Synthesis of 2,2,4-Trisubstituted-1,2-dihydroquinazolines

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Synthesis of 2,2,4-trisubstituted-1,2-dihydroquinazolines **6** from readily available 2-aminobenzonitrile (**1**) is described. The scope and limitations of the method are discussed.

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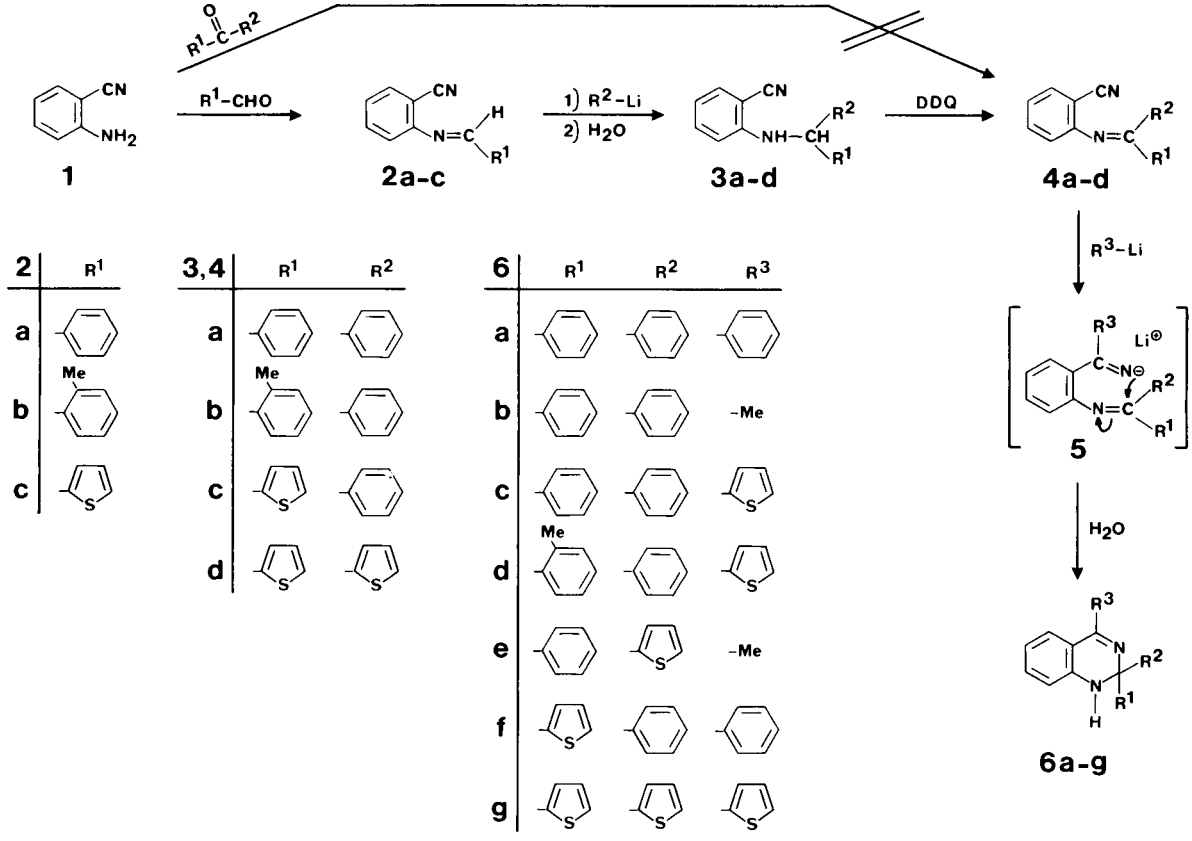
We have reported recently [1] a chemoselective addition reaction of phenyllithium to the methyleneamino moiety of Schiff's base **2a** obtained from 2-aminobenzonitrile (**1**) and benzaldehyde (Scheme I). The resultant amine **3a** is readily dehydrogenated by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give Schiff's base **4a**. It should be noted that compound **4a** could not be obtained in the attempted condensation reaction of **1** with benzophenone. The opposite chemoselectivity, that is, the addition to the cyano group, is observed upon treatment of **4a** with either phenyllithium or methyllithium. The adducts **5a** and **5b** undergo spontaneous cyclization to give, in high overall yields, the respective trisubstituted dihydroquinazolines **6a** and **6b**, the first two members of this previously unknown class of compounds.

We now report the scope and limitations of our route to 2,2,4-trisubstituted-1,2-dihydroquinazolines **6**. Further synthetic studies have been strongly encouraged by the recent finding that **6a** and **6b** bind with DNA, apparently to form a complex with the DNA major groove only [2]. This selective binding may have important ramifications for future design and synthesis of molecular probes within this new class of compounds for studying DNA stereochemistry and dynamics [3]. The DNA binding studies of **6** described here and other derivatives will be reported in due course.

As shown in Scheme I the method is suitable for the preparation of dihydroquinazolines **6** trisubstituted with aryl and heteroaryl groups. By properly choosing the aromatic aldehyde R^1-CHO for the synthesis of Schiff's base

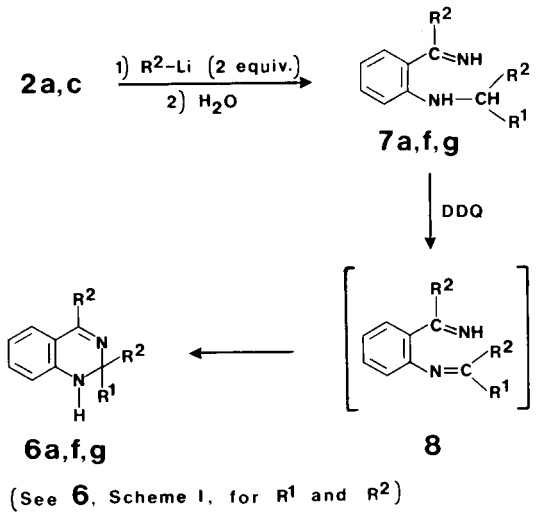
Scheme I



2, and lithium reagents R^2-Li and/or R^3-Li for the subsequent addition reactions, the three substituents at a 1,2-dihydroquinazoline system can be identical as in **6a**, **6g**, one can be different as in **6c**, **6f** or all three aromatic groups can be different as in **6d**. An alkyl group R^3 can also be introduced at position 4 with the use of a lithium reagent R^3-Li, as exemplified by the synthesis of **6b** and **6e**.

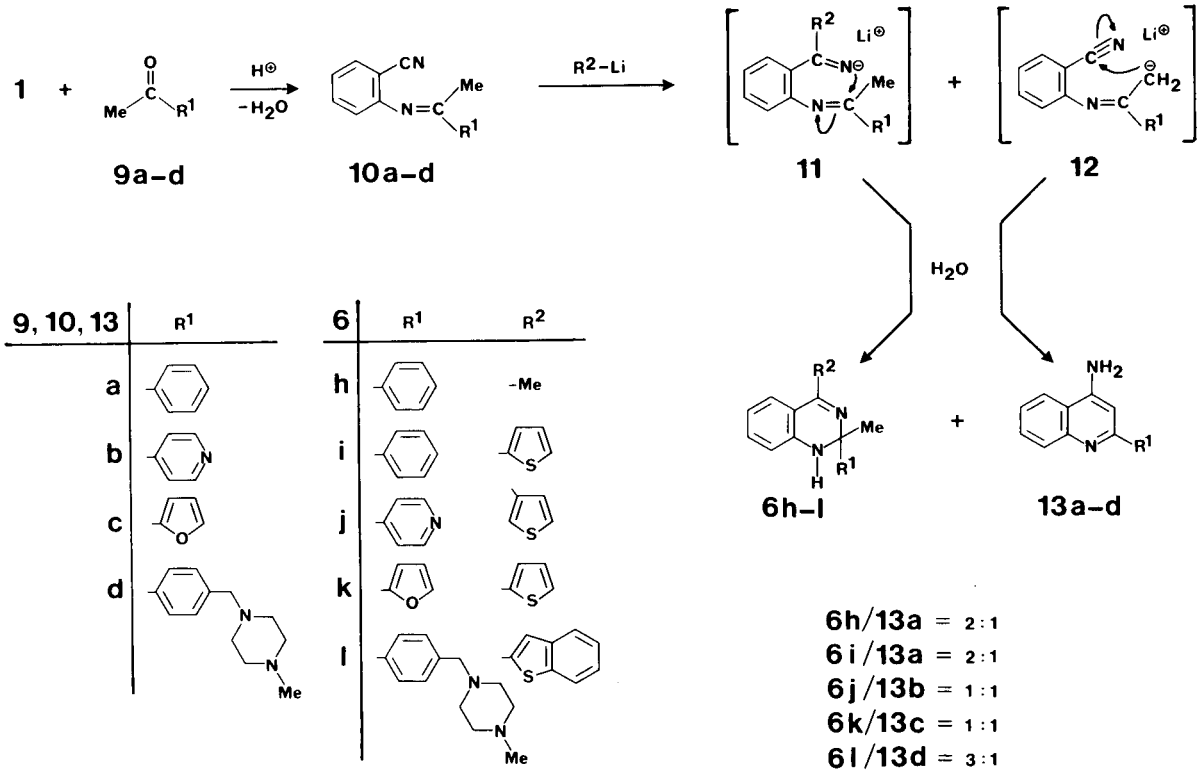
A modification of the method for the preparation of **6** with three identical aromatic substituents and for the preparation of **6** with two identical aromatic substituents at positions 2 and 4, is presented in Scheme II. In this approach the Schiff's base **2** is reacted with an excess of a lithium reagent to produce adduct **7**, which, without isolation, is treated with DDQ. The resultant intermediate product **8** undergoes cyclization to dihydroquinazoline **6**. This route to appropriately substituted **6** is preferred over that given in Scheme I. The route of Scheme II is simpler and results in higher yields of final products. On the other hand, neither method is suitable for the preparation of a dihydroquinazoline **6** with an alkyl group at position 2. Thus, while the addition reaction of **2a-c** with alkyllithium reagents R^2-Li proceeded smoothly to give the corresponding adducts **3** (Scheme I, R^2 = alkyl), the latter compounds failed to be dehydrogenated in the presence of DDQ under a variety of experimental conditions. The corresponding dialkyl adducts **7** (Scheme II, R^2 = alkyl) were stable in the presence of DDQ as well. In addition, **1** could not be condensed with dialkyl ketones to produce the corresponding Schiff's bases **4** (Scheme I, R^1 and R^2 = alkyl), the required precursors for 2,2-dialkyl-substituted **6**.

Scheme II



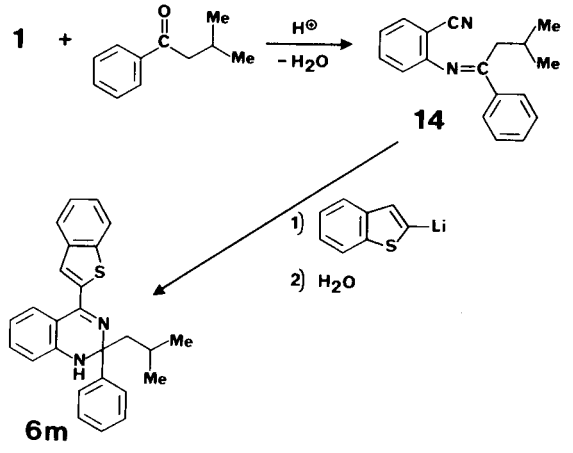
We have found, however, that in contrast to the unsuccessful condensations of dialkyl ketones and diaryl ketones with **1**, the alkyl aryl ketones and alkyl heteroaryl ketones **9** can be condensed with **1** to give the corresponding Schiff's bases in a high yield. The methyl derivatives **10a-d** thus obtained (Scheme III) react with organolithium reagents to produce the corresponding **6** through cyclization of the intermediate adduct **11**. A disturbing side reac-

Scheme III



tion in this preparation is lithiation of the methyl group of **10**. The resultant anion **12** then undergoes an intramolecular cyclization to give a quinoline **13** [4]. Of several solvents studied [5], ether was found to be the best medium for the synthesis of **6**. The ratios of **6/13** for the reactions conducted in ether are given in Scheme III. As can be seen from the first two entries, the reactions of either methyllithium and 2-thienyllithium with Schiff's base **10a** give the same ratio of **6/13**. On the other hand, the relative yields of the two products depend strongly on the electronic nature of the substituent R^1 in **10**. The electron-withdrawing 4-pyridinyl and 2-furanyl groups in **10b** and **10c**, respectively, facilitate the undesired lithiation reaction because the resultant anions **12** are stabilized by these substituents. The electron-donating 4-alkylphenyl group in **10d** has an opposite effect which strongly favors the formation of the corresponding adduct **11**, and subsequently results in an increased yield of dihydroquinazoline **6l**. The undesired lithiation reaction does not take place with higher homologues of **10** [6], as exemplified in Scheme IV for the synthesis of **6m** from Schiff's base **14** [7].

Scheme IV



We have thus shown that only with the exception of 2,2-dialkyl-substituted derivatives, a large number of other 2,2,4-trisubstituted-1,2-dihydroquinazolines **6** can conveniently be prepared from readily available starting materials.

EXPERIMENTAL

Phenyllithium (2 *M* in cyclohexane/ether), methyllithium (1.4 *M* in ether), and *n*-butyllithium (2.6 *M* in hexanes) were obtained from Aldrich. Solutions of 2-thienyllithium and 2-benzo[*b*]thienyllithium in ether were generated from thiophene (0.36 ml, 4.5 mmoles) and benzo[*b*]thiophene (0.6 g, 4.5 mmoles, respectively, by treatment with *n*-butyllithium (1.0 ml, 2.6 mmoles) at 0° for 15 minutes [8]. 3-Thienyllithium in ether (10 ml) was generated from 3-bromothiophene (0.25 ml, 2.6 mmoles) and *n*-butyllithium (1.0 ml, 2.6 mmoles) at −30° [8]. All reaction with organolithium reagents were conducted in ether distilled from sodium benzophenone ketyl immediately before use and under static pressure of nitrogen. The glassware was dried at 140°, assembled hot, and cooled in a stream of nitrogen. The liquids were transferred with syringes. Melting points (Pyrex capillary) are uncorrected. Mass spectra (70 eV) and Fourier-transform infrared spectra (neat) were recorded on a Varian MAT spectrometer and a Bomem Michelson-100 instrument, respectively. Unless stated otherwise, ^{1}H nmr spectra were obtained on a Varian VXR-400 (400 MHz) spectrometer at 25°. The spectra were taken in deuteriochloroform solutions (0.05 M) with tetramethylsilane as an internal standard.

General Procedure for Preparation of Schiff's Bases **2a-c**.

The condensation of **1** (1.18 g, 10 mmoles) with the appropriate aldehyde (11 mmoles) in toluene (30 ml) in the presence of molecular sieves 4A for 5 hours at 50° is more convenient than the previously described [1] acid-catalyzed reaction. Removal of the toluene and the excess aldehyde under reduced pressure gave the corresponding Schiff's bases **2a-c** (98-99%) which were used without further purification. The following data were obtained for samples crystallized from hexanes.

2-[(Phenylmethylene)amino]benzonitrile, **2a**.

Obtained from **1** and benzaldehyde, mp 109-111° (reported [1] mp 109-111°).

2-[[(2-Methylphenyl)methylene]amino]benzonitrile, **2b**.

Obtained from **1** and 2-methylbenzaldehyde, mp 104-106°; ^{1}H nmr: δ 2.65 (s, 3H), 7.16 (d, J = 8 Hz, 1H), 7.26 (m, 2H), 7.31 (t, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 8.75 (s, 1H).

Anal. Calcd. for $C_{15}H_{12}N_2$: C, 81.76; H, 5.49. Found: C, 81.84; H, 5.51.

2-[(2-Thienylmethylene)amino]benzonitrile, **2c**.

Obtained from **1** and 2-thiophenecarboxaldehyde, mp 106-107°; ms: m/e 211 (84), 212 (100, M$^+$); ^{1}H nmr: (60 MHz) δ 7.05-7.75 (m, 7H), 8.57 (s, 1H).

Anal. Calcd. for $C_{12}H_8N_2S$: C, 67.90; H, 3.80. Found: C, 67.71; H, 3.85.

General Procedure for Preparation of Schiff's Bases **4a-d**.

The respective compound **2** (4.0 mmoles) in ether (50 ml) was reacted with a lithium reagent (4.1 mmoles) at 0° for 1 hour. The mixture was then quenched with water (0.1 ml), filtered, concentrated, and dissolved in benzene (50 ml). This solution of crude **3** was treated wiht DDQ (0.93 g, 4.1 mmoles), and the resultant mixture was stirred at 60° for 2 hours (Note: the use of toluene [1] gives lower yields of **4**). Then the mixture was cooled, washed with aqueous solution of sodium hydroxide (5%, 3 x 25 ml), dried over sodium sulfate and concentrated under reduced pressure. Compounds **4** were obtained by chromatography on silica gel (hexanes/triethylamine, 9:1). Solid samples **4a**, **4c** and **4d** were additionally crystallized from hexanes.

2-[(Diphenylmethylene)amino]benzonitrile, **4a**.

Obtained from **2a** and phenyllithium; yield 90%, mp 118-119° (reported [1] mp 118-119°).

2-[[(2-Methylphenyl)phenylmethylene]amino]benzonitrile, **4b**.

Obtained from **2b** and phenyllithium, yield 86%; ir: 1620, 2220 cm^{-1}; ^{1}H nmr: (60 MHz) δ 2.12 and 2.34 (2s, 2.4 H and 0.6 H,

respectively: two diastereomers; see footnote [7]), 6.60-7.80 (m, 13 H).

Anal. Calcd. for $C_{21}H_{16}N_2$: C, 85.10; H, 5.44. Found: C, 84.95; H, 5.49.

2-[[Phenyl(2-thienyl)methylene]amino]benzonitrile, **4c**.

Obtained from **2c** and phenyllithium, yield 85%, mp 165-167°; ir: 1620, 2221 cm^{-1}; ms: m/e 287 (48), 288 (100, M^+); ^1H nmr: (60 MHz) δ 6.65-7.62 (m).

Anal. Calcd. for $C_{18}H_{12}N_2S$: C, 74.97; H, 4.20. Found: C, 75.06; H, 4.21.

2-[[(Di(2-thienyl)methylene]amino]benzonitrile, **4d**.

Obtained from **2c** and 2-thienyllithium, yield 87%, mp 154-155°; ir: 2223 cm^{-1}; ms: m/e 211 (76), 293 (36), 294 (100, M^+); ^1H nmr: (60 MHz) δ 6.87-7.62 (m).

Anal. Calcd. for $C_{16}H_{10}N_2S_2$: C, 65.28; H, 3.42. Found: C, 65.45; H, 3.40.

Schiff's bases **10a-c** and **14**.

Compounds **10a-c** were prepared in the *p*-toluenesulfonic acid-catalyzed condensation of **1** with the appropriate ketone in toluene, as described [4]. A new compound **14** was prepared in a similar manner.

2-[(3-Methyl-1-phenylbutylidene)amino]benzonitrile, **14**.

Obtained from **1** and 3-methyl-1-phenyl-1-butanone, yield 70%, an oil after chromatography on silica gel (hexanes/triethylamine, 9:1); ir: 1635, 2223 cm^{-1}; ms: m/e 205 (100), 219 (46), 220 (51), 247 (59), 261 (47), 262 (66, M^+); ^1H nmr: (60 MHz) δ 0.80 (d, J = 7 Hz, 6H), 1.90 (m, 1H), 2.62 (d, J = 7 Hz, 2H), 6.87 (d, J = 8 Hz, 1H), 7.13 (t, J = 8 Hz, 1H), 7.41-7.66 (m, 5H), 7.92 (d, J = 7 Hz, 2H).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.39; H, 6.92. Found: C, 82.30; H, 6.93.

2-[[1-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]ethylidene]amino]benzonitrile, **10d**.

Compound **10d** could not be prepared using the method described above. The modified procedure is given below.

A mixture of 4-(4-methylpiperazin-1-ylmethyl)benzonitrile (0.86 g, 4 mmoles) [prepared from 4-(bromomethyl)benzonitrile and 1-methylpiperazine, mp 66-68° (from hexanes); ^1H nmr: (60 MHz) δ 2.28 (s, 3H), 2.46 (s, 8H), 3.56 (s, 2H), 7.50 (d, J = 8 Hz, 2H), 7.62 (d, J = 8 Hz, 2H)] and methylmagnesium bromide (7 mmoles) in ether (50 ml) was stirred under reflux for 12 hours and then quenched with a saturated solution of ammonium chloride (5 ml). The quenched mixture was stirred at 23° for 30 minutes. The ether was dried over sodium sulfate, evaporated, and the residue was distilled on a Kugelrohr (100°/0.2 mm Hg) to give 0.78 g (85%) of 1-[4-(4-methylpiperazin-1-ylmethyl)phenyl]ethanone (**9d**) as an oil; ^1H nmr: (60 MHz) δ 2.28 (s, 3H), 2.46 (s, 8H), 2.58 (s, 3H), 3.56 (s, 2H), 7.50 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{14}H_{20}N_2O$: C, 72.37; H, 8.68. Found: C, 72.15; H, 8.75.

In the preparation of **10d**, a mixture of **1** (0.24 g, 2 mmoles), **9d** (0.70 g, 3 mmoles), glacial acetic acid (50 ml), and toluene (50 ml) was heated under reflux for 12 hours with azeotropic removal of water, then concentrated under reduced pressure, cooled, and treated with ether (100 ml). The ether was washed with a cold solution of sodium bicarbonate (10%, 3 x 20 ml), dried over sodium sulfate and concentrated. Compound **10d** was isolated by chromatography on silica gel (hexanes/triethylamine/ethanol, 7:2:1), yield 64%, mp 64-66°; ir: 1636, 2224 cm^{-1}; ms: m/e 99 (100), 261 (74), 332 (68, M^+); ^1H nmr: δ 2.27 (s, 3H), 2.29 (s, 3H), 2.49 (m, 8H), 3.57 (s, 2H), 6.89 (d, J = 8 Hz, 1H), 7.15 (t, J = 8 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 7.55 (t, J = 8 Hz, 1H), 7.64 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28. Found: C, 76.05; H, 7.32.

General Procedure for Preparation of Dihydroquinazolines, **6a-m**.

A solution of **4**, **10** or **14** (3 mmoles) in ether (50 ml) was treated dropwise at −10° with an organolithium reagent (3.1 mmoles). The mixture was stirred at 0° for 2 hours and quenched with water (0.1 ml), and the ether solution was filtered and concentrated. Dihydroquinazolines **6** were isolated by chromatography on silica gel (hexanes/triethylamine, 7:3). Solid products were additionally crystallized from hexanes or toluene/hexanes.

2,2,4-Triphenyl-1,2-dihydroquinazoline, **6a**.

Obtained from **4a** and phenyllithium [1], yield 99%.

4-Methyl-2,2-diphenyl-1,2-dihydroquinazoline, **6b**.

Obtained from **4a** and methyllithium [1], yield 67%.

2,2-Diphenyl-4-(2-thienyl)-1,2-dihydroquinazoline, **6c**.

Obtained from **4a** and 2-thienyllithium, yield 85%, mp 203-204°; ir: 1608, 3398 cm^{-1}; ms: m/e 289 (100), 365 (5), 366 (4, M^+); ^1H nmr: δ 4.76 (br s, 1H), 6.71 (t, J = 8 Hz, 1H), 6.82 (d, J = 8 Hz, 1H), 7.05-7.60 (m, 15H).

Anal. Calcd. for $C_{24}H_{18}N_2S$: C, 78.64; H, 4.95. Found: C, 78.65; H, 5.01.

2-(2-Methylphenyl)-2-phenyl-4-(2-thienyl)-1,2-dihydroquinazoline, **6d**.

Obtained from **4b** and 2-thienyllithium, yield 72%, an oil; ir: 1610, 3400 cm^{-1}; ms: m/e 289 (100), 303 (69), 379 (7), 380 (11, M^+); ^1H nmr: δ 2.28 (s, 3H), 4.55 (br s, 1H), 6.72 (t, J = 8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 7.04-7.55 (m, 14H).

Anal. Calcd. for $C_{25}H_{20}N_2S$: C, 78.91; H, 5.30. Found: C, 78.71; H, 5.55.

4-Methyl-2-phenyl-2-(2-thienyl)-1,2-dihydroquinazoline, **6e**.

Obtained from **4c** and methyllithium, yield 65%, mp 101-102°; ir: 1622, 3388 cm^{-1}; ms: m/e 227 (100), 303 (5), 304 (7, M^+); ^1H nmr: δ 2.43 (s, 3H), 4.73 (br s, 1H), 6.64 (d, J = 8 Hz, 1H), 6.70 (t, J = 8 Hz, 1H), 6.82 (m, 1H), 6.89 (m, 1H), 7.20-7.35 (m, 6H), 7.52 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{19}H_{16}N_2S$: C, 74.95; H, 5.30. Found: C, 75.01; H, 5.34.

2,4-Diphenyl-2-(2-thienyl)-1,2-dihydroquinazoline, **6f**.

Obtained from **4c** and phenyllithium, yield 91%, mp 220-221°; ir: 1612, 3382 cm^{-1}; ms: m/e 289 (100), 365 (9), 366 (6, M^+); ^1H nmr: δ 4.86 (br s, 1H), 6.67 (t, J = 8 Hz, 1H), 6.78 (d, J = 8 Hz, 1H), 6.92 (m, 2H), 7.10 (d, J = 8 Hz, 1H), 7.24-7.36 (m, 5H), 7.45 (m, 3H), 7.63 (m, 4H).

Anal. Calcd. for $C_{24}H_{18}N_2S$: C, 78.65; H, 4.95. Found: C, 78.20; H, 5.05.

2,2,4-Tri(2-thienyl)-1,2-dihydroquinazoline, **6g**.

Obtained from **4d** and (2-thienyl)lithium, yield 66%, mp 181-182°; ir: 1608, 3378 cm^{-1}; ms: m/e 295 (100), 377 (25), 378 (36, M^+); ^1H nmr: δ 4.74 (br s, 1H), 6.80 (t, J = 8 Hz, 1H), 6.82 (d, J =

8 Hz, 1H), 6.91 (m, 2H), 7.03 (m, 2H), 7.14 (m, 1H), 7.24 (m, 2H), 7.32 (t, J = 8 Hz, 1H), 7.48 (m, 2H), 7.58 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{20}H_{14}N_2S_3$: C, 63.44; H, 3.73. Found: C, 63.49; H, 3.74.

2,4-Dimethyl-2-phenyl-1,2-dihydroquinazoline, **6h**.

Obtained from **10a** and methyllithium, yield 63%; mp 66-68°, ir: 1626, 3387 cm^{-1}; ms: m/e 159 (31), 221 (100), 236 (4, M^+); ^1H nmr: δ 1.82 (s, 3H), 2.37 (s, 3H), 4.38 (br s, 1H), 6.59 (d, J = 8 Hz, 1H), 6.67 (t, J = 8 Hz, 1H), 7.18-7.35 (m, 5H), 7.56 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.31; H, 6.83. Found: C, 81.26; H, 6.86.

2-Methyl-2-phenyl-4-(2-thienyl)-1,2-dihydroquinazoline, **6i**.

Obtained from **10a** and 2-thienyllithium, yield 61%, mp 129-130°; ir: 1608, 3392 cm^{-1}; ms: m/e 227 (33), 289 (100), 303 (4), 304 (3, M^+); ^1H nmr: δ 1.87 (s, 3H), 4.56 (br s, 1H), 6.68 (t, J = 8 Hz, 1H), 6.73 (d, J = 8 Hz, 1H), 7.09 (m, 1H), 7.16-7.31 (m, 5H), 7.39 (m, 1H), 7.43 (m, 1H), 7.47 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{19}H_{16}N_2S$: C, 74.95; H, 5.30. Found: C, 75.06; H, 5.33.

2-Methyl-2-(4-pyridinyl)-4-(3-thienyl)-1,2-dihydroquinazoline, **6j**.

Obtained from **10b** and 3-thienyllithium, yield 45%, mp 225-227°; ir: 1612, 3227 cm^{-1}; ms: m/e 227 (45), 290 (100), 305 (3, M^+); ^1H nmr: δ 1.89 (s, 3H), 4.54 (br s, 1H), 6.70 (t, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.26 (m, 2H), 7.38 (m, 2H), 7.46 (dd, J = 4.4 Hz, J = 1.6 Hz, 2H), 7.61 (m, 1H), 8.52 (dd, J = 4.4 Hz, J = 1.6 Hz, 2H).

Anal. Calcd. for $C_{18}H_{15}N_3S$: C, 70.76; H, 4.95. Found: C, 70.57; H, 4.96.

2-(2-Furanyl)-2-methyl-4-(2-thienyl)-1,2-dihydroquinazoline, **6k**.

Obtained from **10c** and 2-thienyllithium, yield 43%, mp 95-97°; ir: 1607, 3379 cm^{-1}; ms: m/e 279 (100), 293 (5), 294 (2, M^+); ^1H nmr: δ 1.90 (s, 3H), 4.57 (br s, 1H), 6.16 (m, 1H), 6.21 (m, 1H), 6.63 (d, J = 8 Hz, 1H), 6.73 (t, J = 8 Hz, 1H), 7.11 (m, 1H), 7.22 (t, J = 8 Hz, 1H), 7.32 (m, 1H), 7.41 (m, 1H), 7.44 (m, 1H), 7.53 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79. Found: C, 69.35; H, 4.81.

4-(2-Benzo[*b*]thienyl)-2-methyl-2-[4-(4-methylpiperazin-1-ylmethyl)-phenyl]-1,2-dihydroquinazoline, **6l**.

Obtained from **10d** and 2-benzo[*b*]thienyllithium, yield 74%, mp 81-83°, mp >250° for **6l**·3HBr·½ H_2O (from ethanol, prepared using a general procedure [9]); ir: 1610, 3391 cm^{-1}; ms: m/e 99 (13), 277 (31), 351 (49), 451 (100), 466 (8, M^+); ^1H nmr: δ 1.88 (s, 3H), 2.27 (s, 3H), 2.45 (m, 8H), 3.45 (s, 2H), 4.54 (br s, 1H), 6.74 (t, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 7.28 (t, J = 8 Hz, 1H), 7.37 (m, 2H), 7.52 (d, J = 8 Hz, 2H), 7.57 (d, J = 8 Hz, 1H), 7.63 (s, 1H), 7.80 (m, 1H), 7.86 (m, 1H).

Anal. Calcd. for $C_{29}H_{30}N_4S$·3HBr·½ H_2O: C, 48.46; H, 4.77. Found: C, 48.34; H, 4.74.

4-(2-Benzo[*b*]thienyl)-2-(2-methylpropyl)-2-phenyl-1,2-dihydroquinazoline, **6m**.

Obtained from **14** and 2-benzo[*b*]thienyllithium, yield 96%, and oil; ir: 1610, 3393 cm^{-1}; ms: m/e 205 (15), 339 (100), 395 (2), 396 (1, M^+); ^1H nmr: δ 0.89 and 0.92 (2d, J = 7 Hz, 6H), 1.87 (m, 1H), 2.07 (m, 2H), 4.50 (br s, 1H), 6.71 (t, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 7.16-7.60 (m, 8H), 7.65 (s, 1H), 7.78-7.99 (m, 3H).

Anal. Calcd. for $C_{26}H_{24}N_2S$: C, 78.75; H, 6.10. Found: C, 79.03; H, 5.87.

Dihydroquinazolines **6a**, **6f**, **6g**: Method of Scheme II.

A mixture of Schiff's base **2** (3 mmoles) and an aryllithium (or heteroaryllithium) reagent (7 mmoles) in ether (50 ml) was stirred at 0° for 2 hours and then quenched with water (0.15 ml), filtered, and concentrated under reduced pressure. The residue was treated with a solution of DDQ (0.8 g, 3.5 mmoles) in benzene (50 ml), and the resultant mixture was stirred at 60° for 2 hours followed by workup as described above: compound (yield), **6a** (97%), **6f** (86%), **6g** (85%). Grignard reagents can be substituted for the organolithium compounds with comparable results.

Quinolin-4-amines **13a-d**.

After the respective 2-methyl-substituted dihydroquinazoline **6h-l** (see preparation of diphydroquinazolines **6a-m**) had been eluted from the chromatography column, the subsequent elution (hexanes/triethylamine/ethanol, 6:3:1) gave the respective aminoquinoline **13a-d**. Compounds **13a-c** were identical with those obtained previously in the lithium diisopropylamide-induced cyclization of the respective **10a-c** [4].

2-[4-(4-Methylpiperazin-1-ylmethyl)phenyl]quinolin-4-amine, **13d**.

Obtained in the reaction of **10d** with 2-benzo[*b*]thienyllithium, yield 23%, an oil; ms: m/e 234 (100), 261 (79), 332 (58, M^+); ^1H nmr: δ 2.33 (s, 3H), 2.52 (m, 8H), 3.54 (s, 2H), 5.31 (br s, 2H, exchangeable with deuterium oxide), 7.03 (s, 1H), 7.39 (d, J = 8 Hz, 2H), 7.41 (t, J = 8 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.83 (d, J = 8 Hz, 1H), 7.96 (d, J = 8 Hz, 2H), 8.07 (d, J = 8 Hz, 1H).

Anal. Calcd. for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28. Found: C, 75.58; H, 7.38.

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[5] An attempted use of hexanes or tetrahydrofuran caused solubility problems and side reactions with organolithium reagents, respectively.

[6] We have shown previously (see reference [4]) that 2-[(1-phenylpropylidene)amino]benzonitrile, the simplest higher homologue of **10a**, is not lithiated in the presence of lithium diisopropylamide.

[7] It should be noted that *E*/*Z* isomerism applies to Schiff's bases **2**, **4b**, **4c**, **10**, and **14**. As shown by ^1H nmr nOe experiments, compounds **2**

and **10** are single *E* diastereomers, while the remaining compounds are obtained as diastereomeric mixtures. The stereochemistry of Schiff's bases is not relevant to this work, and will be presented in due course; for a leading review, see: R. Knorr, *Chem. Ber.*, **113**, 2441 (1980).

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