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Abstract

A new method is presented for the synthesis of 2-aminoquinazolines, which is based on a Chan–Evans–Lam coupling of (2-formylphenyl)boronic acids with guanidines. Relatively mild conditions involving the use of inexpensive CuI as a catalyst and methanol as a solvent permit the application of the method to a wide range of substrates. Nonsubstituted, N-monosubstituted, and N,N-disubstituted guanidines can be used as reactants to give the corresponding 2-aminoquinazolines in moderate yields from readily available (2-formylphenyl)boronic acids.

Key words

guanidines, Chan–Evans–Lam coupling, quinazolines, copper catalysis, formylphosphonic acids

2-Aminoquinazoline is an important substructure for the development of pharmaceutically relevant compounds, especially for the discovery of kinase inhibitors.\textsuperscript{1–6} A number of methods for the construction of 2-aminoquinazolines are known.\textsuperscript{7–18} However, there are only a few approaches that exploit guanidines as reaction components. ortho-Halobenzaldehydes and aryl ketones can be condensed with guanidines in most cases if they contain an additional electron-withdrawing group that facilitates an SNAr reaction.\textsuperscript{3,6,13,14,17,18} For nonactivated substrates, a copper-catalyzed amination of guanidines with aryl bromides has been described as a useful method for accessing 2-aminoquinazolines.\textsuperscript{19} However, the reaction conditions are very harsh (DMF, 120 °C), which limits the scope of this approach.

The Chan–Evans–Lam coupling\textsuperscript{20–24} is an attractive C–N bond-forming reaction that proceeds under relatively mild copper-catalyzed conditions and tolerates alcoholic solvents. To our knowledge, the only precedent for accessing quinazoline derivatives by using Chan–Evans–Lam coupling is a synthesis of quinazolomimines by amination of N,N-disubstituted guanidines, formed in situ, with (2-cyanoaryl)boronic acids.\textsuperscript{25} To facilitate our kinase-inhibitor-development program, we examined whether the Chan–Evans–Lam coupling might also be applicable to the synthesis of aminoquinazolines under mild conditions by using readily available reagents.

A screening of the reaction conditions was performed for the synthesis of unsubstituted quinazoline-2-amine (3). Representative results are reported in Table 1 (see Supporting Information (SI) for the full set of experiments). Due to the polarity of the product 3, its purification by chromatography was difficult, and it was therefore purified by trituration from ethyl acetate. An identical scale and workup were applied in all experiments to permit comparison of the effects of other reaction parameters. Methanol as a reaction solvent, CuI as a catalyst, and K\textsubscript{2}CO\textsubscript{3} as a base were found to be productive conditions for the formation of quinazoline-2-amine (3) from (2-formylphenyl)boronic acid (1) and guanidine hydrochloride (2a) (Table 1, entries 1 and 2).

Excess amounts of the base and guanidine were beneficial in improving the yield of product 3 (Table 1, entry 2). Other copper catalysts [CuCl and Cu(OAc)\textsubscript{2}] were found to be less efficient than CuI (entries 3 and 4). The use of KOH as base improved the yield of product 3 when an excess of guanidine was used (entries 5 and 6). EtOH could also be successfully used as the reaction solvent (entry 7). Guanidine carbonate (2b) as a reactant gave a reduced yield of quinazoline 3 (entries 8 and 9). All the experiments listed in Table 1 were performed open to air to ensure reoxidation.
of the copper catalyst. Performing the reaction under an oxygen atmosphere or adding hydrogen peroxide did not substantially improve the yield of product 3 (see SI).

Next, (2-formylphenyl)boronic acid (1) was treated with a range of guanidines under the most productive reaction conditions (Table 1, entry 6).26 Both N-monosubstituted guanidines 4a-g and N,N-disubstituted guanidines (4h-j) provided the corresponding 2-aminooxazolines 5a-j in fairly good yields (Table 2).

Several (2-formylphenyl)boronic acids 6a-f were next explored as substrates for the synthesis of aminoquinazolines 7a-f and 8a-f (Table 3). Both guanidines 2a and 4a gave the expected products but the isolated yields were generally somewhat higher in the case of the N-methyl-substituted guanidine 4a (Table 3; entries 3 and 4, 5 and 6, 7 and 8).

Boronic acid derivatives such as the pinacolate ester 9a and the trifluoroborate 9b were also competent substrates, providing aminoquinazoline derivative 5a in yields comparable to those from boronic acid 1 (Scheme 1). These results complement the relatively few reported cases of the use of boronic acid derivatives as partners for Chan–Evans–Lam coupling.27,28

In contrast, the boronic acids 10a and 10b bearing a keto group were found to be unsuitable reaction partners for the synthesis of the corresponding quinazolines 11a and 11b (Scheme 2). In the case of these substrates, complex mixtures were obtained containing the O-arylation products 12a and 12b as the only identifiable byproducts. The failure of (2-acylphenyl)boronic acids 10a and 10b to give the expected products implies that the formation of an arylidene guanidine is the first step in the synthesis of aminoquinazolines 3, 5, 7, and 8, followed by intramolecular arylation.

### Table 1 Chan–Evans–Lam Conditions for the Synthesis of 2-Aminoquinazoline (3)

| Entry | Solvent | Temp (°C) | Reactant (equiv) | Catalyst | Base (equiv) | Yield (%) |
|-------|---------|-----------|-----------------|-----------|-------------|-----------|
| 1     | MeOH    | 70        | 2a (1.5)        | Cul      | K$_2$CO$_3$ (2.5) | 31        |
| 2     | MeOH    | 70        | 2a (2.5)        | Cul      | K$_2$CO$_3$ (3)   | 44        |
| 3     | MeOH    | 70        | 2a (2.5)        | Cu(OAc)$_2$ | K$_2$CO$_3$ (3) | 35        |
| 4     | MeOH    | 70        | 2a (2.5)        | CuCl     | K$_2$CO$_3$ (3)   | 23        |
| 5     | MeOH    | 70        | 2a (1.5)        | Cul      | KOH (1.5)      | 34        |
| 6     | MeOH    | 70        | 2a (3)          | Cul      | K$_2$CO$_3$ (3)   | 51 (65)$^c$ |
| 7     | EtOH    | 90        | 2a (3)          | Cul      | -             | 52        |
| 8     | MeOH    | 70        | 2b (3)          | Cul      | K$_2$CO$_3$ (3)   | 17        |
| 9     | MeOH    | 70        | 2b (1.5)        | Cul      | KOH (3)        |           |

$^a$ Reactions were performed open to the air, reaction time: 12–17 h.
$^b$ Purified by trituration with EtOAc to a purity of >98%.
$^c$ NMR yield with 1,3,5-trimethoxybenzene as an internal standard.

### Table 2 Guanidine Scope for the Synthesis of Aminoquinazolines

| Entry | Guanidine R1 | R2 | Product | Yield (%) |
|-------|-------------|----|---------|-----------|
| 1     | 4a$^b$      | H  | Me      | 5a        | 63        |
| 2     | 4b$^c$      | H  | Ph      | 5b        | 56        |
| 3     | 4c$^b$      | H  | Bn      | 5c        | 66$^d$    |
| 4     | 4d$^b$      | H  | Ph(CH$_3$)$_2$ | 5d | 52        |
| 5     | 4e$^b$      | H  | Me(CH$_3$)$_2$ | 5e | 54        |
| 6     | 4f$^b$      | H  | cyclopentyl | 5f | 55        |
| 7     | 4g$^b$      | H  | Cy      | 5g        | 37        |
| 8     | 4h$^b$      | Me | Me      | 5h        | 43        |
| 9     | 4i$^b$      | (CH$_3$)$_3$ | Si | 47        |
| 10    | 4j$^b$      | (CH$_3$)$_2$O(CH$_3$)$_2$ | Sj | 39        |

$^a$ Purified by column chromatography unless stated otherwise.
$^b$ Hydrochloride salt.
$^c$ Carbonate salt.
$^d$ Purified by trituration with EtOAc.
In summary, 2-aminoquinazolines can be obtained by Chan–Evans–Lam coupling of (2-formylphenyl)boronic acids with guanidines. The relatively mild reaction conditions permit the use of this method for the synthesis of pharmacologically relevant compounds bearing a 2-aminoquinazoline scaffold.

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**Supporting Information**
Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707080. Supporting Information

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(26) Quinazolin-2-amine (3): Typical Procedure

A mixture of guanidine hydrochloride (2a; 765 mg, 8 mmol) and KOH (441 mg, 8 mmol) was dissolved in MeOH (30 mL) and the mixture was stirred for 10 min at r.t. (2-Formylphenyl)boronic acid (1; 400 mg, 2.67 mmol) was added in one portion followed by CuI (76 mg, 0.44 mmol), and the resulting mixture was heated at 70 °C overnight. The mixture was then concentrated under reduced pressure and partitioned betweenaq NH4Cl (30 mL) and EtOAc (120 mL). The organic layer was washed with brine, dried (Na2SO4), and concentrated under reduced pressure. The crude product was purified by titration with EtOAc (3 mL) to give a slightly beige solid; yield: 198 mg (51%); mp 194–196 °C.

1H NMR (400 MHz, DMSO-d6): δ = 9.10 (s, 1 H), 7.78 (d, J = 8.9 Hz, 1 H), 7.67 (t, J = 8.5 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 6.82 (s, 2 H). 13C NMR (101 MHz, DMSO-d6): δ = 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LC/MS: m/z [M + H]+ calcd for C16H16N3O: 266.1293; found: 266.1292.

1H NMR (400 MHz, DMSO-d6): δ = 8.90 (s, 1 H), 7.78 (d, J = 8.9 Hz, 1 H), 7.67 (t, J = 8.5 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 6.82 (s, 2 H). 13C NMR (101 MHz, DMSO-d6): δ = 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LC/MS: m/z [M + H]+ calcd for C16H16N3O: 266.1293; found: 266.1292.

1H NMR (400 MHz, DMSO-d6): δ = 9.10 (s, 1 H), 7.78 (d, J = 8.9 Hz, 1 H), 7.67 (t, J = 8.5 Hz, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 6.82 (s, 2 H). 13C NMR (101 MHz, DMSO-d6): δ = 162.4, 160.9, 151.2, 134.1, 127.9, 124.5, 122.0, 119.5. LC/MS: m/z [M + H]+ calcd for C16H16N3O: 266.1293; found: 266.1292.