Versatile Novel Syntheses of Imidazoles†

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A novel ring transformation/desulfurization of substituted 2-methyl-1,2,4-thiadiazolium salts **2** provides a versatile entry to imidazoles **3** with a variety of substituents. Simple one-pot procedures combine the preparation of starting 1,2,4-thiadiazolium salts **2** from *N*-(thiocarbonyl)-*N*′-methylamidines **1** or 1,2,4-dithiazolium triiodides **6** with the ring transformation/desulfurization to the imidazoles **3**. Alternatively, *N*-(thiocarbonyl)-*N*′-methylamidines **1** can be transformed to imidazoles **3** or to 1-substituted imidazoles **5** via S-methylation and elimination of methylthiol. In the same manner, a new entry to 4*H*-imidazoles **8** could be developed.

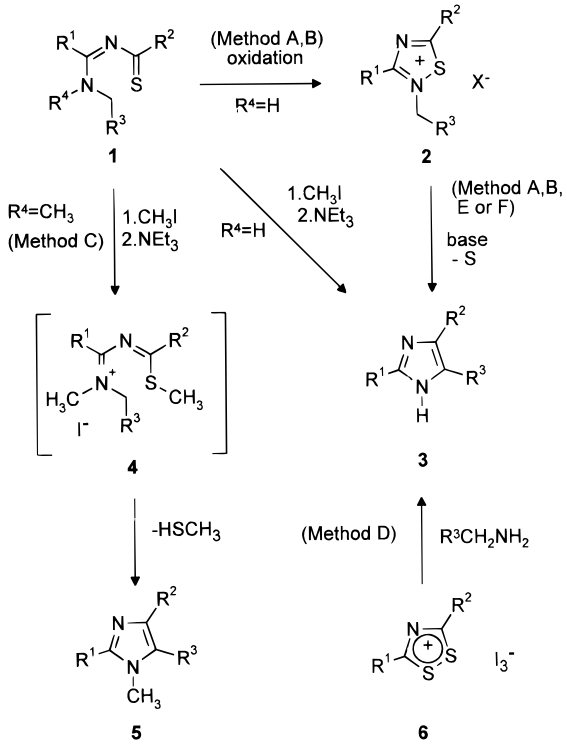
Introduction

Despite the numerous known syntheses of the imidazole ring, it is surprising that special substitution patterns such as in 2-aryl-5-(*N*,*N*-dialkylamino)imidazole-4-carboxylates are as yet difficult to synthesize.[1] Hence, there is still a need to develop general routes to this heterocyclic system. Possibilities of constructing the imidazole skeleton by ring closure of a C−N−C−N−C precursor have rarely been investigated.[1] Thus, base-catalyzed cyclization of *N*-cyano-*N*′-methylamidines with COO-alkyl, CN, or COPh substituents at the methyl group affords 4-aminoimidazoles with electron-withdrawing substituents at position 5,[2−4] while ring closure of 2-azavinamidinium salts in the presence of sodium amide gives 4-(dimethylamino)imidazoles.[5] Condensed imidazoles were obtained by desulfurization of 3-[(acylamino)methyl]tetrahydro-1,3-thiazine-2-thiones in the presence of trifluoroacetanhydride.[6] We now report novel and very versatile routes to imidazoles **3**, **5**, and **8** starting from *N*-(thiocarbonyl)amidines **1** as a C−N−C−N−C building block or from 1,2,4-dithiazolium salts **6**. In two of these syntheses (methods A and B), a new type of ring transformation of intermediate 1,2,4-thiadiazolium salts **2** is involved.

Results and Discussion

The general background of the synthesis of imidazoles **3** was derived from a recently developed efficient access to pyrroles based on the ring transformation/desulfurization of 2-methyl-1,2-thiazolium salts that could be obtained by oxidative ring closure of *β*-aminovinyl thiocarbonyl compounds.[7−9] Extending this concept to the N-analogous 2-methyl-1,2,4-thiadiazolium salts **2** should give rise to the formation of imidazoles **3**. We therefore approached the in-situ oxidative cyclization of substituted *N*-methyl-*N*′-(thiocarbonyl)amidines **1** by applying hydrogen peroxide in methanol (method A) or iodine in the presence of triethylamine (method B). The expected 1,2,4-thiadiazolium salts **2** undergo smooth desulfurization/ring transformation to imidazoles **3**, already in the reaction mixture in most cases (Scheme 1). High yields of **3** were obtained with a wide substitution pattern. It turns out that electron-withdrawing substituents R^3 such as alkoxycarbonyl, cyano, aryl, or hetoaryl are required. In the case of aminocarbonyl or 4-nitrophenyl substituents R^3 the reaction is slower and intermediate 2-methyl-1,2,4-thiadiazolium salt **2h** (R^3 = $CONH_2$) and the 2*H*-1,3,5-thiadiazines **10d** (R^3 = 4-$NO_2C_6H_4$) and **10h** (R^3 = $CONH_2$) (see Scheme 3) can be isolated easily. The transformation of alkoxycarbonyl-substituted compounds **1** (R^3 = COOalkyl) is fast. A corresponding intermediate **2e** (R^3 = COOMe) could only be isolated under strongly acidic conditions (see the Experimental Section). The thiadiazolium salts **2e** and **2h** as well as the 2*H*-1,3,5-thiadiazines **10d** and **10h** could be desulfurized and rearranged to the corresponding imidazoles **3e** (R^3 =

Scheme 1



† Dedicated to Professor Dr. Horst Hartmann on the occasion of his 60th birthday.

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Table 1. Synthesis of Imidazoles 3 and 5

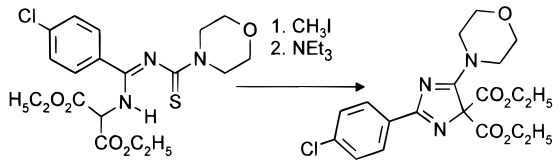
entry	product	R^1	R^2	R^3	substrate	reagent	solvent	yield[a] (%)/ method	mp (°C) (solvent)
1	**3a**	C_6H_5	$N(CH_2)_5$	CO_2CH_3	**1a**	I_2/NEt_3	EtOAc	86/B	176−177 (MeOH)
2	**3b**	4-ClC_6H_4	$N(CH_2CH_2)_2O$	$CO_2C_2H_5$	**1b**	I_2/NEt_3	EtOAc	91/B	212−213 (EtOH/H_2O)
3	**3c**	4-ClC_6H_4	$N(CH_2CH_2)_2O$	CN	**1c**	H_2O_2	MeOH	93/A	251.5 (MeOH)
4	**3d**	4-ClC_6H_4	$N(CH_2CH_2)_2O$	4-$NO_2C_6H_4$	**1d**	I_2/NEt_3	EtOH	94/B	308−310 (EtOH)
5					**10d**	NEt_3	EtOH	92/G	
6	**3e**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	CO_2CH_3	**1e**	H_2O_2	MeOH	96/A	190−191[b] (MeOH)
7					**2e**	NEt_3	MeOH	98/E	
8	**3f**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	$CO_2C(CH_3)_3$	**1f**	H_2O_2	MeOH	94/A	163−164 (EtOAc/hexane)
9	**3g**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	CO_2Bn	**1g**	H_2O_2	MeOH	94/A	192−193 (EtOH)
10	**3h**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	$CONH_2$	**10h**	NEt_3	MeOH	95/G	247−249 (DMF/Et_2O)
11					**2h**	$KHCO_3$	MeOH	82/F	
12	**3i**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	COC_6H_5	**1i**	I_2/NEt_3	EtOAc	65/B	212−214 (EtOH)
13	**3j**	4-$CH_3OC_6H_4$	$N(CH_3)_2$	CO_2CH_3	**1j**	I_2/NEt_3	MeOH	96/B	122−122.5 (Et_2O/hexane)
14	**3k**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2NCH_3$	CO_2CH_3	**1k**	I_2/NEt_3	EtOAc	73/B	153−155 (MeOH)
15	**3l**	3,4-$OCH_2OC_6H_3$	$N(CH_2CH_2)_2O$	CO_2CH_3	**1l**	H_2O_2	MeOH	95/A	232−233 (AcOH/H_2O)
16	**3m**	4-$CF_3C_6H_4$	$N(CH_2CH_2)_2O$	CO_2CH_3	**1m**	H_2O_2	MeOH	93/A	203−204 (EtOAc/hexane)
17	**3n**	4-BrC_6H_4	$N(CH_2CH_2)_2O$	CO_2CH_3	**1n**	I_2/NEt_3	EtOH	94/B	213−214.5 (EtOAc/hexane)
18					**1n**	CH_3I/NEt_3	MeOH	80/C	
19	**3o**	3-$NO_2C_6H_4$	$N(CH_2CH_2)_2O$	CO_2CH_3	**1o**	H_2O_2	MeOH	84/A	221−222 (MeCN)
20	**3p**	CH_3	$N(CH_2CH_2)_2O$	CO_2CH_3	**1p**	H_2O_2	MeOH	88/A	142−143[c] (Et_2O)
21	**3q**	C_6H_5	OC_2H_5	CO_2CH_3	**1q**	I_2/NEt_3	EtOH	94/B	177−179 (CH_2Cl_2/hexane)
22	**3r**	C_6H_5	SC_2H_5	CO_2CH_3	**1r**	I_2/NEt_3	EtOH	93/B	183−184 (EtOAc/hexane)
23	**3s**	C_6H_5	C_6H_5	$CO_2C_2H_5$	**1s**	I_2/NEt_3	EtOAc	90/B	178−180[d,e] (EtOAc/hexane)
24	**3t**	C_6H_5	C_6H_5	CO_2CH_3	**6a**	$H_2NCH_2R^3$	MeCN	73/D	191−193 (EtOAc/hexane)
25	**3u**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CO_2CH_3	**6b**	$H_2NCH_2R^3$	MeCN	80/D	182−183[f] (EtOAc/hexane)
26	**3v**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	CN	**6b**	$H_2NCH_2R^3$	MeCN	58/D	200−201.5 ($CHCl_3$)
27	**3w**	4-ClC_6H_4	4-ClC_6H_4	$CO_2C_2H_5$	**6c**	$H_2NCH_2R^3$	DMF	46/D	208−209 (EtOAc/hexane)
28	**5a**	4-ClC_6H_4	$N(CH_2CH_2)_2O$	CO_2CH_3	**1x**	CH_3I/NEt_3	MeOH	84/C	142−143 (MeOH)
29	**5b**	4-$CH_3OC_6H_4$	$N(CH_2CH_2)_2O$	CO_2CH_3	**1y**	CH_3I/NEt_3	MeOH	87/C	106−107 (CH_2Cl_2/hexane)

[a] Yield of purified material. Crystal change at [b]180−182 °C, [c]122 °C, [d]167−169 °C, [e](lit.[18] 166−167 °C, lit.[19] 173−175 °C), [f]147−148 °C.

COOMe), **3d** (R^3 = 4-$NO_2C_6H_4$), and **3h** (R^3 = $CONH_2$), respectively, by treatment with bases (methods E, F, and G). The transformation of the 1,2,4-thiadiazolium salt **2h** to the imidazole **3h** could also be effected in a stepwise manner (method G) via the corresponding 2H-1,3,5-thiadiazine (**10h**) (see the Experimental Section) as an isolated intermediate. For 2*H*-1,3,5-thiadiazines **10**, alternative 4*H*- or 5*H*-isomers were considered, but ^{13}C NMR shift of the sp^3 ring carbon atom fits best to the structure **10** if the NMR simulation program (ACD-CNMR 1.1. and ACD-HNMR 1.0.) is applied to both possible isomers.

Naturally N,N-disubstituted *N*′-(thiocarbonyl)amidines **1** (R^4 = methyl) can not be oxidized to 1,2,4-thiadiazolium salts **2**. In order to gain access to 1-substituted imidazoles **5**, these amidines **1** were S-methylated with methyl iodide in the presence of triethylamine (method C). Intermediate *N*-imidoylisothioimidates **4** would be expected, but loss of methylthiol afforded imidazoles **5** already in the reaction mixture. The application of method C to N-monosubstituted (thiocarbonyl)amidines **1** (R^4 = H) gives rise to the same imidazoles **3** similarly to the oxidative routes (methods A and B) but in somewhat lower yields. Unlike **1**, the bis(ethoxycarbonyl)methyl-substituted (thiocarbonyl)amidine **7** lacks a CH_2 group at the N-atom and thus affords the 4*H*-imidazole-4,4-dicarboxylate **8** (Scheme 2) when subjected to the S-alkylation procedure (method C). This example represents an interesting new synthesis of 4*H*-imidazoles.[10] The structure of **8** was proved by X-ray crystal analysis.[29] Sometimes while handling the 4*H*-imidazole-4,4-dicarboxylate **8** (e.g., upon longer heating during recrystallization), partial transformation to the corresponding aromatic 1*H*-imidazole **3b** was observed.

Scheme 2



7 **8**

Finally, an extremely short synthesis of imidazoles **3** (R^1 = R^2 = aryl) was discovered by reaction of 3,5-diaryl-1,2,4-dithiazolium triiodides **6** with glycinates or aminoacetonitrile (see Table 1, entries 24−27) (method D). This ring transformation of 1,2,4-dithiazolium salts to imidazoles **3** comprises nucleophilic ring opening[11] to give (thiocarbonyl)amidines **1** (R^4 = H), oxidation of the (thiocarbonyl)amidines to 1,2,4-thiadiazolium salts **2** (X^- = I) by the triiodide anion, and conversion of the salts **2** to the imidazoles **3**. If the corresponding 1,2,4-dithiazolium perchlorates **16** rather than the triiodides **6** were reacted with $R^3CH_2NH_2$ no imidazoles **3** were obtained but instead *N*-(thioacyl)amidines **1** (see Scheme 4) due to the lack of an oxidizing counterion.

Taking into consideration both the known mechanism of the conversion of *β*-aminovinyl thiocarbonyl compounds to pyrroles and the observation of intermediates **2** and **10** in the newly developed synthesis of imidazoles **3**, the following reaction mechanism is proposed for the oxidative transformation of (thiocarbonyl)amidines **1** to imidazoles **3** (see Scheme 3). Oxidation of (thiocarbonyl)-amidines **1** causes ring closure to 1,2,4-thiadiazolium salts **2** as previously shown for other (thiocarbonyl)-amidines.[12−14] Deprotonation of the NCH_2 position of **2**

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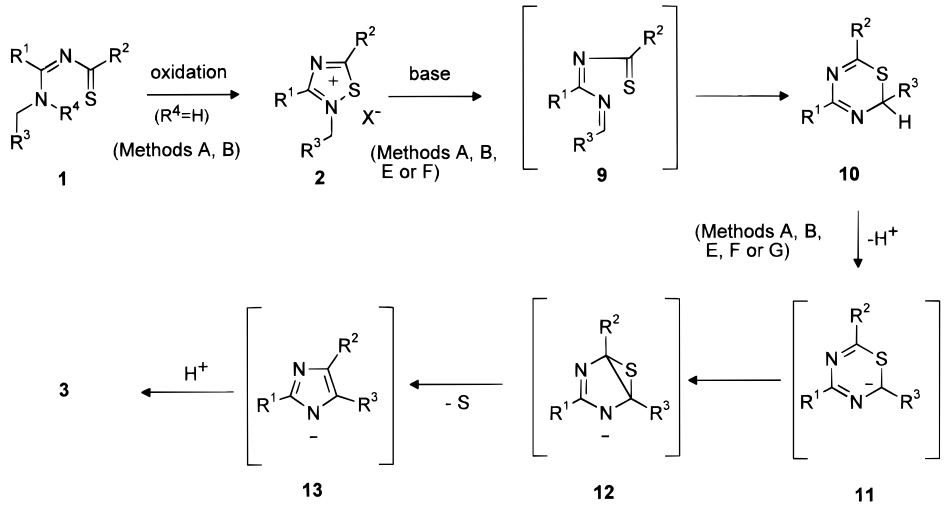
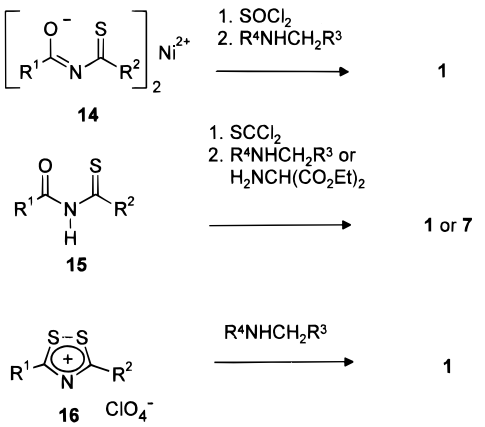
Scheme 3



Scheme 4



initiates ring opening to *N*-(thiocarbonyl)-*N′*-alkylideneamidines **9**. The latter undergo electrocyclic ring closure to 2*H*-1,3,5-thiadiazines **10**. Further deprotonation causes desulfurization under ring contraction via anionic species **11** and **12**. Final protonation of the resulting imidazole anions affords the products **3**. Ring contraction by base-catalyzed desulfurization of 1,3,5-thiadiazines was reported in the 4*H*-2,4,6-triaryl series.[15]

Regardless of this multistep character, the one-pot synthesis of imidazoles **3** from (thiocarbonyl)amidines **1** is a very efficient and novel route to this heterocyclic ring system. It allows a wide scope of substituents especially with disubstituted amino, alkoxy, or alkylthio groups for R^2 at position 4. Until now, such substituent patterns were rarely obtained by ring-closure synthesis[5,16] but by substituent modification (e.g., pharmaceutically active 4-(dialkylamino)imidazole-5-carboxylates were obtained by reductive alkylation of N-unsubstituted 4-aminoimidazole-5-carboxylates[17]). The syntheses of imidazoles **3**, **5**, and **8** from **1** and **7** demonstrate a considerable extension of this type of ring synthesis starting from a C−N−C−N−C precursor.

The starting materials **1** and **7** were obtained by adopting known procedures, e.g., reaction of amines with either 3,5-diaryl-1,2,4-dithiazolium salts **16**,[11] *N*-(thiocarbonyl)imidoyl chlorides obtained by O−Cl exchange from corresponding Ni^{2+} chelates **14** with thionyl chloride,[20,21] or *N*-acylthioureas **16** with thiophosgene[22] (see Scheme 4).

Experimental Section

General Methods. All solvents were purchased from commercial sources and used as received unless otherwise stated. The reactions and the purities of compounds were monitored by TLC performed on precoated silica gel plates with a fluorescent indicator (Merck 60 F_{254}). Merck Kieselgel 60 (0.040−0.063) was used for column chromatography. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 spectrometer with the solvent peak as the reference. Elemental analyses were performed with a Leco CHNS-932 apparatus.

3,5-Diaryl-1,2,4-dithiazolium triiodides **6**,[11,23] 3,5-diaryl-1,2,4-dithiazolium perchlorate **16** ($R_1 = R_2 = C_6H_5$),[11] benzoylthiocarbamic acid *O*-ethyl ester **15** ($R^1 = C_6H_5$, $R^2 = OC_2H_5$)[24] and benzoyldithiocarbamic acid ethyl ester **15** ($R^1 = C_6H_5$, $R^2 = SC_2H_5$)[25] and Ni^{2+} chelate **14** ($R^1 = C_6H_5$, $R^2 = N(CH_2)_5$)[20] were prepared according to literature procedures.

Preparation of Starting Materials and Precursors. General Procedure for the Preparation of *N′,N′*-Disubstituted *N*-Acylthioureas 15 (Adopted from Ref 11). A stirred solution of acyl chloride (R^1COCl) (0.1 mol) and KSCN (11.7 g, 0.12 mol) in dry MeCN (150 mL) was refluxed (for time see below). After the mixture was cooled to rt, a solution of the corresponding amine (0.12 mol) in MeCN (40 mL) was added dropwise (temperature maintained below 50 °C). The mixture was stirred for 30 min and poured into an ice/water mixture (500 mL), again with stirring. The precipitate was collected and recrystallized from EtOH/H_2O. The yields given were not optimized.

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1-[*N*-Benzoyl(thiocarbamoyl)]piperidine [$R^1 = C_6H_5$, $R^2 = N(CH_2)_5$]: 2 h reflux, yield 80%, colorless solid; mp 126−128 °C (lit.[26] mp 122−123 °C).

4-[*N*-(4-Chlorobenzoyl)(thiocarbamoyl)]morpholine [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 40 min reflux, yield 65%, colorless solid; mp 152−153 °C (lit.[26] mp 153−154 °C).

4-[*N*-(4-Methoxybenzoyl)(thiocarbamoyl)]morpholine [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 2 h reflux, yield 74%, colorless solid; mp 136−137 °C (lit.[27] mp 134 °C).

***N*-(4-Methoxybenzoyl)-*N*′,*N*′-dimethylthiourea [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_3)_2$]:** 2 h reflux, yield 51%, colorless solid; mp 127−128 °C (lit.[26] mp 121−122 °C).

1-[*N*-(4-Methoxybenzoyl)(thiocarbamoyl)]-4-methylpiperazine [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_{2CH_2})_2NCH_3$]: 2 h reflux, yield 72%, colorless solid; mp 171−173 °C. Anal. Calcd for $C_{14}H_{19}N_3O_2S$: C, 57.31; H, 6.53; N, 14.33; S, 10.93. Found: C, 57.29; H, 6.76; N, 14.36; S, 10.90.

4-[*N*-[3,4-(Methylenedioxy)benzoyl](thiocarbamoyl)]morpholine [$R^1 = 3,4\text{-}OCH_2OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 1 h reflux, yield 77%, colorless solid; mp 173−174 °C. Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 53.20; H, 4.48; N, 9.69; S, 10.88.

4-[*N*-[4-(Trifluoromethyl)benzoyl](thiocarbamoyl)]morpholine [$R^1 = 4\text{-}CF_3C_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 2 h reflux, yield 63%, colorless solid; mp 167−169 °C. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2S$: C, 49.05; H, 4.12; N, 8.80; S, 10.07. Found: C, 49.04; H, 4.46; N, 8.47; S, 9.83.

4-[*N*-(4-Bromobenzoyl)(thiocarbamoyl)]morpholine [$R^1 = 4\text{-}BrC_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 2 h reflux, yield 52%, colorless solid; mp 159−160 °C. Anal. Calcd for $C_{12}H_{13}BrN_2O_2S$: C, 43.78; H, 3.98; N, 8.51. Found: C, 43.67; H, 3.83; N, 8.69.

4-[*N*-(3-Nitrobenzoyl)(thiocarbamoyl)]morpholine [$R^1 = 3\text{-}NO_2C_6H_4$, $R^2 = N(CH_2CH_2)_2O$]: 40 min reflux, yield 36%, colorless solid; mp 154−155 °C. Anal. Calcd for $C_{12}H_{13}N_3O_4S$: C, 48.80; H, 4.44; N, 14.23; S, 10.86. Found: C, 48.80; H, 4.12; N, 14.21; S, 10.89.

4-[*N*-Acetyl(thiocarbamoyl)]morpholine [$R^1 = CH_3$, $R^2 = N(CH_2CH_2)_2O$]. N-Acetyldithiocarbamic acid ethyl ester [28] (16.3 g, 0.1 mol) was heated with morpholine (8.7 g, 0.1 mol) in EtOH (120 mL) for 0.5 h, followed by evaporation of the solvent. Acetone was added and the product precipitated with hexane: colorless solid, yield 42%; mp 132−133 °C. Anal. Calcd for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88. Found: C, 44.83; H, 6.41; N, 14.75.

Ni^{2+}-Chelates 14 were prepared according to the literature procedure.[20]

$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$: light brown solid, yield 91%; mp 299 °C dec. Anal. Calcd for $C_{24}H_{24}Cl_2N_4O_4S_2Ni$: C, 46.03; H, 3.86; N, 8.95. Found: C, 45.90; H, 3.81; N, 8.94.

General Procedure for the Preparation of [Amino(thiocarbonyl)]amidines 1 ($R^4 = H$) Starting from Nickel Chelates 14 (Adopted from Ref 21). Ni^{2+} chelate **14** (10 mmol) was suspended in dry CCl_4 (60 mL). A solution of $SOCl_2$ (3.14 g, 20 mmol) in CCl_4 (10 mL) was added under stirring over a period of 30 min. The mixture was gently warmed (about 50 °C) for 30 min. After the mixutre was cooled to rt, the precipitated $NiCl_2$ was removed by suction filtration and washed with CCl_4 (50 mL). The combined filtrates were evaporated to give the corresponding crude yellow imidoyl chloride, which was used without further purification [$R^1 = C_6H_5$, $R^2 = N(CH_2)_5$: yield 67%; $R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$: yield 68%]. The crude product (15 mmol) was suspended in dry THF (80 mL) and combined with $H_2NCH_2R^3 \cdot HCl$ (15 mmol). A solution of Et_3N (3.1 g, 30 mmol) in THF (20 mmol) was added dropwise with stirring. The mixture was refluxed and magnetically stirred for 2 h. After the mixture was cooled to rt, $Et_3NH^+Cl^-$ was filtered off and washed with THF (50 mL). The combined solutions were evaporated to dryness and crystallized from EtOH/water (50 mL, 9:1).

***N*-[(Methoxycarbonyl)methyl]-*N*′-[piperidin-1-yl(thiocarbonyl)]benzamidine (1a) [$R^1 = C_6H_5$, $R^2 = N(CH_2)_5$, $R^3 = CO_2CH_3$, $R^4 = H$]:** colorless solid, yield 66%; mp 111−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 2 H), 1.56 (m, 4 H), 3.64 (m, 2 H), 3.70 (s, 3 H), 4.02 (m, 2 H), 4.11 (d, $J = 4.8$ Hz, 2 H), 5.8 (br, 1 H), 7.30−7.45 (m, 5 H); ^{13}C NMR δ 24.3, 25.5, 25.9, 43.9, 48.5, 50.2, 52.3, 127.5, 128.6, 130.7, 133.6, 157 (br), 170.4, 188 (br). Anal. Calcd for $C_{16}H_{21}N_3O_2S$: C, 60.16; H, 6.63; N, 13.16; S, 10.04. Found: C, 60.18; H, 6.68; N, 13.20; S, 10.08.

4-Chloro-*N*-[(ethoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]benzamidine (1b) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CO_2C_2H_5$, $R^4 = H$]: colorless solid, yield 50%; mp 140−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $J = 7.1$ Hz, 3 H), 3.56 (m, 2 H), 3.64 (m, 2 H), 3.74 (br, 2 H), 4.07 (br, 2 H), 4.08 (d, $J = 4.7$ Hz, 2 H), 4.15 (q, $J = 7.1$ Hz, 2 H), 5.8 (br, 1 H), 7.32 (s, 4 H); ^{13}C NMR δ 14.2, 44 (br), 47.8, 49.0, 61.8, 66.3, 66.6, 129.0, 137.1, 131.8 (br), 157 (br), 169.6, 188 (br). Anal. Calcd for $C_{16}H_{20}ClN_3O_3S$: C, 51.96; H, 5.45; N, 11.36; S, 8.67. Found: C, 51.73; H, 5.65; N, 11.06; S, 8.60.

General Procedure for the Preparation of [Amino(thiocarbonyl)]amidines 1 and 7 Starting from Acylthioureas 15 (Adopted from Ref 22). A solution of $SCCl_2$ (4.85 g, 42 mmol) in dry acetone (15 mL) was added to a stirred solution of *N*′,*N*′-disubstituted *N*-acylthiourea **15** (40 mmol) in dry acetone (150 mL). After 15 min of stirring the solvent was evaporated. The remaining yellow crude product was dissolved in dry MeCN (140 mL) and combined with $H_2NCHR^3R^4$ HCl (40 mmol). A solution of Et_3N (8.1 g, 80 mmol) in MeCN (20 mL) was added dropwise with stirring. After 10 min, EtOH (20 mL) was added and the solvent of the reaction mixture removed by rotary evaporation. The residue was recrystallized by dissolution in hot EtOH (80 mL) and then by the dropwise addition of water (10 mL) to the hot solution. After cooling, the product was collected and recrystallized. If no crystals were formed the solution was poured into water (250 mL) and extracted three times with EtOAc (about 100 mL). The organic layer was washed with water, dried with Na_2SO_4, and then concentrated and purified by chromatography (short column, silica gel) using EtOAc/hexane. In most cases, it was possible to observe traces (but up to 23% for **1i**) of the corresponding imidazole **3** in the reaction mixture. All substances are colorless solids if not otherwise stated. In some cases, not all ^{13}C NMR signals appeared or were broad.

4-Chloro-*N*-(cyanomethyl)-*N*′-[morpholino(thiocarbonyl)]benzamidine (1c) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CN$, $R^4 = H$]: yield 47%; mp 172−174 °C; ^{1}H NMR (DMSO-d_6) δ 3.62 (m, 4 H), 3.89 (m, 2 H), 3.99 (m, 2 H), 4.29 (s, 2 H), 7.34 (d, $J = 8.5$ Hz, 2 H), 7.51 (d, $J = 8.5$ Hz, 2 H), 8.57 (s, 1 H); ^{13}C NMR δ 29.8, 47.6, 48.7, 65.7, 65.9, 117.7, 128.5, 129.9, 131.4, 135.4, 156.9, 188.9. Anal. Calcd for $C_{14}H_{15}ClN_4OS$: C, 52.09; H, 4.68; N, 17.36; S, 9.93; Cl, 10.98. Found: C, 52.00; H, 4.67; N, 17.17; S, 9.93; Cl; 11.19.

4-Chloro-*N*-[morpholino(thiocarbonyl)]-*N*′-(4-nitrobenzyl)benzamidine (1d) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = 4\text{-}NO_2C_6H_4$, $R^4 = H$]: yield 53%; mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (m, 2 H), 3.70 (m, 2 H), 3.81 (br, 2H), 4.14 (m, 2 H), 4.63 (d, $J = 5.9$ Hz, 2 H), 7.31−7.38 (m, 4 H), 7.47 (d, $J = 8.7$ Hz, 2 H), 8.18 (d, $J = 8.7$ Hz, 2 H). Anal. Calcd for $C_{19}H_{19}ClN_4O_3S$: C, 54.48; H, 4.57; N, 13.38; S, 7.65. Found: C, 54.36; H, 4.61; N, 13.41; S, 7.63.

4-Methoxy-*N*-[(methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]benzamidine (1e) [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CO_2CH_3$, $R^4 = H$]: yield 56%; mp 153−155 °C; ^{1}H NMR ($CDCl_3$) δ 3.54 (m, 2 H), 3.64 (m, 2 H), 3.71 (br, 2H), 3.71 (s, 3 H), 3.77 (s, 3 H), 4.10 (m, 4 H), 5.9 (br, 1 H), 6.83−6.87 (m, 2 H), 7.36−7.39 (m, 2 H); ^{13}C NMR δ 44 (br), 47.7, 49.0, 52.4, 55.3, 66.2, 66.6, 114.1, 125.5, 129.3, 158 (br), 161.7, 170.4, 189 (br). Anal. Calcd for $C_{16}H_{21}N_3O_4S$: C, 54.68; H, 6.02; N, 11.96; S, 9.12. Found: C, 54.67; H, 6.28; N, 11.92; S, 9.00.

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***N*-[(*tert*-Butoxycarbonyl)methyl]-4-methoxy-*N*′-[morpholino(thiocarbonyl)]benzamidine (1f) [R^1 = 4-CH_3-OC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = $CO_2C(CH_3)_3$, R^4 = H]:** yield 64% (column chromatography); mp 152 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 3.54 (m, 2 H), 3.63 (m, 2 H), 3.66 (br, 2 H), 3.76 (s, 3 H), 3.99 (d, J = 5.2 Hz, 2 H), 4.11 (m, 2 H), 5.8 (br, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 2 H); ^{13}C NMR δ 28.0, 44.8 (br), 47.6, 48.9, 55.3, 66.3, 66.6, 82.4, 114.0, 125.8, 129.3, 157.5 (br), 161.6, 168.9, 189.5 (br). Anal. Calcd for $C_{19}H_{27}N_3O_4S$: C, 57.99; H, 6.92; N, 10.68; S, 8.15. Found: C, 58.01; H, 6.86; N, 10.70; S, 8.08.

***N*-[(Benzyloxycarbonyl)methyl]-4-methoxy-*N*′-[morpholino(thiocarbonyl)]benzamidine (1g) [R^1 = 4-CH_3-OC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2Bn, R^4 = H]:** yield 71% (column chromatography); mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 2.61(m, 2 H), 3.63 (m, 4 H), 3.76 (s, 3 H), 4.10 (m, 2H), 4.15 (d, J = 5.3 Hz, 2 H), 5.14 (s, 2 H), 5.9 (br, 1 H), 6.85 (d, J = 8.7 Hz, 2 H), 7.32 (s, 5 H), 7.37 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 44.3 (br), 47.6, 48.9, 55.3, 66.2, 66.6, 67.2, 114.1, 125.5, 128.3, 128.6, 128.7, 129.3, 135.2, 158 (br), 161.6, 169.8, 190 (br). Anal. Calcd for $C_{22}H_{25}N_3O_4S$: C, 61.80; H, 5.90; N, 9.83; S, 7.50. Found: C, 61.60; H, 5.94; N, 9.53; S, 7.25.

***N*-[(Aminocarbonyl)methyl]-4-methoxy-*N*′-[morpholino(thiocarbonyl)]benzamidine (1h) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = $CONH_2$, R^4 = H]:** yield 42%; mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 3.51 (m, 2 H), 3.57 (m, 2 H), 3.71 (m, 2 H), 3.78 (s, 3 H), 3.80 (s, 2 H), 3.98 (m, 2 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.08 (s, 1H), 7.38 (d, J = 8.7 Hz, 2 H), 7.38 (br, 1 H), 7.96 (br, 1H); ^{13}C NMR δ 44.7, 47.2, 48.5, 55.3, 65.8, 66.0, 113.5, 125.7, 129.7, 157.4, 160.9, 170.9, 188.9. Anal. Calcd for $C_{15}H_{20}N_4O_3S$: C, 53.55; H, 5.99; N, 16.66; S, 9.53. Found: C, 53.35; H, 6.23; N, 16.38; S, 9.49.

***N*-(Benzoylmethyl)-4-methoxy-*N*′-[morpholino(thiocarbonyl)]benzamidine (1i) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = COC_6H_5, R^4 = H]:** yield 21%; mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 3.56 (m, 2 H), 3.68 (m, 2 H), 3.76 (m, 2 H), 3.80 (s, 3 H), 4.16 (m, 2 H), 4.89 (d, J = 4.5 Hz, 2 H), 6.5 (br, 1 H), 6.90 (m, 2 H), 7.44−7.64 (m, 5 H), 7.95 (m, 2 H); ^{13}C NMR δ 47.7, 49.1, 55.4, 66.2, 66.6, 114.1, 125.7, 128.0, 129.0, 129.3, 134.3, 134.4, 158 (br), 161.8, 190 (br), 194.1. Anal. Calcd for $C_{21}H_{23}N_3O_3S$: C, 63.45; H, 5.83; N, 10.57. Found: C, 63.55; H, 5.79; N, 10.68.

***N*-[(Dimethylamino)(thiocarbonyl)]-4-methoxy-*N*′-[(methoxycarbonyl)methyl]benzamidine (1j) [R^1 = 4-CH_3-OC_6H_4, R^2 = $N(CH_3)_2$, R^3 = CO_2CH_3, R^4 = H]:** yield 50%; mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3 H), 3.34 (s, 3 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 4.10 (d, J = 4.4 Hz, 2 H), 6.0 (br, 1 H), 6.83 (d, J = 8.7 Hz, 2 H), 7.36 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 40.4, 42.7, 44.5, 52.8, 55.7, 114.4, 126.2, 129.6, 161.9, 170.9. Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19; N, 13.58. Found: C, 54.64; H, 6.19; N, 13.52.

4-Methoxy-*N*-[(methoxycarbonyl)methyl]-*N*′-[(1-methylpiperazin-4-yl)(thiocarbonyl)]benzamidine (1k) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2NCH_3$, R^3 = CO_2CH_3, R^4 = H]: colorless oil, yield 51% (column chromatography); crude product was used without further purification; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.31 (m, 2 H), 2.40 (m, 2 H), 3.72 (s, 3 H), 3.76 (m, 2H), 3.77 (s, 3 H), 4.16 (m, 2 H), 4.12 (d, J = 5.2 Hz, 2 H), 5.9 (br, 1 H), 6.85 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.8 Hz, 2 H); ^{13}C NMR δ 44.0, 45.8, 47.0, 48.6, 52.4, 54.5, 54.6, 55.3, 114.0, 125.6, 129.2, 157 (br), 161.6, 170.5, 189 (br).

3,4-(Methylenedioxy)-*N*-[(methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]benzamidine (1l) [R^1 = 3,4-$OCH_2OC_6H_3$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = H]: yield 46%; mp 191−193 °C; ^{1}H NMR ($CDCl_3$) δ 3.60 (m, 2 H), 3.68 (m, 2 H), 3.73 (s, 3 H), 3.77 (br, 2 H), 4.12 (d, J = 5.4 Hz, 2 H), 4.15 (m, 2 H), 5.8 (br, 1 H), 5.98 (s, 2 H), 6.78 (d, J = 8.0 Hz, 1 H), 6.88 (d, J = 1.7 Hz, 1 H), 6.95 (dd, J = 8.0, 1.7 Hz, 1 H); ^{13}C NMR δ 44.2, 47.8, 49.0, 52.5, 66.3, 66.6, 101.7, 108.1, 108.5, 122.2, 127.2, 147.9, 149.9, 170.2. Anal. Calcd for $C_{16}H_{19}N_3O_5S$: C, 52.59; H, 5.24; N, 11.50; S, 8.77. Found: C, 52.41; H, 5.38; N, 11.14; S, 8.63.

***N*-[(Methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]-4-(trifluoromethyl)benzamidine (1m) [R^1 = 4-$CF_3C_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = H]:** yield 72.5% (column chromatography); mp 132−133 °C; ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 2 H), 3.67 (m, 2 H), 3.73 (s, 3 H), 3.78 (br, 2 H), 4.10 (m, 4 H), 5.9 (br), 7.52 (d, J = 8.2 Hz, 2 H), 7.63 (d, J = 8.2 Hz, 2 H); ^{13}C NMR δ 44 (br), 47.9, 49.0, 52.6, 66.2, 66.6, 124 (q), 125.7 (d, J = 3.5 Hz), 128.1, 132.5 (q), 137, 170.0. Anal. Calcd for $C_{16}H_{18}F_3N_3O_3S$: C, 49.35; H, 4.66; N, 10.79; S, 8.23. Found: C, 49.08; H, 4.91; N, 10.69; S, 7.93.

4-Bromo-*N*-[(methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]benzamidine (1n) [R^1 = 4-BrC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = H]: yield 55%; mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 3.56 (m, 2 H), 3.64 (m, 2 H), 3.70 (s, 3 H), 3.73 (br, 2 H), 4.08 (m, 4H), 5.9 (br, 1 H), 7.26 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H); ^{13}C NMR δ 44.1 (br), 47.9, 49.0, 52.6, 66.3, 66.6, 129.2, 132.0, 170.1. Anal. Calcd for $C_{15}H_{18}N_3O_3S\cdot 1H_2O$: C, 43.06; H, 4.82; N, 10.05; S, 7.66. Found: C, 42.91; H, 4.87; N, 10.11; S, 7.77.

***N*-[(Methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]-3-nitrobenzamidine (1o) [R^1 = 3-$NO_2C_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = H]:** yield 57%; mp 199−201 °C; ^{1}H NMR (DMSO-d_6) δ 3.59 (m, 2 H), 3.65 (m, 2 H), 3.69 (s, 3 H), 3.74 (m, 2 H), 3.95 (m, 2 H), 4.07 (d, J = 5.7 Hz, 2 H), 7.76 (m, 2 H), 8.15 (m, 1 H), 8.33 (m, 1 H), 8.74 (br, 1 H); ^{13}C NMR δ 43.4, 47.4, 48.8, 52.1, 65.7, 66.0, 122.7, 125.1, 125.5, 130.2, 134.5, 147.3, 156,4, 170.2, 188.8. Anal. Calcd for $C_{15}H_{18}N_4O_5S$: C, 49.17; H, 4.95; N, 15.30; S, 8.75. Found: C, 49.03; H, 4.65; N, 15.35; S, 8.70.

***N*-[(Methoxycarbonyl)methyl]-*N*′-[morpholino(thiocarbonyl)]acetamidine (1p) [R^1 = CH_3, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = H]:** yield 40% (column chromatography); mp 118.5−120 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 3.57 (m, 4 H), 3.67 (s, 3 H), 3.70 (m, 2 H), 3.96 (d, J = 5.2 Hz, 2 H), 4.15 (m, 2 H), 5.61 (t, br, 1 H); ^{13}C NMR δ 18.1, 43.0, 47.6, 49.2, 52.3, 66.4, 66.6, 157.0, 170.5, 190.3. Anal. Calcd for $C_{10}H_{17}N_3O_3S$: C, 46.31; H, 6.61; N, 16.21. Found: C, 46.55; H, 6.80; N, 15.91.

***N*-[Ethoxy(thiocarbonyl)]-*N*′-[(methoxycarbonyl)methyl]benzamidine (1q) (R^1 = C_6H_5, R^2 = OC_2H_5, R^3 = CO_2CH_3, R^4 = H):** yield 27% (column chromatography); mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, br, 3 H), 3.76 (s, 3 H), 4.23 (s, br, 2 H), 4.32 (d, J = 6.7 Hz, 2 H), 6.07 (s, br, 1 H), 7.35−7.48 (m, 5 H); ^{13}C NMR δ 13.8, 43.9, 52.7, 67.8, 127.7, 128.8, 131.3, 133.0, 160.2, 169.8, 201.3. Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.69; H, 5.75; N, 10.00; S, 11.44. Found: C, 55.54; H, 5.70; N, 9.92; S, 11.38.

***N*-[(Ethylthio)(thiocarbonyl)]-*N*′-[(methoxycarbonyl)methyl]benzamidine (1r) (R^1 = C_6H_5, R^2 = SC_2H_5, R^3 = CO_2CH_3, R^4 = H):** yield 35% (column chromatography); mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.4 Hz, 3 H), 3.04 (q, J = 7.4 Hz, 2 H), 3.74 (s, 3 H), 4.20 (br, 2 H), 6.18 (br, 1 H), 7.35−7.53 (m, 5 H); ^{13}C NMR δ 13.4, 31.2, 44.0, 52.6, 128.1, 128.8, 131.4, 156.2, 169.7. Anal. Calcd for $C_{13}H_{16}N_2O_2S_2$: C, 52.68; H, 5.44; N, 9.45. Found: C, 52.69; H, 5.35; N, 9.38.

4-Chloro-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-*N*′-[morpholino(thiocarbonyl)]benzamidine (1x) [R^1 = 4-ClC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = CH_3]: yield 55%; mp 150−152 °C; ^{13}C NMR ($CDCl_3$) δ 39.2, 47.8, 49.1, 51.3, 52.2, 66.2, 66.5, 128.7, 129.4, 130.2, 136.0, 156.9, 169.7, 189.6. Anal. Calcd for $C_{16}H_{20}ClN_3O_3S$: C, 51.96; H, 5.45; N, 11.36; S, 8.67; Cl, 9.58. Found: C, 51.88; H, 5.62; N, 11.25; S, 8.46, Cl, 9.73.

4-Methoxy-*N*-[(methoxycarbonyl)methyl]-*N*-methyl-*N*′-[morpholino(thiocarbonyl)]benzamidine (1y) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3, R^4 = CH_3]: yield 48%; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 2.92 (s, 3 H), 3.60 (m, 4 H), 3.48 (br, 2 H), 3.69 (s, 3 H), 3.77 (s, 3 H), 4.02 (m, 2 H), 4.16 (s, br, 2 H), 6.85 (d, J = 8.2 Hz, 2 H), 7.15 (d, J = 8.2 Hz, 2 H); ^{13}C NMR δ 39.4 (br), 47.7, 49.1, 51.5 (br), 52.1, 55.2, 66.3, 66.6, 113.7, 124.1, 129.6, 160.2, 160.7, 169.9, 190.1. Anal. Calcd for $C_{17}H_{23}N_3O_4S$: C, 55.87; H, 6.34; N, 11.50. Found: C, 55.74; H, 6.45; N, 11.53.

***N*-[Bis(ethoxycarbonyl)methyl]-4-chloro-*N*′-[morpholino(thiocarbonyl)]benzamidine (7):** yield 55%; mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 6 H), 3.55 (m, 2 H), 3.65 (m, 4 H), 4.08 (m, 2 H), 4.23 (m, 4 H), 5.18 (d, J = 6.3 Hz, 1 H), 6.18 (br, 1 H), 7.33−7.39 (m, 4 H); ^{13}C NMR δ 14.0, 48.0, 49.1, 58.6, 62.8, 66.2, 66.5, 129.0, 129.1, 131.0, 137.3,

155.5, 166.1, 189.3. Anal. Calcd for $C_{19}H_{24}ClN_3O_5S$: C, 51.64; H, 5.47; N, 9.51; S, 7.26. Found: C, 51.43; H, 5.53; N, 9.51, S, 7.22.

Preparation of *N*-[(Ethoxycarbonyl)methyl]-*N′*-(thiobenzoyl)-4-benzamidine (1s) ($R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = CO_2C_2H_5$, $R^4 = H$) Starting from 1,2,4-Dithiazolium Salt 16. A solution of Et_3N (2.02 g, 20 mmol) in dry MeCN (10 mL) was added dropwise to a stirred solution of **16** (3.55 g, 10 mmol) and ethyl glycinate hydrochloride (1.4 g, 10 mmol) in dry MeCN (70 mL). After the mixture was stirred for 30 min and the precipitated sulfur filtered off, water (200 mL) was added. The mixture was extracted three times with EtOAc. The organic phase was washed with water and dried with Na_2SO_4. Chromatography on silica gel with hexane/EtOAc afforded 1.82 g of the product **1s** and 0.4g of the imidazole **3s**: red oil, yield 56% (column chromatography); ^{13}C NMR δ 14.1, 44.9, 62.0, 127.9, 128.1, 128.7, 128.9, 131.6, 131.7, 133.1, 141 (br), 159 (br), 160.3. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.66; N, 8.57.

Preparation of 2-[(Methoxycarbonyl)methyl]-3-(4-methoxyphenyl)-5-morpholino-1,2,4-thiadiazolium Perchlorate (2e) [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CO_2CH_3$, $X = ClO_4^-$]. H_2O_2 (1.7 mL, 30% aqueous solution) was added dropwise with cooling to a solution of the (thiocarbonyl)amidine **1e** (1.76 g, 5 mmol) in AcOH (30 mL). After 5 min, $HClO_4$ (0.8 g, 5.5 mmol, 70% aqueous solution) was added. The product was precipitated by dilution with Et_2O, filtered off by suction filtration, washed with Et_2O, and recrystallized from EtOH: colorless crystals; yield 54%; mp 175−177 °C; ^1H NMR (DMSO-d_6) δ 3.57 (m, 2 H), 3.71 (s, 3 H), 3.79 (m, 4 H), 3.86 (s, 3 H), 3.97 (m, 2 H), 5.25 (s, 2 H), 7.16 (d, J = 8.9 Hz, 2 H), 7.74 (d, J = 8.9 Hz, 2 H); ^{13}C NMR δ 47.8, 51.0, 51.6, 53.2, 55.8, 64.8, 65.2, 115.0, 117.8, 132.0, 163.2, 167.2, 171.1, 176.7. Anal. Calcd for $C_{16}H_{20}ClN_3O_8S$: C, 42.72; H, 4.48; N, 9.34; S, 7.13. Found: C, 42.43; H, 4.61; N, 9.42; S, 7.21.

Preparation of [(2-Aminocarbonyl)methyl]-3-(4-methoxyphenyl)-5-morpholino-1,2,4-thiadiazolium Iodide (2h) [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CONH_2$, $X = I^-$]. A 3.36 g (10 mmol) portion of the (thiocarbonyl)amidine **1h** was dissolved in EtOH (100 mL) with stirring and heating. This was then further combined with a solution of I_2 (2.54 g, 10 mmol) in EtOH (70 mL). After 5 min, Et_3N (1.01 g, 10 mmol) dissolved in EtOH (10 mL) was added dropwise. During cooling to rt the product precipitated. It was filtered by suction, washed first with EtOH and then with Et_2O, and finally dried: colorless solid; yield 3.74 g (81%); mp 176−180 °C dec; ^1H NMR (DMSO-d_6) δ 3.59 (s, br, 2 H), 3.78 (s, 4 H), 3.86 (s, 3 H), 3.95 (s, 2 H), 4.94 (s, 2 H), 7.19 (d, J = 8.9 Hz, 2 H), 7.71 (s, 1 H), 7.74 (d, J = 8.9 Hz, 1 H), 7.91 (s, 1 H); ^{13}C NMR δ 47.6, 51.4, 52.0, 55.9, 64.9, 65.3, 114.8, 118.5, 132.0, 162.9, 166.7, 170.7, 177.35. Anal. Calcd for $C_{15}H_{19}IN_4O_3S$: C, 38.97; H, 4.14; N, 12.12. Found: C, 38.75; H, 4.04; N, 12.41.

Preparation of 4-(4-Chlorophenyl)-2-(4-nitrophenyl)-6-morpholino-2*H*-1,3,5-thiadiazine (10d) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = 4\text{-}NO_2C_6H_4$]. A solution of I_2 (1.27 g, 5 mmol) in EtOH (50 mL) was added to a hot solution of the (thiocarbonyl)amidine **1d** (2.1 g, 5 mmol) in EtOH followed by the addition of Et_3N (0.51 g, 5 mmol) dissolved in EtOH (10 mL). After the oxidation was complete as confirmed by TLC, the same quantity of Et_3N solution was added and the resulting solution heated to reflux for 2 min. After cooling, the precipitate was filtered off, washed with EtOH, and dried: colorless solid; yield 81.5%; mp 179−181 °C dec; ^1H NMR ($CDCl_3$) δ 3.78 (br s, 6 H), 4.09 (br s, 2 H), 6.02 (s, 1 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.75 (d, J = 8.7 Hz, 2 H), 8.16 (d, J = 8.6 Hz, 2 H), 8.24 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 46 (br), 48 (br), 64.5, 66.5, 123.9, 128.2, 128.8, 129.2, 136.1, 136.7, 147.2, 147.8, 162.4, 163.5. Anal. Calcd for $C_{19}H_{17}ClN_4O_3S$: C, 54.74; H, 4.11; N, 13.44; S, 7.69. Found: C, 55.05; H, 4.14; N, 13.30; S, 7.48.

Preparation of 2-(Aminocarbonyl)-4-(4-methoxyphenyl)-6-morpholino-2*H*-1,3,5-thiadiazine (10h) [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CONH_2$]. A 2.31 g (5 mmol) portion of **2h** was dissolved in MeOH (60 mL) with stirring and heating and was combined with a solution of Et_3N (0.51 g, 5 mmol) in MeOH (60 mL). The solid formed during cooling was filtered off by suction, washed first with MeOH and then with Et_2O, and dried: yield 95%; mp 167−170 °C dec; ^1H NMR (DMSO-d_6) δ 3.68 (br s, 6 H), 3.79 (s, 3 H) 3.97 (br, 2 H), 5.49 (s, 1 H), 6.92 (d, J = 8.9 Hz, 2 H), 7.75 (s, 1 H), 7.87 (s, 1 H), 8.17 (d, J = 8.9 Hz, 2 H); ^{13}C NMR δ 45.8 (br), 46.3 (br), 55.3, 64.6, 65.9, 113.2, 129.6, 129.8, 161.3, 161.4, 162.5, 170.8. Anal. Calcd for $C_{15}H_{18}N_4O_3S$: C, 53.87; H, 5.43; N, 16.76; S, 9.59. Found: C, 53.72; H, 5.31; N, 16.83; S, 9.76.

Synthesis of Imidazoles. General Procedure for the Preparation of the Imidazoles 3 by Oxidation of [Amino(thiocarbonyl)]amidines 1. For yields of pure compounds, methods, and solvents see Table 1.

Method A (H_2O_2). [Amino(thiocarbonyl)]amidine **1** (10 mmol) was dissolved in MeOH (60 mL) with heating and stirring. Excess H_2O_2 (about 15 mmol, 30% aqueous solution) was added, and the solution was refluxed for 5 min. After further stirring for 30 min, water (100 mL) was added. Stirring was continued for a further 30 min. The resulting precipitate was collected, washed with water, and dried. To remove the sulfur the product was treated with a short column (silica gel) and was eluted with hexane. If all sulfur was removed, the imidazole **3** was eluted with EtOAc or $CHCl_3$/MeOH mixture.

Method B (I_2). [Amino(thiocarbonyl)]amidine **1** (10 mmol) and Et_3N (2.55 g, 25 mmol) were dissolved in EtOH (60 mL) or EtOAc (60 mL) with heating and stirring. A solution of I_2 (2.54 g, 10 mmol) in EtOH or EtOAc (about 50 mL) was added. If EtOAc was used as solvent $Et_3NH^+I^-$ precipitated; this could be dissolved by addition of 20 mL of EtOH. After 1 h of stirring at rt, the EtOAc solution was washed with water, dried with Na_2SO_4. and purified with silica gel (see Method A). In the case of EtOH as solvent, water (100 mL) was added and the precipitate filtered off by suction, washed with water, dried, and purified by column chromatography (see above). Alternatively, the removal of sulfur was possible by dissolving the product in AcOH. Filtration of the sulfur and addition of water to the AcOH solution afforded the imidazole **3**.

All compounds are colorless solids, if not otherwise stated.

Methyl 2-Phenyl-5-piperidinoimidazole-4-carboxylate (3a) [$R^1 = C_6H_5$, $R^2 = N(CH_2)_5$, $R^3 = CO_2CH_3$]. Method B: ^1H NMR (CF_3CO_2D) δ 1.51 (br, 2 H), 1.71 (br, 4 H), 3.51 (m, 4 H), 3.74 (s, 3 H), 7.19−7.29 (m, 3 H), 7.51 (d, 2 H); ^{13}C NMR δ 23.8, 26.5, 55.9, 57.7, 113.0, 125.3, 129.6, 132.2, 135.9, 146.3, 149.6, 162.6. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.73. Found: C, 67.32; H, 6.43; N, 14.66.

Ethyl 2-(4-Chlorophenyl)-5-morpholinoimidazole-4-carboxylate (3b) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CO_2C_2H_5$]. Method B: ^1H NMR (CF_3CO_2D) δ 1.19 (tr, J = 7.2 Hz, 3 H), 3.45 (m, 4 H), 3.86 (m, 4 H), 4.29 (q, J = 7.2 Hz, 2 H), 7.31 (d, J = 8.6 Hz, 2 H), 7.56 (d, J = 8.6 Hz, 2 H); ^{13}C NMR δ 15.1, 52.1, 67.0, 68.8, 109.7, 121.2, 131.0, 132.9, 144.3, 145.2, 148.4, 162.5. Anal. Calcd for $C_{16}H_{18}ClN_3O_3$: C, 57.23; H, 5.40; N, 12.52. Found: C, 57.04; H, 5.61; N, 12.34.

2-(4-Chlorophenyl)-5-morpholinoimidazole-4-carbonitrile (3c) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CN$]. Method A: ^1H NMR (CF_3CO_2D) δ 4.09 (m, 4 H), 4.43 (m, 4 H), 7.89−7.92 (m, 2 H), 8.06−8.09 (m, 2 H); ^{13}C NMR δ 50.1, 68.2, 86.6, 112.2, 121.0, 130.9, 133.2, 145.0, 146.2, 151.7. Anal. Calcd for $C_{14}H_{13}ClN_4O$: C, 58.23; H, 4.54; N, 19.41; Cl, 12.28. Found: C, 58.20; H, 4.58; N, 19.15; Cl, 12.09.

2-(4-Chlorophenyl)-4-morpholino-5-(4-nitrophenyl)-imidazole (3d) [$R^1 = 4\text{-}ClC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = 4\text{-}NO_2C_6H_4$]. Method B: red solid; ^1H NMR (CF_3CO_2D) δ 3.63 (m, 4 H), 4.38 (m, 4 H), 7.86 (d, J = 8.6 Hz, 2 H), 8.08 (d, J = 8.6 Hz, 2 H), 8.32 (d, J = 8.9 Hz, 2 H), 8.69 (d, J = 8.9 Hz, 2 H); ^{13}C NMR δ 52.5, 69.1, 121.9, 122.0, 127.2, 130.4, 130.5, 133.0, 135.3, 141.3, 143.8, 145.1, 150.4. Anal. Calcd for $C_{19}H_{17}ClN_4O_3$: C, 59.30; H, 4.45; N, 14.56. Found: C, 59.15; H, 4.41; N, 14.43.

Methyl 2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxylate (3e) [$R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = N(CH_2CH_2)_2O$, $R^3 = CO_2CH_3$]. Method A: ^1H NMR (CF_3CO_2D) δ 3.44 (m, 4 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 3.85 (m, 4 H), 6.89 (d J = 8.7 Hz, 2 H), 7.60 (d, J = 8.7 Hz, 2 H); ^{13}C NMR δ 51.5, 55.1, 57.0, 68.3, 108.0, 114.8, 117.5, 131.2, 145.6, 147.9, 162.4, 166.2.

Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.55; H, 6.04; N, 13.24. Found: C, 60.58; H, 5.95; N, 13.20.

***tert*-Butyl 2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxylate (3f) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = $CO_2C(CH_3)_3$].** Method A: ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9 H), 3.48 (m, 4 H), 3.79 (s, 3 H), 3.81 (m, 4 H), 6.90 (d, J = 8.9 Hz, 2 H), 7.73 (d, J = 8.9 Hz, 2 H), 9.48 (br, 1 H); ^{13}C NMR δ 28.6, 49.9, 55.3, 66.9, 81.2, 106.9, 114.2, 121.9, 127.2, 144.6, 155.8, 159.4, 160.8. Anal. Calcd for $C_{19}H_{25}N_3O_4$: C, 63.49; H, 7.01; N, 11.69. Found: C, 63.55; H, 7.08; N, 11.71.

Benzyl 2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxylate (3g) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2Bn]. Method A: ^{1}H NMR (CF_3CO_2D) δ 3.79 (m, 4 H), 4.02 (m, 4 H), 4.19 (s, 3 H), 5.70 (s, 2 H), 7.39 (d, J = 8.9 Hz, 2 H), 7.68 (s, 5 H), 8.11 (d, J = 8.9 Hz, 2 H); ^{13}C NMR δ 52.1, 57.6, 68.6, 72.8, 109.1, 115.3, 118.1, 131.5, 131.8, 132.3, 135.7, 146.4, 148.4, 162.6, 166.8. Anal. Calcd for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found: C, 67.28; H, 5.88; N, 10.74.

4-Benzoyl-2-(4-methoxyphenyl)-5-morpholinoimidazole (3i) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = COC_6H_5]. Method B: yellow crystals; ^{1}H NMR ($CDCl_3$) δ 3.12 (m, 4 H), 3.45 (m, 4 H), 3.80 (s, 3 H), 6.80 80 (d, J = 8.8 Hz, 2 H), 7.45−7.54 (m, 3 H), 7.88−7.91 8m, 2 H), 7.99 (d, J = 8.8 Hz, 2 H), 11.33 (s, 1 H); ^{13}C NMR δ 51.2, 55.3, 66.2, 114.1, 116.6, 121.6, 128.2, 128.5, 128.6, 131.8, 139.2, 148.2, 157.9, 161.1, 183.5. Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.07; H, 5.62; N, 11.49.

Methyl 5-(Dimethylamino)-2-(4-methoxyphenyl)imidazole-4-carboxylate (3j) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_3)_2$, R^3 = CO_2CH_3]. Method B: ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 6 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 6.93 (d, J = 8.9 Hz, 2 H), 7.82 (d, J = 8.9 Hz, 2 H), 9.6 (br, 1 H); ^{13}C NMR δ 41.7, 51.1, 55.3, 104.0, 113.7, 121.9, 127.3, 145.4, 157.6, 160.2, 160.8. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.07; H, 6.22; N, 15.27. Found: C, 60.99; H, 6.14; N, 15.24.

Methyl 2-(4-Methoxyphenyl)-5-(1-methylpiperazin-4-yl)imidazole-4-carboxylate (3k) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2NCH_3$, R^3 = CO_2CH_3]. Method B: ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.53 (m, 4 H), 3.56 (m, 4 H), 3.80 (s, 6 H), 6.88 (d, J = 8.9 Hz, 2 H), 7.76 (d, J = 8.9 Hz, 2 H), 9.68 (br s, 1 H); ^{13}C NMR δ 46.2, 49.2, 51.3, 55.0, 55.4, 104.7, 114.2, 121.8, 127.4, 145.5, 156.9, 160.0, 160.8. Anal. Calcd for $C_{17}H_{22}N_4O_3$: C, 61,80; H, 6.71; N, 16.96. Found: C, 61.85; H, 6.80; N, 16.84.

Methyl 2-[3,4-(Methylenedioxy)phenyl]-5-morpholinoimidazole-4-carboxylate (3l) [R^1 = 3,4-$OCH_2OC_6H_3$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method A: ^{1}H NMR (CF_3CO_2D) δ 3.90 (m, 4 H), 4.27 (s, 3 H), 4.32 (m, 4 H), 6.28 (s, 2 H), 7.19 (d, J = 8.3 Hz, 1 H), 7.51 (d, J = 1.8 Hz, 1 H), 7.65 (dd, J = 8.8, 1.7 Hz, 1 H); ^{13}C NMR δ 52.1, 55.7, 68.8, 105.4, 108.6, 109.1, 112.1, 116.2, 126.1, 146.0, 148.4, 152.0, 155.9, 162.9. Anal. Calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 58.01; H, 5.17; N, 12.67.

Methyl 5-Morpholino-2-[4-(trifluoromethyl)phenyl]-imidazole-4-carboxylate (3m) [R^1 = 4-$CF_3C_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method A: ^{1}H NMR ($CDCl_3$) δ 3.54 (m, 4 H), 3.83 (m, 4 H), 3.85 (s, 3 H), 7.66 (d, J = 8.2 Hz, 2 H), 7.98 (d, J = 8.2 Hz, 2 H), 9.97 (s br, 1 H); ^{13}C NMR δ 49.7, 51.6, 66.8, 106.2, 123.8 (q, J = 272.4 Hz), 125.8 (d, J = 3.6 Hz), 126.0, 131.3 (q, J = 32.8 Hz), 132.1, 143.6, 156.6, 159.9. Anal. Calcd for $C_{16}H_{16}F_3N_3O_3$: C, 54.08; H, 4.54; N, 11.83. Found: C, 54.04; H, 4.86; N, 11.85.

Methyl 2-(4-Bromophenyl)-5-morpholinoimidazole-4-carboxylate (3n) [R^1 = 4-BrC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method B: ^{1}H NMR (DMSO-d_6) δ 3.37 (m, 4 H), 3.71 (m, 4 H), 3.78 (s, 3 H), 7.65 (d, J = 8.6 Hz, 2 H), 8.04 (d, J = 8.6 HZ, 2 H), 12.71 (s, 1 H); ^{13}C NMR δ 49.6, 51.2, 66.2, 105 (br), 122.8, 128.4, 128.7, 131.8, 143 (br), 156 (br), 159.5. Anal. Calcd for $C_{15}H_{16}BrN_3O_3$: C, 49.19; H, 4.40; N, 11.48; Br, 21.82. Found: C, 49.15; H, 4.27; N, 11.50; Br, 21.72.

Methyl 5-Morpholino-2-(3-nitrophenyl)imidazole-4-carboxylate (3o) [R^1 = 3-$NO_2C_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method A: ^{1}H NMR (CF_3CO_2D) δ 4.16 (m, 4 H), 4.49 (s, 3 H), 4.54 (m, 4 H), 8.26 (t, J = 8.2 Hz, 1 H), 8.74 (d, J = 7.9 Hz, 1 H), 8.94 (d, J = 8.4 Hz, 1 H), 9.27 (s, 1 H); ^{13}C NMR δ 52.3, 55.8, 68.6, 110.0, 125.0, 125.1, 130.5, 134.0, 135.8, 142.9, 148.6, 151.1, 162.4. Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.21; H, 4.85; N, 16.86. Found: C, 53.91; H, 4.60; N, 16.91.

Methyl 2-Methyl-5-morpholinoimidazole-4-carboxylate (3p) [R^1 = CH_3, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method A: ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 3.39 (m, 4 H), 3.74 (s, 3 H), 3.77 (m, 4 H), 10.0 (br, 1 H); ^{13}C NMR δ 14.4, 49.8, 51.2, 66.8, 104.4, 145.0, 156.3, 159.8. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.22; H, 6.71; N, 18.66. Found: C, 53.17; H, 6.81; N, 18.80.

Methyl 5-Ethoxy-2-phenylimidazole-4-carboxylate (3q) (R^1 = C_6H_5, R^2 = OC_2H_5, R^3 = CO_2CH_3). Method B: ^{1}H NMR (CF_3CO_2D) δ 1.68 (m, 3 H), 4.24, 4.25 (2s, 3 H), 4.80 (m, 2 H), 7.74−8.06 (m, 5 H); ^{13}C NMR δ 15.9, 55.8, 76.2, 108.5, 119.1, 129.6, 132.5, 137.0, 144.9, 153.1, 163.0. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.29; H, 5.63; N, 11.18.

Methyl 5-(Ethylthio)-2-phenylimidazole-4-carboxylate (3r) (R^1 = C_6H_5, R^2 = SC_2H_5, R^3 = CO_2CH_3). Method B: ^{1}H NMR (CF_3CO_2D) δ 1.54 (t, J = 7.4 Hz, 3 H), 3.35 (q, J = 7.4 Hz, 2 H), 4.29 (s, 3 H), 7.77−8.11 (m, 5 H); ^{13}C NMR δ 15.2, 31.2, 55.8, 122.2, 125.4, 129.5, 132.2, 137.0, 139.1, 150.5, 162.5. Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.47; H, 5.47; N, 10.66; S, 11.91.

Ethyl 2,5-Diphenylimidazole-4-carboxylate (3s) (R^1 = R^2 = C_6H_5, R^3 = $CO_2C_2H_5$). Method B: ^{1}H NMR (CF_3CO_2D) δ 1.58 (t, J = 7.2 Hz, 3 H), 4.78 (q, J = 7.2 Hz, 2 H), 7.83−8.33 (m, 10 H); ^{13}C NMR δ 14.6, 67.3, 122.1, 122.7, 126.6, 129.8, 131.4, 131.9, 132.7, 134.6, 137.3, 142.9, 149.9, 162.9. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.05; H, 5.60; N, 9.56.

General Procedure for the Preparation of the Imidazoles 3 and 5 by Methylation of [Amino(thiocarbonyl)]-amidines 1. For yields of pure products and methods see Table 1.

Method C. A mixture of [amino(thiocarbonyl)]amidine **1** (10 mmol), EtOH (70 mL), and MeI (1.57 g, 11 mmol) was gently warmed (about 50 °C) for 15 min. After the addition of Et_3N (1.12 g, 11 mmol), the solution was refluxed for 30 min. After cooling, the solvent was removed under reduced pressure, and the residue was purified by column chromatography using hexane/EtOAc (6:4). All compounds are colorless solids.

Ethyl 2-(4-Bromophenyl)-5-morpholinoimidazole-4-carboxylate (3n) [R^1 = 4-BrC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. For spectroscopic data see method B above.

Methyl 2-(4-chlorophenyl)-3-methyl-5-morpholinoimidazole-4-carboxylate (5x) [R^1 = 4-ClC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]: ^{1}H NMR (CF_3CO_2D) δ 4.04 (s, 4 H), 4.45 (s, 3 H), 4.52 (s, 3 H), 4.55 (s, 4 H), 7.97−8.11 (m, 4 H); ^{13}C NMR δ 39.0, 52.7, 55.6, 69.0, 112.4, 121.5, 133.0, 133.4, 144.1, 146.6, 149.8, 163.2. Anal. Calcd for $C_{16}H_{18}ClN_3O_3$: C, 57.23; H, 5.40; N, 12.52; Cl, 10.56. Found: C, 57.29; H, 5.74; N, 12.51; Cl, 10.57.

Methyl 3-methyl-2-(4-methoxyphenyl)-5-morpholinoimidazole-4-carboxylate (5y) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]: ^{1}H NMR ($CDCl_3$) δ 3.33 (m, 4 H), 3.75 (s, 3 H), 3.79 (m, 4 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 6.93 (d, J = 8.8 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 2 H); ^{13}C NMR δ 35.5, 51.0, 51.1, 55.4, 67.0, 108.9, 114.0, 122.0, 131.0, 149.3, 158.0, 160.6, 160.8. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.61; H, 6.39; N, 12.68. Found: C, 61.61; H, 6.33; N, 12.57.

General Procedure for the Preparation of the Imidazoles 3 by Reaction of the 1,2,4-Dithiazolium Triiodides 6 with Amines. Method D. Dithiazolium triiodide **6** (30 mmol) and $H_2NCH_2R^3$·HCl (30 mmol) were dissolved in MeCN (150 mL). A solution of Et_3N (6.06 g, 60 mmol) in MeCN (10 mL) was added dropwise with stirring (exothermic reaction). After further stirring for 15 min, the same quantity of Et_3N solution was added again. Stirring was continued for 30 min. Precipitated sulfur was filtered off, and the filtrate was poured into water. After extraction with EtOAc (three times with 100 mL), the combined organic phases were washed with water and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography using hexane/EtOAc.

Methyl 2,5-diphenylimidazole-4-carboxylate (3t) (R^1 = R^2 = C_6H_5, R^3 = CO_2CH_3): ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3 H), 7.33−7.90 (m, 10 H), 10.56 (br, 1 H); ^{13}C NMR (CF_3CO_2D) δ 55.4, 121.0, 122.1, 125.9, 129.2, 130.9, 131.2, 132.0, 134.0, 136.6, 142.4, 149.3, 162.6. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.31; H, 5.06; N, 10.10.

Methyl 2,5-bis(4-methoxyphenyl)imidazole-4-carboxylate (3u) (R^1 = R^2 = 4-$CH_3OC_6H_4$, R^3 = CO_2CH_3): ^{1}H NMR (DMF-d_7) δ 3.81 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 7.03 (d, J = 8.9 Hz, 2 H), 7.09 (d, J = 8.9 Hz, 2 H), 7.99 (d, J = 8.8 Hz, 2 H), 8.23 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (DMF-d_7) δ 51.4, 55.6, 55.7, 113.8, 114.8, 122 (br), 123.3, 125.6, 128.4, 131.3, 145 (br), 148.0, 140.4, 161.3. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.59; H, 5.39; N, 8.48.

2,5-Bis(4-methoxyphenyl)imidazole-4-carbonitrile (3v) (R^1 = R^2 = 4-$CH_3OC_6H_4$, R^3 = CN): ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3 H), 3.84 (s, 3 H), 7.08 (d, J = 8.9 Hz, 2 H), 7.14 (d, J = 8.9 Hz, 2 H), 7.83 (d, J = 8.9 Hz, 2 H), 7.98 (d, J = 8.9 Hz, 2 H); IR (cm^{-1}) 2250. Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.77. Found: C, 70.90; H, 4.96; N, 13.76.

Ethyl 2,5-bis(4-chlorophenyl)imidazole-4-carboxylate (3w) (R^1 = R^2 = 4-ClC_6H_4, R^3 = $CO_2C_2H_5$): ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3 H), 4.34 (q, J = 7.1 Hz, 2 H), 7.32−7.50 (m, 4 H), 7.85−7.96 (m, 4 H); ^{13}C NMR (CF_3CO_2D) δ 14.6, 67.4, 121.0, 122.4, 124.8, 131.1, 131.7, 133.0, 133.2, 141.6, 141.7, 144.7, 148.9, 162.5. Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_2$: C, 59.85; H, 3.91; N, 7.76; Cl, 19.63. Found: C, 59.64; H, 3.92; N, 7.81; S, 19.91.

Preparation of Imidazoles 3 by Basic Treatment of 1,2,4-Thiadiazolium Salts 2. Methyl 2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxylate (3e) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = CO_2CH_3]. Method E. A solution of the thiadiazolium salt **2e** (2.25 g, 5 mmol) and Et_3N (0.5 g, 5 mmol) in MeOH (50 mL) was refluxed for 2 min. After cooling, the solvent was removed under reduced pressure and the residue purified by column chromatography with hexane/EtOAc. This afforded 1.55 g of the colorless product (spectroscopic data see method A above).

2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxamide (3h) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = $CONH_2$]. Method F. A saturated aqueous $KHCO_3$ solution (50 mL) was added to a solution of the 1,2,4-thiadiazolium salt **2h** (4.61 g, 10 mmol) in MeOH (50 mL). The mixture was refluxed for 15 min. After cooling, the product precipitated. This material was filtered off, dried, and purified by column chromatography with $CHCl_3$, affording 2.47 g of colorless crystals: ^{1}H NMR (DMSO-d_6) δ 3.03 (m, 4 H), 3.73 (m, 4 H), 3.78 (s, 3 H), 6.97 (d, J = 8.9 Hz, 2 H), 8.87 (br, 2 H), 7.99 (d, J = 8.6 Hz, 2 H), 12.58 (s, 1 H); ^{13}C NMR δ 51.8, 55.3, 66.4, 114.1, 114.4, 122.5, 127.4, 144.1, 152.4, 159.8, 161.1. Anal. Calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53. Found: C, 59.36; H, 6.26; N, 18.25.

Preparation of Imidazoles 3 by Basic Treatment of the 1,3,5-Thiadiazines 10. For yields see Table 1.

Method G. Et_3N (0.51 g, 5 mmol) was added to a suspension of 1,3,5-thiadiazine **10** (5 mmol) in EtOH (50 mL). After 2 h of reflux, the solvent was removed under reduced pressure and the residue purified by column chromatography.

2-(4-Chlorophenyl)-4-morpholino-5-(4-nitrophenyl)imidazole (3d) [R^1 = 4-ClC_6H_4, R^2 = $N(CH_2CH_2)_2O$, R^3 = 4-$NO_2C_6H_4$]. For spectroscopic data see method B.

2-(4-Methoxyphenyl)-5-morpholinoimidazole-4-carboxamide (3h) [R^1 = 4-$CH_3OC_6H_4$, R^2 = $N(CH_2CH_2)_2O$, R^3 = $CONH_2$]. For spectroscopic data see method F.

Preparation of Diethyl 2-(4-Chlorophenyl)-5-morpholino-4H-imidazole-4,4-dicarboxylate (8) via Methylation of [Amino(thiocarbonyl)]amidine 7. A mixture of [amino(thiocarbonyl)]amidine **7** (2.21 g, 5 mmol), EtOH (70 mL), and MeI (0.78 g, 5.5 mmol) was gently warmed (about 50 °C) for 15 min. Et_3N (0.56 g, 5.5 mmol) was added and the mixture refluxed for 30 min. After cooling, the solvent was reduced to 30 mL. Crystallization in a refrigerator (−20 °C) afforded 1.78 g (87%) of the product: colorless crystals; mp 107.5−108 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6 H), 3.67 (br s, 2 H), 3.77 (br s, 4 H), 3.96 (br s, 2 H), 4.25, 4.26 (2 q, J = 7.1 Hz, 4 H), 7.35 (d, J = 8.6 Hz, 2 H), 8.13 (d, J = 8.6 HZ, 2 H); ^{13}C NMR δ 13.9, 48.0, 49.6, 63.1, 66.4, 66.7, 88.3, 128.4, 130.4, 130.5, 137.5, 164.8, 177.4, 178.3. Anal. Calcd for $C_{19}H_{22}ClN_3O_5$: C, 55.95; H, 5.44; N, 10.31. Found: C, 56.08; H, 5.79; N, 10.32.

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