Microwave assisted synthesis of [4, 5-e] [1, 3, 4]thia- diazin-7-yl] hydrazine Derivatives

Javad Azizian , [1] Ramin Miri , [2] Mohammad Kazem Mohammadi [1]

[1]*Factually of Science, Islamic Azad University, Science and Research Branch, Tehran, Iran. Fax : +98-7126224402 . E – mail : mohammadi@iauahvaz.ac.ir*
[2]*Medicinal & Natural Products Chemistry Research Center , Shiraz University of Medical Sciences , Shiraz , Iran*
[3]*Factually of science , Ahvaz Branch Islamic Azad University , Ahvaz , Iran .*

Abstract - New pyrimido [4, 5-e] [1, 3, 4]thia- diazin-7-yl] hydrazines were synthesized via the cyclocondensation of alkyl-2-phenylhydrazinecarbodithioates as a binucleophile with 5-bromo-2,4-dichloro-6-methylpyrimidine as a bielectrophile , and replacement of C-7 chloro atom by hydrazine in ethanol as the solvent . This method has advantages over methods currently described in the literature for the construction of such heterocyclic ring systems.

Keywords: Heterocyclization ; 5-Bromo-2,4-dichloro-6-methylpyrimidine ; Pyrimido[4,5-e][1,3,4]thiadiazine ; Binucleophile ; Bielectrophile .

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 were described as nucleoside analogues,[1,2] antiinflammatory, hypotensive, diuretic,3,4 and phosphodiesterase inhibitor[2] agents. Pyrimido[4,5- e][1,3,4]thiadiazines were synthesized from pyrimidines. Previous routes to such a system involved the heterocyclization of 6-hydrazino-substituted uracils with isothio- cyanates and N-bromosuccinimide, [1–5]condensation of 2,4-di- chloro-5-nitro-6- methylpyrimidine with dithizone6 via the Smiles rearrangement, reaction of thiosemicarbazide with 4,5-dihalo- pyrimidines, [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-1H-[1,3,4]thiadiazino[5,6-b]quinoxalines. [11]

A more efficient method for achieving such a transformation , would be the reaction of a substituted or unsubstantiated hydrazine with 4,6-dichloropyrimidine-5-carbaldehyde allowing formation of the desired ring system in a single step. Such a similar transformation was known for chloroformylpyridines, [12] and condensations of hydrazine itself with such pyrimidinylaldehydes and pyrimidinylketones were reported, [13 ,14] and related transformations were carried out on solid support to yield pyrimidone products. [15]

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-7H-pyrazolo[4,5-e]pyrimidin-4-ylidene)amino]-aniline was reported. [16 , 17]

The synthesis was involved heterocyclization of alkyl-2-phenylhydrazinecarbodithioates as bifunctional nucleophiles with 2,3-dichloro-quinoxaline as an electrophile. To extend the scope of this strategy, we were explored other electrophilic species that could successfully undergo similar reaction.

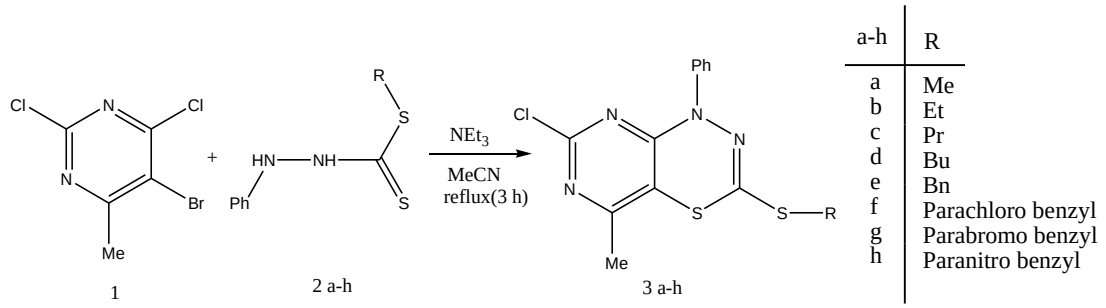
Experimental

Instruments

The 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}C-NMR 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.

General Procedure For the Preparation of Pyrimido[4,5-e][1,3,4]thia- diazines 3a–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 irradiated in microwave owen for the time priods. 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–h.(scheme 1)



Scheme 1.

Characteristic data for compounds (3a,3b) :

7-Chloro-5-methyl-3-(methylsulfanyl)-1-phenyl-1H-pyrimido[4,5-e]- [1,3,4]thiadiazine

(3a):

yellow powder, yield 64%, mp 160 °C. IR (KBr, 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-1H-pyrimido[4,5-e][1,3,4]- thiadiazine ***(3b)****:*

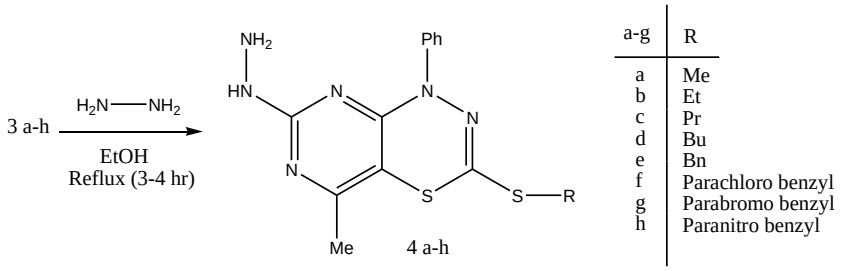
yellow powder, yield 58%, mp 106–108 °C. IR (KBr, cm^{-1}): 870, 1600, 2900, 2950. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, Me, J 7.5 Hz), 2.35 (s, 3H, 8-Me), 3.1 (q, 2H, S–CH_2, J 7.5 Hz), 7.2–7.6 (m, 5H). ^{13}C NMR ($CDCl_3$) δ. 13.4 , 15.570, 21.343, 107.500, 123.695, 126.416, 128.622, 141.305, 143.492, 158.437, 158.523, 164.141 , MS, m/z: 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.

All characteristic data for other compounds (3 c-g) , proved the structural formula .

As shown in Scheme 1, starting alkyl-2-phenylhydrazine- carbodithioates (2 a-h) underwent heterocyclization with 5-bromo-2,4-dichloro-6-methylpyrimidine 1 [18] in boiling acetonitrile in the presence of triethylamine to afford 7-chloro-5-methyl 1-phenylpyrimido[4,5-e][1,3,4]thiadiazines (3a-h).

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

A mixture of each compound 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)



a-g	R
a	Me
b	Et
c	Pr
d	Bu
e	Bn
f	Parachloro benzyl
g	Parabromo benzyl
h	Paranitro benzyl

Scheme 2.

Characteristic data for new compounds (4a-4h) :

*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 (m , 1H, NH) , 7.1–7.6 (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: 320, 319, 318, 317, 272, 46. 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300. ^{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), 3.72 (m, 2H, NH_2), 6 (m , 1H, NH), 7.2–7.6 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.65 ,21.34 , 25.83 , 115.8 , 118.5 ,129.3 , 131.2 , 145 , 152.9 , 154.4 , 161.7 , 163.8 . MS, m/z: 234, 233, 232, 231, 272,60. 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300. ^{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 (m , 1H, NH), 7.1–7.6 (m,

5H).^{13}CNMR ($CDCl_3$) δ 13.1 , 21.34 ,24 , 31.6 , 115.8 , 118.5 ,129.3 , 131.2 , 145 , 152.9 , 154.4 , 161.7 , 163.8 . MS, m/z: 348,347, 346, 345, 272, 74. 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300 . ^{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), 3.72 (m, 2H, NH_2), 6 (m , 1H, NH) 7.1–7.6 (m, 5H) .^{13}C NMR($CDCl_3$) δ 14.25 , 22.65, 21.34 , 27.50 , 31.81 , 115.8 , 118.5 ,129.3 , 131.2 , 145 , 152.9 , 154.4 , 161.7 , 163.8. MS, m/z: 362,361,360,359 , 272, 88. 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.72 (m, 2H, NH_2), 4.28 (s , -CH_2-), 6 (m , 1H, NH) , 7–7.7 (m, 10H).^{13} CNMR δ 21.34 , 42.2 5 , 119.52 , 130.24 , 131.58, 132.73, 133.64 ,133.81 ,142.12 ,150.39 , 156.85 , 165.53 . MS, m/z: 396,395,394,393,272, 91. 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, 4.6; 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300 . ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.72 (m, 2H, NH_2), 4.85 (s , -CH_2-), 6 (m , 1H, NH) , 7–7.7 (m, 9H). ^{13}CNMR ($CDCl_3$) δ 21.34 , 43.31 , 130.24 , 133.24, 133.91 , 135.87 , 137.31 , 143.47 , 150.39 , 156.85 , 165.53 . Found (%): C, 53.27; H, 3.92; N, 19.54; S, 18.05. Calc. for $C_{19}H_{17}ClN_6S_2$ (%): C, 53.2; 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}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300 . ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.72 (m, 2H, NH_2), 4.80 (s , -CH_2-), 6 (m , 1H, NH) , 7–7.7 (m, 9H). ^{13}CNMR ($CDCl_3$) δ 21.34 , 43.15 , 123.65 , 130.24 , 133.81, 136.36 , 138.73, 144.58 ,150.39 , 156.85 , 165.53 . MS, m/z: 473, 472, 471, 470, 272, 170. 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] thiadiazin-7-yl)hydrazine **(4h)**:*

Yellow powder, yield 66%, mp 172-174°C. IR (KBr, cm^{-1}): 1200, 1400-1600, 2900, 3050, 3210 , 3250 , 3300. ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H, 8-Me), 3.72 (m, 2H, NH_2), 5.15 (s , -CH_2-), 6 (m , 1H, NH) , 7–7.7 (m, 9H). ^{13}C NMR ($CDCl)_3$ δ 21.34 , 44.20, 125.19 , 130.24 , 133.81 , 134.27 , 150.39 , 152.58 , 154.41, 156.85 , 165.53 . MS, m/z: 442, 441, 440, 439, 272, 168. 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.

Results and discussion

The structures assigned to compounds 3a-h were substantiated by spectral data. The ^{1}H NMR spectra were devoid of the signals at δ 6.0 and 9.0 ppm for NH groups of precursors 2a-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 proofs came from their IR spectra, which lacked the N–H stretching frequencies of their precursor's 2a-h and confirm the presence of the methyl group and the chlorine atom in compounds 3a-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 alkyl thio groups from compounds 3a–h and

4 a-h, which is in line with the proposed structure as shown in Scheme 2.

Hence, the condensation of 5-bromo-2,4-dichloro-6-methylpyrimidine 1 with alkyl-2-phenylhydrazine- carbodithioates(2 a-h) in the presence of triethylamine as a base was investigated. After a short reaction screening process, it was shown that such a transformation to form 7-chloro-5-methyl-1-phenylpyrimido[4,5-e][1,3,4]thiadiazines (3 a-h) was indeed possible (Scheme 1) and proceeds more efficiently in the presence of base and in acetonitril rather than alcoholic solvents.

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(3-g),could be easily replaced by hydrazine in boiling ethanol and C–Cl stretching bands were devoid in IR spectra of compounds(4a–h). (Scheme 2) .

The structure of 1-(3-(Aryl –Alkyl thio)-5-methyl-1-phenyl -1H-pyrimido[4,5-e] [1,3,4] thiadiazin-7-yl)hydrazine (4 a-h) were shown in Figure 2.

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 was 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 a simple steps to a diverse range of pyrimido[4,5-e] [1,3,4] thiadiazin-7-yl)hydrazine. Such chloro derivatives were known to undergo a wide range of transformations including nucleophilic displacements with hydrazine. This work was represented a new, general method for preparation of the pyrimido [4,5-e] [1,3,4] thiadiazin-7-yl)hydrazine system which had advantages over existing methods .

Acknowledgment:

The authors thanks Mr . Dr . M.M.Ghanbari and Mrs.Dr . Sheikholeslami for valuable helps .

References

[1]O. Haruo, T. Hiroshi and S. Masakazu, Nucleic Acids Res., spec. publ. 5 (Symp. Nucleic Acids Chem., 6th), 1978, 251.

[2]O. Haruo, T. Hiroshi , K. Emi , *J. Carbohydr. Nucleosides* , **1978 ,** 5 , 329 .

[3] N. Tatehiko , F. Sumiyasu , *Japan. Kokai,* 78 28,192 (Cl. C07D513/ 04), Mar 1978 (*Chem. Abstr* , 59905 , 89(1978).

[4]N. Tatehiko , F. Sumiyasu, *Japan. Kokai,* 78 31,694 (Cl. C07D487/04), Mar 1978 (*Chem. Abstr* , 109596 , 89 , (1978).

[5] N. Tatehiko , F. Sumiyasu , *Chem. Pharm. Bull* , **1979 ,** 27 , 1965 .

[6] M. Rahimizadeh, M. M. Heravi , A. Malekan , *Indian. J. Heterocycl. Chem*, **1997** , 6 , 223 .

[7]A. J. Elliott , *J. Heterocycl. Chem,* **1981** , 18 , 799.

[8] C. S. Madhukar , J. D. Rajesh , *Indian J. Chem*. *Sect B* , **1996,** 35B**,** 251.

[9]M. Bakavoli, M. Nikpour , M. Rahimizadeh , *J. Heterocycl. Chem* , 2007 , 44 , 463 .

[10] M. Bakavoli, M. Rahimizadeh, A. Shiri, H. Eshghi , M. Nikpour . *Heterocycles*, 2008 , **75,** 1745 .

[11]M. Bakavoli, M. Nikpour , M. Rahimizadeh , *Phosphorus Sulfur Silicon Relat. Elem* , **2005** , 180 , 2265.

[12] B. M . Lynch, M. A.Khan, H. C.Teo , F. Pedrotti , *Can. J. Chem* , **1988** , 66 , 420–428 .

[13] F.Seela , H.Steker , *Helv. Chim. Acta* , **1986** , 69 , 1602–1613 .

[14] A.Gomtsyan, S. Didomenico, L. Chih-Hung, A. O.Stewart, S. S.Bhagwat, E. A.Kowaluk , M. F.Jarvis , *Bioorg. Med. Chem. Lett* , **2004** , 14 , 4165–4168 .

[15] Y.Zhang, G. Jin, B. Illarionov, A.Bacher, M.Fischer , M.Cushman , *J. Org. Chem* , 2007 , **72** , 7176–7184 .

[16]T. M. C.Tan, F.Yang, H. Fu, M. S.Raghavendra , Y. J.Lam . *Comb. Chem* , **2007** , 9 , 210–218 .

[17]D.Briel, R.Aurich, U.Egerland , K.Unverferth . *Pharmazie* , **2005 ,** 60 , 732–735 .

[18]M. Bakavoli, M. Nikpour , M. Rahimizadeh . *J. Heterocycl. Chem* , 2006 , **43** , 1327 .