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Research Article

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Design and Synthesis of Novel (3-(2,2-Dihaloethenyl)-2,2-Dimethylcyclo-Propyl)(1H-1,2,4-Triazol-1-yl)Methanone Compounds with Fungicidal Activity

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ABSTRACT

Fungicide resistance has created a challenge for the agrochemical industry to discover and commercialize novel molecules or newer modes of action. Bearing in mind the characteristic indicators of the known Triazole fungicides, this study urged the synthesis of novel compounds. In the present study, the active 1,2,4-triazole moiety and the carbonyl group of 3-(2,2-dihaloethenyl)-2,2-dimethylcyclopropane carboxylic acids were combined to synthesize novel compounds. The structural data was elucidated on the basis of spectral and analytical data. These novel compounds were screened for their fungicidal activity. The results show promising antifungal activity displayed by these novel compounds.

Keywords: 1,2,4-Triazoles; Dihaloethenyl-2,2-dimethylcyclo propane derivatives; Antifungal activity

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INTRODUCTION

Fungicides are the most important micro biocides which take care of the fungi that affect the crops. They are either chemically synthesized compounds or biological agents that protect the crops or plants by inhibiting the growth of fungi or the fungal spores. They are used in agriculture or are used to treat fungal infections in animals. Many chemical classes of compounds were introduced during the period 1945 to 1970 [1,2]. Triazoles are one of the important classes of fungicides used to prevent fungal growth on turf grass, agricultural crops and for crop protection. 1,2,4-Triazole is an important class of heterocyclic ring which shows antibactericidal, insecticidal and fungicidal activities. It consists of numerous members, such as cyproconazole, epoxyconazole, flusilazole, flutriafol, metconazole, myclobutanil, propiconazole, prothioconazole, tebuconazole, and tetraconazole. The mode of action of these fungicides is the inhibition of C14-demethylase enzyme which plays an important role in sterol production. This results in the abnormal fungal growth leading to death of the fungus [3-7]. Structures of some of the commercially available triazole fungicides are shown in Table 1.

Recently, a series of novel amide derivatives containing 1,2,4-triazole moiety were synthesized and characterized [8]. The compounds were the derivatives of 1-(2,4-dichlorophenol)-3-aryl-2-(1*H*-1,2,4-triazol-1-yl) prop-2-en-1-one. These compounds showed antifungal and antibacterial activities. They exhibited high inhibitory activity against the plant fungi *Pellicularia sasakii*, and *Gibberella zeae* and bacteria *Ralstonia solanacearum.*

The performance of some or most of the fungicides have been affected at some stage or the other. Use of a particular fungicide over and over again for a long time on the crops gives rise to resistance of the fungal pathogens towards that type of fungicide or drugs. Resistance pathogens and residue problems cause negative impact on the environment and have become major problem worldwide. It is therefore necessary to design new compounds which are used in fewer amounts [9]. The introduction of new and innovative fungicides is an essential element to provide

sustained control of major crop disease [10]. The new molecules should be discovered by either within the established mode of action or with newer modes of action.

Design of Novel Compounds

The present study reports the synthesis of new 1,2,4-triazole compound which show fungicidal activity. Considering the structural similarity and the characteristic symptoms of the known Triazole fungicides, this study prompted the preparation of novel compounds. The synthesis involves the 3-(2,2-dihaloethenyl)-2,2-dimethyl cyclopropane carboxylic acid derivatives as one of the starting material which reacts with sodium 1,2,4-Triazole to form novel compounds. The halogens are known to enhance the fungicidal activity of the compounds.

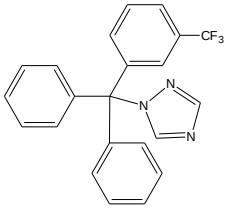
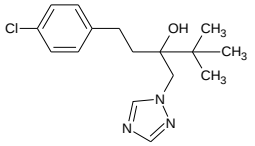
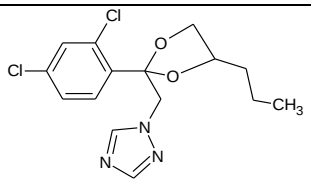
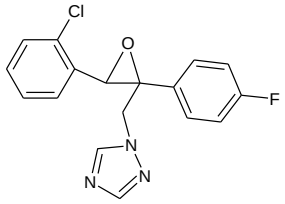
Common name	Chemical name	Structure	Reference
Fluotrimazole	1-(3-trifluoro methyl)-1H-1,2,4-trizole		[4]
Tebuconazole	(RS)-1-p-chlorophenyl-4,4-dimethyl-3-(1H-1,2,4-triazol-1-yl methyl)pentan-3-ol		[5]
Propioconazole	1-((2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl)methyl)-1H-1,2,4-triazole		[6]
Epoxiconazole	1-(((2R,3S)-3-(2-chloro phenyl)-2-(4-fluorophenyl)-2-oxiranyl) methy)-1H-1,2,4-triazole		[7]

Table 1: Structures and names of some of the commercially available triazole fungicides

EXPERIMENTAL SECTION

Materials and Reagents

Commercially available 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane carboxylic acid and 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid were procured from a regional agrochemical company. Potassium carbonate and 1,2,4-Triazole were obtained from Hi-Media. The reagents and solvents used were of analytical grade and were used without further purification.

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel GF254 plates using UV/Iodine as visualizing agent and Merck's silica gel (60-120 mesh) was used for column purification. Nuclear Magnetic resonance (NMR) spectra of the synthesized compounds were obtained using Varian Mercury plus spectrophotometer (USA) at 300 MHz using $CDCl_3$ as a solvent and tetramethyl silane (TMS) as an internal standard. The chemical shifts are reported in ppm (δ units) downfield from TMS. The coupling constants are reported in Hz. NMR spectra was recorded in SAIF-IIT Mumbai, Powai. Infrared spectra were recorded on FT-IR, Nicolet iS5 from Thermoscientific. The solid samples were prepared by using KBr pellets method and liquid samples by diluting with CCl_4. IR spectra were recorded in Research Department of Chemistry-B.

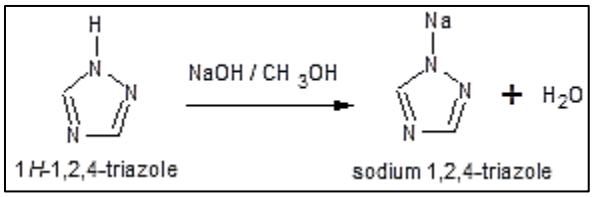
N. Bandodkar college of Science, Thane. All the conversions and yields were rounded up to the nearest significant value.

Methods

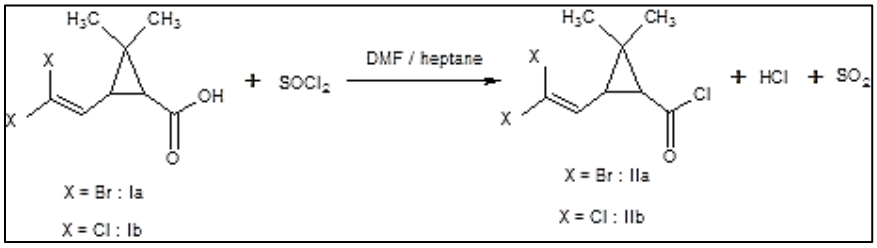
All reactions were done in a three neck round bottom flask with magnetic stirrer bar, condenser and thermometer pocket in a heating water bath and a magnetic stirrer. Sodium 1,2,4-triazole was prepared by reacting 1,2,4-Triazole with sodium hydroxide in methanol as a solvent. The solvent is completely evaporated to give the sodium salt (Scheme 1). The general process for producing (3-(2,2-dihaloethenyl)-2,2-dimethylcyclopropyl)(1*H*-1,2,4-triazol-1-yl)methanone involves the formation of the acid chlorides (Scheme 2) of the 3-(2,2-dihaloethenyl)-2,2-dimethylcyclopropane carboxylic acids and their reaction with sodium 1,2,4-triazole (Scheme 3).

Synthesis of Compounds

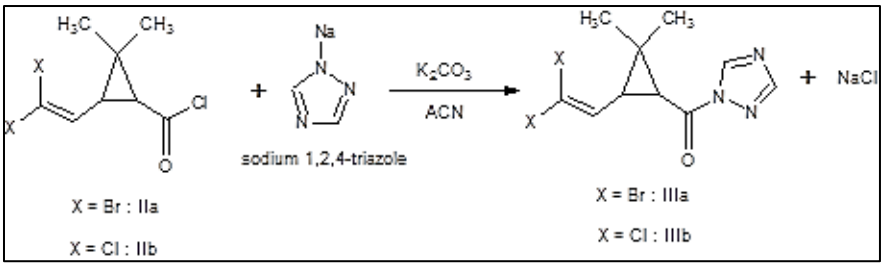
The general route for the synthesis of the novel 1,2,4-triazole compounds is outlined in Schemes 1-3.



Scheme 1: General synthetic route for preparation of sodium 1,2,4-triazole



Scheme 2: General synthetic route for preparation of 3-(2,2-dihaloethenyl)-2,2-dimethylcyclopropane-1- carbonyl chloride



Scheme 3: General synthetic route for preparation of (3-(2,2-dihaloethenyl)-2,2-dimethyl cyclopropyl)(1H-1,2,4-triazol-1-yl)methanone

Sodium 1, 2, 4-Triazole

Methanol (15 ml) and 1-H-1,2,4-triazole (6.9 gm) were charged at room temperature into a 100 ml 2-neck round bottom flask equipped with a magnetic stirrer, thermometer pocket and a condenser and the reaction mixture was cooled to 0-5°C while stirring for 10-15 minutes. A hazy solution was obtained. A clear solution of the NaOH (4 gm) in methanol (30 ml) was slowly added to the reaction mixture over a period of 20 minutes. After addition, the reaction mixture was stirred for 1 hour at 10°C and then heated to 60°C to remove methanol under vacuum. Subsequently, the product was dried under vacuum at 40°C for 4-5 hours to get a white solid (9 gm).

Compound IIa:

3-(2,2-dibromoethenyl)-2,2-dimethylcyclo propane-1- carbonyl chloride (Scheme 2). A solution of heptane (10 ml), 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane carboxylic acid (Ia, 0.01moles, 2.98 gm), thionyl chloride (0.03 moles, 2.2 ml) and DMF (3-4 drops) were heated to 60°C. Evolution of gas was observed on heating. The reaction mass was stirred at 60°C for a period of 3 hours. During this time the reaction mass is a clear slightly brownish

solution. Reaction progress was monitored by TLC using the solvent system 10% ethyl acetate in hexane. After completion of the reaction, the reaction mixture was cooled to 40°C and the solvent was distilled out under vacuum completely to procure the compound 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane-1- carbonyl chloride (IIa) which was then used as it is for further reaction.

Compound IIIa:
(3-(2,2-dibromoethenyl)-2,2-dimethylcyclo propyl)(1H-1,2,4-triazol-1-yl)methanone (Scheme 3). A thin slurry of acetonitrile (20 ml), sodium 1,2,4-triazole (0.51 g) and potassium carbonate (0.35 g) were stirred for a period of 15 minutes at 25-30°C. A solution of 3-(2, 2-dibromoethenyl)-2, 2-dimethylcyclopropane carbonyl chloride IIa (1.58 g) in acetonitrile (5 ml) was slowly added to the above slurry over a few minutes and the reaction mass was stirred for 1 hour. The reaction progress was monitored by TLC using hexane: ethyl acetate in the ratio (90:10) to check the completion of reaction. After completion of reaction, the reaction mass acidified by adding 2 N hydrochloric acid to it and the pH was adjusted to 2. The slurry was extracted with dichloromethane. The two layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate and concentrated to get white solids (1.4 g). Melting point: 82°C.
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.357 (s, 3H); δ 1.407 (s, 3H); δ2.37 (t, 1H); δ 3.25 (d, 2H); δ 6.81 (d, 1H); δ 8.04 (s, 1H); δ 8.89 (s, 1H). IR: 1712, 1508, 1052, 665 cm^{-1}. Mass spectra: The molecular ion peak $(M+H)^+$ appears at 350.

Compound IIb:
3-(2,2-dichloroethenyl)-2,2-dimethylcyclo propane-1-carbonyl chloride (Scheme 2). A solution of heptane (10 ml), 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (Ib, 2.09 g), thionyl chloride (2.2 ml) and DMF (3-4 drops) were heated to 60°C. Evolution of gas was observed on heating. The reaction mass was stirred at 60°C for a period of 3.5 hours. During this time the reaction mass is a clear slightly brownish solution. Reaction progress was monitored by TLC using the solvent system 10% ethyl acetate in hexane. After completion of the reaction, the reaction mixture was cooled to 40°C and the solvent was distilled out under vacuum completely to procure the compound 3-(2,2-dichloromoethenyl)-2,2-dimethylcyclopropane-1- carbonyl chloride (IIb) which was then used as it is for further reaction.

Compound IIIb:
(3-(2,2-dichloroethenyl)-2,2-dimethylcyclo propyl)(1H-1,2,4-triazol-1-yl)methanone (Scheme 3). A thin slurry of acetonitrile (20 ml), sodium 1,2,4-triazole (0.51 g) and potassium carbonate (0.35 g) were stirred for a period of 15 minutes at 25-30°C. A solution of 3-(2, 2-dichloroethenyl)-2, 2-dimethylcyclopropane carbonyl chloride IIb (1.14 g) in acetonitrile (5 ml) was slowly added to the above slurry over a few minutes and the reaction mass was stirred for 1 hour. The reaction progress was monitored by TLC using hexane: ethyl acetate in the ratio (90:10) to check the completion of reaction. After completion of reaction, the reaction mass acidified by adding 2N hydrochloric acid to it and the pH was adjusted to 2. The slurry was extracted with dichloromethane. The two layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate and concentrated to get white solids (1.0 g). Melting point: 90°C.
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.381 (s, 3H); δ 1.431 (s, 3H); δ2.47 (t, 1H); δ 3.24 (d, 2H); δ 6.32 (d, 1H); δ 8.04 (s, 1H); δ 8.9 (s, 1H). IR: 1710, 1728, 1520, 1409, 809 cm^{-1}. Mass spectra: The molecular ion peak $(M+H)^+$ appears at 260.

Antifungal Activity
The Zone of Inhibition method was used for testing the antifungal activity of the synthesized novel triazole compounds IIIa and IIIb.

Materials
Commercially available Nutrient Agar, Agar powder, distilled water, sodium chloride, absolute ethanol and Ketoconazole antibiotic KT30 were obtained from Hi-Media. White coloured fungus growing on Papaya fruit (Carica papaya) was used for the efficacy studies. Approximately 1 gram of the white coloured fungus was removed carefully with the help of a sterilized spatula and added to brine solution (0.875%).

Preparation of the Discs
Compounds IIIa and IIIb were dissolved in DMSO solvent to prepare solutions of 2 mg/ml concentration. Sterilized discs (6 mm) prepared from Whatmann no 1 filter paper were impregnated with these solutions of the compounds.

Sterilized discs of 6 mm were prepared by impregnating them with DMSO which was used as a control. Ketoconazole discs (2 mg/disc) were obtained from Hi-Media served as a positive control.

Preparation of Nutrient Agar Plates

Agar media was prepared by dissolving Nutrient Agar (2.8 gm), Agar powder (1.5 gm) in distilled water (100 gm) to make a clear solution. This agar solution (15-20 ml) was dispensed to petri dishes with covers and sterilized. The petri dishes were inoculated with 0.5 mL of inoculum which was prepared as described earlier, by using sterile pipette, taken from seven day old culture of fungus. The discs of compounds IIIa and IIIb were distributed on the petri dishes. Discs prepared with DMSO served as a control while those with ketoconazole (2 mg/disc) served as positive control. The petri dishes were kept in the autoclave at 27-30°C for three days. All the tests were carried out in duplicate.

RESULTS AND DISCUSSION

Synthesis and Characterization

To summarize, novel triazole compounds were prepared in good yields by a simple and practical process and their fungicidal activity was studied. The structure of new compounds IIIa and IIIb were confirmed by recording IR, ^{1}H NMR and mass spectra. The IR spectra of the novel compounds showed the disappearance of the strong peak of C=O in the acid compound Ia and Ib at 1680 cm^{-1}. The formation of compound IIIa and IIIb was proved by the presence of characteristic strong peak of the C=O at 1710 cm^{-1} of the amide group and C-N bond stretching and bending vibrations at 1508 and 1408 cm^{-1}.

The formation of the compound IIIa from the corresponding carboxylic acid chloride (IIa) was confirmed in the NMR spectra by the appearance of two proton singlets at 8.89 ppm and 8.03 ppm which are characteristic of an N-substituted 1,2,4-triazole. The three protons of each methyl appear as singlets in the region of 1.357 ppm and 1.407 ppm. The signal due to vinyl proton appears as a doublet in the region at 6.81 ppm and the proton next to the carbonyl group appears as a doublet at 3.25 ppm. Finally the other proton attached to the cyclopropyl ring appears as a triplet at 2.37 ppm as it couples with the protons of the neighbouring carbon atoms.

The mass spectrum of IIIa showed molecular ion peak at m/z = 350.

The formation of the compound IIIb from the corresponding carboxylic acid chloride was confirmed in the NMR spectra by the appearance of two proton singlets at 8.9 ppm and 8.04 ppm which are characteristic of an N-substituted 1,2,4-triazole.

The three protons of each methyl appear as singlets in the region of 1.381 ppm and 1.431 ppm. The signal due to vinyl proton appears as a doublet in the region at 6.32 ppm and the proton next to the carbonyl group appears as a doublet at 3.24 ppm. Finally the other proton attached to the cyclopropyl ring appears as a triplet at 2.47 ppm as it couples with the protons of the neighbouring carbon atoms.

The mass spectrum of IIIa showed molecular ion peak at m/z = 260.

Fungicidal Efficacy

Antifungal activity of the synthesized compounds on papaya fruit fungus was evaluated by the zone of inhibition method using impregnated discs. Compounds IIIa and IIIb showed a zone of inhibition confirming the antifungal activity of these compounds. The data on measurement of the zone of inhibition in mm is listed in Table 2.

Compound	Zone of Inhibition in mm
Ketoconazole	25
Compound IIIa	10
Compound IIIb	15
DMSO disc	0

Table 2: Measurement of the zones of inhibition

The initial exploration of the fungicidal activity of the compounds (3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropyl)(1H-1,2,4-triazol-1-yl)methanone and (3-(2,2-dichloroethenyl)-2,2-dimethyl cyclopropyl)(1H-1,2,4-triazol-1-yl)methanone showed comparable fungicidal activity with respect to the known fungicide ketoconazole.

Stereochemistry of the Compounds

The novel synthesized compounds (IIIa and IIIb) have 2 chiral centres (C1 and C3); hence there are 4 isomers possible for these compounds. Also, due to the substituted cyclopropane ring structure, two geometrical isomers are present. There are two cis and two trans isomers for the compounds IIIa and IIIb. The possible stereoisomers of the compounds IIIa and IIIb are presented in Figure 1.

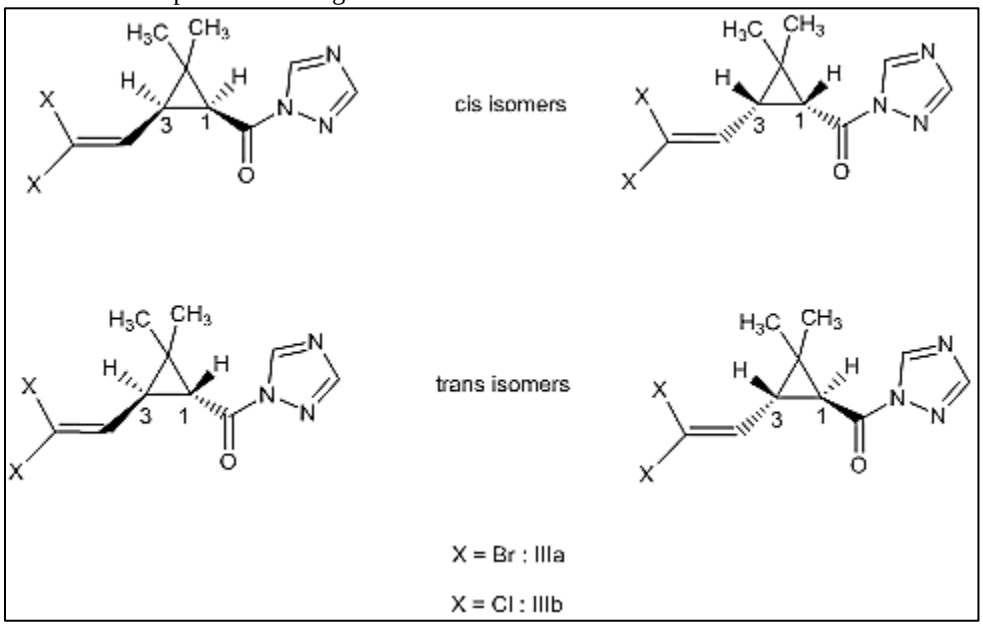


Figure 1: Isomers of compounds IIIa and IIIIb

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REFERENCES

[1] PE Russell. *Plant Pathol*. **2006**, 55, 585-594.
[2] M Vince; S Theodor. *American Phytophathol Society*. **2011**.
[3] M Montgomery; B Paulsrud. *Integrated Pest Management*. **2006**.
[4] G Jager; H Buchel. *Patent Bayer*. **1970**.
[5] G Holmwood; KH Buchel; K Lurssen; PE Frohberger; W Brandes. *Patent Bayer.* **1984**.
[6] VR Gustaaf; H Jan; W Lourens. *Patent Janssen Pharmaceutica*. **1975**.
[7] J Bernd; M Norbert; EP Heinrich; A Eberhard. *Patent BASF AG*. **1984**.
[8] R Tang; L Jin; C Mou; J Yin; S Bai; D Hu; J Wu; S Yang; B Song. *Chem Central J*. **2013**, 7, 30.
[9] D Sharma; B Narasimhan; P Kumar; A Jalbout. *European J Med C.* **2009**, 44, 1119-1127.
[10] L Andy. *Plant Protection Sci*. **2015**, 51, 4, 163-169.