Synthesis and selected reactions of hydrazides containing an imidazole moiety

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Abstract: The preparation of two types of imidazole derivatives bearing a hydrazide group was achieved by treatment of the corresponding esters with NH2NH2 · H2O in MeOH at room temperature. In the case of 4-(ethoxycarbonyl)-1H-imidazole 3-oxides 3, hydrazides of type 1 were formed with retention of the N-oxide structure (Scheme 1). Interestingly, due to a strong H-bonding, no deoxygenation of the N-O function could be achieved even by treatment of 3 with Raney-Ni. The second type, 2-[(1H-imidazol-2-yl)sulfanyl]acetohydrazides 2, was obtained from 1H-imidazole-2(3H)-thiones 4 in two steps via S-alkylation with methyl bromoacetate, followed by treatment with NH2NH2 · H2O (Scheme 2). An imidazole 7, containing both types of hydrazide groups, was prepared analogously from ethyl 2,3-dihydro-2-thioxo-1H-imidazole-4-carboxylate 4d (Scheme 4). Both types of hydrazides, 1 and 2, were transformed successfully to the corresponding acylhydrazones 8 and 9, respectively (Scheme 5). Furthermore, it has been shown that hydrazides of type 1 are useful starting materials for the synthesis of 1,2,4-triazole-3-thiones 11 and 1,3,4-thiadiazole-2-amines 12, bearing an imidazole 3-oxide moiety (Scheme 7).

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Synthesis and Selected Reactions of Acid Hydrazides Containing an Imidazole Moiety

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The preparation of two types of imidazole derivatives bearing a hydrazide group was achieved by treatment of the corresponding esters with $NH_2NH_2 \cdot H_2O$ in MeOH at room temperature. In the case of 4-(ethoxycarbonyl)imidazole 3-oxides **3**, hydrazides of type **1** were formed with retention of the *N*-oxide structure (*Scheme 1*). Interestingly, due to a strong hydrogen bonding, no deoxygenation of the N→O function could be achieved even by treatment of **3** with *Raney*-nickel. The second type, 2-[(imidazol-2-yl)sulfanyl]acetohydrazides **2**, was obtained from 1*H*-imidazole-2(3*H*)-thiones **4** in two steps *via* S-alkylation with methyl bromoacetate followed by treatment with $NH_2NH_2 \cdot H_2O$ (*Scheme 2*). An imidazole **7**, containing both types of hydrazide groups, was prepared analogously from ethyl 2,3-dihydro-2-thioxoimidazole-4-carboxylate **4d** (*Scheme 4*). Both types of hydrazides, **1** and **2**, were transformed successfully into the corresponding acylhydrazones **8** and **9**, respectively (*Scheme 5*). Furthermore, it has been shown that hydrazides of type **1** are useful starting materials for the synthesis of 1,2,4-triazole-3-thiones **11** and 1,3,4-thiadiazole-2-amines **12**, bearing an imidazole 3-oxide residue (*Scheme 7*).

1. Introduction. – In a series of our recent publications, various syntheses of imidazole derivatives including optically active products were reported [1]. It is well documented that some imidazole derivatives such as imidazole *N*-oxides [2], imidazole-2-thiones [3] or 2-sulfanylimidazoles [4] show diverse biological activities. On the other hand, imidazole *N*-oxides were used for the preparation of more complex *N*-heterocles *via* Pd-catalyzed direct arylation [5], and in the case of optically active derivatives, they were applied as promising ligands for asymmetric allylation of aromatic aldehydes [6].

Acyl hydrazides were widely reported as biologically active compounds, and similar properties were shown for their derivatives, *e.g.*, hydrazones, semicarbazones, and thiosemicarbazones [7]. Furthermore, acid hydrazides are privileged starting materials for the preparation of various heterocycles like 1,2,4-triazoles, 1,3,4-thiadiazoles, 1,3,4-oxadiazoles, etc. [8].

The goal of the present study was the synthesis of acid hydrazides containing differently substituted imidazole moieties starting with corresponding esters described in our recent publications. For the first time, acid hydrazides derived from 3-oxidoimidazole carboxylic acids and the influence of the oxido function on the reactivity of the hydrazide unit and *vice versa* will be reported. In addition, the synthesis of corresponding hydrazones as representative derivatives is presented.

2. Results and Discussion. – For the synthesis of imidazole containing acid hydrazides of types **1** and **2**, the typical protocol based on the treatment of the corresponding ethyl carboxylates with $NH_2NH_2 \cdot H_2O$ [9] was applied, and the expected products were obtained in high yields.

The imidazole *N*-oxides **3** bearing the ester group at C(4) were easily available from the reaction of 2-hydroxyimino-3-oxobutanoate with the corresponding primary

amine and CH_2O [1g][10]. Treatment with $NH_2NH_2 \cdot H_2O$ in MeOH at room temperature led to the products **1a**–**1c**, which were obtained as crystalline materials in good yields (*Scheme 1*). Their structures were determined on the basis of their spectroscopic data. The presence of the *N*-oxido function was evidenced by the diagnostic high field shifted H–C(2) signal at 8.60 – 8.37 ppm.

Scheme 1

Finally, the structure of **1b** was established by X-ray crystallography (*Figure*). The N(4)–H group forms bifurcated H-bonds. One interaction is an intramolecular H-bond with the adjacent oxide O(1)-atom to form a loop, which can be described by a graph set motif [12] of S(6). The second interaction is an intermolecular H-bond with the oxide O-atom of a neighboring molecule. This interaction links pairs of molecules related by a centre of inversion into dimers and the motif thus formed can be described by a graph set motif of $R^2_{,2}(12)$. The same two molecules are also linked by a H-bond between the NH_2 group and the oxide O-atom. The motif in this case is $R^2_{,2}(14)$. The other H-atom of the NH_2 group forms an intermolecular H-bond with the hydrazide O(2)-atom of a different neighboring molecule. This interaction links these molecules into centrosymmetric dimers and can be described by a graph set motif of $R^2_{,2}(10)$. The combination of all intermolecular H-bonds links the molecules into two-dimensional layer networks which lie parallel to the (001) plane. The Ph rings from adjacent layers interdigitate.

Figure. *ORTEP Plot* [11] of the molecular structure of **1b** (with 50% probability ellipsoids; arbitrary numbering of the atoms)

Interestingly, in contrast to the ester **3a**, the attempted 'sulfur-transfer reaction' [1a] aimed at obtaining of the corresponding imidazole-2-thione from the acid hydrazide **1a** was unsuccessful. Moreover, the typical thermal isomerization of 2-unsubstituted imidazole *N*-oxide derivatives to the corresponding imidazol-2-ones was not achieved even after heating of **1a** in boiling toluene. Finally, the attempted deoxygenation with *Raney*-Ni, which was performed smoothly in many other cases of imidazole *N*-oxides [1c–1e], did not afford the expected products. All these facts point out that the presence of the hydrazide function strongly influences the reactivity of the oxido function, most likely as a result of a strong intramolecular H-bond between the hydrazide N–H and the oxide O-atom.

The second type of acid hydrazides **2** presented in this study was obtained *via S*-alkylation of imidazole-2-thiones **4** with methyl bromoacetate and subsequent conversion of the ester function (*Scheme 2*). A convenient access to the differently substituted starting materials **4** is the so-called 'sulfur-transfer reaction' [1a][1e], in which the 2-unsubstituted imidazole *N*-oxide is treated with a cycloaliphatic thioketone. The crystalline hydrazides **2a**–**2c** were obtained in good yields.

Scheme 2

Another method used for the incorporation of an ester group into the side chain of imidazoles consists of the condensation of α-hydroxyimino ketones with CH_2O and an appropriate α-amino acid ester [1e]. In that case, the ester group is placed in the

α-position of the side chain at N(1). Unexpectedly, by treatment with $NH_2NH_2 \cdot H_2O$, even under very mild conditions, the imidazole *N*-oxides **5a**–**5b** were converted into the α-(imidazol-1-yl)carboxylic acids **6a**–**6b** in nearly quantitative yields (*Scheme 3*). The preservation of the *N*-oxide function was confirmed by the ^{1}H-NMR spectra, which showed the typical absorption for H–C(2) at 8.13 for **2a** and 8.36 ppm for **2b**, respectively.

Scheme 3

Starting with 2-thioxoimidazole-4-carboxylate **4d**, which was obtained in analogy to the corresponding N-Ph amide [1g] by the 'sulfur-transfer reaction' with **3b**, subsequent alkylation with methyl bromoacetate and treatment with two equivalents of $NH_2NH_2 \cdot H_2O$ led to the bis-hydrazide **7** (*Scheme 4*). The latter represents an example in which the structure elements of type **1** and type **2** are combined.

Scheme 4

Both types of easily available acid hydrazides, **1** and **2**, are attractive starting materials for further syntheses involving the hydrazide group. In the present study, they were used for the formation of hydrazones with various aldehydes and ketones [3]). In the case of acid hydrazides **1b** and **1c**, the reactions with benzaldehyde, adamantan-2-one, and cyclohexanone, respectively, in MeOH occurred smoothly at room temperature and yielded the expected hydrazones **8a**–**8f** in high yields. The analogous reactions with

[3]) For some recent articles on synthesis and biological interest of acylhydrazones see [7a][8a][13].

acetophenone required acid catalysis (AcOH in EtOH, reflux) to give **8e** and **8f** (*Scheme 5*), whereas with benzophenone no hydrazone was obtained.

A series of hydrazones of type **9** derived from hydrazides **2a**–**2c** was prepared by using some of aromatic aldehydes and cyclohexanone. The reactions were carried out in boiling EtOH in the presence of catalytic amounts of AcOH, and in all cases the products were isolated as crystalline materials (*Scheme 5*).

Scheme 5

In contrast to hydazide **1a**, which did not undergo the 'sulfur transfer reaction' upon treatment with 2,2,4,4-tetramethylcyclobutane-1,3-dithione, the analogous reaction with hydrazide hydrazone **8c** afforded, after 24 h at room temperature in CH_2Cl_2, the expected imidazol-2-thione derivative **4e** in 88% yield (*Scheme 6*). It is worth mentioning that corresponding *N*-Me and *N*-Ph-substituted 3-oxidoimidazole-4 carboxamides react under similar conditions [1g], whereas the transformation of 4-methyl- and 4-phenylimidazole-3-oxides is complete within *ca.* 30 min. This result confirms the importance of the H-bonding between the amide and hydrazide function and the N→O group for the tuning of the reactivity of imidazole *N*-oxide as a 1,3-dipol [1a].

Scheme 6

The reaction of acid hydrazides with isothiocyanates is a typical procedure applied for the preparation of 1,3,4-thiadiazoles or 1,2,4-triazole-3-thiones [14]. The two-steep reactions led initially to thiosemicarbazides, which subsequently undergo

cyclocondensation under acidic or basic reaction conditions. Using these methods, hydrazide **1b** was smoothly converted into triazole thione **11** by heating of thiosemicarbazide **10** in aqueous NaOH solution, whereas after stirring of a solution of **1b** in conc. H_2SO_4 at room temperature, thiadiazole **12** was obtained in high yield (*Scheme 7*).

Scheme 7

3. Conclusions. – The presented results show that differently substituted imidazole *N*-oxides containing an ester group can be easily transformed into the corresponding acid hydrazides without loss of the *N*-oxide function. To the best of our knowledge, there are no such examples of azaheterocyclic *N*-oxides reported to date. The presence of the hydrazide function and the *N*-oxide group offer a unique opportunity for their exploration in the synthesis of more complex heterocycles, which are potentially useful building blocks for the preparation of products with biological activity. Some imidazole derivatives containing hydrazide [15] or hydrazone moieties [16] were reported as potential pharmaceuticals, a fact, which is also reflected by several patents, *e.g.* [17].

In addition, imidazole *N*-oxides can be transformed into imidazole-2-thiones, which may be used for syntheses of another class of acid hydrazides containing the imidazole unit. These products can also be considered as potentially useful starting materials for the preparation of diverse polyheterocycles.

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Experimental Part

1. General. M.p.: *Melt-Temp. II* (*Aldrich*); uncorrected. IR Spectra: *NEXUS FT-IR* spectrophotometer; in KBr; absorptions in cm^{-1}. ^1H- and $^{13}C\{^1H\}$-NMR Spectra: *Bruker Avance III 600* using solvent signal as reference; δ in ppm; coupling constants *J* in Hz. Assignments of signals in ^{13}C-NMR spectra were made on the basis of HMQC experiments. EI-HR-MS: *Bruker Esquire LC* spectrometer, ESI-HR-MS: *Finnigan MAT-95* instrument. Optical rotations were determined on a *PERKIN-ELMER 241 MC* polarimeter for $\lambda = 589$ nm.

2. *Starting Materials*. All solvents are commercially available and were used as received. Imidazole *N*-Oxides **3a**,**b**,**c** and **5a**,**b**, and 1*H*-imidazole-2-thiones **4a**–**c** were prepared following known procedures [1a][1e]. 2,2,4,4-Tetramethylcyclobutane-1,3-dithione was prepared by thionation of 2,2,4,4-tetramethylcyclobutane-1,3-dione using P_2S_5 as a thionating reagent [18].

3. *General Procedure for the Synthesis of Hydrazides* **1**. To a soln. of freshly prepared imidazole *N*-oxide ester **3** (10 mmol) in MeOH (5 ml), was added $NH_2NH_2 \cdot H_2O$ (20 mmol). The mixture was stirred for 16 h at r.t., the solvent was evaporated under vacuum, and the residue was crystallized from MeOH.

*1,5-Dimethyl-3-oxido-1*H-*imidazole-4-carboxyhydrazide* (**1a**). Yield: 1.02 g (65%). Colorless crystals. M.p. 242–246° (decomp., MeOH). IR (KBr): 3309*s*, 3261*s* (N–H), 1648v*s* (C=O), 1601v*s*, 1530*m*, 603*m*. ^{1}H-NMR ((D$_6$)DMSO): 11.58 (br. *s*, NH); 8.37 (*s*, H–C(2)); 4.49 (br. *s*, NH$_2$); 3.54 (*s*, MeN); 2.48 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 159.3 (C=O); 133.3, 120.7 (C(4), C(5)); 126.6 (C(2)); 32.2 (MeN); 9.3 (Me). HR-ESI-MS: 171.0874 ([*M*+H]$^+$, $C_6H_{11}N_4O_2$; calc. 171.0876).

*1-Benzyl-5-methyl-3-oxido-1*H-*imidazole-4-carboxyhydrazide* (**1b**): Yield: 1.353 g (55%). Colorless crystals. M.p. 228–230° (decomp., MeOH). IR (KBr): 3296v*s* (NH), 1661v*s* (C=O), 1604v*s*, 1579*m*, 977*m*. ^{1}H-NMR ((D$_6$)DMSO): 11.57 (br. *s*, NH); 8.60 (*s*, H–C(2)); 7.40–7.21 (*m*, 5 arom. H); 5.21 (*s*, CH$_2$); 4.51 (br. *s*, NH$_2$); 2.42 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 159.2 (C=O); 136.0, 121.3 (C(4), C(5)); 130.0 (1 arom. C); 129.4, 128.6, 127.6 (5 arom. CH); 126.6 (C(2)); 48.6 (CH$_2$); 9.6 (Me). HR-ESI-MS: 247.1191 ([*M*+H]$^+$, $C_{12}H_{15}N_4O_2$; calc. 247.1190).

*1-Cyclohexyl-5-methyl-3-oxido-1*H-*imidazole-4-carboxyhydrazide* (**1c**): Yield: 1.428 g (60%). Colorless crystals. M.p. 170–172° (MeOH). IR (KBr): 3305*s*, 3271*s* (NH), 1655vs (C=O), 1600v*s*, 1544*m*, 1416*m*, 1281*m*. ^{1}H-NMR ((D$_6$)DMSO): 11.63 (br. *s*, NH); 8.58 (*s*, H–C(2)); 4.49 (br. *s*, NH$_2$); 4.09–4.00 (*m*, CH); 2.55 (*s*, Me); 1.96–1.76 (*m*, 4 cyclohexyl H); 1.70–1.57 (*m*, 3 cyclohexyl H); 1.46–1.35 (*m*, 2 cyclohexyl H); 1.22–1.11 (*m*, 1 cyclohexyl H). ^{13}C-NMR ((D$_6$)DMSO): 159.4 (C=O); 129.2, 120.3 (C(4), C(5)); 124.2 (C(2)); 55.0 (CH); 33.0, 25.4, 25.0 (5 cyclohexyl CH$_2$); 9.33 (Me). HR-EI-MS: 239.1494 ([*M*+H]$^+$, $C_{11}H_{19}N_4O_2$; calc. 239.1502).

Treatment of ethyl α-(imidazol-1-yl)carboxylates **5** with $NH_2NH_2 \cdot H_2O$ following the same procedure led to the corresponding carboxylic acids **6**.

*(*S*)-2-(4,5-Dimethyl-3-oxido-1*H-*imidazol-1-yl)propanoic Acid* (**6a**). Yield: 1.656 g (90%). Yellowish oil. $[\alpha]_D^{20}$ = +74 (c = 1, MeOH). IR (film): 1683v*s* (C=O),

1633*m*, 1568*m*, 1410*m*, 1337*m*. ^{1}H-NMR (CD_3OD): 8.18 (*s*, H–C(2')); 4.63 (*q*, *J* = 7.2, CH); 2.16, 2.15 (2*s*, 2 Me); 1.68 (*d*, *J* = 7.2, Me). ^{13}C-NMR (CD_3OD): 174.8 (C=O); 124.8, 122.7 (C(4'), C(5')); 124.3 (C(2')); 57.0 (CH); 17.2 (Me); 7.3, 5.6 (2 imidazole Me). HR-EI-MS: 185.0921 ([*M*+H]$^+$, $C_8H_{13}N_2O_3$; calc. 185.0927).

*(*S*)-2-(4,5-Dimethyl-3-oxido-1*H*-imidazol-1-yl)-3-methylbutanoic Acid* (**6b**). Yield: 1.844 g (87%). Yellowish oil. $[\alpha]_D^{20}$ = +34 (c = 1, MeOH). IR (film): 1671v*s* (br. C=O), 1633*m*, 1558*m*, 1411*m*, 1333*m*. ^{1}H-NMR (CD_3OD): 8.36 (*s*, H–C(2')); 4.21 (*d*, *J* = 10.6, CHN); 2.42–2.35 (*m*, CH); 2.22, 2.15 (2*s*, 2 Me); 1.03 (*d*, *J* = 6.5, Me); 0.83 (*d*, *J* = 7.1, Me). ^{13}C-NMR (CD_3OD): 178.8 (C=O); 125.2, 122.6 (C(4'), C(5')); 124.8 (C(2')); 63.5 (CHN); 31.9 (CH); 17.9, 17.6 (2 Me); 7.4, 5.6 (2 imidazole Me). HR-EI-MS: 213.1232 ([*M*+H]$^+$, $C_{10}H_{17}N_2O_3$; calc. 213.1240).

4. *General Procedure for the Synthesis of Hydrazides* **2**. To a soln. of an imidazole-2-thione **4** (1 mmol) in CH_2Cl_2 (5 ml) was added methyl bromoacetate (1 mmol). The mixture was stirred for 48 h at r.t., then, the solvent was evaporated under vacuum, and the residue was used immediately without further purification. The oily residue was dissolved in EtOH (5 ml) and $NH_2NH_2 \cdot H_2O$ (2 mmol) was added. The mixture was heated under reflux for 2 h, the solvent was evaporated under vacuum, and the residue was crystallized from MeOH.

2-[(1-Benzyl-4,5-dimethylimidazol-2-yl)sulfanyl]acetohydrazide (**2a**). Yield: 0.225 g (88%). Colorless crystals. M.p. 127–129° (MeOH). IR (KBr): 3321*s* (NH), 1671v*s* (C=O), 1420*m*, 722*m*. ^{1}H-NMR ($CDCl_3$): 9.88 (br. *s*, NH); 7.26–6.91 (*m*, 5 arom. H); 4.99 (*s*, CH_2N); 3.48 (*s*, CH_2S); 2.10, 1.96 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 170.2 (C=O); 138.6 (C(2')); 136.0, 134.6, 125.3 (1 arom. C, C(4'), C(5')); 129.0, 127.9, 126.2 (5 arom. CH); 47.9 (CH_2N); 35.4 (CH_2S); 12.7, 9.2 (2 Me). HR-EI-MS: 291.1275 ([*M*+H]$^+$, $C_{14}H_{19}N_4OS$; calc. 291.1280).

2-[(1-Cyclohexyl-4,5-dimethylimidazol-2-yl)sulfanyl]acetohydrazide (**2b**). Yield: 0.212 g (75%). Colorless crystals. M.p. 117–119° (MeOH). IR (KBr): 3314*s*, 3226*s* (br., NH), 1676v*s* (C=O), 1615v*s*, 1523*m*, 1413*m*, 1003*m*. ^{1}H-NMR ($CDCl_3$): 10.0 (br. *s*, NH); 3.97–3.93 (*m*, CH); 3.63 (*s*, CH_2S); 2.16, 2.11 (2*s*, 2 Me); 2.03–1.71 (*m*, 7 cyclohexyl H); 1.39–1.18 (*m*, 3 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 170.5 (C=O); 137.9 (C(2')); 134.2, 124.6 (C(4'), C(5')); 57.2 (CH); 35.2 (CH_2S); 31.7, 26.2, 25.2 (5 cyclohexyl CH_2); 12.6, 10.6 (2 Me). HR-EI-MS: 283.1589 ([*M*+H]$^+$, $C_{13}H_{23}N_4OS$; calc. 283.1588).

2-[(1-Benzyl-4,5-diphenylimidazol-2-yl)sulfanyl]acetohydrazide (**2c**). Yield: 0.323 g (76%). Colorless crystals. M.p. 112–115° (MeOH). IR (KBr): 3329*s*, 3276*s* (NH), 1673v*s* (C=O), 1601v*s*, 1453*m*, 1436*m*, 701*m*. ^{1}H-NMR ($CDCl_3$): 9.96 (br. *s*, NH); 7.38–6.82 (*m*, 15 arom. H); 4.90 (*s*, CH_2N); 3.67 (*s*, CH_2N). ^{13}C-NMR ($CDCl_3$): 170.2 (C=O); 142.3, 131.1, 129.2 (3 arom. C); 138.2, 133.5 (C(4'), C(5')); 136.0 (C(2')); 131.0, 130.1, 129.1, 128.8, 128.6, 127.9, 126.8, 126.6, 126.4 (15 arom. CH); 48.1 (CH_2N); 34.6 (CH_2S). HR-EI-MS: 415.1583 ([*M*+H]$^+$, $C_{24}H_{23}N_4OS$; calc. 415.1588).

5. *General Procedure for the Synthesis of 1*H-*Imidazole-2-thiones* **4**. To a magnetically stirred soln. of 1*H*-imidazole N-oxide (1 mmol) in CH_2Cl_2 (1 ml), a soln. of 2,2,4,4-tetramethylcyclobutane-1,3-dithione [18][19] (0.6 mmol) in CH_2Cl_2 (1 ml) was added dropwise. The addition was complete after *ca.* 10 min, and stirring was continued for 24 h, while a little precipitate was formed. Then, the solvent was removed under reduced pressure, the resulting solid was washed with hexane, and filtered. The crude product was recrystallized from MeOH.

*Ethyl 1-Benzyl-5-methyl-2-thioxo-1*H-*imidazole-4-carboxylate* (**4d**). Yield: 0.146 g (53%). Colorless crystals. M.p. 205–207° (decomp., MeOH). IR (KBr): 1706v*s*

(C=O), 1417v*s*, 1335*m*, 721*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.87 (br. *s*, NH); 7.35–7.21 (*m*, 5 arom. H); 5.36 (*s*, CH_2); 4.22 (*q*, *J* = 7.1, MeC*H*$_2$O); 2.28 (*s*, Me); 1.26 (*t*, *J* = 7.1, *Me*CH$_2$O). ^{13}C-NMR ((D$_6$)DMSO): 164.3 (C=S); 159.1 (C=O); 136.6, 115.8 (C(4), C(5)); 135.4 (1 arom. C); 129.1, 127.9, 127.2 (5 arom. CH); 60.9 (MeC*H*$_2$O); 47.0 (CH_2); 14.5 (*Me*CH$_2$O); 10.9 (Me). HR-ESI-MS: …… ([*M*+H]$^+$, $C_{14}H_{17}N_2O_2S$; calc. 227.1005).

N-*(2-Adamantylidenamino)-1-benzyl-5-methyl-2-thioxo-1*H-*imidazole-4-carboxamide* (**4e**). Yield: 0.345 g (88%). Colorless crystals. M.p. 284–286° (decomp., MeOH). IR (KBr): 3293*s* (NH), 3140*s*, 3063*s*, 1616v*s* (C=O), 1510*m*, 1496*m*, 1406*m*, 1365*m*. ^{1}H-NMR (D$_6$)DMSO): 12.78 (br. *s*, NH); 9.99 (br. *s*, imidazol NH); 7.36–7.23 (*m*, 5 arom. H); 5.34 (*s*, CH_2); 3.32, 2.55 (2br. *s*, 2 adamantyl CH); 2.28 (br. *s*, Me); 1.99–1.75 (*m*, 12 adamantyl H). ^{13}C-NMR ((D$_6$)DMSO): 162.5 (C=O); 155.5 (C=S); 136.8 (C=N); 133.3, 117.9 (C(4), C(5)); 130.0 (1 arom. C); 129.1, 127.9, 127.3 (5 arom. CH); 46.9 (CH_2); 39.1, 37.8, 36.3, 31.6, 27.6 (9 adamantyl C); 10.7 (Me). HR-ESI-MS: 395.1895 ([*M*+H]$^+$, $C_{22}H_{27}N_4O_2S$; calc. 395.1900).

6. *Synthesis of 1-Benzyl-2-[(2-hydrazino-2-oxoethyl)sulfanyl]-5-methylimidazole-4-carboxyhydrazide* (**7**). To a soln. of imidazole-2-thione **4d** (267 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added methyl bromoacetate (153 mg, 1 mmol). The mixture was stirred for 48 h at r.t., the solvent was evaporated under vacuum, and the residue was used for the following reaction without further purification. The oily residue was dissolved in EtOH (5 ml) and $NH_2NH_2.H_2O$ (2 mmol) was added. The mixture was stirred for 16 h at r.t., the solvent was evaporated under vacuum, and the residue was crystallized from MeOH. Yield of **7**: 0.293 g (88%). Colorless crystals. M.p. 194–198° (MeOH). IR (KBr): 3315*vs* (N−H), 3203*m*, 1664v*s* (C=O), 1612v*s*, 1594*m*, 1495*m*, 734*m*. ^{1}H-NMR ($CDCl_3$): 9.26, 8.99 (2br. *s*, 2 NH); 7.36–7.05 (*m*, 5

arom. H); 5.15 (*s*, CH_2N); 4.30 (br. *s*, 2 NH_2); 3.73 (*s*, CH_2S); 2.38 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 167.3, 162.9 (2 C=O); 140.3, 131.0 (C(4), C(5)); 136.6 (C(2)); 133.9 (1 arom. C); 129.3, 128.1, 126.9 (5 arom. CH); 47.2 (CH_2N); 35.1 (CH_2S); 10.0 (Me). HR-EI-MS: 335.1286 ([*M*+H]$^+$, $C_{14}H_{19}N_6O_2S$; calc. 335.1285).

7. *General Procedure for the Synthesis of* **8a**–**8f**. To a stirred soln. of a hydrazide **1** (1 mmol) in MeOH (4 ml) at 20º, an equimolar quantity of the carbonyl component (bezaldehyde, adamantan-2-one, cyclohexanone) was added slowly. The mixture was stirred for 16 h at r.t., the soln. was concentrated, the resulting solid was treated with Et_2O, filtered, and crystallized from MeOH.

1-Benzyl-N-*(benzylidenamino)-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8a**). Yield: 0.308 g (92%). Colorless crystals. M.p. 232–234° (decomp., MeOH). IR (KBr): 3086*m*, 1667v*s* (C=O), 1607v*s*, 1594*m*, 1558*m*, 1461*m*. ^{1}H-NMR ($CDCl_3$): 13.80 (br. *s*, NH); 8.20 (*s*, H–C=N); 7.79–7.77 (*m*, 2 arom. H; H–C(2)); 7.41–7.15 (*m*, 8 arom. H); 5.07 (*s*, CH_2); 2.67 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 156.3 (C=O); 149.0 (C=N); 134.1, 122.2 (C(4), C(5)); 133.0, 132.2 (2 arom. C); 130.3, 129.6, 129.3, 128.6, 127.8, 127.3 (10 arom. CH); 125.3 (C(2)); 49.6 (CH_2); 9.8 (Me). HR-ESI-MS: 335.1503 ([*M*+H]$^+$, $C_{19}H_{19}N_4O_2$; calc. 335.1503).

N-*(Benzylidenamino)-1-cyclohexyl-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8b**). Yield: 0.229 g (70%). Colorless crystals. M.p. 206–208° (decomp., MeOH). IR (KBr): 3109*m*, 1671v*s* (C=O), 1608v*s*, 1592*m*, 1417*m*, 1270*m*. ^{1}H-NMR ($CDCl_3$): 13.89 (br. *s*, NH); 8.21 (*s*, H–C=N); 7.85 (*s*, H–C(2)); 7.80–7.78 (*m*, 2 arom. H); 7.39–7.37 (*m*, 3 arom. H); 3.98–3.93 (*m*, CHN); 2.70 (*s*, Me); 2.09–1.96 (*m*, 4 cyclohexyl H); 1.70–1.42 (*m*, 5 cyclohexyl H); 1.30–1.23 (*m*, 1 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 156.5 (C=O); 148.8 (C=N); 134.2 (1 arom. C); 131.2, 121.4 (C(4), C(5)); 130.2, 128.6, 127.8 (5 arom. CH); 122.6 (C(2)); 55.7 (CH); 33.7, 25.4, 24.9 (5

cyclohexyl CH_2); 9.6 (Me). HR-ESI-MS: 327.1816 ([*M*+H]$^+$, $C_{18}H_{23}N_4O_2$; calc. 327.1816).

N-*(2-Adamantylidenamino)-1-benzyl-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8c**). Yield: 0.302 g (80%). Colorless crystals. M.p. 260–262° (decomp., MeOH). IR (KBr): 3181*m* (NH), 3042*m*, 1682v*s* (C=O), 1602v*s*, 1547*m*, 1255*m*. ^{1}H-NMR ($CDCl_3$): 13.35 (br. *s*, NH); 7.76 (*s*, H–C(2)); 7.41–7.38 (*m*, 3 arom. H); 7.13–7.12 (*m*, 2 arom. H); 5.07 (*s*, CH_2); 3.23, 2.87 (2br. *s*, 2 adamantyl CH); 2.64 (*s*, Me); 2.05–1.80 (*m*, 12 adamantyl H). ^{13}C-NMR ($CDCl_3$): 168.5 (C=O); 156.1 (C=N); 133.1, 122.7 (C(4), C(5)); 131.8 (1 arom. C); 129.6, 129.2, 127.1 (5 arom. CH); 125.0 (C(2)); 49.5 (CH_2); 39.4, 39.1, 37.9, 36.4, 32.8, 27.8 (9 adamantyl C); 9.8 (Me). HR-ESI-MS: 379.2132 ([*M*+H]$^+$, $C_{22}H_{27}N_4O_2$; calc. 379.2128).

N-*(2-Adamantylidenamino)-1-cyclohexyl-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8d**). Yield: 0.260 g (70%). Colorless crystals. M.p. 226–228° (decomp., MeOH). IR (KBr): 3104*w* (NH), 1679v*s* (C=O), 1596v*s*, 1416*m*. ^{1}H-NMR ($CDCl_3$): 13.47 (br. *s*, NH); 7.77 (*s*, H–C(2)); 3.96–3.90 (*m*, CHN); 3.22, 2.85 (2br. *s*, 2 adamantyl CH); 2.68 (*s*, Me); 2.09–2.02 (*m*, 2 cyclohexyl H); 2.01–1.82 (*m*, 12 adamantyl H, 1 cyclohexyl H); 1.81–1.75 (*m*, 2 cyclohexyl H); 1.57–1.38 (*m*, 4 cyclohexyl H); 1.30-1.21 (*m*, 1 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 168.1 (C=O); 156.5 (C=N); 130.7, 121.9 (C(4), C(5)); 122.4 (C(2)); 55.6 (CHN); 39.4, 39.3, 39.1, 37.9, 36.4, 33.7, 32.7, 27.8, 25.4, 24.8 (9 adamantyl C, 5 cyclohexyl C); 9.5 (Me). HR-ESI-MS: 371.2441 ([*M*+H]$^+$, $C_{21}H_{31}N_4O_2$; calc. 371.2442).

1-Benzyl-N-*(cyclohexylidenamino)-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8e**). Yield: 0.320 g (98%). Colorless crystals. M.p. 220–222° (decomp., MeOH). IR (KBr): 3081*s*, 2930*s*, 1667v*s* (C=O), 1602v*s*, 1559*m*, 1452*m*. ^{1}H-NMR ($CDCl_3$): 13.46 (br. *s*, NH); 7.77 (*s*, H–C(2)); 7.40–7.38 (*m*, 3 arom. H); 7.13–7.11 (*m*, 2

arom. H); 5.06 (*s*, CH_2); 2.63 (*s*, Me); 2.63–2.43 (*m*, 4 cyclohexyl H); 1.73–1.67 (*m*, 4 cyclohexyl H); 1.64–1.60 (*m*, 2 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 161.8 (C=O); 156.1 (C=N); 133.1, 122.6 (C(4), C(5)); 131.8 (1 arom. C); 129.5, 129.2, 127.1 (5 arom. CH); 125.1 (C(2)); 49.5 (CH_2); 35.4, 28.1, 27.0, 26.1, 25.7 (5 cyclohexyl C); 9.8 (Me). HR-ESI-MS: 327.1814 ([*M*+H]$^+$, $C_{18}H_{23}N_4O_2$; calc. 327.1816).

1-Cyclohexyl-N-*(cyclohexylidenamino)-5-methyl-3-oxido-1*H-*imidazole-4-carboxamide* (**8f**). Yield: 0.239 g (75%). Colorless crystals. M.p. 218–220° (decomp., MeOH). IR (KBr): 3084*m*, 2931v*s*, 1685v*s* (C=O), 1596v*s*, 1538*m*, 1416*m*, 1261*m*. ^{1}H-NMR ($CDCl_3$): 13.47 (br. *s*, NH); 7.82 (*s*, H–C(2)); 3.97–3.91 (*m*, CHN); 2.68 (*s*, Me); 2.46–2.43 (*m*, 4 cyclohexyl H); 2.07–2.05 (*m*, 2 cyclohexyl H); 1.97–1.95 (*m*, 2 cyclohexyl H); 1.78–1.66 (*m*, 5 cyclohexyl H); 1.65–1.60 (*m*, 2 cyclohexyl H); 1.58–1.39 (*m*, 4 cyclohexyl H); 1.30–1.21 (*m*, 1 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 161.5 (C=O); 156.3 (C=N); 130.8, 121.8 (C(4), C(5)); 122.5 (C(2)); 55.6 (CHN); 35.5, 33.7, 28.1, 27.0, 26.1, 25.7, 25.4, 24.8 (10 cyclohexyl C); 9.54 (Me). HR-ESI-MS: 319.2129 ([*M*+H]$^+$, $C_{17}H_{27}N_4O_2$; calc. 319.2128).

8. *General Procedure for the Synthesis of* **8g**,**h** *and* **9a**–**g**: A soln. of hydrazide **1** or **2** (1 mmol) in EtOH (4 ml) and an equimolar amount of the carbonyl component (4-methoxy-, 4-dimethylamino-, 4-methylsulfanylbenzaldehyde, cyclohexanone) and a catalytic amount of AcOH was heated to reflux for 4 h. After cooling to r.t., the solvent was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2 and, after addition of $NaHCO_3$, stirred for 0.5 h. The mixture was filtered, the solvent evaporated under reduced pressure, and the residue was purified by crystallization from MeOH.

1-Benzyl-5-methyl-3-oxido-N-*(1-phenylethylidenamino)-1*H-*imidazole-4-carboxamide* (**8g**). Yield: 0.261 g (76%). Colorless crystals. M.p. 222–226° (decomp., MeOH). IR (KBr): 3061*m*, 2914*m*, 1678v*s* (C=O), 1602v*s*, 1546*m*, 1269*m*, 705*m*. ^{1}H-

NMR ($CDCl_3$): 13.71 (br. *s*, NH); 7.90–7.88 (*m*, 2 arom. H); 7.82 (*s*, H–C(2)); 7.42–7.36 (*m*, 6 arom. H); 7.16–7.14 (*m*, 2 arom. H); 5.09 (*s*, CH_2); 2.67 (*s*, imidazole Me); 2.39 (*s*, MeC=N). ^{13}C-NMR ($CDCl_3$): 156.2 (C=O); 153.0 (C=N); 138.1, 132.1 (2 arom. C); 133.0, 122.6 (C(4), C(5)); 129.6, 129.4, 129.3, 128.2, 127.2, 126.8 (12 arom. C); 125.2 (C(2)); 49.6 (CH_2); 14.5 (*Me*C=N); 9.8 (imidazole Me). HR-ESI-MS: 349.1664 ([*M*+H]$^+$, $C_{20}H_{21}N_4O_2$; calc. 349.1659).

1-Cyclohexyl-5-methyl-3-oxido-N-*(1-phenylethylidenamino)-1*H-*imidazole-4-carboxamide* (**8h**). Yield: 0.238 g (70%). Colorless crystals. M.p. 264–268° (decomp., MeOH). IR (KBr): 3080*m*, 2937*s* 1675v*s* (C=O), 1601v*s*, 1553*m*, 1417*m*, 1273*m*. ^{1}H-NMR ($CDCl_3$): 13.67 (br. *s*, NH); 7.94–7.92 (*m*, 2 arom. H, H–C(2)); 7.41–7.39 (*m*, 3 arom. H); 4.03–3.98 (*m*, CHN); 2.75 (*s*, imidazole Me); 2.43 (*s*, MeC=N); 2.14–2.00 (*m*, 4 cyclohexyl H); 1.64–1.45 (*m*, 4 cyclohexyl H); 1.34–1.25 (*m*, 2 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 156.2 (C=O); 152.9 (C=N); 138.1 (1 arom. C); 131.2, 121.8 (C(4), C(5)); 129.4, 128.2, 126.8 (5 arom. CH); 122.8 (C(2)); 55.8 (CHN); 33.7, 25.4, 24.8 (5 cyclohexyl C); 14.5 (*Me*C=N); 9.6 (Me). HR-ESI-MS: 341.1975 ([*M*+H]$^+$, $C_{19}H_{25}N_4O_2$; calc. 341.1972).

2-(1-Benzyl-4,5-dimethylimidazol-2-yl)sulfanyl-N-*[(4-methoxyphenyl) methylenamino]acetamide* (**9a**). Yield: 0.237 g (57%). Colorless crystals. M.p. 130–132° (MeOH). IR (KBr): 3186*m* (br.), 3067*m* (br.), 1664v*s* (C=O), 1606v*s*, 1407*m*, 1245*m*. ^{1}H-NMR ($CDCl_3$): 12.82 (br. *s*, NH); 8.12 (*s*, H–C=N); 7.72–6.89 (*m*, 9 arom. H); 5.08 (*s*, CH_2N); 3.84 (*s*, MeO); 3.61 (*s*, CH_2S); 2.24, 2.05 (2*s*, 2 imidazole Me). ^{13}C-NMR ($CDCl_3$): 166.0 (C=O); 161.4 (C=N); 147.8 (arom. C–O); 139.3 (C(2')); 135.9, 125.5 (C(4'), C(5')); 134.1(1 arom. C); 129.3, 129.0, 128.0, 126.6, 126.3, 114.1 (10 arom. C); 55.4 (MeO); 48.1 (CH_2N); 36.3 (CH_2S); 12.7, 9.2 (2 imidazole Me). HR-EI-MS: 409.1701 ([*M*+H]$^+$, $C_{22}H_{24}N_4O_2S$; calc. 409.1694).

2-(1-Benzyl-4,5-dimethylimidazol-2-yl)sulfanyl-N-*[(4-dimethylaminophenyl) methylenamino]acetamide* (**9b**). Yield: 0.337 (80%). Colorless crystals. M.p. 75–79° (MeOH). IR (KBr): 3203*m* (br.), 3023*m* (br.), 2917*s* (br.), 1679v*s* (C=O), 1608v*s*, 1525*m*, 1360*m*, 1180*m*. ^{1}H-NMR ($CDCl_3$): 12.52 (br. *s*, NH); 8.05 (*s*, H–C=N); 7.64–6.66 (*m*, 9 arom. H); 5.07 (*s*, CH_2N); 3.60 (*s*, CH_2S); 3.01 (*s*, Me_2N); 2.23, 2.04 (2*s*, 2 imidazole Me). ^{13}C-NMR ($CDCl_3$): 165.6 (C=O); 151.9 (C=N); 148.8 (arom. C–N); 139.3 (C(2')); 135.9 (1 arom. C); 134.2, 121.6 (C(4'), C(5')); 129.2, 129.0, 127.9, 126.32, 126.29, 111.6 (10 arom. C); 48.0 (CH_2N); 40.2 (Me_2N); 36.3 (CH_2S); 12.7, 9.2 (2 imidazole Me). HR-EI-MS: 422.2009 ([*M*+H]$^+$, $C_{23}H_{28}N_5OS$; calc. 422.2010).

2-(1-Benzyl-4,5-dimethylimidazol-2-yl)sulfanyl-N-*(cyclohexylidenamino) acetamide* (**9c**). Yield: 0.322 g (87%). Colorless crystals. M.p. 124–130° (MeOH). IR (KBr): 3207*m* (br., NH), 3061*m* (br.), 1667v*s* (C=O), 1406*m*, 718*m*. ^{1}H-NMR ($CDCl_3$): 11.81 (br. *s*, NH); 7.33–6.99 (*m*, 5 arom. H); 5.04 (*s*, CH_2N); 3.61 (*s*, CH_2S); 2.54–2.42 (*m*, 4 cyclohexyl H); 2.12, 2.03 (2*s*, 2 imidazole Me); 1.75–1.61 (*m*, 6 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 166.7 (C=O); 160.9 (C=N); 140.0 (C(2')); 135.9 (1 arom. C); 134.1, 125.2 (C(4'), C(5')); 129.0, 127.9, 126.2 (5 arom. CH); 48.0 (CH_2N); 36.2 (CH_2S); 35.4, 28.3, 27.0, 26.1, 25.7 (5 cyclohexyl CH_2); 12.6, 9.2 (2 imidazole Me). HR-EI-MS: 371.1879 ([*M*+H]$^+$, $C_{20}H_{27}N_4OS$; calc. 371.1901).

2-(1-Cyclohexyl-4,5-dimethylimidazol-2-yl)sulfanyl-N-*[(4-methylsulfanyl-phenyl)methylenamino]acetamide* (**9d**). Yield: 0.152 g (37%). Colorless crystals. M.p. 76–78° (MeOH). IR (KBr): 3296*m*, (br., NH), 3058*m,* 1667v*s* (C=O), 1596v*s*, 1505*m*, 1363*m*. ^{1}H-NMR ($CDCl_3$): 13.11 (br. *s*, NH); 8.05 (*s*, H–C=N); 7.66–7.21 (*m*, 4 arom. H); 3.99–3.95 (*m*, CHN); 3.70 (*s*, CH_2S); 2.49 (*s*, MeS); 2.19, 2.18 (2*s*, 2 imidazole Me); 2.05–1.72 (*m*, 7 cyclohexyl H); 1.42–1.18 (*m*, 3 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 166.5 (C=O); 147.2 (C=N); 141.6 (C(2')); 138.6, 130.6 (C(4'), C(5')); 134.9

(1 arom. C); 128.0, 125.8, 124.8 (5 arom. C); 57.4 (CHN); 36.2 (CH_2S); 31.7, 26.2, 25.2 (5 cyclohexyl CH_2); 15.2 (MeS); 12.7, 10.5 (2 imidazole Me). HR-EI-MS: 417.1767 ($[M+H]^+$, $C_{21}H_{29}N_4OS_2$; calc. 417.1778).

2-(1-Cyclohexyl-4,5-dimethylimidazol-2-yl)sulfanyl-N-*[(4-methoxyphenyl) methylenamino]acetamide* (**9e**). Yield: 0.288 g (72%). Colorless crystals. M.p. 96–102° (MeOH). IR (KBr): 3203*m* (br., NH), 2917*s* (br.), 1664v*s* (C=O), 1607v*s*, 1512*m*, 1418*m*, 1307*m*, 1250*m*. ^{1}H-NMR ($CDCl_3$): 12.96 (br. *s*, NH); 8.05 (*s*, H–C=N); 7.69–6.86 (*m*, 4 arom. H); 3.99–3.96 (*m*, CHN); 3.83 (*s*, MeO); 3.70 (*s*, CH_2S); 2.19, 2.18 (2*s*, 2 imidazole Me); 2.05–1.74 (*m*, 7 cyclohexyl H); 1.42–1.18 (*m*, 3 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 166.4 (C=O); 147.6 (C=N); 147.6 (1 arom. C–O); 141.6, 126.7 (C(4'), C(5')); 138.6 (C(2')); 129.3, 124.7, 114.1 (5 arom. C); 57.4 (CHN); 55.3 (MeO); 36.2 (CH_2S); 31.7, 26.2, 25.2 (5 cyclohexyl CH_2); 12.6, 10.5 (2 imidazole Me). HR-EI-MS: 401.1986 ($[M+H]^+$, $C_{21}H_{29}N_4O_2S$; calc. 401.2007).

2-(1-Benzyl-4,5-diphenylimidazol-2-yl)sulfanyl-N-*[(4-methylsulfanylphenyl) methylenamino]acetamide* (**9f**). Yield: 0.390 g (71%). Colorless crystals. M.p. 154–156° (MeOH). IR (KBr): 3296*m* (br., NH), 3058*m* (br.), 1683v*s* (C=O), 1596v*s*, 1433*m*, 702*m*. ^{1}H-NMR ($CDCl_3$): 12.90 (br. *s*, NH); 7.87 (*s*, H–C=N); 7.50–6.92 (*m*, 19 arom. H); 5.01 (*s*, CH_2N); 3.83 (*s*, CH_2S); 2.47 (*s*, MeS). ^{13}C-NMR ($CDCl_3$): 165.9 (C=O); 148.1 (C=N); 143.1, 141.7, 131.2, 129.7 (4 arom. C); 137.9, 133.6 (C(4'), C(5')); 135.8 (C(2')); 130.9, 130.4, 129.3, 129.2, 128.9, 128.5, 128.01, 127.98, 127.1, 126.6, 126.5, 125.8 (1 arom. C, 19 arom. CH); 48.3 (CH_2N); 35.6 (CH_2S); 15.2 (MeS). HR-EI-MS: 549.1770 ($[M+H]^+$, $C_{32}H_{29}N_4OS_2$; calc. 549.1778).

2-(1-Benzyl-4,5-diphenylimidazol-2-yl)sulfanyl-N-*(cyclohexylidenamino) acetamide* (**9g**). Yield: 0.329 g (67%). Colorless crystals. M.p. 166–168° (MeOH). IR (KBr): 3321*s* (br., NH), 3026*m*,1679v*s* (C=O), 1602v*s*, 1453*m*, 1433*m*, 701*m*. ^{1}H-NMR

($CDCl_3$): 11.38 (br. *s*, NH); 7.36–6.92 (*m*, 15 arom. H); 4.97 (*s*, CH_2N); 3.93 (*s*, CH_2S); 2.34–1.93 (*m*, 4 cyclohexyl H); 1.62–1.03 (6 cyclohexyl H). ^{13}C-NMR ($CDCl_3$): 166.3 (C=O); 161.4 (C=N); 143.6, 131.2 (C(4'), C(5')); 135.7 (C(2')); 131.0, 130.9, 129.7, 129.0, 128.8, 128.3, 128.2, 127.9, 126.9, 126.7, 126.6 (3 arom. C, 15 arom. CH); 48.3 (CH_2N); 35.3 (CH_2S); 34.6, 27.8, 26.7, 25.4, 25.3 (5 cyclohexyl CH_2). HR-EI-MS: 495.2207 ($[M+H]^+$, $C_{30}H_{31}N_4OS$; calc. 495.2214).

9. *Synthesis of 1-{[(1-Benzyl-5-methyl-3-oxidoimidazolium-4-yl)-4-carbonyl]amino}-3-methylthiourea* (**10**): A mixture of **1b** (247 mg, 1 mmol) and methyl isothiocyanate (80 mg, 1.1 mmol) in EtOH (5 ml) was heated to reflux for 2 h. The formed product **10** was then filtered off, washed with Et_2O, and crystallized from MeOH. Yield: 0.257 g (90%). Colorless crystals. M.p. 224–228° (MeOH). IR (KBr): 3271v*s* (NH), 3097*s* (br.), 1682v*s* (C=O), 1599v*s*, 1557*m*, 740*m*. ^{1}H-NMR ((D_6)DMSO): 12.39, 9.34 (2br. *s*, 2 NH); 8.71 (*s*, H–C(2)); 8.00 (br. *s*, NH); 7.42–7.24 (*m*, 5 arom. H); 5.25 (*s*, CH_2N); 2.85 (*d*, J = 4.3, Me); 2.43 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 182.6 (C=O); 135.8 (C=S); 131.3, 121.3 (C(4'), C(5')); 130.2 (1 arom. C); 129.5, 128.7, 127.7 (5 arom. CH); 126.8 (C(2')); 48.7 (CH_2N); 31.4 (MeN); 9.8 (Me). HR-ESI-MS: 320.1174 ($[M+H]^+$, $C_{14}H_{19}N_5O_2S$; calc. 320.1103).

10. *Synthesis of 1-Benzyl-4-(4,5-dihydro-4-methyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)-5-methyl-1*H*-imidazole 3-Oxide* (**11**). A mixture of **10** (320 mg, 1 mmol) and a 2% aq. soln. of NaOH (5 ml) was heated to reflux for 2 h. Then, the soln. was neutralized with AcOH and the formed precipitate was filtered off and crystallized from MeOH. Yield of **11**: 0.217 g (72%). Colorless crystals. M.p. 244–248° (MeOH). IR (KBr): 3161*s* (NH), 1564*m*, 1457*m*, 1341*m*, 698*m*. ^{1}H-NMR ((D_6)DMSO): 14.02 (br. *s*, NH); 8.58 (*s*, H–C(2)); 7.43–7.29 (*m*, 5 arom. H); 5.23 (*s*, CH_2N); 3.50 (*s*, MeN); 2.14 (*s*, Me). ^{13}C-NMR ((D_6)DMSO): 168.1 (C=S); 142.6 (triazol C(3)); 136.1, 118.0

(imidazole C(4), C(5)); 129.5, 128.63, 127.8 (5 arom. CH); 128.60 (1 arom. C); 126.5 (imidazole C(2)); 49.2 (CH_2N); 31.7 (MeN); 9.4 (Me). HR-ESI-MS: 302.1068 ([*M*+H]$^+$, $C_{14}H_{16}N_5OS$; calc. 302.0997).

11. *Synthesis of 1-Benzyl-5-methyl-4-(5-methylamino-1,3,4-thiadiazol-2-yl)-1*H-*imidazole 3-Oxide* (**12**). A soln. of **10** ((320 mg, 1 mmol) in conc. H_2SO_4 (5 ml) was kept at r.t. for 1 d. After neutralization of the soln. with diluted NH_4OH, the solid product was filtered off, dried, and crystallized from MeOH. Yield of **12**: 0.162 g (54%). Yellowish crystals. M.p. 214–216° (decomp., MeOH). IR (KBr): 3201*m* (br.), 3127*s*, 2963*s* (br.), 1517*m*, 1261*m*, 1096*m*, 1031*m*, 800*m*. ^{1}H-NMR ((D$_6$)DMSO): 8.57 (*s*, H–C(2)); 7.52 (br. *s*, NH); 7.41–7.26 (*m*, 5 arom. H); 5.24 (*s*, CH_2N); 2.89 (*d*, *J* = 4.8, MeN); 2.49 (*s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 169.9, 144.7 (thiadiazol C(2), C(5)); 136.3, 123.0 (imidazole C(4), C(5)); 129.4, 128.5, 127.6 (5 arom. CH); 125.3 (imidazole C(2)); 124.0 (1 arom. C); 48.9 (CH_2N); 31.7 (MeN); 10.1 (Me). HR-ESI-MS: 302.1068 ([*M*+H]$^+$, $C_{14}H_{16}N_5OS$; calc. 302.1076).

12. *X-Ray Crystal Structure Determination of* **1b** (*Table* and *Figure*)[4]). All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer [20] using MoK_α radiation (λ = 0.71073 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. Data reduction was performed with *CrysAlisPro* [20]. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction using spherical harmonics [20] was applied. The space group was determined from packing considerations, a statistical

[4]) CCDC-838434 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre*, *via* www.ccdc.cam.ac.uk/data_request/cif.

analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections were merged. The data collection and refinement parameters are given in the *Table*. A view of the molecule is shown in the *Figure*. The structure was solved by direct methods using *SHELXS97* [21], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The hydrazide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the Me group). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. The weighting scheme was based on counting statistics and included a factor to downweight the intense reflections. A correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from [22a], and the scattering factors for H-atoms were taken from [23]. Anomalous dispersion effects were included in F_c [24]; the values for f' and f'' were those of [22b]. The values of the mass attenuation coefficients are those of [22c]. The *SHELXL97* program [25] was used for all calculations.

Table. *Crystallographic Data for Compound* **1b**

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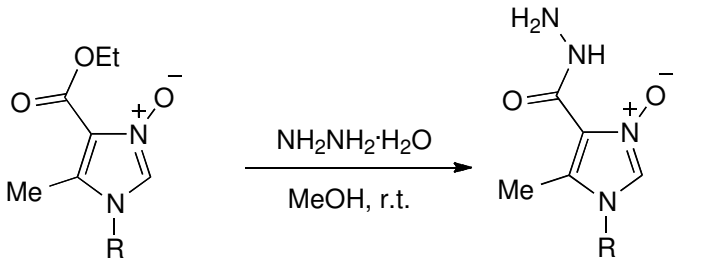
Table. *Crystallographic Data for Compound* **1b**

Crystallized from		MeOH
Empirical formula		$C_{12}H_{14}N_4O_2$
Formula weight [g mol^{-1}]		246.27
Crystal color, habit		pale-yellow, prism
Crystal dimensions [mm]		0.28 × 0.30 × 0.30
Temperature [K]		160(1)
Crystal system		triclinic
Space group		$P\bar{1}$
Z		2
Reflections for cell determination		7053
2θ range for cell determination [°]		5–59
Unit cell parameters	a [Å]	6.8168(2)
	b [Å]	7.6666(2)
	c [Å]	11.7286(4)
	α [°]	97.379(3)
	β [°]	93.255(3)
	γ [°]	101.516(3)
	V [Å^3]	593.49(3)
D_X [g cm^{-3}]		1.378
μ(MoK_α) [mm^{-1}]		0.0977
Scan type		ω
$2\theta_{(max)}$ [°]		58.5
Transmission factors (min; max)		0.855; 1.000
Total reflections measured		10252
Symmetry independent reflections		2815
Reflections with $I > 2\sigma(I)$		2618
Reflections used in refinement		2815
Parameters refined		177
Final $R(F)$ [$I > 2\sigma(I)$ reflections]		0.0412
$wR(F^2)$ (all data)		0.1054
Weights:	$w = [\sigma^2(F_o^2) + (0.0466P)^2 + 0.2729P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$	
Goodness of fit		1.038
Secondary extinction coefficient		0.013(4)
Final Δ_{max}/σ		0.001
$\Delta\rho$ (max; min) [e Å^{-3}]		0.33; -0.41

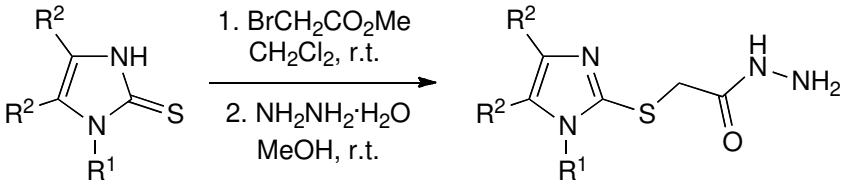
Scheme 1



3a R = Me
b R = Bn
c R = *c*Hex

1a R = Me
b R = Bn
c R = *c*Hex

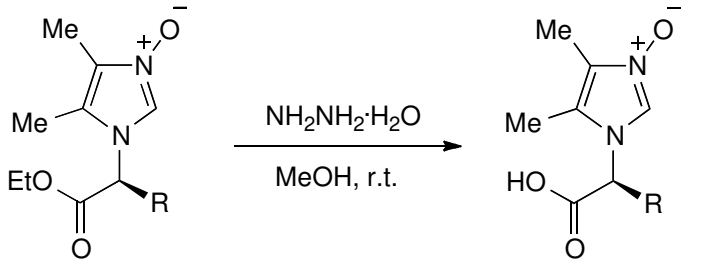
Scheme 2



4a R^1 = Bn, R^2 = Me
b R^1 = *c*Hex, R^2 = Me
c R^1 = Bn, R^2 = Ph

2a R^1 = Bn, R^2 = Me
b R^1 = *c*Hex, R^2 = Me
c R^1 = Bn, R^2 = Ph

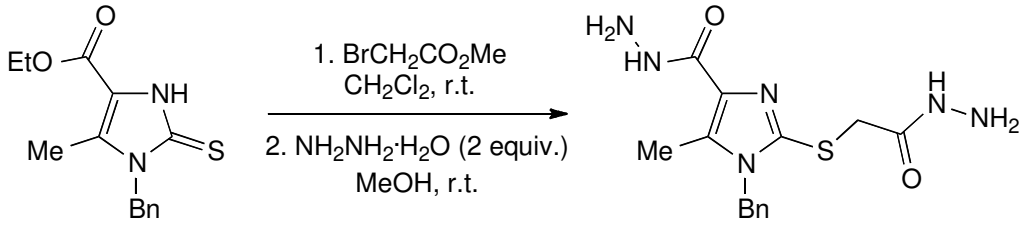
Scheme 3



5a R = Me
b R = Me_2CH

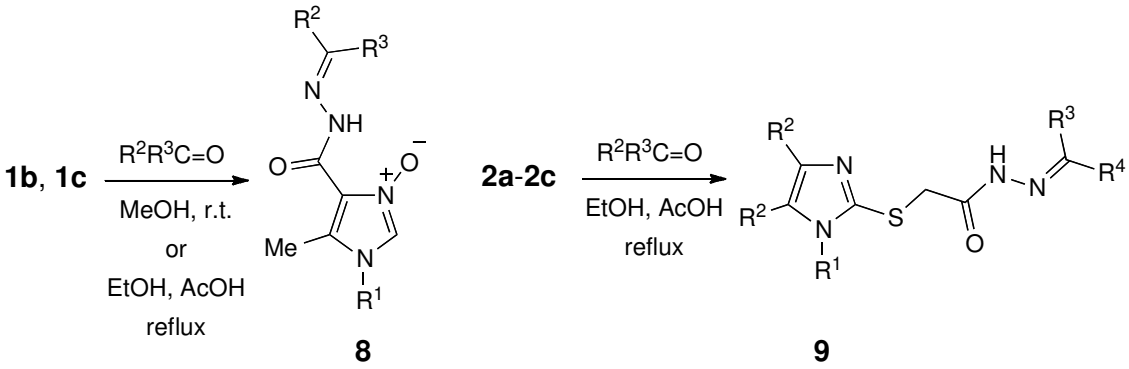
6a R = Me
b R = Me_2CH

Scheme 4



4d **7**

Scheme 5

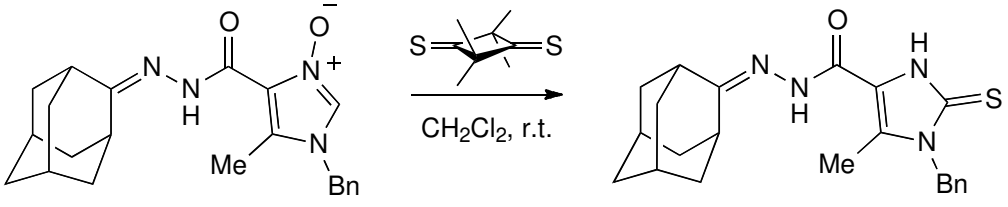


8a R^1 = Bn, R^2 = H, R^3 = Ph
b R^1 = *c*Hex, R^2 = H, R^3 = Ph
c R^1 = Bn, R^2-R^3 = Ad
d R^1 = *c*Hex, R^2-R^3 = Ad
e R^1 = Bn, R^2-R^3 = -$(CH_2)_5$-
f R^1 = *c*Hex, R^2-R^3 = -$(CH_2)_5$-
g R^1 = Bn, R^2 = Me, R^3 = Ph
h R^1 = *c*Hex, R^2 = Me, R^3 = Ph

Ad =

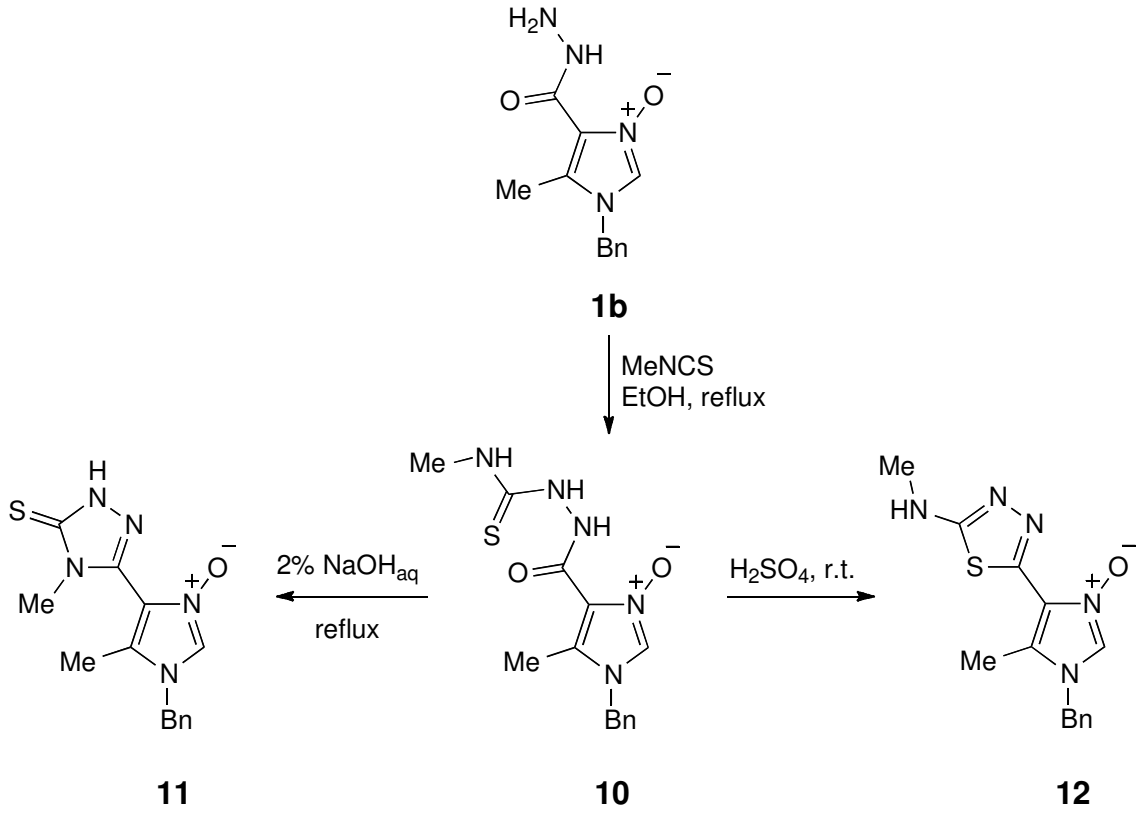
9a R^1 = Bn, R^2 = Me, R^3 = H, R^4 = 4-$MeOC_6H_4$
b R^1 = Bn, R^2 = Me, R^3 = H, R^4 = 4-$Me_2NC_6H_4$
c R^1 = Bn, R^2 = Me, R^3-R^4 = -$(CH_2)_5$-
d R^1 = *c*Hex, R^2 = Me, R^3 = H, R^4 = 4-$MeSC_6H_4$
e R^1 = *c*Hex, R^2 = Me, R^3 = H, R^4 = 4-$MeOC_6H_4$
f R^1 = Bn, R^2 = Ph, R^3 = H, R^4 = 4-$MeSC_6H_4$
g R^1 = Bn, R^2 = Ph, R^3-R^4 = -$(CH_2)_5$-

Scheme 6

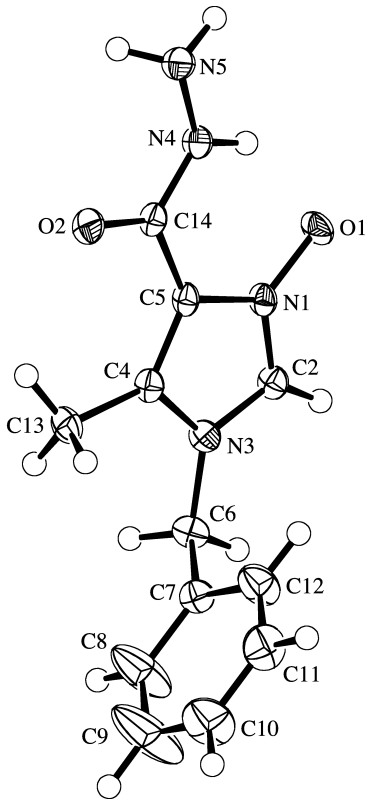


8c **4e**

Scheme 7



Figure



Graphical Abstract