Synthesis of Pyrazinothienopyrimidine Derivatives by the Application of the Intramolecular and Intermolecular Aza-Wittig Reaction/Heterocyclization

Gerardo Blanco, José M. Quintela,* Carlos Peinador*

Departamento de Química Fundamental, Facultad de Ciencias, Universidad de A Coruña, 15071 A Coruña, Spain
Fax +34(981)167000; E-mail: jqqoqf@udc.es; E-mail: capeveqo@udc.es.

Received 23 November 2007; revised 21 January 2008

Abstract: Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine derivatives **6** were synthesized by the intermolecular aza-Wittig reaction of *N*-heteroaryl phosphazene derivatives with carboxylic acid chlorides. The heterocyclization occurs via imidoyl chloride intermediates derived from phosphazenes **4a**,**b**, obtained in a one-step process from α-azidothieno[2,3-*b*]pyrazine carboxylic acid **3**. Moreover, cyclic pyrazinothienopyrimidines were prepared, in a two-step procedure, from amides and azidothienopyrazine-α-carbonyl chloride using an intramolecular aza-Wittig heterocyclization reaction strategy.

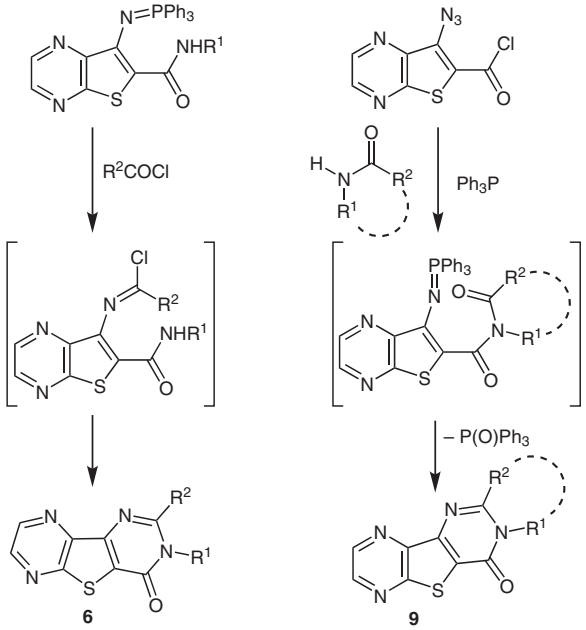
Key words: heterocycles, Wittig reaction, nitrogen, azides, cyclizations

Fused pyrimidines have been the focus of great interest in organic chemistry due to the broad spectrum of biological properties of these compounds and their practical usefulness as reagents for the fine and industrial chemistry. Compounds containing a fused pyrimidine ring play a very important part in the biochemistry of the living cell and have attracted attention in the past few years owing to their wide range of biological activity, particularly in cancer and virus research.[1] Among these heterocyclic compounds, thienopyrimidines are of special significance.[2] It is known, for example, that derivatives of this family show significant antifungal and antibacterial properties,[3] whereas others possess anticonvulsant and angiotensin receptor antagonistic activities.[4] We have previously reported on the synthesis of novel tri- and tetracyclic ring systems, containing the thienopyrimidine skeleton with anti-inflammatory and antihistaminic activity.[5] However, aza-analogue compounds incorporating an S-heterocycle fused to a pyrazine nucleus have been so far poorly utilized. Among the diazines, the pyrazine motif is an important heterocycle, as not only are these units embedded in a variety of natural products and designed molecules which exhibit citotoxicity against certain human cancer cells, but they also serve as precursors to a range of related structures.[6] In addition, substituted pyrazine motifs are often to be found in compounds with applications as anticancer agents, including currently marketed drugs[7] and those recently reported.[8]

We have been interested in the preparation and the reactivity of *N*-(heteroaryl)phosphazenes and, in previous work, we described the facile synthesis of condensed heterocycles via intramolecular aza-Wittig reactions,[9] including highly efficient and regioselective synthesis of substituted pyrazinothienopyrimidinones and bis(pyrazinothienopyrimidinyl)benzenes.[10] As an extension of this work we now report the preparation of novel *N*-(heteroaryl)phosphazenes and their employment in the synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines by way of an intramolecular or intermolecular aza-Wittig reaction followed by heterocyclization.

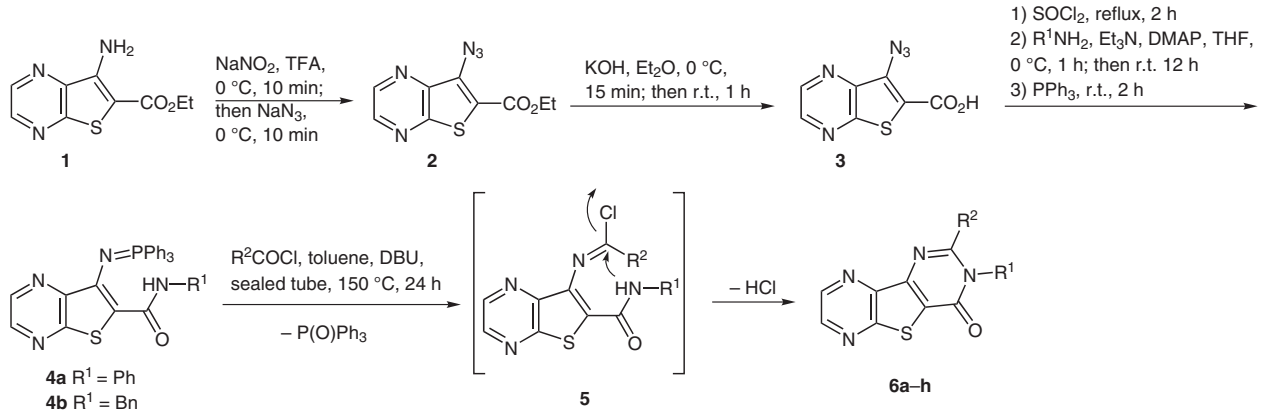
The strategy used for the development of these compounds is depicted in Scheme 1. They can be synthesized by two different ways. Pyrazinothienopyrimidines **6** were synthesized by the intermolecular aza-Wittig reaction of *N*-heteroaryl phosphazene derivatives having secondary amide functions with carboxylic acid chlorides followed by heterocyclization. Cyclic pyrazinothienopyrimidines **9** were prepared in a two-step procedure from amides and azidothienopyrazine-α-carbonyl chloride. Reaction of the crude imides with triphenylphosphine effects an intramolecular aza-Wittig reaction to afford the desired compounds in good to moderate yields.

The synthesis of *N*-heteroaryl phosphazene precursors **4a**,**b** to construct the target pyrazinothienopyrimidinones **6** is summarized in Scheme 2. At first, the reaction of the readily available heterocyclic β-enamino ester **1**[10b] with



Scheme 1 Synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines

SYNTHESIS 2008, No. 9, pp 1397–1403
Advanced online publication: 18.03.2008
DOI: 10.1055/s-2008-1072514; Art ID: T18407SS



Scheme 2 Synthesis of pyrazinothienopyrimidinones **6a–h**

sodium nitrite in TFA affords the azido derivative **2**. The formation of 7-azidothienopyrazine-6-carboxylate **2** was established by IR spectroscopy; the IR spectrum of the reaction mixture showed a strong absorption at 2102 cm^{-1} attributable to the N_3 group. After stirring at room temperature for two hours with ethanolic potassium hydroxide, followed by reprotonation of the carboxylate salt, 7-azidothieno[2,3-*b*]pyrazine-6-carboxylic acid (**3**) was isolated in 99% yield. The preparation of the required secondary aminophosphazene precursors **4** was carried out, in a one-step synthesis, by sequential reaction of 7-azidothieno[2,3-*b*]pyrazine-6-carboxylic acid (**3**) with thionyl chloride, aniline or benzylamine in the presence of triethylamine/4-dimethylaminopyridine, and triphenylphosphine. After stirring for 12 hours at room temperature, the azide derivative **3** was totally consumed, and column chromatography of the final reaction mixture allowed the isolation of 7-(triphenylphosphoranylideneamino)thiophene[2,3-*b*]pyrazine-6-carboxamides **4a** (R^1 = Ph) and **4b** (R^1 = Bn). Phosphazene derivatives **4a** and **4b** were obtained in good global yields (69% and 58%, respectively) for the conversion of **3** → **4** in a one-pot process.

Finally, the synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones **6a–h** was examined by the intermolecular aza-Wittig reaction and heterocyclization. An anhydrous toluene solution of the corresponding phosphazene **4a** or **4b** and the respective acid chlorides was heated in a sealed tube at 150 °C for 24 hours in the presence of DBU. The products obtained from these thermal treatments were chromatographed, thus allowing the isolation of nitrogen heterocyclic derivatives **6a–h** (Scheme 2 and Table 1). The method proved to be general and afforded the desired products in unoptimized yields of 73–90%.

The reaction of phosphazenes with carboxylic acid chlorides to give heterocyclic compounds has been reported by Eguchi,[11] Molina,[12] Wamhoff,[13] Ding,[14] and Zbiral et al.[15] They have shown that upon warming or in the presence of tertiary amines, imidoyl chlorides are formed, which react with internal nucleophiles to afford various heterocycles. Consequently, in the formation of pyrazinothienopyrimidinones, chloroimidoyl derivatives **5** are assumed to be the key intermediates in the consecutive reaction even though **5** could not be detected due to its high reactivity. Pyrimidoannulation occurs via intramolecular attack of the corresponding amide-donor nucleophile to give tricyclic compounds **6** through elimination of hydrogen chloride (Scheme 2).

Table 1 Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6**

Product	R^1	R^2	Yield (%)	Mp (°C)
6a	Ph	Me	73	214–215
6b	Ph	Et	90	284–285
6c	Ph	*i*-Pr	81	205–206
6d	Ph	Ph	80	260–261 (dec.)
6e	Bn	Me	82	114–115
6f	Bn	Et	76	180–181 (dec.)
6g	Bn	*i*-Pr	79	278–280 (dec.)
6h	Bn	Ph	85	249–250 (dec.)

The structural elucidation of the pyrazinothienopyrimidinones **6a–h** was established following their analytical and spectral data, and confirmed by the X-ray crystal structure determination of a monocrystal of **6b** (R^1 = Et; R^2 = Ph). The NH group of carboxamide derivatives **4a**,**b** showed a strong absorption band at 3049–3037 cm^{-1} in the IR spectra, and it appears at δ = 10.38 as a singlet, and at δ = 12.06 as a triplet, respectively, in the ^1H NMR spectra. After heterocyclization, the spectra of pyrazinothienopyrimidinones **6a–h** did not include these types of signals but displayed typical absorption bands for the R^2 substituent of the pyrimidine ring. In the crystal structure of **6b** the ethyl group adopts a coplanar disposition with the pyrazinothienopyrimidinone ring, whereas the dihedral angle between the mean planes defined by the pyrazinethienopyrimidinone nucleus and the phenyl group is approximately 90° (Figure 1).

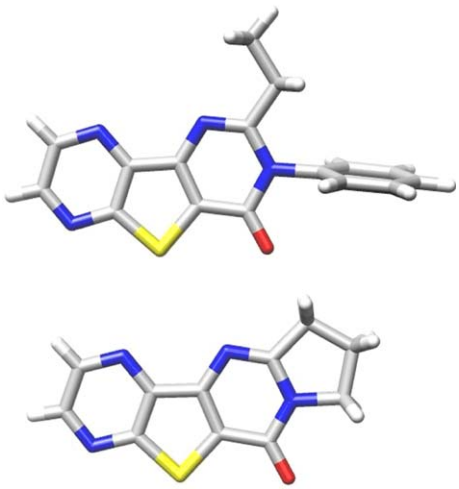
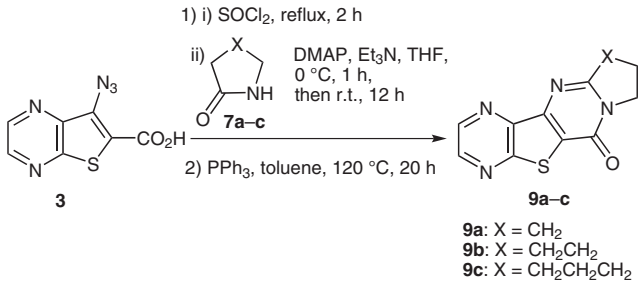


Figure 1 Crystal structures of **6b** (top) and **9a** (bottom). Color labeling scheme is as follows: S (yellow), O (red) N (blue), C (gray), H (light gray).

In an extension of this work, and since this method is not applicable to substrates in which R^1 and R^2 are tethered, we speculated that treating 7-azidothieno[2,3-*b*]pyrazine-6-carboxylic acid (**3**) with thionyl chloride, cyclic amides, and triphenylphosphine would lead to cyclic pyrazinothienopyrimidinones **9**. Thus, reaction involving the coupling between 7-azidothieno[2,3-*b*]pyrazine-6-carbonyl chloride and cyclic amides, such as γ-butyrolactam, δ-valerolactam, or ε-caprolactam could allow access to pyrazinothienopyrimidinones, a class of compounds that are particularly challenging to synthesize using existing technologies. Practically, these proposals worked out as planned. In fact, in a two-step procedure lactams **7a–c** were coupled with the azido derivative **3** and cyclized to afford pyrazinothienopyrimidinones (Scheme 3, Table 2). At first, thionyl chloride converted the carboxylic acid group into an acid chloride and subsequent N-acylation of the amide in the presence of DMAP and Et_3N gave the desired imides, which were used directly in the cyclization to generate the five-, six-, and seven-membered pyrazinothienopyrimidines **9** by reaction with triphenylphosphine in toluene at 120 °C. The separation of the products **9** from triphenylphosphine oxide, the inevitable by-product in the aza-Wittig reaction, was done by chromatography, thus resulting in the isolation of pure cyclic pyrazinothienopyrimidines **9a–c** in acceptable yields (53–58%).

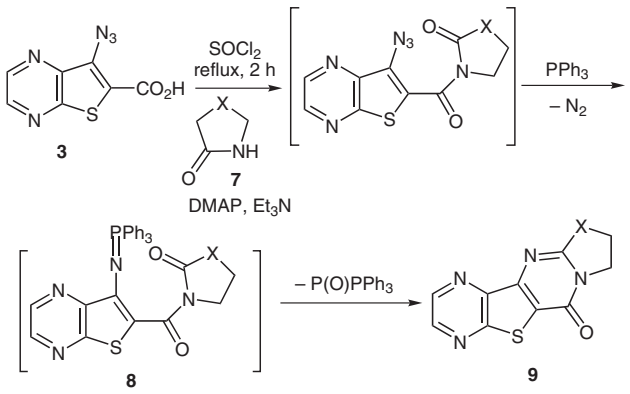


Scheme 3 Synthesis of cyclic pyrazinothienopyrimidinones **9a–c**

Table 2 Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **9**

Product	X	Yield (%)	mp (°C)
9a	CH_2	58	144–145
9b	CH_2CH_2	53	219–220
9c	$CH_2CH_2CH_2$	54	189–190

One reasonable mechanistic proposal for this sequence begins with the formation of acyl chloride. Standard coupling with the lactam to form an imide and subsequent treatment with triphenylphosphine could afford the key phosphazene intermediates **8**, which by aza-Wittig intramolecular heterocyclization reaction provide the desired cyclic pyrazinothienopyrimidine products **9** (Scheme 4). When a toluene solution of the crude imide, obtained by treatment of **3** with thionyl chloride and γ-butyrolactam, was treated with triphenylphosphine for approximately six hours at room temperature, the IR spectra of the reaction mixture showed the total disappearance of the azide band around 2100 cm^{-1} associated with the N_3 group. From the resulting crude material, α-amide phosphazene **8a** was isolated by column chromatography as the only reaction product. When a toluene solution of **8a** was heated at reflux temperature for 20 hours, it underwent intramolecular heterocyclization to provide the expected cyclic pyrazinothienopyrimidine **9a** in 99% yield. The structural determination of phosphazene derivative **8a** was achieved following their analytical and spectral data. In the case of noncyclic amides, cyclization was not observed due to the imide hydrolysis.[16] Isolation of the corresponding amide in the reaction mixture confirms the imide hydrolysis and the poor reactivity to form cyclization products. The structure of **9a** was independently confirmed by X-ray crystal structure analysis (Figure 1).



Scheme 4 Proposed mechanism to cyclic pyrazinothienopyrimidinones **9a–c**

In conclusion, the intermolecular aza-Wittig reaction of *N*-heteroaryl phosphazene derivatives, having secondary amide functions, with carboxylic acid chlorides followed by heterocyclization provided an efficient synthesis of pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones **6** via imidoyl chloride intermediates derived from *N*-phen-

yl-7-(triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-carboxamide (**4a**) and *N*-benzyl-7-(triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-carboxamide (**4b**), respectively, which were obtained in a one-step process from 7-azidothieno[2,3-*b*]pyrazine-6-carboxylic acid (**3**). On the other hand, cyclic pyrazinothienopyrimidines **9** were prepared in a two-step procedure from amides and azidothienopyrazine-α-carbonyl chloride using an intramolecular aza-Wittig heterocyclization reaction strategy. These results indicate the importance and utility of these phosphazenes as versatile building blocks in the preparation of complex polycyclic compounds. Moreover, this process represents a novel reaction sequence in the preparation of cyclic pyrazinothienopyrimidinones, a class of compounds that are particularly challenging to synthesize access using existing technologies.

All reagents were commercial grade chemicals from freshly opened containers. Merck 60 F_{254} foils were used for TLC and Merck 60 (230–400 mesh) silica gel for flash chromatography. NMR spectra were recorded on a Bruker Avance 300 (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively) or a Bruker Avance 500 spectrometer (500 MHz and 125 MHz for ^{1}H and ^{13}C, respectively) in $CDCl_3$ as solvent, and the chemical shifts are expressed in ppm relative to TMS at δ = 0.00 for ^{1}H and to $CDCl_3$ at δ = 77.1 for ^{13}C NMR spectra. IR spectra were recorded as KBr disks on a Bruker VECTOR 22 spectrophotometer. Mass spectrometry experiments were carried out in a Thermo MAT 95 XP spectrometer. Melting points were measured using Stuart Scientific SMP3 apparatus and are uncorrected. Microanalyses were performed by the elemental analyses general service of the University of A Coruña on a Carlo Erba EA-1108 instrument.

Ethyl 7-aminothieno[2,3-*b*]pyrazine-6-carboxylate (**1**) was prepared according to a literature procedure.[10b]

Ethyl 7-Azidothieno[2,3-*b*]pyrazine-6-carboxylate (2)

To a suspension of **1** (2.00 g, 9 mmol) in TFA (40 mL) cooled to 0 °C was added $NaNO_2$ (1.24 g, 18 mmol), and to this was added gradually NaN_3 (1.75 g, 27 mmol), the mixture was stirred at 0 °C for 10 min. Then, Et_2O (40 mL) was added at 0 °C, the mixture was poured into H_2O (400 mL), and the resulting suspension was extracted with Et_2O (4 × 100 mL). The combined extracts were washed with H_2O (2 × 100 mL) and brine (2 × 100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the resulting material was purified by column chromatography on silica gel using hexanes–EtOAc (10:1) as eluent; yield: 2.10 g (95%); pale yellow crystals; mp 70–71 °C (Et_2O–*n*-hexane).

IR (KBr): 2102, 1719, 1690, 1552, 1510, 1466, 1412, 1385, 1361, 1295, 1234, 1195, 1139, 1080, 1048, 1017, 868, 848, 816, 762, 438 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.1 Hz, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 8.67 (d, *J* = 2.3 Hz, 1 H), 8.70 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 14.2, 62.1, 119.3, 133.5, 141.8, 143.4, 144.1, 154.2, 160.8.

MS (FAB): *m*/*z* = 250 (100%).

Anal. Calcd for $C_9H_7N_5O_2S$: C, 43.37; H, 2.83; N, 28.10; S, 12.86. Found: C, 43.52; H, 2.98; N, 28.29; S, 12.67.

7-Azidothieno[2,3-*b*]pyrazine-6-carboxylic Acid (3)

To a solution of **2** (2.20 g, 9 mmol) in Et_2O (100 mL) cooled to 0 °C was added aq 2 M KOH (100 mL). After stirring at 0 °C for 15 min, and at r.t. for 1 h, the mixture was cooled in ice again, aq 2 M HCl (50 mL) was added and then extracted with EtOAc (3 × 100 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give **3**, which was used in the following step without further purification; yield: 1.78 g (99%); yellow-brown solid; mp 139–140 °C (dec.) (EtOAc).

IR (KBr): 3092, 2118, 1695, 1556, 1462, 1344, 1285, 1194, 1086, 1047, 988, 864, 764, 708, 510 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 2.3 Hz, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 142.0, 144.5, 192.4.

MS (FAB): *m*/*z* = 222 (25%).

Anal. Calcd for $C_7H_3N_5O_2S$: C, 38.01; H, 1.37; N, 31.66; S, 14.50. Found: C, 37.82; H, 1.20; N, 31.42; S, 14.36.

7-(Triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazines 4; General Procedure

A mixture of **3** (0.2 g, 0.9 mmol) and $SOCl_2$ (3 mL) was refluxed for 2 h. $SOCl_2$ was removed under reduced pressure, and to the resulting residue was added anhyd THF (15 mL), DMAP (0.01 g, 0.09 mmol), and anhyd Et_3N (0.38 mL, 2.7 mmol). After cooling in an ice-bath, the corresponding primary amine (0.9 mmol) was added gradually, and the mixture was stirred at 0 °C for 1 h, and at r.t. for 12 h. Next, Ph_3P (0.30 g, 1.1 mmol) was added, and the mixture was stirred at r.t for 2 h. The solvent was removed under reduced pressure and the resulting material was purified by column chromatography.

***N*-Phenyl-7-(triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-carboxamide (4a)**

Silica gel (hexanes–EtOAc, 8:2); yield: 69%; yellow solid; mp 193–194 °C (dec.) (EtOAc–hexane).

IR (KBr): 3037, 1642, 1592, 1545, 1886, 1437, 1342, 1223, 1193, 1118, 749, 717, 692, 529 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.97–7.05 (m, 1 H), 7.16–7.25 (m, 2 H), 7.33–7.60 (m, 11 H), 7.70–7.80 (m, 6 H), 7.83 (d, *J* = 2.3 Hz, 1 H), 8.24 (d, *J* = 2.3 Hz, 1 H), 12.06 (s, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 119.8, 123.2, 128.5, 128.6, 128.7, 130.8, 131.9, 131.9, 132.2, 132.4, 132.5, 138.5, 139.0, 141.7, 143.2, 144.5, 154.9, 162.5.

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 17.4.

MS (FAB): *m*/*z* = 531 (100%).

Anal. Calcd for $C_{31}H_{23}N_4OPS$: C, 70.17; H, 4.37; N, 10.56; S, 6.04. Found: C, 70.42; H, 4.18; N, 10.73; S, 6.12.

***N*-Benzyl-7-(triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-carboxamide (4b)**

Silica gel (CH_2Cl_2–EtOAc, 9:1); yield: 58%; yellow solid; mp 220–221 °C (dec.) (CH_2Cl_2–EtOAc).

IR (KBr): 3049, 1627, 1544, 1514, 1434, 1209, 1187, 1133, 1107, 756, 690, 559, 519 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.71 (d, *J* = 5.9 Hz, 2 H), 7.21–7.36 (m, 11 H), 7.41–7.49 (m, 3 H), 7.56–7.66 (m, 6 H), 7.85 (d, *J* = 2.3 Hz, 1 H), 8.23 (d, *J* = 2.3 Hz, 1 H), 10.38 (t, *J* = 5.9 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 43.2, 126.9, 127.8, 128.3, 128.4, 131.1, 131.6, 131.6, 132.1, 132.3, 132.4, 138.3, 139.5, 141.4, 142.8, 144.6, 154.7, 164.6.

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 15.6.

MS (FAB): *m*/*z* = 545 (100%).

Anal. Calcd for $C_{32}H_{25}N_4OPS$: C, 70.57; H, 4.63; N, 10.29; S, 5.89. Found: C, 70.32; H, 4.48; N, 10.53; S, 5.92.

Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-ones 6; General Procedure

A solution of the corresponding phosphazene **4** (0.1 mmol) in anhyd toluene (10 mL) was introduced in a glass tube, and the appropriate acid chloride (0.13 mmol) and DBU (0.2 mmol) were added. The glass tube was sealed and the mixture was heated at 150 °C for 24 h. After cooling, the solvent was removed under reduced pressure and the resulting material was purified by column chromatography [silica gel (hexanes–EtOAc, 7:3)].

2-Methyl-3-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6a)

Yield: 73%; white crystals; mp 214–215 °C (EtOAc–*n*-hexane).

IR (KBr): 1679, 1561, 1538, 1486, 1426, 1374, 1328, 1256, 1193, 1160, 1074, 1041, 760, 696, 656, 428 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.30–7.34 (m, 2 H), 7.54–7.63 (m, 3 H), 8.75 (d, *J* = 2.3 Hz, 1 H), 8.88 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 Hz, $CDCl_3$): δ = 24.3, 124.5, 127.7, 129.9, 130.3, 137.0, 143.0, 143.9, 144.3, 148.5, 158.2, 158.5, 158.7.

MS (FAB): *m*/*z* = 295 (100%).

Anal. Calcd for $C_{15}H_{10}N_4OS$: C, 61.21; H, 3.42; N, 19.04; S, 10.89. Found: C, 61.03; H, 3.68; N, 19.17; S, 10.67.

2-Ethyl-3-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6b)

Yield: 90%; white crystals; mp 284–285 °C (EtOAc–*n*-hexane).

IR (KBr): 1677, 1557, 1539, 1509, 1480, 1342, 1231, 1160, 1079, 870, 744, 707, 646, 499, 452, 428 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.4 Hz, 3 H), 2.63 (q, *J* = 7.4 Hz, 2 H), 7.30–7.36 (m, 2 H), 7.53–7.65 (m, 3 H), 8.75 (d, *J* = 2.3 Hz, 1 H), 8.91 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 11.8, 29.5, 124.4, 128.0, 129.8, 130.1, 136.6, 143.0, 144.1, 144.2, 148.6, 158.2, 158.8, 162.3.

MS (FAB): *m*/*z* = 309 (100%).

Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17; S, 10.40. Found: C, 62.05; H, 3.87; N, 18.39; S, 10.27.

2-Isopropyl-3-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6c)

Yield: 81%; white solid; mp 205–206 °C (EtOAc–*n*-hexane).

IR (KBr): 1675, 1556, 1536, 1491, 1341, 1231, 1162, 1105, 1051, 772, 739, 703, 436 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.7 Hz, 6 H), 2.82 (sept, *J* = 6.7 Hz, 1 H), 7.28–7.34 (m, 2 H), 7.55–7.65 (m, 3 H), 8.74 (d, *J* = 2.3 Hz, 1 H), 8.92 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 21.5, 29.7, 32.9, 124.2, 128.0, 129.7, 130.1, 136.7, 142.9, 144.1, 148.8, 158.3, 158.9, 166.1.

MS (FAB): *m*/*z* = 323 (100%).

Anal. Calcd for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38; S, 9.95. Found: C, 63.58; H, 4.16; N, 17.55; S, 9.90.

2,3-Diphenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6d)

Yield: 80%; pale yellow solid; mp 260–261 °C (dec.) (EtOAc–*n*-hexane).

IR (KBr): 1666, 1533, 1487, 1442, 1339, 1175, 1126, 1070, 777, 761, 696, 544, 441 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.28 (m, 4 H), 7.29–7.32 (m, 1 H), 7.36–7.45 (m, 5 H), 8.80 (d, *J* = 2.3 Hz, 1 H), 8.93 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 Hz, $CDCl_3$): δ = 125.1, 128.0, 128.9, 129.0, 129.2, 129.5, 129.8, 134.6, 137.0, 143.2, 144.2, 144.4, 148.6, 158.4, 158.6, 159.0.

MS (FAB): *m*/*z* = 357 (50%).

Anal. Calcd for $C_{20}H_{12}N_4OS$: C, 67.40; H, 3.39; N, 15.72; S, 9.00. Found: C, 67.21; H, 3.52; N, 15.49; S, 9.12.

3-Benzyl-2-methylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6e)

Yield: 82%; white crystals; mp 114–115 °C (EtOAc–*n*-hexane).

IR (KBr): 1668, 1562, 1540, 1514, 1454, 1386, 1337, 1185, 1140, 1095, 1045, 951, 865, 761, 721, 693, 545, 500, 438 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.74 (s, 3 H), 5.52 (s, 2 H), 7.22–7.26 (m, 2 H), 7.31–7.38 (m, 3 H), 8.75 (d, *J* = 2.3 Hz, 1 H), 8.87 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 23.4, 47.7, 126.3, 126.7, 128.1, 128.5, 128.6, 129.1, 132.0, 134.9, 142.9, 144.0, 144.3, 158.6.

MS (FAB): *m*/*z* = 309 (70%).

Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17; S, 10.40. Found: C, 62.23; H, 3.77; N, 18.29; S, 10.65.

3-Benzyl-2-ethylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6f)

Yield: 76%; yellow solid; mp 180–181 °C (dec.) (EtOAc–*n*-hexane).

IR (KBr): 1673, 1539, 1510, 1450, 1345, 1185, 1141, 1100, 946, 733, 695, 524, 439 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (t, *J* = 7.4 Hz, 3 H), 2.98 (q, *J* = 7.4 Hz, 2 H), 5.56 (s, 2 H), 7.22–7.27 (m, 2 H), 7.35–7.41 (m, 3 H), 8.77 (d, *J* = 2.3 Hz, 1 H), 8.91 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 Hz, $CDCl_3$): δ = 11.7, 28.7, 46.9, 124.1, 126.5, 128.0, 129.1, 135.2, 143.0, 144.1, 144.2, 148.4, 158.3, 159.1, 162.4.

MS (FAB): *m*/*z* = 323 (20%).

Anal. Calcd for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38; S, 9.95. Found: C, 63.02; H, 4.25; N, 17.49; S, 9.87.

3-Benzyl-2-isopropylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6g)

Yield: 79%; pale yellow solid; mp 278–280 °C (dec.) (EtOAc–*n*-hexane).

IR (KBr): 1671, 1556, 1537, 1509, 1442, 1141, 1104, 947, 732, 695, 442 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.7 Hz, 6 H), 3.26 (sept, *J* = 6.7 Hz, 1 H), 5.57 (s, 2 H), 7.15–7.21 (m, 2 H), 7.29–7.37 (m, 3 H), 8.73 (d, *J* = 2.3 Hz, 1 H), 8.90 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 21.5, 32.7, 46.5, 126.3, 127.5, 127.9, 129.1, 135.6, 142.9, 144.0, 144.1, 148.5, 159.0, 166.2.

MS (FAB): *m*/*z* = 337 (30%).

Anal. Calcd for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.65; S, 9.53. Found: C, 64.38; H, 4.89; N, 16.52; S, 9.26.

3-Benzyl-2-phenylpyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (6h)

Yield: 85%; white solid; mp 249–250 °C (dec.) (EtOAc–*n*-hexane).

IR (KBr): 1668, 1549, 1494, 1445, 1374, 1341, 1188, 1140, 1116, 1083, 1041, 869, 769, 704, 661, 515, 441 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, 2 H), 6.93–6.99 (m, 2 H), 7.20–7.25 (m, 3 H), 7.39–7.43 (m, 4 H), 7.46–7.51 (m, 1 H), 8.74 (d, *J* = 2.3 Hz, 1 H), 8.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 49.4, 125.0, 127.2, 127.5, 127.8, 128.5, 128.5, 128.7, 130.3, 134.5, 135.8, 139.8, 143.0, 144.1, 144.3, 160.0, 163.3.

MS (FAB): *m*/*z* = 371 (100%).

Anal. Calcd for $C_{21}H_{14}N_4OS$: C, 68.09; H, 3.81; N, 15.12; S, 8.66. Found: C, 68.33; H, 3.64; N, 15.35; S, 8.54.

Cyclic Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidinones 9; General Procedure

A mixture of **3** (0.20 g, 0.9 mmol) and $SOCl_2$ (3 mL) was heated at reflux temperature for 2 h. After cooling to r.t., the solvent was removed under reduced pressure. The resulting solid was dissolved in anhyd THF (8 mL), and DMAP (0.01 g, 0.09 mmol) and the corresponding lactam **7a–c** (0.9 mmol) were added to the solution. After cooling to 0 °C (ice-bath), anhyd Et_3N (0.38 mL, 2.7 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h, and at r.t. for 12 h, and the solvent was removed under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 (50 mL) and washed with aq 1 M HCl (50 mL) and H_2O (2 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Then the resulting material was transferred to a glass tube and anhyd toluene (10 mL) and PPh_3 (0.3 g, 1.1 mmol) were added. The glass tube was sealed and the mixture was heated at 120 °C for 20 h. After cooling to r.t. the solvent was removed under reduced pressure and the resulting material was purified by silica gel chromatography (CH_2Cl_2–EtOAc, 8:2) to afford the desired pyrazinothienopyrimidines **9**.

9,10-Dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrrolo[1,2-*a*]pyrimidin-6(8*H*)-one (9a)

Yield: 58%; brown crystals; mp: 144–145 °C (CH_2Cl_2–EtOAc).

IR (KBr): 1674, 1589, 1484, 1436, 1177, 1118, 997, 765, 751, 720, 693, 535, 505, 441 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35–2.48 (dt, *J* = 7.4, 8.0 Hz, 2 H), 3.36 (t, *J* = 8.0 Hz, 2 H), 4.35 (t, *J* = 7.4 Hz, 2 H), 8.74 (d, *J* = 2.3 Hz, 1 H), 8.86 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (125 Hz, $CDCl_3$): δ = 19.9, 32.4, 47.3, 123.9, 142.9, 143.9, 144.3, 150.2, 157.5, 158.0, 163.4.

MS (FAB): *m*/*z* = 245 (30%).

Anal. Calcd for $C_{11}H_8N_4OS$: C, 54.09; H, 3.30; N, 22.94; S, 13.13. Found: C, 53.82; H, 3.56; N, 22.83; S, 13.24.

8,9,10,11-Tetrahydro-6*H*-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrido[1,2-*a*]pyrimidin-6-one (9b)

Yield: 53%; pale yellow solid; mp 219–220 °C (CH_2Cl_2–EtOAc).

IR (KBr): 1667, 1556, 1537, 1507, 1345, 1191, 1143, 1091, 762, 440 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96–2.15 (m, 4 H), 3.21 (t, *J* = 6.6 Hz, 2 H), 4.20 (t, *J* = 6.6 Hz, 2 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.85 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 19.1, 21.9, 31.8, 43.1, 123.2, 142.7, 144.0, 144.2, 148.3, 158.1, 158.6, 158.8.

MS (FAB): *m*/*z* = 259 (100%).

Anal. Calcd for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.72; H, 4.18; N, 21.63; S, 12.54.

9,10,11,12-Tetrahydropyrazino[2″,3″:4′,5′]thieno[3′,2′:4,5]pyrimido[1,2-*a*]azepin-6(8*H*)-one (9c)

Yield: 54%; orange solid; mp 189–190 °C (CH_2Cl_2–EtOAc).

IR (KBr): 1659, 1559, 1539, 1513, 1346, 1195, 1137, 1095, 781, 439 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80–1.98 (m, 6 H), 3.23–3.33 (m, 2 H), 4.48–4.55 (m, 2 H), 8.72 (d, *J* = 2.3 Hz, 1 H), 8.85 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 25.0, 27.6, 29.6, 37.4, 43.4, 142.8, 144.1, 145.9, 148.2, 157.4, 158.2, 158.5, 163.6.

MS (FAB): *m*/*z* = 273 (100%).

Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.16; H, 4.60; N, 20.32; S, 11.94.

1-{[7-(Triphenylphosphoranylideneamino)thieno[2,3-*b*]pyrazine-6-yl]carbonyl}pyrrolidin-2-one (8a)

A mixture of **3** (0.20g, 0.9 mmol) and $SOCl_2$ (3 mL) was heated at reflux temperature for 2 h. After cooling to r.t., the solvent was removed under reduced pressure. The resulting solid was dissolved in anhyd THF (8 mL), and DMAP (0.01 g, 0.09 mmol) and γ-butyrolactam (0.08 g, 0.9 mmol) were added to the solution. After cooling to 0 °C, anhyd Et_3N (0.38 mL, 2.7 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h, and at r.t. for 12 h, and Ph_3P (0.3 g, 1.1 mmol) was added to the resulting material and the mixture was stirred at r.t. for 8 h. The solvent was removed under reduced pressure and the resulting material was purified by silica gel chromatography (CH_2Cl_2–EtOAc, 8:2) to afford the phosphazene **8a**; yield: 57%; yellow solid; mp 240–242 °C (dec.) (CH_2Cl_2–EtOAc).

IR (KBr): 1745, 1621, 1543, 1505, 1436, 1344, 1296, 1254, 1228, 1186, 1137, 1107, 717, 551, 532, 516, 435 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91–2.40 (m, 4 H), 4.01 (t, *J* = 6.9 Hz, 2 H), 7.35–7.52 (m, 9 H), 7.68–7.79 (m, 6 H), 7.82 (d, *J* = 2.3 Hz, 1 H), 8.22 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR (75 Hz, $CDCl_3$): δ = 17.9, 32.8, 46.6, 128.1, 128.2, 131.3, 131.3, 131.7, 132.5, 132.6, 133.1, 138.4, 142.1, 144.5, 147.5, 155.9, 164.9, 173.0.

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 11.5.

MS (FAB): *m*/*z* = 523 (20%).

Anal. Calcd for $C_{29}H_{23}N_4O_2PS$: C, 66.65; H, 4.44; N, 10.72; S, 6.14. Found: C, 66.72; H, 4.38; N, 10.73; S, 6.01.

X-ray Crystallographic Data for Compounds 6b and 9a

The crystal and molecular structure of **6b** and **9a** were determined by X-ray diffraction studies.[17,18] Crystals were mounted on a glass fiber and transferred to the cold gas stream of the diffractometer Bruker Smart APEX. Data were recorded with Mo-Kα radiation (λ = 0.71073 Å) in ω-scan mode. The structures were solved by the direct method and refined anisotropically on F^2. Methyl groups were refined using rigid groups and other hydrogens were refined using a riding method.

Compound 6b

Suitable crystal for an X-ray diffraction analysis was grown from EtOH. Yellow prism, FW = 308.36; orthorhombic, space group *P*, *a* = 7.527(5) Å, *b* = 19.500(5) Å, *c* = 19.602(5) Å; *V* = 2877(2) Å^3; *Z* = 8; D_{calcd} = 1.424 mg m^{-3}, F(000) = 1280; *T* = 298 (2) K.

Compound 9a

Suitable crystal for an X-ray diffraction analysis was grown from EtOH. Yellow prism, F = 244.27; monoclinic, space group *P*2(1)/*c*, *a* = 7.7222(8) Å, *b* = 10.4362(11) Å, *c* = 12.5784(13) Å; *β* = 93.577(2)°; *V* = 1011.72(18) Å^3; *Z* = 4; D_{calcd} = 1.604 mg m^{-3}, F(000) = 504; *T* = 298 (2) K.

Acknowledgment

This work was supported by the Xunta de Galicia (Spain) and FEDER (Project PGIDIT06PXIB103224PR). One of us (G.B.) thanks University of A Coruña for a predoctoral fellowship.

References

(1) For recent contributions, see: (a) Cushman, M.; Sambaiah, T.; Jin, G.; Illarionov, B.; Fischer, M.; Bacher, A. *J. Org. Chem.* **2004**, *69*, 601. (b) Haraguchi, K.; Kubota, Y.; Tanaka, H. *J. Org. Chem.* **2004**, *69*, 1831. (c) Depecker, G.; Patino, N.; Giorgio, C. D.; Terreux, R.; Cabrol-Bass, D.; Bailly, C.; Aubertin, A.-M.; Condom, R. *Org. Biomol. Chem.* **2004**, *2*, 74.

(2) For reviews on the synthesis and biological activity of thienopyridines, see: (a) Litvinov, V. P.; Dotsenko, V. V.; Krivokolysko, S. G. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 864. (b) Bakhite, E. A.-G. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 929.

(3) (a) Chambhare, R. V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**, *38*, 89. (b) Walter, H. WO Patent 9914202, **1999**; *Chem. Abstr.* **1999**, *130*, 252368.

(4) (a) Sishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35*, 351. (b) Santagati, M.; Modica, M.; Santagati, A.; Russo, F.; Spampinato, S. *Pharmazie* **1996**, *51*, 7.

(5) (a) Quintela, J. M.; Peinador, C.; González, L.; Devesa, I.; Ferrándiz, M. L.; Alcaraz, M. J.; Riguera, R. *Biorg. Med. Chem.* **2003**, *11*, 863. (b) Quintela, J. M.; Peinador, C.; González, L.; Iglesias, R.; Paramá, A.; Alvarez, F.; Sanmartín, M.; Riguera, R. *Eur. J. Med. Chem.* **2003**, *38*, 265. (c) Rioja, I.; Ubeda, A.; Terencio, M. C.; Guillén, I.; Riguera, R.; Quintela, J. M.; Peinador, C.; González, L.; Alcaraz, M. J. *Eur. J. Pharmacol.* **2000**, *397*, 207. (d) Quintela, J. M.; Peinador, C.; González, L. M.; Rioja, I.; Terencio, M. C.; Ubeda, A.; Alcaraz, M. J.; Riguera, R. *J. Med. Chem.* **1999**, *42*, 4720. (e) Quintela, J. M.; Peinador, C.; Veiga, C.; González, L.; Botana, L. M.; Alfonso, A.; Riguera, R. *Bioorg. Med. Chem.* **1998**, *6*, 1911. (f) Quintela, J. M.; Peinador, C.; Veiga, M. C.; Botana, L. M.; Alfonso, A.; Riguera, R. *Eur. J. Med. Chem.* **1998**, *33*, 887. (g) Peinador, C.; Ojea, V.; Quintela, J. M. *J. Heterocycl. Chem.* **1992**, *29*, 1693.

(6) (a) Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433. (b) Pettit, G. R.; Tan, R.; Xu, J.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 995. (c) Immamura, N.; Nishijima, M.; Takadera, T.; Adachi, K.; Sakai, M.; Sano, H. *J. Antibiot.* **1997**, *50*, 8.

(7) (a) Baker, D. C.; Hand, E. S.; Plowman, J.; Rampal, J. B.; Safavy, A.; Haugwitz, R. D.; Narayanan, V. L. *Anticancer Drug Des.* **1987**, *2*, 297. (b) For a recent review, see: Pawar, V. G.; De Borggraeve, W. H. *Synthesis* **2006**, 2799.

(8) For a recent example, see: Burns, C. J.; Wilks, A. F.; Bu, X. WO Patent 2005054230, **2005**; *Chem. Abstr*. **2005**, 143, 60004.

(9) For reviews, see: (a) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523. (b) Palacios, F.; Aparicio, D.; Rubiales, G.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2006**, *10*, 2371. (c) Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113. (d) Eguchi, S. *ARKIVOC* **2005**, *(ii)*, 98. (e) Arqués, A.; Molina, P. *Curr. Org. Chem.* **2004**, *8*, 827. (f) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.

(10) (a) Blanco, G.; Quintela, J. M.; Peinador, C. *Tetrahedron* **2007**, *63*, 2034. (b) Blanco, G.; Seguí, N.; Quintela, J. M.; Peinador, C.; Chas, M.; Toba, R. *Tetrahedron* **2006**, *62*, 11124. (c) Vázquez, D.; Peinador, C.; Quintela, J. M. *Tetrahedron* **2004**, *60*, 275. (d) Álvarez-Sarandés, R.; Peinador, C.; Quintela, J. M. *Tetrahedron* **2001**, *57*, 5413.

(11) Okawa, T.; Toda, M.; Eguchi, S.; Kakehi, A. *Synthesis* **1998**, 1467.

(12) Molina, P.; Conesa, C.; Velasco, M. D. *Liebigs Ann./Recl.* **1997**, 107.

(13) Wamhoff, H.; Hermann, S.; Stölben, S.; Nieger, M. *Tetrahedron* **1993**, *49*, 581.

(14) Ding, M.-W.; Huang, N.-Y.; He, H.-W. *Synthesis* **2005**, 1601.

(15) Zbiral, E.; Bauer, E.; Stroh, J. *Monatsh. Chem.* **1971**, *102*, 168.

(16) Lowe-Ma, C. K.; Nissan, R. A.; Wilson, W. S. *J. Org. Chem.* **1990**, *55*, 3755.

(17) Crystallographic data (excluding structure factors) for **6b** and **9a** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers **6b**: CCDC 668435, and **9a**: CCDC 668436. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 33603 or e-mail: deposit@ccdc.cam.ac.uk).

(18) Sheldrick, G. M. *SHELXL-97 Program*; University of Göttingen: Germany, **1997**.