

Simple and efficient heterocyclization method for synthesis of new 1,5-tetra alkyl-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine derivatives

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Abstract: New 1,5-tetra alkyl methyl- phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine were synthesized via the cyclo condensation of 2-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-2-methylhydrazine with phenylthioisothiocyanate and further replacement of chlorine atom on the seven number position of pyrimido[4, 5- e][1, 3, 4]thiadiazin by appropriate secondary amines in simple and efficient methods.

Keywords: Heterocyclization, Methylpyrimidine, Methylhydrazine, Phenylthioisothiocyanate.

Introduction

Pyrimidines are of chemical and pharmacological interest [1,2] and compounds containing the pyrimidine ring system have been shown to possess antitumor, antibacterial, antifungal, antimalarial and anticonvulsant activities [3-4]. Some of these compounds are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia [5]. Furthermore, several pyrimidines are used in polymer and supramolecular chemistry [6, 7]. Conjugated molecules which have a pyrimidine core as the key unit have received much attention and they are prospective candidates for light emitting devices [8] and molecular wires [9]. The biological activities of pyrimido[4, 5- e][1, 3, 4]thiadiazines, as a very important class of pyrimidin derivatives [10-13], persuaded us to search for efficient synthetic methods for this class of heterocyclic compounds. Previously, we described the formation of fused [1, 3, 4]thiadiazines by the condensation of alkyl-2-phenyl hydrazine carbodithioates with heterocyclic poly halides [14,15].

In our continuing work on design of new pyrimidin ring systems, we are interested to incorporate a pyrimidine group in one of the phenyl rings. The reason for this is that pyrimidine derivatives comprise a diverse and interesting group of drugs. The subject has been discussed recently [14,15]. Earlier, a comprehensive review concerning pyrimidines had been published by Brow [16].

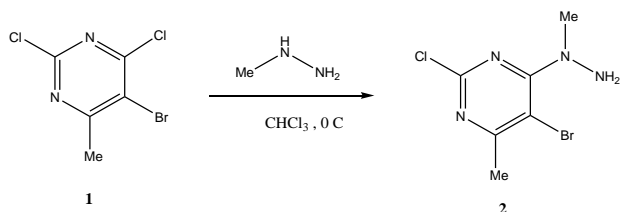
Herein we report the synthesis of new pyrimidothiadiazines via the reaction of 5-bromo-2,4-dichloro-6-methylpyrimidine with methyl hydrazine to form 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)hydrazine. This product then reacted with phenyl isothiocyanate to produce 7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine. The chlorine atom in this compound, finally replaced with secondary amines (Schemes 1-3).

Results and discussion

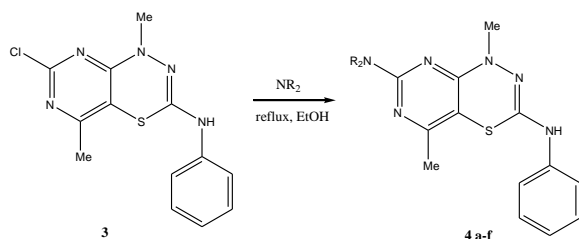
As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds, we report herein a simple synthesis of functionalized tetra alkyl- -phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine (4a-f)

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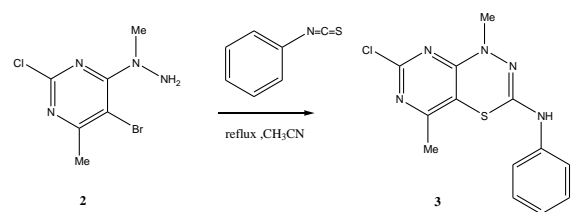
using simple starting materials from selective hetero cyclization around the pyrimidine ring. Our strategy for the synthesis of tetra alkyl- -phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine 4a-f, which are potential precursors for further heterocyclic systems is a secondary amine substitution of the chlorine atom of 7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine to produce 4a-f.



Scheme1: preparation of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine.



Scheme2: N7,N7,1,5-tetramethyl-N3-phenyl-1H-pyrimido [4,5-e] [1,3,4]thiadiazine-3,7-diamine.



Scheme3: 7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido [4,5-e][1,3,4]thiadiazin-3-amine.

The structures assigned to compounds (4a-f) were substantiated by spectral data. The ^1H NMR spectra were devoid of the signals at 2.66 ppm (δ) for N-Me groups of precursor's 3 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 decrease the N-H stretching frequencies of their precursor's 2 and confirm the formation of thiadiazin ring and view the new stretching frequencies for C-H at about 1450-1600 for new arriving aromatic ring. Presence of the methyl group and the chlorine atom in compounds 3a-f by two stretching frequencies at about 2900 and 850 cm^{-1} ,

respectively. In new compounds (4a-f), the replace of chlorine atom were approved with the loss of frequencies at about 850 cm^{-1} . In ^{13}C NMR spectra, signal at about 172 ppm for chlorine atom in compounds (3) were showed further downfield shifts to 164 ppm, approximately with replacing with secondary amines.

In order to demonstrate the efficiency and the applicability of the method, the reaction of a series of secondary amines with (3) were carried out to give the corresponding products in good yields under identical reaction conditions. The scope of the reaction was also demonstrated by the synthesis of 4 using 3 and secondary amines as starting material. The reaction proceeded at refluxing ethanol to yield the desired product in moderate yield. The reaction shown in scheme 2 and 3 proceeded only when acetonitril and ethanol were used as the solvent.

Conclusion

In summary, we have developed a new, simple, and Efficient method for the synthesis of 7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine, and 1,5-tetra alkyl- phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine for potential synthetic and pharmacological interest. The good yields of the products, the mild reaction conditions, and the use of simple starting materials are the main advantages of this method. The reactions were performed under neutral conditions and the substances were mixed without any activation or modification. The simplicity of this method makes it an interesting alternative to other approaches.

Experimental

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 ^1H 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 ^1H and ^{13}C NMR spectra were referenced to external SiMe_4 . 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 [17].

General Procedure for the Preparation of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine:

The solutions of methyl hydrazin (10 ml) in chloroform (15 ml) and 5-Bromo- 2, 4- dichloro- 6-methyl pyrimidine (1) in chloroform (15 ml) were cooled to -5 °C in refrigerator. These solutions were added together with severe stirring in 15 min approximately. Then the solvent was removed in reduced pressure and washed with water. The residue then recrystallized in ethanol to afford pure product (2) in high yield (80%). the melting point of product was 100 °C (Scheme 1).

IR (KBr, cm^{-1}): 840, 2900, 2960, 3280, 3360, ^1H NMR (300 MHz, CDCl_3): δ : 2.52 (s, 3H, CH_3), 3.38 (s, 3H, N- CH_3), 4.2 (s, 2H, NH_2); ms:m/z, 250 (58%), 252 (75%), 254(19%).

General Procedure For the Preparation of 7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine:

A mixture of compound 2 (2.5 mmol, 0.61 g), phenyl iso thiocyanate (2.5 mmol, 0.337 gr) and triethylamine (1mL) in acetonitrile (10mL) was refluxed under an atmosphere of nitrogen for 3 hr. 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 pure product (Scheme 2).

7-chloro-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine(3) :

White powder, yield 58%, mp 106–108 °C. IR (KBr, cm^{-1}): 870, 1600, 2900, 2950, 3150. ^1H NMR (CDCl_3) δ : 2.46 (s, 3H, Me, J 7.5 Hz), 2.85 (s, 3H, N-Me), 5.21 (s, 1H, N-H, J 7.5 Hz), 6.57-7.34 (m, 5H). ^{13}C NMR (CDCl_3) δ : 18.51(Me), 32.18(N-Me), 118.52, 121.11, 128.92, 133.76, 144.29, 156.47, 172.31 (Ph-Cl). Found (%): C, 51.11; H, 3.90; N, 22.95; S, 10.57. Anal. Calc. for $\text{C}_{14}\text{H}_{13}\text{ClN}_4\text{S}_2$ (%): C, 51.06; H, 3.96; N, 22.90; S, 10.49.

General Procedure for the Reaction of 3 with secondary amines:

A mixture of compound 3 (3 mmol) in ethanol (20 ml) was heated under reflux with appropriate secondary amines (excess) for 4 h. after the completion of reaction (monitored by tlc (chloroform/hexan 2;1) , The solvent was removed and the residue was washed with water and then crystallized from

ethanol to give pure products (4a–h). (Scheme 3, Table 1).

***N,N*,1,5-tetramethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine(4a):**

^1H NMR (300 MHz, CDCl_3) δ : 2.32 (s, 3H , Ph-Me), 2.63 (s, 6H, NR_2), 2.66 (s, 3H, N-Me), 6.72-7.35 (Ph). ^{13}C NMR (300 MHz, CDCl_3) δ : 21.67, 35.2, 43.79, 110.46, 120.7, 124.13, 132.91, 151.3, 164.6, 167.2. Anal. Calc. for $\text{C}_{15}\text{H}_{18}\text{N}_6\text{S}$ (%): C 57.30; H 5.77; N 26.73; S 10.20. found: C 57.41; H 5.71; N 26.98; S 10.35.

***N,N*-diethyl-1,5-dimethyl-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine(4b):**

^1H NMR (300 MHz, CDCl_3) δ : 1.41 (t , 6H , NR_2), 2.46 (s , 3H , Ph-Me), 3.55 (q, 4H, NMe_2), 4.83 (s, 1H, N-H), 6.62-7.2 (m, 5H, Ph). ^{13}C NMR (300 MHz, CDCl_3) δ : 17.21, 21.6, 35.75, 117.3, 122.31, 125.89, 132.3, 157.71, 161.6, 166.62. Anal. Calc. for $\text{C}_{17}\text{H}_{22}\text{N}_6\text{S}$ (%): C 59.62; H 6.48; N 24.54; S 9.36 . found: C 59.48; H 6.39; N 24.67; S 9.49 .

***N,N*-diisopropyl-1,5-dimethyl-N-3-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazine-3,7-diamine(4c):**

^1H NMR (300 MHz, CDCl_3) δ : 1.73 (t, 6H, NR_2), 2.63 (s, 3H, Ph-Me), 2.86 (s, 3H, N-Me), 4.69 (N-H). ^{13}C NMR (300 MHz, CDCl_3) δ : 19, 24.21, 34.65, 45.2, 120.7, 122.57, 127.1, 134.79, 153.3, 155, 158.74, 163, Anal. Calc. for $\text{C}_{19}\text{H}_{26}\text{N}_6\text{S}$ (%): C 61.59; H 6.48; N 24.54; S 9.36. found: C 61.7; H 6.53; N 25; S 9.31.

***1,5*-dimethyl-N-phenyl-7-(piperidin-1-yl)-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine(4d):**

^1H NMR (300 MHz, CDCl_3) δ : 1.68 (m, 6H, NR_2), 2.58 (t, 3H, Ph-Me), 2.93 (t, 4H, NR_2), 5.1, (N-H), 6.87-7.32, (m, 5H). ^{13}C NMR (300 MHz, CDCl_3) δ : 19.1, 35.67, 38.93, 48.23, 65.86, 155.4, 157.75, 164.34, 169.32. Anal. Calc. for $\text{C}_{18}\text{H}_{22}\text{N}_6\text{S}$ (%): C 60.99; H 6.26; N 23.71; S 9.05. found: C 61.63; H 6.3; N 23.47; S 9.68.

***1,5*-dimethyl-7-morpholino-N-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine(4e):**

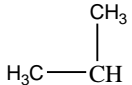
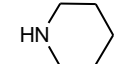
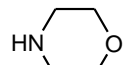
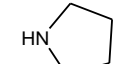
^1H NMR (300 MHz, CDCl_3) δ : 1.62 (m, 6H, NR_2), 2.64 (t, 3H, Ph-Me), 2.93 (t, 4H, NR_2), 5.1 (N-H), 6.87-7.32 (m, 5H). ^{13}C NMR (300 MHz, CDCl_3) δ : 22.34, 37.45, 39.17, 47.84, 69.92, 160.62, 162.36, 165.03, 174.28. Anal. Calc. for $\text{C}_{17}\text{H}_{20}\text{N}_6\text{OS}$ (%): C 57.28; H 5.66 ; N 23.58; S 9.00. found: C 57.83; H 5.77 ; N 23.16; S 9.36.

1,5-dimethyl-N-phenyl-7-(pyrrolidin-1-yl)-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine(4f):

¹H NMR (300 MHz, CDCl₃) δ: 1.60 (m, 6H, NR₂), 2.55 (t, 3H, Ph-Me), 2.84 (t, 4H, NR₂), 5.46 (N-H), 6.45-7.13 (m, 5H). ¹³C NMR (300 MHz, CDCl₃) δ:

19.1, 32.13, 39.82, 46.00, 66.81, 158.92, 157.19, 168.30, 172.35. Anal. Calc. for C₁₇H₂₀N₆S(%): C 59.97; H 5.92; N 24.69; S 9.42. found: C 60.1; H 5.85; N 24.89; S 9.4.

Table 1: prepared compound (4a-f) from the reaction of 3 with secondary amines.

Compound	m.p(°C)	Yield (%)	R
4a	166-168	64	CH ₃ -
4b	177-178	68	CH ₃ -CH ₂ -
4c	160-162	71	
4d	180-181	70	
4e	184-185	73	
4f	178-179	77	

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