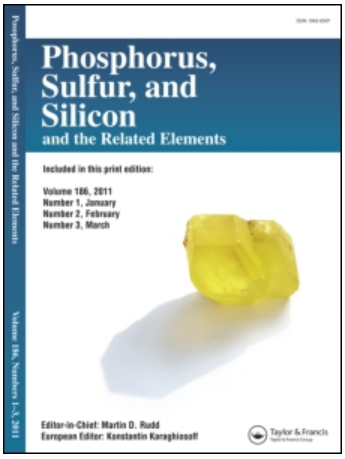

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Synthesis of a Novel Heterocyclic System, [1,2,4] Triazino[1,2-*a*]Pyrimido [4,5-*e*] [1,3,4] Thiadiazines

Majid M. Heravi[ab]; Mohammad Bakherad[b]; Mohammad Rahimzadeh[b]; Mehdi Bakavoli[b]; Mitra Ghassemzadeh[c]

[a] Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran [b] Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran [c] Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

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Synthesis of a Novel Heterocyclic System, [1,2,4] Triazino[1,2-*a*]Pyrimido [4,5-e] [1,3,4] Thiadiazines

Majid M. Heravi
Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran and Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

Mohammad Bakherad
Mohammad Rahimzadeh
Mehdi Bakavoli
Department of Chemistry, School of Sciences, Ferdowsi University of Mashhad, Mashhad, Iran

Mitra Ghassemzadeh
Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran

Substituted 6-chloro-pyrimido[4,5-e][1,3,4] thiadiazine was converted to the corresponding 6-hydrazino derivative by treatment with hydrazine hydrate in DMF/Et_3N. The latter was converted to various substituted [1,2,4]triazino[1,2-a] pyrimido[4,5-e][1,3,4]thiadiazines.

Keywords Hydrazine hydrate; pyrimidines; pyrimidothiodiazines; thiadiazines; triazines

Broad biological and pharmacological activities of various thiadiazine fused rings have been extensively investigated,[1] *s*-Triazolo[3,4-b][1,3,4]thiadiazines have been demonstrated to show a wide spectrum of pharmacological activities such as antiinflammatory, analgesic, and antifungal activities.[2] Nitrophenylfurfurylidene-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines have shown antibacterial and antiviral activities.[3] The synthesis of 1,3,4-thiadiazines[4] and imidazo[1,5-d][1,3,4]thiadiazines have been reported.[5] Synthesis of some tricyclic compounds derived from [1,3,4]thiadiazine have been

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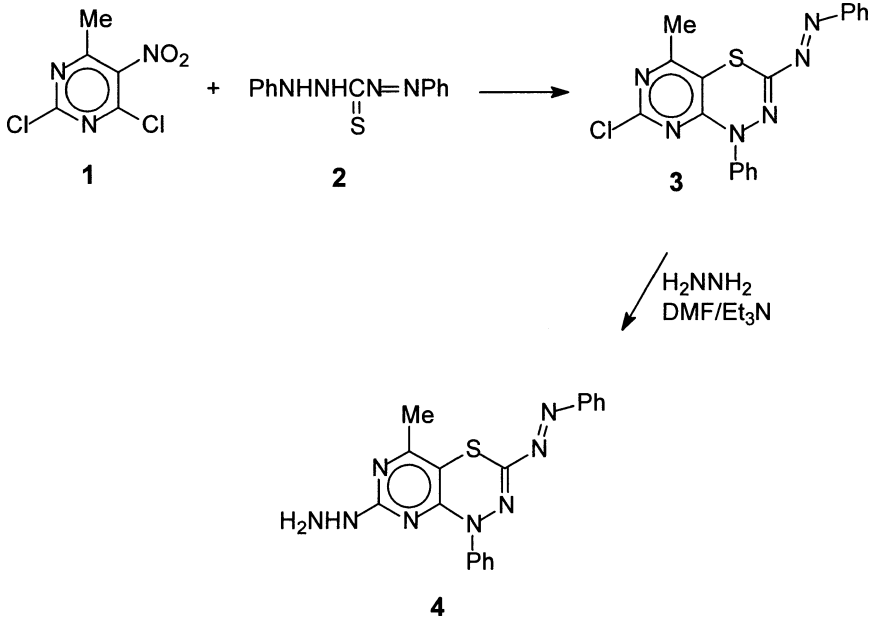
Address correspondence to Majid M. Heravi, Azzahra University, Department of Chemistry, School of Sciences, Vanak, Tehran, Iran. E-mail: mmh1331@yahoo.com

recently reported.[6] Synthesis and reactions of some pyrimido[4,5-e][1,2,4]thiadiazines[7] and pyrido[1,3,4]thiadiazines[8] also have been reported.

We have reported recently on the synthesis of substituted 6-chloro[4,5-e][1,3,4] thiadiazines[9a] and triazolo[4,3-a]pyrimido[4,5-e][1,3,4]thiadiazines.[9b] Armed with these experiences and the availability of starting material and prompted by the varied biological properties of fused [1,3,4] thiadiazines, a project aimed at the synthesis of other tricyclic compounds derived from pyrimido[4,5-e][1,3,4] thiadiazines was undertaken. The results of such studies are described in this article.

We have recently reported the synthesis of a 6-chloropyrimido[4,5-e][1,3,4] thiadiazine **3**[7] from the reaction of 2,6-dichloro-3-methyl-5-nitropyrimidine **1** with dithizone **2**. Compound **3** was found to react smoothly with hydrazine in DMF in the presence of triethyl amine to yield the corresponding 6-hydrazino derivative **4** (Scheme 1).



SCHEME 1

In the view of ring extensions to obtain tricyclic compounds derived from 1,3,4-thiadiazine and to investigate their possible biological activities, compound **4** reacted with phenacyl bromide in refluxing ethanol to afford a crystalline pure compound which was

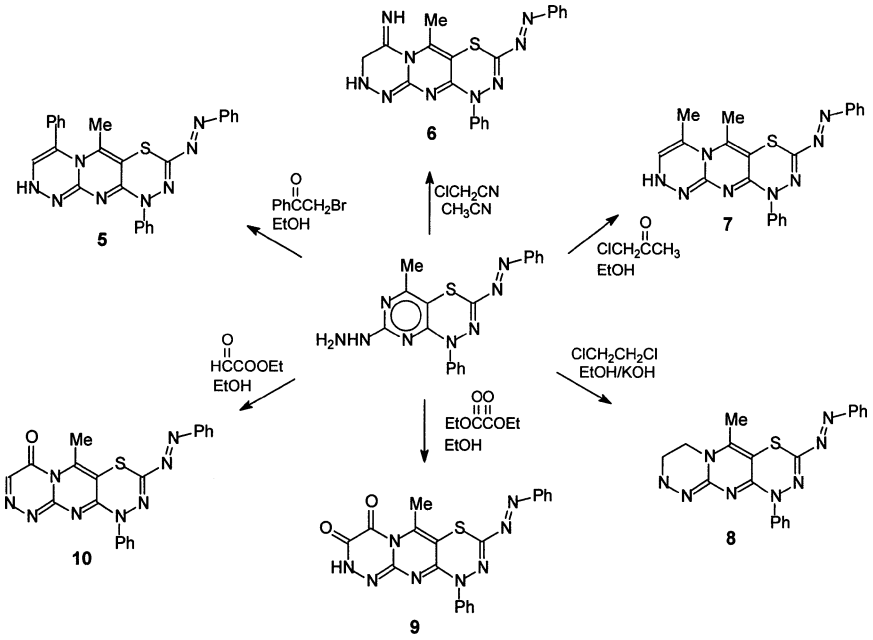
identified to be 11-methyl-4,9-diphenyl-2-phenylazo-4H-[1,2,4]triazino[1,2-a]pyrimido[4,5-e][1,3,4] thiadiazine **5**.

Next, we payed attention to the synthesis of this tricyclic system with imino groups on the 1,2,4-triazine ring. The reaction of **4** with chloroacetonitrile in acetonitrile gave 9-imino-11-methyl-4-phenyl-2-phenylazo-4H-[1,2,4]triazino[1,2-a]pyrimido[4,5-e][1,3,4] thiadiazine **6**.

Compound **4** was refluxed in ethanol with chloroacetone to afford 9, 11-dimethyl-4-phenyl-2-phenylazo-4H[1,2,4]triazino[1,2-a] pyrimido[4,5-e][1,3,4] thiadiazine **7**.

Reaction of **4** with 1,2-dichloroethane in the presence of KOH in ethanol ensued smoothly and gave 11-methyl-4-phenyl-2-phenylazo-5,6-dihydro[1,2,4]triazino[1,2-a] pyrimido[4,5-e][1,3,4] thiadiazine **8** in a 57% yield.

Compound **4** reacted with diethyloxalate in refluxing ethanol to yield 11-methyl-4-phenyl-2-phenylazo-4H-[1,2,4]triazino[1,2-a] pyrimido[4,5-e][1,3,4]thiadiazine–8,9-dione **9**; and finally, the reaction of **4** with glyoxalic acid monohydrate afforded 11-methyl-4-phenyl-2-phenylazo-4H-[1,2,4]triazino[1,2-a]pyrimido[4,5-e][1,3,4]thiadiazine-9-one **10** (Scheme 2).



SCHEME 2

EXPERIMENTAL SECTION

M.P.'s were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Shimatzu spectrometer as KBr disc. ^{1}HNMR spectra were recorded on a Bruker (100 MHz) instrument using TMS as internal standard. Mass spectra were obtained from Varian CH-7 at 70 eV. Microanalyses were performed at the Research Institute of Petroleum Industry, Tehran, Iran.

Synthesis of Compound 5

Compound **4** (0.37 g, 0.001 mol) and phenacyl bromide were refluxed in ethanol (10 mL) for 5 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under reduced pressure. The crude residue was basified by NaOH and the crude product was crystallized from EtOH to yield the title compound. Yield: 70%, m.p.: 160–1 °C, ^{1}HNMR δ($CDCl_3$): 2.40(s, 3H, CH_3), 5.66(s, 1H, triazine-H), 6.1(s, 1H, NH), 7.16–7.93(m, 15H, aromatic protons). IR, $\tilde{\nu}$(KBr disc): 3150 cm^{-1}, MS, m/z, M+, 476. Elemental analysis $C_{26}H_{20}N_8S$ calcd. C, 65.54; H, 4.20; N, 23.53; S, 6.73; found: C, 65.48; H, 4.26; N, 23.47; S, 6.52.

Synthesis of Compound 6

Compound **4** (0.37 g, 0.001 mol) and chloroacetonitrile (0.15 g, 0.12 mL, 0.002 mol) were refluxed in EtOH (5 mL) for 6 h. The solvent was evaporated to dryness and the crude residue was subjected directly to column chromatography using $CHCl_3$ as an eluent to afford compound 6. Yield: 60%, m.p.: 245–6 °C, ^{1}HNMR δ($CDCl_3$): 2.25(s, 3H, CH_3), 4.65(s, 1H, NH), 6.5(s, 1H, NH imine), 7.24–7.86(m, 10H, aromatic protons). IR, $\tilde{\nu}$(KBr disc): 3200 cm^{-1}, MS, m/z, M+, 415. Elemental analysis $C_{20}H_{17}N_9S$ calcd. C, 57.83; H, 4.10; N, 30.36; S, 7.71; found: C, 57.68; H, 4.19; N, 30.32; S, 7.58.

Synthesis of Compound 7

Compound **4** (0.37 g, 0.001 mol) and chloroacetone (0.18 g, 0.002 mol) were refluxed in EtOH (5 mL) for 6 h. The progress of the reaction was monitored by TLC. After the reaction was complete the solvent was evaporated under reduced pressure. The crude residue was subjected directly to column chromatography to give pure **7**. Yield: 50%, m.p.: 290–1 °C, ^{1}HNMR δ(DMSO-d_6): 2.36(s, 3H, CH_3), 2.54 (s, 3H, CH_3), 5.49(s, 1H, triazine-H), 5.95 (s, 1H, NH), 7.52–7.97 (m, 10H, aromatic

protons). IR, $\tilde{\nu}$(KBr disc): 3100 cm^{-1}, MS, m/z, M+, 414. Elemental analysis $C_{21}H_{18}N_8S$ calcd. C, 60.07; H, 4.35; N, 27.65; S, 7.73; found: C, 60.78; H, 4.43; N, 26.88; S, 7.75.

Synthesis of Compound 8

Compound **4** (0.37 g, 0.001 mol) and dichloroethane (0.19 g, 0.16 mL, 0.002 mol) were refluxed in DMF (5 mL) and KOH (0.12 g, 0.002 mol) for 5 h. The solution was poured into water (5 mL). The solid was column chromatographed using $CHCl_3$ as an eluent to afford pure **8**. Yield: 57%, m.p.: 240–2 °C, ^{1}HNMR δ($CDCl_3$): 2.65(s, 3H, CH_3), 3.65(m, 4H, 2 CH_2), 4.62 (s, broad, 1H, NH), 7.55–7.99(m, 1H, aromatic protons). IR, $\tilde{\nu}$(KBr disc): 3150 cm^{-1}, MS, m/z, M+, 404. Elemental analysis $C_{20}H_{18}N_8S$ calcd. C, 39.70; H, 4.48; N, 27.86; S, 7.96; found: C, 59.57; H, 4.22; N, 27.75; S, 7.99.

Synthesis of Compound 9

Compound **4** (0.37 g, 0.001 mol) and diethyloxalate (0.14 g, 0.15 mL, 0.001 mol) were refluxed in ethanol (10 mL) for 4 h and water (2 mL) was added. The precipitated solid was filtered and washed with water to afford pure **9**. Yield: 75%, m.p.: 258–9 °C, ^{1}HNMR δ(DMSO-d_6): 2.24(s, 3H, CH_3), 7.39–7.87 (m, 10H, aromatic protons), 11.28 (s, 1H, NH). IR, $\tilde{\nu}$(KBr disc): 3200 cm^{-1}, MS, m/z, M+, 430. Elemental analysis $C_{20}H_{14}N_8O_2S$ calcd. C, 55.81; H, 3.26; N, 26.04; S, 7.44; found; C, 55.78; H, 3.34; N, 25.98; S, 7.45.

Synthesis of Compound 10

Compound **4** (0.37 g, 0.001 mol) and glyoxalic acid (0.09 g, 0.001 mol) were refluxed for 4 h. The progress of the reaction was monitored by TLC. To this solution water (2 mL) was added. The crude solid was filtered and washed with water to yield the pure product. Yield: 82%, m.p.: 273–4°C, ^{1}HNMR δ($CDCl_3$): 2.25(s, 3H, CH_3), 5.61(s, 3H, CH_3), 5.61 (s, 1H, triazine-H), 7.24–7.91(m, 10H, aromatic protons). IR, $\tilde{\nu}$(KBr disc): 1710 cm^{-1}, MS, m/z, M+, 414. Elemental analysis $C_{20}H_{14}N_8OS$ calcd. C, 57.97; H, 3.38; N, 27.05; S, 7.73; found: C, 57.88; H, 3.51; N, 26.94; S, 7.58.

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