Synthesis of Novel Heterocyclic System
[1,2,4] Triazolo [4,3,a] pyrimido [4,5-e] [1,3,4] thiadiazines

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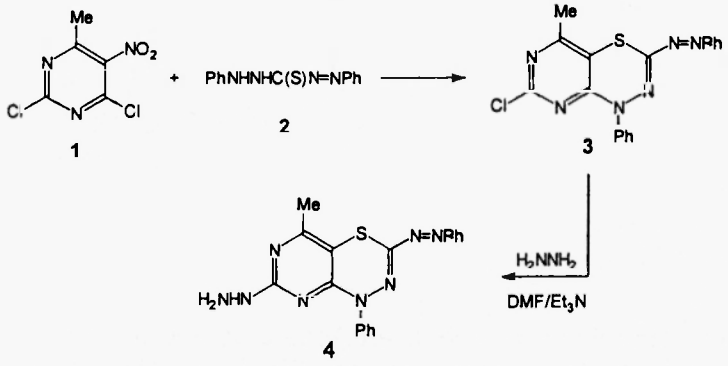
Abstract. Substituted 6-chloropyrimido [4,5-e] [1,3,4] thiadiazine was converted to the corresponding 6-hydrazino derivative by treatment with hydrazine hydrate in DMF/ Et_3N. The latter was used for the syntheses of a various substituted [1,3,4] triazolo [4,3-a] pyrimido [4,5-e] [1,3,4] thiadiazines.
Keywords. Thiadiazine, Dithizone, pyrimidine, trizoles, heterocyclization.

Introduction

1,2,4-Triazoles and n-bridged heterocycles derived from them are found to be associated with diverse pharmacological activities (1). The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically important drugs (2). The pyrimidine ring is seen frequently in many drugs, a biological active compounds and natural products (3). Broad biological and pharmacological activities of various thiadiazines fused ring has been extensively investigated (4).
We have recently reported on the synthesis of substituted 6-chloro [4,5-e] [1,3,4] thiadiazines (5). Armed with this experience, availability of starting material and prompted by the various biological properties of fused [1,3,4] thiadiazines, a project aimed at the synthesis of tricyclic compounds derived from pyrimido [4,5-e] [1,3,4] thiadiazines was undertaken. In this communication we wish to report the synthsis of novel heterocyclic system [1,3,4] triazolo [4,3-a] pyrimido [4,5-e] [1,3,4] thidiazines.
6-Chloropyrimido [4,5-c] [1,3,4] thiadiazine 3 was synthesized from the reaction of 2,6-dichloro-3-methyl-5-nitropyrimidine 1 with dithizone **2**. Compound 3 was found to react smoothly with hydrazine hydrate in DMF in the presence of triethylamine to yield the corresponding 6-hydrazino derivative **4** (Scheme 1).



Scheme 1

For ring extension and obtain tricyclic compound containing 1,2,4-triazole nucleus in order to study their possible biological activities, compound **4** was reacted with trimethyl orthoformate in refluxing EtOH in presence of catalytic amount of H_2SO_4 to obtain

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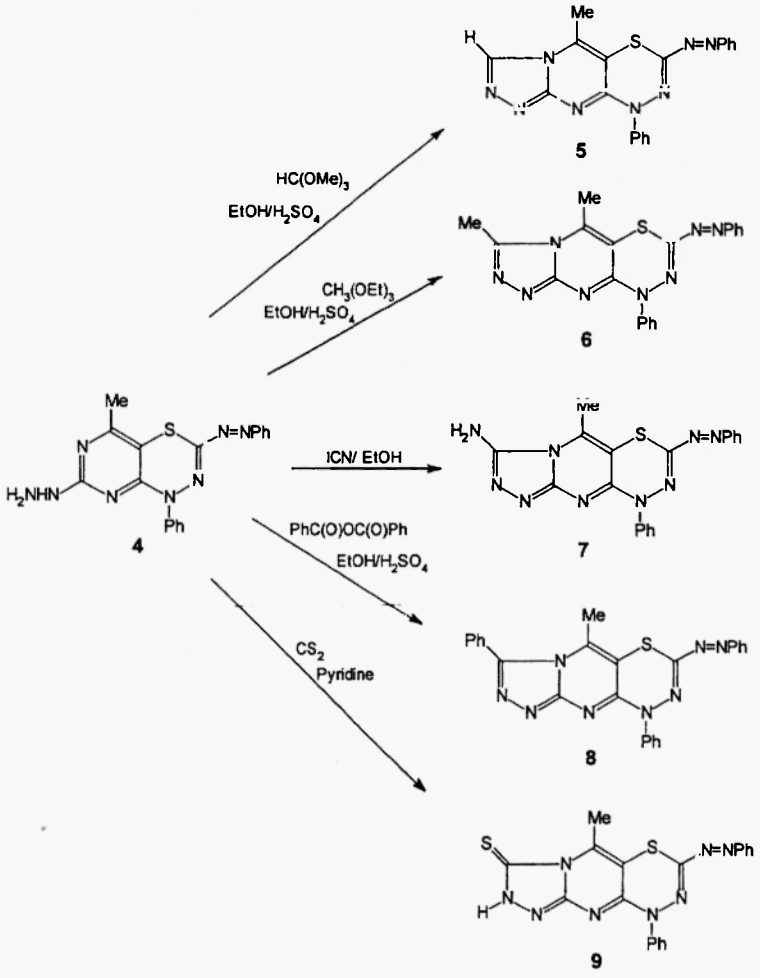
10-mathyl-4-phenyl-2-phenylazo [1,2,4] triazolo [4,3-a] pyrimodo [4,5-e] [1,3,4] thidiazine **5**. Reaction of 4 with triethyl orthoacetate in refluxing EtOH in the presence of catalytic amount of H_2SO_4 gave 8,10-dimethyl derivative **6**. When **4** was reacted with cyanogen iodide 8-amino derivative **7** was obtained. Reaction of **4** with benzoic anhydride in the presence of catalytic amount of H_2SO_4 gave 4,8-diphenyl compound **8**. At last when **4** was reacted with carbon disulfide in pyridine **8** and (7H)-thione **9** was isolated. These reactions are illustrated in Scheme 2.



Scheme 2

Experimental

Melting points were determined on a Reichert Apparatus and are uncorrected. IR spectra were recorded on a Shimatzu spectrometer as KBr discs. ^{1}HNMR 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 Research Center of Petroleum of Iran.

Synthesis of Compound 4

Compound **3** (0.01 mol, 3.8 g), hydrazine hydrate (0.02 mol, 0.64 g, 0.62 mL) and triethyl amine (2 mL) were refluxed in DMF (50 mL) for 3 hrs. The solvent was evaporated off

under reduced pressure and to the crude water (3 mL) was added. The solid was filtered off, washed with water and crystallized from EtOH/ H_2O 50/50 to afford the compound **4**. Yield 75%, mp; 232-3°C, ^{1}HNMR δ($CD_3C(O)CD_3$-d_6): 2.36(s, 3H, CH_3), 3.3(s, 2H, NH_2), 6.99(s, 1H, NH),7.5-7.95 (m, 10H, 2Ph). IR, $\tilde{\upsilon}$ (KBr disc): 3260, 3300 cm^{-1}, MS, m/z, M+, 376. Elemental analysis $C_{18}H_{16}N_8S$ calcd. C 57.45, H 4.25, N 29.78, S 8.52; found C 55.37, H 4.20, N 29.89, S 8.21.

Synthesis of compound 5

Compound 4 (0.001 mol, 0.38 g), trimethyl orthoformate (0.002 mol, 0.21 g, 0.2 mL) and sulfuric acid (0.5 mL) in ethanol (5 mL) were refluxed for 3hrs. The solvent was evaporated off under reduced pressure. To the crude water (3 mL) was added. The solid was filtered off, washed with water and crystallized from EtOH / H_2O 50 / 50 to afford the product. Yield 77%, mp; 267-8°C, ^{1}HNMR δ(CD_3OD): 2.66(s, 3H, CH_3), 7.5-8 (m, 10H, 2Ph), 9.2 (s, 1H, H of triazole). MS, m/z, M^+, 380. Elemental analysis $C_{19}H_{14}N_8S$ calcd. C 59.06, H 3.62, N 29.01, S 8.31; found C 58.9, H 3.72, N 28.82, S 8.43.

Synthesis of compound 6

Compound 4 (0.001 mol, 0.38 g), triethyl orthoacetate and sulfuric acid (0.5 mL) were refluxed in ethanol for 4 hrs.The solvent was evaporated off under reduced pressure. To the crude, water was added and filtered off. The solid was washed with water and purified by column chromatography using $CHCl_3$ as eluent to afford the titled compound. Yield 57%, mp; 284-5°C, ^{1}HNMR δ($CDCl_3$): 2.05(s, 3H, CH_3), 2.34(s, 3H, CH_3), 7.26-7.98 (m, 10H, 2Ph), MS, m/z, M^+, 400. Elemental analysis $C_{20}H_{16}N_8S$ calcd. C 60.00, H 4.00, N 28.00, S 8.00; found C 59.71, H 3.83, N 27.84, S 7.82.

Synthesis of compound 7

Compound 4 (0.001 mol, 0.38 g) and cyanogen iodide (0.001 mol, 0.15 g) were refluxed in ethanol (7 mL) for 3.5 hrs. The solvent was evaporated off under reduced pressure. To the crude, water (5 mL) was added. The precipitated solid was purified by column chromatography using $CHCl_3$ as eluent. Yield 62%, mp; 245-7°C, ^{1}HNMR δ($CDCl_3$): 2.31(s, 3H, CH_3), 6.95(s, 2H, NH_2), 7.26-7.97 (m, 10H, 2Ph). IR, $\tilde{\upsilon}$ (KBr disc): 3230 cm^{-1}, MS, m/z, M^+, 401. Elemental analysis $C_{19}H_{15}N_9S$ calcd. C 56.85, H 3.74, N 31.42, S 7.99; found C 64.88, H 3.78, N 24.10, S 7.91.

Synthesis of compound 8

Compound 4 (0.001 mol, 0.38 g), benzoic anhydride (0.001 mol, 0.22 g) and sulfuric acid (0.5 mol) were refluxed in ethanol (5 mL) for 5 hrs. To this mixture after cooling water (5 mL) was added. The precipitated solid was filtered off and purified by column chromatography $CHCl_3$ as eluent to afford the pure titled compound. Yield 75%, mp; 292-3°C, ^{1}HNMR δ ($CDCl_3$): 2.29 (s, 3H, CH_3), 7.26-7.93 (m, 15H, 3Ph). MS, m/z, M^+, 462. Elemental analysis $C_{25}H_{18}N_8S$ calcd. C 64.93, H 3.89, N 24.24, S 6.94; found C 64.88, H 3.78, N 24.10, S 7.85.

Synthesis of compound 9

Compound 4 (0.001 mol, 0.38 g) and carbon disulfide (0.002 mol, 0.15 g, 0.12 mL) were refluxed in pyridine (5 mL) for 5 hrs. The solvent was evaporated to dryness under reduce

pressure. To the crude water (5 mL) was added. The precipitated solid was filtered off and crystallized from EtOH to yield compound **9**. Yield 55%, mp; 226-8°C, ^{1}HNMR δ($CDCl_3$): 2.34(s, 3H, CH_3), 7.25-7.98 (m, 10H, 2Ph), IR, $\tilde{\upsilon}$ (KBr disc): 3250 cm^{-1}, MS, m/z, M^+, 418. Elemental analysis $C_{19}H_{14}N_8S_2$ calcd. C 54.54, H 3.35, N 26.80, S 15.31; found C 54.36, H 3.45, N 20.61, S 15.23.

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