Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 64 (2008) 1333–1344
www.elsevier.com/locate/tet

Application of the aza-Wittig reaction to the synthesis of pyrazinothienotriazolopyrimidinones: a new tetracyclic ring system

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

Departamento de Química Fundamental, Facultad de Ciencias, Universidad de A Coruña, 15071 A Coruña, Spain

Received 17 October 2007; received in revised form 5 November 2007; accepted 16 November 2007
Available online 22 November 2007

Abstract

A simple one-pot and efficient method is described for the synthesis of pyrazinothienopyrimidines **6** by domino processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization. A tandem aza-Wittig reaction of phosphazenes **7**, derived from **6**, with heterocumulenes (isocyanates, carbon disulfide or carbon dioxide) generates the pyrazinothienotriazolopyrimidinones **9**, **11** and **12**, respectively. Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **15** and bis(pyrazinothienotriazolopyrimidinones) **17** were synthesized by the intermolecular aza-Wittig reaction of phosphazenes **7** with acyl chlorides or α,ω-dichlorides followed by heterocyclization via imidoyl chloride intermediate **16**. Further S-alkylation of **11** and reaction of **6** with phosgeniminium chloride produce 2-alkylthio- and 2-*N*,*N*-dimethylaminopyrazinothienotriazolopyrimidinones **13** and **19**, respectively.

1. Introduction

The large number of biologically active molecules that contain heterocyclic rings has made synthetic studies of new heterocyclic rings very attractive,[1] stimulated by recent reports that showed anti-tumour activity in a wide range of polyheterocyclic compounds isolated from marine organisms.[2] In this context, nitrogen- and sulfur-containing rings are among the most useful heterocycles and their utility has been widely demonstrated, as a consequence of their exciting biological properties and their role as pharmacophores of considerable historical importance.[3]

Pyrimidine moiety has been widely employed in the design of biologically active agents, and compounds containing a fused pyrimidine have attracted attention in the past few years owing to their wide range of biological activity, particularly in cancer and virus research.[4] Among its fused bicyclic, the thienopyrimidines are of great importance because of their remarkable biological activities.[5] We have previously reported on the synthesis of novel tri- and tetracyclic ring systems, containing the thienopyrimidine skeleton, with anti-inflammatory and anti-histaminic activity.[6] Among the diazines, the pyrazine ring system is found in marine metabolites which exhibit mild cytotoxicity against certain human cancer cells,[7] and it is also present in other biologically natural products.[8] Besides, substituted pyrazine motifs are often to be found in compounds with applications as anti-cancer agents, including currently marketed drugs[9] and those recently reported.[10] On the other hand, a large number of compounds containing the 1,2,4-triazole nucleus are responsible for a variety of biological responses, including applications as anti-tumour and anti-inflammatory agents.[11] The introduction of a triazole and pyrazine moieties to the thienopyrimidine system is expected to influence the biological activities significantly. Although there are a few examples of pyrazinothienopyrimidine scaffolds, no reports exist describing the synthesis of pyrazino-[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidines.

The aza-Wittig reaction has become one of the most important synthetic method for constructing novel C═N, N═N and S═N double bonds, especially in the preparation

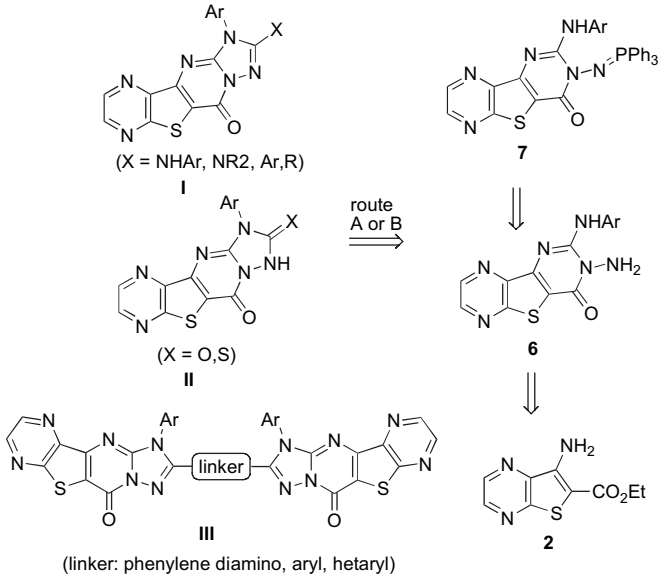
* Corresponding authors.
E-mail address: capeveqo@udc.es (C. Peinador).

0040-4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.11.059

of nitrogen-containing heterocyclic compounds. Phosphazenes, nitrogen analogues of phosphorus ylides, are versatile intermediates in modern synthetic chemistry.[12] Moreover, phosphazenes have proved to be useful building blocks for the synthesis of functionalized imine compounds, and numerous research papers and several reviews have appeared describing the general use of phosphazenes as reagents and intermediates in organic synthesis,[13] including the synthesis of heterocyclic natural products by the aza-Wittig method.[14] Recently, we have reported the synthesis of fused pyrimidines based on the tandem aza-Wittig heterocumulene-mediated annulation strategy.[15] As a part of our continuing investigations on the aza-Wittig reaction and with the aim of designing new polyheterocyclic systems with potential biological interest, this paper reports a general method for the preparation of derivatives of the unknown ring system pyrazino[2′,3′:4,5]-thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidine, which contains the thienopyrimidine, pyrazine and 1,2,4-triazole subunits.

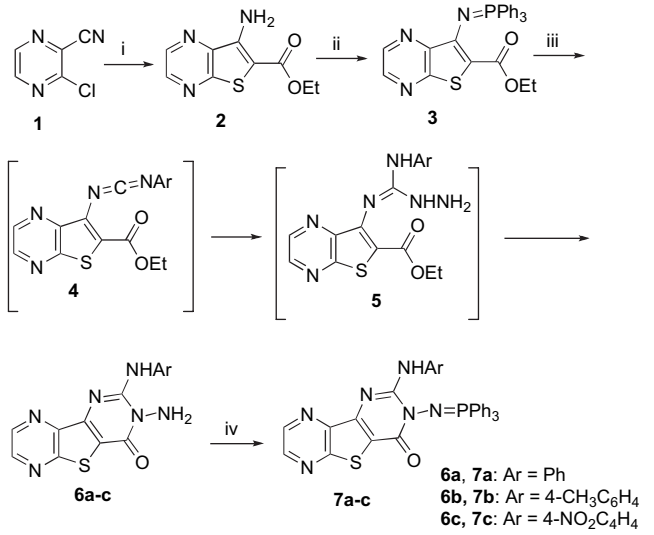
2. Results and discussion

The strategy used for the development of these compounds was focused as shown in Scheme 1. The pyrazinothienopyrimidinones **6** appear to serve as a good building blocks for these heterocycles. They can be synthesized from the readily available heterocyclic β-enamino ester **2**. We tried the preparation of the tetracyclic fused skeletons type **I** and **II** and bis(triazolothienotriazolopyrimidines) type **III** by two different ways. The first one (route A) involves an aza-Wittig-type reaction of phosphazenes **7**, derived from pyrazinothienopyrimidines **6**, with heterocumulenes (carbon dioxide, carbon disulfide or isocyanates) or aroyl or alkanoyl chlorides to give a 1,3,5-hexatriene or imidoyl chloride intermediate, which after subsequent intramolecular heterocyclization, generated the functionalized 1,2,4-triazole ring with the corresponding amino-donor nucleophile in the final step. The second way (route B) is based on the reaction of pyrazinothienopyrimidines **6** with phosgeniminium chloride.



Scheme 1. Retrosynthetic pathhway for the synthesis of pyrazinothienopyrimidines **I**, **II** and **III**.

The synthesis of pyrazothienopyrimidinones **6** and phosphazenes **7** from easily accessible ethyl 3-aminothieno[2,3-*b*]-pyrazine-2-carboxylate **2** is summarized in Scheme 2. Beginning with 2-chloro-3-cyanopyrazine **1**, obtained following the Johnston procedure starting from 3-cyanopyrazine,[16] treatment with ethyl mercaptoacetate afforded enaminoester **2** in 98% yield. The phosphazene **3**, readily prepared by the reaction of **2** with hexachloroethane–triphenylphosphine–triethylamine,[17] can be used as synthetic intermediate of new substituted pyrazinothienopyrimidines **6a–e** by domino processes involving aza-Wittig/intermolecular nucleophilic addition/intramolecular cyclization.



Scheme 2. Synthesis of pyrazinothienopyrimidinones **6** and phosphazenes **7**. Reagents and conditions: (i) $HSCH_2CO_2Et$, Na_2CO_3, EtOH, reflux, 4 h; (ii) C_2Cl_6, $(C_6H_5)_3P$, NEt_3, THF, sealed tube; (iii) (a) ArNCO, THF, room temperature, 3 h; (b) NH_2NH_2; (iv) C_2Cl_6, $(C_6H_5)_3P$, NEt_3, toluene, 100 °C, sealed tube.

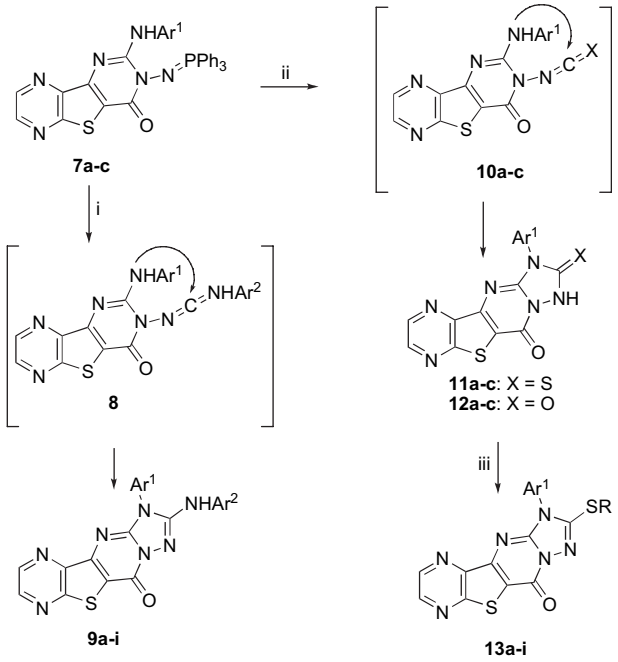
Pyrimido-annulation occurs via a heterocumulene moiety, available from the reaction of the phosphazene **3** and an aromatic isocyanate, which, in turn, was conveniently converted, by a one-pot procedure, into the corresponding fused heterocycle **6**, via initial nucleophilic addition of hydrazine to the carbodiimide cumulenic system **4** to give the guanidine intermediate **5** followed by intramolecular hetero conjugate addition annulation (Scheme 2). The regioselectivity of the reaction can be rationalized in terms that the (triphenylphosphoranylidene)amino derivative **5** cyclizes to give **6** across the strong nucleophilic hydrazine group rather than the arylamine one.[18] The participation of carbodiimides **4** and (triphenylphosphoranylidene)amino intermediates **5** in process of this class has been confirmed experimentally.[15]

Structural elucidation of compounds **6** was accomplished from the analytical and spectral data. The mass spectra showed the expected molecular ion peaks and the IR spectra showed a strong bands at ν=3344–3129 cm^{-1}, attributed to the NH

and NH_2 groups, and a C=O absorption at 1682–1665 cm^{-1}, while in the ^1H NMR spectra, the NH and NH_2 protons are found, as a singlets, at δ=10.29–8.79 and δ=5.99–4.82, respectively, in addition to the set of signals due to the H-7 and H-8 protons of the pyrazine ring. The most salient features of the ^1H NMR and ^{13}C NMR spectra are summarized under Section 4.

Due to the apparent feasibility of this reaction, and the good yields of tricyclic compounds **6a–c**, we decided to extend the heterocyclization in order to obtain new tetracyclic structures. Compounds **6a–c** were converted into novel functionalized heteroaryl phosphazenes **7a–c** upon reaction with triphenylphosphine–hexachloroethane and triethylamine. These phosphazenes **7**, precursors of the target molecules **9**, **11–15** and **17**, were isolated as stable solid compounds in good yields (75–83%).

As reported in Scheme 3, cyclization occurred when phosphazenes **7** react with heterocumulenes, such as isocyanates, carbon disulfide or carbon dioxide, yielding the interesting fused rings systems **9**, **11** and **12**. The phosphazenes **7a–c** were first reacted with aromatic isocyanates, in THF at room temperature, affording in few hours the cyclized products **9a–i** which were isolated and purified on a silica gel column with CH_2Cl_2/AcOEt as eluent. On the basis of these results we investigated the reactivity of iminophosphoranes **7a–c** towards other heterocumulenes, as carbon dioxide or carbon disulfide. Heating phosphazenes **7** in sealed tube at 100 °C with carbon disulfide in THF gave rise to the fused tetracyclic ring compounds **11a–c** in good yields. On the other hand, 1,3-dihydro-3-arylpyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2-4-triazolo[1,5-*a*]pyrimidin-3,10-dione compounds **12a–c** were obtained in moderate yields when phosphazenes **7** were allowed to react with carbon dioxide in THF. The significantly low yield of the reaction might be due to the low solubility of carbon dioxide in the organic solvent. The optimized results are summarized in Table 2. S-alkylation of **11** with alkylating reagents, such as iodomethane, benzyl chloride or chloroacetonitrile, in the presence of potassium carbonate, gave the alkylthioderivatives **13a–i** in good yields (74–97%) (Scheme 3, Table 3).



Scheme 3. Synthesis of pyrazinothienotriazolopyrimidinones **9a–i**, **11a–c**, **12a–c** and **13a–i**. Reagents and conditions: (i) Ar^2NCO, THF, room temperature, 3–4 h; (ii) CX_2, THF, 100 °C, 3 h (CS_2), 8 h (CO_2); (iii) RX, CH_3CN, K_2CO_3, 60 °C, 0.5–2 h.

In Scheme 3, the reaction pattern for compounds **7a–c** and aromatic isocyanates, carbon dioxide and carbon disulfide is reported, while in Tables 1–3 a complete set of reaction products **9a–i**, **11a–c**, **12a–c** and **13a–i** are reported. Considering these final reported results, the first step in each reaction sequence was the aza-Wittig-type reaction between the iminophosphorane **7** with the heterocumulene (aromatic isocyanate, carbon disulfide or carbon dioxide) to provide triphenylphosphine oxide and a 1-azadiene cumulenic moiety, as a highly reactive intermediate, and these reactive cumulenic systems were cyclized to give the 1,2,4-triazole ring with the corresponding amino-donor nucleophile in the final step.

Table 1
Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **9a–i**

Compd	Ar^1	Ar^2	Yield (%)	Mp (°C)
9a	C_6H_5	C_6H_5	83	>300
9b	C_6H_5	4-CH_3-C_6H_4	95	>300
9c	C_6H_5	4-NO_2-C_6H_4	99	>300 (dec)
9d	4-CH_3-C_6H_4	C_6H_5	82	>300
9e	4-CH_3-C_6H_4	4-CH_3-C_6H_4	88	>300
9f	4-CH_3-C_6H_4	4-NO_2-C_6H_4	99	>300 (dec)
9g	4-NO_2-C_6H_4	C_6H_5	77	>300
9h	4-NO_2-C_6H_4	4-CH_3-C_6H_4	72	>300
9i	4-NO_2-C_6H_4	4-NO_2-C_6H_4	91	>300 (dec)

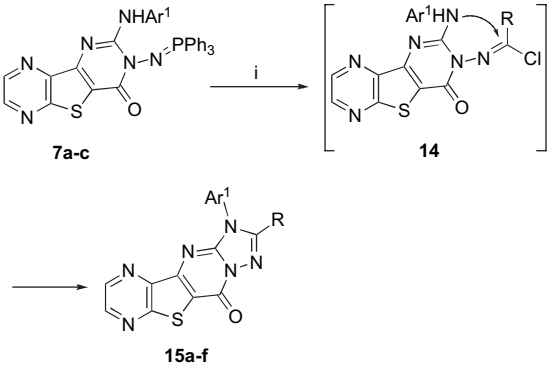
Table 2
Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **11a–c** and **12a–c**

Compd	Ar^1	X	Yield (%)	Mp (°C)
11a	C_6H_5	S	97	287–289
11b	4-CH_3-C_6H_4	S	87	>300 (dec)
11c	4-NO_2-C_6H_4	S	72	>300
12a	C_6H_5	O	55	>300
12b	4-CH_3-C_6H_4	O	53	>300 (dec)
12c	4-NO_2-C_6H_4	O	42	>300 (dec)

Table 3
Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **13a–i**

Compd	Ar^1	R	Yield (%)	Mp (°C)
13a	C_6H_5	CH_3	93	>300 (dec)
13b	C_6H_5	$CH_2C_6H_5$	97	295–297
13c	C_6H_5	CH_2CN	89	>300
13d	4-CH_3-C_6H_4	CH_3	82	>300
13e	4-CH_3-C_6H_4	$CH_2C_6H_5$	89	239–240
13f	4-CH_3-C_6H_4	CH_2CN	84	>300
13g	4-NO_2-C_6H_4	CH_3	81	>300
13h	4-NO_2-C_6H_4	$CH_2C_6H_5$	74	277–279
13i	4-NO_2-C_6H_4	CH_2CN	90	>300

The next step of this study was the preparation of pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **15a–f** by an initial aza-Wittig reaction between the phosphazenes **7** and alkanoyl or aroyl chlorides and subsequent intramolecular heterocyclization (Scheme 4, Table 4), revealing the preferential reactivity of the iminophosphorane group of compounds **7**, compared to the amino moiety, towards electrophilic reagents.[12c] Chloroimidoyl derivatives **14** are assumed to be the key intermediates in the consecutive reactions even though **14** could not be detected due to its high reactivity, and these reactive intermediates were cyclized to give the 1,2,4-triazole ring with the corresponding amino-donor nucleophile to afford tetracyclic compounds **15** through elimination of hydrogen chloride.



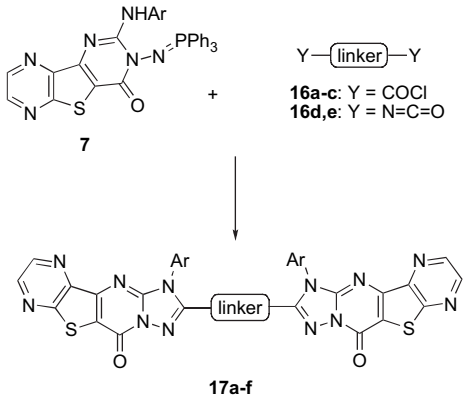
Scheme 4. Synthesis of pyridothieno-1,2,4-triazolopyrimidinones **15a–f**. Reagents and conditions: (i) RCOCl, THF, NEt_3, room temperature, 3–8 h.

Table 4
Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **15a–f**

Compd	Ar^1	R	Yield (%)	Mp (°C)
15a	C_6H_5	CH_3	60	220 (dec)
15b	C_6H_5	C_6H_5	72	>300
15c	4-CH_3-C_6H_4	CH_3	70	>300
15d	4-CH_3-C_6H_4	C_6H_5	91	>300
15e	4-NO_2-C_6H_4	CH_3	71	>300
15f	4-NO_2-C_6H_4	C_6H_5	92	>300

We next considered the possibility to extend this design strategy to the preparation of bis(pyrazinothienotriazolopyrimidines) **17**. Thus, we reacted phospazene **7** with α,ω-dichlorides, as isophthaloyl chloride, terephtaloyl chloride and 2,6-pyridinedicarbonyl dichloride, or diisocyanates, as 1,3- and 1,4-phenylene diisocyanate, under similar reaction conditions to those shown in Schemes 3 and 4, which cleaning furnished the new bis(tetraheterocyclic) compounds **17a–f** (Scheme 5, Table 5). In compounds **17**, two pyrazinothienotriazolopyrimidine skeletons are linked via their respective C-2′ carbon atoms by a 1,3-phenylene, 1,4-phenylene, 2,6-pyridine, 1,3-phenylene diamino or 1,4-phenylene diamino chain. Isolated yields of these interesting heterocycles ranged from moderate to good (50–71%). Once again all new compounds showed spectroscopic and characterization data in accord with the proposed structures.

Finally, it seemed possible that the 1,2,4-triazolo ring could be alternatively derived by an efficient one-pot process

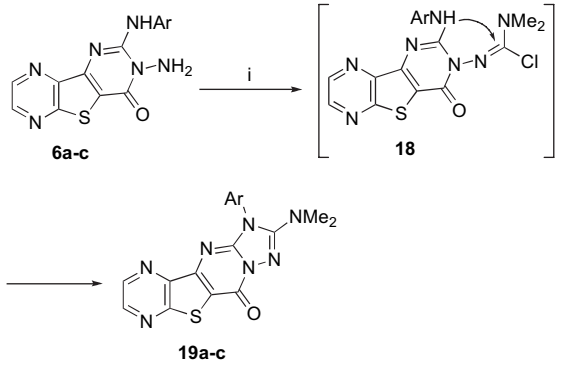


Scheme 5. Synthesis of bis(pyrazinothienotriazolopyrimidines) **17a–f**.

Table 5
Bis(pyrazinothienotriazolopyrimidines) **17a–f**

Compd	Ar	Linker	Yield (%)	Mp (°C)
17a	C_6H_5	1,4-C_6H_4	62	>300
17b	C_6H_5	1,3-C_6H_4	67	>300
17c	C_6H_5	2,6-C_6H_3N	71	>300
17d	C_6H_5	1,4-$C_6H_4(NH)_2$	67	250 (dec)
17e	4-$CH_3C_6H_4$	1,4-$C_6H_4(NH)_2$	55	250 (dec)
17f	C_6H_5	1,3-$C_6H_4(NH)_2$	50	260 (dec)

employing phosgeniminium chloride as starting material. *N*,*N*-Dichloromethylenedimethylammonium salts, particularly *N*,*N*-dichloromethylenedimethylammonium chloride (Viehe's salt) are stable but reactive building blocks for heterocyclic synthesis.[19] We had previously used this transformation in the preparation of fused biologically active heterocyclic ring systems, including natural products.[20] In the presented synthetic approach an useful general method for the formation of pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **19** has been derived. On treatment with *N*,*N*-dimethylmethyleneiminium chloride in refluxing 1,2-dichloroethane **6a–c** gave directly **19** in moderate to good yields (Scheme 6, Table 6). The conversion of **6** into **19** involves an initial nucleophilic chlorine substitution to give the chloroamidine **18**, as highly reactive intermediate, which easily undergoes ring closure across the arylamino group to the fused triazole ring.



Scheme 6. Synthesis of pyridothieno-1,2,4-triazinepyrimidones **19a–c**. Reagents and conditions: (i) $Cl_2C{=}NMe_2Cl$, CH_2Cl_2, reflux, 1 h.

Table 6
Pyrazino[2′,3′:4,5]thieno[3,2-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-4(3*H*)-ones **19a–c**

Compd	Ar	Yield (%)	Mp (°C)
19a	C_6H_5	87	>300
19b	4-CH_3-C_6H_4	71	>300
19c	4-NO_2-C_6H_4	60	>300

Compounds **9**, **11–13**, **15**, **17** and **19** were unambiguously characterized from their spectroscopic data, mass spectrometric data and elemental analyses (see Section 4). For example, the mass spectrum of **9e** shows the molecular ion peak at *m/z*=440 with 100% abundance. The IR spectrum reveals N–H and C=O absorption bands at 3263 cm^{-1} and 1688 cm^{-1}, respectively. The ^1H NMR spectrum of **9e** shows two singlets at δ=2.29 and 2.49 due to the CH_3 groups, while the NH proton resonates as a singlet at δ=9.05 ppm. The signals attributable to the H-6 and H-7 aromatic protons of the pyrazine ring are found at δ=8.82 and 8.86 as doublets. The ^{13}C NMR spectroscopic data for **9e** show the signals of C=O and the two CH_3 at δ=157.0 ppm and 20.9 ppm and 21.5 ppm, respectively. The structure of **9i** was independently confirmed by X-ray crystal structure analysis (Fig. 1).

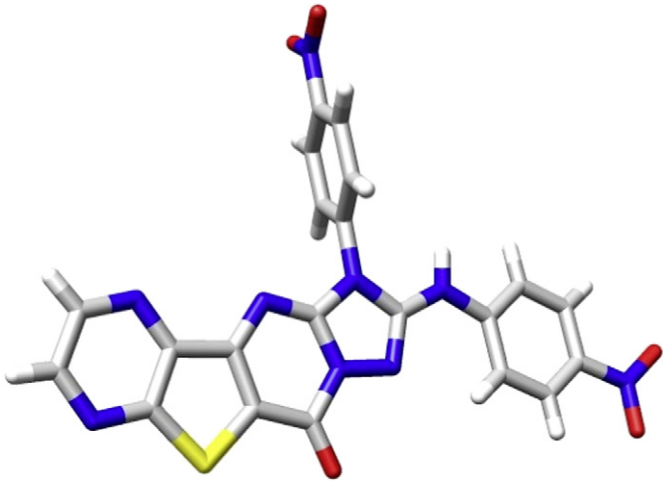


Figure 1. Crystal structure of compound **9i**. Solvent molecules have been omitted for clarity.

3. Conclusions

In conclusion, a method based on a tandem aza-Wittig reaction of phosphazenes **7** with heterocumulenes, as isocyanates, carbon disulfide and carbon dioxide, or acyl chlorides that allows the formation of tetracyclic fused ring systems with the biologically important pyrazine, thienopyrimidine and 1,2,4-triazole moieties is reported. These results indicate the importance and utility of these phosphazenes as versatile building blocks in the preparation of complex polycyclic compounds. The method utilizes easily accessible starting materials and allows mild reaction conditions, straightforward product isolation and good yields.

4. Experimental section

4.1. General

All reagents used were commercial grade chemicals from freshly opened containers. Merk 60 HF254+366 foils were used for thin layer chromatography and Merk 60 (230–400 mesh) silica gel for flash chromatography. NMR spectra were obtained in a Bruker Avance 500 equipped with a dual cryoprobe for ^1H and ^{13}C and a Bruker Avance 300 spectrometers. TMS was used as an internal reference. IR spectra were recorded as potassium bromide disks. Mass spectrometry experiments were carried out in a Fision VG-Quattro 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.

4.2. Ethyl 3-aminothieno[2,3-b]pyrazine-2-carboxylate **2**

To a solution of 2-chloro-3-cyanopyrazine **1**[16] (5.00 g, 35.80 mmol) in EtOH (100 mL) were added Na_2CO_3 (4.24 g, 40 mmol) and ethyl thioglycolate (5.33 g, 40 mmol) and the resultant reaction mixture was stirred at reflux temperature for 4 h and poured into water (200 mL). The precipitated product was filtered by suction, washed with water and purified by flash chromatography using CH_2Cl_2/AcOEt (90:10; v/v) as eluent to give **2** (7.05 g, 90%); mp 120–121 °C (lit.[15b] 120–121 °C).

4.3. 3-Amino-2-arylaminopyrazino[2′,3′:4,5]thieno-[3,2-d]pyrimidin-4(3H)-one **6**

To a solution of phosphazene **4**[15b] (3 g, 6.2 mmol) in dry THF (60 mL) was added the appropriate isocyanate (7.45 mmol) and the mixture was stirred at room temperature under Ar for 3–4 h. Then, the solvent was removed under reduced pressure and Et_2O (60 mL) was added to the precipitate triphenylphosphine oxide. The reaction mixture was filtered and the solvent removed. To the solution of residue prepared above in ethanol (60 mL) was added hydrazine hydrate (0.28 g, 7.45 mmol, 85%). The mixture was stirred for 30 min at room temperature and the resulted solid was isolated by filtration and purified by column chromatography on silica gel eluting with a hexanes–AcOEt gradient from 50% to 100% ethyl acetate to give **6** as a yellow solid.

4.3.1. 3-Amino-2-phenylaminopyrazino[2′,3′:4,5]-thieno[3,2-d]pyrimidin-4(3H)-one (**6a**)

Yield 99%; mp: 243–245 °C. IR (KBr) 3344, 3302, 3270, 3184 (NH), 1673 (C=O), 1594, 1548, 1524 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.82 (s, 2H, NH_2), 7.10–7.20 (m, 1H, ArH), 7.40–7.50 (m, 2H, ArH), 7.82–7.88 (m, 2H, ArH), 8.68 (d, 1H, *J*=2.3 Hz, H-7), 8.79 (s, 1H, NH_2), 8.84 (d, 1H, *J*=2.3 Hz, H-8). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 114.4, 121.6, 124.0, 129.1, 138.8, 143.6, 143.9, 144.9, 148.6, 152.3, 157.4, 158.2. MS (EI) *m/z* 310 (M^+, 20). Anal. Calcd for

$C_{14}H_{10}N_6OS$: C, 54.18; H, 3.25; N, 27.08; S, 10.33. Found: C, 54.10; H, 3.34; N, 26.93; S, 10.15.

*4.3.2. 3-Amino-2-(4-methylphenyl)aminopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**6b**)*

Yield 64%; mp: 255–256 °C. IR (KBr) 3342, 3299, 3272, 3129 (NH), 1665 (C=O), 1592, 1553, 1523, 1478 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.29 (s, 3H, CH_3), 5.87 (s, 2H, NH_2), 7.17–7.20 (m, 2H, ArH), 7.79–7.82 (m, 2H, ArH), 8.80 (d, 1H, J=2.3 Hz, H-7), 8.91 (d, 1H, J=2.3 Hz, H-8), 9.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 20.4, 113.4, 121.1, 128.9, 132.4, 135.6, 142.9, 143.3, 144.2, 148.1, 151.8, 156.8, 157.6. MS (FAB) *m/z* 325 [$(MH)^+$, 100]. Anal. Calcd for $C_{15}H_{12}N_6OS$: C, 55.54; H, 3.73; N, 25.91; S, 9.89. Found: C, 55.56; H, 3.64; N, 25.77; S, 9.95.

*4.3.3. 3-Amino-2-(4-nitrophenyl)aminopyrazino-[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**6c**)*

Yield 73%; mp: 260 °C (dec). IR (KBr) 3286, 3485 (NH), 1682 (C=O), 1561, 1542, 1510, 1485 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 5.99 (s, 2H, NH_2), 8.28–8.32 (m, 2H, ArH), 8.36–8.41 (m, 2H, ArH), 8.88 (d, 1H, J=2.3 Hz, H-7), 9.00 (d, 1H, J=2.3 Hz, H-8), 10.29 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 116.2, 120.7, 125.1, 142.5, 143.7, 143.8, 145.1, 145.3, 147.9, 151.6, 157.3, 158.1. MS (FAB) *m/z* 356 [$(MH)^+$, 40]. Anal. Calcd for $C_{14}H_9N_7O_3S$: C, 47.32; H, 2.55; N, 27.59; S, 9.02. Found: C, 47.14; H, 2.44; N, 27.43; S, 9.15.

*4.4. 2-Arylamino-3-(triphenylphosphoranylideneamino)-pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one **7***

To a mixture of **6** (3.2 mmol), triphenylphosphine (4.8 mmol) and hexachloroethane (3.2 mmol) in dry toluene (30 mL), triethylamine (16.50 mmol) was added dropwise. The reaction mixture was heated at 100 °C in a sealed tube for 48 h. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography using a CH_2Cl_2–AcOEt gradient from 0% to 10% ethyl acetate to give **7** as a yellow solid.

*4.4.1. 2-Phenylamino-3-(triphenylphosphoranylideneamino)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**7a**)*

Yield 83%; mp: 285 °C (dec). IR (KBr) 3257 (NH), 1660 (C=O), 1589, 1543, 1484 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.06–7.14 (m, 1H, ArH), 7.37–7.58 (m, 11H, ArH), 7.78–7.89 (m, 8H, ArH), 8.57 (d, 1H, J=2.3 Hz, H-7), 8.76 (d, 1H, J=2.3 Hz, H-8), 9.77 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 119.5, 123.1, 128.6, 128.7, 129.2, 130.3, 131.6, 131.8, 131.9, 132.3, 132.4, 138.6, 141.9, 142.8, 144.4, 145.4, 150.6, 150.7, 158.0. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 22.8. MS (EI) *m/z* 570 (M^+, 55). Anal. Calcd for $C_{32}H_{23}N_6OPS$: C, 67.36; H, 4.06; N, 14.73; S, 5.62. Found: C, 67.52; H, 3.91; N, 14.56; S, 5.62.

*4.4.2. 2-(4-Methylphenyl)amino-3-(triphenylphosphoranylideneamino)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**7b**)*

Yield 75%; mp: 275 °C (dec). IR (KBr) 3234 (NH), 1665 (C=O), 1589, 1546, 1498 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (s, 3H, CH_3), 7.18–7.25 (m, 2H, ArH), 7.43–7.57 (m, 9H, ArH), 7.68–7.74 (m, 2H, ArH), 7.76–7.89 (m, 6H, ArH), 8.56 (d, 1H, J=2.3 Hz, H-7), 8.76 (d, 1H, J=2.3 Hz, H-8), 9.65 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 20.9, 119.7, 128.6, 128.7, 129.7, 130.3, 131.6, 131.8, 131.8, 132.3, 132.4, 132.7, 136.0, 141.8, 142.8, 144.4, 145.5, 150.8, 150.9, 157.5, 158.0. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 22.8. MS (FAB) *m/z* 585 [$(MH)^+$, 100]. Anal. Calcd for $C_{33}H_{25}N_6OPS$: C, 67.80; H, 4.31; N, 14.37; S, 5.48. Found: C, 67.74; H, 4.25; N, 14.17; S, 5.43.

*4.4.3. 2-(4-Nitrophenyl)amino-3-(triphenylphosphoranylideneamino)pyrazino[2′,3′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (**7c**)*

Yield 77%; mp: >300 °C. IR (KBr) 3221 (NH), 1652 (C=O), 1540, 1507, 1486 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.45–7.60 (m, 9H, HAr), 7.76–7.87 (m, 6H, HAr), 7.98–8.16 (m, 2H, ArH), 8.29–8.35 (m, 2H, ArH), 8.62 (d, 1H, J=2.3 Hz, H-7), 8.81 (d, 1H, J=2.3 Hz, H-8), 10.27 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 118.5, 125.4, 128.7, 128.9, 130.1, 131.4, 132.0, 132.1, 132.2, 132.4, 142.1, 142.5, 143.2, 144.0, 144.4, 144.7, 158.0. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ: 23.4. MS (FAB) *m/z* 616 [$(MH)^+$, 70]. Anal. Calcd for $C_{32}H_{22}N_7O_3PS$: C, 62.43; H, 3.60; N, 15.93; S, 5.21. Found: C, 62.25; H, 3.56; N, 15.74; S, 5.18.

*4.5. 3-Aryl-2-arylaminopyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one **9a**. General procedure*

To a solution of phosphazene **7** (0.09 mmol) in dry THF (5 mL) was added the appropriate isocyanate (0.1 mmol). The mixture was stirred at room temperature under Ar for 3–4 h until the phosphazene had disappeared (TLC monitored). Then, the precipitate obtained was isolated by filtration, washed with THF (2 mL) and subjected to chromatography on silica gel eluting with a CH_2Cl_2–AcOEt gradient from 0% to 10% ethyl acetate to give **9** as a yellow solid.

*4.5.1. 3-Phenyl-2-phenylaminopyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9a**)*

Yield 83%; mp: >300 °C. IR (KBr) 3458 (NH), 1684 (C=O), 1580, 1543, 1488 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 7.05–7.12 (m, 1H, ArH), 7.33–7.42 (m, 2H, ArH), 7.67–7.79 (m, 7H, ArH), 8.82 (d, 1H, J=2.3 Hz, H-6), 8.85 (d, 1H, J=2.3 Hz, H-7), 9.19 (s, 1H, NH). MS (FAB) *m/z* 412 [$(MH)^+$, 95]. Anal. Calcd for $C_{21}H_{13}N_7OS$: C, 61.30; H, 3.18; N, 23.83; S, 7.79. Found: C, 60.98; H, 3.38; N, 23.94; S, 7.47.

*4.5.2. 2-(4-Methylphenyl)amino-3-phenylpyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9b**)*

Yield 95%; mp: >300 °C. IR (KBr) 3287 (NH), 1675 (C=O), 1575, 1524, 1511 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.27 (s, 3H, CH_3), 7.12–7.19 (m, 2H, ArH), 7.55–7.62 (m, 2H, ArH), 7.65–7.78 (m, 5H, ArH), 8.81 (d, 1H, J=2.3 Hz, H-6), 8.84 (d, 1H, J=2.3 Hz, H-7), 9.08 (s, 1H, NH). MS (FAB) *m/z* 426 [$(MH)^+$, 100]. Anal. Calcd for $C_{22}H_{15}N_7OS$: C, 62.10; H, 3.55; N, 23.04; S, 7.54. Found: C, 62.00; H, 3.48; N, 23.16; S, 7.53.

*4.5.3. 2-(4-Nitrophenyl)amino-3-phenylpyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9c**)*

Yield 99%; mp: >300 °C (dec). IR (KBr) 3448 (NH), 1678 (C=O), 1568, 1507 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 7.65–7.80 (m, 5H, ArH), 7.85–8.00 (m, 2H, ArH), 8.22–8.33 (m, 2H, ArH), 8.84 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7), 9.98 (s, 1H, NH). MS (FAB) *m/z* 457 [$(MH)^+$, 60]. Anal. Calcd for $C_{21}H_{12}N_8O_3S$: C, 55.26; H, 2.65; N, 24.55; S, 7.03. Found: C, 55.38; H, 2.58; N, 24.74; S, 6.97.

*4.5.4. 2-(4-Methylphenyl)amino-3-phenylpyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9d**)*

Yield 82%; mp: >300 °C. IR (KBr) 3448 (NH), 1679 (C=O), 1581, 1563, 1514, 1488 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.48 (s, 3H, CH_3), 7.07–7.12 (m, 1H, ArH), 7.35–7.40 (m, 2H, ArH), 7.49–7.53 (m, 2H, ArH), 7.57–7.61 (m, 2H, ArH), 7.67–7.71 (m, 2H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.85 (d, 1H, J=2.3 Hz, H-7), 9.11 (s, 1H, NH). MS (FAB) *m/z* 426 [$(MH)^+$, 50]. Anal. Calcd for $C_{22}H_{15}N_7OS$: C, 62.10; H, 3.55; N, 23.04; S, 7.54. Found: C, 62.40; H, 3.65; N, 22.79; S, 7.46.

*4.5.5. 3-(4-Methylphenyl)-2-(4-methylphenyl)amino-pyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo-[1,5-a]pyrimidin-10(3H)-one (**9e**)*

Yield 88%; mp: >300 °C. IR (KBr) 3263 (NH), 1688 (C=O), 1593, 1581, 1546, 1513, 1490 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 7.17–7.22 (m, 2H, ArH), 7.50–7.55 (m, 2H, ArH), 7.60–7.65 (m, 4H, ArH), 8.82 (d, 1H, J=2.3 Hz, H-6), 8.86 (d, 1H, J=2.3 Hz, H-7), 9.05 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 20.9, 21.5, 115.6, 120.3, 128.5, 129.2, 129.7, 131.0, 132.6, 136.5, 140.7, 143.3, 143.9, 144.9, 148.2, 149.5, 150.4, 152.2, 157.0. MS (FAB) *m/z* 440 [$(MH)^+$, 100]. Anal. Calcd for $C_{23}H_{17}N_7OS$: C, 62.86; H, 3.90; N, 22.31; S, 7.30. Found: C, 62.68; H, 3.91; N, 22.51; S, 7.29.

*4.5.6. 3-(4-Methylphenyl)-2-(4-nitrophenyl)-aminopyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo-[1,5-a]pyrimidin-10(3H)-one (**9f**)*

Yield 99%; mp: >300 °C (dec). IR (KBr) 3251 (NH), 1691 (C=O), 1538, 1568, 1510, 1495 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.50 (s, 3H, CH_3), 7.52–7.56 (m, 2H, ArH), 7.62–7.66 (m, 2H, ArH), 7.98–8.03 (m, 2H, ArH), 8.30–8.35 (m, 2H, ArH), 8.85 (d, 1H, J=2.3 Hz, H-6), 8.88 (d, 1H, J=2.3 Hz, H-7), 9.95 (s, 1H, NH). MS (FAB) *m/z* 471 [$(MH)^+$, 10]. Anal. Calcd for $C_{22}H_{14}N_8O_3S$: C, 56.16; H, 3.00; N, 23.82; S, 6.82. Found: C, 56.32; H, 3.09; N, 24.09; S, 6.64.

*4.5.7. 3-(4-Nitrophenyl)-2-phenylaminopyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9g**)*

Yield 77%; mp: >300 °C. IR (KBr) 3453 (NH), 1684 (C=O), 1580, 1529, 1492 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.05–7.13 (m, 1H, ArH), 7.35–7.44 (m, 2H, ArH), 7.65–7.73 (m, 2H, ArH), 8.06–8.14 (m, 2H, ArH), 8.55–8.62 (m, 2H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7), 9.33 (s, 1H, NH). MS (FAB) *m/z* 457 [$(MH)^+$, 100]. Anal. Calcd for $C_{21}H_{12}N_8O_3S$: C, 55.26; H, 2.65; N, 24.55; S, 7.03. Found: C, 55.21; H, 2.67; N, 24.50; S, 7.15.

*4.5.8. 2-(4-Methylphenyl)amino-3-(4-nitrophenyl)pyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9h**)*

Yield 72%; mp: >300 °C. IR (KBr) 3411 (NH), 1682 (C=O), 1582, 1519, 1491 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.28 (s, 3H, CH_3), 7.17–7.23 (m, 2H, ArH), 7.55–7.60 (m, 2H, ArH), 8.06–8.11 (m, 2H, ArH), 8.52–8.61 (m, 2H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7), 9.22 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 20.9, 116.1, 120.2, 125.8, 129.8, 131.1, 132.7, 136.4, 136.8, 143.5, 143.8, 145.0, 148.2, 148.8, 149.1, 149.7, 152.0, 157.0. MS (FAB) *m/z* 471 [$(MH)^+$, 100]. Anal. Calcd for $C_{22}H_{14}N_8O_3S$: C, 56.16; H, 3.00; N, 23.82; S, 6.82. Found: C, 56.28; H, 2.90; N, 23.90; S, 6.69.

*4.5.9. 3-(4-Nitrophenyl)-2-(4-nitrophenyl)aminopyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**9i**)*

Yield 91%; mp: >300 °C (dec). IR (KBr) 3323 (NH), 1687 (C=O), 1616, 1571, 1524, 1490 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.89–7.95 (m, 2H, ArH), 8.09–8.14 (m, 2H, ArH), 8.27–8.34 (m, 2H, ArH), 8.56–8.63 (m, 2H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7), 10.09 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 116.2, 119.0, 125.7, 125.8, 130.9, 136.7, 143.6, 143.7, 145.2, 148.5, 148.8, 148.9, 152.0, 157.0. MS (FAB) *m/z* 502 [$(MH)^+$, 15]. Anal. Calcd for $C_{21}H_{11}N_9O_5S$: C, 50.30; H, 2.21; N, 25.14; S, 6.39. Found: C, 50.18; H, 2.18; N, 25.23; S, 6.46.

*4.6. 3-Aryl-2-Thioxo(or 2-oxo)pyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one **11** and **12***

To a solution of phosphazene **7** (0.80 mmol) in dry THF (5 mL) was added excess CS_2 or CO_2 (3.5 mmol) under Ar at room temperature. The reaction mixture was heated at 100 °C in a sealed tube for 3 h (CS_2) or 8 h (CO_2) (in the

case of **12a** 8 h at room temperature). The precipitate was separated by filtration, washed with THF (2 mL) and purified by column chromatography using a hexanes–AcOEt gradient from 70% to 100% ethyl acetate to give **11** or **12** as a yellow solid.

*4.6.1. 3-Phenyl-2-thioxopyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**11a**)*

Yield 97%; mp: 287–289 °C. IR (KBr) 3432 (NH), 1711 (C=O), 1699, 1668, 1584, 1471 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.45–7.54 (m, 1H, ArH), 7.55–7.61 (m, 4H, ArH), 8.80 (d, 1H, J=2.3 Hz, H-6), 8.83 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 114.9, 129.0, 129.6, 129.7, 133.5, 143.3, 144.0, 145.0, 148.8, 150.5, 151.6, 157.2. MS (FAB) *m/z* 353 [$(MH)^+$, 100]. Anal. Calcd for $C_{15}H_8N_6OS_2$: C, 51.12; H, 2.29; N, 23.85; S, 18.20. Found: C, 51.13; H, 2.17; N, 23.99; S, 18.26.

*4.6.2. 3-(4-Methylphenyl)-2-thioxopyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**11b**)*

Yield 87%; mp: >300 °C. IR (KBr) 3444 (NH), 1710 (C=O), 1668, 1593, 1533, 1516, 1475 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.36 (s, 3H, CH_3), 7.35–7.40 (m, 2H, ArH), 7.42–7.47 (m, 2H, ArH), 8.82 (d, 1H, J=2.3 Hz, H-6), 8.85 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 21.3, 114.5, 128.8, 129.9, 139.0, 143.2, 143.7, 144.2, 144.8, 148.6, 150.6, 151.5, 157.1. MS (FAB) *m/z* 367 [$(MH)^+$, 100]. Anal. Calcd for $C_{16}H_{10}N_6OS_2$: C, 52.45; H, 2.75; N, 22.94; S, 17.50. Found: C, 52.33; H, 2.76; N, 22.89; S, 17.46.

*4.6.3. 3-(4-Nitrophenyl)-2-thioxopyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**11c**)*

Yield 72%; mp: >300 °C (dec). IR (KBr) 3429 (NH), 1689 (C=O), 1580, 1522, 1504, 1489 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.88–7.92 (m, 2H, ArH), 8.52–8.56 (m, 2H, ArH), 8.76 (d, 1H, J=2.3 Hz, H-7), 8.84 (d, 1H, J=2.3 Hz, H-8). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 115.8, 124.3, 130.5, 136.9, 140.7, 143.0, 145.4, 147.1, 148.9, 149.0, 150.7, 151.8, 157.2. MS (FAB) *m/z* 398 [$(MH)^+$, 45]. Anal. Calcd for $C_{15}H_7N_7O_3S_2$: C, 45.34; H, 1.78; N, 24.67; S, 16.14. Found: C, 45.23; H, 1.79; N, 24.79; S, 16.17.

*4.6.4. 1,3-Dihydro-3-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-3,10-dione (**12a**)*

Yield 55%; mp: >300 °C. IR (KBr) 3449 (NH), 1765 (C=O), 1583, 1543, 1521, 1497, 1487 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.45–7.73 (m, 5H, ArH), 8.82 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 115.6, 127.4, 128.7, 129.5, 132.7, 143.4, 144.1, 144.8, 147.2, 147.6, 150.6, 156.7. MS (FAB) *m/z* 337 [$(MH)^+$, 75]. Anal. Calcd for $C_{15}H_8N_6O_2S$: C, 53.57; H, 2.40; N, 24.99; S, 9.53. Found: C, 53.29; H, 2.17; N, 25.16; S, 9.42.

*4.6.5. 1,3-Dihydro-3-(4-methylphenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-3,10-dione (**12b**)*

Yield 53%; mp: >300 °C (dec). IR (KBr) 3415 (NH), 1656 (C=O), 1593, 1579, 1557, 1518, 1593, 1579, 1557, 1518, 1498 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz) δ: 2.39 (s, 3H, CH_3), 7.31–7.36 (m, 2H, ArH), 7.54–7.59 (m, 2H, ArH), 8.73 (d, 1H, J=2.3 Hz, H-6), 8.80 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 75 Hz) δ: 20.8, 113.6, 126.1, 129.0, 131.4, 136.3, 142.2, 143.4, 144.3, 145.8, 151.2, 156.2. MS (FAB) *m/z* 351 [$(MH)^+$, 100]. Anal. Calcd for $C_{16}H_{10}N_6O_2S$: C, 54.85; H, 2.88; N, 23.99; S, 9.15. Found: C, 54.73; H, 2.78; N, 23.79; S, 9.16.

*4.6.6. 1,3-Dihydro-3-(4-nitrophenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-3,10-dione (**12c**)*

Yield 42%; mp: >300 °C (dec). IR (KBr) 3427 (NH), 1671 (C=O), 1551, 1540, 1523, 1508 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 8.20–8.24 (m, 2H, ArH), 8.45–8.50 (m, 2H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.91 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 116.1, 124.8, 126.6, 132.8, 133.6, 139.4, 143.3, 144.1, 144.7, 146.0, 146.9, 150.9, 156.7. MS (FAB) *m/z* 382 [$(MH)^+$, 20]. Anal. Calcd for $C_{15}H_7N_7O_4S$: C, 47.25; H, 1.85; N, 25.71; S, 8.41. Found: C, 47.13; H, 1.77; N, 25.99; S, 8.27.

*4.7. 2-(Alkylthio)-3-arylpyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one **13**. General procedure*

A mixture of **11** (0.1 mmol), alkyl halide (0.13 mL) and solid potassium carbonate (0.2 mmol) in CH_3CN (5 mL) was stirred for 0.5–2 h at 60 °C. After cooling, the precipitate was filtered, washed with CH_3CN (1 mL) and H_2O (1 mL) and purified by column chromatography using a hexanes–AcOEt gradient from 60% to 100% ethyl acetate to give **13** as a yellow solid.

*4.7.1. 2-(Methylthio)-3-phenylpyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13a**)*

Yield 93%; mp: >300 °C. IR (KBr) 1682 (C=O), 1596, 1591, 1582, 1575, 1559, 1503, 1486 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.85 (s, 3H, CH_3), 7.54–7.69 (m, 5H, ArH), 8.72 (d, 1H, J=2.3 Hz, H-6), 8.80 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 14.0, 117.4, 127.2, 130.4, 130.8, 130.9, 142.5, 143.7, 144.2, 148.8, 150.1, 152.1, 156.0, 158.3. MS (FAB) *m/z* 367 [$(MH)^+$, 60]. Anal. Calcd for $C_{16}H_{10}N_6OS_2$: C, 52.45; H, 2.75; N, 22.94; S, 17.50. Found: C, 52.63; H, 2.45; N, 22.75; S, 17.60.

*4.7.2. 2-(Benzylthio)-3-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13b**)*

Yield (97%); mp: 295–297 °C. IR (KBr) 1702 (C=O), 1587, 1538, 1525, 1503, 1485, 1454 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 4.69 (s, 2H, CH_2), 7.30–7.38 (m, 3H, ArH),

7.41–7.48 (m, 2H, ArH), 7.51–7.63 (m, 5H, ArH), 8.72 (d, 1H, J=2.3 Hz, H-6), 8.81 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 36.3, 117.4, 127.2, 128.4, 129.0, 129.5, 130.4, 130.7, 130.9, 134.3, 142.5, 143.7, 144.2, 148.8, 149.9, 152.1, 154.9, 158.3. MS (FAB) *m/z* 443 [$(MH)^+$, 60]. Anal. Calcd for $C_{22}H_{14}N_6OS_2$: C, 59.71; H, 3.19; N, 18.99; S, 14.49. Found: C, 59.52; H, 3.07; N, 18.70; S, 14.65.

*4.7.3. 2-(Cyanomethylthio)-3-phenylpyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13c**)*

Yield (89%); mp: >300 °C. IR (KBr) 1698 (C=O), 2250 (CN), 1582, 1539, 1507, 1488 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.50 (s, 2H, CH_2), 7.70–7.78 (m, 5H, ArH), 8.86 (d, 1H, J=2.3 Hz, H-6), 8.88 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 75 Hz) δ: 16.8, 115.1, 116.7, 127.8, 130.1, 130.7, 131.0, 143.1, 143.1, 144.9, 148.7, 150.5, 151.4, 152.3, 156.8. MS (FAB) *m/z* 392 [$(MH)^+$, 40]. Anal. Calcd for $C_{17}H_9N_7OS_2$: C, 52.16; H, 2.32; N, 25.05; S, 16.38. Found: C, 52.03; H, 2.32; N, 24.87; S, 15.99.

*4.7.4. 3-(4-Methylphenyl)-2-(methylthio)pyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13d**)*

Yield 82%; mp: >300 °C. IR (KBr) 1691 (C=O), 1593, 1581, 1539, 1516, 1488 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.48 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 7.40–7.45 (m, 4H, ArH), 8.71 (d, 1H, J=2.3 Hz, H-6), 8.79 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 13.9, 21.4, 117.2, 127.0, 128.2, 131.0, 141.3, 142.4, 143.7, 144.2, 148.9, 150.2, 152.2, 156.2, 158.3. MS (FAB) *m/z* 381 [$(MH)^+$, 100]. Anal. Calcd for $C_{17}H_{12}N_6OS_2$: C, 53.67; H, 3.18; N, 22.09; S, 16.86. Found: C, 53.87; H, 3.16; N, 22.01; S, 16.95.

*4.7.5. 2-(Benzylthio)-3-(4-methylphenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13e**)*

Yield 89%; mp: 239–240 °C. IR (KBr) 1706 (C=O), 1538, 1515, 1498, 1485 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.45 (s, 3H, CH_3), 4.67 (s, 2H, CH_3), 7.29–7.48 (m, 9H, ArH), 8.70 (d, 1H, J=2.3 Hz, H-6), 8.79 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 21.3, 36.2, 117.1, 126.9, 128.2, 128.3, 128.9, 129.4, 130.8, 134.3, 141.1, 142.4, 143.7, 144.1, 148.8, 150.0, 152.0, 155.0, 158.2. MS (FAB) *m/z* 457 [$(MH)^+$, 100]. Anal. Calcd for $C_{23}H_{16}N_6OS_2$: C, 60.51; H, 3.53; N, 18.41; S, 14.05. Found: C, 60.27; H, 3.49; N, 18.24; S, 14.00.

*4.7.6. 2-(Cyanomethylthio)-3-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13f**)*

Yield 84%; mp: >300 °C. IR (KBr) 1702 (C=O), 2255 (CN), 1591, 1538, 1515, 1500, 1486 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.48 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.51–7.56 (m, 2H, ArH), 7.60–7.64 (m, 2H, ArH), 8.88 (d, 1H, J=2.3 Hz, H-6), 8.90 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 17.3, 21.4, 115.5, 117.2, 128.1, 128.6, 131.1, 141.5, 143.6, 143.7, 145.4, 149.3, 151.1, 152.0, 153.0, 157.3. MS (FAB) *m/z* 406 [$(MH)^+$, 70]. Anal. Calcd for $C_{18}H_{11}N_7OS_2$: C, 53.32; H, 2.73; N, 24.18; S, 15.82. Found: C, 53.14; H, 2.65; N, 23.99; S, 15.66.

*4.7.7. 2-(Methylthio)-3-(4-nitrophenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13g**)*

Yield 81%; mp: >300 °C (dec). IR (KBr) 1714 (C=O), 1584, 1530, 1505, 1486 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.91 (s, 3H, CH_3), 7.85–7.92 (m, 2H, ArH), 8.48–8.55 (m, 2H, ArH), 8.74 (d, 1H, J=2.3 Hz, H-6), 8.83 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 14.2, 118.2, 125.7, 128.0, 136.1, 142.7, 143.4, 144.4, 148.5, 148.6, 149.5, 151.8, 154.6, 158.3. MS (FAB) *m/z* 412 [$(MH)^+$, 40]. Anal. Calcd for $C_{16}H_9N_7O_3S_2$: C, 46.71; H, 2.20; N, 23.83; S, 15.59. Found: C, 46.57; H, 2.31; N, 24.01; S, 15.77.

*4.7.8. 2-(Benzylthio)-3-(4-nitrophenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13h**)*

Yield 74%; mp: 277–279 °C (dec). IR (KBr) 1704 (C=O), 1584, 1524, 1504, 1485 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.71 (s, 2H, CH_2), 7.30–7.40 (m, 3H, ArH), 7.41–7.49 (m, 2H, ArH), 7.80–7.88 (m, 2H, ArH), 8.43–8.51 (m, 2H, ArH), 8.73 (d, 1H, J=2.3 Hz, H-6), 8.81 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 36.7, 118.1, 125.6, 128.0, 128.6, 129.0, 129.4, 133.9, 136.1, 142.7, 143.3, 144.4, 148.5, 149.2, 151.7, 153.5, 158.2, 162.9. MS (FAB) *m/z* 448 [$(MH)^+$, 90]. Anal. Calcd for $C_{22}H_{13}N_7O_3S_2$: C, 54.20; H, 2.69; N, 20.11; S, 13.15. Found: C, 54.09; H, 2.52; N, 19.96; S, 12.91.

*4.7.9. 2-(Cyanomethylthio)-3-(4-methylphenyl)pyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**13i**)*

Yield 90%; mp: >300 °C (dec). IR (KBr) 1689 (C=O), 2252 (CN), 1585, 1523, 1505, 1489 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.54 (s, 2H, CH_2), 8.02–8.10 (m, 2H, ArH), 8.55–8.63 (m, 2H, ArH), 8.88 (d, 1H, J=2.3 Hz, H-6), 8.91 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 75 Hz) δ: 17.1, 115.4, 116.5, 125.4, 129.1, 135.9, 142.9, 143.2, 145.0, 148.5, 148.6, 150.2, 151.3, 151.4, 156.7. MS (FAB) *m/z* 437 [$(MH)^+$, 50]. Anal. Calcd for $C_{17}H_8N_8O_3S_2$: C, 46.78; H, 1.85; N, 25.68; S, 14.69. Found: C, 47.02; H, 2.12; N, 25.76; S, 14.91.

*4.8. Pyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one **15a**. General procedure*

Acyl chloride (0.08 mmol) and triethylamine (0.10 mmol) were added under argon, at room temperature, to a solution of phosphazene **7** (0.07 mmol) in dry THF (5 mL). The solution was stirred at room temperature for 3 h (for benzoyl chloride 8 h). The precipitate was separated by filtration, washed with THF (1 mL) and purified by column chromatography using a CH_2Cl_2–AcOEt gradient from 0% to 10% ethyl acetate to give **15** as a yellow solid.

*4.8.1. 2-Methyl-3-phenylpyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15a**)*

Yield 60%; mp: 220 °C (dec). IR (KBr) 1698 (C═O), 1586, 1490 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.30 (s, 3H, CH_3), 7.33–7.50 (m, 5H, ArH), 8.83 (d, 1H, J=2.3 Hz, H-6), 8.98 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 12.3, 117.1, 127.4, 130.6, 130.7, 131.4, 142.4, 143.7, 144.3, 149.5, 149.6, 151.6, 152.6, 158.3. MS (FAB) *m/z* 335 [$(MH)^+$, 90]. Anal. Calcd for $C_{16}H_{10}N_6OS$: C, 57.48; H, 3.01; N, 25.14; S, 9.59. Found: C, 57.60; H, 3.09; N, 25.35; S, 9.58.

*4.8.2. 2,3-Diphenylpyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15b**)*

Yield 72%; mp: >300 °C. IR (KBr) 1712 (C═O), 1578, 1539, 1486 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 7.47–7.52 (m, 2H, ArH), 7.51–7.59 (m, 3H, ArH), 7.64–7.66 (m, 5H, ArH), 8.89 (d, 1H, J=2.3 Hz, H-6), 8.92 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 115.2, 125.2, 129.0, 129.4, 129.6, 130.4, 130.8, 132.2, 133.1, 143.6, 143.8, 145.5, 149.9, 151.2, 152.4, 152.7, 157.4. MS (FAB) *m/z* 397 [$(MH)^+$, 70]. Anal. Calcd for $C_{21}H_{12}N_6OS$: C, 63.62; H, 3.05; N, 21.20; S, 8.09. Found: C, 63.46; H, 2.85; N, 21.19; S, 8.04.

*4.8.3. 2-Methyl-3-(4-methylphenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15c**)*

Yield 70%; mp: >300 °C (dec). IR (KBr) 1699 (C═O), 1595, 1542, 1517, 1493 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.50 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.33–7.50 (m, 4H, ArH), 8.71 (d, 1H, J=2.3 Hz, H-6), 8.80 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 12.2, 21.4, 117.0, 127.1, 128.7, 131.1, 141.1, 142.4, 143.8, 144.3, 149.5, 149.8, 151.8, 152.6, 158.4. MS (ESI) *m/z* 349 [$(MH)^+$, 10]. Anal. Calcd for $C_{17}H_{12}N_6OS$: C, 58.61; H, 3.47; N, 24.12; S, 9.20. Found: C, 58.44; H, 3.47; N, 24.26; S, 9.15.

*4.8.4. 3-(4-Methylphenyl)-2-phenylpyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15d**)*

Yield 91%; mp: >300 °C. IR (KBr) 1714 (C═O), 1592, 1578, 1540, 1515, 1487 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.47 (s, 3H, CH_3), 7.30–7.45 (m, 6H, ArH), 7.48–7.56 (m, 1H, ArH), 7.59–7.65 (m, 2H, ArH), 8.72 (d, 1H, J=2.3 Hz, H-6), 8.82 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 21.3, 117.1, 124.3, 127.4, 128.8, 129.4, 129.7, 130.9, 131.8, 140.6, 142.4, 143.8, 144.2, 149.5, 150.2, 152.3, 152.7, 158.4. MS (FAB) *m/z* 411 [$(MH)^+$, 100]. Anal. Calcd for $C_{22}H_{14}N_6OS$: C, 64.38; H, 3.44; N, 20.48; S, 7.81. Found: C, 64.43; H, 3.31; N, 20.36; S, 7.55.

*4.8.5. 2-Methyl-3-(4-nitrophenyl)pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15e**)*

Yield 71%; mp: >300 °C. IR (KBr) 1713 (C═O), 1581, 1527, 1505, 1488 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 2.52 (s, 3H, CH_3), 8.06–8.11 (m, 2H, ArH), 8.56–8.61 (m, 2H, ArH), 8.89 (d, 1H, J=2.3 Hz, H-6), 8.92 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR (DMSO-d_6, 125 Hz) δ: 17.1, 120.3, 130.5, 134.6, 142.2, 148.4, 148.5, 150.3, 153.4, 154.3, 155.1, 156.7, 157.1, 162.0. MS (FAB) *m/z* 380 [$(MH)^+$, 40]. Anal. Calcd for $C_{16}H_9N_7O_3S$: C, 50.66; H, 2.39; N, 25.85; S, 8.45. Found: C, 50.36; H, 2.33; N, 25.91; S, 8.22.

*4.8.6. 3-(4-Nitrophenyl)-2-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**15f**)*

Yield 92%; mp: >300 °C. IR (KBr) 1713 (C═O), 1583, 1556, 1541, 1524, 1487, 1449 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.46–7.52 (m, 2H, ArH), 7.58–7.63 (m, 3H, ArH), 7.72–7.76 (m, 2H, ArH), 8.43–8.48 (m, 2H, ArH), 8.78 (d, 1H, J=2.3 Hz, H-6), 8.87 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 118.2, 123.5, 125.6, 128.5, 129.3, 129.4, 132.5, 137.5, 142.8, 143.4, 144.5, 148.2, 149.1, 149.3, 151.6, 152.4, 158.4. MS (FAB) *m/z* 442 [$(MH)^+$, 20]. Anal. Calcd for $C_{21}H_{11}N_7O_3S$: C, 57.14; H, 2.51; N, 22.21; S, 7.26. Found: C, 57.25; H, 2.62; N, 22.02; S, 7.07.

*4.9. Bis(pyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo-[1,5-a]pyrimidin-10(3H)-ones) **17**. General procedure*

Diacyl chloride (0.05 mmol) and triethylamine (0.26 mmol) were added under argon, at room temperature, to a solution of phosphazene **7** (0.10 mmol) in dry THF (5 mL). The reaction mixture was heated at 150 °C in a sealed tube for 3 h. The precipitate was separated by filtration, washed with THF (1 mL) and purified by column chromatography using a CH_2Cl_2–AcOEt gradient from 0% to 10% ethyl acetate to give **17** as a yellow solid.

*4.9.1. 1,4-Bis(10′-oxo-3′-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl)benzene (**17a**)*

Yield 62%; mp: >300 °C (dec). IR (KBr) 1705 (C═O), 1582, 1537, 1465, 1432 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.61–7.66 (m, 10H, HAr), 7.67 (s, 4H, HAr), 8.74 (d, 2H, J=2.3 Hz, H-5), 8.82 (d, 2H, J=2.3 Hz, H-6). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 127.7, 127.9, 129.4, 129.7, 129.8, 130.6, 130.8, 137.9, 139.5, 142.4, 144.2, 144.3, 144.4, 149.5, 154.8. MS (FAB) *m/z* 715 [$(MH)^+$, 10]. Anal. Calcd for $C_{36}H_{18}N_{12}O_2S_2$: C, 60.50; H, 2.54; N, 23.52; S, 8.97. Found: C, 60.70; H, 2.48; N, 23.63; S, 9.06.

*4.9.2. 1,3-Bis(10′-oxo-3′-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl)benzene (**17b**)*

Yield 67%; mp: >300 °C (dec). IR (KBr) 1695 (C═O), 1599, 1584, 1522, 1496, 1485, 1443 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.37–7.47 (m, 5H, HAr), 7.57–7.63 (m, 6H, ArH), 7.71–7.75 (m, 2H, HAr), 7.81–7.84 (m, 1H, HAr), 8.74 (d, 2H, J=2.3 Hz, H-5), 8.83 (d, 2H, J=2.3 Hz, H-6). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 117.5, 125.4, 127.7, 129.6, 130.1, 130.7, 130.9, 131.8, 132.4, 142.6, 143.6, 144.4, 149.5, 149.9, 150.7, 152.5, 158.4. MS (FAB^+) *m/z* 715

[(MH$^+$), 15]. Anal. Calcd for $C_{36}H_{18}N_{12}O_2S_2$: C, 60.50; H, 2.54; N, 23.52; S, 8.97. Found: C, 60.38; H, 2.34; N, 23.69; S, 8.79.

*4.9.3. 2,6-Bis(10′-oxo-3′-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl)pyridine (**17c**)*

Yield 71%; mp: >300 °C (dec). IR (KBr) 1686 (C=O), 1581, 1488, 1456, 1448, 1436 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.14–7.20 (m, 4H, ArH), 7.39–7.48 (m, 6H, ArH), 8.12–8.19 (m, 1H, ArH), 8.32–8.38 (m, 2H, ArH), 8.75 (d, 2H, J=2.3 Hz, H-5), 8.84 (d, 2H, J=2.3 Hz, H-6). ^{13}C NMR ($CDCl_3$, 125 Hz) δ: 117.4, 127.3, 127.6, 129.6, 130.0, 132.0, 139.0, 142.7, 143.5, 144.5, 144.6, 149.2, 149.8, 149.8, 152.6, 158.5. MS (FAB$^+$) *m/z* 716 [(MH)$^+$, 10]. Anal. Calcd for $C_{35}H_{17}N_{13}O_2S_2$: C, 58.73; H, 2.39; N, 25.44; S, 8.96. Found: C, 58.90; H, 2.44; N, 25.53; S, 9.15.

*4.9.4. 1,3-Bis(10′-oxo-3′-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl)-phenylene diamine (**17d**)*

Yield 67%; mp: 250 °C (dec). IR (KBr) 3272 (NH), 1669 (C=O), 1595, 1574, 1539, 1514, 1486, 1446, 1339 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.66 (s, 2H, NH), 7.05–7.12 (m, 4H, HAr), 7.45–7.52 (m, 6H, HAr), 7.81 (s, 4H, HAr), 8.57 (d, 2H, J=2.3 Hz, H-5), 8.75 (d, 2H, J=2.3 Hz, H-6). ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) *m/z* 745 [(MH)$^+$, 10]. Anal. Calcd for $C_{36}H_{20}N_{14}O_2S_2$: C, 58.06; H, 2.71; N, 26.33; S, 8.61. Found: C, 58.00; H, 2.68; N, 26.24; S, 8.57.

*4.9.5. 1,4-Bis{10′-oxo-3′-(4″-methylphenyl)-pyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl}phenylene diamine (**17e**)*

Yield 55%; mp: 250 °C (dec). IR (KBr) 3341 (NH), 1685 (C=O), 1591, 1578, 1512, 1493, 1443, 1387 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.52 (s, 6H, CH_3), 5.99 (s, 2H, NH), 6.70–6.73 (m, 4H, HAr), 7.35–7.38 (m, 4H, HAr), 7.50 (s, 4H, HAr), 8.69 (d, 2H, J=2.3 Hz, H-5), 8.78 (d, 2H, J=2.3 Hz, H-6). A ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) *m/z* 773 [(MH)$^+$, 20]. Anal. Calcd for $C_{38}H_{24}N_{14}O_2S_2$: C, 59.06; H, 3.13; N, 25.37; S, 8.30. Found: C, 58.98; H, 3.28; N, 25.24; S, 8.47.

*4.9.6. 1,3-Bis(10′-oxo-3′-phenylpyrazino[2′,3′:4,5]thieno-[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-yl)-phenylene diamine (**17f**)*

Yield 50%; mp: 260 °C (dec). IR (KBr) 3271 (NH), 1673 (C=O), 1630, 1544, 1486, 1450, 1339 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 5.14 (s, 2H, NH), 7.37–7.45 (m, 4H, HAr), 7.79–7.88 (m, 10H, HAr), 8.58 (d, 2H, J=2.3 Hz, H-5), 8.77 (d, 2H, J=2.3 Hz, H-6). ^{13}C NMR spectrum could not be obtained due to poor solubility. MS (FAB) *m/z* 745 [(MH)$^+$, 15]. Anal. Calcd for $C_{36}H_{20}N_{14}O_2S_2$: C, 58.06; H, 2.71; N, 26.33; S, 8.61. Found: C, 57.90; H, 2.78; N, 26.34; S, 8.67.

*4.10. 3-Aryl-2-(N,N-dimethylamino)-pyrazino[2′,3′:4,5]-thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one **19***

To a solution of **7** (0.08 mmol) in CH_2Cl_2 (3 mL) was added *N,N*-dichloromethylenedimethylammonium chloride (Viehe's salt) (0.10 mol). The reaction mixture was heated at reflux temperature for 1 h. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography using a CH_2Cl_2–AcOEt gradient from 20% to 30% ethyl acetate to give **19** as a yellow solid.

*4.10.1. 2-(N,N-Dimethylamino)-3-phenylpyrazino-[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]pyrimidin-10(3H)-one (**19a**)*

Yield 87%; mp: >300 °C. IR (KBr) 1684 (C=O), 1580, 1546, 1522, 1491 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.87 (s, 6H, CH_3), 7.52–7.64 (m, 5H, ArH), 8.66 (d, 1H, J=2.3 Hz, H-6), 8.75 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 40.2, 117.6, 124.0, 127.2, 130.0, 130.4, 132.8, 142.1, 143.7, 148.0, 149.5, 152.3, 155.2, 158.0. MS (FAB) *m/z* 364 [(MH)$^+$, 100]. Anal. Calcd for $C_{17}H_{13}N_7OS$: C, 56.19; H, 3.61; N, 26.98; S, 8.82. Found: C, 56.00; H, 3.54; N, 27.17; S, 8.77.

*4.10.2. 2-(N,N-Dimethylamino)-3-(4-methylphenyl)-pyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]-pyrimidin-10(3H)-one (**19b**)*

Yield 71%; mp: >300 °C. IR (KBr) 1694 (C=O), 1596, 1573, 1540, 1515, 1492 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.47 (s, 3H, CH_3), 2.90 (s, 6H, CH_3), 7.36–7.50 (m, 4H, ArH), 8.66 (d, 1H, J=2.3 Hz, H-6), 8.76 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 21.3, 40.2, 117.5, 127.0, 130.2, 130.9, 140.4, 142.1, 143.7, 143.9, 148.0, 149.7, 152.3, 155.3, 158.0. MS (FAB) *m/z* 378 [(MH)$^+$, 100]. Anal. Calcd for $C_{18}H_{15}N_7OS$: C, 57.28; H, 4.01; N, 25.98; S, 8.50. Found: C, 57.09; H, 3.87; N, 25.79; S, 8.32.

*4.10.3. 2-(N,N-Dimethylamino)-3-(4-nitrophenyl)-pyrazino[2′,3′:4,5]thieno[3,2-d]-1,2,4-triazolo[1,5-a]-pyrimidin-10(3H)-one (**19c**)*

Yield 60%; mp: >300 °C. IR (KBr) 1679 (C=O), 1580, 1533, 1502 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.94 (s, 6H, CH_3), 7.92–7.99 (m, 2H, ArH), 8.48–8.56 (m, 2H, ArH), 8.70 (d, 1H, J=2.3 Hz, H-6), 8.79 (d, 1H, J=2.3 Hz, H-7). ^{13}C NMR ($CDCl_3$, 75 Hz) δ: 40.6, 118.6, 125.7, 127.7, 138.1, 142.4, 143.5, 144.0, 147.7, 148.0, 148.8, 152.0, 154.8, 158.0. MS (FAB) *m/z* 409 [(MH)$^+$, 85]. Anal. Calcd for $C_{17}H_{12}N_8O_3S$: C, 50.00; H, 2.96; N, 27.44; S, 7.85. Found: C, 49.81; H, 2.88; N, 27.25; S, 8.03.

5. Crystallographic material

Crystallographic data (excluding structural factors) for **9i** have been deposited in the Cambridge Crystallographic Data Center as supplementary publication number CCDC 664177. 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).

Acknowledgements

We thank to MCyT and FEDER (Grants BQU 2003-00574 and CTQ2006-04728) and the Xunta de Galicia, Spain (Grants PGI-DIT04PXIC10307PN and PGIDIT06PXIB103224PR) for financial support. G.B. acknowledges a predoctoral fellowship from the University of A Coruña.

References and notes

1. For recent reviews of heterocyclic synthesis, see: (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449; (b) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195; (c) Streng, W. H. *Drug Discov. Today* **1997**, *2*, 415; (d) Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *Org. Prep. Proced. Int.* **1998**, *30*, 1; (e) Cinfolini, M. A. *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: London, 1996; Vol. 3.
2. (a) Kane, S. E. *Adv. Drug Res.* **1996**, *28*, 181; (b) Bourguet-Kondracki, M. L.; Martin, M. T.; Guyot, M. *Tetrahedron Lett.* **1996**, *37*, 3457; (c) Kobayashi, M.; Chen, Y.-J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron* **1995**, *51*, 3727; (d) Bonaicha, N.; Amade, P.; Puel, D. *J. Nat. Prod.* **1994**, *57*, 1455; (e) Take, I.; Inouye, Y.; Nakamura, S.; Allandeen, H. S.; Kubo, A. *J. Antibiot.* **1989**, *42*, 107; (f) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, H.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378.
3. (a) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941 and references cited therein; (b) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840; (c) Neuschütz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227; (d) Ihara, M.; Fukumoto, K. *Nat. Prod. Rep.* **1997**, *14*, 413; (e) Taylor, E. C.; Dowling, J. E. *J. Org. Chem.* **1997**, *62*, 1599 and pertinent references cited therein; (f) Jones, G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., McKillop, A., Eds.; Pergamon: Oxford, 1996; Vol. 5; (g) Oikawa, T.; Kanomata, N.; Tada, M. *J. Org. Chem.* **1993**, *58*, 2046.
4. For recent contributions, see: (a) Haraguchi, K.; Kubota, Y.; Tanaka, H. *J. Org. Chem.* **2004**, *69*, 1831; (b) 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.
5. For examples, see: (a) Chambhare, R. V.; Khadse, B. G.; Bobde, A. S.; Bahekar, R. H. *Eur. J. Med. Chem.* **2003**, *38*, 89; (b) Sishoo, C. J.; Shirsath, V. S.; Rathod, I. S.; Yande, V. D. *Eur. J. Med. Chem.* **2000**, *35*, 351; (c) Walter, H. WO9914202, 1999 (*Chem. Abstr.* **1999**, *130*, 252368k); (d) Varvounis, G.; Giannopoulos, T. *Adv. Heterocycl. Chem.* **1996**, *66*, 193.
6. (a) Quintela, J. M.; Peinador, C.; González, L.; Devesa, I.; Ferrándiz, M. L.; Alcaraz, M. J.; Riguera, R. *Bioorg. Med. Chem.* **2003**, *11*, 863; (b) 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; (c) 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.
7. Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433.
8. (a) Pettit, G. R.; Tan, R.; Xu, J.; Ichihara, Y.; Williams, M. D.; Boyd, M. R. *J. Nat. Prod.* **1998**, *61*, 995; (b) Immamura, N.; Nishijima, M.; Takadera, T.; Adachi, K.; Sakai, M.; Sano, H. *J. Antibiot.* **1997**, *50*, 8.
9. (a) Baker, D. C.; Hand, E. S.; Plowman, J.; Rampal, J. B.; Safavy, A.; Haugwitz, R. D.; Narayanan, V. L. *Anti-Cancer Drug Des.* **1987**, *2*, 297; (b) For a recent review, see: Pawar, V. G.; De Borggraeve, W. H. *Synthesis* **2006**, 2799.
10. For a recent example, see: Burns, C. J.; Wilks, A. F.; Bu, X. Worldwide Patent WO2005054230, 2005 (*Chem. Abstr.* **2005**, *143*, 60004o).
11. (a) Palaska, E.; Sahin, G.; Kelicen, P.; Durlu, N. T.; Altinok, G. *Farmaco* **2002**, *57*, 101; (b) Hedge, V. B.; Bis, S. J.; Heo, E. C.; Hamilton, C. T.; Johnson, P. L.; Karr, L. L.; Martin, T. P.; Neese, P. A.; Orr, N.; Tisdell, F. E.; Yap, M. C. H.; Zhu, Y. U.S. Patent 20,020,019,370, 2002 (*Chem. Abstr.* **2002**, *136*, 146541); (c) Ulusoy, N.; Gursoy, A.; Otuk, G. *Farmaco* **2001**, *56*, 947; (d) Mikamo, H.; Yin, X. H.; Hayasaki, Y.; Satoh, M.; Tamaya, T. *Chemotherapy* **2001**, *47*, 377.
12. For recent contributions, see: (a) Cossío, F. P.; Alonso, C.; Lecea, B.; Ayerbe, M.; Rubiales, G.; Palacios, F. *J. Org. Chem.* **2006**, *71*, 2839; (b) Cassidy, M. P.; Oezdemir, A. D.; Padwa, A. *Org. Lett.* **2005**, *7*, 1339; (c) Ding, M.-W.; Huang, N.-Y.; He, H.-W. *Synthesis* **2005**, 1601; (d) Snider, B. B.; Zhon, J. *J. Org. Chem.* **2005**, *70*, 1087; (e) Gil, C.; Braese, S. *Chem.—Eur. J.* **2005**, *11*, 2680; (f) Alajarín, M.; Sánchez-Andrada, P.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2005**, *70*, 1340; (g) Cami-Kobed, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072.
13. 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) Arqués, A.; Molina, P. *Curr. Org. Chem.* **2004**, *8*, 827; (e) Wamhoff, H.; Richardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159; (f) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197; (g) Nitta, M. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU K.K.: Tokyo, 1993; Vol. 9, p 87; (h) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353; (i) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1.
14. (a) Eguchi, S. *Arkivoc* **2005**, 98; (b) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1; (c) Eguchi, S.; Okano, T.; Okawa, T. *Recent Res. Devel. in Organic Chem.* **1997**, 337.
15. (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) Álvarez-Sarandés, R.; Peinador, C.; Quintela, J. M. *Tetrahedron* **2001**, *57*, 5413.
16. Johnston, D. B. R. U.S. Patent 4.442,095, 1984.
17. (a) Appel, R.; Halstenberg, M. *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: London, 1979; p 378; (b) See Ref. 15.
18. Ding, M.-W.; Chen, Y.-F.; Huang, N.-Y. *Eur. J. Org. Chem.* **2004**, 3872.
19. For a review, see: Quintela, J. M.; Peinador, C.; Moreira, M. J.; Alvarez-Sarandés, R. *Recent Res. Devel. in Organic Chem.* **1998**, *2*, 409.
20. (a) Peinador, C.; Quintela, J. M.; Moreira, M. J. *Tetrahedron* **1997**, *53*, 8269; (b) Quintela, J. M.; Peinador, C.; Moreira, M. J. *Tetrahedron* **1995**, *51*, 5901; (c) Peinador, C.; Veiga, C.; Ojea, V.; Quintela, J. M. *Heterocycles* **1994**, *38*, 2065.