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EXPEDIENT SYNTHESIS OF N-SUBSTITUTED 2-AMINOTHIAZOLES

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ABSTRACT: The reaction of α-halo ketones **1** with potassium thiocyanate and amines **3** offers the advantage of an efficient one-pot synthesis of the title compounds **4** from readily available starting materials.

The application of 2-aminothiazoles in therapy and their utilization as agents based on cyclogenase inhibition[1a-d] led to explore a convenient method for their preparation. Typically, 2-aminothiazoles are prepared either by the condensation of α-halo ketones with monosubstituted thioureas[2a-g] or by the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic amine hydrochlorides.[3a,b] α-Thiocyanato carbonyl compounds, in turn, are usually obtained from the corresponding halides as precursors upon reaction with thiocyanate ion.

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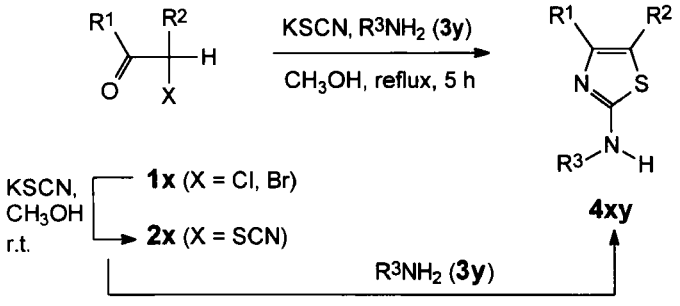
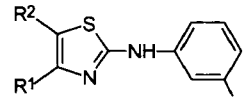
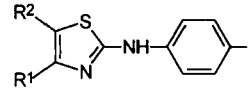
Scheme 1.

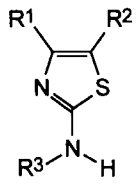


1,2,4 x	R^1	R^2	3 y	R^3	4 y	R^3
a	C_6H_5	CH_3	a	C_6H_5	a	C_6H_5
b	CH_3	C_6H_5	b	$C_6H_5CH_2$	b	$C_6H_5CH_2$
c	CH_3	CH_3	c	3-$H_2NC_6H_4$	c	
d	CH_3	H	d	4-$H_2NC_6H_4$	d	

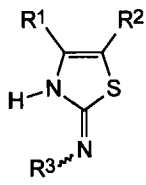
Therefore, a one-pot procedure was designed to directly convert α-halo ketones **1** into 2-aminothiazoles **4**. The transformation was carried out by the reaction of α-halo ketones with potassium thiocyanate and amines **3** in refluxing methanol without isolation of the presumed α-thiocyanato intermediate **2**.

This one-pot procedure can be efficiently applied mainly to primary aromatic and aliphatic amines **3**. The reaction of ketone **1a** with a secondary amine like *N*-methylaniline was sluggish and provided **8ca** only in poor yield. Utilization of primary aliphatic amines as exemplified by benzylamine **3b** afforded the expected thiazoles **4xb**. Reaction of 1,3- and 1,4-diaminobenzenes (**3c, 3d**) with two molar eqivalents of α-halo ketones **1a-c** led to the respective bis[(thiazol-2-yl)amino]-benzenes **4xc** and **4xd** (Scheme 1).

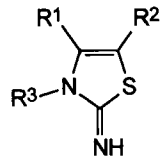
Owing to the ambident nucleophilic character of the thiocyanate ion the reaction with **1x** followed by **3y** may conceivably give rise to heterocyclic structures **4-7**.



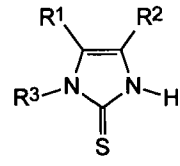
4



5



6



7

The formation of imidazole-2-thiones **7** and of 2-iminothiazoles **6** was ruled out by means of NMR spectroscopy. The chemical shift of the exchangeable proton signal in the range of δ 9.85-10.17 (DMSO-d_6) is in contrast to that of imidazole-2-thiones **7**[4] exhibiting the 3-NH proton signal at lower field (δ 11.88-12.41, DMSO-d_6). Saturation of the exchangeable proton caused a 10% NOE at the *ortho* - protons of the *N*-phenyl group. The ^{1}H NMR spectra of the heterocyclic products with R^3 = benzyl display a doublet of the methylene group and a triplet of the NH group. Upon exchange with deuteriumoxide the methylene doublet turns into a singlet; this rules out the formation of 2-iminothiazoles **5** and **6** and conforms only with the 2-aminothiazole structure **4**. The 2-aminothiazole structure of product **4aa** was ultimately confirmed by X-ray analysis (Figure 1).

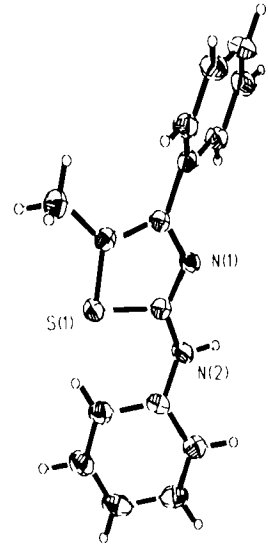
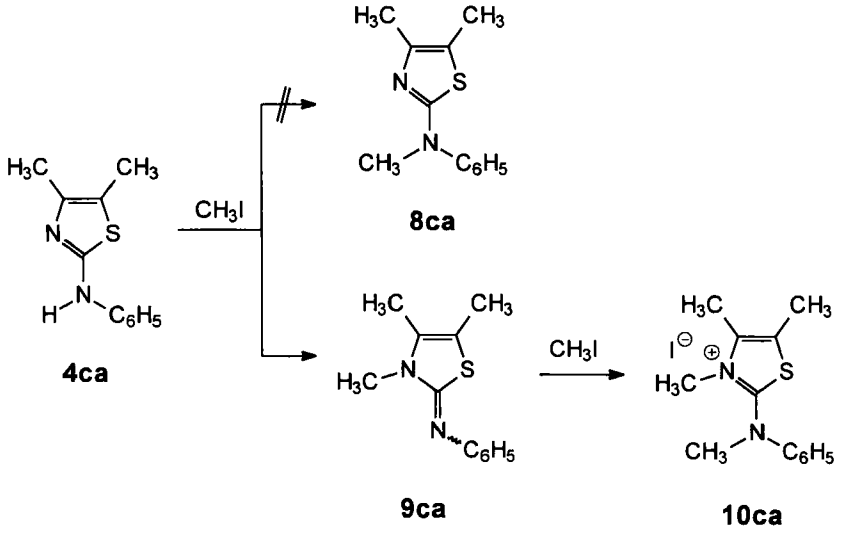


Figure 1.

ORTEP view of **4aa**.[5] The ellipsoids are drawn at the 50% probability level.

Treatment of **4ca** with an excess of methyl iodide first afforded a mono-methylation product. In order to distinguish between methylation at the exocyclic or the endocyclic nitrogen atom a NOE experiment provided the structure proof: Saturation of the *N*-methyl group resulted in a 12% NOE of the 4-methyl signal. This rules out the formation of the *N*-methyl-*N*-phenylthiazole derivative **8ca** and confirms structure **9ca**. After isolation further treatment of **9ca** with excess of methyl iodide afforded the thiazolium salt **10ca** (Scheme 2).

Scheme 2.



EXPERIMENTAL

Spectroscopic data were recorded with the following instruments: Mattson Galaxy Series GL-3020 (IR); Bruker AM 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz); Finnigan MAT 95 (EI-MS 70 eV; FAB-MS Cs gun, 20 KeV, 0.2 μA; HRMS: R = 6000); Hitachi U-3000 (UV); Siemens P4-diffractometer (X-ray). Melting points (mp) were determined with a Kofler hot stage microscope (Reichert). Thin layer chromatography (TLC) was performed on silica gel (Polygram Sil G/UV$_{254}$; Macherey-Nagel).

N-Substituted 2-Aminothiazoles 4xy (x = a - d, y = a; x = a, b; y = b).

General Procedure:

A solution of the α-halo ketone **1x** (**x** = **a**, **b**: X = Br; **x** = **c**, **d**: X = Cl) (0.03 mol) and potassium thiocyanate (4.4 g, 0.045 mol) in methanol (20 mL) was stirred at ambient temperature for 1h. Subsequently, the amine **3y** (**y** = **a, b**) (0.03 mol) was added dropwise and the reaction mixture was heated under reflux for 5 h. After cooling to ambient temperature the precipitate was filtered off and washed with water. Recrystallization from ethanol / water (4:1) afforded slightly yellow crystals **4xy** (**x** = **a** - **d**, **y** = **a**; **x** = **a**, **b**; **y** = **b**). The purity of products **4xy** was checked by TLC (ether / petroleum ether 2:1).

***N*-(5-Methyl-4-phenylthiazol-2-yl)-*N*-phenylamine (4aa):** Yield: 85%; mp 169-170° C; (lit:[6] 168°C); R_f 0.66 (ether / petroleum ether 2:1); IR (KBr): 3217, 3180, 3053, 2916, 2814, 1599, 1570, 1460, 1315, 752, 690 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 242.0 (3.73), 288.5 (3.68); ^1H NMR (DMSO-d_6): δ 2.41 (s, 3H, 5-CH_3), 6.91 (t, J = 7.3 Hz, 1H, 4-H 2-NC_6H_5), 7.26-7.35 (m, 5H 4-C_6H_5) 7.63-7.68 (m, 4H, 2,3,5,6-H 2-NC_6H_5), 10.04 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 11.9 (5-CH_3), 116.3, 145.2, 159.2 (5-C, 4-C, 2-C), 127.0, 127.9, 128.3, 135.1 (4-C, 2,6-C, 3,5-C, 1-C 4-C_6H_5), 116.6, 120.8, 128.9, 141.1 (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); EI-MS (*m/z* (%)): 266 (100, $M^{\bullet+}$), 251 (14, M - CH_3), 150 (27, C_6H_5NHCNS), 147 (22, $C_6H_5C_2CH_2S$), 115 (19, $C_6H_5C_2CH_2$), 104 (18, C_6H_5NHC), 77 (26, C_6H_5); HRMS (*m/z*): Calcd. for $C_{16}H_{14}N_2S$: 266.08777. Found: 266.08776.

***N*-(4-Methyl-5-phenylthiazol-2-yl)-*N*-phenylamine (4ba):** Yield 83%; mp 146-147 °C; R_f 0.63 (ether / petroleum ether 2:1); IR (KBr): 3225, 3182, 3065, 2951, 1597, 1564, 1496, 1460, 758, 694 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.0 (3.81), 320.5 (4.27); ^1H NMR (DMSO-d_6): δ 2.32 (s, 3H, 4-CH_3), 6.93 (t, J = 7.3 Hz, 1H, 4-H 2-NC_6H_5), 7.26-7.38 (m, 3H, 3,5-H 2-NC_6H_5; 4-H 5-C_6H_5), 7.40-7.42 (m, 4H, 2,6-H 2-NC_6H_5; 3,5-H 5-C_6H_5), 7.61 (d, J = 7.8 Hz, 2H, 2,6-H 5-C_6H_5), 10.17 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 16.4 (4-CH_3), 119.0, 143.3, 160.6 (5-C, 4-C, 2-C), 126.7, 128.3, 128.8, 132.2 (4-C, 2,6-C, 3,5-C, 1-C 5-C_6H_5), 116.9, 121.2, 128.9, 141.1 (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); EI-MS (*m/z* (%)): 266 (100, $M^{\bullet+}$), 225 (5, M - CH_3CN), 150 (20, C_6H_5NHCNS), 147 (8, $C_6H_5C_2CH_2S$),

121 (12, C_6H_5CS), 115 (9, $C_6H_5CH_2C_2$), 77 (11, C_6H_5). HRMS (*m/z*): Calcd. for $C_{16}H_{14}N_2S$: 266.08777. Found: 266.08776.

***N*-(4,5-Dimethylthiazol-2-yl)-*N*-phenylamine (4ca):** Yield 86%; mp 107-109 °C (lit.[3a] 107-109 °C); R_f 0.70 (ether / petroleum ether 2:1); IR (KBr): 3240, 3068, 2916, 2822, 1604, 1568, 1498, 1458, 1296, 746, 684 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 237.5 (3.58), 298.5 (4.14); ^1H NMR (DMSO-d_6): δ 2.11 (s, 3H, 5-CH_3), 2.17 (s, 3H, 4-CH_3), 6.87 (t, *J* = 7.3 Hz, 1H, 4-H 2-NC_6H_5), 7.25 (dd, *J* = 7.8, 7.3 Hz, 2H, 3,5-H 2-NC_6H_5), 7.55 (d, *J* = 7.8 Hz, 2H, 2,6-H 2-NC_6H_5), 9.85 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 10.5 (5-CH_3), 14.6 (4-CH_3), 113.5, 142.7, 158.3 (5-C, 4-C, 2-C), 116.4, 120.5, 128.8, 141.7 (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); EI-MS (*m/z* (%)): 204 (100 $M^{\bullet+}$), 189 (76, M - CH_3), 150 (85, C_6H_5NHCNS), 104 (51, C_6H_5NHC), 102 (25), 93 (14, $C_6H_5NH_2$), 77 (50, C_6H_5); HRMS (*m/z*): Calcd. for $C_{11}H_{12}N_2S$: 204.07212. Found: 204.07213.

***N*-(4-Methylthiazol-2-yl)-*N*-phenylamine (4da):** Yield 91%; mp 115-117 °C (lit.[8] 115-117 °C); R_f 0.79 (ether / petroleum ether 2:1); IR (KBr): 3229, 3184, 3101, 2906, 1601, 1541, 1500, 1458, 742, 704 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.5 (3.51), 293.5 (4.14); ^1H NMR (DMSO-d_6): δ 2.21 (d, *J* = 2 Hz, 3H, 4-CH_3), 6.41 (q, *J* = 2 Hz, 1H, 5-H), 6.90 (t, *J* = 7.3 Hz, 1H, 4-H 2-N-C_6H_5), 7.27 (dd, *J* = 7.8, 7.3 Hz, 2H, 3,5-H 2-N-C_6H_5), 7.59 (d, *J* = 7.8 Hz, 2H, 2,6-H 2-NC_6H_5), 10.05 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 17.4 (4-CH_3), 102.1, 147.9, 162.9 (5-C, 4-C, 2-C), 116.6, 120.8, 128.8, 141.3 (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); EI-MS: *m/z* (%) 190 (100, $M^{\bullet+}$), 150 (31, C_6H_5NHCNS), 104 (51, C_6H_5NHC), 102 (33), 77 (34, C_6H_5); HRMS (*m/z*): Calcd. for $C_{10}H_{10}N_2S$: 190.05647. Found: 190.05760.

***N*-Benzyl-*N*-(5-methyl-4-phenylthiazol-2-yl)amine (4ab):**[9] Yield 65%; mp 151-153 °C; R_f 0.56 (ether / petroleum ether 2:1); IR (KBr): 3182, 3078, 2957, 2885, 1574, 1489, 1425, 775, 696 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.5 (4.09), 266.0 (3.99); ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, 5-CH_3), 4.42 (d, *J* = 5.8 Hz, 2H, 2-NCH_2), 7.21-7.37 (m, 8H, 2-$NCH_2C_6H_5$; 3,4,5-H 4-C_6H_5), 7.39 (d, *J* = 8.2 Hz, 2H, 2,6-H 4-C_6H_5), 7.90 (t, *J* = 5.8 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 21.1 (5-CH_3), 47.4 (CH_2), 114.4, 145.0, 164.3 (5-C, 4-C, 2-C), 126.8, 127.4, 128.2,

135.4 (4-C, 2,6-C, 3,5-C, 1-C 4-C_6H_5), 126.7, 127.9, 128.1, 139.4 (4-C, 2,6-C, 3,5-C, 1-C $CH_2C_6H_5$); EI-MS (*m/z* (%)): 280 (91, $M^{\bullet+}$), 176 (21), 151 (100, $C_6H_5CH_2NHCHS$), 148 (36, $C_6H_5C_2CH_3S$), 105 (85, $C_6H_5CH_2NH_2$), 91 (33, $C_6H_5CH_2$), 77 (34, C_6H_5); HRMS (*m/z*): Calcd. for $C_{17}H_{16}N_2S$: 280.10342. Found: 280.10342.

***N*-Benzyl-*N*-(4-methyl-5-phenylthiazol-2-yl)amine (4bb):** Yield 69%; mp 148-150 °C; R_f 0.40 (ether / petroleum ether 2:1); IR (KBr): 3198, 3084, 2933, 2893, 1589, 1464, 1423, 760, 700 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 304.0 (4.22); ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, 4-CH_3), 4.44 (d, *J* = 5.8 Hz, 2H, 2-NCH_2), 7.19-7.38 (m, 10H, 2-$NCH_2C_6H_5$; 5-C_6H_5), 8.10 (t, *J* = 5.8 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6):[7] δ 16.4 (4-CH_3), 47.3 (CH_2), 117.2, 143.3, 165.7 (5-C, 4-C, 2-C), 121.0, 127.3, 128.7, 132.9 (4-C, 2,6-C, 3,5-C, 1-C 5-C_6H_5), 126.9, 127.9, 128.3, 132.9 (4-C, 2,6-C, 3,5-C, 1-C $CH_2C_6H_5$); EI-MS (*m/z* (%)): 280 (98, $M^{\bullet+}$), 189 (23, M - $C_6H_5CH_2$), 176 (28), 147 (34, $C_6H_5C_2CH_2S$), 77 (18, C_6H_5), 28 (100); HRMS (*m/z*): Calcd. for $C_{17}H_{16}N_2S$: 280.10342. Found: 280.10342.

Bis[(thiazol-2-yl)amino]benzenes 4xc and 4xd (x = a - c). General Procedure: A solution of the α-halo ketone **1x** (**x** = **a**, **b**: X = Br; **x** = **c**: X = Cl) (0.06 mol) and potassium thiocyanate (8.7g, 0.09 mol) in methanol (40 mL) was stirred at ambient temperature for 1h. Subsequently, the diamino benzene **3y** (**y** = **c, d**) (3.24 g, 0.03 mol) was added in one portion and the reaction mixture was heated under reflux for 10 h. After cooling to ambient temperature the precipitate was filtered off and washed with water. Recrystallisation from ethanol / water (4:1) afforded slightly yellow crystals **4xy** (**x** = **a-c**, **y** =**c,d**). The purity of products **4xc** and **4xd** was checked by TLC (ether / petroleum ether 2:1).

1,3-Bis[(5-methyl-4-phenylthiazol-2-yl)amino]benzene (4ac): Yield: 83%; mp 115-118 °C; R_f 0.41 (ether / petroleum ether 2:1); IR (KBr): 3632, 3236, 3004, 2922, 1612, 1562, 1479, 1440, 1327, 1167, 1007, 767, 696 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 242.5 (3.43); 290.5 (3.36); ^1H NMR (DMSO-d_6): δ 2.38 (s, 6H, 5-, 5'-CH_3) 7.31 (t, *J* = 7.3 Hz, 2H, 4-H 4-, 4'-C_6H_5), 7.42 (dd, *J* = 7.3, 6.8 Hz, 4H, 3,5-H 4-, 4'-C_6H_5), 7.68 (d, *J* = 6.8 Hz, 4H, 2,6-H 4-, 4'-C_6H_5), 7.20 (m, 3H,

4,5,6-H C_6H_4), 7.88 (s, 1H, 2-H C_6H_4), 10.05 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6):[7] δ 12.0 (5-CH_3), 116.2, 145.3, 159.2, (5-C, 4-C, 2-C), 127.0, 128.1, 128.3, 135.1 (2,6-C, 4-C, 3,5-C, 1-C 4-C_6H_5) 104.8, 110.0, 129.4, 141.8 (2-C, 4,6-C, 5-C, 1,3-C C_6H_4); EI-MS (*m/z* (%)): 454 (4, $M^{\bullet+}$), 281 (100, M - $C_6H_5CH_2C_3NS$), 266 (16, M - $C_6H_5C_3CH_2N_2S$); 205 (14), 165 (24), 147 (28, $C_6H_5C_2CH_2S$), 115 (43, $C_6H_5CH_2C_2$), 77 (26, C_6H_5); Anal. Calcd. for $C_{26}H_{22}N_4S_2$: C, 68.69; H, 4.88; N, 12.32; S, 14.10. Found: C, 68.01; H, 4.94; N, 12.31; S, 14.74.

1,3-Bis[(4-methyl-5-phenylthiazol-2-yl)amino]benzene (4bc): Yield: 78%; mp 175-177 °C; R_f 0.45 (ether / petroleum ether 2:1); IR (KBr): 3186, 3057, 2945, 1610, 1554, 1473, 1429, 754, 692 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 241.5 (3.12), 324.5 (3.57); ^1H NMR (DMSO-d_6): δ 2.34 (s, 6H, 4-, 4'-CH_3), 7.14-7.42 (m, 13H, 4,5,6-H 4-C_6H_5, 4'-C_6H_5, C_6H_4), 8.04 (s, 1H, 2-H C_6H_4) 10.22 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6):[7] δ 16.4 (4-CH_3), 119.1, 143.2, 160.4 (5-C, 4-C, 2-C), 126.7, 128.2, 128.7, 132.2 (4-C, 2,6-C, 3,5-C, 1-C 5-C_6H_5), 104.9, 110.3, 129.3, 141.6 (2-C, 4,6-C, 5-C, 1,3-C C_6H_4); EI-MS (*m/z* (%)): 454 (37, $M^{\bullet+}$), 281 (100, M - $C_6H_5CH_2C_3NS$), 121 (35, C_6H_5CS), 115 (21, $C_6H_5C_2CH_2$), 77 (18, C_6H_5); Anal. Calcd. for $C_{26}H_{22}N_4S_2$: C, 68.69; H, 4.88; N, 12.32; S, 14.10. Found: C, 68.56; H, 5.07; N, 12.23; S, 14.14.

1,3-Bis[(4,5-dimethylthiazol-2-yl)amino]benzene (4cc): Yield 76%; mp 176-179 °C; R_f 0.30 (ether / petroleum ether 2:1); IR (KBr): 3246, 3211, 3061, 2916, 2854, 1612, 1575, 1500, 1429, 1290, 871, 680 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.0 (2.86), 302.0 (3.18); ^1H NMR (DMSO-d_6): δ 2.12 (s, 6H, 4-, 4'-CH_3), 2.18 (s, 6H, 5-, 5'-CH_3), 6.65-6.89 (m, 3H, 4,5,6-H C_6H_4), 7.85 (s, 1H, 2-H C_6H_4), 9.81 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6):[7] δ 10.5 (5-CH_3), 14.6 (4-CH_3), 113.5, 142.6, 159.2 (5-C, 4-C, 2-C), 104.4, 109.4, 129.1, 141.9 (2-C, 4,6-C, 5-C, 1,3-C C_6H_4); EI-MS (*m/z* (%)): 330 (100, $M^{\bullet+}$), 271 (47, M - CH_3CS), 219 (20, M - $CH_3CH_2C_3NS$), 203 (19, M - $CH_3CH_3C_3NSNH$), 144 (27). Anal. Calcd. for $C_{16}H_{18}N_4S_2$: C, 58.15; H, 5.49; N, 16.95; S, 19.40. Found: C, 57.94; H, 5.50; N, 16.16; S, 20.40.

1,4-Bis[(5-methyl-4-phenylthiazol-2-yl)amino]benzene (4ad): Yield 97%; mp 235-238 °C; R_f 0.31 (ether / petroleum ether 2:1); IR (KBr): 3385, 3173, 3061,

2937, 1602, 1548, 1510, 1435, 1294, 767, 700 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 244.5 (3.37), 297.0 (3.36), 321.5 (3.38); ^1H NMR (DMSO-d_6): δ 2.39 (s, 6H, 5-, 5'-CH_3), 7.31 (t, J = 7.3 Hz, 2H, 4-H 4-, 4'-C_6H_5), 7.44 (dd, J = 7.3, 7.3 Hz, 4H, 3,5-H 4-, 4'-C_6H_5), 7.64 (d, J = 7.3 Hz, 4H, 2,6-H 4-, 4'-C_6H_5), 7.58 (s, 4H, C_6H_4), 9.90 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6):[7] δ 11.5 (5-CH_3), 115.6, 145.3, 159.6 (5-C, 4-C, 2-C), 127.0, 127.9, 128.3, 135.4 (2,6-C, 4-C, 3,5-C, 1-C 4-C_6H_5) 117.7, 135.2 (2,3,5,6-C, 1,4-C C_6H_4); EI-MS (*m/z* (%)): 454 (12, $M^{\bullet+}$), 281 (90, M - $C_6H_5CH_2C_3NS$), 147 (22, $C_6H_5C_2CH_2S$), 115 (18, $C_6H_5C_2CH_2$), 105 (100, $C_6H_6N_2$), 77 (58, C_6H_5). Anal. Calcd for $C_{26}H_{22}N_4S_2$: C, 68.69; H, 4.88; N, 12.32; S, 14.10. Found: C, 68.58; H, 4.94; N, 12.23; S, 14.25.

1,4-Bis[(4-methyl-5-phenylthiazol-2-yl)amino]benzene (4bd): Yield 94%; mp 266-268 °C; R_f 0.21 (ether / petroleum ether 2:1); IR (KBr): 3381, 3198, 3053, 2922, 1597, 1579, 1514, 1450, 1292, 756, 694 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.0 (2.93), 336.5 (3.27); ^1H NMR (DMSO-d_6): δ 2.31 (s, 6H, 4-, 4'-CH_3), 7.26-7.52 (m, 10H, 5-, 5'-C_6H_5), 7.57 (s, 4H, C_6H_4), 10.07 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6):[7] δ 16.4 (4-CH_3), 118.4, 143.3, 160.9 (5-C, 4-C, 2-C), 126.6, 128.2, 128.7, 132.3 (4-C, 2,6-C, 3,5-C, 1-C 5-C_6H_5), 118.1, 135.3 (2,3,5,6-C, 1,4-C C_6H_4); EI-MS (*m/z* (%)): 454 (7, $M^{\bullet+}$), 281 (100, M - $C_6H_5CH_2C_3NS$), 165 (18), 121 (27, C_6H_5CS), 103 (16, $C_6H_4N_2$), 91 (18, C_6H_4NH), 77 (24, C_6H_5). Anal. Calcd. for $C_{26}H_{22}N_4S_2$: C, 68.69; H, 4.88; N, 12.32; S, 14.10. Found: C, 68.50; H, 4.96; N, 12.20; S, 14.34.

1,4-Bis[(4,5-dimethylthiazol-2-yl)amino]benzene (4cd): Yield: 85%; mp 257-260 °C; R_f 0.15 (ether / petroleum ether 2:1); IR (KBr): 3225, 3146, 3076, 2920, 1562, 1523, 1444, 1406, 1288, 1209, 814, 704, 507 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 240.0 (2.80), 322.0 (3.24); ^1H NMR (DMSO-d_6):[7] δ 2.10 (s, 6H, 5-, 5'-CH_3), 2.16 (s, 6H, 4-, 4'-CH_3), 7.47 (s, 4H, C_6H_4), 9.71 (br s, 2H, NH, NH); ^{13}C NMR (DMSO-d_6): δ 10.5 (5-CH_3), 14.6 (4-CH_3), 112.7, 142.5, 159.8 (5-C, 4-C, 2-C), 117.6, 135.3 (2,3,5,6-C, 1,4-C C_6H_4); EI-MS (*m/z* (%)): 330 (100, $M^{\bullet+}$), 271 (16, M - CH_3CS), 231 (13, M - $CH_3C_2CH_2NS$), 219 (35, M - $CH_3C_2CH_2NCS$), 203 (25, M - $CH_3C_2CH_3NCSNH$), 165 (13), 159 (13). Anal. Calcd. for $C_{16}H_{18}N_4S_2$: C, 58.15; H, 5.49; N, 16.95; S, 19.40. Found: C, 57.94; H, 5.38; N, 17.14; S, 19.51.

***N*-(3,4,5-Trimethyl-2,3-dihydro-3*H*-thiazol-2-yliden)-*N*-phenylamine (9ca)**: A mixture of **4ca** (0.4 g, 2.00 mmol) and methyl iodide (1.19 g, 8.40 mmol) in acetone (5 mL) was heated under reflux for 5 h. After removal of excess of methyl iodide and the solvent in vacuo, the residue upon treatment with 5% aqueous sodium bicarbonate solution turned crystalline. Recrystallization from methanol / water (4:1) gave colorless crystals **9ca** (0.37 g, 86%); mp 45-47 °C (lit.[10] 42-43 °C) R_f 0.55 (ether / petroleum ether 2:1); IR (KBr): 3068, 2916, 1651, 1604, 1579, 1489, 1332, 898, 765, 696 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 242.0 (3.85), 307.0 (3.74); ^1H NMR (DMSO-d_6): δ 2.20 (s, 3H, 4-CH_3), 2.33 (s, 3H, 5-CH_3), 3.67 (s, 3H, 3-CH_3), 7.07-7.45 (m, 5H, 2-NC_6H_5); ^{13}C NMR (DMSO-d_6):[7] δ 11.0 (5-CH_3), 11.6 (4-CH_3), 34.5 (3-CH_3), 112.2, 138.2, 166.1 (5-C, 4-C, 2-C), 124.0, 128.0, 130.3, 134.1 (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); EI-MS (*m/z* (%)): 218 (100, $M^{\bullet+}$), 164 (12, $C_6H_5NCSNCH_3$), 114 (23, $CH_3NC_2CH_3CH_2S$), 106 (17, $C_6H_5NCH_3$), 91 (36, C_6H_5N), 77 (30, C_6H_5); HRMS (*m/z*): Calcd. for $C_{12}H_{14}N_2S$: 218.08777. Found: 218.09001.

3,4,5-Trimethyl-2-(methylanilino)thiazolium iodide (10ca): A solution of **9ca** (0.3 g, 1.37 mmol) in methyl iodide (1.19 g, 8.4 mmol) and acetone (5 mL) was refluxed for 12 h. After removal of methyl iodide and the solvent in vacuo, the residue was crystallized with ether to give pure **10ca** (0.42 g, 84%); mp 120-123 °C; R_f 0.77 (ethyl acetate); IR (KBr): 3038, 2976, 2935, 2854, 1610, 1531, 1491, 1371, 1132, 775, 707 cm^{-1}; UV ($CHCl_3$, λ_{max} (log ε)): 243.0 (4.07), 304.0 (3.90); ^1H NMR (DMSO-d_6): δ 2.35 (s, 3H, 4-CH_3), 2.44 (s, 3H, 5-CH_3), 3.24 (s, 3H, 3-CH_3), 3.58 (s, 3H, 2-NCH_3), 7.35-7.52 (m, 5H, 2-NC_6H_5); ^{13}C NMR (DMSO-d_6):[7] δ 11.9 (4-CH_3), 11.4 (5-CH_3), 37.4 (3-CH_3), 45.2 (2-NCH_3), 118.1, 144.1, 168.1 (5-C, 4-C, 2-C), 123.7, 127.3, 130.1, 136.2, (2,6-C, 4-C, 3,5-C, 1-C 2-NC_6H_5); FAB-MS HRMS (*m/z*): Calcd. for $C_{13}H_{17}N_2S$: 233.11124. Found: 233.10902.

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R value = 0.0369 based on F and WR2 value = 0.0871 based on F^2 (SHELX93 program) for 1371 observed intensities with $I>2\sigma(I)$. The coordinates, bond distances and angles are deposed at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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