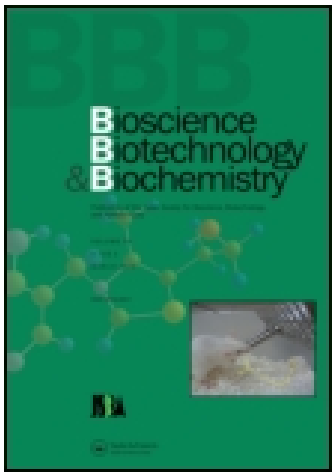

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Synthesis and Fungicidal Activity of Some 5-Membered Heterocyclic Derivatives Containing Benzimidazoles

Lallan Mishra[a], V. K. Singh[a], N. K. Dubey[ab] & A. K. Mishra[ab]
[a] Department of Chemistry, Banaras Hindu University, Varanasi 221005, U.P., India
[b] Department of Botany, Banaras Hindu University, Varanasi 221005, U.P., India
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Note

Synthesis and Fungicidal Activity of Some 5-Membered Heterocyclic Derivatives Containing Benzimidazoles

Lallan MISHRA,† V. K. SINGH, N. K. DUBEY,* and A. K. MISHRA*

*Department of Chemistry and * Department of Botany, Banaras Hindu University, Varanasi 221005, U.P., India*

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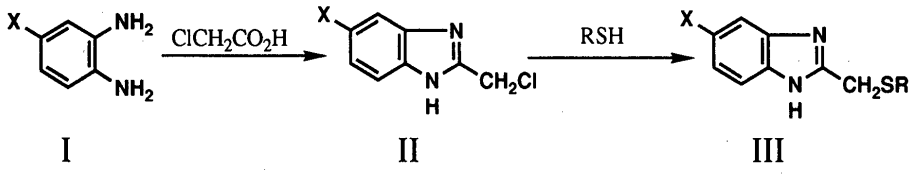
2-Chloromethyl-5*H*/methyl benzimidazoles were condensed with different 2-substituted 5-mercapto-1,3,4-oxadiazoles and thiadiazoles, and 4-amino 2-substituted 5-mercapto-1,2,4-triazoles. The synthesized compounds were characterized and evaluated for their fungicidal activities, and few were found to be better fungicides than those commercially used.

Biologically significant heterocyclic compounds bearing three atoms in the ring, *viz.* 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and 1,2,4-triazoles, have already been well documented in the literature.[1-3] Additionally, the synthetic utility of benzimidazole derivatives for building the various organic heterocycles and for better chemotherapeutic agents has also been reported in the literature.[4] Combining these facts with our interest in the study of various condensed heterocyclic compounds,[5,6] an attempt was made to condense the benzimidazole derivatives with 5-mercapto oxadiazoles, thiadiazoles and triazoles, and to evaluate their fungicidal activity.

All melting point (mp) values were measured by the open capillary method and are uncorrected. NMR spectra were recorded with a JEOL FX 90Q FT NMR spectrophotometer, using TMS as an internal standard in DMSO-d_6. IR spectra were measured with a Perkin Elmer model 783 in potassium bromide.

3-Substituted-5-mercapto-1,2,4-triazoles and 2-substituted-5-mercapto-1,3,4-oxadiazoles/1,3,4-thiadiazoles were prepared according to the procedure in the literature.[7]

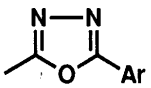
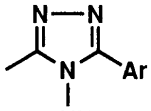
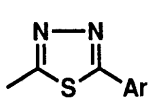
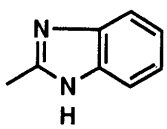
4-Amino-3-substituted-5-(5*H*/methyl benzimidazol-2-yl-methyl)-thio-1,2,4-triazoles and 2-substituted-5-(benzimidazol-2-yl-methyl)-thio-1,3,4-oxadiazoles/1,3,4-thiadiazoles were prepared by the method reported in the literature,[8] whereby a mixture of 2-chloromethyl-5*H*/methyl benzimidazoles and the respective 2-substituted-5-mercapto-1,3,4-thiadiazoles/1,3,4-oxadiazoles and 4-amino-3-substituted- 5-mercapto-1,2,4-triazoles in a 1 : 1 molar ratio (1 mmol each) was refluxed in pyridine (10–15 ml) for 3–4 h (Sheme). The products thus obtained were poured into ice-cold water (100–150 ml), and the resulting solid materials were then washed and recrystallized from ethanol (10–20 ml). The yield was 45–65%. 2-(Benzimidazol-2-yl-methyl)-thiobenzimidazole similarly prepared was purified by recrystallizing from ethanol. The purity of each compound was checked by TLC, using chloroform/acetone as a solvent. The compounds thus prepared



I II III

Scheme. Preparation of Benzimidazole Derivatives.

Table I. Benzimidazole Derivatives

Compound no.	X	R	Ar	mp (°C)	Compound no.	X	R	Ar	mp (°C)
1	H		Ph	166[d]	**15**	H		Ph	178–179
2	H		4-ClPh	180[d]	**16**	H		4-ClPh	204–206
3	H		2-ClPh	168[d]	**17**	H		2-ClPh	194–195
4	H		3-ClPh	162[d]	**18**	H		3-ClPh	186
5	H		4-pyr	248[d]	**19**	H		4-pyr	146–148
6	Me		Ph	162[d]	**20**	Me		Ph	242
7	Me		4-ClPh	185[d]	**21**	Me		3-ClPh	185
8	H		Ph	153					
9	H		4-ClPh	162					
10	H		2-ClPh	153	**22**	Me			108[d]
11	H		3-ClPh	160					
12	H		4-Pyr	160					
13	Me		Ph	158					
14	Me		3-ClPh	162					

ClPh, chlorophenyl; pyr, pyridyl; d, decomposition.

† To whom correspondence should be addressed.

are depicted in Table I and gave satisfactory elemental analysis results.

To test the antifungal properties, cultures of the test fungi *Rhizoctonia solani* and *Helminthosporium oryzae* were maintained in a potato dextrose agar medium. A 10 ml portion of the potato dextrose agar medium was supplemented separately by the requisite amount of each compound (in acetone) to give a final concentration of 500 ppm (w/v), and the fungitoxicity was tested by the poisoned food technique.[9] The final disc cut from the periphery of a seven-day-old culture of the test fungi was inoculated separately in each set. Controlled sets containing only the potato dextrose agar medium were similarly prepared. The percentage inhibition of growth of the fungi in each treatment set was calculated by the formula reported earlier.[10]

Commercially available fungicides, *i.e.*, Dithane M-45 (mancozeb), Agrasan G.N. (phenylmercury acetate), Ceresan (unspecified mercury compounds), and Captan were also tested under similar conditions on the test fungi, and showed a percentage inhibition of 61–65% against *Helminthosporium oryzae* and 65–87% against *Rhizoctonia solani.*

IR spectra of the compounds showed characteristic peaks at 3180–3120 cm^{-1} due to ν_{NH}, in addition to peaks between 3400 and 3250 cm^{-1} due to ν_{NH_2} (only for the triazole series). The peaks observed at 1330–1300 cm^{-1} were assigned to a CH_2S group, whereas triazolyl, thiadiazolyl, oxadiazolyl and benzimidazolyl ring vibrations were observed in the 1010–950 cm^{-1} region.

NMR spectra of the compounds showed a peak at δ 8.8–8.9 ppm due to an NH proton. A high-field shift in position of this proton was observed in the spectra of those compounds bearing a 5-methyl benzimidazolyl group; this is consistent with the electron-releasing nature of the methyl group. The NMR signals originating from aromatic protons were observed in the range of 7.1–8.1 ppm. The protons of the NH_2 group in the triazolyl compounds appeared between 6.5 and 6.8 ppm. Protons of the CH_2S group in all compounds appeared at δ 4.8 ppm, except in the case of the triazolyl compounds, where it was shifted towards a lower field at 5.8 ppm due to the presence of the NH_2 group at the 4-position of the triazole ring. The substituents at the 3-position of the heterocycles did not affect the chemical shift of the CH_2S protons, even in the presence of electron-withdrawing groups.

Compounds 4 and 11 bearing an *m*-chlorophenyl group at the 2-position of the oxadiazolyl and thiadiazolyl rings, in contrast to their phenyl, *o*-chlorophenyl and *p*-chlorophenyl analogues (Table II), were observed to be better fungitoxicants, and heterocycles bearing triazolyl rings also showed potent activity when the phenyl or *m*-chlorophenyl group was present at the 3-position of the ring (**15** and **18**). It can also be seen from Table II that, with compounds bearing an 1,3,4-oxadiazolyl ring, substitution of the *p*-chlorophenyl group at the 2-position decreased the activity when there was no methyl group at the 5-position of the benzimidazolyl group. However, compound 7 bearing a *p*-chlorophenyl group at the 2-position of the oxadiazole ring and a methyl group at the 5-position of the benzimidazole ring showed maximum activity (100% inhibition) toward both of the fungi at 500 ppm.

Thus, the antifungal activity with respect to the structure can generalized as follows: (i) The balance of overall electron density present on both the heterocyclic rings was responsible for the activity. If one ring bears an electron-withdrawing group and the other bears an electron-releasing group, the activity would tend to be a maximum, as seen in the case of compound **7.** However, this generalization calls for a deeper study of electron density calculations to make a quantitative case for all rings. (ii) Keeping the benzimidazole group constant, attachment of the 1,3,4-oxadiazole ring enhanced the antifungal activity, perhaps due to its significant interaction with amino acids in the light of the recent report by Saegusa *et al.*[11] The nature of each fungus is, of course, also responsible for the activity.

The compounds were also tested for their insecticidal activity against *Musca domestica*, *Spodoptera litura*, *Tetranychus cinnabarinus*, and *Cules pipions pallens*, but none of them showed much activity, except for slight inhibition toward emerging mosquito larvae (*Culex pipiens pallens*) at 3–5 ppm. Similarly, none of the compounds showed any herbicidal activity in either pre-emergence, post-emergence or paddy conditions toward *J. millet*, *Oats*, *morning glory*, *velvet leaf* (pre- and post-emergence), nor toward *rice*, *barnyard grass*, *hard stem bulrush* and *arrow head.*

Apart from the antifungal activity toward *R. solani* and *H. oryzae*, all the screening tests were performed at the Takarazuka Research Centre of Sumitomo Chemical Co., Ltd. (Hyogo 665, Japan) by courtsey of Dr. Hiroko Yamazaki.

Table II. Antifungal Activity† of Each Compound at 500 ppm

Compound no.[a]	Percentage inhibition of growth	
	H. oryzae	*R. solani*
1	73.5	65.2
2	39.7	21.2
3	75.0	56.2
4	89.7	69.4
5	49.8	32.0
6	65.3	61.3
7	100.0	100.0
8	74.3	69.8
9	52.5	39.0
10	68.2	49.8
11	91.2	89.5
12	54.5	21.3
13	71.3	64.5
14	81.2	60.4
15	92.5	74.5
16	45.3	20.0
17	52.3	39.8
18	89.3	61.2
19	30.0	29.3
20	81.2	70.5
21	82.5	71.2
22	81.3	61.3

[a] Compound numbers are the same as those shown in Table I.
† Activity is within the ±5% range.

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