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One-Step Conversion of 2-Amino-*N*′-arylbenzamidines into 3-Aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles Using 4,5-Dichloro-1,2,3-dithiazolium Chloride

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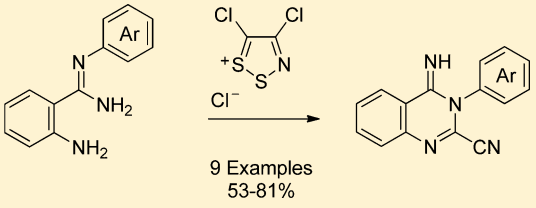
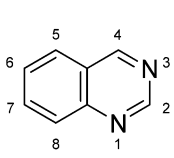
Supporting Information

ABSTRACT: 2-Amino-*N*′-arylbenzamidines react with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) in the presence of Hünig's base (2 equiv) to give in one step 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles in 53−81% yields. Nine examples are presented along with the single-crystal X-ray structure of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile. Furthermore, the behavior of the latter toward both acid and base hydrolysis is investigated. All new compounds are fully characterized, and a mechanistic rationale for the formation of the iminoquinazolines is provided.

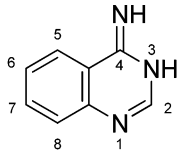


1. INTRODUCTION

Quinazoline (benzo[*a*]pyrimidine) is the parent heterocycle of an important group of compounds that find application as components in pharmaceuticals, agrochemicals, dyes, sensors, polymers, and organic electronics. As such, there are extensive reviews on the synthesis, chemistry, and properties of quinazolines.[1] The quinazoline skeleton is found in many natural products.[2]



Quinazoline



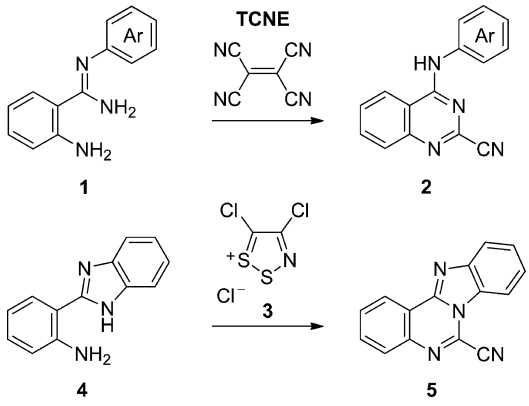
Quinazolin-4(3*H*)-imine

An interesting quinazoline subclass is quinazolin-4(3*H*)-imine, the structure of which is featured in biologically active compounds that behave as cholinesterase inhibitors,[3] cMET kinase inhibitors,[4] or modulators of chemokine CCR3 activity[5] or exhibit antiproliferative[6] or cardiotonic activities.[7]

Recent methods for the preparation of quinazolin-4(3*H*)-imines include the palladium-catalyzed three-component reaction of carbodiimide, isocyanide, and a nucleophile,[8] the three-step synthesis of 3-aryl-2-halo-4(3*H*)-quinazoliniminium halides from readily accessible heteroenyne-allenes,[9] the reaction of anthranilonitrile with triethyl orthoformate,[10] the single-step synthesis from simple carbonyl compounds, primary amines, or amino acid methyl esters and 2-azido-5-nitrobenzonitrile,[11] and a one-pot cyclization of 2-(dichloroisocyanido)benzonitrile with α-amino ketones.[12]

Recently, we reinvestigated the reaction of 2-amino-*N*′-arylbenzamidines **1**[13] with tetracyanoethylene (TCNE),[14] which affords the 4-anilinoquinazoline-2-carbonitriles **2** in moderate to good yields[15] (Scheme 1), and considered replacing expensive TCNE with 4,5-dichloro-1,2,3-dithiazolium chloride **3** (Appel salt) that is easily prepared from chloroacetonitrile and disulfur dichloride.[16] The use of Appel salt **3** for the two-step introduction of C−C≡N via the synthesis of neutral 1,2,3-dithiazoles (step 1) and their subsequent ring transformation to cyanoheteroarenes (step 2) has been well demonstrated,[17] and excellent reviews on the chemistry of 1,2,3-dithiazoles have appeared.[18] While the reaction of 2-cyano-(4-chloro-5*H*-1,2,3-dithiazolylidenamino)-benzenes with selected alkoxides gave 4-alkoxyquinazoline-2-carbonitriles,[19] there is only one report for an analogous two-step preparation of 4-(alkylamino)pyrido[2,3-*d*]pyrimidine-2-carbonitriles from 2-aminopyridine-3-carbonitriles.[17i] Furthermore, a similar reaction between Appel salt **3** and 2-(1*H*-

Scheme 1. Preparation of 4-Anilinoquinazolines 2 and the Cyanobenzimidazoquinazoline 5



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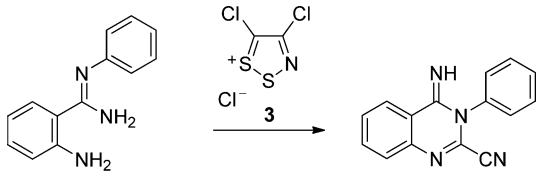
benzo[*d*]imidazol-2-yl)aniline **4** gave directly cyanobenzimidazoquinazoline **5** in 50% yield[20] (Scheme 1).

Surprisingly, the reaction between 2-amino-*N*′-arylbenzamidines **1** and Appel salt **3** did not result in the expected 4-anilinoquinazoline-2-carbonitrile **2** but rather afforded the isomeric 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitrile **6** (Scheme 2). To the best of our knowledge, this represents

Scheme 2. Preparation of 4-Iminoquinazoline-2-carbonitrile 6a



the first synthesis of a 2-cyano-substituted quinazolin-4(3*H*)-imine, which is worthy of note since nitriles can readily be subsequently modified into a wide variety of other functionalities.[21] The results of our discovery are presented herein.

2. RESULTS AND DISCUSSION

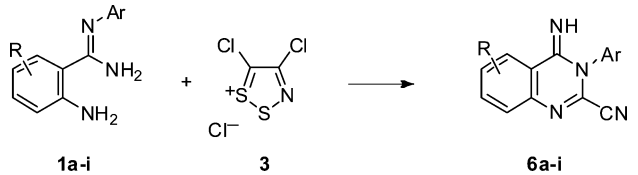
The reaction between anilines and 4,5-dichloro-1,2,3-dithiazolium chloride **3** typically produce the neutral (4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzenes.[16a,22] However, in a few cases where an *ortho* nucleophilic side chain is present on the arylamine, the product isolated arises as a result of an in situ ring transformation affording the more stable heteroarene.[20,23]

Thus, treating 4,5-dichloro-1,2,3-dithiazolium chloride **3** (Appel salt) with 2-amino-*N*′-phenylbenzamidine **1a** proceeded to give 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) and not the expected 4-anilinoquinazoline-2-carbonitrile (**2**) (Scheme 2) directly as a one-pot process. Analysis of the reaction mixture by TLC failed to detect the presence of any intermediate.

4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) was isolated as colorless needles, mp 141−142 °C (from cyclohexane) [mp (DSC) onset 143.9 °C, peak max 146.2 °C], which differed considerably from that of 4-anilinoquinazoline-2-carbonitrile (**2**) mp (DSC) onset 211.7 °C, peak max 212.5 °C (from $CHCl_3$). Interestingly, our melting point for the anilinoquinazoline **2** was also significantly different from that reported in the literature (lit.[15] mp 84−85 °C), despite matching closely with the reported ^1H, ^{13}C NMR and IR spectra. Furthermore, mass spectrometry of the iminoquinazoline **6a** gave a parent ion at *m*/*z* (EI) 246 Da (M^+, 34%), which in combination with elemental analysis gave a molecular formula of $C_{15}H_{10}N_4$, supporting a compound that was isomeric with the anilinoquinazoline **2**. Further observed differences between the two isomers could be seen in the IR and NMR spectra: 4-anilinoquinazoline-2-carbonitrile (**2**) gave a nitrile stretching frequency of ν(C≡N) 2247 cm^{-1}, while 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) gave a nitrile stretching frequency of ν(C≡N) 2239 cm^{-1}. The ^{13}C NMR spectrum showed 13 separate signals for both isomers, 7 of which were CH (by DEPT-135 NMR). However, the most downfield and upfield signals for the iminoquinazoline **6a** appeared at 153.3 and 111.3 ppm, respectively, while those for anilinoquinazoline **2** appeared at 157.5 and 115.1 ppm. Both compounds also had different R_f values of silica gel TLC plates R_f **6a** (DCM/*t*-BuOMe, 9:1) 0.48 vs R_f **2** (DCM/*t*-BuOMe, 9:1) 0.52 indicating the iminoquinazoline **6a** was the more polar of the two. Any ambiguity in the structural assignment was addressed by solving the single-crystal X-ray structure for 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (Figure S1, Supporting Information).

Optimization of Iminoquinazoline Formation. By screening the type and equivalents of the organic base used, the reaction of Appel salt **3** and 2-amino-*N*′-phenylbenzamidine (**1a**) was partially optimized. Typically, 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) was treated with 2-amino-*N*′-phenylbenzamidine (**1a**) (51 mg, 0.24 mmol) in DCM (4 mL) at ca. 20 °C for 4 h followed by the addition of base at ca. 20 °C and an additional 2 h of stirring, protected from moisture with $CaCl_2$ drying tube. When pyridine (2−4 equiv) was used as base only traces of the iminoquinazoline **6a** were obtained, while more basic trialkylamines such as Et_3N (2−4 equiv) or Hünig's base (i-Pr_2NEt) (2−4 equiv) gave 55−61 and 72−75% yields, respectively. Interestingly, increasing the base strength further by using the bicyclic amidine DBU (2−3 equiv) led to low product yields (32−36%). With this data in mind, we reacted 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) with various substituted 2-amino-*N*′-arylbenzamidines **1b−i** in the presence of Hünig's base (2 equiv) and obtained the iminoquinazolines **6b−i**, respectively (Table 1).

Table 1. Reaction of 4,5-Dichloro-1,2,3-dithiazolium Chloride (3) with 2-Amino-*N*′-arylbenzamidines 1[a]



entry	Ar	R	yield of **6a−i** (%)
1	Ph	H	**6a** (73)
2	4-MeC_6H_4	H	**6b** (81)
3	4-$MeOC_6H_4$	H	**6c** (74)
4	4-FC_6H_4	H	**6d** (57)
5	4-ClC_6H_4	H	**6e** (65)
6	4-BrC_6H_4	H	**6f** (63)
7	3,4-$Cl_2C_6H_3$	H	**6g** (65)
8	Ph	4,5-$(MeO)_2$	**6h** (53)
9	4-$MeOC_6H_4$	4,5-$(MeO)_2$	**6i** (61)

[a]Compounds **3** (50 mg, 0.24 mmol) and **1** (0.24 mmol) in DCM (4 mL) were reacted at ca. 20 °C for 4 h followed by the addition of i-Pr_2NEt (2 equiv) at ca. 20 °C and an additional 2 h of stirring, protected from moisture with a $CaCl_2$ drying tube.

As seen from Table 1, reaction yields range between 53 and 81%. For the unsubstituted benzamidines (R = H) the yields were affected by the nature of the *N*-aryl group. Neutral or electron-rich Ar groups (Ar = Ph, 4-Tol, and 4-$MeOC_6H_4$, entries 1−3) gave higher yields (73−81%); however, where the Ar group was less electron rich (Ar = 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, and 3,4-$Cl_2C_6H_3$, entries 4−7) the yields dropped (57−65%). The reaction also tolerated electron-rich dimethoxy-substituted benzamidines, which gave the expected iminoquinazolines **6h** and **6i** in moderate yields, 53 and 61%, respectively (entries 8 and 9).

Some Chemistry of 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (6a). On close inspection, the two

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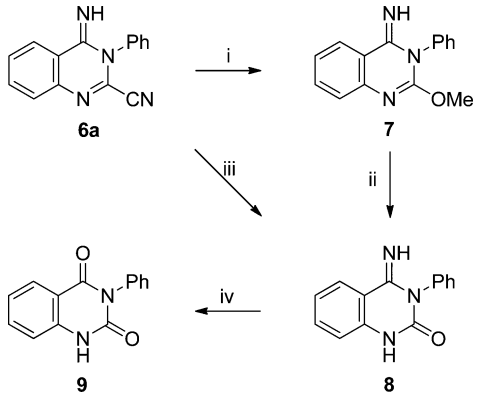
quinazoline isomers **2** and **6a** can in theory be isomerized into each other via a Dimroth rearrangement.[24] Furthermore, treatment of 3-alkyl- or 3-benzyl-4-imino-3,4-dihydroquinazolines with NaOH was known to afford products of the Dimroth rearrangement: the 4-alkylamino- and 4-benzylaminoquinazoline isomers.[11] The isomerization of the iminoquinazoline **6a** into the 4-anilinoquinazoline **2** via acid or base catalysis was therefore investigated.

Initially, solutions of the iminoquinazoline **6a** in either dry toluene, toluene in the presence of Hünig's base, or in neat Hünig's base heated to ca. 110 °C indicated that the iminoquinazoline **6a** was stable to these conditions. However, reaction of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) in the presence of NaOH (1 equiv) in MeOH at ca. 67 °C for 3 h gave 2-methoxy-3-phenylquinazolin-4(3*H*)-imine (**7**) in quantitative yield (99%). The use of milder bases such as K_2CO_3 and Na_2CO_3 led to lower yields (70%), while the use of amine bases such as Hünig's base, pyridine, or DMAP in MeOH led to complex reaction mixtures. Interestingly, further treatment of 2-methoxy-3-phenylquinazolin-4(3*H*)-imine (**7**) with HCl (10%) at ca. 67 °C for 30 min led to the quantitative formation of 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**8**)[25] (99%). Furthermore, the quantitative conversion of the iminoquinazoline **6a** into 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**8**) could also be achieved as a one-pot process. Finally, hydrolysis of the iminoquinazolinone **8** with 1 N NaOH at ca. 20 °C for 7 d gave the known 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**9**)[26] in 90% yield (Scheme 3).

Scheme 3[a]

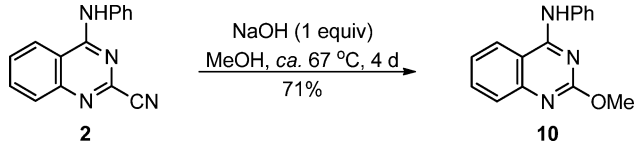


[a]Reagents and conditions: (i) NaOH (1 equiv), MeOH, ca. 67 °C, 3 h, 99%; (ii) 10% HCl, ca. 67 °C, 30 min, 99%; (iii) NaOH (1 equiv), MeOH, ca. 67 °C, 3 h, then 10% HCl, ca. 60 °C, 20 min, 99%; (iv) 1 N NaOH, ca. 20 °C, 7 d, 90%.

Interestingly, similar treatment of 4-anilinoquinazoline-2-carbonitrile (**2**) with NaOH (1 equiv) in MeOH at ca. 67 °C for 4 d led to substitution of the nitrile to afford the known 4-anilino-2-methoxyquinazoline (**10**)[27] in good yield (71%) (Scheme 4).

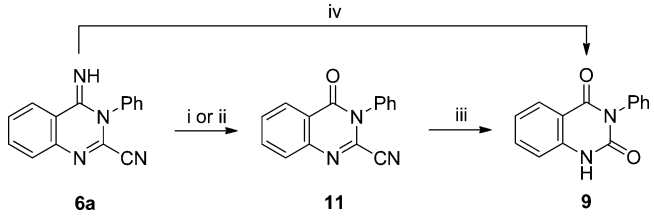
In contrast, direct treatment of the iminoquinazoline **6a** with either TFA (1 equiv) in DMSO, DMF, or DMA at ca. 20 °C or at ca. 100 °C or in the presence of HCl (1 equiv) in THF/water (1:1) also failed to give the Dimroth rearranged product but did afford the known 4-oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**11**)[28] in high yield. When 2 or more equiv of HCl was used, 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**9**)

Scheme 4. Preparation of 4-Anilino-2-methoxyquinazoline (10)



was obtained in 92–99% yields. Interestingly, heating the dihydroquinazolinone **11** in the presence of HCl (1 equiv) in THF/water (1:1) at ca. 65 °C gave no reaction, but treatment with HCl (2 equiv) after 3 d at ca. 65 °C afforded 3-phenylquinazoline-2,4(1*H*,3*H*)-dione (**9**)[26] in 96% yield (Scheme 5).

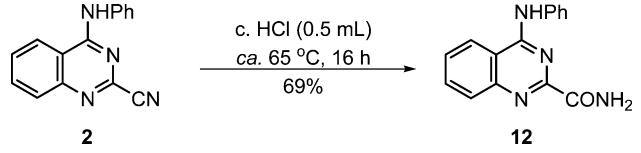
Scheme 5[a]



[a]Reagents and conditions: (i) TFA (1 equiv), DMSO, 20–100 °C, 2 d, 99%; (ii) HCl (1 equiv), THF/H_2O (1:1), 65 °C, 1 d, 87%; (iii) HCl (2 equiv), THF/H_2O (1:1), 65 °C, 3 d, 96%; (iv) HCl (4 equiv), THF/H_2O (1:1), 65 °C, 1.5 d, 99%.

In contrast to the above, similar treatment of the isomer anilinoquinazoline **2** with HCl (1 equiv) in THF/water (1:1) at ca. 65 °C for 24 h gave no hydration, hydrolysis, or isomerization, and the compound was recovered unchanged. Nevertheless, reaction in the presence of neat concd HCl at ca. 65 °C for 16 h gave 4-anilinoquinazoline-2-carboxamide (**12**) in 69% yield (Scheme 6). These studies provided support for the fact that the iminoquinazoline **6a** and the anilinoquinazoline **2** were not interconvertable under acid conditions.

Scheme 6. Preparation of 4-Anilinoquinazoline-2-carboxamide (12)



Mechanistic Rationale for the Formation of the Iminoquinazolines 6. There are two possible routes to the iminoquinazolines **6**: the Appel salt **3** condenses with 2-amino-*N*′-arylbenzamidines at the primary aniline amine to give adduct **13**, or alternatively, condensation at the amidino secondary amine provided adduct **14**. These can then undergo intramolecular cyclizations via a common spirocyclic intermediate **15** which undergoes cleavage affording the observed iminoquinazoline **6** (Scheme 7).

Unfortunately, we were unable to isolate any intermediates that could provide support for either proposal. However, we note that amidines typically undergo alkylation to give the more basic amine which is typically the secondary amine,[29] and this may explain why formation of the 4-anilinoquinazoline-2-

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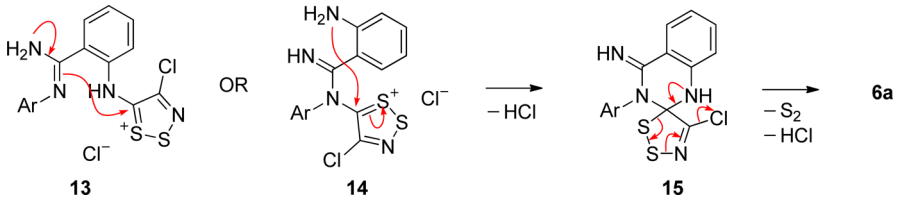
Scheme 7. Mechanistic Rationale for the Formation of the Quinazolinimine 6a



carbonitrile (**2**) was not observed. Studies to further understand this transformation are presently underway.

3. CONCLUSIONS

Treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **3** with 2-amino-*N*′-arylbenzamidines **1a**–**i** directly affords 3-aryl-4-imino-3,4-dihydroquinazoline-2-carbonitriles **6a**–**i** in moderate to good yields (53–81%). The reaction provides a convenient route to C-2 cyano-substituted quinazolin-4(3*H*)-imines.

4. EXPERIMENTAL SECTION

4.1. General Methods and Materials. Reactions were protected from atmospheric moisture by $CaCl_2$ drying tubes. All volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed thin-layer chromatography (TLC) plates (Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography[30] was used throughout for all non-TLC scale chromatographic separations using silica gel 60 (less than 0.063 mm). Melting points were determined using a hotstage microscope apparatus. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a UV/vis spectrophotometer, and inflections are identified by the abbreviation "inf". IR spectra were recorded on a FTIR spectrometer with a Ge ATR accessory, and strong, medium, and weak peaks are represented by s, m, and w, respectively. ^{1}H and ^{13}C NMR spectra were recorded either on a 300 MHz machine (at 300 and 75 MHz, respectively) or on a 500 MHz machine (at 500 and 125 MHz, respectively). ^{13}C NMR multiplicity assignments were determined using APT of DEPT NMR experiments. Deuterated solvents were used for the homonuclear lock, and the signals are referenced to the deuterated solvent peaks. Low-resolution (EI) mass spectra were recorded on a GC–MS with direct inlet probe. 4,5-Dichloro-1,2,3-dithiazolium chloride (**3**),[16] 2-amino-*N*′-arylbenzamidines **1a**–**g**,[13] and TCNE[14b] were prepared according to the literature.

4.2. Preparation of 2-Amino-*N*′-arylbenzamidines 1h and 1i. *4.2.1. (Z)-2-Amino-4,5-dimethoxy-N′-phenylbenzamidine (**1h**).* Typical procedure: To stirred 4,5-dimethoxyanthranilonitrile (957 mg, 5.36 mmol) at ca. 20 °C was added portionwise powdered anhydrous $AlCl_3$ (706 mg, 5.36 mmol). The reaction mixture was then heated (ca. 100 °C) until a homogeneous melt formed. To this was added aniline (489 μL, 5.36 mmol) and the mixture was heated for 4 h and then allowed to cool to ca. 20 °C. The resultant solid mass was then crushed and slurried in 12.5% NaOH (40 mL). The resulting mixture was extracted (DCM), washed (H_2O), and dried (Na_2SO_4). Removal of the volatiles followed by chromatography (*t*-BuOMe/EtOH, 9:1) of the residue gave the title compound **1h** (178 mg, 12%) as colorless needles: mp 172–173 °C (from cyclohexane/EtOH); R_f 0.40 (*t*-BuOMe/EtOH, 90:10); λ_{max} (DCM)/nm 234 (log ε 4.56), 267 (4.30), 337 (4.04); ν_{max}/cm^{-1} 3435w and 3343w (NH_2), 3279w, 3117w, 3009w, 2961w, 2934w, 2911w, 2905w, 2858w, 2830w (Ar CH), 1632m, 1587w, 1562m, 1514m, 1483m, 1458w, 1446w, 1412w, 1391m, 1285w, 1265w, 1223s, 1174w, 1113w, 1069w, 1024w, 1001w, 964w, 912w, 876w, 843m, 777w; δ_H (300 MHz; $CDCl_3$) 7.36 (2H, dd, *J* 7.7, 7.7), 7.07 (1H, dd, *J* 7.5, 7.5), 7.00–6.95 (3H, m), 6.26 (1H, s), 5.81 (2H, br s), 4.70 (2H, br s), 3.87 (3H, s), 3.83 (3H, s); δ_C (75 MHz; $CDCl_3$) 155.7 (s), 152.1 (s), 148.9 (s), 143.6 (s), 140.7 (s), 129.5 (d), 122.9 (d), 121.9 (d), 111.6 (d), 107.9 (s), 100.7 (d), 57.0 (q), 55.7 (q); *m*/*z* (EI) 271 (M$^+$, 100%), 254 (37), 239 (50), 211 (6), 193 (7), 179 (41), 163 (36), 147 (6), 135 (14), 120 (7), 93 (30), 77 (33), 65 (9), 51 (11). Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.51; H, 6.26; N, 15.40.

*4.2.2. (Z)-2-Amino-4,5-dimethoxy-N′-(4-methoxyphenyl)-benzamidine (**1i**).* Similar treatment of 4,5-dimethoxyanthranilonitrile (723 mg, 4.06 mmol), powdered anhydrous $AlCl_3$ (535 mg, 4.06 mmol), and *p*-anisidine (500 mg, 4.06 mmol) at ca. 20 °C gave the title compound **1i** (151 mg, 12%) as colorless plates: mp 174–175 °C (from EtOH); R_f 0.47 (*t*-BuOMe/EtOH, 60:40); λ_{max} (DCM)/nm 234 (log ε 4.52), 266 (4.21), 336 (3.99); ν_{max}/cm^{-1} 3458w, 3433w and 3348w (NH_2), 3308w, 3011w (Ar CH), 2994w, 2957w, 2936w, 2837w, 1635s, 1603m, 1587m, 1558m, 1518m, 1501s, 1466m, 1447m, 1414w, 1385m, 1346w, 1271m, 1215s, 1184m, 1171m, 1103m, 1067w, 1038w, 1018m, 999m, 964w, 854m, 835m, 814w, 777m; δ_H (300 MHz; $CDCl_3$) 6.95 (1H, s), 6.92 (4H, m), 6.26 (1H, s), 5.82 (2H, br s), 4.74 (2H, br s), 3.86 (3H, s), 3.83 (3H, s), 3.81 (3H, s); δ_C (75 MHz; $CDCl_3$) 156.2 (s), 155.6 (s), 152.0 (s), 143.5 (s), 141.8 (s), 140.7 (s), 122.8 (d), 114.8 (d), 111.6 (d), 108.1 (s), 100.7 (d), 57.0 (q), 55.7 (q), 55.5 (q); *m*/*z* (EI) 301 (M$^+$, 83%), 284 (19), 269 (18), 241 (3), 226 (3), 179 (38), 163 (13), 148 (5), 135 (10), 123 (100), 108 (63), 92 (7), 80 (9), 77 (6), 64 (4), 52 (5). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.82; H, 6.35; N, 13.86.

4.3. Preparation of 3-Aryl-3,4-dihydro-4-iminoquinazoline-2-carbonitriles 6a–i. *4.3.1. 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**).* Typical procedure: To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) in DCM (4 mL) at ca. 20 °C was added 2-amino-*N*′-phenyl-benzamidine (**1a**) (51 mg, 0.24 mmol). After 4 h, to the reaction mixture was added Hünig's base (83.5 μL, 0.48 mmol) and the mixture allowed to stir at ca. 20 °C for an additional 2 h. The reaction mixture was then adsorbed onto silica and chromatography (*n*-hexane) to give traces of S_8, followed (*n*-hexane/DCM, 80:20) by 4-chloro-5*H*-1,2,3-dithiazol-5-one (8 mg, 20%). Further elution (DCM/*t*-BuOMe, 90:10) gave the title compound **6a** (43 mg, 73%) as colorless needles: mp 141–142 °C (from cyclohexane), mp (DSC) onset 143.9 °C, peak max 146.2 °C (from cyclohexane); R_f 0.48 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 237 inf (log ε 4.25), 245 inf (4.18), 255 (4.13), 265 (4.19), 274 (4.11), 298 inf (3.77), 311 (3.94), 324 (3.99), 340 inf (3.85); ν_{max}/cm^{-1} 3341w, 3308w (NH), 3071w (Ar CH), 2239w (C≡N), 1643m, 1605w, 1574w, 1560m, 1491w, 1472w, 1462m, 1348m, 1302m, 1283m, 1227w, 1217w, 1167m, 1138m, 1030w, 1007w, 997w, 876w, 827w, 800w, 760s; δ_H (300 MHz; $CDCl_3$) 8.25 (1H, d, *J* 6.9), 7.69–7.63 (5H, m), 7.54 (1H, ddd, *J* 7.4, 7.4, 1.8), 7.44–7.40 (2H, m), 6.71 (1H, br s); δ_C (125 MHz; $CDCl_3$) 153.3 (s), 143.2 (s), 135.0 (s), 133.4 (d), 131.3 (d), 131.2 (s), 131.0 (d), 129.9 (d), 129.0 (d), 128.4 (d), 125.6 (d), 122.5 (s), 111.3 (s); *m*/*z* (EI) 246 (M$^+$, 34%), 245 (M$^+$ – H, 100), 236 (7), 219 (17), 192 (11), 160 (8), 141 (7), 129 (7), 118 (12), 113 (11), 111 (12), 102 (25), 97 (17), 91 (20), 85 (19), 83 (17), 77 (64), 71 (25), 69 (26), 64 (46), 57 (48). Anal. Calcd for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 73.02; H, 3.95; N, 22.67.

*4.3.2. 4-Imino-3-p-tolyl-3,4-dihydroquinazoline-2-carbonitrile (**6b**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with (*Z*)-2-amino-*N*′-*p*-tolylbenzamidine (**1b**) (54 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6b** (51 mg, 81%) as beige needles: mp 155–156 °C (from *n*-hexane/DCM); mp (DSC) onset 158.6 °C, peak max 160.9 °C (from *n*-hexane/DCM); R_f 0.60 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 231 (log ε 4.27), 255 (4.08), 264 (4.14), 274 (4.07), 298 inf (3.72), 310 (3.89),

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323 (3.94), 342 inf (3.79); ν_{max}/cm^{-1} 3292w (NH), 3040w, 3009w (Ar CH), 2924w, 2907w, 2887w, 2874w, 2243w (C≡N), 1641s, 1603w, 1578m, 1566w, 1510m, 1464m, 1352m, 1323s, 1308m, 1292w, 1240w, 1225w, 1186m, 1180m, 1146m, 1111w, 1026w, 1002w, 956w, 839m, 814w, 789m, 768s; δ_H (300 MHz; $CDCl_3$) 8.26 (1H, d, *J* 8.1), 7.70−7.6 (2H, m), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.8), 7.44 (2H, d, *J* 8.1), 7.28 (2H, d, *J* 8.4), 6.34 (1H, br s), 2.47 (3H, s); δ_C (75 MHz; $CDCl_3$) 153.5 (s), 143.3 (s), 141.7 (s), 133.4 (d), 132.2 (s), 131.7 (d), 131.3 (s), 129.8 (d), 128.6 (d), 128.3 (d), 125.7 (d), 122.4 (s), 111.3 (s), 21.4 (q); *m*/*z* (EI) 260 (M^+, 12%), 259 (M^+ − H, 49), 239 (9), 224 (8), 207 (31), 179 (8), 169 (11), 163 (44), 149 (12), 133 (25), 119 (10), 113 (28), 106 (20), 97 (29), 91 (67), 77 (22), 69 (37), 65 (31), 57 (30). Anal. Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.69; H, 4.54; N, 21.58.

*4.3.3. 4-Imino-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2-carbonitrile (**6c**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-*N*′-(4-methoxyphenyl)benzamidine (**1c**) (58 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6c** (49 mg, 74%) as orange needles: mp 140−141 °C (from *n*-hexane/DCM); mp (DSC) onset 142.8 °C, peak max 144.3 °C (from *n*-hexane/DCM); R_f 0.42 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 232 (log ε 4.26), 255 (4.09), 265 (4.14), 273 (4.07), 298 inf (3.73), 310 (3.90), 324 (3.95), 342 inf (3.80); ν_{max}/cm^{-1} 3312w, 3281w, 3262w (NH), 3075w, 3057w, 3011w (Ar CH), 2963w, 2934w, 2909w, 2835w, 2243w (C≡N), 1634s, 1607m, 1587m, 1576w, 1560m, 1510s, 1472m, 1462m, 1437w, 1354m, 1344w, 1321s, 1306s, 1283m, 1250s, 1234s, 1182s, 1167m, 1148m, 1136w, 1115w, 1057w, 1032m, 999w, 968w, 951w, 891w, 879w, 858m, 841s, 824m, 779m, 770s; δ_H (300 MHz; $CDCl_3$) 8.27 (1H, d, *J* 7.8), 7.72−7.62 (2H, m), 7.52 (1H, ddd, *J* 7.4, 7.4, 1.7), 7.32 (2H, d, *J* 9.0), 7.14 (2H, d, *J* 9.0), 6.89 (1H, br s), 3.91 (3H, s); δ_C (75 MHz; $CDCl_3$) 161.3 (s), 153.5 (s), 143.2 (s), 133.3 (d), 131.6 (s), 130.1 (d), 129.7 (d), 128.6 (d), 128.2 (d) 127.0 (s), 125.6 (d), 122.5 (s), 116.1 (d), 111.4 (s), 55.6 (q); *m*/*z* (EI) 276 (M^+, 92%), 275 (M^+ − H, 100), 261 (54), 259 (43), 250 (7), 234 (11), 210 (24), 181 (9), 159 (12), 154 (28), 149 (13), 129 (14), 122 (16), 102 (52), 97 (26), 95 (30), 91 (21), 83 (27), 77 (31), 71 (28), 69 (39), 64 (22), 59 (33), 57 (57). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.61; H, 4.28; N, 20.14.

*4.3.4. 3-(4-Fluorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**6d**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-*N*′-(4-fluorophenyl)-benzamidine (**1d**) (55 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6d** (36 mg, 57%) as beige needles: mp 163−163.5 °C (from *n*-hexane/DCM); mp (DSC) onset 167.9 °C, peak max 169.2 °C (from *n*-hexane/DCM); R_f 0.52 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 235 inf (log ε 4.19), 255 (4.09), 263 (4.14), 273 (4.08), 299 inf (3.75), 310 (3.90), 323 (3.95), 339 inf (3.81); ν_{max}/cm^{-1} 3304w, 3285w (NH), 3075w, 3048w, 3009w (Ar CH), 2241w (C≡N), 1638s, 1599m, 1578m, 1564w, 1508s, 1462m, 1418w, 1372w, 1346m, 1317s, 1288m, 1244w, 1227m, 1177m, 1150m, 1096w, 1026w, 1003w, 881w, 851m, 839m, 831m, 822m, 789w, 764s; δ_H (300 MHz; $CDCl_3$) 8.21 (1H, d, *J* 7.5), 7.74−7.64 (2H, m), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.5), 7.45−7.32 (4H, m); δ_C (75 MHz; $CDCl_3$) 165.4 (s), 162.0 (d, $^1J_{CF}$ 252.9), 153.8 (s), 143.0 (s), 133.5 (d), 131.1 (d, $^3J_{CF}$ 9.1), 130.0 (d), 128.5 (d), 125.4 (d), 122.2 (s), 118.2 (d, $^2J_{CF}$ 22.7), 111.2 (s); *m*/*z* (EI) 264 (M^+, 26%), 263 (M^+ − H, 100), 245 (12), 236 (3), 209 (1), 154 (6), 147 (7), 132 (3), 102 (27), 95 (32), 90 (7), 75 (29), 63 (7). Anal. Calcd for $C_{15}H_9FN_4$: C, 68.18; H, 3.43; N, 21.20. Found: C, 68.29; H, 3.30; N, 21.12.

*4.3.5. 3-(4-Chlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**6e**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-*N*′-(4-chlorophenyl)-benzamidine (**1e**) (59 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6e** (44 mg, 65%) as colorless needles: mp 209−210 °C (from *n*-hexane/DCM); mp (DSC) onset 198.9 °C, peak max 200.6 °C (from *n*-hexane/DCM); R_f 0.61 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 228 (log ε 4.41), 253 inf (4.17), 264 (4.18), 273 (4.11), 298 inf (3.79), 310 (3.94), 323 (3.99), 340 inf (3.85); ν_{max}/cm^{-1} 3304w (NH), 3053w (Ar CH), 2241w (C≡N), 1643s, 1597w, 1574w, 1566w, 1493m, 1466m, 1406w, 1350m, 1315s, 1292m, 1246w, 1223w, 1172m, 1155w, 1090m, 1067w, 1049w, 1022w, 1001w, 970w, 948w, 879w, 841m, 812w, 785w, 775s; δ_H (300 MHz; $CDCl_3$) 8.21 (1H, d, *J* 8.1), 7.71−7.64 (2H, m), 7.65 (2H, d, *J* 8.4), 7.56 (1H, ddd, *J* 7.4, 7.4, 1.4), 7.38 (2H, d, *J* 8.7), 5.70 (1H, br s); δ_C (75 MHz; $CDCl_3$) 153.8 (s), 143.0 (s), 137.5 (s), 133.7 (s), 133.6 (d), 131.3 (d), 130.9 (s), 130.4 (d), 130.1 (d), 128.6 (d), 125.4 (d), 122.1 (s), 111.2 (s); *m*/*z* (EI) 282 (M^++2, 10%), 281 (M^++1, 36), 280 (M^+, 31), 279 (M^+-H, 100), 244 (12), 154 (8), 149 (4), 113 (7), 111 (21), 102 (30), 90 (10), 75 (26), 63 (8). Anal. Calcd for $C_{15}H_9ClN_4$: C, 64.18; H, 3.2; N, 19.96. Found: C, 64.34; H, 3.10; N, 19.92

*4.3.6. 3-(4-Bromophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**6f**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-*N*′-(4-bromophenyl)-benzamidine (**1f**) (69 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6f** (49 mg, 63%) as orange needles: mp 191−192 °C (from *n*-hexane/DCM); mp (DSC) onset 191.7 °C, peak max 193.6 °C (from *n*-hexane/DCM); R_f 0.75 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 231 (log ε 4.54), 253 inf (4.25), 263 (4.23), 273 (4.15), 299 inf (3.85), 311 (4.00), 323 (4.06), 339 inf (3.94); ν_{max}/cm^{-1} 3298w (NH), 3086w, 3049w, 3028w, 3011w (Ar CH), 2243w (C≡N), 1688w, 1641s, 1593m, 1564m, 1489m, 1400w, 1348m, 1319m, 1290m, 1244w, 1223w, 1175m, 1155w, 1070w, 1018m, 1001m, 970w, 880w, 839m, 808m, 785m, 775s; δ_H (300 MHz; $CDCl_3$) 8.18 (1H, d, *J* 7.8), 7.79 (2H, d, *J* 8.7), 7.70−7.64 (2H, m), 7.55 (1H, ddd, *J* 7.4, 7.4, 1.8), 7.31 (2H, d, *J* 8.7), 6.86 (1H, br s); δ_C (125 MHz; $CDCl_3$) 153.7 (s), 143.0 (s), 134.3 (d), 133.6 (d), 130.8 (s), 130.6 (d), 130.1 (d), 128.6 (d), 125.6 (s), 125. (d), 122.1 (s), 111.2 (s); *m*/*z* (EI) 326 (M^+ + 2, 29%), 325 (M^+ + 1, 98), 324 (M^+, 30), 323 (M^+ − H, 100), 259 (3), 244 (32), 209 (5), 207 (5), 192 (5), 155 (14), 122 (18), 102 (42), 90 (23), 76 (33), 63 (16), 50 (17). Anal. Calcd for $C_{15}H_9BrN_4$: C, 55.41; H, 2.79; N, 17.23. Found: C, 55.41; H, 2.70; N, 17.15.

*4.3.7. 3-(3,4-Dichlorophenyl)-4-imino-3,4-dihydroquinazoline-2-carbonitrile (**6g**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-*N*′-(3,4-dichlorophenyl)benzamidine (**1g**) (67 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6g** (49 mg, 65%) as beige plates: mp 175−176 °C (from *n*-pentane/DCM); mp (DSC) onset 176.6 °C, peak max 180.5 °C (from *n*-pentane/DCM); R_f 0.77 (DCM/*t*-BuOMe, 90:10); λ_{max} (DCM)/nm 230 (log ε 4.41), 252 inf (4.19), 264 (4.17), 273 (4.08), 299 inf (3.79), 310 (3.93), 323 (3.97), 339 inf (3.85); ν_{max}/cm^{-1} 3265w (N*H*), 3092w, 3044w, 3019w, 3007w (Ar CH), 2953w, 2924w, 2853w, 2241w (C≡N), 1620s, 1601m, 1574m, 1562m, 1472m, 1462m, 1389w, 1354m, 1337m, 1256w, 1231m, 1182w, 1132m, 1119w, 1055m, 1034m, 1022w, 970w, 928w, 876m, 854w, 827m, 770s; δ_H (300 MHz; $CDCl_3$) 8.12 (1H, d, *J* 7.2), 7.73 (1H, d, *J* 8.7), 7.70−7.65 (2H, m), 7.60−7.54 (2H, m), 7.30 (1H, dd, *J* 8.4, 2.4); δ_C (125 MHz; $CDCl_3$) 154.1 (s), 142.8 (s), 135.9 (s), 133.9 (s), 134.8 (s) 133.7 (d), 132.5 (s), 131.1 (d), 130.5 (s), 130.2 (d), 128.8 (d), 128. (d), 125.1 (d), 121.7 (s), 111.1 (s); *m*/*z* (EI) 317 (M^+ + 2, 43%), 315 (M^+, 100), 313 (M^+ − 2, 21), 304 (6), 285 (18), 280 (43), 272 (10), 270 (10), 260 (25), 258 (56), 244 (8), 230 (14), 223 (28), 216 (85), 186 (29), 136 (19), 109 (26), 103 (64), 96 (27), 90 (20), 76 (40), 64 (81), 57 (38). Anal. Calcd for $C_{15}H_8Cl_2N_4$: C, 57.17; H, 2.56; N, 17.78. Found: C, 57.24; H, 2.5; N, 17.69.

*4.3.8. 4-Imino-6,7-dimethoxy-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6h**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-4,5-dimethoxy-*N*′-(phenyl)benzamidine (**1h**) (64 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6h** (38 mg, 53%) as colorless needles: mp 230 °C (sub) (from acetone); mp (DSC) onset 260.8 °C, peak max 263.2 °C (from acetone); R_f (*t*-BuOMe/EtOH, 60:40) 0.59; λ_{max} (DCM)/nm 229 (log ε 4.58), 249 inf (4.56), 257 inf (4.61), 266 (4.66), 275 inf (4.62), 314 (3.98), 329 (4.05), 355 (4.05), 372 inf (4.00), 393 inf (3.67); ν_{max}/cm^{-1} 3304w, 3287w (NH), 3100w, 3073w, 3013w (Ar CH), 2976w, 2940w, 2870w, 2830w, 2237w (C≡N), 1628m, 1609s, 1570m, 1512s, 1493m, 1470m, 1454m, 1433w, 1381m, 1348m, 1304m, 1277m, 1229m, 1204m, 1182w, 1125m, 1055m, 1038w, 1003m, 995m, 934w, 876w, 856m, 841m, 822m, 793m, 781m, 765m;

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δ_H (300 MHz; $CDCl_3$) 7.72−7.66 (4H, m), 7.44−7.41 (2H, m), 7.08 (1H, s), 6.34 (1H, br s), 4.01 (3H, s), 4.00 (3H, s); δ_C (75 MHz; $CDCl_3$) 153.6 (s), 152.7 (s), 151.1 (s), 138.7 (s), 134.9 (s), 131.3 (d), 131.1 (d), 129.5 (s), 129.1 (d), 116.2 (s), 111.5 (s), 109.0 (d), 105.6 (d), 56.5 (q), 56.3 (q); *m*/*z* (EI) 306 (M^+, 31%), 305 (83), 289 (11), 261 (5), 236 (3), 193 (2), 149 (8), 129 (10), 111 (7), 97 (13), 83 (13), 77 (37), 71 (15), 69 (27), 57 (26), 51 (10). Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.55; H, 4.42; N, 18.38.

*4.3.9. 4-Imino-6,7-dimethoxy-3-(4-methoxyphenyl)-3,4-dihydroquinazoline-2-carbonitrile (**6i**).* Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride (**3**) (50 mg, 0.24 mmol) with 2-amino-4,5-dimethoxy-*N*′-(4-methoxyphenyl)benzamidine (**1i**) (71 mg, 0.24 mmol) at ca. 20 °C gave the title compound **6i** (49 mg, 61%) as pale yellow needles: mp 234−235 °C (from acetone); mp (DSC) onset 254.5 °C, peak max 255.4 °C (from acetone); R_f 0.73 (*t*-BuOMe/EtOH, 90:10); λ_{max} (DCM)/nm 232 (log ε 4.68), 248 (4.62), 255 inf (4.61), 268 (4.61), 276 inf (4.55), 316 (4.01), 330 (4.10), 358 (4.10), 392 (3.73); ν_{max}/cm^{-1} 3289w (NH), 3100w, 3055w, 3024w and 3015w (Ar CH), 2984w, 2963w, 2943w, 2914w, 2866w, 2827w, 2237w (C≡N), 1640m, 1632m, 1607m, 1587w, 1578w, 1512s, 1458m, 1429w, 1414w, 1377m, 1339w, 1318w, 1308w, 1298m, 1275s, 1252s, 1221w, 1198m, 1186w, 1167m, 1121s, 1107m, 1063w, 1032m, 1017w, 995m, 953w, 882m, 868m, 837s; δ_H (300 MHz; $CDCl_3$) 7.66 (1H, s), 7.32 (2H, d, *J* 8.7), 7.13 (2H, d, *J* 8.7), 7.05 (1H, s), 6.51 (1H, br s), 4.00 (3H, s), 3.99 (3H, s), 3.91 (3H, s); δ_C (75 MHz; $CDCl_3$) 161.5 (s), 153.7 (s), 153.1 (s), 151.2 (s), 138.8 (s), 130.3 (d), 130.2 (s), 127.2 (s), 116.3 (s), 116.3 (d), 111.7 (s), 109.1 (d), 105.8 (d), 56.5 (q), 56.3 (q), 55.7 (q); *m*/*z* (EI) 336 (M^+, 89%), 335 (100), 321 (41), 305 (8), 245 (42), 159 (14), 122 (5), 107 (15), 92 (14), 77 (32), 64 (12), 51 (10). Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.44; H, 4.84; N, 16.60.

4.4. Base Hydrolysis of 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (6a) (Scheme 2). *4.4.1. 2-Methoxy-3-phenylquinazolin-4(3H)-imine (**7**) from the Iminoquinazoline **6a** (Reaction Conditions i).* To solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL), and the stirred mixture was heated at ca. 67 °C for 3 h and then allowed to cool to ca. 20 °C. The reaction mixture was then diluted (H_2O), neutralized (10% HCl), and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **7** (25 mg, 99%) as pale yellow plates: mp (DSC) onset 126.3 °C, peak max 128.4 °C (from DCM/*n*-pentane, 60:40); R_f 0.40 (*t*-BuOMe/DCM, 20:80); λ_{max} (DCM)/nm 234 (log ε 4.35), 240 inf (4.32), 247 inf (4.22), 265 inf (3.94), 275 (3.98), 284 inf (3.91), 305 inf (3.69), 316 (3.81), 329 (3.69); ν_{max}/cm^{-1} 3310w, 3277w (NH), 3260w, 3061w, 2951w, 2924w, 2853w, 1643s, 1634m, 1605s, 1582s, 1481m, 1472m, 1454w, 1437m, 1371m, 1360m, 1323s, 1308m, 1298m, 1261w, 1242w, 1233w, 1184m, 1171m, 1144m, 1119w, 1074w, 1049m, 1030m, 976m, 962m, 905w, 870w, 833w, 806m, 764s; δ_H (500 MHz; $CDCl_3$) 8.20 (1H, d, *J* 7.5), 7.61−7.57 (3H, m), 7.54−7.51 (1H, m), 7.44 (1H, dd, *J* 0.5, 0.5), 7.30−7.27 (3H, m), 3.92 (3H, s); δ_C (125 MHz; $CDCl_3$) 156.6 (s), 152.0 (s), 144.7 (s), 135.1 (s), 132.9 (d), 130.1 (d), 129.3 (d), 129.0 (d), 125.7 (d), 125.4 (d), 124.5 (d), 119.5 (s), 55.1 (q); *m*/*z* (EI) 251 (M^+, 22%), 250 (100), 235 (11), 119 (6), 91 (6), 77 (8). Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.63; H, 5.27; N, 16.82

*4.4.2. 4-Imino-3-phenyl-3,4-dihydroquinazolin-2(1H)-one (**8**) from the Quinazolinimine **7** (Reaction Conditions ii).* To solution of 2-methoxy-3-phenylquinazolin-4(3*H*)-imine (**7**) (25.1 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of 10% HCl (0.5 mL), and the stirred mixture was heated at ca. 67 °C for 30 min and then allowed to cool to ca. 20 °C. The reaction mixture was then neutralized (10% K_2CO_3) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **8** (23.5 mg, 99%) as colorless plates: mp (DSC) onset 218.4 °C, peak max 223.7 °C (from MeOH) (lit.[25] mp 214−218 °C); R_f (DCM/*t*-BuOMe, 70:30) 0.32; λ_{max} (DCM)/nm 234 (log ε 4.58), 246 inf (4.37), 294 inf (3.88), 306 (4.07), 318 (4.01); ν_{max}/cm^{-1} 3294w, 3206w, 3152w and (NH), 3090w and 3065w (Ar CH), 2997w, 2934w, 2891w, 2852w, 1688s (C═O), 1614s, 1491m, 1447m, 1406m, 1294s, 1267m, 1171m, 1157m, 1142m, 1117w, 1069w, 1042w, 962w, 907w, 864w, 839w, 829w, 791s, 775m, 756s; δ_H (500 MHz; CD_2Cl_2) 9.00 (1H, br s), 8.15 (1H, br s), 7.60 (2H, dd, *J* 6.8, 6.8), 7.54 (1H, dd, *J* 7.3, 7.3), 7.46 (1H, dd, *J* 7.6, 7.6), 7.32 (2H, d, *J* 7.5), 7.16 (1H, dd, *J* 7.5, 7.5), 6.87 (1H, d, *J* 8.0), 6.78 (1H, br s); δ_C (125 MHz; CD_2Cl_2) one quaternary carbon missing 150.9 (s), 137.4 (s), 135.5 (s), 133.5 (d), 130.5 (d), 129.9 (d), 129.6 (d), 127.3 (d), 123.4 (d), 116.0 (s), 115.2 (d); *m*/*z* (EI) 238 (MH^+, 3%), 237 (M^+, 20), 236 (100), 195 (1), 145 (1), 118 (14), 104 (2), 91 (14), 77 (6), 65 (6). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.93; H, 4.54; N, 17.61.

*4.4.3. 4-Imino-3-phenyl-3,4-dihydroquinazolin-2(1H)-one (**8**) from the Quinazolinimine **6a** (Reaction Conditions iii).* To solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL), and the stirred mixture was heated at ca. 67 °C for 3 h and then allowed to cool to ca. 20 °C. The reaction mixture was then acidified (10% HCl), and the volatiles were evaporated under reduced pressure. The remaining solid was then dissolved (H_2O), neutralized (10% K_2CO_3), and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **8** (23.4 mg, 99%) as colorless plates, mp (DSC) onset 218.4 °C, peak max 223.7 °C (from MeOH) (lit.[25] mp 214−218 °C) identical to the sample described above.

*4.4.4. 3-Phenylquinazoline-2,4(1H,3H)-dione (**9**) from the Quinazolinimine **8** (Reaction Conditions iv).* To 4-imino-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**8**) (23.7 mg, 0.1 mmol) was added a solution of 1 N NaOH (1 mL) and the reaction mixture allowed to stir at ca. 20 °C for 7 d. The reaction mixture was then neutralized (10% HCl) and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **9** (21.5 mg, 90%) as colorless plates: mp (DSC) onset 281.2 °C, peak max 281.8 °C (lit.[26] mp 281−282 °C) (from cyclohexane/EtOH, 1:1); R_f 0.52 (DCM/*t*-BuOMe, 80:20); λ_{max} (DCM)/nm 229 (log ε 4.17), 242 inf (3.97), 309 (3.47), 3.19 (3.39); ν_{max}/cm^{-1} 3213w, 3198w, 3122w, 3080w, 3057w, 3020w, 3003w (Ar CH), 2941w, 2899w, 2808w, 1726m (C═O), 1697w, 1659s (C═O), 1626m, 1611m, 1591m, 1518w, 1493m, 1445m, 1400m, 1341w, 1327w, 1288m, 1273w, 1240w, 1150m, 1072w, 1026w, 1017w, 876w, 866w, 817w, 783w, 752s; δ_H (300 MHz; $CDCl_3$) 9.52 (1H, s), 8.15 (1H, dd, *J* 1.5, 1.5), 7.60−7.49 (4H, m), 7.34−7.30 (2H, m), 6.94 (1H, d, *J* 8.1); δ_C (75 MHz; $CDCl_3$) one quaternary carbon missing 162.5 (s), 151.4 (s), 138.6 (s), 135.4 (d), 134.8 (s), 129.5 (d), 128.9 (d), 128.8 (d), 128.5 (d), 123.6 (d), 115.1 (d), 114.8 (s); *m*/*z* (EI) 238 (M^+, 100%), 237 (31), 146 (51), 119 (100), 93 (48), 90 (17), 77 (8), 64 (22).

4.5. Base Hydrolysis of 4-Anilinoquinazoline-2-carbonitrile (2) (Scheme 3). *4.5.1. 4-Anilino-2-methoxyquinazoline (**10**).* To solution of 4-anilinoquinazoline-2-carbonitrile (**2**) (24.6 mg, 0.1 mmol) in MeOH (0.5 mL) was added a solution of NaOH (4 mg, 0.1 mmol) in MeOH (0.5 mL), and the stirred mixture was heated at ca. 67 °C for 4 d and then allowed to cool to ca. 20 °C. The reaction mixture was then diluted (H_2O), neutralized (10% HCl), and extracted (*t*-BuOMe). The organic extracts were then washed (H_2O) and dried (Na_2SO_4). Removal of the volatiles gave the title compound **10** (17.8 mg, 71%) as pale yellow plates: mp (DSC) onset 198.4 °C, peak max 200.9 °C, dec onset 206.1 °C, peak max 208.9 °C (lit.[27] mp 198−200 °C) (from DCM/*n*-pentane, 60:40); R_f 0.45 (DCM/*t*-BuOMe, 80:20); λ_{max} (DCM)/nm 234 (log ε 4.46), 278 (4.17), 295 inf (4.02), 322 inf (4.06), 335 (4.71), 349 inf (4.08); ν_{max}/cm^{-1} 3161w, 3051w (Ar CH), 2986w, 1620m, 1599m, 1568s, 1530m, 1497s, 1470m, 1445s, 1416m, 1373s, 1323s, 1292w, 1259m, 1190w, 1177w, 1138w, 1103w, 1072m, 1030w, 991w, 912w, 879w, 871w, 853w, 841w, 800w, 766m, 754m; δ_H (500 MHz; $CDCl_3$) 7.80−7.76 (3H, m), 7.74−7.69 (2H, m), 7.46 (1H, br s), 7.41 (2H, dd, *J* 7.5, 7.5), 7.37 (1H, ddd, *J* 7.3, 7.3, 2.0), 7.16 (1H, dd, *J* 7.5, 7.5), 4.07 (3H, s);

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δ_C (75 MHz; $CDCl_3$) 162.6 (s), 159.5 (s), 152.1 (s), 138.1 (s), 133.2 (d), 129.1 (d), 127.5 (d), 124.4 (d), 123.8 (d), 121.5 (d), 120.5 (d), 112.3 (s), 54.5 (q); *m*/*z* (EI) 251 (M^+, 46%), 250 ($M^+ - 1$, 100), 235 (11), 220 (26), 207 (7), 144 (6), 116 (9), 110 (6), 90 (9), 77 (20), 65 (14), 51 (11).

4.6. Acid Hydrolysis of 4-Imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (6a) (Scheme 4). *4.6.1. 4-Oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**11**) (Reaction Conditions i).* To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (24.6 mg, 0.1 mmol) in DMSO (1 mL) was added TFA (7.7 μL, 0.1 mmol). The reaction mixture was heated at ca. 100 °C for 2 d and monitored by TLC. When no starting quinazoline remained (by TLC), the reaction mixture was allowed to cool to ca. 20 °C and then neutralized with 10% K_2CO_3, diluted in H_2O (3 mL), and extracted (*t*-BuOMe, 2 × 30 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica, and chromatographed to give the title compound **11** (23.5 mg, 99%) as colorless needles: mp 193−194 °C (lit.[28] mp 196−197 °C) (from cyclohexane/EtOH, 90:10); R_f 0.55 (DCM/*t*-BuOMe, 95:05); λ_{max} (DCM)/nm 232 (log ε 4.14), 249 inf (3.70), 260 inf (3.54), 291 inf (3.71), 303 (3.79), 312 inf (3.73), 327 (3.59); ν_{max}/cm^{-1} 3076w, 3052w (Ar CH), 2239w (C≡N), 1692s (C═O), 1605m, 1599m, 1584m, 1560m, 1491m, 1466m, 1462m, 1342s, 1323m, 1279s, 1236w, 1211w, 1159w, 1117w, 1107w, 1088w, 1076w, 1022w, 1009w, 972w, 893w, 885w, 847w, 799w, 777s, 768s; δ_H (500 MHz; $CDCl_3$) 8.37 (1H, d, *J* 5.0), 7.92−7.86 (2H, m), 7.69 (1H, dd, *J* 7.5, 7.5), 7.63−7.60 (3H, m), 7.43−7.41 (2H, m); δ_C (75 MHz; $CDCl_3$) 160.1 (s), 146.5 (s), 135.4 (d), 135.2 (s), 131.5 (s), 130.7 (d), 130.3 (d), 130.1 (d), 128.7 (d), 128.2 (d), 127.5 (d), 123.0 (s), 111.0 (s); *m*/*z* (EI) 247 (M^+, 100%), 219 (51), 192 (7), 166 (6), 129 (6), 119 (48), 102 (13), 90 (12), 77 (71), 63 (8), 51 (32).

*4.6.2. 4-Oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**11**) (Reaction Conditions ii).* To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (24.6 mg, 0.1 mmol) in THF/H_2O (1:1) (1 mL) was added concd HCl (9 μL, 0.1 mmol). The reaction mixture was heated at ca. 65 °C for 24 h and monitored by TLC. When no starting quinazoline remained (by TLC), the reaction mixture was allowed to cool to ca. 20 °C and then neutralized with 10% K_2CO_3 and extracted (*t*-BuOMe, 2 × 30 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica and chromatographed to give the title compound **11** (21.5 mg, 87%), as colorless needles: mp 193−194 °C (lit.[28] mp 196−197 °C) identical to that described above.

*4.6.3. 3-Phenylquinazoline-2,4(1H,3H)-dione (**9**) from the Quinazolinone **11** (Reaction Conditions iii).* To a stirred solution of 4-oxo-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**11**) (23.7 mg, 0.1 mmol) in THF/H_2O (1:1) (1 mL) was added concd HCl (18 μL, 0.2 mmol). The reaction mixture was heated at ca. 65 °C for 3 d and monitored by TLC. When no starting quinazoline remained (by TLC) the reaction mixture was allowed to cool to ca. 20 °C and then neutralized with 10% K_2CO_3 and extracted (*t*-BuOMe, 60 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica, and chromatographed to give the title compound **9** (22.8 mg, 96%) as colorless plates: mp (DSC) onset 281.2 °C, peak max 281.8 °C (lit.[26] mp 281−282 °C)identical to authentic sample.

*4.6.4. 3-Phenylquinazoline-2,4(1H,3H)-dione (**9**) from the Quinazolinimine **6a** (Scheme 4, Reaction Conditions iv).* To a stirred solution of 4-imino-3-phenyl-3,4-dihydroquinazoline-2-carbonitrile (**6a**) (24.6 mg, 0.1 mmol) in THF/H_2O (1:1) (1 mL) was added concd HCl (56 μL, 0.4 mmol). The reaction mixture was heated at ca. 65 °C for 1.5 d and monitored by TLC. When no starting quinazoline remained (by TLC), the reaction mixture was allowed to cool to ca. 20 °C, neutralized with 10% K_2CO_3, and extracted (*t*-BuOMe, 60 mL). The combined organic phases were dried (Na_2SO_4), adsorbed onto silica, and chromatographed to give the title compound **9** (23.6 mg, 99%) as colorless plates: mp (DSC) onset 281.2 °C, peak max 281.8 °C (lit.[26] mp 281−282 °C) (from cyclohexane/EtOH, 1:1) identical to an authentic sample.

4.7. Hydration of 4-Anilinoquinazoline-2-carbonitrile (2). *4.7.1. 4-Anilinoquinazoline-2-carboxamide (**12**).* To 4-anilinoquinazoline-2-carbonitrile (**2**) (24.6 mg, 0.10 mmol) was added concd HCl (0.5 mL). The reaction mixture was heated at ca. 65 °C for 16 h and monitored by TLC. When no starting material remained the reaction mixture was allowed to cool to ca. 20 °C and neutralized with 6 M NaOH followed by precipitation and filtration of the title compound **12** (18.2 mg, 69%) as colorless needles: mp (DSC) onset 229.6 °C, peak max 230.1 °C (from THF/*n*-pentane, 60:40); R_f 0.48 (THF/DCM, 50:50); λ_{max} (DCM)/nm 339 (log ε 4.22); ν_{max}/cm^{-1} 3505w, 3414w, 3289w and 3186w (NH), 1680w, 1638m, 1626m, 1609w, 1566s, 1531m, 1493m, 1487s, 1447m, 1416s, 1368m, 1315w, 1302w, 1292w, 1256w, 1213w, 1157w, 1134w, 1096w, 1078w, 1030w, 989w, 910w, 883w, 870w, 847w, 796w, 768m, 758s; δ_H (500 MHz; $CDCl_3$) 9.98 (1H, s), 8.61 (1H, d, *J* 10.0), 7.97−7.90 (4H, m), 7.88 (1H, br s), 7.70 (1H, dd, *J* 7.5, 7.5), 7.68 (1H, br s), 7.43 (2H, dd, *J* 7.5, 7.5), 7.17 (1H, dd, *J* 7.5, 7.5); δ_C (75 MHz; $CDCl_3$) 165.7 (s), 158.4 (s), 154.5 (s), 149.5 (s), 139.0 (s), 133.7 (d), 128.7 (d), 128.6 (d), 127.6 (d), 124.1 (d), 123.2 (d), 122.4 (d), 114.9 (s); *m*/*z* (EI) 264 (M^+, 92%), 219 (100), 192 (5), 129 (5), 110 (14), 92 (13), 77 (35), 65 (8), 51 (16). Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.26; H, 4.69; N, 20.92.

4.5. X-ray Crystallographic Studies. Data were collected on an Oxford-Diffraction Supernova diffractometer, equipped with a CCD area detector utilizing Mo Kα radiation (λ = 0.71073 Å). A suitable crystal was attached to glass fibers using paratone-N oil and transferred to a goniostat where they were cooled for data collection. Unit cell dimensions were determined and refined by using 6074 ($3.02 \leq \theta \leq 28.90°$) reflections. Empirical absorption corrections (multiscan based on symmetry-related measurements) were applied using CrysAlis RED software.[31] The structure was solved by direct methods using SIR92[32] and refined on F^2 using full-matrix least-squares using SHELXL97.[33] Software packages used: CrysAlis CCD[31] for data collection, CrysAlis RED[31] for cell refinement and data reduction, WINGX for geometric calculations,[34] and DIAMOND[35] for molecular graphics. The non-H atoms were treated anisotropically. The hydrogen atom attached to N3 was located on a difference Fourier map, whereas all other hydrogen atoms were placed in calculated, ideal positions and refined as riding on their respective carbon atoms.

*4.5.1. Crystal refinement data for compound **6a**:* $C_{15}H_{10}N_4$, *M* = 246.27, orthorhombic, space group *Pbca*, *a* = 16.3251(4) Å, *b* = 6.7320(2) Å, *c* = 21.6139(5) Å, *V* = 2375.4(2) Å^3, *Z* = 8, *T* = 100(2) K, ρ_{calcd} = 1.377 g cm^{-3}, $2\theta_{max}$ = 53. Refinement of 176 parameters on 2460 independent reflections out of 10391 measured reflections (R_{int} = 0.0236) led to R_1 = 0.0363 [$I > 2\sigma(I)$], wR_2 = 0.1119 (all data), and *S* = 1.080 with the largest difference peak and hole of 0.193 and −0.206 e^{-3}, respectively.

Crystallographic data for compound **6a** have been deposited with the Cambridge Crystallographic Data Centre with deposit no. CCDC-952956. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441223336033; or e-mail: deposit@ccdc.cam.ac.uk.

■ ASSOCIATED CONTENT

Supporting Information

Copies of 1D ^1H and ^{13}C NMR spectra of all new compounds. Single-crystal X-ray structure of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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