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Synthetic studies on 3-arylquinazolin-4-ones: intramolecular nucleophilic aromatic substitution reaction of 2-carboxamido-3-arylquinazolin-4-ones and its application to the synthesis of secondary aryl amines

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Abstract—The general synthesis and a novel intramolecular nucleophilic aromatic substitution (S_NAr) reaction of 2-carboxamido-3-arylquinazolin-4-ones, a potentially useful scaffold in the field of medicinal chemistry, are described. The synthetic utility of the S_NAr reaction as a tool for the synthesis of secondary aryl amines, including diaryl amines, is also demonstrated.

1. Introduction

3-Arylquinazolin-4-one has been extensively utilized as a core structure in the field of medicinal chemistry, as represented by methaqualone and its related derivatives (Fig. 1).[1] For example, researchers from Pfizer have recently discovered a novel potent AMPA receptor antagonist CP-465,022 based on 3-(2-chlorophenyl)-6-fluoroquinazolin-4-one as the template.[2] It should be noted that CP-465,022 exists as a separable mixture of atropisomers and its anticonvulsant activity resides in only one of the atropisomers [i.e., (+)-CP-465,022]. The relationship between the atropisomeric property and biological activity makes 3-arylquinazolin-4-one an intriguing structure. The 3-arylquinazolin-4-one motif can also be found in natural products, as exemplified by benzomalvin A,[3] circumdatin F[4] and tryptanthrin.[5] Thus, 3-arylquinazolin-4-one is an important and potentially useful structural motif for the design and synthesis of biologically active molecules.[6] Here we describe in detail the synthesis of 2-carboxamido-3-arylquinazolin-4-ones and their intramolecular nucleophilic aromatic substitution (S_NAr) reaction. Application of the intramolecular S_NAr reaction to the synthesis of secondary aryl amines, including diaryl amines, is also described.[7]

2. Results and discussion

2.1. Synthesis of 2-carboxamido-3-arylquinazolin-4-ones

As a part of our synthetic studies on 3-arylquinazolin-4-ones for the development of biologically active molecules, we designed and targeted the 2-carboxamido-3-arylquinazolin-4-ones (e.g., **10** and **12**–**16**), and the general synthesis was investigated starting from 2-ethoxycarbonyl-3-arylquinazolin-4-ones (**9a**–**g**) as the key intermediates (Scheme 1). The synthesis of **9a**–**g** commenced with the acylation of the aromatic amines **6a**–**g** ($ClCOCO_2Et$, pyridine) to obtain the oxalamic acid esters **7a**–**g** (Scheme 1), which were then subjected to dehydrative cyclization to form **9a**–**g** using the following two methods. The first (Method A) is that used for the synthesis of several natural quinazoline alkaloids:[8,9] compounds **7a**–**g** were treated with I_2, PPh_3 and *i*-Pr_2NEt at room temperature to give a mixture of the iminobenzoxadines **8a**–**g** and quinazolin-4-ones **9a**–**g**, which, without separation, were treated with pyrrolidine in AcOH/THF (1:10) under refluxing conditions to provide the desired 3-arylquinazolin-4-ones **9a**–**g** in moderate to good overall yields. However, this method requires tedious chromatographic separation of the desired products (i.e., iminobenzoxazine and quinazolin-4-one) from the co-product triphenylphosphine oxide and excess triphenylphosphine, which makes this protocol less attractive particularly in the

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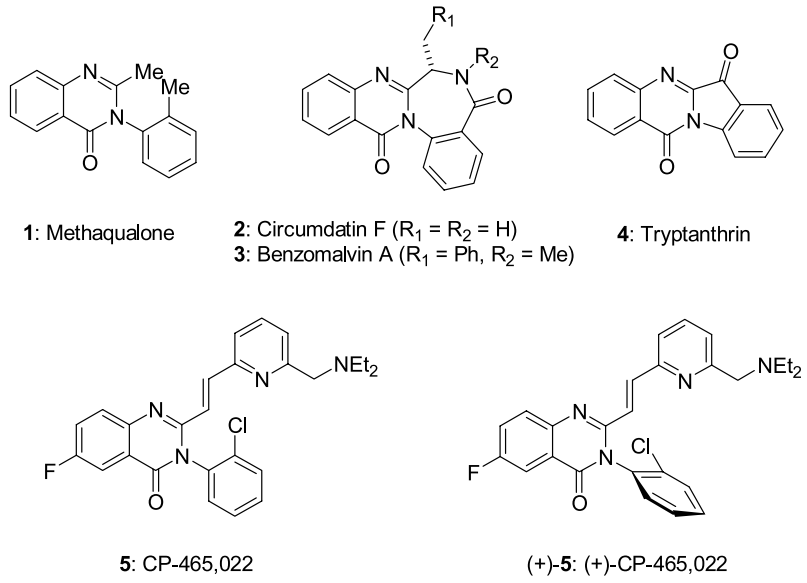
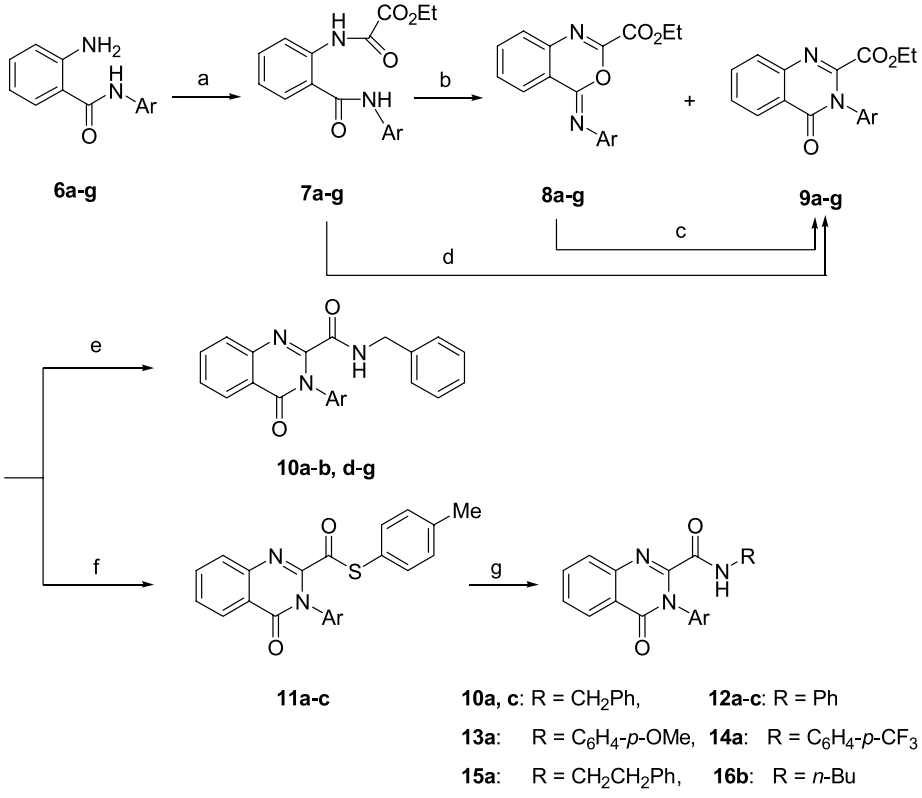
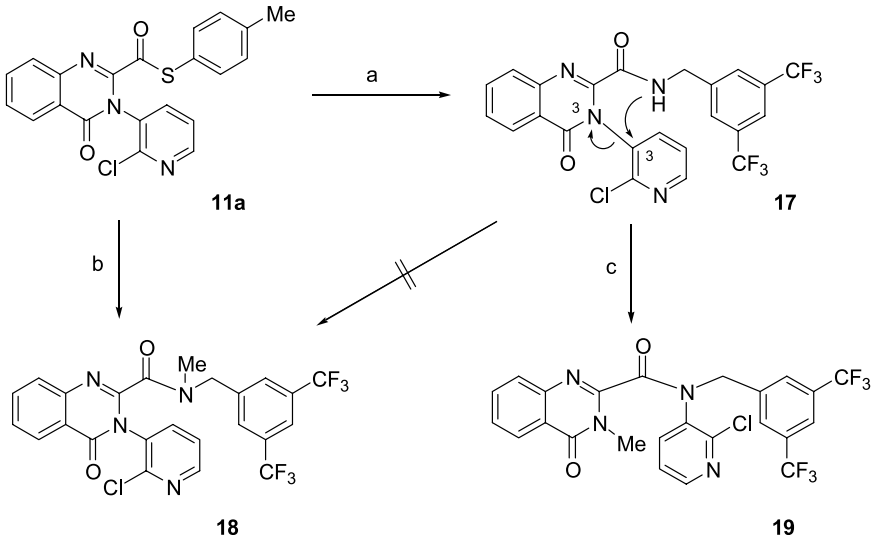


Figure 1. Representative biologically active molecules that possess the 3-arylquinazolin-4-one structural motif.



Scheme 1. Synthesis of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones. Reagents and conditions: (a) $ClCOCO_2Et$ (1.2 equiv), pyridine (1.5 equiv), THF, 0 °C, 90–98%; (b) I_2 (3 equiv), PPh_3 (3 equiv) *i*-Pr_2NEt (10 equiv), CH_2Cl_2, 0 °C to rt; (c) pyrrolidine (1.2 equiv), THF/AcOH (10:1), reflux, 46–94% (2 steps); (d) TMSCl (15 equiv), Et_3N (46 equiv), $ClCH_2CH_2Cl$, 40 mM, 80 °C, 84–100%; (e) $AlMe_3$ (4 equiv) $PhCH_2NH_2$ (4 equiv), CH_2Cl_2, 0 °C to rt, 53–100%; (f) *p*-MeC_6H_5SH (4 equiv), $AlMe_3$ (4 equiv), CH_2Cl_2, 0 °C to rt, 60–91%; (g) RNH_2 (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 81–100%.

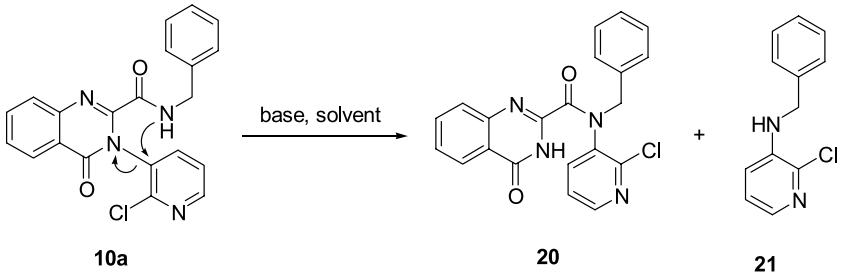


Scheme 2. Reagents and conditions: (a) 3,5-bis(trifluoromethyl)benzylamine (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 100%; (b) *N*-[3,5-bis(trifluoromethyl)]-*N*-methylbenzylamine (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 100%; (c) NaH (1.2 equiv), DMF, 0 °C to rt, then MeI (10 equiv), 0 °C to rt, 81%.

case of large-scale synthesis. The second method (Method B) is based on the protocol appearing in a patent literature,[10] in which several quinazolin-4-ones were prepared by dehydration of 2-carbamoylanilides using trimethylsilyl chloride (TMSCl) in the presence of Et_3N. Using the modified conditions (**7a–g**, TMSCl, Et_3N in 1,2-dichloroethane at 80 °C), the desired 2-ethoxycarbonyl-3-arylquinazolin-4-ones **9a–g** were directly obtained in excellent yields. Two points in the present cyclodehydration process should be noted. The concentration at which the reaction is performed (ca. 40 mM) is important for the clean conversion. Further, the reaction temperature is also an important factor: when the reaction was performed at 40 °C the rate of the reaction was very slow, and at higher temperature (>100 °C) the yields of **9a–g** were significantly reduced.

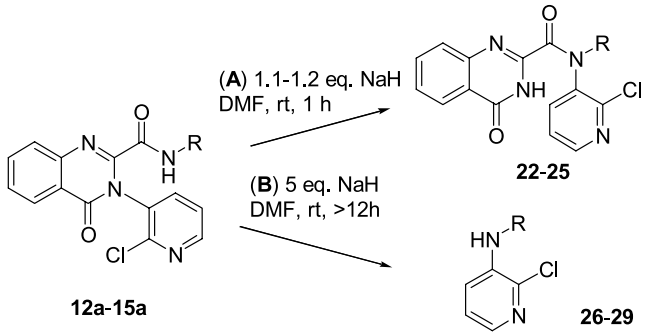
Conversion of the ethyl esters **9a–g** to the corresponding amide derivatives was found not to be trivial because the corresponding carboxylic acids readily underwent decarboxylation.[11] Therefore, we were forced to employ an amidation method that does not require hydrolysis of the ethyl esters **9a–g**. The benzylamide **10a** could be quantitatively produced using dimethylaluminum amide method ($PhCH_2NH_2$, $AlMe_3$).[12] The other benzylamide derivatives **10b** and **10d–g** could also be synthesized in the same manner. In the case of aromatic amines, however, the desired amides could not be obtained reproducibly, presumably due to their low nucleophilicity. After several unfruitful attempts, we reached a general solution for this chemical transformation. Thus, the ethyl esters **9a–c** were first converted to the *p*-tolylthiol esters **11a–c** by the action of sufficiently reactive dimethylaluminum thiolate $Me_2AlSC_6H_4$-*p*-Me (generated in situ from Me_3Al and *p*-MeC_6H_4SH),[13] which were then reacted with an appropriate primary amine in the presence of $AgOCOCF_3$ [THF/toluene (1:1), 60 °C],[14] giving a series of 2-carboxamido-3-arylquinazolin-4-ones (**10a–c**, **12a–c**, **13a**, **14a**, **15a** and **16b**) in high yields. Thus, we have developed an efficient synthetic entry to 2-carboxamido-3-arylquinazolin-4-ones, which comprises the following steps: (i) acylation of aromatic amines **6a–g**, (ii) dehydrative cyclization by the action of TMSCl/Et_3N, (iii) conversion of the ethyl ester to the *p*-tolylthiol ester with $Me_2AlSC_6H_4$-*p*-Me and (iv) $AgOCOCF_3$-mediated amidation.

Table 1. Effects of solvent and molar amount of base on the intramolecular S_NAr reaction



Entry	Reagents and conditions	Product	Yield (%)
1	NaH (1.2 equiv), DMF, rt, 1 h	**20**	76
2	NaH (1.2 equiv), THF, rt, 2 h	**20**	75
3	NaH (3 equiv), toluene, 80 °C, overnight	**20**	85
4	NaH (5 equiv), DMF, rt, overnight	**21**	76

Table 2. Intramolecular S_NAr reaction of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones (**12a–15a**) (**A**) and synthesis of secondary aryl amines from **12a–15a** (**B**)



Entry	Substrate	R	(A)		(B)	
			Product	Yield (%)	Product	Yield (%)
1	**12a**	Ph	**22**	88	**26**	85
2	**13a**	C_6H_4-*p*-OMe	**23**	87	**27**	49
3	**14a**	C_6H_4-*p*-CF_3	**24**	100	**28**	84
4	**15a**	CH_2CH_2Ph	**25**	63	**29**	100

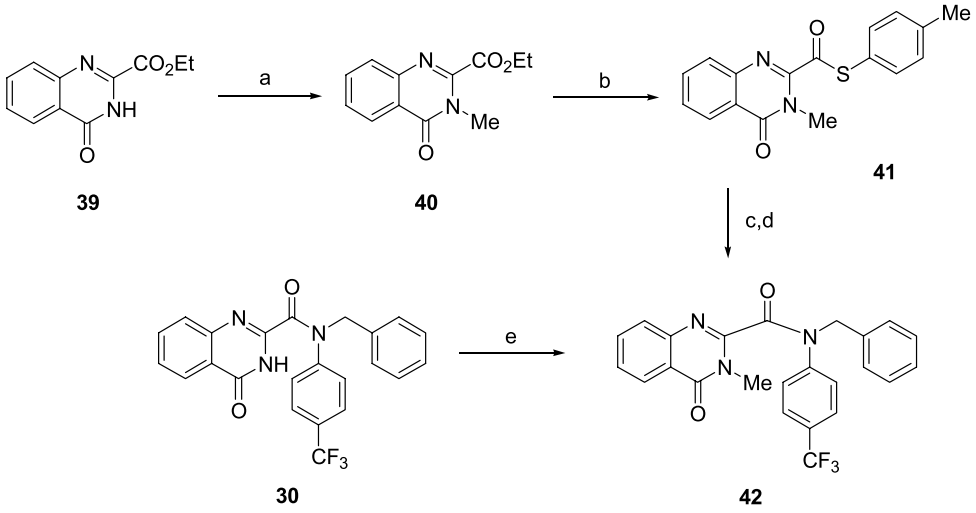
2.2. Intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones

Using the methodology described above, the 2-carboxamido-3-arylquinazolin-4-ones with *N*-[3,5-bis(trifluoromethyl)benzyl] groups, **17** and **18** (Scheme 2), which we had anticipated would possess NK_1 receptor antagonistic activity,[15] were prepared by treatment of **11a** with 3,5-bis(trifluoromethyl)benzylamine and *N*-[3,5-bis(trifluoromethyl)]-*N*-methylbenzylamine in the presence of $AgOCOCF_3$, respectively. To our surprise, treatment of **17** with NaH followed by the addition of MeI exclusively gave the migrated tertiary amide **19** instead of the expected *N*-methylated product **18**. The migration of the N3-pyridyl group was induced by the action of NaH, that is, the amide-nitrogen anion first formed attacked the C3 of the pyridine ring and then the C3–N3 bond was cleaved, resulting in the migration of the pyridyl group. Subsequent trapping of the resultant anion at the N3 of the quinazolinone ring with MeI furnished the migrated tertiary amide **19** (Scheme 2). This unique rearrangement is considered to fall into a category of the intramolecular S_NAr reaction. Intrigued by this unexpected and unprecedented result, we attempted to investigate the scope and limitation of the migration reaction of 2-carboxamido-3-arylquinazolin-4-ones.

We first examined the effects of the solvent and molar amount of base employing the benzyl amide **10a** as a model substrate (Table 1). Upon treatment of **10a** with NaH in DMF at room temperature for 1 h, the tertiary amide **20** was produced in 76% yield (entry 1 in Table 1). The reaction also proceeded smoothly in THF to yield **20**, but a slightly longer reaction time was required (entry 2). In contrast, using toluene as a solvent, heating of the reaction mixture and a prolonged reaction time were required for the reaction to be completed (entry 3). Surprisingly, exposure of **10a** to a fivefold molar excess of NaH in DMF at room temperature overnight resulted in in situ cleavage of **20**, giving rise to the secondary aryl amine **21** as the sole isolatable product after aqueous workup (entry 4). Since we performed the experiment with reagent-grade DMF under aerobic conditions, it was assumed that the unexpected production of **21**

Table 3. Effect of the substituent of the N3 aryl group

Entry	Substrate	X	R	Product	Yield (%)
1	**10b**	*p*-CF_3	CH_2Ph	**30**	95
2	**12b**	*p*-CF_3	Ph	**31**	85
3	**16b**	*p*-CF_3	*n*-Bu	**32**	100
4	**10c**	*o*-CO_2Me	CH_2Ph	**33**	100
5	**12c**	*o*-CO_2Me	Ph	**34**	72
6	**10d**	*p*-CN	CH_2Ph	**35**	95
7	**10e**	*m*-CF_3	CH_2Ph	**36**	0
8	**10f**	*p*-OMe	CH_2Ph	**37**	0
9	**10g**	H	CH_2Ph	**38**	0

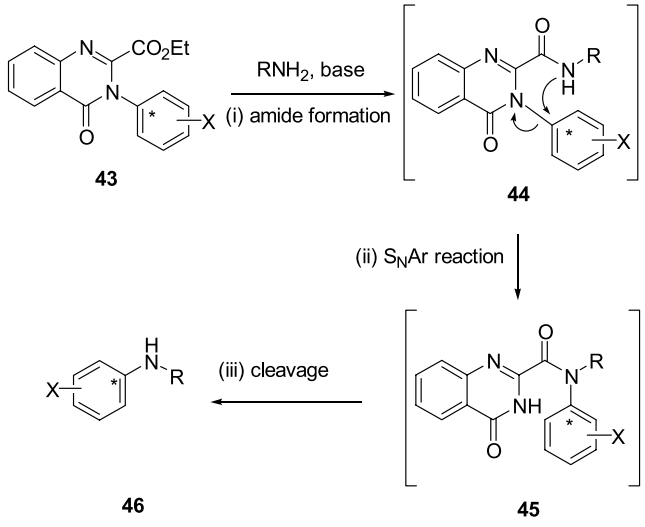


Scheme 3. Reagents and conditions: (a) MeI (5 equiv), NaHMDS (1.2 equiv), DMF, 0 °C to rt, 72%; (b) *p*-MeC_6H_4SH (4 equiv), $AlMe_3$ (4 equiv), CH_2Cl_2, 0 °C to rt, 71%; (c) *p*-(trifluoromethyl)aniline (3 equiv), $AgOCOCF_3$ (1.1 equiv), THF/toluene (1:1), 60 °C, 80%; (d) NaH (1.2 equiv), BnBr (1.5 equiv), DMF, 0 °C to rt, 99%; (e) NaH (1.2 equiv), MeI (10 equiv), DMF, 0 °C to rt, 92%.

could be ascribed to adventitious H_2O absorbed from moisture, generating dry NaOH that is sufficiently reactive to cleave the tertiary amide moiety of **20**.[16]

To validate the substrate scope of the present S_NAr reaction, a variety of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones (**12a**–**15a**) were examined as substrates (Table 2). Upon treatment of the quinazolin-4-ones **12a**–**15a** with 1.1–1.2 equiv of NaH in DMF at room temperature for 1 h, all compounds cleanly furnished the migrated products, that is, 2-*N*-(2-chloro-3-pyridyl)carboxamidoquinazolin-4-one derivatives (**22**–**25**) (Table 2A). On the other hand, when using 5 equiv of NaH (DMF, room temperature, overnight), all quinazolin-4-ones (**12a**–**15a**) delivered the respective secondary aryl amines (**26**–**29**) (Table 2B) in satisfactory yields. These results indicate that aliphatic, benzylic and aromatic amides can be employed in the present reaction.

We then investigated the effect of the substituent of the N3 aryl group as shown in Table 3. It was found that the reactions also proceeded with the N3 phenyl derivatives and that the presence of an electron withdrawing group(s) at the ortho or para position of the N3 phenyl group was essential for the success of the present reaction: *p*-CF_3 (**10b**, **12b** and **16b**), *o*-CO_2Me (**10c** and **12c**) and *p*-CN (**10d**) derivatives cleanly furnished the corresponding migrated tertiary amides [i.e., 2-(*N*-aryl)carboxamidoquinazolin-4-ones **30**–**35**] upon treatment with 1.2 equiv of NaH in DMF at room temperature. On the other hand, *m*-CF_3 (**10e**), *p*-OMe (**10f**) and unsubstituted (**10g**) derivatives did not participate in the present reaction. In these cases, attempts to migrate the N3 aryl group by extending the reaction time and/or forcing the reaction conditions only gave a mixture of several unidentified products. These results imply that the present reaction is based on an S_NAr mechanism.

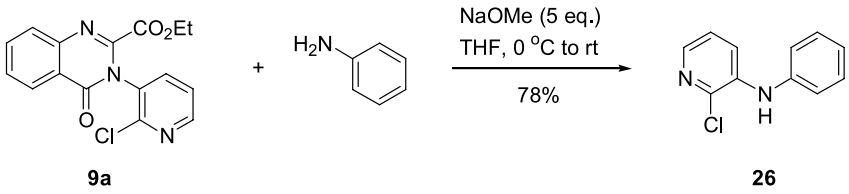


Scheme 4. A cascade process leading to the generation of the secondary aryl amines.

The structures of the migrated products were characterized on the basis of NMR, IR and HRMS spectra. Moreover, in the case of **30**, further structural confirmation was obtained by comparison of the spectroscopic data of the *N*-methylated product **42** with those of authentic sample prepared as described in Scheme 3. Thus, *N*-methylation of the known quinazolin-4-one **39**[11] with sodium bis(trimethylsilyl)amide (NaHMDS) and MeI gave **40**,[17] which was exposed to $Me_2AlSC_6H_4$-*p*-Me to give **41**. Amidation of **41** with 4-(trifluoromethyl)aniline in the presence of $AgOCOCF_3$ and the ensuing *N*-benzylation of the resultant amide (BnBr, NaH) furnished **42** in good overall yield. The spectroscopic properties of this material **42** were indistinguishable from those of the sample obtained from **30** through *N*-methylation (MeI, NaH), thereby unambiguously confirming the structure of **30**.

2.3. Expeditious synthesis of secondary aryl amines

Based on the above results, we surmised that a reaction of the 2-ethoxycarbonyl-3-arylquinazolin-4-ones (**9**) and primary amines in the presence of a base would induce a cascade process comprised of (i) amide formation (**43**→**44**), (ii) intramolecular S_NAr reaction (**44**→**45**) and (iii)

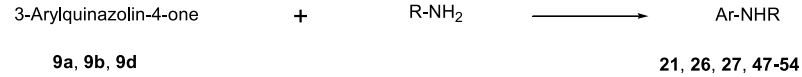


Scheme 5.

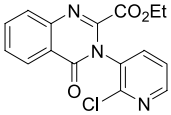
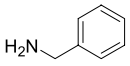
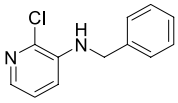
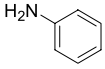
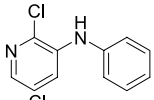
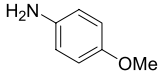
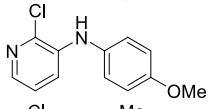
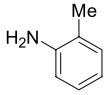
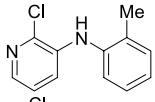
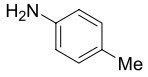
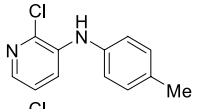
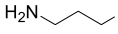
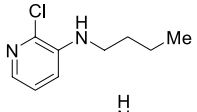
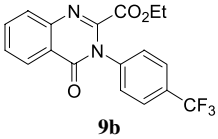
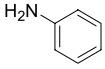
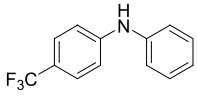
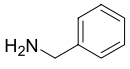
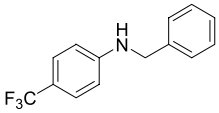
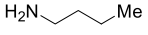
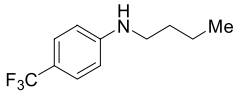
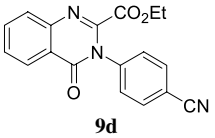
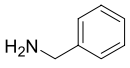
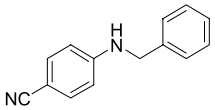
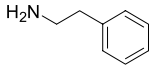
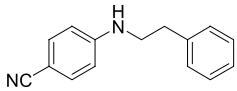
cleavage of the resultant tertiary amide (**45**→**46**), leading to the one-pot generation of secondary aryl amines (Scheme 4).

Consequently, we found that treatment of the ethyl ester **9a** with 1.5 equiv of aniline and 5 equiv of NaOMe in reagent-grade THF at room temperature under aerobic conditions gave the secondary aryl amine **26** in 78% yield (Scheme 5). It should be noted that the cleavage of the tertiary amide intermediate to produce the secondary aryl amine was

Table 4. Expeditious synthesis of secondary aryl amines[a]



9a, **9b**, **9d** — **21**, **26**, **27**, **47-54**

Entry	3-Arylquinazolin-4-one	R-NH_2	Product (Ar-NHR)	Yield (%)
1	 **9a**		 **21**	73
2	**9a**		 **26**	78
3	**9a**		 **27**	49
4	**9a**		 **47**	64
5	**9a**		 **48**	82
6	**9a**		 **49**	64
7	 **9b**		 **50**	59
8	**9b**		 **51**	77
9	**9b**		 **52**	71
10	 **9d**		 **53**	74
11	**9d**		 **54**	81

[a] All reactions were performed using 1.5 equiv of amine and 5 equiv of NaOMe in wet THF at room temperature.

dramatically enhanced by a small amount of H_2O contaminated in the reagent-grade THF.[16] The present cascade reaction was then applied to a series of substrates, and the results are summarized in Table 4. Various aliphatic, benzylic and aromatic amines could be employed in this process. It should be mentioned that the present method does not require strict inert anhydrous reaction conditions and is operationally very simple. It also offers easy access to diaryl amines (e.g., **26**, **27**, **47**, **48** and **50**) that are mainly synthesized via metal-catalyzed cross-coupling reactions.[18]

3. Conclusion

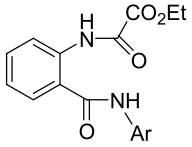
A general synthetic entry to 2-carboxamido-3-arylquinazolin-4-ones and the discovery of their intramolecular S_NAr reaction, which is rarely predictable from conventional heterocyclic chemistry, are described. The requirement for the success of the present migration reaction is the presence of an electron-withdrawing group on the N3 aryl ring, which is consistent with that of usual S_NAr reactions. The present reaction has been applied to the synthesis of secondary aryl amines, including diaryl amines, the notable feature of which is its operational simplicity.

4. Experimental

4.1. General remarks

All reactions sensitive to air and/or moisture were carried out under an atmosphere of argon in oven-dried glassware with anhydrous solvents unless otherwise noted. All anhydrous solvents and reagent grade *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Wako Pure Chemicals Co. Inc. and used without further drying. All other reagents purchased were of the highest commercial quality and used as received unless otherwise stated. Analytical thin layer chromatography was carried out using E. Merck silica gel 60 F_{254} plates (0.25 mm thickness). Open column chromatography was performed on Kanto Chemical silica gel 60N (spherical, neutral). Flash chromatography was carried out using Fuji Silysia silica gel BW300 (200–400 mesh) or Fuji Silysia chromatorex–NH silica gel (100–200 mesh). Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a JEOL JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). Tetramethylsilane was defined as 0 ppm for ^1H NMR and the

Table 5. Physicochemical properties of *N*-(2-aryl-carbamoylphenyl)oxalamic acid ethyl esters (**7a**–**g**)



Compound	Ar	Yield (%)	Mp (°C)	^1H NMR (400 MHz, $CDCl_3$) δ	HRFABMS [(M+H)$^+$], calcd (found)
7a	2-Chloro-3-pyridyl	97	169–171	12.33 (br s, 1H), 8.90 (d, J=7.2 Hz, 1H), 8.77 (d, J=9.2 Hz, 1H), 8.47 (br s, 1H), 8.20 (m, 1H), 7.76 (d, J=7.2 Hz, 1H), 7.65 (t, J=7.2 Hz, 1H), 7.37–7.27 (m, 2H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{16}H_{15}ClN_3O_4$ 348.0751 (348.0739)
7b	–C_6H_4–*p*-CF_3	98	212	12.19 (br s, 1H), 8.64 (d, J=8.4 Hz, 1H), 8.15 (s, 1H), 7.80 (d, J=9.2 Hz, 2H), 7.66 (m, 3H), 7.57 (t, J=7.6 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}F_3N_2O_4$ 381.1062 (381.1046)
7c	–C_6H_4–*o*-CO_2Me	97	173–174	12.16 (br s, 1H), 8.91 (d, J=8.4 Hz, 1H), 8.76 (d, J=9.2 Hz, 1H), 8.09 (d, J=7.2 Hz, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.67–7.57 (m, 2H), 7.31 (t, J=7.2 Hz, 1H), 7.16 (t, J=8.4 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 3.97 (s, 3H), 1.45 (t, J=7.2 Hz, 3H)	$C_{19}H_{19}N_2O_6$ 438.1429 (438.1425)
7d	–C_6H_4–*p*-CN	91	195–197	12.13 (br s, 1H), 8.66 (d, J=9.2 Hz, 1H), 8.15 (br s, 1H), 7.82 (d, J=8.4 Hz, 2H), 7.72–7.63 (m, 3H), 7.58 (m, 1H), 7.23 (m, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}N_3O_4$ 338.1141 (338.1137)
7e	–C_6H_4–*m*-CF_3	98	159–160	(DMSO-d_6) 11.91 (br s, 1H), 10.83 (s, 1H), 8.38 (d, J=8.4 Hz, 1H), 8.20 (s, 1H), 8.01–7.90 (m, 2H), 7.68–7.59 (m, 2H), 7.50 (d, J=8.4 Hz, 1H), 7.35 (m, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.30 (t, J=7.2 Hz, 3H)	$C_{18}H_{16}F_3N_2O_4$ 381.1062 (381.1060)
7f[26]	–C_6H_4–*p*-OMe	96	199–200 (lit.[26] 204–205)	12.39 (br s, 1H), 8.68 (d, J=8.4 Hz, 1H), 7.84 (br s, 1H), 7.66 (d, J=7.2 Hz, 1H), 7.59–7.46 (m, 3H), 7.22 (m, 1H), 6.92 (d, J=9.2 Hz, 2H), 4.42 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.43 (t, J=7.2 Hz, 3H)	$C_{18}H_{19}N_2O_5$ 343.1294 (343.1299)
7g[26]	–Ph	90	158–160 (lit.[26] 160–161)	(DMSO-d_6) 12.06 (br s, 1H), 10.57 (s, 1H), 8.42 (d, J=8.4 Hz, 1H), 7.93 (d, J=7.2 Hz, 1H), 7.73 (d, J=7.2 Hz, 2H), 7.62 (t, J=7.2 Hz, 1H), 7.43–7.27 (m, 3H), 7.14 (t, J=7.2 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.29 (t, J=7.2 Hz, 3H)	$C_{17}H_{17}N_2O_4$ 313.1188 (313.1188)

center line of the triplet of $CDCl_3$ was also defined as 77.0 ppm for ^{13}C NMR. The following abbreviations are used to designate the multipilicities: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Low- and high-resolution mass spectra were recorded on a JEOL SX-102A mass spectrometer under fast atom bombardment (FAB) conditions using *m*-nitrobenzyl alcohol (NBA) as a matrix. Extracted solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4, and solvents were evaporated under reduced pressure.

4.2. Synthesis of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (10a–g, 12a–c, 13a, 14a, 15a, 16b, 17)

4.2.1. *N*-(2-Aryl-carbamoylphenyl)oxalamic acid ethyl esters (7a–g). As a typical example, the preparation of *N*-[2-(2-chloro-3-pyridyl)carbamoylphenyl]oxalamic acid ethyl ester (**7a**) is described. To a solution of aromatic amine **6a**[19] (0.50 g, 2.02 mmol) in THF (10 mL) at 0 °C were added pyridine (0.190 mL, 2.34 mmol) and $ClCOCO_2Et$ (0.270 mL, 2.42 mmol). After being stirred at 0 °C for 15 min, the mixture was concentrated. To the concentrate were added EtOAc and H_2O, and the organic layer was separated. The aqueous layer was extracted with EtOAc. The organic layers were combined, washed with brine, dried, and concentrated to give a pale yellow solid. Crystallization from *i*-Pr_2O gave **7a** (0.68 g, 97%) as pale yellow crystals. The physicochemical properties are described in Table 5.

Similarly, **7b**–**g** were prepared from the known aromatic amines **6b**–**g** (**6b**,[20] **6c**,[21] **6d**,[22] **6e**,[23] **6f**,[24] and **6g**[25]). The physicochemical properties are listed in Table 5.

4.2.2. 3-Aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (9a–g). Two methods (Method A and B) were used for the preparation of **9a**–**g**. As a typical example, the preparation of 3-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester (**9a**) is described.

Method A. To a solution of **7a** (9.50 g, 27.4 mmol) in CH_2Cl_2 (100 mL) cooled at 0 °C were sequentially added *i*-Pr_2NEt (48.0 mL, 276 mmol), PPh_3 (21.6 g, 82.4 mmol) and I_2 (20.9 g, 82 mmol). The mixture was stirred at room temperature for 50 min and then diluted with EtOAc. The organic layer was washed with 10% aqueous Na_2CO_3 and brine, dried, and concentrated. Purification of the residue by open column chromatography (silica gel, 40% EtOAc/hexane) gave a mixture of iminobenzoxazine **8a** and quinazolin-4-one **9a** (10.8 g), which was used in the next reaction without separation.

To a solution of the above mixture in THF (200 mL) were added pyrrolidine (2.80 mL, 33.5 mmol) and AcOH (20 mL). The mixture was heated under reflux for 1 h, cooled to room temperature, and concentrated. The residue was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by open column chromatography (silica gel, 40% EtOAc/hexane) gave **9a** (8.20 g, 94% for the two steps). Crystallization from *i*-Pr_2O gave **9a** as colorless crystals. The physicochemical properties are described in Table 6.

Method B. The following reaction was carried out under an atmosphere of argon. To a solution of **7a** (347 mg, 1.00 mmol) in $ClCH_2CH_2Cl$ (25 mL) were added Et_3N (6.43 mL, 46.0 mmol) and TMSCl (1.90 mL, 15.0 mmol). The mixture was heated under gentle reflux for 1.5 h. After cooling, the mixture was diluted with EtOAc, washed successively with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 50% EtOAc/hexane) gave **9a** as colorless crystals (329 mg, 100%). The physicochemical data were identical with those of **9a** prepared by Method A. Similarly, **9b**–**g** were prepared from **7b**–**g** by Method A and B. The physicochemical properties are listed in Table 6.

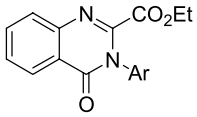
4.3. 3-Aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides (10a–g, 12a–c, 13a, 14a, 15a, 16b, 17)

Two methods (Method A and/or B) were used for the preparation of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides. As the typical examples, the syntheses of *N*-benzyl-3-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (**10a**) by Method A and B are described.

4.3.1. Method A. The following reaction was carried out under an atmosphere of argon. To a solution of benzylamine (0.220 mL, 2.01 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added a solution of $AlMe_3$ (1.0 M solution in hexane, 2.00 mL, 2.00 mmol). The mixture was stirred at room temperature for 1 h and then cooled to 0 °C. To this solution was added quinazolin-4-one **9a** (165 mg, 0.50 mmol), and the mixture was stirred at room temperature for 7 h. The reaction was quenched with saturated aqueous potassium sodium tartrate solution at 0 °C. The resultant mixture was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30→50% EtOAc/hexane) gave **10a** (194 mg, quant.) as a colorless oil. The physicochemical properties are described in Table 7.

4.3.2. Method B. The following reaction was carried out under an atmosphere of argon. To a solution of **11a** (see below) (814 mg, 2.00 mmol) in anhydrous THF/toluene (20 mL, 1:1, v/v) were added benzylamine (0.660 mL, 6.04 mmol) and $AgOCOCF_3$ (486 mg, 2.20 mmol). After being stirred at 60 °C for 1.5 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 and 10% aqueous NH_4OH. The mixture was stirred vigorously at room temperature for ca. 10 min and then insoluble materials were filtered off. The organic layer was extracted with CH_2Cl_2, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 40% EtOAc/hexane) gave **10a** (780 mg, 100%). Similarly, 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxamides (**10b** and **10d**–**g**) were prepared from **9b** and **9c**–**g** by Method A. Compounds **10c**, **12a**–**c**, **13a**, **14a**, **15a**, **16b** and **17** were prepared from the corresponding 4-tolylthiol esters (**11a**–**c**)

Table 6. Physicochemical properties of 3-aryl-3,4-dihydro-4-oxo-quinazoline-2-carboxylic acid ethyl esters (**9a–g**)



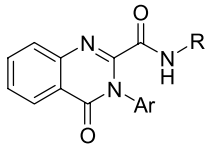
Compound	Ar	Yield (%)		Mp (°C)	NMR[b]	HRFABMS [(M+H)$^+$], calcd (found)
		Method[a] A	Method[a] B			
9a	2-Chloro-3-pyridyl	94	100	95–97	^{1}H NMR δ 8.54 (m, 1H), 8.36 (d, J=7.6 Hz, 1H), 7.94–7.85 (m, 2H), 7.79 (m, 1H), 7.64 (m, 1H), 7.45 (m, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.18 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.3, 160.2, 150.3, 149.6, 146.1, 144.8, 139.1, 135.5, 131.7, 129.3, 128.7, 127.4, 123.1, 121.9, 63.3, 13.7	$C_{16}H_{13}ClN_3O_3$ 330.0645 (330.0650)
9b	–C_6H_4–*p*-CF_3	82	94	151–153	^{1}H NMR δ8.36 (d, J=8.4 Hz, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.80 (d, J=8.0 Hz, 2H), 7.62 (m, 1H), 7.51 (d, J=8.0 Hz, 2H), 4.13 (q, J=7.2 Hz, 2H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.64, 160.60, 146.4, 146.2, 139.4, 135.3, 131.9, 131.6, 129.0, 128.8, 128.4, 127.3, 126.6 (q, J=4.0), 124.9, 122.2, 122.0, 63.0, 13.5	$C_{18}H_{14}F_3N_2O_3$ 363.0956 (363.0943)
9c	–C_6H_4–*o*-CO_2Me	72	87	67–68	^{1}H NMR δ8.34 (d, J=8.4 Hz, 1H), 8.27 (d, J=8.4 Hz, 1H), 7.90–7.80 (m, 3H), 7.70 (m, 1H), 7.63–7.55 (m, 2H), 7.40 (d, J=8.0 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 3.71 (s, 3H), 1.04 (t, J=7.2 Hz, 3H); ^{13}C NMR δ164.6, 161.3, 160.6, 146.6, 146.3, 136.6, 134.9, 133.4, 131.9, 130.4, 129.9, 128.5, 128.33, 128.27, 127.3, 122.2, 62.7, 52.5, 13.5	$C_{19}H_{17}N_2O_5$ 353.1137 (353.1136)
9d	–C_6H_4–*p*-CN	60	89	173–175	^{1}H NMR δ8.34 (br, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.83–7.79 (m, 2H), 7.63 (m, 1H), 7.50 (d, J=9.2 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 1.11 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 160.48, 160.46, 146.2, 145.6, 140.4, 135.4, 133.2, 129.19, 129.15, 128.5, 127.3, 121.9, 117.7, 113.6, 63.2, 13.6	$C_{18}H_{13}N_3O_3$ 320.1035 (320.1034)
9e	–C_6H_4–*m*-CF_3	77	98	112–113	^{1}H NMR δ8.35 (d, J=8.0 Hz, 1H), 7.87 (d, J=3.6 Hz, 2H), 7.78 (d, J=7.6 Hz, 1H), 7.71–7.56 (m, 4H), 4.13 (q, J=7.2 Hz, 2H), 1.05 (t, J=7.2 Hz, 3H)	$C_{19}H_{14}F_3NO_3$ 362.1004 (362.1002)
9f[26]	–C_6H_4–*p*-OMe	46	84	120–121 (lit.[26] 125–126)	^{1}H NMR δ8.35 (d, J=7.6 Hz, 1H), 7.83 (d, J=4.0 Hz, 2H), 7.59 (m, 1H), 7.33–7.26 (m, 2H), 7.04–6.96 (m, 2H), 4.13 (q, J=7.2 Hz, 2H), 3.86 (s, 3H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR δ161.2, 161.0, 160.3, 147.6, 146.6, 134.9, 129.4, 128.41, 128.38, 128.1, 127.3, 122.1, 114.6, 62.7, 55.6, 13.6	$C_{18}H_{17}N_2O_4$ 325.1188 (325.1172)
9g[26]	–Ph	51	98	105–106 (lit.[26] 108–109)	^{1}H NMR δ8.35 (d, J=8.0 Hz, 1H), 7.89–7.80 (m, 2H), 7.60 (m, 1H), 7.54–7.45 (m, 3H), 7.37 (m, 1H), 4.09 (q, J=7.2 Hz, 2H), 1.00 (t, J=7.2 Hz, 3H); ^{13}C NMR δ160.9, 147.2, 146.6, 136.1, 135.0, 129.6, 129.4, 128.5, 128.2, 127.3, 122.2, 62.7, 13.5	$C_{17}H_{15}N_2O_3$ 295.1082 (295.1071)

[a] See Section 4.2.2.
[b] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

and amines by Method B. The physicochemical properties are listed in Table 7.

4.3.3. 3,4-Dihydro-4-oxo-3-(2-chloro-3-pyridyl)-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11a). The following reaction was carried out under an atmosphere of argon. To a solution of *p*-tolylthiol (497 mg, 4.00 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of $AlMe_3$ (1.0 M solution in hexane, 4.00 mL, 4.00 mmol). After being stirred at room temperature for 30 min, the mixture was cooled to 0 °C. To this solution was added quinazolin-4-one **9a** (329 mg, 1.00 mmol) and the mixture was stirred at room temperature for 80 min and then cooled to 0 °C. The reaction was carefully quenched with saturated aqueous potassium sodium tartrate. The resultant mixture was diluted with EtOAc and stirred at room temperature until the layers became clear. The organic layer was separated and washed with brine, dried, and concentrated. Purification of the residue by column chromatography (silica gel, BW300, 15→25% EtOAc/hexane) gave **11a** (356 mg, 87%). Crystallization from *i*-Pr_2O gave **11a** as pale yellow crystals: Mp 203–204 °C (*i*-Pr_2O); IR (film)

Table 7. Physicochemical properties of 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxyamides (**10a–g**, **12a–c**, **13a**, **14a**, **15a**, **16b**, **17**)



Compound	Ar	R	Method[a]	Yield (%)	Mp (°C)	NMR[b]	HRFABMS $[(M+H)^+]$ calcd (found)
10a	2-Chloro-3-pyridyl	$-CH_2Ph$	A B	100 100	Oil	^{1}H NMR δ 8.51 (m, 1H), 8.35 (d, J=9.2 Hz, 1H), 8.09 (br, 1H), 7.86 (m, 1H), 7.81–7.75 (m, 2H), 7.63 (m, 1H), 7.40–7.22 (m, 5H), 4.54 (m, 1H), 4.43 (m, 1H); ^{13}C NMR δ 161.1, 159.3, 149.3, 148.2, 145.3, 144.8, 138.4, 137.0, 135.3, 132.7, 129.0, 128.7, 128.0, 127.7, 127.6, 124.4, 122.9, 121.7, 43.6	$C_{12}H_{16}ClN_4O_2$ 391.0962 (391.0962)
10b	$-C_6H_4-p$-CF_3	$-CH_2Ph$	A	76	227–228	^{1}H NMR δ 8.33 (d, J=6.4 Hz, 1H), 7.90–7.81 (m, 2H), 7.80–7.72 (m, 3H), 7.62 (m, 1H), 7.43–7.30 (m, 6H), 4.46 (d, J=6.4 Hz, 2H)	$C_{23}H_{15}F_3N_3O_2$ 424.1273 (424.1281)
10c	$-C_6H_4-o$-CO_2Me	$-CH_2Ph$	B	91	Oil	^{1}H NMR δ 8.29 (d, J=7.3 Hz, 1H), 8.14 (m, 1H), 7.98 (t, J=5.5 Hz, 1H), 7.83–7.74 (m, 2H), 7.70 (m, 1H), 7.58–7.51 (m, 2H), 7.38 (d, J=7.3 Hz, 1H), 7.33–7.23 (m, 2H), 7.20–7.13 (m, 2H), 4.47 (dd, J=14.7, 5.5 Hz, 1H), 4.34 (dd, J=14.7 Hz, 5.5, 1H), 3.65 (s, 3H); ^{13}C NMR δ 165.3, 162.1, 160.0, 146.5, 145.8, 138.4, 134.7, 133.2, 131.4, 130.0, 128.9, 128.6, 128.3, 127.8, 127.6, 127.5, 12.3, 126.7, 122.1, 52.1, 43.4	$C_{24}H_{20}N_3O_4$ 414.1454 (414.1451)
10d	$-C_6H_4-p$-CN	$-CH_2Ph$	A	53	220–222	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.97 (br s, 1H), 7.86 (m, 1H), 7.82–7.75 (m, 3H), 7.62 (t, J=8.0 Hz, 1H), 7.42–7.31 (m, 5H), 7.28–7.23 (m, 2H), 4.46 (d, J=6.4 Hz, 2H); ^{13}C NMR δ 163.2, 159.1, 145.0, 144.8, 136.7, 135.0, 132.6, 128.9, 128.5, 128.3, 127.7, 127.6, 127.5, 127.2, 121.5, 117.9, 112.5, 43.4	$C_{23}H_{16}N_4O_2$ 381.1351 (381.1358)
10e	$-C_6H_4-m$-CF_3	$-CH_2Ph$	A	93	174–175	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.88–7.78 (m, 2H), 7.77–7.72 (m, 2H), 7.67–7.57 (m, 2H), 7.56–7.48 (m, 2H), 7.38–7.28 (m, 3H), 7.25 (m, 1H), 4.56–4.32 (m, 2H); ^{13}C NMR δ 162.0, 160.1, 146.4, 145.8, 138.3, 137.4, 135.5, 131.8, 129.8, 129.3, 129.1, 128.3, 128.12, 128.05, 127.8, 126.0 (q, J=4.0), 124.70, 124.66, 122.2, 44.0	$C_{23}H_{17}F_3N_3O_2$ 424.1272 (424.1264)
10f	$-C_6H_4$-p-OMe	$-CH_2Ph$	A	96	182–184	^{1}H NMR δ 8.32 (d, J=8.4 Hz, 1H), 7.80 (m, 1H), 7.73 (m, 1H), 7.60–7.53 (m, 2H), 7.37–7.28 (m, 2H), 7.25–7.18 (m, 3H), 7.03–6.97 (m, 2H), 4.46 (d, J=8.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR δ 161.6, 160.2, 159.3, 145.5, 136.9, 134.4, 128.34, 128.29, 128.0, 127.4, 127.3, 126.9, 126.7, 121.6, 113.9, 82.9, 55.1, 43.1	$C_{23}H_{20}N_3O_3$ 386.1504 (386.1505)
10g	–Ph	$-CH_2Ph$	A	78	154–155	^{1}H NMR δ 8.24 (d, J=8.4 Hz, 1H), 7.78–7.63 (m, 4H), 7.55–7.41 (m, 5H), 7.32–7.22 (m, 3H), 7.16 (d, J=6.4 Hz, 1H), 4.38 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 161.6, 160.5, 147.8, 145.8, 137.3, 136.8, 134.7, 128.9, 128.6, 128.4, 127.73, 127.68, 127.6, 127.5, 127.1, 121.8, 43.4	$C_{22}H_{17}N_3O_2$ 356.1399 (356.1382)

Table 7 (*continued*)

Compound	Ar	R	Method[a]	Yield (%)	Mp (°C)	NMR[b]	HRFABMS $[(M+H)^+]$ calcd (found)
12a	2-Chloro-3-pyridyl	–Ph	B	100	213–214	^{1}H NMR δ 9.73 (s, 1H), 8.50 (m, 1H), 8.36 (d, J=8.2 Hz, 1H), 7.94–7.86 (m, 2H), 7.78 (m, 1H), 7.66 (m, 1H), 7.56 (d, J=7.3 Hz, 2H), 7.44 (m, 1H), 7.37–7.29 (m, 2H), 7.15 (m, 1H); ^{13}C NMR δ 161.1, 156.7, 149.3, 148.3, 145.0, 144.6, 138.2, 136.5, 135.5, 132.8, 129.3, 129.1, 128.1, 127.7, 125.2, 123.0	$C_{20}H_{14}ClN_4O_2$ 377.0805 (377.0803)
12b	–C_6H_4–*p*-CF_3	–Ph	B	81	199–200	^{1}H NMR δ 9.58 (s, 1H), 8.36 (d, J=8.2 Hz, 1H), 7.93–7.83 (m, 2H), 7.78 (d, J=8.2 Hz, 2H), 7.65 (m, 1H), 7.54 (d, J=8.2 Hz, 1H), 7.42 (d, J=8.2 Hz, 1H), 7.34 (t, J=8.2 Hz, 2H), 7.15 (m, 1H)	$C_{22}H_{15}F_3N_3O_2$ 410.1116 (410.1116)
12c	–C_6H_4–*o*-CO_2Me	–Ph	B	87	Amorphous	^{1}H NMR δ 9.73 (s, 1H), 8.32 (d, J=8.2 Hz, 1H), 8.16 (d, J=8.2 Hz, 1H), 7.84 (d, J=8.2 Hz, 2H), 7.70 (m, 1H), 7.62–7.47 (m, 4H), 7.38 (d, J=7.3 Hz, 1H), 7.27 (d, J=7.3 Hz, 2H), 7.09 (t, J=7.3 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR δ 165.4, 162.2, 157.3, 146.0, 145.4, 138.6, 136.9, 134.8, 133.3, 131.5, 129.8, 128.93, 128.86, 128.6, 127.9, 127.4, 126.6, 124.8, 122.1, 119.9, 52.2	$C_{23}H_{18}N_3O_4$ 400.1297 (400.1317)
13a	2-Chloro-3-pyridyl	–C_6H_4–*p*-OMe	B	100	178–179	^{1}H NMR δ 9.66 (s, 1H), 8.47 (m, 1H), 8.39 (d, J=8.2 Hz, 1H), 7.92–7.80 (m, 2H), 7.76 (m, 1H), 7.61 (m, 1H), 7.49–7.37 (m, 3H), 6.88–6.77 (m, 2H), 3.75 (s, 3H); ^{13}C NMR δ 161.1, 156.9, 156.5, 149.1, 148.2, 145.0, 144.7, 138.1, 135.3, 132.8, 129.6, 129.1, 128.0, 127.4, 122.9, 121.6, 114.1, 55.3	$C_{21}H_{16}ClN_4O_3$ 407.0911 (407.0914)
14a	2-Chloro-3-pyridyl	–C_6H_4–*p*-CF_3	B	100	118–120	^{1}H NMR δ 9.98 (s, 1H), 8.49 (dd, J=4.5 Hz, 1.8, 1H), 8.34 (d, J=7.3 Hz, 1H), 7.92–7.83 (m, 2H), 7.78 (dd, J=7.3, 1.8 Hz, 1H), 7.68 (d, J=8.2 Hz, 2H), 7.64 (m, 1H), 7.56 (d, J=8.2 Hz, 2H), 7.43 (m, 1H); ^{13}C NMR δ 161.0, 156.9, 149.3, 148.3, 144.8, 144.0, 139.6, 138.2, 135.5, 132.6, 129.5, 128.1, 127.6, 126.6, 126.2 (q, J=4.0), 123.0, 122.5, 121.8, 119.7	$C_{21}H_{13}ClN_4O_2$ 445.0679 (445.0678)
15a	2-Chloro-3-pyridyl	–CH_2CH_2Ph	B	100	Oil	^{1}H NMR δ 8.49 (m, 1H), 8.32 (d, J=8.2 Hz, 1H), 7.90–7.79 (m, 2H), 7.77–7.70 (m, 2H), 7.61 (t, J=7.3 Hz, 1H), 7.42 (dd, J=7.3 Hz, 4.6, 1H), 7.35–7.28 (m, 2H), 7.27–7.17 (m, 2H), 3.63–3.46 (m, 2H), 2.85 (t, J=7.3 Hz, 2H); ^{13}C NMR δ 161.1, 159.3, 149.3, 148.3, 145.3, 144.8, 138.4, 138.3, 135.3, 132.8, 129.0, 128.7, 128.6, 128.0, 127.5, 126.6, 122.9, 121.8, 40.9, 35.4	$C_{22}H_{17}ClN_4O_2$ 405.1118 (405.1125)
16b	–C_6H_4–*p*-CF_3	*n*-Bu	B	96	198–199	^{1}H NMR δ 8.30 (d, J=7.3 Hz, 1H), 7.84 (m, 1H), 7.76 (t, J=8.2 Hz, 2H), 7.63–7.52 (m, 2H), 7.40 (d, J=8.2 Hz, 2H), 3.32–3.20 (m, 2H), 1.57–1.46 (m, 2H), 1.40–1.28 (m, 2H), 0.92 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 161.7, 159.8, 146.1, 145.6, 140.8, 135.1, 130.9, 130.6, 128.9, 128.1, 127.9, 127.4, 126.1 (q, J=4.0 Hz), 125.1, 122.4, 121.9, 39.5, 31.3, 20.0, 13.6	$C_{20}H_{19}F_3N_3O_2$ 390.1429 (390.1428)
17	2-Chloro-3-pyridyl	–C_6H_3−3, 5-$(CF_3)_2$	B	100	Oil	^{1}H NMR δ 8.50–8.39 (m, 2H), 8.34 (d, J=8.2 Hz, 1H), 7.88 (m, 1H), 7.82–7.70 (m, 4H), 7.63 (m, 1H), 7.43 (m, 1H), 4.67–4.54 (m, 2H)	$C_{23}H_{14}ClF_6N_4O_2$ 527.0709 (527.0709)

[a] See Sections 4.3.1 and 4.3.2.
[b] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

3070, 2920, 1698, 1597, 1493, 1465, 1413, 1339, 1279, 1223, 1119, 1076, 1034, 1017, 882, 810, 791, 774 cm^{-1}; ^1H NMR δ 8.48–8.43 (m, 1H), 8.41 (d, J=6.4 Hz, 1H), 8.00 (d, J=8.2 Hz, 1H), 7.94 (m, 1H), 7.73–7.66 (m, 2H), 7.37 (m, 1H), 7.30–7.24 (m, 2H), 7.20 (d, J=8.2 Hz, 2H), 2.35 (s, 3H); HRFABMS calcd for $C_{21}H_{15}ClN_3O_2S$ [$(M+H)^+$] 408.0573, found 408.0583.

4.3.4. 3,4-Dihydro-4-oxo-3-[4-(trifluoromethyl)phenyl]-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11b). Prepared according to the procedure described for **11a**. Yield 60% (colorless crystals): Mp 247 °C (*i*-Pr_2O); IR (film) 3074, 2924, 1690, 1670, 1595, 1495, 1470, 1417, 1329, 1279, 1161, 1122, 1070, 1045, 1021, 891, 848, 805, 776 cm^{-1}; ^1H NMR δ 8.36 (d, J=6.4 Hz, 1H), 8.00–7.88 (m, 2H), 7.73 (d, J=8.4 Hz, 2H), 7.66 (m, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.24–7.15 (m, 4H), 2.35 (s, 3H); HRFABMS calcd for $C_{23}H_{16}F_3N_2O_2S$ [$(M+H)^+$] 441.0884, found 441.0884.

4.3.5. 3,4-Dihydro-4-oxo-3-[2-(methoxycarbonyl)-phenyl]-2-quinazolinecarbothioic acid S-*p*-tolyl ester (11c). Prepared according to the procedure described for **11a**. Yield 91% (a colorless oil); IR (film) 3028, 2952, 1720, 1694, 1594, 1566, 1491, 1465, 1346, 1271, 1188, 1102, 1082, 1049, 962, 883, 810, 758 cm^{-1}; ^1H NMR δ 8.34 (d, J=8.2 Hz, 1H), 8.13 (m, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.88 (m, 1H), 7.68–7.58 (m, 2H), 7.52 (m, 1H), 7.31 (d, J=8.2 Hz, 1H), 7.23–7.13 (m, 4H), 3.71 (s, 3H), 2.32 (s, 3H); ^{13}C NMR δ 187.2, 161.8, 147.0, 145.9, 140.1, 137.1, 134.9, 134.5, 133.4, 131.8, 130.2, 130.0, 129.3, 129.1, 128.6, 127.4, 127.2, 123.5, 122.5, 52.3, 21.3; HRFABMS calcd for $C_{24}H_{19}N_2O_4S$ [$(M+H)^+$] 431.1065, found 431.1074.

4.4. *N*-[3,5-Bis(trifluoromethyl)benzyl]-3-(2-chloro-3-pyridyl)-3,4-dihydro-*N*-methyl-4-oxo-2-quinazolinecarboxamide (18)

Compound **18** was prepared from the 4-tolylthiol ester **11b** and *N*-3,5-bis(trifluoromethyl)benzyl-*N*-methylamine according to the procedure described in 4.3.2 (Method B). A pale yellow foam. Yield 100%. IR (film) 3074, 2936, 1699, 1655, 1604, 1568, 1471, 1414, 1382, 1351, 1281, 1175, 1133, 967, 908, 775 cm^{-1}; ^1H NMR (a 3:2 mixture of *cis–trans* isomers) δ 8.55 (m, 0.4H), 8.46 (m, 0.6H), 8.34 (m, 1H), 8.19 (s, 1H), 8.04–7.75 (m, 4H), 7.68–7.53 (m, 2H), 7.49 (m, 0.4H), 7.40 (m, 0.6H), 5.30 (d, J=15.6 Hz, 0.4H), 4.75 (d, J=15.6 Hz, 0.6H), 4.49 (d, J=15.6 Hz, 0.4H), 4.30 (d, J=15.6 Hz, 0.6H), 3.22 (s, 1.8H), 2.79 (s, 1.2H); HRFABMS calcd for $C_{24}H_{16}ClF_6N_4O_2$ [$(M+H)^+$] 541.0865, found 541.0880.

4.5. Intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones

4.5.1. 3,4-Dihydro-*N*-(substituted)-*N*-(substituted)aryl-4-oxo-2-quinazolinecarboxamides (19, 20, 22–25, 30–35). Typical examples are described for the formation of *N*-benzyl-3,4-dihydro-*N*-methyl-4-oxo-2-quinazolinecarboxamide (**19**) and *N*-benzyl-*N*-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (**20**) by migration of **17a**. Formation of **19**: To a solution of **17a** (82 mg, 0.16 mmol) in DMF (2.5 mL) cooled at 0 °C was added NaH (60% in oil) (7.5 mg, 0.19 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. To this mixture cooled at 0 °C was added MeI (0.100 mL, 1.61 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C and diluted with EtOAc. The organic layer was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30% EtOAc/hexane) gave the migrated product **19** (69 mg, 81%). The physicochemical data are listed in Table 8.

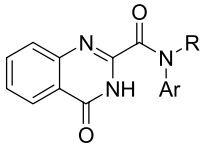
4.5.2. *N*-Benzyl-*N*-(2-chloro-3-pyridyl)-3,4-dihydro-4-oxo-2-quinazolinecarboxamide (20). To a solution of **10a** (900 mg, 2.31 mmol) in reagent grade DMF (20 mL) at 0 °C was added NaH (60% in oil) (110 mg, 2.75 mmol). After being stirred at room temperature for 1 h, the mixture was cooled to 0 °C and the reaction quenched with H_2O and solid NH_4Cl (150 mg). The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, chromatorex–NH, 10% MeOH/$CHCl_3$) gave **20** (680 mg, 76%). Crystallization from EtOAc/hexane gave **20** as colorless crystals. The physicochemical properties are described in Table 8. Similarly, the migrated products **22–25** (Table 2) and **30–35** (Table 3) were obtained from the corresponding amides **12a–15a**, **10b**, **12b**, **16b**, **10c**, **12c** and **10d**. The physicochemical data are listed in Table 8.

4.6. Structural confirmation of the product of the intramolecular S_NAr reaction

4.6.1. 3-Methyl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester (40).[17] The following reaction was carried out under an atmosphere of argon. To a solution of 3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl ester **39**[11] (218 mg, 1.00 mmol) in DMF (10 mL) cooled at 0 °C were added MeI (0.310 mL, 4.98 mmol) and NaHMDS (1.20 mL, 1.20 mmol). After being stirred at room temperature for 100 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc and the organic layer was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, chromatorex–NH, 20% EtOAc/hexane) gave **40**[17] (167 mg, 72%) as colorless crystals: Mp 41 °C (lit[17] 45 °C); IR (film) 2983, 1740, 1684, 1605, 1468, 1377, 1300, 1251, 1115, 1088, 1001, 863, 774 cm^{-1}; ^1H NMR δ 8.32 (d, J=7.6 Hz, 1H), 7.82–7.72 (m, 2H), 7.56 (m, 1H), 4.53 (q, J=7.3 Hz, 2H), 3.65 (s, 3H), 1.48 (t, J=7.3 Hz, 3H); ^{13}C NMR δ 161.39, 161.36, 147.1, 146.4, 134.5, 128.3, 128.0, 126.9, 121.8, 63.3, 32.1, 14.0; HRFABMS calcd for $C_{12}H_{13}N_2O_3$ [$(M+H)^+$] 233.0926, found 233.0921.

4.6.2. 3,4-Dihydro-4-oxo-3-methyl-2-quinazolinecarbothioic acid S-*p*-tolyl ester (41). The following reaction was carried out under an atmosphere of argon. To a solution of *p*-tolylthiol (1.44 g, 11.6 mmol) in anhydrous toluene (20 mL) cooled at 0 °C was added $AlMe_3$ (11.3 mL, 1.03 M solution in hexane, 11.6 mmol). The mixture was allowed to warm to room temperature over 30 min. To this solution was added **40** (673 mg, 2.90 mmol) in anhydrous

Table 8. Physicochemical properties of *N*-(substituted)-*N*-(substituted)ary-3,4-dihydro-4-oxo-2-quinazolinecarboxyamides (**19**, **20**, **22**–**25**, **30**–**35**)



Compound	Ar	R	Mp (°C)	NMR[a]	HRFABMS $[(M+H)^+]$ calcd (found)
20	2-Chloro-3-pyridyl	–Bn	168–169	^{1}H NMR δ 10.17 (br s, 1H), 8.39 (m, 1H), 8.25 (m, 1H), 7.60 (t, J=8.2 Hz, 1H), 7.48 (t, J=7.3 Hz, 1H), 7.36–7.22 (m, 5H), 7.17 (d, J=7.3 Hz, 2H), 6.95 (d, J=8.2 Hz, 1H), 5.72 (d, J=14.7 Hz, 1H), 4.43 (d, J=14.7 Hz, 1H)	$C_{21}H_{16}ClN_4O_2$ 391.0962 (391.0962)
22	2-Chloro-3-pyridyl	–Ph	180–181	^{1}H NMR δ 10.35 (br s, 1H), 8.39 (m, 1H), 8.28 (d, J=8.2 Hz, 1H), 7.75 (d, J=8.2 Hz, 1H), 7.65 (m, 1H), 7.55–7.28 (m, 7H), 7.09 (m, 1H); ^{13}C NMR δ 161.0, 160.8, 149.6, 148.1, 147.3, 146.6, 143.8, 141.1, 138.0, 134.6, 129.5, 128.9, 128.4, 127.9, 126.6, 126.3, 126.2, 123.3, 122.6	$C_{20}H_{14}ClN_4O_3$ 377.0805 (377.0822)
23	2-Chloro-3-pyridyl	–C_6H_4–*p*-OMe	198–200	^{1}H NMR δ 11.0 (br s, 1H), 8.38 (m, 1H), 8.23 (d, J=7.2 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.65 (m, 1H), 7.51 (m, 1H), 7.40–7.27 (m, 3H), 7.09 (m, 1H), 7.02–6.75 (m, 2H), 3.81 (s, 3H); ^{13}C NMR δ 161.1, 160.8, 158.9, 149.3, 147.8, 146.5, 143.9, 138.7, 137.8, 134.6, 133.8, 128.8, 128.4, 127.5, 126.6, 123.2, 122.5, 114.7, 55.4	$C_{21}H_{16}ClN_4O_3$ 407.0911 (407.0927)
24	2-Chloro-3-pyridyl	–C_6H_4–*p*-CF_3	110–112	^{1}H NMR δ 10.63 (br, 1H), 8.43 (d, J=3.7 Hz, 1H), 8.29 (d, J=7.3 Hz, 1H), 7.78 (m, 1H), 7.72–7.59 (m, 3H), 7.55–7.43 (m, 3H), 7.37 (m, 1H), 7.10 (d, J=7.3 Hz, 1H); ^{13}C NMR δ 161.1, 160.0, 149.7, 148.7, 146.4, 143.5, 138.2, 134.7, 129.1, 128.4, 126.7, 126.5 (q, J=4.0), 124.9, 123.4, 122.6, 122.2	$C_{21}H_{12}ClF_3N_4O_2$ 445.0679 (445.0668)
25	2-Chloro-3-pyridyl	–CH_2CH_2Ph	Oil	^{1}H NMR δ 10.40 (br, 1H), 8.40 (m, 1H), 8.25 (m, 1H), 7.60 (m, 1H), 7.48 (m, 1H), 7.34–7.15 (m, 7H), 6.97 (d, J=8.2 Hz, 1H), 4.40 (m, 1H), 3.82 (m, 1H), 3.18 (m, 1H), 3.02 (m, 1H); ^{13}C NMR δ 160.8, 160.3, 149.7, 148.0, 146.6, 143.2, 138.2, 137.8, 134.5, 128.8, 128.75, 128.72, 128.6, 128.4, 126.7, 126.5, 122.8, 122.5, 53.3, 33.3	$C_{22}H_{17}ClN_4O_2$ 405.1118 (405.1113)
30	–C_6H_4–*p*-CF_3	–Bn	172–173	^{1}H NMR δ 10.70 (s, 1H), 8.26 (d, J=7.2 Hz, 1H), 7.70–7.45 (m, 4H), 7.36–7.13 (m, 8H), 5.15 (br s, 2H)	$C_{23}H_{17}F_3N_3O_2$ 424.1273 (424.1277)
31	–C_6H_4–*p*-CF_3	–Ph	169–171	^{1}H NMR δ 10.58 (s, 1H), 8.28 (d, J=7.2 Hz, 1H), 7.69–7.58 (m, 3H), 7.50 (t, J=7.2 Hz, 1H), 7.45–7.23 (m, 7H), 7.18 (d, J=8.0 Hz, 1H)	$C_{22}H_{15}F_3N_3O_2$ 410.1116 (410.1105)
32	–C_6H_4–*p*-CF_3	–*n*-Bu	123–124	^{1}H NMR δ 10.51 (br, 1H), 8.25 (br, 1H), 7.75–7.30 (m, 6H), 7.00 (br, 1H), 3.96 (br, 2H), 1.68 (br, 2H), 1.46–1.33 (m, 2H), 0.98–0.90 (br, 3H)	$C_{20}H_{19}F_3N_3O_2$ 390.1429 (390.1434)
33	–C_6H_4–*o*-CO_2Me	–Bn	Oil	^{1}H NMR δ 10.21 (s, 1H), 8.21 (d, J=8.2 Hz, 1H), 7.83 (d, J=7.3 Hz, 1H), 7.60–7.48 (m, 2H), 7.45–7.39 (m, 2H), 7.32–7.15 (m, 6H), 6.98 (d, J=8.2 Hz, 1H), 5.18 (d, J=14.7 Hz, 1H), 4.90 (d, J=14.7 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR δ 165.9, 161.1, 160.8, 147.0, 144.7, 142.5, 135.5, 134.2, 132.8, 130.9, 130.4, 129.7, 128.4, 128.3, 128.1, 127.9, 127.8, 126.4, 122.4, 55.6, 52.3	$C_{24}H_{20}N_3O_4$ 414.1454 (414.1457)
34[b]	–C_6H_4–*o*-CO_2Me	–Ph	Oil	^{1}H NMR δ 10.06 (br s, 1H), 8.23 (d, J=7.0 Hz, 1H), 8.10 (s, 0.26H), 7.90 (s, 0.74H), 7.75–7.05 (m, 11H), 3.90 (s, 0.78H), 3.78 (s, 2.21H)	$C_{23}H_{18}N_3O_4$ 400.1297 (400.1293)
35	–C_6H_4–*p*-CN	–Bn	149–151	^{1}H NMR δ 10.06 (br s, 1H), 8.26 (d, J=8.0 Hz, 1H), 7.69–7.57 (m, 3H), 7.49 (m, 1H), 7.35–6.95 (m, 8H), 5.18 (br s, 2H)	$C_{23}H_{17}N_4O_2$ 381.1351 (381.1339)

[a] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.
[b] Exists as a 74:26 mixture of *cis*–*trans* isomers at 300 K.

toluene (15 mL) via cannula. After being stirred at room temperature for 1.5 h, the reaction mixture was cooled to 0 °C and treated with saturated aqueous potassium sodium tartrate solution and then with EtOAc. The mixture was stirred at room temperature until the layers became clear. The organic layer was separated, washed with brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 20% EtOAc/hexane) gave *p*-tolylthiol ester **41**, which was further purified by crystallization from *i*-Pr_2O to give pale yellow crystals

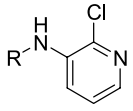
(642 mg, 71%): Mp 120–122 °C; IR (film) 3024, 2921, 1685, 1593, 1564, 1465, 1334, 1297, 1188, 1103, 1011, 918, 882, 809, 773 cm^{-1}; ^1H NMR δ 8.34 (d, J=7.2 Hz, 1H), 7.90–7.79 (m, 2H), 7.61 (m, 1H), 7.46–7.38 (m, 2H), 7.34–7.27 (m, 2H), 3.76 (s, 3H), 2.42 (s, 3H); HRFABMS calcd for $C_{17}H_{15}N_2O_2S$ [$(M+H)^+$] 311.0854, found 311.0843.

4.6.3. *N*-Benzyl-3,4-dihydro-3-methyl-*N*-[4-(trifluoromethyl)phenyl]-4-oxo-2-quinazolinecarboxamide (42). The following reactions were carried out under an atmosphere of argon. To a solution of **41** (150 mg, 0.48 mmol) in anhydrous THF/toluene (1:1, v/v, 6 mL) were added 4-aminobenzotrifluoride (0.180 mL, 1.43 mmol) and $AgOCOCF_3$ (118 mg, 0.53 mmol). The mixture was heated at 60 °C for 2.5 h. After cooling, the mixture was diluted with CH_2Cl_2 and 10% NH_4OH and stirred vigorously at room temperature for a while. Insoluble materials were filtered off, and the filtrate was extracted with CH_2Cl_2. The combined organic layer was dried, and concentrated. The residue was passed through a short plug of silica gel (BW300, 20% EtOAc/hexane) and used in the next reaction without further purification.

To a solution of the above material in DMF (5 mL) cooled at 0 °C were added benzyl bromide (0.070 mL, 0.59 mmol) and NaH (60% in oil) (19 mg, 0.48 mmol). After being stirred at room temperature for 80 min, the mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 30% EtOAc/hexane) gave **42** as a colorless foam: IR (film) 3068, 3036, 1682, 1601, 1519, 1468, 1438, 1401, 1326, 1265, 1169, 1128, 1069, 1012, 967, 849, 776 cm^{-1}; ^1H NMR (exists as a 83:17 mixture of *cis–trans* isomers at 300 K) δ 8.31 (d, J=7.3 Hz, 0.17H), 8.16 (d, J=7.3 Hz, 0.83H), 7.83–7.08 (m, 12H), 5.14 (s, 0.34H), 5.05 (s, 1.66H), 3.61 (s, 0.51H), 3.38 (s, 2.49H); HRFABMS calcd for $C_{24}H_{19}F_3N_3O_2$ [$(M+H)^+$] 438.1429, found 438.1425.

4.6.4. *N*-Methylation of 30. To a solution of **30** (125 mg, 0.30 mmol) in DMF (4 mL) cooled at 0 °C were added MeI (0.180 mL, 2.89 mmol) and NaH (60% in oil) (14 mg, 0.35 mmol). After being stirred at room temperature for 50 min, the mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography

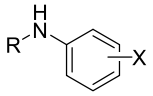
Table 9. Physicochemical properties of *N*-(2-chloro-3-pyridinyl)-*N*-(substituted)amines (**21**, **26**–**29**, **47**–**49**)



Compound	R	Mp (°C)	NMR[a]	HRFABMS [$(M+H)^+$] calcd (found)
21[27]	–CH_2Ph	Oil	^1H NMR δ 7.71 (d, J=4.4 Hz, 1H), 7.40–7.23 (m, 5H), 7.02 (m, 1H), 6.83 (d, J=8.4 Hz, 1H), 4.84 (br s, 1H), 4.39 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 140.6, 137.7, 137.1, 136.7, 128.9, 127.6, 127.1, 123.4, 117.8, 47.4	$C_{12}H_{11}ClN_2$ 219.0689 (219.0688)
26	–Ph	69–71	^1H NMR δ 7.86 (d, J=4.8 Hz, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.40–7.32 (m, 2H), 7.20–7.04 (m, 4H), 6.14 (s, 1H); ^{13}C NMR δ 140.0, 139.3, 138.6, 137.7, 129.7, 123.9, 123.1, 121.20, 121.15	$C_{11}H_{10}ClN_2$ 205.0532 (205.0538)
27	–C_6H_4–*p*-OMe	Oil	^1H NMR δ 7.78 (d, J=4.6 Hz, 1H), 7.18 (d, J=7.3 Hz, 1H), 7.12 (d, J=8.2 Hz, 2H), 7.02 (dd, J=8.2, 4.6 Hz, 1H), 6.92 (d, J=9.2 Hz, 2H), 5.99 (s, 1H), 3.82 (s, 3H); ^{13}C NMR δ 157.0, 139.3, 138.1, 137.4, 132.5, 125.2, 123.1, 119.8, 114.9, 55.5	$C_{12}H_{12}ClN_2O$ 235.0638 (235.0642)
28	–C_6H_4–*p*-CF_3	Oil	^1H NMR δ 7.99 (d, J=4.6 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.58 (d, J=9.1 Hz, 2H), 7.23–7.13 (m, 3H), 6.29 (s, 1H); ^{13}C NMR δ 144.1, 141.5, 136.1, 127.3 (q, J=4.0), 125.1, 123.9, 123.4, 118.8	$C_{12}H_9ClF_3N_2$ 273.0406 (273.0401)
29	–CH_2CH_2Ph	Oil	^1H NMR δ 7.70 (dd, J=4.6, 1.8 Hz, 1H), 7.38–7.30 (m, 2H), 7.29–7.19 (m, 4H), 7.08 (dd, J=8.2, 4.6 Hz, 1H), 6.90 (m, 1H), 4.42 (s, 1H), 3.47–3.37 (m, 2H), 3.00–2.92 (m, 2H); ^{13}C NMR δ 140.5, 138.5, 137.1, 136.3, 128.73, 128.66, 126.7, 123.3, 117.3, 44.4, 35.2	$C_{13}H_{13}ClN_2$ 233.0845 (233.0842)
47	–C_6H_4–*o*-Me	Oil	^1H NMR δ 7.82 (dd, J=3.6, 1.6 Hz, 1H), 7.31 (m, 1H), 7.22 (d, J=3.6 Hz, 2H), 7.13 (m, 1H), 7.08–7.01 (m, 2H), 5.92 (s, 1H), 2.25 (s, 3H); ^{13}C NMR δ 138.5, 138.1, 138.0, 132.4, 131.4, 127.1, 125.2, 123.4, 123.1, 120.6, 17.8	$C_{12}H_{12}ClN_2$ 219.0689 (219.0687)
48[28]	–C_6H_4–*p*-Me	Oil	^1H NMR δ 7.83 (m, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.17 (d, J=8.4 Hz, 2H), 7.09–7.01 (m, 3H), 6.07 (s, 1H), 2.34 (s, 3H); ^{13}C NMR δ 138.7, 138.4, 138.1, 137.2, 133.9, 130.2, 123.1, 122.1, 120.5, 20.9	$C_{12}H_{12}ClN_2$ 219.0689 (219.0695)
49	–*n*-Bu	Oil	^1H NMR δ 7.69 (m, 1H), 7.09 (m, 1H), 6.88 (m, 1H), 3.19–3.10 (m, 2H), 1.71–1.61 (m, 2H), 1.52–1.40 (m, 2H), 0.98 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 140.9, 136.9, 136.0, 123.4, 117.2, 42.9, 31.1, 20.2, 13.8	$C_9H_{14}ClN_2$ 185.0845 (185.0842)

[a] ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

Table 10. Physicochemical properties of *N*-(substituted)anilines (**50–54**)



Compound	X	R	Mp (°C)	NMR[a]	HRFABMS [(M+H)$^+$] calcd (found)
50	*p*-CF_3	–Ph	49–51	^{1}H NMR δ 7.46 (d, J=8.0 Hz, 2H), 7.37–7.28 (m, 2H), 7.14 (d, J=7.2 Hz, 2H), 7.08–6.99 (m, 3H), 5.90 (s, 1H); ^{13}C NMR δ 146.8, 141.1, 129.6, 126.7 (q, J=4.0 Hz), 122.9, 120.0, 115.3	$C_{13}H_{11}F_3N$ 238.0843 (238.0851)
51[29]	*p*-CF_3	–Bn	Oil	^{1}H NMR δ 7.42–7.26 (m, 7H), 6.63 (d, J=8.4 Hz, 2H), 4.37 (s, 1H); ^{13}C NMR δ 150.4, 138.4, 128.8, 127.5, 127.4, 126.6 (q, J=4.0), 126.3, 112.0, 47.8, 29.7	$C_{14}H_{13}F_3N$ 252.1000 (252.1008)
52	*p*-CF_3	–*n*-Bu	Oil	^{1}H NMR δ 7.38 (d, J=8.4 Hz, 2H), 6.58 (d, J=9.2 Hz, 2H), 3.93 (br s, 1H), 3.18–3.08 (m, 2H), 1.67–1.52 (m, 2H), 1.49–1.36 (m, 2H), 1.00–0.92 (m, 3H); ^{13}C NMR δ 150.9, 126.6 (q, J=4.0), 123.7, 118.2, 111.6, 43.2, 31.4, 20.2, 13.8	$C_{11}H_{15}F_3N$ 218.1156 (218.1162)
53[30]	*p*-CN	–Bn	61–63 (lit.[30] 66)	^{1}H NMR δ 7.45–7.28 (m, 7H), 6.60 (d, J=9.2 Hz, 2H), 4.73 (br s, 1H), 4.38 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 151.0, 137.7, 133.8, 128.89, 128.88, 127.7, 127.4, 120.3, 112.5, 47.6	$C_{14}H_{13}N_2$ 209.1079 (209.1078)
54[31]	*p*-CN	–CH_2CH_2Ph	Oil	^{1}H NMR δ 7.44–7.13 (m, 7H), 6.58–6.48 (m, 2H), 4.21 (s, 1H), 3.48–3.38 (m, 2H), 2.95–2.85 (m, 2H); ^{13}C NMR δ 151.0, 138.4, 133.7, 128.8, 128.7, 120.4, 112.3, 100.0, 98.8, 44.2	$C_{15}H_{14}N_2$ 223.1235 (223.1236)

[a] ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were taken in $CDCl_3$.

(silica gel, BW300, 30% EtOAc/hexane) gave amide **42** (118 mg, 92%) as a colorless foam. Spectroscopic data of this material were indistinguishable with those of the authentic sample obtained from **41** (Scheme 3).

4.7. Synthesis of secondary aryl amines (21, 26–35) from the amides (Tables 1 and 2)

As a typical example, the synthesis of *N*-benzyl-*N*-(2-chloro-3-pyridinyl)amine (**21**) from the amide **10a** is described. To a solution of **10a** (100 mg, 0.26 mmol) in reagent grade DMF (5 mL) at 0 °C was added NaH (60% in oil) (51 mg, 1.28 mmol). After being stirred at room temperature overnight, the mixture was cooled to 0 °C and quenched with H_2O. The mixture was diluted and extracted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 10→20% EtOAc/hexane) gave **21**[27] (42 mg, 76%) as a colorless oil. Similarly, the secondary aryl amines (**26–35**) were obtained from the corresponding amides. The physicochemical properties are described in Tables 9 and 10.

4.8. Direct synthesis of secondary aryl amines (21, 26, 27 and 47–54) from 3-aryl-3,4-dihydro-4-oxo-2-quinazolinecarboxylic acid ethyl esters (9a, 9b and 9d) and amines (Table 4)

As a typical example, the preparation of *N*-(2-chloro-3-pyridinyl)-*N*-phenylamine (**26**) by reaction of **9a** with aniline in the presence of NaOMe is described. To a mixture of aniline (21 mg, 0.23 mmol) and NaOMe (41 mg, 0.76 mmol) in reagent grade THF (1 mL) at 0 °C was added **9a** (50 mg, 0.15 mmol). After being stirred at room temperature for 5 h, the mixture was diluted with EtOAc and acidified with AcOH (pH ~4). The mixture was diluted with EtOAc, washed with H_2O and brine, dried, and concentrated. Purification of the residue by flash chromatography (silica gel, BW300, 20% EtOAc/hexane) gave **26** (24 mg, 78%). The physicochemical properties are described in Table 9. Similarly, the secondary aryl amines **21**, **27** and **47–54** were obtained by reaction of **9a**, **9b** and **9d** with the various amines. The results are summarized in Table 4, and the physicochemical properties are listed in Tables 9 and 10.

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