Synthesis and antifungal activity of novel 3-anilino-6-ethylthio-4,5-dihydro-1,2,4,5-tetrazines

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Abstract : Synthesis of some novel 4,5-dihydro-1,2,4,5-tetrazines have been achieved by the interaction of *S*-ethylthiocarbohydrazide and *N*-arylisocyanodichlorides in chloroform medium. A comparative antifungal study has also been carried out on the fungus *Fusarium udum*.

Keywords : Tetrazines, antifungal activity.

Literature contents a number of methods for the synthesis of 1,2,4,5-tetrazines¹. Majority of them² are 3,6-symmetrically disubstituted tetrazines obtained from the treatment of nitrile derivatives of hydrazine or aldehyde with substituted hydrazines. Bansal and coworkers³ have also synthesized 1,2,4,5-tetrazines by the reaction of substituted phenacyl pyridinium bromide with aromatic diazonium salt solution. In this connection, we are reporting the synthesis of some novel dihydro-1,2,4,5-tetrazines by using *N*-aryl/alkylisocyanodichlorides⁴ by a new route.

Results and discussion

S-Ethylthiocarbohydrazide (1) was prepared from thiocarbohydrazide and ethyl iodide (0.01 mol), followed by basification with dilute ammonium hydroxide and crystallization from ethanol.

S-Ethylthiocarbohydrazide (1) (0.01 mol) was treated with *N*-phenylisocyanodichloride (2a) in boiling chloroform to furnish the monohydrochloride of 3-anilino-6-ethylthio-4,5-dihydro-1,2,4,5-tetrazine, yield 80%, m.p. 182 °C. On basification with dilute ammonium hydroxide, it afforded the free base (3a).

The other 1,2,4,5-tetrazines (3b-f) were prepared by expanding the above reaction to different *N*-arylisocyanodichlorides (2b-f), and the related products were obtained in good yields (see Experimental).

Compounds (3a-f) were tested for their antifungal activity against the fungus *Fusarium udum* at 27 ± 2 °C, and some of these compounds (3b,c,f) were found to possess higher activity than that of the standard (Mancozeb) used against the same fungus.

Experimental

The melting points were recorded using hot paraffin bath and are uncorrected. Chemicals used were of A.R. grade. IR spectra were recorded in Nujol mull as well as KBr pellets on a Perkin-Elmer spectrophotometer. PMR spectra were recorded in CDCl₃ with TMS as internal standard. All new compounds showed satisfactory results from elemental analyses (C, H, N and S).

S-Ethylthiocarbohydrazide :

0.01 mol of thiocarbohydrazide was refluxed with 0.01 mol of ethyl iodide in chloroform medium for 1.5 h, when a solid mass was separated out. The compound has been characterized by analysis of the hydroiodide and picrate, and by its conversion into the dibenzaldehyde derivative. It was acidic to litmus and identified as monohydroiodide of *S*-ethylthiocarbohydrazide, yield 82%, m.p. 130 °C. It was basified with dilute ammonium hydroxide and crystallized from ethanol to yield free base *S*-ethylthiocarbohydrazide (1), m.p. 119 °C.

3-Anilino-6-ethylthio-4,5-dihydro-1,2,4,5-tetrazine (3a) :

0.01 mol of *S*-ethylthiocarbohydrazide (1) was refluxed with *N*-phenylisocyanodichloride (2a) in boiling chloroform medium for 4 h. Evolution of hydrogen chloride gas was clearly noticed. After completion of reaction and distilling off chloroform, a sticky mass was obtained. It was repeatedly washed with petroleum ether (60–80 °C), which afforded a deep coloured granular solid. It was crystallized from ethanol. It was found acidic to litmus and on determination of equivalent weight, identified as monohydrochloride of 3-anilino-6-ethylthio-4,5-dihydro-1,2,4,5-tetrazine, yield 80%, m.p. 182 °C. The com-

where, 2a, 3a : Ar = phenyl
 2b, 3b : Ar = *m*-tolyl
 2c, 3c : Ar = *o*-tolyl
 2d, 3d : Ar = *p*-tolyl
 2e, 3e : Ar = *p*-chlorophenyl
 2f, 3f : Ar = *m*-chlorophenyl

Scheme 1

pound on basification with dilute ammonium hydroxide solution afforded a free base (3a).

It was crystallized from ethanol, m.p. 170 °C (Found : C, 51.02; H, 5.48; N, 29.62; S, 13.50. C₁₀H₁₃N₅S requires : C, 51.06; H, 5.53; N, 29.78; S, 13.61%); IR⁵ 3273, 3203 (N-H), 1640 (C=N), 1528 (ArC=C), 1284 (C-N) and 755 (C-S) cm⁻¹; ¹H NMR : δ 1.25, (3H, t, *J* 7 Hz), 2.5 (2H, q, *J* 7 Hz), 6.97–7.26 (2H, s, R-NH), 7.29 (1H, s, Ar-NH), 7.44–7.55 (5H, m, Ar-H); 3b : C₁₁H₁₅N₅S, m.p. 169 °C; 3c : C₁₁H₁₅N₅S, m.p. 158 °C; 3d : C₁₁H₁₅N₅S, m.p. 168 °C; 3e : C₁₀H₁₂N₅SCl,

m.p. 164 °C; 3f : C₁₀H₁₂N₅SCl, m.p. 167 °C.

The compounds 3a-f were assayed for their antifungal activities against the test fungus *Fusarium udum* at 27 ± 2 °C by poisoned food technique⁶. Potato dextrose agar (PDA) was used as a basal medium to evaluate the efficiency of these synthesized products. A chemical fungicide, Mancozeb was used as a standard for this process. Compound (3e) showed comparable activity (73% inhibition) and compounds (3b,c,f) showed highest activity (83, 80 and 78%, respectively) than that (73%) of the standard.

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