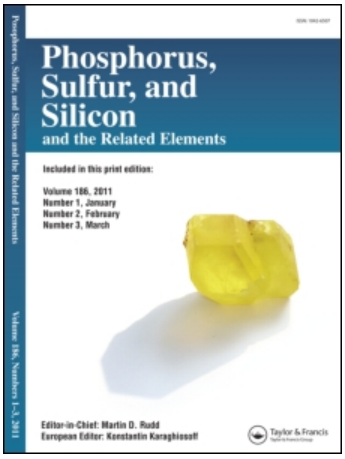

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A New Approach to the Synthesis of Fused Pyrazoles: The Synthesis of New Pyrazolo [4,3-*e*][1,2,4]triazolo-[4,3-*a*]pyrimidine-4(5*H*)-imines

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To cite this Article Davoodnia, A. , Zhiani, R. , Roshani, M. , Bakavoli, M. and Bashash, M.(2007) 'A New Approach to the Synthesis of Fused Pyrazoles: The Synthesis of New Pyrazolo [4,3-*e*][1,2,4]triazolo-[4,3-*a*]pyrimidine-4(5*H*)-imines', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 6, 1219 — 1224
To link to this Article: DOI: 10.1080/10426500601160462
URL: http://dx.doi.org/10.1080/10426500601160462

Phosphorus, Sulfur, and Silicon, 182:1219–1224, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500601160462

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A New Approach to the Synthesis of Fused Pyrazoles: The Synthesis of New Pyrazolo [4,3-*e*][1,2,4]triazolo-[4,3-*a*]pyrimidine-4(5*H*)-imines

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*A new route for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidine-4(5*H*)-imines has been delineated through heterocyclization of suitably functionalized pyrazoles with phenylisothiocyanate followed by methylation, nucleophilic displacement with hydrazine, and finally cyclocondensation with orthoesters.*

Keywords Fused pyrazoles; orthoesters; phenyl isothiocyanates; pyrazolotriazolopyrimidines

INTRODUCTION

In recent years pyrazolotriazolopyrimidines have been the subject of intense research due to the interesting pharmacological activities found for several of their derivatives.[1–3] Among the various pyrazolotriazolopyrimidine ring systems, pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines have been little explored, and there are very few reports on the synthesis and chemical properties of these compounds.[4,5] Derivatives of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines have solely been prepared from suitably functionalized pyrimidines. Other routes to these compounds still remain to be explored. Inspired by these facts and due to our interest in the synthesis of heterocyclic compounds with potential biological activities,[6–10] we were interested to look for specific routes to new derivatives of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines.

Received October 22, 2005; accepted October 22, 2006.
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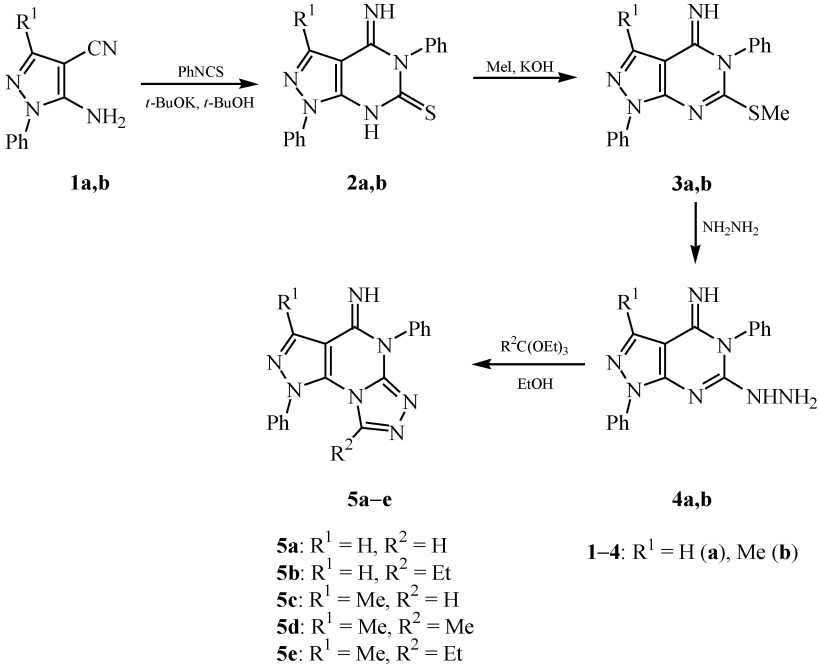
RESULTS AND DISCUSSION

Our synthesis started from suitably functionalized pyrazoles **1a**,**b**,[11] which were converted directly to 6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiones **2a**,**b** when heated at reflux temperature with phenylisothiocyanate in the presence of potassium *tert*-butoxide in *tert*-butanol. Pyrazolopyrimidothiones **2a**,**b** were transformed smoothly to their thiomethyl derivatives **3a**,**b** using methyl iodide in the presence of potassium hydroxide at r.t. Displacement of the thiomethyl group with hydrazine hydrate furnished hydrazino derivatives **4a**,**b**. The latter compounds subsequently underwent cyclocondensation with triethylorthoesters in ethanol on heating to reflux to give the desired tricyclic products, pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*a*]pyrimidines **5a**–**e** (Scheme 1).



SCHEME 1

The structural assignment of compounds **5a–e** was based upon spectral data and elemental analysis. For example, the ^{1}H NMR spectrum of **5c** showed the disappearance of two broad signals belonging to NH_2 and NH moieties of compound **4b**. The mass spectral analysis showed the expected molecular ion peak at m/e 341 for compound **5c**.

In conclusion, the reaction of **1a**,**b** with phenylisothiocyanate in the presence of potassium *tert*-butoxide in *tert*-butanol proceeded smoothly to give the corresponding pyrazolopyrimidothiones **2a**,**b**. Methylation of these compounds was followed by treatment with hydrazine gave **4a**,**b**, which were converted to tricyclic products **5a–e**.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Mass spectra were obtained with a Varian CH-7 instrument at 70 eV. Elemental analyses were performed by Ferdowsi University, Mashhad, Iran.

General Procedure for 2a,b

To a solution of the 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile **1a,b** (10 mmol) and potassium *tert*-butoxide (20 mmol) in *tert*-butanol (50 mL), phenylisothiocyanate (12 mmol) was added. The reaction mixture was heated under reflux for 7 h. After completion of the reaction, the mixture was cooled to r.t. The precipitate was collected and washed with ethanol and chloroform to give compounds **2a** and **2b** as yellow powder in 72% and 76% yields, respectively.

*4-Imino-1,5-diphenyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-d]pyrimidine-6-thione (2a)*

M.p. 242–244°C; ^{1}H NMR (d_6-DMSO): δ 7.2–8.1 (m, 11H, arom-H), 10.3 (br, 2H, NH); MS, *m/z*: 319 (M^+); anal. calcd. for $C_{17}H_{13}N_5S$ (319.38): C, 63.93; H, 4.10; N, 21.93; S, 10.04%. Found: C, 63.89; H, 4.07; N, 21.89; S, 10.08%.

*4-Imino-3-methyl-1,5-diphenyl-1,4,5,7-tetra-hydro-6*H*-pyrazolo[3,4-d] pyrimidine-6-thione (2b)*

M.p. 235–237°C; ^{1}H NMR (d_6-DMSO): δ 2.4 (s, 3H, CH_3), 7.1–8.2 (m, 10H, arom-H), 9.3 (br, 2H, NH); MS, *m/z*: 333 (M^+); anal. calcd. for $C_{18}H_{15}N_5S$ (333.41): C, 64.84; H, 4.53; N, 21.01; S, 9.62%. Found: C, 64.79; H, 4.58; N, 20.98; S, 9.63%.

General Procedure for 3a,b

4-Imino-1,5-diphenyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiones **2a**,**b** (5 mmol) and methyl iodide (5 mmol) were dissolved in EtOH (40 mL) and H_2O (15 mL) containing KOH (10 mmol). The reaction mixture was stirred at r.t. for 5 h. After this time, the

crude product was collected and recrystallized from ethanol to give compounds **3a** and **3b** as a white and a yellow powder in 80% and 86% yields, respectively.

*6-(Methylthio)-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-imine (3a)*

M.p. 162–164°C; ^{1}H NMR (d_6-DMSO): δ 2.7 (s, 3H, CH_3), 7.0–8.2 (m, 11H, arom-H), 9.9 (s br, 1H, NH); MS, *m/z*: 333 (M^+); anal. calcd. for $C_{18}H_{15}N_5S$ (333.41): C, 64.84; H, 4.53; N, 21.01; S, 9.62%. Found: C, 64.87; H, 4.48; N, 20.97; S, 9.65%.

*3-Methyl-6-(methylthio)-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-imine (3b)*

M.p. 147–149°C; ^{1}H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 7.2–8.3 (m, 10H, arom-H), 10.0 (s br, 1H, NH); MS, *m/z*: 347 (M^+); anal. calcd. for $C_{19}H_{17}N_5S$ (347.12): C, 65.68; H, 4.93; N, 20.16; S, 9.23%. Found: C, 65.64; H, 4.98; N, 20.12; S, 9.21%.

General Procedure for 4a,b

6-(methylthio)-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidine-4-imines **3a**,**b** (1 mmol) and hydrazine hydrate (2 mL) were heated at 45°C in ethanol (15 mL) for 10 h. Then the precipitate was collected and recrystallized from ethanol, to give compounds **4a** and **4b** as a white powder in 62% and 87% yields, respectively.

*6-Hydrazino-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-imine (4a)*

M.p. 221–223°C; ^{1}H NMR (d_6-DMSO): δ 4.7 (s br, 2H, NH_2), 6.8–8.3 (m, 11H, arom-H), 9.0 (s br, 1H, NH), 9.2 (s br, 1H, NH); MS, *m/z*: 317 (M^+); anal. calcd. for $C_{17}H_{15}N_7$ (317.14): C, 64.34; H, 4.76; N, 30.90%. Found: C, 64.37; H, 4.73; N, 30.85%.

*6-Hydrazino-3-methyl-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-imine (4b)*

M.p. 239–241°C; ^{1}H NMR (d_6-DMSO): δ 2.6 (s, 3H, CH_3), 5.9 (s br, 2H, NH_2), 7.4–8.0 (m, 10H, arom-H), 9.3 (br, 1H, NH), 10.1 (br, 1H, NH); MS, *m/z*: 331 (M^+); anal. calcd. for $C_{18}H_{17}N_7$(331.37): C, 65.24; H, 5.17; N, 29.59%. Found: C, 65.21; H, 5.22; N, 29.53%.

General Procedure for 5a–e

To a solution of the 6-hydrazino-1,5-diphenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-imine **4a**,**b** (5 mmol) in ethanol (40 mL),

the respective triethylorthoester (7 mmol) was added. The reaction mixture was heated under reflux for 10 h. After completion of the reaction, the mixture was cooled to r.t. The crude product was collected and recrystallized from ethanol to give compounds **5a–e** as white powders.

1,5-Diphenyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]-pyrimidin-4(5H)-imine (5a)

Yield 75%; m.p. 334–336°C; ^{1}H NMR (d_6-DMSO): δ 7.4–8.5 (m, 11H, arom-H), 9.7 (s, 1H, CH of triazole ring), 10.3 (s br, 1H, NH); MS, *m/z*: 327 (M^+); anal. calcd. for $C_{18}H_{13}N_7$(327.34): C, 66.04; H, 4.00; N, 29.95%. Found: C, 66.09; H, 3.96; N, 29.90%.

8-Ethyl-1,5-diphenyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidin-4(5H)-imine (5b)

Yield 74%; m.p. 319–321°C; ^{1}H NMR (d_6-DMSO): δ 1.2 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_3), 3.8 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2), 7.0–8.4 (m, 11H, arom-H), 9.9 (s br, 1H, NH); MS, *m/z*: 355 (M^+); anal. calcd. for $C_{20}H_{17}N_7$(355.40): C, 67.59; H, 4.82; N, 27.59%. Found: C, 67.65; H, 4.80; N, 27.52%.

3-Methyl-1,5-diphenyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidin-4(5H)-imine (5c)

Yield 77%; m.p. 329-331°C; ^{1}H NMR (d_6-DMSO): δ 2.6 (s, 3H, CH_3), 7.4-8.1 (m, 10H, arom-H), 9.5 (s, 1H, CH of triazole ring), 10.2 (s br, 1H, NH); MS, *m/z*: 341 (M^+); anal. calcd. for $C_{19}H_{15}N_7$ (341.37): C, 66.85; H, 4.43; N, 28.72%. Found: C, 66.88; H, 4.41; N, 28.67%.

3,8-Dimethyl-1,5-diphenyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidin-4(5H)-imine (5d)

Yield 85%; m.p. 312–314°C; ^{1}H NMR (d_6-DMSO): δ 2.55 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 7.2–8.1 (m, 10H, arom-H), 9.9 (s br, 1H, NH); MS, *m/z*: 355 (M^+); anal. calcd. for $C_{20}H_{17}N_7$ (355.40): C, 67.59; H, 4.82; N, 27.59%. Found: C, 67.63; H, 4.78; N, 27.54%.

8-Ethyl-3-methyl-1,5-diphenyl-1-pyrazolo[4,3-e][1,2,4]triazolo[4,3-a] pyrimidin-4(5H)-imine (5e)

Yield 78%; m.p. 307–309°C; ^{1}H NMR (d_6-DMSO): δ 1.2 (t, $^3J_{HH}$ = 8.0 Hz, 3H, CH_3), 2.7 (s, 3H, CH_3), 3.7 (q, $^3J_{HH}$ = 8.0 Hz, 2H, CH_2), 7.0–8.2 (m, 10H, arom-H), 9.9 (s br, 1H, NH); MS, *m/z*: 369 (M^+); anal. calcd. for $C_{21}H_{19}N_7$ (369.42): C, 68.28; H, 5.18; N, 26.54%. Found: C, 68.32; H, 5.15; N, 26.49%.

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