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On the synthesis of fused thiazolo[5,4-*d*]isoxazoles and a novel rearrangement involving conversion of 5(4*H*)-isoxazolones to 4(5*H*)-isoxazolones

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The interaction of 4-bromo-3-substituted-(4*H*)-isoxazol-5-ones (**1**) with alkyl/aryl thiocarbamides (**2**), 4-alkyl/aryl thiosemicarbazides (**7**) and 2, 4-disubstituted thiosemicarbazides (**12**) afford 5-alkyl/arylamino-3-substituted-thiazolo [5, 4-*d*]isoxazoles (**3**) and 6-amino/anilino-5-alkyl/arylimino-3-substituted-thiazolo[5, 4-*d*]isoxazoles respectively. An alternate unambiguous one step synthesis is described. The compounds have been characterised by chemical reactions and spectral data.

The compounds containing fused thiazolo[5, 4-*d*]isoxazoles have been reported earlier as one of the derivatives prepared from 4-chloro-2-phenyliminothiazole-5-carboxaldehyde[1]. We now report an alternate synthesis through readily accessible 4-bromo-3-substituted-(4*H*)-isoxazol-5-ones with thiocarbamides and thiosemicarbazides.

On refluxing **1a** and **2a** in ethanol in the presence of pyridine 5-amino-3-phenyl-thiazolo[5, 4-*d*]isoxazole (**3a**) was obtained. It showed characteristic IR absorption bands in KBr at 3393 and 3239 (NH_2), 1649 cm^{-1} (νC=N). Its ^1H NMR spectrum (300 MHz in DMSO-d_6) revealed tautomeric form **3a** showing peaks δ7.50-7.55 (m, 5H, Ar-H), 8.45 and 8.68 (2 singlets, 1H, 2 × −NH; D_2O exchangeable). ^{13}C NMR (300 MHz in DMSO-d_6) showed peaks at 126.4 to 132.75 (6 aromatic carbons), 164 and 159 (2 × *C*=N carbons) and 139.5 (>*C*=*C*< carbons).

Compound **3a** on treatment with alkyl/aryl isothiocyanates (**4**) in alcoholic alkali afforded 5-(3′-alkyl/aryl-thioureido)-3-substituted-thiazolo[5, 4-*d*]isoxazoles (**5**) [Scheme-I]. For **5b** IR (KBr) bands were observed at 3179, 3042 and 1610 cm^{-1}. Its ^1H NMR spectrum showed peaks at δ3.76 (s, 3H, $-OCH_3$), 6.9-7.5 [m, 9H, aromatic H containing two doublets at 6.96 and 7.46 (*J*=6.8 Hz each)], 9.16 and 9.34 (s, 1H, 2 × −NH; D_2O exchangeable). ^{13}C NMR for **5c** showed peaks at 21 (−*C*H_3 carbon), 125.5-135.0 (12 aromatic carbons), 164 and 158 (2 × −*C*=N), 138 (>*C*=C<) and 180 ppm (−*C*=S carbon).

An alternate unambiguous one-step synthesis of **5** was achieved by the interaction of **1** with dithiobiurets (**6**).

Similarly **1** and 4-alkyl/aryl thiosemicarbazides (**7**) in refluxing ethanol and pyridine afforded 6-amino-5-alkyl/arylimino-3-substituted-thiazolo[5,4-*d*]isoxazoles (**8**) which on reaction with aldehydes (**9**) in the presence of sodium acetate afforded Schiff's bases (**10**) (Scheme-II). The relevant spectral data and physical characteristic are listed in Table I.

The structure of **10** has been confirmed by an alternate unambiguous synthesis by the interaction of **1** with thiosemicarbazones (**11**). The compounds thus obtained were identified through undepressed m.m.p., superimposible IR spectra and co-TLC.

2, 4-Diaryl-thiosemicarbazides (**12**) and **1** under similar conditions gave 6-anilino-5-arylimino-3-substituted-thiazolo [5, 4-*d*]isoxazoles (**13**) (Scheme-II). Compounds **13** could also be obtained by the reaction of **1** with 1, 4-diaryl-thiosemicarbazides (**14**). The formation of **13** from **12** and **14** could be rationalised as arising by isomerisation of **12** to **14** during heating as reported earlier by Bose[2].

Compound **3** (0.025 *M*, R=Ph, R′=H) and aqueous sodium hydroxide (0.115 M) were stirred together at ambidient temperature for 4 hr. On acidification with dil. HCl in cold, 3-phenyl-4(5*H*)-isoxazolone[3] (**15a**) was obtained in 78% yield. For **15a** IR (KBr) spectrum showed bands at 3058, 2962, 1806, 1376, 1162, 1078 and 877 cm^{-1}. Its ^1H NMR (300 MHz in $CDCl_3$) spectrum showed peaks at δ3.8 (s, 2H, $-CH_2$),7.20-

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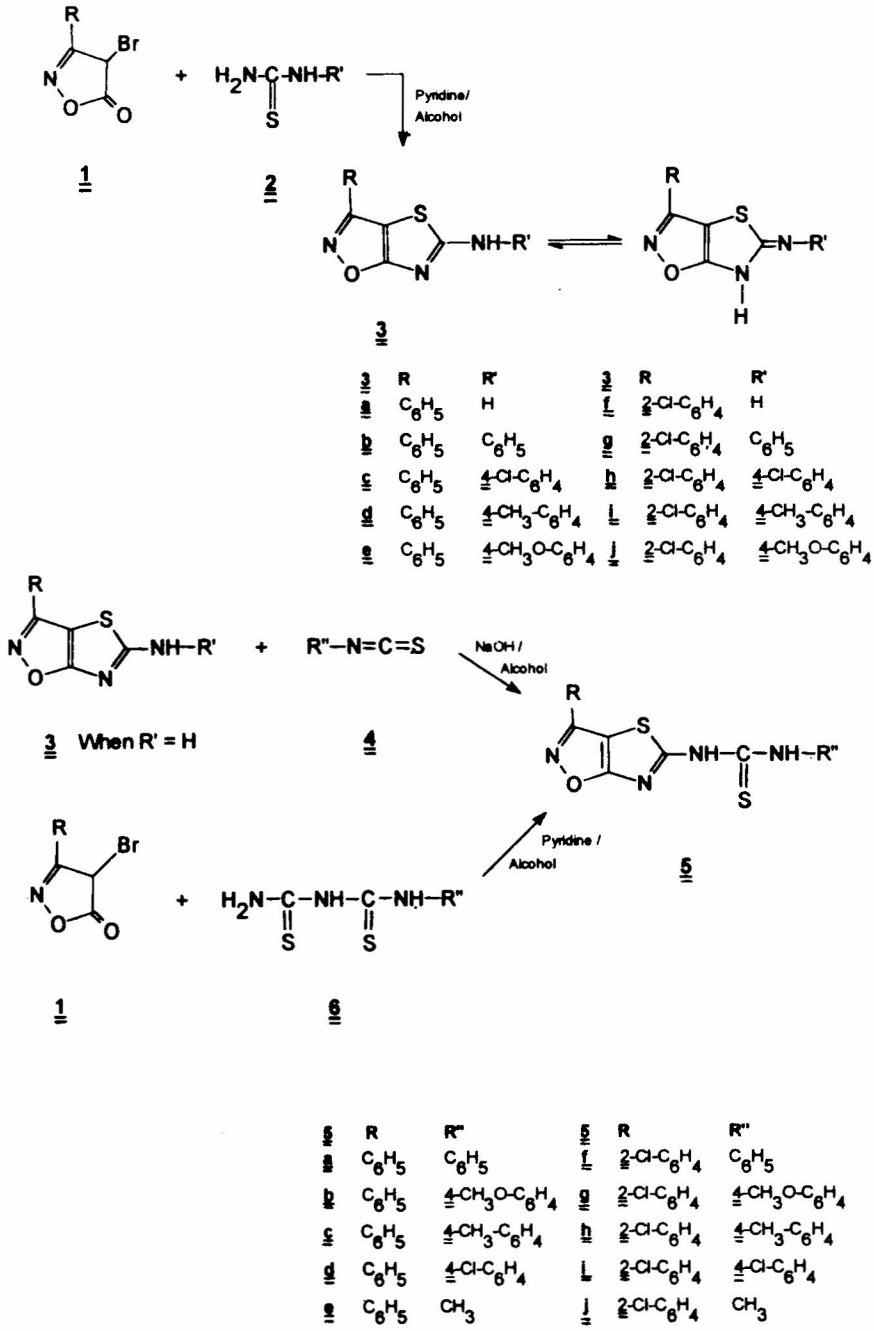


3	R	R'	3	R	R'
a	C_6H_5	H	f	2-Cl-C_6H_4	H
b	C_6H_5	C_6H_5	g	2-Cl-C_6H_4	C_6H_5
c	C_6H_5	4-Cl-C_6H_4	h	2-Cl-C_6H_4	4-Cl-C_6H_4
d	C_6H_5	4-CH_3-C_6H_4	i	2-Cl-C_6H_4	4-CH_3-C_6H_4
e	C_6H_5	4-CH_3O-C_6H_4	j	2-Cl-C_6H_4	4-CH_3O-C_6H_4

5	R	R"	5	R	R"
a	C_6H_5	C_6H_5	f	2-Cl-C_6H_4	C_6H_5
b	C_6H_5	4-CH_3O-C_6H_4	g	2-Cl-C_6H_4	4-CH_3O-C_6H_4
c	C_6H_5	4-CH_3-C_6H_4	h	2-Cl-C_6H_4	4-CH_3-C_6H_4
d	C_6H_5	4-Cl-C_6H_4	i	2-Cl-C_6H_4	4-Cl-C_6H_4
e	C_6H_5	CH_3	j	2-Cl-C_6H_4	CH_3

Scheme I

7.55 (m, 5H, Ar-H). ^{13}C NMR (300 MHz in $CDCl_3$) spectrum showed peaks at 33.98 ($-CH_2$), 126.58-132.15 (6 aromatic carbons), 163.01 ($-C=N$) and 174.63 ($-C=O$). In the mass spectrum (EI), m/z peaks were observed at 161 (M^+), 133, 119, 116, 103, 93, 89 and 77.

The conversion of 5(4*H*)-isoxazolones into 4(5*H*)-isoxazolones opens up a novel approach to the synthesis of the almost inaccessible 4(5*H*)-isoxazolones. The probable mechanism for the formation of **15** could be rationalised as shown in Scheme III. The formation of thiourea could be explained as arising by the thiohydrolysis of the cyanamide formed during the course of the reaction, as hydrogen sulphide was detected in the reaction. The identity of the thiourea was confirmed by TLC and chemical analysis. Small quantities of elemental sulphur were detected in the reaction mixture. It may have probably reacted with the alkali affording sodium sulphide.

Table I—Characterisation data of Schiff's bases **10**

Compd	R	R_1	R_2	m.p. (°C)	Yield (%)
10a	C_6H_5	C_6H_5	C_6H_5	182	80
10b	C_6H_5	C_6H_5	$2-OH-C_6H_4$	178	82
10c*	C_6H_5	C_6H_5	$4-CH_3O-C_6H_4$	198	84
10d	C_6H_5	$4-CH_3-C_6H_4$	C_6H_5	106	85
10e	C_6H_5	$4-CH_3-C_6H_4$	$2-OH-C_6H_4$	102	82
10f	C_6H_5	$4-CH_3-C_6H_4$	$4-CH_3O-C_6H_4$	162	81
10g	C_6H_5	$4-CH_3O-C_6H_4$	C_6H_5	101	84
10h	C_6H_5	$4-CH_3O-C_6H_4$	$2-OH-C_6H_4$	105	82
10i	C_6H_5	$4-CH_3O-C_6H_4$	$4-CH_3O-C_6H_4$	98	84
10j	C_6H_5	$(CH_3)_3-C$	C_6H_5	155	79
10k	C_6H_5	$(CH_3)_3-C$	$2-OH-C_6H_4$	110	78
10l	C_6H_5	$(CH_3)_3-C$	$4-CH_3O-C_6H_4$	108	80
10m	C_6H_5	H	C_6H_5	176	76
10n	C_6H_5	H	$2-OH-C_6H_4$	156	78
10o	C_6H_5	H	$4-CH_3O-C_6H_4$	172	79
10p	$2-Cl-C_6H_4$	C_6H_5	C_6H_5	144	82
10q	$2-Cl-C_6H_4$	C_6H_5	$2-OH-C_6H_4$	141	84
10r	$2-Cl-C_6H_4$	C_6H_5	$4-CH_3O-C_6H_4$	136	86
10s	$2-Cl-C_6H_4$	$4-CH_3-C_6H_4$	C_6H_5	133	85
10t	$2-Cl-C_6H_4$	$4-CH_3-C_6H_4$	$2-OH-C_6H_4$	146	84
10u	$2-Cl-C_6H_4$	$4-CH_3-C_6H_4$	$4-CH_3O-C_6H_4$	132	82
10v	$2-Cl-C_6H_4$	$4-CH_3O-C_6H_4$	C_6H_5	148	84
10w	$2-Cl-C_6H_4$	$4-CH_3O-C_6H_4$	$2-OH-C_6H_4$	144	85
10x	$2-Cl-C_6H_4$	$4-CH_3O-C_6H_4$	$4-CH_3O-C_6H_4$	135	85
10y	$2-Cl-C_6H_4$	$(CH_3)_3-C$	C_6H_5	126	81
10z	$2-Cl-C_6H_4$	$(CH_3)_3-C$	$2-OH-C_6H_4$	140	80
10aa	$2-Cl-C_6H_4$	$(CH_3)_3-C$	$4-CH_3O-C_6H_4$	137	79
10bb	$2-Cl-C_6H_4$	H	C_6H_5	188	77
10cc	$2-Cl-C_6H_4$	H	$2-OH-C_6H_4$	184	76
10dd**	$2-Cl-C_6H_4$	H	$4-CH_3O-C_6H_4$	198	78

Satisfactory C, H, N and S analyses were obtained within 0.3% error

***10c**: PMR : δ3.76 (s, 3H, $-OCH_3$), 6.84-7.93 (m, 14H, ArH), 8.14 (s, 1H, −CH); ^{13}C NMR : 55.71 ($-OCH_3$ carbon), 114.93 (> *C*= *C*< carbon), 126.38-134.56 (18 aromatic carbons), 143.2, 152.5 and 157.4 ppm (− *C*=N carbons)

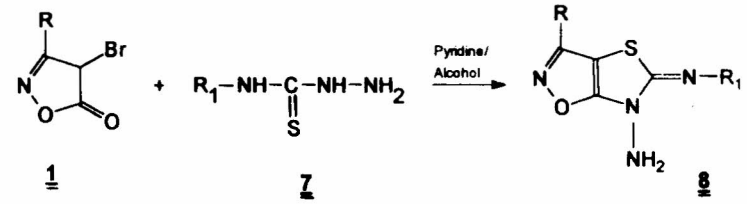
****10dd** : PMR : δ 3.81 (s, 3H, $-OCH_3$), 7.00-7.87 (m, 8H, aromatic H), 8.28 (s, 1H, −CH), 9.44 (s, 1H, −NH); ^{13}C NMR : 55.83 ($-OCH_3$ carbon), 114.73 (> *C*= *C*< carbon), 125.69-132.98 (12 aromatic carbons), 152.0, 162.37 & 164.29 (3 × − *C*=N carbons)

Compound **15a** reacted with bromine in acetic acid in presence of UV light to afford 5-bromo derivative **16a**. Its IR (KBr) spectrum showed bands at 3025, 1813, 1380, 1159, 1080 and 874 cm^{-1}. On reaction with thiocarbamide it gave 5-amino-3-phenyl-thiazolo [4, 5-*d*]isoxazole (**17a**). Its ^1H NMR spectrum revealed tautomeric form of **17a** by showing peaks at δ7.45-7.64 (m, 5H, Ar-H), 8.65 & 8.18 (s, 1H 2× −NH; D_2O exchangeable). ^{13}C NMR spectrum showed peaks at 125.65-132.50 (6 aromatic carbons), 163 and 158 (2× *C*=N), 137.50 (> *C*= *C*< carbons).

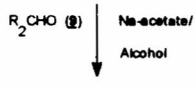
Experimental Section

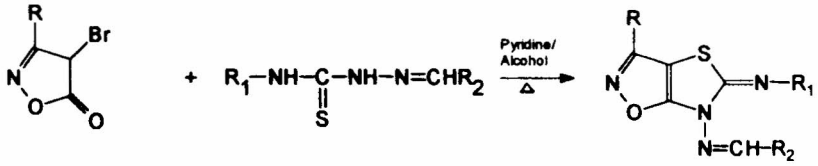
Melting points were determined in open glass capillaries and are uncorrected. IR were recorded on Perkin-Elmer 1600 series FTIR and PMR and ^{13}C NMR on 300 MHz VXRO using DMSO-deuterated solvent. TLC in various solvents showed the compounds to be homogeneous. Compounds **1, 2, 6, 7, 11, 12, 14** were prepared by literature methods[4-9].

5-Alkyl/aryl amino-3-substituted-thiazolo [5, 4-*d*]isoxazoles (3): General procedure. A mixture of **1** (0.01 mole), **2** (0.01 mole) and pyridine (0.02 mole) in ethanol (25 mL) was refluxed for 3 hr, cooled and poured onto crushed ice when compound **3** was obtained. It was recrystallised from ethanol. The compounds **3a-j** were similarly synthesized. **3a**: (m.p. 230°)75%); **3b**: m.p. 96° (85%); **3c**: m.p. 105° (86%); ^1H NMR : δ8.4 (s, 1H, −NH), 6.8-7.8 (m, 9H, ArH); **3d**: m.p. 174° (85%); **3e** : m.p. 124° (85%); **3f**: m.p. 215° (75%); ^1H NMR : δ 8.32 (s, 1H, −NH), 8.58 (s, 1H, −NH), 7.38-7.53 (m, 4H, ArH); ^{13}C NMR :



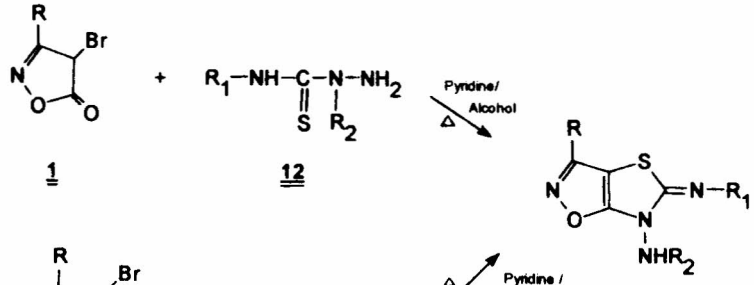
1 7 8





1 11 10

8	R	R_1	8	R	R_1
a	C_6H_5	C_6H_5	f	2-Cl-C_6H_4	C_6H_5
b	C_6H_5	4-CH_3O-C_6H_4	g	2-Cl-C_6H_4	4-CH_3O-C_6H_4
c	C_6H_5	4-CH_3-C_6H_4	h	2-Cl-C_6H_4	4-CH_3-C_6H_4
d	C_6H_5	$(CH_3)_3$-C	i	2-Cl-C_6H_4	$(CH_3)_3$-C
e	C_6H_5	H	j	2-Cl-C_6H_4	H

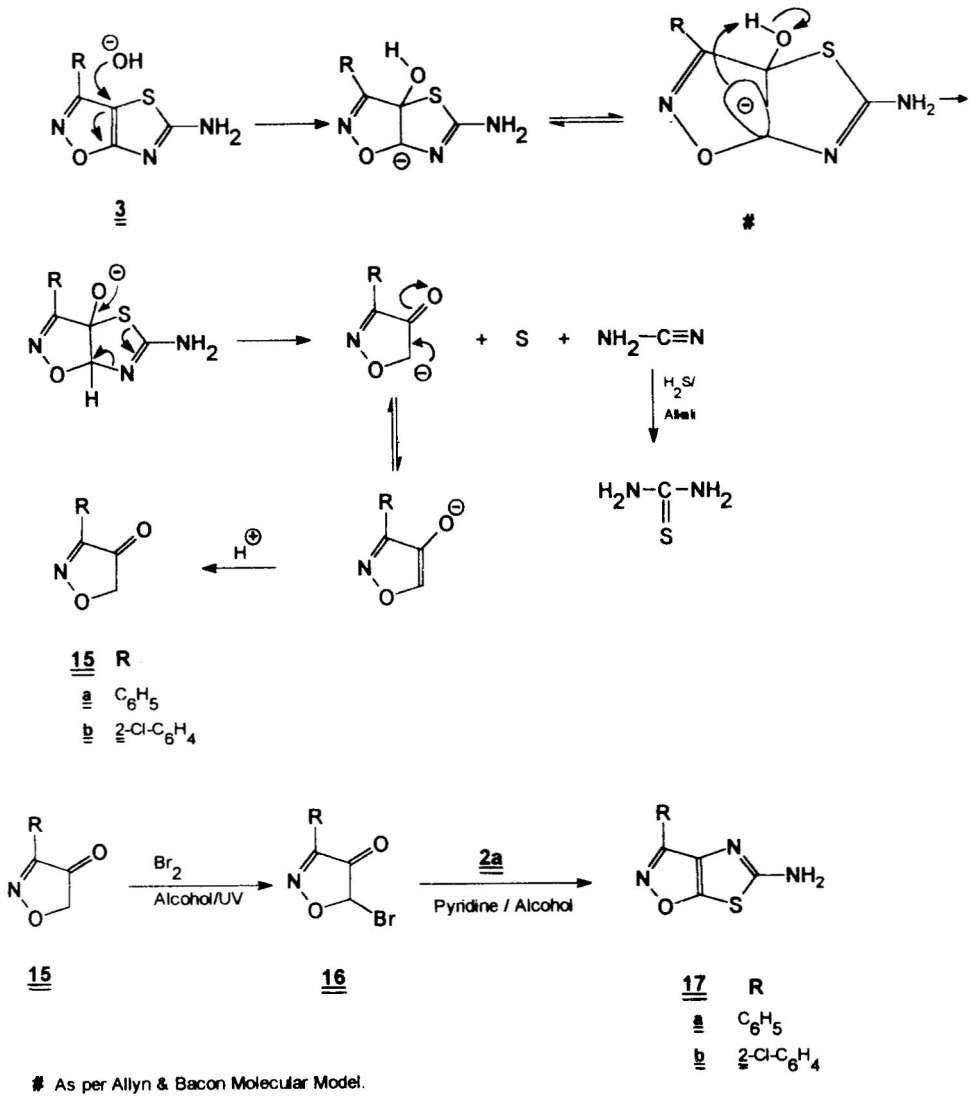


1 12 13

1 14

13	R	R_1	R_2
a	C_6H_5	C_6H_5	C_6H_5
b	C_6H_5	4-CH_3-C_6H_4	C_6H_5
c	C_6H_5	4-CH_3O-C_6H_4	C_6H_5
d	2-Cl-C_6H_4	C_6H_5	C_6H_5
e	2-Cl-C_6H_4	4-CH_3-C_6H_4	C_6H_5
f	2-Cl-C_6H_4	4-CH_3O-C_6H_4	C_6H_5

Scheme II



Scheme III

127.36-133.0 (6 aromatic carbons), 164 and 159 (2× $-C=N$ carbons), 137 ppm ($>C=C<$ carbons); 3 g, m.p. 106° (85%); **3h**: m.p. 152° (87%); **3i**: m.p. 130° (85%); **3j**: m.p. 102° (85%).

5-(3′-Alkyl/aryl thioureido)-3-substituted-thiazolo [5, 4-*d*]isoxazoles (5): General procedure. A mixture of **3** (R′=H, 0.01 mole), **4** (0.01 mole) and NaOH (0.01 mole) in ethanol (25 mL) was refluxed for 3.5 hr, cooled and poured onto crushed ice. It was further brought to *p*H 6 by adding cold dil. HCl when compound **5** separated out. It was recrystallised from dil. ethanol. Compounds **5a-d** were similarly synthesised. **5a**: m.p. 102° (88%); ^{13}C NMR : 124.50-129.20 (12 aromatic carbons), 164.50 and 157.88 (2× $C=N$ carbons), 137.90 ($>C=C<$ carbon), 179.71 ppm ($-C=S$ carbon); **5b**: m.p. 158° (89%); **5c**: m.p. 145° (88%); **5d** : m.p. 140° (86%); ^{1}H NMR : δ 6.82 - 8.10 (m, 9H, ArH), 9.24 and 9.35 (s, 1H, 2× −NH); **5e** : m.p. 149° (70%); **5f** : m.p. 108° (68%); **5g**: m.p. 145° (88%); **5h** : m.p. 141° (87%); **5i** : m.p. 135° (85%); **5j** : m.p. 138°, 72%).

An alternate unambiguous synthesis of 5: General procedure A mixture of **1** (0.01 mole), **6** (0.01 mole) and pyridine (0.02 mole) in ethanol (25 mL) was refluxed for 3 hr, cooled and poured onto crushed ice, when compound **5** was obtained. It was recrystallised from dil. ethanol. Compounds **5a-j** were synthesised and characterised by co-TLC, superimposable IR with authentic samples prepared as described earlier.

6-Amino-5-alkyl/arylimino-3-substituted-thiazolo [5,4-*d*]isoxazoles (8): General procedure. A mixture of **1** (0.01 mole), **7** (0.01 mole) and pyridine (0.02 mole) in ethanol (25 mL) was refluxed for 3 hr, cooled and poured onto crushed ice when compound **8** was obtained. It was recrystallised from dil. ethanol. The compounds **8a-j** were synthesized. **8a**: m.p. 142° (88%); **8b**: m.p. 168°, (89%); IR(KBr) : 3285 and 3185 (νNH_2), 1606 ($\nu C=N$), 1245, 1028 and 755 cm^{-1}; ^1H NMR : δ 3.71 (s, 3H, $-OCH_3$), 9.55 (s, 2H, $-NH_2$; D_2O exchangeable), 6.84-7.54 [m, 9H, aromatic H containing two doublets for 4-methoxyphenyl; at 6.87 (J=9.08 Hz) and 7.43 (J=9.08 Hz)]; ^{13}C NMR : 55.62 ($-OCH_3$ carbon), 113.67 ($>C=C<$ carbons), 114.56-128.59 (12 aromatic carbons), 154.30 and 156.29 ppm ($2\times -C=N$ carbons); **8c**: m.p. 171° (88%); **8d**: m.p. 182° (74%); ^1H NMR : δ1.20 (s, 6H, $2\times -CH_3$), 1.46 (s, 3H, $1\times -CH_3$), 9.76 (s, 2H, $-NH_2$), 7.39-7.61 (m, 5H, ArH); **8e**: m.p. 189° (72%); ^1H NMR : δ9.62 (s, 2H, $-NH_2$), 5.31 (s, 1H, $-NH$), 7.29-7.92 (m, 5H, ArH); **8f** : m.p. 105°C (86%); **8g;** 116° (86%); **8h**: m.p. 122° (89%); ^{13}C NMR: 26 ($-CH_3$ carbon), 112.07 (>C=C< carbons), 117.74-134.90 (12 aromatic carbons), 156.92 and 158.99 ppm (2×-C=N carbons); **8i:** m.p. 155° (75%); **8j**: m.p. 175° (72%).

Schiff's bases (10). A mixture of **8** (0.01 mole), **9** (0.01 mole) and fused sodium acetate (0.01 mole) was refluxed in methanol for 3-4 hr. The reaction mixture was then poured onto crushed ice to get **10**. It was further recrystallised from dil. ethanol. The compounds **10a-dd** were synthesised which are incorporated in Table I.

6-Anilino-5-alkyl/arylimino-3-substituted-thiazolo [5,4-*d*] isoxazoles (13): General procedure. A mixture of compound **1** (0.01 mole), **12** (0.01 mole) and pyridine (0.02 mole) in ethanol (25 mL) was refluxed for 3 hr, cooled and poured onto crushed ice when compound **13** was obtained. It was recrystallised from dil. ethanol. The compounds **13a-f** were similarly synthesised. **13a** : m.p. 102° (86%); IR(KBr) : 3282, 1594, 1454, 1315 and 753 cm^{-1}; ^1H NMR : δ 8.98 (s, 1H, NHAr), 6.99 to 7.69 (m, 15H, aromatic H); ^{13}C NMR : 122.60-129.95 (18 aromatic carbons), 146.15 and 149.45 ($2\times -C=N$ carbons), 113.85 ppm ($>C=C<$ carbons), **13b** : m.p. 148° (84%); **13C** : m.p. 168° (85%); **13d** : m.p. 162° (82%); **13e** : m.p. 142° (84%); ^1H NMR : δ 2.25 (s, 3H, $-CH_3$), 5.48 (s, 1H, $-NH$), 6.87-7.66 (m, 13H, aromatic H); ^{13}C NMR : 20.8 ($-CH_3$ carbon), 119.36 ($>C=C<$ carbons), 120. 17-130.85 (18 aromatic carbons), 149.85 and 145.94 ppm ($2\times -C=N$ carbons); **13f** (134° (85%).

An alternate unambiguous synthesis of 10: General procedure. Compounds **11** were prepared by refluxing 4-alkyl/aryl thiosemicarbazides (**7**) with aldehydes (**9**) in ethanol for 2 hr. The reaction mixture in each case was left overnight, filtered and crystallised from ethanol.

A mixture of **1** (0.01 mole), **11** (0.01 mole) and pyridine (0.02 mole) was then refluxed in ethanol (25 mL) for 3-4 hr, cooled and poured onto crushed ice, when compound **10** was obtained. It was recrystallised from dil. ethanol. Further confirmation of the identity was done by superimposable IR and m.m.p. determination with an authentic sample prepared as described earlier.

An alternate synthesis of 13 : General procedure. A mixture of **14** (0.01 mole), **1** (0.01 mole) and pyridine (0.02 mole) in ethanol (25 mL) was refluxed for 3 hr, cooled and poured onto crushed ice, when compound **13** was obtained. It was recrystallised from dil. ethanol. Its identity was further confirmed with an authentic sample prepared as described earlier.

3-substituted-4(5H)-isoxazolones (15) : General procedure. Compound **3** (R′=H, 0.025 mole) and NaOH (0.115 mole) in distilled water (50 mL) were stirred vigorously for 4-5 hr. It was further acidified to *p*H 6 with cold dil. HCl, when white creamy compound **15** separated out. A strong smell of hydrogen sulphide was perceptible. It was washed several times with cold water and further recrystallised from dil. ethanol. **15a** : m.p. 125° (Lit. 124°) (78%); **15b:** m.p. 96 ° (77%); ^1H NMR : δ 4.4 (s, 1H, $-CH$), 5.55 (s, 1H, $-OH$ tautomeric form), 7.20-7.80 (m, 4H, aromatic H); ^{13}C NMR : 36.5 ($-CH_2$ carbon) 128.0-134.5 (6 aromatic carbons), 163.0 ($-C=N$ carbon) and 173.0 ppm ($>C=O$ carbon).

5-Bromo-3-substituted-4(5H)-isoxazolones (16). Compound **15** (0.01 mole) was dissolved in minimum amount of acetic acid and to it bromine (0.01 mole) in acetic acid was added slowly in the presence of UV light during one hr. The stirring was continued for 30 min and then poured onto crushed ice when compound **16** was obtained. It was recrystallised from chloroform and immediately used for further reaction as it was found to be unstable. **16a** : m.p. 114° (75%); IR (KBr) :

3025, 1815, 1380, 1159, 1080 and 874 cm^{-1}; **16b** : m.p. 106° (77%).

5-Amino-3-substituted-thiazolo[4,5-*d*] isoxazoles (17) : General procedure. Compound **16** (0.01 mole), thiocarbamide (0.02 mole) and pyridine (0.02 mole) in ethanol (20 mL) were refluxed for 3 hr, cooled and poured onto crushed ice when compound **17** was obtained. It was recrystallised from dil. ethanol. **17a**: m.p. 156° (72%); **17b**, (m.p. 144° (71%).

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