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Synthesis of Certain Thiadiazolylthioureas

M. JOLLYAMMA* and T.S. SUJATHA†
Department of Chemistry, Kuriakose Elias College, Mannanam-686 561, India
E-mail: jollysaiku@gmail.com

In this paper, the interaction of isothiocyanates with 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazoline are reported. The reaction in all cases occurred only on the exo amino function and is a versatile method for the synthesis of thiadiazoyl thioureas.

Key Words: Isothiocynate, Thiadiazolines, Thiadiazolylthioureas.

INTRODUCTION

The use of thiourea derivatives as antibacterial, antifungal, antitubercular and antitumor activities is well documented[1-10]. Some of the known heteryl thioureas find use of analytical reagents particularly in colorimetric determinations of noble metals like platinum, gold[11] *etc.* Further 1,2,4-thiadiazole derivatives with thioureido grouping are known to be virucides[12].

3-Amino-4-aryl-5-arylimino-1,2,4,-Δ^2-thiadiazolines (**1**) are reported to resists condensation with isocyanates, isothiocyanates or carbon disulphide under various conditions[13]. It has been found[14-17] that even a feebly basic amino function of a thiourea could be made to condense with isothiocyanate if the reactants are stirred together in a non-aqueous polar solvent like acetonitrile or dimethyl formamide in the presence of strong alkali. This condition has been tried on the case of 3-amino-4-aryl-5-arylimino-Δ^2-1,2-4-thiadiazolines and was found to be succesful. The condensation in all the cases examined occurred on the exo amino function. In the present investigation, the reaction of isothiocyanates with the thiadiazoline derivatives were carried out in acetonitrile in the presence of powdered sodium hydroxide.

EXPERIMENTAL

The IR (KBr) spectra were run on a Perkin-Elmer 397 infrared spectrophotometer, UV spectra in methanol on a Hitachi UV-220A spectrophotometer and ^{1}H NMR in $CDCl_3$ on R-24-B Hitachi 300 MHz high resolution NMR spectrometer with TMS as an internal standard. The mass spectra were taken on a Hewlett Packard HP-5995 mass spectrometer. Melting points were determined on a Thomas-Hoover immersion type melting point apparatus and are uncorrected and the purity of the products were confirmed by TLC.

†Department of Chemistry, M.M.N.S.S. College, Kottiyam-691 571, India.

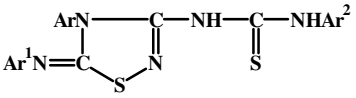
Interaction of 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazoline with aryl isothiocyanate: In a typical experiment, 3-amino-4-phenyl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazoline (2.9 g, 0.01 mol) and powdered sodium hydroxide (0.4 g, 0.01 mol) were stirred together in acetonitrile. An equimolar amount of phenyl isothocyanate (1.35 g, 0.01 mol) in acetonitrile (3 mL) was added dropwise to the reaction mixture. The mixture was stirred well till the smell of isothiocyanate disappeared or a drop of the reaction mixture poured in to water did not separate any oily layer. Then the reaction mixture was diluted with water, filtered to remove any insolubles and neutralized with dilute hydrochloric acid. A white precipitate was obtained. It was redissolved in dilute sodium hydroxide and again precipitated with dilute acid, collected on a filter, washed, dried (3 g, 81 %) and crystallized from ethanol when colourless needles of 1-phenyl-3-(4-phenyl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazol-3-yl)thiourea were obtained (m.p. 176 ºC). It was found to contain only one compound on TLC analysis and responded dehydrosulphurization test with ammonical silver nitrate solution. Analysis found: C = 63.9, H = 4.7, N = 16.1, S = 14.9 % required for $C_{23}H_{21}N_5S_2$, C = 64.0, H = 4.9, N = 16.2, S = 14.8 %; UV (MeOH) λ_{max}: 215, 245, 280 nm; IR (KBr, ν_{max}, cm^{-1}): 3395 and 3205 (s, N-H), 2925 (w, C-H), 1650 (s, C=N), 1590 (s, C=C), 1500 (s, C=S), 1055 (s) and 880 (w, ring skeletal vib. of 1,2,4-thiadiazoline); NMR ($CDCl_3$) δ: 2.2 (s, 6H, 2xCH_3 of xylyl), 7.5-8.1 (m, 14H, 13Ar-H), 12.0 (s, 1H, NH-Ar) mass m/z (%): 431 (M^+, 30.8), 340 (16.3), 338 (4.1), 296 (3.1), 268 (99.2), 254 (19.5), 253 (3.2), 222 (42.5), 209 (8.5), 105 (8.2), 163 (2.3), 93 (7.1), 135 (6.2), 77 (7.9).

Similar condensation reaction of other 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazolines with aryl and alkyl isothiocynates were conducted. The analytical data and physical constants of the resulting thiadiazolylthioureas are given in Tables 1 and 2.

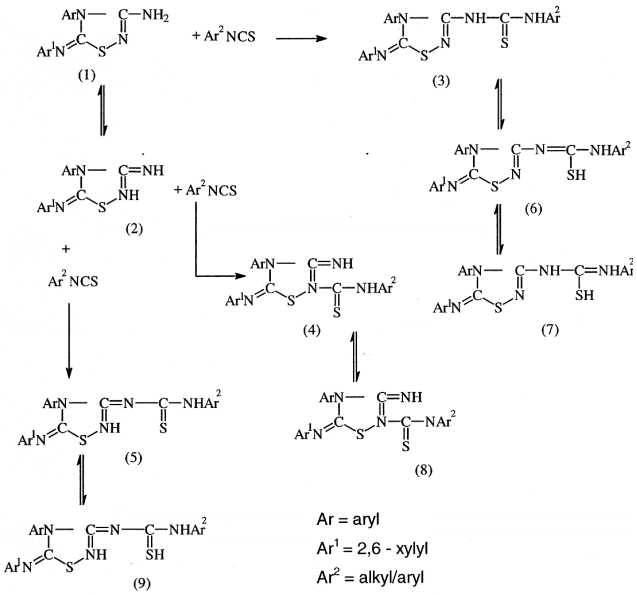
RESULTS AND DISCUSSION

An equimolar mixture of 3-amino-4-phenyl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazoline (**1**) and phenylisothiocyanate was stirred in acetonitrile in the presence of powdered sodium hydroxide. The reaction was seemed complete when the pungent smell of isothiocyanate disappeared or when a drop of the reaction mixture when diluted formed a clear solution without any oily film on the surface. Then the reaction mixture was diluted with water and neutralized with hydrochloric acid. The precipitate was filtered, washed with cold water and dried. The presence of only one spot on a TLC showed it to be single compound, m.p. 176 ºC. From elemental analysis its molecular composition was found to be $C_{23}H_{21}N_5S_2$, indicating that only one molecule of the isothiocyanate has condensed with the thiadiazoline and the product is a 1:1 adduct. Since thiadiazoline could exist in two tautomeric forms (**1**) or (**2**), the product may exist as (**3-5**) or its tautomeric structures (**6-9**).

TABLE-1
ADDITION PRODUCT OF ARYL ISOTHIOCYANATES WITH
3-AMINO-5-ARYLIMINO-4-ARYL-Δ^2-1,2,4-THIADIAZOLINES

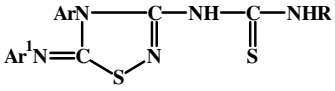


Compd.	Ar	Ar^1	Ar^2	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Found (calcd.)			
							C	H	N	S
a	Phenyl	2,6-Xylyl	Phenyl	$C_{23}H_{21}N_5S_2$	176	81	63.9 (64.0)	4.7 (4.9)	16.1 (16.2)	14.9 (14.8)
b	Phenyl	2,6-Xylyl	*p*-Tolyl	$C_{24}H_{23}N_5S_2$	166	77	64.5 (64.7)	4.7 (4.7)	15.6 (15.7)	14.3 (14.4)
c	*p*-Tolyl	2,6-Xylyl	Phenyl	$C_{24}H_{23}N_5S_2$	144	75	64.6 (64.7)	4.6 (4.7)	15.4 (15.7)	14.4 (14.4)
d	*p*-Tolyl	2,6-Xylyl	*p*-Tolyl	$C_{25}H_{25}N_5S_2$	157	72	65.2 (65.3)	5.3 (5.4)	15.1 (15.2)	14.0 (13.9)
e	*p*-Anisyl	2,6-Xylyl	*p*-Anisyl	$C_{25}H_{26}N_5O_2S_2$	104	69	60.9 (61.0)	5.3 (5.3)	14.1 (14.2)	12.8 (13.0)
f	*p*-Phenetyl	2,6-Xylyl	Phenyl	$C_{25}H_{26}N_5O_2S_2$	175	71	61.2 (61.0)	5.1 (5.3)	14.3 (14.2)	13.1 (13.0)
g	Phenyl	2,5-Xylyl	Phenyl	$C_{23}H_{21}N_5S_2$	156	74	63.8 (64.0)	4.8 (4.9)	16.1 (16.2)	14.9 (14.8)
h	Phenyl	2,5-Xylyl	*p*-Anisyl	$C_{24}H_{23}N_5S_2$	182	81	64.6 (64.7)	4.6 (4.7)	15.1 (15.7)	14.5 (14.4)
i	Phenyl	2,5-Xylyl	*p*-Anisyl	$C_{24}H_{23}N_5OS_2$	171	70	62.4 (62.5)	4.9 (5.0)	15.3 (15.2)	13.8 (13.9)



Scheme-I

TABLE-2
ADDITION PRODUCT OF ALKYL ISOTHIOCYANATES WITH
3-AMINO-4-ARYL-5-ARYLIMINO-Δ^2-1,2,4-THIADIAZOLINES



Compd.	Ar	Ar^1	R	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Found (calcd.)			
							C	H	N	S
a	Phenyl	2,6-Xylyl	Methyl	$C_{18}H_{19}N_5S_2$	177	95	58.4 (58.5)	5.0 (5.1)	18.8 (18.9)	17.2 (17.3)
b	Phenyl	2,6-Xylyl	*n*-Propyl	$C_{20}H_{23}N_5S_2$	135	90	60.3 (60.4)	5.8 (5.8)	17.5 (17.6)	16.1 (16.1)
c	*p*-Anisyl	2,6-Xylyl	*n*-Propyl	$C_{20}H_{25}N_5OS_2$	149	88	57.7 (57.8)	5.9 (6.0)	16.7 (16.8)	15.4 (15.4)
d	Phenyl	2,5-Xylyl	Methyl	$C_{18}H_{19}N_5S_2$	136	94	58.3 (58.5)	5.1 (5.1)	18.7 (18.9)	17.2 (17.3)
e	*p*-Tolyl	2,5-Xylyl	Methyl	$C_{19}H_{21}N_5S_2$	142	94	59.4 (59.5)	5.4 (5.5)	18.3 (18.2)	16.6 (16.7)
f	*p*-Tolyl	2,5-Xylyl	Ethyl	$C_{20}H_{23}N_5S_2$	154	92	60.2 (60.4)	5.7 (5.8)	17.6 (17.6)	16.2 (16.1)
g	*p*-Tolyl	2,5-Xylyl	*n*-Propyl	$C_{21}H_{25}N_5S_2$	134	90	61.2 (61.3)	6.0 (6.1)	17.0 (17.0)	15.4 (15.6)

The adduct obtained in the present reaction undergoes dehydrosulphurization with sodium plubite solution indicating that it contain $-NH-\underset{\underset{S}{\|}}{C}-NH-$ or a group $=N-\underset{\underset{S}{\|}}{C}-NH_2$ in its structure. Structure (**4** and **5**) is ruled out since they do not contain such grouping. The adduct gave a positive dehydrosulphurization test with ammoniacal silver nitrate and proved its structure to be (**3**).

The IR, UV and NMR and mass spectral data are also in agreement with 1-phenyl-3-(4-phenyl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazol-3-yl)thiourea structure (**3**). The PMR spectrum of the adduct (**3**) showed one NH proton in the region δ 12.0. The other NH proton was observed along with the aromatic protons in the region δ 7.5-8.1. The NH_2 protons of the starting material, 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazoline was observed[18] in the region δ 4.9 as a singlet. Due to the electron withdrawing nature of the substitutents in the adduct, the NH proton is found to be shifted to higher δ value. Both the NH signals are found to disappear when the spectra is run in the presence of D_2O. The signals due to the other substitutents were observed in the same region as shown by the parent thiadiazoline.

Similar condensations of the thiadiazolines with different aryl isothiocyanates yielded the thiadiazolylthiourea derivatives listed in Table-1. The condensation of alkyl isothiocyanates with various 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazolines yielded different thiadiazolylthiourea derivatives listed in Table-2.

From the above observations it is obvious that the thiourea derivatives obtained by the condensation of 3-amino-4-aryl-5-arylimino-Δ^2-1,2,4-thiadiazolines with aryl or alkyl isothiocyanates occurred on the amino group at position 3 of the 1,2,4-thiadiazoline and the product is a 1:1 adduct.

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