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Base-catalyzed synthesis of quinazolines in aqueous medium

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ABSTRACT

An alternative green protocol and step economy for the synthesis of quinazoline has been developed. The reaction of readily available 2-aminobenzonitriles with various organometallic reagents led to *ortho*-aminoaryl N—H ketimine species. The subsequent base catalysed N—C bond formation with various isothiocyanates afforded quinazoline scaffolds in aqueous medium. The salient features of this protocol are use of readily available inexpensive precursors, water as a green environmentally benign solvent, short reaction time, operational simplicity, easy workup procedure and good functional group tolerance.

Significant attention has been attached to the study and development of organic transformations in aqueous media in last two decades [1]. A reaction is considered ideal if it proceeds in a green reaction medium in the presence of benign reagents without the use of hazardous organic solvents, metal complexes. Furthermore the development of environmentally friendly catalytic processes is currently one of the greatest challenges for the chemists [2]. In this regard, development of a green methodology utilizing water as a green, non-toxic and non-flammable solvent has become one of the prime goals in sustainable chemistry, hence large number of environmentally friendly novel protocols have been developed over the past two decades [1].

Quinazolines are privileged *N*-heterocyclic structure motifs that are well-known for their wide range of utility in life-saving synthetic pharmaceutical [3], these scaffolds are associated with anticancer activity for example **Gefitinib** is a tyrosine kinase inhibitor drug, like gefitinib, **Erlotinib** also receptor tyrosine kinase inhibitor which act on the (EGRF), while **Lapatinib** (**1**) is an U.S. FDA approved drug used for the treatment of breast cancer and other solid tumours. **Alfuzosin** (**2**) is used for the treatment of benign prostatic hyperplasia and **Doxazosin** (**3**) is used for the treatment of prostate enlargement and high blood pressure, and also this scaffold is associated with anti-hypertensive, anti-malarial, anti-bacterial anti-inflammatory, anti-tuberculosis properties (Fig. 1) [3].

Due to diverse range of pharmacological activities of the substituted 2-aminoquinazoline derivatives, considerable attention was drawn towards their synthesis and consequently various synthetic methods were also reported for their preparation [4]. Few approaches reported for the construction of substituted 2-aminoquinazolines are: for example Mahajan et al. reported the synthesis of 2-*sec*-amines quinazolines [5] from condensation reaction of guanidines with aldehydes, Zhao et al. obtained the same from 2-bromobenzaldehyde and guanidines as the starting materials and copper(I) iodide as a catalyst [6] and very recently Zhu co-workers disclosed the formation of quinazoline by palladium-catalyzed intramolecular C—H amidination [7] with isonitriles and *N*-arylamidines and, Neuville and his group also developed a method for the construction of 2-aminoquinazolines scaffolds from boronic acids, amines and cyanamides as a starting precursors [8]. The above maintained synthetic protocols are among the few fruitful strategies. However, large number of existing protocols encounter several disadvantages, like risky starting materials, expensive transition metal complexes, additives, oxidants, multistep synthesis, ligands and toxic solvents. Hence development of economical and green strategies is needed for the construction of substituted quinazolines derivatives.

Previously our group developed a metal free synthesis of *N*,4-disubstituted quinazoline as shown in (Scheme 1 Eq. (1)), these synthesis rely on the reaction of isothiocyanates with 2-amino-benzophenone and ammonium acetate to furnish the corresponding product catalysed by iodine [9]. In general 2-amino-arylphenones were prepared from starting precursors 2-aminobenzonitriles and organometallic reagents initially led to the formation of *ortho*-aminoketimine, followed by acid hydrolysis of this intermediate [9,10], where as it requires an additional ammonium source for the quinazoline ring formation in our previ-

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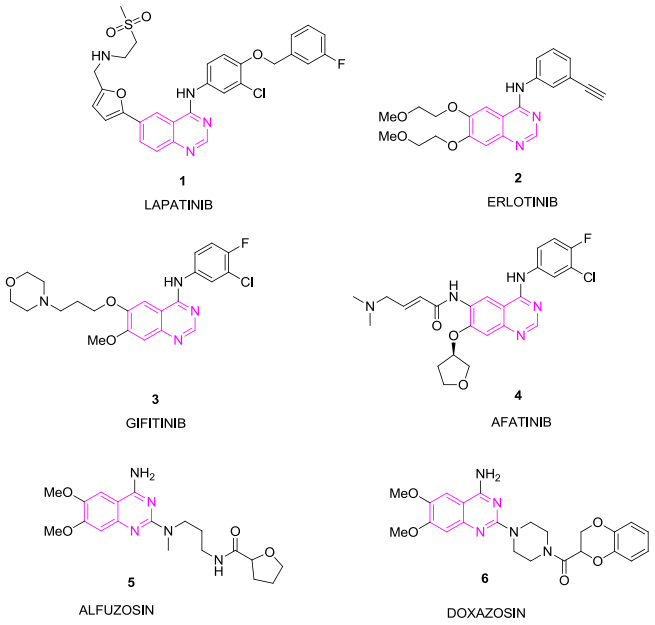
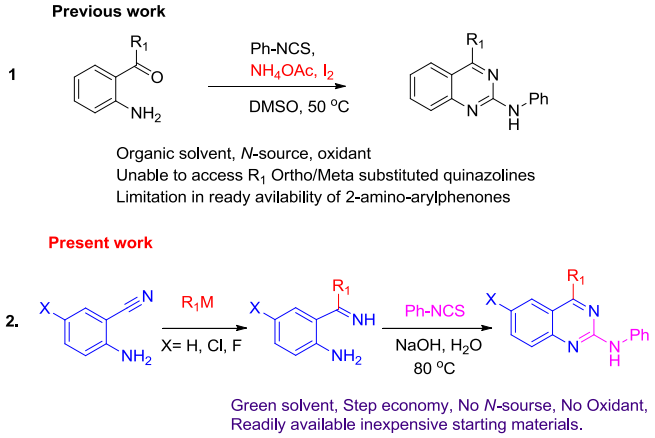


Fig. 1. Quinazolines as medicinal agents.

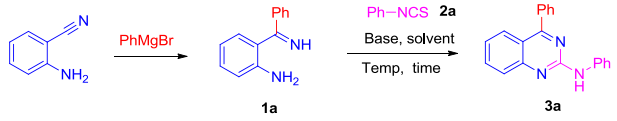


Scheme 1. Synthesis of quinazolines.

ous method. It was also observed that *meta* and *ortho* substituted 2-aminoaryl ketones did not tolerate the reaction conditions due to steric effect [9]. To overcome this limitation and taking into account the step and atom economy, we envisioned that a direct synthesis of quinazoline from the *ortho*-aminoketimine species should be a viable and attractive approach to this important class of compounds, further more we discovered that such transformations could be facilitated via a transition metal-free catalyzed, base promoted and using water as a environmentally benign solvent in our strategy. Therefore the present protocol relies on generation of *ortho*-aminoketimine species and its subsequent usage in the formation of quinazolines. In continuation with previous work, herein we report a novel, step economy and environmentally benign protocol by using sodium hydroxide as a base in water for the construction of *N*,4-disubstituted quinazolines (Scheme 1).

ortho-Aminoketimine was prepared from the reaction of 2-aminobenzonitrile with aryl magnesium bromide [10,11]. Then the reaction of *ortho*-aminoketimine (**1a**) and phenylisothiocyanate (**2a**) with NaOH (2.0 equiv) in DMSO stirred at room temperature for 12 h, provided the desired product quinazoline **3a** in 31% yield (Table 1, entry 1). When the reaction temperature was

Table 1
Optimization of the reaction conditions.[a,b]



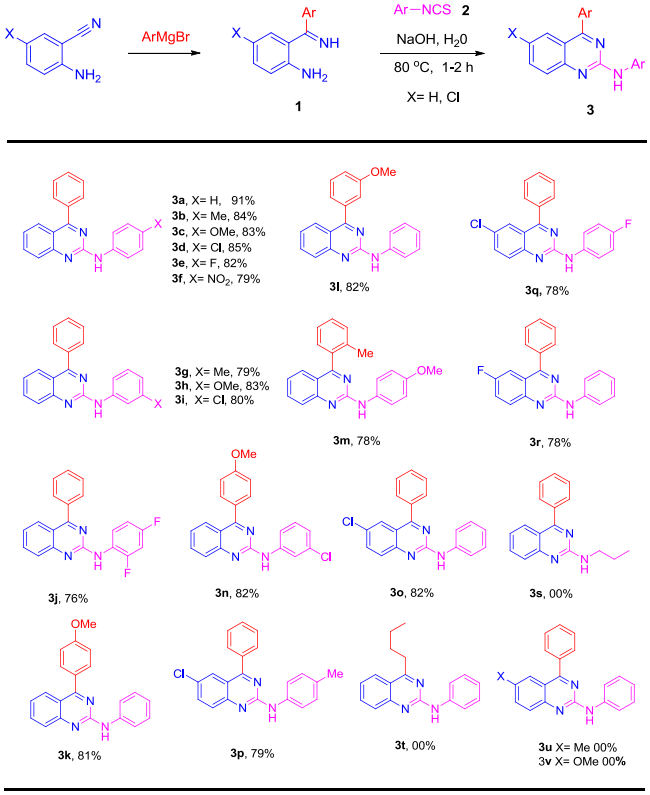
Entry	Solvent	Base (equiv)	Temp	Time	Yield[b] (%)
1	DMSO	NaOH (2.0)	rt	12 h	31
2	DMSO	NaOH (2.0)	60	8 h	52
3	CH_3CN	NaOH (2.0)	60	9 h	39
4	Dioxane	NaOH (2.0)	60	8 h	42
5	DMF	NaOH (2.0)	60	3 h	61
6	H_2O	NaOH (2.0)	60	2 h	71
7	H_2O	NaOH (2.0)	80	2 h	82
8	H_2O	KOH (2.0)	80	2 h	69
9	H_2O	K_2CO_3 (2.0)	80	2 h	42
10	H_2O	Cs_2CO_3 (2.0)	80	2 h	39
11	H_2O	NaOH (3.0)	80	2 h	91
12	H_2O	NaOH (4.0)	80	2 h	91

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (x equiv.) and solvent (3 mL) at 80 °C for 2 h.
[b] Isolated yield.

raised to 60 °C, the reaction was completed within 8 h, however moderate yield (52%) was observed. To improve the yields, various solvents such as CH_3CN, DMF and dioxane were screened, among all DMF provide better yields within 3 h under same reaction conditions (Table 1, entries 2–5). Interestingly the reaction proceeds efficiently under the polar solvent. Considering the sustainable chemistry we invoked water as a solvent and to our delight the reaction was proceeded quickly and reaction yield was observed 71%, (Table 1 entry 6). Based on the solvent screening H_2O was recognized as a better solvent in terms of yields and reaction time [12]. Subsequently we increased the temperature to 80 °C the reaction was completed within 2 h with 82% of yield (Table 1 entry 7). Then we investigated different bases and their influence on the reaction. Thus various bases like K_2CO_3, Cs_2CO_3 and KOH were tested among all NaOH was observed to be more effective (Table 1, entries 8–10). The equivalent of NaOH was also studied, raising the quantity of NaOH from 2.0 equiv to 3.0 equiv. provided the product **3a** in 91% of yield (Tabel 1, entry 11), however further raising the NaOH equivalent 3.0–4.0 did not improve the yields [12]. Thus the optimized reaction conditions for this reaction are *ortho*-aminoketimine (1.0 mmol), isothiocyanate (1.0 mmol) and NaOH (3.0 equiv) in water at 80 °C in 1–2 h, and hence chosen for the synthesis of *N*,4-disubstituted quinazolines.

With suitable reaction conditions in hand (Table 1, entry 11), the scope and the electronic nature and their positions on the phenylisothiocyanate was investigated, and the results are summarized in Scheme 2. A series of *para*-substituted electronic-withdrawing and electronic-donating phenylisothiocyanates like methyl, methoxy, chloro, fluoro and nitro groups were well tolerated and gave the corresponding *N*,4-disubstituted quinazoline (**3a**-**3f**) in good to excelent yields, subsequently *meta*-substituted phenylisothiocyanate like methyl, methoxy and chloro were also examined, when the reaction proceed smoothly and offered the corresponding products (**3g**-**3i**) in good to excellent yields. The disubstituted isothiocyanate also well tolerated under the reaction conditions and provided corresponding product **3j** in good yields, demonstrating that substituents on phenylisothiocyanates do not influence the outcome of the reaction.

To further examine the different types of *ortho*-aminoketimines (**1**), *ortho*, *meta* and *para* substituents present on the phenyl ring, it

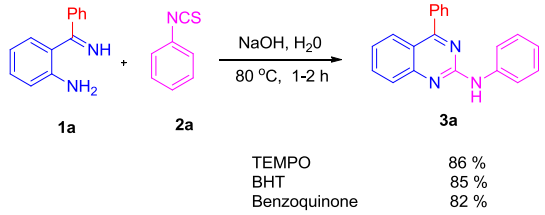


Scheme 2. Synthesis of substituted quinazolines.[a,b] [a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (3 equiv.) and solvent (3 mL) at 80 °C for 2 h. [b]Isolated yield.

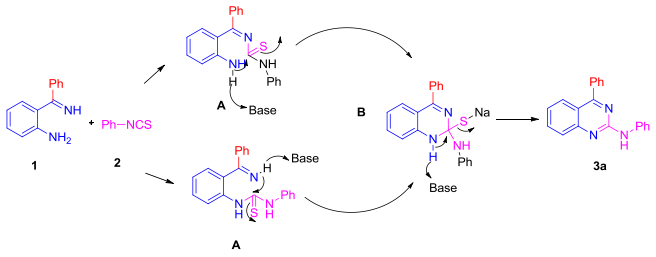
was found that they were well tolerated under the standard conditions and led to the formation of corresponding products in good to excellent yields (**3k-3n**). The reaction also tolerated chloro and fluoro substituents on *ortho*-aminoketimines (**1**) with different substituted phenylisothiocyanates to afford the corresponding products (**3o-3r**) in excellent yields. However, alkyl isothiocyanate and *ortho*-aminoalkylketamine were not tolerated under the standard conditions (**3s-3t**). Also, both 2-(imino(phenyl)methyl)-4-methylaniline and 4-methoxy bearing substrate failed to yield the corresponding products (**3u-3v**).

For the better understanding of reaction mechanism, firstly the involvement of radical intermediate in the reaction was checked by a series of control experiments when the reaction was performed with starting precursors **1a** with **2a** under standard condition in the presence of radical quenchers TEMO, benzoquinone and BHT, we found that the reaction was unaffected, indicating that the reaction proceeds through ionic pathway during the course of the reaction (Scheme 3).

Based on the above results and from the previous literature data and our own previous work [13,14] we propose a possible reaction mechanism for the formation of quinazoline as outlined below Scheme 4.



Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism.

As described in Scheme 4, firstly, *ortho*-aminoketimine **1a** reacts with phenylisothiocyanate **2a** to offer the thiourea intermediate **A**, subsequently intramolecular nucleophilic attack of the amine or imine group on the thiocarbonyl carbon gave the cyclised product **B** via N—C bond formation. The intermediate **B** on aromatization offered **3a** with subsequently generation of **S** and H_2O.

In conclusion, we have successfully developed a step economy and sustainable synthetic methodology for the construction of highly valuable substituted quinazolines by using starting precursor 2-aminobenzonitrile, Grignard reagent, phenylisothiocyanate, NaOH and H_2O as a solvent at 80 °C. This methodology possess several advantages like transition-metal free protocol, use of readily available and inexpensive sodium hydroxide as a base, use of water as a green and renewable solvent with step economy. We strongly believe that this methodology will useful for the construction of highly valuable quinazolines in an economical and sustainable manner.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151186.

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