Synthesis of Novel α-Amino-*N*-substituted Thioacetimidates

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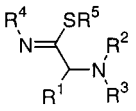
Introduction

Glycineamidines **2** are useful synthetic building blocks for the synthesis of aminoimidazoliums,[1] aryliminopiperazine-2,3-diones,[2] and novocaine derivatives.[3] The analogous α-amino-*N*-substituted thioacetimidates **1** are also potentially useful intermediates; however, few of them have been previously reported.[4] α-Amino-thioacetimidate derivatives were shown to exhibit herbicidal activity.[4b] In general, thioimidates are known to be very useful synthetic precursors in organic chemistry.[4c]



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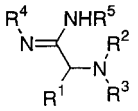

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Imidoyl halides are versatile intermediates[5] and are usually prepared by reaction of phosgene, thionyl chloride, oxalyl chloride, or phosphorus pentachloride with amides.[5] The major disadvantage of imidoyl halides is their inherent instability and, since they are particularly susceptible to hydrolysis, they are rarely isolated and purified prior to use. 1-Imidoylbenzotriazoles provide stable alternatives since they are substantially more stable and easier to isolate than the corresponding imidoyl halides.[6] The benzotriazolyl moiety in imidoylbenzotriazoles can be exchanged for various nucleophiles,[6a,d] and photolysis leads to 1,2-disubstituted benzimidazoles.[6c]

Previous preparations of 1-imidoylbenzotriazoles comprise: (i) treatment of *N*-aryl secondary amides with phosphorus oxychloride in the presence of triethylamine and subsequent trapping of the resultant imidoyl chloride with benzotriazole;[6b] (ii) treatment of amides with 1,1′-sulfinylbenzotriazole[6a,c] (generated in situ from 1-trimethylsilylbenzotriazole and thionyl chloride); (iii) via a benzotriazole-mediated Beckmann type rearrangement of oximes.[7]

1-α-Amino-substituted 1-imidoylbenzotriazoles have not been reported previously. We now disclose an efficient novel synthetic route to such benzotriazoles **5a**−**k** via insertions of isonitriles **3a**−**d** into the benzotriazole nitrogen−carbon bond of *N*-(aminoalkyl)benzotriazoles **4a**−**f** and subsequent nucleophilic displacement of the benzotriazole moiety using thiols to give novel α-amino thioacetimidates **1a**−**g**.

Results and Discussion

N-(Aminoalkyl)benzotriazoles **4a**−**f** were formed by well-established procedures involving condensation of benzotriazole, an aldehyde, and a secondary amine in water (**4a**−**d**),[8] or by reflux under Dean−Stark conditions in benzene (**4e**−**f**)[9] (Scheme 1). Although they frequently crystallized as the pure benzotriazol-1-yl isomer, such *N*-(aminoalkyl)benzotriazoles usually exist in solution as an equilibrating mixture of Bt^1 and Bt^2 isomers. The reactivity of both isomers is identical or very similar, since they both ionize to the same species.[6e]

The isonitriles **3a**−**d** were prepared from the corresponding amides[10] (92−99%) and were usually generated and used in situ.

Reaction of the aromatic **3a**−**c** or aliphatic isonitriles **3d** with *N*-(aminoalkyl)benzotriazoles **4a**−**f** in the presence of catalytic boron trifluoroetherate in THF at 20 °C gave crude 1-imidoylbenzotriazoles **5a**−**k** in excellent yields (Table 1). Only the Bt^1 isomers of imidoylbenzotriazoles **5a**−**i**,**k** were observed even when a mixture of the Bt^1 and Bt^2 isomers of *N*-(aminoalkyl)benzotriazoles **4a**−**f** were used, a result of isomerization of the starting materials. However, **5j** was obtained as a mixture of the Bt^1 and Bt^2 isomers. The reactions were complete within 1 h, and the products were purified by recrystallization where possible (**5a**,**c**,**d**,**f**,**h**,**i**,**j**) (87−97%). Compounds **5b**,**g**,**k** were purified by flash column chromatography (96%, 94%, and 87%, respectively). Attempts to purify imidoylbenzotriazole **5e** (45%) by column chromatography afforded a significant amount of the corresponding amide **6** (32%) as well as a trace of novel amidine **7** (5%) (Scheme 1). In general, 1.05−1.10 equiv of the isonitrile gave the products with approximately 95% purity following extractive workup. All 1-imidoylbenzotriazoles, except **5k**, could be used for the next step without recrystallization or purification by column chromatography.

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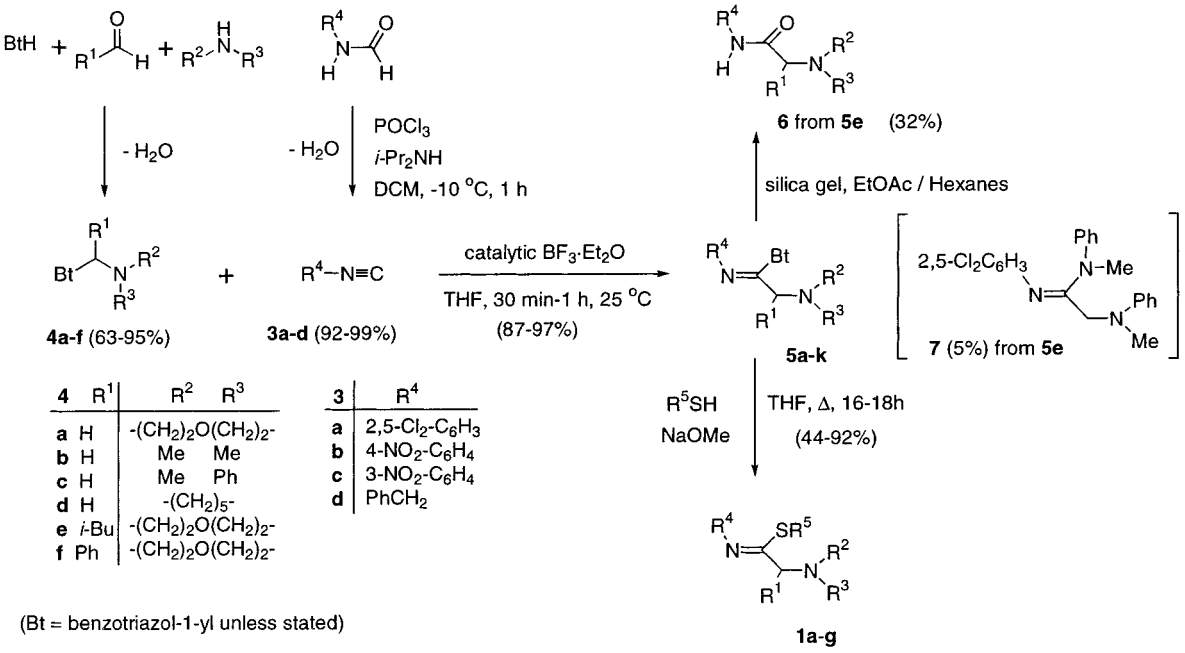
Scheme 1[a]



4	R^1	R^2 R^3
a	H	$-(CH_2)_2O(CH_2)_2-$
b	H	Me Me
c	H	Me Ph
d	H	$-(CH_2)_5-$
e	*i*-Bu	$-(CH_2)_2O(CH_2)_2-$
f	Ph	$-(CH_2)_2O(CH_2)_2-$

3	R^4
a	2,5-Cl_2-C_6H_3
b	4-NO_2-C_6H_4
c	3-NO_2-C_6H_4
d	$PhCH_2$

[a] For yields of **1a**−**g** and **5a**−**k**, see Tables 1 and 2. For compounds **4a**−**b**,**d**−**f** Bt = benzotriazol-1-yl (Bt^1) and benzotriazol-2-yl (Bt^2) in ratios from 1:1 to 4:1. For compound **5j** Bt = Bt^1:Bt^2 in a 1:2.6 ratio.

Table 1. 1-Imidoylbenzotriazoles 5a−k

5	R^1	R^2	R^3	R^4	yield[a] (%)
a	H	$-(CH_2)_2O(CH_2)_2-$		2,5-$Cl_2C_6H_3$	92
b	H	Me	Me	2,5-$Cl_2C_6H_3$	96[b]
c	H	$-(CH_2)_2O(CH_2)_2-$		4-NO_2-C_6H_4	93
d	H	$-(CH_2)_2O(CH_2)_2-$		3-NO_2-C_6H_4	97
e	H	Me	Ph	2,5-$Cl_2C_6H_3$	90 (45)[c]
f	H	Me	Ph	3-NO_2-C_6H_4	91
g	H	$-(CH_2)_2O(CH_2)_2-$		$C_6H_5CH_2$	94[b]
h	H	$-(CH_2)_5-$		4-NO_2-C_6H_4	88
i	^{i}Bu	$-(CH_2)_2O(CH_2)_2-$		3-NO_2-C_6H_4	87
j	Ph	$-(CH_2)_2O(CH_2)_2-$		2,5-$Cl_2C_6H_3$	89
k	H	$-(CH_2)_5-$		2,5-$Cl_2C_6H_3$	87[b]

[a] Isolated by recrystallization unless stated. [b] Purified by flash column chromatography. [c] Isolated by column chromatography, crude yield ca. 90%, isolated yield 45% due to significant hydrolysis to amide **6** (32%).

Attempts were unsuccessful in carrying out the analogous isonitrile insertion reactions to prepare α-thio- or α-alkoxy-*N*-substituted thioacetimidates from α-thioalkyl- and α-alkoxyalkyl-benzotriazoles, respectively.

α-Amino thioacetimidates **1a**−**g** resulted from the nucleophilic displacement in refluxing THF of the benzotriazolyl moiety in **5a**,**c**,**e**,**g**,**i** by an appropriate aliphatic or aromatic thiolate anion, generated in situ from a thiol and sodium methoxide (Scheme 1). Purification by column chromatography on silica gel for compounds **1a**,**b**,**d**−**g**, and recrystallization for **1c**, led to isolated yields of 44−92% (Table 2). Since the starting material **5** and product **1** often have virtually identical retention factors, they could not be separated by column chromatography unless **5** was completely consumed.

The structures of compounds **1a**−**g** and **5a**−**k** were confirmed by ^{1}H and ^{13}C NMR and mass spectroscopy and elemental analyses. Badly defined peaks and poorly resolved ^{1}H and ^{13}C NMR spectra were often obtained at room temperature for the pure α-amino thioacetimidates **1a**−**g** and for 1-imidoylbenzotriazole **5i**; this was due to the slow rotation around the C=N double bond. This was

Table 2. α-Amino *N*-Substituted Thioacetimidates 1a−g

1	R^1	R^2	R^3	R^4	R^5	yield[a] (%)
a	H	$-(CH_2)_2O(CH_2)_2-$		2,5-$Cl_2C_6H_3$	4-MeC_6H_4	44
b	H	$-(CH_2)_2O(CH_2)_2-$		2,5-$Cl_2C_6H_3$	$C_6H_5CH_2$	53
c	H	Me	Ph	2,5-$Cl_2C_6H_3$	Ph	92[b]
d	H	$-(CH_2)_2O(CH_2)_2-$		4-$NO_2C_6H_4$	4-MeC_6H_4	44
e	H	$-(CH_2)_2O(CH_2)_2-$		$C_6H_5CH_2$	4-MeC_6H_4	46
f	H	$-(CH_2)_2O(CH_2)_2-$		$C_6H_5CH_2$	4-^{t}Bu-2-MeC_6H_3	75
g	^{i}Bu	$-(CH_2)_2O(CH_2)_2-$		3-$NO_2C_6H_4$	4-MeC_6H_4	59

[a] Isolated by column chromatography unless stated. [b] Isolated by recrystallization.

particularly evident for the C=N carbon at ca. 165−170 ppm and the adjacent methylene carbon at 58−64 ppm in the ^{13}C NMR spectra of thioacetimidates **1a**,**c**,**d**,**g** and 1-imidoylbenzotriazole **5i**. Sometimes the C=N carbon signal was extremely broad and barely visible; therefore, integration of the ^{13}C NMR spectra became necessary in order to verify the presence of these signals. The positions of the C=N carbon signal in the ^{13}C NMR spectra was similar to that observed in previously reported 1-imidoylbenzotriazoles (typically around 155 ppm)[6a,b] and thiazoles (typically around 165−170 ppm).[11] Increased acquisition times and temperatures of 60 °C for the NMR acquisitions usually afforded better resolved spectra, but occasionally led to decomposition, i.e., as in the case of **1a**.

Conclusion

We have reported an efficient Lewis acid catalyzed isonitrile insertion reaction leading to highly substituted α-amino-substituted 1-imidoylbenzotriazoles **5a**−**k**, stable alternatives to imidoyl halides. Nucleophilic displacement of the benzotriazolyl moiety in **5a**,**c**,**e**,**g**,**i** using a variety of thiols led to novel highly functionalized α-amino thioacetimidates **1a**−**g**.

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Experimental Section

General Comments. Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using tetramethylsilane as the internal standard. The ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent $CDCl_3$ peak as the internal reference. Elemental analyses (C, H, N) were carried out on a Carlo Erba-1106 instrument. Column chromatography was carried out on silica gel (230−400 mesh). THF was distilled from Na and benzophenone under a nitrogen atmosphere prior to use. *N*-(Aminoalkyl) benzotriazoles **4a**−**d** were prepared in high yields (63−95%) by condensation of benzotriazole, formaldehyde, and a secondary amine in water.[8,12] *N*-(Aminoalkyl)benzotriazoles **4e**−**f** were prepared by reflux of benzotriazole, an aldehyde, and a secondary amine under Dean−Stark conditions in benzene.[9] The isonitriles **3a**−**d** were prepared quantitatively from the corresponding amides using phosphorus oxychloride in the presence of diisopropylamine at −10 °C[10] and used immediately, or, if stored under inert atmosphere in the freezer, within 24 h.

1-(3-Methyl-1-morpholinobutyl)benzotriazole (4e). Compound **4e** was crystallized from ethanol as white needles (63%); it was present as a 1:1 mixture of Bt^1 and Bt^2 isomers, mp 89−91 °C; ^{1}H NMR ($CDCl_3$) [for both isomers unless stated] δ 0.88−1.02 (m, 12H), 1.36−1.58 (m, 2H), 2.12−2.46 (m, 4H), 2.56−2.70 (m, 8H), 3.60−3.79 (m, 8H), 5.51−5.68 (m, 2H), 7.35−7.44 (m, 3H, 2H for Bt^1 isomer and 1H for Bt^2 isomer), 7.48 (t, J = 7.5 Hz, 1H, Bt^2 isomer), 7.60 (d, J = 8.9 Hz, 1H, Bt^2 isomer), 7.86−7.92 (m, 2H, Bt^1 isomer), 8.09 (d, J = 8.3 Hz, 1H, Bt^2 isomer). ^{13}C NMR ($CDCl_3$) [for both isomers] δ 22.1, 22.3, 22.5, 24.6, 39.5, 39.7, 48.4, 48.9, 66.8, 66.9, 77.7, 84.6, 109.8, 118.1, 119.9, 123.7, 126.1, 127.2, 133.8, 143.4, 145.5. Anal. Calcd for $C_{15}H_{22}N_4O$: C, 65.75; H, 8.09; N, 20.45. Found: C, 65.31; H, 8.28; N, 20.37.

Preparation of 1-Imidoylbenzotriazoles 5a−k. Imidoylbenzotriazoles **5a**−**k** were prepared by the reaction of *N*-(aminoalkyl)benzotriazoles **4a**−**f** and an appropriate isonitrile **3a**−**d**. Boron trifluoride etherate (5−10 drops) was added to a solution of *N*-(aminoalkyl)benzotriazole (5 mmol) in dry THF at 20 °C. After stirring for 10 min, 1.05−1.10 equiv of the crude isonitrile (5.25−5.50 mmol) in THF was added. The reaction mixture was stirred for 30 min to 1 h. Ethyl acetate was added, and the organic layer was washed with three portions of water. The organic layer was separated, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to yield the desired 1-imidoylbenzotriazole in a good yield. Further purification was achieved by recrystallization with EtOH. In the cases of **5b**,**g**,**e**,**k**, flash column chromatography was used to get an analytically pure sample; however, prolonged time on the column led to rapid hydrolysis of the desired compound, as demonstrated by the conversion of **5e** → **6**.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-morpholinoethylidene]-2,5-dichloroaniline (5a).** Compound **5a** was crystallized from ether as white plates (92%), mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 2.43−2.48 (m, 4H), 3.41−3.45 (m, J = 4.7 Hz, 4H), 4.16 (s, 2H), 7.05−7.12 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 53.3, 56.1, 66.6, 115.5, 120.0, 120.7, 123.0, 124.6, 125.8, 129.7, 130.3, 131.4, 132.5, 145.5, 146.5, 154.7. Anal. Calcd for $C_{18}H_{17}Cl_2N_5O$: C, 55.40; H, 4.39; N, 17.94. Found: C, 55.46; H, 4.48; N, 17.95.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-dimethylaminoethylidene]-2,5-dichloroaniline (5b).** Compound **5b** was obtained as a pale yellow oil following column chromatography using ethyl acetate/hexanes (1:3) (96%); ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 6H), 3.98 (s, 2H), 7.03−7.13 (m, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 45.6, 55.9, 115.3, 119.9, 121.3, 123.3, 124.9, 125.5, 129.4, 130.5, 131.4, 132.6, 144.9, 146.4, 155.6. Anal. Calcd for $C_{16}H_{16}Cl_2N_5$: C, 55.18; H, 4.34; N, 20.11. Found: C, 54.85; H, 4.36; N, 19.96. HRMS (FAB) calcd for $C_{16}H_{16}Cl_2N_5$ (M + 1): 348.0783. Found: 348.0788.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-morpholinoethylidene]-4-nitroaniline (5c).** Compound **5c** was crystallized from ethanol as pale yellow plates (93%), mp 164−165 °C; ^{1}H NMR ($CDCl_3$) δ 2.43−2.48 (m, 4H), 3.43−3.48 (m, 4H), 4.14 (s, 2H), 7.13 (d, J = 8.9 Hz, 2H), 7.54 (dt, J = 1.0, 7.4 Hz, 1H), 7.64 (dt, J = 1.0, 7.4 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 8.7 Hz, 2H), 8.41 (d, J = 8.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 53.2, 54.9, 66.5, 115.1, 120.0, 120.1, 124.7, 125.9, 129.7, 131.1, 144.1, 146.5, 153.0, 153.3. Anal. Calcd for $C_{18}H_{18}N_6O_3$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.18; H, 5.09; N, 23.21.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-morpholinoethylidene]-3-nitroaniline (5d).** Compound **5d** was crystallized from ethanol as white plates (97%), mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 2.45−2.50 (m, 4H), 3.48−3.53 (m, 4H), 4.13 (s, 2H), 7.39 (d, J = 8.4 Hz, 1H), 7.50−7.68 (m, 3H), 8.02−8.08 (m, 2H), 8.16 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 53.2, 54.5, 66.6, 115.3, 115.5, 119.0, 120.1, 125.9, 126.6, 129.5, 129.7, 131.2, 146.6, 148.0, 148.5, 154.5. Anal. Calcd for $C_{18}H_{18}N_6O_3$: C, 59.01; H, 4.95; N, 22.94. Found: C, 59.09; H, 5.03; N, 22.95.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-(*N*-methylanilino)ethylidene]-2,5-dichloroaniline (5e).** Compound **5e** was obtained as yellow plates following column chromatography using ethyl acetate/hexanes (1:15) (45%), mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H), 5.19 (s, 2H), 6.40−6.46 (m, 3H), 6.74 (t, J = 7.4 Hz, 1H), 6.90 (dd, J = 2.4, 8.7 Hz, 1H), 7.17 (t, J = 7.1 Hz, 2H), 7.28 (t, J = 8.1 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 39.8, 54.0, 112.2, 115.3, 117.7, 119.3, 120.0, 120.5, 124.0, 125.8, 129.2, 129.8, 129.9, 131.5, 132.5, 144.7, 146.4, 147.0, 153.8. Anal. Calcd for $C_{21}H_{17}N_5Cl_2$: C, 61.47; H, 4.18; N, 17.07. Found: C, 61.28; H, 4.15; N, 17.03.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-(*N*-methylanilino)ethylidene]-3-nitroaniline (5f).** Compound **5f** was crystallized from ethanol as white plates (91%), mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 5.25 (s, 2H), 6.35 (d, J = 7.8 Hz, 2H), 6.70 (dt, J = 0.9, 6.9 Hz, 1H), 6.92−6.96 (m, 1H), 7.07−7.14 (m, 2H), 7.31 (t, J = 8.1 Hz, 1H), 7.49−7.56 (m, 2H), 7.62 (dt, J = 1.2, 7.7 Hz, 1H), 7.76−7.82 (m, 1H), 8.17 (dd, J = 1.2, 8.1 Hz, 1H), 8.34 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 39.6, 52.9, 112.2, 112.6, 115.1, 118.0, 120.1, 123.8, 125.9, 129.0, 129.1, 129.8, 131.4, 146.4, 147.0, 147.4, 148.1, 152.5. Anal. Calcd for $C_{21}H_{18}N_6O_2$: C, 65.27; H, 4.70; N, 21.75. Found: C, 65.33; H, 4.85; N, 21.80.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-morpholinoethylidene]-benzylamine (5g).** Compound **5g** was obtained as a pale yellow oil following column chromatography using ethyl acetate/hexanes (1:3) (94%); ^{1}H NMR ($CDCl_3$) δ 2.63−2.67 (m, 4H), 3.63−3.68 (m, 4H), 4.25 (s, 2H), 5.10 (s, 2H), 7.26−7.50 (m, 6H), 7.55 (dt, J = 1.2, 7.7 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 53.5, 53.8, 53.9, 66.8, 115.6, 119.6, 125.2, 126.9, 127.5, 128.5, 129.0, 131.6, 139.6, 146.5, 153.8. HRMS (FAB) calcd for $C_{19}H_{21}N_5O$: 336.1824. Found 336.1791.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-piperidinoethylidene]-4-nitroaniline (5h).** Compound **5h** was crystallized from ethanol as white plates (88%), mp 155 °C (decomp); ^{1}H NMR ($CDCl_3$) δ 1.29 (br s, 6H), 2.36 (br s, 4H), 4.10 (s, 2H), 7.11 (d, J = 9.0 Hz, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.28 (d, J = 9.0 Hz, 2H), 8.41 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 23.5, 25.7, 54.3, 55.7, 115.3, 120.1, 120.1 124.6, 125.8, 129.6, 131.3, 143.9, 146.6, 153.5, 154.2. Anal. Calcd for $C_{19}H_{20}N_6O_2$: C, 62.62; H, 5.53; N, 23.06. Found: C, 62.52; H, 5.67; N, 22.88. HRMS (FAB) calcd for $C_{19}H_{20}N_6O_2$: 365.1726. Found 365.1693.

***N*-[1-(1*H*-Benzotriazol-1-yl)-4-methyl-2-morpholinopentylidene]-3-nitroaniline (5i).** Compound **5i** was crystallized from ethanol as pale yellow plates (87%), mp 150−153 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.1 Hz, 6H), 1.58−1.73 (m, 1H), 1.74−1.92 (m, 2H), 2.50−2.65 (m, 4H), 3.47−3.64 (m, 4H), 4.61 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.42−7.58 (m, 3H), 7.89−7.98 (m, 2H), 8.12 (d, J = 8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 22.5, 22.9, 26.0, 38.2, 51.0, 65.4, 67.1, 114.3, 115.4, 118.8, 120.2, 125.6, 125.9, 129.4, 129.4, 131.5, 146.2, 147.6, 148.7, 155.9. Anal. Calcd for $C_{22}H_{26}N_6O_3$: C, 62.54; H, 6.20; N, 19.89. Found: C, 62.16; H, 6.50; N, 19.88.

***N*-[1-(Benzotriazolyl)-2-morpholino-2-phenylethylidene]-2,5-dichloroaniline (5j).** This compound was crystallized from ethanol as yellow microcrystals (89%), mp 186−187 °C, the

(12) (a) Burckhalter, J. H.; Stephens, V. C.; Hall, L. A. R. *J. Am. Chem. Soc.* **1952**, *74*, 3868. (b) Smith, J. R. L.; Sadd, J. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1181.

product was obtained as a mixture of Bt^2 and Bt^1 isomers (2.6:1, respectively); ^{1}H NMR ($CDCl_3$) [both isomers unless stated] δ 2.50−2.53 (m, 4H, Bt^1 isomer), 3.11−3.14 (m, 4H, Bt^2 isomer), 3.46−3.52 (m, 4H, Bt^1 isomer), 3.67−3.70 (m, 4H, Bt^2 isomer), 5.99 (s, 1H, Bt^1 isomer), 6.17 (s, 1H, Bt^2 isomer), 6.55−7.65 (m, 22H), 7.89 (d, J = 8.3 Hz, 1H, Bt^2 isomer) 8.09 (d, J = 8.4 Hz, 1H, Bt^1 isomer). ^{13}C NMR ($CDCl_3$) [both isomers] δ 48.9, 49.0, 67.1, 67.3, 109.4, 110.0, 110.4, 110.7, 113.6, 113.7, 117.6, 117.9, 119.7, 119.9, 120.0, 120.4, 123.9, 124.5, 127.8, 128.4, 128.5, 128.7, 128.8, 129.0, 129.6, 129.9, 130.2, 133.2, 133.5, 133.7, 134.5, 135.5, 140.8, 141.4, 143.3, 143.9, 145.2, 145.8. Anal. Calcd for $C_{24}H_{21}Cl_2N_5O$: C, 61.81; H, 4.54; N, 15.02. Found: C, 61.71; H, 4.72; N, 14.88.

***N*-[1-(1*H*-Benzotriazol-1-yl)-2-piperidinoethylidene]-2,5-dichloroaniline (5k).** Compound **5k** was obtained as a pale yellow oil following column chromatography using ethyl acetate/hexanes (1:2) (87%); ^{1}H NMR ($CDCl_3$) δ 1.27 (br s, 6H), 2.36 (br s, 4H), 4.11 (s, 2H), 7.02−7.12 (m, 2H), 7.34 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 23.5, 25.6, 54.3, 56.8, 115.5, 119.8, 120.7, 122.8, 124.2, 125.5, 129.4, 130.0, 131.3, 132.2, 145.6, 146.4, 155.3. Anal. Calcd for $C_{19}H_{19}Cl_2N_5$: N, 18.04. Found: N, 17.79. HRMS (FAB) calcd for $C_{19}H_{19}Cl_2N_5$: 388.1096. Found 388.1092.

Preparation of α-Amino Thioacetimidates 1a−g. 1-Imidoyl benzotriazole **5** (3 mmol), an appropriate thiol (1.1 equiv), and sodium methoxide (1 equiv) were heated under reflux in dry THF for 16−18 h under a nitrogen atmosphere. Ethyl acetate was then added to the reaction mixture, which was washed with 1% NaOH, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to yield either an oily residue that was purified by column chromatography on silica gel using hexanes/ethyl acetate mixtures (**1a**,**b**,**d**−**g**), or a solid which was recrystallized from ethanol (**1c**).

4-Methylphenyl *N*-(2,5-Dichlorophenyl)-2-morpholinothioacetimidate (1a). Compound **1a** was obtained as yellow needles following column chromatography using hexanes/ethyl acetate (10:1) (44%), mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.39−2.46 (m, 4H), 3.17 (s, 2H), 3.62−3.68 (m, 4H), 6.81 (br s, 1H), 6.94 (dd, J = 2.2, 8.5 Hz, 1H), 7.14 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 2.9 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H). It was not possible to obtain satisfactory ^{13}C NMR spectra for this compound due to poor resolution as explained in the text. Attempts to heat the sample to either 60 °C (in $CDCl_3$) or 100 °C (in $CD_3C_6D_5$) led to substantial decomposition. Anal. Calcd for $C_{19}H_{20}Cl_2N_2OS$: C, 57.72; H, 5.10; N, 7.09. Found: C, 57.69; H, 5.19; N, 6.92.

Benzyl *N*-(2,5-Dichlorophenyl)-2-morpholinothioacetimidate (1b). Compound **1b** was obtained as a pale yellow oil following column chromatography using hexanes/ethyl acetate (3:1) (53%); ^{1}H NMR ($CDCl_3$) δ 2.38−2.45 (m, 4H), 3.12 (s, 2H), 3.58−3.68 (m, 4H), 4.24 (s, 2H), 6.73 (d, J = 2.5 Hz, 1H), 6.94 (dd, J = 2.5, 8.5 Hz, 1H), 7.18−7.32 (m, 4H), 7.33−7.39 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 34.3, 53.5, 61.1, 66.6, 120.3, 122.1, 123.9, 127.0, 128.4, 129.1, 130.5, 132.7, 137.5, 148.5, 172.7. Anal. Calcd for $C_{19}H_{20}Cl_2N_2OS$: C, 57.72; H, 5.10; N, 7.09. Found: C, 57.75; H, 5.22; N, 6.81. HRMS (FAB) calcd: 395.0752. Found: 395.0755.

Phenyl *N*′-(2,5-Dichlorophenyl)-2-(*N*-methyl-*N*-phenylamino)thioacetimidate (1c): Compound **1c** was obtained as white needles following recrystallization from EtOH/ethyl acetate (92%), mp 107−108 °C; ^{1}H NMR ($CDCl_3$) (at 60 °C) δ 2.30 (s, 3H), 4.11 (s, 2H), 6.64−6.77 (m, 4H), 6.89 (dd, J = 1.8, 8.7 Hz, 1H), 7.18−7.24 (m, 3H), 7.29−7.35 (m, 3H), 7.50−7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) (at 60 °C) δ 39.2, 58.8, 112.5, 117.3, 120.4, 122.1, 124.5, 128.4, 129.0, 129.4, 129.5, 130.6, 132.6, 135.4, 147.8, 148.7, 166.4. Anal. Calcd for $C_{21}H_{18}Cl_2N_2S$: C, 62.84; H, 4.52; N, 6.98. Found: C, 62.45; H, 4.67; N, 6.86.

4-Methylphenyl *N*-(4-Nitrophenyl)-2-morpholinothioacetimidate (1d). Compound **1d** was obtained as pale yellow needles following column chromatography using hexanes/ethyl acetate (4:1) (44%), mp 148−149 °C; ^{1}H NMR ($CDCl_3$) (at 60 °C) δ 2.36−2.39 (m, 7H), 3.15 (s, 2H), 3.66−3.70 (m, 4H), 6.93 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 8.20 (d, J = 7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.2, 53.1, 63.1, 66.8, 119.9, 125.1, 125.3, 129.8, 135.9, 140.1, 144.1, 155.9, 167.4* [*Quaternary carbon signal very small, but integration shows it to be present. After attempted high-temperature NMR experiments, this peak at ca. 168 ppm shows up more clearly, but significant decomposition of the compound is observed by the appearance of new signals in the aromatic region.] Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.17; H, 6.07; N, 11.23.

4-Methylphenyl *N*-Benzyl-2-morpholinothioacetimidate (1e). Compound **1e** was obtained as pale yellow plates following column chromatography using hexanes/ethyl acetate (3:1) (46%), mp 73−75 °C; ^{1}H NMR ($CDCl_3$) (at 60 °C) δ 2.18−2.24 (m, 4H), 2.36 (s, 3H), 3.01 (s, 2H), 3.55−3.61 (m, 4H), 4.67 (s, 2H), 7.15 (d, J = 7.9 Hz, 2H), 7.22−7.28 (m, 1H), 7.30−7.43 (m, 4H), 7.51 (d, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) (at 60 °C) δ 21.1, 52.7, 56.7, 63.8, 66.8, 126.6, 126.7, 127.8, 128.3, 129.4, 136.0, 139.2, 139.6, 161.7. Anal. Calcd for $C_{20}H_{24}N_2OS$: C, 70.55; H, 7.10; N, 8.23. Found: C, 70.32; H, 7.21; N, 8.00.

4-(*tert*-Butyl)-2-methylphenyl *N*-benzyl-2-morpholinothioacetimidate (1f). Compound **1f** was obtained as a pale orange oil after purification by column chromatography using hexanes/ethyl acetate (3:1) (75%); ^{1}H NMR ($CDCl_3$) (at 60 °C) δ 1.31 (s, 9H), 2.10−2.20 (m, 4H), 2.45 (s, 3H), 3.00 (s, 2H), 3.46−3.58 (m, 4H), 4.74 (s, 2H), 7.10−7.45 (m, 7H), 7.57 (d, J = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 21.1, 31.3, 34.4, 53.1, 57.0, 64.2, 66.9, 126.6, 126.7, 127.9, 128.4, 129.9, 130.2, 133.8, 139.6, 139.8, 149.7, 161.7. Anal. Calcd for $C_{24}H_{32}N_2OS$: C, 72.68; H, 8.13; N, 7.06. Found: C, 73.28; H, 8.38; N, 7.44.

4-Methylphenyl *N*-(3-Nitrophenyl)-2-morpholino-(2-isobutyl)thioacetimidate (1g). Compound **1g** was obtained as a pale yellow oil following column chromatography using hexanes/ethyl acetate (5:1) (59%); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 6H), 1.42−1.51 (m, 1H), 1.59−1.81 (m, 2H), 2.33 (s, 3H), 2.35−2.44 (m, 2H), 2.62−2.71 (m, 2H), 3.38 (dd, J = 5.9, 8.1 Hz, 1H), 3.62−3.68 (m, 4H), 7.09−7.18 (m, 3H), 7.35 (d, J = 8.6 Hz, 2H), 7.45 (t, J = 8.1 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.88−7.94 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.1, 22.4, 22.7, 25.0, 35.5, 48.8, 64.0, 67.4, 114.6, 118.4, 125.8, 125.8, 129.6, 129.8, 135.9, 139.9, 148.6, 150.7, 168.8. HRMS (FAB) for $C_{23}H_{29}N_3O_3S$ calcd: 428.2008. Found: 428.2008.

***N*-(2,5-Dichlorophenyl)-2-(*N*-methylanilino)acetamide (6).** Compound **6** was obtained as pale yellow prisms following column chromatographic purification of compound **5e** using hexanes/ethyl acetate (15:1) (32%), mp 111−112 °C; ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 3.99 (s, 2H), 6.82 (d, J = 7.8 Hz, 2H), 6.89 (t, J = 7.4 Hz, 1H), 7.00 (dd, J = 2.4, 8.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.32 (t, J = 8.1 Hz, 2H), 8.53 (d, J = 2.4 Hz, 1H), 9.16 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 40.1, 59.8, 112.0, 113.8, 119.5, 121.0, 124.6, 129.4, 129.6, 133.4, 134.8, 149.0, 168.9. Anal. Calcd for $C_{15}H_{14}N_2Cl_2O$: C, 58.27; H, 4.56; N, 9.06. Found: C, 58.29; H, 4.55; N, 9.10.

***N*′-(2,5-Dichlorophenyl)-*N*-methyl-2-(*N*-methylanilino)-*N*-phenylethanimidamide (7).** This compound was obtained as a pale yellow oil following column chromatography of compound **5e** using hexanes/ethyl acetate (15:1) (5%); ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H), 3.33 (s, 3H), 3.91 (s, 2H), 6.25 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 7.3 Hz, 1H), 6.77 (dd, J = 2.5, 8.5 Hz, 1H), 7.08−7.26 (m, 6H), 7.33−7.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 38.7, 40.8, 53.2, 112.2, 116.9, 122.1, 123.1, 126.7, 126.9, 128.7, 129.6, 129.9, 132.3, 145.3, 147.5, 148.5, 157.8. HRMS (FAB) for $C_{22}H_{21}N_3Cl_2$ calcd: 398.1191. Found: 398.1230.

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