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Some Reactions of 4,6-Diaminopyrimidinethione

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Reaction of 4,6-diamino-2(1H)-pyrimidinethione (1) with p-toluene-sulfonyl hydrazine, nitrous acid and carbon disulfide afforded the compounds (2, 3) and (4) respectively. Compound (3) easily reacted with anthranilic acid, semicarbazide thiosemicarbazide and acid hydrazides and gave the polynuclearheterocyclic compounds (5, 6_{a,b}) and (8_{a,b}) respectively. Also, compound (4) yielded the tricyclic compound 7 when reacted with ethylchloroformate. The purpose of this article is synthesis of biologically active polynuclear heterocyclic compounds.

Keywords Tetrazopyrimidinethione; triazolopyridine; polynuclear heterocycle

INTRODUCTION

As an extension of our studies on pyrimidine and pyrimidine thione derivatives, as synthons to prepare fused heterocyclic compounds,^{1,2} we have synthesized new compounds for use as antischistosomal, such as tricyclic and hexacyclic compounds, since some of pyrimidine and pyrimidinethione derivatives have provided to be active antiviral,^{3,4} antimicrobial,^{5,6} and anticancer.⁷

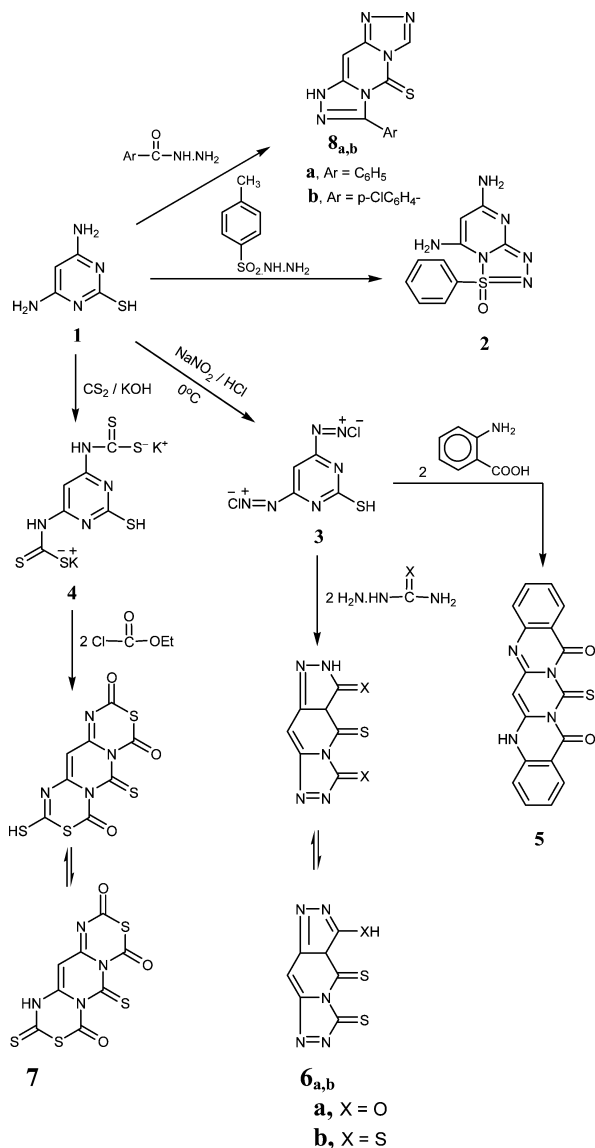
CHEMISTRY

Heating a ternary mixture of malononitrile and thiourea in presence of sodium ethoxide in ethanol under reflux yielded 4,6-diamino-2(1H)-pyrimidinethione (1).⁸

Reaction of (1) with p-toluenesulfonyl hydrazine gave 4,6-diamino-(3-oxo-3-p-tolyl)-thia-(1,2,4)-triazolo-[5,4a]pyrimidine (2). The structure of (2) was elucidated from its correct spectral data (Table I).

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SCHEME 1

On the other hand, when compound (**1**) was allowed to react with nitrous acid and carbon disulfide, it afforded the unseparated intermediates (**3**) and (**4**), respectively.^{1,2} Treatment of the tetrazonium salt (**3**) with anthranilic acid yielded the polynuclear heterocyclic compound **5** (Table I).

TABLE I Characterization Data of Products 2-8_b

Compound	M.P.°C solvent	Yield %	IR cm ⁻¹	¹ H NMR (ppm)
2	280–281 n-butanol	52	1590 (C=N), 1335 (S=O), 1370–1325 (S=N), 3300–3200 (NH ₂)	2.5 (s, 3H, CH ₃), 7.5–8 (m, 4H, aromatic), 5.1–5.6 (broad, 4H, 2NH ₂)
5	268–70 DMF	47	1660 (C=O), 3190 (NH), 1460 (C=S)	6.1 (s, 1H, NH), 7.2–7.9 (m, 8H, 2Ph), 6.8 (s, 1H pyrimidyl)
6_{a=}	229 n-butanol	55	1450 (C=S), 1470 (C=S), 3195 (NH)	7.2 (s, 1H pyrimidyl), 6.8 (broad, 1H, NH)
6_b	253 n-butanol	58	1440 (C=S), 1650 (C=O), 3180 (NH)	7.1 (s, 1H pyrimidyl), 10.1 (broad, 1H, NH)
7	218–20 ethanol	61	1670 (C=O), 1650 (C=O), 1635 (C=O), 1455 (C=S), 3180 (NH)	6.8 (broad, 1H, NH), 7.2 (s, 1H pyrimidyl)
8_a	261 A.A.	43	1450 (C=S), 3200 (NH), 1580 (C=N)	7.1 (s, 1H pyrimidyl), 6.8 (broad, 1H, NH), 7–7.8 (m, 5H, phenyl)
8_b	273–5 A.A.	49	1455 (C=S), 1590 (C=N), 3190 (NH)	7.2 (s, 1H, pyrimidyl), 6.2 (broad, 1H, NH), 7.2–7.9 (m, 4H, phenyl)

DMF: dimethyl formate; A.A.: acetic acid.

Also, compound (**3**) reacted with semicarbazide and thiosemicarbazide and gave the tricyclic compounds (**6_{a,b}**); the structure of these compounds was confirmed from their correct spectral data (Table I).

On the other hand when the dipotassium salt (**4**) was allowed to react with ethylchloroformate it gave the tricyclic compound (**7**) (Table I).

Reaction of the tetrazonium salt (**4**) with benzoylhydrazine and p-chlorobenzoylhydrazine afforded the tricyclic compounds (**8_{a,b}**) (Table I).

EXPERIMENTAL

All melting points were uncorrected and were determined on electric melting point apparatus. ¹H NMR spectra (DMSO-d₆ and CDCl₃), were carried out on a Bruker Avance 300 MHz spectrometer using TMS as internal reference chemical shift in δ, ppm).

Reaction of Compound (1) with p-Toluenesulfonyl Hydrazine—Formation of (2)

A mixture of compound **1** (1.42 g, 0.01 mol) and p-toluenesulfonyl hydrazine (1.86 g, 0.01 mol) in n-butanol (30 ml) was heated under reflux for 15 h; the solid produced after cooling was collected and crystallized from n-butanol into compound (**2**) m.p. 289–80°C.

Reaction of Compound (1) with Nitrous Acid—Formation of the Intermediate (3)

To an ice-cold solution of (**1**) (3 g) in dilute hydrochloric acid (35 ml), contained in 250 ml beaker, a solution of sodium nitrite (2.5 g) in cold water (20 ml) was added slowly. The resulting tetrazonium salt solution was stirred for 15 min at 0°C and used in the next experiments without isolation.

Reaction of 3 with Anthranilic Acid—Formation of (5)

To the tetrazonium salt solution **3** (2.2 g, 0.01 mol) anthranilic acid was added (1.37 g, 0.01 mol) and the mixture was stirred for 8 h, concentrated by evaporation under vacuum. The solid produced was collected and crystallized from dimethylformamide into compound (**5**), m.p. 268°C.

Reaction of (3) with Semicarbazide and Thiosemicarbazide—Formation of (6_{a,b})

To the tetrazonium salt solution (**3**) (2.2 g, 0.01 mol), semicarbazide (0.75 g, 0.01 mol) and/or thiosemicarbazide (0.91 g, 0.01 mol) was added, and the reaction mixture was stirred for 12 h; the solid produced was collected and crystallized from n-butanol, **6_a**, m.p. 229°C, **6_b**, m.p. 253°C.

Reaction of 1 with Carbon Disulfide—Formation of the Dipotassium Salt (4)

A mixture of (**1**), (1.42 g, 0.01 mol) and potassium hydroxide (0.39 g, 0.01 mol) in carbon disulfide (60 ml) was heated on water bath at 60°C for 1 h; the reaction mixture was left to cool and used in the next experiment without separation.

Reaction of the Dipotassium Salt (4) with Ethylchloroformate—Formation of (7)

A mixture of (4), (3.7 g, 0.01 mol) and ethylchloroformate (0.96 g, 0.01 mol) was heated on water bath for 2 h; the solid produced after cooling was collected and crystallized from ethanol into compound (7), m.p. 218°C.

Reaction of the Tetrazonium Salt with Acid Hydrazide, Formation of (8_{a,b})

To the tetrazonium salt solution (4) (3.7 g, 0.01 mol), benzoylhydrazine (1.3 g, 0.01 mol) and/or p-chlorobenzoylhydrazine (1.7 g, 0.01 mol) was added, and the reaction mixture was stirred for 18 h at room temperature, then concentrated by evaporation under reduced pressure, the solid produced was collected, washed with water and recrystallized from acetic acid into compounds 8_{a,b}, m.p. of 8_a 261°C, m.p. of 8_b 284°C.

CONCLUSION

The above work enables us to synthesize some new biologically active polynuclear heterocyclic compounds from simple monocyclic heterocyclic compounds.

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