3b (133,23); C3 (135,91); C9a (140,23); C3c (145,13); C10 (146,85); C11a (147,30); C7a (153,13); C=O (161,30).
4c 	97	195 (EtOH)	2,07(s,3H); 5,61 (t,2H, J=1,92 Hz, H3',H4'); 6,2 (t,2H, J=1,92 Hz, H2',H5'); 6,83-6,87(m,5HAr); 8,5 (s, 1H pyridine).	C methyl (17,07); C2 (101,20); C3' (108,17); C4' (108,17); C10 (127,25); C2' (127,53); C5' (127,53); C9 (128,58); C11 (129,54); C3a(130,01); C3(131,21); C5 (134,52); C4 (134,90); C8(146,25); C6 (146,75); C7a (151,70);C=O (163,54).
4d 	80	153 (Ethyl acetate)	0,92-0,98(t,2H, J=2 Hz); 2,15-2,37(q,3H,J=2Hz) ;2,38(s,3H); 6,39 (t,2H, J=2 Hz H3',H4'); 6,75 (t,2H, J=2 Hz H2',H5'); 8,45(s, 1H pyridine).	H_3 C ethyl (13,51); H_3C methyl(14,67); H_2C ethyl (17,87); C3' (109,51); C4' (109,51); C2' (109,93); C5' (109,93); C2 (120,97); C3a (126,26); C5 (127,25); C3 (127,63); C4 (141,41); C6 (144,76); C7a (147,05); CO (163,51).

Preparation of pyrido[3',2':4,5]thieno[2,3-e] pyrrolo[1,2-a]pyrazine-4-(5H)one **5(a-d)**; General Procedure :

A solution of compound **4(a-d)** in o-dichlorobenzene (30 ml) is heated at reflux (180 °C) for 30 min and then allowed to cool. Th solution of cyclohexane is added and the precipitated product is isolated by suction, and dried.

Products	Yields (%)	MP(°C)	^{1}H NMR (δ en ppm)	^{13}C NMR (δ en ppm)
5a 	97	245 (EtOH)	1,59-3,06(m,8H); 6,42 (dd, $J_{2,1}$=3,06 Hz, $J_{2,3}$=3,84Hz,H-2 pyrrole); 7,04 (dd, $J_{1,2}$=3,06 Hz, $J_{1,3}$=1,22 Hz,H-1 pyrrole); 7,26 (dd, $J_{3,2}$=3,84 Hz, $J_{3,1}$=1,22 Hz, H-3 pyrrole); 7,98(s,1H pyridine); 11,3(s broad,1H(NH))	C10 (17,15); C12 (20,98); C11 (21,89); C9 (25,70); C2 (108,08); C1 (111,53); C3 (115,20);C5a (120,17); C12c (122,29); C3a (127,44); C12b (128,43); C8a (129,04); C12a (134,25), C6a (142,68); C8 (150,18); C=O (161,40).
5b 	98	270 (EtOH)	2,28(m,4H); 5,36 (dd, $J_{2,3}$=3,84 Hz, $J_{2,1}$=3,06 Hz,H-2 pyrrole); 5,95(dd, $J_{1,2}$=3,06 Hz, $J_{1,3}$=1,22 Hz,H-1 pyrrole); 6,23(dd, $J_{3,1}$=1,22 Hz, $J_{3,2}$=3,84 Hz,H-3 pyrrole); 6,52-6,62(m,4HAr); 7,54(s,1Hpyridine);11,5(s broad,1H(NH))	C10 (25,48); C9 (28,34); C5a (95,75); C14d (110,03); C2 (114,23); C3a(118,37); C3 (118,54); C1 (123,53); C14c (126,42); C12 (127,18); C13 (127,89); C14b(129,41); C14 (135,60); C11 (136,17); C8a (138,83)C8 (143,58); C10a (144,85); C14a (150,34); C6a (150,52); C=O (160,35).
5c 	77	280 (EtOH)	2,05(s,3H); 5,31 (dd, $J_{2,3}$=3,84 Hz, $J_{2,1}$=3,06 Hz,H-2pyrrole); 5,77 (dd, $J_{1,3}$=1,22 Hz, $J_{1,2}$=3,06 Hz,H-1pyrrole); 6,86 (dd, $J_{3,2}$=3,84 Hz, $J_{3,1}$=1,22 Hz,H-3pyrrole); 7,1-7,3(m,5HAr); 8,17(s,1Hpyridine);11,5(s broad,1H(NH)	C methyl (17,93);C5a (108,18); C2 (109,40); C3 (126,74); C1 (127,11); C14 (127,80); C13 (128,24);C10b (128,54); C12 (128,90) ; C3a (129,51); C10a (134,01), C9 (136,65) ; C10 (137,39); C11(146,16) ; C6a (146,95) ; C8 (150,79) ; C=O (160,55).
5d 	96	290 (Ethyl-acetate)	0,77(t,3H); 0,93(q,2H); 2,57(s,3H); 6,08 (dd, $J_{2,3}$=3,84 Hz, $J_{2,1}$=3,06 Hz,H-2 pyrrole ; 6,63(dd, $J_{1,2}$=3,06 Hz, $J_{1,3}$=1,22 Hz,H-1 pyrrole); 7,22(dd, $J_{3,1}$=1,22 Hz, $J_{3,2}$=3,84 Hz,H-3 pyrrole);7,64(s,1Hpyridine); 11,25(s broad ,1H(NH)).	H_3C ethyl (12,45); H_3C methyl (15,10); H_2C ethyl (23,30); C5a (106,93); C2 (107,75); C1 (109,82); C3 (110,29); C10b (118,97); C3a (124,53); C10a (126,36); C9 (127,56); C10 (127,93); C6a (141,70); C8 (145,14); CO (153,77).

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