SYNTHESIS OF SOME 3-ARYLIMINO-5-(N-4-METHOXYBENZYLIDENE-HYDRAZONO)-1,2,4-DITHIAZOLIDINES

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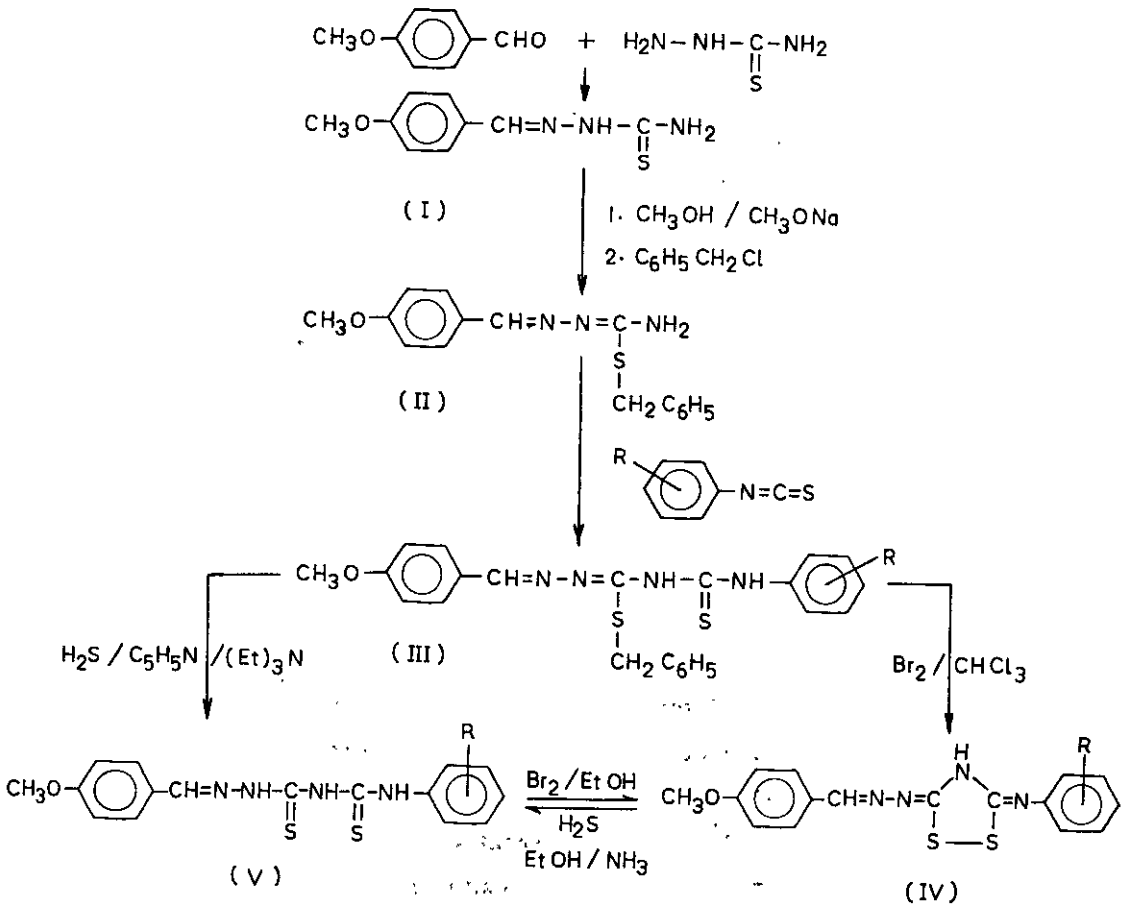
Abstract - A simple and convenient synthesis of some 3-arylimino-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidines (IV a-e) has been achieved by oxidative debenzylation and cyclization of the corresponding 5-aryl-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiurets (III a-e) which in turn were prepared by the condensation of certain potentially active S-benzyliso-4-methoxybenzylidenethiosemicarbazone (II) with appropriate aryl isothiocyanate. These dithiazolidines have been characterized by their synthesis through alternative routes (Scheme 1), elemental analyses and also by ir spectra.

The chemistry of substituted 1,2,4-dithiazolines and dithiazolidines has been of considerable interest to this research group[1-4]. Thiosemicarbazides and thiosemicarbazones have been known for their activity against viruses, protozoa, small pox and certain kinds of tumour[5-8]. Certain thiosemicarbazides have been also reported to possess fungicidal activity[9] due to presence of toxophoric >N-C(=S)- grouping and several substituted heterocyclic compounds having this active moiety are also on record[10-11]. In the present communication, attempts have been made to combine the toxicity of aldehyde molecule with the toxophoric activity of thiosemicarbazides with a view to synthesise certain isodithiobiurets, dithiobiurets and their heterocyclic oxidation products having potential biological activity.

In view of these facts, we now report the synthesis of certain hitherto unknown 5-aryl-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiurets (III a-e) and their facile conversion to the related 3-arylimino-5-(N-4-methoxybenzylidene-hydrazono)-1,2,4-dithiazolidines (IV a-e).

The procedure consists of treating the 4-methoxybenzaldehyde thiosemicarbazone (I) with benzyl chloride in methanol in presence of sodium methoxide, and the resulting S-benzyliso-4-methoxybenzaldehyde thiosemicarbazone (II) was condensed with appropriate aryl isothiocyanate to afford 5-aryl-1-(4-methoxybenzylidene-amino)-2-S-benzyliso-2,4-dithiobiurets (III a-e). The latter in chloroform solution was treated with molecular bromine when the benzyl group of these was

SCHEME-1



Where, III-V
a, R = Cl-3
b, R = Cl-4
c, R = CH_3-3
d, R = OCH_3-3
e, R = OC_2H_5-4

eliminated as benzyl bromide followed by ring closure to the related 3-arylimino-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidines (IV a-e). These compounds have also been obtained by the oxidation of the related 5-aryl-1-(4-methoxybenzylideneamino)-2,4-dithiobiurets (V a-e) which after reductive debenzylation of the related isodithiobiurets (III a-e) with hydrogen sulphide in pyridine-triethylamine were obtained and also by reduction of (IV) with H_2S in ethanolic ammoniacal solution. Their structural assignments were based on mixed melting point technique and spectral studies too.

EXPERIMENTAL

All melting points were determined with a Kofler hot stage apparatus by open capillary tube method and are uncorrected. IR spectra were recorded on Perkin-Elmer Spectrophotometer (Model 720) in nujol.

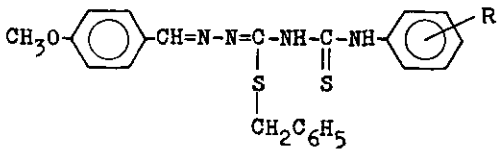
The precursor 4-methoxybenzaldehyde thiosemicarbazone (I) was obtained by the condensation of 4-methoxybenzaldehyde and thiosemicarbazide following known method[12]. The benzylation of (I) was affected with benzyl chloride in presence of sodium methoxide in methanol.

5-Aryl-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiurets (III a-e) .- A mixture of 4-chlorophenyl isothiocyanate (2.02 g, 0.0119 M) and S-benzyliso-4-methoxybenzaldehyde thiosemicarbazone (II) (3.57 g, 0.0119 M) in benzene (20 ml) was refluxed for 4-6 h on a steam bath. The excess of solvent was removed under reduced pressure and semi solid residue was repeatedly washed with petroleum ether (bp 40-60°C) followed by addition of a little ethanol. The crude isodithiobiuret thus obtained was crystallized from ethanol. (III b) 3.0 g (67%), mp 160°C.

Similarly other 5-aryl-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiurets were prepared by the condensation of S-benzyliso-4-methoxybenzaldehyde thiosemicarbazone with different aryl isothiocyanates (Table 1).

3-Arylimino-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidines (IV a-e).- The following procedures are typical to the methods used to prepare new derivatives of dithiazolidines.

Table 1 – 5-Aryl-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiurets (III a-e)[a]



Compd.	R	mp °C	Yield %	ir bands in Nujol[13-15] cm^{-1}	assignments
IIIa	Cl-3	130	65	3210m	NH
				1115, 1145vs, 1205w	N-C(=S)-N
IIIb	Cl-4	160	67	3205m	NH
				1120, 1150vs, 1200w	N-C(=S)-N
IIIc	CH_3-3	140	55	3200m	NH
				1120, 1145vs, 1210w	N-C(=S)-N
IIId	CH_3O-3	154	51	3200m	NH
				1100, 1140vs, 1200w	N-C(=S)-N
IIIe	C_2H_5O-4	87	69	3210m	NH
				1125, 1150vs, 1220w	N-C(=S)-N

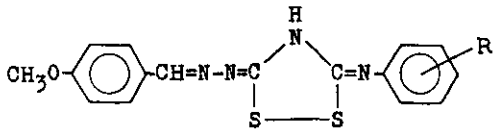
[a]Elemental analyses (C,H,N,S), in all of these compounds, are in agreement within ± 0.30 of the theoretical values.

Method A: Oxidative debenzylation of III a-e .– 5-(3-Chlorophenyl)-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiuret (IIIa) (2 g, 0.004 M) which was made into paste with little chloroform was treated with molecular bromine till the colour of bromine persisted. The reaction mixture warmed up considerably evolving fumes of benzyl bromides. It was allowed to stand over 45 min and, thereafter, repeatedly washed with ether. The treatment with a little ethanol separated out the hydrobromide of 3-(3-chlorophenylimino)-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidines as a solid mass. Free base (IVa) was obtained by treating this with ammonia solution (sp.gr. 0.90) and crystallised from ethanol in 70% yield. (IVa) mp 243°C. Other derivatives (IIIb-e) were similarly oxidised to their corresponding dithiazolidines (IVb-e) (Table 2).

Method B: Oxidation of V a-e .—

The oxidation of 5-(3-chlorophenyl)-1-(4-methoxybenzylideneamino)-2,4-dithiobiuret (Va) (2 g, 0.005 M) (Table 3) with bromine in dilute ethanol followed by addition of excess of ether afforded the hydrobromide of the corresponding 3-(3-chlorophenylimino)-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidine. The treatment of this with ammonia solution yielded the free base (IVa) which was crystallised from ethanol. Yield 1.42 g (72%). Similarly the remaining derivatives (V b-e) were oxidatively cyclodehydrogenated (Table 2).

Table 2 - 3-Arylimino-5-(N-4-methoxybenzylidenehydrazono)-1,2,4-dithiazolidines (IV a-e)[a]



Compd.	R	mp °C	Yield[b] %	ir bands in Nujol[13-15] cm^{-1}	assignments
IVa	Cl-3	243	70	480s	S-S
			(72)	1615s	C=N
IVb	Cl-4	123	72	480s	S-S
			(70)	1620s	C=N
IVc	CH_3-3	178	73	485s	S-S
			(59)	1610s	C=N
IVd	CH_3O-3	124	63	490s	S-S
			(67)	1620s	C=N
IVe	C_2H_5O-4	118	59	485s	S-S
			(70)	1610s	C=N

[a]Elemental analyses (C,H,N,S), in all of these compounds, are in agreement within ± 0.30 of the theoretical values.

[b]Numbers in parentheses indicate yield obtained by method B.

5-Aryl-1-(4-methoxybenzylideneamino)-2,4-dithiobiurets(V a-e) .—

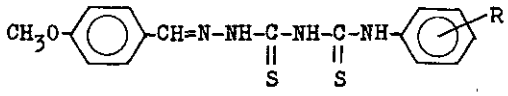
The methods below are typical among those used to prepare new derivatives of the

2,4-dithiobiurets.

Method A: Reductive debenzylation of III a-e .—

5-(3-Chlorophenyl)-1-(4-methoxybenzylideneamino)-2-S-benzyliso-2,4-dithiobiuret (2 g, 0.004 M) was accordingly dissolved in pyridine-triethylamine solution (1:6) and subjected to the stream of H_2S for 4 h. The resulting reaction mixture was filtered, poured over crushed ice and acidified with dilute hydrochloric acid getting precipitated the expected 5-(3-chlorophenyl)-1-(4-methoxybenzylideneamino) -2,4-dithiobiuret (Va). It was filtered and crystallised from ethanol in 50% yield, (Va) mp 175°C. The remaining isodithiobiurets (III b-e) were also reduced to their corresponding dithiobiurets (V b-e) (Table 3).

Table 3 – 5-Aryl-1-(4-methoxybenzylideneamino)-2,4-dithiobiurets (V a-e)[a]



Compd.	R	mp °C	Yield[b] %	ir bands in Nujol[13-15] cm^{-1}	assignments
Va	Cl-3	175	50	1145m	N-C(=S)-N
			(49)	1620s	C=N
Vb	Cl-4	130	57	1145m	N-C(=S)-N
			(50)	1620s	C=N
Vc	CH_3-3	161	42	1150m	N-C(=S)-N
			(61)	1615s	C=N
Vd	CH_3O-3	143	45	1145m	N-C(=S)-N
			(55)	1615s	C=N
Ve	C_2H_5O-4	168	61	1150m	N-C(=S)-N
			(61)	1620s	C=N

[a]Elemental analyses (C,H,N,S), in all of these compounds, are in agreement within ± 0.30 of the theoretical values.

[b]Numbers in parentheses indicate yield obtained by method B.

Method B: Reduction of IV .—

A stream of dry hydrogen sulphide was passed for 4 h in the dithiazolidine (IVa)

(2 g, 0.005 M) dissolved in hot ethanolic ammoniacal solution (25 ml). The clear solution on dilution with water or acidification afforded the related 2,4-dithiobiurets(Va). It was crystallised from ethanol, yield 0.98 g (49%), mp 175°C (Table 3).

These compounds, in all the cases, were substantiated in terms of microanalyses, which were in good accord with calculated values, mixed melting point technique, spectral evidences and also with their synthesis through alternative routes (Scheme 1).

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