N-Functionalized Benzotriazole-1-carboximidoyl Chlorides: Synthetic Equivalents for Isocyanide Dichlorides

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Readily prepared *N*-functionalized benzotriazole-1-carboximidoyl chlorides are proposed as stable and novel isocyanide dichloride synthetic equivalents. Subsequent condensations of these new intermediates afford polysubstituted guanidines, *S*-aryl isothioureas, and 2-aminoquinazolin-4-thiones.

Introduction

Isocyanide dichlorides,[1] including *N*-acyl[2] and *N*-sulfonyl[3] derivatives, undergo nucleophilic substitution with various nucleophiles to provide access to carbodiimides, guanidines, chloroformamidines, thioesters, isoureas, isothioureas, carbonimidates, and five- and six-membered heterocycles.[1] Preparative routes to isocyanide dichlorides[4] include (i) the reaction of isothiocyanates with chlorine,[5] (ii) the reaction of isocyanates with phosphorus pentachloride,[5a] (iii) the addition of chlorine to isocyanides,[6,7] (iv) the reaction of monosubstituted formanilides with a mixture of thionyl chloride and sulfuryl chloride,[7] (v) the addition of dichlorocarbenes to azides[8] or azabicyclobutanes,[9] and (vi) the reaction of trisubstituted ureas with carbon tetrachloride in the presence of triphenyl phosphine or with phosphorus pentachloride.[10] While many isocyanide dichlorides can be made in satisfactory yields by these methods, these compounds are often strongly corrosive, toxic, and sensitive toward hydrolysis,[4,11] properties that decrease their convenience for possible applications.

Our earlier investigations have shown that the replacement of the halogen atom in such synthons as α-chloroalkyl ethers and α-chloroalkylamines by a benzotriazole moiety provides stable and nontoxic synthetic equivalents.[12] We now describe the synthesis of novel *N*-functionalized benzotriazole-1-carboximidoyl chlorides and their use as stable isocyanide dichloride synthetic equivalents.

Results and Discussion

A one-step reaction of easily available *N*-chlorobenzotriazole (**1**)[13] with isonitriles **2a**−**f** in chloroform at room temperature conveniently affords *N*-functionalized benzotriazole-1-carboximidoyl chlorides as approximately equimolar mixtures of the Bt^1 (**3a**−**f**) and Bt^2 (**4a**−**f**) isomers (Scheme 1). Benzyl, benzotriazolylmethyl, tosylmethyl, and aryl isonitriles **2** all afford almost quantitative total yields of the expected adducts **3a**−**f** and **4a**−**f**. For analytical purposes, we isolated some of the individual isomers by extraction and recrystallization (**3a**−**d** and **4b**,**d**) or column chromatography (**3e**, **4e**). Thus, in the ^{1}H NMR spectrum of crude material obtained in the reaction of [(*p*-methylphenyl)sulfonylmethyl]isonitrile (**2b**) with compound **1**, the Me and CH_2 signals for isomers **3b** and **4b** appeared as singlets with the same integral intensity at 2.46, 2.45, and 5.16, 5.19 ppm, respectively. Complex superposition of the aromatic signals is observed at 7.30−8.20 ppm. In the spectra of individual isomers **3b** and **4b**, characteristic patterns for the four nonequivalent protons of the Bt^1 moiety showed at 7.52−8.13 ppm, and two typical multiplets of the AA′BB′ spin system of Bt^2 group showed at 7.48−7.51 and 7.90−7.93 ppm, respectively. In contrast with isocyanide dichlorides, compounds **3a**−**f** and **4a**−**f** are high melting crystalline compounds, stable on storage, insensitive to air and moisture, nonvolatile, and odorless.

For further synthetic transformations, the mixtures of **3a**−**f** with the corresponding **4a**−**f** were used without separation for the sequential displacement of the chlorine atom and the benzotriazole moiety to prepare polysubstituted guanidines **10**, *S*-arylisothioureas **11**, and 2-aminoquinazoline-4-thiones **13**.

Thus, *N*-functionalized 1*H*-benzotriazole-1-carboximidoyl chlorides **3a**−**f** and 2*H*-benzotriazole-2-carboximidoyl chlorides **4a**−**f** condensed with primary and secondary aliphatic and primary aromatic amines, in the presence of triethylamine in dry methylene chloride, to afford the corresponding *N*,*N*′-functionalized 1*H*-benzotriazole-1-carboximidamides **6a**−**j** and 2*H*-benzotriazole-2-carboximidamides **7a**−**j** in overall yields of 45−92%.

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Scheme 1

3, 4	a	b	c	d	e	f
R^1	$PhCH_2$	$TsCH_2$	$BtCH_2$	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	3-$NO_2C_6H_4$
Overall yield (%)	79	93	83	90	85	70

Scheme 2

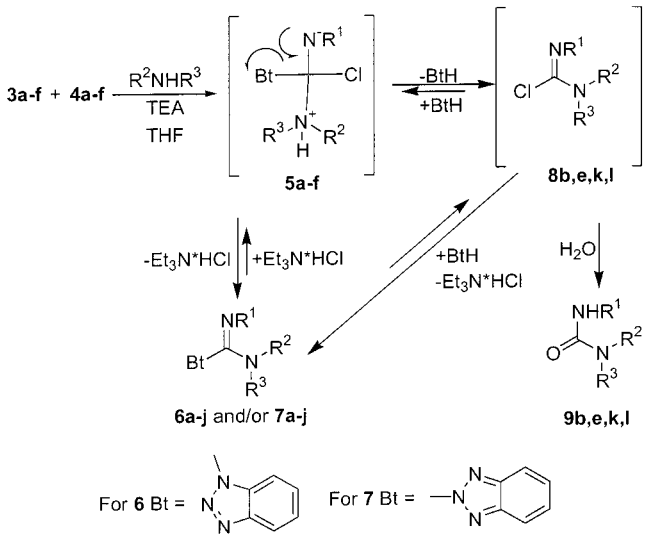

Table 1. Preparation of Benzotriazole-1-carboximidamides 6 and 7

6 + **7**, **9**	reaction time, h	R^1	R^2	R^3	yield of **6** + **7**	yield of **9**
a	4	$TsCH_2$	*i*-butyl	H	62	0[a]
b	4	$BtCH_2$	allyl	allyl	45	32
c	72	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	H	65	0[a]
d	78	$TsCH_2$	$(CH_2)_2O(CH_2)_2$		78	0[a]
e	4	4-$NO_2C_6H_4$	*i*-butyl	H	60	40
–	72	–	–	–	89	0[a]
f	15	4-$CH_3C_6H_4$	$(CH_2)_2O(CH_2)_2$		81	0[a]
g	1	4-$CH_3C_6H_4$	$(CH_2)_4$		80	0[a]
h	30	4-$CH_3C_6H_4$	ethyl	ethyl	78	0[a]
i	1	4-$CH_3C_6H_4$	*n*-propyl	H	70	0[a]
j	2	3-$NO_2C_6H_4$	$(CH_2)_2O(CH_2)_2$		92	0[a]
k	4	$BtCH_2$	*i*-butyl	H	0[a]	65
l	3	$C_6H_5CH_2$	$(CH_2)_2O(CH_2)_2$		0[a]	57

[a] Compound was not isolated.

The preparation of compounds **6**,**7b** and **6**,**7e** was accompanied by the formation of the disubstituted **9b** or trisubstituted urea **9e**, which apparently was formed by the hydrolysis of nonisolated chloroformamidines **8b**,**e** during workup. Ureas **9k**,**l** were the sole products isolated from **3**,**4k** and **3**,**4l** (Scheme 2, Table 1). Benzotriazole-substituted carboximidoyl chlorides **3**,**4d** and **3**,**4f**, activated by a nitro group in the *N*-phenyl moiety, gave the best yields of carboximidamides **6**,**7e** and **6**,**7j** (89 and 92% respectively). In contrast, *N*-benzyl and *N*-(benzotriazol-1-yl)methyl carboximidoyl chlorides **3**,**4a**,**c** either gave lower yields of desired compounds (**6**,**7b**, 45%), or did not form compounds at all (**6**,**7k**,**l**) (Table 1). *N*,*N*′-Functionalized 1*H*-benzotriazole-1-carboximidamides **6a**−**j** and 2*H*-benzotriazole-2-carboximidamides **7a**−**j** were used without separation of isomers for further transformations. However, the individual Bt^1 isomers (**6b**,**c**,**e**−**j**) and/or Bt^2 isomers (**7a**,**b**,**d**,**f**−**h**) were isolated for analytical purposes.

In both the ^1H and ^{13}C NMR spectra, the signals of the N(CH_2−)$_2$ and N(CH_2CH_2−) groups in compounds **6b**,**f**−**h**, and **7b**,**d**,**f**−**j** appeared as broad singlets due to hindered rotation around amide-type C−N bonds. *N*,*N*′-Disubstituted carboximidamides **6c**,**e**,**i**, and **7a** are potentially tautomeric. Nevertheless, *N*-(4-nitrophenyl)- and *N*-[(4-methylphenyl)sulfonyl]methyl derivatives **6c**,**e**, and **7a** demonstrate well-resolved ^1H and ^{13}C NMR spectra of the single tautomeric form, as depicted in Scheme 2. For the *N*-(4-methylphenyl)-*N*′-propyl-substituted compound **6i**, a strong broadening of the signals of the N′CH_2− group and CH-7 fragment of the benzotriazole moiety is observed in both the ^1H and ^{13}C NMR spectra. It may indicate fast (on the NMR time scale) exchange of the proton between NH and N′H positions.

A benzotriazole moiety can in many ways be compared to a halogen substituent.[12] Compounds **3a**−**f** and **4a**−**f** provide models for the investigation of the relative reactivity of a Bt group and chlorine. Thus, condensation of compound **3d** with isobutylamine during 4 h gave a mixture of compounds **6**,**7e** (60%) and **9e** (40%). Increasing the reaction time for up to 72 h gave products **6e** and **7e** in almost quantitative yield. This suggests that the displacement of the Bt group is as fast as that of the chlorine atom, but that the chloro intermediates **8** are less stable thermodynamically than the benzotriazole-substituted analogues **6** and **7**, which become the major products after establishment of the equilibrium. It is surprising that mixtures of compounds **6** + **7** and compound **8** were formed competitively since a halogen is a much better leaving group than benzotriazole.[14a] Thus, acylbenzotriazoles[14b] and α-benzotriazolyl ketones[14c] are usually less reactive than the corresponding acyl chlorides and α-chloro ketones. However, the present result suggests that when chlorine and benzotriazole are connected to the same carbon center, a benzotriazole moiety has a lability comparable with that of a chlorine atom; implications of this conclusion are under investigation.

Early syntheses of guanidines from isocyanide dichlorides[1] were performed with an excess of the amine and led exclusively to symmetrically substituted products. Syntheses of unsymmetrical guanidines from isocyanide dichlorides by sequential displacement of two chlorine atoms were reported only for *N*-acyl or *N*-tosyl derivatives.[15]

Reactions of the mixtures of benzotriazole-carboximidamides **6c**,**e** and **7c**,**e** with amines in refluxing THF during 2−3 d lead to unsymmetrical tetrasubstituted guanidines **10a**,**b** in 68−69% yields (Scheme 3). Sharp and well-resolved signals of the compound **10a** (R^2 = *i*-Bu) in both ^1H and ^{13}C NMR spectra indicate that **10a** exists in solution ($CDCl_3$, rt) exclusively as the −N*H*-*i*-Bu tautomer. The NH proton signal is observed as a

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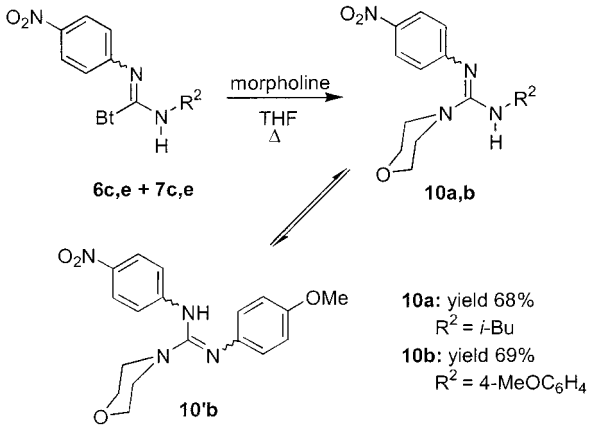
Scheme 3



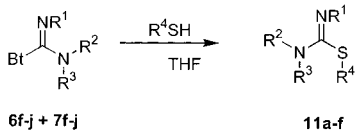
broad singlet at 4.10 ppm. In contrast, two different NH signals at 5.58 and 5.95 ppm (integral ratio 7:3) are observed under the same conditions for compound **10b** (R^2 = 4-methoxyphenyl). Aromatic, morpholine, and MeO groups appear as a single set of relatively (compared to compound **10a**) broad signals. Perhaps, this compound exists as a mixture of 4-MeO−C_6H_4−NH− tautomer **10b** and 4-$NO_2C_6H_4$−NH− tautomer **10′b** in the molar ratio 7:3, respectively. We estimated the parameters of this tautomeric system by using AM1 semiempirical calculations. The results obtained ($\Delta\Delta G_{\mathbf{10b-10'b}} = -0.34$ kcal/mol or **10b:10′b** = 60:40) are in good agreement with the experimental data.

Isothioureas are known as specific inhibitors of inducible nitric oxide synthase,[16a−d] and *S*-alkyl isothioureas are useful synthons in organic chemistry.[16e] However, there were no general synthetic procedures described previously for the preparation of *S*-aryl-*N*,*N*,*N*′-substituted isothioureas.

Reactions of mixtures of compounds **6f**−**j** and **7f**−**j** with aryl thiols at room temperature in dry THF during 15−36 h readily afford *S*-aryl isothioureas **11a**−**f** in 80−88% yields (Scheme 4). According to the ^{1}H NMR (rt, $CDCl_3$) spectrum, a potentially tautomeric compound **11c** (R^1 = 4-Me−C_6H_4, R^2 = *n*-Pr, R^3 = H, R^4 = 4-Cl−C_6H_4) exists exclusively in the NH−Pr form.

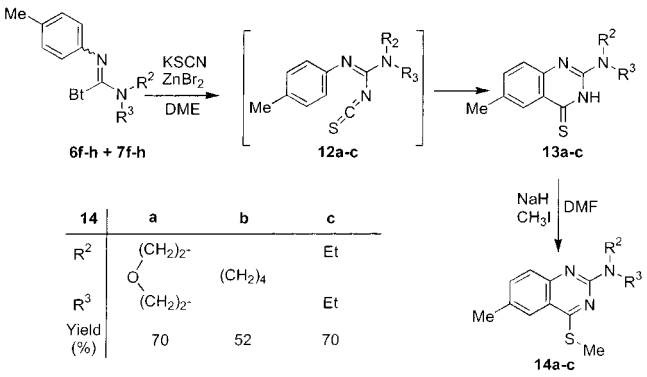
Reactions of compounds **6f**−**h** and **7f**−**h** with potassium thiocyanate, leading to 2-aminoquinazolin-4-thiones **13a**−**c**, demonstrate the synthetic equivalency of **6f**−**h**, **7f**−**h**, and the analogous chloroformamidines.[17] This reaction required a 2-fold excess of potassium thiocyanate and zinc bromide as a catalyst. A complete conversion of the starting materials in refluxing 1,2-dimethoxyethane according to TLC control needed about 7−8 h to give crude compounds **13a**−**c** in good yields. We suggest that the cyclization process takes place via nonisolated intermediates **12a**−**c**, which undergo cyclization *in situ* to give the 2-aminoquinazoline derivatives **13a**−**c**. Analysis of 1,3-quinazoline-4-thiones **13a**−**c** by ^{1}H NMR (DMSO-d_6 and $CDCl_3$) showed a complex superposition of broad signals in both the aliphatic and aromatic regions due

Scheme 4



11	a	b	c	d	e	f
R^1	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	3-$NO_2C_6H_4$	4-$CH_3C_6H_4$
R^2	$-(CH_2)_2-O-(CH_2)_2-$	$-(CH_2)_2-O-(CH_2)_2-$	*n*-Propyl	$-(CH_2)_4-$	$-(CH_2)_2-O-(CH_2)_2-$	Et
R^3			H			Et
R^4	4-$CH_3C_6H_4$	4-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4
Yield (%)	85	88	80	88	87	80

Scheme 5



14	a	b	c
R^2	$-(CH_2)_2-O-(CH_2)_2-$	$-(CH_2)_4-$	Et
R^3			Et
Yield (%)	70	52	70

to the tautomeric nature of these compounds. However, *S*-methylation of the crude products **13a**−**c** with methyl iodide in the presence of sodium hydride in DMF gave compounds **14a**−**c** in overall 50−70% yields (Scheme 5). 2-Amino-4-(methylthio)quinazolines **14a**−**c** were completely characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analyses.

Conclusions

The preparation of *N*-functionalized benzotriazole-substituted carboximidoyl chlorides **3a**−**f** and **4a**−**f** as stable and easily accessible synthetic equivalents to isocyanide dichlorides has been described. These derivatives are sequentially condensed with amines, aryl thiols, and potassium thiocyanate to afford entries to polysubstituted guanidines **10**, *S*-aryl isothioureas **11**, and 2-aminoquinazoline-4-thiones **13**, respectively.

Experimental Section

General Methods. Melting points were determined with a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz respectively) using $CDCl_3$ as a solvent. Tetrahydrofuran (THF) was distilled under nitrogen, immediately before use, from sodium/benzophenone. Column chromatography was conducted with silica gel 230−400 mesh. All the other reagents were of reagent grade and were used without purification. Thermodynamic properties of compounds **10b** and **10′b** were calculated by Mopac 6 using method AM1.

General Procedure for the Preparation of Compounds 3 and 4. A solution of 1-chlorobenzotriazole (765 mg, 5 mmol)

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in chloroform (30 mL) was slowly added to a solution of an isonitrile **2** (5 mmol) in chloroform (30 mL) with stirring at room temperature. After the complete conversion of the starting materials, the crude mixtures of compounds **3a**−**f** (Bt[1] isomers) and **4a**−**f** (Bt[2] isomers) were used for the preparation of derivatives **6a**−**j** and **7a**−**j** without separation. Since Bt[1] isomer is more soluble in organic solvents, it can be separated from Bt[2] isomer by extraction with an appropriate solvent followed by recrystallization from the same solvent. Separation of isomer of **3e** was performed by column chromatography (ethyl ether/pentane, 2/8).

***N*-(4-Nitrophenyl)-1*H*-benzotriazole-1-carboximidoyl Chloride (3d).** This compound was isolated from acetone as light yellow needles: mp 218−220 °C; ^{1}H NMR δ 6.76 (d, J = 8.8 Hz, 2H), 7.66 (t, J = 7.7 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 8.12 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.4 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 113.5, 119.8, 120.2, 124.3, 126.5, 129.6, 130.3, 142.6, 144.9, 145.6, 149.5. Anal. Calcd for $C_{13}H_8ClN_5O_2$: C, 51.76; H, 2.67. Found: C, 51.76; H, 2.58.

***N*-(4-Nitrophenyl)-2*H*-benzotriazole-2-carboximidoyl Chloride (4d).** This compound was separated from **3d** by washing with cold acetone. Yellow microcrystals were obtained after evaporation of the solvent: mp 213−214 °C; ^{1}H NMR δ 7.39 (d, J = 7.8 Hz, 2H), 7.56−7.58 (m, 2H), 7.95−7.97 (m, 2H), 8.38 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ 119.3, 121.4, 114.3, 121.8, 125.2, 130.2, 146.0, 150.0. Anal. Calcd for $C_{13}H_8ClN_5O_2$: C, 51.76; H, 2.67; N, 23.21. Found: C, 51.55; H, 2.71; N, 23.01.

General Procedure for the Preparation of Compounds 6 and 7. A mixture of an amine (1.37 mmol) and triethylamine (1.37 mmol) was added to a suspension of *N*-functionalized benzotriazole-carboximidoyl chlorides **3** and **4** and was allowed to react for 72 h. The reaction mixture was then washed with water and dried over $MgSO_4$. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The residue obtained was separated by column chromatography on silica gel to afford compounds **6** and **7** in approximately equimolar amounts. Analytical samples of these compounds were also purified by recrystallization.

***N*-[1*H*-Benzotriazol-1-yl(morpholino)methylidene]-4-methylaniline (6f).** This compound was isolated as white prisms from ethyl acetate/hexanes: mp 141−142 °C; ^{1}H NMR δ 2.06 (s, 3H), 3.38 (br s, 4H), 3.82 (br s, 4H), 6.43 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.2 Hz, 2H), 7.30−7.38 (m, 3H), 7.98 (d, J = 8.7 Hz, 1H); ^{13}C NMR δ 20.6, 46.7, 66.3, 110.4, 119.9, 120.1, 124.5, 128.6, 129.2, 132.0, 132.4, 141.9, 143.9, 144.8. Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.09; H, 6.09; N, 21.79.

***N*-[2*H*-Benzotriazol-2-yl(morpholino)methylidene]-4-methylaniline (7f).** This compound was isolated as yellow prisms from ethyl acetate/hexanes: mp 155−156 °C; ^{1}H NMR δ 2.11 (s, 3H), 3.29 (br s, 4H), 3.79−3.82 (m, 4H), 6.49 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 7.37−7.40 (m, 2H), 7.81−7.84 (m, 2H); ^{13}C NMR δ 20.7, 46.5, 66.2, 118.8, 121.0, 127.7, 129.1, 132.4, 143.7, 143.8, 143.9. Anal. Calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.43; H, 5.83; N, 21.95.

***N*-Isobutyl-*N*′-(4-nitrophenyl)urea (9e).** This compound was isolated as yellow prisms from ethanol: mp 195−196 °C; ^{1}H NMR δ 0.93 (d, J = 6.8 Hz, 6H), 1.83−1.75 (m, 1H), 3.06 (t, J = 6.2 Hz, 2H), 6.12 (t, J = 5.4 Hz, 1H), 7.55 (d, J = 9.2 Hz, 2H), 8.01 (d, J = 9.2 Hz, 2H), 8.78 (br s, 1H); ^{13}C NMR δ 19.7, 28.4, 46.8, 116.5, 124.7, 140.7, 146.5, 154.8. Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.79; H, 6.68; N, 17.94.

Procedure for Preparation of Compounds 10. A mixture of compounds **6c**,**e** + **7c**,**e** (1 mmol) and morpholine (90 mg, 1.03 mmol) were dissolved in THF (15 mL). The reaction was allowed to occur in refluxing THF for 96 h. The reaction was monitored by TLC until the disappearance of the starting materials **6c**, **e** + **7c**, **e** was noted. The THF was then removed under reduced pressure and the residue was purified by flash chromotography ((i) ethyl acetate/hexane 1/1, (ii) ethyl alcohol).

Tautomeric Mixture of *N*-(4-Methoxyphenyl)-*N*′-(4-nitrophenyl)-4-morpholinecarboximidamide (10b) and *N*-(4-Methoxyphenyl)-*N*′-(4-nitrophenyl)-4-morpholinecarboximidamide (10′b). This mixture was isolated as yellow prisms from ethanol: mp 176−178 °C; ^{1}H NMR δ 3.34−3.37 (m, 4H), 3.66 (br s, 4H), 3.77 (s, 3H), 5.58 (br s, 0.7H), 5.95 (br s, 0.3H), 6.82 (d, J = 8.4 Hz, 2H), 6.91−6.94 (m, 4H), 8.04 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 46.9, 55.4, 66.2, 114.7, 121.0, 122.3, 125.3, 133.9, 141.9, 152.1, 155.9, 157.0. Anal. Calcd for $C_{18}H_{20}N_4O_4$: N, 15.72. Found: N, 16.02.

Procedure for the Synthesis of Isothioureas 11. A mixture of compounds **6f**−**j** and **7f**−**j** (0.85 mmol) was dissolved in dry THF (10 mL) under argon. An appropriate thiophenol (0.85 mmol) in THF (5 mL) was added slowly to the stirred mixture and was allowed to react for 15−48 h at room temperature. After the complete conversion of the starting materials (TLC control), the solvent was removed under reduced pressure, and the crude product obtained was purified by column chromatography with a mixture of ethyl acetate/hexanes as an eluent.

4-Chlorophenyl-*N*-(4-methylphenyl)-4-morpholinecarbimidothioate (11b). The compound was purified by column chromatography with ethyl acetate/pentane as eluent. The light yellow oil, obtained after evaporation of the solvents, was crystallized during 2 days to give off-white prisms: mp 67−68 °C; ^{1}H NMR δ 2.28 (s, 3H), 3.54 (br s, 8H), 6.63 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 20.8, 48.3, 66.3, 121.4, 128.9, 129.0, 131.5, 132.2, 132.6, 133.1, 147.1, 152.8. Anal. Calcd for $C_{18}H_{19}ClN_2OS$: C, 62.33; H, 5.52; N, 8.08. Found: C, 62.51; H, 5.71; N, 8.16.

Procedure for the Synthesis of 6-Methyl-4-methylthio-2-aminoquinazolines 14a−**c.** Potassium thiocyanate (2 equiv, dry powder) and zinc bromide (1.1 equiv, dry powder) were added to a solution of the mixture of compounds **6f**−**h** + **7f**−**h** (1 equiv) in 1,2-dimethoxyethane (70 mL) under argon atmosphere. The reaction mixture was kept at reflux for 6−8 h until the complete conversion of the starting materials **6f**−**h** + **7f**−**h** (TLC control). A dark yellow suspension was obtained and cooled to room temperature, and then water (100 mL) was added. The product was extracted four times with methylene chloride (1 × 350 mL and 3 × 50 mL), the organic extracts were dried over $MgSO_4$, and the solvent was removed to dryness under reduced pressure to give a crude compound **13a**−**c**. Compound **13a**−**c** (1 equiv) was dissolved in DMF (2 mL) at room temperature, and then a slight excess of sodium hydride (1.2 equiv) was added and the reaction mixture was stirred for 10−15 min before the addition of a solution of methyl iodide (1.2 equiv). The stirring was continued for 1 h at room temperature. The product **14a**−**c** was precipitated with ice water, filtered off, washed with water, dried in vacuo, and purified by column chromatography.

6-Methyl-4-(methylthio)-2-morpholinoquinazoline (14a) The compound was purified by column chromatography with ethyl ether/pentane as eluent, and yellow prisms were obtained after evaporation of the solvents: mp 128−129 °C; ^{1}H NMR δ 2.42 (s, 3H), 2.61 (s, 3H), 3.79−3.82 (m, 4H) 3.91−3.94 (m, 4H), 7.44 (s, 2H), 7.61 (s, 1H); ^{13}C NMR δ 12.5, 21.2, 44.5, 66.9, 118.7, 122.8, 125.8, 131.9, 135.6, 148.6, 157.2, 171.0. Anal. Calcd for $C_{14}H_{17}N_3OS$: C, 61.06; H, 6.22; N, 15.26. Found: C, 61.01; H, 6.33; N, 15.22.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and CHN analysis data for compounds **3a**−**c**,**e**, **4b**,**e**,**f**, **6b**,**c**,**e**,**g**−**j**, **7a**,**b**,**d**,**g**,**h**, **9b**,**k**,**l**, **10a**, **11a**,**c**−**f**, and **14b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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