A New Synthesis of *N*-Substituted-2-alkyl(or aryl)quinazolin-4-amines by Amide Base-Mediated Cyclization of Carboximidamides Derived from 2-(Trifluoromethyl)benzenamine

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A one-pot preparation of carboximidamides (amidines) **11-14** involves treatment of amides **2-5** with phosphorus pentachloride followed by the treatment of the resultant crude imidoyl chlorides **7-10** with ammonia. Amidines **11-14** are cyclized to quinazolines **20-26** in lithium alkylamide- or dialkylamide-mediated reactions.

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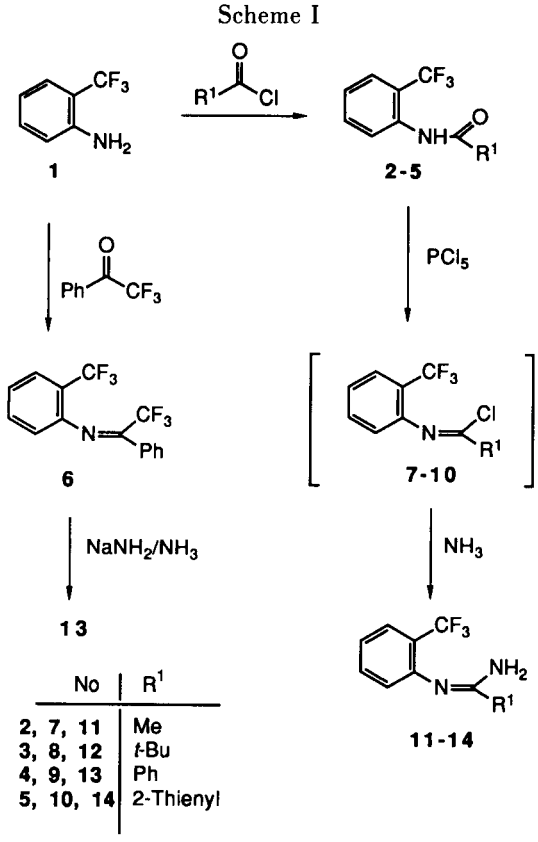
Many *N*-substituted quinazolin-4-amines have been synthesized and found to exhibit a variety of biological activities. Compounds of this class are stimulants [1], antidepressants [1], antihistamines [2], antimalarials [3], biocides [4], and plant-growth regulators [5]. An anti-HIV-1 activity has also been noted recently for some derivatives [6]. A general synthetic route to these compounds involves the preparation of quinazolines containing a nucleofugic group in the C-4 position, usually chloro, followed by displacement of the C-4 function with an amine [7].

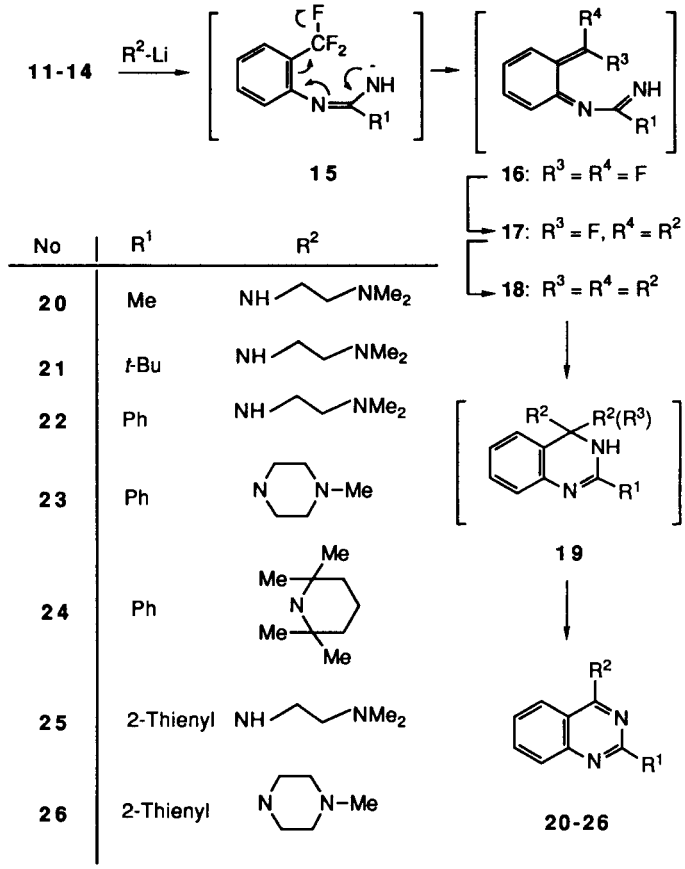
In this paper we report a new synthetic approach to the title quinazolines, in which the construction of the quinazoline ring system and introduction of the amino substituent occur in the same reaction. More specifically, carboximidamides (amidines) such as **11-14** (Scheme I) derived from 2-(trifluoromethyl)benzenamine (**1**) are cyclized directly to 4-quinazolin-4-amines, such as **20-26**, upon treatment with a lithium alkylamide or dialkylamide reagent (Scheme II). Each fluorine of the trifluoromethyl substituent of the amidine is successfully displaced by a series of internal nucleophilic processes, and the resulting quinazoline contains the amino function of the lithium reagent incorporated in the C-4 position. The proposed intermediacy of **15-19** is based on our mechanistic studies on a

Scheme I



No	R^1
2, 7, 11	Me
3, 8, 12	*t*-Bu
4, 9, 13	Ph
5, 10, 14	2-Thienyl

Scheme II



No	R^1	R^2
20	Me	NH–(CH2)3–NMe2
21	*t*-Bu	NH–(CH2)3–NMe2
22	Ph	NH–(CH2)3–NMe2
23	Ph	N(CH2CH2)2N–Me
24	Ph	2,6-dimethylmorpholin-4-yl
25	2-Thienyl	NH–(CH2)3–NMe2
26	2-Thienyl	N(CH2CH2)2N–Me

similar amide base-mediated cyclization of ketimines derived from **1** which produces *N*-substituted quinolin-4-amines [8]. The successful preparation of quinazolines **20-26** by a modification of this novel cyclization approach greatly expands the scope of the chemistry of the anionically activated trifluoromethyl group in heterocyclic synthesis [8-10]. It should be noted that starting compound **1** is commercially available and inexpensive.

Efficient acylation [8a] of **1** was followed by treatment of the resultant amides **2-5** with phosphorus pentachloride to give imidoyl chlorides **7-10** which then, without isolation, were allowed to react with ammonia [11] to furnish the respective amidines **11-14**. The method does not require chromatography and produces analytically pure amidines in an overall yield in the range of 70-78%. In an alternative synthesis of benzenecarboximidamide **13** the ketimine **6** derived from **1** and 2,2,2-trifluoro-1-phenylethanone was treated with sodium amide in liquid ammonia. Similar nucleophile addition reactions followed by elimination of the trifluoromethyl group are rare [10].

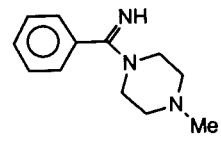
The ^{1}H nmr spectrum of ethanimidamide **11** was consistent with the presence of two diastereomers in the ratio of 1:1. The remaining compounds **12-14** were single (*Z*)-diastereomers as shown by proton nOe experiments. Briefly, irradiation of the amino protons in **12-14** gave the expected nOe enhancements for C6H of the benzenamine portion as a characteristic highest-field aromatic doublet in the spectrum and for the adjacent protons of the substituent R^1. A similar irradiation of the latter protons gave the nOe signal for the adjacent amino group only [12].

The cyclizations of **11-14** proceeded at +5° in ether or at +50° in benzene and in both cases produced the corresponding quinazolines **20-26** in similar yields in the range of 36-57%. A careful analysis of a crude mixture containing quinazoline **20** revealed the absence of a quinoline product which could have originated from ionization of the starting ethanimidamide **11** at the methyl group [8]. This high chemoselectivity shows that quinazolines substituted at position 2 with a primary or secondary alkyl group can also be obtained by this cyclization method.

An interesting result is the successful preparation of a highly sterically congested quinazoline **24**. This compound could not be prepared in attempted reactions of 4-chloro-2-phenylquinazoline with 2,2,6,6-tetramethylpiperidine or its lithio derivative under a variety of experimental conditions. On the other hand, the reaction of 4-chloro-2-phenylquinazoline with *N,N*-dimethyl-1,2-ethanediamine or *N*-methylpiperazine furnished the respective quinazolines **22** and **23** identical to the quinazolines of the corresponding cyclization reactions of benzenecarboximidamide **13**.

The cyclization method, thus, is suitable for the synthesis of sterically congested quinazolin-4-amines and in the synthesis of derivatives for which the corresponding 4-chloroquinazolines are not readily available. Although chromatographic purification was required, a simple flash chromatography was sufficient in all cases studied. A quinazoline was always eluted first, followed by additional, much more polar products.

In order to gain an insight into side reactions, selected mixtures containing quinazolines **23** and **25** were analyzed in more detail. Chromatography gave the respective amidines **27** and **28** as the second major products in 10-15%



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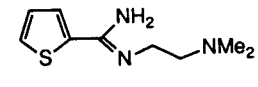

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yields and a large number of minor unidentified compounds. The yields of **27** and **28** increased to 40-60% and the quinazoline formation was suppressed for the reactions conducted in benzene at +5°. The competitive formation of **27, 28** apparently originates from the addition reaction of an amide base to the C=N function of non-ionized starting amidines **13, 14** or intermediate products derived from **16-18**, which is followed by elimination of an anionic benzenamine function from the resultant adduct. It has been shown previously that such a trifluoromethyl-substituted anion and derivatives are unstable and undergo a number of complex transformations [9].

EXPERIMENTAL

Ether, tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl immediately before use. Flash chromatography was conducted with silica gel as an adsorbent. Melting points (Pyrex capillary) are not corrected. Unless stated otherwise ^{1}H nmr spectra were obtained at 400 MHz at 25° in deuteriochloroform solutions with tetramethylsilane as an internal reference. Coupling constants smaller than 1.5 Hz are not reported.

Amides **3-5** were prepared by using the procedure [8a] for the preparation of **2** and crystallized from aqueous ethanol.

N-[2-(Trifluoromethyl)phenyl]-2,2-dimethylpropanamide, **3**.

This compound had mp 93-94°, yield 96%; ^{1}H nmr: δ 1.33 (s, 9H), 7.21 (t, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.80 (br s, exchangeable with deuterium oxide, 1H), 8.25 (d, J = 8 Hz, 1H); ms: m/z 57 (100), 161 (27), 245 (M^+, 25).

Anal. Calcd. for $C_{12}H_{14}F_3NO$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.68; H, 5.77; N, 5.63.

N-[2-(Trifluoromethyl)phenyl]benzamide, **4**.

This compound had mp 143-145°, yield 84%; ^{1}H nmr: δ 7.28 (t, J = 8 Hz, 1H), 7.50-7.68 (m, 5H), 7.88 (m, 2H), 8.24 (br s, exchangeable with deuterium oxide, 1H), 8.45 (d, J = 8 Hz, 1H); ms: m/z 105 (100), 265 (M^+, 26).

Anal. Calcd. for $C_{14}H_{10}F_3NO$: C, 63.39; H, 3.80; N, 5.28. Found: C, 63.21; H, 3.89; N, 5.20.

N-[2-(Trifluoromethyl)phenyl]thiophene-2-carboxamide, **5**.

This compound had mp 129-131°, yield 85%; ^{1}H nmr: δ 7.16 (dd, J = 4 and 5 Hz, 1H), 7.26 (t, J = 8 Hz, 1H), 7.57-7.67 (m, 4H), 8.10 (br s, exchangeable with deuterium oxide, 1H), 8.40 (d, J = 8 Hz, 1H); ms: m/z 111 (100), 271 (M^+, 36).

Anal. Calcd. for $C_{12}H_8F_3NOS$: C, 53.13; H, 2.97; N, 5.16. Found: C, 53.05; H, 2.97; N, 5.12.

2,2,2-Trifluoro-1-phenyl-*N*-[2-(trifluoromethyl)phenyl]ethanimine, **6**.

A solution of **1** (1.93 g, 10 mmoles), 2,2,2-trifluoro-1-phenylethanone (2.09 g, 10 mmoles), and *p*-toluene sulfonic acid (0.06 g) in toluene (35 ml) was heated under reflux for 36 hours with azeotropic removal of water. Flash chromatography (hexanes/*N*,*N*-diethylethanamine, 9:1) gave 2.76 g (73%) of **6** as an oil; ^{1}H nmr: δ 6.43 (d, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 7.22-7.40 (m, 6H), 7.64 (d, J = 8 Hz, 1H); ms: m/z 248 (100), 317 (M^+, 34).

Anal. Calcd. for $C_{15}H_9F_6N$: C, 56.79; H, 2.86; N, 4.42. Found: C, 56.87; H, 2.90; N, 4.35.

General Procedure for Preparation of Amidines **11-14**.

An amide **2-5**, (10 mmoles) was added to a suspension of phosphorus pentachloride (2.16 g, 10.5 mmoles) in dry benzene (30 ml). The mixture was stirred 15 minutes 50° and then concentrated under reduced pressure. Dry benzene (50 ml) was added to the residue and the solution was concentrated again to remove traces of hydrogen chloride and phosphoryl chloride. A solution of the resultant crude imidoyl chloride, **7-10**, in dry tetrahydrofuran (30 ml) in an open pressure vessel was cooled to −40° under a nitrogen atmosphere. Dry ammonia was bubbled through the solution until the total volume reached 35 ml. The vessel was sealed and allowed to stand at 23° for 10 hours and then cooled to −40°, opened, and allowed to warm slowly to 23°. After removal of tetrahydrofuran on a rotary evaporator the residue was treated with water (2 ml) and extracted with ether (3 x 35 ml). Hexanes (20 ml) were added to the ether and the mixture was dried with sodium sulfate. Removal of the solvent on a rotary evaporator gave an amidine, **11-14**. Solid compounds **12-14** were crystallized from hexanes or hexanes/ethanol.

N'-[2-(Trifluoromethyl)phenyl]ethanimidamide, **11**.

This compound was obtained as an oil, yield 70%; ^{1}H nmr: δ 1.75 and 2.13 (2s, 3H, *Z* and *E* isomers), 4.35 and 4.75 (2 br s, 2H, exchangeable with deuterium oxide, *Z* and *E*), 6.70-7.63 (m, 4H); ms: m/z 186 (57), 202 (M^+, 100).

Anal. Calcd. for $C_9H_9F_3N_2$: C, 53.46; H, 4.48; N, 13.86. Found: C, 53.28; H, 4.56; N, 13.70.

2,2-Dimethyl-*N'*-[2-(trifluoromethyl)phenyl]propanimidamide, **12**.

This compound had mp 60-61°, yield 75%; ^{1}H nmr: δ 1.30 (s, 9H), 4.32 (br s, 2H, exchangeable with deuterium oxide), 6.86 (d, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.43 (t, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H); ms: m/z 40 (100), 149 (77), 167 (84), 229 (52), 244 (M^+, 38).

Anal. Calcd. for $C_{12}H_{15}F_3N_2$: C, 59.00; H, 6.19; N, 11.47. Found: C, 59.12; H, 6.24; N, 11.38.

N'-[2-(Trifluoromethyl)phenyl]benzenecarboximidamide, **13**.

This compound had mp 106-107°, yield 78%; ^{1}H nmr: δ 4.76 (br s, 2H, exchangeable with deuterium oxide), 6.86 (d, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 7.44-7.53 (m, 4H), 7.68 (d, J = 8 Hz, 1H), 7.89 (m, 2H); ms: m/z 248 (69), 264 (M^+, 100).

Anal. Calcd. for $C_{14}H_{11}F_3N_2$: C, 63.63; H, 4.20; N, 10.60. Found: C, 63.73; H, 4.24; N, 10.55.

N'-[2-(Trifluoromethyl)phenyl]-2-thiophenecarboximidamide, **14**.

This compound had mp 107-109°, yield 71%; ^{1}H nmr: δ 4.74 (br s, 2H, exchangeable with deuterium oxide), 7.04-7.14 (m, 3H), 7.44-7.49 (m, 3H), 7.66 (d, J = 8 Hz, 1H); ms: m/z 254 (84), 270 (M^+, 100).

High resolution ms. Calcd. for $C_{12}H_9F_3N_2S$ m/z 270.0438; observed m/z 270.0433.

Preparation of Amidine **13** from Imine **6**.

A solution of sodium amide prepared from liquid ammonia (10 ml) and sodium (0.25 g, 11 mg-atoms) in the presence of ferric chloride (20 mg) was treated with a solution of ketimine **6** (0.48 g, 1.5 mmoles) in tetrahydrofuran (5 ml). The mixture was stirred under reflux for 2.5 hours and then quenched by dropwise addition of ethanol (2.5 ml) in ether (20 ml). The dry-ice condenser was removed, and ammonia was allowed to evaporate. Then the mixture was treated with a saturated solution of ammonium chloride (2.5 ml). The organic layer was dried (sodium sulfate) and concentrated on a rotary evaporator. Chromatography (hexanes/*N*,*N*-diethylethanamine/ethanol, 7:2:1) gave 0.22 g (65%) of **13** identical with the amidine obtained from amide **4** as described above.

General Procedure for Preparation of Quinazolines **20-26**.

A solution of an amine (*N*,*N*-dimethyl-1,2-ethanediamine, *N*-methylpiperazine or 2,2,6,6-tetramethylpiperidine, 5 mmoles) in dry benzene (10 ml) was treated with *n*-butyllithium (2.5 *M* in hexanes, 2 ml, 5 mmoles) at +5°, and the resultant mixture was stirred at +5° for 15 minutes before treatment with a solution of an amidine, **11-14**, (1 mmole) in anhydrous benzene (10 ml). The mixture was stirred at +50° for 8 hours and then cooled to +23° and quenched with water. The benzene layer was concentrated on a rotary evaporator. Chromatography (hexanes/*N*,*N*-diethylethanamine/ethanol, 7:2:1) was followed by crystallization of a solid quinazoline **20**, **24**, **25** from hexanes or hexanes/ether. An oil, **21-23**,**26**, was dissolved in ethanol (5 ml) and the resultant solution was treated with phosphoric acid or hydrogen bromide in ethanol (1 *M*, 2 ml, 2 mmoles). The resultant precipitate of a salt was crystallized from aqueous ethanol.

The reaction in ether was conducted at +5° for 2 hours and worked up as described above.

N-[2-(Dimethylamino)ethyl]-2-methylquinazolin-4-amine, **20**.

This compound had mp 107-108°, yield 47%; ^{1}H nmr: δ 2.32 (s, 6H), 2.62 (t, J = 6 Hz, 2H), 2.64 (s, 3H), 3.68 (m, 2H; t, J = 6 Hz, 2H, after treatment with deuterium oxide), 6.53 (br s, 1H, exchangable with deuterium oxide), 7.39 (t, J = 8 Hz, 1H), 7.68 (t, J = 8 Hz, 1H), 7.73 (d, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H); ms: chemical ionization (2-methylpropane) m/z 160 (48), 231 (M^++1, 100).

Anal. Calcd. for $C_{13}H_{18}N_4$: C, 67.79; H, 7.88; N, 24.33. Found: C, 67.82; H, 7.85; N, 24.20.

N-[2-Dimethylamino)ethyl]-2-(1,1-dimethylethyl)quinazolin-4-amine, **21**.

This compound was obtained as an oil, yield 41%; ^{1}H nmr: (60 MHz) δ 1.45 (s, 9H), 2.31 (s, 6H), 2.63 (t, J = 6 Hz, 2H), 3.75 (m, 2H; t, J = 6 Hz, 2H, after treatment with deuterium oxide), 6.50 (br s, 1H, exchangeable with deterium oxide), 7.2-8.0 (m, 4H); ms: chemical ionization (2-methylpropane) m/z 109 (65), 202 (65), 273 (M^++1, 100). The phosphate salt, **21**·2½HH_3PO_4·2H_2O, had mp 178-179°.

Anal. Calcd. for $C_{16}H_{24}N_4$·2½H_3PO_4·2H_2O: C, 34.72; H, 6.46; N, 10.12. Found: C, 34.60; H, 6.38; N, 10.04.

N-[2-(Dimethylamino)ethyl]-2-phenylquinazolin-4-amine, **22**.

This compound was obtained as an oil, yield 57%; ^{1}H nmr: (60 MHz) δ 2.30 (s, 6H), 2.63 (t, J = 6 Hz, 2H), 3.82 (m, 2H, t, J = 6 Hz, 2H, after treatment with deuterium oxide), 6.62 (br s, 1H, exchangeable with deuterium oxide), 7.20-8.10 (m, 7H), 8.67 (m, 2H); ms: chemical ionization (2-methylpropane) m/z 293 (M^++1, 100). The phosphate salt, **22**·2HBr·H_2O, had mp 282-283°.

Anal. Calcd. for $C_{18}H_{20}N_4$·2HBr·H_2O: C, 45.78; H, 5.12; N, 11.87. Found: C, 45.76; H, 5.15; N, 11.82.

4-(4-Methylpiperazin-1-yl)-2-phenylquinazoline, **23**.

The compound was obtained as an oil, yield 49%; ^{1}H nmr: (60 MHz) δ 2.40 (s, 3H), 2.66 (t, J = 5 Hz, 4H), 3.92 (t, J = 5 Hz, 4H), 7.25-8.15 (m, 7H), 8.65 (m, 2H); ms: chemical ionization (2-methylpropane) m/z 305 (M^++1, 100). The phosphate salt, **23**·1½H_3PO_4·H_2O, had mp 154-155°.

Anal. Calcd. for $C_{19}H_{20}N_4$·1½H_3PO_4·H_2O: C, 48.61; H, 5.69; N, 11.94. Found: C, 48.57; H, 5.68; N, 11.99.

2-Phenyl-4-(2,2,6,6-tetramethylpiperidin-1-yl)quinazoline, **24**.

This compound had mp 126-127°, yield 36%; ^{1}H nmr: δ 0.70 (s, 6H), 1.50-1.78 (m, 12H, including s, 6H, at δ 1.62), 7.48-7.58 (m, 4H), 7.81 (t, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.52 (d, J = 8 Hz, 1H), 8.67 (m, 2H); ms: m/z 330 (100), 345 (M^+, 3).

Anal. Calcd. for $C_{23}H_{27}N_3$: C, 79.96; H, 7.88; N, 12.16. Found: C, 79.84; H, 7.85; N, 12.22.

N-[2-(Dimethylamino)ethyl]-2-(2-thienyl)quinazolin-4-amine, **25**.

This compound had mp 109-111°, yield 40%; ^{1}H nmr: (60 MHz) δ 2.30 (s, 6H), 2.63 (t, J = 6 Hz, 2H), 3.80 (m, 2H; t, J = 6 Hz, 2H, after treatment with deuterium oxide), 6.70 (br s, 1H, exchangeable with deuterium oxide), 7.10-8.20 (m, 7H); ms: chemical ionization (2-methylpropane) m/z 228 (83), 299 (M^++1, 100).

High resolution ms: chemical ionization (methane). Calcd. for $C_{16}H_{19}N_4S$ (M^++1) m/z 299.1330; observed m/z 299.1320.

4-(4-Methylpiperazin-1-yl)-2-(2-thienyl)quinazoline, **26**.

This compound was obtained as an oil, yield 46%; ^{1}H nmr: (60 MHz) δ 2.38 (s, 3H), 2.64 (t, J = 5 Hz, 4H), 3.88 (t, J = 5 Hz, 4H), 7.12-8.05 (m, 7H); ms: m/z 83 (78), 211 (63), 240 (100), 310 (M^+, 20).

High resolution ms: Calcd. for $C_{17}H_{18}N_4S$ m/z 310.1252; observed m/z 310.1261.

The hydrobromide salt, **26**·2HBr, had mp >325°.

Anal. Calcd. for $C_{17}H_{18}N_4S$·2HBr: C, 43.23; H, 4.27; N, 11.86. Found: C, 43.19; H, 4.25; N, 11.77.

Compounds **27** and **28**.

After quinazolines **23** and **25** had been isolated by chromatography the subsequent elution with hexanes/*N*,*N*-diethylethanamine/ethanol (6:2:2) gave the respective compounds **27** and **28**. These oily products were transformed into crystalline hydrobromides as described for the quinazolines.

1-(Iminophenylmethyl)-4-methylpiperazine, **27**.

The yields were 40% (benzene, +5°) and 10% (ether, +5°; benzene, +50°); ^{1}H nmr: (60 MHz) δ 2.33 (s, 3H), 2.45 (t, J = 5 Hz, 4H), 3.46 (t, J = 5 Hz, 4H), 5.90 (br s, 1H), 7.41 (s, 5H); ms: chemical ionization (2-methylpropane) m/z 121 (38), 204 (M^++1, 100). The hydrobromide salt, **27**·2HBr, had mp 299-300°.

Anal. Calcd. for $C_{12}H_{17}N_3$·2HBr: C, 39.47; H, 5.24; N, 11.51. Found: C, 39.45; H, 5.21; N, 11.45.

N'-[2-(Dimethylamino)ethyl]-2-thiophenecarboximidamide, **28**.

The yields were 60% (benzene, +5°) and 15% (ether, +5°, benzene, +50°); ^{1}H nmr: (60 MHz) δ 2.30 (s, 6H), 2.60 (t, J = 6 Hz, 2H), 3.45 (t, J = 6 Hz, 2H), 5.50 (br s, 2H), 7.10 (t, J = 4 Hz, 1H), 7.40 (d, J = 4 Hz, 2H); ms: chemical ionization (2-methylpropane) m/z 110 (100), 198 (M^++1, 54). The hydrobromide salt, **28**·2HBr, had mp 262-265°.

Anal. Calcd. for $C_9H_{15}N_3S$·2HBr: C, 30.10; H, 4.77; N, 11.70. Found: C, 30.40; H, 4.79; N, 11.64.

Acknowledgment.

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