One-pot three-component synthesis of bis[2-(methylthio)-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes

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Three-component reactions of ethyl 2-methylthio-4-[(triphenylphosphanylidene)amino] thiazole-5-carboxylate with aromatic diisocyanates and secondary amines produced novel bis[2-methylthio-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes in the presence of EtONa in 67–93% yields. This method provides an effective synthesis of nitrogen-containing heterocycles with the advantages of mild reaction conditions, simple operation and good yields. The structures of the products were confirmed by ^{1}H NMR, IR, MS and elemental analysis.

Keywords: three-component reaction, thiazole, pyrimidine, thiazolo[4,5-*d*]pyrimidine, benzene, synthesis

Thiazolopyrimidines as purine antagonists are known to have potential biological importance.[1,2] In general, they are widely used in the fields of medicine and pesticides.[3–5] The [4,5-*d*] isomer of thiazolopyrimidine can be considered as the 7-thia analogues of guanine and adenine due to the replacement of a nitrogen by a sulfur atom at position 7 of the purine ring. Numerous thiazolo[4,5-*d*]pyrimidine derivatives have been reported for their interesting biological and pharmaceutical activities. For example, many derivatives of this ring system were found to have CNS-depressant properties and antifungal, antimicrobial,[6] anti-HIV,[7] antituberculosis[8] and herbicidal activities.[9] The large number of biologically active molecules that contain heterocyclic rings has made synthetic studies of new heterocyclic rings very attractive. Particularly, polyfunctionalised heterocyclic compounds play important roles in the drug discovery process.[10–14] Therefore, it is not surprising that research on the synthesis of polyfunctionalised heterocyclic compounds has received significant attention. In recent years, attention has been increasingly paid to the synthesis of bis-heterocyclic compounds. Recently, we have been interested in the synthesis of fused pyrimidinones *via* aza-Wittig reaction of β-ethoxycarbonyliminophosphoranes with aromatic isocyanates and subsequent reaction with various nucleophiles under mild conditions.[15,16] As a continuation of our research for new biologically active heterocycles, here we report an efficient synthesis of bis[2-(methylthio)-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes, a series of compounds which have not been reported before.

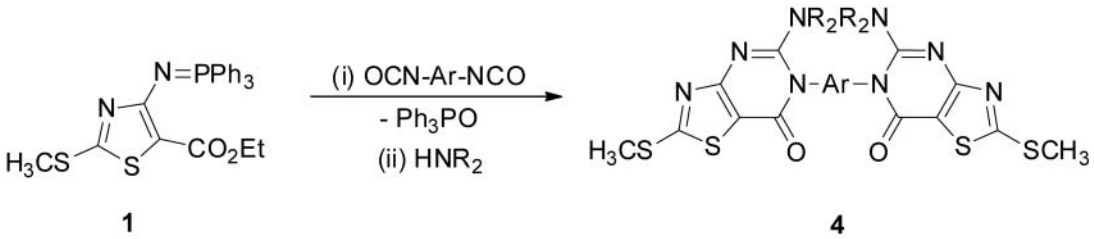
Results and discussion

The iminophosphorane **1** was synthesised according to the literature procedure and had identical physical and spectra properties to those reported previously.[17] Reaction of iminophosphorane **1** with aromatic diisocyanates, followed by *in situ* heterocyclisation of the intermediate carbodiimide, by a secondary amine, resulted directly in the formation of the corresponding bis[2-(methylthio)thiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes and triphenylphosphine oxide, as outlined in Scheme 1.

The results are listed in Table 1.

The iminophosphorane **1** reacted with aromatic diisocyanates to give intermediate carbodiimides **2**. The reaction proceeded smoothly in THF at room temperature. Subsequent reaction of the carbodiimides **2** with secondary amines at room temperature gave intermediate guanidines **3** *via* initial nucleophilic addition of amines to the carbodiimide. Even in refluxing toluene, **3** did not cyclise. However, in dry 1,2-dichloroethane and in the presence of a catalytic amount of EtONa, compounds **3** were converted smoothly to the 1,4-bis[2-methylthio-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes **4** in satisfactory yields at room temperature. We found that heterocyclisation occurred *via* nucleophilic displacement from the neighbouring ester group to give the target compounds **4** by intramolecular elimination of ethanol. Irrespective of the nature of the aryl (Ar) group in the diisocyanate the cyclisation proceeded very smoothly and with the same regioselectivity. The reaction pathway is shown in Scheme 2.

The structures of compounds **4** were fully confirmed by IR, ^{1}H NMR and MS data. The mass spectra of the products showed the expected molecular ion peaks and the IR spectra showed a strong C=O absorption band at 1682–1695 cm^{-1}. For example, the electrospray ionisation mass spectrum (ESI-MS) for **4e** showed the expected molecular ion peaks which showed *m/z* at 629 $(M + H)^+$ and the two-dimensional ionisation pattern is in accord with the proposed structure. The IR spectrum (KBr) for **4e** showed a strong absorption at 1685 cm^{-1} assigned to the C=O group. IR absorption spectra of thiazoles are generally characterised by the presence of two bands around 1260–1215 and 1090–1020 cm^{-1} corresponding to C–S–C moiety. In the ^{1}H NMR spectrum, the $-SCH_3$ protons appeared at 2.47 ppm as singlet, in addition to the aromatic proton multiplets which absorbed in the region 7.23–7.51 ppm.



1 **4**

Scheme 1 Synthesis of bis[2-(methylthio)thiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes

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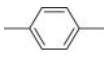
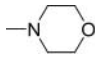
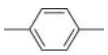
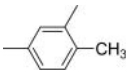
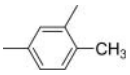
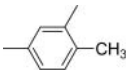
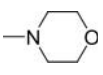
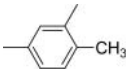
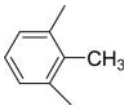
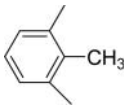
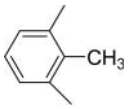
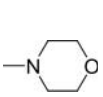
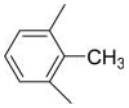
Table 1 Preparation of bis[2-(methylthio)-7-oxothiazolo[4,5-*d*]-pyrimidin-6(7*H*)-yl]benzenes

Compd	Ar	NR_2	Yield/%[a]
4a		NEt_2	87
4b		NPr^i_2	76
4c			93
4d			91
4e		NEt_2	83
4f		NPr^i_2	72
4g			88
4h			80
4i		NEt_2	77
4j		NPr^i_2	67
4k			82
4l			78

[a] Isolated yields based on iminophosphorane **1**.

Conclusion

In summary, we developed a new approach for the one-pot three-component synthesis of bis[2-(methylthio)-7-oxothiazolo-[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes. This approach provides an effective way to synthesise this aryl-linked nitrogen-containing heterocycles, with the advantages of the mild reaction conditions, simple operation and good yields.

Experimental

Melting points were determined using a TKHG model X-4 apparatus and were uncorrected. IR spectra were recorded on a Nicolet 7500 NXR IR spectrometer as KBr pellets with absorption given in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance III 300 NMR spectrometer and chemical shifts (δ) are given in ppm using $(CH_3)_4Si$ as an internal reference (δ = 0). Mass spectral data were obtained on a Finnigan LCQ Advantage MAX mass spectrometer. Elementary analyses were taken on a Perkin-Elmer CHN 2400 elemental analysis instrument.

*Synthesis of bis[2-(methylthio)-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzenes* (**4**)*; general procedure*

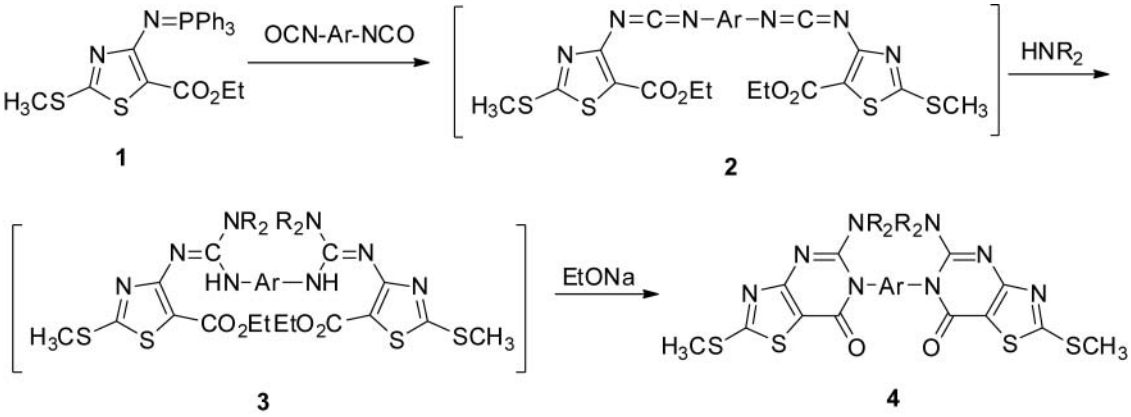
An aromatic diisocyanate (0.003 mol) was added to the solution of iminophosphorane **1** (2.9 g, 0.006 mol) in THF (10 mL) at 0–5 °C. When the iminophosphorane **1** reacted with the aromatic diisocyanate, triphenylphosphine oxide was formed. After the reaction mixture was stirred for 5–6 h at 0–5 °C, the solvent was removed under reduced pressure and Et_2O/petroleum ether (b.p. 60–90 °C 1:2; 12 mL) was added to precipitate triphenylphosphine oxide. Then triphenylphosphine oxide was removed by filtration. Removal of the solvent gave carbodiimides **2**, which were used directly without further purification. A secondary amine (0.006 mol) was added to the solution of **2** prepared above in CH_2Cl_2 (10 mL) to give the intermediate guanidines **3**. After the reaction mixture was stirred for 2–3 h, the solvent was removed and EtONa in anhydrous EtOH (8 mL, 10%) was added. The mixture was stirred for 3–5 h at room temperature. The solution was evaporated and the residue was recrystallised from EtOH to give the target compound **4**. TLC using Merck 60 F-254 silica gel plates was used to follow the progress of every reaction.

*1,4-Bis[5-(diethylamino)-2-methylthio-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzene* (**4a**): White crystals; m.p. 215–216 °C; IR (KBr): 2306, 1685 (C=O), 1556, 1441, 1213, 1118, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (t, *J* = 7.2 Hz, 12H, 4 × CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.61 (q, *J* = 7.2 Hz, 8H, 4 × CH_2), 7.26–7.62 (m, 4H, ArH); ESI-MS *m/z*: 615 $(M + H)^+$. Anal. Calcd for $C_{26}H_{30}N_8O_2S_4$: C, 50.79; H, 4.92; N, 18.23. Found: C, 50.83; H, 3.86; N 18.15%.

*1,4-Bis[5-(diisopropylamino)-2-methylthio-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl] benzene* (**4b**): White crystals; m.p. 241–242 °C; IR (KBr): 2306, 1687 (C=O), 1542, 1442, 1223, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, *J* = 7.2 Hz, 24H, 8 × CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.91–3.07 (m, 4H, 4 × CH), 7.14–7.55 (m, 4H, ArH); ESI-MS *m/z*: 671 $(M + H)^+$. Anal. Calcd for $C_{30}H_{38}N_8O_2S_4$: C, 53.70; H, 5.71; N, 16.70. Found: C, 53.82; H, 5.76; N 16.65%.

*1,4-Bis[2-methylthio-5-morpholino-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzene* (**4c**): White crystals; m.p. 267–269 °C; IR (KBr): 3306, 1687 (C=O), 1540, 1451, 1242, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.47 (s, 6H, 2 × SCH_3), 3.08 (t, *J* = 4.8 Hz, 8H, 4 × NCH_2), 3.46 (t, *J* = 4.8 Hz, 8H, 4 × OCH_2), 7.24–7.63 (m, 4H, ArH); ESI-MS *m/z*: 643 $(M + H)^+$. Anal. Calcd for $C_{26}H_{26}N_8O_4S_4$: C, 48.58; H, 4.08; N, 17.43. Found: C, 48.46; H, 4.16; N, 17.48%.

*1,4-Bis[2-methylthio-5- piperidino-7-oxothiazolo[4,5-*d*]pyrimidin-6(7*H*)-yl]benzene* (**4d**): White crystals; m.p. > 300 °C; IR (KBr): 3303, 1688 (C=O), 1543, 1455, 1244, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22–1.45 (m, 20H, 10 × CH_2), 2.47 (s, 6H, 2 × SCH_3),



Scheme 2

7.28–7.72 (m, 4H, ArH); ESI-MS *m/z*: 639 $(M + H)^+$. Anal. Calcd for $C_{28}H_{30}N_8O_2S_4$: C, 52.64; H, 4.73; N, 17.54. Found: C, 52.57; H, 4.75; N, 17.65%.

2,4-Bis[5-(diethylamino)-2-methylthio-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4e**): White crystals; m.p. > 300 °C; IR (KBr): 3308, 2940, 1685 (C=O), 1552, 1458, 1343, 1212 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (t, *J* = 7.2 Hz, 12H, 4 × CH_3), 2.34 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.58 (q, *J* = 7.2 Hz, 8H, 4 × NCH_2), 7.23–7.51 (m, 3H, 3H, ArH); ESI-MS *m/z*: 629 $(M + H)^+$. Anal. Calcd for $C_{27}H_{32}N_8O_2S_4$: C, 51.57; H, 5.13; N, 17.82. Found: C, 51.66; H, 5.07; N, 17.71%.

2,4-Bis[5-(diisopropylamino)-2-methylthio-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4f**): White crystals; m.p. 265–266 °C; IR (KBr): 3307, 2941, 1687 (C=O), 1553, 1415, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, *J* = 7.2 Hz, 24H, 8 × CH_3), 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.91–3.07 (m, 4H, 4CH), 7.24–7.64 (m, 3H, ArH); ESI-MS *m/z*: 685 $(M + H)^+$. Anal. Calcd for $C_{31}H_{40}N_8O_2S_4$: C, 54.36; H, 5.89; N, 16.36. Found: C, 54.27; H, 5.81; N, 16.33%.

2,4-Bis[2-methylthio-5-morpholino-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4g**): White crystals; m.p. 287–289 °C; IR (KBr): 3296, 1687 (C=O), 1540, 1451, 1112, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 3.08 (t, *J* = 4.8 Hz, 8H, 4 × NCH_2), 3.46 (t, *J* = 4.8 Hz, 8H, 4 × OCH_2), 7.21 -7.61 (m, 3H, ArH); ESI-MS *m/z*: 657 $(M + H)^+$. Anal. Calcd for $C_{27}H_{28}N_8O_4S_4$: C, 49.37; H, 4.30; N, 17.06. Found: C, 49.45; H, 4.19; N, 17.01%.

2,4-Bis[2-methylthio-5- piperidino-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4h**): White crystals; m.p. > 300 °C; IR (KBr): 2978, 1689 (C=O), 1553, 1457, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22–1.45 (m, 20H, 10 × CH_2), 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 7.28–7.72 (m, 4H, ArH); ESI-MS *m/z*: 653 $(M + H)^+$. Anal. Calcd for $C_{29}H_{32}N_8O_2S_4$: C, 53.35; H, 4.94; N, 17.16. Found: C, 53.41; H, 4.87; N, 17.23%.

2,6-Bis[5-(diethylamino)-2-methylthio-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4i**): White crystals; m.p. > 300 °C; IR (KBr): 3308, 2940, 1685 (C=O), 1552, 1458, 1343, 1212 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.03 (t, *J* = 7.2 Hz, 12H, 4 × CH_3), 2.34 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.58 (q, *J* = 7.2 Hz, 8H, 4 × NCH_2), 7.23–7.51 (m, 3H, 3H, ArH); ESI-MS *m/z*: 629 $(M + H)^+$. Anal. Calcd for $C_{27}H_{32}N_8O_2S_4$: C, 51.57; H, 5.13; N, 17.82. Found: C, 51.69; H, 5.09; N, 17.77%.

2,6-Bis[5-(diisopropylamino)-2-methylthio-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4j**): White crystals; m.p. 265–266 °C; IR (KBr): 3307, 2941, 1687 (C=O), 1553, 1415, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.05 (d, *J* = 7.2 Hz, 24H, 8 × CH_3), 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 2.91–3.07 (m, 4H, 4CH), 7.24–7.64 (m, 3H, ArH); ESI-MS *m/z*: 685 $(M + H)^+$. Anal. Calcd for $C_{31}H_{40}N_8O_2S_4$: C, 54.36; H, 5.89; N, 16.36. Found: C, 54.29; H, 5.83; N, 16.31%.

2,6-Bis[2-methylthio-5-morpholino7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4k**): White crystals; m.p. 267–269 °C; IR (KBr): 3296, 1687 (C=O), 1540, 1451, 1112, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 3.08 (t, *J* = 4.8 Hz, 8H, 4 × NCH_2), 3.46 (t, *J* = 4.8 Hz, 8H, 4 × OCH_2), 7.21–7.61 (m, 3H, ArH); ESI-MS *m/z*: 657 $(M + H)^+$. Anal. Calcd for $C_{27}H_{28}N_8O_4S_4$: C, 49.37; H, 4.30; N, 17.06. Found: C, 49.40; H, 4.21; N, 17.13%.

2,6-Bis[2-methylthio-5- piperidino-7-oxothiazolo[4,5-d*]pyrimidin-6(7*H*)-yl]toluene* (**4l**): White crystals; m.p. > 300 °C; IR (KBr): 2978, 1689 (C=O), 1553, 1457, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22–1.45 (m, 20H, 10 × CH_2), 2.35 (s, 3H, CH_3), 2.47 (s, 6H, 2 × SCH_3), 7.28–7.72 (m, 4H, ArH); ESI-MS *m/z*: 653 $(M + H)^+$. Anal. Calcd for $C_{29}H_{32}N_8O_2S_4$: C, 53.35; H, 4.94; N, 17.16. Found: C, 53.44; H, 4.86; N, 17.20%.

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References

1 R.M. Shaker, *Arkivoc*, 2012 (**i**), 1.
2 A. Fernandez-Mato, G. Blanco, J.M. Quintela and C. Peinador, *Tetrahedron*, 2008, **64**, 3446.
3 Y. Liang, H.W. He and Z.W. Yang, *J. Heterocycl. Chem.*, 2011, **48**, 88.
4 R.J. Zeng, Z.C. Zhou, Z.X. Wang and X.F. Li, *Chin. J. Org. Chem*., 2008, **28**, 1624.
5 M. Chhabria, I. Rathod, K. Vala and P. Patel, *Med. Chem. Res*., 2011, **20**, 1450.
6 Y. Liang, S. Fan, W.Y. Mo and H.W. He, *J. Fluorine Chem.*, 2007, **128**, 879.
7 N.S. Habib, R. Soliman, A. EI-Tombary, S. EI-Hawash and O.G. Shaaban, *Arch. Pharm. Res.*, 2007, **30**, 1511.
8 A.M. Khairy and W.M. Basyouni, *J. Sulfur Chem*., 2010, **31**, 551.
9 Q.Y. Ren, Y.J. Liang, H.W. He, L.W. Fu and Y.C. Gu, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6713.
10 S. Peyman, I.M. David and D. Minoo, *Mol. Divers.*, 2012, **16**, 231.
11 G. Blanco and C. Peinador, *Tetrahedron*, 2008, **64**, 1136.
12 C. Blackburn, A. Achab, A. Elder, S. Ghosh, J. Guo, G. Harriman and M. Jones, *J. Org. Chem*., 2005, **70**, 10206.
13 F. Palacios, C. Alonso, D.T. Aparicio, G. Rubiales and J. Santos, *Tetrahedron*, 2007, **63**, 523.
14 S. Pedeboscq, D. Gravier, F. Casadebaig, G. Hou, A. Gissot, F.D. Giorgi, F. Ichas, J. Cambar and J.P. Pometan, *Eur. J. Med. Chem.*, 2010, **45**, 2473.
15 Z.D. Fang and J.Q. Liu, *Chin. J. Org. Chem.*, 2011, **31**, 2102.
16 Z.D. Fang and X.H. Wei, *J. Chem. Res.*, 2012, **36**, 612.
17 H. Wamhoff, S. Herrmann, S. Stolben and M. Nieger, *Tetrahedron*, 1993, **49**, 581.