An Acid-Catalysed Conversion of 2-(4-Quinazolinylamino)benzoic Acid into 2-(2-Aminophenyl)-4(1*H*)-Quinazolinone

Helen F. Sneddon,* Sean M. Lynn

GlaxoSmithKline R&D Ltd, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK
Fax +44(1438)768302; E-mail: helen.f.sneddon@gsk.com

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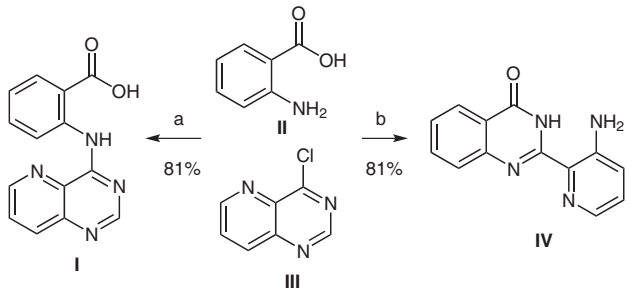
Abstract: An acid-catalysed conversion of *N*-arylcarboxy-4-quinazolinones into 2-(2-aminoaryl)-4(1*H*)-quinazolinones has been observed. This reaction allows for a nucleophilic aromatic substitution reaction between aminobenzoic acids and 4-chloroquinazolines to form *N*-arylcarboxy-4-quinazolinones to be followed in situ by a conversion into 2-(2-aminoaryl)-4(1*H*)-quinazolinones in a one-pot tandem process.

Key words: rearrangement, tandem reaction, nucleophilic aromatic substitution, bicyclic compounds, fused ring systems

N-Arylcarboxy-4-quinazolinamines (such as may be accessed from intermediate **I**) have long been of interest for their anti-inflammatory properties.[1] On attempting to isolate the product of an acid-catalysed nucleophilic aromatic substitution reaction between aminobenzoic acid **II** and 4-chloropyrido[3,2-*d*]pyrimidine (**III**), the unexpected product from an acid-catalysed rearrangement, 2-(3-amino-2-pyridinyl)-4(1*H*)quinazolinone (**IV**) was observed (Scheme 1).

Quinazolinones such as **IV** are a common scaffold, with over 16000 2-phenyl-4(1*H*)-quinazolinone-containing compounds currently listed in the literature.[2]

A repeat of the reaction in the absence of HCl yielded the expected product of nucleophilic aromatic substitution (**I**). When 2-(pyrido[3,2-*d*]pyrimidin-4-ylamino)benzoic acid (**I**) was heated with HCl, complete conversion into 2-(3-amino-2-pyridinyl)-4(1*H*)-quinazolinone (**IV**) was observed.



Scheme 1 *Reagents and conditions*: (a) *i*-PrOH, 140 °C, 1 h; (b) HCl, *i*-PrOH, 140 °C, 1 h.

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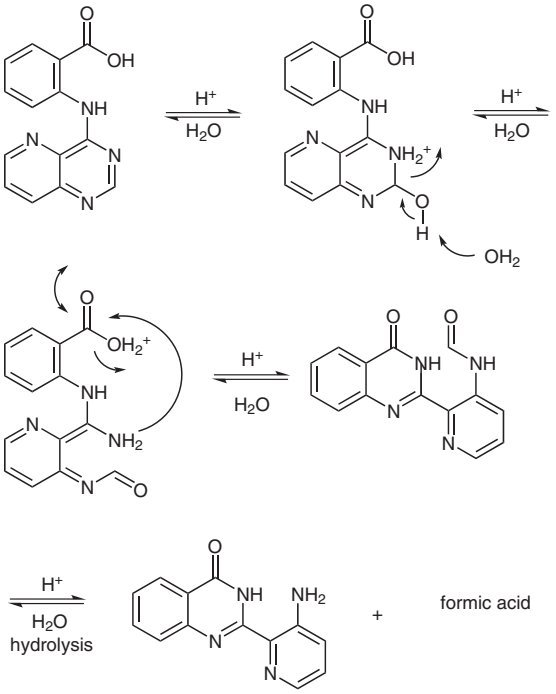
The heating of *N*-arylcarboxy-4-quinazolinamine **I** to 80 °C in DMSO for 48 hours using real-time elevated temperature NMR confirmed that no thermal rearrangement was observed, consistent with the conversion into quinazolinone **IV** being acid-catalysed. A possible mechanism for this reaction is shown in Scheme 2. Support for this possible mechanism is offered by the observation of formic acid in an NMR sample of the crude reaction mixture.



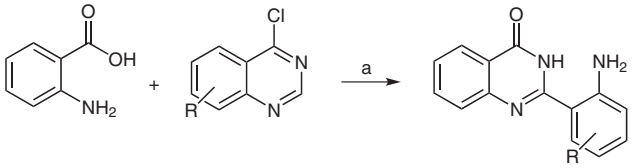
Scheme 2 Proposed mechanism

Intramolecular condensations of aromatic acids with pyrimidines have long been known.[3] Conditions reported in the literature for such condensations include H_2SO_4,[4] $SOCl_2$[5] and pyridine in acetic anhydride.[6] However, to the best of our knowledge, the condensation of an aromatic acid with a pyrimidine nitrogen, with the concomitant ring opening of the pyrimidine and loss of the C2 carbon of the pyrimidine ring (presumably as formic acid under aqueous acid-catalysed conditions) has yet to be reported.

The observed reaction highlights a potential instability of *N*-arylcarboxy-4-quinazolinamines to acidic conditions. In addition this reaction may also allow an additional route to the direct preparation of 2-(2-aminoaryl)-4(1*H*)-

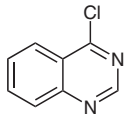
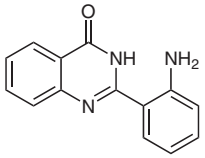
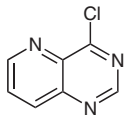
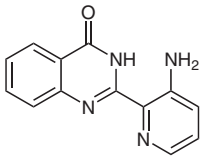
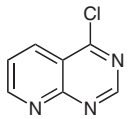
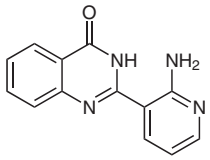
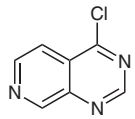
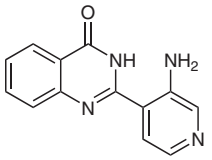
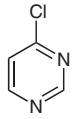
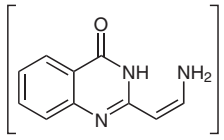
quinazolinones from 4-haloquinzolines and aminobenzoic acids.

Aminobenzoic acid has been shown to react with a range of quinazolines (Scheme 3, Table 1).



Scheme 3 *Reagents and conditions*: (a) HCl, *i*-PrOH, 140 °C, 1 h.

Table 1 Products of the Reaction of Aminobenzoic Acid with Various Haloquinazolines

Entry	Quinazoline	Product	Yield (%)[a]
1			76
2			81
3			66
4			80
5			0

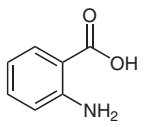
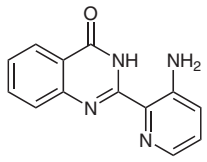
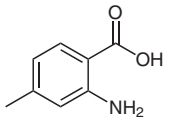
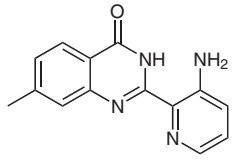
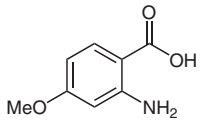
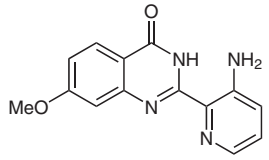
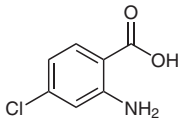
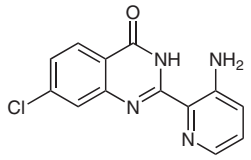
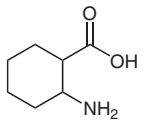
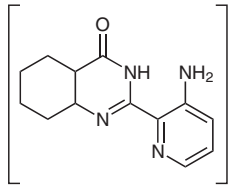
[a] Isolated yield.

The reaction worked well with various pyridopyrimidines (Table 1, entries 2–4), however the attempted reaction with 4-chloropyrimidine (Table 1, entry 5) showed no discernable quinazolinone formation.

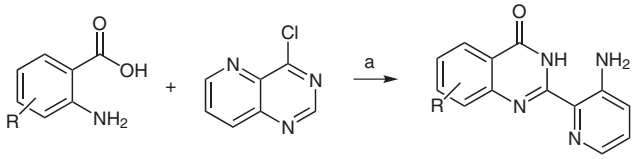
The reaction with 4-chloropyrido[3,2-*d*]pyrimidine has been shown to occur with a range of aminobenzoic acids (Scheme 4, Table 2).

The reaction gave higher yields with electron-rich aromatic amines (Table 2, entries 2 and 3), than with the electron-poor aromatic amine (Table 2, entry 4). The attempted reaction with a non-aromatic acid (Table 2, entry 5) showed multiple products, but no discernable product analogous to the previous reactions.

Table 2 Products of the Reaction of 4-Chloropyrido[3,2-*d*]pyrimidine with Various Aminobenzoic Acids

Entry	Aminobenzoic acid	Product	Yield (%)[a]
1			81
2			79
3			74
4			41
5			0

[a] Isolated yield.

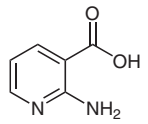
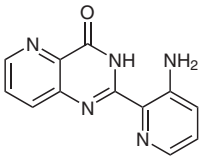
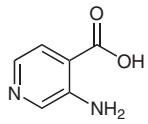
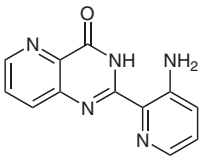
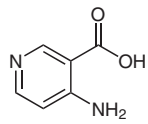
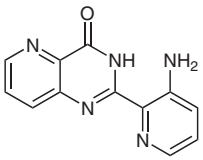


Scheme 4 *Reagents and conditions*: (a) HCl, *i*-PrOH, 140 °C, 1 h.

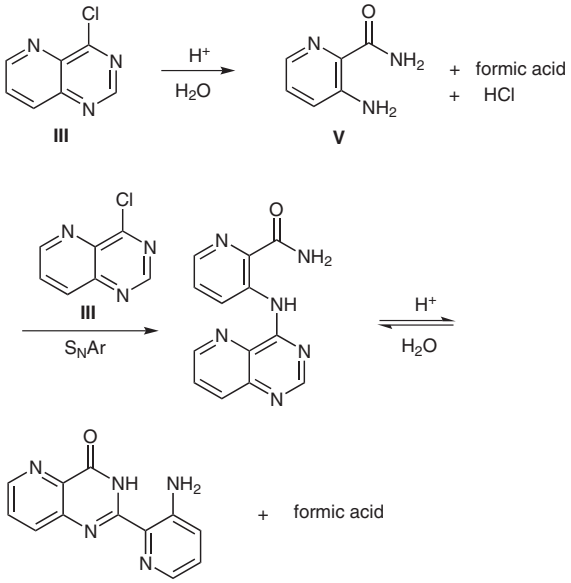
Interestingly, attempts to carry out the reaction with aminopyridine carboxylic acids all yielded small amounts of the same product (Table 3), which is thought to derive from self-condensation of 4-chloropyrido[3,2-*d*]pyrimidine.

It should be noted that the aminopyridine carboxylic acids (Table 3, entries 1–3) are likely to be protonated under these conditions, and as such are less nucleophilic. It is possible that under these conditions, hydrolysis of the 4-chloropyrido[3,2-*d*]pyrimidine (**III**) followed by nucleophilic addition of the resulting 3-amino-2-pyridinecarbox-

Table 3 Products of the Reaction of 4-Chloropyrido[3,2-*d*]pyrimidine with Various Aminopyridine Carboxylic Acids

Entry	Aminopyridine carboxylic acid	Product	Yield (%)[a]
1			16
2			10
3			11

[a] Isolated yield.



Scheme 5 Proposed mechanism for self-condensation of quinazolinones

amide (**V**) to residual 4-chloropyrido[3,2-*d*]pyrimidine (**III**) occurs, which may then be followed by condensation as before (Scheme 5).[7]

In summary an apparently novel reaction of *N*-arylcarboxy-4-quinazolinamines[8] has been observed, highlighting the instability of such substrates to acidic conditions. In addition this reaction may also allow an additional route to the direct preparation of 2-(2-aminoaryl)-4(1*H*)-quinazolinones from 4-haloquinzolines and aminobenzoic acids which may be of use when other methods are not appropriate.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

With thanks to Sean Hindley for HPLC purification of the products shown in Table 3 (entries 2 and 3).

References and Notes

(1) Gineinah, M. M.; El-Sherbeny, M. A.; Nasr, M. N.; Maarouf, A. R. *Arch. Pharm. (Weinheim, Ger.)* **2002**, 556.
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(7) Traces of self-condensation product (12% by LC–MS) also appeared to have been present in the attempted reaction with 2-aminocyclohexylcarboxlic acid (Table 2, entry 5).
(8) **Typical Procedure**: A suspension of 2-aminobenzoic acid (83 mg, 0.604 mmol) and 4-chloropyrido[3,2-*d*]pyrimidine (100 mg, 0.604 mmol) in *i*-PrOH (4 mL) and 2 M HCl (1 mL) was heated in a sealed vial in a microwave to 140 °C for 1 h. The crude reaction mixture was concentrated under reduced pressure, and triturated with Et_2O to yield the product as a pale yellow solid (116 mg, 81%).[9]
(9) Lower-yielding reactions and those yielding multiple by-products were purified by reverse-phase flash column chromatography, or by mass-directed HPLC.