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Iminophosphoranes in heterocyclic chemistry. A simple one-pot synthesis of pyridothienopyridazines and pyrimidothienopyridazines

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Abstract—Iminophosphoranes, 6-(2-ethoxycarbonylvinyl)-3,4-diphenyl-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*]pyridazine **1a**, 6-(2-cyanovinyl)-3,4-diphenyl-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*]pyridazine **1b**, and 6-(4-aryliminomethylene)-3,4-diphenyl-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*] pyridazine **5a–c** react with heterocumulenes such as iso(thio)cyanates, carbon dioxide and carbon disulfide to give directly the title compounds in an aza-Wittig/electrocyclic-ring closure process. The *N*-heteroaryliminophosphoranes **8a**,**b** underwent an unusual pyridine ring closure under Vilsmeier conditions to form the pyridothienopyridazines **10a**,**b**.

1. Introduction

The use of iminophosphoranes has been emerging as reagents and intermediates in organic synthesis for its utility in synthesis of C=N double bond-containing compounds, in particular nitrogen heterocyclic compounds via inter- and intramolecular aza-Wittig reactions. Annelation of ring systems with *N*-heterocycles by means of an aza-Wittig reaction has recently been widely utilized because of the availability of functionalized iminophosphoranes. In recent years, numerous research papers and several review articles have appeared describing the varied use of iminophosphoranes as a valuable tool for the construction of nitrogen-containing heterocycles.[1]

In this context, iminophosphorane-mediated synthesis of heterocyclic ring systems has developed remarkably in recent years, which is obviously linked to the rapid progress in the preparation of functionalized iminophosphoranes.[2] These compounds can react with carbonyl compounds to form imines, and with isocyanates, isothiocyanates, carbon dioxide and carbon disulfide, to afford the corresponding heterocumulenes.[3] The intramolecular aza-Wittig reaction is a powerful tool for the synthesis of **5–7** membered nitrogen heterocycles such as oxazoles,[4] quinazolin-4(3H)-ones,[5] 1,4-benzodiazepin-5-ones,[6] iminolactams[7] or azolinones[5a] and the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocyclization, the tandem aza-Wittig and cyclization sequence, has been utilized for the synthesis of many important nitrogen heterocycles.[8] Therefore, the tandem aza-Wittig and cyclization sequence has been shown to be a useful method for the construction of fused indoles,[9] pyridines,[10] pyrimidines[11] and isoquinoline [12] derivatives.

The *N*-heteroaryliminophosphoranes have proved to be very versatile building blocks for the construction of manifold heterocondensed systems, and fused nitrogen heterocycles have been prepared, via the intermolecular aza-Wittig reaction and heterocyclization, recently.[13] Following our studies directed towards the development of new synthetic methods of nitrogen heterocycles based on heterocyclization reactions of azahexatriene compounds, we have previously published the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy.[14]

2. Results

During the last years we have been interested in the synthesis of substituted heterocycles containing the thienopyridine and thienopyrimidine systems with the aim of finding compounds with antinflammatory and antihistaminic activities.[13] As a further extension of the aza-Wittig-type methodology we report herein a new general synthesis for the pyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine and pyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine ring systems.

Keywords: iminophosphorane; aza-Wittig; pyridothienopiridazine; pyrimidothienopyridazine.

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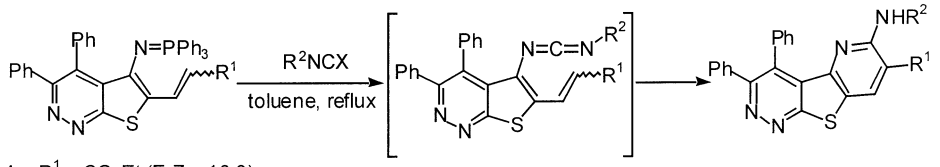
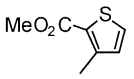
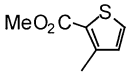


1a: $R^1 = CO_2Et$ (E:Z = 10:0)
1b: $R^1 = CN$ (E:Z= 4:1)

2a-m **3a-m**

3	X	R^1	R^2	t (h)	%	3	X	R^1	R^2	t (h)	%
a	O	CO_2Et	C_6H_5	1	92	**h**	S	CO_2Et		14	53
b	O	CO_2Et	4-Cl-C_6H_4	4	63	**i**	O	CN	C_6H_5	2	76
c	O	CO_2Et	4-F-C_6H_4	3	76	**j**	O	CN	4-F-C_6H_4	1	51
d	O	CO_2Et	4-MeO-C_6H_4	3	66	**k**	O	CN	4-MeO-C_6H_4	10	86
e	O	CO_2Et	4-Me-C_6H_4	4	59	**l**	O	CN	*i*-Pr	5	51
f	O	CO_2Et	C_6H_{11}	4	91	**m**	S	CN		20	69
g	O	CO_2Et	*i*-Pr	5	70						

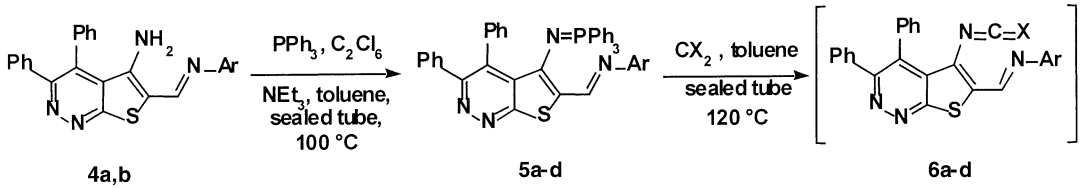
Scheme 1.

For the construction of diaza isosters of pharmaceutically relevant bi- or tricyclic systems, *vic*-disubstituted diazines can be regarded as valuable precursors. Pyridazines and heterocyclic annelated pyridazines continue to attract considerable attention for their applications in agriculture and in particular for their biological activity for use as potential drugs.[15] The recent discovery of Pyridazomycin,[16] a new antifungal antibiotic, and Zazissine,[17] a new cytotoxic guanidine alkaloid, both containing this heteroarene system, will most probably stimulate even broader interest in 1,2-diazine chemistry. Whereas, pyridine-annulated sulfur-containing heterocycles have been studied extensively,[18] comparatively little is known about aza-analogous systems in which an *S*-heterocycle is fused to a pyridazine nucleus. Recently, our researches have been devoted to the synthesis of condensed tricyclic systems of potential biological activity with a thiophene ring fused to a pyridazine system.[19]

This paper reports detailed results on the facile synthesis of pyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine and pyrimido-[4′,5′:4,5]thieno[2,3-*c*]pyridazine derivatives involving an aza-Wittig type reaction heterocyclization sequence.

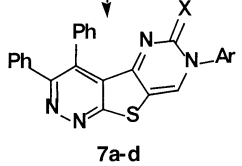
3. Discussion

The iminophosphoranes of heterocyclic and heteroaromatic β-enamino esters and β-enamino nitriles have proved to be very versatile synthons for the construction of hetero-condensed systems.[1c] The key iminophosphoranes **1a**,**b** and **5a**–**d** are easily prepared from 5-amino-3,4-diphenyl-thieno[2,3-*c*]pyridazine-6-carboxaldehyde.[19c] The approach to the above mentioned triheterocyclic systems is based on the stepwise formation of the pyridine ring following the aza-Wittig/electrocyclic ring closure strategy. The reaction of *N*-heteroaryliminophosphoranes **1a**–**b** with several



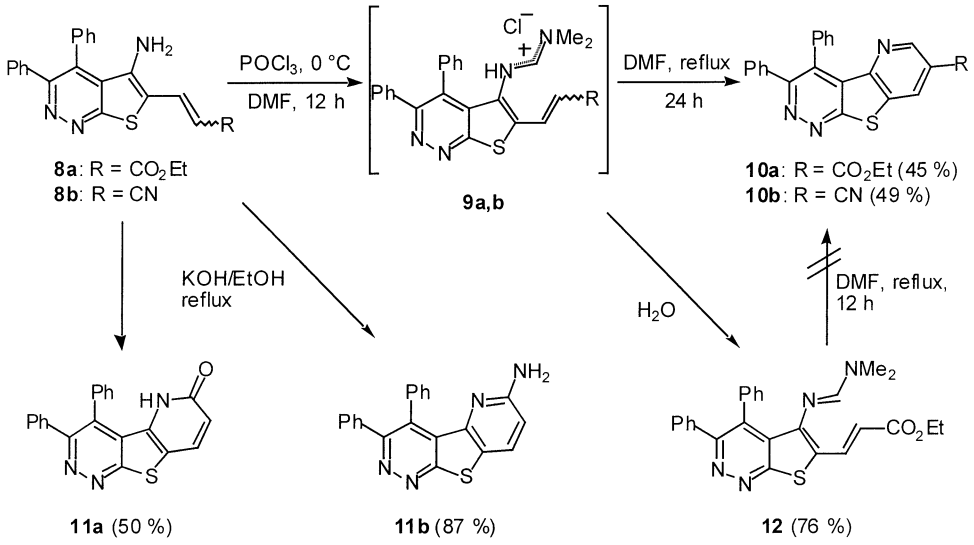
4a,b **5a-d** **6a-d**

4	Ar	X	t (h)	Product	%
a	C_6H_5	O	8	**7a**	94
a	C_6H_5	S	10	**7b**	91
b	4-MeO-C_6H_4	O	18	**7c**	94
b	4-MeO-C_6H_4	S	19	**7d**	84



7a-d

Scheme 2.



Scheme 3.

aromatic and aliphatic iso(thio)cyanates in dry toluene at reflux temperature leads directly to the pyrido-[2′,3′:4,5]thieno[2,3-*c*]pyridazine derivatives **3a**–**m** (Scheme 1). Presumably, the conversion involves an initial aza-Wittig reaction between the iminophosphorane and the isocyanate to give a carbodiimide (**2**) as highly reactive intermediate which undergoes electrocyclic ring closure followed by [1,3-*H*] shift to afford the final product **3** in moderate to good yields. The structure of compounds **3** was determined by microanalyses and spectral data. In the ^{1}H NMR spectra, the characteristic chemical shifts of the amino group are found at δ=4.91–12.03 ppm, and those of H-8 at δ=8.14–8.94 ppm as singlets, while the ^{13}C NMR spectra showed a signal at δ=135.0–137.1 ppm due to the C-8 carbon.

Similarly, the expected imine derivatives **4** were obtained in high yields by reaction of 5-amino-3,4-diphenylthieno-[2,3-*c*]pyridazine-6-carbaldehyde with aromatic primary amines in refluxing EtOH–AcOH.[20] The desired key intermediates iminophosphoranes **5** were obtained very readily from aldimines **4** in high yields by treatment with the triphenylphosphine/triethylamine/hexachloroethane system in dry toluene (known as the Appel method and often used even in recent literatures)[21]. Heating iminophosphoranes **5** in sealed tube at 120°C with carbon dioxide or carbon disulfide in toluene gave 1,5-diaza-1,3,5-hexatriene intermediates **6**, which contains cumulated double bonds at the one end. A thermally induced 6π-electrocyclization of 1,5-diaza-1,3,5-hexatrienes **6** followed by a [1,3] hydrogen shift affords the pyrimidine ring to yield the cyclization products **7** (Scheme 2). Unfortunately, all attempts at the direct conversion of compounds **4** into the pyrimidothieno-pyridazine system by treatment with iso(thio)cyanates followed by electrocyclic ring closure failed, resulting in a complex mixture of unidentified products (TLC control). Compounds **7** were characterized from their spectroscopic data and mass spectrometric data. The mass spectra showed the expected molecular ion peak and the IR spectra exhibited one strong absorption band at ν=1660–1690 or 1590–1610 cm^{-1} due to the carbonyl or thiocarbonyl groups, respectively. In the ^{1}H NMR spectra, the characteristic chemical shifts of the H-5 are found at δ=8.34–9.28 ppm as singlets. Low solubilities of **7a**–**d** in common deuterated solvents did not allow to obtain a good ^{13}C NMR spectra.

On the other hand, we found that, under Vilsmeier conditions, tricyclic pyridothienopyridazine derivatives **10** were produced from 5-vinylthienopyridazines **8**[19c], accompanied by loss of dimethylamine. The heterocyclization of **8a**,**b** occurred smoothly with an excess of the Vilsmeier reagent (mole ratio 1:6) at 0°C followed by prolonged reflux in *N*,*N*-dimethylformamide. The structure of compounds **10** were unambiguously deduced from their spectral data and elemental analyses. The most salient features of the ^{1}H NMR and ^{13}C NMR spectra are summarized on Experimental. The mechanism of the heterocyclization[22] probably includes an initial *N*-formylation of the aminovinylthieno-pyridazine **8** to give an intermediate dimethyliminium salt **9**. Then, nucleophilic attack of the chloride ion on the *N*-alkyl moiety provokes simultaneous electrocyclic ring closure. As a final step, aromatization of the 2,3-dihydropyridine occurs, via elimination of dimethylamine, to give the fused pyridines **10a**,**b**. When intermediate **9a** was treated with ice instead of refluxing, compound **12** was obtained, which cannot be transformed in **10a** by refluxing in DMF (Scheme 3).

Finally, when vinylthienopyridazines **8a**,**b** were treated with potassium hydroxide in ethanol pyridothienopyridazines **11a**,**b** were obtained by intramolecular cyclization. The molecular structure was supported by the spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra) and elemental analyses.

4. Conclusion

The above methods demonstrate that the tandem aza-Wittig/electrocyclization strategy provides a new entry to a variety

of the tricyclic pyridothienopyridazine and pyrimidothienopyridazine systems. Advantages of the present method are: easy availability of starting materials, good yields in the iminophosphorane preparation as well as in the cyclization step, and experimental simplicity of the one-pot procedure.

5. Experimental

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded as potassium bromide disks on a Perkin–Elmer 783 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC 200F instrument at room temperature. Mass spectra were obtained on 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 flash chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the elemental analyses general service of the University of La Coruña.

5.1. General procedure for the synthesis of 3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazines (3a–m)

To a solution of **1a** or **1b**[19a] (100 mg) in toluene (5 mL) the appropriated iso(thio)cyanate (1.1 equiv.) was added, and the mixture was heated at reflux for 1–20 h; after cooling the solvent was evaporated, the crude was slurred with ether (5 mL) and the solid formed was filtered off and recrystallized from acetone/CH_2Cl_2.

5.1.1. Ethyl 3,4-diphenyl-6-phenylaminopyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3a). (92%); mp 221–223°C. IR (KBr, cm^{-1}): 1690 (CO), 1570, 1500, 1440, 1230, 760, 700. ^{1}H NMR δ($CDCl_3$): 1.48 (t, 3H, J=7.1 Hz, CH_3), 4.46 (q, 2H, J=7.1 Hz, OCH_2), 6.83–7.12 (m, 5H, C_6H_5), 7.22–7.69 (m, 10H, C_6H_5), 8.83 (s, 1H, H-8), 10.42 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 62.1 (CH_2), 109.7 (C-7), 118.6, 121.6, 123.9, 126.6, 127.7, 127.9, 128.0, 128.8, 129.0, 130.2, 130.5, 133.3, 135.5 (C-8), 137.0, 139.2, 150.6, 153.2, 157.5, 165.1, 166.5 (CO). MS (FAB, *m*/*z*, %): 503 [$(MH)^+$, 46], 351 (12), 288 (35), 214 (30), 197 (34), 181 (100). Anal. calcd for $C_{30}H_{22}N_4O_2S$: C, 71.69; H, 4.41; N, 11.15. Found C, 71.91; H, 4.38; N, 10.98.

5.1.2. Ethyl 6-(4-chlorophenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3b). (63%); mp 245–247°C. IR (KBr, cm^{-1}): 1680 (CO), 1610, 1570, 1400, 1210, 800, 700. ^{1}H NMR δ($CDCl_3$): 1.47 (t, 3H, J=7.1 Hz, CH_3), 4.48 (q, 2H, J=7.1 Hz, OCH_2), 6.83, 6.92 (AA′BB′ system, 4H, J=9.0 Hz, C_6H_4), 7.19–7.64 (m, 10H, C_6H_5), 8.81 (s, 1H, H-8), 10.37 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 62.2 (OCH_2), 109.7 (C-7), 120.3, 124.4, 126.5, 126.6, 127.8, 128.0, 128.1, 128.8, 129.1, 130.2, 130.6, 133.3, 135.6 (C-8), 136.9, 137.8, 150.7, 153.1, 157.6, 166.6 (CO). MS (EI, *m*/*z*, %): 538 (M^++2, 34), 356 (M^+, 100), 455 (37), 398 (11), 245 (23), 121 (27), 199 (28), 111 (28). Anal. calcd for $C_{30}H_{21}N_4O_2SCl$: C, 67.09; H, 3.94; N, 10.43. Found C, 67.00; H, 4.03; N, 10.53.

5.1.3. Ethyl 6-(4-fluorophenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3c). (76%); mp 200–202°C. IR (KBr, cm^{-1}): 1690 (CO), 1590, 1510, 1240, 800, 700. ^{1}H NMR δ($CDCl_3$): 1.48 (t, 3H, J=7.1 Hz, CH_3), 4.45 (q, 2H, J=7.1 Hz, OCH_2), 6.61–6.90 (m, 4H, C_6H_4), 7.20–7.37 (m, 10H, C_6H_5), 8.82 (s, 1H, H-8), 10.30 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 62.1 (OCH_2), 119.6 (C-7), 115.4 (J=22.7 Hz, C-3′, C-5′), 120.5 (J=7.1 Hz, C-2′, C-6′), 124.0, 126.6, 127.8, 128.0, 129.0, 130.2, 130.6, 133.3, 135.3 (C-8), 135.6, 136.9, 150.7, 157.5, 162.7 (J=250.5 Hz, C-4′), 166.6 (CO). MS (EI, *m*/*z*, %): 520 (M^+, 100), 473 (31), 447 (21), 237 (35), 95 (40). Anal. calcd for $C_{30}H_{21}N_4O_2SF$: C, 69.22; H, 4.07; N, 10.76. Found C, 68.93; H, 4.03; N, 10.77.

5.1.4. Ethyl 6-(4-methoxyphenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3d). (66%); mp 199–201°C. IR (KBr, cm^{-1}): 1690 (CO), 1570, 1500, 1240, 1200, 800, 700, 600. ^{1}H NMR δ($CDCl_3$): 1.47 (t, 3H, J=7.1 Hz, CH_3), 3.79 (s, 3H, OCH_3), 4.45 (q, 2H, J=7.1 Hz, OCH_2), 6.54, 6.85 (AA′BB′ system, 4H, J=9.0 Hz, C_6H_4), 7.15–7.34 (m, 10H, C_6H_5), 8.80 (s, 1H, H-8), 10.21 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 55.3 (OCH_3), 62.0 (CH_2), 109.4 (C-7), 114.1, 120.6, 123.4, 126.7, 127.7, 127.9, 128.8, 130.2, 130.6, 132.7, 133.3, 135.5, 135.7 (C-8), 137.0, 150.9, 153.4, 154.5, 157.5, 165.2, 166.6 (CO). MS (EI, *m*/*z*, %): 532 (M^+, 100), 485 (15), 459 (6), 243 (21), 207 (14), 77 (10). Anal. calcd for $C_{31}H_{24}N_4O_3S$: C, 69.91; H, 4.54; N, 10.52. Found C, 70.31; H, 4.50; N, 10.41.

5.1.5. Ethyl 6-(4-methylphenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3e). (59%); mp 200–202°C. IR (KBr, cm^{-1}): 1690 (CO), 1610, 1520, 1220, 800, 700, 610. ^{1}H NMR δ($CDCl_3$): 1.47 (t, 3H, J=7.1 Hz, CH_3), 2.28 (s, 3H, $C_6H_4CH_3$), 4.48 (q, 2H, J=7.1 Hz, OCH_2), 6.80–6.89 (m, 4H, C_6H_4), 7.21–7.61 (m, 10H, C_6H_5), 8.80 (s, 1H, H-8), 10.29 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 20.8 ($C_6H_4CH_3$), 62.0 (CH_2), 109.6 (C-7), 119.0, 123.6, 126.7, 127.7, 127.9, 128.9, 129.4, 130.2, 130.5, 133.3, 135.5 (C-8), 136.7, 137.0, 150.8, 157.7, 165.2, 166.7, 167.5 (CO). MS (EI, *m*/*z*, %): 516 (M^+, 100), 469 (37), 443 (21), 235 (35), 90 (37). Anal. calcd for $C_{31}H_{24}N_4O_2S$: C, 72.07; H, 4.68; N, 10.85. Found C, 72.26; H, 4.60; N, 10.91.

5.1.6. Ethyl 6-cyclohexylamino-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3f). (91%); mp 235–237°C. IR (KBr, cm^{-1}): 3330 (NH), 1700 (CO), 1600, 1225, 810, 720. ^{1}H NMR δ($CDCl_3$): 1.06–1.72 (m, 10H, CH_2), 1.42 (t, 3H, J=7.1 Hz, CH_3), 3.30–3.34 (m, 1H, NCH), 4.32 (q, 2H, J=7.1 Hz, CH_2), 7.19–7.32 (m, 10H, C_6H_5), 7.92 (d, 1H, J=8.8 Hz, NH), 8.65 (s, 1H, H-8). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 23.8, 25.7, 32.5 (CH_2), 46.9 (NCH), 61.3 (OCH_3), 108.1 (C-7), 120.9, 127.8, 127.9, 128.1, 130.2, 130.3, 132.1, 132.4, 134.0, 135.2 (C-8), 136.9, 155.7, 156.8, 164.5, 166.5 (CO). MS (EI, *m*/*z*, %): 508 (M^+, 100), 479 (62), 426 (53), 352 (18), 195 (22), 55 (51). Anal. calcd for $C_{30}H_{28}N_4O_2S$: C, 70.84; H, 5.55; N, 11.02. Found C, 70.73; H, 5.86; N, 10.98.

5.1.7. Ethyl 6-isopropylamino-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine-7-carboxylate (3g). (70%); mp 195–197°C. IR (KBr, cm^{-1}): 3340 (NH), 1700

(CO), 1600, 1580, 1500, 1230, 800, 710. ^{1}H NMR δ($CDCl_3$): 0.89 [d, 6H, J=6.3 Hz, $CH(CH_3)_2$], 1.41 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.45 (m, 1H, NCH), 4.36 (q, 2H, J=7.0 Hz, OCH_2), 7.22–7.39 (m, 10H, C_6H_5), 7.70 (d, 1H, J=7.8 Hz, NH), 8.63 (s, 1H, H-8). ^{13}C NMR δ($CDCl_3$): 14.2 (OCH_2CH_3), 22.6 [$CH(CH_3)_2$], 61.3 (OCH_2), 108.0 (C-7), 120.9, 127.7, 127.9, 130.4, 134.0, 135.0 (C-8), 135.5, 136.9, 151.4, 155.6, 156.7, 165.4, 166.2 (CO). MS (EI, *m/z*, %): 468 (M^+, 100), 453 (83), 439 (53), 421 (26), 407 (52), 189 (59). Anal. calcd for $C_{27}H_{24}N_4O_2S$: C, 69.21; H, 5.16; N, 11.96. Found C, 69.48; H, 5.38; N, 11.93.

5.1.8. Ethyl 6-(2-methoxycarbonylthiophen-3-ylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]-pyridazine-7-carboxylate (3h). (53%); mp 266–268°C. IR (KBr, cm^{-1}): 1710, 1690 (CO), 1580, 1370, 1250, 700. ^{1}H NMR δ($CDCl_3$): 1.48 (t, 3H, J=7.1 Hz, OCH_2CH_3), 3.93 (s, 3H, OCH_3), 4.56 (q, 2H, J=7.1 Hz, OCH_2), 6.46, 6.86 (AA′BB′ system, 2H, J=5.4 Hz, H-4′, H-5′), 7.20–7.40 (m, 10H, C_6H_5), 8.94 (s, 1H, H-8), 12.03 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 14.3 (OCH_2CH_3), 51.8 (OCH_3), 62.2 (OCH_2), 108.5, 111.4 (C-7), 122.1, 125.7, 127.8, 127.9, 128.3, 129.1, 130.2, 130.7, 133.7, 135.9 (C-8), 136.8, 144.9, 151.4, 157.5, 161.0, 164.2, 165.4 (CO). MS (EI, *m/z*, %): 566 (M^+, 100), 461 (58), 433 (14), 230 (28), 57 (18). Anal. calcd for $C_{30}H_{22}N_4O_4S_2$: C, 63.59; H, 3.91; N, 9.89. Found C, 63.31; H, 3.95; N, 10.02.

5.1.9. 7-Cyano-3,4-diphenyl-6-phenylaminopyrido[2′,3′:4,5]-thieno[2,3-*c*]pyridazine (3i). (76%); mp 249–251°C. IR (KBr, cm^{-1}): 3420 (NH), 2220 (CN), 1610, 1560, 1440, 760, 710. ^{1}H NMR δ($CDCl_3$): 6.86–7.33 (m, 16H, C_6H_5+ H-8), 8.38 (s, 1H, NH). ^{13}C NMR δ($CDCl_3$): 96.2 (C-7), 115.7 (CN), 118.8, 122.9, 124.7, 126.4, 127.8, 128.1, 129.2, 130.2, 130.3, 133.0, 135.9, 136.7, 136.9 (C-8), 138.1, 150.4, 152.7, 157.8. MS (EI, *m/z*, %): 455 (M^+, 97), 361 (14), 228 (21), 213 (27), 77 (100). Anal. calcd for $C_{28}H_{17}N_5S$: C, 73.83; H, 3.76; N, 15.37. Found C, 73.61; H, 3.70; N, 15.50.

5.1.10. 7-Cyano-6-(4-fluorophenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine (3j). (51%); mp 264–266°C. IR (KBr, cm^{-1}): 3400 (NH), 2220 (CN), 1570, 1420, 1240, 840, 710. ^{1}H NMR δ($CDCl_3$): 6.67–6.88 (m, 4H, C_6H_4), 6.99 (s, 1H, NH), 7.16–7.50 (m, 10H, C_6H_5), 8.37 (s, 1H, H-8). ^{13}C NMR δ($CDCl_3$): 95.8 (C-7), 115.7 (CN), 115.8 (J=22.7 Hz, C-3′, C-5′), 121.2 (J=8.5 Hz, C-2′, C-6′), 124.6, 127.8, 127.9, 128.1, 129.0, 130.2, 130.3, 132.9, 134.0, 135.8, 136.5, 136.9 (C-8), 150.3, 152.9, 156.2, 158.6 (J=242.7 Hz, C-4′), 164.6. MS (EI, *m/z*, %): 473 (M^+, 100), 444 (10), 361 (25), 222 (35), 95 (54). Anal. calcd for $C_{28}H_{16}N_5SF$: C, 71.02; H, 3.41; N, 14.79. Found C, 71.30; H, 3.30; N, 14.62.

5.1.11. 7-Cyano-6-(4-methoxyphenylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine (3k). (86%); mp 253–255°C. IR (KBr, cm^{-1}): 3410 (NH), 2210 (CN), 1600, 1560, 1510, 1420, 1300, 800, 710. ^{1}H NMR δ($CDCl_3$): 3.82 (s, 3H, OCH_3), 6.59, 6.80 (AA′BB′ system, 4H, J=8.8 Hz, C_6H_4), 6.90 (s, 1H, NH), 7.15–7.27 (m, 10H, C_6H_5), 8.33 (s, 1H, H-8). ^{13}C NMR δ($CDCl_3$): 55.4 (CH_3), 95.6 (C-7), 114.4, 115.9 (CN), 121.4, 124.7, 127.9, 128.1, 128.8, 130.2, 130.3, 132.9, 136.8 (C-8), 150.5, 153.3, 155.6, 164.5. MS (EI, *m/z*, %): 485 (M^+, 100), 470 (27), 243 (11), 77 (23). Anal. calcd for $C_{29}H_{19}N_5OS$: C, 71.73; H, 3.94; N, 14.42. Found C, 71.66; H, 3.83; N, 14.44.

5.1.12. 7-Cyano-6-isopropylamino-3,4-diphenylpyrido-[2′,3′:4,5]thieno[2,3-*c*]pyridazine (3l). (51%); mp 266–268°C. IR (KBr, cm^{-1}): 3360 (NH), 2220 (CN), 1600, 1560, 1260, 770, 700. ^{1}H NMR δ($CDCl_3$): 0.91 (d, 6H, J=6.3 Hz, CH_3), 3.31–3.54 (m, 1H, NCH), 4.91 (d, 1H, J=7.8 Hz, NH), 7.21–7.41 (m, 10H, C_6H_5), 8.16 (s, 1H, H-8). ^{13}C NMR δ($CDCl_3$): 22.5 (CH_3), 42.7 (NCH), 93.3 (C-7), 116.1 (CN), 121.8, 126.7, 127.8, 128.1, 129.9, 130.4, 133.8, 135.7, 136.4 (C-8), 136.5, 150.8, 154.9, 156.9, 164.8. MS (EI, *m/z*, %): 421 (M^+, 77), 406 (100), 378 (36), 188 (17), 77 (12). Anal. calcd for $C_{25}H_{19}N_5S$: C, 71.23; H, 4.54; N, 16.61. Found C, 71.41; H, 4.62; N, 16.77.

5.1.13. 7-Cyano-6-(2-methoxycarbonylthiophen-3-ylamino)-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazine (3m). (69%); mp 256–258°C. IR (KBr, cm^{-1}): 3320 (NH), 2210 (CN), 1690 (CO), 1590, 1450, 1260, 780. ^{1}H NMR δ($CDCl_3$): 3.92 (s, 3H, OCH_3), 6.41, 6.97 (AA′BB′ system, 2H, J=5.4 Hz, H-4′, H-5′), 7.18–7.49 (m, 10H, C_6H_5), 8.42 (s, 1H, H-8), 10.74 (s, 1H, NH) ^{13}C NMR δ($CDCl_3$): 52.2 (OCH_3), 97.2 (C-7), 108.6, 115.0 (CN), 121.2, 125.7, 126.3, 127.8, 128.1, 128.6, 129.0, 130.1, 130.4, 131.4, 133.8, 135.4, 136.5, 137.1 (C-8), 144.6, 150.0, 151.3, 157.8, 164.5, 164.8 (CO). MS (EI, *m/z*, %): 519 (M^+, 56), 487 (18), 461 (100), 426 (13), 216 (19), 149 (27), 103 (32). Anal. calcd for $C_{28}H_{17}N_5O_2S_2$: C, 64.72; H, 3.30; N, 13.48. Found C, 64.41; H, 3.15; N, 13.81.

5.2. General procedure for the synthesis of 6-(4-aryliminomethylen)-3,4-diphenyl-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*]pyridazines (5a,b)

A mixture of the appropriated heterocyclic amine[20] (250 mg), triphenylphosphine (1.5 equiv.), hexachloroethane (1.5 equiv.) and triethylamine (2.5 equiv.) in toluene (15 mL) was heated in a sealed tube at 100°C for 24 h. After cooling the solid formed was filtered off, washed with water and recrystallized from EtOH/CH_2Cl_2.

5.2.1. 3,4-Diphenyl-6-(4-phenyliminomethylen)-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*] pyridazine (5a). (81%); mp 233–235°C. IR (KBr, cm^{-1}): 1550; 1460; 1410; 1160; 1110; 700. ^{1}H NMR ($CDCl_3$): 6.60–6.65 (m, 2H, C_6H_5); 6.84–7.45 (m, 28H, C_6H_5); 8.17 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$): 121.1; 125.5; 126.9; 127.1; 127.3; 127.5; 128.5; 128.8; 130.2; 130.6; 130.9; 131.9; 132.0; 132.2; 133.4; 134.3; 134.8; 135.8; 137.9; 147.3; 151.4; 154.1 (CHN); 156.3; 163.4. ^{31}P NMR ($CDCl_3$): 7.2. MS (FAB, *m/z*, %): 667 [$(MH)^+$, 13]; 217 (100); 262 (25); 183 (39); 183 (38). Anal. calcd for $C_{43}H_{31}N_4PS$: C, 77.46; H, 4.69; N, 8.40. Found C, 77.68; H, 4.35; N, 8.59.

5.2.2. 6-(4-Methoxyphenyliminomethylen)-3,4-diphenyl-5-[(triphenylphosphoranylidene)amino]thieno[2,3-*c*] pyridazine (5b). (91%); mp 275–277°C. IR (KBr, cm^{-1}): 1610; 1490; 1460; 1430; 1410; 1250; 700. ^{1}H NMR ($CDCl_3$): 3.81 (s, 3H, CH_3); 6.61, 6.70 (AA′BB′ system, 4H, J=9.3 Hz, C_6H_4); 6.90–7.45 (m, 25H, C_6H_5); 8.20 (s, 1H, CHN). ^{13}C NMR ($CDCl_3$): 55.4 (OCH_3); 113.8; 122.4;

127.7; 130.2; 130.7; 130.9; 131.9; 132.0; 134.0; 134.8; 137.8; 144.4; 146.4; 152.0 (NCH); 156.2; 157.9; 163.3. ^{31}P NMR ($CDCl_3$): 6.8. MS (FAB, *m/z*, %): 697 [$(MH)^+$, 13]; 683 (13); 316 (20); 288 (45); 262 (32); 183 (100). Anal. calcd for $C_{44}H_{33}N_4OPS$: C, 75.84; H, 4.77; N, 8.04. Found C, 76.20; H, 4.54; N, 7.88.

5.3. General procedure for the synthesis of 3,4-diphenyl-8-(thi)oxo-6,7-dihydropyrimido[2′,3′:4,5]thieno[2,3-*c*]-pyridazines (7a–d)

A mixture of the appropriated iminophosphorane **5a**,**b** (150 mg), an excess of solid carbon dioxide or carbon disulfide in toluene (10 mL) was heated in a sealed tube at 115°C in an argon atmosphere. After cooling, the solvent was removed under reduced pressure and the crude product was recrystallized or purified by flash chromatography to yield **7a**–**d**.

5.3.1. 6,7-Dihydropyrimido-3,4,7-triphenyl-6-oxo[4′,5′:4,5]-thieno[2,3-*c*]pyridazine (7a). (94%); recrystallized from EtOH/CH_2Cl_2; mp>300°C. IR (KBr, cm^{-1}): 1690 (CO); 1490; 1340; 700. ^{1}H NMR (DMSO-d_6): 7.29–7.30 (m, 10H, C_6H_5); 7.52 (broad s, 5H, C_6H_5N); 9.14 (s, 1H, H-8). MS (FAB, *m/z*, %): 434 [$(MH^+)+1$, 100]; 433 [$(MH)^+$, 40]; 330 (21). Anal. calcd for $C_{26}H_{16}N_4OS$: C, 70.20; H, 3.73; N, 12.95. Found C, 69.99; H, 3.86; N, 12.88.

5.3.2. 6,7-Dihydropyrimido-3,4,7-triphenyl-6-thioxo-[4′,5′:4,5]thieno[2,3-*c*]pyridazine (7b). (91%); recrystallized from CH_2Cl_2; mp>300°C. IR (KBr, cm^{-1}): 1606; 1471; 1341; 1192; 760; 696. ^{1}H NMR (DMSO-d_6): 7.24–7.60 (m, 15H, C_6H_5); 9.28 (s, 1H, H-8). MS (FAB, *m/z*, %): 450 [$(MH^+)+1$, 100]; 449 [$(MH)^+$, 51]; 346 (10); 274 (17). Anal. calcd for $C_{26}H_{16}N_4S_2$: C, 69.62; H, 3.60; N, 12.49. Found C, 69.97; H, 3.50; N, 12.12.

5.3.3. 7-(4-Methoxyphenyl)-3,4-diphenyl-6-oxo-6,7-dihydropyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (7c). (94%); recrystallized from CH_2Cl_2; mp 291–293°C. IR ((KBr, cm^{-1}): 1660 (CO); 1500; 1250; 840; 690. ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, CH_3); 6.99 (d, 2H, J=8.8 Hz, C_6H_4); 7.24–7.40 (m, 12H, $C_6H_5+C_6H_4$); 8.27 (s, 1H, H-8). MS (FAB, *m/z*, %): 464 [$(MH^+)+1$, 100]; 463 [$(MH)^+$, 42]; 197 (13); 181 (66). Anal. calcd for $C_{27}H_{18}N_4O_2S$: C, 70,11; H, 3,92; N, 12,11. Found C, 70.26; H, 4.13; N, 12.00.

5.3.4. 3,4-Diphenyl-7-(4-methoxyphenyl)-6-thioxo-6,7-dihydropyrimido[4′,5′:4,5]thieno[2,3-*c*]pyridazine (7d). (84%); purified by flash chromatography using CH_2Cl_2/AcOEt (12:1) as eluent; mp 256–258°C. IR (KBr, cm^{-1}): 1590; 1380; 1130; 1230; 690. ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, CH_3); 7.02 (d, 2H, J=8.8 Hz, C_6H_4); 7.24–7.42 (m, 12H, $C_6H_5+C_6H_4$); 8.34 (s, 1H, H-8). MS (FAB, *m/z*, %): 480 [$(MH)^+ +1$, 100]; 479 [$(MH)^+$, 49]. Anal. calcd for $C_{27}H_{18}N_4OS_2$: C, 67.76; H, 3.79; N, 11.71. Found C, 67.50; H, 3.70; N, 11.95.

5.4. General procedure for the synthesis of 3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]pyridazines (10a,b)

Over DMF (10 mL) at −10°C was added dropwise $POCl_3$ (0.1 mL, 2.5 equiv.), and the mixture was stirred for 1 h; **8a** or **b** (150 mg) was added in portions at that temperature, and the mixture was stirred overnight at room temperature. Afterward the reaction mixture was heated at reflux for 24 h; after cooling, ice was added, and the solid formed was filtered off and purified by flash chromatography using CH_2Cl_2/AcOEt (25:1) as eluent.

5.4.1. Ethyl 3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]-pyridazine-7-carboxylate (10a). (45%); mp 198–200°C. IR (KBr, cm^{-1}): 1710 (CO), 1590, 1300, 1140, 1010, 780, 700. ^{1}H NMR δ($CDCl_3$): 1.42 (t, 3H, J=7.3 Hz, CH_3), 4.45 (q, 2H, J=7.3 Hz, OCH_2), 7.23–7.43 (m, 10H, C_6H_5), 8.87 (d, 1H, J=2.0 Hz, H-6), 9.12 (d, 1H, J=2.0 Hz, H-8). ^{13}C NMR δ($CDCl_3$): 14.2 (CH_3), 61.9 (OCH_2), 125.3 (C-7), 127.2, 127.8, 127.9, 128.9, 128.5, 130.2, 130.4, 132.2 (C-8), 133.0, 134.8, 135.8, 136.6, 148.2 (C-6), 151.7, 164.4 (CO). MS (FAB, *m/z*, %): 412 [$(MH)^+$, 100], 304 (14). Anal. calcd for $C_{24}H_{17}N_3O_2S$: C, 70.05; H, 4.16; N, 10.21. Found C, 69.88; H, 4.04; N, 10.28.

5.4.2. 7-Cyano-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]-pyridazine (10b). (49%); mp 264–266°C. IR (KBr, cm^{-1}): 2220 (CN), 1440, 1320, 750, 690. ^{1}H NMR δ($CDCl_3$): 7.24–7.48 (m, 10H, C_6H_5), 8.55 (d, 1H, J=1.9 Hz, H-6), 8,73 (d, 1H, J=1.9 Hz, H-8). ^{13}C NMR δ($CDCl_3$): 108.8 (C-7), 116.1 (CN), 126.7, 128.0, 128.4, 130.0, 130.4, 132.6, 134.4 (C-8), 134.9, 135.4, 136.3, 148.8 (C-6), 151.4, 157.9, 163.8. MS (EI, *m/z*, %): 364 (M^+, 98), 363 (100), 335 (29), 262 (6), 182 (13), 168 (19). Anal. calcd for for $C_{22}H_{12}N_4S$: C, 72.51; H, 3.32; N, 15.37. Found C, 72.25; H, 3.49; N, 15.59.

5.4.3. 6-Oxo-3,4-diphenyl-5,6-dihydropyrido[2′,3′:4,5]-thieno[2,3-*c*]pyridazine (11a). A solution of **8a** (150 mg, 0.374 mmol) and KOH (42 mg, 0.748 mmol) in EtOH (13 mL) was refluxed for 2.5 h. The solvent was evaporated, CH_2Cl_2 (25 mL) was added and the solution was washed with water and dried with Na_2SO_4. After the solvent was evaporated, the crude obtained was purified by flash chromatography using CH_2Cl_2/AcOEt (1:1) as eluent to yield **7** (66 mg, 50%); mp: 254–256°C (dec.). IR (KBr, cm^{-1}): 3360 (NH), 1670 (CO), 1570, 1510, 1440, 840, 700. ^{1}H NMR δ(DMSO-d_6): 6.92 (d, 1H, J=8.8 Hz, H-7), 7.28–7.33 (m, 10H, C_6H_5), 8.40 (d, 1H, J=8.8 Hz, H-8), 10.66 (br s, 1H, NH). MS (EI, *m/z*, %): 355 (M^+, 75), 354 (100), 326 (29), 297 (24), 154 (25), 113 (21), 77 (55). Anal. calcd for $C_{21}H_{13}N_3SO$: C, 70.97; H, 3.69; N, 11.82. Found C, 70.88; H, 3.48; N, 11.99.

5.4.4. 6-Amino-3,4-diphenylpyrido[2′,3′:4,5]thieno[2,3-*c*]-pyridazine (11b). A solution of **8b** (150 mg, 0.424 mmol) and KOH (47 mg, 0.847 mmol) in EtOH (13 mL) was refluxed for 1 h. The solvent was evaporated, CH_2Cl_2 (25 mL) was added and the solution was washed with water and dried with Na_2SO_4. After the solvent was evaporated, the crude obtained was purified by flash chromatography using CH_2Cl_2/AcOEt (9:1) as eluent to yield **8** (130 mg, 87%); mp 256–258°C. IR (KBr, cm^{-1}): 3470, 3320 (NH_2), 1620, 1580, 1410, 1300, 1100, 820, 760. ^{1}H NMR δ(DMSO-d_6): 5.71 (br s, 2H, NH_2), 6.78 (d, 1H, J=9.3 Hz, H-7), 7.22–7.33 (m, 10H, C_6H_5), 8.15 (d, 1H, J=9.3 Hz, H-8). ^{13}C NMR *d* (DMSO-d_6): 112.5 (C-7), 123.0, 127.5, 127.9, 128.1, 128.2, 130.6, 130.8, 133.6,

132.8 (C-8), 134.6, 134.7, 146.4, 156.4, 158.0, 164.0. MS (FAB, *m/z*, %): 355 [$(MH)^+$, 100], 181 (11). Anal. calcd for $C_{21}H_{14}N_4S$: C, 71.16; H, 3.98; N, 15.81. Found C, 71.35; H, 4.09; N, 15.46.

5.4.5. 6-[(*E*)-2-Ethoxycarbonylvinyl]-5-dimethylaminomethylenamino-3,4-diphenylthieno[2,3-*c*]pyridazine (12). Over DMF (10 mL) at −10°C was added dropwise $POCl_3$ (0.1 mL, 2.5 equiv.), and the mixture was stirred for 1 h; **8a** (0.150 g, 0.373 mmol) was added in portions at that temperature, and the mixture was stirred overnight at room temperature. Afterward, ice was added and the solid formed was filtered off and recrystallized from acetone/CH_2Cl_2 to yield **12** (130 mg, 76 %); mp 256–258°C. IR (KBr, cm^{-1}): 1710 (CO); 1650; 1610; 1310; 1200; 740. ^1H NMR ($CDCl_3$): 1.33 (t, 3H, J=7.1 Hz, OCH_2CH_3); 2.46 (s, 3H, NCH_3); 2.65 (s, 3H, NCH_3); 4.25 (c, 2H, J=7.0 Hz, OCH_2); 6.34 (d, 1H, J=15.6 Hz, H-2′); 6.76 (s, 1H, NCH); 7.07–7.27 (m, 10H, C_6H_5); 7.85 (d, 1H, J=15.6 Hz, H-1′); ^{13}C NMR δ($CDCl_3$): 14.3 (OCH_2CH_3); 33.6, 39.9 (NCH_3); 60.6 (OCH_2); 119.5 (C-2′); 127.3; 127.4; 127.7; 129.4; 130.3; 133.3; 134.4; 135.2 (C-1′); 137.0; 154.0 (NCH); 156.0; 162.0; 166.6 (CO). MS (IE, *m/z*, %): 456 (M^+, 100); 383 (90); 340 (24); 326 (10); 77 (11). Anal. calcd for $C_{26}H_{24}N_4SO_2$: C, 68.40; H, 5.30; N, 12,27. Found C, 68.08; H, 5.53; N, 11.90.

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