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A Simple and Efficient Approach for the Synthesis of 2-Aminated Quinazoline Derivatives via Metal Free Oxidative Annulation

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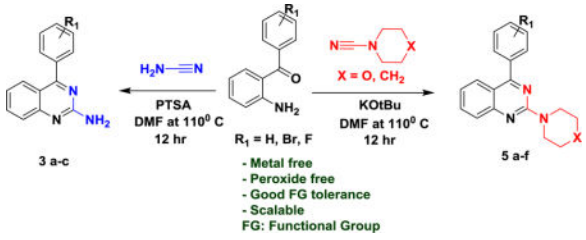
Abstract

A simple and efficient approach for the synthesis of 2-aminoquinazoline derivatives in moderate to good yields. This reaction employs mild reaction conditions, is metal-free and utilizes readily available starting materials making it a more viable reaction for the scale up synthesis and ligand diversity. Notably, this methodology allows the synthesis of 2-aminoquinazolines using a free amine or cyclic amine enabling structural diversity and good atom economy.

Graphical abstract



Keywords

Quinazolines; Oxidative Annulation; Metal Free; Heteroaromatic

Designing a simple and efficient chemical reaction sequence that provides maximum structural diversity with few synthetic steps to yield small heterocyclic molecules with interesting biological function is a challenge to both medicinal and synthetic chemists.[1] As a representative of heterocyclic molecules, 2-aminoquinazolines are drug-like scaffolds and exhibit wide range of biological activities such as potent, selective, and orally efficacious inhibitors of receptor tyrosine kinase c-Kit, represented by the 5,6-dihydro-pyridinone **1**[2]

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Supplementary data

General experimental procedures, Mass and NMR spectral data for compounds are provided in supporting information.

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along with a 2¢-deoxynucleotide analogue **2**[3] (figure 1). The 2-aminoquinazoline and quinazoline scaffold is also represented in FDA-approved pharmaceuticals including the antihypertensive agent Prazosin **(3)** and the anti-cancer agent Gefitinib **(4)** (figure 1).

Diverse ranges of pharmacological activities of 2-aminoquinazoline derivatives have sparked considerable interest in their synthesis using versatile and scalable methods.[4–6] There are very few approaches that describe the construction of 2-aminoquinazolines (scheme 1). For example, 2-aminoquinazoline derivatives have been developed using arylboronic acids as a precursor (scheme 1, A).[4] In 2005, Mahajan reported a microwave-promoted synthesis of quinazolines from N-arylamidines and aldehydes (scheme 1, B).[5] Alternatively, the reaction of 2-halophenyl ketone with guanidine derivatives in the presence of copper catalyst yielded 2-aminoquinazoline derivatives (scheme 1, C).[6] These reactions suffer from harsh reaction conditions using microwaves, use of reactive metal catalysts and expensive boronated pre-functionalized starting materials, which limits ligand diversity and scale up processes.

Pandya *et al* have explored the metal catalyzed transformation of small heterocycles including the C-H functionalization.[7,8] Herein, we report a metal-free and simple reaction scheme for the synthesis of 2-aminated (primary and tertiary amines) quinazoline derivatives using readily available starting materials producing moderate to high yields. Our initial efforts commenced by designing unsubstituted 2-amino derivatives of the quinazoline scaffold using unsubstituted cynamide (1 eq.) and 2-aminobenzophenone (1eq.). To identify suitable reaction conditions, we started our investigation with PTSA (p-toluene sulfonic acid) (1 eq.) as a catalyst for the reaction in THF (table 1, entry 1). These conditions produced the desired product (**7a**) in moderate yields (61%). To our delight, the yield was increased to 75% when changing the solvent to DMF, also in the presence of PTSA (table 1, entry 2). Decreasing the reaction temperature to 70°C produced the desired product in a low yield (table 1, entry 5) and at room temperature the reaction did not produce product (table 1, entry 6). Notably, after basifying reaction conditions using KOtBu, the reaction produced moderate yields (table 1, entry 3 & 4).

The reaction of 4-morpholinecarbonitrile (1 eq.) with 2-aminobenzophenone (1eq.) produced a cyclic amine at the 2-position of the quinazoline core. To our surprise, the reaction gave good yield when KOtBu used over the PTSA. (table 2, entry 1 & 2).

With the optimized reaction conditions in hand, further exploration for the scope of substrate and functional group tolerance was explored. The reaction with strong electron withdrawing groups **(7b, 9b, 9e)** present on the aromatic ring of the acyl phenyl ring resulted in the good yield compared to weak electron withdrawing **(7c, 9c, 9f)** and unsubstituted aromatic ring **(7a, 9a, 9d)** shown in scheme 2.

Structure conformation of the synthesized compounds was confirmed by ^{1}H & ^{13}C NMR and mass spectrometry (supplemental information). Lastly, to dually confirm the synthesis of 2-aminoquinazolines, overnight evaporation of the compound **9e** dissolved in ethyl acetate and hexane (3:1) gave a single crystal for the x-ray analysis illustrated in figure 2.

Plausible reaction mechanism for 2-aminoquinazoline formation mediated by acid or base is shown in scheme 3. Weak acid PTSA carried out the protonation of the cyano group's

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nitrogen, which increases the electrophilic nature of the cyanamide carbon.[9] This allows the amine to attack the electrophilic carbon forming the amidine intermediate. This intermediate undergoes cyclization followed by elimination of a water molecule to produce the 2-aminoquinazoline. Conversely, base-mediated proton removal of the amine yields a strong nucleophile capable of reacting with the cyanamide carbon, followed by ring closure afforded product. In summary, acid increases cyanamide carbon electrophilicity, while base increases nucleophilicity, which is one of the key steps in the reaction kinetics.

In conclusion, we have developed a simple and efficient approach for the synthesis of 2-aminoquinazoline derivatives in moderate to good yields. The advantage of this reaction is its mild and metal free reaction conditions. This methodology allows the synthesis of a 2-aminoquinazoline core functionalized with a free amine as chemical handle for the further structural diversity generating a potentially biologically important compound library.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Metal-free reaction conditions for the synthesis of 2-aminoquinazolines
- Mild reaction conditions for the synthesis of 2-aminoquinazolines
- Functionalization of the biologically relevant quinazoline scaffold
- Scalable synthesis for 2-aminoquinazolines

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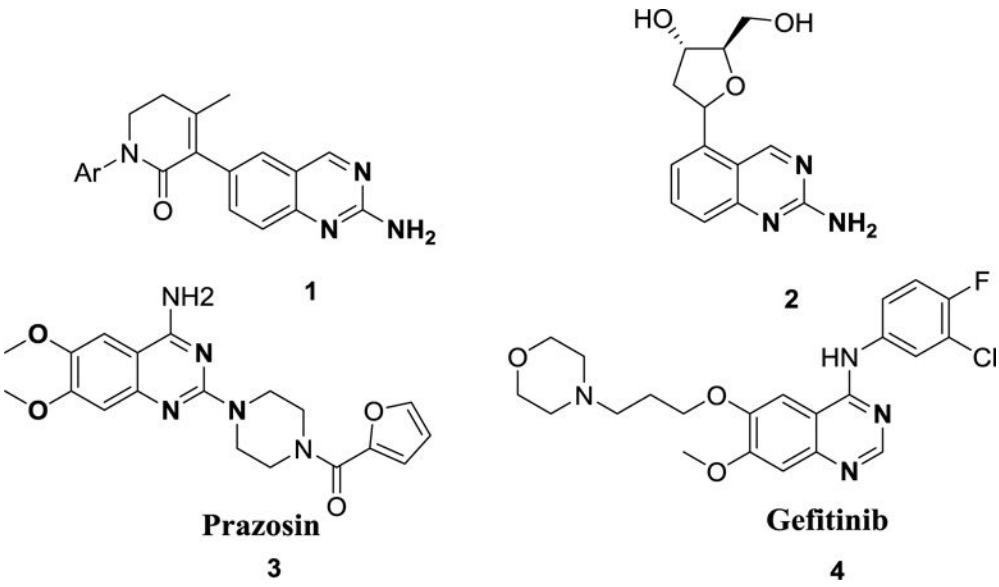

Figure 1.

Selected examples of tyrosine kinase receptor inhibitors (**1**), 2¢-deoxynucleotide analogue (**2**) and pharmaceutical drugs Prazosin (**3**) and Gefitinib (**4**), possessing the quinazoline scaffold.

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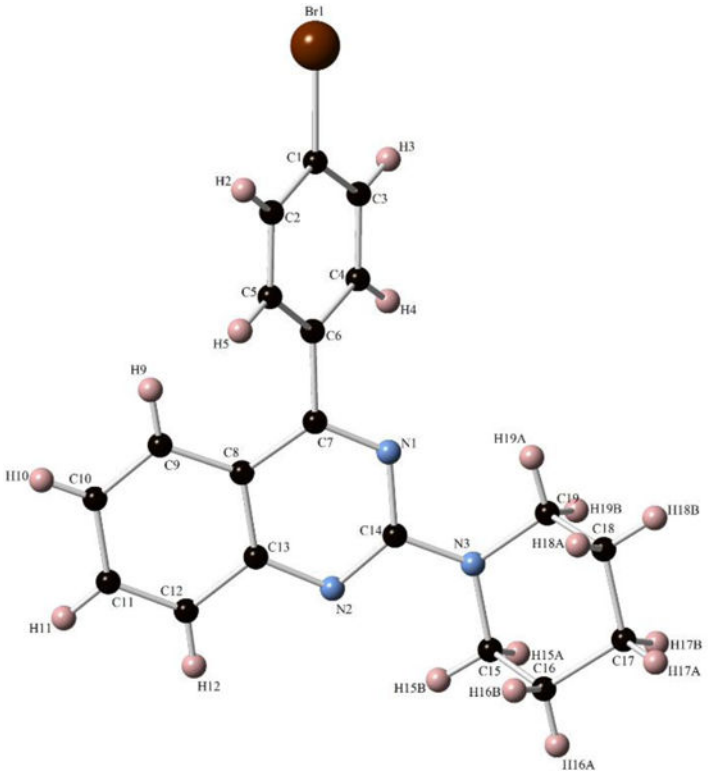
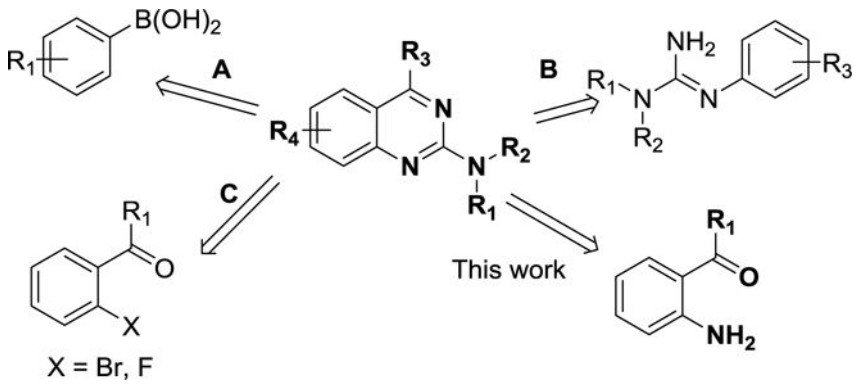


Figure 2.
X-ray crystal structure of 2-aminoquinazoline **9e**.



Scheme 1.
Retrosynthetic analysis of the 2-aminoquinazoline scaffold.

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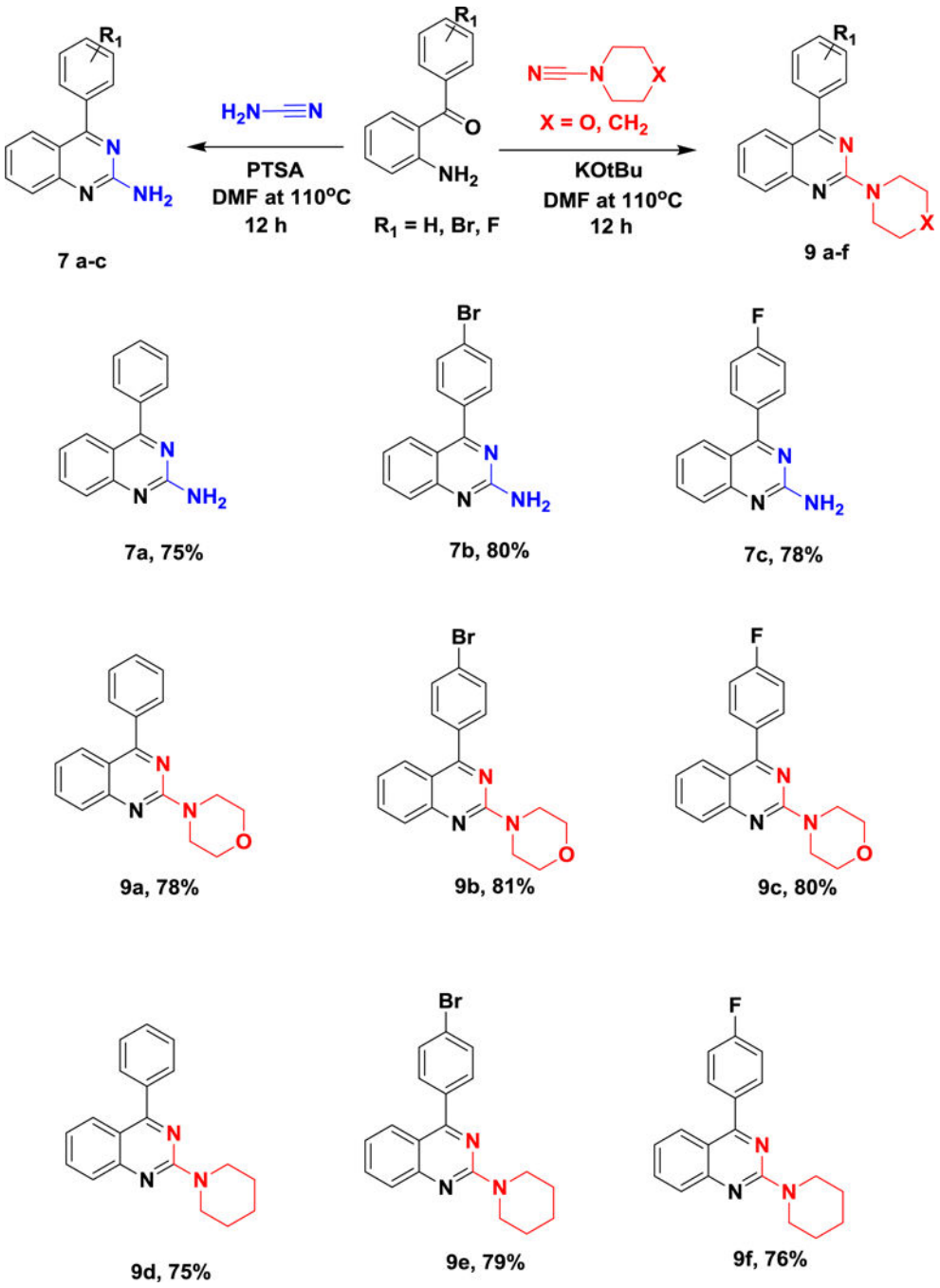

Scheme 2.

Substrate scope used in the synthesis of 2-aminoquinazoline derivatives.

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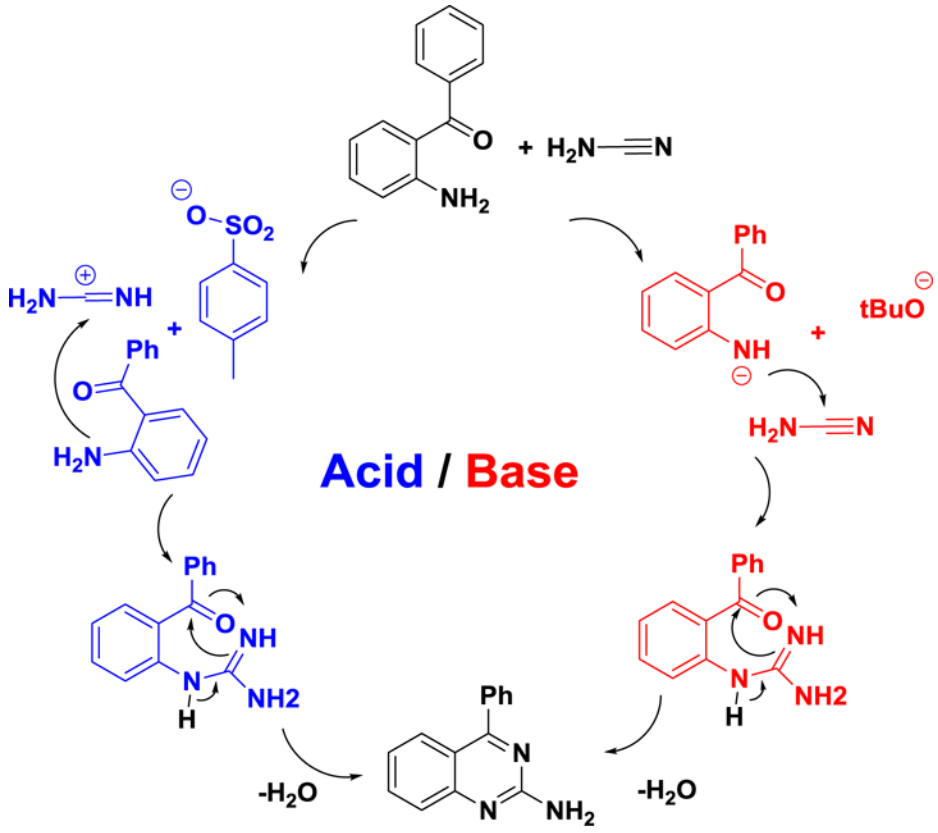

Scheme 3.
Plausible reaction mechanism for a metal free cascade cyclization.

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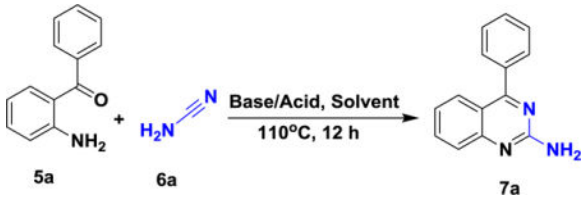
Table 1

Optimization of reaction conditions for the unsubstituted 2-aminoquinazoline derivatives.



5a 6a 7a

entry	acid/base	equivalent	solvent	yields (%)[c]
1	PTSA	1	THF	61
2	PTSA	1	DMF	75
3	KOtBu	0.5	DMF	55
4	KOtBu	1	DMF	65
5[a]	PTSA	1	DMF	8
6[b]	PTSA	1	DMF	0

[a] Reaction Carried out at 70° C.

[b] Reaction carried out at room temperature.

[c] Isolated yields (flash chromatography). PTSA: *para* toluene sulfonic acid

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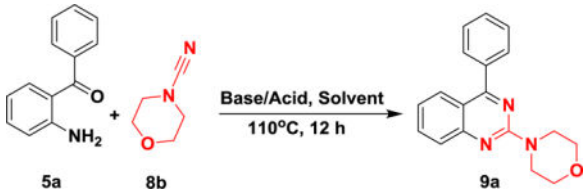
Table 2

Optimization of reaction conditions for substituted cyclic 2-aminoquinazoline derivatives.



entry	acid/base	equivalent	solvent	yields (%)[a]
1	PTSA	1	DMF	66
2	KOtBu	1	DMF	78

[a]Isolated Yields (Flash Chromatography).