Pergamon

Tetrahedron 56 (2000) 9343–9349

TETRAHEDRON

Synthesis of 4-Arylaminoquinazolines and 2-Aryl-4-arylaminoquinazolines from 2-Aminobenzonitrile, Anilines and Formic Acid or Benzaldehydes

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Received 5 June 2000; revised 5 September 2000; accepted 21 September 2000

Abstract—2-Aminobenzonitrile treated with anilines in the presence of aluminium chloride gave respective 2-amino-*N*-arylbenzamidines. 4-Arylaminoquinazolines lacking a substituent at the 2 position were obtained directly by heating 2-amino-*N*-arylbenzamidines in formic acid; in similar conditions other carboxylic acids did not react with the amidines. The latter when treated with aldehydes afforded 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines readily oxidizable by potassium permanganate to 2-aryl-4-arylaminoquinazolines.

Introduction

Recently, there has been a renewed interest in 4-arylaminoquinazolines connected with reports on high biological activity of the compounds, particularly as potential antitumor drugs.[1–3]

Despite the interest in the biological activity of 4-arylaminoquinazolines almost no progress in their synthesis has been published. 4-Arylaminoquinazolines are usually obtained from 4-chloro[4] or 4-mercaptoquinazolines[5] reaction with anilines. Yields of the synthesis do not exceed 50%.[6] Some 4-arylaminoquinazolines have been prepared from 4(3*H*)-quinazolinone and an aniline hydrochloride in the presence of phosphorus pentaoxide and *N*,*N*-dimethylcyclohexylamine.[7] 4-Phenylaminoquinazoline itself has also been obtained by desulfurization of 4-phenylaminoquinazolin-2-thione on Raney nickel W7.[8,11] Surprisingly, besides our preliminary report,[16] no paper describes 4-arylaminoquinazoline synthesis from 2-amino-*N*-arylbenzamidines involving formation of two C–N bonds (Fig. 1).

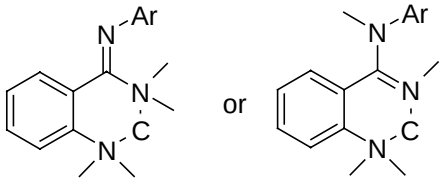

Figure 1.

Keywords: *o*-aminobenzonitrile; amidines; acidity; quinazolines; synthesis.
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The reason could lie in a shortage of information on syntheses and properties of 2-amino-*N*-arylbenzamidines. It has been reported that 2-amino-*N*-(2-aminophenyl)benzamidine can be prepared in a reaction of 2-nitroaniline sulfate with 2-nitrobenzonitrile followed by the reduction of both nitro groups in forming 2-nitro-*N*-(2-nitrophenyl)-benzamidine.[9] A similar method has been used for the synthesis of 2-amino-*N*-phenylbenzamidine.[10] The latter compound has also been obtained by reduction of 4-phenylamino-1,2,3-benzotriazine with hydrazine and Raney nickel.[9]

Results and Discussion

Synthesis of 2-amino-*N*-arylbenzamidines

Searching for an efficient method of 2-amino-*N*-arylbenzamidine synthesis, we checked a reaction of 2-aminobenzonitrile[12] with aniline carried out in the presence of anhydrous aluminium chloride (Scheme 1; Table 1).

A preliminary attempt performed under typical conditions (equimolar amounts of all reagents and the catalyst)[13] gave low yields of the amidines. For example, the reaction between 2-aminobenzonitrile, aniline and aluminium chloride gave mainly tricycloquinazoline (**2**)[14] and 2-(2-aminophenyl)-4-phenylaminoquinazoline (**3**)[15] (Fig. 2).

Much better yields of the amidines were obtained using 50% excess of anilines and aluminium chloride compared with the amount of *o*-aminobenzonitrile. The yields depended on the substituent on the benzene ring in the starting anilines. Strongly electron withdrawing substituents lowered a yield

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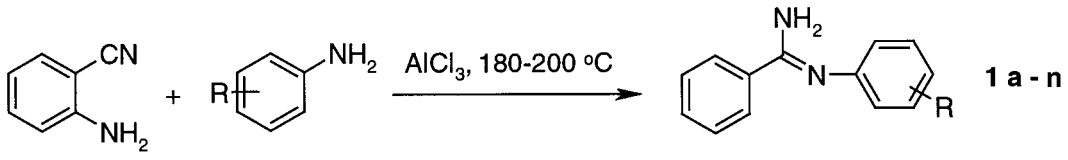


Scheme 1.

Table 1. 2-Amino-*N*-arylbenzamidines obtained in reactions of 2-aminobenzonitrile with anilines

Amidine	R	Amidine	R
1a	H	**1h**	3-Cl
1b	2-Me	**1i**	4-Cl
1c	3-Me	**1j**	3,4-diCl
1d	4-Me	**1k**	2-Br
1e	2,4-diMe	**1l**	3-Br
1f	3,4-diMe	**1m**	4-Br
1g	2-Cl	**1n**	3-I

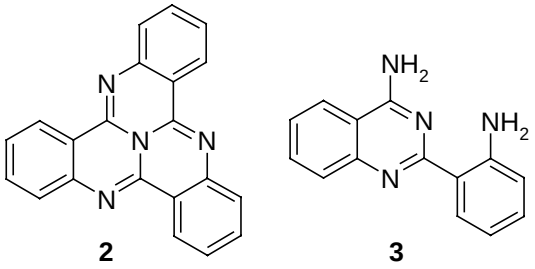


Figure 2.

(3,4-dichloroaniline) or prevented (nitroanilines) the formation of amidines, presumably due to the low nucleophilicity of the amino group in these anilines. Surprisingly, use of an anisidine or 3,4-methylenedioxyaniline led to the formation of tricycloquinazoline and some tars. The latter results may be explained assuming coordination of the catalyst by alkoxy groups what prevents the formation of the expected amidines.

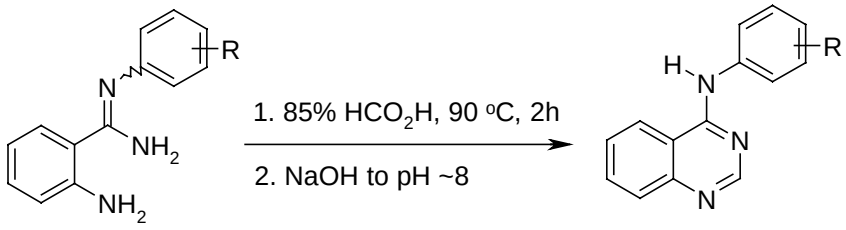
Synthesis of 4-arylaminoquinazolines from 2-amino-*N*-arylbenzamidines and formic acid

As we have already mentioned 2-amino-*N*-arylbenzamidines and hot formic acid afford 4-arylaminoquinazolines in good yields (Scheme 2, Table 2).[16] Unfortunately this reaction can only be applied to the synthesis of 2-unsubstituted 4-arylaminoquinazolines. Therefore, we assumed that the formyl group formally present in formic acid and not the carboxylic one is critical for formation of a quinazoline system in the reaction studied.

Synthesis of 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines and of 2-aryl-4-arylaminoquinazolines from 2-amino-*N*-arylbenzamidines and benzaldehydes

Based on the known reaction of 2-aminobenzamidine hydrochloride with aldehydes,[18] we performed several reactions of 2-amino-*N*-arylbenzamidines with benzaldehyde or its ring substituted derivatives obtaining the expected crude 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines as the main products. (Scheme 3, Table 3)

Attempts to purify the compounds by recrystallization and column chromatography led to deterioration in elemental analysis results. Careful ^{1}H NMR spectral checking showed a very characteristic signal at ca. 9.8 ppm (a signal of the N–H hydrogen atom from the arylamino group in 4-arylaminoquinazolines) indicating that the dihydroquinazolines are readily oxidized to the quinazolines in samples purified by chromatography. This signal was usually more intense than that of the crude material. Nevertheless, for some

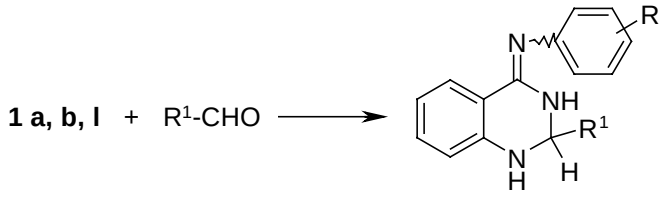


Scheme 2.

Table 2. Yields and melting points of 4-arylaminoquinazolines obtained in the reaction of 2-amino-*N*-arylbenzamidines with formic acid

R	Yield [%]	Mp [°C]	R	Yield [%]	Mp [°C]
H	82	200–221	3-I	92	232–234
2-Me	70	82–84	4-Me	84	191–193
2-Br	73	131–132	4-Cl	92	194–195
3-Me	84	196–197	4-Br	91	189–190
3-Cl	90	199–200	3,4-diMe	83	196.5–198
3-Br	92	216–217	3,4-diCl	92	219–220

dihydroquinazolines, we were able to determine their melting points, ^{1}H NMR and MS spectra. The spectral analysis showed that all the products have the structure of anils. The latter are better stabilized by resonance than 4-arylamino tautomers. We have not undertaken any attempts to work in anoxic conditions that would probably allow the preparation of analytically pure samples of the anils. Instead, some of the crude compounds were treated with potassium permanganate in acetone to get corresponding aromatic quinazolines (Scheme 4).



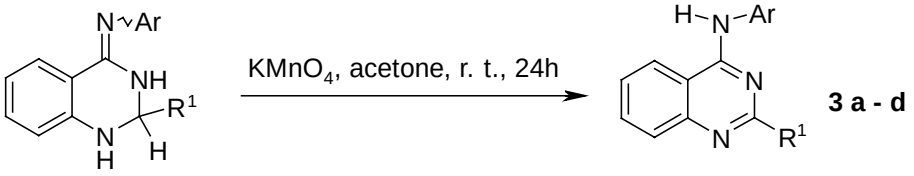
Scheme 3.

Table 3. Yields and melting points of crude 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines

Amidine	R^1	Product	Yield [%]	Mp [°C]
1a	Ph	**2aa**	59	125–126
1a	3-MeC_6H_4	**2ab**	45	157–159
1b		**2bc**	71	140–142
1l		**2ld**	74	148–150
1a	4-$MeOC_6H_4$	**2ae**	45	203–206
1b		**2bf**	7	114–117
1l		**2lg**	21	108–110
1a	4-Cl	**2ah**	77	215–220
1a	4-Br	**2ai**	83	229–233
1a	3,4-diClC_6H_3	**2aj**	76	134–135
1b		**2bk**	25	80–83
1l		**2lm**	36	94–96
1a	1-Methylethyl	**2an**	75	121–125

The results of such treatment we collected in Table 4. Yields of the quinazolines obtained are moderate when calculated from the starting dihydroquinazolines but usually low when calculated based on the starting amidines.

We have achieved some improvement in yields of 2-aryl-4-arylaminoquinazolines calculated based on the starting amidines omitting separation of the dihydroquinazolines and treating them with potassium permanganate following a change of the solvent; thus ethanol used in the first stage was replaced by acetone. The scope of such one-pot syntheses (Scheme 5) is showed in Table 5. It is worth mentioning that the method is also successful for a preparation of 2-alkyl-4-arylaminoquinazolines. A synthesis of 2-(2-methylethyl)-4-phenylaminoquinazoline, separated as its hydrochloride in 53% yield, may serve as an example.



Scheme 4.

Table 4. Yields of 2-aryl-4-arylaminoquinazolines obtained by a treatment of the corresponding crude 2,3-dihydroquinazoline derivatives with potassium permanganate

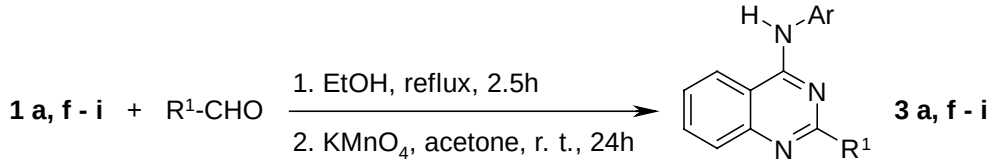
Substrate	Product	Yield [%] calcd on a dihydroquinazoline	Yield [%] calcd on an amidine
2aa	**3a**	69	41
2ah	**3b**	56	43
2ai	**3c**	88	73
2lm	**3d**	56	20

Spectroscopic and other physicochemical properties of the amidines and dihydroquinazolines

We characterized the synthesized compounds by standard MS and ^{1}H NMR spectra. 2-Amino-*N*-arylbenzamidines give moderately intense (over 40%) molecular peaks. As a rule, starting radical-cations decompose via four main routes: by the elimination of hydrogen atom (M^+-1 peaks), by the elimination of ammonia (M^+-17 peaks), by the elimination of *o*-aminobenzonitrile (M^+-118 peaks) and by the elimination of the respective substituted aniline radicals ($M^+-ArNH^{\cdot}$ peaks). The latter process leads to the formation of the protonated *o*-aminobenzonitrile (*m*/*z*=119 peaks). In MS spectra of 2-amino-*N*-arylbenzamidines with *o*-substituted *N*-aryl group another possible route of fragmentation appears. It involves departure of the *o*-substituent (halogen atom, methyl radical) from a molecular radical-cation. Fragmentation pattern fully supports the analysis of synthesized compounds.

In MS spectra of the synthesized 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines molecular peaks are weak (less than 10%). Instead, peaks M-1, M-2 and M-3 are intensive, the latter often being main ones. The peaks mentioned probably arise from a molecular radical-cation by departures of hydrogen atoms. They can leave from the positions 1, 2 or 3 of the hetero-ring. There were also observed peaks probably identical with the molecular peaks and fragmentation routes of the corresponding 2-arylquinazolines and 2-aryl-4-arylaminoquinazolines. These results support an assumption that, in contrast to a liquid phase, in a gas phase both tautomeric forms of 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines are present (another is 2-aryl-4-arylamino-1,2-dihydroquinazoline form).

The most characteristic feature of the ^{1}H NMR spectra of 2-amino-*N*-arylbenzamidines is the presence of two broadened two-proton signals of the aromatic amino (6.7–6.9 ppm) and the amidine amino (5.5–6.3 ppm) groups. The presence of these two signals indicates that in the compounds studied, the two benzene rings are conjugated through a double amidine carbon–nitrogen bond in the



Scheme 5.

Table 5. The scope of one-pot synthesis of 2-aryl-4-aminoquinazolines from 2-amino-*N*-arylbenzamidines and aldehydes

Amidine	R^1	Product
1a	Ph	**3a**
1k	4-$MeOC_6H_4$	**3f**
1l		**3g**
1a	3-MeC_6H_4	**3h**
1a	2-methylethyl	**3i**

solution phase. In the spectra there were no signals that could be attributed to the possible tautomers. We also recorded UV-VIS spectra of the *meta* and *para*-substituted 2-amino-*N*-arylbenzamidines in solutions of different pHs to determine of pK_a values of the compounds.[17] The values shown in Table 6 fulfil the Hammet equation ($\rho=-2.5$, $r=0.985$).

The relatively high ρ value indicates that the imino nitrogen atom is the site of the first protonation step (Scheme 6).

Conclusions

The synthesis of 4-arylaminoquinazolines and their 2-aryl derivatives presented here is the most general among known methods. We have shown the method can also be applied in synthesis of 2-alkyl-4-arylaminoquinazolines though the latter compounds were rather away from our interest. The described method allows the preparation of many derivatives with either electron-withdrawing or electron-donating groups as aryl substituents. Yields of the products are from moderate to good. The method starts from commercially available 2-aminobenzonitrile; other reagents are simple and cheap. The elaborated syntheses also suffers from some limitations. It cannot be applied in the synthesis of nitro- and alkoxy-derivatives. Unfortunately alkoxy groups cannot be present either in starting aminobenzonitrile or aniline. Thus, a first step of the synthesis, namely the preparation of amidines, requires further investigation.

Table 6. pK_a values of 2-amino-*N*-arylbenzamidines

Amidine	pK_a	Amidine	pK_a
1a	8.80±0.16	**1d**	9.10±0.07
1c	8.95±0.15	**1i**	8.09±0.17
1h	7.68±0.13	**1m**	8.05±0.12
1l	7.89±0.16	**1e**	8.98±0.16

Some conclusions drawn from the spectra of 2-amino-*N*-arylbenzamidines and 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines may be helpful in elucidation of the reaction mechanisms. Neither the formation of 2-amino-*N*-arylbenzamidines nor the formation of 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazolines is clear yet. Investigations concerning the mechanisms are in progress.

Experimental

General

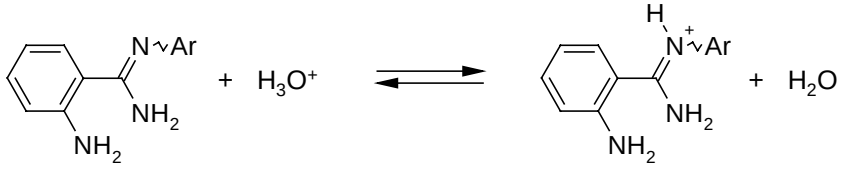
MS spectra were made on Shimadzu GCMS QP-2000 apparatus (EI method). ^{1}H NMR spectra were made on Varian XL-300 in DMSO-d_6 (spectra made in acetone-d_6 are indicated in the text below). UV-VIS spectra were made on Shimadzu UV-2102 PC apparatus. Melting points (not corrected) were collected on Boetius HMK apparatus.

Synthesis of 2-amino-*N*-arylbenzamidines

General procedure. An aniline (15 mmol) and *o*-aminobenzonitrile (10 mmol) were carefully heated until a homogenous melt. Anhydrous aluminium chloride (15 mmol) was added in many portions with swirling. The resulted mixture was then heated at 180–200°C during 1 h. Then 10% hydrochloric acid (25 ml) was added, and after dissolving the post-reaction mixture, 2 M sodium hydroxide solution was added until pH=6. the obtained solution was extracted with chloroform (3×10 ml). The aqueous layer was separated and basified with 2 M sodium hydroxide solution. The white precipitate was filtered off, washed with water until neutral reaction, air dried, and crystallized from a benzene–petroleum ether (bp 40–60°C) mixture.

1a. (1.80 g, 57%) as white plates, mp 146–147°C (147–148°C).[15]

1b. (2.26 g, 67%) as a white solid, mp 107–108°C; [Found:



Scheme 6.

C, 74.61; H, 6.40 N, 18.71. $C_{14}H_{15}N_3$ requires C, 74.64; H, 6.71; N, 18.65%]; δ_H 3.36 (3H, s, Me), 5.97 (2H, s, NH_2-aliph.), 6,49–6.54 (1H, m, 5), 6.69–7.72 (1H, m, 3), 6.76–6.79 (2H, m, 2′+6′), 6.87 (2H, s, NH_2-arom.), 7.06–7.15 (3H, m, 4+3′+5′), 7.50–7.53 (1H, m, 6); *m/z* 225 (48, M^+), 208 (17), 119 (38), 107 (100), 106 (71), 92 (18), 91 (16), 77 (10), 65 (30), 39 (11%).

1c. (1.22 g, 36%), as a white solid, mp 123–124°C; [Found: C, 74.93; H, 6.73; N, 18.45. $C_{14}H_{15}N_3$ requires C, 74.64; H, 6.71; N, 18.65%]; δ_H 2.29 (3H, s, Me), 5.98 (2H, bs, NH_2-aliph.), 6.49–6.54 (1H, m, 5), 6.65–6.71 (3H, m, 3+2′+4′), 6.80–6.83 (3H, m, NH_2-arom.+5′), 7.07–7.11 (1H, m, 4), 7.18–7.23 (1H, m, 6′), 7.49–7.51 (1H, m, 6); *m/z* 225 (43, M^+), 224 (26), 208 (17), 119 (37), 118 (21), 107 (100), 106 (54), 92 (22), 91 (25), 79 (10), 78 (10), 77 (15), 65 (42), 64 (12), 63 (11), 53 (12), 52(13), 43(10), 41 (29%).

1d. (2.06 g, 61%), as a white solid, mp 152–153°C; [Found: C, 74.89; H, 6.54; N, 18.61. $C_{14}H_{15}N_3$ requires C, 74.64; H, 6.71; N, 18.65%]; δ_H 2.27 (3H, s, Me), 5.97 (2H, bs, NH_2-aliph.), 6.49–6.54 (1H, m, 5), 6.69–6.71 (1H, m, 3), 6.76–6.86 (2H, m, 2′+6′), 6.87 (2H, bs, NH_2-arom.), 7.06–7.15 (3H, m, 4 +3′+5′), 7.50–7.53 (1H, m, 6); *m/z* 225 (49, M^+), 224 (14), 208 (17), 119 (38), 107 (100), 106 (71), 92 (18), 91 (16), 65 (30), 39 (11%).

1e. (0.68 g, 19%), as white crystals, mp 92–93°C; [Found: C, 75.10; H, 7.13; N 17.56. $C_{15}H_{17}N_3$ requires C, 75.28; H, 7.16; N, 17.56%]; δ_H (acetone-d_6) 2.12 (3H, s, 2′-Me), 2.26 (3H, s, 4′-Me), 5,50 (2H, s, NH_2-aliph.), 6.52–6.57 (1H, m, 5), 6.70–6.72 (1H, m, 3), 6.76–6.79 (3H, m, NH_2-arom.+6′), 6.96–6.97 (1H, m, 5′), 7.02 (1H, s, 3′), 7.09–7.14 (1H, m, 4), 7.55–7.57 (1H, m, 6); *m/z* 239 (66, M^+), 238 (18), 224 (31), 223 (11), 222 (31), 221 (14), 122 (12), 121 (100), 120 (59), 119 (58), 118 (21), 112 (10), 111 (10), 106 (66), 103 (14), 92 (32), 91 (22), 79 (13), 78 (11), 77 (35), 65 (35), 53 (11), 52 (14), 41 (25%).

1f. (1.58 g, 44%), as white needles, mp 109–112°C; [Found: C, 75.34; H, 7.19; N, 17.62. $C_{15}H_{17}N_3$ requires C, 75.28; H, 7.16; N, 17.56%]; δ_H 2.18 (3H, s, 3′-Me), 2.20 (3H, s, 4′-Me), 5.94 (2H, s, NH_2-aliph.), 6.48–6.53 (1H, m, 5), 6.57–6.60 (1H, m, 3), 6.67–6.71 (2H, m, 5+2′), 6.87 (2H, s, NH_2-arom.), 6.87–7.11 (2H, m, 4+6′), 7.48–7.51 (1H, m, 6); *m/z* 239 (52, M^+), 238 (20), 222 (16), 122 (11), 121 (100), 120 (52), 119 (44), 118 (15), 112 (11), 106 (70), 103 (11), 92 (23), 91 (17), 79 (11), 78 (74), 77 (35), 65 (28), 51 (11), 39 (19%).

1g. (0,77 g, 21%), as a white–yellow solid, mp 123–125°C; [Found: C, 63.46; H, 4.89; N, 17.17. $C_{13}H_{12}ClN_3$ requires C, 63.55; H, 4.92; N, 17.10%]; δ_H 6.25 (2H, bs, NH_2-aliph.), 6.50–6.55 (1H, m, 5), 6.69–6.72 (1H, m, 3), 6.76 (2H, bs, NH_2-arom.), 6.97–7.02 (2H, m, 5′+6′), 7.08–7.13 (1H, m, 4), 7.24–7.29 (1H, m, 4′), 7.43–7.46 (1H, m, 3′), 7.49–7.51 (1H, m, 6); *m/z* 245 (36, M^+), 228 (14), 210 (36), 129 (34), 128 (10), 127 (100), 119 (74), 118 (32), 105 (19), 92 (50), 91 (32), 90 (16), 78 (11), 77 (10), 76 (11), 75 (32), 66 (13), 65 (60), 64 (24), 63 (27), 52 (20), 51 (18), 50 (15), 41 (13), 39 (38), 38 (15%).

1h. (1.47 g, 40%), as a canary-yellow solid, mp 104–106°C; [Found: C, 63.49; H, 4.93; N, 17.13. $C_{13}H_{12}ClN_3$ requires C, 63.55; H, 4.92; N, 17.10%]; δ_H 6.28 (2H, s, NH_2-aliph.), 6.53–6.57 (1H, m, 5), 6.73–6.76 (3H, m, NH_2-arom.+3), 6.85–6.87 (1H, m, 6′), 6.93 (1H, s, 2′), 4.04–7.06 (1H, m, 4′), 7.04–7.06 (1H, m, 4′), 7.10–7.15 (1H, m, 4), 7.32–7.37 (1H, m, 5′), 7.54–7.56 (1H, m, 6); *m/z* 245 (19, M^+), 228 (23), 129 (28), 127 (85), 119 (100), 118 (31), 111 (12), 105 (19), 92 (49), 91 (24), 75 (27), 66 (11), 65 (52), 64 (24), 63 (19), 52 (14), 51 (13), 39 (27%).

1i. (1.40 g, 38%), as white plates, mp 161–162°C; [Found: C, 63.60; H 4.81; N 17.05. $C_{13}H_{12}ClN_3$ requires C, 63.55; H, 4.92; N, 17.10%]; δ_H (acetone-d_6) 5.83 (2H, bs, NH_2-aliph.), 6.54–6.60 (1H, m, 4), 6.67 (2H, bs, NH_2-arom.), 6.77–6.79 (1H, m, 3), 6.92–6.95 (2H, m, 3′+5′), 7.10–7.15 (1H, m, 5), 7.30–7.33 (2H, m, 2′+6′), 7.57–7.59 (1H, m, 6); *m/z* 245 (42, M^+), 228 (19), 129 (31), 127 (100), 119 (82), 118 (32), 105 (17), 92 (45), 91 (26), 75 (22), 65 (48), 64 (18), 63 (17), 53 (11), 52 (12), 41 (26), 40 (12%).

1j. (0.21 g, 5%), as a white solid, mp 130–131°C; [Found: C, 55.80; H, 3.96; N, 14.98. $C_{13}H_{11}Cl_2N_3$ requires C, 56.14; H, 3.99; N, 15.11%]; δ_H 6.42 (2H, s, NH_2-aliph.), 6.49–6.53 (1H, m, 5), 6.69–6.71 (3H, m, NH_2-arom.+2′), 6.84–6.86 (2H, m, 3), 7.10–7.20 (2H, m, 4+5), 7.49–7.51 (2H, m, 6+6′); *m/z* 279 (30, M^+), 278 (8), 264 (9), 262 (13), 165 (7), 164 (5), 163 (38), 162 (7), 161 (61), 122 (10), 119 (100), 118 (45), 109 (10), 92 (44), 91 (30), 90 (18), 75 (11), 66 (10), 65 (42), 64 (20), 63 (24), 53 (17), 52 (11), 51 (10), 43 (12), 41 (29), 40 (14%).

1k. (2.39 g, 55%), as a white solid, mp 127–129°C; [Found: C, 53.77; H, 4.25; N, 14.42. $C_{13}H_{12}BrN_3$ requires C, 53.81; H, 4.17; N, 14.48%]; δ_H 6.24 (1H, bs, NH_2-aliph.), 6.49–6.45 (1H, m, 5), 6.67–6.72 (1H, m, 3), 6.78 (2H, bs, NH_2-arom.), 6.90–6.98 (2H, m, 5′+6′), 7.08–7.13 (1H, m, 4), 7.23–7.33 (1H, m, 4′), 7.49–7.51 (1H, m, 5′), 7.60–7.63 (1H, m, 4); *m/z* 291 (22, $(M+2)^+$), 289 (22, M^+), 274 (8), 272 (8), 210 (54), 193 (16), 173 (58), 171 (59), 119 (100), 118 (42), 105 (30), 97 (10), 93 (20), 92 (77), 91 (48), 90 (18), 77 (16), 76 (27), 75 (25), 66 (21), 65 (91), 64 (34), 63 (34), 52 (25), 51 (22), 50 (21), 41 (16), 39 (61), 38 (21%).

1l. (1.57 g, 36%), as a white solid, mp 98–99°C; [Found: C, 54.01; H, 4.17; N, 14.44. $C_{13}H_{12}BrN_3$ requires C, 53.81; H, 4.17; N, 14.48%]; δ_H 6.29 (2H, bs, NH_2-aliph.), 6.53–6.56 (1H, m, 5), 6.73–6.76 (3H, m, NH_2-arom.+3), 6.89–6.91 (1H, m, 6′), 7.07–7.20 (3H, m, 4+2′+4′), 7.26–7.31 (1H, m, 5′), 7.53–7.56 (1H, m, 6); *m/z* 289 (24, M^+), 288 (13), 274 (11), 173 (36), 171 (37), 119 (100), 118 (33), 105 (20), 93 (18), 92 (64), 91 (30), 90 (11), 76 (23), 75 (18), 66 (15), 65 (69), 64 (23), 63 (24), 52 (17), 51 (12), 50 (16), 41 (11), 39 (37), 38 (13%).

1m. (1.65 g, 38%), as white plates, mp 167–168°C; [Found: C, 53.80; H, 4.19; N, 14.40. $C_{13}H_{12}BrN_3$ requires C, 53.81; H, 4.17; N, 14.48%]; δ_H 6.20 (2H, bs, NH_2-aliph.), 6.49–6.54 (1H, m, 5), 6.69–6.72 (1H, m, 5), 6.77 (2H, bs, NH_2-arom.), 6.82–6.85 (2H, m, 3′+5′), 7.07–7.12 (1H, m, 4), 7.44–7.47 (2H, m, 2′+6′), 7.50–7.53 (1H, m, 5); *m/z* 289 (71, M^+), 173 (47), 171 (49), 119 (100), 118 (24), 105 (21), 92 (58), 91 (28), 90 (11), 76 (22), 75 (18), 66 (12), 65 (62),

64 (20), 63 (23), 52 (15), 51 (12), 59 (18), 41 (12), 39 (34), 38 (12%).

1n. (1.92 g, 38%), as a white solid, mp 108–110°C; [Found: C, 46.34; H, 3.57; N, 12.47. $C_{13}H_{12}IN_3$ requires C, 46.31; H, 3.59; N, 12.46%]; δ_H (acetone-d_6) 5.88 (2H, bs, NH_2-aliph.), 6.55–6.61 (1H, m, 5), 6.63 (2H, bs, NH_2-arom.), 6.77–6.80 (1H, m, 3), 6.95–6.97 (1H, m, 6′), 7.09–7.16 (2H, m, 4+4′), 7.32–7.38 (2H, m, 2′+5′), 7.57–7.59 (1H, m, 6); *m/z* 337 (59, M^+), 336 (42), 320 (19), 219 (53), 119 (82), 118 (41), 105 (20), 97 (11), 93 (19), 92 (100), 91 (4), 90 (11), 77 (11), 76 (33), 75 (11), 66 (18), 65 (83), 64 (32), 63 (27), 53 (19), 52 (16), 51 (22), 43 (17), 41 (47), 40 (20), 31 (25%).

Reactions of 2-amino-*N*-arylbenzamidines with aldehydes

General method. 2-Amino-*N*-arylbenzamidine (1.5 mmol) was added to a solution of an aldehyde in ethanol (7.5 cm^3, 0.24 M). The reaction mixture was boiled for 2.5 h, then solvent was evaporated under reduced pressure. The residue was crystallized form a water–ethanol mixture.

Synthesis of 4-arylamino-2-arylquinazolines from dihydroquinazolines

A crude 2-aryl-4-arylimino-1*H*-2,3-dihydroquinazoline (1.5 mmol) in acetone (20 cm^3) was added to potassium permanganate (0.28 g, 1.6 mmol) dissolved in acetone (80 cm^3). Reaction mixture was stirred for 24 h at ambient temp. Then 0.5 M aqueous solution of Na_2SO_3 was added to decrease the permanganate color. The precipitate was filtered off, filtrate was evaporated under reduced pressure, and the residue was crystallized form an ethanol–water mixture.

3a. (3.07 g, 69%), as yellow plates, mp 151–152°C, (mp 152°C).[19]

3b. (2.78 g, 56%), as a yellow solid, mp 157–158°C; [Found: C, 72.51; H, 4.31; N, 12.57. $C_{20}H_{14}ClN_3$ requires C, 72.62; H, 4.27; N, 12.70%]; δ_H 7.19–7.20 (1H, m, 4″), 7.46–7.51 (2H, m, 3″+5″), 7.57–7.66 (3H, m, 6+3′+5′), 7.88–7.92 (2H, m, 7+8), 7.94–7.97 (2H, m, 2″+6″), 8.42–8.45 (2H, m, 2′+6′), 8.58–8.60 (1H, m, 5), 9.94 (1H, s, NH); *m/z* 331 (60, M^+), 330 (100), 295 (3), 294 (3), 241 (3), 239 (8), 166 (8), 148 (10), 147 (10), 102 (18), 77 (9), 52 (10%).

3c. (4.97 g, 88%), as a yellow solid, mp 159–161°C; [Found: C, 63.99; H, 3.81; N, 11.05. $C_{20}H_{14}BrN_3$ requires C, 63.85; H, 3.75; N, 11.17%]; δ_H 7.20–7.22 (1H, m, 4″), 7.47–7.52 (2H, m, 3″+5″), 7.62–7.65 (1H, m, 6), 7.70–7.73 (2H, m, 3′+5′), 7.88–7.89 (2H, m, 7+8), 7.96–7.99 (2H, m, 2″+6″), 8.36–8.39 (2H, m, 2′+6′), 8.59–8.61 (1H, m, 5), 9.93 (1H, s, NH); *m/z* 376 (100, $(M+2)^+-1$), 375 (65, M^+), 374 (93), 296 (15), 294 (17), 285 (8), 283 (10), 218 (7), 192 (12), 148 (28), 102 (41), 77 (32), 76 (29), 75 (27), 65 (12), 52 (34), 51 (20), 41 (21), 35 (18%).

3d. (3.74 g, 56%), as a yellow solid, mp 187–188°C; [Found: C, 53.95; H, 2.66; N, 9.50. $C_{20}H_{12}BrCl_2N_3$ requires C, 54.21; H, 2.73; N, 9.48%]; δ_H 7.34–7.43 (2H, m, 4″+5″), 7.60–7.65 (1H, m, 6), 7.69–7.72 (1H, m, 5′), 7.85–7.90 (3H, m, 7+8+6″), 8.29–8.31 (1H, m, 6′), 8.41 (1H, s, 2″), 8.47–8.52 (2H, m, 5+2′), 9.98 (1H, s, NH); *m/z* 444 (100, $(M+2)^+-1$), 443 (43, M^+), 442 (58), 365 (5), 364 (10), 363 (7), 362 (8), 275 (8), 273 (10), 164 (16), 147 (12), 102 (12), 76 (12), 75 (17), 64 (15), 52 (20), 51 (16), 41 (10%).

One-pot synthesis of 4-arylamino-2-arylamino-quinazolines from 2-amino-*N*-arylbenzamidines and aldehydes

An aldehyde (1.8 mmol.), 2-amino-*N*-arylbenzamidine (1.5 mmol.) and ethanol (7.5 cm^3) were boiled for 2.5 h. The solvent was evaporated under reduced pressure, and then acetone (20 cm^3) was added followed by potassium permanganate (1.6 mmol.) dissolved in acetone (80 cm^3). The remainder of the procedure was performed as described above.

3a. (2.76 g, 62%) as a yellow solid, mp 150–152°C, (mp 152°C).[19]

3f. (2.25 g, 37%), as an orange solid, mp 176–178°C; [Found: C, 62.01; H, 4.05; N, 10.34. $C_{21}H_{16}BrN_3O$ requires C, 62.08; H, 3.97; N, 10.34%]; δ_H 3.81 (3H, s, OMe), 6.97–7.00 (2H, m, 3′+5′), 7.32–7.34 (1H, m, 4″), 7.53–7.62 (2H, m, 6+5Prime;), 7.70–7.73 (1H, m, 3), 7.83–7.86 (3H, m, 7+8+3Prime;), 8.18–8.21 (2H, m, 2Prime;+6Prime;), 8.48–8.51 (1H, m, 5), 9.90 (1H, s, NH); *m/z* 405 (14, M^+), 404 (4), 328 (4), 327 (25), 326 (100), 324 (3), 312 (3), 311 (9), 283 (8), 282 (26), 281 (7), 192 (12), 163 (15), 141 (10%).

3g. (3.41 g, 56%), as an off-white solid, mp 173–175°C; [Found: C, 62.14; H, 4.02; N, 10.31. $C_{21}H_{16}BrN_3O$ requires C, 62.08; H, 3.97; N, 10.34%]; δ_H 3.86 (3H, s, OMe), 7.07–7.10 (2H, m, 3′+5′), 7.34–7.37 (1H, m, 4Prime;), 7.41–7.47 (1H, m, 5Prime;), 7.58–7.64 (1H, m, 6), 7.86–7.87 (2H, m, 7+8), 7.98–8.00 (1H, m, 6Prime;), 8.41–8.46 (3H, m, 2′+6′+2Prime;), 8.54–8.56 (1H, m, 5), 9.95 (1H, s, NH); *m/z* 405 (2, M^+), 118 (9), 77 (10), 32 (13), 31 (100), 30 (13%).

3h. (1.54 g, 33%), as a yellow solid, mp 141–142°C; [Found: C, 80.87; H, 5.43; N, 13.56. $C_{21}H_{17}N_3$ requires C, 81.00; H, 5.50; N, 13.49%]; δ_H 2.52 (3H, s, Me), 7.18–7.20 (1H, m, 4Prime;), 7.31–7.33 (1H, m, 4′), 7.38–7.43 (1H, m, 5′), 7.46–7.52 (2H, m, 3Prime;+5Prime;), 7.61–7.65 (1H, m, 6), 7.88–7.89 (2H, m, 7+8), 7.99–8.02 (2H, m, 2Prime;+6Prime;), 8.24–8.26 (1H, m, 6′), 8.31 (1H, s, 2′), 8.59–8.61 (1H, m, 5), 9.89 (1H, s, NH); *m/z* 311 (60, M^+), 310 (100), 219 (9), 218 (5), 192 (4), 156 (5), 91 (11), 77 (8), 65 (11), 52 (7%).

3i. (2.37 g, 53%), as a white solid (separated as a hydrochloride), mp 102–110°C; [Found: C, 68.04; H, 5.98; N, 14.12. $C_{17}H_{18}N_3Cl$ requires C, 68.34; H, 6.07; N, 14.06%]; δ_H 1.30 (6H, d, *J*=6.6 Hz, CHMe_2,), 3.10–3.18 (1H, m, C*H*–Me), 7.25–7.27 (1H, m, 4Prime;), 7.45–7.51 (2H, m, 3Prime;+5Prime;), 7.73–7.78 (1H, m, 6), 7.88–8.04 (4H, m, 7+8+2Prime;+6Prime;), 8.79–8.81 (1H, m, 5), 11.0 (1H, bs, NH); *m/z* 263 (16, M^+), 262 (14), 235 (12),

223 (17), 222 (100), 220 (16), 110 (10), 77 (23), 52 (12), 31 (21%).

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