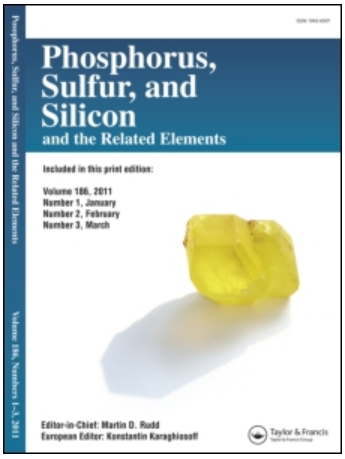

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Synthesis of New (Pyrimido[4,5-*e*][1,3,4] thiadiazin-7-yl)hydrazine Derivatives

Javad Azizian[a]; Ramin Miri[b]; Mohammad Kazem Mohammadi[a]; Fatemeh Sheikholeslami Farahani[a]; Javad Hosseini[a]; Mohsen Nikpour[c]
[a] Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran [b] Medicinal & Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran [c] Faculty of Science, Islamic Azad University, Ahvaz Branch, Ahvaz, Iran

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SYNTHESIS OF NEW (PYRIMIDO[4,5-*e*][1,3,4] THIADIAZIN-7-YL)HYDRAZINE DERIVATIVES

Javad Azizian,[1] Ramin Miri,[2] Mohammad Kazem Mohammadi,[1] Fatemeh Sheikholeslami Farahani,[1] Javad Hosseini,[1] and Mohsen Nikpour[3]

[1]*Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran*
[2]*Medicinal & Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[3]*Faculty of Science, Islamic Azad University, Ahvaz Branch, Ahvaz, Iran*

New (pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazines were synthesized via the cyclocondensation of alkyl-2-phenylhydrazinecarbodithioates as bidentate nucleophiles with 5-bromo-2,4-dichloro-6-methylpyrimidine as an electrophile and further replacement of chlorine atom on the seven number position of pyrimido[4,5-e][1,3,4]thiadiazin by hydrazine in boiling ethanol.

Keywords Bidentate nucleophile; 5-bromo-2,4-dichloro-6-methylpyrimidine; electrophile; heterocyclization; pyrimido[4,5-*e*][1,3,4]thiadiazine

INTRODUCTION

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 are described as nucleoside analogues,[1,2] and anti-inflammatory, hypotensive, diuretic,[3,4] and phosphodiesterase inhibitor agents.[2] 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 fused [1,3,4]thiadiazines by the condensation of alkyl-2-phenylhydrazinecarbodithioates with heterocyclic polyhalides.[11,12] A more efficient method for achieving such a transformation would be the reaction of a substituted or unsubstituted hydrazine with 4,6-dichloropyrimidine-5-carbaldehyde, which

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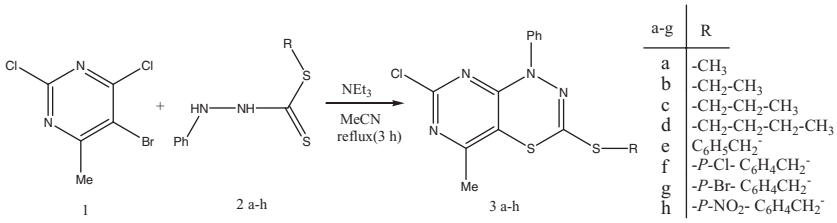
Address correspondence to Javad Azizian, Faculty of Science, Islamic Azad University, Science and Research Branch, Tehran, Iran. E-mail: azizian@cc.sbu.ac.ir

would allow formation of the desired ring system in a single step. Such a similar transformation has been reported for chloroformylpyridines[13]; condensations of hydrazine itself with such pyrimidinylaldehydes and pyrimidinylketones were reported[14,15] and related transformations were carried out on solid support to yield pyrimidone products.[16] Such a transformation of 4,6-dichloro-2-phenylpyrimidine-5-carbaldehyde and phenylhydrazine proceeding with concomitant displacement of a second hydrazine molecule to form N-[(1,6-diphenyl-7-H-pyrazolo[4,5-e]pyrimidin-4-ylidene)amino]aniline was reported.[17,18]

RESULTS AND DISCUSSION

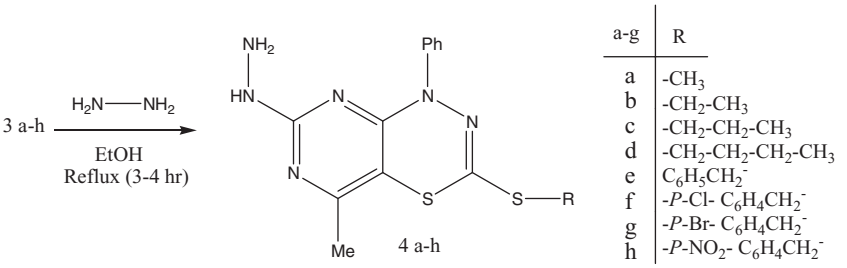
Our strategy for the synthesis of (pyrimido[4,5-*e*][1,3,4]thiadiazin-7-yl)hydrazines **4a–h**, which are potential precursors for further heterocyclic systems, is a hydrazine substitution of the chlorine atom of 3-alkylsulfanyl-7-chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazines **3a–h**. Compounds **3a–e** were recently prepared,[11] and new compounds **3f–h** were prepared by the same procedure. The structures assigned to compounds **3f–h** were substantiated by spectral data. The ^{1}H NMR spectra were devoid of the signals at *ca.* 6.0 and 9.0 ppm (δ) for NH groups of the precursor's **2f–h** 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 proof came from their IR spectra, which lacked the N–H stretching frequencies of their precursor's **2f–h** and confirmed the presence of the methyl group and the chlorine atom in compounds **3f–h** 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 **3f–h** and **4a–h**, which is in line with the proposed structure as shown in Schemes 1 and 2.



Scheme 1 Preparation of pyrimido[4,5-*e*][1,3,4]thiadiazines.

Hence, the condensation of 5-bromo-2,4-dichloro-6-methylpyrimidine 1 with alkyl-2-phenylhydrazinecarbodithioates (**2f–h**) in alkaline acetonitrile afforded a group of pyrimido[4,5-e][1,3,4]thiadiazine derivatives. The orientation of this reaction was recently determined.[11,19]

Microanalytical data for compounds **3a–h** had no significant difference with the expected data. We also found that the chlorine atom in the 7-position of the products **3a–h** could be easily replaced by hydrazine in boiling ethanol, and C–Cl stretching bands were absent in IR spectra of compounds **4a–h** (Scheme 2). The structures of 1-(3-(aryl-alkyl thio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (**4a–h**) are shown in Scheme 2.



Scheme 2 General procedure for the reaction of pyrimido[4,5-*e*][1,3,4]thiadiazines with hydrazine.

CONCLUSION

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 hydrazine is a convenient and general procedure for preparation of new pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives. In the majority of cases, this methodology was allowed access in simple steps to a diverse range of (pyrimido[4,5-*e*][1,3,4]thiadiazin-7-yl)hydrazine. This work represents a new, general method for preparation of the (pyrimido[4,5-*e*][1,3,4]thiadiazin-7-yl)hydrazines, which are useful precursors for the synthesis of novel heterocyclic systems.

EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. Infrared spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer. All the chemical shifts were quoted in ppm using the high-frequency positive convention; the ^{1}H and ^{13}CNMR spectra were referenced to external $SiMe_4$. 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. 5-Bromo-2,4-dichloro-6-methylpyrimidine was prepared according to the published procedure.[20]

General Procedure for the Preparation of Pyrimido[4,5-e][1,3,4]thiadiazines 3f–h

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 **3f–h** (Scheme 1).

3-(4-Chlorobenzylthio)-7-chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine (3f). Yellow powder, 60% yield, mp 135–136°C, IR (KBr cm^{-1}): 865, 1670, 2930, 2960. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, Ph-Me), 4.31 (s, 2H,S-CH_2), 7.25–7.77 (m, 9H).^{13}CNMR ($CDCl_3$) δ 22.1(Ph- Me), 45.5 (-S-CH_2-), 131.1, 132.9, 133.5, 135.2, 137.3, 146.6, 154.6(2 Ph), 157.3(Ph-Cl), 164.3, 173.56. m/z, 436(5%), 434(32%),

432(44%), 277(10%), 275(32%). Found (%): C, 52.61; H, 3.29; N, 13.02; S, 14.75. Calc. for $C_{19}H_{14}Cl_2N_4S2$ (%): C, 52.66; H, 3.26; N, 12.93; S, 14.80.

3-(4-Bromobenzylthio)-7-chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1, 3,4]thiadiazine (3g). Yellow powder, 54% yield, mp 128–130°C, IR (KBr cm^{-1}): 850, 1620, 2900, 2950. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H, Ph-Me), 4.25 (s, 2H,S-CH_2), 7.28–7.70 (m, 9H) ^{13}CNMR ($CDCl_3$) δ 22.7(Ph- Me), 43.5 (−S−CH_2−), 122.2, 130.8,134.5, 137.9, 140.0, 143.7,149.6 (2 Ph), 156.0(Ph-Cl), 167.4, 170.4 m/z, 480(19%), 478(75%), 476(58%), 277(5%), 275(15%). Found (%): C, 47.71; H, 5.92; N, 11.77; S, 13.39. Calc. for $C_{19}H_{14}BrClN_4S2$ (%): C, 47.76; H, 2.95; N, 11.73; S, 13.42.

3-(4-Nitrobenzylthio)-7-chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1, 3,4]thiadiazine (3h). Yellow powder, 63% yield, mp 147–149°C, IR (KBr cm $^{-1}$): 860, 1580, 2900, 2970. ^{1}H NMR ($CDCl_3$) δ, 2.31 (s, 3H, Ph-Me), 4.35 (s, 2H,S−CH_2), 7.35–7.88 (m, 9H).^{13}C NMR ($CDCl)_3$ δ 23.1(Ph- Me), 44.0(−S−CH_2−), 124.3, 131.8, 133.0, 136.7, 153.4, 151.6, 155.9, 158.3, 166.3, 174.8 m/z, 445(12%), 443(38%), 277(15%), 275(48%). Found (%): C, 51.43; H, 3.10; N, 15.73; S, 14.49. Calc. for $C_{19}H_{14}ClN_5O_2S_2$ (%): C, 51.41; H, 3.18; N, 15.78; S, 14.45.

General Procedure for the Reaction of 3a–h with Hydrazine

A mixture of each of compounds 3a–h (5 mmol) in ethanol (20 mL) was heated under reflux with hydrazine (excess) for 4 h. The solvent was removed, and the residue was washed with water and then crystallized from ethanol to give products 4a–h (Scheme 2).

1-(5-Methyl-3-(methylthio)-1-phenyl-1H-pyrimidio[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (4a). Yellow powder, yield 60%, mp 195–197°C. IR (KBr, cm^{-1}): 1200, 1400–1600, 2900, 3050, 3210, 3250, 3300. ^{1}H NMR ($CDCl_3$) 2.35 (s, 3H, 8-Me), 2.52 (s, 3H, S−Me), 3.72 (m, 2H, NH_2), 6.14 (m, 1H, NH), 7.10–7.63 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 15.5(S-Me), 21.7(Ph-Me), 107.5, 123.6, 126.4, 128.6, 141.3(Ph), 143.4, 158.4, 158.5, 164.1. MS, m/z: 318. Found (%): C, 49.10; H, 4.4; N, 26.44; S, 20.19. Calc. for $C_{13}H_{14}N_6S_2$ (%): C, 49.04; H, 4.43; N, 26.39; S, 20.14.

1-(3-(Ethylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (4b). Yellow powder, yield 67%, mp 160–162°C. IR (KBr, cm^{-1}): 1250, 1420–1600, 2930, 3050, 3200, 3270, 3285. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, Me, J 7.5 Hz), 2.38 (s, 3H, 8-Me), 3.16 (q, 2H, S−CH_2, J 7.5 Hz), 3.72 (m, 2H, NH_2), 6.53 (m, 1H, NH), 7.21–7.65 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.65,21.34 (S-Et), 25.83 (Ph-Me), 115.8, 118.5,129.3, 131.2, 145.1(Ph), 152.9, 154.4, 161.7, 163.8. MS, m/z: 332. Found (%): C, 50.64; 4.91; N, 25.26; S, 19.33. Calc. for $C_{14}H_16N_6S_2$ (%): C, 50.58; H, 4.85; N, 25.28; S, 19.29.

1-(5-Methyl-1-phenyl-3-(propylthio)-1H-pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (4c). Yellow powder, yield 70%, mp 152–154°C. IR (KBr, cm^{-1}): 1235, 1440–1610, 2950, 3000, 3230, 3265, 3310. ^{1}H NMR ($CDCl_3$) δ .92 (t, 3H, Me), 1.85 (m, 2H, −CH_2−), 2.84 (t, 2H, S−CH_2, J 7.5 Hz), 3.72 (m, 2H, NH_2), 6.67 (m, 1H, NH), 7.18–7.63 (m, 5H).^{13}C NMR ($CDCl_3$) δ 13.1 (S-Pr), 21.3(Ph-Me),24(S-Pr), 31.6 (S-Pr), 113.2, 117.0,128.5, 132.8, 147.3(Ph), 153.3, 156.7, 160.1, 165.9. MS, m/z: 346. Found (%): C, 52.05; H, 4.90; N, 24.29; S, 18.45. Calc. for $C_{15}H_{16}N_6S_2$ (%): C, 52.00; H, 4.85; N, 24.26; S, 18.51.

1-(3-(Butylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (4d). Yellow powder, yield 65%, mp 149–150°C. IR (KBr, cm^{-1}): 1180, 1420–1650, 2920, 3070, 3215, 3275, 3350. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, Me, J 7.5

Hz), 2.33 (s, 3H, 8-Me), 3.1 (q, 2H, S—CH_2, J 7.5 Hz), 3.75 (m, 2H, NH_2), 6.42 (m, 1H, NH) 7.17–7.63 (m, 5H). ^{13}C NMR($CDCl_3$) δ 14.25 (S-Bu), 21.34 (Ph-Me), 22.65 (S-Bu), 27.50(S-Bu), 31.81 (S-Bu), 112.3, 118.1,128.1, 133.5(Ph), 143.6, 152.0, 155.7, 163.9, 165.1. MS, m/z: 360. Found (%): C, 53.38; H, 5.46; N, 23.38; S, 17.82. Calc. for $C_{16}H_{20}N_6S_2$ (%): C, 53.31; H, 5.59; N, 23.31; S, 17.79.

1-(3-(Benzylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-7-yl)hydrazine (4e). Yellow powder, yield 75%, mp 148–150°C. IR (KBr, cm^{-1}): 1230, 1450–1635, 2925, 3000, 3255, 3285, 3290. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.72 (m, 2H, NH_2), 4.28 (s, —CH_2—), 6.18 (m, 1H, NH), 7.08–7.72 (m, 10H).^{13}C NMR δ 21.3(Ph-Me), 42.2(S—CH_2—), 119.5, 130.2, 131.5, 132.7,133.6,133.8,142.1,150.3, 156.8, 165.5. MS, m/z: 394. Found (%): 57.87; H, 4.65; N, 21.36; S, 16.30. Calc. for $C_{19}H_{18}N_6S_2$ (%): C, 57.84; H, 4.61; N, 21.3; S, 16.26.

1-(3-(4-Chlorobenzylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4] thiadiazin-7-yl)hydrazine (4f). Yellow powder, yield 80%, mp 180–182°C. IR (KBr, cm^{-1}): 1215, 1420–1675, 2940, 3100, 3200, 3220, 3310. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.70 (m, 2H, NH_2), 4.85 (s, —CH_2—), 6.56 (m, 1H, NH), 7.15–7.71 (m, 9H).^{13}C NMR ($CDCl_3$) δ 21.7(Ph-Me), 43.3(S-CH_2), 130.7, 133.2, 133.9, 135.8, 137.3, 143.4, 151.5, 156.2, 166.8. MS, m/z: 430(19%), 428(60%). Found (%): C, 53.27; H, 3.92; N, 19.54; S, 18.05. Calc. for $C_{19}H_{17}ClN_6S_2$ (%): C, 53.21; H, 3.99; N, 19.59; S, 17.95.

1-(3-(4-Bromobenzylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4] thiadiazin-7-yl)hydrazine (4g). Yellow powder, yield 76%, mp 189–191°C. IR (KBr, cm^{-1}): 1210, 1440–1680, 2880, 3080, 3185, 3260, 3355. ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, 8-Me), 3.75 (m, 2H, NH_2), 4.80 (s, —CH_2—), 6.72 (m, 1H, NH), 7.34–7.78 (m, 9H). ^{13}C NMR ($CDCl)_3$ δ 21.9(Ph-Me), 44.2(S—CH_2—), 125.1, 130.2, 133.8, 134.2, 150.3, 152.5, 154.4, 156.8, 165.5. MS, m/z: 474(54%), 472(54%). Found (%): C, 48.12; H, 3.66; N, 17.81; S, 13.49. Calc. for $C_{19}H_{17}BrN_6S_2$ (%): C, 48.20; H, 3.62; N, 17.75; S, 13.55.

1-(3-(4-Nitrobenzylthio)-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thia diazin-7-yl)hydrazine (4h). Yellow powder, yield 66%, mp 172–174°C. IR (KBr, cm^{-1}): 1225, 1410–1620, 2900, 3050, 3210, 3280, 3300. ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H, 8-Me), 3.73 (m, 2H, NH_2), 5.15 (s, —CH_2—), 6.83 (m, 1H, NH), 7.59–7.74 (m, 9H). ^{13}C NMR ($CDCl)_3$ δ 22.4 (Ph-Me), 44.2(S—CH_2—), 126.7, 131.9, 133.1, 137.3, 153.1, 155.8, 157.2, 160.8, 169.2. MS, m/z: 439. Found (%): C, 51.88; H, 3.93; N, 22.34; S, 14.63. Calc. for $C_{19}H_{17}N_7O_2S_2$ (%): C, 51.92; H, 3.90; N, 22.31; S, 14.59.

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