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Synthesis of 2-(substituted)-5-(benzotriazomethyl)-1,3,4-oxadiazole for anti-fungal activity

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Abstract

Synthesis of (ethyl 2- (1H Benzo [d] [1, 2, 3] triazole –1- yl] acetate) and (2H – benzo [d] [1, 2, 3] triazole – 1 – yl aceto hydrazine) along with their derivatives has been done. The entire synthesized compounds were characterized by UV, IR & ^{1}H-NMR spectroscopy. The Antimicrobial activity of the synthesized compounds was evaluated, on albino rats. The present investigation deals with the synthesized compounds possessing good Anti- fungal activity.

Key words: Esterification, Benztriazole**,** Anti- fungal activity.

INTRODUCTION

1, 2, 3 Benztriazoles were reported have potential fungicidal activity and antiphrastic activity. Similarly1, 3, 4-Oxadiazole derivatives were also reported to possess fungicidal, Herbicidal, pesticidal, insecticidal, antihistaminic antiamoebic, hypnotic, analgesic and anti- Inflammatory activity.

As part of our ongoing study of the design and synthesis of novel heterocyclic compounds. We have recently reported the synthesis of Poly heterocyclic compounds. Literature survey reveals that substituted 1, 3, 4-oxadiazole derivative posses broad spectrum biological activities, which include Antimicrobial [1-3], Anticancer [4, 5], Anti-inflammatory [6-8], Anticonvulsant [9, 10], Anti-tuberculosatic [11, 12], Insecticidal activity [13, 14].

1, 2, 3 benzotriazole derivative also show several pharmacological activities viz. antimicrobial activity, anti inflammatory, anti analgesic activity, anti cancer etc. On the basis of our observation the parent research work was carried out to synthesize 1, 2, 3 triazole substituted 1, 3, 4 oxadiazoles and to further evaluate anti- fungal activity.

RESULTS AND DISCUSSION

These compounds were synthesized with the objective of developing better anti-fungal molecules with maximum percentage of yield and optimal antifungal activity.

It was observed that aromatic compounds .All the synthesized compounds were effective against all the four stains; this activity might be due to the presence of two nuclei Benztriazole and Oxadiazole. Compound D_2 was most effective; Compound D_3 was less effective than compound D_2 . Compounds D_4, D_5 exhibited less fungal activity.

Further Investigation with appropriate structural modification of the title compound may result in therapeutically useful products.

Table 1: Anti- fungal activity of Synthesized compounds

Compound Code	Zone of Inhibition (mm)			
	C. albicans	*A. niger*	*A. flavus*	*Alternaria altenata*
D_1	12	9	8	8
D_2	7	15	10	11
D_3	10	7	15	8
D_4	8	8	7	8
D_5	6	8	10	10

MATERIALS AND METHODS

All the chemicals were procured from S.D Fine Mumbai and C.D.H. New Delhi. They were on analytical grade and were purified by the established methods. Melting points were determined by open capillary tubes method Purity and homogeneity of the compounds was routinely determined by thin layer chromatography on glass plates using silica gel G as absorbent and solvent system Benzene : Methanol (8:2) Spots were visualized by iodine vapor by irradiation with UV light. ^{1}H-NMRspectra was recorded on Brucker spetrospin dpx300 Spectrometer using 5-15% solutions in DMSO-D6 (TMS as internal standard). The Synthetic Procedure involved the following five steps.

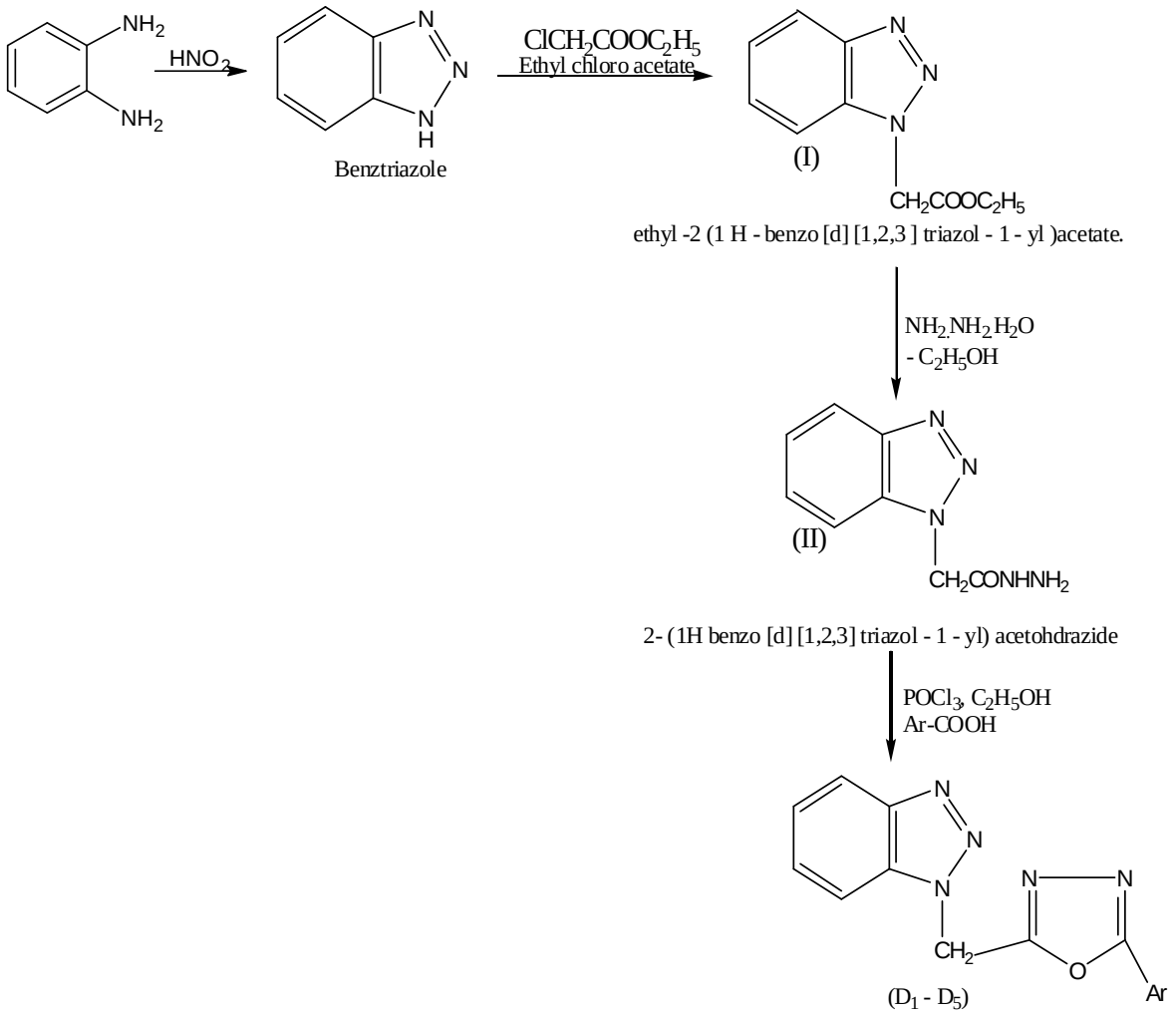
Experimental

STEP-1

***The Synthesis of Benztriazole*:**

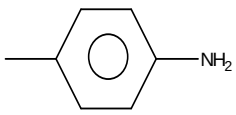
In a mixture of 11.5ml. glacial acetic acid and 30 ml. water, 0.1M o-phenylenediamine was dissolved and then added a solution of 0.1M $NaNO_2$ in 15 ml. of water, stirred continuously for 15 minutes. The temperature was maintained at 12^0 C, chilled in ice bath and product (I) was collected by filtration. The yield obtained was 65% and M.P. was 99^0 C.

Scheme 1

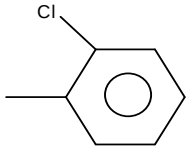


Ar = Aromatic Acids-

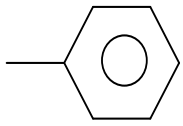
(D_1)



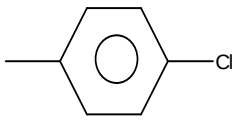
(D_2)



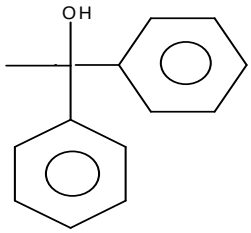
(D_3)



(D_4)



(D_5)



STEP-II

Synthesis of ethyl 2-(1H Benzo [d] [1, 2, 3] triazole – 1- yl] acetate). (I):

A mixture of Benztriazole (0.01 mole), ethyl chloro acetate (0.01 mole) & potassium carbonate 3gm in acetone 60ml was stirred for 6 hours. The solvent was removal under reduced pressure & the solid mass so obtained was extracted with ether (diethyl ether). The ether was removed under reduced pressure to get needle shaped Brown crystals.

Yield: 89%, M.P- 60^0C, λ max 1400-1600 (Ar), 1690 (ester gp.), 2100-2200 (N=N), 3000-3100 cm^{-1} (alkyl gp), ^{H}NMR (δ ppm) 7.4 - 8.00 (m, Ar) 3.5 (S, 2H, CH_2), 4.2 (Q, 2H, CH_2), 2.5 (T, 3H, CH_3).

STEP-III

Synthesis of (2H – benzo [d] [1, 2, 3] triazole – 1 – yl aceto hydrazine). (II) :

An ethanolic solution of Compound (I) (0.01mole) & Hydrazine hydrate (20ml.) of room temp. Was stirred for 4 hours & then refluxed on water bath for 3 hours the excess, solvent was removal by distillation. The solid crystals so separated were filtered. Washed with cold water & Reacystalised from ethanol.

Yield – 80% M.P- 120^0C , λ max IR 1400-1600 (Ar), 1750 (CONH), 3400 (NH^2), 2100-2200 (N=N), 3000-3100 (alkyl gp.) ^{H}NMR (δ ppm) 7.4 -8.00 (M, Ar), 3.5 (S, 2H, CH_2), 3.0 (S, 2H, NH_2), 5.4 (S, 1H, NH).

STEP- IV-

Procedure (D_1-D_5)

Compound (II) (0.01mole) was refluxed with different amino acid (0.01 mole) is the presence of phosphoryl oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_1---D_5.

Synthesis of 5 – (Benztriazole 1- yl – methyl) – 2 – phenyl – 1, 3, 4 – oxadiazole **(D_1):**

Compound (II) (0.01mole) was refluxed with p-amino benzoic acid (0.01 mole) is the presence of phosphorus oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_1.

Yield – 49%, M.P. – 185-186^0C, λ max.IR 3422 (NH_2), 2898-2983 (alkyl gp), 1400-1600 (M Ar), 1123 (Ester Linkage), 2363 (N=N). ^{H}NMR (δ ppm) 5.9 (S, 2H, NH_2), 7.6 -7.8 (M, Ar ring A), 6.5- 6.8 (M, Ar ring B), 3.35 (S, 2H, CH_2).

Synthesis of 5-(Benztriazole 1 – yl – methyl) – 2 – (2 – chloro phenyl) 1, 3, 4- oxadiazole **(D_2) :**

Compound (II) (0.01mole) was refluxed with o-chloro benzoic acid (0.01 mole) is the presence of phosphorus oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_2.

Yield – 52%, M.P. – 170-172^{0}C, λ max .IR 3898 -2983 (Alkyl gp), 1400- 1600(M, Ar region), 1123 (Ester linkage), 2363 (N=N). ^{H}NMR (δ ppm)
7.6 -7.8 (M, Ar ring A), 6.5- 6.8 (M, Ar ring B), 3.35 (S, 2H, CH_2).

Synthesis of 5 – (Benztriazole 1 – yl – methyl) – 2 – (4-chloro phenyl) 1, 3, 4 – oxadiazole **(D_3):**
Compound (II) (0.01mole) was refluxed with benzoic acid (0.01 mole) is the presence of phosphorus oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_3.
Yield – 50%, M.P. – 178-179^{0}C, λ max.IR, 3898 -2983 (Alkyl gp), 1400- 1600(M, Ar region), 1123 (Ester linkage), 2363 (N=N). ^{H}NMR (δ ppm) 7.5 -7.7 (M, Ar ring A), 6.5- 6.8 (M, Ar ring B), 3.35 (S, 2H, CH_2).

Synthesis of 5 – (Benztriazole 1 – yl – methyl) –2 – (4 – amino phenyl) 1,3,4 – oxadiazole **(D_4):**
Compound (II) (0.01mole) was refluxed with 4- chloro benzoic acid (0.01 moles) is the presence of phosphorus oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_4.

Yield – 55%, M.P. – 167-168^{0}C, λ max.IR, 3898 -2983 (Alkyl gp), 1400- 1600 (M, Ar region), 1123 (Ester linkage), 2363 (N=N). ^{H}NMR (δ ppm) 7.6 -7.8 (M, Ar ring A), 6.4- 6.9 (M, Ar ring B), 3.36 (S, 2H, CH_2).

Synthesis of 5 – (Benzotriazole 1 – yl – methyl) -2 – (di phenyl methanol) 1,3, –oxadiazole **(D_5):**
Compound (II) (0.01mole) was refluxed with benzilic acid (0.01 mole) is the presence of phosphorus oxy chloride (10 ml) for 6 hours. The content then were poured into ice- cold water & basified with sodium bi carbonate solution. The separated solid was filtered & recrystallised from ethanol to give derivative D_5.

Yield – 51%, M.P. – 159-160^{0}C, λ max.IR 3550 (OH), 2898-2983 (Alkyl gp), 1400-1600 (M, Ar region), 1123 (Ester linkage), 2363 (N=N).). ^{H}NMR (δ ppm) 7.3 -7.5 (M, Ar ring A), 7.9- 8.1 (M, Ar ring B), 4.6 (S, OH) 3.36 (S, 2H, CH_2).

Determination of Anti- fungal activity:
All the synthesized compounds were screened for antifungal activity on agar plates using Saboraund's medium by cup-plate technique. The fungal cultures were *C. albicans, A .niger, A. flavus, Alternaria alternata*. The standard drug used for the present study was streptomycin. The concentration of the synthesized compounds and standard drugs were taken as 50 µg/ml. All the compounds were dissolved in DMF. In order to account for the effect due to DMF, a blank was also performed.

CONCLUSION

These compounds were synthesized with the objective of developing better antifungal molecules with maximum percentage of yield and optimal antifungal activity.

It was observed that halogen substituted aromatic compounds were more active than unsubstituted aromatic compounds and aromatic compounds were more active than alkyl substituted compounds[12]. All the synthesized compounds were effective against all the four strains; this activity might be due to the presence of three nuclei; Benztriazole, Thiadiazole and 4-Thaizolidinone in one structure. Compound D_2; was most effective; the activity could be due to presence of phenyl and p-bromo phenyl ring. Compound D_3 was less effective than compound D_2; it might be due to presence of only p- chlorophenyl ring Compounds D_4 and D_5 exhibited less antifungal activity; the activity could be due to the absence of aromatic nucleus or presence of alkyl groups.

Further investigation with appropriate structural modification of title compound may result in therapeutically useful products.

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