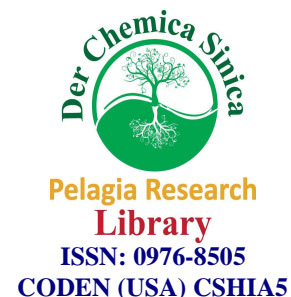




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A new route to the preparation of spiroheterocyclic compounds

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ABSTRACT

Owing to the extensive pharmacological importance, heterocyclic compounds are often synthesized with varying substituents. The main objective of such synthesis is to study the activity related aspects of pharmacophore groups of the heterocyclic compounds and to enhance the yield of the compounds if found significantly active. Since spiro heterocycles are expected to be pharmacologically active, compounds viz., N-[1-acetyl-7,9-diphenyl-4-oxa-8-thia-1,2-diazaspiro(4.5)dec-2-en-3-yl]acetamide and N-[1-acetyl-7,9-diphenyl-4,8-dithia-1,2-diazaspiro(4.5)dec-2-en-yl]acetamide have been synthesized and characterized by C,H,N analysis, IR, ¹H-NMR and ¹³C-NMR data.

Key words: Spiro Heterocycle, N- [1-acetyl-7,9-diphenyl-4-oxa-8-thia-1,2-diazaspiro(4.5)dec-2-en-3-yl] acetamide, N- [1-acetyl-7,9-diphenyl-4,8-dithia-1,2-diazaspiro(4.5)dec-2-en-yl] acetamide, Pharmacophore groups, Physiological effect.

INTRODUCTION

Heterocycles are an important class of compounds as they find wide application as analgesic agents, tranquilizers, neurotransmitters besides other pharmacologically active products [1,2]. Amoxicillin, an antibiotic; ranitidine, an antagonist of the H₂ histamine receptor for the treatment of gastric ulcers; hydrochlorothiazide and furosemide, diuretics; acetaminophen, an analgesic; digoxin, a cardiac glycoside; penicillin-V, an antibiotic; etc. contain heterocyclic ring as a part of their structures [1]. Chemists synthesise many hundreds of thousands of organic compounds for various reasons. Heterocycles are synthesized with a focus on studying the physiological effects that these compounds can trigger and the synthetic routes that can provide with greater supply of these compounds than that nature can produce.

Thiadiazoles, oxadiazoles and triazoles are five membered rings associated with diverse biological and pharmacological properties [3]. Thiadiazoles are any of several isomeric five membered heterocycles having two carbon atoms, one nitrogen atom, one sulphur atom and one double bond. Oxadiazolines are five membered heterocycles having two carbon atoms, one nitrogen atom, one oxygen atom and one double bond. Thiadiazoline derivatives are active as antimicrobial antiviral and insecticidal agents [4]. Some thiadiazolines like 5-arylimino-1,2,4-thiadiazolines were found to exhibit control efficacy *in vivo*, especially against cucumber downy mildew (pseudoperonospora cubensis). The fungitoxic properties of the compounds strongly suggested that their primary mode of action is the inhibition of SH-enzyme. Among the series of compounds 5-(4-chlorophenylimino)-2-methyl-3-phenyl-1,2,4-thiadiazoline was most active against cucumber downy mildew[5].

Thiadiazolines also exhibit hypoglycemic and antitubercular properties [6-9]. There are few general routes to obtain 1,3,4-thiadiazolines. Holmberg and Sandstrom proposed the reaction between an aldehyde or a ketone with substituted thiohydrazides[10]. Taylor et al. found that 1,3-dipolar cycloaddition between chlorodiazabutadiene and thiourea rendered 4-amidine-1,3,4-thiadiazolines[11]. However, the preparation of this heterocyclic ring is mostly achieved by hetero cyclization of thiosemicarbazones, as reported by Andreae et al., Somogyi and Kubota et al. [12-15]. Several 1,3,4 thiadiazoline derivatives have been prepared from several ketones (diarylketones, indanones and tetralone) via the corresponding thiosemicarbazones [16,17].

In this context, it has been intended to prepare some spiro heterocycles of biological interest, characterize them by using the physical data and undertake the study of pharmacological activities in a separate project later.

MATERIALS AND METHODS

Benzaldehyde (Merck), acetic anhydride (Merck), acetone (SRL) were purified appropriately. Semicarbazide hydrochloride (Loba Chemie) and thiosemicarbazide (Himedia Laboratories) were purified by recrystallisation. Silica Gel G (Qualigens) was used for TLC. IR spectra were recorded on a Shimadzu IR-Affinity-1 Instrument. ¹H-NMR and ¹³C-NMR spectra on Bruker 300 MHz spectrometer. C,H,N analysis was carried out at STIC, Cochin University of Science and Technology, Cochin.

Synthesis of N-(1-acetyl-7,9-diphenyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-2-en-3-yl) acetamide (iv)
1.7 g 2,6-diphenyltetrahydro-4H-thiopyran-4H-one semicarbazone (ii) was dissolved in 5ml of pyridine and added with 1.5 ml of acetic anhydride. Then the mixture was heated over a water bath at 100°C with magnetic stirring and heating was continued for 2 hours. Then the reaction mixture was poured into ice water. Pale white coloured solid of N-(1-acetyl-7,9-diphenyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-2-en-3-yl)acetamide(iv) was separated, filtered and dried. Then it was recrystallized from ethanol.

Melting point: 184⁰C, Yield: 74%; IR (cm⁻¹): 3446(NH str.), 3028(aromatic C-H str.), 1627(C=O str.), 1602(C=N str), 1259 (C-N str.); ¹H NMR (ppm): 8.3(1H, s, NH-amide), 7.4-7.2(10H, m, aromatic -H), 3.8-3.7(2H, t, methine-H at C-7 and C-9), 2.6-2.5(4H, d, methylene-H at C-6 and C-10), 1.3(6H, s, acetyl CH₃); ¹³C NMR (ppm): 164(CO of acetyl group), 153(Carbon at C-5),

140(Ipso carbons of phenyl rings), 128-127(other carbons in aromatic ring), 50-44(Carbons at C-6,C-7,C-9 and C-10), 36(CH₃ of acetyl group).

Synthesis of N-(1-acetyl -7,9-diphenyl-4,8-dithia-1,2-diazaspiro[4.5]dec-2-en-3-yl) acetamide(v)

1.7 g of 2,6-diphenyltetrahydro-4H-thiopyran-4-one thiosemicarbazone (iii) was dissolved in 5ml of pyridine and added with 1.5 ml of acetic anhydride. Then the mixture was heated over a water bath at 100°C with magnetic stirring and heating was continued for 2 hours. Then the reaction mixture was poured into ice water. Yellow coloured solid of N-(1-acetyl-7,9-diphenyl-4,8-dithia-1,2-diazaspiro[4.5]dec-2-en-3-yl)acetamide(v) was separated, filtered and dried. Then it was recrystallized from ethanol.

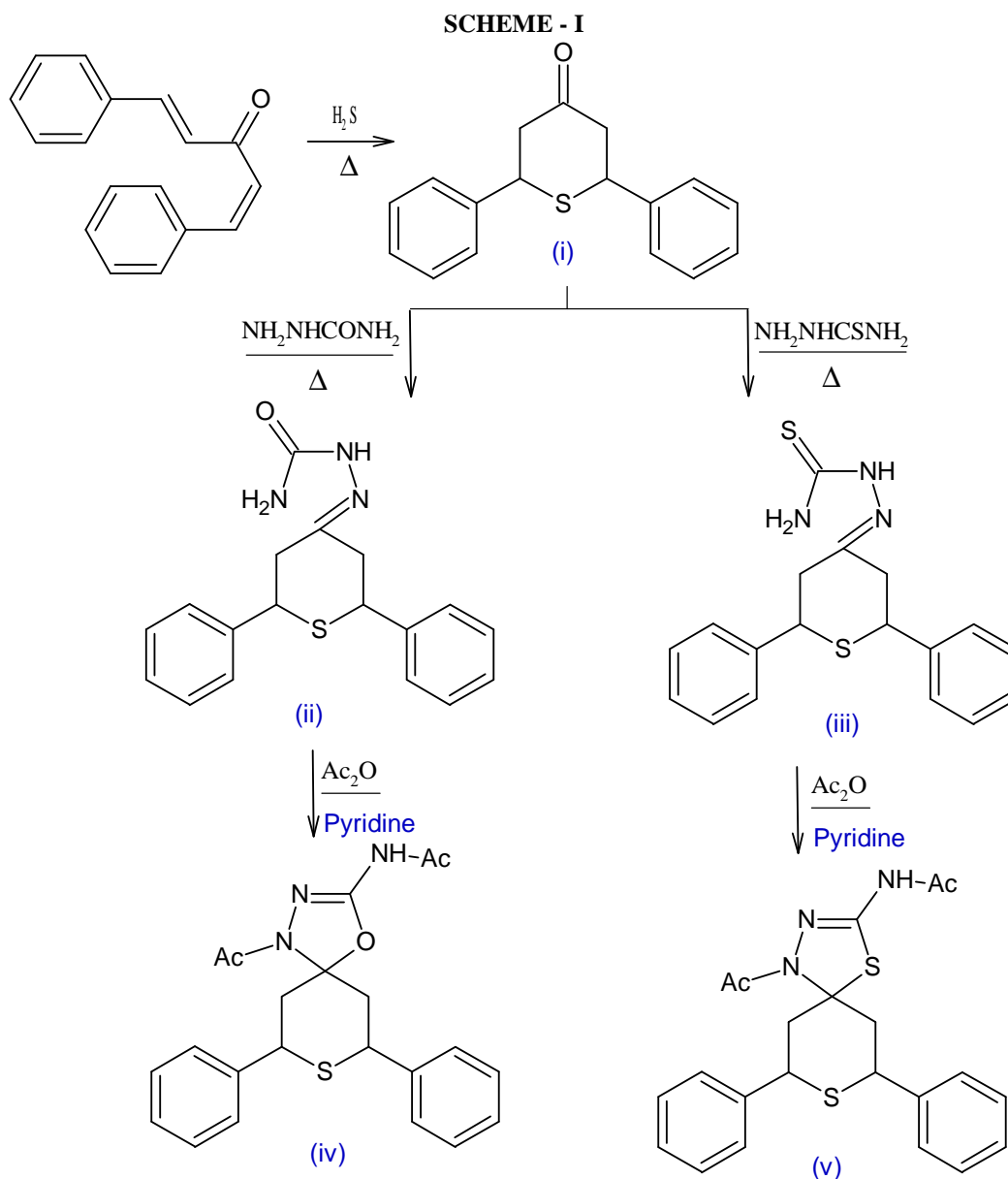
Melting point: 120⁰C, Yield: 81%; IR (cm⁻¹): 3396(NH str.), 3028(aromatic C-H str.), 1618(C=O str.), 1490(C=N str), 1234 (C-N str.), 696(C-S str.); ¹H-NMR (ppm): 8.8-8.7(1H, s, NH-amide), 7.4-7.2(10H, m, aromatic -H), 3.7-3.6(2H, t, methine-H at C-7 and C-9), 2.8-2.7(4H, d, methylene-H at C-6 and C-10), 1.4-1.3(6H, s, acetyl CH₃); ¹³C-NMR (ppm): 170(CO of acetyl group), 141(Carbon at C-5), 140(Ipso carbons of phenyl rings), 128-127(other carbons in aromatic ring), 46-45(Carbons at C-6, C-7,C-9 and C-10 of six membered heterocyclic ring), 23(CH₃ of acetyl group).

RESULTS AND DISCUSSION

The compound 2,6-diphenyl tetrahydro-4H-thiopyran-4-one(i) was prepared according to the literature method [18,19]. The semicarbazone and thiosemicarbazone derivatives were prepared based on the available procedure [20]. The target compounds N-(1-acetyl-7,9-diphenyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-2-en-3-yl)acetamide(iv) and N-(1-acetyl -7,9-diphenyl-4,8-dithia-1,2-diazaspiro[4.5]dec-2-en-3-yl)acetamide(v) were synthesized by the method described in the materials and methods section.

The preliminary laboratory analysis and C,H,N analysis revealed the formation of the compound(iv). The IR data showed the characteristic stretching frequencies as follows. 3446 cm⁻¹ for NH, 3028 cm⁻¹ for aromatic CH, 1627 cm⁻¹ for carbonyl group and 1602 cm⁻¹ for C=N stretching, 1259 cm⁻¹ for C-N str. besides other characteristic frequencies. The ¹H-NMR data supported the structure of the compound as predicted(iv) in the **Scheme-1** i.e., δ 8.3 corresponds to NH of amide group, δ 7.4-7.2 corresponds to aromatic hydrogens, δ 3.8 -3.7 are assigned to methine protons, δ 2.6-2.5 are assigned to methylene protons and δ 1.3 corresponds to acetyl protons of spiro ring substituent. The various peak assignments of ¹³C-NMR spectrum also confirm the assigned structure to compound(iv).

Similarly the formation of compound(v) also was revealed from preliminary laboratory analysis and C,H,N analysis. The IR data showed the characteristic stretching frequencies as follows. 3396 cm⁻¹ for NH, 3028 cm⁻¹ for aromatic CH, 1618 cm⁻¹ for carbonyl group and 1490 cm⁻¹ for C=N stretching besides other characteristic frequencies. The ¹H-NMR data supported the structure of the compound as predicted(v) in the **Scheme-1** i.e., δ 8.8-8.7 corresponds to NH of amide group, δ 7.4-7.2 corresponds to aromatic hydrogens, δ 3.7-3.6 are assigned to the methine protons, δ 2.8-2.7 corresponds to methylene protons, δ 1.4-1.3 corresponds to acetyl protons of spiro ring substituent.



The various peak assignments of ^{13}C -NMR spectrum also confirm the assigned structure to compound (v). The ^1H -NMR and ^{13}C -NMR data were assigned to the compounds with the help of chem office 2005.

The synthetic route followed to obtain the spiro heterocyclic compounds (iv and v) is simple besides giving higher yield of the product. Further it has been planned to make an indepth study on the anticipated biological activities of these compounds (iv and v).

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