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Synthesis of Some Heterocyclic Compounds Containing Two Nitrogen Atoms

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Hydrazines and substituted hydrazines have tendency to take part into substitution as well as condensation reaction. The condensation with suitable carbonyl compounds give hydrazones. These hydrazones undergo cyclization under suitable conditions and form two nitrogen atom containing heterocyclic ring systems. These compounds have pronounced antibacterial properties and also acts as promoters of various organic reactions. But these are highly toxic and less curative. These compounds have a big range of biological activity due to the versatility of their application in the synthesis of drugs, polymers and dyes.

Key Words: Synthesis, Heterocyclic compounds.

INTRODUCTION

Many hydrazide[1,2] with varying substituents in the pyridine ring have been found to exhibit pronounced antitubercular activity. Alicyclic hydrazides have also been shown to possess a wide range of biological activity[3,4]. Heterocyclic compounds derived from hydrazides find numerous application in many fields and the most investigated amongst these are in biological activities. Of the various types of heterocyclic compounds derived from hydrazides, the 1,3 4-oxadizoles deserve special attention due to its versatility in drug synthesis, production of polymers, preparation of dyes in photography as light screening agents and as scintillators.

A group of 1,3,4-oxadiazolin-5-ones and 1,3,4-oxadiazolin-5-thiones exhibit antitubercular activity[5,6]. 2-(4´-Pyridyl)-1,3,4-oxadiazolin-5-one is active against mycobacterium tuberculosis and mycobacterium leprae and has some advantages over isoniazid[7]. Oxadizolin-5-ones and 5-thiones also possess analgesic, antipyretic and antiphlogistic properties[8].

2-[5´-Nitrophenyl-(2´)]-1,3,4-thiadiazolin-5-ones have been particularly well investigated for their fungicidal and bactericidal properties[9-11]. Some simpler compounds in the series are found to possess important physiological activity, *e.g.*, anticonvulsive and antiparalytic activity shown by 2-amino-5-phenyl 1,3,4-thiadiazole and 2´-phenyl-1,3,4-thiadizolin-5-one[12], hypnotic and sedative action shown by 2-hydroxyphenyl-1,3,4-thiadiazole[13]

bacterial and hypoglycemic effectiveness shown by sulphonamide derivatives of these diazoles[14] *etc*.

Amongst other important uses of the 1,3,4-thiadiazoles are in the stablizing and preparation of macromolecular materials[15,16], as dye stuffs particularly anthraquinone and vat dyes, in photography as tone improvers[17] and development accelerators[18], as light screening agents and optical brightners[19] and on account of their scintillation properties[20].

EXPERIMENTAL

Sulphuric acid bath were taken for melting point determination. Melting point was determined in open capillaries and is uncorrected. For high melting solids, melting points were determined by using an electrical apparatus. Organic solvents were dried and purified by following the specific method prescribed for them. Infrared spectra were obtained from different sources, potassium bromide disc were used. Significant infrared absorptions are mentioned in the experimental section at appropriate places.

Thin layer chromatography (TLC)

TLC was done in routine manner to follow the progress of the reactions and judgement of the purity of compounds. The purity of compounds in many cases was judged by performing TLC using two or three solvent systems. Silica gel G (BDH) was used as absorbent. TLC plates were prepared by dipping microscope slides in slurry of the adsorbent in chloroform and allowing the solvent to evaporate. The spot on the chromatograms were detected by exposing the developed TLC plates to iodine vapour. The following solvent systems were generally used for TLC (i) benzene, (ii) benzene/ethanol (10:1), (iii) benzene/ethyl acetate (10:1), (iv) ethyl acetate/methanol (5:1), (v) chloroform/methanol (5:1) and (vi) chloroform/ethanol (5:2).

Preparation of 2-*p*-nitrobenzyl-5-phenyl-1,3,4-thiadiazole

Preparation of *p*-nitro phenyl acetic acid (Step-I): *p*-Nitrobenzylcyanide (12 g) conc. Sulphuric acid (36 g) and water 35 mL were heated under reflux for 0.5 h following the method of Vogel[21] and then diluted with equal volume of water and cooled. The separated solid was collected by filtration and washed with water several times. Re-crystallization of the solid from hot water gave the pure *p*-nitrophenyl acetic acid (10.2 g) m.p. 151-152ºC (Lit m.p. 151ºC).

Preparation of ethyl *p*-nitro phenyl acetate (Step-II): A mixture of *p*-nitro phenyl acetic acid (12 g) absolute ethanol (25 mL) and conc. sulphuric acid (1 mL) was heated on a water bath for 1 h and then left overnight at room temperature. The separated solid was filtered off, washed with ice water and then with aqueous sodium bicarbonate (10 %). It was

finally washed with ice cold water and recrystallized from ethanol to furnish the pure ester as a white crystalline solid (115 g) m.p. 64ºC (Lit m.p. 63.3ºC)[22].

Preparation of *p*-nitro phenyl acetate hydrazides (Step-III): Hydrazine hydrate (3.25 mL 100 %) was added to a solution of ethyl-*p*-nitro phenyl acetate (10 g) in ethanol (25 mL) and the mixture was heated under reflux for 2 h. After which solid separated out. This was left at room temperature for 1 h and then in a cooling chamber when white solid separated out completely from the solution. The solid was filtered off and recrystallized from methanol to furnish the pure hydrazide compound (7.5 g) m.p. 165ºC (Lit. m.p. 167ºC).

Preparation of final product (Step-IV): The thiadiazole was prepared by reaction between *p*-nitro phenyl acetic acid hydrazide, benzoyl chloride by passing H_2S gas; the condensation was done under a variety of conditions.

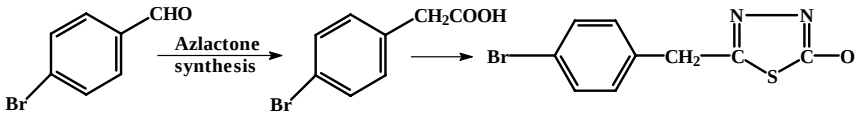
In pyridine medium: A mixture of *p*-nitro phenyl acethydrazide (0.5 g) benzoyl chloride (0.4 mL) and pyridine (1 mL) was taken in a small round bottom flask fitted with a delivery tube through which H_2S gas was passed in the reaction mixture and heated under reflux on a water bath. The reaction was followed by TLC, which showed almost complete disappearance of the starting materials after 4 h of heating. After that pyridine was removed by distillation. The residue on cooling deposited a yellow solid. This was washed with benzene and ethanol. It was then recrystallized from ethanol to furnish 2-*p*-nitrobenzyl-5-phenyl-1,3,4-thiadizole as yellow needles (0.45 g) m.p. 68ºC.

By direct heating: A mixture of *p*-nitro phenyl acethydrazide (0.5 g) and benzoyl chloride (0.4 mL) was heated under reflux by passing H_2S gas slowly in the reaction mixture for 5 h, when TLC examination showed the reaction to be completed. The reaction mixture was then left in an ice chest overnight. After 24 h, the yellow solid which had separated from the reaction mixture was triturated with aqueous sodium bicarbonate, washed with cold water and was recrystallized from ethanol to give the pure thiadiazole (0.40 g) m.p. and mixed m.p. 66-68ºC.

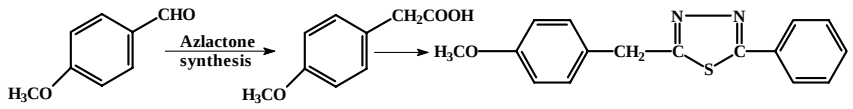
In pyridine medium at room temperature: Pyridine (1 mL) was added to a mixture of *p*-nitro phenyl acethydrazide (0.5 g) benzoyl chloride (0.4 mL) placed in a small round bottom flask and set aside at room temperature by passing H_2S gas. The reaction was followed by TLC, which showed that there was practically no trace of the starting material after 4 d. On treating the reaction mixture with benzene and light petroleum a yellow solid separated which was removed by filtration and washed with ethanol. Re-crystallization of the solid from ethanol gave the pure thiadiazole (0.15 g) mp and mixed mp 68ºC.

In similar way, the following compounds were synthesized by the condensation of suitable hydrazide with benzoyl chloride. The substituted phenyl acetic acids required for the synthesis of these compounds were all prepared from the corresponding substituted benzaldehyde by azalactone synthesis under different conditions.

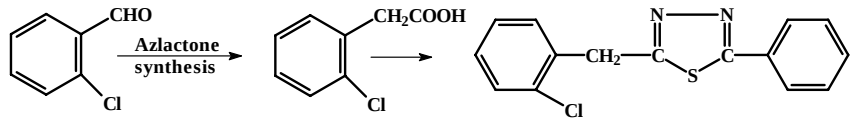
Preparation of 2-*p*-bromobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction between *p*-bromophenyl acet-hydrazide and benzoyl chloride.



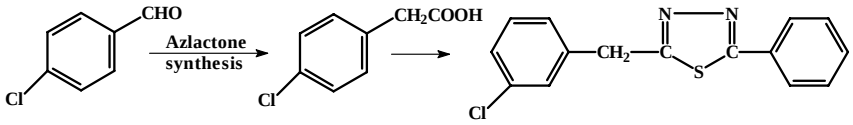
Preparation of 2-*p*-methoxybenzyl-5-phenyl-1,3,4-thiadiazole: By reaction *p*-methoxyphenyl acet-hydrazide, benzoyl chloride and H_2S gas.



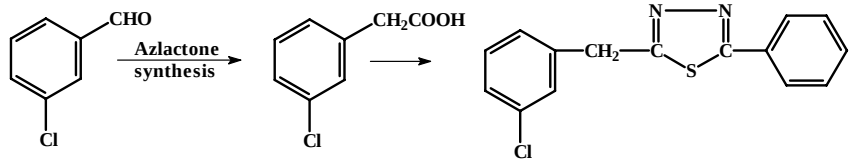
Preparation of 2-*o*-chlorobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction between *o*-chlorophenyl acethydrazide benzoyl chloride and H_2S gas.



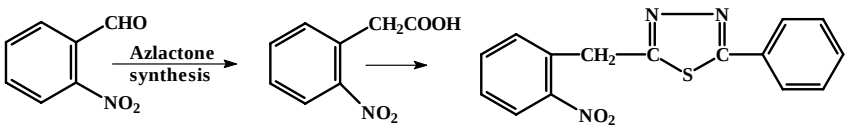
Preparation of 2-*p*-chlorobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction between *p*-chlorophenyl acethydrazide benzoyl chloride and H_2S gas.



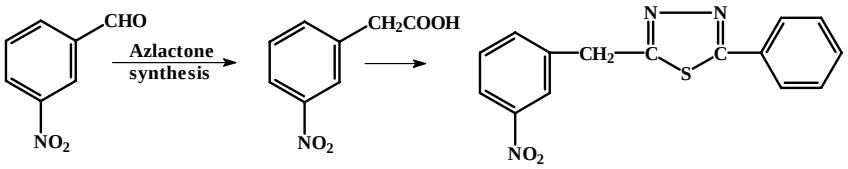
Preparation of 2-*m*-bromobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction *m*-chlorophenyl acethydrazide benzoyl chloride and H_2S gas.



Preparation of 2-*o*-nitrobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction between *o*-nitrophenyl acetic acid hydrazide benzoyl chloride by passing H_2S gas.

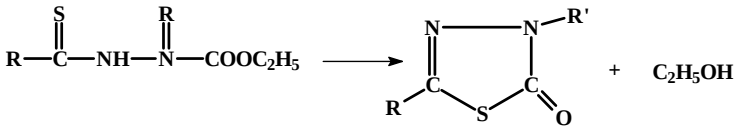


Preparation of 2-*m*-nitrobenzyl-5-phenyl-1,3,4-thiadiazole: By reaction between *m*-nitrophenyl acetic acid hydrazide benzoyl chloride by passing H_2S gas.



RESULTS AND DISCUSSION

1,3,4-Thiadiazoles have been prepared from ester derivatives of monothioacyl hydrazide with elimination of alcohol.



As we had easy access to a number of substituted phenyl acetic acids, we chose to convert them into the respective hydrazides for their cyclization into 1,3,4-oxadiazoles. The method of cyclization of diacyl hydrazides for this purpose appeared suitable from several considerations amongst which were the wide choice of dehydrating agents available, the constraints of our laboratory resources and above all, a simple alternative synthetic procedure being easily available for establishing the identity of the cyclized product.

The phenyl acetic acid hydrazides were treated with benzoyl chloride in the presence of H_2S gas and suitable condensing agents, such as phosphorous pentaoxide, pyridine etc. The initial reaction between the reactants gave diacyl hydrazides which then cyclized in presence of H_2S gas to form 2,5-disubstituted-1,3,4-thiadiazole. The products were characterized by elemental analysis and their spectral characteristics (Table-1).

The general scheme adopted for the synthesis was according to scheme given below:

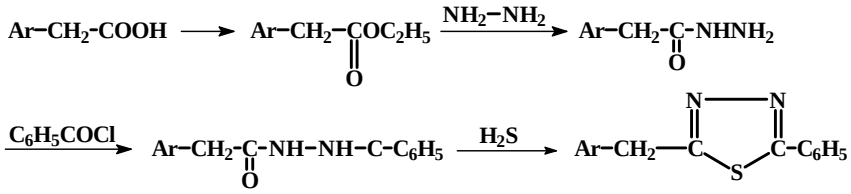


TABLE-1
ANALYTICAL AND IR SPECTRAL DATA OF PRODUCTS

S. No.	Compound/(m.f.)	Elemental Analysis Calcd. (Found)%	IR (KBr, cm^{-1})
1	2-*p*-Nitrobenzyl-5-phenyl-1,3,4-thiadiazole ($C_5H_{11}N_3O_2S$)	N = 14.50 (14.14) S = 10.50 (10.77)	1590 ν(C=N) 1505 ν(NO_2 *arom.*) 2920 ν(C–N) 760 ν(C–S)
2	2-*p*-Bromophenyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_2SBr$)	N = 8.20 (8.45) S = 9.75 (9.66)	1580-1505 ν(C=N) for sub. benzene ring 2910 ν(C–H) 755 ν(C–S)
3	2-*p*-Methoxybenzyl-5-phenyl-1,3,4-thiadiazole ($C_{16}H_{14}ON_2S$)	N = 10.15 (9.92) S = 11.50 (11.34)	1585-1580 ν(C=N) for sub. benzene ring 2920 ν(C–H) 775 ν(C–S)
4	2-*o*-Chlorobenzyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_2Cl_3$)	N = 9.60 (9.77) S = 11.40 (11.16)	1590-1575 ν(C=N) for sub. benzene ring 2920 ν(C–H) 785 ν(C–S)
5	2-*p*-Chlorobenzyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_2Cl_5$)	N = 10.15 (9.77) S = 11.40 (11.16)	1590-1585 ν(C=N) for sub. benzene ring 2920 ν(C–H) 785 ν(C–S)
6	2-*m*-Chlorobenzyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_2Cl_5$)	N = 9.85 (9.77) S = 11.00 (11.16)	1605-1580 ν(C=N) for sub. benzene ring 2900 ν(C–H) 760 ν(C–S)
7	2-*o*-Nitrobenzyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_3O_2S$)	N = 13.95 (14.14) S = 10.50 (10.77)	1590 ν(C=N) 1575 ν(NO_2 *arom.*) 2920 ν(C–N) 785 ν(C–S)
8	2-*m*-Nitrobenzyl-5-phenyl-1,3,4-thiadiazole ($C_{15}H_{11}N_3O_2S$)	N = 14.00 (14.14) S = 11.00 (10.77)	1590 ν(C=N) 1505 ν(NO_2 *arom.*) 2920 ν(C–N) 765 ν(C–S)

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