Organic & Biomolecular Chemistry

Accepted Manuscript

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DOI: 10.1039/C9OB00349E

COMMUNICATION

I_2-Catalyzed Oxidative Synthesis of *N*,4-Disubstituted Quinazolines and Quinazoline Oxides

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A easy and efficient approach to the synthesis of *N*,4-disubstituted quinazoline-2-amine and oxides is described, this transformation proceeds smoothly in the presence of molecular iodine. The metal-free protocol presented here is insensitive to air moisture and operationally simple. This versatile and synthetic methodology is broadly applicable to a variety of N,4-disubstituted quinazoline-2-amine and oxides and synthesized in good to excellent yields starting from readily available inexpensive precursors.

Quinazoline and their derivatives represent a medicinally and pharmaceutically important class of heterocyclic motifs that are found as the core structural skeletons in a variety of drug molecules. This scaffold is associated with anticancer, anti-tuberculosis, anti-hypertensive, antibacterial, anti-inflammatory, and anti-malarial properties (Figure 1).[1] Therefore, the development of novel synthetic methods for quinazolines and their derivatives has gained considerable attention from chemists in a wide range over the past decade.[2-5] Among the family of Quinazolines, 2,4-disubstituted quinazolin-2-amine/N,4-disubstituted quinazoline 3-oxide derivatives received particular attention because of their potential pharmacological activity. The synthesis of such compounds remains challenging, wherein multiple steps, high temperature transition metals are routinely required and the overall efficiency of these multistep syntheses is frequently unsatisfactory.[6a,6b,6c] The most common approach for the synthesis of these scaffolds were nucleophilic substitution reactions of aryl or alkyl amines with 2-chloroquinazolines, Qiang Zhu *et al* reported the synthesis of 4-amino-2-substituted quinozoline by using *N*-arylamidines and isonitriles via palladium catalyzed intramolecular C-H amidination.[7] Also Neuville *et al* reported copper-promoted three component synthesis of 2-aminoquinazolines involving cyanamides, arylboronic acids and amines.[8] Recently, Swanth and co-workers reported synthesis of quinazoline-3-oxide via a palladium catalyzed azide-isocyanide coupling/cyclocondensation reaction.[9] Philippe Ratel *et al* obtained quinazoline-3-oxide over two steps from ethoxycarbonyl isothiocyanate with the amino oximes in EtOAc which offered thiourea followed by ethanol reflux.[10] However many of the reported methodologies encounter drawbacks such as use of expensive transition metals catalyst, bases and oxidants. Thus it is desirable to develop an efficient protocol for the synthesis of *N*,4-disubstituted quinazolines using readily available inexpensive starting materials.

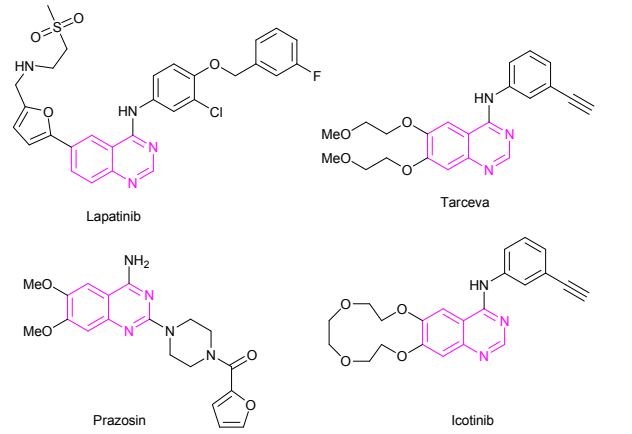

Figure 1. Selected examples of compounds containing Quinazoline moiety

On the other hand, iodine-mediated approaches were found to be highly efficient alternatives for transition metal catalysts in N-C, N-N, N-S bond formation reactions because iodine is low in cost, readily available, and nontoxic.[11] Recently we reported a metal-free synthesis of 4,5-disubstituted/N-fused 3-amino-1,2,4-triazoles and 3-substituted 5-amino-1,2,4-thiazole by utilising molecular iodine.[12] In continuation of this program, herein we report the development of one-pot three component reaction for functionalized quinazoline/oxide derivatives via reactions of isothiocyanate with 2-amino-benzophenone and ammoniumacetate/(2-aminophenyl)(phenyl)methanone oxime to furnish the corresponding *N*,4-disubstituted quinazolines and quinazoline oxides catalyzed by iodine. This reaction leads to an excellent yields of products in lesser time when carried out in DMSO at moderate or room temperature.

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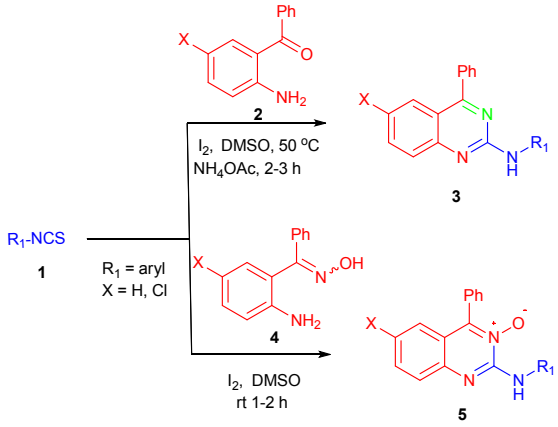
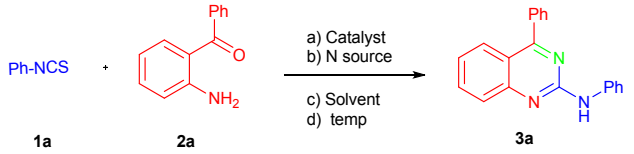
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme1. *N*,4-Disubstituted Quinazolin-2-Amine/4-aryl-2-(arylamino)quinazoline-3-oxide

Initially, we started the synthesis of *N*,4-diphenylquinazolin-2-amine by taking phenylisothiocyanate (**1a**), 2-aminobenzophenone (**2a**), and ammonium acetate as a nitrogen source in presence of I_2 (0.3 equiv) in DMSO and stirred the mixture at room temperature (25 °C) for 8 h to provide the desired product **3a** in 16% yield. Encouraged by this result, further increase in iodine resulted in moderate yields (Table 1, entries 2 and 3). When the reaction was performed at elevated temperature (50 °C) a complete conversion of starting material to desired product (**3a**, 45%) was observed in 3 h. To improve the reaction yields, we screened various solvents (CH_3CN, DMF and 1,4-Dioxane) under the same conditions and the results are summarized in Table 1. Next, we studied the amount of iodine, raising the quantity of iodine from 0.3 equiv to 0.5 equiv provided the product **3a** in 95% yield (Table 1, entry 8). Further increase did not improve the yield. Subsequently other nitrogen sources were also studied such as urea, $(NH_4)_2CO_3$, NH_4Cl and NH_4HCO_3 which showed a lower yield of **3a** (Table 1, entries 10-13).[13] Then, NH_4OAc was identified as the most effective one affording superior results. Accordingly the optimized reaction conditions are: isothiocyanate (1.0 mmol), 2-aminobenzophenone (1.0 mmol), ammonium acetate (6.0 equiv) and iodine (0.5 equiv) in DMSO at 50 °C for the synthesis of *N*,4-disubstituted quinazolin-2-amine **3a.**

Table 1. Optimization of the reaction conditions[a]

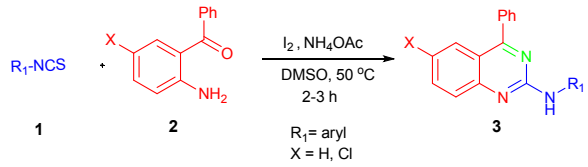


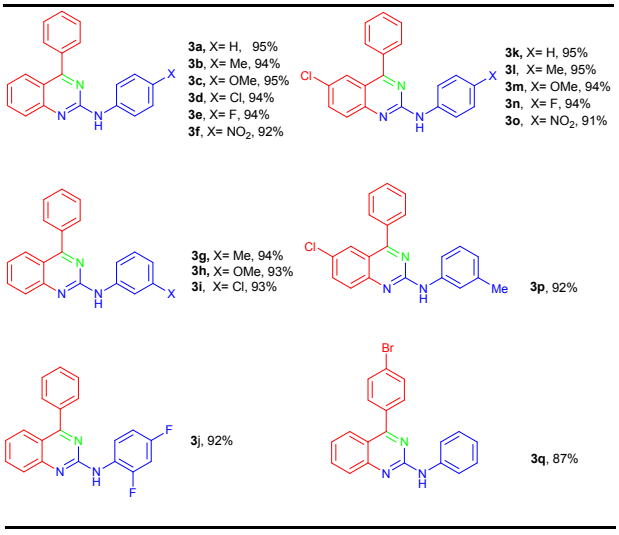
Entry	Solvent	Catalyst	N source (6.0 equiv)	Temperature (°C)	Yield (%)[b]
1	DMSO	I_2 (0.3)	NH_4OAc	rt	16
2	DMSO	I_2 (0.5)	NH_4OAc	rt	43
3	DMSO	I_2 (1.0)	NH_4OAc	rt	49
4	DMSO	I_2 (0.3)	NH_4OAc	50	45
5	CH_3CN	I_2 (0.3)	NH_4OAc	50	40
6	DMF	I_2 (0.3)	NH_4OAc	50	35
7	1,4-Dioxane	I_2 (0.3)	NH_4OAc	50	25
8	DMSO	I_2 (0.5)	NH_4OAc	50	95
9	DMSO	I_2 (1.0)	NH_4OAc	75	95
10	DMSO	I_2 (0.5)	Urea	50	trace
11	DMSO	I_2 (0.5)	$(NH_4)_2CO_3$	50	15
12	DMSO	I_2 (0.5)	NH_4Cl	50	10
13	DMSO	I_2 (0.5)	NH_4HCO_3	50	20

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol) and catalyst (x equiv) NH_4OAc (6.0 equiv) in solvent (3 mL) at 50 °C temperature for 3 h. [b]Isolated yield.

With the optimized reaction conditions in hand, we next explored the scope and generality of the reaction using wide variety of isothiocyanates (**1**) under the established reaction conditions and the results are summarized in Scheme 2. The results indicated that a wide range of substituted groups, such as methyl, methoxy, chloro, fluoro and nitro presenting on isothiocyanate, were well tolerated under the standard conditions and offered the corresponding *N*,4-disubstituted quinazolin-2-amine (**3a**-**3i**) in good to excellent yields. The 2,4-difluorophenyl isothiocyanate was also applied in the reaction successfully to provide the corresponding **3j** in 92% yield. The effect of substituent on 2-aminobenzophenone has also been studied in the presence of an electron-withdrawing group at 5th position of 2-aminobenzophenone. The results disclosed that the reactions proceeded smoothly and well tolerated a wide range of functional groups, including methyl, methoxy, chloro, fluoro, and nitro groups on isothicyanate, to obtain the corresponding products (**3k**-**3p**) in good to excellent yields. (2-Aminophenyl)(4-bromophenyl)methanone with phenyl isothiocyanate (**1a**) gave the desired product **3q** in 87 % yield. Use of either alkyl isothiocyanates or 2-aminophenyl alkyl ketones did not give the desired products. Also, meta/ortho-substituted aryl ketone substrates did not give the products.

Scheme 2. Synthesis of *N*,4-Disubstituted Quinazolin-2-Amines[a,b]

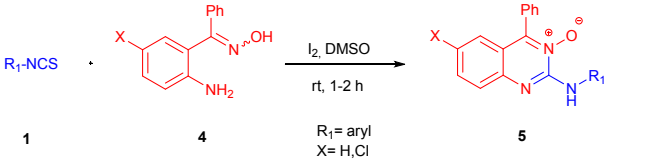


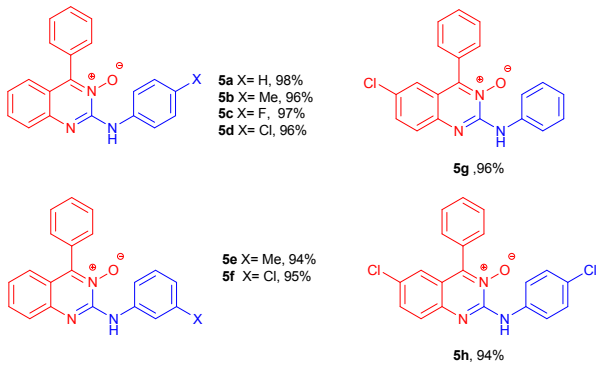


[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), ammonium acetate (6.0 equiv) and iodine (0.5 equiv) in DMSO at 50 ^{0}C for 2-3 h. [b]Isolated yield

With consistent results in hand, we replaced the 2-aminobenzophenone (**2**) with (2-aminophenyl)(phenyl)methanone oxime[14] (**4**) in the presence of I_2 (0.5 equiv) in DMSO at room temperature for 2 h, to obtain 4-phenyl-2-(phenylamino)quinazoline 3-oxide (**5a**, 95% yield) instead of expected *N*,5-diphenylbenzo[d][1,2,6]oxadiazepin-2-amine. Further we investigated the substrate scope of phenyl isothiocyanate (Scheme 3). In general, phenyl isothicyanate (**1**) bearing both electron-donating and electron-withdrawing groups on the benzene ring worked well to deliver the desired products (**5a**-**5f**) in good to excellent yields. In addition, electron withdrawing substrate (2-amino-5-chlorophenyl)(phenyl)methanone oxime(**4**) still had good reactivity, to afford the corresponding products (**5g** and **5h**) in excellent yields. Interestingly a mixture or *E* and *Z*-oximes (**4**) can be used as starting materials and can be effectively converted into products, without any significant effect on reaction time or yield.

Scheme 3. Synthesis of the *N*,4-Disubstituted Quinazoline 3-oxide[a b]

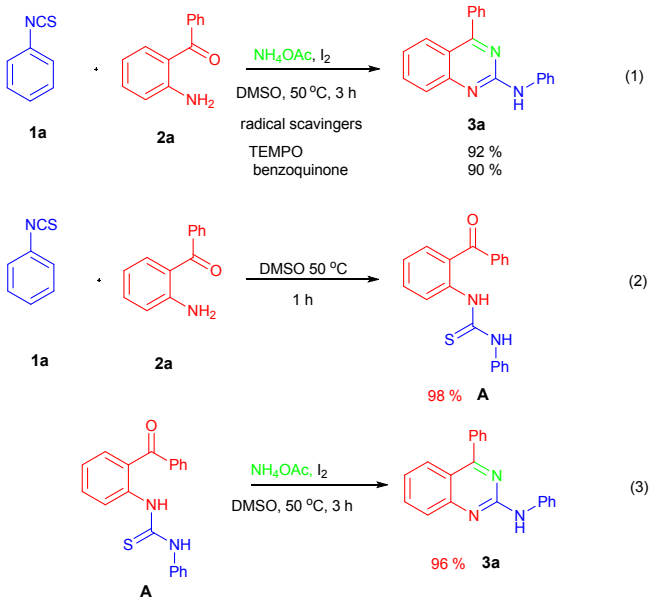




[a]Reaction conditions: **1** (1.0 mmol), **4** (1.0 mmol) and iodine (0.5 equiv) in DMSO at rt for 2-3 h. [b]Isolated yields

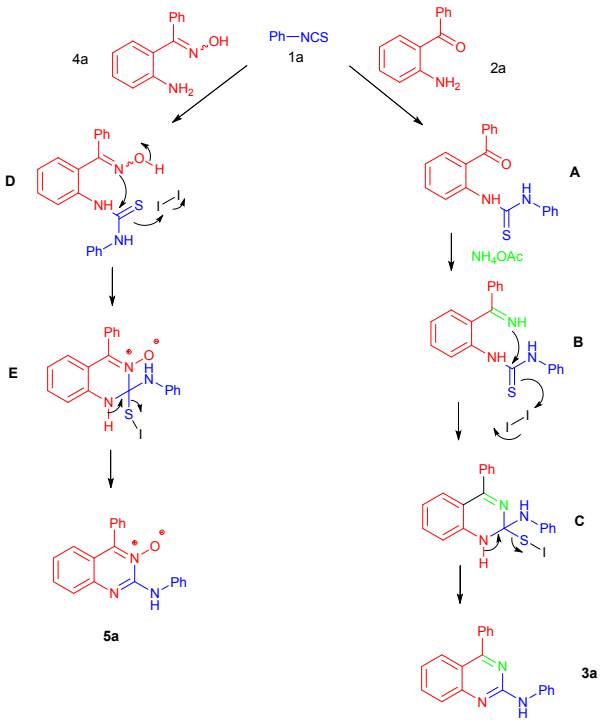
A series of control experiments was subsequently carried out to develop a deeper understanding of the reaction mechanism (Scheme 4). To check the involvement of radical intermediates in the reaction, under the standard reaction condition even in presence of TEMPO, benzoquinone, gave the corresponding compound **3a** in 92 and 90% yields, respectively (Scheme 4, eq 1), indicating the non-involvement of radicals during the course of the reaction. Next, we isolated the thiourea intermediate (**A**), by conducting the reaction of **1a** with 2-aminobenzophenone, whose structure was confirmed by ^{1}H, ^{13}C and HRMS (Scheme 5, eq 2). Under the standard reaction conditions intermediate **A** gave **3a**, indicating that **A** might be the intermediate for this transformation (Scheme 4, eq 3).

Scheme 4. Control experiments



On the basis of the above experimental results and reports in the literature,[9,12,13,16] we proposed the possible reaction mechanism for the formation of *N*,4-disubstituted quinazolin-2-amine/ *N*,4-disubstituted quinazoline-3-oxide as shown in Scheme 5.

Scheme 5. Proposed reaction mechanism



Initially, **1a** condensed with **2a** to afford thiourea intermediate **A**. Next, intermediate **A** reacts with NH_4OAc to give imine intermediate **B**, followed by intramolecular attack of the imine NH group onto the thiocarbonyl carbon with concomitant trapping of the S anion to afford the cyclised product **C.** Intermediate **C** on aromatization affords **3a** with subsequently generation of S and HI. Similarly, when **1a** condensed with **4a** gives thiourea intermediate **D** which leads to the formation of cyclised **E** via N-C and S-I bond formation. Upon aromatization of **E** with the generation of HI and S affords the desired product **5a**.

Conclusions

In summary, we have developed a new strategy for the constructing of *N*,4-disubstituted quinazolin-2-amine/4-aryl-2-(arylamino)quinazoline- 3-oxide from isothiocyanate, 2-amino benzophenone and (2-aminophenyl)(phenyl)methanone oxime under iodine catalysis. This methodology possesses several advantages, such as metal free protocol, the use of molecular iodine and readily available isothioctanates, 2-amino benzophenones and ammonium acetates. We believe that this methodology will find useful application for the synthesis of valuable quinazolines/quinazoline oxides in economical manner.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

The author J. N thank the UGC, New Delhi for financial support in the form of fellowships.

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