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Steric and Electronic Influence of Substituents on the Formation of 1,2,4-Thiadiazolines

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Oxidation of binary mixtures of 1-aryl-3-(2',6'-xylyl)thiourea and thiourea in acidic alcoholic solution yields 3-amino-4-aryl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazolines. A study of steric and electronic influence of substituents on the formation of 1,2,4-thiadiazolines has also been done. The rearrangement of the *bis*(formamidine)sulphide to amidinothiourea derivative has been found to be governed by the steric effect.

Key Words: Thioureas, Thiadiazolines.

INTRODUCTION

Research on new substances possessing antibacterial activity has attracted considerable attention owing to continuous increase in bacterial resistance[1]. Further, infection caused by various micro-organisms pose a serious challenge to the medical community and need for an effective therapy has led to the search for novel antibacterial agents[2]. Substituted thiadiazoline derivatives are an important class of compounds having various biological activities like antibacterial[3], anticancer[4], antiviral[5] and antifungal[6]. Based on the above observations and earlier investigations[7-21], here in are reported the synthesis of various 1,2,4-thiadiazoline derivatives.

Among the many methods reported for the synthesis of 1,2,4-thiadiazoline derivatives, oxidation of binary mixtures of thioureas have been used as a general method[9-21]. In these oxidations one molecule each of the thioureas is involved in the building up of the thiadiazoline. The structure of the final product formed is found to depend on the substitution pattern of the amidinothiourea intermediate which is formed by the isomerization of the *bis*(amidino)sulphide salt. During the isomerization of the *bis*(amidino)sulphide salt, of the two amidino groups, an unsubsituted[13-19] or alkyl substituted[16] amidino group is found to migrate to the aryl substituted nitrogen of the other amidino group. It has also been observed that if the aryl substituents on an amidino group are different, the amidino group which migrates preferentially goes to the nitrogen which bears the more electron releasing aryl group[15-17]. The mode of isomerization is not altered even though one of *ortho*-positions of aryl

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group is substituted by a methyl group[13]. Two products (**6** and **7**) were isolated, when both the *ortho*-positions were substituted by methyl groups[20]. The above observations prompted us to study the electronic and steric influence during the oxidation of 1-aryl-3-(2',6'-xylyl)thiourea and thiourea (aryl = *p*-tolyl, *p*-anisyl, *p*-phenetyl and *o*-phenetyl).

EXPERIMENTAL

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 HEW-LETT PACKARD HP-5995 mass spectrometer. Melting points were determined by capillary method and are uncorrected and the purity of the products were confirmed by TLC.

Oxidation of binary mixtures of 1-aryl-3-(2',6'-xylyl) thioureas and thiourea: In a typical experiment, a mixtures of 1-phenyl-3-(2',6'-xylyl)thiourea (6.05 g, 0.025 mol) and thiourea (1.9 g, 0.025 mol) in 1:1 ethanol-water mixture (200 mL) containing conc. HCl (6 mL, 32 %, 0.025mol) and oxidized with hydrogen peroxide (6 mL, 30 %, 0.05 mol). Colloidal sulphur started separating as evidenced by a pale yellow turbidity. During the addition of H_2O_2, the reaction mixture was warmed on a water bath. When the oxidation was complete the reaction mixture was cooled and filtered. The filtrate on basification yielded a white precipitate derived from the mixed oxidation. It was then collected, dried and crystallized from benzene-petroleum ether mixture when shining plates of the base were obtained (m.p. 168 ºC, 6.6 g, 89 %). TLC examination of this product showed the presence of only one compound and it was identified as 3-amino-4-phenyl-5-(2',6'-xylyl)imino-Δ^2-1,2,4-thiadiazoline (**6**). Analysis found (%): C 64.8, H 5.4, N 18.8, S 10.6, required (%) for $C_{16}H_{16}N_4S$, C 64.9, H 5.4, N 18.9, S 10.8; UV (MeOH) λ_{max}: 220, 250, 260 nm; IR (KBr, ν_{max}, cm^{-1}), 3450 and 3220 (s, N=H), 2970 (s), 2870 (m, C-H) 1640 (w, C=N), 1620 (s, NH_2),1025 (m) and 810 (ring skeletal vibrations of 1,2,4-thiadiazoline); NMR ($CDCl_3$) δ: -2.1 (s, 6H, 2 × CH_3 of xylyl), 4.9 (s, 2H, NH_2), 7.0-7.7 (non-resolved multiplet; 8H, Ar-H); Mass m/z (%) 296, (M^+, 93.3), 254 (25.2), 222 (44.3), 204 (10.1), 16.3 (1.5), 91 (30.4), 91 (30.4), 79 (17.9).

Other binary mixtures of 1-aryl-3-(2',6'-xylyl)thioureas with thiourea were similarly oxidized and worked up. The related 3-amino-4-aryl-5-xylylimino-Δ^2-1,2,4-thiadiazolines (**6a-e**) were obtained in a good yield. The melting points, elemental analysis and yield of the products, were listed in Table-1.

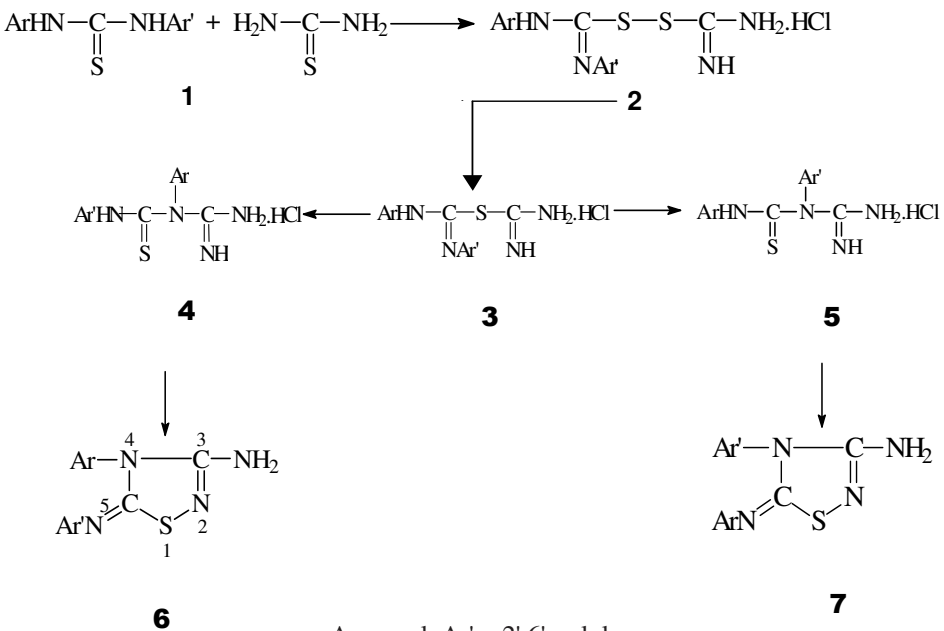
RESULTS AND DISCUSSION

Equimolar mixture of 1-phenyl-3-(2',6'-xylyl)thiorea (**1**) and thiourea on hydrogen peroxide oxidation afforded a compound **6** (**Scheme-I**). Reduction of **6** with hydrogen sulphide in acidic medium and subsequent decomposition with sodium bicarbonate afforded 2',6'-xylylisothiocyanate and phenylguanidine carbonate. Oxidation of the

solution obtained after reduction yielded the original base **6** back. The interconversion between amidinothiourea **5** and the original base by oxidation-reduction reactions supports the structure **6**.

TABLE-1

Compd.	Ar	Ar'	m.f.	Elemental analysis (%): Found (reqd.)				m.p. (ºC)	Yield (%)
				C	H	N	S		
6a	Phenyl	2',6'-Xylyl	$C_{16}H_{16}N_4S$	64.8 (64.9)	5.4 (5.4)	18.8 (18.9)	10.6 (10.8)	168	89
6b	*p*-Tolyl	2',6'-Xylyl	$C_{17}H_{18}N_4S$	65.7 (65.8)	5.7 (5.8)	17.9 (18.0)	10.3 (10.3)	161	77
6c	*p*-Anisyl	2',6'-Xylyl	$C_{17}H_{18}N_4OS$	62.3 (62.5)	5.3 (5.5)	17.1 (17.1)	9.9 (9.8)	141	75
6d	*p*-Phenetyl	2',6'-Xylyl	$C_{18}H_{20}N_4OS$	63.8 (63.6)	5.9 (5.9)	16.5 (16.6)	9.4 (9.3)	83	72
6e	*o*-Phenetyl	2',6'-Xylyl	$C_{18}H_{20}N_4OS$	63.7 (63.9)	5.7 (5.9)	16.5 (16.6)	9.4 (9.3)	146	70



Ar = aryl; Ar' = 2',6'-xylyl

Scheme-I

The structure **6** was confirmed, based on the products of reductive cleavage, elemental analysis, spectral analysis and alternative synthesis.

Unlike in the oxidation of binary mixtures reported earlier, the oxidation of 1-phenyl-3-(2',6'-xylyl)thiourea and thiourea forms 3-amino-4-phenyl-5-(2',6'-xylyl) imino-Δ^2-1,2,4-thiadiazoline (**6**) in which the more electron rich xylyl group is at 5-position. In the isomerization of monosulphide **3** the migration of the unsubstituted amidino group occurred on to the nitrogen carrying the less electron releasing phenyl group. This is contrary to earlier observations[14,17]. This can be attributed to the steric hindrance created by the two methyl groups at the *ortho* positions of the phenyl group which hinders the approach of the amidino group to that nitrogen.

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