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5-Amino-3H-1,2,4-Dithiazole-3-Thione as a Synthon: New Synthesis of 2-Thioureidobenzheteroazoles

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ABSTRACT

*New and efficient one pot syntheses of 2-thioureidobenzimidazole (**V**), 2-thioureidobenzoxazole (**VI**), and 2-thioureidobenzothiazole (**VII**) have been developed. The target compounds were obtained in good yields by condensing the title synthon commonly known as isoperthiocyanic acid (**I**) with 1,2-diaminobenzene (**II**), 2-aminophenol (**III**), and 2-aminothiophenol (**IV**), respectively, in various organic solvent and in the solid state.*

INTRODUCTION

Thiourea and its derivatives have generated a great deal of interest, since they represent the common building block of a number of heterocyclic systems [1]. For several years, benzheteroazole derivatives have attracted the attention of synthetic organic chemists, due to the wide spectrum of their chemotherapeutic properties [2]. However, there appear to be no reports in the literature on 2-thioureidobenzimidazole and 2-thioureidobenzoxazole.

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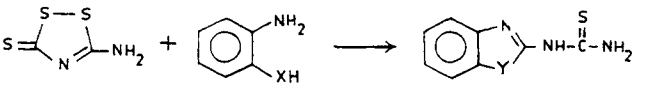
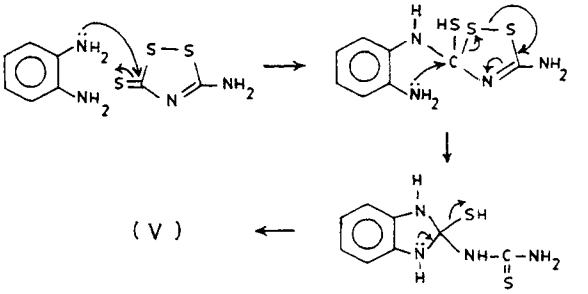
RESULTS AND DISCUSSION

In this article, we wish to report efficient one-pot syntheses of 2-thioureidobenzimidazole (**V**), 2-thioureidobenzoxazole (**VI**), and 2-thioureidobenzothiazole (**VII**) from readily accessible 1,2-diaminobenzene (II), 2-aminophenol (**III**), and 2-aminothiophenol (**IV**), respectively, by condensation with the synthon 5-amino-3H-1,2,4-dithiazole-3-thione (**I**) in both solid and solution states.



I X = NH II, O III, S IV Y = NH V, O VI, S VII

The proposed mechanism is supported by the observation that elemental sulfur and H_2S are generated during the reaction.



(V)

Attempts to prepare **V** from 2-aminobenzi-

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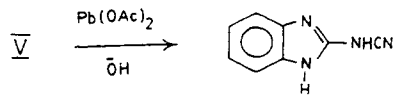
midazole through the corresponding isothiocyanate failed. An alternative method was therefore adopted to give additional support for the structure of **V**. Dehydrogenative desulfurization of **V** yielded 2-cyanamidobenzimidazole (**VIII**), whose spectral characteristics were similar to those reported by Wittenbrook [3].



(VIII)

Polymorphism was observed when (**VI**) was crystallized from various alcoholic solvents. It did not give any color with alcoholic ferric chloride, showing the absence of a phenolic hydroxyl.

The results of the experimental conditions used to define an optimum set are presented in Table 1.

EXPERIMENTAL

Isoperthiocyanic acid was prepared following the method of Kalson [4]. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H NMR spectra were obtained by use of a Jeol FX-90Q instrument at 89.55 MHz, with TMS as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5995 GC-MS spectrometer. The UV spectra were recorded on an SP8-400 Pye-Unicam spectrophotometer and Beckmann HPLC model 330, coupled with a Hewlett-Packard 1040 HPLC diode array detector. Elemental analyses were performed on a Carlo-Erba elemental analyzer, model 1106.

2-Thioureidobenzimidazole (**IV**)

Solid State Condensation of **I** *and* **II**. A mixture of **I** (7.5 g, 0.05 mol) and **II** (5.54 g, 0.05 mol) was placed in a china dish and heated with stirring on a steam bath. Within 10 minutes, the mixture melted to a dark brown paste with copious evolution of hydrogen sulfide. After 2 hours, the reaction mixture was cooled and extracted with 1N aqueous sodium hydroxide (4 × 50 mL). The extract was filtered, and the filtrate was cooled and neutralized to pH 7, initially by adding 2N hydrochloric acid and finally with a pH 7 phosphate buffer solution. When the mixture was left overnight in the refrigerator, the precipitation was completed. The solid material was collected, washed with water, and dried. The product obtained was leached with 2N hydrochloric acid (100 mL) and left to stand at room temperature for 4 hours. The acid-insoluble product was filtered, washed well with water, and dried (5.9 g), and the washings were added to the acid solution. A small portion (100 mg) of the product was purified by preparative TLC, using silica gel and benzene ethyl acetate (3:2 ratio) as the eluent. Material (75 mg, 49%) with R_f 0.61 crystallized as slender needles from propanol to yield the title compound, mp 194–196°C (decomp): λ_{max} (MeOH) 286 nm; ν_{max} (KBr) 3455, 3290, 3100, 1650, 1590, 1455, 1340, 1280, 1130, 1070, and 740 cm^{-1}; ^{1}H NMR [$(CD_3)_2SO$] δ 7.30 (4H, m), 9.06 (1H, s; exchangeable with D_2O), 10.18 (1H, s; exchangeable with D_2O), 11.12 (2H, m; exchangeable with D_2O); m/z (% abundance) 192 (100, M^+), 176 (12), 175 (66), 159 (47), 133 (41), 105 (22); HPLC [MeOH:H_2O(60:40)] 0.75 mL/min, R_t = 1.66 min. Found C, 49.54%; H, 4.196%; N, 29.16%. $C_8H_8N_4S$ requires C, 49.9%; H, 4.19%; and N, 29.14%.

The acid soluble part, kept in an ice-cold bath, was neutralized with 2N aqueous sodium hydroxide and finally adjusted with a buffer solution to pH 7 and then left in the refrigerator for 6 hours. The pale yellowish brown precipitate that had

TABLE 1 Reaction Conditions

Solution Number	*Medium*	*Reactant*	*Mole Ratio*	*Reactant*	*Mole Ratio*	*Temperature (°C)*	*Duration (Hours)*	*Yield (%)*
1	Solid state	I	1.00	II	1.06	100	2	53.6
2	Solid state	I	0.98	III	1.00	120–130	2	73[a]
3	Solid state	I	1.20	IV	1.00	140–145	1.5	25
4	THF	I	1.25	II	1.00	65	26	83.8
5	THF	I	1.00	III	1.00	65	33	86[a]
6	Methanol	I	1.03	II	1.00	65	28.5	89
7	Methanol	I	1.00	III	1.00	65	26	67.3[b]
8	Abs ethanol	I	1.20	II	1.00	80	22.5	96
9	Abs ethanol	I	1.25	III	1.00	80	30	77.7[a]
10	Abs ethanol	I	1.00	IV	1.00	80	26	60
11	Dioxan	I	1.10	II	1.00	100	20	79.4
12	Dioxan	I	1.00	III	1.00	100	30	88[b]
13	Dioxan	I	1.00	IV	1.00	100	26	53

[a]Mp 210–211°C (recrystallized from propanol/butanol).
[b]Mp 205–206°C (recrystallized from ethanol/isopropanol).

formed was filtered off, washed with water, and dried (730 mg) and found to be **V**. The overall yield of **V** was found to be 53.6%.

Condensation of **I** *and* **II** *in Organic Solvent Media.* A typical procedure: **I** (3.30 g, 0.022 mol) and **II** (1.94 g, 0.018 mol) in absolute ethanol (30 mL) was refluxed for 22 hours. The solvent was distilled from the reaction mixture and the residue treated with aqueous sodium hydroxide (1N, 3 × 25 mL) and then filtered. The filtrate was carefully neutralized to pH 7 and kept in a refrigerator for 8 hours. The precipitate (3.22 g, 96%) that had formed was collected, washed with water, and dried. It was found to be chromatographically homogeneous. Recrystallization from propanol yielded **V**, identical with the compound described earlier.

2-Cyanamidobenzimidazole (**VIII**)

To a suspension of **V** (1.92 g, 0.01 mol) in boiling water (15 mL), 15 mL of hot aqueous lead acetate (4.16 g, 0.01 mol) was added with stirring. A black precipitate of lead sulfide separated out immediately. The reaction mixture was then boiled for 10 minutes and cooled in ice, and the lead sulfide was filtered off. The colorless filtrate was acidified at 0–5°C by careful addition of glacial acetic acid (7 mL) and left in the refrigerator for 3 hours. The precipitate obtained was filtered off, washed with ice-cold water (3 × 10 mL), and dried (1.19 g, 70%). Recrystallization from acetonitrile afforded cream-colored microcrystals, mp 275–280°C (decomp) with softening at 240°C (Ref. [3], mp 275–285°C (decomp) with softening at 240°C); ν_{max} (KBr) 2175 cm^{-1} (s): *m/z* (%, abundance) M^+ 158 (base peak), 131 (9.1), 105 (4.2), 104 (12.9), 90 (9.4).

2-Thioureidobenzoxazole (**VI**)

(a) **I** (3.1 g, 0.0204 mol) and **III** (2.18 g, 0.02 mol) were placed in a 50 mL conical flask. The flask was immersed in an oil bath initially maintained at 120°C. A copious evolution of hydrogen sulfide occurred within 5 minutes. The bath temperature was then gradually increased to 125°C and maintained between 125 and 130°C for 2 hours. The workup of the reaction mixture was carried out as described earlier. The acid insoluble product (2.8 g, 73%) was recrystallized from isopropyl alcohol to give cream-colored, slender needles of **VI**, mp 205–206°C; λ_{max} (MeOH): 315 nm; ν_{max} (KBr); 3345, 3240, 3170, 3120, 1620, 1600, 1575, 1450, 1230, 1060, 740 cm^{-1}; ^1H NMR [$(CD_3)_2SO$] δ 7.75 (4H, m), 8.73 (1H, s; exchangeable with D_2O), 9.91 (1H, s; exchangeable with D_2O), and 11.75 (1H, s; exchangeable with D_2O); *m/z* (% abundance) M 193 (43) 176 (3) 134 (base peak), 105 (10) 91 (11) 79 (23); HPLC [MeOH:H_2O (60:40)] 0.75 mL/min, R_t = 2.60 min; found C, 49.67%; H, 3.63%; N, 22.18%. $C_8H_7N_3SO$ requires C, 49.72%; H, 3.65%; N, 21.75%.

(b) A magnetically stirred suspension of **I** (1.5 g, 0.01 mol) and **III** (1.09 g, 0.01 mol) in peroxide-free dioxane (30 mL) was refluxed for 30 hours. The mixture was cooled, the precipitated sulfur filtered off, and the filtrate evaporated on a steam bath. The residue left behind was worked up, as described earlier. The acid insoluble product (1.7 g, 88%) was recrystallized from propanol to give cream-colored, slender needles of VI, mp 211–212°C.

2-Thioureidobenzothiazole (**VII**)

A magnetically stirred suspension of **I** (1.5 g, 0.01 mol) and **IV** (1.2 mL, 0.0112 mol) in absolute ethanol was refluxed for 26 hours under a nitrogen atmosphere. The reaction mixture was cooled, and the solvent was evaporated on a steam bath. The residue was refluxed with benzene (15 mL) for 5 minutes, cooled, and filtered. The precipitate (1.41 g, 60%) was recrystallized from ethanol as slender needles, mp 205–206°C (Ref. [5], 206–207°C); ν_{max} (KBr) 3320, 3180, 1610, and 1190 cm^{-1}.

The solid state condensation of **I** and **IV** was effected, the temperature being maintained between 140 and 145°C, and the workup was carried out as described earlier. The product was recrystallized twice from ethanol and found to be **VII**.

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