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Synthesis of new fungitoxic 5-aryl-4,5,6,7-tetrahydrobenzo-thazolon [3,2-a] [1,3,5]-thriazine-3-thiones

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Abstract

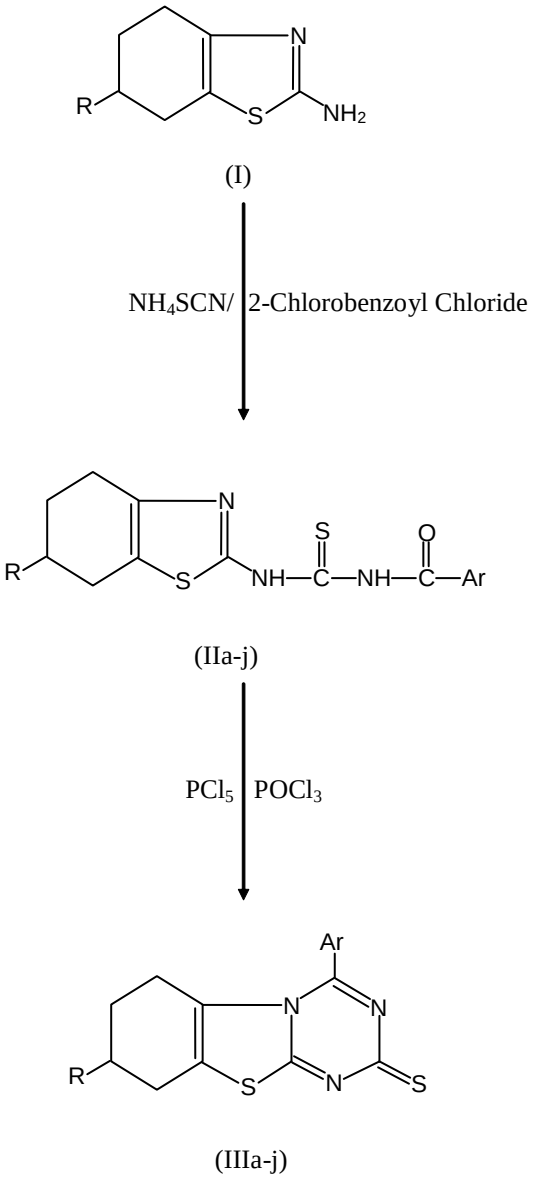
2-Bromo-6-methyl cyclohexanone on boiling with thiourea gave 2-amino-4-methyl-4,5,6,7-tetrahydrobenzothiazole (I), which inturn were treated with mixture of NH_4SCN and aroyl halides in acetone followed by addition of 2-amino-5-phenyl-1,3,4-thiadiazole gives N^1-aroyl-N^3-(4,5,6,7)-tetrahydrobenzothiazole-2-yl-thioureas (II*a-j*) compounds (II*a-j*) further reacted with a mixture of $POCl_3$ and PCl_5 to yield 5-aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5]-triazine-3-thione (III*a-j*). Antifungal activity of the prepared compounds have been compared with Dithane M-45 against *Puccinia recondita* and *Ustilagonuda var. maydis* and the results correlated with their structural features.

Introduction

Thiazolyl derivatives have been used for the treatment of bacterial[1-3] and in pharmaceutical and biological field[4,5].

Keeping the above observation in view, 4,5,6,7-tetrahydrobenzothiazoles nucleus has been fused with 1,3,5-triazine nucleus, resulting the title compounds 5-aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5]-triazine-3-thione which might result in the fungicides of enhanced potency. The presence of thione function (>C=S) at position 3 in these compounds is expected to enhance their fungitoxicity[6]. The reaction sequence leading to the formation of title compounds is given in the scheme-I.

2-Bromo-6-methylcyclohexanone were prepared by treating 2-methylcyclo-hexanone and bromine in cold, which were converted to 2-amino-4,5,6,7-tetrahydro-benzothiazole (I) treating 2-chlorocyclohexanone thiourea and ethanol. It can also be prepared by condensation of 2-bromo-6-methylcylcohexanone with thiourea. Benzothiazoles (I) on treating with a mixture of NH_4SCN and aroyl halides in acetone gives N^1-aroyl-N^3-(4,5,6,7)-tetrahydro-benzothiazole-2-yl-thioureas (II*a-j*). These thioureas (II*a-j*) on treatment with a mixture of $POCl_3$ and PCl_5 gives 5-aryl-4,5,6,7-tetrahydro-benzothiazolo [3,2-a] [1,3,5]-triazine-3-thione (III*a-j*).



Ar : IIIa,f = $-C_6H_5$, IIIb,g = o–ClC_6H_4, IIIc, h = p–ClC_6H_4, IIIe,j = p–$CH_3C_6H_4$

R : IIIa,e = –H, IIIf–j = $-CH_3$

Scheme-I

Antifungal activity :

The antfungal activity of the ten title compounds (III*a-j*) and their precursors thioureas (II*a-j*) were evaluated against the fungi *Puccinia recondita* and *Ustilagonuda var. maydis* at 1000, 100 and 10 ppm concentration. Dithane M-45 a standard commercial fungicide, was also tested under similar conditions for comparing the results.

All the compounds were more active against *Ustilagonuda. var. maydis* as compared with *Puccinia recondita*. Most of the compounds showed the significant antifungal activity at 1000 ppm against both the fungal species but their toxicity decreased markedly on lower concentration (100 & 10 ppm). The compounds II*a*, III*b*, & IV*c* exhibited fungitoxicity of the order of Dithane M-45 at 1000 ppm against both the test fungi. Their activity decreased markedly at lower concentrations (100 & 10 ppm) except in case of the compounds III*b*, which inhibited 42-44% growth of both the fungal species even at 10 ppm concentration.

Experimental

Melting point were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin Elemer spectrophotometer (cm^{-1}) and PMR spectra in $CDCl_3$ were recorded on a EM 360L (60 MHz) ^{1}HNMR spectrometer using TMS as internal standard using TMS as internal reference (chemical shifts in δ ppm).

Synthesis of 2-amino-4,5,6,7-tetrahydrobenzothiazole (I) :

Freshly distilled 2-chlorocyclohexanone

(0.03 mol), thioureas (0.03 mol) and ethanol (30 ml) was refluxed on a steam bath for 10 hours. Solvent was removed under reduced pressure and the residue (hydrochloride salt) allowed to cool. It was washed with a small volume of ether to remove any unreacted Ketone and neutralized by aqueous NH_3 solution and allowed to stand till a solid product (free base separated out). The product was recrystallized from ethanol as colourless needles, yield, 3.3 gm, 70% of theory. Similarly condensation of 2-bromo-6-methylcyclohexanone with thioureas in boiling 15 hours gave 2-amino-4-methyl-4,5,6,7-tetrahydrobenzothiazole yield 69% of the theory.

Synthesis of N^1-Aroyl-N^3-(4,5,6,7)-tetrahydrobenzothiazole-2-yl) thioureas (IIa-j) :

A mixture of NH_4SCN (0.12 mol) and aroyl halides (0.12 mol) in acetone (160 ml) was heated under reflux for half hours followed by addition of powered 2-amino-5-phenyl-1,3,4-thiadiazole (0.12 mol) and the mixture was further refluxed for 2 hours. The excess of acetone was evaporated and ice cold water was added to the residue. The product thus precipitated was washed with NH_4OH followed by water and recrystallized from ethanol acetone mixture.

Table1. Characterization data of N^1-Aroyl-N^3-(4,5,6,7)-tetrahydrobenzothiazole-2-yl) thioureas(II*a-j*)

Compd. No.	Ar group	R group	Yield (%)	M.P. (^{0}C)
II*a*[*]	C_6H_5	H	72	150
b	2-ClC_6H_4	H	73	162
c	4-ClC_6H_4	H	75	166
d	p-FC_6H_4	H	71	187
e	p-$CH_3C_6H_4$	H	76	183
f[**]	C_6H_5	CH_3	72	172
g	2-ClC_6H_4	CH_3	71	182
h	4-ClC_6H_4	CH_3	74	186
i	p-FC_6H_4	CH_3	75	190

[*] IR(KBr) : 1635 (cyclic N-H), 1665 (C=O), 1620 (C=N), 1225 (C=S) cm^{-1}

[**] IR (KBr) : 3285 (N-H), 1660 (C=O), 1620 (C=N), 1220 (C=S) cm^{-1}

Synthesis of 5-aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5]-triazine-3-thione (IIIa-j) :

N^1-aroyl-N^3-(4,5,6,7-terahydrobenzothiazoles-2-yl)-thioureas (0.015 mol) was refluxed with a mixture of $POCl_3$ (15 ml) and PCl_5 (3.1 gm, 0.015 mol) for 3 hours. The excess of $POCl_3$ was removed under reduced pressure and crushed ice was added to the residue. The product thus precipitated was filtered, washed with water and recrystallized from ethanol.

Table 2. Characterization data of 5-aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5] -triazine-3-thiones (III*a-j*)

Compd. No.	Ar group	R group	Yield (%)	M.P. (^{0}C)
III*a*	C_6H_5	H	71	127
b	o-ClC_6H_4	H	73	133
c	p-ClC_6H_4	H	75	137
d	p-FC_6H_4	H	71	131
e*	p-$CH_3C_6H_4$	H	74	124
f**	C_6H_5	CH_3	77	132
g	o-ClC_6H_4	CH_3	74	137
h	p-ClC_6H_4	CH_3	78	142
i	p-FC_6H_4	CH_3	76	148
j	p-$CH_3C_6H_4$	CH_3	74	156

* IR(KBr) : 1635 (cyclic C=N), 1100 (C=S), 1375 (C–S–C) cm^{-1}

^{1}HNMR (DMSO-d_6) δ : 2.2 (3H, s, –CH_3); 7.2–8.2 (4H, m, Ar–H), 1.7-1.9 (4H, m, 5 & 6 CH_2), 2.65-2.45 (3H, m, 4 & 7 CH_2)

** IR (KBr) : 1632 (cyclic C=N), 1220 (C=S), 1365 (C–S–C) cm^{-1}

^{1}HNMR (DMSO-d_6) δ : 2.3 (3H, s, –CH_3); 7.3–8.1 (5H, m, Ar–H)

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References

1. N. Anand, *Burgers Medicinal Chemistry,* Ed. M.B. Wolf, (Wiley-Inter Science), New York (1979).
2. P.K. Sharma, S.N. Shawhney, A. Gupta, G.B. Singh and S. Ravi, *Indian J. Chem.; 37B,* 371 (1998).
3. S. Uingkar, A.S. Badade, B.G. Khadse, *Indian Journal of Heterocyclic Chemistry, 11(1),* 35-38 (2001).
4. K. Brown, J.F Cavalla, D. Green and A.B Wilson; *Nature* (London), *219,* 164 (1968).
5. B.S. Ganguli, B. Singh and P.S. Fernandes; *Indian J. Heterocyclic Chem., 3,* 269 (1994).
6. J.G. Horsefall and S. Rich, Contribs., Boyce Thompson Inst., *16,* 361 (1951).