Synthesis of 1,3,5-thiadiazines from formamidinothiocarbamide

D. T. Tayade, M. E. Shelke*, J. S. Wagmare and R. C. Panpaliya

Department of Chemistry, Mahatama Fule Mahavidyalaya, Warud-444 906, Maharashtra, India
Department of Chemistry, Jijamata Mahavidyalaya, Buldhana, Maharashtra, India

E-mail: meshelke@rediffmail.com

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Abstract: Novel series of 2-substitutedamino-4-(2-imino-4-thiobiureto-S-yl-carbamidino)-6-substitutedimino-1,3,5-thiadiazines (3a-f) and 2-substitutedamino-4-(4-imino-6-substitutedimino-1,3,5-thiadiaz-2-yl)-6-substitutedimino-1,3,5-thiadiazines (Sa-f) has been obtained by basification of their hydrochlorides (la-O) and (4a-f) respectively. The latter were synthesized by the interaction of 1-formamidino-3-thioamido-N-substitutedformamidinothiocarbamides (la-O) and N-substitutedisocyanodichloride in 1 : 1 and 1 : 2 molar ratio respectively which were prepared initially by the condensation of aryllalkylisothiocyanate and 1,3-diformamidinothiocarbamide in 1 : 1 molar ratio. The structure of all these compounds were established on the basis of elemental analysis, IR and PMR spectral data.

Keywords: 1,3,5-Thiadiazines, synthesis, substitutedthiocarbamides.

The literature survey reveals that the heterocyclic compounds having 1,3,5-thiadiazines nucleus enhanced pharmaceutical, medicinal, agricultural and industrial values. The synthetic applications of N-substitutedisocyanodichlorides have been investigated and shown to have enough potential in the synthesis of nitrogen and sulphur containing heterocyclic compounds thus aim to synthesize 1,3,5-thiadiazines, reaction of N-aryl/alkylisocyanodichloride have been carried out with different 1-formamidino-3-thioamido-N-substitutedformamidinothiocarbamides in 1 : 1 and 1 : 2 molar ratios.

Experimental

All chemicals used were of analar grade. N-Substitutedisocyanodichlorides were prepared according to literature method. Melting point of all synthesized compounds was 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 CDCl₃ and DMSO-d₆. 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.

The parent compound 1-formamidino-3-thioamido-N-substitutedformamidinothiocarbamide (la-f) was prepared by refluxing the mixture of 1,3-diformamidinothiocarbamide with aryl/alkylisothiocyanate in 1 : 1 molar ratio in aceton ethanol medium for 4 h on water bath.

Synthesis of 1-formamidino-3-thioamido-N-phenylformamidinothiocarbamide (Ia) : Mixture of 1,3-diformamidinothiocarbamide (0.01 m), phenylisothiocyanate (0.01 m) in carbon tetrachloride (30 ml) was refluxed on water bath for 4 h in 1 : 1 molar ratio. The mixture was filtered and filtrate during distillation yielded the crystals of Ia. Yield 80%; m.p. 264 °C; IR spectra of compound shows v(N-H) 3356.6, v(C-H)(Ar) 3131.3, v(C=N) 1635.4, v(C-N) 1294.7, v(C=S) group 1197.7, v(C-S) 777.9 and v(C=NH) grouping 1688.4 cm⁻¹. The PMR spectra of compounds showed signals due to N-H protons at 8 6.7776 ppm, Ar-H at 8 7.4657 ppm and the signal at 8 3.155 ppm is due to moisture in DMSO-~ and 8 1.25 ppm is due to DMSO. Elemental analysis (Found: C, 40.35; H, 4.10; N, 33.02; S, 21.48. Calcd.: C, 40.67; H, 4.40; N, 33.22; S, 21.69%).

Similarly, other compounds (Ib-f) were synthesized and enlisted in Table 1.

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-phenylformamidinothiocarbamide (0.01 m) (Ia) was suspended in carbon tetrachloride medium (25 ml). To this a solution of N-phenylisocyanodichloride (0.01 m) was added in 1 : 1 molar proportions. The reaction mixture was refluxed on water bath for 4 h. During heating evaluation of hydro-
gen chloride gas was observed and tested with moist blue litmus paper. Cooling the reaction mixture and distilled off excess solvent crystals were separated out. And crystallized 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)). On basification of (2a(i)) with ammonium hydroxide solution afforded free bases (3a(i)). It was recrystallised from aqueous ethanol, m.p.195 °C.

Similarly, other compounds, (2a(ii) to 2f(iv)) were synthesized from (1a-f) and which on basification yielded thiadiazines (3a(ii) to 3a(iv)) and (3b(ii) to 3f(iv)) by above mention method and enlisted in Table 2.

Properties of compound (3a(i)):

It is light brown crystalline solid having m.p.195 °C. From analytical data, molecular formula is C17H16N8S2, molecular weight 396. IR spectra of compound shows v(N-H) 3359.5, v(C-H)(Ar) 2924.7, v(C=N) 1642.2, v(C-N) 1293.3, v(C=S) grouping 1173.7, v(C-S) 778.2 and v(C=NH) grouping 1506.1 cm⁻¹. The PMR spectra of compound showed signals due to 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 and the signal at δ 2.7-3.1 ppm is due to moisture in DMSO-d6 and δ 0.75-2.2 ppm is due to DMSO. Elemental analysis (Found : C, 51.49; H, 3.99; N, 28.14; S, 16.12. Calcd. : C, 51.52; H, 4.04; N, 28.28; S, 16.16%). From these spectral, elemental and chemical data the compound (3a(i)) is 2-phenylamino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-phenylimino-1,3,5-thiadiazine.

Properties of compound (3b(i)):

It is pale yellow crystalline solid having m.p. 190 °C. From analytical data, molecular formula is C13H16N8S2, molecular weight 348. IR spectra of compound shows v(N-H) 3355.1, v(C-H)(Ar) 2922.4, v(C=N) 1687.7, v(C-N) 1294.5, v(C-S) grouping 1193.6, v(C-S) 776.9, v(C=NH) grouping 1506.1 cm⁻¹. The PMR spectra of compound showed signals due to 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 and the signal at δ 2.7-3.1 ppm is due to moisture in DMSO-d6 and δ 0.75-2.2 ppm is due to DMSO. Elemental analysis (Found : C, 51.49; H, 3.99; N, 28.14; S, 16.12. Calcd. : C, 51.52; H, 4.04; N, 28.28; S, 16.16%). From these spectral, elemental and chemical data the compound (3b(i)) is 2-phenylamino-4-(2-imino-4-thiobiureto-5-yl-carbamidino)-6-phenylimino-1,3,5-thiadiazine.

Table 1. Physical data of the synthesised compounds

| Compd. | R            | Yield (%) | M.p. (°C) | Molecular weight | Molecular formula |
|--------|--------------|-----------|-----------|------------------|------------------|
| 1a     | Phenyl       | 80        | 264       | 295              | C10H13N5S2       |
| 1b     | p-Chlorophenyl| 75        | 272       | 329              | C10H12N7S2Cl     |
| 1c     | p-Tolyl      | 82        | 254       | 310              | C11H16N7S2       |
| 1d     | Ethyl        | 73        | 230       | 247              | C6H13N7S2        |
| 1e     | Methyl       | 84        | 218       | 233              | C9H11N7S2        |
| 1f     | t-Butyl      | 79        | 256       | 275              | C9H17N7S2        |

*All compounds gave satisfactory C, H, N and S analysis.

Table 2. Physical data of the synthesised compounds

| Compd. | R            | R1        | Yield (%) | M.p. (°C) |
|--------|--------------|-----------|-----------|-----------|
| 3a(i)  | Phenyl       | Phenyl    | 68        | 195       |
| 3a(iv) | Phenyl       | t-Butyl   | 65        | 182       |
| 3b(i)  | Ethyl        | Phenyl    | 62        | 190       |
| 3b(iii)| Ethyl        | Ethyl     | 73        | 177       |
| 3c(i)  | p-Chlorophenyl| Phenyl    | 68        | 207       |
| 3c(ii) | p-Chlorophenyl| p-Chlorophenyl | 79 | 219 |
| 3c(iii)| p-Chlorophenyl| Ethyl     | 74        | 191       |
| 3d(i)  | Phenyl       | Phenyl    | 72        | 203       |
| 3d(ii) | Phenyl       | p-Chlorophenyl | 76 | 227 |
| 3d(iii)| Ethyl        | Ethyl     | 59        | 187       |
| 3d(iv) | t-Butyl      | Ethyl     | 54        | 181       |
| 3e(i)  | Phenyl       | Phenyl    | 62        | 184       |
| 3e(ii) | p-Chlorophenyl| p-Chlorophenyl | 69 | 189 |
| 3e(iii)| Ethyl        | Ethyl     | 76        | 172       |
| 3f(iv) | t-Butyl      | R-Butyl   | 59        | 176       |
| 3f(i)  | Ethyl        | Phenyl    | 62        | 265       |
| 3f(ii) | Phenyl       | Phenyl    | 62        | 285       |
| 3f(iii)| Ethyl        | Ethyl     | 89        | 245       |
| 3f(iv) | R-Butyl      | Phenyl    | 77        | 254       |
| 5a(i)  | Phenyl       | Phenyl    | 75        | 245       |
| 5b(i)  | Ethyl        | Phenyl    | 67        | 272       |
| 5b(ii) | Ethyl        | Phenyl    | 69        | 226       |
| 5b(iii)| Ethyl        | Ethyl     | 73        | 235       |
| 5c(i)  | p-Chlorophenyl| Phenyl    | 59        | 279       |
| 5c(ii) | p-Chlorophenyl| p-Chlorophenyl | 62 | 294 |
| 5c(iii)| Ethyl        | Phenyl    | 69        | 252       |
| 5c(iv) | p-Chlorophenyl| t-Butyl  | 74        | 254       |
| 5d(i)  | t-Butyl      | Phenyl    | 72        | 269       |
| 5d(ii) | p-Chlorophenyl| Phenyl    | 79        | 289       |
| 5d(iii)| t-Butyl      | Phenyl    | 81        | 212       |
| 5d(iv) | t-Butyl      | R-Butyl   | 68        | 223       |
| 5e(i)  | Methyl       | Phenyl    | 54        | 239       |
| 5e(ii) | Phenyl       | Phenyl    | 59        | 264       |
| 5e(iii)| Ethyl        | Ethyl     | 68        | 231       |
| 5e(iv) | Phenyl       | Ethyl     | 71        | 242       |
| 5f(i)  | t-Butyl      | Phenyl    | 81        | 264       |
| 5f(ii) | R-Butyl      | Phenyl    | 69        | 281       |
| 5f(iii)| Ethyl        | Phenyl    | 74        | 238       |
| 5f(iv) | R-Butyl      | Phenyl    | 69        | 234       |

*All compounds gave satisfactory C, H, N and S analysis.
From this spectral, elemental and chemical data the compound (3b(i)) is 2-ethylamino-4-(4-imino-6-phenylimino-1,3,5-thiadiazine-2-yl)-6-phenylimino-1,3,5-thiadiazine hydrochloride (4a(i)).

On basification of (4a(ii)) with ammonium hydroxide solution afforded free base (5a(i)). It was recrystallised from aqueous ethanol, m.p. 265 °C.

Similarly, other compounds, (4a(ii) to 4f(iv)) were synthesized from (la-f). And which on basification yielded other thiadiazines (5a(ii) to 5a(iv)) and (5b(ii) to 5f(iv)) by above mention method and enlisted in Table 2.

Properties of compound (5a(i)):

It is ivory crystalline solid having m.p. 265 °C. From analytical data; molecular formula $\text{C}_{24}\text{H}_{19}\text{N}_{9}\text{S}_{2}$, molecular weight 497. IR spectra of compound shows $\nu$(N-H) 3308.4, $\nu$(C-H)(Ar) 3146.6, $\nu$(C=N) 1666.1, $\nu$(C=S) 1626.9, and $\nu$(C=O) 1007.6 cm$^{-1}$. The PMR spectra of compound showed signals due to Ar-NH protons at $\delta$ 8.63 ppm, Ar-H protons at $\delta$ 7.14–7.18 ppm and the signal at $\delta$ 2.58–2.59 ppm is due to moisture in DMSO.

Properties of compound (5b(i)):

It is bricks red crystalline solid having m.p. 245 °C. From analytical data; molecular formula $\text{C}_{20}\text{H}_{19}\text{N}_{9}\text{S}_{2}$, molecular weight 348. IR spectra of compound shows $\nu$(N-H) 3383.9 and $\nu$(C-H)(Ar) 3146.6, $\nu$(C=N) 1660.5, $\nu$(C=S) 1332.7, $\nu$(C=S) 1154.2, and $\nu$(C=O) 1007.6 cm$^{-1}$. The PMR spectra of compound showed signals due to Ar-NH protons at $\delta$ 8.63 ppm, Ar-H protons at $\delta$ 7.14–7.18 ppm and the signal at $\delta$ 2.58–2.59 ppm is due to moisture in DMSO.

Scheme 1

\[
\text{H}_2\text{C} \xrightarrow{-\text{NH}} \text{NH-C} \xrightarrow{\text{NH}} \text{NH} \xrightarrow{\text{NH-C}} \text{S} \xrightarrow{\text{C-N-R}} \text{R}
\]

Scheme 2

\[
\text{H}_2\text{C} \xrightarrow{-\text{NH}} \text{NH-C} \xrightarrow{\text{NH}} \text{NH} \xrightarrow{\text{NH-C}} \text{S} \xrightarrow{\text{C-N-R}} \text{R}
\]

where, $R_1$ = phenyl, $p$-chlorophenyl, $p$-tolyl, ethyl, methyl, $t$-butyl

$R_2$ = phenyl, $p$-chlorophenyl, ethyl, $t$-butyl

Synthesis of 2-phenylamino-4-(4-imino-6-phenylimino-1,3,5-thiadiaz-2-yl)-6-phenylimino-1,3,5-thiadiazine (5a(i)):

1-Formamidino-3-thioamido-$N$-phenylformamidinothiocarbamide (0.01 m) (1a) was suspended in acetone ethanol medium (25 ml). To this a solution of $N$-phenylisocyanodichloride (0.02 m) was added. The reaction mixture was refluxed on water bath for 12 h. During heating evolution of hydrogen chloride gas was observed and tested with moist blue litmus paper. After cooling the reaction mixture and distilled off excess solvent, solid crystals were separated out. And crystallized from aqueous ethanol. Yield 73%, m.p. 272 °C and identified as 2-phenylamino-4-(4-imino-6-phenylimino-1,3,5-thiadiaz-2-yl)-6-phenylimino-1,3,5-thiadiazine hydrochloride (4a(i)).
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