A SYNTHESIS FOR SOME NEW THIENO[2,3-*b*:4,5-*b*']-DIPYRIDINES

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Abstract- An efficient method is proposed for the preparation of substituted thieno[2,3-*b*:4,5-*b*']dipyridines **(2a-h**, **3a-g**, and **5a-e)**, based on the Friedländer synthesis of 3-amino-5-cyano-7-ethoxy-2-formyl-4-phenylthieno[2,3-*b*]pyridine **(1)** with acyclic, cyclic, heterocyclic and α,β–unsaturated ketones. In addition, the reaction of **1** with guanidine sulfate yielded the fused triheterocyclic pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine system **(6)**.

Numerous *N*-heteroaromatic carbaldehydes are extensively used as versatile synthetic building blocks for the preparation of condensed heterocyclic systems.[1] The formation of ring compounds from substituted heterocyclic amino aldehydes is often the method of choice for the synthesis of polycondensed materials consisting of many fused rings.[2]

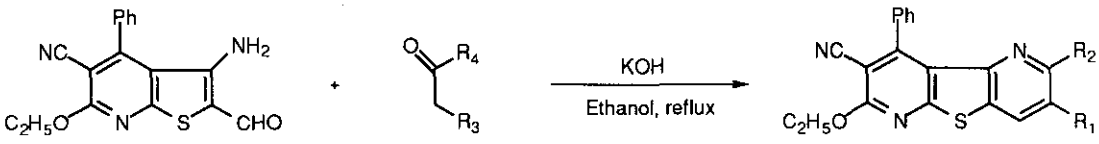
The thieno[2,3-*b*]pyridines are the isosters of classical quinolines. Some thieno[2,3-*b*]pyridines showed antimicrobial activity similar to[3] or greater than[4] nalixidic acid and many heterocyclic compounds containing the thienopyridine moiety are known to have major pharmacological activity specially like antiinflamatory,[5] antianaphilactic,[6] hypocholesterolenic[7] and antipyretic[8] agents. Also some of them inhibit platelet aggregation,[9] possess potential antineoplastic activity[10] or have good vasodilating and hypotensive properties.[11] In addition to various pharmacological properties, thieno[2,3-*b*]pyridines are useful intermediates in the synthesis of tri- and tetracyclic heterocyclic compounds.[12]

This assessment prompted us, in a continuation of our research into the synthesis of novel polyheterocyclic compounds of pharmacological interest containing a thiophene central nucleus,[13] to prepare new thienodipyridine derivatives based on the use of the Friedländer quinoline synthesis, a reaction that continues to attract the attention of synthetic chemists.[14] The Friedländer condensation of appropriated *o*-amino aldehydes seemed a most promising

synthetic sequence for the construction of such systems, since fully aromatic substrates are obtained and the direction of annelation is unequivocally determined by the location of the functional groups in the substrate.

Thus, 3-amino-5-cyano-7-ethoxy-2-formyl-4-phenylthieno[2,3-*b*]pyridine **(1)**, a suitable starting compound for our proposed synthesis, could be obtained from the corresponding carbonitrile precursor[13c] by a reaction with diisobutylaluminium hydride. A Friedländer condensation of this compound with aromatic and aliphatic ketones under a catalytic alkaline condition (ethanolic potassium hydroxide) led to substituted thienodipyridines **(2a-g)**. Similarly, treatment of **1** with ethyl acetoacetate gave the expected compound **(2h)**.

Scheme 1



1 *2a-h*

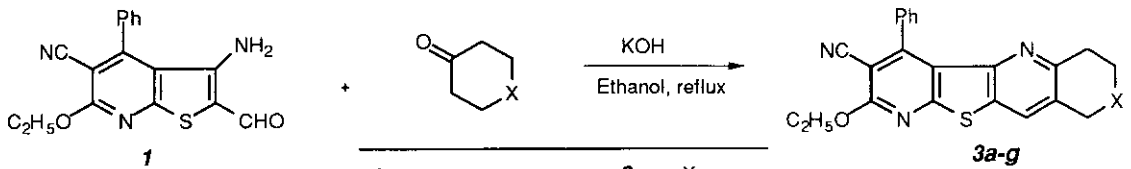
2	R_1	R_2	R_3	R_4	*2*	R_1	R_2	R_3	R_4
a	H	CH_3	H	CH_3	***e***	H	*p*-ClC_6H_4	H	*p*-ClC_6H_5
b	CH_3	CH_3	CH_3	CH_3	***f***	H	*m*-$NO_2C_6H_4$	H	*m*-$NO_2C_6H_4$
c	H	CH_2CH_3	CH_3	CH_3	***g***	H	2-Pyridyl	H	2-Pyridyl
d	H	C_6H_5	H	C_6H_5	***h***	$CO_2C_2H_5$	CH_3	$CO_2C_2H_5$	CH_3

It should be noted that the condensation of amino aldehyde **(1)** with unsymetrical aliphatic ketones gives two different products depending on which α–carbon is used for bond formation. Ring closure under the base catalyzed condensation of **1** with ethyl methyl ketone was found to occur preferentyally at the α-methylene carbon, even though the isomeric product **(2c)** has been also isolated in a lower yield from the reaction mixture.

Similarly, various polycyclic compounds containing a fused terminal thienopyridine moiety **(3a-g)** were easily obtained by Friedländer condensation of the heterocyclic amino aldehyde **(1)** with cyclic ketones and heterocyclic 6-membered ring ketones. The direction of annelation and the position of the heteroatom(s) are defined by the participating functional groups. The availability and structural variety of cyclic ketones provide an easy and direct access to a number of fused heterocyclic systems for which in many cases alternate annelation methods are not readily available. All of the isolated compounds **(3a-g)** presented a characteristic singlet between $\delta = 7.55$ and $\delta = 7.90$ for the H-10 hydrogen in the ^1H nmr spectra, and the EI-mass spectra showed the expected molecular ion peak. Furthermore, the absence of the

characteristic bands of the amine group in the ir spectra indicated the condensation products to be **3**. Salient features of the ^1H nmr, ^{13}C nmr, ir and ms spectra are given in Experimental.

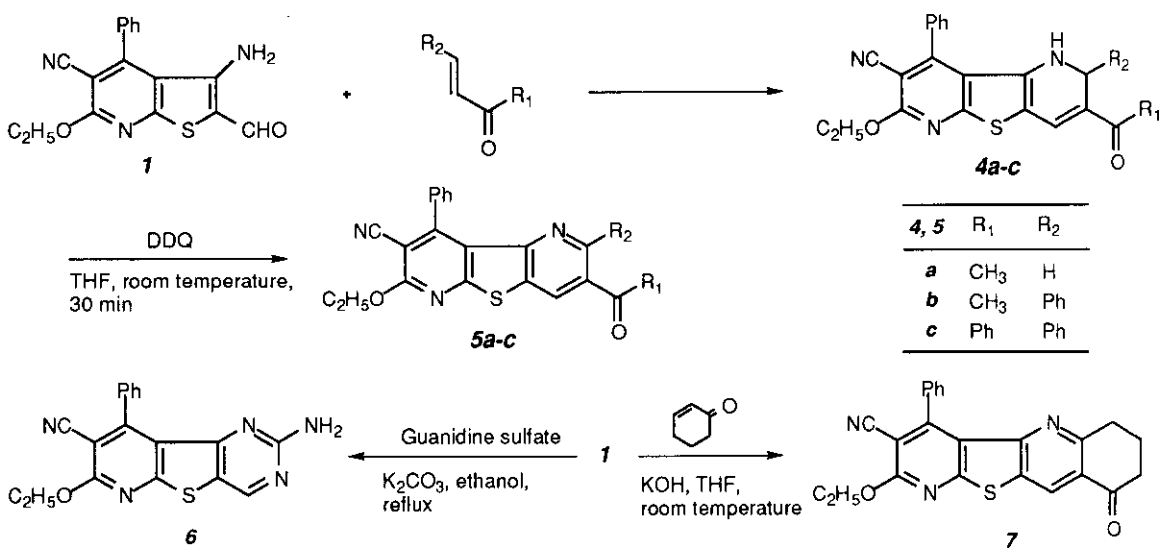
Scheme 2



3	X	3	X
a	NCH_3	e	CH_2
b	$NCOC_6H_5$	f	S
c	$NCO_2C_2H_5$	g	CH_2CH_2
d	O		

The reaction of amino aldehyde **(1)** with an appropriated α,β-unsaturated ketone in tetrahydrofurane containing a catalytic amount of ethanolic potassium hydroxide, gave thieno[2,3-*b*:4,5-*b*']dipyridines **(5)**. Annelation occurs *via* conjugated 1,4-addition and subsequent cyclization to the 1,2-dihydro derivatives **(4)** as intermediates, which could be oxidized to the fully aromatic compounds to give **5**. In some cases, the intermediate dihydrothienodipyridines **(4b,c)** were isolated and these were oxidized to thienodipyridines **(5)** by a reaction with DDQ in tetrahydrofurane for a few hours. In the cases of methyl vinyl ketone and 2-cyclohexenone, the intermediates **(4)** were unstable and underwent spontaneous oxidation to the thienodipyridines **(5a** and **7)** respectively.

Scheme 3



4, 5	R_1	R_2
a	CH_3	H
b	CH_3	Ph
c	Ph	Ph

The structure of these compounds were consistent with their elemental analyses and spectral data. Thus, compounds **(4b,c)** present a characteristic doublet (δ = 5.64 and δ = 5.86,

respectively) corresponding to the H-2 hydrogen and other doublet (δ = 4.49 for **4b** and δ = 4.51 for **4c**), exchangeable with deuterium, which can be attributed to *N*-bounded hydrogen at the position 1. On other hand, the ^{13}C nmr spectra of compounds **(4b,c)** showed one signal (δ = 52.2-52.7) for the carbon at position 2 on the newly synthesized pyridine ring. The ^{1}H nmr spectra of compounds **(5)** showed one singlet which appears at δ = 8.25-8.68 corresponding to the H-10 on this triheterocyclic system.

Finally, a condensation reaction of compound **(1)** with guanidine sulfate in refluxing ethanol gave pyridothienopyrimidine **(6)** which presented a characteristic resonance at δ = 8.70 in the ^{1}H nmr spectrum for the H-4 and its mass spectrum showed an intense peak at m/z = 347 corresponding to the molecular ion.

EXPERIMENTAL SECTION

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. Ir spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^{1}H and ^{13}C nmr spectra were obtained on a Bruker AC200F instrument at room temperature. Mass spectra were obtained at 70 eV by using a VG4 spectrometer. The silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the silica gel 60 (230-400 mesh) employed for medium-pressure chromatography (mplc) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

Reaction of carbaldehyde (1) with aliphatic, aromatic, cyclic or heterocyclic ketones (2a-g, 3a-g); General Procedure:

A solution of **1** (0.10 g, 0.31 mmol), the appropriate ketone (0.37 mmol) and a few drops of KOH (ethanolic, 10%) in ethanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc. A product was isolated by filtration and recrystallization, or evaporation of the solvent under reduced pressure and the residue purified by mplc.

8-Cyano-7-ethoxy-9-phenyl-2-methylthieno[2,3-*b*:4,5-*b*']dipyridine **(2a)**. Recrystallized from ethanol/acetone; yield (60 %); mp 238-240 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1540; 1370; 1340. ^{1}H Nmr δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3); 2.31 (s, 3H, CH_3); 4.65 (q, 2H, J = 7.1 Hz, OCH_2); 7.11 (d, 1H, J = 8.3 Hz, H-3); 7.52 (s, 5H, C_6H_5); 7.94 (d, 1H, J = 8.3 Hz, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 24.7 (CH_3); 64.2 (OCH_2); 95.3 (C-8); 115.0 (CN); 119.8 (C-9a); 120.7 (C-3); 127.7; 128.1; 129.3; 129.4; 130.1; 133.5; 148.8; 154.3; 155.9; 163.2; 164.7. Ms (EI, *m/z*, %): 345 (M^+,100); 316 (47); 303 (45); 300 (38); 288 (32); 286 (11). *Anal.* Calcd $C_{20}H_{15}N_3OS$: C, 69.55; H, 4.38; N, 12.17. Found C, 69.69; H, 4.32; N, 12.03.

8-Cyano-7-ethoxy-2,3-dimethyl-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridine **(2b)**. Purified by mplc using as eluent hexane/dichloromethane (1:1); yield (61 %); mp 199-201 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1560; 1540; 1495; 1400; 1340. ^{1}H Nmr δ ($CDCl_3$): 1.49 (t, 3H, J = 7.1 Hz, CH_3); 2.24 (s, 3H, CH_3); 2.32 (s, 3H, CH_3); 4.65 (q, 2H, J = 7.1 Hz,

OCH_2); 7.53 (s, 5H, C_6H_5); 7.79 (s, 1H, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 19.6, 22.8 (CH_3); 64.1 (OCH_2); 95.1 (C-8); 115.2 (CN); 120.1 (C-9a); 127.7; 128.9; 129.4; 129.7; 130.3; 133.6; 146.6; 153.7; 155.1; 163.0; 164.3. Ms (EI, *m/z*, %): 359 (M^+, 22); 330 (7); 317 (9); 314 (7); 302 (5). *Anal.* Calcd $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69. Found C, 70.07; H, 4.85; N, 11.54.

8-Cyano-7-ethoxy-2-ethyl-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridine **(2c)**. Purified by mplc using as eluent hexane/dichloromethane (1:1); yield (10 %); mp 192-194 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1560; 1540; 1380; 1340. ^1H Nmr δ ($CDCl_3$): 0.96 (t, 3H, J = 7.5 Hz, CH_3); 1.53 (t, 3H, J = 7.1 Hz, CH_3); 2.60 (q, 2H, J = 7.5 Hz, CH_2); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.1 (d, 1H, J = 8.3 Hz, H-3); 7.52 (s, 5H, C_6H_5); 7.99 (d, 1H, J = 8.3 Hz, H-4). ^{13}C Nmr δ ($CDCl_3$): 12.6, 14.3 (CH_3); 30.8 (CH_2); 64.2 (OCH_2); 95.7 (C-8); 115.0 (CN); 120.0 (C-9a); 120.1 (C-3); 128.3 (C-4a); 127.1, 129.1, 129.2, 130.1, 133.9 (C_6H_5, C-4); 148.5; 154.4; 160.8; 163.2; 164.7. Ms (EI, *m/z*, %): 359 (M^+, 100); 331 (25); 330 (46); 317 (34); 314 (25). *Anal.* Calcd for $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69. Found C, 70.29; H, 4.83; N, 11.53.

8-Cyano-7-ethoxy-2,9-diphenylthieno[2,3-*b*:4,5-*b*']dipyridine **(2d)**. Recrystallized from ethanol/dichloromethane; yield (87 %); mp 231-233 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1380; 1340. ^1H Nmr δ ($CDCl_3$): 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.30-7.63 (m, 10H, $2C_6H_5$); 7.78 (d, 1H, J = 8.5 Hz, H-3); 8.11 (d, 1H, J = 8.5 Hz, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.3 (OCH_2); 95.8 (C-8); 114.8 (CN); 116.9 (C-3); 120.0 (C-9a); 126.6; 128.4; 128.8; 129.0; 129.2; 129.7; 130.8; 134.3; 138.0; 149.3; 153.8; 154.5; 163.3. Ms (EI, *m/z*, %): 407 (M^+, 100); 378 (24); 365 (26); 362 (30). *Anal.* Calcd for $C_{25}H_{17}N_3OS$: C, 73.69; H, 4.21; N, 10.31. Found C, 73.60; H, 4.38; N, 10.37.

2-(4-Chlorophenyl)-8-cyano-7-ethoxy-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridine **(2e)**. Recrystallized from ethanol/dichloromethane; yield (60 %); mp 242-244 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1400; 1340. ^1H Nmr δ ($CDCl_3$): 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.24-7.63 (m, 9H, C_6H_5); 7.74 (d, 1H, J = 8.5 Hz, H-3); 8.14 (d, 1H, J = 8.5 Hz, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.4 (OCH_2); 95.9 (C-8); 114.8 (CN); 116.6 (C-3); 119.9 (C-9a); 130.0 (C-4a); 127.9; 128.5; 128.6; 128.7; 129.0; 131.0; 134.3; 135.2; 136.5 (C_6H_5, C_6H_4Cl, C-4); 149.3; 152.6; 154.5; 163.4; 165.1. Ms (EI, *m/z*, %): 441 (M^+, 100); 412 (20); 399 (26); 385 (14). *Anal.* Calcd for $C_{25}H_{16}ClN_3OS$: C, 67.95; H, 3.65; N, 9.51. Found C, 68.08; H, 3.51; N, 9.62.

8-Cyano-7-ethoxy-2-(3-nitrophenyl)-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridine **(2f)**. Recrystallized from ethanol/dichloromethane; yield (65 %); mp 259-261 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1520; 1340; 1020. ^1H Nmr δ ($CDCl_3$): 1.54 (t, 3H, J = 7.1 Hz, CH_3); 4.69 (q, 2H, J = 7.1 Hz, OCH_2); 7.42-8.41 (m, $9H_{arom}$); 7.80 (d, 1H, J = 8.5 Hz, H-3); 8.20 (d, 1H, J = 8.5 Hz, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.5 (OCH_2); 96.1 (C-8); 114.6 (CN); 117.2; 119.6 (C-9a); 121.2 (C-3); 131.1 (C-4a); 103.6; 123.7; 128.5; 128.6; 129.3; 129.6; 131.3; 132.7; 134.0; 140.0; 148.7 (C_6H_5, $C_6H_4NO_2$, C-4); 149.6; 151.5; 154.7; 163.5; 165.1. Ms (EI, *m/z*, %): 452 (M^+, 11). *Anal.* Calcd for $C_{25}H_{16}N_4O_3S$: C, 66.36; H, 3.56; N, 12.38. Found C, 66.41; H, 3.40; N, 12.56.

8-Cyano-7-ethoxy-9-phenyl-2-(2-pyridyl)thieno[2,3-*b*:4,5-*b*']dipyridine **(2g)**. Recrystallized from ethanol/dichloromethane; yield (63 %); mp 249-251 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1380; 1340. ^1H Nmr δ ($CDCl_3$): 1.55 (t, 3H, J = 7.1 Hz, CH_3); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.37-7.64 (m, $8H_{arom}$); 8.19 (d, 1H, J = 8.5 Hz, H-3); 8.47

(d, 1H, J = 8.5 Hz, H-4); 8.60 (d, J = 5.0 Hz, $1H_{arom}$). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.4 (OCH_2); 95.8 (C-8); 114.8 (CN); 118.0; 119.8 (C-9a); 121.1 (C-3); 123.7; 128.4; 128.8; 128.9; 131.0; 131.5; 134.5; 136.5; 148.8; 153.3; 154.3; 155.5; 163.4; 165.8. Ms (EI, *m/z*, %): 408 (M^+, 100); 381 (17); 379 (16); 363 (22). *Anal.* Calcd for $C_{24}H_{16}N_4OS$: 70.57; H, 3.95; N, 13.72. Found C, 70.64; H, 3.80; N, 13.55.

3-Cyano-2-ethoxy-8-methyl-4-phenyl-6,7,8,9-tetrahydropyrido[3',2':4,5]thieno[3,2-*b*]-1,6-naphthyridine **(3a)**. Recrystallized from ethanol; yield (70 %); mp 210-212 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1580; 1550; 1345. ^1H Nmr δ ($CDCl_3$): 1.52 (t, 3H, J = 7.1 Hz, CH_3); 2.44 (s, 3H, NCH_3); 2.67-2.77 (m, 4H, CH_2CH_2); 3.62 (s, 2H, CH_2N); 4.63 (q, 2H, J = 7.1 Hz, OCH_2); 7.50 (s, 5H, C_6H_5); 7.67 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 32.2 (CH_2); 45.8 (NCH_3); 52.8, 57.4 (CH_2); 64.1 (OCH_2); 95.1 (C-3); 115.0 (CN); 119.5 (C-4a); 127.5; 127.6; 127.8; 128.4; 129.3; 133.3; 147.5; 152.3; 153.9; 163.1; 164.5. Ms (EI, *m/z*, %): 400 (M^+, 61); 399 (100); 371 (26); 357 (17); 356 (20); 328 (32). *Anal.* Calcd for $C_{23}H_{20}N_4OS$: C, 68.98; H, 5.03; N, 13.99. Found C, 68.79; H, 5.12; N, 14.18.

3-Cyano-2-ethoxy-8-ethoxycarbonyl-4-phenyl-6,7,8,9-tetrahydropyrido[3',2':4,5]thieno[3,2-*b*]-1,6-naphthyridine **(3b)**. Recrystallized from ethanol; yield (63 %); mp 193-195 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1700 (CO); 1550. ^1H Nmr δ ($CDCl_3$): 1.27 (t, 3H, J = 7.1 Hz, CH_3); 1.52 (t, 3H, J = 7.1 Hz, CH_3); 2.71 (t, 2H, J = 5.9 H, CH_2z); 3.68 (t, 2H, J = 5.9 Hz, CH_2); 4.17 (q, 2H, J = 7.1 Hz, OCH_2); 4.62 (q, 2H, J = 7.1 Hz, OCH_2); 4.69 (s, 2H, CH_2N); 7.46-7.51 (m, 5H, C_6H_5); 7.79 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.3, 14.6 (CH_3); 31.9, 41.2, 45.1 (CH_2); 61.6, 64.2 (OCH_2); 95.2 (C-3); 114.8 (CN); 119.3 (C-4a); 126.5; 127.6; 129.0; 129.2; 129.4; 133.3; 147.6; 152.3; 154.0; 155.4; 163.2; 164.6. Ms (EI, *m/z*, %): 458 (M^+, 14); 430 (23); 429 (100); 357 (38); 328 (13). *Anal.* Calcd for $C_{25}H_{22}N_4O_3S$: C, 65.49; H, 4.84; N, 12.22. Found C, 65.37; H, 4.98; N, 12.15.

8-Benzoyl-3-cyano-2-ethoxy-4-phenyl-6,7,8,9-tetrahydropyrido[3',2':4,5]thieno[3,2-*b*]-1,6-naphthyridine **(3c)**. Recrystallized from ethanol/acetone; yield (75 %); mp 250-252 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1645 (CO); 1550; 1425; 1345. ^1H Nmr δ ($CDCl_3$): 1.55 (t, 3H, J = 7.1 Hz, CH_3); 2.50 (br s, 2H, CH_2); 3.69 (br s, 2H, CH_2); 4.70 (q, 2H, J = 7.1 Hz, OCH_2); 4.97 (br s, 2H, CH_2); 740-7.50 (m, 10H, $2C_6H_5$); 7.90 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 32.7; 44.3; 50.6 (CH_2); 64.3 (OCH_2); 95.5 (C-3); 114.9 (CN); 119.4 (C-4a); 126.1; 126.9; 127.8; 128.6; 129.2; 129.3; 130.1; 133.4; 135.4; 148.0; 151.6; 154.2; 163.4; 164.8; 171.0 (CO). Ms (EI, *m/z*, %): 490 (M^+,14); 105 (100). *Anal.* Calcd for $C_{29}H_{22}N_4O_2S$: C, 71.00; H, 4.52; N, 11.42. Found C, 71.14; H ,4.44; N, 11.48.

3-Cyano-2-ethoxy-4-phenyl-6,7-dihydro-9*H*-pyrano[3,4-*e*]thieno[3,2-*b*:5,4-*b'*]dipyridine **(3d)**. Purified by mplc using as eluent hexane/dichloromethane (1:3); yield (40 %); mp 220-222 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1340. ^1H Nmr δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3); 2.72 (t, 2H, J = 5.8 Hz, CH_2); 3.99 (t, 2H, J = 5.8 Hz, CH_2); 4.64 (q, 2H, J = 7.1 Hz, OCH_2); 4.82 (s, 2H, CH_2); 7.50 (s, 5H, C_6H_5); 7.67 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 31.7 (CH_2); 64.2; 65.7; 67.4 (OCH_2); 95.3 (C-3); 114.9 (CN); 119.5 (C-4a); 125.9; 127.7; 128.0; 128.9; 129.2; 129.4; 133.4; 147.8; 151.3; 154.1; 163.3; 164.6. Ms (EI, *m/z*, %): 387 (M^+, 100); 358 (15); 345 (32); 330 (15); 328 (24). *Anal.* Calcd for $C_{22}H_{17}N_3O_2S$: C, 68.20; H, 4.42; N, 10.85. Found C, 68.08; H, 4.30; N, 10.71.

3-Cyano-2-ethoxy-4-phenyl-6,7,8,9-tetrahydropyrido[3',2':4,5]thieno[3,2-*b*]quinoline **(3e)**. Recrystallized from ethanol/acetone; yield (60 %); mp 215-217 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1340; 1150. ^1H Nmr δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3); 1.79 (m, 4H, CH_2-CH_2-CH_2-CH_2); 2.60 (m, 2H, CH_2); 2.83 (m, 2H, CH_2); 4.63 (q, 2H, J = 7.1

Hz, OCH_2); 7.50 (s, 5H, C_6H_5); 7.70 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 22.6; 22.8; 29.1; 32.4 (CH_2); 64.0 (OCH_2); 94.9 (C-3); 115.1 (CN); 119.7 (C-4a); 127.6; 128.4; 129.2; 129.3; 129.9; 130.4; 133.5; 146.8; 153.7; 155.3; 163.0; 164.4. Ms (EI, *m/z*, %): 385 (M^+, 100); 356 (20); 343 (23); 328 (22). *Anal.* Calcd for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.97; N, 10.90. Found C, 71.53; H, 5.11; N, 10.93.

3-Cyano-2-ethoxy-4-phenyl-6,7-dihydro-9*H*-thiopyran[3,4-*e*]thieno[3,2-*b*:5,4-*b'*]dipyridine **(3f)**. Recrystallized from ethanol/acetone; yield (56 %); mp 255-257 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550; 1345; 1275. ^1H Nmr δ ($CDCl_3$): 1.53 (t, 3H, J = 7.1 Hz, CH_3); 2.89 (s, 4H, CH_2CH_2); 3.81 (s, 2H, CH_2); 4.64 (q, 2H, J = 7.1 Hz, OCH_2); 7.49-7.52 (m, 5H, C_6H_5); 7.57 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 26.4; 29.3; 33.4 (CH_2); 64.2 (OCH_2); 95.3 (C-3); 114.9 (CN); 119.4 (C-4a); 127.7; 128.2; 128.8; 128.9; 129.3; 129.4; 133.4; 147.6; 154.0; 154.2; 163.2; 164.6. Ms (EI, *m/z*, %): 403 (M^+,100); 361 (18); 328 (37); 313 (16); 300 (11). *Anal.* Calcd for $C_{22}H_{17}N_3OS_2$: C, 65.49; H, 4.25; N, 10.41. Found C, 65.59; H, 4.27; N, 10.27.

3-Cyano-2-ethoxy-4-phenyl-7,8,9,10-tetrahydrocyclohepteno[*e*]thieno[3,2-*b*:5,4-*b'*]dipyridine **(3g)**. Purified by mplc using as eluent hexane/dichloromethane (3:1); yield (49 %); mp 179-181 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1550. ^1H Nmr δ ($CDCl_3$): 1.52 (t, 3H, J = 7.1 Hz, CH_3); 1.51-1.84 (m, 6H, CH_2); 2.26-2.83 (m, 4H, CH_2); 4.64 (q, 2H, J = 7.1 Hz, OCH_2); 7.49-7.56 (m, 5H, C_6H_5); 7.55 (s,1H, H-11). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 26.5; 28.1; 32.3; 35.6; 39.3 (CH_2); 64.0 (OCH_2); 95.0 (C-3); 115.2 (CN); 120.0 (C-4a); 127.6; 128.7; 129.3; 129.5; 129.7; 133.5; 136.3; 146.2; 153.7; 161.1; 162.9; 164.3. Ms (EI, *m/z*, %): 399 (M^+, 86); 357 (15); 354 (8). *Anal.* Calcd for $C_{24}H_{21}N_3OS$: C, 72.15; H, 5.30; N, 10.52. Found C, 72.28; H, 5.37; N, 10.59.

Ethyl 8-cyano-7-ethoxy-2-methyl-9-phenylthieno[2,3-*b*:4,5-*b'*]dipyridine-3-carboxylate (2h):

A solution of **1** (0.10 g, 0.31 mmol) and a catalytic amount of piperidine in ethyl acetoacetate (5 ml) was refluxed for 3 h. The solid formed was filtered off and recrystallized from ethanol/acetone to obtain **2h** (0.020 g, 16 %); mp 206-209 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1720 (CO); 1550; 1340; 1240. ^1H Nmr δ ($CDCl_3$): 1.41 (t, 3H, J = 7.1 Hz, CH_3); 1.54 (t, 3H, J = 7.1 Hz, CH_3); 2.55 (s, 3H, CH_3); 4.38 (q, 2H, J = 7.1 Hz, OCH_2); 4.68 (q, 2H, J = 7.1 Hz, OCH_2); 7.51-7.55 (m, 5H, C_6H_5); 8.63 (s, 1H, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.2 ($\mathbf{C}H_3CH_2O$); 14.4 ($\mathbf{C}H_3CH_2O$); 25.0 (CH_3); 61.4 (OCH_2); 64.5 (OCH_2); 95.9 (C-8); 114.7 (CN); 119.1 (C-9a); 122.5; 127.8; 128.0; 129.3; 129.6; 132.6; 133.1; 150.9; 155.1; 157.2; 163.7; 165.9; 166.2. Ms (EI, *m/z*, %): 417 (M^+, 100); 389 (25); 344 (20); 286 (19). *Anal.* Calcd for $C_{23}H_{19}N_3OS$: C, 66.17; H, 4.59; N, 10.07. Found C, 66.24; H, 4.45; N, 10.05.

3-Acetyl-8-cyano-7-ethoxy-9-phenylthieno[2,3-*b*:4,5-*b'*]dipyridine (5a):

To a suspension of **1** (0.10 g, 0.31 mmol) and methyl vinyl ketone (0.025 g, 0.37 mmol) in EtOH (10 ml) a catalytic amount of KOH (10% ethanolic) was added. The reaction mixture was stirred at room temperature for 22 h. The solid formed was filtered off and purified by mplc usind as eluent CH2Cl2/hexane (2:1) to obtain **5a** and a mixture of **4a** and **5a**. This mixture was dissolved in THF (7 ml), and an excess of DDQ was added. The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue purified by mplc. Elution with dichloromethane/hexane (2:1) afforded **5a** (0.072 g, 66 % overall from 1); mp 179-181 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1690 (CO); 1555; 1390; 1345. ^1H Nmr δ ($CDCl_3$): 1.56 (t, 3H, J = 7.1 Hz, CH_3); 2.65 (s, 3H, CH_3); 4.70 (q, 2H, J = 7.1 Hz, OCH_2); 7.51-7.60 (m, 5H, C_6H_5); 8.68 (d, 1H, J = 2.0 Hz, H_{arom}); 8.96 (d,

1H, J = 2.1 Hz, H_{arom}). ^{13}C Nmr δ (CD)Cl_3: 14.4 (CH_3); 26.9 ($\mathbf{C}H_3CO$); 64.7 (OCH_2); 96.5 (C-8); 114.5 (CN); 119.1 (C-9a); 128.2; 129.0; 129.8; 130.0; 131.4, 133.4 (C_6H_5, C-4, C-4a); 147.4 (C-2); 152.7; 155.4; 163.9; 166.3; 195.8 (CO). Ms (EI, *m/z*, %): 373 (M^+, 95); 372 (100); 344 (96); 331 (35). *Anal.* Calcd for $C_{21}H_{15}N_3O_2S$: C, 67.55; H, 4.05; N, 11.35. Found C, 67.59; H, 4.09; N, 11.32.

3-Acetyl-8-cyano-7-ethoxy-2,9-diphenyl-1,2-dihydrothieno[2,3-*b*:4,5-*b*']dipyridine (4b):

To suspension of **1** (0.10 g, 0.31 mmol) and *trans* 4-phenyl-3-buten-2-one (0.054 g, 0.37 mmol) in EtOH (10 ml) a catalytic amount of KOH (10% ethanolic) was added. The reaction mixture was refluxed for 20 min. The solid formed was filtered off and recrystallized from ethanol/dichloromethane to obtain **4b**; yield (62%); mp 222-225 °C. (KBr, cm^{-1}): 3400 (NH); 2220 (CN); 1635 (CO); 1550; 1470. ^1H Nmr δ ($CDCl_3$): 1.49 (t, 3H, J = 7.1 Hz, CH_3); 2.37 (s, 3H, CH_3); 4.49 (d, 1H, J = 3.2 Hz, NH); 4.60 (q, 2H, J = 7.1 Hz, OCH_2); 5.64 (d, 1H, J = 3.3 Hz, NHC**H**); 7.04-7.63 (m, 11H, $2C_6H_5$, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.3 (CH_3); 24.9 (CH_3); 52.2 (C-2); 64.3 (OCH_2); 94.9 (C-8); 105.6; 114.3 (CN); 115.9; 124.6; 125.6; 127.7; 127.9; 128.4; 129.2; 129.4; 130.6; 130.8; 132.7; 140.2; 142.4; 151.8; 161.7; 164.9; 194.5 (CO). Ms (EI, *m/z*, %): 451 (M^+, 56); 449 (40); 374 (100). *Anal.* Calcd for $C_{27}H_{21}N_3O_2S$: C, 71.82; H, 4.68; N, 19.30. Found C, 71.98; H, 4.47; N, 19.15.

3-Benzoyl-8-cyano-7-ethoxy-2,9-diphenyl-1,2-dihydrothieno[2,3-*b*:4,5-*b*']dipyridine (4c) and 3-cyano-2-ethoxy-4-phenyl-6,7-dihydropyrido[3',2':4,5]thieno[3,2-*b*]quinolin-9(8*H*)-one (7):

To a solution of aldehyde **(1)** (0.10 g, 0.31 mmol) and appropriate α-β unsaturated ketone (0.37 mmol) in THF (6 ml) a catalytic amount of KOH (10% ethanolic) was added. The reaction mixture was stirred at room temperature for 10 min (**5c**) or 72 h (**7**). The solvent was evaporated under reduced pressure and the residue purified by mplc.

3-Benzoyl-8-cyano-7-ethoxy-2,9-diphenyl-1,2-dihidrothieno[2,3-*b*:4,5-*b*']dipyridine. **(4c)**. Purified by mplc using as eluent dichloromethane/hexane (3:1); yield (46 %); mp 234-236 °C. Ir (KBr, cm^{-1}): 3420 (NH); 2220 (CN); 1610 (CO); 1560; 1470. ^1H Nmr δ ($CDCl_3$): 1.49 (t, 3H, J = 7.1 Hz, CH_3); 4.51 (d, 1H, J =3.6 Hz, NH); 4.59 (q, 2H, J = 7.1 Hz, OCH_2); 5.86 (d, 1H, J = 3.7 Hz, NHC**H**); 7.11-7.65 (m, 16H, $3C_6H_5$, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.3 (CH_3); 52.7 (C-2); 64.3 (OCH_2); 94.9 (C-8); 106.0; 114.3 (CN); 115.8; 123.9; 125.5; 127.7; 127.9; 128.3; 128.4; 128.5; 129.3; 129.4; 130.7; 131.1; 132.9; 134.0; 138.9; 140.2; 142.6; 152.0; 161.8; 165.1; 193.8 (CO). Ms (EI, *m/z*, %): 513 (M^+, 15); 511 (21); 436 (12); 408 (13). *Anal.* Calcd for $C_{32}H_{23}N_3O_2S$: C, 74.83; H, 4.51; N, 8.18. Found C, 74.70; H, 4.75; N, 8.23.

3-Cyano-2-ethoxy-4-phenyl-6,7-dihydropyrido[3',2':4,5]thieno[3,2-*b*]quinolin-9(8*H*)-one **(7)** Purified by mplc using as eluent dichloromethane/hexane (3:1); yield (50 %); mp 225-227 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1680 (CO); 1550; 1340 . ^1H Nmr δ ($CDCl_3$): 1.55 (t, 3H, J = 7.1 Hz, CH_3); 2.15 (q, 2H, J = 6.5 Hz, CH_2); 2.68 (t, 2H, J = 6.5 Hz, CH_2); 2.83 (t, 2H, J = 6.1 Hz, CH_2); 4.69 (q, 2H, J = 7.1 Hz, OCH_2); 7.50-7.55 (m, 5H, C_6H_5); 8.68 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 21.8, 32.5, 38.6 (CH_2); 64.6 (OCH_2); 96.1 (C-3); 114.6 (CN); 119.0 (C-9a); 125.2; 127.8; 129.2; 129.5; 129.6; 133.2; 152.3; 155.4; 160.7; 163.9; 166.7; 197.3 (CO). Ms (EI, *m/z*, %): 399 (M^+, 100); 398 (32); 370 (23); 357 (39); 354 (17). *Anal.* Calcd for $C_{23}H_{17}N_3O_2S$: C, 69.15; H, 4.29; N, 10.52. Found C, 69.30; H, 4.15; N, 10.69.

8-Cyano-7-ethoxy-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridines (5b,c); General Procedure:

A solution of **4b,c** (0.25 mmol) and DDQ (0.25 mmol) in THF (3 ml) was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was recrystallized or purified by mplc.

3-Acetyl-8-cyano-7-ethoxy-2,9-diphenylthieno[2,3-*b*:4,5-*b*']dipyridine. **(5b)**. Recrystallized from ethanol/dichloromethane; yield (88 %); mp 191-193 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1680 (CO); 1550; 1500; 1450; 1410. ^{1}H Nmr δ ($CDCl_3$): 1.57 (t, 3H, J = 7.1 Hz, CH_3); 2.12 (s, 3H, CH_3); 4.70 (q, 2H, J = 7.1 Hz, OCH_2); 7.20-7.56 (m, 10H, $2C_6H_5$); 8.26 (s, 1H, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 30.4 (CH_3CO); 64.6 (OCH_2); 96.1 (C-8); 114.5 (CN); 119.3 (C-9a); 128.2; 128.3; 128.9; 129.2; 129.3; 129.5; 129.6; 130.7; 131.3; 133.6; 138.6; 150.1; 154.1; 155.0; 163.7; 166.0; 203.3 (CO). Ms (EI, *m/z*, %): 449 (M^+, 100); 434 (12); 420 (13); 407 (22). *Anal.* Calcd for $C_{27}H_{19}N_3O_2S$: C, 72.14; H, 4.26; N, 9.35. Found C, 72.30; H, 4.32; N, 9.10.

3-Benzoyl-8-cyano-7-ethoxy-2,9-diphenylthieno[2,3-*b*:4,5-*b*']dipyridine. **(5c)**. Purified by mplc using as eluent dichloromethane/hexane (1:1); yield (90 %); mp 198-200 °C. Ir (KBr, cm^{-1}): 2220 (CN); 1660 (CO); 1555; 1540; 1410; 1380. ^{1}H Nmr δ ($CDCl_3$): 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.71 (q, 2H, J = 7.1 Hz, OCH_2); 7.08-7.68 (m, 15H, $3C_6H_5$); 8.25 (s, 1H, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.6 (OCH_2); 96.2 (C-8); 114.6 (CN); 119.5 (C-9a); 127.8; 128.3; 128.4; 128.9; 129.0; 129.3; 129.6; 129.9; 130.9; 131.4; 131.6; 133.5; 133.7; 136.5; 138.1; 150.2; 154.4; 155.1; 163.7; 165.8; 196.8 (CO). Ms (EI, *m/z*, %): 511 (M^+, 100); 482 (12); 469 (12); 454 (11); 441 (44). *Anal.* Calcd for $C_{32}H_{21}N_3O_2S$: C, 75.13; H, 4.18; N, 8.21. Found C, 75.30; H, 4.08; N, 8.32.

2-Amino-8-cyano-7-ethoxy-9-phenylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine (6):

A mixture of **1** (0.20 g, 0.62 mmol), guanidine sulfate (0.15 g, 0.68 mmol) and K_2CO_3 (0.094 g, 0.68 mmol) in ethanol (20 ml) was refluxed for 5 h. The solid formed was filtered off and purified by mplc using as eluent dichloromethane/ethanol (99:1) to yield **6** (0.11 g, 50%); mp 241-243 °C. Ir (KBr, cm^{-1}): 3495, 3395 (NH); 2220 (CN); 1620; 1550; 1345. ^{1}H Nmr δ ($CDCl_3$): 1.56 (t, 3H, J = 7.1 Hz, CH_3); 4.66 (q, 2H, J = 7.1 Hz, OCH_2); 4.73 (br s, 2H, NH_2, exchangeable with deuterium); 7.52 (m, 5H, C_6H_5); 8.70 (s, 1H, H-4). ^{13}C Nmr δ ($CDCl_3$): 14.4 (CH_3); 64.6 (OCH_2); 95.9 (C-8); 114.6 (CN); 118.2; 119.1 (C-4a, C-9a); 127.9; 129.2; 129.8; 133.1 (C_6H_5); 152.2 (C-4); 155.8; 157.1; 160.6; 164.3; 167.3. Ms (EI, *m/z*, %): 347 (M^+, 45); 346 (15); 318 (33). *Anal.* Calcd for $C_{18}H_{13}N_5OS$: C, 62.23; H, 3.77; N, 20.16. Found C, 62.30; H, 3.84; N, 20.22.

ACKNOWLEDGMENTS

Financial support (Project 10303B93) from the Xunta de Galicia are gratefully acknowledged. The nmr, mass spectra and elemental analyses facilities were kindly provided by Servicios Generales de Apoyo a la Investigacion of the University of La Coruña.

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Received, 3rd July, 1995