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: A novel intramolecular nucleophilic aromatic substitution reaction of 2-carboxamido-3-arylquinazolin-4-one derivatives induced by base treatment and its application to the expeditious synthesis of secondary aryl amines, including diaryl amines, are described.

Key words: heterocycles, nucleophilic aromatic substitutions, amines, tandem reactions, medicinal chemistry

3-Arylquinazolin-4-one is a structural motif that is widely found in medicinal chemistry and natural product chemistry, as exemplified by methaqualone (**1**),[2] circumdatin F (**2**),[3] benzomalvin A (**3**)[4] and tryptanthrin (**4**)[5] (Figure 1). Due to its potential utility, 3-arylquinazolin-4-one has been extensively utilized as a core structure in the field of medicinal chemistry. For example, researchers from Pfizer have recently succeeded in the discovery of a new potent AMPA receptor antagonist, CP-465,022 (**5**), based on 3-(2-chlorophenyl)-6-fluoroquinazolin-4-one as the template.[6] It is noteworthy that CP-465,022 exists as a separable mixture of atropisomers and that the anticonvulsant activity resides in only one of the atropisomers [i.e., (+)-CP-465,022]. Such a relationship between the atropisomeric property and biological profile also makes 3-arylquinazolin-4-one as an intriguing motif.

We have been engaged in the synthesis of a series of 3-arylquinazolin-4-one derivatives, represented by **11** (Scheme 1). The synthesis was commenced with the acylation of the known amide **6**[7] to give the ethyl ester **7** in high yield. Dehydrative cyclization of **7** under Snider's conditions[8,9] produced a mixture of the iminobenzoxazine **8** and quinazolinone **9**, which, without separation, was treated with pyrrolidine to provide the quinazolinone **9** in good overall yield. Exposure of **9** to dimethylaluminium thiolate[10] led to the thiol ester **10**, which was reacted with *N*-methyl-3,5-bis(trifluoromethyl)benzylamine in the presence of $AgOCOCF_3$[11] to give the amide **11** in 100% yield. The related amide **12** was similarly obtained from **10** using 3,5-bis(trifluoromethyl)benzylamine. To our surprise, treatment of **12** with NaH in DMF at room temperature followed by the addition of MeI led to the exclusive formation of the tertiary amide **13** (81% yield) and

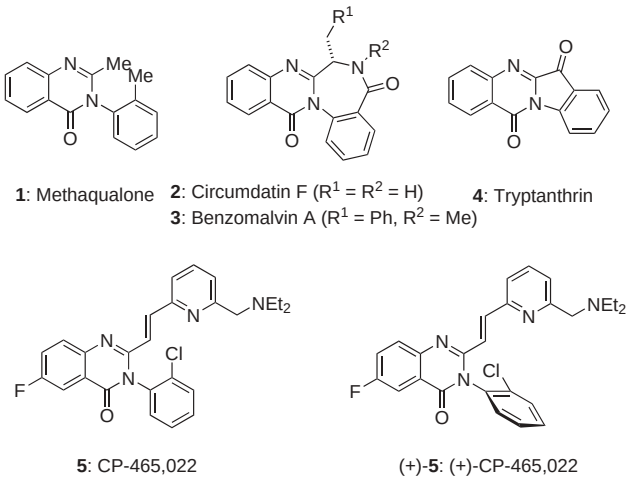

Figure 1 Representative bioactive molecules and natural products that possess the 3-arylquinazolin-4-one structural motif

the expected N-methylated product **11** was not observed.[12]

Thus, migration of the aryl group at the N3 position, presumably via nucleophilic aromatic substitution (S_NAr), was induced by the action of NaH, leading to the tertiary amide **13** after trapping of the resultant anion with MeI (Scheme 1). In this communication, we describe a novel intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones and its synthetic utility as a tool for the synthesis of secondary aryl amines, including diaryl amines.

To validate the scope and limitation of the present S_NAr reaction, we first prepared a variety of 2-carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones **12** (Table 1). Upon treatment of the quinazolin-4-ones with 1.2 equivalents of NaH in DMF at room temperature, all compounds cleanly furnished the migrated products, i.e., 2-*N*-(2-chloro-3-pyridyl)carboxamidoquinazolin-4-one derivatives **14**, indicating that aliphatic, benzylic and aromatic amides are well tolerated in the present reaction.[13]

We also investigated the effect of the substitution of the N3 aryl group (Table 2). It was revealed that the reaction proceeded in N3 phenyl derivatives **15a**–**g** and the presence of an electron withdrawing group(s) at the *ortho* or *para* position of the N3 phenyl group is essential for the success of the present reaction: *p*-CF_3, *p*-CN and

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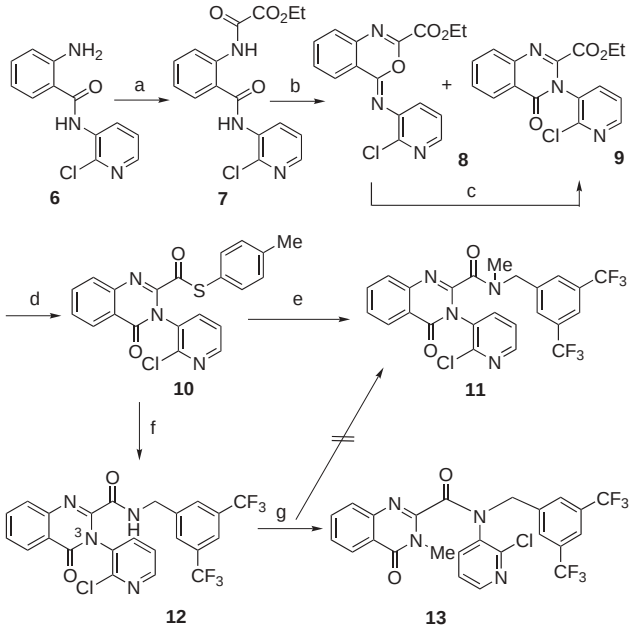
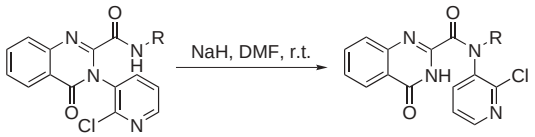


Scheme 1 *Reagents and conditions*: (a) $ClCOCO_2Et$, pyridine, THF, 0 °C, 97%; (b) I_2, PPh_3, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to r.t.; (c) pyrrolidine, THF–HOAc (10:1), reflux, 91% (2 steps); (d) *p*-MeC_6H_5SH, $AlMe_3$, CH_2Cl_2, 0 °C to r.t., 87%; (e) *N*-methyl-3,5-bis(trifluoromethyl)benzylamine, $AgOCOCF_3$, THF–toluene (1:1), 60 °C, 100%; (f) 3,5-bis(trifluoromethyl)benzylamine, $AgOCOCF_3$, THF–toluene (1:1), 60 °C, 100%; (g) NaH, DMF, 0 °C to r.t., 1 h then MeI, 0 °C to r.t., 1 h, 81%.

o-CO_2Me derivatives cleanly furnished the corresponding tertiary amides (i.e., 2-*N*-arylcarboxamidoquinazolin-4-ones **16a**–**g**; entries 1–7) upon treatment with 1.1–1.2 equivalents of NaH in DMF at room temperature. On the other hand, *m*-CO_2Me, *p*-OMe and unsubstituted derivatives (**15h**–**j**; entries 8–10) 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.

Table 1 Intramolecular S_NAr Reaction of 2-Carboxamido-3-(2-chloro-3-pyridyl)quinazolin-4-ones **12**[a]

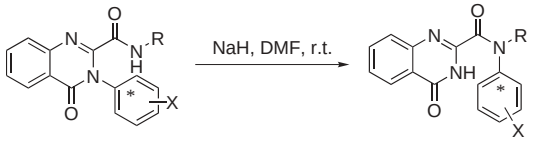


12a–e **14a–e**

Entry	**12**, **14**	R	Yield (%)
1	**a**	Ph	88
2	**b**	C_6H_4-*p*-OMe	87
3	**c**	C_6H_4-*p*-CF_3	100
4	**d**	Bn	76
5	**e**	CH_2CH_2Ph	63

[a] All reactions were performed using 1 equiv of the 3-arylquinazolin-4-one **12** and 1.2 equiv of NaH in DMF at r.t.

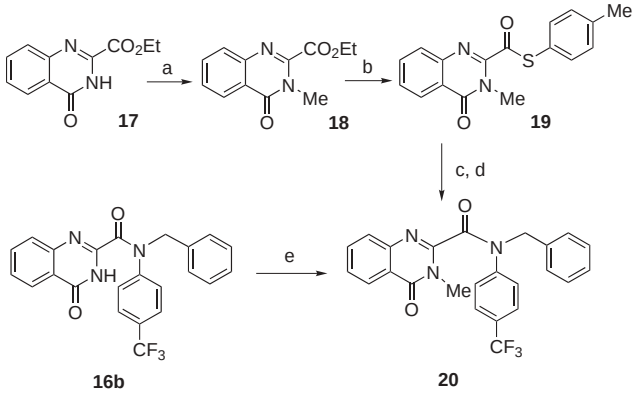
Table 2 Effect of a Substituent of the N3 Aryl Group



15a–j **16a–j**

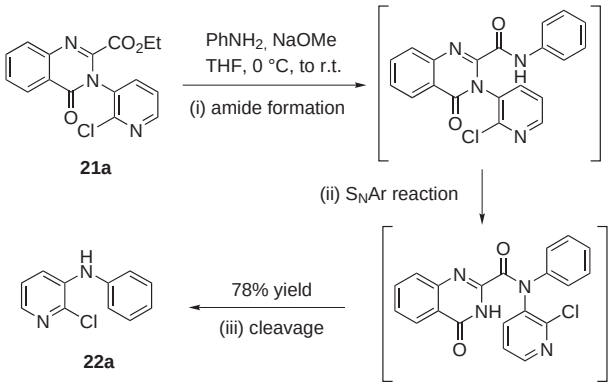
Entry	**15**, **16**	X	R	Yield (%)
1	**a**	*p*-CF_3	Ph	85
2	**b**	*p*-CF_3	Bn	95
3	**c**	*p*-CF_3	*n*-Bu	100
4	**d**	*p*-CN	Bn	95
5	**e**	*o*-CO_2Me	Ph	72
6	**f**	*o*-CO_2Me	C_6H_4-*m*-CF_3	89
7	**g**	*o*-CO_2Me	Bn	100
8	**h**	*m*-CO_2Me	Ph	0
9	**i**	*p*-OMe	Bn	0
10	**j**	H	Bn	0

At this stage, the structural confirmation of the products of the present intramolecular S_NAr reaction (i.e., the migrated products **13**, **14** and **16**) was made by comparison of the spectroscopic data of the N-methylated compound **20** derived from **16b** with those of an authentic sample prepared from the ethyl 4-quinazolone-2-carboxylate (**17**)[14] in 4 steps (Scheme 2).



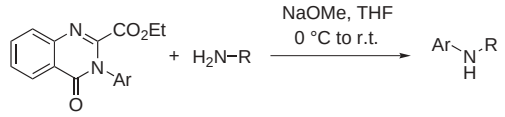
Scheme 2 Structural confirmation of the tertiary amide **16b**. *Reagents and conditions*: (a) MeI, NaHMDS, DMF, 0 °C to r.t., 72%; (b) *p*-MeC_6H_4SH, $AlMe_3$, toluene, 0 °C to r.t., 71%; (c) 4-(trifluoromethyl)aniline, $AgOCOCF_3$, THF–toluene (1:1), 60 °C, 80%; (d) NaH, BnBr, DMF, 0 °C to r.t., 99%; (e) NaH, MeI, DMF, 0 °C to r.t., 92%.

Based on the above results, we have thus established an expeditious method for the synthesis of secondary aryl amines: we found that treatment of the ethyl ester **21a** with 1.5 equivalents of aniline and 5.0 equivalents of NaOMe (THF, 0 °C to r.t.) led to the generation of the secondary aryl amine **22a** (Scheme 3). The present process should be a cascade reaction comprised of (i) amide formation, (ii) intramolecular S_NAr reaction, and (iii) cleavage of the resultant tertiary amide. The cascade reaction was then applied to a series of substrates and the results are summarized in Table 3. Various aliphatic, benzylic and aromatic amines could be employed in this process.[15] It is worth mentioning that the present method does not require inert anhydrous conditions and is operationally very simple. It also offers easy access to diaryl amines (e.g., **22a–c**, **22f**) that are mainly synthesized via metal-catalyzed cross-coupling reactions.[16]



Scheme 3 Cascade process leading to the generation of the secondary aryl amine

Table 3 Expeditious Synthesis of the Secondary Aryl Amines[a]



a: Ar = 2-chloro-3-pyridyl
b: Ar = C_6H_4-*p*-CF_3
c: Ar = C_6H_4-*p*-CN

Entry	22	Ar	R	Yield (%)
1	**a**	2-Chloro-3-pyridyl	Ph	78
2	**b**	2-Chloro-3-pyridyl	C_6H_4-*p*-Me	82
3	**c**	2-Chloro-3-pyridyl	C_6H_4-*o*-Me	64
4	**d**	2-Chloro-3-pyridyl	Bn	73
5	**e**	2-Chloro-3-pyridyl	*n*-Bu	64
6	**f**	C_6H_4-*p*-CF_3	Ph	59
7	**g**	C_6H_4-*p*-CF_3	Bn	77
8	**h**	C_6H_4-*p*-CF_3	*n*-Bu	71
9	**i**	C_6H_4-*p*-CN	Bn	74
10	**j**	C_6H_4-*p*-CN	CH_2CH_2Ph	81

[a] All reactions were carried out using 1.0 equiv of 3-arylquinazolin-4-one, 1.5 equiv of amine and 5.0 equiv of NaOMe in THF at 0 °C to r.t.

In conclusion, we have discovered a novel intramolecular S_NAr reaction of 2-carboxamido-3-arylquinazolin-4-ones. Application of the present reaction to the synthesis of secondary aryl amines, including diaryl amines, has also been demonstrated.

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(12) Premixing MeI and **12** prior to the addition of NaH led to a mixture of the migrated tertiary amide **13** (58%) and *N*-methylated compound **11** (31%).
(13) **Representative Procedure for the Intramolecular S_NAr Reaction**: To a solution of **12a** (40.5 mg, 0.108 mmol) in DMF (1.5 mL) cooled at 0 °C was added NaH (60% in oil, 5.2 mg, 0.13 mmol) and the reaction mixture was stirred at

r.t. for 1 h. The reaction was quenched by the addition of H_2O and solid NH_4Cl (ca 20 mg). The resultant mixture was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, $CHCl_3$ then 5% MeOH–$CHCl_3$) gave **14a** (35.6 mg, 88%) as a colorless solid.

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(15) **Representative Procedure for the Synthesis of Secondary Aryl Amines**: To a solution of **21a** (50 mg, 0.15 mmol) in THF (1 mL) cooled at 0 °C were added aniline (21 mg, 0.23 mmol) and NaOMe (41 mg, 0.76 mmol). After being stirred at r.t. for 5 h, the reaction mixture was diluted with EtOAc and neutralized with HOAc. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by flash chromatography (silica gel, 20% EtOAc–hexane) gave **22a** (24 mg, 78%) as a colorless oil.

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