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EFFICIENT SYNTHESIS OF NOVEL AZO COMPOUNDS BASED ON PYRIMIDO[4,5-*E*][1,3,4]THIADIAZINE

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ABSTRACT. Some new 5-bromo-2,4-dichloro-6-alkylpyrimidines were prepared by sequential treatment of 6-alkyl-pyrimidin-2,4(1*H*,3*H*)-diones with bromine and phosphoryl chloride. Condensation of the dithizone with 5-bromo-2,4-dichloro-6-alkylpyrimidines in alkaline acetonitrile achieved 5-alkyl-7-chloro-3-phenylazo-1-phenyl-*1H*-pyrimido[4,5-*e*][1,3,4] thiadiazines. 7-chlorine atom of these compounds was replaced by secondary amines in boiling ethanol to afford their 7-amino derivatives.

KEY WORDS: Azo dyes, 5-Bromo-2,4-dichloro-6-alkyllpyrimidines, Dithizone, Cyclocondensation, Pyrimido[4,5- e][1,3,4]thiadiazine

INTRODUCTION

A variety of biological activities of pyrimido[4,5-*e*][1,3,4]thiadiazines is a strong motive to search for more efficient synthetic methods for this class of heterocyclic compounds. These compounds have been described as anti-inflammatory, hypotensive, diuretic [1, 2], phosphodiesterase inhibitor [2] and nucleoside analogues [3] agents. A patent literature disclosed that pyrimido[4,5-*e*][1,3,4]thiadiazines are good candidates for dyeing of polyesters [4]. Condensation of dithizone with 2,4-dichloro-6-methyl-5-nitro-pyrimidine via the smile's rearrangement, is an efficient rout for the preparation of this heterocyclic system [5]. In a previous communication [6] we had described a new approach for the formation of pyrimido[4,5-*e*][1,3,4]thiadiazines by condensation of alkyl-2-phenylhydrazinecarbodithioates with 5-bromo-2,4-dichloro-6- methylpyrimidine. This strategy was extended in the present research for preparing of novel group of coloring azo compounds.

RESULTS AND DISCUSSION

In this research we exhibit the synthesis of new 1-(5-alkyl-7-chloro- 1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-yl)-2-phenyldiazenes by condensation of 5-bromo-2,4-dichloro-6-alkyl-(phenyl)pyrimidines **3a-e** with dithizone **4** as shown in Scheme 1. One of the key starting materials **3a** was prepared earlier [7] and compounds **3b-e** were synthesized by treatment of 5-bromo-6-alkyl-pyrimidin-2,4(1*H*,3*H*)-diones **2b-e** with phosphoryl chloride. The latter compounds were prepared *via* bromination of 6-alkyl-pyrimidin-2,4(1*H*,3*H*)-diones **1b-e** in water as shown in Scheme 2.

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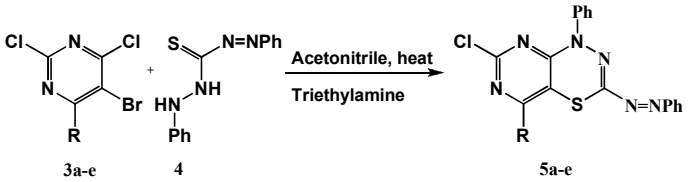
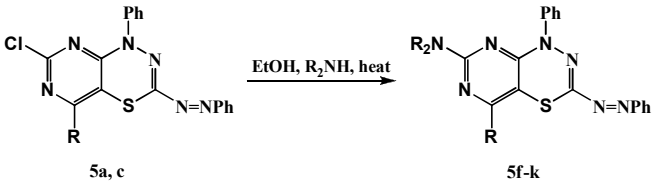


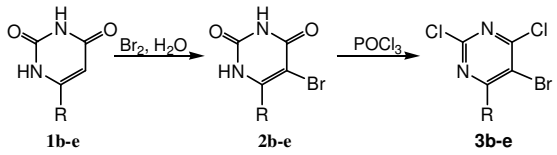
R= a: methyl, b: ethyl, c: propyl, d:isopropyl, e: phenyl



f: R= methyl, R_2NH= piperidine
g: R= methyl, R_2NH= morpholine
h: R= methyl, R_2NH= 4-methylpiperazine
i: R= propyl, R_2NH= piperidine
j: R= propyl, R_2NH= morpholine
k: R= propyl, R_2NH= 4-methylpiperazine

Scheme 1. Preparation of compounds **5a-k**.

Structure assignments of compounds **2b-e** and **3b-e** are based upon spectral and microanalytical data. ^{1}H NMR spectrum of the compounds **2b-e** lacked the signal of vinyl proton of number 5 position. This result was confirmed by mass spectra, when it showed the two molecular ions, by 78 and 80 *m/z* more than the molecular ion of each precursor **1b-e**. ^{1}H NMR and IR spectra of compounds **3b-e** do not show the signals and vibration bands of NH moieties, which has been regarded to compounds **2b-e** and their mass spectra confirmed the existence of two chlorines and a bromine by exhibition of M, M+2, M+4 and M+6 molecular ions with the ratio of 9, 15, 7, 1, respectively.



R= b:ethyl, c: propyl, d:isopropyl, e: phenyl

Scheme 2. Preparation of precursor **2b-e**.

The structures assigned to compounds **5a-e** are verified by their spectral and microanalytical data. The ^{1}H NMR spectrum of compound 4 presented the signals around δ 6.0 and 9.0 ppm belonging to NH moieties, which were devoided in the ^{1}H NMR spectra of products **5a-e**. This result also amplified by appearance of signals of aromatic protons and signals at δ 1-2.8 ppm for

alkyl group of precursor **3a-e**. IR spectra of compounds **5a-e** lacked the stretching vibration bands at around 3350 cm^{-1} regarding to N-H bonds of the precursor **4**, but showed some bands at 2900-3000 cm^{-1} due to symmetric and asymmetric stretching vibration of C-H bonds of alkyl groups belonged to precursor **3a-e**. These results plus the observation of M and M+2 ions in the mass spectra of compounds **5a-e** by the ratio 3:1, indicates the situation of [1,3,4]thiadiazine ring around positions **4** and **5** of the pyrimidine ring.

In the earlier communications 3D molecular structure of the condensed product of dithizone analogs with 5-bromo-2,4-dichloro-6-methylpyrimidine **3a** was strongly evidenced by X-ray crystallography [6, 8].

Microanalytical data of compounds **5a-e** have no significant difference with the expected data. We also found that the chlorine atom in the number 7 position of products is easily replaced by secondary amines in boiling ethanol and C-Cl stretching band disappeared in IR spectra of compounds **5f-k**.

In conclusion the condensation of 5-bromo-2,4-dichloro-6-alkyl(and phenyl)pyrimidine with dithizone afforded novel 3-phenylazo-1-phenyl-*1H*-pyrimido[4,5-*e*][1,3,4]thiadiazines with the magenta color. Further replacement of chlorine with secondary amines is also a general procedure for preparation of 7-amino-3-phenylazo-1-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives with blue color.

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}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 either synthetic compound was tested by TLC using chloroform as mobile phase. Alkyl-2-phenylhydrazinecarbodithioates were prepared according to the earlier procedure [9, 10].

General procedure for the preparation of 5-bromo-6-alkyl-pyrimidin-2,4(1H,3H)-diones ***2b-e***. To a suspension of either 6-alkyl-pyrimidine-2,4(1*H*,3*H*)-dione **1b-e** (20 mmol) in water (40 mL), bromine (3.2 g, 20 mmol) was added with vigorous stirring. Stirring was continued for further 30 min and then the mixture was heated to boil and then kept for overnight to give a white precipitate. The precipitate was filtered off, washed with warm water and dried at 80 ^oC.

*5-Bromo-6-ethylpyrimidine-2,4(1H,3H)-dione (**2b**).* This compound was obtained as a white powder in 70% yield, m.p. 265-267 ^oC (dec), IR: 3170 cm^{-1} (NH), 1580 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d6) δ, 1.15 (t, 3H, CH_3, J = 7.5 Hz), 2.37 (q, 2H, 5-CH_2, J = 7.5 Hz), 11.35 (s, 1H, N_1H), 11.45 (s, 1H, N_3H); ms: m/z, 218 (80%), 220 (80%).

*5-Bromo-6-propylpyrimidine-2,4(1H,3H)-dione (**2c**).* This compound was obtained as a white powder in 80% yield, m.p. 260-261 ^oC (dec), IR: 3200 cm^{-1} (NH), 1550 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d6) δ, 1.05 (t, 3H, CH_3, J = 7.3 Hz), 1.57 (sextet, 2H, CH_2), 2.45 (t, 2H, 5-CH_2, J = 7.6 Hz), 11.35 (s, 1H, N_1H), 11.45 (s, 1H, N_3H); ms: m/z, 232 (80%), 234 (80%).

*5-Bromo-6-(1-methylethyl)pyrimidine-2,4(1H,3H)-dione (**2d**).* This compound was obtained as a white powder in 75% yield, m.p. 252-253 ^oC (dec), IR: 3250 cm^{-1} (NH), 1600 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d6) δ, 0.95 (d, 6H, 2CH_3, J = 7.2 Hz), 2.55 (m, 1H, 5-CH), 11.30 (s, 1H, N_1H), 11.40 (s, 1H, N_3H); ms: m/z, 232 (90%), 234 (90%).

*5-Bromo-6-phenylpyrimidine-2,4(1H,3H)-dione (**2e**)*. This compound was obtained as a white powder in 85% yield, m.p. 243-244 ^{o}C (dec), IR: 3200 cm^{-1} (NH), 1570 cm^{-1} (C=O); ^{1}H NMR: (DMSO-d6) δ, 7.1-7.4 (m, 5H, aromatic), 11.50 (s, 1H, N_1H), 11.65 (s, 1H, N_3H); ms: m/z, 266 (60%), 268 (60%).

*General procedure for the preparation of 5-bromo-2,4-dichloro-6-alkylpyrimidine (**3b-e**)*. A mixture of 5-bromo-6-alkyl-pyrimidine-2,4(1*H*,3*H*)-dione **2b-e** (10 mmol) in phosphoryl-chloride (10 mL) was heated under reflux for 3 h. The excess phosphorylchloride was removed in *vacuo* and the residue was added to ice. The precipitate was extracted by chloroform (2 x 10 mL), dried by sodium sulfate and then evaporated under an efficient hood.

*5-Bromo-2,4-dichloro-6-ethylpyrimidine (**3b**)*. This compound was obtained as a viscose liquid in 60% yield, ^{1}H NMR: ($CDCl_3$) δ, 1.25 (t, 3H, CH_3, J = 7 Hz), 2.62 (q, 2H, 5-CH_2, J = 7 Hz); ms: m/z, 254 (54%), 256 (89%), 258 (42%), 260 (6%).

*5-Bromo-2,4-dichloro-6-propylpyrimidine (**3c**)*. This compound was obtained as a viscose liquid in 70% yield, ^{1}H NMR: ($CDCl_3$) δ, 1.15 (t, 3H, CH_3, J = 7.2 Hz), 1.80 (sextet, 2H, CH_2), 2.72 (t, 2H, 5-CH_2, J = 7.2 Hz); ms: m/z, 268 (56%), 270 (91%), 272 (43%), 274 (6%).

*5-Bromo-2,4-dichloro-6-(1- methylethyl)pyrimidine (**3d**)*. This compound was obtained as a viscose liquid in 50% yield, ^{1}H NMR: ($CDCl_3$) δ, 1.10 (d, 6H, $2CH_3$, J = 7.5 Hz), 2.83 (m, 1H, 5-CH); ms: m/z, 268 (64%), 270 (97%), 272 (50%), 274 (7%).

*5-Bromo-2,4-dichloro-6-phenylpyrimidine (**3e**)*. This compound was obtained as a viscose liquid in 70% yield, ^{1}H NMR: ($CDCl_3$) δ, 7.5-7.8 (m, aromatic); ms: m/z, 302 (36%), 304 (60%), 306 (28%), 308 (4%).

*General procedure for the preparation of pyrimido [4,5-e][1,3,4]thiadiazines **5a-e***. A mixture of either 5-bromo2,4-dichloro-6-alkyl(and phenyl)pyrimidine **3a-e** (2.5 mmol), dithizone **4** (2.5 mmol) and triethylamine (1 mL) in acetonitrile (20 mL) was boiled under reflux for 15 min. 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 with ethanol to give products **5a-e**.

1-*(7-Chloro-5-methyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5a**)*. This compound was obtained as a magenta powder in 90% yield, m.p. 271-273 ^{o}C (dec); IR (KBr disk) ν: 950 cm^{-1}, 1700 cm^{-1}, 2950 cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ, 2.31 (s, 3H, 5-CH_3), 7.5-8 (m, 10H); m/z, 382, 380, 277, 275. Anal. calcd. for $C_{18}H_{13}ClN_6S$: C, 56.77; H, 3.44; N, 22.07; S, 8.42. Found: C, 56.52; H, 3.5; N, 22.20; S, 8.13.

1-*(7-Chloro-5-ethyl-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5b**)*. This compound was obtained as a magenta powder in 85% yield, m.p. 262-264 ^{o}C (dec); IR (KBr disk) ν: 940 cm^{-1}, 1730 cm^{-1}, 2970 cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ, 1.23 (t, 3H, CH_3, J = 7.3 Hz), 2.52 (q, 2H, 5-CH_2, J = 7.3 Hz), 7.5-8 (m, 10H); m/z, 396, 394, 291, 289. Anal. calcd. for $C_{19}H_{15}ClN_6S$: C, 57.79; H, 3.83; N, 21.28; S, 8.12. Found: C, 58.06; H, 3.96; N, 21.04; S, 7.82.

*1-(7-Chloro-1-phenyl-5-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5c**)*. This compound was obtained as a magenta powder in 80% yield, m.p. 255-257 ^{o}C (dec); IR (KBr disk) ν: 960 cm^{-1}, 1750 cm^{-1}, 2930 cm^{-1}; ^{1}H NMR: ($CDCl_3$) δ, 1.12 (t, 3H, CH_3, J = 7.4

Hz), 1.74 (sextet, 2H, CH_2), 2.63 (t, 2H, 5-CH_2, J = 7.4 Hz), 7.5-8 (m, 10H); m/z, 410, 408, 305, 303. Anal. calcd. for $C_{20}H_{17}ClN_6S$: C, 58.75; H, 4.19; N, 20.55; S, 7.84. Found: C, 59.06; H, 4.35; N, 20.32; S, 7.51.

*1-(7-Chloro-5-(1-methylethyl)-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5d**)*. This compound was obtained as a magenta powder in 85% yield, m.p. 249-251 ^oC (dec); IR (KBr disk) ν: 9300 cm^{-1}, 1770 cm^{-1}, 2960 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 1.05 (d, 6H, $2CH_3$, J = 7.5 Hz), 2.75 (m, 1H, 5-CH), 7.5-8 (m, 10H); m/z, 410, 408, 305, 303. Anal. calcd. for $C_{20}H_{17}ClN_6S$: C, 58.75; H, 4.19; N, 20.55; S, 7.84. Found: C, 58.91; H, 4.31; N, 20.28; S, 7.56.

*1-(7-Chloro-1,5-diphenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5e**)*. This compound was obtained as a magenta powder in 92% yield, m.p. 292-294 ^oC (dec); IR (KBr disk) ν: 930 cm^{-1}, 1770 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 7.5-8.3 (m, aromatic); m/z, 444, 442, 339, 337. Anal. calcd. for $C_{23}H_{15}ClN_6S$: C, 62.37; H, 3.41; N, 18.97; S, 7.24. Found: C, 62.58; H, 3.62; N, 18.73; S, 6.95.

*General procedure for the reaction of **5b**,**c**,**e** with secondary amines*. A mixture of either compound **5a**,**c** (5 mmol) in ethanol (20 mL) was heated under reflux with 2 mL of either morpholine, piperidine or 1-methylpiprazine for 6 h. The solvent was removed and the residue was washed with water and then crystallized from ethanol to give the products **5f-k**.

1-(5-*Methyl-1-phenyl-7-(piperidin-1-yl)-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5f**)*. This compound was obtained as a blue powder in 70% yield, m.p. 250-252 ^oC (dec); IR (KBr disk) ν: 2950 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 1.4-1.8 (m, 6H, $((CH_2)_3$-$CH_2N)$, 2.27 (s, 3H, 5-CH_3), 3.5 (t, 4H, $2(CH_2N)$, J = 6 Hz), 7.5-8 (m, 10H); m/z, 429, 324. Anal. calcd. for $C_{23}H_{23}N_7S$: C, 64.31; H, 5.40; N, 22.83; S, 7.46. Found: C, 64.59; H, 5.67; N, 22.49; S, 7.22.

1-(5-*Methyl-7-(morpholin-4-yl)-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5g**)*. This compound was obtained as a blue powder in 75% yield, m.p. 255-257 ^oC (dec); IR (KBr disk) ν: 2920 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 2.25 (s, 3H, 5-CH_3), 3.6 (s, 8H, CH_2-(O and N)), 7.5-8 (m, 10H); m/z, 431, 326. Anal. calcd. for $C_{22}H_{21}N_7OS$: C, 61.23; H, 4.91; N, 22.72; S, 7.43. Found: C, 61.32; H, 5.12; N, 22.51; S, 7.22.

*1-(5-Methyl-7-(4-methylpiperazin-1-yl)-1-phenyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5h**)*. This compound was obtained as a blue powder in 60% yield, m.p. 240-242 ^oC (dec); IR (KBr disk) ν: 2980 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 2.3-2.6 (m, 10H, $CH_3N(CH_2)_2$ and 5-CH_3), 3.6 (t, 4H, $2(CH_2N)$, J = 6.1 Hz), 7.5-8 (m, 10H); m/z, 444, 339. Anal. calcd. for $C_{23}H_{24}N_8S$: C, 62.14; H, 5.44; N, 25.21; S, 7.21. Found: C, 62.33; H, 5.63; N, 24.96; S, 7.03.

*2-Phenyl-1-(1-phenyl-7-(piperidin-1-yl)-5-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)diazene (**5i**)*. This compound was obtained as a blue powder in 65% yield, m.p. 241-243 ^oC (dec); IR (KBr disk) ν: 2950 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 1.12 (t, 3H, CH_3, J = 7.2 Hz), 1.4-1.8 (m, 8H, $((CH_2)_3$-CH_2N, CH_2), 2.63 (t, 2H, 5-CH_2, J = 7.2 Hz), 3.5 (t, 4H, $2(CH_2N)$, J = 6 Hz), 7.5-8 (m, 10H); m/z, 457, 352. Anal. calcd. for $C_{25}H_{27}N_7S$: C, 65.62; H, 5.95; N, 21.43; S, 7.01. Found: C, 65.51; H, 5.72; N, 21.28; S, 6.79.

*1-(7-(Morpholin-4-yl)-1-phenyl-5-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5j**)*. This compound was obtained as a blue powder in 70% yield, m.p. 235-237 ^oC

(dec); IR (KBr disk) ν: 2900 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 1.12 (t, 3H, CH_3, J = 7.4 Hz), 172 (sextet, 2H, CH_2), 2.63 (t, 2H, 5-CH_2, J = 7.2 Hz), 3.6 (s, 8H, CH_2-(O and N)), 7.5-8 (m, 10H); m/z, 459, 354. Anal. calcd. for $C_{24}H_{25}N_7OS$: C, 62.72; H, 5.48; N, 21.33; S, 6.98. Found: C, 67.56; H, 5.55; N, 21.52; S, 6.72.

*1-(7-(4-Methylpiperazin-1-yl)-1-phenyl-5-propyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-yl)-2-phenyldiazene (**5k**)*. This compound was obtained as a blue powder in 55% yield, m.p. 229-231 ^oC (dec); IR (KBr disk) ν: 2980 cm^{-1}; ^1H NMR: ($CDCl_3$) δ, 1.12 (t, 3H, CH_3, J = 7.1 Hz), 1.74 (sextet, 2H, CH_2), 2.3-2.6 (m, 9H, $CH_3N(CH_2)_2$ and 5-CH_2), 3.6 (t, 4H, 2(CH_2N), J = 6 Hz), 7.5-8 (m, 10H); m/z, 472, 367. Anal. calcd. for $C_{25}H_{28}N_8S$: C, 63.53; H, 5.97; N, 23.71; S, 6.78. Found: C, 65.34; H, 6.17; N, 23.93; S, 6.54.

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