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Synthesis of new trisubtitued imdidazole compounds in solvent free condition

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Abstract- Treatment of 7-chloro-1-phenylpyrimido[4,5-e][1,3,4]thiadiazines with hydrazine in boiling ethanol gave corresponding7-hydrazinyl derivatives. Diazotization of the latter compounds acheived a mixture of 5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine and 9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazines. Ratio of these two group of products determined by ^{1}HNMR studies and no significant preference was observed for their formation. Efforts for separation of the products were unsuccessful and its reason is discussed.

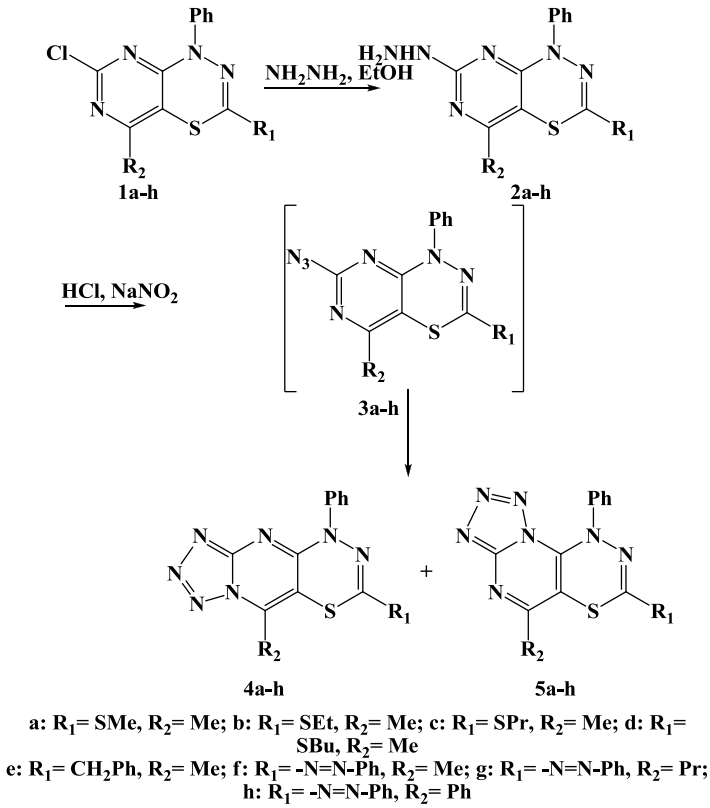
Keywords: diazotization, imidazole, solvent free.

Introduction

The growing pharmaceutical and agrochemical interests for fused pyrimidines has focused the attention of organic chemists to search for efficient and general routes to these molecules in synthetically useful yields. Fused N,S containing pyrimidines are a class of fused heterocycles which have been described as being antiviral [1-7], antifungal [8], nucleoside analogues [9], agrochemicals [10] and enzyme inhibitors [11-13] agents. These reports and pursuing of our research on synthesis of privilege compounds [12-15], are strong motives for us to prepare a novel group of this class of heterocycles in the present study.

Results and discussion

The current study presents the synthesis of tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazines**4a-h**. This synthesis is based on the diazotization of 7-hydrazinyl-1-phenylpyrimido[4,5-e][1,3,4]thiadiazines**2a-h** in aqueous media, which are prepared by replacement of 7-chlorine atom of 7-chloro-1-phenylpyrimido[4,5-*e*][1,3,4]thiadiazines**1a-h**with hydrazine in boiling ethanol (Scheme 1).



a: R_1= SMe, R_2= Me; b: R_1= SEt, R_2= Me; c: R_1= SPr, R_2= Me; d: R_1= SBu, R_2= Me
e: R_1= CH_2Ph, R_2= Me; f: R_1= -N=N-Ph, R_2= Me; g: R_1= -N=N-Ph, R_2= Pr; h: R_1= -N=N-Ph, R_2= Ph

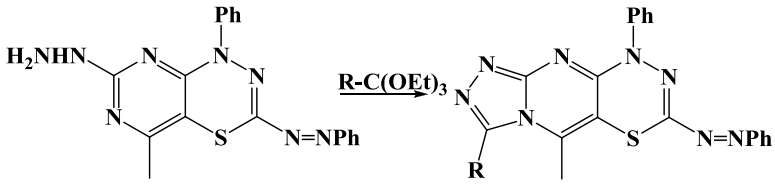
Scheme 1: preparation of compounds **2a-h, 3a-h** and **4a-h**.

The structural assignments of the synthetic compounds were based upon the spectral and microanalytical data.

IR spectra of 7-hydrazinyl-1-phenylpyrimido[4,5-*e*][1,3,4]thiadiazines**2a-h** was devoid of the stretching vibration band at 800-1000 cm^{-1} due to C-Cl functionalityof **1a-h**, but showed some vibrational bands at 3450 & 3300 cm^{-1} belonging to their $NHNH_2$ moieties. Further proof came from the ^1H NMR spectra, which showed the appearance of two broad signals in δ 6ppm and 4.2 ppm belonging to NH and NH_2 moiety of compounds **2a-h** respectively. These results and also

lacking of isotopic pattern of chlorine atom in the mass spectra of compounds **2a-h** strongly verified their structure assignment.

In a previous communication, heterocyclization of 7-hydrazinyl-5-methyl-1-phenyl-3-phenyldiazenyl-1*H*-pyrimido [4,5-*e*][1,3,4]thiadiazine**2f** with orthoesters was studied by NOE technique and it showed that 1*H*-[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazines have been formed as sole product [16] (Scheme 2).



2f

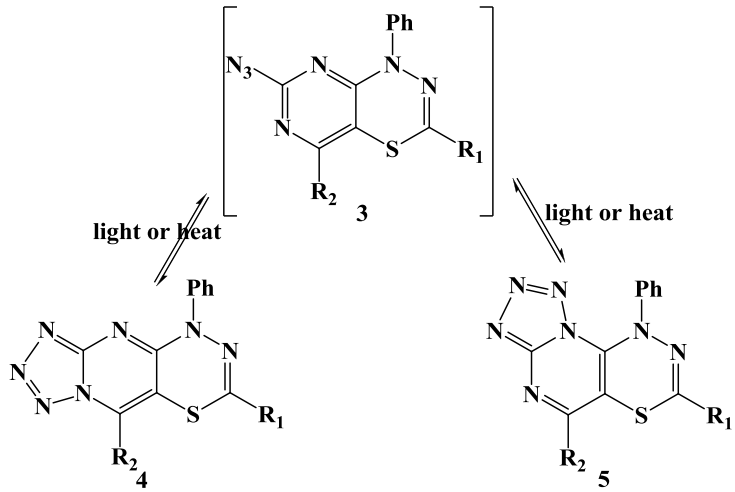
Scheme 2: Condensation of compound 2f with orthoesters.

The aforementioned spectral data is the major evidence for theformation of tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazines**4a-h** in comparison with thetetrazolo[5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazines**5a-h**.

IR spectra of the product of diazotization of compounds **2a-h** did not show neithervibrational bands at 3450 & 3300 cm^{-1} belonging to their $NHNH_2$ moietiesof procursors nor vibrational band at around 2000 cm^{-1} due to azide group of reactive intermediates **3a-h**.^{1}HNMR spectra of these compounds did not showtwo broad signals in δ 6ppm and 4.2 ppm belonging to NH and NH_2 moiety of compounds **2a-h** but exhibit two assignable signals for the pyrimidine adjucent CH_2 or CH_3 group of products **4a-h** and **5a-h**.

For example, diazotization of 7-hydrazinyl-5-methyl-3-(methylsulfanyl)-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine**2a** in water, afforded a yellow powder, which was divided to two different fractions from the precursor in TLC. ^{1}HNMR of this mixture exhibited three signals in aliphatic range in δ 2.32, 2.55 and 2.88 ppm with the ratio 40, 100 and 60 respectively, which are easily assignable to pyrimidine adjucent methyl of product **5a**, SCH_3 of both products and pyrimidine adjucent methyl of product **4a**respectively as shown in supplemetary document. Due to anisotropic effect of tetrazole ring the chemical shift of **4a** pyrimidine-methyl group is deshielded compared to that in **5a**. We found that the ratio of structures varied in the different cases and no preference was observed. Surprising results were found in the separation of these isomers. Since the heterocyclic structure of**5** is more polar than its isomer **4**, the separation of

them by a suitable preparative TLC is possible. We also observed that these two products of each cases separated in a silicagel plate with chloroform-methanole (95/5), but each fraction exhibited a ^{1}HNMR spectrum similar to the nonseparated mixture`s spectrum and showed two fractions in its TLC. These findings and the existance of wel known tautomerism between tetrazole and azido forms in a lot of tetrazoles, are leading us to suggest the rapid equilibrium of each forms **4**&**5** with the azide form **3** as shown in Scheme 3 as a reasonable mechanism for explanation these observations.



Scheme 3: Mechanism of mutual conversion of isomers **4** and **5**

Experimental

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}HNMR (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. Precursors **2a-f**&**1g,h**were prepared according to the previous published reports [16-18].

General procedure for the preparation of compounds **2g,h**

A solution of either7-chloro-1-phenyl-3-phenyldiazenyl-5-propyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine (0.408 gr, 1mmol) or 7-chloro-1,5-diphenyl-3-phenyldiazenyl-1*H*-pyrimido[4,5-*e*] [1,3,4]thiadiazine (0.442 gr, 1mmol) in ethanol (20 ml) was heated under reflux to boiling and then hydrazine hydrate (2ml) was added. Heating was continued for 3hr with

vigorous stirring. The reaction mixture was filtered after cooling to room temperature and recrystallized from ethanol to achieve compounds **2g,h**.

7-Hydrazinyl-1-phenyl-3-phenyldiazenyl-5-propyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine **2g**

This compound was obtained as a blue powder in 85% yield, mp265-266^{o}C (dec); IR (KBr disk): ν, 1750 cm^{-1}, 2930 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 1.10 (t, 3H, CH_3), 1.72 (sextet, 2H, CH_2), 2.61 (t, 2H, 5-CH_2), 4.2 (br, 2H, NH_2), 6 (br, 1H, NH), 7.5-8 (m, 10H); m/z, 404. *Anal*. Calcd. for $C_{20}H_{20}N_8S$: C, 59.39; H, 4.98; N, 27.70; S, 7.93.Found: C, 59.16; H, 5.12; N, 27.42; S, 7.71.

7-Hydrazinyl-1,5-diphenyl-3-phenyldiazenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine **2h**

This compound was obtained as a blue powder in 90% yield, mp 300-302 ^{o}C (dec); IR (KBr disk):ν, 1770 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 4.2 (br, 2H, NH_2), 6.2 (br, 1H, NH), 7.5-8.3 (m, 15H, aromatic); m/z, 438. Anal. Calcd. for $C_{23}H_{18}N_8S$: C, 63.00; H, 4.14; N, 25.55; S, 7.31. Found: C, 63.25; H, 4.32; N, 25.31; S, 6.98.

General procedure for diazotization of compounds 7-hydrazinyl-1-phenylpyrimido[4,5-e][1,3,4]thiadiazines **2a-h**

A solution of either compounds **2a-h** (1mmol) in conc. hydrochloric acid (5ml) was diluted by water (5ml) and cooled in an ice bath. A cooled solution of sodium nitrit (0.4 gr) in water (5ml) was dropwisely added to the previous solution and stirred for 2hr in ice bath. The reaction mixture was neutralized by sodium hydroxide solution and filtered. The precipitant washed by hot ethanole and dried in 80 ^{o}C to obtaine compounds **4a-h** and **5a-h**.

9-Methyl-7-(methylsulfanyl)-5-phenyl-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (**4a**)

This compound was obtained as a yellow powder in 70% combined yield, mp170 177 ^{o}C, IR (KBr disk):ν, 1560 cm^{-1}, 2900 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ , 2.55 (s, 3H, S- CH_3), 2.88 (s, 0.6 x 3H, 9-CH_3), 7.2-7.6 (multiplet,5H); m/z, 329.

5-Methyl-7-(methylsulfanyl)-9-phenyl-9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-*e*][1,3,4] thiadiazine (**5a**)

This compound was obtained as a yellow powder in 70% combined yield, mp170 177 ^{o}C, IR (KBr disk):ν, 1560 cm^{-1}, 2900 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ , 2.32 (s, 0.4 x 3H, 5-CH_3), 2.55 (s, 3H, S- CH_3), 7.2-7.6 (multiplet,5H); m/z, 329.

7-(Ethylsulfanyl)-9-methyl-5-phenyl-5*H*-tetrazolo [1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (**4b**)

This compound was obtained as a yellow powder in 60% combined yield, mp116-121ºC, IR (KBr disk):ν, 1600 cm^{-1}, 2900 cm^{-1}, 2950 cm^{-1} ; ^{1}HNMR:($CDCl_3$) δ, 1.38 (t, 3H, CH_3), 2.90 (s, 0.5 x 3H, 9-CH_3) , 3.12 (q, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H); m/z, 343.

7-(Ethylsulfanyl)-5-methyl-9-phenyl-9*H*-tetrazolo [5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazine (**5b**)

This compound was obtained as a yellow powder in 60% combined yield, mp116-121ºC, IR (KBr disk):ν, 1600 cm^{-1}, 2900 cm^{-1}, 2950 cm^{-1} ; ^{1}HNMR:($CDCl_3$) δ, 1.38 (t, 3H, CH_3), 2.35 (s, 0.5 x 3H, 5-CH_3) , 3.12 (q, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H); m/z, 343.

9-Methyl-5-phenyl-7-(propylsulfanyl)-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-][1,3,4]thiadiazine (**4c**)

This compound was obtained as a yellow powder in 80% combined yield, mp95-102 ºC, IR (KBr disk): ν, 1650 cm^{-1}, 2900 cm^{-1}, 2950 cm^{-1}; HNMR:($CDCl_3$) δ, 1.10 (t, 3H, CH_3), 1.72 (sextet, 2H,CH_2), 2.90 (s, 0.6 x 3H, 9-CH_3), 3.09 (t, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H), m/z, 357.

5-Methyl-9-phenyl-7-(propylsulfanyl)-9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-][1,3,4]thiadiazine (**5c**)

This compound was obtained as a yellow powder in 80% combined yield, mp95-102 ºC, IR (KBr disk): ν, 1650 cm^{-1}, 2900 cm^{-1}, 2950 cm^{-1}; HNMR:($CDCl_3$) δ, 1.10 (t, 3H, CH_3), 1.72 (sextet, 2H,CH_2), 2.35 (s, 0.4 x 3H, 5-CH_3), 3.09 (t, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H), m/z, 357.

7-(Butylsulfanyl)-9-methyl-5-phenyl-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (**4d**)

This compound was obtained as a yellow powder in 70% combined yield, mp70-78ºC, IR (KBr disk):ν, 1600 cm^{-1}, 2900 cm^{-1}, 2960 cm^{-1}; ^{1}HNMR:($CDCl_3$) δ, 0.97 (t, 3H,CH_3), 1.33-1.85 (multiplet, 4H, 2CH_2), 2.90 (s, 0.4 x 3H, 9-CH_3) , 3.12 (t, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H) m/z, 371.

7-(Butylsulfanyl)-5-methyl-9-phenyl-9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazine (**5d**)

This compound was obtained as a yellow powder in 70% combined yield, mp70-78ºC, IR (KBr disk):ν, 1600 cm^{-1}, 2900 cm^{-1}, 2960 cm^{-1}; ^{1}HNMR:($CDCl_3$) δ, 0.97 (t, 3H,CH_3), 1.33-1.85 (multiplet, 4H, 2CH_2), 2.36 (s, 0.6 x 3H, 5-CH_3) , 3.12 (t, 2H,S-CH_2), 7.2-7.6 (multiplet, 5H) m/z, 371.

7-(Benzylsulfanyl)-9-methyl-5-phenyl-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-][1,3,4]thiadiazine (**4e**)

This compound was obtained as a yellow powder in 90% combined yield, mp131-138^{o}C, IR (KBr disk): ν, 1550 cm^{-1}, 2900 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 2.89 (s, 0.3 x 3H, 9-CH_3), 4.31 (s, 2H,S-CH_2), 7.2-7.5 (multiplet, 10H); m/z, 405.

7-(Benzylsulfanyl)-5-methyl-9-phenyl-9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-][1,3,4]thiadiazine (**5e**)

This compound was obtained as a yellow powder in 90% combined yield, mp131-138^{o}C, IR (KBr disk): ν, 1550 cm^{-1}, 2900 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 2.36 (s, 0.7 x 3H, 5-CH_3), 4.31 (s, 2H,S-CH_2), 7.2-7.5 (multiplet, 10H); m/z, 405.

9-Methyl-5-phenyl-7-phenyldiazenyl-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (4f)

This compound was obtained as a blue powder in 90% combined yield,mp 280-287^{o}C (dec)**;** IR (KBr disk): ν, 1700 cm^{-1}, 2950 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 2.90 (s, 0.5 x 3H, 9-CH_3), 7.2-8(multiplet, 10H); m/z, 387.

5-Methyl-9-phenyl-7-phenyldiazenyl-9*H*-tetrazolo[5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazine (**5f**)

This compound was obtained as a blue powder in 90% combined yield,mp 280-287^{o}C (dec)**;** IR (KBr disk): ν, 1700 cm^{-1}, 2950 cm^{-1}, 2940 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 2.35 (s, 0.5 x 3H, 8-CH_3), 7.2-8(multiplet, 10H); m/z, 387.

5-Phenyl-7-phenyldiazenyl-9-propyl-5*H*-tetrazolo[1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (**4g**)

This compound was obtained as a blue powder in combined 85% yield, mp263-273 ^{o}C (dec); IR (KBr disk):ν, 1750 cm^{-1}, 2930 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 1.15 (t, 3H, CH_3), 1.77 (sextet, 2H, CH_2), 3.21 (t, 0.6 x 2H, 9-CH_2), 7.5-8 (m, 10H); m/z, 415.

9-Phenyl-7-phenyldiazenyl-5-propyl-9*H*-tetrazolo [5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazine (**5g**)

This compound was obtained as a blue powder in combined 85% yield, mp263-273 ^{o}C (dec); IR (KBr disk):ν, 1750 cm^{-1}, 2930 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 1.15 (t, 3H, CH_3), 1.77 (sextet, 2H, CH_2), 2.58 (t, 0.4 x 2H, 5-CH_2), 7.5-8 (m, 10H); m/z, 415.

5,9-Diphenyl-7-phenyldiazenyl-5*H*-tetrazolo [1',5':1,2]pyrimido[4,5-*e*][1,3,4]thiadiazine (**4h**)

This compound was obtained as a magenta powder in 92% combined yield, mp290-297ºC (dec); IR (KBr disk):ν, 1770 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 7.5-8.3 (m, aromatic); m/z, 449.

5,9-Diphenyl-7-phenyldiazenyl-9*H*-tetrazolo [5',1':2,3]pyrimido[4,5-*e*][1,3,4]thiadiazine (**5h**)

This compound was obtained as a magenta powder in 92% combined yield, mp290-297ºC (dec); IR (KBr disk):ν, 1770 cm^{-1}; ^{1}HNMR: ($CDCl_3$) δ, 7.5-8.3 (m, aromatic); m/z, 449.

Conclusion

In conclusion diazotization of compounds 7-hydrazinylpyrimido[4,5-e][1,3,4]thiadiazines afforded two groups of 5*H*-tetrazolo [1',5':1,2]pyrimido[4,5-*e*][1,3,4] thiadiazines and 9*H*-tetrazolo [5',1':2,3]pyrimido[4,5-*e*] [1,3,4]thiadiazines with no significant preference.

Acknowledgments

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