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Research Article

Synthesis & characterization of N-thiadiazolyl thiazolidinone derivatives

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ABSTRACT

Thiazolidine-4-ones containing thiazole moiety. It had been syhthesised by 6-aminocoumarin, isatin, primary amines, and aromatic aldehydes. Present article is sincere attempt to synthesis of a series of {2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one derivatives} (3a-3e). The synthetic approach involves the cyclocondensation of the appropriate Schiff bases with α-mercaptoalkanoic acid in glacial acetic acid. Here suitably substituted Schiff's bases(2a-2e) obtained by the reaction of appropriate aminothiadiazole(1) derivative with different substituted aromatic aldehydes. The synthesised complexes have been identified by their melting point, R_f values and interpreted by their spectral studies like IR, ^{1}H NMR & Mass.

Key words: *Thiosemicarbazide, Thiazolidinone, Glacial acetic acid, Aromatic*

INTRODUCTION

Heterocyclic compounds occupy a central position among those molecules that makes life possible. The chemistry of heterocyclic compounds has been an interesting field of study for a long time. 1,3,4-thiadiazole[1] derivatives posses interesting biological activities[2-10] probably conferred to them due to strong aromaticity of the ring system which leads to great in vivo stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring[11] . Compounds carrying the thiazolidinone ring have been reported to demonstrate a wide range of pharmacological activities[12] which include antimicrobial activity[13,14], antifungal activity[15], CFTR inhibitor[16], antitumor[17,18], anti inflammatory[19], anticonvulsant[20]. Thiazolidinone ring can be prepared by nucleophilic addition of thioglycolic/thiolactic acid to C=N double bond[21-23].

MATERIALS AND METHOD

2-Phenyl-3-(5-Phenyl-1,3,4-Thiadiazol-2-yl)-1,3 Thiazolid in-4-one derivatives are synthesized using three steps: synthesis of phenyl thiadiazolamine, synthesis of schiff's base, and synthesis of thiazolidinone derivatives. Melting points were determined by open capillaries on tempo apparatus. The completion of reaction and purity was checked by HPTLC pre-coated plates. IR spectra was recorded on spectrometer using KBr pressed pellet technique. ^{1}HNMR spectra was recorded on BRUKER 300 (MHZ) NMR spectrometer.

SYNTHESIS OF 5-PHENYL-1,3,4-THIAZOL-2-AMINE (1)

Thiosemicarbazide (0.025 mol) was suspended in a 1,4-dioxane (30ml) and strirr with the addition of benzoic acid(0.03mol). Then $POCl_3$ was added at 0°C. The mixture was heated at 85°C for 5hrs and left to room temperature. Evaporate the solvent and pour that solid mass into ice cold water (30ml) with good stirring. Basify the mixture to $_p$H-9 by the addition of 40% NaOH solution. Cool room temperature, the precipitate was filtered and give washings with cold water to remove all the coloured matter, the product was dried and collect it & recrystalized from ethanol. Melting point of the compound is 211-213^{o}C with 89.6% yield.

SYNTHESIS OF 5-PHENYL-*N*-[PHENYLMETHYLIDENE]-1,3,4-THIADIAZOL-2-AMINE (2a):
To 1 equivalent of compound **1** add 5 equivalent of benzaldehyde in ethanol(25ml) with 0.5ml acetic anhydride and refluxed for 8hrs and cooled. The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a 500ml beaker. The product was filtered and dried. The product was purified by recrystallization from chloroform. Yield 34.05%, melting point 207-211°C

SYNTHESIS OF *N*-{[4-(DIMETHYLAMINO) PHENYL]METHYLIDENE}-5-PHENYL-1,3,4-THIADIAZOL-2-AMINE (2b):
To 1 equivalent of compound **1** add 5 equivalent of 4-(dimethylamino) benzaldehyde in ethanol (25ml) with 0.5ml acetic anhydride and refluxed for 8hrs and cooled. The solid thus obtained was collected through filtration if not, pour the reaction mixture into crushed ice and collect the product. Recrystalization from chloroform. Yield 54.7%, melting point 253-257°C.

SYNTHESIS OF 4-{[(5-PHENYL-1,3,4-THIADIAZOL-2-YL)IMINO]METHYL}PHENOL (2c):
To 1 equivalent of compound **1** add 5 equivalent of 4-hydroxy benzaldehyde in ethanol(25ml) with 0.5ml acetic anhydride and refluxed for 8hrs and cooled. The solid thus obtained was collected through filtration if not, pour the reaction mixture into crushed ice and collect the product. Recrystalization from chloroform. Yield 39.8%, melting point 243-251°C.

SYNTHESIS OF *N*-[(4-NITROPHENYL)METHYLIDENE]-5-PHENYL-1,3,4-THIADIAZOL-2-AMINE (2d):
To 1 equivalent of compound **1** add 5 equivalent of 4-nitro benzaldehyde in ethanol(25ml) with 0.5ml acetic anhydride and refluxed for 8hrs and cooled. The solid thus obtained was collected through filtration if not, pour the reaction mixture into crushed ice and collect the product. Recrystalization from chloroform. Yield 42.4%, melting point 217-222°C.

SYNTHESIS OF *N*-[(4-METHOXYPHENYL)METHYLIDENE]-5-PHENYL-1,3,4-THIADIAZOL-2-AMINE (2e):
To 1 equivalent of compound **1** add 5 equivalent of 4-methoxy benzaldehyde in ethanol (25ml) with 0.5ml acetic anhydride and refluxed for 8hrs and cooled. The solid thus obtained was collected through filtration if not, pour the reaction mixture into crushed ice and collect the product. Recrystalization from chloroform. Yield 36.2%, melting point 204-206°C.

SYNTHESIS OF2-PHENYL-3-(5-PHENYL-1,3,4-THIADIAZOL-2YL)-1,3-THIAZOLIDIN-4-ONE (3a):
To the Schiff's base (2a) add thioglycolic acid in equimolar ratio and reflux the above mixture using glacial acetic acid as a solvent for 10-12 hrs, cool then mix the reaction mixture with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystalized from ethanol. Yield 73.1%, melting point 204-209°C.
IR (cm^{-1} KBr): C-S-C-str (688.85), C=N-str (1690), C=O-str (1735), N-CH_2-str (2864), Ar-CH Str (3037.40), Ar-C=C-Str (1558.20); **^{1}HNMR ppm (DMSO):** δ7.2-7.9(H,m,ArH), δ 2.5(2H,s,CH_2), δ 6.5(H,s,CH).

SYNTHESIS OF 2-(4-DIMETHYLAMINOPHENYL-3-(5-PHENYL-1,3,4-THIADIAZOL-2YL)-1,3-THIAZOLIDIN-4-ONE (3b):
To the Schiff's base (2b) add thioglycolic acid in equimolar ratio and reflux the above mixture using glacial acetic acid as a solvent for 10-12 hrs, cool then mix the reaction mixture with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystalized from ethanol. Yield 54.7%, melting point 201-204°C.
IR (cm^{-1} KBr): C-S-C-str (688.85), C=N-str (1690), C=O-str (1735), N-CH2-str (2864), Ar-C-H Str (3037.40), Ar-C=C Str (1558.20); **^{1}HNMR ppm (DMSO):** δ 7.2-7.9(9H,m,ArH), δ 2.54(2H,s,CH_2), δ 5.969(H,s,CH), δ 3.010 H of $N(CH_3)_2$.

SYNTHESIS OF 2-(4-HYDROXYPHENYL-3-(5-PHENYL-1,3,4-THIADIAZOL-2YL)-1,3-THIAZOLIDIN-4-ONE (3c):
To the Schiff's base (2c) add thioglycolic acid in equimolar ratio and reflux the above mixture using glacial acetic acid as a solvent for 10-12 hrs, cool then mix the reaction mixture with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystalized from ethanol. Yield 77.7%, melting point 217-223°C.
IR (cm^{-1}KBr): C-S-C-str (689), C=N-str (1068), C=O-str (1697), NCH_2-str(2902.98), OH-str (3550.42), Ar C=C-str (1560); **^{1}HNMR ppm (DMSO):** δ 7.2-8.3(9H,m,ArH) δ 2.543(2H,s,CH_2) , δ 5.9(H,s,CH) , δ 13.043(s,1H,OH).

SYNTHESIS OF 2-(4-NITROPHENYL-3-(5-PHENYL-1,3,4-THIADIAZOL-2YL)-1,3-THIAZOLIDIN-4-ONE (3d):
To the Schiff's base (2d) add thioglycolic acid in equimolar ratio and reflux the above mixture using glacial acetic acid as a solvent for 10-12 hrs, cool then mix the reaction mixture with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystalized from ethanol. Yield 54.92%, melting point 201-205°C.
IR (cm^{-1} KBr): Thiadiazole (1066), C-S-C-str (687.30),C=N-str (1687), C=O(1817),NCH_2-str (2900.95), Ar-C-H-Str (3030.66), Ar-C=C-Str (1550.97); **^{1}HNMR ppm (DMSO):** δ 7.2-7.9(9H,m,ArH,), δ 2.54(2H,s,CH_2), δ 5.969(H,s,CH) .

SYNTHESIS OF 2-(4-METHOXYPHENYL-3-(5-PHENYL-1,3,4-THIADIAZOL-2YL)-1,3-THIAZOLIDIN-4-ONE (3e):
To the Schiff's base (2e) add thioglycolic acid in equimolar ratio and reflux the above mixture using glacial

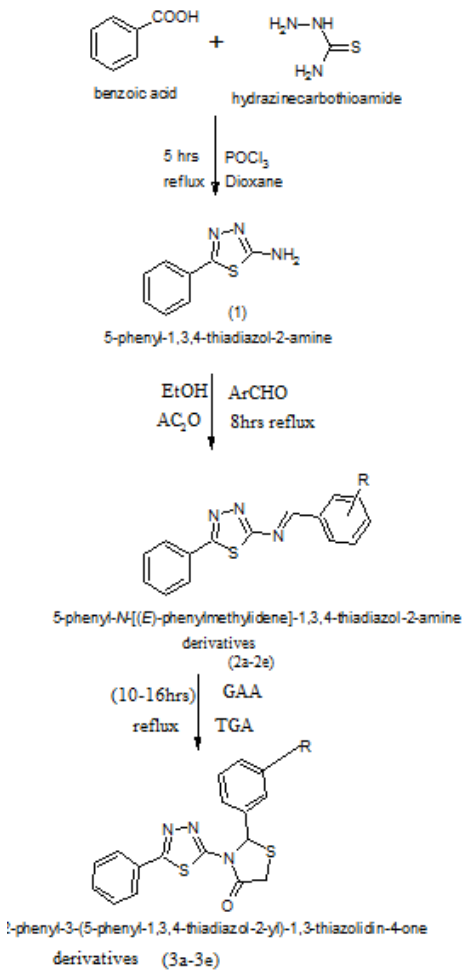
acetic acid as a solvent for 10-12 hrs, cool then mix the reaction mixture with sodium carbonate (10%). The resultant neutral solid is poured into crushed ice, collect the solid after more washings with cold water. Recrystalized from ethanol. Yield 72.19%, melting point 227-230°C.
IR (cm^{-1} KBr): C-S-C-str (689.59),C=N-str (1691), C=O-str (1816), N-CH_2-str (2903.40), Ar-C-H Str (3035.33), Ar-C=C Str (1558.83)

Table 1. represents the substitutions of synthesized derivatives with their respective R_f values.

Compound	R	R_f value
3a	H	0.29
3b	$N(CH_3)_2$	0.38
3c	4-OH	0.29
3d	4-NO_2	0.39
3e	4-OCH_3	0.31

Solvent system to monitor TLC(precoated)= n-Hexane:Ethyl acetate(8:2)

Scheme



RESULTS AND DISCUSSION

In our present investigation, different derivatives of 2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3-thiazo lidin-4-one (3a-3j). In synthetic scheme benzoic acid on reaction with thiosemicarbazide yielded 5-phenyl-1,3,4-thiadiazol-2-amine **1** which on reaction with different aromatic aldehydes afforded 5-phenyl-*N*-[(*E*)-phenylmethylidene]-1,3,4-thiadiazol-2-amine derivatives **(2a-2e) .** The comp ounds **2(a-e)** on treatment with thioglycolic acid in presence of $ZnCl_2$ gave 2-phenyl-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1,3-thiazolidin-4-one **(3a-3e).** The stru ctures of the compounds were confirmed by melting points, UV-Visible spectroscopy, IR spectra in ^{1}H NMR and MASS spectral data. The structures of compounds **(3a-3e)** were confirmed on basis of spectral data. IR spectrum showed absorption peaks at 688 cm^{-1} for the C-S-C of thiadiazole and absorption peaks around 1600cm^{-1} and 2900 cm^{-1} for the C=O & NCH_2S of thiazolidinone respectively. The ^{1}HNMR spectra exhibiting multiple peaks attributed to the protan at δ 7.2- 8 indicating the presence of aromatic protan while siglets at δ 2.5(CH_2), δ 5.9 (CH) indicating the thiazolidinone linkage.

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