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Synthesis of Certain 3-(Alkyl/Arylthioureido)-5-Alkylimino-4-Alkyl-1,2,4-Δ^2-Thiadiazolines

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Condensation of 5-alkylimino-3-amino-4-alkyl-1,2,4-Δ^2-thiadiazolines and alkyl/aryl isothiocyanates in a basic medium yields 3-(alkyl/aryl thioureido)-5-alkylimino-4-alkyl-1,2,4-Δ^2-thiadiazolines. Their structures have been established by chemical analysis and spectral data. The steric effects of alkyl or aryl groups do not affect the course of the reaction.

INTRODUCTION

A survey of the chemical literature reveals that a compound with an amine function reacts with isothiocyanates forming substituted thioureas. There are several reports that thiourea derivatives exhibit antibacterial[1], antifungal,[2, 3] antitubercular[4] and antitumour[5,6] activities. Some of the heterylthioureas known find use in the colorimetric determination of noble metals like platinum, gold[7] etc. These heterocyclic compounds find wide application in pharmacology[8]. The observations quoted are encouraging enough to stimulate further investigation in this direction.

The attack of an isothiocyanate and isocyanate on a heterocyclic ring system bearing an exocyclic as well as an endocyclic amino function has been the subject of active investigation. 3-Amino-4-aryl-5-arylimino-1,2,4-Δ^2-thiadiazolines are reported to resist condensation with isocyanates, isothiocyanates or carbon disulphide under various conditions[9,10]. The thiadiazolines were therefore stirred with equivalent amounts of isothiocyanate in acetonitrile or dimethyl formamide in the presence of strong alkali. After completion of the reaction, as indicated by the disappearance of the pungent smell of the isothiocyanate the reaction mixture was neutralised to give only one product in good yield in all the cases.

EXPERIMENTAL

Infrared spectra (KBr) were recorded on a Perkin-Elmer 397 spectrophotometer, PMR spectra on a R24-B Hitachi (60 MHz) spectrometer using TMS as an internal standard.

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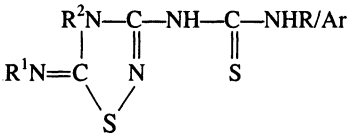
3-Amino thiadiazoles used for the preparation of thiourea derivatives were prepared by the oxidation of mixtures of 1,3-dialkylthroureas and thiourea.

Preparation of title compounds: To powdered NaOH (0.05 mol) suspended in dimethyl formamide (10 mL) containing 3-amino-4-alkyl-5-alkylimino-1,2,4-Δ^2-thiadiazoline (0.05 mol) isothiocyanate (0.05 mol) was added gradually with stirring. Stirring was continued till the pungent smell of isothiocyanate vanished. Completion of the reaction was tested by adding two drops of the reaction mixture into cold water (10 mL) when a clear solution was obtained. The reaction mixture was then poured into cold water (150 mL), filtered to remove any unreacted 3-amino thiadiazoles and the filtrate neutralised with 1% HCl. The resulting solid was crystallised (Table-1) TLC analysis showed purity of the compound.

TABLE-1

1-ALKYL/ARYL-3-(4-ALKYL-5-ALKYLIMINO-Δ^2-1,2,4-THIADIAZOL-3-YL) THIOUREA



Substituents			Yield	m.p.	m.f.	% Found (Required)	
R^1	R^2	R/Ar	(%)	(°C)		S	N
Benzyl	Benzyl	Methyl	30	125	$C_{18}H_{19}N_5S_2$	16.98 (17.34)	18.88 (18.97)
Benzyl	Benzyl	Ethyl	32	124	$C_{19}H_{21}N_5S_2$	16.36 (16.71)	18.20 (18.28)
Benzyl	Benzyl	*n*-Propyl	34	120	$C_{20}H_{23}N_5S_2$	15.77 (16.12)	17.60 (17.63)
Benzyl	Benzyl	Isopropyl	33	126	$C_{20}H_{23}N_5S_2$	15.80 (16.12)	17.59 (17.63)
Benzyl	Benzyl	Butyl	30	103	$C_{21}H_{25}N_5S_2$	15.23 (15.57)	17.01 (17.03)
Benzyl	Benzyl	Phenyl	30	115	$C_{23}H_{21}N_5S_2$	14.79 (14.84)	16.22 (16.26)
Benzyl	Benzyl	*p*-Tolyl	32	118	$C_{24}H_{23}N_5S_2$	14.27 (14.38)	15.69 (15.73)
Benzyl	Benzyl	*p*-Anisyl	31	130	$C_{24}H_{23}N_5S_2O$	13.38 (13.47)	14.69 (14.73)
Benzyl	Benzyl	*o*-Phenetyl	30	152	$C_{25}H_{25}N_5S_2O$	13.36 (13.47)	14.68 (14.73)

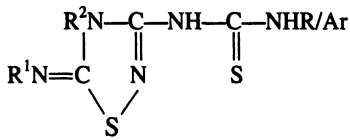
RESULTS AND DISCUSSION

An equimolar mixture of 3-amino-4-benzyl-5-benzylimino-1,2,4-Δ^2-thiadiazoline and methyl isothiocyanate, in the presence of equivalent quantity of powdered sodium hydroxide was stirred in dimethyl formamide for about 4 h. The reaction

was deemed complete when the pungent smell of the isothiocyanate disappeared. The reaction mixture on dilution, filtration and subsequent neutralisation yielded a product. TLC examination of this product showed the presence of only a single component. Only one molecule of the isothiocyanate condensed with the 1,2,4-thiadiazole as the product formed from elemental analysis was found to be a 1 : 1 adduct. The molecular composition was found to be $C_{18}H_{19}N_5S_2$. In all cases studied, the chromatogram showed only one product.

TABLE-2

1-ALKYL/ARYL-3-(4-ALKYL-5-ALKYLIMINO-Δ^2-1,2,4-THIADIAZOL-3-YL) THIOUREA

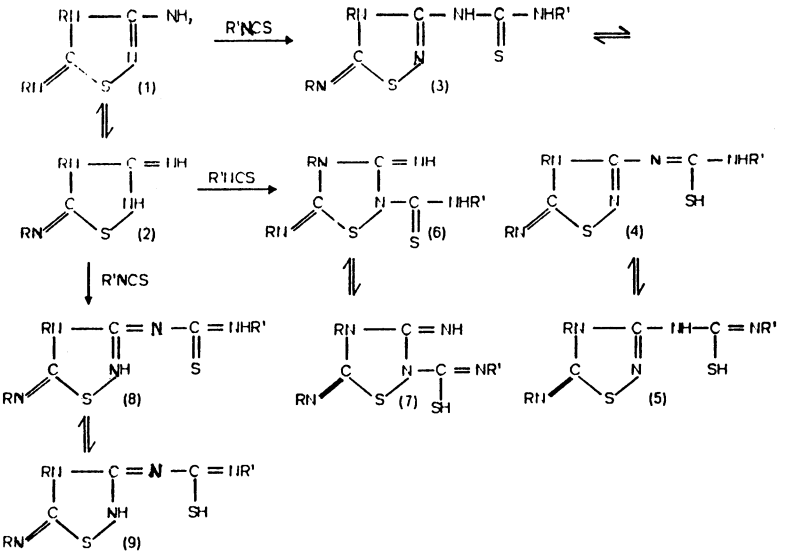


Substituents			Yield	m.p.	m.f.	% Analysis, Found (Required)	
R^1	R^2	R/Ar	%	(°C)		S	N
Propyl	Propyl	Methyl	–	–	$C_{10}H_{19}N_5S_2$	23.04 (23.44)	25.62 (25.64)
Propyl	Propyl	Ethyl	30	84	$C_{11}H_{21}N_5S_2$	21.92 (22.29)	24.38 (24.39)
Propyl	Propyl	Propyl	33	112	$C_{12}H_{23}N_5S_2$	20.94 (21.26)	23.23 (23.25)
Propyl	Propyl	Isopropyl	32	99	$C_{12}H_{23}N_5S_2$	20.98 (21.26)	23.18 (23.25)
Propyl	Propyl	Butyl	30	148	$C_{13}H_{25}N_5S_2$	19.97 (20.32)	22.18 (22.22)
Propyl	Propyl	Phenyl	30	150	$C_{15}H_{25}N_5S_2$	19.00 (19.10)	20.78 (20.89)
Propyl	Propyl	*p*-Tolyl	33	135	$C_{16}H_{23}N_5S_2$	17.98 (18.33)	20.01 (20.05)
Propyl	Propyl	*p*-Chloro phenyl	31	131	$C_{15}H_{20}N_5S_2Cl$	17.29 (17.34)	18.89 (18.97)
Propyl	Propyl	*p*-Anisyl	30	125	$C_{16}H_{23}N_5S_2O$	17.48 (17.53)	19.09 (19.17)

The product with the molecular formula $C_{18}H_{19}N_5S_2$ was found to be soluble in aqueous akali and was reprecipitated on neutralisation. On warming with alkaline lead acetate it was found to undergo dehydrosulphurisation indicating that the thiocarbamoyl function is attached to the 3-amino group. A thiocarbamoyl derivative which does not have an —NH—C(=S)—NH or N—C(=S)—NH_2 group would never give blackening with alkaline lead acetate. Hence the product contains an HN—C(=S)—NH grouping and the structure is (3).

Klayman[11, 12] reported during his studies on a large number of thioureas (including heterocyclic thioureas) that the differences in the rate of hydrolysis of

S-methyl derivative could be used as a means of distinguishing differently substituted thioureas. On treatment with aqueous sodium hydroxide solution the S-alkyl derivatives of 1-substituted thioureas hydrolysed at room temperature releasing methyl mercaptan whereas 1,3-disubstituted thioureas released mercaptan only on heating for 30 seconds at 100°C.



The condensation product was found to evolve methyl mercaptan when it was methylated and subsequently treated with warm alkali. This fact again confirms that the condensation has occurred on the exocyclic nitrogen atom.

The PMR spectrum of 1-methyl-3-(4-benzyl-5-benzylimino-Δ^2-1,2,4-thiadiazol-3-yl) thiourea showed the following absorptions. A doublet at δ 2.95 (3H) due to the 3 methyl protons of the —HN—C(=S)—NH—CH_3 group, a singlet at δ 3.95 (2H) due to the two methylenic protons of the benzyl group, another singlet at δ 4.65 (2H) due to the two methylenic protons of 5-benzylimino group. Aromatic protons appear as a broad multiplet between δ 6.4 and 6.9 (10H). A broad quartet between δ 7.0 and δ 7.3 (1H) due to the NH protons of the NH-Me group and a broad singlet between δ 9.2 and δ 9.6 (1H) due to —NH adjacent to the thiadiazoline ring which is more acidic than the NH—Me group.

The condensation of the two thiadiazoles with different isothiocyanates in the presence of powdered sodium hydroxide yielded the thiadiazolyl thiourea drivatives. The products obtained also answered the dehydrosulphurisation test as well as Klayman's test, indicating that condensation occurred on the exo amino group.

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