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Synthesis and Structural Studies of 2,5- Diaryl/Dialkylimino-1,3,4-Thiadiazolidines and their Acetyl and Nitroso Derivatives

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ABSTRACT

Synthesis with Spectral analysis of some 2,5-Symmetrically substituted -1,3,4-thiadiazolidines(II) have been achieved through innovative route by the interaction of 1,6-diaryl/dialkyl-2,5-bithioureas(I) with iodine containing KI and NaOH. The interaction involved the oxidative cyclisation of the compound by elimination of hydrogen sulphide gas. The compound (II) thus prepared, were successfully acetylated by acetic anhydride and glacial acetic acid. The nitroso derivatives were also prepared from compound (II) and the structure of all these compounds were established on the basis of elemental analysis, IR and PMR spectral data.

Keyword: 5-membered ring system with N & S, Diaza derivative of thiophene, Vital important drug, Pesticides.

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INTRODUCTION

Heterocyclic chemistry is called as one of the mostintriguing and complex branch of organic chemistry Five-membered heterocycles, such as imidazole, oxazole, thiazole, oxadiazole and thiadiazole, are common and typically possess biological activities. In the recent decades, the synthesis of substituted thiadiazoles and related compounds has attracted considerable attention because these compounds constitute the structural frameworks of several naturally occurring compounds. In recent decades, research has indicated that the thiadiazole ring is an important framework with broad-spectrum biological activity. 1,3,4 Thiadiazolidine containing compounds show a widespectrum of biological activities such as carbonic anhydrase inhibitors, analgesic, antiinflammatory, anti-bacterial etc. Thiadiazolidines are of vital importance as drugs. These ring systems have been successfully incorporated in commercial drugs and pesticides in past and still offers chances to various new types to increase their activities. Thiadiazolidines are the five membered ring systems in which two Nitrogen and sulphur atoms are present. They can also called as diazo deterivative[4] of thiophene in which two –CH= grouping have been replaced by –N=. The synthetic applications of aryl isocynodichloride have been investigated earlier. The reagent, which was first prepared by Nef [8], has been shown to have enough potentiality in the synthesis of Nitrogen and Sulphur containing 5 & 6- membered heterocyclic compound. Therefore, it appeared sufficiently interesting to prepare aryl isocynodichloride and use these reagents as intermediate in the synthesis of nitrogen and sulphur containing heterocyclic compound. With this aim in mind, N-phenylisocynodichloride was prepared and its reaction with substituted thiosemicarbazides have been carried out and 1, 3, 4,-thiadiazolidines have been isolated in good yield.

MATERIALS AND METHOD

In this section the oxidative cyclisation of 1, 6-diaryl/dialkyl-2,5-dithiobiureas have been undertaken with the help of iodine solution containing KI and NaOH. The product thus obtain were converted into their acetyl as well as nitroso derivative. The reagent for synthesis of 2, 5-symmetrically substituted 1,3,4-thiadiazolidine describe here were prepared as follow-

Preparation of aryl/alkyl isothiocynate

A facile and general protocol for the preparation of isothiocyanates from alkyl and aryl amines relies on a tosyl chloride mediated decomposition of a dithiocarbamate salts that are generated in situ by treatment of amines with carbon disulfide and triethylamine. Various aryl/alkyl isothiocyanates have been prepared in good yield.

Preparation of 1,6-diaryl/dialkyl 1,2,5-dithiobiurea (I)

These were prepared involving the reaction of alkyl/aryl isothiocyanates with hydrazine hydrate in 2:1 ratio. A mixture of aryl/alkyl isothiocyanates and hydrazinehydrate(15 ml) was refluxed for 4 h. The excess of hydrazine hydrate was removed in vacumn and the residue was triturated with water, filtered off, dried and recrystallized from ethanol to give colorless crystals.

Interaction of 1,6-diaryl/dialkyl-2,5-dithiobiurea (I) with excess iodine containing. KI and NaOH

Formation of 2, 5-diaryl/dialkylimino-1, 3, 4-thiadiazolidines (II)

a**) Synthesis of 2, 5-diphenylimino-1, 3, 4-thiadiazolidine (IIa)**

1, 6-Diphenyl-2, 5-dithiobiurea (Ia) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white colored product separated out which on crystallization from ethanol gave colorless 2,5-diphenylimino-1,3,4-thiadiazolidine (IIa),

b) Synthesis of 2,5-di-o-tolylimino-1,3,4-thiadiazolidine (IIb)

1, 6-Di-o-tolyl-2,5-dithiobiurea (Ib) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white colored product separated out which on crystallization from ethanol gave colorless 2,5-di-o-tolylimino-1,3,4-thiadiazolidine (IIb).

c) Synthesis of 2,5-di-m-tolylimino-1,3,4-thiadiazolidine (IIc)

1, 6-Di-m-tolyl-2,5-dithiobiurea (Ic) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white colored product separated out which on crystallization from ethanol gave colorless 2,5-di-m-tolylimino-1,3,4-thiadiazolidine (IIc),

d) Synthesis of 2,5-di-p-tolylimino-1,3,4-thiadiazolidine (IId)

1,6-Di-p-tolyl-2,5-dithiobiurea (Id) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white

colored product separated out which on crystallization from ethanol gave colorless 2,5-di-m-tolylimino-1,3,4-thiadiazolidine (IId),

e) Synthesis of 2,5-di-o-chlorophenylimino-1,3,4-thiadiazolidine (IIe)

1,6-di-o-chlorophenyl-2,5-dithiobiurea (Ie) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white colored product separated out which on crystallization from ethanol gave colorless 2,5-di-o-chlorophenylimino -1,3,4-thiadiazolidine (IIe)

f) Synthesis of 2,5-di-p-chlorophenylimino-1,3,4-thiadiazolidine (IIf)

1, 6-di-p-chlorophenyl-2,5-dithiobiurea (If) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when off white colored product separated out which on crystallization from ethanol gave colorless 2,5-di-p-chlorophenylimino -1,3,4-thiadiazolidine (IIf),

g) Synthesis of 2,5-di-t-butylimino-1,3,4-thiadiazolidine (IIg)

1,6-di-t-butyl-2,5-dithiobiurea (Ig) was made into paste in a china dish. To this was added the solution of iodine was made up by mixing potassium iodide and NaOH. The iodine solution was added in excess till no further decolourisation took place. The reaction involves evolution of hydrogen sulphide gas. The reaction mixture was allowed to stand for 6-7 hrs, when the granular product separated out, which on crystallization from ethanol gave c 2,5- di-t-butylimino -1,3,4-thiadiazolidine (IIg),

Acetylation of 2,5-diaryl/dialkylimino-1,3,4- thiadiazolidine(II) by acetic acid in 1:1 ratio

IIa ,IIb, IIc , IId, IIe , IIf, IIg, (0.01 mole)on refluxing with acetic anhydride (0.01mole) and glacial acetic acid (10ml) for 1hr,followed by dilution with water afforded (IIIa, IIIb, IIIc,IIId, IIIe, IIIf & IIIg). The products were crystallized from ethanol.

Interaction of 2,5-diaryl/dialkylimino-1,3,4- thiadiazolidine(II) and Sodium Nitrite with conc. HCl (Nitrous acid)

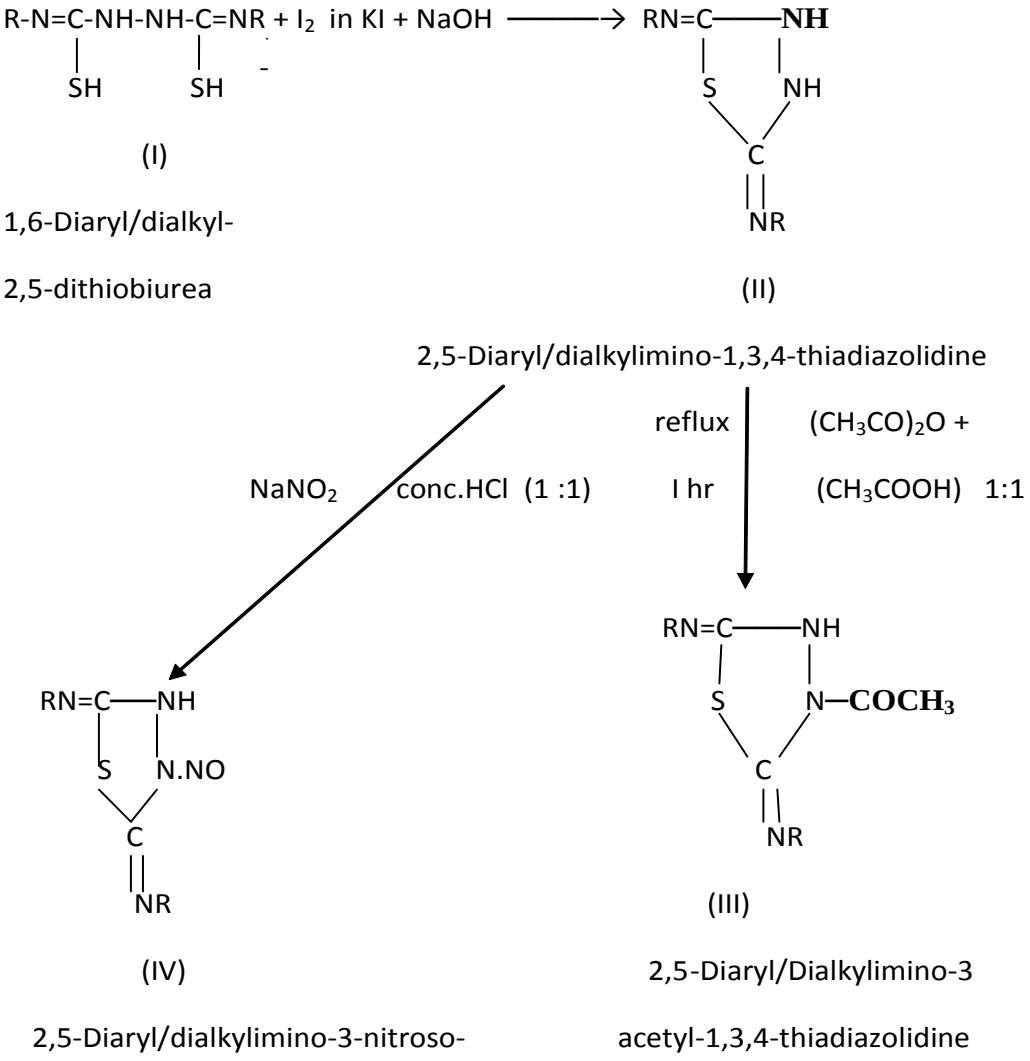
Formation of 2,5-diaryl/dialkylimino- 3-nitroso-1,3,4- thiadiazolidine

IIa ,IIb, IIc , IId, IIe , IIf, IIg, (0.01 mole) was made into solution with conc. HCl . To this acidic solution 5ml of 20% sodium nitrite was added with continuous stirring. The reaction mixture was

allowed to stand for 2 hrs for completion of reaction. It was filtered through bucher and washed with water to give (IVa, IVb, IVc, IVd ,IVe, IVf & IVg). The products were crystallized form.

Reaction scheme

The formation of 2,5-diaryl/dialkylimino-1,3,4-thiadiazolidine (II) and their acetyl derivative (III) as well as nitroso derivative (IV) can be stated as-



Where- R=in Ia, IIa, IIIa and IVa = Phenyl

R=in Ib, IIb, IIIb and IVb = o-tolyl

R= in Ic, IIc, IIIc and IVc = m-tolyl

R=in Id, IId, IIId and IVd = p-tolyl

R=in Ie, IIe, IIIe and IVe = o-chlorophenyl

R=in If, IIf, IIIf, and IVf = p-chlorophenyl

R=in Ig, IIg, IIIg and IVg = t-butyl

RESULTS AND DISCUSSION

The reaction of 1,6 Diphenyl -2-5-dithiourea (Ia) was made into paste with ethanol. To this ethanolic paste was added iodine solution containing KI & NaOH with constant stirring. The colour of iodine initially disappered with evolution of H_2S gas. But the addition was continued until no further decolurisation of iodine took place and violet colour persisted. The reaction mixture was allowed to stand 3-4 hrs .To ensure the completion of reaction. when off white colour product (IIa) separates out was crystallized from ethanol. The compound was found to be acidic to litmus The compound was insoluble in water but soluble in organic solvent like acetone , chloroform, alcohol etc. The IR analysis showed the presence of following absorption band due to ᵛNH(3212 cm-1),ᵛC=N(1597 cm-1), ᵛC-N(1335 cm-1) ,ᵛN-N(1190cm-1), ᵛC-S(693 cm-1).The PMR spectrum of the product showed peaks due to aromatic protons at δ(7.9 to 7.5ppm)and N-H proton at δ(9.5 ppm) synthesis and structural. On the basis of above facts the compound (IIa) has been assigned the structure as 2,5-Diphenylimino-1,3,4-thiozolidine. Compound compound (IIb-IIg)were synthesized by extending the reaction of 1,6,Diaryl/Dialkyl and iodine and KI and NaOH and Related 1,3,4,thiadiazolidine (IIb-IIg) were Isolated in Good Yield. 2,5-diphenylimino-1,3,4-thiadiazolidine (IIa) on Refluxing with Glacial acetic acid and acetic anhydriode mixture in 1:1 ratio for one hour followed by distallitation with water afforded a solid (IIIa) crysallized with ethanol M.P.180 C .The (IIIa) gave positive test for N,S element and for –COCH3 Group. The elemental analysis of the product indicated its Molecular formula C16H14N4SO (Found C=61.75%, H=4, 38%, N=17, 88%, S=10.15%) calculated for (C16H1N4SO C=61.93%, H=4, 51%, N=18.06%, S=10,32%) The IR analysis showed the presence of following absorption band due to ᵛNH(3211 cm-1),ᵛC=N(1597 cm-1), ᵛC-N(1310 cm-1) ,ᵛN-N(1189cm-1), ᵛC-S(693 cm-1), ,ᵛC=O(1640 cm-1), On the basis of above facts the compound (IIIa) has been assigned the structure as 2,5-diphenylimine -3-1,3,4-thiadiozolidine. The other related acetyl derivatives (IIIb-IIIg) were prepared by extending the above reaction. 2,5-diphenylimino-1,3,4-thiadiazolidine (IIa) was mixed with conc HCL. To This Solution was added 5 ml of 20% sodium nitrate with continuous stirring. The reaction mixture was allowed to stand for 2 hrs for completion of reaction. The product was crystallized from ethanol. The product was identified as 2,5-diphenylimino-3-nitroso-1,3,4 thiadiazolidine (IV a)M.P. 190. The (IVa) gave positive test for N & S element. The elemental analysis of the product identified it m.f.C14 H11 N5 SO (Found N=24.23%,S=10,90%) calculated for C14 H11 N5 SO(N=24,45%

& S=11,18%) On the basis of above facts the compound (IVa) has been assigned the structure as 2,5-diphenylimine -3-nitroso-1,3,4-thiadiozolidine.The other related acetyl derivatives (IVb-IVg) were prepared by extending the above reaction.

Table 1: Formation of 2, 5-diaryl/dialkylimino-3- acetyl-1, 3, 4-thiadiazolidines (III) Reactants: Formation of 2, 5-diaryl/dialkylimino-1,3,4-thiadiazolidines(II)and acetic anhydride

S No.	2,5-diaryl/dialkylimino-1,3,4-thiadiazolidines(II)	2,5-diaryl/dialkylimino-3 -acetyl-1,3,4-thiadiazolidines(III)	M.P	Mol.Formula	Elemental analysis(%) Found(Calculated)			
					C	H	N	S
1	2,5-diphenylimino-1,3,4 -thiadiazolidine (IIa)	2,5-diphenylimino-3- acetyl -1,3,4- -thiadiazolidine (IIIa)	180	$C_{16}H_{14}N_4SO$	61.75 (61.93)	*4.38* (4.51)	17.88 (18.06)	10.15 (10.30)
2	2,5-di-o-tolylimino-1,3,4-thiadiazolidine (IIb)	2,5-di-o-tolylimino-3- acetyl-1,3,4-thiadiazolidine (IIIb)	146	$C_{18}H_{18}N_4SO$	63.81 (63.90)	5.26 (5.32)	16.35 (16.56)	9.28 (9.46)
3	2,5-di-m-tolylimio-1,3,4-thiadiazolidine (IIc)	2,5-di-m-tolylimino-3- acetyl-1,3,4-thiadiazolidine (IIIc)	152	$C_{18}H_{18}N_4SO$	63.76 (63.90)	5.18 (5.32)	16.40 (16.56)	9.45 (9.46)
4	2,5-di-p-tolylimino-1,3,4-thiadiazolidine (IId)	2,5-di-p-tolylimino-3- acetyl- -1,3,4-thiadiazolidine (IIId)	178	$C_{18}H_{18}N_4SO$	63.72 (63.90)	5.20 (5.32)	16.38 (16.56)	9.26 (9.46)
5	2,5-di-o-chlorophenylimino-1,3,4- thiadiazolidine (IIe)	2,5-di-o-chlorophenylimino--3-acetyl- -1,3,4-thiadiazolidine (IIIe)	110	$C_{14}H_{12}N_4SOCl$	52.43 (52.66)	3.55 (3.76)	17.38 (17.55)	9.86 (10.03)
6	2,5-di-p-chlorophenylimino-1,3,4- thiadiazolidine (IIf)	2,5-di-p-chlorophenylimino-3-acetyl- 1,3,4-thiadiazolidine (IIIf)	250	$C_{14}H_{12}N_4SOCl$	52.36 (952.66)	3.58 (3.76)	17.30 (17.55)	9.87 (10.03)
7	2,5-di-t-butylimino-1,3,4-thiadiazolidine (IIg)	2,5-di-t-butylimino-3- acetyl-1,3,4-thiadiazolidine (IIIg)	160	$C_{14}H_{12}N_4SO$	53.18 (53.33)	7.85 (8.14)	20.53 (20.74)	11.50 (11.83)

Table 2: Formation of 2, 5-diaryl/dialkylimino-3- nitroso-1, 3, 4-thiadiazolidines (IV):

Reactants: Formation of 2, 5-diaryl/dialkylimino-1,3,4-thiadiazolidines(II)and sodium nitrite and conc. HCl(Nitrous acid)

SN	2,5-diaryl/dialkylimino-1,3,4-thiadiazolidines **(II)**	2,5-diaryl/dialkylimino-3-nitroso-1,3,4-thiadiazolidines **(IV)**	M.P	Mol..Formula	Elemental analysis(%) Found(Calculated)	
1	2,5-diphenylimino-1,3,4-thiadiazolidine (IIa)	2,5-diphenylimino-3-nitroso- -1,3,4 -thiadiazolidine (IVa)	190	$C_{14}H_{11}N_5SO$	24.23 (24.45)	10.90 (11.1)
2	2,5-di-o-tolylimino-1,3,4-thiadiazolidine (IIb)	2,5-di-o-tolylimino-3-nitroso-1,3,4-thiadiazolidine (IVb)	166	$C_{16}H_{15}N_5SO$	21.30 (24.45)	9.70 (9.94)
3	2,5-di-m-tolylimino-1,3,4-thiadiazolidine (IIc)	Synthesisof 2,5-di-m-tolylimino-3-nitroso-1,3,4-thiadiazolidine (IVc)	169	$C_{16}H_{15}N_5SO$	21.37 (21.53)	9.64 (9.84)
4	2,5-di-p-tolylimino-1,3,4-thiadiazolidine (IId)	2,5-di-p-tolylimino-3-nitroso- -1,3,4-thiadiazolidine (IVd)	178	$C_{16}H_{15}N_5SO$	21.36 (21.53)	9.62 (9.84)
5	2,5-di-o-chlorophenylimino-1,3,4-	2,5-di-o-chlorophenylimino-3-nitroso-1,3,4-	123	$C_{14}H_9N_5SOCl$	16.84	9.50 (9.69)

	thiadiazolidine (IIe)	thiadiazolidine (IVe)			(16.96)	
6	2,5-di-p-chlorophenylimino-1,3,4-thiadiazolidine (IIf)	2,5-di-p-chlorophenylimino-3-nitroso-1,3,4-thiadiazolidine (IVf)	210	$C_{14}H_9N_5SOCl$	16.72 (16.96)	9.44 (9.69)
7	2,5-di-t-butylimino-1,3,4-thiadiazolidine (IIg)	2,5-di-t-butylimino-3-nitroso- 1,3,4-thiadiazolidine (IVg)	155	$C_{10}H_{19}N_4SO$	27.08 (27.23)	12.20 (12.45)

CONCLUSION

The thiadiazole ring is an important framework with broad-spectrum biological activity. 1,3,4 Thiadiazolidine containing compounds show a wide spectrum of biological activities such as carbonic anhydrase inhibitors, analgesic, anti-inflammatory, anti-bacterial etc. Thiadiazolidines are of vital importance as drugs. These ring systems have been successfully incorporated in commercial drugs and pesticides in past and still offers chances to various new types to increase their activities.

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