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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF 2-(1, 2, 3 –BENZOTRIZOL -1-YL-ACETATE) THIAZOLIDINE ACETIC ACID ETHYL ESTER USING DIETHYL ACETYLENE DICARBOXYLATE (DEAD) WITH THIOSEMICARBAZONE DERIVATIVES

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ABSTRACT

In the present investigation newer and simple synthetic methods of 2- (1, 2, 3- benzotriazol -1- yl – methyl) thiozolidine acetic ethylester is described. Benzotriazole 1 is converted to carbothioamide 3 by reaction with ethylchloroacetate followed by thiosemicarbazide. The compound 3 is converted to corresponding thiazolidine compound by treatment with Diethyl Acetylene Dicarboxylate (DEAD) With Thiosemicarbazone Derivatives. Structural elucidation is accomplished by IR, and 1 H NMR spectraldataof thesynthesized compounds. Based on the antibacterial studies of the compound 1 and 2, it can be concluded that compound 2 showed (plate-1)high activity against Escherichia coli (gram -negative bacteria) at 100µgconcentration then compound 1.

INTRODUCTION

Azoles are most important in the history of heterocyclic chemistry and also extensively as important synthons in organic synthesis. The versatile chemotherapeutical activities of azoles, a significant amount of research activity have been directed towards this class. Synthesis and activity of benzotriazole derivatives as antiprotozoal agents (Kopanska *et al.*, 2004) (inhibitors of Acanathamoeba castellanii) have been reported in the literature. Benzotriazole acts as raw metrials in many organic syntheses (Purohit and SrivastaVa 1992; Krasavin 2005) and has proven to be fertile source of Pharmaceutical agents such as antimicrobial (Al-omran *et al.*, 2002), anticonvulsant, anti-inflammatory (Dawood *et al.*, 2006), antitumor (Al-Soud *et al.*, 2003) etc. Some derivatives of benzotriazoles are reported as agonists of peroxisome proliferator activated receptors (Sparatore *et al.*, 2006). Synthesis and biological activity of1H-benzotriazol analogues as inhibitors of the NT pase / helicase and of some related Flavivirade has been extensively investigate (Bretner *et al.*, 2005). Thiazolidinones have a broad spectrum of pharmacological properties i.e.antibacterial (Altintas *et al.*, 2005), antifungal (Liu *et al.*, 2000), ntiinflammatory (Vazzana *et al.*, 2004), anticonvulsant (Gursoy and Terzioglu 2005) etc. Thiazolidinones, substituted at the position two, its derivatives and analogues exhibit unusually high in vitro activity against Mycobacterium tuberculosis (Sobin 1952). Several derivatives of alkoxyphthalimide have been synthesized (Sharma *et al.*, 2006; Banu *et al.*, 2000) and reported to demonstrate a wide range of pharmacological activities i.e. anticancer, antimalarial (Ure and Perassalo 2000), antiepileptic (Singh *et al.*, 2004) etc.

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RESULTS AND DISCUSSION

The key intermediate used for the synthesis of both series of the final compounds was 2-(1,2,3- benzotriazol-1-yl-acetate)hydrazine carbothioamide 3, which in turn was prepared by the reaction of 1H-benzotriazole 1 with ethylchloroacetate in the presence of K_2CO_3 as a base, followed by condensation with thiosemicarbazide. Formation of 3 was confirmed by the presence of N-H stretching peaks at 3378 and 3237 cm-1 in IR and a multiplet at δ 8.3 for NH.NH.C=S.NH2 group in 1HNMR spectra. Then the compound reacted with DEAD to form hetrocyclisation. And The synthesised compounds were tested for antibacterial activity against Escherichia Coli (gram-negativebacteria) and Staphylococcus aureus (gram- positive bacteria).

Experimental section

Melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were recorded on Nicolet 380 -

FT-IR Spectrophotometer using KBr Pellets (γ max in cm^{-1}). Thin layer chromatography (TLC) was performed using glass plates, coated with Silica gel (ACME) of 0.25mm thickness. Sports were visualized using iodine chamber. Usual workup and column chromatographic purification. (60-120 mess Ethyl acetate: petroleum ether). The solvents and reagents used for the synthesis were purified by the standard methods. Petroleum ether refers to the fraction of b.p 60-80. Anhydrous sodium sulphate was used as the drying agent. The synthesized compounds were tested for antibacterial activity.

Synthesis of Benzotriazole

Dissolved 10.8g of (0.1 mol) of 0 -phenylenediamine (1) in a mixture of 12g (11.5ml 0.2mol) of glacial acetic acid 30ml of water contained in a 250ml beaker and then added 7.5g (0.11mol) of sodium nitrite in 15ml of water in one portion, continue stirring for 15 minutes. Collect by vacuum filtration the pale brown solid and dissolve boiling water with charcoal and filter, dried and Usual workup and column chromatographic purification(Ethylacetate : Petrolium ether). m.p 95 - 99˚c. Swati Ojha (2007) reported the same melting point. Synthesis of Ethyl - (1,2,3 benzotriazol) - 1 - y1 acetate (I) To a solution of benzotriazole (1) (0.01mole, 1.19g) inacetone, ethylchloroacetate (0.01mole, 1.06ml) was added drop-wise and K_2CO_3 (0.01mole,2.76g) was used as a base. The reacting mixture was refluxed for 7 hr. On a water bath and filtered hot. Solvent was evaporated from the filtrate to yield the product as white, shining crystals. Recrystallization was carried out from ethanol. The purity was checked on a TLC (Silica gel). Using a mixture of benzene and methanol in the ratio 3:1 by volume Usual workup and column chromatographic purification (Ethylacetate: Petrolium ether)Yield 66%); m.p. 72˚C IR (KBr, cm-1): 2987 (C-H str., CH3),2934 (C-H str., CH2), 1742 (C=O str.), 1600 (C=N str.), 1028.82(C-O str.); 1HNMR (CDCl3, δ): 7.65 (m, 4H, Ar-H),4.20(q, 2H, COOCH2CH3), 3.65 (s, 2H,NCH2), 1.28 (t,3H, COOCH2CH3)

Synthesis of 2 - (1,2,3 - benzotriazol - 1 yl - acetate-hydrazine carbothioamide (II)

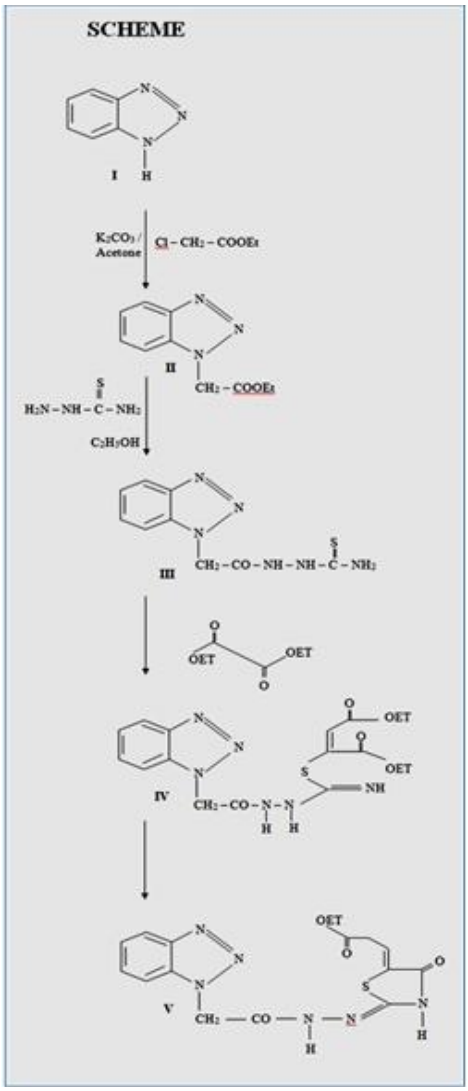
An equimolar mixture of (I) (0.01mole, 2.5g) and thiosemicarbazide (0.01mole, 0.9g) in acetone was refluxed for 8-10 hr. The reaction mixture was allowed to cool and the obtained yellow solid was recrystallised from alcohol. The purity of the compound was checked on a TLC (Silica gel) using a mixture of benzene and methanol 3:1 by volume. The spots were identified with iodine vapour in an iodine chamber Usual workup and column chromatographic purification (Ethylacetate: Petrolium ether) (Yield 81%); m.p

Synthesis of 2 - (1,2,3 - benzotrizol - 1 -yl - acetate) thiazolidine acetic acid ethyl ester(III)

To a solution of 2-(1,2,3-benzotriazol -1- yl- acetate)-ydrazine carbothioamide (2.50g) 0.01mol and diethyl acetylene dicarboxylate (DEAD) (0.01mol,0.3ml) and ethyl acetate (100ml) was added to a solution. The solution was stirred at ambient temperature for 3h. The resulting yellow precipitate was filtered, washed with ethyl acetate, a yellow solid was separated which was than recrystallized from ethanol water. The purity of a compound was checked on a TLC (Silica gel) using a mixture of benzene and methanol 3:1 by volume. The spots were identified with iodine vapour in an iodine chamber. Usual workup and columnchromatographic purification (Ethylacetate : Petrolium ether) (Yield95%) m.p. 242˚ C.IR (KBr, cm-1): 3449, 3380 (N-H str.), 1787.20, 1662.67 (C=O str.), 1603.71 (C=N str.),695 (C-S-C str.); 1H NMR(CDCl3, δ): 8.13 (s, 1H,CONH), 7.1-7.5 (m, 4H, Ar-H), 5.8 (s, 1H, NH of thiazolidinone ring), 4.1 (s, 2H, CH2), 3.8 (s, 2H,NCH2).

Bacterial activity

Based on the antibacterial studies of the compounds 1 and 2, it can be concluded that compound 2 showed (Plate - 1) high activity against Escherichia coli (gram-negative bacteria) at 100 µg concentration then compound 1.



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