Syntheses of Some 3,5-Diaryl-4*H*-1,2,4-triazole Derivatives and their Antifungal Activity

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Abstract. Syntheses of a series of 3, 5-diaryl-4*H*-1, 2, 4-triazole derivatives are described. In this present work, 4-amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole(**1**) was converted to *N,N'*-bis[3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine(**2**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) in good yields by treatment with aldehydes OHC-C₆H₄-CHO and Ar-CHO respectively. The compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) were reduced with NaBH₄ to afford the corresponding compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediamine (**4**) and 3-phenyl-5-*p*-tolyl-4-[4-methyl benzylamino]-4*H*-1,2,4-triazole (**5**) respectively. The newly synthesized compounds were characterized by spectral and elemental analyses. All the synthesized compounds were tested for their antifungal activity against *P.oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum*.

Keywords: 1, 2, 4-Triazole, Benzoylhydrazone, Hydrazine hydrate, Antifungal activity.

Introduction

The chemistry of heterocyclic compounds continuously to be an explore field in the organic chemistry. The importance of triazole derivative lies in the field that these have occupied a unique position in heterocyclic chemistry due to their antimicrobial activity¹⁻³.

1, 2, 4-Triazoles and their derivatives represent one of the most biologically active classes of compounds, possessing a wide range of therapeutic properties⁴. In views of these observations and in continuation of our earlier work⁵⁻¹¹ on the syntheses of some 1,2,4- and 1,2,3- triazole derivatives, we now report the syntheses of some more triazoles derived from 4-amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole and their antifungal activity.

Compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) were obtained by the condensation of 4-amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole (**1**) with aldehydes OHC-C₆H₄-CHO and Ar-CHO in glacial acetic acid respectively. Compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediamine (**4**) and 3-phenyl-5-*p*-tolyl-4-[4-methyl benzylamino]-4*H*-1,2,4-triazole (**5**) were obtained from compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) by using NaBH₄ as a reducing agent.

Experimental

Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries and are uncorrected. IR spectra (KBr in cm⁻¹) were recorded on a Jasco FT-IR 5300 spectrophotometer and PMR spectra (DMSO-d₆) on a Varian EM-390 spectrometer using TMS as an internal standard (chemical shift in δ ppm). Mass spectra were recorded on a Jeol JMS-D 300 Mass spectrometer operating at 70 eV. The purity of the compounds was confirmed by TLC using silica gel G and purified by column chromatography. For TLC, Merck silica gel 60 G plate was used. For column chromatography, Merck silica gel 60 (0.063-0.200 mm) was used. The necessary chemicals were obtained from Merck and Fluka. All compounds showed satisfactory elemental analyses.

4-Amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole (**1**)

Ethyl *p*-methylbenzoate benzoylhydrazone (0.01 mol) was reacted with hydrazine hydrate (0.01 mol) in 40 mL of 1-propanol and the mixture was refluxed for 30 h. On cooling the mixture, separated crude product was filtered, dried, washed with 30 mL of benzene. The insoluble part in benzene was recrystallized from 1-propanol to yield the compound (**1**), (yield 85%), m.p. 284 °C, Anal.Calc. for C₁₅H₁₄N₄: C, 71.92; H, 5.54; N, 22.29%; Found: C, 72.02; H, 5.20; N, 22.56%. IR (KBr): 3344,3248 (NH₂), 1620 (C=N) and 825,767,695 cm⁻¹ (aromatic ring); PMR: δ 2.37 (1H,s,CH₃); 6.28 (2H,s, NH₂), 7.31 (2H,d, Ar-H), 7.49 (3H,m, Ar-H),7.97 (2H,d, Ar-H) and 8.11 ppm (2H,m, Ar-H); MS : *m/z* 209 (M⁺) other peaks were observed at 157,141,126,104,85,73 and 45 .

N,N'-Bis[3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**)

Compound (**1**) (0.01 mol) was reacted with corresponding aldehyde (OHC-C₆H₄-CHO) (0.01 mol) in 30 mL of glacial acetic acid and the mixture was refluxed for 5 h. On cooling the mixture, poured into a beaker containing 80 mL of ice water. The precipitate formed was filtered, dried and the product was recrystallized from acetic acid to yield the compound (**2**), (yield 85%), m.p. 305 °C, Anal.Calc. for C₃₈H₃₀N₈: C, 78.15; H, 5.78; N, 15.89%; Found: C, 77.98; H, 5.91; N, 15.91%. IR (KBr): 1598 (C=N) and 698cm⁻¹ (aromatic ring); PMR: δ 2.52 (6H,s,2CH₃); 7.32 (4H,d, Ar-H), 7.50 (6H,s, Ar-H), 7.72 (4H,d, Ar-H),7.81 (4H,m, Ar-H), 7.92 (4H,s, Ar-H) and 8.70 ppm (2H,s, C-H); MS : *m/z* 237 (M⁺) other peaks were observed at 189,169,131,116,83 and 48 .

3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**)

Compound (**1**) (0.01 mol) was reacted with corresponding aldehyde (Ar-CHO) (0.01 mol) in the presence of 30 mL of glacial acetic acid; was refluxed for 5 h. On cooling the mixture, poured into a beaker containing 80 mL of ice water. The precipitate formed was filtered, dried and the product was recrystallized from ethanol-water (1:1) to yield the compound (**3**), (yield 90%), m.p. 180 °C, Anal.Calc. for C₂₃H₂₀N₄: C, 78.28; H, 5.75; N, 15.92%; Found: C,

78.21; H, 5.93; N, 15.93%. IR (KBr): 1600 (C=N) and 695 cm^{-1} (aromatic ring); PMR: δ 2.35 (3H,s,CH₃), 2.45 (3H,s,CH₃), 7.32 (4H,d, Ar-H), 7.40 (4H,m, Ar-H), 7.70 (3H,m, Ar-H), 7.81 (2H,m,Ar-H), 7.95 (2H,m, Ar-H) and 8.60 ppm (1H,s, C-H); MS : m/z 239 (M⁺) other peaks were observed at 188,139,126,118, 96,79 and 41.

N,N'-Bis[3-phenyl-5-*p*-tolyl-4H-1,2,4-triazolyl]-1,4-xylenediamine (**4**)

The corresponding compounds (**2**) (0.01 mol) was dissolved in 60 mL of dried methanol and NaBH₄ (0.01 mol) was added in small portion of the solution. The mixture was refluxed for 30 min and then allowed to cool. After evaporation at 35 °C under reduced pressure, the solid residue was washed with cold water. After drying, the solid product was recrystallized from ethanol to yield the compound (**4**), (yield 85%), m.p. 325 °C, Anal.Calc. for C₃₈H₃₄N₈: C, 78.38; H, 5.88; N, 15.88%; Found: C, 77.58; H, 5.90; N, 15.89%. IR (KBr): 3306 (N-H), 1618 (C=N) and 819,768,731,692 cm^{-1} (aromatic ring); PMR: δ 2.52 (6H,s,2CH₃); 3.65 (4H, d, 2CH₂), 7.10 (2H,t, 2NH), 6.55 (4H,s, Ar-H), 7.39 (4H,m, Ar-H), 7.55 (6H,s, Ar-H) and 7.88 ppm (8H,m, Ar-H); MS : m/z 236 (M⁺) other peaks were observed at 199,159,129,126,96,76 and 47.

3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylamino]-4H-1,2,4-triazole (**5**)

The corresponding compounds (**3**) (0.01 mol) was dissolved in 60 mL of dried methanol and NaBH₄ (0.01 mol) was added in small portion of the solution. The mixture was refluxed for 30 minutes and then allowed to cool. After evaporation at 35 °C under reduced pressure, the solid residue was washed with cold water. After drying, the solid product was recrystallized from ethyl acetate to yield the compound (**5**), (yield 92%) m.p. 182 °C, Anal.Calc. for C₂₃H₂₂N₄: C, 77.84; H, 6.25; N, 15.87%; Found: C, 78.16; H, 6.18; N, 15.82%. IR (KBr): 3302 (N-H), 1616 (C=N) and 825,770,695 cm^{-1} (aromatic ring); PMR: δ 2.31 (3H,s, CH₃); 2.46 (3H, s, CH₃), 3.72 (2H,d,CH₂), 5.31 (1H,t, NH), 6.71 (2H,d, Ar-H), 6.95 (2H,d, Ar-H), 7.33 (2H,d, Ar-H), 7.51 (2H,m, Ar-H), 7.85 (4H,d, Ar-H) and 7.88 ppm (1H,m, Ar-H); MS: m/z 235 (M⁺) other peaks were observed at 179,149,129,116,89,75 and 51.

Antifungal activity

Four compounds were evaluated for their fungicidal activity against *P.oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum* at 1000 ppm, 500 ppm and 100 ppm concentrations, respectively by food poisoning of solidified agar technique¹²⁻¹⁴. The inhibitory activities were compared with commercial fungicide Griseofulvin (standard drug) under similar conditions. The mould cultures used were 7 days old. The results are presented in Table 1. The percentage inhibition after the incubation for 24, 48 and 72 h was calculated by following equation:

$$\text{Percentage inhibition} = (C-T) \times 100/C$$

Where, C= Diameter of Fungus colony (mm) in control plates

T= Diameter of Fungus colony (mm) in treated plates

It is obvious from the fungicidal screening results that the most of compounds have significant fungi toxicity at 1000 ppm against all of five fungi, but the fungi toxicity decreases considerably upon dilution. The result indicates that all these compounds showed very good activity against *P.oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum*. (Table 1). From the above observation it is clear that the 1, 2, 4-triazole derivatives are more active and play a prominent role in the antifungal activity.

Table 1. Evaluation of antifungal activity of the compounds.

Compd	Average percentage inhibition after 72 hours														
	<i>P. oryzae</i>			<i>B. cinerea</i>			<i>A. niger</i>			<i>C. albicans</i>			<i>T. rubrum</i>		
	1000	500	100	1000	500	100	1000	500	100	1000	500	100	1000	500	100
	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm	ppm
2	88	80	68	77	59	55	74	53	38	69	51	39	72	62	56
3	92	80	79	75	52	52	93	63	44	62	51	37	80	66	58
4	92	84	79	91	82	74	91	67	47	69	54	44	76	67	52
5	92	80	68	91	82	74	90	63	62	64	56	45	78	66	57
Standard (Griseofulvin)	100	84.6	66.3	99.4	84.6	71.0	98.8	84.6	71.0	99.6	84.6	68.3	99.8	82.5	71.0
Control	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00

Results and Discussion

Compound 4-amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole(**1**) required as a starting material was obtained in one pot reaction with ethyl *p*-methylbenzoate benzoylhydrazone and hydrazine hydrate. Compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-phenyl-5-*p*-tolyl-4-[4-methylbenzylidenamino]-4*H*-1,2,4-triazole (**3**) were obtained by the condensation of compound 4-amino-3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazole(**1**) with aldehydes OHC-C₆H₄-CHO and Ar-CHO in glacial acetic acid. In the reduction of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**), the formation of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediamine (**4**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylamino]-4*H*-1,2,4-triazole (**5**) were possible due to possibility of the reduction of the hetero ring. However, the reduction was performed on the imino group of compounds *N,N'*-Bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) without affecting the hetero ring by using NaBH₄ as the selective reducing agent. (Scheme 1)

All synthesized compounds containing 1,2,4-triazole moiety is more active and plays a prominent role in antifungal activity. The structures of all the compounds are confirmed by IR, PMR, & MS spectral data, and are further supported by correct elemental analyses. The IR spectra of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-phenyl-5-*p*-tolyl-4-[4-methylbenzylidenamino]-4*H*-1,2,4-triazole (**3**) showed characteristic absorption bands between 1575 and 1600 cm⁻¹ (C=N). The PMR characteristic signals of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediimine (**2**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylidenamino]-4*H*-1,2,4-triazole (**3**) were observed at δ 8.58-8.78 ppm (1H, s, N=CH). The IR spectra of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediamine (**4**) and 3-Phenyl-5-*p*-tolyl-4-[4-methyl benzylamino]-4*H*-1,2,4-triazole (**5**) showed characteristic absorption bands between 3200-3310 cm⁻¹(NH). The PMR characteristic signals of compounds *N,N'*-bis [3-phenyl-5-*p*-tolyl-4*H*-1,2,4-triazolyl]-1,4-xylenediamine (**4**) and 3-phenyl-5-*p*-tolyl-4-[4-methylbenzylamino]-4*H*-1,2,4-triazole (**5**) were a triplet at δ 5.30-6.30 ppm (1H, t, NH) and as a doublet at δ 3.63-4.15 ppm (2H, d, CH₂).

Scheme 1.

Conclusion

In conclusion, a series of 3,5-diaryl-4*H*-1,2,4-triazole derivatives were synthesized and characterized. The structure of all the compounds are confirmed by IR, PMR & MS spectral data, and are further supported by correct elemental analysis. All these compounds containing 1,2,4- triazole moiety is more active and plays a prominent role in antifungal activity. All compounds showed significant and comparable activity with Griseofulvin against *P.oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum* at 1000 ppm concentration.

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