Synthesis of 2,3-Dihydroimidazo[2,1-*b*]thiazole Derivatives *via* Cyclization of *N*-Allylimidazoline-2-thiones

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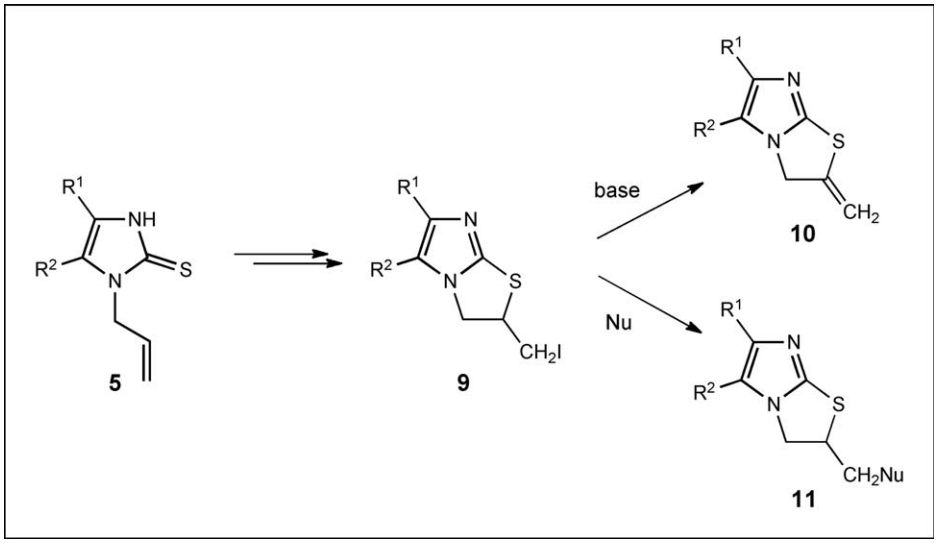

A novel method for the preparation of 2,3-dihydroimidazo[2,1-*b*]thiazole **9** by iodination and subsequent cyclization of the easily available *N*-allylimidazoline-2-thiones **5**, is described. Selected transformations of the iodomethyl derivatives **9**, leading to methylidene compounds **10** or the sulfide **11** (Nu = RS), via elimination with a base or via substitution with an enolizable imidazoline-2-thione (the term ''1,3-dihydroimidazole-2-thione'' will be used alternatively), respectively, are presented.

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INTRODUCTION

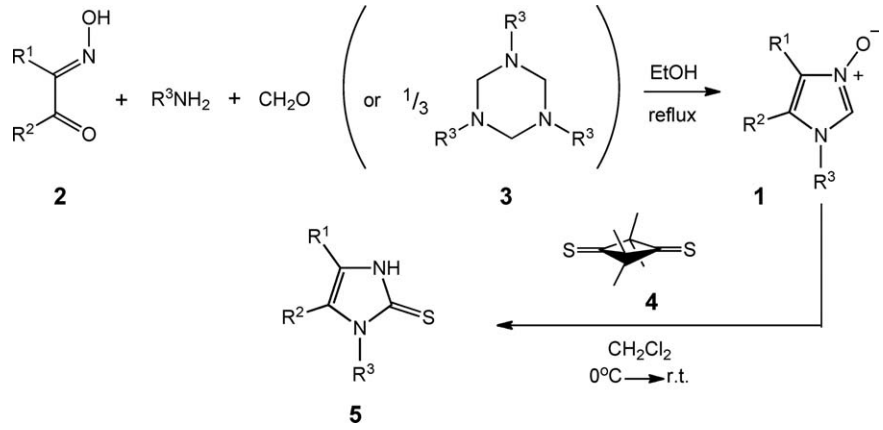
In a series of recent articles, a convenient approach to 2-unsubstituted imidazole *N*-oxides **1**, including optically active derivatives, has been reported [2]. In general, the applied method is based on the condensation of α-(hydroxyimino)ketones **2** with a primary aliphatic amine and formaldehyde. Alternatively, the corresponding hexahydro-1,3,5-triazines **3**, being trimers of formaldehyde imines, can be used (Scheme 1).

Irrespective of the substitution pattern, the reaction of **1** with 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4**) resulted in the ''sulfur transfer reaction'' leading to 1,3-dihydroimidazole-2-thiones **5** in high-yield [2b,2d,3]. In addition to *N*-alkyl and *N*-cycloalkyl substituted imidazole *N*-oxides **1**, some of the corresponding *N*-allyl derivatives were also obtained in good yields [2a]. However, the latter have not been explored for further conversions yet.

In spite of the fact that *N*-allyl-1,3-dihydroimidazole-2-thiones seem to be attractive starting materials for diverse cyclization reactions involving the allyl group, there are only few reports on their synthesis available to date. The first approach, reported already in 1895, was the condensation of *N*-allylthiourea with 2-hydroxy-1,2-diphenylethanone (benzoine) [4]. The second synthesis described the condensation of isothiocyanic acid and acetals of *N*-allyl α-aminoacetaldehyde [5]. In addition, the reaction of allylisothiocyanate with glucosamine is reported to yield the desired product [6], and the analogous condensation with 1-amino-3-methylbutan-2-one gave *N*-allyl-5-isopropylimidazoline-2-thione [7].

The goal of this study was the preparation of a series of less known *N*-allyl-1,3-dihydroimidazole-2-thiones and their subsequent cyclization to corresponding fused *N*,*S*-heterocycles. Heterocyclic thiones with an allyl-substituted *N*-atom attached to the C=S group are known

Scheme 1



to undergo an intramolecular 1,5-cyclization to yield fused thiazoles. Thus, treatment of the *N*-allyltriazolethione **6** with iodine in ethanol at room temperature gave the thiazolo[2,3-*c*][1,2,4]triazole hydroiodide **7** [8] (Scheme 2). The analogous bromide was obtained from the reaction with bromine in chloroform.

To the best of our knowledge, there are no analogous reactions with imidazoline thiones, described so far. However, in the case of benzimidazoline-2-thiones, a similar cyclization has been observed [9].

RESULTS AND DISCUSSION

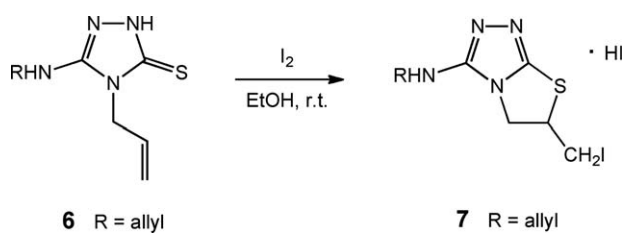
In accordance with the known procedure [2], heating of 1,3,5-triallylhexahydro-1,3,5-triazine (**3a**, R^3 = allyl) and 3-(hydroxyimino)butan-2-one (**2a**, $R^1 = R^2$ = Me) in ethanol gave the expected 1-allyl-4,5-dimethylimidazole *N*-oxide (**1a**) in 78% yield (Scheme 1, Table 1). The imidazoline-2-thione **5a** was prepared from **1a** by treatment with 0.5 mol equivalents of **4** in dichloromethane at room temperature. The same procedures were applied for the synthesis of **5b**–**5f**.

Solutions of the purified imidazoline-2-thiones **5** in ethanol were treated with iodine at room temperature, and the corresponding hydroiodides **8** precipitated directly from the reaction mixture. The subsequent neutralization with aqueous sodium acetate solution gave 2,3-dihydroimidazo[2,1-*b*]thiazoles **9** as crystalline products, with the exception of **9e** (Scheme 3, Table 1).

The structure of products **9** was proved by means of spectroscopic methods. For example, the ^{13}C-NMR spectrum of **9b** showed the signals for three imidazole C-atoms at 145.3, 141.7, and 133.6 ppm as well as two triplets for CH_2 groups at 49.3 and 7.3 ppm (assigned to CH_2N and CH_2I, resp.), and a doublet for a CH group at 52.2 ppm.

The presence of the iodomethyl group in compounds **9** enables further transformation with basic and nucleophilic agents. In fact, treatment of **9a** with triethylamine in ethanol afforded, after elimination of HI, the exomethylidene derivative **10a**. Furthermore, the attempted substitution of iodide with potassium cyanide, carried out either in acetone or in ethanol, led to the same elimination product **10a**. On the other hand, the reaction of **9f** with the enolizable 1,4,5-trimethylimidazoline-2-thione (**5g**) in ethanol, led successfully to the sulfide **11** in good yield (Scheme 4).

Scheme 2



6 R = allyl **7** R = allyl

Table 1

Synthesis of 1-allylimidazole *N*-oxides **1**,1-allyl-1,3-dihydroimidazole-2-thiones **5**, and 2,3-dihydro-2-(iodomethyl)imidazo[2,1-*b*]thiazoles **9**.

				Yield [%]		
	R^1	R^2	R^3	**1**	**5**	**9**
a	Me	Me	All[a]	78	84	36
b	MeCO	Me	All	54	71	65
c	EtO_2C	Me	All	36	52	61
d	PhNHCO	Me	All	77	89	74
e	Me	Ph	All	[b]	39[c]	39
f	Ph	Ph	All	73 [2a]	76	52

[a] All = allyl.
[b] Not isolated in pure form.
[c] Overall yield starting from **3a** via **1e.**

Scheme 3

CONCLUSIONS

The presented study shows that treatment of the easily available *N*-allyl-1,3-dihydroimidazole-2-thiones **5** with iodine results in the cyclization leading to imidazo[2,1-*b*]thiazole derivatives **9**, bearing an iodomethyl group as an additional reaction center. As selected transformations of these products, the elimination of HI and the substitution with 1,4,5-trimethylimidazoline-2-thione, as an example of an *S*-nucleophile, are presented.

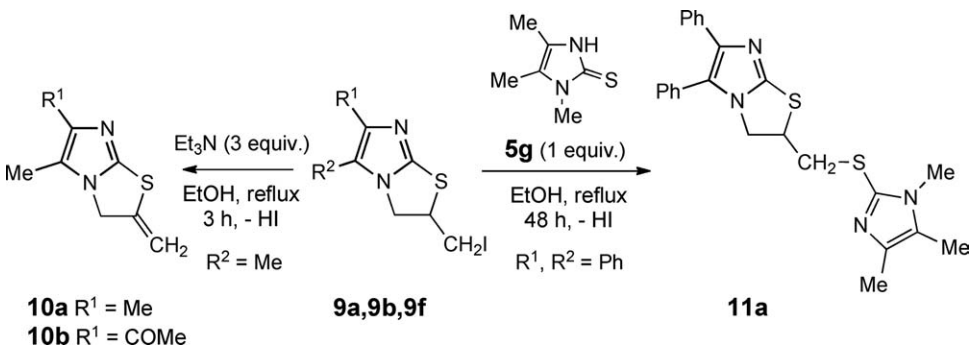
The importance of imidazo[2,1-*b*]thiazoles is well documented, as many derivatives of them display diverse biological activities [10] (see also [11]). The presented synthetic approach supplements the already reported methods for the preparation of 2,3-dihydroimidazo[2,1-*b*]thiazoles, which are based on reactions either of appropriate imidazole or thiazole derivatives. In the case of imidazole derivatives, the bis-alkylation of imidazoline-2-thiones with 1,2-dibromoethane was most frequently applied [12]. Another approach is the thermal cyclization of *N*-vinylimidazoline-2-thiones, which leads to the aromatized fused system [13]. The non-aromatized parent system was obtained via a formal vinyl transfer reaction of the parent imidazoline-2-thione with *S*-vinyl-*S*-(4-methylphenyl)-*N*-tosylimine [14]. The reactions starting with 1,3-thiazole derivatives are described to a comparable extent. As a typical example, the cyclocondensation of an α-bromoacetophenone with 2-amino-1,3-thiazoles can be mentioned [11a]. A very recent report deals with a multistep procedure, in which the alkylation of 2-amino-1,3-thiazole with propargyl bromide and subsequent cyclization are the key steps [11c]. In the light of the already reported approaches, our method, presented in this article, enlarges the number of synthetic tools for the preparation of new, diversely substituted imidazo[2,1-*b*]thiazoles. Of special importance is the availability of differently substituted α-(hydroxyimino)ketones **2**, which are key starting materials for the presented multi-step procedure.

EXPERIMENTAL

Melting points were determined in capillaries using a Melt-Temp II apparatus (Aldrich) and are uncorrected. IR Spectra were recorded on a NEXUS FT-IR spectrophotometer as KBr pellets; absorptions in cm^{-1}. ^1H- and ^{13}C-NMR spectra were measured on a Tesla BS567A (80 MHz) or Varian Gemini 200 (200 and 50 MHz, resp.) instrument or a Bruker AC 400 instrument (400 and 100 MHz, resp.) in a suitable solvent ($CDCl_3$, CD_3OD or DMSO-d_6); chemical shifts (δ) were given in ppm (TMS = 0 ppm), coupling constants *J* in Hz. The multiplicity of the ^{13}C signals was deduced from DEPT spectra. The HRMS spectra were registered on a Finnigan MAT-95 instrument.

Synthesis of 4,5-disubstituted 1-allyl-1*H*-imidazole 3-oxides (1a–f). In the cases of **1a**, **1d**, **1e**, and **1f**, the solution of 1,3,5-triallylhexahydro-1,3,5-triazine (**3a**, 0.69g, 3.3 mmol) and the corresponding α-(hydroxyimino)ketone of type **2** (10 mmol) in ethanol (15 mL) was refluxed for the required time (ca. 3 h, TLC monitoring, silica gel, MeOH). The solvent was removed under reduced pressure and the crude product was

Scheme 4



washed several times with Et_2O and purified thereby. In the cases of **1b** and **1c**, a solution of **3a** (0.94g, 4.5 mmol) in Et_2O (2 mL) was added to the magnetically stirred and cooled solution (water/ice external bath) of the corresponding α-(hydroxyimino)ketone **2** (10 mmol) in 5 mL Et_2O. When the addition was complete, the cooling bath was removed and the stirring was continued for 24 h at room temperature. Then, the colorless precipitate was filtered off and purified by flash chromatography (SiO_2). Acetone was used first as an eluent to remove the remaining **2**, followed by a mixture of ethyl acetate and MeOH (1:1). Next, the same reaction was repeated using recovered **2**. The combined fractions of the crude product **1** were purified by recrystallization from an appropriate solvent. The 1-allyl-4-methyl-5-phenyl-1*H*-imidazole 3-oxide (**1e**) could not be obtained in pure form and, therefore, the crude product was converted immediately into the corresponding imidazole-2-thione **5e**. The protocol for the synthesis of thiones of type **5**, as well as spectroscopic and analytical data for 1-allyl-4,5-diphenyl-1*H*-imidazole 3-oxide (**1f**), were already reported [2a].

1-Allyl-4,5-dimethyl-1H-imidazole 3-oxide (1a). The crude product was purified by flash chromatography on silica using AcOEt with increasing amounts of MeOH (up to 1:1 ratio) to give **1a** in 78% yield (1.19 g). Light yellow semi-solid, hygroscopic. IR (KBr): ν 3100–2900vs (br.), 1627m, 1443m, 1393s, 1378s, 1335s, 1187m, 1148m, 1004m, 926m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.18 (s, 1H, H—C(2)); 5.91–5.72 (m, 1H, —CH=); 5.26–4.95 (m, 2H, $=CH_2$); 4.37–4.34 (m, 2H, $—CH_2—$); 2.13, 2.06 (2s, 6H, 2Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 131.3 (d, —CH=); 126.3, 125.2 (2s, C(4), C(5)); 121.3 (d, C(2)); 118,5 (t, $=CH_2$); 47.8 (t, $—CH_2—$); 8.3, 7.0 (2q, 2 Me). EI-HRMS: 152.0975 (M^+, $C_8H_{12}N_2O^+$; calcd. 152.0950).

4-Acetyl-1-allyl-5-methyl-1H-imidazole 3-oxide (1b). Yield 0.97 g (54%). Colorless crystals, mp 39–40°C (CH_2Cl_2/Et_2O). IR (KBr): ν 3117s, 1660vs, 1557s, 1420m, 1407m, 1333m, 1274m, 1145m, 950m, 731m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.93 (s, 1H, H—C(2)); 6.15–5.68 (m, 1H, —CH=); 5.46–5.04 (m, 2H, $=CH_2$); 4.54–4.44 (m, 2H, $—CH_2—$); 2.82 (s, 3H, MeCO); 2.48 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 191.3 (s, C=O); 132.0, 129.6 (2s, C(4), C(5)); 130.2 (d, —CH=); 125.6 (d, C(2)); 119.6 (t, $=CH_2$); 47.6 (t, $—CH_2—$); 30.6 (q, *Me*CO); 9.9 (q, Me). EI-HRMS: 180.0905 (M^+, $C_9H_{12}N_2O_2^+$; calcd. 180.0899).

Ethyl 1-allyl-5-methyl-3-oxido-1H-imidazole-4-carboxylate (1c). The crude product was purified by flash chromatography on silica using AcOEt with increasing amounts of MeOH (up to 1:1 ratio) to give **1c** in 36% yield (0.76 g). Colorless semi-solid. IR (KBr): ν 3150–2950s, 1706vs, 1458m, 1326m, 1285m, 1180m, 1091m, 742m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 8.27 (s, 1H, H—C(2)); 6.03–5.84 (m, 1H, —CH=); 5.36–5.06 (m, 2H, $=CH_2$); 4.61–4.58 (m, 2H, $—CH_2—$); 4.40 (q, J = 7.1, 2H, MeCH_2O); 2.46 (s, 3H, Me); 1.39 (t, J = 7.1, 3H, *Me*CH_2O). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 158.8 (s, C=O); 131.8, 121.6 (2s, C(4), C(5)); 130.4 (d, —CH=); 126.8 (d, C(2)); 118.7 (t, $=CH_2$); 60.5 (t, MeCH_2O); 47.6 (t, CH_2N); 13.8 (q, *Me*CH_2O); 9.5 (q, Me). EI-HRMS: 210.1017 (M^+, $C_{10}H_{14}N_2O_3^+$; calcd. 210.1004).

1-Allyl-5-methyl-3-oxido-N-phenyl-1H-imidazole-4-carboxamide (1d). Yield 1.98 g (77%). Yellow solid, mp 115–117°C (CH_2Cl_2/Et_2O). IR (KBr): ν 3119m, 1664m, 1621s, 1598s, 1565s, 1498m, 1447m, 1418m, 1309m, 1277m, 759m. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 12.90 (s, 1H, NH); 7.88 (s, 1H, H—C(2)); 7.77–7.61 (m, 2 arom. H); 7.44–6.99 (m, 3 arom. H); 6.07–5.67 (m, 1H, —CH=); 5.46–5.03 (m, 2H, $=CH_2$); 4.52–4.42 (m, 2H, $—CH_2—$); 2.63 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 157.2 (s, C=O); 138.0, 131.7, 121.9 (3s, 1 C(Ph), C(4), C(5)); 130.2 (d, —CH=); 128.9, 125.2, 124.1, 120.5 (4d, 5 CH(Ph), C(2)); 119.9 (t, $=CH_2$); 47.8 (t, $—CH_2—$); 9.55 (q, Me). EI-HRMS: 257.1173 (M^+, $C_{14}H_{15}N_3O_2^+$; calcd. 257.1164).

Synthesis of 1,3,5-triallylhexahydro-1,3,5-triazine (3a). The allylamine (50 mL, 38 g, 0.67 mol) was carefully dissolved in methanol (80 mL) and cooled to 0°C. Then, solid paraformaldehyde (21 g, 0.7 mol) was added in small portions, the obtained suspension was allowed to reach r.t. and was stirred overnight. Next day, the solvent was removed *in vacuo* and the oil was short-path distilled at 95–100°C/2 mm Hg to give **3a** in 84% yield. All spectra of **3a** corresponded with literature data [15].

Synthesis of 4,5-disubstituted 1-allyl-2,3-dihydroimidazole-2-thiones (5a–f). To the magnetically stirred solution of *N*-oxide **1** (10 mmol) in CH_2Cl_2 (30 mL), the solution of 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**4**, 0.95 g, 5.5 mmol) in dichloromethane (8 mL) was added at 0°C. After the ice-bath was removed, stirring was continued overnight. The solvent was removed to dryness, the residue was washed with two portions of ether (10 mL each), and the crude product was recrystallized from an appropriate solvent.

1-Allyl-2,3-dihydro-4,5-dimethylimidazole-2-thione (5a). Yield 1.40 g (84%). Light yellow crystals, mp 147–149°C ($CHCl_3$/Et_2O). IR (KBr): ν 3166m, 3088s, 2949m, 2923m, 1661w, 1497m, 1431m, 1412m, 1397m, 1236m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 12.17 (br. s, 1H, NH); 6.16–5.69 (m, 1H, —CH=); 5.30–4.92 (m, 2H, $=CH_2$); 4.71–4.61 (m, 2H, $—CH_2—$); 2.08, 2.04 (2s, 6H, 2 Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 157.5 (s, C=S); 131.7 (d, —CH=); 121.3, 119.9 (2s, C(4), C(5)); 116.7 (t, $=CH_2$); 46.3 (t, $—CH_2—$); 8.7, 8.6 (2q, 2Me). EI-HRMS: 168.0726 (M^+, $C_8H_{12}N_2S^+$; calcd. 168.0721).

4-Acetyl-1-allyl-2,3-dihydro-5-methylimidazole-2-thione (5b). Yield 1.39 g (71%). Pale yellow crystals, mp 145–148°C (MeOH). IR (KBr): ν 3150–2900vs, 1641vs, 1596m, 1492m, 1414s, 1385m, 1375m, 1353m, 1262m, 1177m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 11.74 (br. s, 1H, NH); 5.90–5.71 (m, 1H, —CH=); 5.18–4.94 (m, 2H, $=CH_2$); 4.79–4.29 (m, 2H, $—CH_2—$); 2.42, 2.40 (2s, 6H, 2 Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 186.1 (s, C=O); 162.2 (s, C=S); 134.2, 124.2 (2s, C(4), C(5)); 130.4 (d, —CH=); 117.6 (t, $=CH_2$); 46.3 (t, $—CH_2—$); 28.5 (q, *Me*CO); 10.9 (q, Me). EI-HRMS: 196.0681 (M^+, $C_9H_{12}N_2OS^+$; calcd. 196.0670).

Ethyl 1-allyl-2,3-dihydro-5-methyl-2-thioxoimidazole-4-carboxylate (5c). The crude product was purified by flash chromatography on silica using AcOEt to give **5c** in 52% yield (1.17 g). Colorless crystals, mp 146–148°C ($CHCl_3$/petroleum ether). IR (KBr): ν 3150–2900s (br.), 1698 vs, 1497m, 1462m, 1417s, 1372m, 1359m, 1267m, 1173m, 1158m, 1088m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 11.10 (br. s, 1H, NH); 6.01–5.82 (m, 1H, —CH=); 5.28–5.04 (m, 2H, $=CH_2$); 4.81–4.74 (m, 2H, $—CH_2—$); 4.34 (q, J = 7.1, 2H, MeCH_2O); 2.47 (s, 3H, Me); 1.38 (t, J = 7.1, 3H, *Me*CH_2O). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 162.4 (s, C=S); 158.6 (s, C=O); 134.8, 115.5 (2s, C(4), C(5)); 130.7 (d, —CH=); 117.4 (t, $=CH_2$); 60.8 (t,

Me*C*H_2O); 46.3 (t, CH_2N); 13.9 (q, *Me*CH_2O); 9.9 (q, Me). EI-HRMS: 226.0777 (M^+, $C_{10}H_{14}N_2O_2S^+$; calcd. 226.0776).

1-Allyl-2,3-dihydro-5-methyl-N-phenyl-2-thioxoimidazole-4-carboxamide (5d). Yield 2.43 g (89%). Colorless solid, mp 259–262°C (decomp.) (EtOH). IR (KBr): ν 3252m, 3200–2900s (br.), 1640vs, 1599m, 1533m, 1497m, 1447s, 1403m, 1362m, 761m. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 12.53, 9.56 (2br.s, 2H, 2 NH); 7.60–7.56 (m, 2 arom. H); 7.32–7.24 (m, 2 arom. H); 7.07–6.99 (m, 1 arom. H); 5.92–5.76 (m, 1H, ═CH═); 5.12 (dd, J = 10.4, 1.2, 1H); 4.92 (dd, J = 17.2, 1.4, 1H); 4.66–4.64 (m, 2H, ═CH_2═); 2.38 (s, 3H, Me). ^{13}C-NMR (50 MHz, DMSO-d_6): δ 161.6, 156.5 (2s, C═O, C═S); 138.4, 133.4, 117.7 (3s, 1 C(Ph), C(4), C(5)); 131.9 (d, ═CH═); 128.8, 123.8, 119.7 (3d, 5 CH(Ph)); 116.8 (t, ═CH_2); 45.6 (t, ═CH_2═); 9.9 (q, Me). EI-HRMS: 273.0940 (M^+, $C_{14}H_{15}N_3OS^+$; calcd. 273.0936).

1-Allyl-2,3-dihydro-4-methyl-5-phenylimidazole-2-thione (5e). The crude *N*-oxide **1e** prepared according to the general protocol was subsequently transformed into **5e** by treatment with **4** in CH_2Cl_2 solution [3]. Pure product was obtained by flash chromatography on silica using acetone, then MeOH, in 39% overall yield (0.83 g). Colorless needles, mp 164–165°C (EtOH). IR (KBr): ν 3150–2900vs (br.), 1599m, 1506s, 1485m, 1424m, 1388m, 1243m, 1198m, 763m, 700m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 12.39 (br. s, 1H, NH); 7.46–7.40 (m, 3 arom. H); 7.32–7.27 (m, 2 arom. H); 5.95–5.76 (m, 1H, ═CH═); 5.20–4.88 (m, 2H, ═CH_2); 4.62–4.58 (m, 2H, ═CH_2═); 2.16 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 158.8 (s, C═S); 132.1 (d, ═CH═); 130.2, 128.8, 128.7 (3d, 5 CH(Ph)); 128.3, 127.4, 122.2 (3s, 1 C(Ph), C(4), C(5)); 117.3 (t, ═CH_2); 46.9 (t, ═CH_2═); 9.3 (q, Me). EI-HRMS: 230.0882 (M^+, $C_{13}H_{14}N_2S^+$; calcd. 230.0878).

1-Allyl-2,3-dihydro-4,5-diphenylimidazole-2-thione (5f). Yield 2.22 g (76%). Colorless crystals, mp 293–296°C (EtOH). IR (KBr): ν 3100–2900vs (br.), 1508m, 1493s, 1482s, 1425m, 1397m, 1388m, 1238m, 1199m, 918m, 773s, 702s. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 11.36 (br. s, 1H, NH); 7.48–7.43 (m, 3 arom. H); 7.35–7.31 (m, 2 arom. H); 7.24 (s, 5 arom. H); 5.93–5.77 (m, 1H, ═CH═); 5.18–4.89 (m, 2H, ═CH_2); 4.62–4.57 (m, 2H, ═CH_2═). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 160.7 (s, C═S); 131.9 (d, ═CH═); 134.2, 128.5, 127.4, 125.4 (4s, 2 C(Ph), C(4), C(5)); 131.1, 129.6, 129.1, 128.8, 128.0, 126.4 (6d, 10 CH(Ph)); 117.8 (t, ═CH_2); 47.1 (t, ═CH_2═). EI-HRMS: 292.1047 (M^+, $C_{18}H_{16}N_2S^+$; calcd. 292.1034).

Synthesis of 5,6-disubstituted 2,3-dihydro-2-(iodomethyl)-imidazo[2,1-*b*]thiazoles (9a–f). To a solution (or suspension) of the corresponding imidazoline-2-thione **5** (10 mmol) in dry ethanol (*ca*. 20 mL), an equimolar amount of nicely powdered iodine (2.54 g) was added in small portions, and vigorous stirring was continued for 24 h at room temperature. The resulting mixture was cooled and the yellow precipitate of crude **8** was filtered off. After evaporation of the solvent, the residue was washed with few portions of ether, filtered off and combined. If necessary, the crude hydroiodide **8** was recrystallized from hot EtOH. The obtained salt was suspended in ethanol (*ca*. 10 mL), an aqueous solution (5%) of AcONa (1.64 g, 20 mmol) was added, and stirring was continued for 1 h at room temperature. The resulting product **9** was filtered off and crystallized from an appropriate solvent.

2,3-Dihydro-2-iodomethyl-5,6-dimethylimidazo[2,1-b]thiazole (9a). The isolated hydroiodide **8a** was dissolved in ethanol (*ca*. 5 mL), an aqueous solution (5%) of AcONa (20 mmol) was added, and the solution was stirred for 30 min at room temperature. The mixture was extracted with chloroform, the combined organic phases were washed with an aqueous solution (10%) of $Na_2S_2O_3$, dried ($CaCl_2$), and after filtration the solvent was evaporated. The crude product was purified by flash chromatography on silica ($CHCl_3$) to give 1.06 g (36%) of **9a** as a colorless solid; mp 83–86°C (decomp., $CHCl_3$). IR (KBr): ν 3010–2870vs (br.), 1585m, 1483s, 1452m, 1421m, 1382m, 1367m, 1314m, 1227m, 1187m, 807m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.42–4.29 (m, 1H); 4.00–3.85 (m, 2H); 3.45 (dd, J = 10.2, 4.7, 1H); 3.31 (t, J = 10.5, 1H); 2.02, 1.99 (2s, 6H, 2 Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 143.2, 137.8, 121.3 (3s, 3 C(imidazole)); 51.9 (d, CH); 49.4 (t, CH_2N); 12.8, 8.8 (2q, 2 Me); 8.1 (t, CH_2I). EI-HRMS: 293.9689 (M^+, $C_8H_{11}IN_2S^+$; calcd. 293.9688).

Selected Data for ***8a***. Yellow crystals. mp 146–149°C (decomp., EtOH). IR (KBr): 3054vs (br.), 2960–2870vs, 1646m, 1498m, 1442m, 1176m. ^{1}H-NMR (80 MHz, CD_3OD): δ 5.18–4.93 (m, 1H); 4.54 (dd, J = 12.0, 7.7, 1H); 4.35 (dd, J = 12.0, 4.0, 1H); 3.78 (s, 1H); 3.74 (d, J = 5.8, 1H); 2.25 (s, 6H, 2 Me).

6-Acetyl-2,3-dihydro-2-iodomethyl-5-methylimidazo[2,1-b]thiazole (9b). Yield 2.09 g (65%). Yellow crystals, mp 152–153°C (EtOH). IR (KBr): ν 1655vs, 1547s, 1492m, 1464m, 1411w, 1370s (br.), 1282m, 1212m, 1178m, 1158s, 951m, 548m. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.52–4.45 (m, 1H); 4.13–4.04 (m, 2H); 3.54 (dd, J = 10.4, J = 4.0, 1H); 3.36 (t, J = 10.8, 1H); 2.48, 2.42 (2s, 6H, 2 Me). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.0 (s, C═O); 145.3, 141.7, 133.6 (3s, 3 C(imidazole)); 52.2 (d, CH); 49.3 (t, CH_2N); 27.3 (q, *Me*CO); 11.2 (q, Me); 7.3 (t, CH_2I). EI-HRMS: 321.9648 (M^+, $C_9H_{11}IN_2OS^+$; calcd. 321.9637).

Selected data for ***8b***. Yellow needles, mp 178–180°C (EtOH). IR (KBr): ν 3040–2750vs (br.), 1664vs, 1590m, 1525m, 1483m, 1412s, 1340m, 1303m, 1239m, 1179m. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.01–4.94 (m, 1H); 4.50 (dd, J = 12.0, 7.6, 1H); 4.25 (dd, J = 12.0, 4.0, 1H); 3.79–3.71 (m, 2H); 2.53, 2.44 (2s, 6H, 2 Me).

Ethyl 2,3-dihydro-2-iodomethyl-5-methylimidazo[2,1-b]thiazole-6-carboxylate (9c). The crude **8c** was suspended in ethanol (5 mL), an aqueous solution (5%) of AcONa (20 mmol) was added, and the solution was stirred for 30 min at room temperature. The mixture was extracted with few portions of chloroform, the combined organic phases were washed with an aqueous solution (10%) of $Na_2S_2O_3$ and dried ($CaCl_2$), and the solvent was evaporated to give **9c** in 61% overall yield (2.14 g). Colorless solid, mp 130–134°C (decomp., $CHCl_3$). IR (KBr): ν 1694vs, 1497s, 1459m, 1396m, 1376m, 1345m, 1195m, 1173s, 1157s, 1089m, 782m. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.53–4.48 (m, 1H); 4.27 (q, J = 7.2; Me*C*H_2O); 4.15 (dd, J = 11.6, 7.2, 1H); 4.05 (dd, J = 11.6, 4.0, 1H); 3.53 (dd, J = 10.4, 4.8, 1H); 3.38 (t, J = 10.4, 1H); 2.46 (s, 3H, Me); 1.31 (*t*, J = 7.0, *Me*CH_2O). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 163.1 (s, C═O); 146.6, 135.0, 132.8 (3s, 3 C(imidazole)); 60.4 (t, Me*C*H_2O); 52.2 (d, CH); 49.7 (t, CH_2N); 14.4, 10.9 (2q, 2 Me); 7.8 (t, CH_2I). EI-HRMS: 351.9779 (M^+, $C_{10}H_{13}IN_2O_2S^+$; calcd. 351.9742).

2,3-Dihydro-2-iodomethyl-5-methyl-N-phenylimidazo[2,1-b]thiazole-6-carboxamide (9d). Yield 2.97 g (74%). Colorless crystals, mp 195–203°C (decomp., EtOH). IR (KBr): ν 3281m,

1656s, 1593s, 1569m, 1523s, 1490s, 1440s, 1385m, 1301m, 1235m, 1189m, 1173m, 756m. ^{1}H-NMR (200 MHz, DMSO-d_6): δ 9.68 (br s, 1H, NH); 7.84–7.80 (m, 2 arom. H); 7.34–7.26 (m, 2 arom. H); 7.07–7.00 (m, 1 arom. H); 4.86–4.80 (m, 1H); 4.36 (dd, J = 11.6, 7.6, 1H); 4.05 (dd, J = 11.6, 4.8, 1H); 3.75–3.65 (m, 2H); 2.53 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 161.1 (s, C=O); 144.5, 139.0, 134.3, 132.6 (4s, 1 C(Ph), 3 C(imidazole)); 128.5, 122.9, 119.7 (3d, 5 CH(Ph)); 53.2 (d, CH); 49.1 (t, CH_2N); 10.4 (t, CH_2I); 10.2 (q, Me). EI-HRMS: 398.9917 (M^+, $C_{14}H_{14}IN_3OS^+$; calcd. 398.9902).

2,3-Dihydro-2-iodomethyl-6-methyl-5-phenylimidazo[2,1-b]thiazole (9e). Workup analogous to that described for **9a** gave 1.39 g (39%) of **9e** as a colorless semi-solid after column chromatography (silica, $CHCl_3$/AcOEt 9:1). IR (KBr): ν 1603m, 1492m, 1474m, 1457s, 1423m, 1376m, 764m, 700m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.49–7.42 (m, 2 arom. H); 7.36–7.29 (m, 3 arom. H); 4.54–4.41 (m, 1H); 4.18 (d, J = 5.2, 2H); 3.61–3.41 (m, 2H); 2.28 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 146.2, 140.1, 130.7, 129.7 (4s, C(Ph), 3 C(imidazole)); 128.8, 127.7, 127.3 (3d, 5 CH(Ph)); 52.2 (d, CH); 51.2 (t, CH_2N); 14.0 (q, Me); 7.7 (t, CH_2I). EI-HRMS: 355.9851 (M^+, $C_{13}H_{13}IN_2S^+$; calcd. 355.9844).

*Selected data for **8e**.* Pale yellow solid, mp 108–109°C (decomp., $CHCl_3$). IR (KBr): ν 3000–2450vs (br.), 1624m, 1598m, 1504m, 1515m, 1200m, 766m, 749m, 701m. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.51 (s, 5 arom. H); 5.37–5.04 (m, 1H); 4.69 (dd, J = 12.0, 7.2, 1H); 4.28 (dd, J = 12.0, 4.0, 1H); 4.01–3.75 (m, 2H); 2.43 (s, 3H, Me).

2,3-Dihydro-2-iodomethyl-5,6-diphenylimidazo[2,1-b]thiazole (9f). Yield 2.17 g (52%). Colorless solid, mp 173–176°C (decomp., EtOH). IR (KBr): ν 1600m, 1504m, 1475s, 1456m, 1441m, 1336m, 1123w, 965w, 772s, 700s. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.52–7.33 (m, 7 arom. H); 7.28–7.17 (m, 3 arom. H); 4.57–4.50 (m, 1H); 4.20 (dd, J = 11.6, 6.8, 1H); 4.13 (dd, J = 11.6, 4.0, 1H); 3.61 (dd, J = 10.4, 4.8, 1H); 3.53 (t, J = 10.6, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.2, 142.2, 134.0, 130.2, 127.0 (5s, 2 C(Ph), 3 C(imidazole)); 130.8, 129.2, 129.1, 128.5, 128.3, 126.9 (6d, 10 CH(Ph)); 52.4 (d, CH); 51.2 (t, CH_2N); 7.7 (t, CH_2I). EI-HRMS: 418.0009 (M^+, $C_{18}H_{11}IN_2OS^+$; calcd. 418.0002).

*Selected data for **8f**.* Pale yellow solid, mp 212–218°C (decomp., EtOH). IR (KBr): ν 3050–2700vs (br.), 1514s, 1443m, 1173m, 1100m, 769s, 733m, 698s. ^{1}H-NMR (80 MHz, $CDCl_3$): δ 7.52, 7.38 (2s, 10 arom. H); 5.19–4.94 (m, 1H); 4.65 (dd, J = 12.0, 7.4, 1H); 4.32 (dd, J = 12.0, 4.5, 1H); 3.83 (d, J = 6.4, 2H).

Synthesis of 5,6-disubstituted 2,3-dihydro-2-methylidenimidazo[2,1-*b*]thiazoles (10). To a solution of **9** (1.0 mmol) in ethanol (5 mL), freshly distilled Et_3N (3.0 mmol, 0.30 g) was added and the resulting solution was refluxed for 3 h. The mixture was cooled to room temperature, filtered through a Celite plug, and the solvents were evaporated. Purification by flash chromatography (silica, $CHCl_3$) gave pure substance.

2,3-Dihydro-5,6-dimethyl-2-methylidenimidazo[2,1-b]thiazole (10a). Yield 53 mg (32%). Mp 107–110°C ($CHCl_3$). Decomposes during the storage at room temperature. IR (KBr): ν 2922s (br.), 1624m, 1482s, 1443s, 1374m, 1304m, 1266m, 1170m, 862m. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.39 (q-like, J ≈ 2.3, 1H); 5.29 (q-like, J ≈ 2.5, 1H); 4.67 (t, J = 2.5, 2H); 2.11 (s, 6H, 2 Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 142.9, 142.5, 137.3, 121.4 (4s, 4 C); 107.9 (t, $=CH_2$); 49.8 (t, CH_2); 12.9, 8.9 (2q, 2 Me).

6-Acetyl-2,3-dihydro-5-methyl-2-methylidenimidazo[2,1-b]thiazole (10b). Yield 0.12 g (62%). Mp 82–85°C (CH_2Cl_2/hexane). IR (KBr): ν 1656vs, 1631m, 1550s, 1499m, 1460m, 1379s, 1356m, 1187m, 1166m, 951m, 891m. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.40 (q-like, J ≈ 2.3, 1H); 5.31 (q-like, J ≈ 2.7, 1H); 4.70 (t, J = 2.4, 2H); 2.44, 2.41 (2s, 6H, 2 Me). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.0 (s, C=O); 144.9, 141.0, 140.5, 137.2 (4s, 4 C); 109.5 (t, $=CH_2$); 49.2 (t, CH_2); 27.3 (q, *Me*CO); 11.0 (q, Me). EI-HRMS: 194.0529 (M^+, $C_9H_{10}IN_2OS^+$; calcd. 194.0515).

Synthesis of 2,3-dihydro-5,6-diphenyl-2-{[(1,4,5-trimethyl-1*H*-imidazol-2-yl)sulfanyl]methyl}imidazo[2,1-*b*]thiazole (11). A mixture of equimolar amounts of **9f** (0.8 g, 1.9 mmol) and 1,4,5-trimethyl-2,3-dihydroimidazole-2-thione (**5g**, 0.27 g, 1.9 mmol) in ethanol (10 mL) was heated to reflux for 48 h. Then, half of the solvent was evaporated, the resulting solution treated with AcONa (0.35g, 5% aqueous solution), vigorously stirred, and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were dried ($CaCl_2$), filtered, and the solvent was evaporated to dryness. The resulting solid was purified by column chromatography (silica, $CHCl_3$/AcOEt 1:1) to give 0.26 g (32%) of **11** as a colorless solid. Mp 155–157°C (acetone). IR (KBr): ν 2920m, 1602m, 1504m, 1477m, 1458s, 1441s, 1394m, 1335m, 1123m, 769m, 697s. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41–7.07 (m, 10 arom. H); 4.55–4.50 (m, 1H); 4.22 (dd, J = 11.6, 6.8, 1H); 4.07 (dd, J = 11.6, 4.8, 1H); 3.70–3.62 (m, 1H); 3.45 (s, 3H, MeN); 3.36 (dd, J = 14.0, 7.2, 1H); 2.13, 2.07 (2s, 6H, 2 Me). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 147.4, 142.4, 136.1, 134.4, 132.3, 130.4, 127.6, 126.4 (8s, 8 C); 129.1, 129.0, 128.3, 128.2, 126.9, 126.7 (6d, 10 CH(Ph)); 52.0 (d, CH); 49.9, 39.4 (2t, 2 CH_2); 31.6, 11.5, 9.1 (3q, 3 Me). EI-HRMS: 432.1453 (M^+, $C_{24}H_{24}N_4S_2^+$; calcd. 432.1442).

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