A SYNTHESIS OF NEW PYRIDO[2',3':4,5]THIENO[2,3-*c*]-PYRIDAZINE DERIVATIVES

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Abstract- 5-Amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde is formed by DIBAL reduction from the corresponding cyano precursor 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbonitrile **(1)**. A variety of substituted pyrido[2',3':4,5]thieno[2,3-*c*]pyridazines were synthesized from 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde **(2)** by Friedländer condensation with acyclic, cyclic, heterocyclic or α,β-unsatured ketones and other active methylene compounds.

Pyridazine derivatives and heterocycle-annelated pyridazines have aroused great interest in the past few years due to their wide spectrum of interesting pharmacological activities observed.[1] Whereas pyridine-annelated sulfur-containing heterocycles have been studied extensively,[2] comparatively little is known about aza-analogue systems in which an *S*-heterocycle is fused to a pyridazine nucleus. In a previous paper[3] we reported the synthesis of polyheterocycles containing the pyrimido[4´,5´:4,5]thieno[2,3-*c*]pyridazine skeleton in expectation of some biological activities. In a search of the literature it is surprising that pyridothienopyridazines have been practically ignored.[4] Following this research line and in continuation of our work on the studies on *S*-, *N*-heterocyclic compounds, we describe here a convenient approach to substituted pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine derivatives as isosteres of pharmaceutically relevant pyridothienopyrimidines.[5]

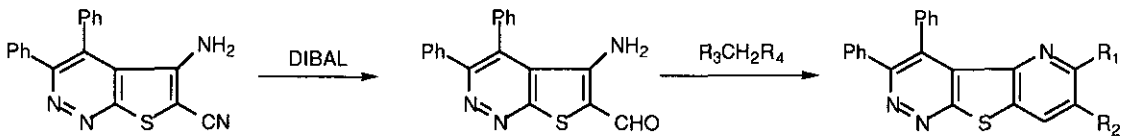
The formation of ring structures from substituted starting materials has very wide applicability for the annelation of heterocyclic systems and is often the method of choice for the elaboration of polycondensed materials composed of multiple fused rings. This construction method predeterminates the direction of ring growth and generally permits the direct and regiospecific production of functional groups and/or substituents in the newly formed heterocyclic ring. Whereas annelation reactions involving suitable aromatic hydrocarbon compounds carrying

the aminoaldehyde moiety provide synthetic entry into heterocyclic systems[6] and numerous *N*-heteroaromatic carbaldehydes are extensively used as versatile building blocks for the preparation of condensed heterocyclic compounds,[7] the chemistry of thienopyridazinecarbaldehydes so far has not been studied.

The 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde **(2)**, a suitable starting compound for our proposed synthesis, could be detained by diisobutylaluminium hydride (DIBAL) reduction to the corresponding cyano precursor **(1)**.[8] This new aldehyde opens a direct route from the preparation of thienopyridazine series by annelation of the pyridine ring to a preformed thienopyridazine nucleus based on the use of the Friedländer quinoline synthesis.[9]

Condensation of the aminoaldehyde **(2)** with aromatic and aliphatic ketones under a catalytic alkaline conditions (ethanolic potassium hydroxide) yielded the expected Friedländer products **(3a-e)** in moderate yields. Thus aryl methyl ketones are readily transformed into 6-aryl derivatives **(3a-c)** and the base-catalyzed reaction of **2** with aliphatic ketones gave pyridothienopyridazines **(3d,e)**.

Scheme 1



1 *2* *3a-k*

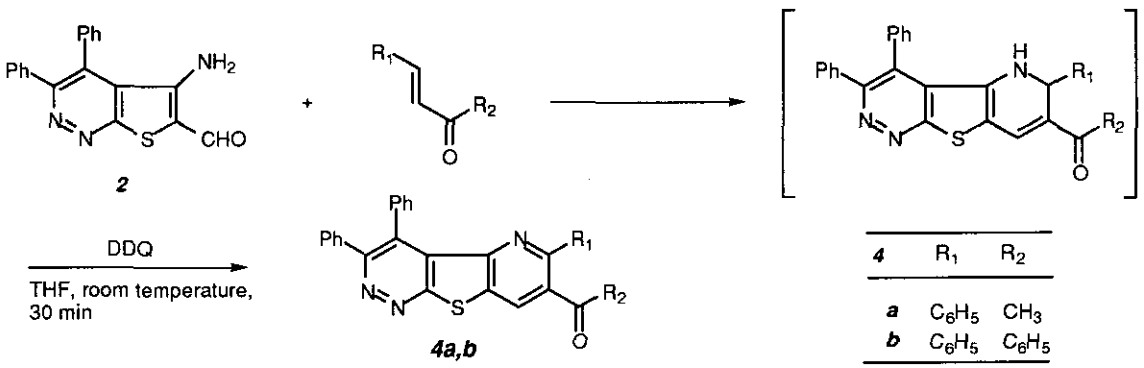
3	R_1	R_2	R_3	R_4	*3*	R_1	R_2	R_3	R_4
a	C_6H_5	H	H	COC_6H_5	***g***	CH_3	$CO_2C_2H_5$	$COCH_3$	$CO_2C_2H_5$
b	*p*-ClC_6H_4	H	H	CO-*p*-ClC_6H_4	***h***	NH_2	CN	CN	CN
c	2-Pyridyl	H	H	CO-2-Pyridyl	***i***	NH_2	C_6H_5	CN	C_6H_5
d	CH_3	H	H	$COCH_3$	***j***	NH_2	$CO_2C_2H_5$	CN	$CO_2C_2H_5$
e	CH_3	CH_3	CH_3	$COCH_3$	***k***	OH	CN	CN	$CO_2C_2H_5$
f	CH_3	$COCH_3$	$COCH_3$	$COCH_3$					

It should be noted that the condensation of **2** with asymmetrical aliphatic ketones occurred in only one direction on ring closure, although it may principally give two different products depending on which α-carbon is used for bond formation. Ring closure in the same base-catalyzed condensation of **2** with ethyl methyl ketone which was found to occur preferentially at the α-methylene carbon affords compound **(3e)**. The isomeric product, detected by nmr spectroscopy in the reaction mixture, has not been isolated.

Annelation reactions of β-diketones and β-keto esters with **2** are greatly facilitated by the presence of a double activated α-methylene group and, as expected, only one directed ring closure is observed. Thus, the reaction of **2** with 2,4-pentanedione and ethyl acetoacetate affords **3f** and **3g**, respectively. Cyclization reaction with malononitrile takes place *via* intramolecular addition of the amino group to the cyano function on the intermediate produced by initial intermolecular condensation to give 6-amino-7-cyano-3,4-diphenylpyrido[2',3':4,5]-thieno[2,3-*c*]pyridazine **(3h)**. Similarly, the reaction product of **2** with phenylacetonitrile lead to the corresponding triheterocyclic compound **(3i)**, and the base-catalyzed condensation of **2** with ethyl cyanoacetate affords a mixture of pyridothienopyridazines **(3j)** and **(3k)** in 36% and 47% yield, respectively.

The reaction of the aminoaldehyde **(2)** with an appropriate α,β-unsaturated ketones such as *trans*-4-phenyl-3-buten-2-one and *trans*-benzylideneacetophenone gave **4a,b**. Annelation occurs *via* conjugated 1,4-addition and subsequent cyclization to the 1,2-dihydro derivative as intermediate, which could be oxidized to the aromatic compound.

Scheme 2



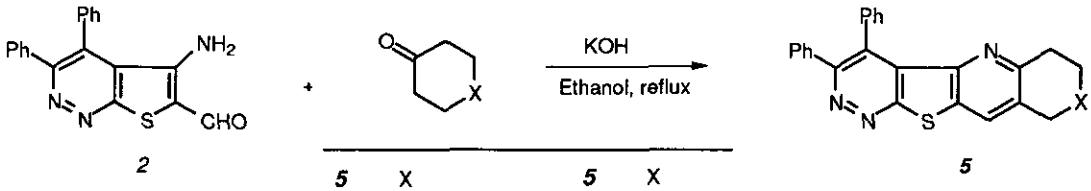
4	R_1	R_2
a	C_6H_5	CH_3
b	C_6H_5	C_6H_5

Similarly, various polycyclic compounds containing a fused terminal thienopyridazine moiety **(5a-g)** were easily obtained by Friedländer condensation of the heterocyclic amino aldehyde **(2)** *with cyclic ketones and heterocyclic 6-membered ring ketones.* The structural variety of cyclic ketones provides a direct access to a number of polyheterocyclic systems for which in many cases alternate annelation methods are not readily available.

The structures of these compounds were assigned by elemental analyses as well as ir, mass, and nmr spectral data.

In conclusion, we synthesized a number of pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine derivatives by use of Friedländer's approach.

Scheme 3



2

5	X	5	X
a	NCH_3	e	S
b	$NCOC_6H_5$	f	CH_2
c	$NCO_2C_2H_5$	g	CH_2CH_2
d	O		

5

EXPERIMENTAL SECTION

All reagents used were commercial grade chemicals. Melting points were determined on a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded as potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^1H 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 VG-QUATTRO 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 liquid 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.

5-Amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde (2):

To a solution of **1** (0.20 g, 0.61 mmol) in dry THF (10 ml) diisobutylaluminium hydride (1.2 ml, 1.5 M in toluene, 1.4 mmol) was added dropwise at -10 °C. The reaction mixture was stirred for 2 h and then 25% H_2SO_4 (3 ml) was added. The stirring was continued overnight at room temperature. The organic layer was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (20 ml). The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated. The solid formed was recrystallized from EtOH to afford **2** (0.15 g, 71%) as orange crystals; mp 270-272 °C. Ir (KBr, cm^{-1}): 3450; 3300; 3200 (NH); 1640 (CO); 1550; 1525; 1450. ^1H Nmr δ ($CDCl_3$): 6.25 (br s, 2H, NH_2); 7.19-7.53 (m, 10H, C_6H_5); 9.84 (s, 1H, CHO). ^{13}C Nmr δ ($CDCl_3$): 110.8; 124.2; 128.1, 128.5, 129.2, 129.3, 129.6, 129.8, 130.3, 132.8 (C_6H_5); 135.0; 136.1; 146.8; 155.4; 185.7 (CHO). Ms (EI, *m/z*, %): 331 (M^+,100); 302 (13); 285 (25); 273 (14); 241 (14); 215 (12). *Anal.* Calcd for $C_{19}H_{13}N_3OS$: C, 68.86; H, 3.95; N, 12.68. Found C, 68.97; H, 3.83; N, 12.59.

Reaction of carbaldehyde (2) with aliphatic, aromatic ketones or nitriles (3a-e, 3g, 3i-k); General Procedure:

A solution of **2** (0.10 g, 0.30 mmol), the appropriate ketone (0.37 mmol) and a few drops of 10% KOH (ethanolic) in ethanol (10 ml) was refluxed until all starting material had disappeared as checked by tlc. The resulting mixture was worked up in one of the following ways: (A) After cooling, a product was isolated by filtration and recrystallized from ethanol/CH_2Cl_2. (B) The solvent was evaporated under reduced pressure and the residue purified by mplc.

3,4,6-Triphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3a)**. Recrystallized from ethanol/CH_2Cl_2; pale brown solid; yield (50%); mp 209-211 °C. Ir (KBr, cm^{-1}): 1490; 1440; 1400; 1290; 1240. ^1H Nmr δ ($CDCl_3$): 7.28-7.63 (m, 15H, $3C_6H_5$); 7.96 (d, 1H, J = 8.5 Hz, H-7); 8.29 (d, 1H, J = 8.5 Hz, H-8). ^{13}C Nmr δ ($CDCl_3$): 119.7; 126.7; 127.7; 127.8; 127.9; 128.2; 128.5; 129.4; 129.9; 130.5; 131.5; 133.8; 134.0; 135.3; 136.7; 137.6; 148.5; 154.3; 157.0; 164.2. Ms (EI, *m/z*, %): 415 (M^+, 60); 414 (70); 384 (11); 382 (11); 307 (12). *Anal.* Calcd for $C_{27}H_{17}N_3S$: C, 78.05; H, 4.12; N, 10.11. Found C, 78.19; H, 4.07; N, 10.15.

6-(4-Chlorophenyl)-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3b)**. Recrystallized from ethanol/CH_2Cl_2; pale yellow crystals; yield (40%); mp 235-237 °C. Ir (KBr, cm^{-1}): 1590; 1565; 1490; 1440; 1430; 1400 ^1H Nmr δ ($CDCl_3$): 7.25-7.50 (m, 14H, $2C_6H_5$ +C_6H_4); 7.89 (d, 1H, J = 8.6 Hz, H-7); 8.27 (d, 1H, J = 8.6 Hz, H-8). ^{13}C Nmr δ ($CDCl_3$): 119.4; 127.9; 128.2; 128.6; 129.9; 130.4; 131.6; 134.0; 135.2; 135.5; 136.0; 136.6; 148.5; 153.0; 157.0; 164.1. Ms (EI, *m/z*, %): 451 (M^++2, 34); 449 (M^+, 93); 448 (100); 420 (11); 416 (12); 384 (11). *Anal.* Calcd for $C_{27}H_{16}N_3ClS$: C, 72.07; H, 3.58; N, 9.34. Found C, 72.01; H, 3.53; N, 9.41.

3,4-Diphenyl-6-(2-pyridyl)pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3c)**. Recrystallized from ethanol/CH_2Cl_2; brown solid; yield (55%); mp 236-238 °C. Ir (KBr, cm^{-1}): 3050; 1590; 1570; 1550; 1540; 1490; 1440. ^1H Nmr δ ($CDCl_3$): 7.22-7.64 (m, $13H_{arom}$); 8.35 (d, 1H, J = 8.6 Hz, H-7); 8.61 (dt, 1H, J = 4.9 Hz, J = 0.8 Hz); 8.67 (d, 1H, J = 8.6 Hz, H-8). ^{13}C Nmr δ ($CDCl_3$): 120.9; 121.3; 124.0; 127.9; 128.2; 129.9; 130.5; 131.7; 134.2; 135.1; 135.6; 136.7; 147.9; 148.7; 153.6; 155.0; 157.0; 164.1. Ms (EI, *m/z*, %): 416 (M^+, 74); 412 (100); 383 (10); 208 (14). *Anal.* Calcd for $C_{26}H_{16}N_4S$: C; 74.98; H, 3.87; N, 13.45. Found C, 75.19; H, 3.70; N, 13.33.

6-Methyl-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3d)**. Purified by mplc using CH_2Cl_2/AcOEt as eluent; pale yellow crystals; yield (62%); mp 176-178 °C. Ir (KBr, cm^{-1}): 3050; 2910; 1600; 1575; 1550; 1490; 1440; 1400. ^1H Nmr δ ($CDCl_3$): 2.37 (s, 3H, CH_3); 7.25-7.45 (m, 11H); 8.09 (d, 1H, J = 8.3 Hz). ^{13}C Nmr δ ($CDCl_3$): 24.3 (CH_3); 123.6; 127.5; 127.8; 128.1; 128.2; 130.4; 130.5; 130.7; 132.4; 133.3; 135.1; 136.8; 156.4; 156.8; 164.0. Ms (EI, *m/z*, %): 353 (M^+, 68); 352 (100); 324 (11); 320 (16). *Anal.* Calcd for $C_{22}H_{15}N_3S$: C, 74.76 ; H, 4.28; N, 11.89. Found C, 74.92; H, 4.16; N, 11.81.

6,7-Dimethyl-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3e)**. Recrystallized from ethanol/CH_2Cl_2; brown crystals; yield (60%); mp 207-209 °C. Ir (KBr, cm^{-1}): 3050; 1440; 1400; 1285. ^1H Nmr δ ($CDCl_3$): 2.28 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 7.26-7.34 (m, 10H, $2C_6H_5$); 7.90 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 19.9, 22.9 (CH_3); 127.5; 127.8; 128.0; 128.1; 130.5; 130.7; 133.0; 133.2; 133.5; 134.6; 137.0; 145.6; 155.9; 156.7; 163.9. Ms (EI, *m/z*, %): 367 (M^+, 52); 366 (100); 334 (16); 323 (7); 200 (10). *Anal.* Calcd for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.43. Found C, 75.02; H, 4.51; N, 11.29.

Ethyl 6-Methyl-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-7-carboxylate **(3g)**. Purified by mplc using CH_2Cl_2/AcOEt as eluent; pale yellow crystals; yield (67%); mp 171-173 °C. Ir (KBr, cm^{-1}): 3050; 2990; 1710 (CO); 1580; 1550; 1520; 1490; 1440. ^1H Nmr δ ($CDCl_3$): 1.43 (t, 3H, J = 7.1 Hz, CH_3); 2.60 (s, 3H, CH_3); 4.42 (q, 2H, J = 7.1 Hz, OCH_2); 7.26-7.47 (m, 10H, $2C_6H_5$); 8.75 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 14.2 ($\mathbf{C}H_3CH_2O$); 25.0 (CH_3); 61.7 (OCH_2); 125.2; 127.5; 127.6; 127.9; 128.3; 128.4; 130.3; 130.5; 132.2; 132.9; 133.3; 135.8; 136.5; 150.0; 157.0; 157.3; 164.6; 165.6 (CO). Ms (EI, *m/z*, %): 425 (M^+, 100); 396 (64); 322 (14); 295 (7). *Anal.* Calcd for $C_{25}H_{19}N_3O_2S$: C, 70.57; H, 4.50; N, 9.87. Found C, 70.49; H, 4.64; N, 9.71.

6-Amino-3,4,7-triphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3l)**. Purified by mplc using hexane/CH_2Cl_2/AcOEt (4:1:1) as eluent; yellow crystals; yield (57%); mp 255-257 °C. Ir (KBr, cm^{-1}): 3500, 3400 (NH); 1600; 1440; 1300. ^1H Nmr δ ($CDCl_3$): 4.36 (s, 2H, NH_2); 7.24-7.50 (m, 15H, $3C_6H_5$); 7.87 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 124.9; 126.1; 127.5; 127.8; 128.0; 128.1; 128.5; 129.3; 130.5; 132.0; 133.8; 134.6; 137.1; 145.9; 154.1; 156.4; 164.4. Ms (EI, *m/z*, %): 430 (M^+, 100); 429 (100); 412 (11); 397 (10). *Anal.* Calcd for $C_{27}H_{18}N_4S$: C, 75.33; H, 4.21; N, 13.01. Found C, 75.22; H, 4.28; N, 12.88.

Ethyl 6-Amino-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine-7-carboxylate **(3j)**. Purified by mplc using CH_2Cl_2/AcOEt (20:1) as eluent and recrystallized from ethanol; red solid; yield (36%); mp 242-244 °C. Ir (KBr, cm^{-1}): 3400, 3300 (NH_2); 1620 (CO); 1560; 1510; 1500. ^1H Nmr δ ($CDCl_3$): 1.36 (t, 3H, J = 7.1 Hz, CH_3); 4.32 (q, 2H, J = 7.1 Hz, OCH_2); 4.72 (br s, 2H, NH_2); 7.18-7.50 (m, 10H, $2C_6H_5$); 8.27 (s, 1H, H-8). Ms (EI, *m/z*, %): 426 (M^+, 100); 397 (29); 381 (53); 379 (36); 352 (52); 322 (15). *Anal.* Calcd for $C_{24}H_{18}N_4O_2S$: C, 67.59; H, 4.25; N, 13.14. Found C, 67.48; H, 4.17; N, 13.26.

7-Cyano-6-hydroxy-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(3k)**. Purified by mplc using CH_2Cl_2/AcOEt (20:1) as eluent; pale brown solid; yield (47%); mp >291 °C. Ir (KBr, cm^{-1}): 3310 (NH); 2210 (CN); 1660; 1650; 1510; 1450. ^1H Nmr δ ($CDCl_3$): 7.30-7.62 (m, 10H, $2C_6H_5$); 8.35 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 98.9 (C-7); 115.7 (CN); 127.7; 128.0; 128.8; 130.0; 130.1; 132.4; 135.0; 136.8; 141.0; 156.8; 160.7; 164.1. Ms (EI, *m/z*, %): 380 (M^+, 96); 379 (100); 351 (27); 322 (19); 296 (11). *Anal.* Calcd for $C_{22}H_{12}N_4OS$: C, 69.46; H, 3.18; N, 4.21. Found C, 69.66; H, 3.03; N, 4.38.

7-Acetyl-6-methyl-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (3f):

A solution of **2** (0.15 g, 0.45 mmol), 2,4-pentadienone (0.07 g, 0.58 mmol) and a few drops of piperidine in THF (10 ml) was refluxed for 9 h. The solvent was evaporated under reduced pressure and the residue was purified by mplc using CH_2Cl_2/AcOEt (10:1) as eluent to afford **3f** (65 mg, 34%) as pale yellow crystals; mp 180-192 °C. Ir (KBr, cm^{-1}): 1690 (CO); 1560; 1500; 1390. ^1H Nmr δ ($CDCl_3$): 2.50 (s, 3H, CH_3); 2.66 (s, 3H, CH_3); 7.25-7.46 (m, 10H, $2C_6H_5$); 8.49 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 24.8, 29.4 (CH_3); 127.5; 127.6; 127.9; 128.2; 128.4; 130.3; 130.5; 131.4; 132.2; 132.9; 135.5; 135.7; 136.6; 149.5; 155.6; 157.1; 164.5; 199.4 (CO). Ms (EI, *m/z*, %): 395 (M^+, 75); 394 (100); 322 (11). *Anal.* Calcd for $C_{24}H_{17}N_3OS$: C, 72.89; H, 4.33; N, 10.62. Found C, 72.78; H, 4.40; N, 10.76.

6-Amino-7-cyano-3,4-diphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (3h):

A solution of **2** (0.10 g, 0.30 mmol), malononitrile (0.025 g, 0.37 mmol) and a few drops of piperidine in THF (10 ml) was stirred at room temperature for 7 h. A product was isolated by filtration and recrystallized from ethanol/acetone to afford **3h** (0.85 g, 90%) as yellow crystals; mp 288-290 °C. Ir (KBr, cm^{-1}): 3490, 3350 (NH); 2210 (CN); 1610; 1520; 1440; 1420. ^1H Nmr δ ($CDCl_3$): 4.89 (s, 2H, NH_2); 7.22-7.42 (m, 10H, $2C_6H_5$); 8.25 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 93.5 (C-7); 115.8 (CN); 123.9; 126.5; 127.6; 127.9; 128.3; 128.5; 130.2; 130.4; 133.0; 135.9; 136.4 (C-8); 150.9; 156.1; 157.0; 164.7. Ms (EI, *m/z*, %): 379 (M^+, 100); 361 (19); 350 (14); 346 (10); 322 (8). *Anal.* Calcd for $C_{22}H_{13}N_5S$: C, 69.64; H, 3.45; N, 18.46. Found C, 69.78; H, 3.33; N, 18.42.

Reaction of carbaldehyde (2) with α,β-unsaturated ketones; General Procedure for 4a,b:

A solution of **2** (0.10 g, 0.30 mmol), the appropriate ketone (0.37 mmol) and a few drops of 10% KOH (ethanolic) in THF (10 ml) was stirred at room temperature until all starting material had disappeared as checked by tlc. The solvent was evaporated under reduced pressure and the residue was purified by mplc using as eluent CH_2Cl_2/AcOEt (20:1 for **4a**, 50:1 for **4b**). A solution of the solid and DDQ (0.07 g, 0.30 mmol) in THF (10 ml) was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure and the residue was purified by mplc using CH_2Cl_2/AcOEt (15:1) as eluent for **4a** or recrystallized from ethanol/CH_2Cl_2 for **4b**.

7-Acetyl-3,4,6-triphenylpyrido[2',3':4,5]thieno[2,3-*c*]pyridazine (**4a**). Pale yellow crystals. Yield (43%); mp 238-240 °C. Ir (KBr, cm^{-1}): 1700 (CO); 1500; 1440; 1400. ^1H Nmr δ ($CDCl_3$): 2.16 (s, 3H, CH_3); 7.22-7.48 (m, 15H, $3C_6H_5$); 8.36 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 30.4 (**C**H_3CO); 127.4; 127.9; 128.0; 128.2; 128.4; 129.5; 129.6; 130.2; 130.5; 131.1; 133.3; 133.5; 135.8; 136.5; 138.2; 149.3; 154.1; 157.3; 164.5; 203.1 (CO). Ms (EI, *m/z*, %): 458 (M^+, 30); 457 (68); 384 (15). *Anal.* Calcd for $C_{27}H_{19}N_3O_2S$: C, 75.96; H, 4.40; N, 9.16. Found C, 76.13; H, 4.23; N, 9.27.

7-*Benzoyl-3,4,6-triphenylpyrido[2',3':4,5]thieno[2,3-c]pyridazine* (**4b**). *Pale brown crystals. Yield (80%); mp* 273-275 °C. Ir (KBr, cm^{-1}): 1660 (CO); 1590; 1500; 1480; 1440. ^1H Nmr δ ($CDCl_3$): 7.05-7.71 (m, 20H, $4C_6H_5$); 8.36 (s, 1H, H-8). ^{13}C Nmr δ ($CDCl_3$): 127.9; 128.0; 128.2; 128.4; 128.6; 129.1; 129.5; 129.9; 120.1; 130.5; 132.0; 133.0; 133.4; 133.8; 134.0; 135.8; 136.0; 136.4; 137.7; 149.3; 154.6; 157.2; 164.4; 196.4 (CO). Ms (EI, *m/z*, %): 519 (M^+, 18); 414 (2); 77 (100). *Anal.* Calcd for $C_{34}H_{21}N_3OS$: C, 78.59; H, 4.07; N, 8.09. Found C, 78.67; H, 3.91; N, 7.92.

Reaction of carbaldehyde (2) with heterocyclic ketones; General Procedure for 5a-g:

A solution of **2** (0.10 g, 0.30 mmol), the appropriate ketone (0.37 mmol) and a few drops of 10% KOH (ethanolic) in ethanol (10 ml) was stirred at room temperature until all starting material had disappeared as checked by tlc. The resulting mixture was worked up in one of the following ways: (A) After cooling, a product was isolated by filtration and recrystallized from a suitable solvent. (B) The solvent was evaporated under reduced pressure and the residue was purified by mplc.

8-Methyl-3,4-diphenyl-6,7,8,9-tetrahydropyridazino[4',3':4,5]thieno[3,2-*b*][1,6]naphthyridine (**5a**). Recrystallized from ethanol; brown solid; yield (61%); mp 202-204 °C. Ir (KBr, cm^{-1}): 2940; 1540; 1480; 1440; 1400; 1380. ^1H Nmr δ ($CDCl_3$): 2.47 (s, 3H, NCH_3); 2.69-2.84 (m, 4H, CH_2CH_2); 3.70 (s, 2H, CH_2N); 7.24-7.45 (m, 10H, $2C_6H_5$); 7.83 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 32.2 (CH_2); 45.8 (NCH_3); 52.6, 57.5 (CH_2); 127.4; 127.8; 128.0; 128.1; 130.4; 130.5; 130.9; 132.6; 133.3; 134.8; 136.9; 146.7; 153.1; 156.8; 163.9. Ms (EI, *m/z*, %): 408 (M^+, 87); 393 (7); 364 (42); 334 (8). *Anal.* Calcd for $C_{25}H_{20}N_4S$: C, 73.50; H, 4.93; N, 13.72. Found C, 73.68; H, 4.85; N, 13.76.

8-Benzoyl-3,4-diphenyl-6,7,8,9-tetrahydropyridazino[4',3':4,5]thieno[3,2-*b*][1,6]naphthyridine (**5b**). Recrystallized from ethanol/CH_2Cl_2; white solid; yield (83%); mp 245-247 °C. Ir (KBr, cm^{-1}): 1620 (CO); 1580; 1440; 1400. ^1H Nmr δ ($CDCl_3$): 2.82 (br s, 2H, CH_2); 3.72 (br s, 2H, CH_2); 5.02 (br s, 2H, CH_2); 7.25-7.48 (m, 15H, $3C_6H_5$);

8.09 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 32.7; 44.3; 45.0 (CH_2); 127.0; 127.6; 127.9; 128.2; 128.6; 129.1; 130.2; 130.3; 130.5; 133.3; 135.0; 135.3; 136.8; 147.2; 152.5; 157.0; 164.0; 170.0 (CO). Ms (EI, *m/z*, %): 498 (M^+, 7); 393 (4); 105 (100). *Anal.* Calcd for $C_{31}H_{22}N_4OS$: C, 74.68; H, 4.45; N, 11.24. Found C, 74.52; H , 4.25; N, 11.38.

Ethyl 3,4-Diphenyl-6,7,8,9-tetrahydropyridazino[4',3':4,5]thieno[3,2-*b*][1,6]naphthyridine-8-carboxylate **(5c)**. Recrystallized from ethanol/CH_2Cl_2; white solid; yield (63%); mp 203-205 °C. Ir (KBr, cm^{-1}): 3020; 1690 (CO); 1480; 1430; 1410. ^{1}H Nmr δ ($CDCl_3$): 1.29 (t, 3H, J = 7.1 Hz, CH_3); 2.77 (t, 2H, J = 6.0 H, CH_2); 3.74 (t, 2H, J = 6.0 Hz, CH_2); 4.18 (q, 2H, J = 7.1 Hz, OCH_2); 4.77 (s, 2H, CH_2N); 7.24-7.46 (m, 10H, $2C_6H_5$); 7.95 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 14.6 (CH_3); 32.0, 41.2, 45.4 (CH_2); 61.8 (OCH_2); 127.5; 127.9; 128.2; 128.2; 130.3; 130.5; 133.2; 133.4; 135.0; 136.8; 147.0; 153.1; 155.4; 156.7; 164.0. Ms (EI, *m/z*, %): 466 (M^+, 100); 437 (74); 393 (46); 364 (23); 334 (12). *Anal.* Calcd for $C_{27}H_{22}N_4O_2S$: C, 69.51; H, 4.75; N, 12.01. Found C, 69.69; H, 4.69; N, 12.16.

3,4-Diphenyl-6,7-dihydro-9*H*-pyrano[3",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(5d)**. Purified by mplc using CH_2Cl_2/ethanol (99:1) as eluent; brown solid; yield (63%); mp 225-227 °C. Ir (KBr, cm^{-1}): 3050; 1540; 1525; 1485; 1460; 1440; 1400. ^{1}H Nmr δ ($CDCl_3$): 2.78 (t, 2H, J = 5.8 Hz, CH_2); 4.02 (t, 2H, J = 5.8 Hz, CH_2); 4.88 (s, 2H, CH_2); 7.26-7.46 (m, 10H, $2C_6H_5$); 7.83 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 31.7 (CH_2); 65.6; 67.5 (OCH_2); 126.4; 127.5; 127.9; 128.1; 128.2; 130.3; 130.5; 131.1; 132.9; 133.3; 134.9; 136.8; 146.9; 152.1; 156.9; 163.9. Ms (EI, *m/z*, %): 395 (M^+, 67); 364 (34); 336 (34); 309 (13). *Anal.* Calcd for $C_{24}H_{17}N_3OS$: C, 72.89; H, 4.33; N, 10.62. Found C, 72.98; H, 4.16; N, 10.45.

3,4-Diphenyl-6,7-dihydro-9*H*-thiopyrano[3",4":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(5e)**. Recrystallized from ethanol; brown solid; yield (61%); mp 249-251 °C. Ir (KBr, cm^{-1}): 1525; 1480; 1440; 1410; 1395. ^{1}H Nmr δ ($CDCl_3$): 2.93 (s, 4H, CH_2CH_2); 3.86 (s, 2H, CH_2); 7.27-7.46 (m, 10H, $2C_6H_5$); 7.92 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 26.3; 30.0; 33.5 (CH_2); 127.5; 127.8; 128.1; 128.2; 129.2; 130.3; 130.4; 131.2; 133.0; 133.3; 134.8; 136.8; 147.7; 154.8; 156.8; 163.9. Ms (EI, *m/z*, %): 411 (M^+, 100); 378 (15); 365 (30); 348 (8); 336 (12). *Anal.* Calcd for $C_{24}H_{17}N_3S_2$: C, 70.05; H, 4.16; N, 10.21. Found C, 70.23; H, 4.04; N, 10.37.

3,4-Diphenyl-6,7,8,9-tetrahydropyridazino[4',3':4,5]thieno[3,2-*b*]quinoline **(5f)**. Purified by mplc using CH_2Cl_2 as eluent; yellow crystals; yield (64%); mp 244-246 °C. Ir (KBr, cm^{-1}): 2940; 1525; 1490; 1440; 1400. ^{1}H Nmr δ ($CDCl_3$): 1.82 (t, 4H, J = 3.14, CH_2-CH_2-CH_2-CH_2); 2.62 (br s, 2H, CH_2); 2.90 (br s, 2H, CH_2); 7.27-7.46 (m, 10H, $2C_6H_5$); 7.85 (s, 1H, H-10). ^{13}C Nmr δ ($CDCl_3$): 22.5; 22.7; 29.4; 32.5 (CH_2); 127.4; 127.8; 128.0; 128.1; 130.4; 130.5; 132.6; 133.4; 133.7; 134.6; 137.0; 145.9; 156.1; 156.7; 164.0. Ms (EI, *m/z*, %): 393 (M^+, 16); 392 (25); 334 (5). *Anal.* Calcd for $C_{25}H_{19}N_3S$: C, 76.31; H, 4.87; N, 10.68. Found C, 76.48; H, 4.75; N, 10.61.

3,4-Diphenyl-7,8,9,10-tetrahydro-6*H*-cyclohepta[1",2":5',6']pyrido[2',3':4,5]thieno[2,3-*c*]pyridazine **(5g)**. Purified by mplc using CH_2Cl_2 as eluent; pale yellow crystals; yield (52%); mp 220-222 °C. Ir (KBr, cm^{-1}): 2910; 1525; 1480; 1450; 1400. ^{1}H Nmr δ ($CDCl_3$): 1.59-1.85 (m, 6H, CH_2); 2.73-2.90 (m, 4H, CH_2); 7.24-7.46 (m, 10H, $2C_6H_5$); 7.89 (s, 1H, H-11). ^{13}C Nmr δ ($CDCl_3$): 26.5, 28.0, 32.3, 35.8, 39.3 (CH_2); 127.4; 127.8; 128.0; 128.1; 130.1; 130.5; 130.6; 133.2; 133.5; 134.6; 137.1; 139.5; 145.3; 156.7; 161.8; 164.0. Ms (EI, *m/z*, %): 407 (M^+, 57); 406 (100); 374 (7). *Anal.* Calcd for $C_{26}H_{21}N_3S$: C, 76.63; H, 5.19; N, 10.31. Found C, 76.49; H, 5.27; N, 10.46.

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