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Convenient synthesis of new pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives

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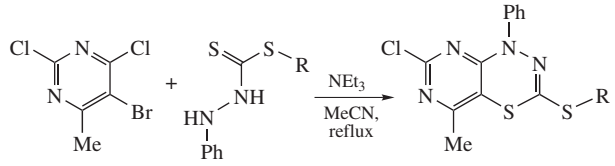
New 3-alkylsulfanyl-7-chloro-5-methyl-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazines were synthesized *via* the cyclocondensation of alkyl-2-phenylhydrazinecarbodithioates with 5-bromo-2,4-dichloro-6-methylpyrimidine in basic acetonitrile.

The biological activities of pyrimido[4,5-*e*][1,3,4]thiadiazines persuaded us to search for efficient synthetic methods for this class of heterocyclic compounds, which have been described as nucleoside analogues,[1,2] antiinflammatory, hypotensive, diuretic,[3,4] and phosphodiesterase inhibitor[2] agents.

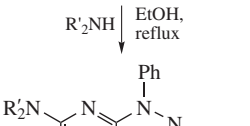
Pyrimido[4,5-*e*][1,3,4]thiadiazines have been synthesized from pyrimidines. Previous routes to such a system involved the heterocyclization of 6-hydrazino-substituted uracils with isothiocyanates and *N*-bromosuccinimide,[1–5] condensation of 2,4-dichloro-5-nitro-6-methylpyrimidine with dithizone[6] *via* the Smiles rearrangement, reaction of thiosemicarbazide with 4,5-dihalopyrimidines,[7] cyclocondensation of thiosemicarbazide with 5-bromobarbituric acid[8] and condensation of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine with carbon disulfide and alkyl halides[9] or isothiocyanates.[10] Previously, we described the formation of 1-phenyl-1*H*-[1,3,4]thiadiazino[5,6-*b*]quinoxalines.[11] The synthesis involved heterocyclization of alkyl-2-phenylhydrazinecarbodithioates as bifunctional nucleophiles with 2,3-dichloroquinoxaline as an electrophile. To extend the scope of this strategy, we explored other electrophilic species that could successfully undergo similar reaction.

As shown in Scheme 1, starting alkyl-2-phenylhydrazinecarbodithioates **2** underwent heterocyclization with 5-bromo-2,4-dichloro-6-methylpyrimidine **1**[12] in boiling acetonitrile in the presence of triethylamine to afford 7-chloro-5-methyl-1-phenylpyrimido[4,5-*e*][1,3,4]thiadiazines **3**.

The structures assigned to compounds **3** were substantiated by spectral data.† The ^{1}H NMR spectra were devoid of the signals



2, **3**: **a** R = Me **d** R = Bu
b R = Et **e** R = CH_2Ph
c R = Pr



4: **a** R = Et, R'_2 = $(CH_2)_2O(CH_2)_2$
b R = Et, R'_2 = $(CH_2)_4$
c R = Pr, R'_2 = $(CH_2)_2O(CH_2)_2$
d R = Pr, R'_2 = $(CH_2)_4$
e R = CH_2Ph, R'_2 = $(CH_2)_2O(CH_2)_2$
f R = CH_2Ph, R'_2 = $(CH_2)_4$

4a–f

Scheme 1

at δ 6.0 and 9.0 ppm for NH groups of precursors **2** and showed further downfield shifts for aromatic protons and a signal at 2.35 ppm for the methyl group of precursor **1** indicating the construction of a thiadiazine ring around the 4- and 5-positions of the pyrimidine ring. Further proofs came from their IR spectra, which lacked the N–H stretching frequencies of their precursors **2** and confirm the presence of the methyl group and the chlorine atom in compounds **3** by two stretching frequencies at about 2900 and 850 cm^{-1}, respectively. Mass spectra showed the expected molecular ion peak and the fragmentation pattern indicated the loss of alkylthio groups from compounds **3a–e**, which is in line with the proposed structure as shown in Scheme 2.

Microanalytical data for compounds **3** had no significant difference with the expected data. We also found that the chlorine atom in the 7-position of the products can be easily

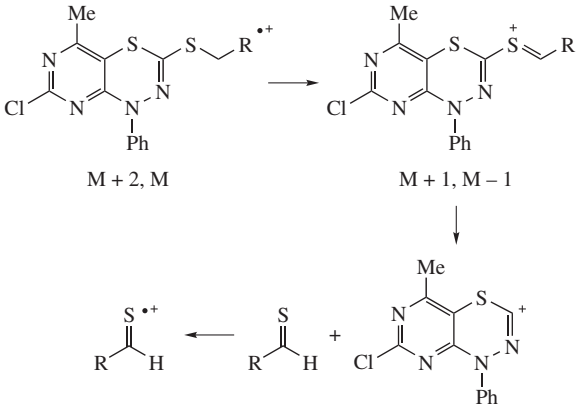
† The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. The purity of all of the new compounds was tested by TLC using chloroform as a mobile phase.

*General procedure for the preparation of pyrimido[4,5-*e*][1,3,4]thiadiazines* **3a–e**. A mixture of compound **1** (2.5 mmol, 0.61 g), alkyl-2-phenylhydrazinecarbodithioate **2** (2.5 mmol) and triethylamine (1 ml) in acetonitrile (10 ml) was refluxed under an atmosphere of nitrogen for 3 h. After the reaction was completed, the mixture was cooled to room temperature and then evaporated under reduced pressure. The residue was washed with water and crystallized from ethanol prior to washing with light petroleum 40–60 to give products **3a–e**.

*7-Chloro-5-methyl-3-(methylsulfanyl)-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine* **3a**: yellow powder, yield 64%, mp 160 °C. IR (KBr, ν/cm^{-1}): 850, 1550, 2900, 2940. ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H, 8-Me), 2.52 (s, 3H, S–Me), 7.2–7.6 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 15.570, 21.343, 107.500, 123.695, 126.416, 128.622, 141.305, 143.492, 158.437, 158.523, 164.141. MS, *m*/*z*: 324, 323, 322, 321, 277, 275, 46. Found (%): C, 48.44; H, 3.50; N, 17.20; S, 19.69. Calc. for $C_{13}H_{11}ClN_4S_2$ (%): C, 48.36; H, 3.43; N, 17.35; S, 19.86.

*7-Chloro-3-(ethylsulfanyl)-5-methyl-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine* **3b**: yellow powder, yield 58%, mp 106–108 °C. IR (KBr, ν/cm^{-1}): 870, 1600, 2900, 2950. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, Me, *J* 7.5 Hz), 2.35 (s, 3H, 8-Me), 3.1 (q, 2H, S–CH_2, *J* 7.5 Hz), 7.2–7.6 (m, 5H). MS, *m*/*z*: 338, 337, 336, 335, 277, 275, 60. Found (%): C, 49.80; H, 3.90; N, 16.75; S, 18.88. Calc. for $C_{14}H_{13}ClN_4S_2$ (%): C, 49.92; H, 3.89; N, 16.63; S, 19.04.

For characteristics of compounds **3c–e**, see Online Supplementary Materials.



Scheme 2

replaced by secondary amines in boiling ethanol and C–Cl stretching bands were devoid in IR spectra of compounds **4a–f**.‡ The orientation of cyclization was confirmed by single crystal X-ray diffraction analysis. The structure of 3-(ethylsulfanyl)-5-methyl-1-phenyl-7-tetrahydro-1*H*-1-pyrrolyl-1*H*-pyrimido[4,5-*e*]-[1,3,4]thiadiazine **4b**[13] is shown in Figure 1.

In conclusion, the condensation of 5-bromo-2,4-dichloro-6-methylpyrimidine with alkyl-2-phenylhydrazinecarbodithioates and further replacement of the 7-chlorine atom with secondary amines is a convenient and general procedure for preparation of new pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives.

‡ *General procedure for the reaction of* **3b**,**c**,**e** *with secondary amines.* A mixture of each compound **3b**,**c**,**e** (5 mmol) in ethanol (20 ml) was heated under reflux with either morpholine (2.0 g) or pyrrolidine (1.8 g) for 4 h. The solvent was removed and the residue was washed with water and then crystallized from ethanol to give products **4a–f**.

*4-[3-(Ethylsulfanyl)-5-methyl-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-7-yl]morpholine* **4a**: green powder, yield 70%, mp 122–124 °C. IR (KBr, ν/cm^{-1}): 1600, 2900, 2940. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, Me, *J* 7.4 Hz), 2.25 (s, 3H, 8-Me), 3.1 (q, 2H, S–CH_2, *J* 7.4 Hz), 3.57 (m, 8H, CH_2–O, CH_2–N), 7.2–7.6 (m, 5H). MS, *m*/*z*: 387. Found (%): C, 55.88; H, 5.40; N, 18.14; S, 16.42. Calc. for $C_{18}H_{21}N_5OS_2$ (%): C, 55.79; H, 5.46; N, 18.07; S, 16.55.

*3-(Ethylsulfanyl)-5-methyl-1-phenyl-7-tetrahydro-1*H*-1-pyrrolyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine* **4b**: green powder, yield 65%, mp 132–134 °C. IR (KBr, ν/cm^{-1}): 1620, 2900, 2930. ^{1}H NMR ($CDCl_3$) δ: 1.35 (t, 3H, Me, *J* 7.2 Hz), 1.93 (t, 4H, 2C*H*$_2$CH$_2$N, *J* 6 Hz), 2.27 (s, 3H, 8-Me), 3.1 (q, 2H, S–CH_2, *J* 7.2 Hz), 3.38 (br, 4H, 2CH_2N), 7.2–7.6 (m, 5H). MS, *m*/*z*: 371. Found (%): C, 58.32; H, 5.78; N, 18.72; S, 17.12. Calc. for $C_{18}H_{21}N_5S_2$ (%): C, 58.19; H, 5.70; N, 18.85; S, 17.26.

For characteristics of compounds **4c–f**, see Online Supplementary Materials.

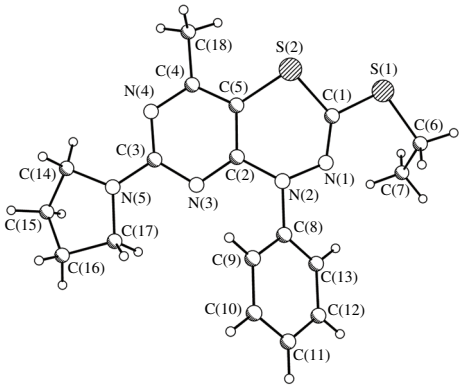


Figure 1 ORTEP drawing of structure **4b**.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2008.09.020.

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