DIRECT SYNTHETIC APPROACH TO *N*-SUBSTITUTED 1-AMINO-2,3-DIHYDRO-1*H*-IMIDAZOLE-2-THIONES

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Abstract - In an efficient one-pot procedure, the title compounds (**8**) were obtained by the reaction of α-halo ketones (**1**) with potassium thiocyanate and monosubstituted hydrazines (**3**). The reaction is considered to proceed *via* the formation of azo-alkenes (**5**) and thiocyanic acid. These intermediates, in turn, undergo a [3+2] cycloaddition reaction; the resultant azomethine imine cycloadducts (**6**) are transformed into the final products (**8**). The structure of compounds (**8**) has been confirmed by utilization of various NMR techniques.

INTRODUCTION

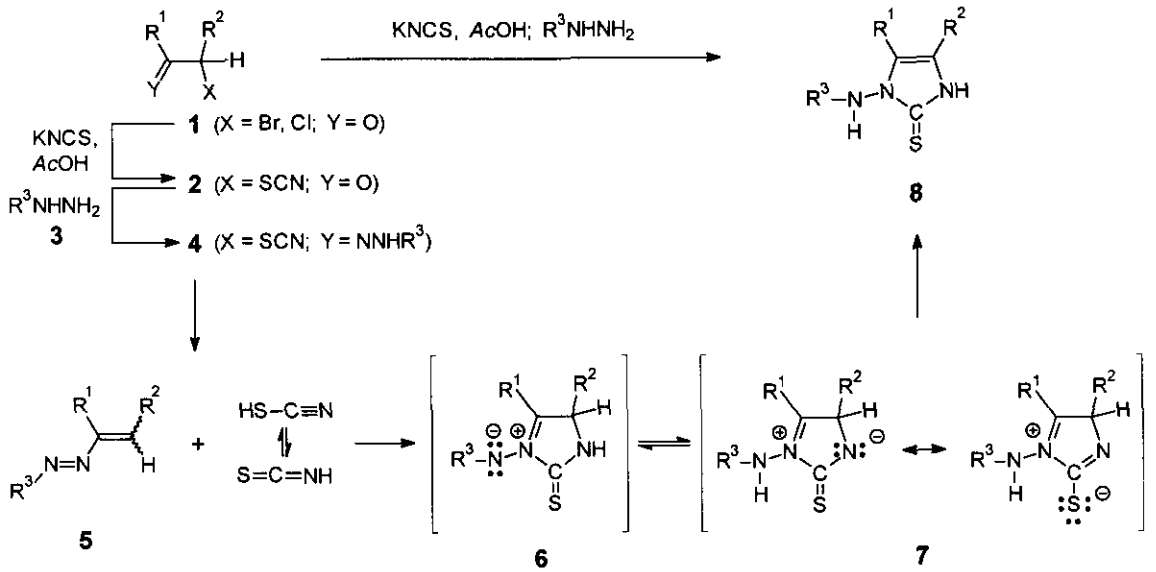
Current interest in *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones (**8**) has been aroused by reports on the industrial applicability and various biological activities associated with a number of 1-substituted imidazole-2-thione derivatives. 1-Methylimidazole-2-thione (Methimazole®) is used for the treatment of thyroid gland disorder,[1a] while other derivatives serve for the treatment of arthritis[1b,c] and cardiovascular disorders,[1d,e] and also as HIV-1 reverse transcriptase inhibitors.[1f] In addition, anti-inflammatory activities[1g] and, more recently, antioxidant properties[1h] have been reported as well.

RESULTS AND DISCUSSION

The reaction of α-halo ketones (**1**) with potassium thiocyanate and the appropriate monosubstituted hydrazine (**3**) affords *N*-substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thione derivatives (**8**). This multistep reaction was carried out in an efficient one-pot procedure. This reaction is considered to follow the reaction path as outlined in Scheme 1. In the first step the α-halo ketone (**1**) is presumed to react with potassium thiocyanate, and the first-formed α-thiocyanato carbonyl compound (**2**) is converted by the hydrazine (**3**) into the hydrazone (**4**). In the course of a 1,4-elimination reaction, two intermediates, the

corresponding azo-alkene[2a] (**5**) and thiocyanic acid,[3] are formed. These intermediates subsequently undergo a [3+2] cycloaddition reaction;[2b] the azo-alkene (**5**) reacts as an isoelectronic hetero-allyl anion equivalent and thiocyanic acid (or isothiocyanic acid) as dipolarophile. The resultant cycloadduct, the heterocyclic azomethine imine intermediate (**6**) is anticipated to equilibrate with the zwitterion (**7**) by a proton transfer from the thiourea NH to the more basic exocyclic nitrogen atom. Eventually, 1,2-hydrogen shift from 4-C to 3-N provides the final product (**8**).

Scheme 1



1, 2	R^1	R^2	3	R^3
a	CH_3	CH_3	**a**	C_6H_5
b	CH_3	C_6H_5	**b**	4-$O_2NC_6H_4$
c	C_6H_5	CH_3	**c**	4-$CH_3C_6H_4$
d	$(CH_2)_4$		**d**	4-$CH_3OC_6H_4$
			e	4-ClC_6H_4
			f	$C_6H_5CH_2$

4 - 8 (*e.g.* **8ab**: R^1, R^2 = **a**, R^3 = **b**)

The structure of the novel *N*-monosubstituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones (**8**) has been spectroscopically confirmed, in particular by various NMR experiments.

The ^{1}H-NMR spectra of the isomeric imidazoles (**8ba**) and (**8ca**) having a phenyl group at position 4 and 5, respectively, permit an unambiguous structure assignment. The ^{1}H-NMR spectrum of compound (**8ba**) exhibits the aromatic proton signals as clearly separated multiplets (Figure 1). The signals of the 4-phenyl protons are shifted to lower field with respect to the *N*-phenyl protons; the *ortho* protons of the 4-phenyl

group resonate at lowest field. The geometry optimized structure[4] of **8ba** (Figure 1) suggests that presumably due to the closely coplanar orientation of the 4-phenyl and the imidazole rings, the latter induces the anisotropic deshielding effect on the *ortho*-protons of the 4-phenyl group.[5]

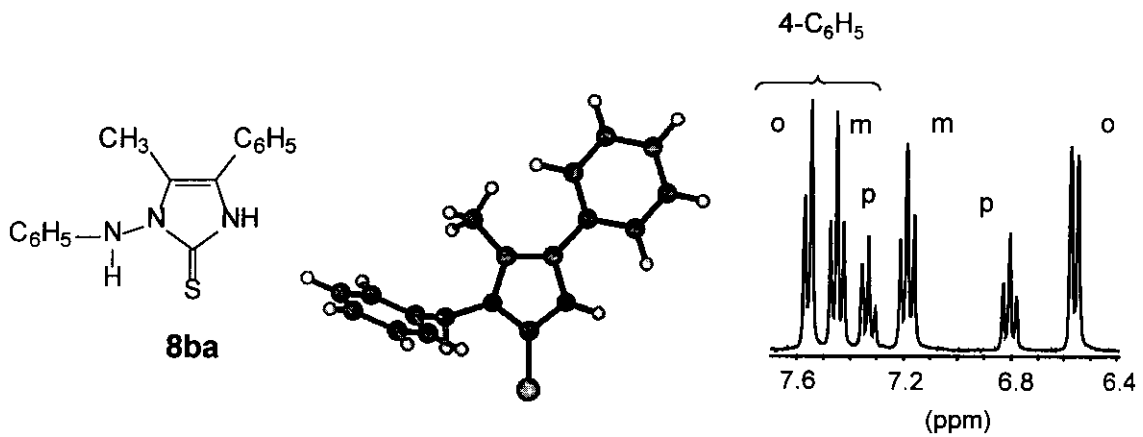


Figure 1. Geometry optimized structure and ^{1}H-NMR aromatic region of **8ba**.

By contrast, all 5-phenyl proton signals of the imidazole (**8ca**) are displayed as an unresolved multiplet at low field, while the *N*-phenyl protons give rise to well separated multiplets at higher field (Figure 2). This spectral feature is rationalized by the lack of coplanarity between 5-phenyl and the imidazole ring, both rings being almost perpendicular to each other due to steric interference of the former with the 1-*N*-amino substituent and the 4-methyl group (*cf.* structure drawing of **8ca** in Figure 2).

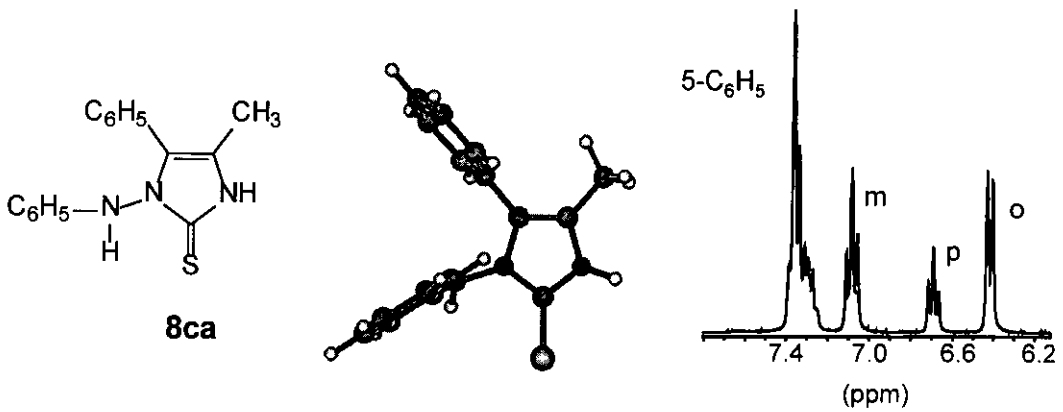


Figure 2. Geometry optimized structure and ^{1}H-NMR aromatic region of **8ca**.

The structure assignments also provide evidence that the conversion of the starting compounds (**1**) into the heterocyclic products (**8**) proceeds through the reactions shown in Scheme 1. Furthermore, these results rule out the possibility of an alternative reaction path as observed in the related reaction of α-chloro aldimines and potassium thiocyanate;[6] according to that reaction path the formation of isomeric imidazoles with the substituents R^1 and R^2 formally exchanged would be expected.

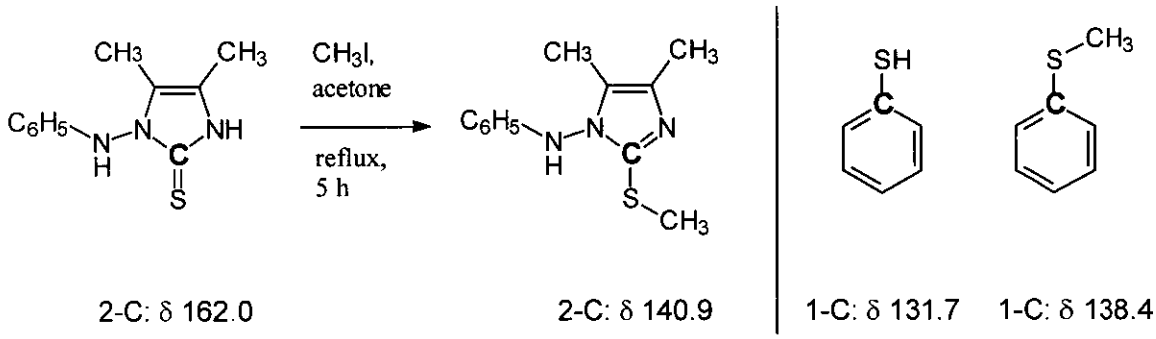
The two NH signals (exchangeable with D_2O) of compounds (**8**) exhibited in the ranges δ 8.69 - 8.93 and δ 11.88 -12.41 are attributed to the amino substituent at 1-N and to the 3-NH, respectively. The downfield signal of the latter is indicative of a thiourea moiety with a marked resonance contribution from the zwitterionic structure [>N–C(=S)–NH– ↔ >N–C(–S^-)=N^+H–]. Based on this assignment of the NH signals the two methyl group signals of **8aa** (R^1, R^2 = CH_3) were analyzed by means of NOE-DIFF-spectroscopy. Saturation of the 3-NH signal caused 18% NOE at the 4-methyl group. The same experiment applied to the exchangeable proton of the 1-phenylamino substituent resulted in a 10% NOE at the high field *ortho*-proton signals of the *N*-phenyl substituent.

Furthermore, the infrared spectra are in agreement with the thione form of compounds (**8**). An S-H stretching vibration[7a] is missing; the characteristic absorption pattern in the range of 3400-2700 cm^{-1} results from stretching vibrations both of C-H (aromatic substituents) and of N-H (1-N-NH and 3-NH, the latter thiourea-like). The absorption band in the range of 700-770 cm^{-1} is attributed to the N-C-S deformation vibration of the thiourea moiety.[7b]

The UV spectra of compounds (**8**) show two major absorption bands corresponding to those of diphenylamine.[8] The 1-(4-nitrophenylamino) derivatives (**8xb**, **x** = **a** - **d**) display also a shoulder above 320 nm due to the nitro group. As compared to compounds (**8xy**, **x** = **a**, **d**; **y** = **a**, **b**) with alkyl groups in both positions 4 and 5, the 5-phenyl substituent of compounds (**8cy**, **y** = **a** - **f**) does not alter the appearance of the UV spectra. By contrast, the UV spectra of compounds (**8by**, **y** = **a**, **b**) with the 4-phenyl group show an additional absorption at about 300 nm superimposed to the diphenylamine-like spectrum of **8**. This absorption is similar to that of *m*-aminobiphenyl,[9] a close structural resemblance of the 1-amino-4-phenylimidazole portion of **8by** (**y** = **a**, **b**).

As exemplified by compound (**8aa**), the 2-thione function has been confirmed excluding the sulphanyl function of a conceivable tautomer. For this purpose the imidazole-2-thione (**8aa**) was methylated and converted into the 2-methylsulfanylimidazole derivative (**9aa**) (Scheme 2). The chemical shifts of 2-C in compounds (**8aa**) and (**9aa**) were compared with those of the aromatic 1-C in thiophenol (δ 131.7) and methylsulfanylbenzene (δ 138.4).[10a,b] The 1-C shifts of both latter compounds compare well with the 2-C shift (δ 140.9) of the 2-methylsulfanylimidazole derivative (**9aa**) but are markedly different from that of 2-C (δ 162.0) in compound (**8aa**), thus indicating the thione structure of compounds (**8**) with 2-C shifts in this range.

Scheme 2.



2-C: δ 162.0 2-C: δ 140.9 1-C: δ 131.7 1-C: δ 138.4

EXPERIMENTAL

Spectroscopic data were recorded on the following instruments: MATTSON Galaxy Series GL-3020 (IR; KBr; [cm^{-1}]); Bruker AM 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz; DMSO-d_6; δ); MAT 95 (EI-MS 70 eV [m/z] (%)); HITACHI U-3000 (UV; $CHCl_3$, λ_{max} [nm], (log ε)). Melting points (mp [°C]) were determined with a Kofler hot stage microscope (Reichert). Thin layer chromatography (TLC) was carried out on silica gel (Polygram Sil G/UV_{254}).

***N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thiones; Method A :** To a stirred solution of the α-halo ketone (**1**) (**1a**, **1d**, X = Cl; **1b**, **1c**, X = Br) (2.5 mmol) in acetic acid (10 mL) was added finely ground potassium thiocyanate (0.37 g, 3.8 mmol) at ambient temperature. After 1 h, phenylhydrazine (**3a**) (0.27 g, 2.5 mmol) was added dropwise. The reaction mixture turned red, the temperature rose, and after 1-2 h the product began to separate. Stirring was continued for another 2 h, ether (15 mL) was added to complete the precipitation of the product (**8xa**; **x** = **a** - **d**), which was filtered off and washed with water (2 x 20 mL). Recrystallization from ethanol afforded colorless crystals (**8xa**), the purity was checked with TLC. In order to remove colored impurities the crude product was dissolved in 5% NaOH and extracted with dichloromethane. Neutralization of the aqueous layer with 10% HCl induced precipitation of the pure (by TLC) product (**8xa**). For the preparation of **8da** the reaction was carried out in methanol with a few drops of acetic acid added. ^{1}H- and ^{13}C-NMR data are collected in Tables 1 and 2.

Procedure B : To a stirred solution of the α-halo ketone (**1**) (**1a**, **1d**, X = Cl; **1b**, **1c**, X = Br) (2.5 mmol) in DMF (10 mL) was added finely ground potassium thiocyanate (0.37g, 3.8 mmol) at ambient temperature. After stirring for 1 h, hydrazine (**3b**, **3c**) or hydrazine hydrochloride (**3d**·HCl, **3e**·HCl, **3f**·HCl) (2.5 mmol) dissolved in DMF (3 mL) was added dropwise. Stirring was continued for 5 h, and upon addition of water, the resultant precipitate was filtered off. Recrystallization from ethanol afforded the pure (TLC) product (**8xb**; **x** = **a** - **d**; **8cc**, **8cd**, **8ce**, **8cf**). ^{1}H- and ^{13}C-NMR data are collected in Tables 1 and 2.

Table 1: ^{1}H-NMR Data of *N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thiones (**8**).

	R^1	R^2	R^3	1-N-NH[a]	3-NH[a]
8aa	2.01 (s)	1.89 (s)	6.47 (d, J = 7.7 Hz), 6.77 (t, J = 7.1 Hz), 7.15 (dd, J = 7.7, 7.1 Hz)	8.72	11.88
8ba	2.19 (s)	7.33 (t, J = 7.8 Hz), 7.45 (dd, J = 7.8, 7,3 Hz), 7.54 (d, J = 7.3 Hz)	6.55 (d, J = 7.8 Hz), 6.80 (t, J = 7,3 Hz), 7.19 (dd, J = 7.8, 7.3 Hz)	8.93	12.10
8ca	7.25-7.38 (m)	2.14 (s)	6.41 (d, J = 8.2 Hz), 6.69 (t, J = 7.6 Hz), 7.08 (dd, J = 8.2, 7.6 Hz)	8.87	12.41
8da	1.69 (m, 5,6-CH_2CH_2), 2.22 (m, 4-CH_2), 2.35 (m, 7-CH_2)		6.49 (d, J = 7.8 Hz), 6.77 (t, J = 7.3 Hz), 7.15 (dd, J = 7.8, 7,3 Hz)	8.69	11.98
8ab	2.02 (s)	1.87 (s)	6.55, 6.58, 8.08, 8.11 (AA'BB', J = 8.8 Hz)[b]	10.04	12.19
8bb	2.17 (s)	7.34 (t, J = 7.6 Hz), 7.42 (dd, J = 7.6, 7,0 Hz), 7.56 (d, J = 7.0 Hz)	6.67, 6.70, 8.10, 8.13 (AA'BB', J = 8.8 Hz)[b]	10.20	12.83
8cb	7.26-7.34 (m)	2.14 (s)	6.54, 6.57, 8.01, 8.04 (AA'BB', J = 9.4 Hz)[b]	10.21	12.65
8db	1.69 (m, 5,6-CH_2CH_2), 2.10 (m, 4-CH_2), 2.36 (m, 7-CH_2)		6.58, 6.61, 8.07, 8.10 (AA'BB', J = 8.7 Hz)[b]	10.01	12.23
8cc	7.31-7.35 (m)	2.11 (s)	2.12 (s), 6.43, 6.46, 7.12, 7.15 (AA'BB', J = 8.8 Hz)[b]	8.71	12.41
8cd	7.30-7.37 (m)	2.13 (s)	3.61 (s), 6.41, 6.44, 7.11, 7.15 (AA'BB', J = 8.8 Hz)[b]	9.14	12.40
8ce	7.31-7.35 (m)	2.12 (s)	6.32, 6.35, 6.88, 6.91 (AA'BB', J = 8.3 Hz)[b]	9.13	12.49
8cf	7.33-7.42 (m)	2.05 (s)	3.97 (d, J = 6.2 Hz, CH_2), 7.07-7.11 (m), 7.19 (m)	6.01 (t, J = 6.2 Hz)	12.24

[a] br s. [b] A = 2,6-H ar, B = 3,5-H ar; the determination of J is based on the assumption of an AB quartet.[11]

2,3-Dihydro-4,5-dimethyl-1-phenylamino-1*H*-imidazole-2-thione (8aa) (Method A)**:** Yield: 61%; mp 217-219°C; R_f 0.65 (ether/ethyl acetate 9:1); IR: 3169, 3072, 2943, 2806, 2752, 704; UV: 279.5 (3.97); 241.5 (3.77); MS: 219 (100, $M^{\bullet+}$), 190 (27, M - C_2H_5), 127 (57, M - C_6H_5NH), 77 (9, C_6H_5). Anal. Calcd for $C_{11}H_{13}N_3S$: C, 60.25; H, 5.97; N, 19.16; S, 14.62. Found: C, 60.30; H, 5.75; N, 19.20; S, 14.54.

2,3-Dihydro-5-methyl-4-phenyl-1-phenylamino-1*H*-imidazole-2-thione (8ba) (Method A)**:** Yield: 69%; mp 226-228°C; R_f 0.84 (ether/ethyl acetate 9:1); IR: 3136, 3065, 2924, 2742, 763; UV: 283.5 (4.20), 297.5 (4.19), 241.5 (4.03); MS: 281 (100, $M^{\bullet+}$), 189 (40, M - C_6H_5NH), 131 (62,

M - C_6H_5NHNCS), 93 (62, $C_6H_5NH_2$), 77 (29, C_6H_5). Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30 ; H, 5.37; N, 14.93; S, 11.39. Found: C, 68.32; H, 5.30; N, 14.79; S, 11.25.

Table 2: ^{13}C-NMR Data of *N*-Substituted 1-Amino-2,3-dihydro-1*H*-imidazole-2-thiones (**8**).

	2-C, 4-C, 5-C[a]	R^1	R^2	R^3
8aa	160.8, 117.1, 122.0	7.7	8.9	112.2, 119.5, 128.8, 147.1[b]
8ba	161.9, 121.5, 123.8	9.2	126.3, 127.2, 127.3, 128.7[c]	112.4, 119.7, 128.8, 147.0[b]
8ca	161.6, 119.5, 126.5	127.5 127.7, 128.1, 128.6[b]	9.9	112.2, 119.2, 128.8, 147.0[b]
8da	160.8, 120.0, 124.9	19.3 (7-CH_2), 20.1 (4-CH_2), 21.1 (5-CH_2), 21.8 (6-CH_2)		112.4, 119.6, 128.8, 147.2[b]
8ab	160.7, 117.9, 121.7	7.6	9.1	111.3, 125.8, 139.4, 153.0[d]
8bb	160.7, 120.3, 126.1	10.0	127.0, 128.1, 128.5, 128.7[c]	111.4, 125.7, 139.2, 152.9[d]
8cb	162.1, 122.1, 123.5	126.5, 127.6, 128.5, 128.8[c]	9.1	111.6, 125.8, 139.6, 152.8[d]
8db	161.1, 121.1, 124.6	19.2 (7-CH_2), 20.1 (4-CH_2), 21.5 (5-CH_2), 21.8 (6-CH_2)		111.5, 125.8, 139.4, 153.2[d]
8cc	161.5, 119.5, 127.6	127.7, 127.9, 128.1, 128.8[b]	11.0	20.0 (CH_3), 112.5, 126.6, 129.1, 144.8[b]
8cd	161.4, 119.5, 126.5	127.7, 127.9, 128.2, 128.9[b]	10.0	55.1 (CH_3O), 113.9, 114.2, 140.8, 153.0[c]
8ce	161.6, 119.8, 126.5	127.5, 127.9, 128.3, 128.6[e]	10.0	113.4, 122.8, 128.9, 146.1[b]
8cf	158.6, 124.9, 127.8	127.6, 127.8, 128.0, 128.3[c]	9.7	53.3 (CH_2), 119.5, 127.3, 129.2, 136.1[f]

[a] The assignment of the 4-C and 5-C signals was achieved by means of HMQC-spectra. [b-e] Order of phenyl signals: [b] 2,6-C, 4-C, 3,5-C, 1-C; [c] 2,6-C, 3,5-C, 1-C, 4-C; [d] 2,6-C, 3,5-C, 4-C, 1-C; [e] 4-C, 1-C, 2,6-C, 3,5-C; [f] 4-C, 2,6-C, 3,5-C, 1-C.

2,3-Dihydro-4-methyl-5-phenyl-1-phenylamino-1*H*-imidazole-2-thione (8ca) (Method A)**:** Yield: 72%; mp 212-214°C; R_f 0.71 (ether/ethyl acetate 9:1); IR: 3263, 3047, 3036, 2907, 744; UV: 288.5 (4.21), 241.0 (3.95); MS: 281 (100, $M^{\bullet+}$), 248 (7, M - SH), 221 (23, M - HNCSH), 189 (11, M - C_6H_5NH), 131 (6, M - C_6H_5NHNCS), 93 (65, $C_6H_5NH_2$), 77 (14, C_6H_5). Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30 ; H, 5.37; N, 14.93; S, 11.39. Found: C, 68.27; H, 5.26; N, 14.85; S, 11.28.

2,3,4,5,6,7-Hexahydro-1-phenylamino-1*H*-benzimidazole-2-thione (8da)[2b] (Method A)**:** Yield: 80% (Method A); mp 207-209°C; R_f 0.72 (ether/ethyl acetate 9:1); IR: 3306, 3163, 3098, 2947, 752; UV:

281.5 (4.11), 241.5 (3.88); MS: 245 (100, $M^{\bullet+}$), 153 (44, M - C_6H_5NH), 93 (72, $C_6H_5NH_2$), 68 (24, C_5H_8).

2,3-Dihydro-4,5-dimethyl-1-(4-nitrophenylamino)-1*H*-imidazole-2-thione (8ab) (Method B): Yield: 93%; mp 275-280°C; R_f 0.35 (ether/ethyl acetate 9:1); IR: 3204, 3102, 2957, 1595, 1346, 748; UV: 332.0 (sh, 3.87), 292.5 (4.18), 240.5 (3.81); MS: 264 (59, $M^{\bullet+}$), 138 (21, $O_2NC_6H_4NH_2$), 127 (100, M - $O_2NC_6H_4NH$), 68 (19, M - $O_2NC_6H_4NHNCSH$). Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.99 ; H, 4.58; N, 21.20; S, 12.13. Found: C, 50.56; H, 4.23; N, 20.90; S, 12.01.

2,3-Dihydro-5-methyl-1-(4-nitrophenylamino)-4-phenyl-1*H*-imidazole-2-thione (8bb) (Method B): Yield: 90%; mp 250-253°C; R_f 0.21 (ether/ethyl acetate 9:1); IR: 3186, 3080, 2928, 1597, 1342, 750; UV: 334.0 (sh, 3.78), 298.5 (4.38), 302.5 (4.37), 240.5 (3.98); MS: 326 (21, $M^{\bullet+}$), 190 (100, M - $O_2NC_6H_4N$), 131 (35, M - $O_2NC_6H_4NHNCS$), 77 (13, C_6H_5). Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.17; S, 9.82. Found: C, 59.04 ; H, 4.28 ; N, 17.00; S, 9.38.

2,3-Dihydro-4-methyl-1-(4-nitrophenylamino)-5-phenyl-1*H*-imidazole-2-thione (8cb) (Method B): Yield: 84%; mp 260-262°C; R_f 0.48 (ether/ethyl acetate 9:1); IR: 3265, 3057, 2920, 2714, 1595, 1344, 746; UV: 320.5 (sh, 4.01), 281.5 (4.23), 239.5 (3.89); MS: 326 (100, $M^{\bullet+}$), 280 (43, M - NO_2), 267 (84, M - HNCS), 189 (52, M - $O_2NC_6H_4NH$), 131 (52, M - $O_2NC_6H_4NHNCS$), 117 (50, M - $O_2NC_6H_4NHNCSN$), 105 (50), 77 (33, C_6H_5). Anal. Calcd for $C_{16}H_{14}N_4O_2S$: C, 58.88; H, 4.32; N, 17.17; S, 9.82. Found: C, 58.28 ; H, 4.36 ; N, 16.69; S, 9.41.

2,3,4,5,6,7-Hexahydro-1-(4-nitrophenylamino)-1*H*-benzimidazole-2-thione (8db) (Method B): Yield: 87%; mp 261-262°C; R_f 0.28 (ether/ethyl acetate 9:1); IR: 3188, 3082, 2941, 2858, 1601, 1342, 775, 499; UV: 321.5 (sh) (4.04), 284.0 (4.28), 242.0 (3.91); MS: 290 (53, $M^{\bullet+}$), 231 (56, M - HNCS), 153 (100, M - $O_2NC_6H_4NH$), 138 (52, $O_2NC_6H_4NH$), 108 (33, $C_6H_8N_2$), 73 (35, NCSNH). Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.78; H, 4.86; N, 19.30; S, 11.04. Found: C, 53.69; H, 4.75; N, 19.35; S, 10.70.

2,3-Dihydro-4-methyl-1-(4-methylphenylamino)-5-phenyl-1*H*-imidazole-2-thione (8cc) (Method B): Yield: 89%; mp 192-194°C; R_f 0.47 (ether/ethyl acetate 9:1); IR: 3259, 3057, 2912, 2835, 2714, 760; UV: 290.0 (4.24), 244.5 (4.05); MS: 295 (60, $M^{\bullet+}$), 190 (100, M - $CH_3C_6H_4N$), 131 (48, C_9H_9N), 107 (85, $CH_3C_6H_4NH_2$), 77 (17, C_6H_5); Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22; S, 10.85. Found: C, 68.95; H, 5.77; N, 14.30; S, 10.94 .

2,3-Dihydro-1-(4-methoxyphenylamino)-4-methyl-5-phenyl-1*H*-imidazole-2-thione (8cd) (Method B): Yield: 89%; mp 220-222°C; R_f 0.38 (ether/ethyl acetate 9:1); IR: 3261, 3059, 2999, 2912, 2714, 702; UV: 289.0 (4.26), 242.5 (4.19); MS: 311 (77, $M^{\bullet+}$), 280 (30, M - CH_3O), 190 (100, M - $CH_3OC_6H_4N$), 131 (25, C_9H_8NH), 123 (75, $CH_3OC_6H_4NH_2$), 108 (40, $CH_3OC_6H_5$), 77 (10, C_6H_5); Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49; S, 10.30. Found: C, 64.85; H, 5.61; N, 13.23; S, 10.09.

1-(4-Chlorophenylamino)-2,3-dihydro-4-methyl-5-phenyl-1*H*-imidazole-2-thione (8ce) (Method B): Yield: 76%; mp 212 °C; R_f 0.43 (ether/ethyl acetate 9:1); IR: 3227, 3059, 2916, 2712, 810, 698; UV:

286.5 (4.28), 243.0 (4.07); MS: 317 (11, M + 2), 315 (31, $M^{\bullet+}$), 282 (35, M - SH), 190 (55, M - ClC_6H_4N), 131 (65, C_9H_9N), 127 (100, $ClC_6H_4NH_2$), 77 (10, C_6H_5). Anal. Calcd for $C_{16}H_{14}N_3ClS$: C, 60.85; H, 4.47; N, 13.31; Cl: 11.23; S, 10.13. Found: C, 60.95; H, 4.38; N, 13.40; Cl, 11.32; S, 10.38.

1-Benzylamino-2,3-dihydro-4-methyl-5-phenyl-1*H*-imidazole-2-thione (8cf) (Method B)**:** Yield: 65%; mp 198-202°C; R_f 0.69 (ether/ethyl acetate 9:1); IR: 3250, 3059, 2932, 2722, 758; UV: 288.5 (4.20), 242.0 (3.82); MS: 295 (5, $M^{\bullet+}$), 190 (100, M - $C_6H_5CH_2N$), 130 (11, M - $C_6H_5CH_2NHNCSH$), 105 (16, C_6H_5CHNH), 91 (25, $C_6H_5CH_2$), 77 (17, C_6H_5). Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22; S, 10.85. Found: C, 68.84; H, 5.91; N, 14.48; S, 10.86.

4,5-Dimethyl-2-methylsulfanyl-1-phenylamino-imidazole (9aa): A mixture of **8aa** (0.25 g, 1.11 mmol) and methyl iodide (1.19 g, 8.40 mmol) in acetone (5 mL) was heated under reflux for 5 h.. Excess of methyl iodide and the solvent were removed *in vacuo*; the residue upon treatment with 5% aqueous sodium bicarbonate solution turned crystalline: 0.22 g (82%) **9aa**; mp 198°C (ethanol); R_f 0.28 (ether); IR: 3219, 3105, 2999, 2918; UV: 265.0 (3.78), 243.5 (3.97); ^{1}H-NMR: 1.88 (3H, s, 4-CH_3), 2.05 (3H, s, 5-CH_3), 2.40 (3H, s, CH_3S), 6.38 (2H, d, J = 7.8 Hz, 2,6-H ar), 6.79 (1H, t, J = 7.3 Hz, 4-H ar), 7.17 (2H, dd, J = 7.8, 7.3 Hz, 3,5-H ar), 9.01 (1H, exchangeable, br s, HN); ^{13}C-NMR: 7.7 (5-CH_3), 13.0 (4-CH_3), 14.1 (CH_3S), 124.5 (4-C), 131.4 (5-C), 140.9 (2-C), 111.8, 119.8, 129.1, 147.0 (2,6-C, 4-C, 3,5-C, 1-C of C_6H_5NH); MS: 233 (100, $M^{\bullet+}$), 141 (70, M - C_6H_5NH), 93 (80, $C_6H_5NH_2$), 77 (15, C_6H_5). Anal. Calcd for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01; S, 13.74. Found: C, 61.35; H, 6.40; N, 18.00; S, 13.45.

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