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# Synthesis and Characterization of some Halogen containing Triazolotriazinoindoles as Possible Fungicides

**ATMA RAM MISRA, MAYA MANI TRIPATHI and ABU SHAHMA**

Department of Chemistry, Shri Durga Ji Post Graduate College,
Chandeshwar and Shibli National PG College, Azamgarh (India).

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**ABSTRACT**

Certain 6H-5-aryl-9-halo-1,2,4-triazolo[3',4':3,4]-1,2,4-triazino [5,6-b]-indoles (4a-1) and 5H-1-aryl-8-halo-1,2,4-triazolo [4',3':3,4]-1,2,4-Triazino [5,6-b]-indoles (5a-1) have been prepared in good yields, characterization of new compounds has been done means of spectral data and elemental analysis. The fungicidal activity of synthesized compounds have been evaluated against *A. niger* and *F. oxysporium.*

**Key words:** *A. niger, F. oxysporium,* Agar Plate Technique, Indoles, Spectral analysis.

## INTRODUCTION

In continuation of our research on the synthesis of biologically important heterocyclic compounds herein we report the Synthesis and antifungal activity of some traizolotriazinoiondoles (Scheme 1). 1,2,4-Triazole derivatives are known to exhibit various types of useful biological activity like fungicidal[1-3], herbicidal[4,5] and insecticidal[6-8]. Similarly indoles nucleus is also associated with broad spectrum of pesticidal activities like fungicidal[9], antimicrobial[10-12] etc. 1,2,4-triazines fused with an indole nucleus have reported as potential drugs[13-14]. In the light of the above background the title compounds triazoltriazoindoles have been synthesized with the hope that the fusion of biolable 1,2,4-triazole, 1,2,4-triazine and indole nuclei might results the fungicides of enhanced potency.

5-Haloisotins were condensed with thiosemicarbazide to obtain 8-halo-3-mercapto-1,2,4-triazino [5,6-b]-indoles (1a,b). Hydrazinolysis of (Ia, b) yielded 8-halo-3-hydrazino-1,2,4-triazino [5,6-b]-indoles (2a,b). The reaction of these hydrazines with aromatic aldehydes afforded the hydrazones (3a-1). Cyclization of these hydrazones employing thionyl chloride resulted in the formation of 6H-5-aryl-9-halo-1,2,4-triazolo [3',4':3,4]-1,2,4-triazino [5,6-b)-indoles (4a-1). The above hydrazones are also cyclised employing bromine in acetic acid. The products obtained by this cyclization are found to be different from that of thionyl chloride catalyzed reaction and are new characterized as 5H-1-aryl-8-halo-1,2,4-triazolo [4',3':2,3]-1,2,4-triazino [5,6-b]-indoles) (5a-1).

In order to study the mode of cyclization, the hydrazones (4a-f) were subjected to thionyl

chloride catalyzed cyclization and cyclization using bromine in acetic acid. In all the cases the two types of cyclization yielded different compounds. The structures of these cyclized products were confirmed by elemental analysis and mass spectral data. The appearance of a base peak at mlz, 320 along with a M+2 peak at mlz 322 with one third intensity of the former for the compounds (5a) is consistent with the molecular formula $C_{16}H_9ClN_6$. The apperance of an intense molecular ion peak in this mass spectrum also indicates the aromatic nature of angularly fused triazolotriazino indoles. The mass spectrum of linearly cyclized triazolotriazinoindole (6a) shows, fairly intense molecular ion peak at mlz, 320 (60%) along with the M+2 peak at mlz 322 (20%) confirming its assigned molecular formula $C_{16}H_9ClN_6$. The base peak in this case was seen at mlz 103, which can be attributed to molecular ion of benzonitrile formed by the initial fragmentation of the triazole ring. The molecular ion peak in the case however was not the base peak indicating the less aromatic character of the linearly cyclized product.

**Antifungal activity**

The compounds (3a-1) (4a-1) and (5a-1) were screened for their antifungal activity against *A. niger* and *F. oxysprium* at 1000, 100 and 10 ppm concentrations following the Agar Plate Technique[15]. It is appeared from screening data that all the compounds were more active against *Helminthosporium oryze* as compared with *Aspergillous niger* but their difference was marginal. Most of the compounds showed the significant antifungal activity of 1000 ppm against both the fungal species but their toxicity decreased markedly at lower concentrations (100 and 10 ppm). The compounds 6b and 6c exhibited fungitoxicity of the order of Dithane M-45 at 1000 ppm against both the fungi. However, their activity decreased markedly at lower concentration (100 and 10 ppm) except in case of the compound 6c which inhibited 54-56 growth of both the fungal species even at 10 ppm concentration. In spite of the fact that the compounds (3a-1) have a performed open chain skeleton of trizolotriazinoindoles (4a-1 and 5a-1) where the chain is closed resulting in a more planar and compact system. This is in conformity with the earlier observations that the compact size and planarity of molecule often enhance its pesticidal activity[16-17]. It was noted that the introduction of chloro group is more effective that the of methyl or methoxy group. The overall results are not so encouraging as one would expect from the combined performance of the fused biolabile nuclei i.e. 1,2,5-trizene and 1,2,4-triazole.

## EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra in KBr were recorded on a Jasco FT/IR-460 plus Fourier Transform infrared spectrophotometer. $^1$HNMR spectra were scanned on a bruker ultraspec 500 MHz/ AMX 400 MHz spectrometer using DMSO as solvent chemical shift are expressed in δ ppm spectra were recorded on JEOL SX 102/DA-6000 mass spectrophotometer using Argon/Xenon (6KV, 10mA) as the FAB gas with m-nitrobenzyl alcohol as the matrix.

**Table 1: Characterization data of 6H-5-aryl-9-halo-1,2,4-triazolo [3',4':3,4]-1,2,4-triazino [5,6-b]-indoles (IV a-l) and Characterization data of 5H-1-aryl-8-holo-1,2,4-trizolo [4',3':2,3]-1,2,4-triazino [5,6-b]-indoles (Va-l)**

| Comp. No. | R | Molecular Formula | m.p. (°C) | Yield (%) | Anal. (%) found (Cald). C | H | N |
|---|---|---|---|---|---|---|---|
| X=Cl | | | | | | | |
| IVa* | H | $C_{16}H_{11}N_6Cl$ | 310 | 68 | 61.41 (61.44) | 03.10 (03.11) | 26.09 (26.12) |
| b | p-Cl | $C_{16}H_{10}N_6Cl_2$ | 210 | 70 | 56.95 (53.93) | 02.49 (02.52) | 23.61 (23.59) |
| c | o-Cl | $C_{16}H_{10}N_6Cl_2$ | 208 | 65 | 53.95 (53.93) | 02.51 (02.52) | 23.57 (23.59) |

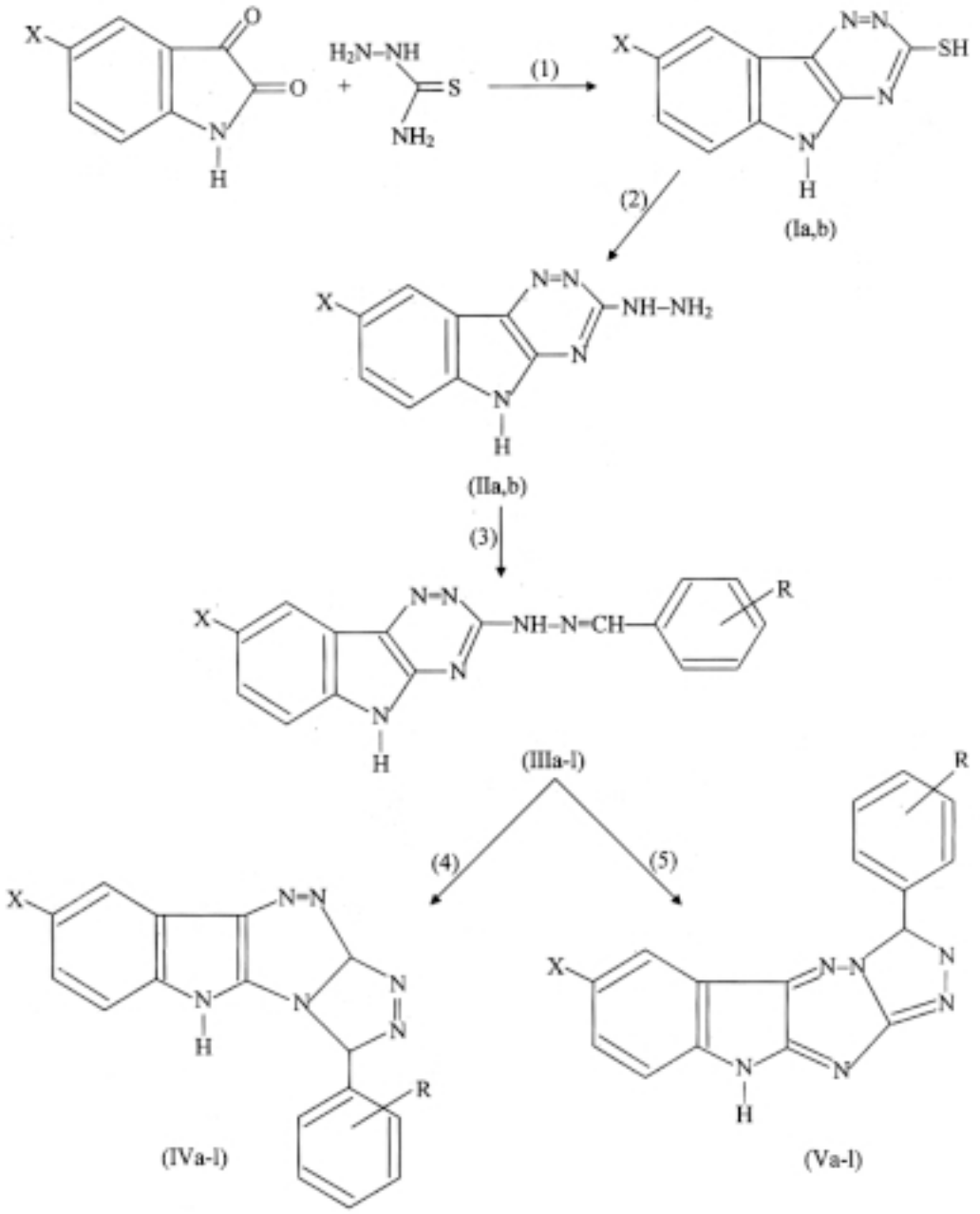
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| d | p-$CH_3$ | $C_{17}H_{13}N_6Cl$ | 265 | 66 | 60.81 (60.80) | 04.54 (03.57) | 25.06 (25.03) |
| e | o-$OCH_3$ | $C_{17}H_{13}N_6OCl$ | 262 | 71 | 58.01 (58.03) | 03.39 (03.41) | 23.86 (23.89) |
| f | p-$OCH_3$ | $C_{17}H_{13}N_6OCl$ | 278 | 75 | 58.05 (58.03) | 03.42 (03.41) | 23.90 (23.89) |
| **X=Br** | | | | | | | |
| g | H | $C_{16}H_{11}N_6Br$ | 295 | 72 | 52.43 (52.45) | 02.75 (02.73) | 22.92 (22.95) |
| h | p-Cl | $C_{16}H_{10}N_6ClBr$ | 261 | 64 | 47.95 (47.94) | 02.23 (02.24) | 20.95 (20.97) |
| i | o-Cl | $C_{16}H_{10}N_6ClBr$ | 258 | 73 | 47.92 (47.94) | 02.21 (02.24) | 20.98 (20.97) |
| j | p-$CH_3$ | $C_{17}H_{13}N_6Br$ | 232 | 66 | 56.65 (53.68) | 03.17 (03.15) | 22.09 (22.10) |
| k | o-$OCH_3$ | $C_{17}H_{13}N_6OBr$ | 245 | 68 | 51.49 (51.51) | 03.00 (03.03) | 21.19 (21.21) |
| l | p-$OCH_3$ | $C_{17}H_{13}N_6OBr$ | 285 | 67 | 51.48 (51.51) | 03.01 (03.03) | 21.22 (21.21) |
| **X=Cl** | | | | | | | |
| V a | H | $C_{16}H_9N_6Cl$ | 305 | 65 | 59.89 (59.90) | 02.78 (02.80) | 26.21 (26.20) |
| b | o-Cl | $C_{16}H_8N_6Cl_2$ | 259 | 69 | 54.05 (54.08) | 02.21 (02.25) | 23.67 (23.66) |
| c | p-Cl | $C_{16}H_8N_6Cl_2$ | 209 | 73 | 54.07 (54.08) | 02.22 (02.25) | 23.63 (23.66) |
| d | p-$CH_3$ | $C_{17}H_{11}N_6Cl$ | 274 | 75 | 60.95 (60.98) | 03.24 (03.28) | 25.09 (25.11) |
| e | o-$OCH_3$ | $C_{17}H_{11}N_6OCl$ | 281 | 74 | 58.21 (58.20) | 03.15 (03.13) | 23.94 (23.96) |
| f | p-$OCH_3$ | $C_{17}H_{11}N_6OCl$ | 283 | 68 | 58.18 (58.20) | 03.10 (03.13) | 23.97 (23.96) |
| **X=Br** | | | | | | | |
| g | H | $C_{16}H_9N_6Br$ | 308 | 26 | 52.62 (52.60) | 02.43 (02.46) | 23.79 (23.81) |
| h | o-Cl | $C_{16}H_8N_6ClBr$ | 265 | 61 | 48.05 (48.06) | 02.01 (02.00) | 21.00 (21.02) |
| i | p-Cl | $C_{16}H_8N_6ClBr$ | 206 | 65 | 48.02 (48.06) | 02.03 (02.00) | 21.00 (21.02) |
| j | p-$CH_3$ | $C_{17}H_{11}N_6Br$ | 276 | 72 | 53.79 (53.82) | 02.88 (02.90) | 22.14 (22.16) |
| k | o-$OCH_3$ | $C_{17}H_{11}N_6OBr$ | 259 | 76 | 51.63 (51.64) | 02.75 (02.78) | 21.27 (21.26) |
| l | p-$OCH_3$ | $C_{17}H_{11}N_6OBr$ | 264 | 70 | 51.66 (51.64) | 02.79 (02.78) | 21.21 (21.26) |

*IB (KBr): 3175 (N-H), 1580 (>C=C< of aromatic ring), 3050 (aromatic C-H), 1590 (C-N), 1055 (-N=N-), 1625 (cyclic <C=N-), 695 (C-Cl).

$^1$H NMR (DMSO-$d_6$) δ: 10.02 (1H, indole NH), 5.05 (s, 2H, of two CH-N), 6.25-7.55 (m, 8H, Ar-H)

** IB (KBr): 3170 (N-H), 1583 (>C=C<of aromatic ring) 3060 (aromatic C-H), 1580 (C-N), 1620 (Cyclic< C=N), 690 (C-Cl)

$^1$H NMR (DMSO-$d_6$) δ: 10.12 (1H, indole NH), 6.20-7.60 (m, 7H, Ar-H), 3.5 (s, 3H, $OCH_3$




X : a-g=Cl; h-l=Br

R : a,g=H; b,h=p-Cl; c,i=o-Cl; d,j=p-$CH_3$, l,k=o-$CH_3$, f,l=p-$OCH_3$

(1) $K_2CO_3/H_2O$ (2) $N_2H_4.H_2O$ (3) Ar–CHO/AcOH (4) $SOCl_2$ (5) $Br_2$/AcOH

**Scheme 1.**

**Synthesis of 8-halo-3-mercapto-1,2,4-triazilo [5,6-b]-indoles (Ia, b)**

8-Halo-3-mercapto-1,2,4-triazino [5,6-b]-indoles were synthesized by condensation of 5-haloisatin and thiosemicarbazide following the method of Gladyen *et al*.,[18]. Thus 5-haloisatin (1.0 mol), thiosemicarbazide (1.2 mol) and K2CO3 solution in water refluxed in ethanol for 2 hrs. Then solvent was removed by evaporation obtained solid was recrystallized from DMF. All the prepared indoles well agreed with their analytical data already reported in the literature[18].

**Synthesis of 8-halo-3-yl-hydrazino-1,2,4-triazino [5,6-b]-indoles (IIa,b)**

The corresponding 9-halo-3-mercapto-1,2,4-trizino [5,6-b]-indoles (1a,b) (0.01 mol) was refluxed with hydrazine hydrate (10 ml) 98% with occasional shaking for 1 to 1.5 hrs. The resulting solid product was recrystallized from aqueous DMF to yield fine pale yellow crystals. 8-Chloro or bromo--3-yl-hydrazino-1,2,4-triazino [5,6-b] indoles were prepared by the above procedure which well agreed with their analytical data already reported in the literature[19].

**Synthesis of 8-halo-1,2,4-triazino [5,6-b]-indoles-3-yl hydrazones (IIIa-l)**

A solution of 8-halo-3-yl hydrazino-1,2,4-triazino [5,6-b]-indoles (2a,b) 5m mol and substituted benzldehyde (5m mol) in alcohol (50 ml) was refluxed for 2 hrs. The reaction mixture on removal of alcohol, yield the corresponding hydrazones, the resulting solid was filtered and recrystalized from aqueous DMF to yield to the title compounds (3a-1). Compounds (3a). IR (KBr) max in $cm^{-1}$; 3180 (N-H), 2950 (C-H) aliphatic), 1590 (C=C of aromatic ring), 3050 (aromatic C-H), 1580 (C-N), 1050 (N-N), 1625 (Cyclic (>C=N-), 690 (C-Cl). $^1$HNMR ($CDCl_3$) δ in ppm; 6.24 (s, 1H, -NH-exchangeable), 10.01 (s, 1H, indole NH) 5.20 (s, 1H, CH=N-), 6.24-7.52 (m, 8H, Ar-H).

**Synthesis of 6H-5-aryl-9-halo-1,2,4-triazolo [3',4':3,4]-1,2,4-triazino [5,6-b]-indoles (IVa-l)**

A mixture of approptriate hydrazones (1.0 mol) and thionyl chloride (10 ml) was refluxed on a water bath for 4 hours. The excess of thionyl chloride was removed by distillation under reduced pressure. The residue was washed with hot petroleum ether and cooled. The product so obtained was recrystallized from DMF to yield powdery crystals of the title compounds. The structure was assigned on the basis of analytic and spectral data, which are given in the table 1.

**Synthesis of 5H-1-aryl-8-halo-1,2,4-triazolo [3',4':2,3]-1,2,4-triazino [5,6-b]-indoes (Va-l)**

A solution of corresponding aromatic aldedhye,1,2,4-triazino-[5,6-b]-indoles]-3-yl hydrazones (1.0 mol) in galacial acetic acid was treated with bromine (1.2 mol) in acetic acid and stirred at an ambient temperatures for five hours. The reaction mixture was cooled and diluted with water. The precipitated solid product was filtered. The crude product was recrystallization from DMF to give the 5H-1-aryl-8-halo-1,2,4-triazolo [5,6-b]-indoles. All the prepared titled compounds with their characterization data m.p., yield, molecular formula, elemental analysis and spectral data as foot-note are recorded in Table 1.

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