One-Pot Three-Step Synthesis of Pyrazinothienopyrimidines Using Tandem Aza-Wittig/Electrocyclic Ring Closure

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Abstract: A facile and efficient one-pot procedure for the preparation of pyrazino[3′,2′:4,5]thieno[3,2-*d*]pyrimidines following a tandem aza-Wittig/electrocyclic ring closure strategy is described. The one-pot, three-step reaction between 3-amino-2-formylthieno[2,3-*b*]pyrazine, primary amines, dichlorotriphenylphosphine and heterocumulenes, proceeded effectively and the yields of the products were higher than in the stepwise process. The products can also be prepared directly by a one-pot, two-step reaction using the same aldehyde, dichlorotriphenylphosphine and isocyanates. The advantages of the present method are easily accessible starting materials, experimental simplicity of the one-pot procedure, and good yields.

Key words: heterocycles, Wittig reaction, electrocyclic reactions, phosphazenes, cyclizations

Heterocyclic compounds occur very widely in nature and are essential to life and their synthesis has been subject of great interest due to their wide applicability.[1] These structures represent a class of molecules that act as ligands for various biological receptors with a high degree of binding affinity. In this context, an increasingly important area of ligand design involves the synthesis and study of new bridging ligands and, in the recent years, new ring construction processes have appeared that involves the preparation of new fused nitrogen and sulfur heterocycles and their use as chelating ligands.[2] Among these heterocyclic compounds, thienopyrimidines[3] and substituted pyrazine[4] motifs are of special significance.

The tandem aza-Wittig/electrocyclic ring closure of phosphazenes with heterocumulenic compounds has been widely used for the synthesis of many types of five- and six-membered N-heterocycles.[5] This approach has also been used by us for the preparation of triheterocyclic systems bearing various substituents in the pyridine ring.[6]

We have previously reported on the synthesis of novel tri- and tetracyclic ring systems with anti-inflammatory, antihistaminic and antiprotozoal activity.[7] In the frame of a development of novel synthetic methodology for the preparation of biologically active N-heterocyclic fused structures, we report here an efficient, one-pot procedure for the preparation of pyrazino[3′,2′:4,5]thieno[3,2-*d*]pyrimidines following a tandem aza-Wittig/electrocyclic ring closure strategy. The one-pot, three-step reaction proceeded effectively, and the yields of the products were higher than in the stepwise process. The advantages of the present method are easily accessible starting materials, experimental simplicity of the one-pot procedure, and good yields. We also wish to report the preparation of the pyrazinothienopyrimidine core directly by using a one-pot, two-step methodology.

Our efforts were directed towards the development of a one-pot, three-step reaction, which affords products in good yield in order to confirm the effectiveness of the one-pot process. The desired products **6** were prepared as shown in Scheme 1. Thus, a one-pot, three-step procedure involving sequential addition of aminoaldehyde **1**, primary amines, dichlorotriphenylphosphine and heterocumulenes such as isocyanates, carbon disulfide or carbon dioxide, could allow access to pyrazinothienopyrimidinones **6**. The starting material for all of the following chemistry was 7-amino-6-formylthieno[2,3-*b*]pyrazine (**1**), which was prepared by reduction of previously reported 3-amino-2-cyanothieno[2,3-*b*]pyrazine with diisobutylaluminium hydride. The synthesis of **3-**phenyl-2-phenylimino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (**6a**) was selected for establishing the effectiveness of the one-pot, three-step reaction. First, aminoaldehyde **1**, aniline, and a catalytic amount of piperidine were mixed in ethanol and heated at reflux for approximately one hour. The solvent was evaporated to dryness under reduced pressure then toluene was added followed by triphenylphosphine, hexachloroethane, and triethylamine and the reaction mixture was heated at 100 °C. After removing the solvent, a toluene solution containing the phenyl isocyanate was added, the reaction flask sealed, and the reaction mixture heated at 120 °C for approximately eight hours. The material obtained by this thermal treatment was purified by chromatography to give the pure pyrazinothienopyrimidine **6a** in 73% yield.

We found that the yield obtained using the one-pot, three-step synthesis was higher than that obtained from the stepwise process. Thus, treatment of aldehyde **1** with aniline in the presence of a catalytic amount of piperidine in refluxing ethanol for one hour (reaction monitored by TLC) led to the corresponding aldimine **2a** in 72% yield. The key intermediate phosphazene **3a** was obtained from **2** as an orange solid in 65% yield by treatment with the triphenylphosphine, triethylamine, hexachloroethane system[8] in anhydrous toluene. Reaction of phosphazene **3a** with phenyl isocyanate at 120 °C in a sealed tube for approximately eight hours resulted in the formation of

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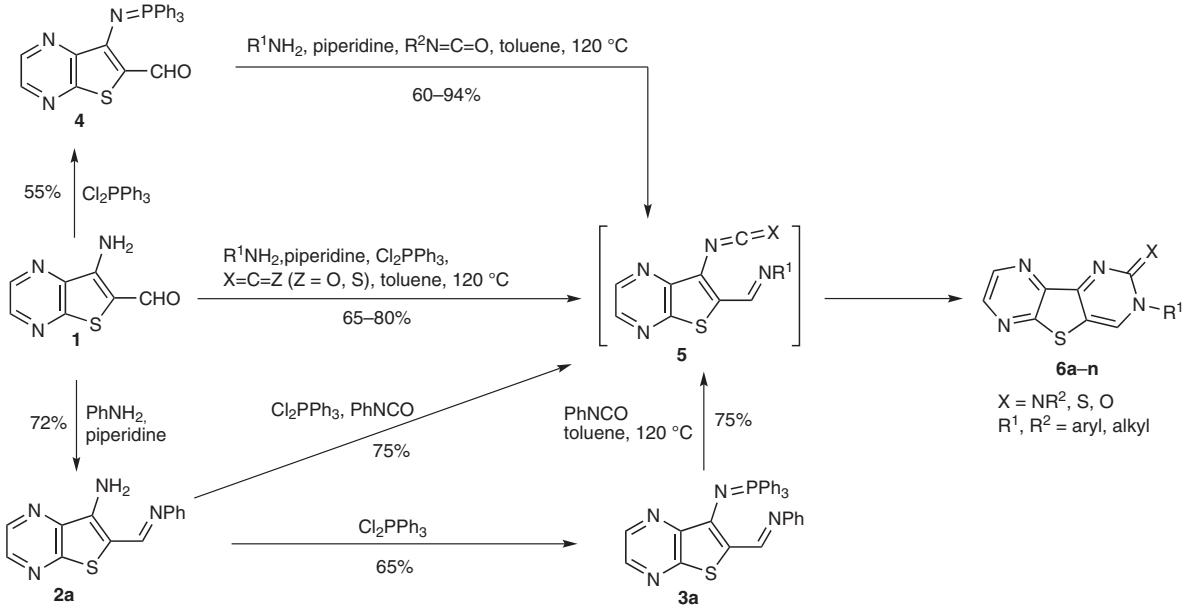


Scheme 1 One-pot and stepwise syntheses of pyrazinothienopyrimidines **6a–n**

triphenylphosphine oxide and the desired triheterocyclic compound **6a** as a yellow solid in 75% yield. We also carried out the direct reaction of aldimines **2a** with dichlorodiphenylphosphine prepared in situ (using C_2Cl_6/PPh_3/Et_3N), and phenylisocyanate, which afforded **6a** in 75% yield. Nevertheless, the total yield of the desired tricyclic compound **6a** using phosphorane **4**, obtained by reaction of **1** with dichlorotriphenylphosphine, aniline and phenylisocyanate was comparable to the protocol described above, but was lower than that in the one-pot, three-step synthesis (Scheme 1).

These preliminary experiments allowed us to design a general *one-pot* procedure for the preparation of the pyrazinothienopyrimidine core. The scope of the method was established by synthesizing fourteen compounds **6a–n** varying the primary amine and the heterocumulene utilized. To this end, the one-pot, three-step reaction sequence between aminoaldehyde **1**, aromatic and aliphatic primary amines, dichlorotriphenylphosphine, and isocyanates provided the disubstituted pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines **6a–j** in a straightforward manner (Table 1, entries 1–10). Triheterocyclic compounds **6a–j** were obtained in good overall yields (65–80%) for the conversion **1**→**6**, involving three reaction steps in a one-pot process.

Having established an efficient preparation with isocyanates, the potential application of the one-pot procedure using other heterocumulenes was explored. In this context, the application of the procedure employing carbon disulfide or carbon dioxide instead of isocyanates gave rise to the fused pyrimidines **6k–n** in good yields (entries 11–14, Table 1). The formation of these compounds can also be understood to occur by aza-Wittig reaction between the initially formed phosphazenes **3** and carbon dioxide or carbon disulfide to give the corresponding isocyanate as intermediates.[9] Heating this intermediate in anhydrous toluene at 120 °C causes it to cyclize spontaneously to the corresponding fused pyrimidinone compounds **6k–n**. It is worth mentioning that the isolation of pure cyclic pyrazinothienopyrimidine **6k** was not possible because of diffi-

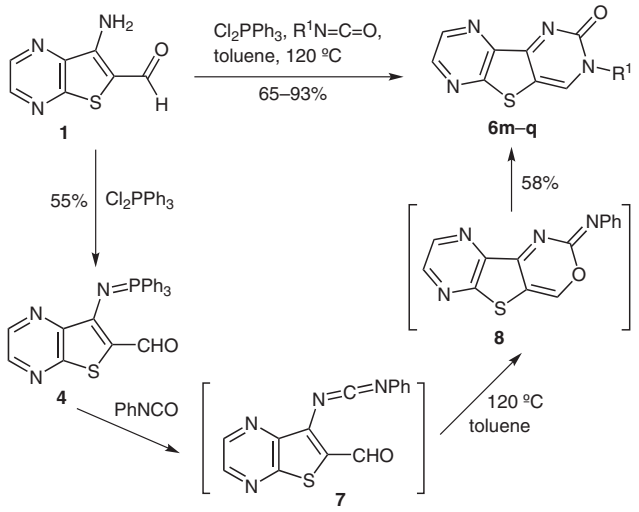
Table 1 Pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidines **6a–q**

	Compd	X	R^1	Yield (%)	Mp (°C)
1	**6a**	PhN	Ph	73	160–161
2	**6b**	4-MeC_6H_4N	Ph	65	135–137 (dec.)
3	**6c**	4-$O_2NC_6H_4N$	Ph	80	247–248
4	**6d**	BuN	Ph	66	140–141 (dec.)
5	**6e**	*i*-PrN	Ph	71	110–111 (dec.)
6	**6f**	PhN	Bu	67	234–236
7	**6g**	4-MeC_6H_4N	Bu	76	249–250
8	**6h**	4-$O_2NC_6H_4N$	Bu	77	265–267
9	**6i**	BuN	Bu	77	111–113 (dec.)
10	**6j**	*i*-PrN	Bu	79	140–142
11	**6k**	S	Ph	70[a]	–
12	**6l**	S	Bu	80	142–143
13	**6m**	O	Ph	60	225–226
14	**6n**	O	Bu	58	233–235
15	**6o**	O	4-MeC_6H_4	93	260–262 (dec.)
16	**6p**	O	4-$O_2NC_6H_4$	70	>300
17	**6q**	O	*i*-Pr	68	241–243 (dec.)

[a] Yield determined by ^{1}H NMR analysis of reaction mixture.

culties in separating the product from triphenylphosphine oxide, the inevitable byproduct of the aza-Wittig reaction.

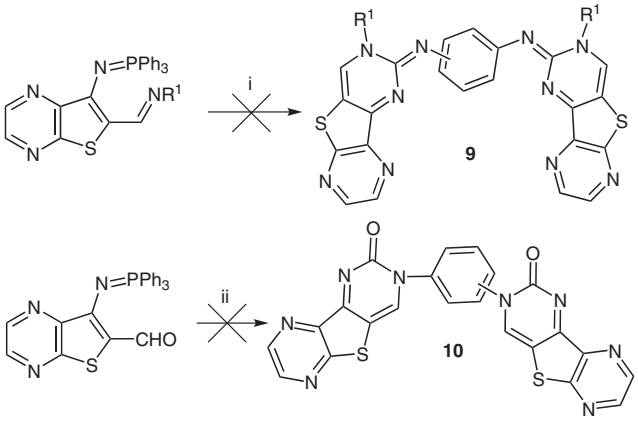
On the other hand, in one-pot processes, the sequential treatment of aminoaldehyde **1** with dichlorotriphenylphosphine (prepared in situ in the same reaction flask) and isocyanates in anhydrous toluene at reflux, led to the corresponding pyrazinothienopyrimidines **6o–q** directly in good yields, confirming the effectiveness of these one-pot, two-step reactions (Scheme 2 and Table 1, entries 13–17). We also carried out the reaction of phosphazene **4** with isocyanates, affording pyrido[2′,3′:4,5]thieno[2,3-*d*] in good to excellent yields (65–93%). The yield in the one-pot, two-step synthesis was higher than those obtained using the step-wise process. Presumably, the **1→6m–q** conversion involves initial aza-Wittig reactions between the generated phosphazene **4** (from reaction of aminoaldehyde **2** with dichlorotriphenylphosphine) and isocyanates, to afford carbodiimides **7**. By heating in toluene at reflux, these highly reactive intermediates underwent a 6π-electrocyclization involving their conjugated hexatriene fragment to give an unstable 1,3-oxazine-2-imine **8** which, by a Dimroth-type rearrangement of the lactone–lactam, underwent ring opening and closure to finally yield the pyrazinothienopyrimidines **6m–q**.



Scheme 2 One-pot and stepwise preparations of pyrazinothienopyrimidines **6m–q**

We reasoned that by thermal treatment with diisocyanates, the phosphazenes **3** and **4** could transform into pyrazinothienopyrimidines **9** and **10**, respectively, following a similar mechanistic sequence to that involved in the conversions **3→6** and **4→6** (Scheme 3). Unfortunately, when toluene solutions of compounds **3** and **4** and diisocyanates (1,3- an 1,4-phenylene diisocyanate), were heated at 120 °C for one hour in a sealed tube, only very complex reaction mixtures were obtained.

Structural elucidation of compounds **6** was accomplished from their analytical and spectral data. For example, the IR spectrum of **6f** exhibited a strong band at ν = 1627 cm^{-1} due to the imino group. Their ^1H NMR spectrum showed



Scheme 3 Attempted synthesis of bis(pyrazinothienopyrimidines) **9** and **10**. *Reagents and conditions*: (i) $C_6H_4(NCO)_2$, toluene, 120 °C; (ii) $C_6H_4(NCO)_2$, piperidine, toluene, 120 °C.

two doublets at δ = 8.58 and 8.67 ppm (*J* = 2.3 Hz) due to the pyrazine ring, and two triplets at δ = 1.02 ppm (*J* = 7.3 Hz) and δ = 4.09 ppm (*J* = 7.3 Hz) due to the CH_3 and NCH_2 protons, respectively. The ^{13}C NMR spectroscopic data for **6f** showed signals arising from the C=O (δ = 162.4 ppm) and CH_2 carbons (δ = 13.8, 19.9, 29.9 and 53.8 ppm). The FAB spectrum of **6f** showed a strong molecular ion peak (*m*/*z* = 336) with 100% abundance. The structure of **6f** was independently confirmed by X-ray crystal structure analysis (Figure 1). In the crystal structure of **6f** the pyrazinothienopyrimidine ring is planar. The dihedral angle between the mean planes defined by the pyrazinothienopyrimidine nucleus and the phenyl ring is 65°.

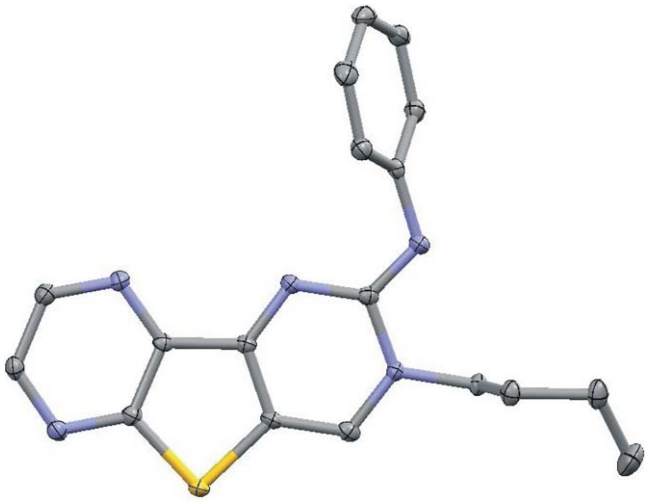


Figure 1 Crystal structure of **6f**. Solvent molecules and hydrogen atoms have been omitted for clarity. Color labeling scheme is as follows: S (yellow), N (blue), C (gray).

In summary, we have presented herein a novel and efficient methodology for the synthesis of disubstituted pyrazinothienopyrimidines through processes which involve tandem aza-Wittig/electrocyclic ring closure of phosphazenes with heterocumulenic compounds. These

structures are assembled from readily available starting materials in a simple one-pot procedure in high yields, under mild reaction conditions. This procedure presents all the advantages associated with one-step domino processes, such as reduction of reaction time, molecular diversity, no need for purification of intermediates and minimization of costs and waste production.

All reagents were commercial grade chemicals from freshly opened containers. Merck 60 F_{254} foils were used for thin layer chromatography and Merck 60 (230–400 mesh) silica gel was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance 300 (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively) or a Bruker Avance 500 (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 (δ = 0.00 ppm) for ^{1}H and to $CDCl_3$ (δ = 77.1 ppm) for ^{13}C. ^{31}P NMR spectra were obtained using a Bruker Avance 300 with 85% phosphoric acid as standard. IR spectra were recorded as KBr disks on a Bruker VECTOR 22 spectrophotometer. Mass spectrometry experiments were carried out using 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.

3-Amino-2-cyanothieno[2,3-*b*]pyrazine was prepared starting from commercial 3-cyanopyrazine according to a literature procedure.[10]

The crystal and molecular structure of **6f** was determined by X-ray diffraction studies.[11] Crystals were mounted on 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 direct methods and refined anisotropically[12] on F^2. Methyl groups were refined using rigid groups and other hydrogens were refined using a riding method.

7-Amino-6-formylthieno[2,3-*b*]pyrazine (1)

To a solution of 3-amino-2-cyanothieno[2,3-*b*]pyrazine (2 g, 11 mmol) in anhydrous THF (150 mL) cooled to –15 °C, DIBAL-H (1.5 M in toluene, 15.1 mL, 22.7 mmol) was added dropwise, and the reaction mixture was stirred at the same temperature for 2 h. MeOH (5 mL) was added and the reaction mixture was stirred for 5 min and then poured into ice-cooled HCl (1 M, 90 mL) and stirred for 30 min. The THF was removed under reduced pressure and the aqueous solution was extracted with Et_2O (15 × 50 mL). The organic layers were dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting material was purified by column chromatography on silica gel (hexanes–EtOAc, 70:30) to give **1**.

Yield: 1.0 g (50%); orange solid; mp 185–187 °C.

IR (KBr): 3331 (NH_2), 1621 (C=O), 1606, 1566, 1530, 1487, 1350 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.80 (s, 2 H, NH_2), 8.63 (d, *J* = 2.3 Hz, 1 H), 8.67 (d, *J* = 2.3 Hz, 1 H), 9.81 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 109.6, 140.9, 141.4, 145.1, 145.5, 157.7, 185.2.

MS (EI): *m*/*z* (%) = 179 (100) [M^+].

Anal. Calcd for $C_7H_5N_3S$: C, 46.92; H, 2.81; N, 23.45; S, 17.89. Found: C, 46.74; H, 3.00; N, 23.28; S, 17.75.

7-Amino-6-[(*N*-phenylimino)methyl]thieno[2,3-*b*]pyrazine (2a)

A mixture of 3-aminothieno[2,3-*b*]pyrazine-2-carbaldehyde (**1**; 0.5 g, 2.8 mmol), aniline (0.33 mL, 3.6 mmol) and a catalytic amount of piperidine in EtOH (20 mL) was refluxed until the aldehyde disappeared (~1.5 h, monitored by TLC). After cooling, the precipitated solid was filtered off and recrystallized (EtOH) to yield **2a**.

Yield: 0.51 g (72%); red crystals; mp 184–186 °C (dec.).

IR (KBr): 3434 (NH_2), 1540, 1481, 1465, 1359 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.73 (br s, 2 H), 7.20–7.28 (m, 3 H), 7.36–7.45 (m, 2 H), 8.56 (d, *J* = 2.3 Hz, 1 H), 8.27 (s, 1 H), 8.60 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 109.5, 120.9, 126.0, 129.2, 140.9, 141.0, 142.1, 142.6, 151.5, 154.2, 156.4.

MS (FAB): *m*/*z* (%) = 255 (100).

Anal. Calcd for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03; S, 12.61. Found: C, 61.07; H, 4.37; N, 22.18; S, 12.35.

6-[(*N*-Phenylimino)methyl]-7-[(triphenylphosphoranylidene)amino]thieno[2,3-*b*]pyrazine (3a)

To a mixture of **2a** (0.25 g, 0.98 mmol), Ph_3P (0.39 g, 1.47 mmol) and hexachloroethane (0.35 g, 1.47 mmol) in anhydrous toluene (10 mL), Et_3N (0.34 mL, 2.46 mmol) was added dropwise. The reaction mixture was heated at 100 °C with stirring in a sealed tube for approximately 2 h (monitored by TLC). After cooling, the resulting solid was filtered off and recrystallized (EtOAc) to give **3a**.

Yield: 0.33 g (65%); orange solid; mp 205–207 °C (dec.).

IR (KBr): 1550, 1462, 1410 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.10–7.55 (m, 14 H), 7.65–7.90 (m, 6 H), 7.97 (d, *J* = 2.3 Hz, 1 H), 8.23 (d, *J* = 2.3 Hz, 1 H), 9.32 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 121.4, 125.2, 128.2, 128.4, 129.0, 131.5, 132.6, 132.9, 138.8, 141.4, 145.8, 145.9, 141.7, 152.6, 153.6, 156.5.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 8.06.

MS (FAB): *m*/*z* (%) = 515 (90).

Anal. Calcd for $C_{31}H_{23}N_4PS$: C, 72.36; H, 4.51; N, 10.89; S, 6.23. Found: C, 71.96; H, 4.78; N, 11.07; S, 5.96.

6-Formyl-7-[(triphenylphosphoranylidene)amino]thieno[2,3-*b*]pyrazine (4)

To a mixture of aldehyde **1** (0.3 g, 1.67 mmol), Ph_3P (0.66 g, 2.51 mmol) and hexachloroethane (0.59 g, 2.51 mmol) in anhydrous toluene (15 mL), Et_3N (0.42 mL, 4.19 mmol) was added dropwise. The reaction mixture was heated at 100 °C in a sealed tube for 1.5 h (monitored by TLC). After cooling, the solvent was removed under reduced pressure and the residue was subjected to chromatography on silica gel (CH_2Cl_2) to give **4**.

Yield: 0.40 g (55%); yellow solid; mp 230–232 °C (dec.).

IR (KBr): 1622 (C=O), 1494, 1468, 1430, 1348 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.46 (m, 6 H), 7.49–7.54 (m, 3 H), 7.77–7.83 (m, 6 H), 7.99 (d, *J* = 2.3 Hz, 1 H), 8.31 (d, *J* = 2.3 Hz, 1 H), 10.74 (s, 1 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 128.5, 128.6, 131.0, 131.8, 131.9, 131.9, 132.6, 132.6, 139.2, 143.4, 157.9, 184.3.

^{31}P NMR ($CDCl_3$, 121.5 MHz): δ = 9.67.

MS (FAB): *m*/*z* (%) = 440 (100).

Anal. Calcd for $C_{25}H_{18}N_3OPS$: C, 68.33; H, 4.13; N, 9.56; S, 7.30. Found: C, 68.56; H, 3.98; N, 9.69; S, 7.06.

One-Pot Synthesis of Pyrazinothienopyrimidines 6a–n; General Procedure

A mixture of aminoaldehyde **1** (0.1 g, 0.56 mmol), the appropriate amine (benzylamine or aniline) (0.67 mmol) and a catalytic amount of piperidine in EtOH (10 mL) was refluxed for 1–2 h (monitored

by TLC). After cooling, the solvent was removed to dryness under reduced pressure, a solution of Ph_3P (0.22 g, 0.84 mmol) and hexachloroethane (0.20 g, 0.84 mmol) in anhydrous toluene (10 mL) was added, then Et_3N (0.19 mL, 1.40 mmol) was added dropwise. The reaction flask was sealed and the mixture was heated at 100 °C for 1–2 h (monitored by TLC). After cooling to r.t., the solvent was removed under reduced pressure and a solution of the appropriate heterocumulene (isocyanate, CS_2 or CO_2; 0.67 mmol) in anhydrous toluene (5 mL) was added in the same reaction flask. The flask was sealed and the reaction mixture containing the phosphazene and heterocumulene was heated at 120 °C for ~8 h until the phosphazene had disappeared (monitored by TLC). After cooling to r.t., the solvent was removed under reduced pressure, Et_2O (5 mL) was added, and the mixture was stirred at r.t. for 1–3 h. The resulting material formed was filtered off and purified by column chromatography on silica gel (EtOAc–CH_2Cl_2, 30→40%).

3-Phenyl-2-phenylimino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6a)
Yield: 73%; yellow crystals; mp 160–161 °C.

IR (KBr): 1670, 1624, 1599, 1549, 1539, 1498, 1430, 1339, 1280 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.10–7.18 (m, 1 H), 7.31–7.43 (m, 4 H), 7.48–7.59 (m, 5 H), 8.36 (s, 1 H), 8.74 (d, *J* = 2.3 Hz, 1 H, H-7), 8.86 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.7, 121.6, 126.2, 129.3, 129.3, 129.7, 129.8, 140.6, 143.4, 144.3, 147.0, 150.2, 152.5, 154.8, 162.8, 165.0.

MS (EI): *m*/*z* (%) = 278 (20) [$M^+ - C_6H_5$].

Anal. Calcd for $C_{20}H_{13}N_5S$: C, 67.59; H, 3.69; N, 19.70; S, 9.02. Found: C, 67.36; H, 3.79; N, 19.52; S, 9.19.

3-Phenyl-2-(4-methylphenyl)imino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6b)
Yield: 65%; yellow crystals; mp 135–137 °C (dec.).

IR (KBr): 1627, 1590, 1490, 1452, 1349, 1322, 1305 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 2.43 (s, 3 H), 7.13–7.18 (m, 4 H), 7.32–7.36 (m, 5 H), 8.35 (s, 1 H), 8.73 (d, *J* = 2.3 Hz, 1 H, H-7), 8.85 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.3, 112.6, 125.9, 128.5, 128.5, 129.5, 130.3, 139.2, 140.1, 143.3, 144.5, 146.9, 152.1, 154.9, 155.8, 162.7, 164.7.

MS (FAB): *m*/*z* (%) = 370 (20) $[MH]^+$.

Anal. Calcd for $C_{21}H_{15}N_5S$: C, 68.27; H, 4.09; N, 18.96; S, 8.68. Found: C, 68.45; H, 3.87; N, 18.72; S, 8.49.

3-Phenyl-2-(4-nitrophenyl)imino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6c)
Yield: 80%; yellow crystals; mp 247–248 °C.

IR (KBr): 1628, 1551, 1504, 1453 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.46–7.52 (m, 5 H), 7.73–7.77 (m, 2 H), 8.24–8.28 (m, 2 H), 8.42 (s, 1 H), 8.78 (d, *J* = 2.3 Hz, 1 H, H-7), 8.88 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 113.4, 125.1, 125.3, 126.2, 127.5, 129.6, 130.4, 131.5, 142.2, 142.6, 144.1, 145.6, 147.3, 151.2, 162.4, 163.3.

MS (FAB): *m*/*z* (%) = 401 (30) $[MH]^+$.

Anal. Calcd for $C_{20}H_{12}N_6O_2S$: C, 59.99; H, 3.02; N, 20.99; S, 8.01. Found: C, 59.83; H, 2.91; N, 20.73; S, 7.80.

2-*n*-Butylimino-3-phenyl-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6d)
Yield: 66%; green crystals; mp 140–141 °C (dec.).

IR (KBr): 1627, 1599, 1577, 1503, 1471, 1422, 1365, 1346 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (t, *J* = 7.3 Hz, 3 H), 1.40–1.54 (m, 2 H), 1.86–2.00 (m, 2 H), 4.09 (t, *J* = 7.3 Hz, 2 H), 6.94–7.04 (m, 1 H), 7.27–7.38 (m, 4 H), 7.88 (s, 1 H), 8.58 (d, *J* = 2.3 Hz, 1 H, H-7), 8.67 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.8, 19.9, 29.9, 53.8, 107.9, 122.0, 123.0, 128.6, 142.5, 143.2, 143.7, 146.0, 148.8, 149.0, 160.9, 162.5.

MS (FAB): *m*/*z* (%) = 336 (60) $[MH]^+$.

Anal. Calcd for $C_{18}H_{17}N_5S$: C, 64.45; H, 5.11; N, 20.88; S, 9.56. Found: C, 64.32; H, 4.92; N, 20.53; S, 9.40.

2-Isopropylimino-3-phenyl-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6e)
Yield: 71%; yellow solid; mp 110–111 °C (dec.).

IR (KBr): 1631, 1575, 1549, 1486, 1438 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.52 (d, *J* = 6.8 Hz, 6 H), 5.30 (sept, *J* = 6.8 Hz, 1 H), 7.39–7.46 (m, 5 H), 8.35 (s, 1 H), 8.70 (d, *J* = 2.3 Hz, 1 H, H-7), 8.83 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 21.8, 51.2, 112.6, 121.7, 123.1, 125.1, 140.4, 143.2, 146.6, 151.2, 154.5, 157.1, 160.2, 167.8.

MS (FAB): *m*/*z* (%) = 322 (40) $[MH]^+$.

Anal. Calcd for $C_{17}H_{15}N_5S$: C, 63.53; H, 4.70; N, 21.79; S, 9.98. Found: C, 63.37; H, 4.58; N, 22.01; S, 9.89.

3-*n*-Butyl-2-phenylimino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6f)
Yield: 67%; purple crystals; mp 234–236 °C.

IR (KBr): 1627, 1577, 1503, 1471, 1422, 1365, 1346 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.02 (t, *J* = 7.3 Hz, 3 H), 1.40–1.54 (m, 2 H), 1.86–2.00 (m, 2 H), 4.09 (t, *J* = 7.3 Hz, 2 H), 6.96–7.04 (m, 1 H), 7.28–7.36 (m, 4 H), 7.88 (s, 1 H), 8.58 (d, *J* = 2.3 Hz, 1 H), 8.67 (d, *J* = 2.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.8, 19.9, 29.9, 53.8, 107.9, 122.0, 123.0, 128.6, 142.5, 143.2, 143.7, 146.0, 148.7, 149.0, 161.0, 162.4.

MS (FAB): *m*/*z* (%) = 336 (100) $[MH]^+$.

Anal. Calcd for $C_{18}H_{17}N_5S$: C, 64.45; H, 5.11; N, 20.88; S, 9.56. Found: C, 64.14; H, 5.29; N, 20.78; S, 9.32.

3-*n*-Butyl-2-(4-methylphenyl)imino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6g)
Yield: 76%; purple crystals; mp 249–250 °C.

IR (KBr): 1628, 1582, 1493, 1470, 1421, 1362 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.00 (t, *J* = 7.3 Hz, 3 H), 1.40–1.50 (m, 2 H), 1.87–1.96 (m, 2 H), 2.31 (s, 3 H), 4.06 (t, *J* = 7.3 Hz, 2 H), 7.08–7.13 (m, 2 H), 7.17–7.21 (m, 2 H), 7.85 (s, 1 H), 8.56 (d, *J* = 2.3 Hz, 1 H, H-7), 8.66 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.9, 20.0, 21.0, 30.0, 53.8, 107.6, 122.8, 129.3, 131.2, 142.5, 143.3, 143.7, 146.1, 149.0, 152.0, 160.9, 162.5.

MS (FAB): *m*/*z* (%) = 350 (100) $[MH]^+$.

Anal. Calcd for $C_{19}H_{19}N_5S$: C, 65.30; H, 5.48; N, 20.04; S, 9.18. Found: C, 64.97; H, 5.26; N, 20.17; S, 9.01.

3-(*n*-Butyl)-2-(4-nitrophenyl)imino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6h)
Yield: 77%; brown solid; mp 265–267 °C.

IR (KBr): 1624, 1523, 1480, 1417, 1363, 1320 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.04 (t, *J* = 7.3 Hz, 3 H), 1.45–1.54 (m, 2 H), 1.91–1.99 (m, 2 H), 4.19 (t, *J* = 7.3 Hz, 2 H), 7.40–7.45 (m, 2 H), 8.07 (s, 1 H), 8.17–8.21 (m, 2 H), 8.67 (d, *J* = 2.3 Hz, 1 H, H-7), 8.77 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.8, 20.0, 30.2, 54.5, 110.6, 123.3, 125.0, 141.9, 142.7, 143.1, 143.8, 146.7, 150.4, 156.0, 161.2, 162.6.

MS (FAB): *m*/*z* (%) = 381 (30) $[MH]^+$.

Anal. Calcd for $C_{18}H_{16}N_6O_2S$: C, 56.83; H, 4.24; N, 22.09; S, 8.43. Found: C, 56.67; H, 4.18; N, 22.15; S, 8.49.

3-*n*-Butyl-2-*n*-butylimino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6i)
Yield: 77%; yellow solid; mp 111–113 °C (dec.).

IR (KBr): 1662, 1635, 1541, 1466, 1411, 1377, 1337 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.00 (t, *J* = 7.3 Hz, 6 H), 1.39–1.52 (m, 4 H), 1.86–1.94 (m, 4 H), 4.12–4.16 (m, 4 H), 8.27 (s, 1 H), 8.71 (d, *J* = 2.3 Hz, 1 H, H-7), 8.85 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.7, 26.5, 31.0, 53.4, 112.2, 143.2, 144.0, 146.7, 154.1, 155.1, 162.2, 163.8.

MS (FAB): *m*/*z* (%) = 316 (100) $[MH]^+$.

Anal. Calcd for $C_{16}H_{21}N_5S$: C, 60.92; H, 6.71; N, 22.20; S, 10.17. Found: C, 60.85; H, 6.58; N, 22.12; S, 10.34.

3-*n*-Butyl-2-isopropylimino-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6j)
Yield: 79%; brown solid; mp 140–142 °C.

IR (KBr): 1659, 1632, 1522, 1464, 1334 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.01 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.38–1.41 (m, 2 H, CH_2), 1.53 (d, *J* = 6.8 Hz, 6 H, CH_3), 1.78–1.84 (m, 2 H), 3.88 (t, *J* = 7.3 Hz, 2 H), 4.62–4.69 (sept, *J* = 6.8 Hz, 1 H), 8.41 (s, 1 H), 8.69 (d, *J* = 2.3 Hz, 1 H, H-7), 8.94 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.8, 19.5, 23.4, 29.9, 43.9, 46.8, 116.6, 143.5, 143.7, 144.3, 151.5, 157.8, 160.7, 163.4.

MS (FAB): *m*/*z* (%) = 302 (100) $[MH]^+$.

Anal. Calcd for $C_{15}H_{19}N_5S$: C, 59.77; H, 6.35; N, 23.24; S, 10.64. Found: C, 59.64; H, 6.29; N, 23.38; S, 10.51.

3-*n*-Butyl-2-thioxo-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6l)
Yield: 80%; orange solid; mp 142–143 °C.

IR (KBr): 1598, 1492, 1438, 1374 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.03 (t, *J* = 7.3 Hz, 3 H), 1.45–1.54 (m, 2 H), 1.98–2.05 (m, 2 H), 4.64 (t, *J* = 7.3 Hz, 2 H), 8.45 (s, 1 H), 8.73 (d, *J* = 2.3 Hz, 1 H, H-7), 8.89 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.7, 20.0, 30.1, 59.4, 118.0, 142.0, 143.8, 144.0, 146.9, 157.6, 162.2, 180.1.

MS (FAB): *m*/*z* (%) = 277 (20) $[MH]^+$.

Anal. Calcd for $C_{12}H_{12}N_4S_2$: C, 52.15; H, 4.38; N, 20.27; S, 23.20. Found: C, 52.22; H, 4.25; N, 20.09; S, 22.98.

2-Oxo-3-phenyl-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6m)
Yield: 60%; pale-yellow solid; mp 225–226 °C.

IR (KBr): 1676 (C=O), 1454, 1376 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.52–7.65 (m, 5 H), 8.42 (s, 1 H), 8.80 (d, *J* = 2.3 Hz, 1 H, H-7), 8.93 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 112.6, 126.3, 129.7, 129.8, 140.6, 143.4, 144.3, 147.0, 154.7, 162.8, 165.0.

MS (FAB): *m*/*z* (%) = 281 (15) $[MH]^+$.

Anal. Calcd for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99; S, 11.44. Found: C, 60.34; H, 3.09; N, 19.63; S, 10.95.

3-*n*-Butyl-2-oxo-pyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6n)
Yield: 58%; yellow solid; mp 233–235 °C.

IR (KBr): 1639 (C=O), 1499, 1470, 1445, 1417, 1359 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 0.99 (t, *J* = 7.4 Hz, 3 H), 1.40–1.50 (m, 2 H), 1.86–1.94 (m, 2 H), 4.14 (t, *J* = 7.5 Hz, 2 H), 8.30 (s, 1 H), 8.71 (d, *J* = 2.3 Hz, 1 H, H-7), 8.84 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.6, 19.9, 31.0, 53.3, 112.1, 142.6, 143.1, 144.0, 146.6, 155.0, 162.1, 163.7.

MS (FAB): *m*/*z* (%) = 261 (50) $[MH]^+$.

Anal. Calcd for $C_{12}H_{12}N_4OS$: C, 55.37; H, 4.65; N, 21.52; S, 12.32. Found: C, 55.11; H, 4.17; N, 21.41; S, 11.88.

Preparation of Pyrazinothienopyrimidines 6m–q; Typical Procedure

A solution of aminoaldehyde **1** (0.1 g, 0.56 mmol), Ph_3P (0.22 g, 0.84 mmol), hexachloroethane (0.20 g, 0.84 mmol), and Et_3N (0.19 mL, 1.40 mmol) in anhydrous toluene (10 mL) was heated at 100 °C for 1–2 h (monitored by TLC) in a sealed reaction flask. After cooling to r.t., the solvent was removed under reduced pressure and a solution of the appropriate isocyanate (0.67 mmol) in anhydrous toluene (5 mL) was added in the same reaction flask. The flask was sealed and the reaction mixture containing the phosphazene and heterocumulene was heated at 120 °C for ~8 h until the phosphazene had disappeared (monitored by TLC). After cooling to r.t., the solvent was removed under reduced pressure, Et_2O (5 mL) was added, and the mixture was stirred at r.t. for 1–3 h. The resulting material formed was filtered off and purified by column chromatography on silica gel (EtOAc–CH_2Cl_2, 50→100%) to give **6m** (71% yield), **6n** (65% yield), and **6o–q** as pure compounds.

3-(4-Methylphenyl)-2-oxo-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6o)
Yield: 93%; yellow solid; mp 260–262 °C (dec.).

IR (KBr): 1671 (C=O), 1623, 1526, 1428, 1350, 1278 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.42 (s, 3 H), 7.29–7.35 (m, 2 H), 7.37–7.42 (m, 2 H), 8.39 (s, 1 H), 8.72 (d, *J* = 2.3 Hz, 1 H, H-7), 8.84 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.6, 112.4, 125.8, 130.1, 138.0, 139.7, 143.2, 144.5, 146.8, 154.7, 162.6, 164.6, 171.1.

MS (FAB): *m*/*z* (%) = 295 (40) $[MH]^+$.

Anal. Calcd for $C_{15}H_{10}N_4OS$: C, 61.21; H, 3.42; N, 19.04; S, 10.89. Found: C, 61.52; H, 3.25; N, 19.15; S, 10.28.

3-(4-Nitrophenyl)-2-oxo-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6p)
Yield: 70%; yellow solid; mp >300 °C.

IR (KBr): 1657 (C=O), 1614, 1521, 1494, 1465, 1416, 1348, 1317 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ = 7.76–7.80 (m, 2 H), 8.34 (s, 1 H), 8.42–8.46 (m, 2 H), 8.76 (d, *J* = 2.3 Hz, 1 H, H-7), 8.90 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 111.9, 124.5, 128.3, 141.7, 143.6, 145.9, 147.2, 147.3, 147.6, 153.9, 162.3, 164.2.

MS (FAB): *m*/*z* (%) = 281 (25) $[MH^+ - NO_2]$.

Anal. Calcd for $C_{14}H_7N_5O_3S$: C, 51.69; H, 2.17; N, 21.53; S, 9.86. Found: C, 51.06; H, 2.47; N, 21.02; S, 9.97.

3-Isopropyl-2-oxo-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6q)

Yield: 68%; yellow solid; mp 241–243 °C (dec.).

IR (KBr): 1647 (C=O), 1524, 1503, 1466, 1374, 1349, 1272 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.53 (d, *J* = 6.8 Hz, 6 H), 5.30 (sept, *J* = 6.8 Hz, 1 H), 8.34 (s, 1 H), 8.70 (d, *J* = 2.3 Hz, 1 H, H-7), 8.83 (d, *J* = 2.3 Hz, 1 H, H-8).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 22.1, 51.2, 112.6, 140.3, 142.8, 143.2, 146.6, 154.9, 162.2, 162.8.

MS (FAB): *m*/*z* (%) = 247 (90) $[MH]^+$.

Anal. Calcd for $C_{11}H_{10}N_4OS$: C, 53.64; H, 4.09; N, 22.75; S, 13.02. Found: C, 53.98; H, 4.38; N, 23.05; S, 13.19.

2-Oxo-3-phenyl-2,3-dihydropyrazino[2′,3′:4,5]thieno[3,2-*d*]pyrimidine (6m)

To a solution of phosphazene **4** (0.1 g, 0.23 mmol) in anhydrous THF (5 mL) was added phenyl isocyanate (0.27 mmol). The reaction mixture was heated at 120 °C in a sealed tube for ~8 h until the phosphazene had disappeared (monitored by TLC). The solution was concentrated to dryness, and the residual material was purified by column chromatography on silica gel (EtOAc–CH_2Cl_2, 50→100%) to give **6m** (58% yield), whose properties were identical to those of the compound obtained by the one-pot procedure.

X-ray Crystallographic Data for Compound 6f

Suitable crystals for an X-ray diffraction analysis were grown from EtOH. Formula weight: 668.86; Crystal system: monoclinic; Space group: P2(1)/c; Unit cell dimensions: *a* = 10.7553(3) Å, *b* = 13.6974(4) Å, *c* = 12.3887(4) Å, *a* = 90°, *b* = 115.752(2)°, *g* = 90°; *V* = 1643.84(8) $Å^3$; *Z* = 2; D (calcd) = 1.351 mg m^{-3}; F(000) = 700; *T* = 100 (2) K.

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(11) Crystallographic data (excluding structure factors) for **6f** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 692136. 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].

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