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Graphical Abstract

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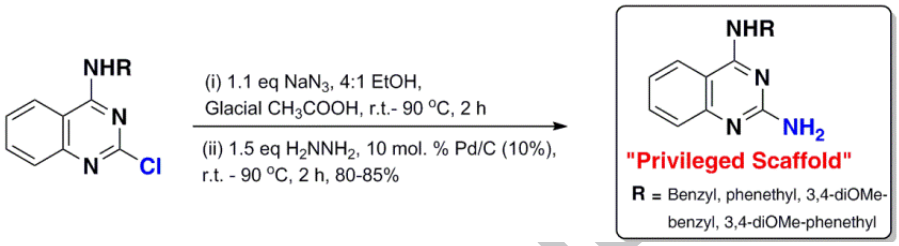

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Facile approaches toward the synthesis of N^4-monosubstituted quinazolin-2,4-diamines

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ABSTRACT

The amination of quinazoline-based heterocyclics is of significant interest due to its privileged structure and application in the development of bioactive compound libraries, as well as in the synthesis of readily convertible building blocks. The current approaches generally result in low yields, utilize harsh conditions and/or rely on expensive catalysts. After examining three different approaches to synthesize N^4-monosubstituted quinazolin-2,4-diamines, we developed an efficient and mild synthetic method to prepare quinazolin-2,4-diamines in 80–85% yield.

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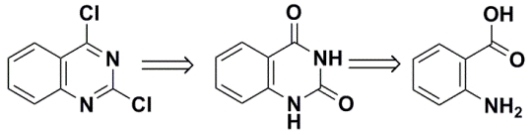
Introduction

Substituted quinazolin-2,4-diamines (Fig. 1) and related ring scaffolds, have substantial utility in medicinal chemistry and drug development. From cancer to diabetes to microbiology and more, there is an ever-growing list of quinazoline-based derivatives with a wide range of bioactive profile.[1-4]

Figure 1. N^2, N^4-Disubstituted quinazolin-2,4-diamine ring scaffold.

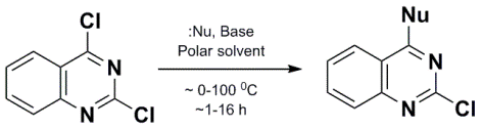
Synthetically, substituted quinazolin-2,4-diamines are generally prepared from a monocyclic starting precursor such as anthranillic acid, that is first converted to a bicyclic quinazoline ring template using urea to obtain quinazolin-2,4(1*H*, 3*H*)-dione. Subsequently, it is chlorinated to afford 2,4-dichloroquinazoline (2,4-DCQ), which can be functionalized at the C2 and C4 positions to synthesize diverse compound libraries (Scheme 1).[5-10]

In another approach, cyanoimidation and tandem reductive cyclization of 2-nitrobenzaldehyde was used to prepare N^4-substituted-2,4-diaminoquinazolines.[11]



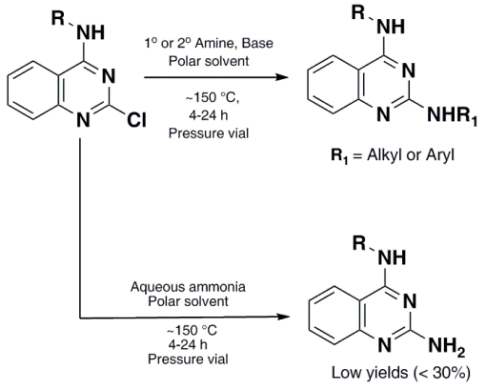
Scheme 1. Typical retrosynthetic approach toward 2,4-DCQ scaffold.

Due to its chemical nature, the quinazoline carbons at the C2 and C4 positions are electron deficient. This property is exploited in functionalizing 2,4-DCQ template by employing nucleophilic aromatic substitution (NAS) conditions to replace the C4 halogen with alkyl/aromatic amines (2-chloro-N^4-monosubstituted quinazolin-4-amines). This is a relatively straightforward approach that requires moderate reaction conditions (Scheme 2).[10, 12, 13]



Scheme 2. Commonly utilized approach toward C-4 functionalization of 2,4-DCQ.

However, amination at the C2 position, to obtain N^2,N^4-disubstituted quinazolin-2,4-diamines, requires harsher conditions due to the inherent electrochemical nature of the carbon at that position. The deactivation of that position toward nucleophilic attack when the C4 halogen is substituted with electron-donating groups prevents its efficient functionalization.[14, 15] Generally, C2 amination using alkyl or arylamines in an aprotic, high-boiling point solvent along with a quenching base under high temperature (at or above 150 °C) and pressure, yields the desired C2 amine-functionalized quinazolines in moderate to good yields. That being said, a similar approach using ammonia is not readily transferable to prepare N^4-monosubstituted quinazolin-2,4-diamines (C2 = NH_2) which are desirable compounds in biological activity screening studies (Scheme 3).[16, 17]

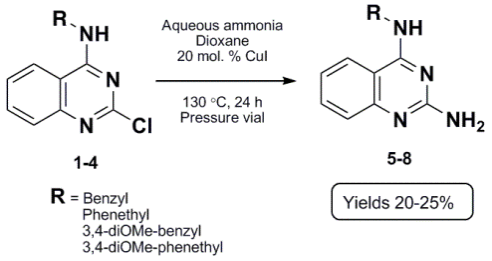


Scheme 3. Common synthetic approaches toward C2-amine functionalized quinazolines.

Results and discussion

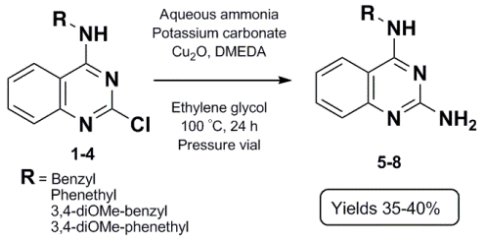
As part of our on-going efforts to develop C2-amine-based quinazolines, we herein present three viable approaches toward achieving this functionalization in moderate to good yields. In the evolution of our method development, we utilized 2-chloro-N^4-monosubstituted quinazolin-4-amines **1**–**4** (R = benzyl-, phenethyl, 3,4-dimethoxybenzyl and 3,4-dimethoxyphenethyl, Scheme 4) as starting precursors that were synthesized in-house.

In the first C2 amination approach using aqueous ammonia, we explored the utility of copper iodide (CuI) as a catalyst. The reaction conditions employed 20 mol.% CuI with 1,4-dioxane and aqueous ammonia (1:3 ratio v/v) heated at 130 °C in a sealed pressure vial for 24 h (Scheme 4, Method 1A, Supporting Information).[18]



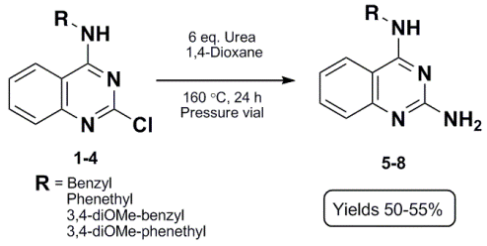
Scheme 4. C2 Amination using CuI to obtain C2-amine functionalized quinazolines.

While the approach was successful in facilitating the reaction (although not when attempted with sodium iodide), the yields were generally low (quinazolines **5**–**8**, 20–25%). In addition, we encountered difficulty in preventing ammonia escaping from the pressure vial during the reaction time period of 24 h due to seal breaking. An improved variation of this preliminary reaction is based on the work described by Renaud and co-workers, where CuI is replaced with copper (I) oxide (Cu_2O) and equimolar amounts of a diamine ligand, such as dimethylethylenediamine (DMEDA). This reaction was run under highly basic conditions (20 eq. potassium carbonate and 40 eq. aqueous ammonia) and heated in ethylene glycol at 100 °C in a sealed pressure vial for 24 h (Scheme 5, Method 1B, Supporting Information).[18] This modified approach was more successful in facilitating the reaction and provided better yields (35–40%) compared to Scheme 4, although the overall yield was still moderate. While we didn't encounter any ammonia leaks, the workup was more elaborate and time-consuming.



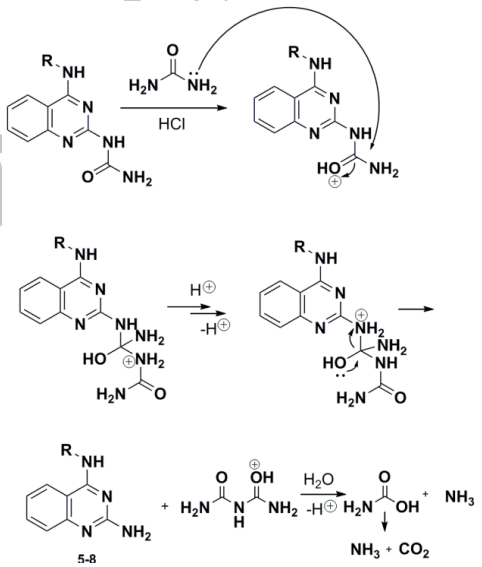
Scheme 5. Modified Cu_2O-based approach toward C2-amine functionalized quinazolines.

Our second approach, utilizing urea, was more promising. The reaction conditions used were straightforward. The starting 2-chloro-N^4-monosubstituted quinazolin-4-amines (**1**–**4**) were heated with 6 equivalents of urea in anhydrous 1,4-dioxane at 160 °C in a sealed pressure vial for 24 h (Scheme 6, Method 2, Supporting Information).



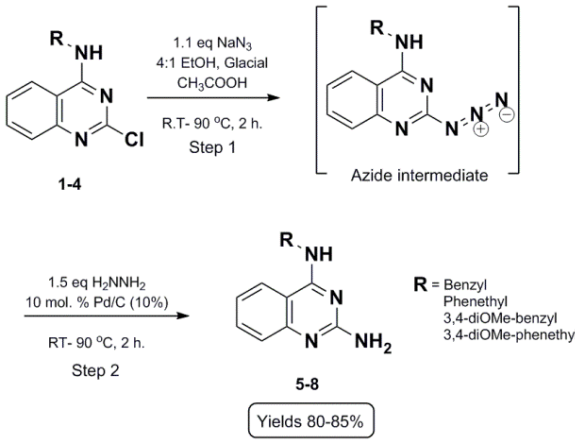
Scheme 6. Urea-based pressure vial approach toward C2-amine functionalized quinazolines.

While this condition was initially intended for the synthesis of C2-urea-based quinazolines, we were pleasantly surprised to observe a good amount of hydrolyzed C2-amine products (**5**–**8**, 50–55% yield, Scheme 6). Interestingly, the symmetry of urea is one of the driving forces in this reaction, as similar attempts with asymmetric amides (e.g. acetamide and methylcarbamate) were not successful in producing similar outcomes. The proposed mechanism of quinazoline-urea hydrolysis via an addition-elimination pathway to afford compounds **5**–**8** is shown in Scheme 7.



Scheme 7. Proposed mechanism of C2-urea-based quinazoline hydrolysis to obtain C2-amine functionalized quinazolines.

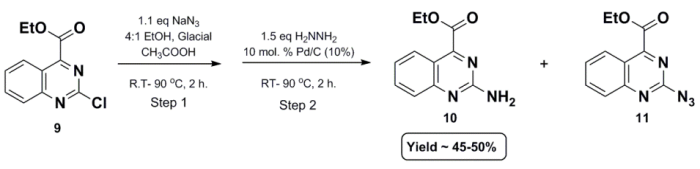
Our final approach, utilizes a two-step, one-pot reaction process that goes via a C2-azide (-N_3) intermediate (Scheme 8). Of the three methods discussed, this utilized the mildest conditions (maximum temperature of 90 °C, under reflux with no pressure vial set-up), with shortest reaction time (3 h) and provided the best yield (≥80%). Initially, the starting 2-chloro-N^4-monosubstituted quinazolin-4-amine (**1**–**4**) was heated with sodium azide (NaN_3) in 3:1 ethanol and glacial acetic acid for 2 h at 90 °C. After allowing the contents to cool to room temperature, 10 mol.% of Pd/C (10%) was added to the solution followed by slow addition of 1.5 eq. hydrazine ($H_2NNH_2.H_2O$) before re-heating the contents at 90 °C for 2 h (Scheme 8). To our satisfaction, this one-pot condition, gave very good yields (80–85%, Scheme 8, Method 3, Supporting Information).[19-24]



Scheme 8. One-pot synthesis of N^4–monosubstituted quinazoline-2,4-diamines

In order to explore the C2 selectivity of this method in the presence of quinazoline substrates with susceptible functional groups, we used ethyl 2-chloroquinazoline-4-carboxylate **9**, which possess an ethyl ester group at C4 position. Treatment of **9** under similar conditions provided the desired C2 amine **10** in lower yield (45-50%, Scheme 9). Interestingly, we were able to isolate the C2 azide **11** in 20% yield which supports the proposed mechanism shown in Scheme 7.

It is very evident that this one-pot approach carries many advantages compared to the other approaches used to synthesize N^4-monosubstituted-quinazolin-2,4-diamines. The conditions are milder and the reaction time is drastically reduced. Furthermore, the C2-azide intermediate can be isolated if needed in structure-activity relationship (SAR) studies. The significantly higher yields are attributed to straightforward workup step that involves simple filtration of the Pd/C catalyst, followed by removal of the ethanol/acetic acid in vacuo without the need for further purification using column chromatography. Importantly, the reaction can be carried out to isolate C2-azides in the presence of susceptible functional groups such as C4 esters. Some limitations to utilizing this approach, particularly the second step involving Pd/C based reduction, is that these conditions may not be suitable to halogen-containing quinazoline substrates which can potentially lead to dehalogenation during azide reduction.

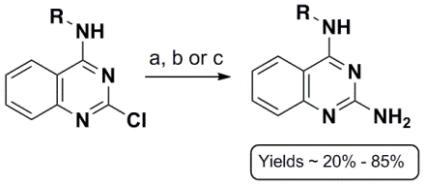


Scheme 9. One-pot synthesis of ethyl 2-aminoquinazoline-4-carboxylate (**10**)

Conclusion

In summary, we investigated three approaches (summarized in Table 1) toward the synthesis of N^4,N^2-disubstituted quinazolin-2,4-diamines. Among them, the one-pot reaction via an azide intermediate provided very good yields (80–85%) and was identified as a mild and efficient method to prepare novel quinazoline-based compound libraries for drug screening.

Table 1. Summary of three potential routes to C2-amine-based quinazolines



Parameters	a. Copper-Catalyzed	b. Urea-based Hydrolysis	c. Azide reduction
Time	24 h	24 h	4 h
Temp. (°C)	130 or 100	160	90, reflux
Setup	Sealed pressure vial	Sealed pressure vial	RB flask
Solvent	Dioxane or Ethylene glycol	Dioxane	Ethanol and Glacial acetic acid
Amine source	Aq. Ammonia	Urea	Sodium azide
Purification	Column	Column	No column
% Yield	20–25	50–55	80–85
Workup	Elaborate	Easy	Easy

Acknowledgements

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Supplementary data

Supplementary data associated with this article including complete experimental procedures and product characterization data can be found, in the online version, at http://

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