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Reaction of 1-Aryl-, 1,3-Diaryl- and 1-Alkyl-3-aryl-*S*-alkyl-isothioureas with 4-Alkyl/Aryl Thiosemicarbazides : Formation of 4-Alkyl/Aryl-3-arylamino-5-mercapto-1,2,4-triazoles and 2,5-Diarylamino-1,3,4-thiadiazoles

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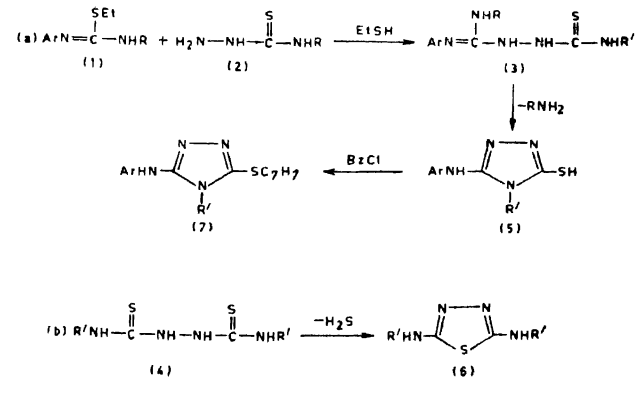
The interaction of 1-aryl-, 1,3-diaryl- and 1-alkyl-3-aryl-*S*-alkylisothioureas (1) with 4-alkyl/aryl thiosemicarbazides (2) has been found to afford 4-alkyl/aryl-3-arylamino-5-mercapto-1,2,4-triazoles (5) in good yield. 2,5-Diarylamino-1,3,4-thiadiazoles (6) is also formed as a minor product. A probable mechanism is suggested for the formation of these products.

THE varied pharmacological properties reported for 1,2,4-triazole and 1,3,4-thiadiazole derivatives[1] continues to draw the attention of chemists towards the synthesis of these using novel procedures. It was reported earlier from these laboratories that reaction of cyanamide with 4-alkyl/aryl thiosemicarbazide hydrochlorides in acid medium results in the formation of 2-alkyl/arylamino-5-amino-1,3,4-thiadiazoles and 4-alkyl/aryl-3-amino-5-mercapto-1,2,4-triazoles through the intermediate formation of 1-amidino-4-alkyl/arylthiosemicarbazides[2]. It has also been found that *S*-alkylisothioureas were found to react with amines, both aromatic[3] and aliphatic[4], to yield substituted guanidines. Taking clue from the above reactions it was decided to examine the reaction of 1-aryl-, 1,3-diaryl- and 1-alkyl-3-aryl-*S*-alkylisothioureas with 4-alkyl/aryl thiosemicarbazides. It was expected that thiosemicarbazides being basic, would undergo condensation with the *S*-alkyl derivative yielding an intermediate amidinothiosemicarbazide which could subsequently cyclise to 5-mercapto-1,2,4 triazole or a 1,3,4-thiadiazole derivative.

In the present study, reaction of an equimolar mixture of 1-phenyl-2-*S*-ethylisothiourea (1a) and 4-phenyl thiosemicarbazide (2a) was carried out in ethanolic medium yielding an alkali-soluble and an alkali-insoluble products The isolated alkali-insoluble product was analysed for $C_{14}H_{12}N_4S$. This compound did not answer dehydrosulphurisation test with sodium plumbite solution showing the absence of any $-NH-(C=S)-NH-$ or $N-(C=S)-NH_2$ grouping. When this product was treated with benzyl chloride and alkali it yielded a benzyl derivative (7a). It was identified as 3-mercapto-4-phenyl-5-phenylamino-1,2,4-triazole (5a). The structure was confirmed by comparison with an authentic sample prepared alternatively[5]. The alkali-insoluble product analysed for $C_{14}H_{12}N_4S$. It also did not show the dehydrosulphurisation test. It was identified as 2,5-diphenylamino-1,3,4-thiadiazole (6a) by comparison with an authentic sample[6].

In the light of the above observations the reaction was extended to other 1-aryl-, 1,3-diaryl- and 1-alkyl-3-aryl-*S*-ethylisothioureas (1) and 4-alkyl/aryl thiosemicarbazides (2) and in almost all the cases both 5 and 6 were isolated in varying yields.

A plausible mechanism for the formation of 5 should involve the intermediacy of a 1-(*N*-arylamidino)-4-arylthiosemicarbazide (3). The evolution of alkyl mercaptan implies the formation of such an intermediate. Here the *S*-ethylisothiourea (1) could undergo a nucleophilic displacement of ethyl mercaptan by the attack of the primary amino group of 2 resulting in the formation of the intermediate 3. The formation of 5 could be explained



4; R′ = Aryl Scheme 1

by the nucleophilic displacement of ammonia by the attack of the nitrogen (near the thioketo group) carrying the alkyl/aryl substituent. Attack with this nitrogen invariably occurred as it was more nucleophilic than the amidino nitrogen atoms and hence only the possibility of elimination of RNH_2 or $ArNH_2$ remained. Of these two the one with the aryl substituent was retained, as the aryl ring offered more stability to the product. The postulated intermediate 3 could not be isolated due to its thermal instability (Scheme 1a).

The formation of 6 on the other hand could be explained by the formation of a 1,6-diaryl-2,5-dithiobiurea (4) intermediate which in turn could be obtained by the attack of 4-aryl thiosemicarbazide (2) with its *N*-amino group on another molecule of 2 displacing hydrazine under the reaction conditions. Independently it has been proved that thiosemicarbazide on prolonged heating in an organic solvent forms 2,5-dithiobiurea. The intermediate 4 could then undergo thermal cyclisation with the evolution of hydrogen sulphide thereby resulting in 6. The product 6 thus, being a by-product, was obtained comparatively in small quantities (Scheme 1b).

Experimental

The 4-alkyl/aryl thiosemicarbazides (2) were prepared by the condensation of the appropriate isothiocyanate with excess hydrazine hydrate at ice-cold temperature. 1-Arylthioureas were prepared by the isomerisation of arylaminethiocyanate in aqueous solution[7]. 1,3-Diaryl- and 1-alkyl-3-arylthioureas were prepared by the condensation of one equivalent each of the respective alkyl/aryl isothiocyanate and arylamine.

The purity of the products was ascertained by tlc. All melting points were determined in a silicon-bath and are uncorrected. Satisfactory elemental analyses were obtained for all compounds.

Ir spectra (KBr) were recorded on a Perkin-Elmer 397 spectrophotometer, ^1H nmr spectra (DMSO ; TMS) on a Varian EM-360 (60 MHz) spectrometer and mass spectra on a Hewlett-Packard HP 5995 spectrometer.

Interaction of 1-aryl-, 1,3-diaryl- and 1-alkyl-3-aryl-S-ethylisothioureas (1) *and 4-alkyl/aryl thiosemicarbazides* (2). *Formation of 4-alkyl/aryl-3-arylamino-5-mercapto-1,2,4-triazole* (5) *and 2,5-diarylamino-1,3,4-thiadiazole* (6) :

(*i*) *Reaction of 1-aryl-S-ethylisothiourea* (1; *Ar=aryl, R=H) and 4-alkyl/aryl thiosemicarbazides* (2) : In a typical experiment 1-phenylthiourea (7.6 g, 0.05 mol) was refluxed with ethyl iodide (7.8 g. 0.05 mol) in ethanol for 15–20 min. The reaction mixture was then diluted with water, filtered to remove any insolubles and neutralised with sodium bicarbonate solution. The oily 1-phenyl-2*S*-ethylisothiourea (1a) was extracted into ether. 4-Phenyl thiosemicarbazide (2a ; 8.35 g, 0.05 mol) was then added to the ether extract and the reaction mixture was heated on a water-bath for about 20 h with occassional addition of ethanol until the evolution of ethyl mercaptan ceased. The reaction mixture was then washed with boiling

TABLE 1 – PHYSICAL DATA OF 4-ALKYL/ARYL-3-ARYLAMINO-5-MERCAPTO-1,2,4-TRIAZOLE (5 ; AR = ARYL, R'=ALKYL/ARYL)*

Compd. no.	R'	Ar	Mol. formula	Yield %	M.p.** °C
5a	C_6H_5	C_6H_5	$C_{14}H_{12}N_4S$	45	209[a]
b	p-$CH_3O-C_6H_4$	C_6H_5	$C_{15}H_{14}N_4SO$	60	230
c	p-$Cl-C_6H_4$	p-$Cl-C_6H_4$	$C_{14}H_{10}N_4Cl_2S$	42	268
d	p-$CH_3-C_6H_4$	C_6H_5	$C_{15}H_{14}N_4S$	21	178
e	p-$CH_3-C_6H_4$	p-$CH_3-C_6H_4$	$C_{16}H_{16}N_4S$	50	197
f	p-$CH_3-C_6H_4$	p-$Cl-C_6H_4$	$C_{15}H_{13}N_4ClS$	65	248
g	C_6H_5	p-$C_2H_5O-C_6H_4$	$C_{16}H_{16}N_4SO$	15	175
h	p-$C_2H_5O-C_6H_4$	C_6H_5	$C_{16}H_{16}N_4SO$	18	210
i	p-$C_2H_5-O-C_6H_4$	p-$CH_3-C_6H_4$	$C_{17}H_{18}N_4SO$	28	190
j	p-$CH_3-C_6H_4$	p-$C_2H_5O-C_6H_4$	$C_{17}H_{18}N_4SO$	30	197
k	p-$C_2H_5O-C_6H_4$	p-$C_2H_5O-C_6H_4$	$C_{18}H_{20}N_4SO_2$	32	222
l	p-$C_2H_5O-C_6H_4$	p-$Cl-C_6H_4$	$C_{16}H_{15}N_4ClSO$	65	225
m	p-$Cl-C_6H_4$	p $C_2H_5O-C_6H_4$	$C_{16}H_{15}N_4ClSO$	28	243
n	p-$CH_3O-C_6H_4$	p-$CH_3-C_6H_4$	$C_{16}H_{16}N_4SO$	68	227
o	p-$CH_3O-C_6H_4$	p-$Cl-C_6H_4$	$C_{15}H_{13}N_4ClSO$	65	261
p	p-$CH_3O-C_6H_4$	p-$C_2H_5O-C_6H_4$	$C_{17}H_{18}N_4SO_2$	40	202
q	p-$CH_3-C_6H_4$	p-$CH_3O-C_6H_4$	$C_{16}H_{16}N_4SO$	55	201
r	n-C_4H_9	p-$Cl-C_6H_4$	$C_{12}H_{15}N_4ClS$	10	197
s	CH_3	C_6H_5	$C_9H_{10}N_4S$	12	201
t	CH_3	p-$CH_3-C_6H_4$	$C_{10}H_{12}N_4S$	15	231
u	CH_3	p-$Cl-C_6H_4$	$C_9H_9N_4ClS$	25	269
v	C_6H_5	p-$CH_3-C_6H_4$	$C_{15}H_{14}N_4S$	10	204
w	C_6H_5	p-$Cl-C_6H_4$	$C_{14}H_{11}N_4ClS$	20	216

*Satisfactory elemental analyses were obtained for all compounds. **Lit.[6] m.p. (°C) : [a]208.

TABLE 2 – SPECTRAL DATA OF COMPOUNDS 5*

Compd. no.	*m/z* observed (%)/calcd.	ν_{max} cm^{-1}	δ
5a	268 (M^+, 100) 268	3 380s, 3 100m, 1 590s, 1 490s, 1 220s	–
b	– 298	3 320s, 3 100m, 1 590s, 1 490s, 1 240s	3.9 (3H, s), 7.0 – 7.6 (10H, m), 8.3 (1H, s)
c	336 (M^+, 100) 336	3 360s, 3 100m, 1 610s, 1 540s, 1 470s, 1 310s, 1 220s	7.2 – 7.7 (8H, m), 8.6 (1H, s), 11.3 (1H, s)
d	– 282	3 620s, 3 400w, 2 900w, 1 580s, 1 320s, 1 210s	–
e	296 (M^+, 100) 296	3 400s, 3 100m, 1 600s, 1 490s, 1 315s, 1 220s	2.2 (3H, s), 2.5 (3H, s), 7.0 – 7.6 (8H, m), 8.2 (1H, s), 11.4 (1H, s)
f	316.4 (M^+, 59.8) 317	3 360s, 3 100m, 1 590s, 1 470s, 1 320s, 1 220s	–
i	– 326	3 360m, 3 100m, 2 900m, 1 600s, 1 490m, 1 320s 1 220s	1.0 – 1.3 (3H, t), 2.0 (3H, s), 3.8 – 4.2 (2H, q), 6.8 – 7.5 (8H, m), 8.0 (1H, s)
j	– 326	3 260w, 3 080m, 2 900m, 1 590s, 1 470s, 1 310s, 1 220s	–
k	– 356	3 260w, 3 080m, 2 920m, 1 600s, 1 490s, 1 300s, 1 240s	–
l	– 347	3 200m, 1 600s, 1 480s, 1 310s, 1 240s, 1 210s	–
m	346.5 (M^+, 19.80) 347	3 390s, 3 100m, 1 610s, 1 540s, 1 470s, 1 310s, 1 220s	–
n	– 312	3 230s, 1 590s, 1 490s, 1 310s, 1 240s, 1 210s	–
o	– 333	3 360s, 3 100m, 2 940m, 1 600s, 1 490s, 1 320s, 1 240s	3.8 (3H, s), 7.0 – 7.7 (8H, m), 8.4 (1H, s), 11.6 (1H, s)
p	342.5 (M^+, 44.2) 342	3 220w, 3 070m, 2 900m, 1 600s, 1 470s, 1 290s, 1 220b	–
q	312.5 (M^+, 37) 312	–	–
r	– 283	–	0.8 – 1.7 (7H, m), 4.0 – 4.3 (2H, t), 7.3 – 7.7 (4H, m), 9.0 (1H, s), 11.2 (1H, s)
v	– 282	3 100m, 2 920w, 1 600s, 1 480s, 1 310s, 1 220s	2.2 (3H, s), 6.9 – 7.6 (9H, m), 8.2 (1H, s), 11.4 (1H, s)

TABLE 3 – PHYSICAL AND SPECTRAL DATA OF 2,5-DIARYLAMINO-1,3,4-THIADIAZOLE (6 ; R′ = ARYL)*

Compd. no.	R	R′	Molecular formula	M.p.** °C	ν_{max} cm^{-1}	δ
6a	C_6H_5	C_6H_5	$C_{14}H_{11}N_4S$	247[a]	–	–
	p-$CH_3-C_6H_4$	p-$CH_3-C_6H_4$	$C_{16}H_{16}N_4S$	250[b]	–	–
c	p-Cl–C_6H_4	p-Cl–C_6H_4	$C_{14}H_{10}N_4Cl_2S$	261	3 400w, 3 200m, 3 000m, 1 590s, 1 460s, 1 300m	–
d	p-$C_2H_5O-C_6H_4$	p-$C_2H_5O-C_6H_4$	$C_{18}H_{20}N_4SO_2$	215	3 200m, 3 100m, 1 540s, 1 240s	1.0–1.3 (6H, t), 3.8–4.2 (4H, q), 6.8–7.5 (8H, m), 9.6 (2H, s)
e	p-$CH_3O-C_6H_4$	p-$CH_3O-C_6H_4$	$C_{16}H_{16}N_4SO_2$	232	3 400m, 3 200w, 3 000w, 1 590m, 1 470s, 1 230s	3.7 (6H, s), 6.8–7.6 (8H, m), 9.6 (2H, s)

*Satisfactory elemental analyses were obtained for all compounds.
**Lit.[6] m.p. (°C) : [a]247, [b]248.

TABLE 4 – PHYSICAL AND SPECTRAL DATA OF 4-ARYL-3-ARYLAMINO-5-BENZYLTHIO-1,2,4-TRIAZOLES (7 ; Ar = ARYL, R′ = ARYL)*

Compd. no.	R′	Ar	Mol. formula	Yield %	M.p. °C
7a	C_6H_5	C_6H_5	$C_{21}H_{16}N_4S$	50	140
b	p-$CH_3O-C_6H_4$	C_6H_5	$C_{22}H_{20}N_4SO$	80	156
c	p-Cl–C_6H_4	p-Cl–C_6H_4	$C_{21}H_{14}N_6Cl_2S$	55	171
d	p-$CH_3-C_6H_4$	C_6H_5	$C_{22}H_{20}N_4S$	40	139
e	p-$CH_3-C_6H_4$	p-$CH_3-C_6H_4$	$C_{23}H_{22}N_4S$	48	129
f	p-$CH_3-C_6H_4$	p-Cl–C_6H_4	$C_{22}H_{19}N_4ClS$	30	150
g	p-$C_2H_5O-C_6H_4$	p-Cl–C_6H_4	$C_{23}H_{21}N_4ClSO$	60	175
h	p-$CH_3O-C_6H_4$	p-$CH_3-C_6H_4$	$C_{23}H_{22}N_4SO$	37	149
i	p-$CH_3O-C_6H_4$	p-Cl–C_6H_4	$C_{22}H_{19}N_4ClSO$	85	176
j	C_6H_5	p-Cl–C_6H_4	$C_{21}H_{17}N_4ClS$	38	149

7g : δ 1.0–1.3 (3H, t), 3.8–4.2 (2H, q), 4.3 (2H, s), 6.8–7.6 (14H, m) ; *m/z* 436.4 (M^+, 8.5%).
7i : δ 3.7 (3H, s), 4.3 (2H, s), 6.8–7.7 (14H, m).
*Satisfactory elemental analyses were obtained for all compounds.

water to remove any unreacted starting material. Trituration of the residue with dilute sodium hydroxide solution (2%) yielded an alkali-soluble and an alkali-insoluble portion. Acidification of the alkaline extract yielded 3-mercapto-4-phenyl-5-phenylamino-1,2,4-triazole (5a) which was crystallised from ethanol as white shining needles (45%), m.p. 209° (lit.[5] 208°). The alkali-insoluble portion crystallised from DMF/ethanol as colourless plates and was identified as 2,5-diphenylamino-1,3,4-thiadiazole (6a), m.p. 247° (lit.[6] 247°). The characterisation data of other 1,2,4-triazoles (5) and 1,3,4-thiadiazoles (6) are listed in Tables 1–3.

Benzylation of 5a. *Formation of 3-benzylthio-4-phenyl-5-phenylamino-1,2,4-triazole* (7a) : A solution of 5a (2.68 g, 0.01 mol) in ethanolic alkali was treated with benzyl chloride (1.27 g, 0.01 mol) and the reaction mixture kept stirred. The resulting white precipitate of 3-benzylthio-4-phenyl-5-phenylamino-1,2,4-triazole (7a) separated after about 30 min, was crystallised from ethanol as shining white needles (50%), m.p. 140°. The other 4-aryl-3-arylamino-5-benzylthio-1,2,4-triazoles (7) obtained thus are listed in Table 4.

(*ii*) *Reaction of 1,3-diaryl-S-ethylisothiourea* (1 ; *Ar=R=aryl) and 4-aryl thiosemicarbazide* (2) : 1-3-Diphenylthiourea (5, 7 g, 0.025 mol) was refluxed with ethyl iodide (3.9 g, 0.025 mol) in ethanol for about 20 min. The reaction mixture, after dilution and neutralisation with sodium bicarbonate solution, was extracted into ether, and then 4-phenyl thiosemicarbazide (2a ; 4.2 g, 0.025 mol) was added to the ether extract. The mixture was heated for about 20 h, when the evolution of ethyl mercaptan ceased. The reaction mixture on washing with boiling water, followed by dissolution in dilute sodium hydroxide solution (5%) yielded an alkali-insoluble portion which was identified as 2,5-diphenylamino-1,3,4-thiadiazole (6a), m.p.

247° (lit.[6] 247°). Comparison with the sample (6a) obtained in the previous reaction (i) showed both to be the same. The alkaline filtrate on acidification afforded 3-mercapto-4-phenyl-5-phenylamino-1,2,4-triazole (5a ; 30%), m.p. 210° (lit.[5] 208°). This was found to be identical with the sample (5a) obtained earlier. Benzylation of this triazole (2.68 g, 0.01 mol) yielded 3-benzylthio-4-phenyl-5-phenylamino-1,2,4-triazole (7a ; 28%), m.p. 140°. It was crystallised from ethanol as shining colourless needles.

*(iii) Reaction of 1-alkyl-3-aryl-*S*-ethylisothiourea (1 ; Ar=aryl, R=alkyl) with 4-aryl thiosemicarbazide (2) :* In another reaction, 1-ethyl-3-phenyl-thiourea (4.5 g, 0 025 mol) was refluxed with ethyl iodide (3.9 g, 0.025 mol) in ethanol for 20 min. The reaction mixture was then diluted, neutralised with sodium bicarbonate solution and extracted in ether. The ether extract was then heated with (4.2 g, 0.025 mol) 4-phenyl thiosemicarbazide (2a). The reaction proceeded as before and working up of the reaction mixture as in the previous case yielded an alkali-soluble product which was identified as 3-mercapto-4-phenyl-5-phenylamino-1,2,4-triazole (5a ; 15%), m p. 208° (lit.[5] 208°). It was shown to be identical with 5a obtained before. The alkali-insoluble portion was identical with 2,5-diphenyl-amino-1,3,4-thiadiazole (6a), m.p. 247° (lit.[6] 247°).

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References

1. A. R. KATRITZKY and A. J. BOULTON, *Adv. Heterocycl. Chem.*, 1968, **9**, 165.
2. L. KOSHY and C. P. JOSHUA, *Indian J. Chem., Sect. B*, 1986, **25**, 530.
3. G. B. L. SMITH, *J. Am. Chem. Soc.*, 1929, **51**, 477.
4. R. PHILLIPS and H. T. CLARKE, *J. Am. Chem. Soc.*, 1923, **45**, 1755.
5. L. E. A. GODFREY and F. KURZER, *J. Chem. Soc.*, 1962, 3561.
6. P. P. PATEL and G. C. CHAKRAVARTI, *J. Indian Inst. Sci., Sect. A*, 1930, **13**, 85.
7. C. P JOSHUA and K. N. RAJASEKHARAN, *Chem. Ind. (London)*, 1974, 750.