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Synthesis of 1-Substituted-2-thio-1*H*-4-[(2-imino-4-thiobiureto-5-yl) guanyl]-6-substituted amino-1,2-dihydro-s-triazines

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Series of 1-substituted-2-thio-1*H*-4-[(2-imino-4-thiobiureto-5-yl)-guanyl]-6-substitutedamino-1,2-dihydro-s-triazines **(4a(i)–4f(iv))** have been obtained by the isomerization of 2-substituted amino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-substitutedimino-1,3,5-thiadiazines **[3a(i)–3f(iv)]** in presence of ethanolic sodium bicarbonate solution, which have been obtained by basification of their hydrochlorides **[2a(i)–2f(iv)]** which are synthesized by the interaction of 1-formamidino-3-thioamido-N-substituted formamidinothiocarbamides **(1a–f)** and N-aryl/alkylisocyanodichlorides. The latter were prepared initially by the condensation of N-aryl/alkylisothiocyanate and 1,3-diformamidinothiocarbamide. The structure of all these compounds was established on the basis of elemental analysis and IR and NMR spectral data.

Key Words: Formamidinothiocarbamides, 1,3,5-Thiadiazines, s-Triazine, Synthesis.

INTRODUCTION

The heterocyclic compounds containing triazine nucleus gain immense importance in human life. Due to their applications in pharmaceutical, industrial, medicinal, agricultural values, s-triazines possess potential therapeutic value[1] for several diseases. Some s-triazines act as antibacterial[2, 3], antiinflammatory[4], antidiabetic[5], hypoglycemic agent[6] and muscle relaxant[7]. In view of the various utilities of these compounds in various fields and as a part of the wider programme of research labs to provide alternative routes for the synthesis of various 6-membered heterocyclic compounds, it was thought interesting to investigate the isomerization of 1,3,5-thiadiazines to s-triazines.

EXPERIMENTAL

All chemicals used were of AnalaR grade. N-aryl/alkyl isocyanodichlorides were prepared according to literature method[8]. Melting points of all synthesized compounds were determined in open capillary and uncorrected, IR spectra were recorded on Perkin-Elmer spectrometer in the range 4000-400 cm^{-1} in Nujol mull as KBr pellets. PMR spectra were recorded with TMS as internal standard using $CDCl_3$ and DMSO-d_6. TLC checked the purity of the compounds on silica gel-G plates with layer thickness of 0.3 mm. All compounds gave satisfactory C, H, N and S elemental analysis.

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Synthesis of 1-formamidino-3-thioamido-N-phenylformamidino-thiocarbamide (1a)

Mixture of 1,3-diformamidinothiocarbamide (0.01 m), N-phenylisothiocyanate (0.01 m) in carbon tetrachloride (30 mL) was refluxed on a water bath for 4 h. The mixture was filtered and the filtrate during distillation yielded the crystals of **1a**. Yield 80%; m.p. 264°C; IR (KBr, cm^{-1}) ν(N—H) 3356.6, ν(C—H) (Ar) 3131.3, ν(C=N) 1635.4, ν(C—N) 1294.7, ν(C=S) 1197.7, ν(C—S) 777.9, ν(C=NH) 1688.4. ^{1}H NMR (DMSO-d_6: δ ppm) N—H protons at δ 6.77 ppm, Ar-H at δ 7.46 ppm and the signals at δ 3.15 ppm are due to moisture in DMSO-d_6 and the signal at δ 1.25 ppm is due to DMSO. Elemental analysis (%), Found (Calcd.): C 40.35 (40.67), H 4.10 (4.40), N 33.02 (33.22), S 21.48 (21.69).

Similarly, other compounds **(1b–f)** were synthesized.

Synthesis of 2-phenylamino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-phenylimino-1,3,5-thiadiazine [3a(i)]

1-Formamidino-3-thioamido-N-phenylformamidinothiocarbamides (0.01 m) **(1a)** was suspended in carbon tetrachloride medium (25 mL). To this a solution of N-phenylisocyanodichloride (0.01 m) was added. The reaction mixture was refluxed on a water bath for 4 h. During heating evolution of hydrogen chloride gas was observed and tested with moist blue litmus paper. On cooling the reaction mixture and distilling off excess solvent, crystals were separated out and recrystallized from aqueous ethanol. Yield 72%, m.p. 210°C and identified as 2-phenylamino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-phenylimino-1,3,5-thiadiazine hydrochloride **[2a(i)]**. Basification of **[2a(i)]** with ammonium hydroxide solution afforded free base **[3a(i)]**. It was recrystallized from aqueous ethanol. m.p. 195°C

Similarly, other compounds **[2a(ii)–2f(iv)]** were synthesized from **(1a–f)** which on basification yielded thiadiazines **[3a(ii)–3a(iv)]** and **[3b(ii)–3f(iv)]** by the above mention method.

Compound [3a(i)]: A light brown crystalline solid having m.p. 195°C. From analytical data, m.f. is $C_{17}H_{16}N_8S_2$, m.w. 396. IR (KBr, cm^{-1}) ν(N—H) 3359.5, ν(C—H, arom.) 2924.7, ν(C=N) 1642.2, ν(C—N) 1293.3, ν(C=S) 1173.7, ν(C—S) 778.2, ν(C=NH) 1506.1. ^{1}H NMR (DMSO-d_6: δ ppm) Ar-H protons at δ 7.04–7.71 ppm, Ar-NH protons at δ 6.68–6.87 ppm, N—H protons at δ 4.2–4.3 ppm. The signal at δ 2.7–3.1 ppm is due to moisture in DMSO-d_6 and the signal at δ 0.75–2.2 ppm is due to DMSO. Elemental analysis (%), Found (Calcd.): C 51.49 (51.52), H 3.99 (4.04), N 28.14 (28.28), S 16.12 (16.16).

Compound [3b(i)]: A pale yellow crystalline solid having m.p. 190°C. From analytical data, m.f. is $C_{13}H_{16}N_8S_2$, m.w. 348. IR (KBr, cm^{-1}) ν(N—H) 3355.1, ν(C—H, arom.) 2922.4, ν(C=N) 1687.7, ν(C—N) 1294.5, ν(C=S) 1193.6, ν(C—S) 776.9, ν(C=NH) 1448.2, ν(C—H) 2852.4. ^{1}H NMR (DMSO-d_6: δ ppm) Ar-H protons at δ 7.4–7.5 ppm, thiadiazino protons at δ 6.84–7.1, —CH_2 protons at δ 2.95, —CH_3 protons at δ 1.24–1.63 ppmand the signal at δ 2.11–2.15 ppm and 2.55–2.56 ppm is due to moisture in DMSO. Elemental analysis (%), Found (Calcd.): C 44.35 (44.83); H 4.42 (4.6); N 33.05 (32.18); S 18.22 (1839).

Synthesis of 1-phenyl-2-thio-1*H*-4-[(2-imino-4-thiobiureto-5-yl)guanyl]-6-phenylamino-1,2-dihydro-s-triazine [4a(i)]

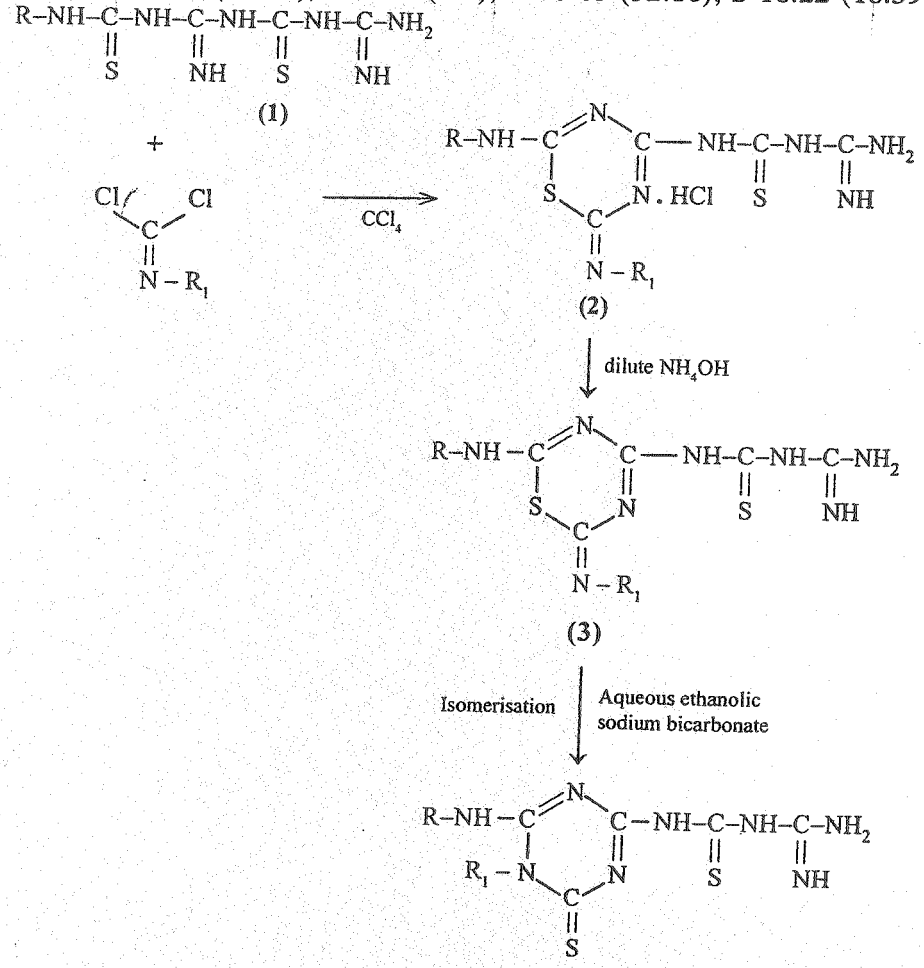
2-phenylamino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-phenylimino-1, 3,5-thiadiazines **[3a(i)]** was suspended in 5% aqueous ethanolic sodium bicarbonate solution and refluxed for 2 h. during heating reactant went into solvent. When excess solvent was distilled off, needle-shaped pale yellow crystals separated out. It was recrystallized from glacial acetic acid and identified as 1-phenyl-2-thio-1*H*-4-(2-imino-4-thiobiureto-5-yl)guanyl]-6-phenylamino-1,2-dihydro-s-triazine **[4a(i)]**. Yield 62%, m.p. 185°C. Similarly, other compounds **[4a(ii)–4a(iv)]** and **[4b(ii)–4f (iv)]** were isomerized from **[3a(ii)–3a(iv)]** and **[3b(ii)–3f(iv)]** by the above mentioned method and enlisted in Table-1.

TABLE-I
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS [4a(i) to 4f(iv)]

Compd. No.	R	R_1	m.p. (°C)	Yield	m.f.
4a(i)	Phenyl	Phenyl	185	62	$C_{17}H_{16}N_8S_2$
4a(ii)	Phenyl	*p*-Chlorophenyl	191	59	$C_{17}H_{15}N_8S_2Cl$
4a(iii)	Phenyl	Ethyl	179	71	$C_{13}H_{16}N_8S_2$
4a(iv)	Phenyl	*t*-Butyl	167	69	$C_{15}H_{20}N_8S_2$
4b(i)	Ethyl	Phenyl	182	63	$C_{13}H_{16}N_8S_2$
4b(ii)	Ethyl	*p*-Chlorophenyl	194	75	$C_{13}H_{15}N_8S_2Cl$
4b(iii)	Ethyl	Ethyl	174	69	$C_9H_{16}N_8S_2$
4b(iv)	Ethyl	*t*-Butyl	159	71	$C_{11}H_{20}N_8S_2$
4c(i)	*p*-Chlorophenyl	Phenyl	192	65	$C_{17}H_{15}N_8S_2Cl$
4c(ii)	*p*-Chlorophenyl	*p*-Chlorophenyl	203	57	$C_{17}H_{14}N_8S_2Cl_2$
4c(iii)	*p*-Chlorophenyl	Ethyl	195	58	$C_{13}H_{15}N_8S_2Cl$
4c(iv)	*p*-Chlorophenyl	*t*-Butyl	181	71	$C_{15}H_{19}N_8S_2Cl$
4d(i)	*p*-Tolyl	Phenyl	194	79	$C_{18}H_{18}N_8S_2$
4d(ii)	*p*-Tolyl	*p*-Chlorophenyl	209	65	$C_{18}H_{17}N_8S_2Cl$
4d(iii)	*p*-Tolyl	Ethyl	191	59	$C_{14}H_{19}N_8S_2$
4d(iv)	*p*-Tolyl	*t*-Butyl	172	72	$C_{16}H_{22}N_8S_2$
4e(i)	Methyl	Phenyl	171	65	$C_{12}H_{14}N_8S_2$
4e(ii)	Methyl	*p*-Chlorophenyl	169	71	$C_{12}H_{13}N_8S_2Cl$
4e(iii)	Methyl	Ethyl	164	62	$C_8H_{14}N_8S_2$
4e(iv)	Methyl	*t*-Butyl	174	68	$C_{10}H_{18}N_8S_2$
4f(i)	*t*-Butyl	Phenyl	181	65	$C_{15}H_{20}N_8S_2$
4f(ii)	*t*-Butyl	*p*-Chlorophenyl	178	69	$C_{15}H_{19}N_8S_2Cl$
4f(iii)	*t*-Butyl	Ethyl	152	71	$C_{11}H_{20}N_8S_2$
4f(iv)	*t*-Butyl	*t*-Butyl	168	73	$C_{13}H_{24}N_8S_2$

Compound [4a(i)]: A pale yellow crystalline solid having m.p. 185°C, m.f. is $C_{17}H_{16}N_8S_2$. IR (KBr, cm^{-1}) ν(N—H) 3373.9, ν(C—H) (Ar) 3150.0, ν(C=N) 1669.0, ν(C=NH) 1572.4, ν(C—N) 1181.3, ν(C—S) 995., ν(C—S) 596.5. ^1H NMR (DMSO-d_6: δ ppm) Ar-NH protons at δ 8.19–8.2 ppm, Ar-H protons at δ 6.6–7.2 ppm, NH_2 protons at δ 5.9–6.107 ppm, NH protons at δ 6.9–7.2 ppm and the signal at δ 3.25–3.47 ppm is due to moisture in DMSO-d_6. Elemental analysis (%), Found (Calcd.): C 51.49 (51.52), H 3.99 (4.04), N 28.14 (28.28), S 16.12 (16.16).

Compound [4b(i)]: An ivory crystalline solid having m.p. 182°C, m.f. is $C_{13}H_{16}N_8S_2$. IR (KBr, cm^{-1}) ν(N—H) 3387.3, ν(C—H, arom.) 3147.7, ν(C=N) 1666.7, ν(C—N) 1305.3, ν(C=S) 1178.0, ν(C—S) 746-9. ^1H NMR (DMSO-d_6: δ ppm) Ar-H protons at δ 8.15 ppm, triazino NH protons at δ 6.69 ppm, NH_2 protons at δ 5.83 ppm, —CH_3 protons at δ 3.31 ppm, —CH_3 protons at δ 2.52–2.54 ppm. The signal at δ 1.24 ppm is due to moisture in DMSO-d_6. δ 0.844–0.869 ppm is due to moisture in DMSO. Elemental analysis (%), Found (Calcd.): C 44.35 (44.83), H 4.42 (4.6), N 33.05 (32.18), S 18.22 (18.39).



where R = phenyl, *p*-chlorophenyl, *p*-tolyl, ethyl, methyl, *t*-butyl; R_1 = phenyl, *p*-chlorophenyl, ethyl, *t*-butyl

Scheme-I

RESULTS AND DISCUSSION

The parent compound 1-formamidino-3-thioamido-N-substitutedformamidino-thiocarbamides **(1a–f)** was prepared by the interaction of 1,3-diformamidinothiocarbamide (0.01 m) with N-aryl/alkylisothiocyanate (0.01 m) in carbon tetrachloride medium for 4 h on a water bath. The compounds **(1a–f)** were then further reacted with N-aryl/alkylisocyanodichlorides in 1 : 1 molar proportion in carbon tetrachloride medium for 4 h. During heating, evolution of hydrogen chloride gas was noticed as tested with moist blue litmus paper.

On cooling the reaction mixture and distilling off excess solvent, needle-shaped crystals were isolated. These were acidic to litmus and were identified as monohydrochlorides of 2-substituted-amino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-substitutedimino-1,3,5-thiadiazines **[2a(i)–2f(iv)]**. These on basification with aqueous ammonium hydroxide solution afford free bases **[3a(i)–3f(iv)]**, which on boiling in presence of ethanolic sodium bicarbonate solution to isomerize into 1-substituted-2-thio- (1H)-4-[(2-imino-4-thiobiureto-5-yl) guanyl]-6-substitutedamino-1,2-dihydro-s-triazines **[4a(i)–4f(iv)]** (see **Scheme-I** on previous page).

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