

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 -unsaturated 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 paper³ 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

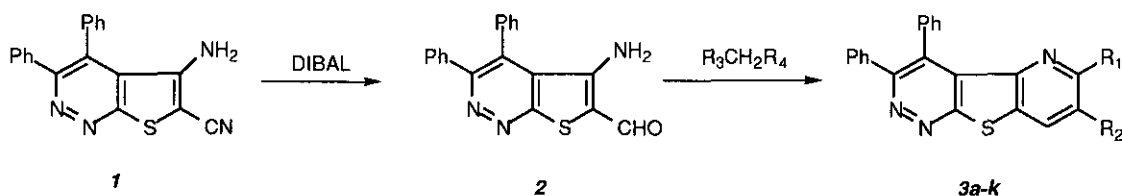
The formation of ring structures from substituted starting materials has very wide applicability for the annelation of heterocyclic systems and is often the method of choice for the elaboration of polycondensed materials composed of multiple fused rings. This construction method predeterminates the direction 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 systems⁶ 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 obtained 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



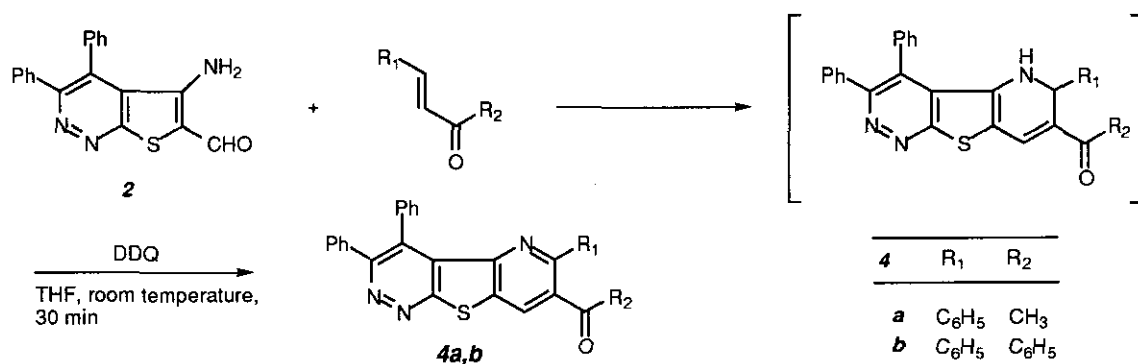
3	R ₁	R ₂	R ₃	R ₄	3	R ₁	R ₂	R ₃	R ₄
a	C ₆ H ₅	H	H	COCH ₃	g	CH ₃	CO ₂ C ₂ H ₅	COCH ₃	CO ₂ C ₂ H ₅
b	<i>p</i> -ClC ₆ H ₄	H	H	CO- <i>p</i> -ClC ₆ H ₄	h	NH ₂	CN	CN	CN
c	2-Pyridyl	H	H	CO-2-Pyridyl	i	NH ₂	C ₆ H ₅	CN	C ₆ H ₅
d	CH ₃	H	H	COCH ₃	j	NH ₂	CO ₂ C ₂ H ₅	CN	CO ₂ C ₂ H ₅
e	CH ₃	CH ₃	CH ₃	COCH ₃	k	OH	CN	CN	CO ₂ C ₂ H 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.

Annulation 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 phenylacetone nitrile 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**. Annulation 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

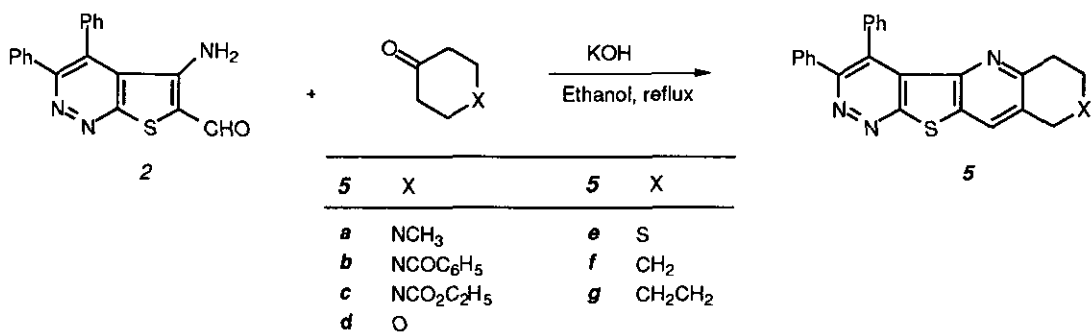


Similarly, various polycyclic compounds containing a fused terminal thienopyridazine moiety (**5a-g**) were easily obtained by Friedländer condensation of the heterocyclic amino aldehyde (**2**) with cyclic ketones and heterocyclic 6-membered ring ketones. The structural variety of cyclic ketones provides a direct access to a number of polyheterocyclic systems for which in many cases alternate annulation 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



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 ¹³C 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 HF₂₅₄₊₃₆₆ used for analytical thin layer chromatography and the silica gel 60 (230-400 mesh) employed for medium-pressure liquid chromatography (mpc) 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% H₂SO₄ (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 CH₂Cl₂ (20 ml). The organic layer was washed with H₂O, dried (Na₂SO₄) 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 (CDCl₃): 6.25 (br s, 2H, NH₂); 7.19-7.53 (m, 10H, C₆H₅); 9.84 (s, 1H, CHO). ¹³C Nmr δ (CDCl₃): 110.8; 124.2; 128.1, 128.5, 129.2, 129.3, 129.6, 129.8, 130.3, 132.8 (C₆H₅); 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 C₁₉H₁₃N₃OS: 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 ethano/CH₂Cl₂. (B) The solvent was evaporated under reduced pressure and the residue purified by mpc.

3,4,6-Triphenylpyrido[2',3':4,5]thieno[2,3-c]pyridazine (**3a**). Recrystallized from ethanol/CH₂Cl₂; pale brown solid; yield (50%); mp 209-211 °C. Ir (KBr, cm⁻¹): 1490; 1440; 1400; 1290; 1240. ¹H Nmr δ (CDCl₃): 7.28-7.63 (m, 15H, 3C₆H₅); 7.96 (d, 1H, *J* = 8.5 Hz, H-7); 8.29 (d, 1H, *J* = 8.5 Hz, H-8). ¹³C Nmr δ (CDCl₃): 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 C₂₇H₁₇N₃S: 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/CH₂Cl₂; pale yellow crystals; yield (40%); mp 235-237 °C. Ir (KBr, cm⁻¹): 1590; 1565; 1490; 1440; 1430; 1400. ¹H Nmr δ (CDCl₃): 7.25-7.50 (m, 14H, 2C₆H₅ + C₆H₄); 7.89 (d, 1H, *J* = 8.6 Hz, H-7); 8.27 (d, 1H, *J* = 8.6 Hz, H-8). ¹³C Nmr δ (CDCl₃): 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 C₂₇H₁₆N₃ClS: 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/CH₂Cl₂; brown solid; yield (55%); mp 236-238 °C. Ir (KBr, cm⁻¹): 3050; 1590; 1570; 1550; 1540; 1490; 1440. ¹H Nmr δ (CDCl₃): 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). ¹³C Nmr δ (CDCl₃): 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 C₂₆H₁₆N₄S: 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 mpic using CH₂Cl₂/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 (CDCl₃): 2.37 (s, 3H, CH₃); 7.25-7.45 (m, 11H); 8.09 (d, 1H, *J* = 8.3 Hz). ¹³C Nmr δ (CDCl₃): 24.3 (CH₃); 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 C₂₂H₁₅N₃S: 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/CH₂Cl₂; brown crystals; yield (60%); mp 207-209 °C. Ir (KBr, cm⁻¹): 3050; 1440; 1400; 1285. ¹H Nmr δ (CDCl₃): 2.28 (s, 3H, CH₃); 2.37 (s, 3H, CH₃); 7.26-7.34 (m, 10H, 2C₆H₅); 7.90 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 19.9, 22.9 (CH₃); 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 C₂₃H₁₇N₃S: 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 mpic using CH₂Cl₂/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 (CDCl₃): 1.43 (t, 3H, *J* = 7.1 Hz, CH₃); 2.60 (s, 3H, CH₃); 4.42 (q, 2H, *J* = 7.1 Hz, OCH₂); 7.26-7.47 (m, 10H, 2C₆H₅); 8.75 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 14.2 (CH₃CH₂O); 25.0 (CH₃); 61.7 (OCH₂); 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 C₂₅H₁₉N₃O₂S: 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 (**3i**). Purified by mpc using hexane/CH₂Cl₂/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 (CDCl₃): 4.36 (s, 2H, NH₂); 7.24-7.50 (m, 15H, 3C₆H₅); 7.87 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 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 C₂₇H₁₈N₄S: 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 mpc using CH₂Cl₂/AcOEt (20:1) as eluent and recrystallized from ethanol; red solid; yield (36%); mp 242-244 °C. Ir (KBr, cm⁻¹): 3400, 3300 (NH₂); 1620 (CO); 1560; 1510; 1500. ¹H Nmr δ (CDCl₃): 1.36 (t, 3H, *J* = 7.1 Hz, CH₃); 4.32 (q, 2H, *J* = 7.1 Hz, OCH₂); 4.72 (br s, 2H, NH₂); 7.18-7.50 (m, 10H, 2C₆H₅); 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 C₂₄H₁₈N₄O₂S: 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 mpc using CH₂Cl₂/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 (CDCl₃): 7.30-7.62 (m, 10H, 2C₆H₅); 8.35 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 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 C₂₂H₁₂N₄OS: 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 mpc using CH₂Cl₂/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 (CDCl₃): 2.50 (s, 3H, CH₃); 2.66 (s, 3H, CH₃); 7.25-7.46 (m, 10H, 2C₆H₅); 8.49 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 24.8, 29.4 (CH₃); 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 C₂₄H₁₇N₃OS: 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 (CDCl₃): 4.89 (s, 2H, NH₂); 7.22-7.42 (m, 10H, 2C₆H₅); 8.25 (s, 1H, H-8). ¹³C Nmr δ (CDCl₃): 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 C₂₂H₁₃N₅S: 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 mpc using as eluent $\text{CH}_2\text{Cl}_2/\text{AcOEt}$ (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 mpc using $\text{CH}_2\text{Cl}_2/\text{AcOEt}$ (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. $^1\text{H Nmr } \delta$ (CDCl_3): 2.16 (s, 3H, CH_3); 7.22-7.48 (m, 15H, $3\text{C}_6\text{H}_5$); 8.36 (s, 1H, H-8). $^{13}\text{C Nmr } \delta$ (CDCl_3): 30.4 (CH_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 $\text{C}_{27}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$: 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. $^1\text{H Nmr } \delta$ (CDCl_3): 7.05-7.71 (m, 20H, $4\text{C}_6\text{H}_5$); 8.36 (s, 1H, H-8). $^{13}\text{C Nmr } \delta$ (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 $\text{C}_{34}\text{H}_{21}\text{N}_3\text{OS}$: 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 mpc.

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. $^1\text{H Nmr } \delta$ (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, $2\text{C}_6\text{H}_5$); 7.83 (s, 1H, H-10). $^{13}\text{C Nmr } \delta$ (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 $\text{C}_{25}\text{H}_{20}\text{N}_4\text{S}$: 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. $^1\text{H Nmr } \delta$ (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, $3\text{C}_6\text{H}_5$);

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 $\text{C}_{31}\text{H}_{22}\text{N}_4\text{OS}$: 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. ^1H Nmr δ (CDCl_3): 1.29 (t, 3H, $J = 7.1$ Hz, CH_3); 2.77 (t, 2H, $J = 6.0$ Hz, 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, $2\text{C}_6\text{H}_5$); 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 $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_2\text{S}$: 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 mpls 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. ^1H 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, $2\text{C}_6\text{H}_5$); 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 $\text{C}_{24}\text{H}_{17}\text{N}_3\text{OS}$: 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. ^1H Nmr δ (CDCl_3): 2.93 (s, 4H, CH_2CH_2); 3.86 (s, 2H, CH_2); 7.27-7.46 (m, 10H, $2\text{C}_6\text{H}_5$); 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 $\text{C}_{24}\text{H}_{17}\text{N}_3\text{S}_2$: 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 mpls using CH_2Cl_2 as eluent; yellow crystals; yield (64%); mp 244-246 °C. Ir (KBr, cm^{-1}): 2940; 1525; 1490; 1440; 1400. ^1H Nmr δ (CDCl_3): 1.82 (t, 4H, $J = 3.14$, $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2$); 2.62 (br s, 2H, CH_2); 2.90 (br s, 2H, CH_2); 7.27-7.46 (m, 10H, $2\text{C}_6\text{H}_5$); 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 $\text{C}_{25}\text{H}_{19}\text{N}_3\text{S}$: 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 mpls using CH_2Cl_2 as eluent; pale yellow crystals; yield (52%); mp 220-222 °C. Ir (KBr, cm^{-1}): 2910; 1525; 1480; 1450; 1400. ^1H 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, $2\text{C}_6\text{H}_5$); 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 $\text{C}_{26}\text{H}_{21}\text{N}_3\text{S}$: C, 76.63; H, 5.19; N, 10.31. Found C, 76.49; H, 5.27; N, 10.46.

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