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SYNTHESES AND ANTIFUNGAL ACTIVITY OF 3-ARYLMETHYL-5-ARYLOXYMETHYL-2-METHYLISOXAZOLIDINES

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Abstract

Reaction of sodium salt of allyl alcohol with 2-chloro-5-phenyl-1,3,4-thiadiazole gave 2-allyloxy-5-phenyl-1,3,4-thiadiazole **2**. Compounds **4a** and **4b** could be obtained through the reaction of nitrone **3** with **2**. Reaction of compound **2** with nitrone **5** afforded the final compound **6**. Antifungal activity of all compounds was less than ketoconazole.

Introduction

In recent years, systemic fungal infections in man have increased considerably. The population most sensitive to such infections are immunocompromised patients, such as acquired immune deficiency syndrome (AIDS) patients undergoing cancer chemotherapy and organ transplantation [1-3].

Since the discovery of the first antifungal azoles, namely, clotrimazole, miconazole and econazole [4], several effective azole derivatives, namely ketoconazole, itraconazole and fluconazole have been introduced [5-6] (Fig. 1).

In spite of the introduction of several novel antifungal agents, the number of available drugs with sufficient efficacy to treat mycoses remains limited. Therefore, we have decided to synthesize the title compounds as possible effective antifungal compounds. In this work, we studied the effect of arylmethyl in position 3 (compound 6) and aryloxymethyl in position 5 (compounds **4** and **4b**) on antifungal activity.

Keywords: Antifungal activity; Isoxazolidines; Syntheses of isoxazolidines

Results and Discussion

The common approach for the synthesis of isoxazolidine compounds is the 1,3,-dipolar cycloaddition reaction of ketonitrones with substituted double bonds [7-9]. The title compounds could be synthesized according to Scheme 1.

Reaction of allyl alcohol with 2-chloro-5-phenyl-1,3,4-thiadiazole in the presence of sodium afforded 2-allyloxy-5-phenyl-1,3,4-thiadiazole (**2**). 1,3-Dipolar cycloaddition of nitrone **3** with compound **2** in refluxing toluene yielded compound **4**. 1,3-Cycloaddition reaction of nitrone is thought to have a concerted mechanism. The regio and stereospecifity of the reaction is highly dependent on the structure of nitrone and dienophiles and involves both electronic and steric factors [10]. The regio and stereospecific 1,3-dipolar cycloaddition of nitrone **3** with compound **2** afforded predominantly the *cis* isomer **4**. The *trans* isomer of compound **4** could not be detected. The structure of compound **4** was determined by ^{1}H NMR spectroscopy. The difference (Δ) between the coupling constants J of H4A and H4B protons and the H_5 proton was 4.5 Hz for compound **4a** and 4.1 Hz for compound **4b** respectively. Similar values have been reported for similar compounds [11].

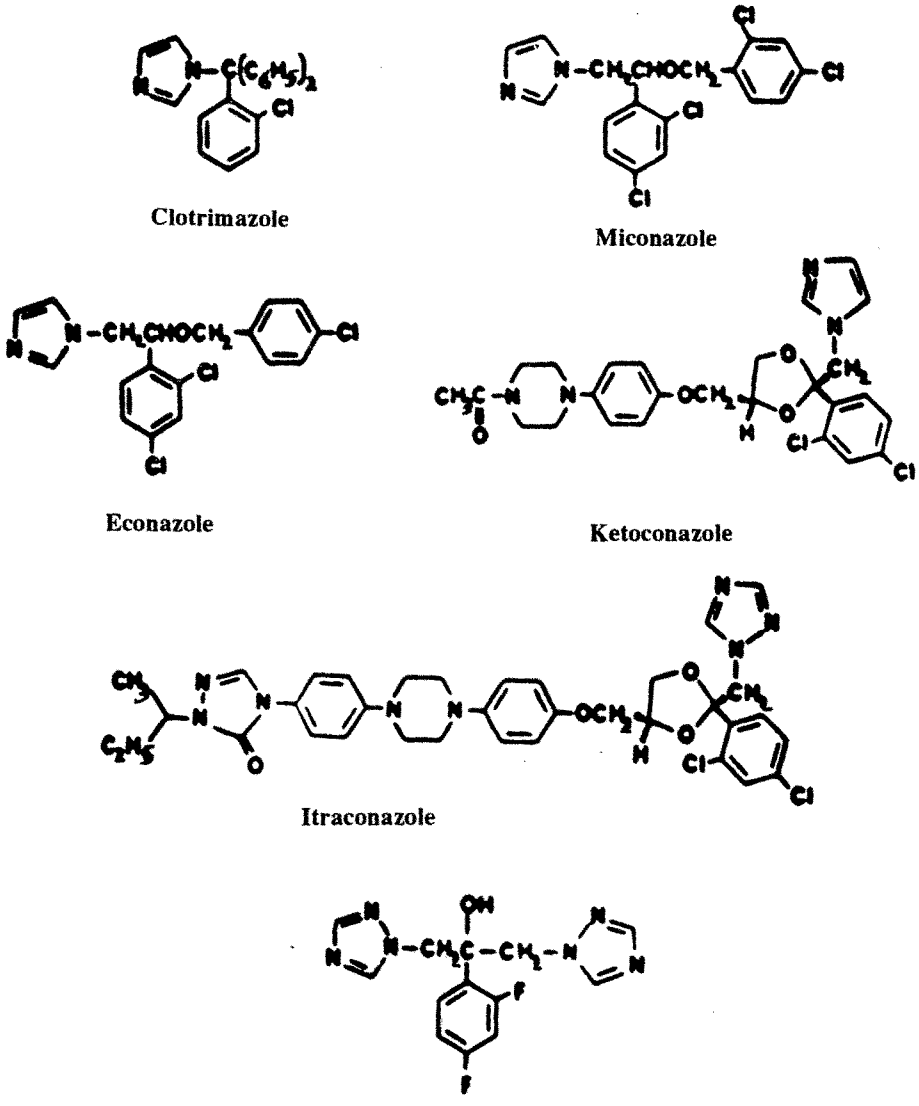


Figure 1

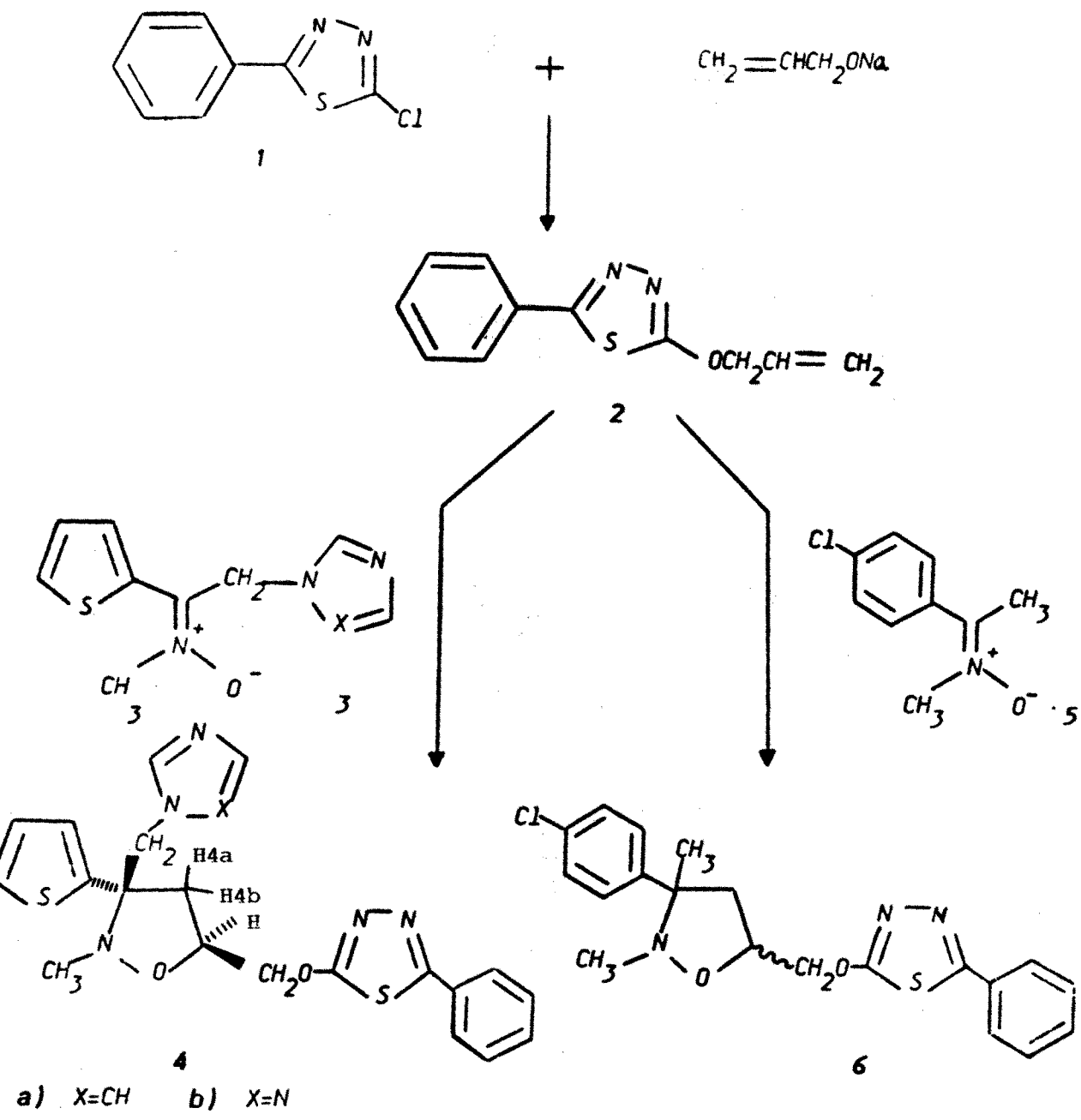
Reaction of N-[*p*-chlorophenylethylidene] methanamine N-oxide (**5**) [9] with compound **2** gave single compound **6**. The stereochemistry of compound **6** could not be determined since both hydrogens 4a and 4b appeared at 2.59 ppm as multiplet.

Antifungal Activity

Compounds **4** and **6** tested against *Candida albicans* (ATCC 10231) and *Aspergillus niger* (ATCC 16404). Ketoconazole was used for comparison. The *in vitro* antifungal activity was assayed in solid agar test and was measured as the minimum inhibitory concentration (MIC) value (Table 1).

Table 1. Antifungal activity of compounds **4** and **6** measured as the minimum inhibitory concentration (MIC, μg/ml)

Compound	*Candida albicans*	*Aspergillus niger*
4a	40	50
4b	>60	>60
6	inactive	inactive
Ketoconazole	20	10



Scheme 1

As can be seen from Table 1, all compounds were less active than ketoconazole. The inactivity of compound **6** demonstrates that the aryl at position 3 in isoxazole ring is required for activity. In addition, compounds **4a** and **4b** were less active than ketoconazole. This shows that phenylthiadiazole ring is not the best aryl group required for activity. Therefore, other aryl groups should be investigated in order to get more active compounds.

Experimental Section

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The UV spectra were recorded using a Perkin-Elmer Model 550 SE. The IR spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The ^{1}H NMR spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal

tetramethylsilane. The mass spectra were run on a Varian Model MAT-311 spectrometer at 70 eV.

2-Allyloxy-5-phenyl-1,3,4-thiadiazole (2)

To a stirring solution of allyl alcohol (11.6 g, 0.2 mole) in dry THF (50 ml) sodium wire (4.6 g, 0.2 atm g) was added. After the reaction was complete, 2-chloro-5-phenyl-1,3,4-thiadiazole (**1**, 9.83 g, 0.05 mole) [12] in THF (30 ml) was added dropwise. After the addition was complete, the stirring was continued for 2 hours. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel) using chloroform-petroleum ether (20: 80) as eluent to give 9.81 g (90%) of **2**; IR (KBr): 3030 (s), 1285 (s), 990 (s), 858 (s) and 743 (s), ^{1}H NMR ($CDCl_3$): 7.78 (m, 2H, aromatic), 7.45 (m, 3H, aromatic), 6.45 (m, 1H, CH=), 5.47 (m, 2H, CH_2=) and 5.07 ppm (d, 2H, OCH_2); ms: m/z (%) 218 (M^+, 80), 178 (12), 145 (10), 129 (91), 121 (100), 115 (81), 103 (37), 89 (14) and 77 (90).

***cis*-3-(1H-1-Imidazol-1-ylmethyl)-2-methyl-3-(2-thienyl)-5-(5-phenyl-1,3,4-thiadiazol-2-yloxymethyl) isoxazolidine (4a)**

A suspension of N-[2-(1H-imidazol-1-yl]-1-(2-thienyl) ethylidene] methanamine-N-oxide (**3**, 4.42 g, 0.02 moles) [9] and compound **2** (6.54 g, 0.03 mole) in toluene (100 ml) was refluxed under nitrogen for 72 hours. The mixture was filtered. The solvent was evaporated and the residue purified by preparative TLC using chloroform-methanol (98: 2) as eluent. The desired compound was crystallized from 2-propanol to give 3.51 g (40%) of **4a**; m.p. 181-183°; UV (CH_3OH): λ_{max} 283 (log ε = 4.28), 235 nm (log ε = 4.26); ^{1}H NMR ($CDCl_3$): 7.52 (m, 8H, aromatic), 6.90 (m, 3H, aromatic), 4.87 (m, 1H, H-C_5), 4.41 (s, 2H, CH_2N), 4.17 (m, 2H, CH_2O), 2.80 (dd, 1H, H-C_4, $J_{4,5}$ = 9.6 Hz, $J_{4a,4b}$ = 13.2 Hz), 2.55 (dd, 1H, H-C_4, $J_{4,5}$ = 5.1 Hz, $J_{4a,4b}$ = 13.2) and 2.45 (s, 3H, CH_3N); ms: m/z (%) 439 (M^+, 3), 395 (10), 317 (19), 313 (85), 221 (10), 176 (50), 177 (15), 161 (21) and 83 (100).

Anal. Calcd. for $C_{21}H_{21}N_5O_2S_2$: C, 57.40; H, 4.78; N, 15.95. Found: C, 57.53; H, 4.59; N, 15.78.

***cis*-3-(1-H-1,2,4-Triazol-1-ylmethyl)-2-methyl-3-(2-thienyl)-5-(5-phenyl-1,3,4-thiadiazol-2-yloxymethyl) isoxazolidine (4b)**

This compound was prepared similar to **4a** in 38% yield; m.p. 152-154° (ethyl acetate); UV (methanol): λ_{max} 285 (logε = 4.37), 236 nm (logε = 4.35), ^{1}H NMR ($CDCl_3$): 7.59 (m, 7H, aromatic), 6.85 (m, 3H, aromatic), 4.68 (m, 1H, H-C_5), 4.41 (s, 2H, CH_2N), 4.10 (m, 2H, CH_2O), 2.80 (dd, 1H, H-C_4, $J_{4,5}$ = 9.4, $J_{4a,4b}$ = 13.2 Hz), 2.72 (dd, 1H, H-C_4, $J_{4,5}$ = 5.3 Hz, $J_{4a,4b}$ = 13.2Hz)) and 2.49 (s, 3H, NCH_3); ms: m/z (%) 440 (M^+, 3), 358 (50), 223 (10), 218 (10), 121 (100), 82 (42) and 77 (35) and 83 (100).

Anal. Calcd. for $C_{20}H_{20}N_6O_2S_2$: C, 54.55; H, 4.55; N, 19.09. Found: C, 54.73; H, 4.69; N, 19.23.

3-(4-Chlorophenyl)-2,3-dimethyl-5-(5-phenyl-1,3,4-thiadiazol-2-yloxymethyl) isoxazolidine (6)

This compound was prepared similar to **4a** in 45% yield, m.p. 142-143° (ethyl acetate); UV (methanol): λ_{max} 220 (log ε = 4.66), 271 nm (log ε = 4.81); ^{1}H NMR ($CDCl_3$): 7.46 (m, 9H, aromatic), 4.60 (m, 1H, H-C_5), 3.66 (m, 2H, CH_2O), 2.59 (m, 2H, CH_2), 2.54 (s, 3H, CH_3N) and 1.25 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{20}ClN_3O_2S$: C, 59.78; H, 4.98; N, 10.46. Found: C, 59.63; H, 4.83; N, 10.58.

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