Synthesis of 1-(alkylamino)- and 1-(dialkylamino)benzimidazoline-2-thiones

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Unlike 1-aminobenzimidazoles, 1-alkylaminobenzimidazoles are thiolated on fusing with sulfur without elimination of the *N*-amino group, yielding the previously unknown 1-(alkylamino)benzimidazoline-2-thiones. These compounds can be more conveniently obtained on a preparative scale by thiolation of 1-alkylacetamidobenzimidazoles with subsequent hydrolytic elimination of the acetyl group. When 1-(dialkylamino)benzimidazoles are fused with sulfur, they are converted into 1-(dialkylamino)benzimidazoline-2-thiones. By alkylation of 1-(methylamino)- and 1-(diethylamino)benzimidazoline-2-thiones with methyl iodide in alkaline media the corresponding 2-(methylthio)benzimidazoles were prepared.

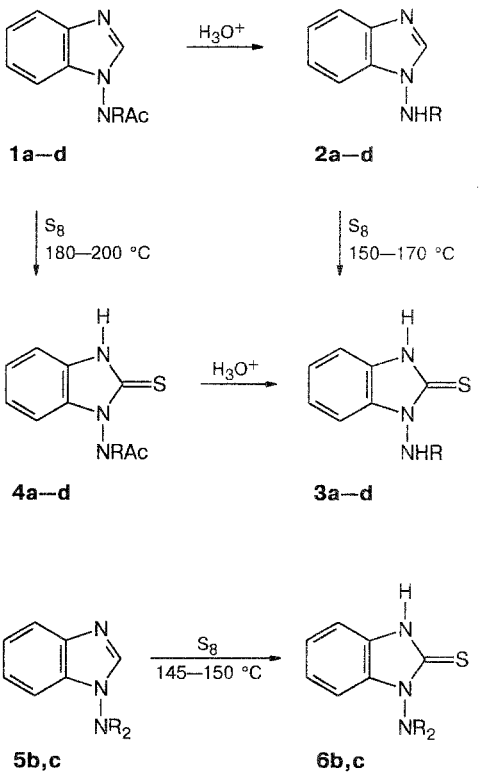
Key words: 1-(alkylamino)- and 1-(dialkylamino)benzimidazoles, thiolation.

We have found previously that during fusion of 1-aminobenzimidazole with sulfur, thiolation of position 2 is preceded by oxidative deamination, and consequently, the reaction yields benzimidazoline-2-thione as the only product.[1] Later, in relation to *N*-benzylidene-aminobenzimidazoles, we found that protection of the amino group prevents it from elimination during thiolation, which makes it possible to synthesize in this way, after hydrolytic elimination of the benzylidene group, *N*-aminoazolinethiones, including 1-amino-benzimidazoline-2-thione.[2]

To solve a number of synthetic problems, we needed 1-(alkylamino)- and 1-(dialkylamino)benzimidazoline-2-thiones, which remained unknown until recently. Since these compounds cannot be synthesized by alkylation of 1-aminobenzimidazoline-2-thione (for compounds of this sort this reaction is known to occur at the sulfur atom), we decided to study thiolation of 1-(alkylamino)- and 1-(dialkylamino)benzimidazoles. One could have expected that the presence of alkyl substituents at the *N*-amino group would be sufficient to prevent deamination. By alkylating 1-acetamidobenzimidazole (**1a**) in acetone in the presence of alkali with subsequent hydrolysis of the acetyl group in the resulting 1-(*N*-alkyl-acetamido)benzimidazoles (**1b—d**) we obtained 1-(methylamino)- (**2b**), 1-(ethylamino)- (**2c**), and 1-(benzylamino)benzimidazoles (**2d**), necessary for our studies (Scheme 1).

We began the synthesis of 1-aminobenzimidazoline-2-thiones with study of thiolation of compound **1a**. We found that heating **1a** with sulfur (180—200 °C) gives

Scheme 1



R = H (**a**), Me (**b**), Et (**c**), Bn (**d**).

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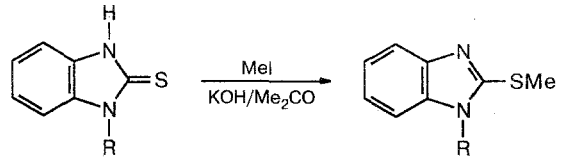
Table 1. ^{1}H NMR spectra of the compounds synthesized

Compound	δ (*J*/Hz)[a]
1b	1.84 (s, 3 H, $COCH_3$); 3.47 (s, 3 H, NCH_3); 7.40 (m, 3 H, H(4)—H(6)); 7.85 (m, 1 H, H(7)); 7.99 (s, 1 H, H(2))
1c	1.09 (t, J = 7.03, 3 H, $CH_2\underline{CH_3}$); 1.80 (s, 3 H, $COCH_3$); 3.75[b] (d. q, ^2J = 14.06, ^3J = 7.33, 1 H, $\underline{CH_2}CH_3$); 4.12[b] (d. q, ^2J = 14.06, ^3J = 7.32, 1 H, $\underline{CH_2}CH_3$); 7.40 (m, 3 H, H(4)—H(6)); 7.85 (m, 1 H, H(7)); 7.94 (s, 1 H, H(2))
1d	1.84 (s, 3 H, CH_3); 4.46[b] (d, J = 14.5, 1 H, CH_2); 5.51[b] (d, J = 14.2, 1 H, CH_2); 7.17 (m, 9 H, H(4)—H(6), H(2′)—H(6′)); 7.39 (s, 1 H, H(2)); 7.78 (m, 1 H, H(7))
3b	2.95 (d, J = 6.2, 3 H, $NH\underline{CH_3}$); 5.60 (q, J = 6.2, 1 H, $\underline{NH}CH_3$); 7.24 (m, 3 H, H(4)—H(6)); 7.35 (m, 1 H, H(7)); 10.71 (s, 1 H, NH)
3c	1.22 (t, J = 7.2, 3 H, $CH_2\underline{CH_3}$); 3.25 (m, 2 H, $\underline{CH_2}CH_3$); 5.48 (t, J = 5.9, 1 H, $\underline{NH}CH_2$); 7.21 (m, 3 H, H(4)—H(6)); 7.34 (m, 1 H, H(7)); 11.13 (s, 1 H, NH)
3d	4.32 (d, J = 5.9, 2 H, $NH\underline{CH_2}$); 5.73 (t, J = 5.9, 1 H, $\underline{NH}$—CH_2); 7.24 (m, 3 H, H(4)—H(6)); 7.49 (m, 1 H, H(7)); 10.84 (s, 1 H, NH)
4a	2.11 (s, 3 H, CH_3); 7.19 (m, 4 H, H(4)—H(7)); 11.10 (s, 1 H, $\underline{NH}CO$); 12.90 (s, 1 H, NH)
4b	1.75 (s, 3 H, $COCH_3$); 3.20 (s, 3 H, NCH_3); 7.30 (m, 4 H, H(4)—H(7)); 13.20 (s, 1 H, NH)
4c	1.19 (t, J = 7.2, 3 H, $CH_2\underline{CH_3}$); 1.90 (s, 3 H, $COCH_3$); 3.81[b] (d. q, ^2J = 14.0, ^3J = 7.20, 1 H, $\underline{CH_2}CH_3$); 4.28[b] (d. q, ^2J = 14.02, ^3J = 7.21, 1 H, $\underline{CH_2}CH_3$); 7.28 (m, 4 H, H(4)—H(7)); 11.40 (s, 1 H, NH)
4d	1.91 (s, 3 H, $COCH_3$); 4.47[b] (d, J = 14.0, 1 H, CH_2); 5.75[b] (d, J = 14.0, 1 H, CH_2); 6.42 (m, 1 H, H(4′)); 7.02 (m, 6 H, H(4)—H(6), H(3′), H(5′)); 7.36 (s, 2 H, H(2′), H(6′))
6b	3.21 (s, 6 H, $2CH_3$); 7.20 (m, 8 H, H(4)—H(6), H(2′)—H(6′)); 7.37 (m, 1 H, H(7)); 11.03 (s, 1 H, NH)
6c	0.98 (t, J = 7.33, 6 H, $2CH_3$); 3.21 (d. q, ^2J = 12.01, ^3J = 7.33, 2 H, $CH_2(H^b)$); 4.10 (d. q, ^2J = 12.02, ^3J = 7.32, 2 H, $CH_2(H^a)$); 7.16—7.26 (m, 3 H, H(4)—H(6)); 7.40 (m, 1 H, H(7)); 10.92 (m, 1 H, NH)
7	2.75 (s, 3 H, SCH_3); 2.95 (s, 3 H, NCH_3); 4.72 (s, 1 H, NH); 7.25 (m, 3 H, H(4)—H(6)); 7.66 (m, 1 H, H(7))
8	0.97 (t, J = 7.32, 6 H, $2CH_2\underline{CH_3}$); 2.68 (s, 3 H, SCH_3); 3.17 (d. q, ^2J = 12.02, ^3J = 7.32, 2 H, $CH_2(H^b)$); 3.49 (d. q, ^2J = 12.01, ^3J = 7.03, 2 H, $CH_2(H^a)$); 7.11 (t, J = 7.33, 1 H, H(5)); 7.18 (t, J = 6.99, 1 H, H(6)); 7.39 (d, J = 7.33, 1 H, H(4)); 7.68 (d, J = 6.99, 1 H, H(7))

[a] The ^{1}H NMR spectra of **4a,b** were recorded in DMSO-d_6; spectra of the other compounds were measured in $CDCl_3$. [b] The protons of the CH_2 group are nonequivalent.

1-acetamidobenzimidazoline-2-thione (**4a**) in 63 % yield. This indicated that replacement of even one hydrogen atom in the amino group of *N*-aminoazoles provides sufficient protection. This inference was further confirmed in relation to compounds **2a,b**, which are thiolated at 150—170 °C yielding 1-(alkylamino)benzimidazoline-2-thiones (**3b—d**). However, this reaction is accompanied by some resinification, and the yields of compounds **3b—d** are low (30—66 %). In order to increase the yields of thiones **3b—d**, we decided to protect as well the second hydrogen atom of the *N*-amino group, and therefore involved 1-(*N*-alkylacetamido)benzimidazoles **1b—d** into thiolation. We found that thiolation of these compounds at 180—200 °C really proceeds more smoothly, and the yields of the resulting 1-(*N*-alkylacetamido)benzimidazoline-2-thiones (**4b—d**) amount to 73—75 %. Further hydrolysis of the latter affords compounds **3b—d** in high yields. The conclusion that the use of *N*-aminoazoles disubstituted at the amino group in thiolation reactions is more favorable is also supported by the fact that fusion of 1-(dialkylamino)benzimidazoles (**5b,c**) with sulfur at 145—150 °C gives 1-(dimethylamino)- and 1-(diethylamino)benzimidazoline-2-thiones (**6b,c**) in 73 and 56 % yields, respectively (Scheme 1).

Using compounds **3b** and **6c** as examples it was shown that these compounds, like other benzimidazoline-2-thiones,[1,6] are alkylated with methyl iodide in an alkaline medium only at the sulfur atom affording 1-(methylamino)- (**7**) and 1-(diethylamino)-2-methylthiobenzimidazoles (**8**).



3b: R = NHMe
6c: R = NEt_2

7: R = NHMe
8: R = NEt_2

It is of interest that the methylene protons of the ethyl groups in compounds **6c** and **8**, unlike those in the starting compound **5c**, become magnetically nonequivalent and are manifested as two two-proton multiplets with chemical shifts of 4.10 and 3.21 ppm for **6c** and 3.49 and 3.17 ppm for **8** (Table 1).

In view of the fact that the amino group in *N*-aminoazoles always has a pyramidal configuration,[3]

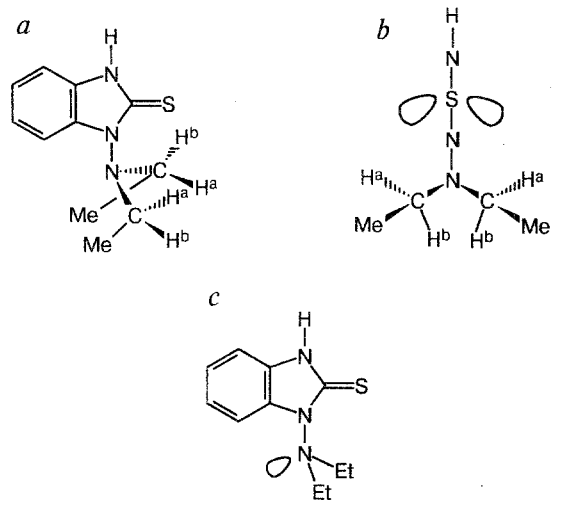


Fig. 1. Conformation of the diethylamino groups in compound **6c** (from data of the ^{1}H NMR spectrum): view from the side (*a*), view along the plane of the rings (*b*), general view (*c*).

this nonequivalence is probably caused by dissimilar anisotropic effects of the sulfur atom on the protons of the CH_2 groups located near it (H^a) and those removed from it (H^b) (Fig. 1, *a*, *b*). The latter indicates that, on the one hand, rotation around the N—C_2H_5 bonds in molecules **6b** and **8** is hindered and, on the other hand, the axis of the lone electron pair directed toward the benzene ring has a pyramidal conformation with respect to the amine nitrogen atom (Fig. 1, *c*). This is the second example of such conformation found in the series of *N*-aminobenzazoles (*cf.* Ref. 4). In the other example this was caused by an intramolecular hydrogen bond.[5] A conformation of this type is likely to be realized in 1-diethylaminobenzimidazole (**5c**) itself, which is indirectly indicated by the fact that this compound is much more difficult to thiolate (due to steric restrictions created by the two ethyl groups) than compound **5b**.

Experimental

IR spectra of compounds **1b—d**, **2c,d**, **3b,c**, and **4a,c,d** were recorded on an IKS-40 spectrophotometer and those of compounds **2b**, **3d**, and **6—8** were obtained on a UR-20 spectrometer in Nujol. ^{1}H NMR spectra of compounds **1b,d** and **4a—d** were run on a Bruker-90 instrument (90 MHz), while those of compounds **1c**, **3b—d**, and **6—8** were obtained on a Unity-300 instrument (300 MHz).

The course of reactions was monitored by TLC on plates with Al_2O_3 of Brockman activity IV using chloroform as the eluent; the plates were visualized by iodine vapor. Melting points were determined in sealed capillaries on a PTP instrument and were not corrected.

Yields, melting points, and data of IR and ^{1}H NMR spectra and elemental analysis of the synthesized compounds are presented in Tables 1 and 2.

Compounds **1a** and **5b,c** were prepared by previously described procedures.[7—9]

1-(*N*-Alkylacetamido)benzimidazoles (1b—d). Powdered KOH (0.45 g, 8 mmol) was added with stirring to a solution of 1-(acetamido)benzimidazole (**1a**) (1.4 g, 8 mmol) in 100 mL of acetone, and after 10—15 min, an equimolar amount of alkyl halide was added. The mixture was stirred for 4 h at ~20 °C. The acetone was evaporated under reduced pressure. The residue, containing some starting compound aside from the reaction product, was dissolved in 30 mL of chloroform, and the solution was passed through a chromatographic column (l = 30 cm, d = 2.5 cm) packed with Al_2O_3 using chloroform as the eluent. Compounds **1b—d** were collected as the first fraction (R_f 0.7—0.8); the next fraction with R_f 0.1 contained recovered compound **1a**.

1-(Alkylamino)benzimidazoles (2b—d). A solution of compound **1b—d** (10 mmol) in 20 mL of conc. HCl was boiled for 1h, cooled, and neutralized with 22% NH_4OH, and the reaction product was extracted with chloroform (2×30 mL). The chloroform was evaporated, and the residue was crystallized from heptane (**2c**) or a heptane—benzene mixture (1 : 1, for compounds **2b,d**). Melting point of compound **2b** was 71—73 °C, which corresponds to the published data.[9]

1-(Alkylacetamido)benzimidazoline-2-thiones (4a—d). A mixture of compound **1a—d** (2 mmol) and powdered sulfur (0.064 g, 2 mmol) was kept at 180—200 °C for 2 h. During the reaction the melt gradually crystallized. After cooling, the product was crystallized from an H_2O—EtOH mixture (1 : 1, for **4a,b,d**) or from an isooctane—benzene mixture (1 : 1, for **4c**).

1-(Alkylamino)benzimidazoline-2-thiones (3a—d). a. A solution of 1-(*N*-alkylacetamido)benzimidazoline-2-thiones (**4a—d**) (2 mmol) in 5 mL of conc. HCl was boiled for 1—2 h, the course of the reaction being monitored by chromatography on Al_2O_3 plates. After cooling the solution was neutralized with 22% ammonia, and the resulting precipitate of thiones **3a—d** was filtered off and crystallized from EtOH (**3a**), benzene (**3b,d**), or isooctane (**3c**). The melting point of thione **3a**, equal to 212—213 °C, coincided with the published data.[1] The melting point of a mixture with an authentic sample of thione **3a** was undepressed.

b. Compound **2b—d** (1.5 mmol) was mixed with sulfur (0.048 g, 1.5 mmol), and the mixture was heated for 1 h at 150—170 °C. After cooling, the melt was dissolved in 10 mL of chloroform, and the solution was passed through a column packed with Al_2O_3 (l = 25 cm, d = 1.5 cm); elution was carried out with chloroform, and the first fraction (R_f 0.6—0.7) was collected. After evaporating the solvent, the residue was crystallized as described in the previous procedure. The melting points of mixtures of the resulting compounds **3b—d** with authentic samples were undepressed.

1-(Dimethylamino)benzimidazoline-2-thione (6b). A mixture of 1-(dimethylamino)benzimidazole (0.24 g, 1.5 mmol) and sulfur (0.048 g, 1.5 mmol) was heated at 145—150 °C for 2 h. After cooling, the melt was dissolved in 5 mL of chloroform, and the solution was passed through a column packed with Al_2O_3 (l = 25 cm, d = 1.5 cm); elution was carried out with chloroform, and the fraction with R_f 0.15 was collected. After evaporating the solvent, the residue was crystallized from a heptane—toluene (5:1) mixture; yield 0.21 g (73 %).

1-(Diethylamino)benzimidazoline-2-thione (6c). A mixture of 1-(diethylamino)benzimidazole (0.43 g, 2.28 mmol) and sulfur (0.074 g, 2.3 mmol) was kept at 145—150 °C for 4 h. After cooling, the reaction mixture was dissolved in 10 mL of chloroform, and the solution was passed through a column packed with Al_2O_3 (l = 20 cm, d = 1.5 cm), and the fraction

Table 2. Some physicochemical and analytical characteristics of the compounds synthesized

Compound	Yield (%)	M.p./°C (solvent)	Molecular formula	Found / Calculated (%)			IR spectrum, ν/nm^{-1}		
				C	H	S	C=N	C=O	NH_2
1b	77	147—149 (isooctane)	$C_{10}H_{11}N_3O$	63.36 63.48	6.17 5.86	—	1615	1692	—
1c	68	75—76 (heptane)	$C_{11}H_{13}N_3O$	65.12 65.01	6.55 6.45	—	1617	1693	—
1d	46	89—90 (isooctane—heptane)	$C_{16}H_{15}N_3O$	72.48 72.43	5.90 5.70	—	1612	1679	—
2c	70	82—84 (heptane)	$C_9H_{11}N_3$	67.11 67.06	6.93 6.88	—	1620	—	3196
2d	87	106—108 (heptane—benzene)	$C_{14}H_{13}N_3$	75.00 74.31	5.81 5.87	—	1605	—	3248
3b	81[a] 30[b]	182—184 (benzene)	$C_8H_9N_3S$	53.42 53.61	4.98 5.06	17.61 17.89	1618	—	3259 3173
3c	99[a] 50[b]	115—117 (isooctane)	$C_9H_{11}N_3S$	55.80 55.93	6.03 5.74	16.75 16.59	1620	—	3245 3141
3d	77[a] 66[b]	158—159 (benzene)	$C_{14}H_{13}N_3S$	66.05 65.86	5.16 5.13	12.76 12.56	1625	—	3255 3155
4a	63	269—271 (water—ethanol)	$C_9H_9N_3OS$	52.35 52.16	4.60 4.38	15.30 15.47	1620	1693	3277 3142
4b	75	208—210 (water—ethanol)	$C_{10}H_{11}N_3OS$	54.35 54.28	5.18 5.01	14.38 14.49	1625	1705	3155
4c	73	129—131 (isooctane)	$C_{11}H_{13}N_3OS$	56.25 56.15	5.67 5.57	13.44 13.62	1630	1705	3160
4d	75	122—124 (benzene)	$C_{16}H_{15}N_3OS$	64.54 64.62	5.20 5.08	10.58 10.78	1620	1708	3145
6b	73	150—152 (heptane—toluene)	$C_9H_{11}N_3S$	56.01 55.93	5.65 5.74	16.62 16.59	1620	—	3155
6c	50	130—131 (heptane)	$C_{11}H_{15}N_3S$	59.82 59.73	6.73 6.78	14.54 14.48	1625	—	3155
7	89	80—82 (isooctane)	$C_9H_{11}N_3S$	56.20 55.93	5.83 5.74	16.70 16.59	1615	—	3220
8	77	Yellow oil	$C_{12}H_{17}N_3S$	61.32 61.25	7.35 7.29	13.67 13.60	1620	—	—

[a] By acid hydrolysis of compounds **4b—d**. [b] By thiolation of compounds **2b—d**.

with R_f 0.2 was collected (elution was carried out with chloroform); yield 0.28 g (56 %).

1-Methylamino-2-(methylthio)benzimidazole (7). Powdered KOH (0.56 g, 0.01 mol) was added to a solution of thione **3b** (1.79 g, 0.01 mol) in 100 mL of acetone, and 10 min later, methyl iodide (0.65 mL, 0.01 mol) was added. The mixture was stirred for 1 h at ~20 °C. The acetone was evaporated under reduced pressure, 30 mL of chloroform was added to the residue, and the precipitate of KI was filtered off and washed with 10 mL of chloroform. The combined chloroform solutions were passed through a column packed with Al_2O_3 (l = 25 cm, d = 3 cm); elution was carried out with chloroform, and the fraction with R_f 0.9 was collected. When the chloroform was evaporated, the residue was crystallized from isooctane; yield 1.73 g (89 %).

1-Diethylamino-2-(methylthio)benzimidazole (8). Finely powdered KOH (0.056 g, 1 mmol) was added to a solution of thione **6c** (0.22 g, 1 mmol) in 15 mL of acetone, and 10 min later, methyl iodide (0.12 mL, 2 mmol) was added. The mixture was stirred for 4 h at ~20 °C, and the acetone was evaporated under reduced pressure. The residue was dissolved in 5 mL of chloroform and passed through a column packed with Al_2O_3 (l = 20 cm, d = 1.5 cm); elution was carried out with chloroform, and the fraction with R_f 0.8 was collected to give 0.18 g (77 %) of a yellowish oil, n_D^{20} 1.5320.

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