Radical-Nucleophilicity Controlled Regiodivergent C-3 vs C-7 Functionalization of Quinoxalin-2(1H)-ones

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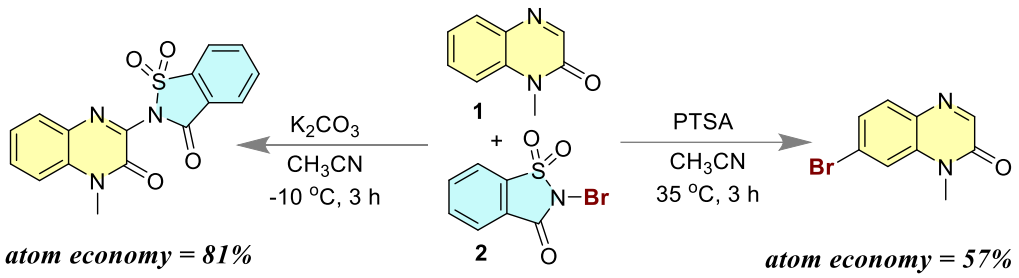
GRAPHIC FOR TOC



ABSTRACT

Here in this article, we have addressed how radical nucleophilicity and temperature controlled the regiodiversity (C-3 *vs* C-7) of quinoxalin-2(1*H*)-one. Following the acquisition of the diversity product, PTSA and potassium carbonate were added within the reaction vessel to further address the selectivity issue for the same methods. And we encompassed an easy-to-follow guide explaining how to obtain 7-bromo-1-methylquinoxalin-2(1H)-one and 2-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide using 1-methylquinoxalin-2(1H)-one and 2-bromobenzo[d]isothiazol-3(2H)-one 1,1-dioxide in acetonitrile solvent.

KEYWORDS

Quinoxalin-2(1*H*)-one; C-3 vs. C-7 Regioselectivity; Aromatic halogenation; Temperature controlled; Imidyl radical

INTRODUCTION

Modern organic synthesis has been influenced by discovery of sustainable and effective process for the production of C-C,[1-2] C-N,[3-4] and C-heteroatom bonds.[5-6] The 20th century witnessed the development of numerous novel synthetic transformations that addressed step economy, selectivity, and sustainability.[7] Many novel radical reaction that has shown significant synthetic potential have been introduced in the recent few decades.[8] Furthermore, both biological science and material science more specifically polymer science have made substantial use of radical chemistry.[9] Recently, radical reactions are now frequently considered and utilised in contemporary organic syntheses as the advantages of radical chemistry become more widely acknowledged and the conduction of mild and selective radical transformation has received more attention in the fields of photochemistry and electrochemistry.[10-17] These developments have been made possible by growing understanding of the key variable that control radical process, including radical polarity, bond dissociation energy (BDEs).[18]

The current difficulty in synthesis is not so much finding novel, elementary reactions involving organic radicals, rather understanding how to carry out these reactions efficiently and selectively.[19]This entails figuring out how to effectively produce radicals, or trap the radicals.[20]The *N*-Br bond energy for NBSA is only 48 Kcal/mole, which is significantly lower than that of comparable bromine precursors such as NBS (62 Kcal/mole) or PNBS (60 Kcal/mole).[21] Furthermore, the amidyl free radical[22] in presence of PTSA was so substantially stabilized that it was unable to function as a nucleophile for the amination reaction.

Additionally, the bromine free radical is now completely free to react with quinoxalin-2(1H)-one to create 7-bromo-1-methylquinoxalin-2(1H)-one and inhibited to produce 2-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide.

Quinoxalin-2(1H)-one and its derivatives have extensive application in medicinal chemistry and the pharmaceutical industry[23]. Additionally, several quinoxalin-2(1H)-one derivatives have demonstrated promise as anticancer medicines by blocking enzymes or pathways that promote the proliferation of cancer cells. Since it targets particular biological[24] pathways or receptors linked to diseases, its structural characteristics make it a useful scaffold for creating and manufacturing novel medications. Since several derivatives have antibacterial[25] and antifungal properties, researchers are interested in using them to create novel antimicrobial drugs[26] as well. In material science, quinoxalin-2(1H)-one derivatives may also find utility in the creation of specific polymers or materials[27]. Because of its adaptability, quinoxalin-2(1H)-one may have its chemical and biological properties changed, which makes it a valuable substance for a range of applications in research and development across multiple scientific domains.

N-Bromosaccharin is useful halogenating reagent due to its stability, low cost and easy to handling. Without any additive, catalyst or oxidising agent breaking of *N*-X bond for direct aromatic halogenation reaction of heteroarenes is one of the most challenging tasks in organic chemistry. On that respect, Nishii and group reported aromatic halogenation by combining NXS with Lewis acid to activate the *N*-X bond for the halogenation of heteroarenes using carborane catalyst.[28] Likewise under very mild condition Ritter and group reported halogenation of heteroarenes by using sulfonyl hypoiodites.[29] Also Csp^2–H imidation of

heterocyclic molecules is already well explored for making of Csp^2–N bonds via metal catalysed cross coupling reactions[30-34]. But doing the same job in mild condition like dissociation of *N*-Br bond from *N*-Bromosaccharin in halogenation and imidation via imidyl radicals without any additive or catalyst in one single pot is quite fascinating. This kind of mild reaction can occur depending on the bond energy of *N*-Br in different bromine precursors.The *N*-Br bond energy for NBSA is only 48 Kcal/mole, which is significantly lower than that of comparable bromine precursors such as NBS (62 Kcal/mole) or PNBS (60 Kcal/mole).[21] Another important function of the SO_2 group is to break the *N*-Br bond of 2-bromobenzo[d]isothiazol-3(2H)-one 1,1-dioxide (NBSA) in acetonitrile solvent and stabilize the imidyl radical that results after the breakage of the *N*-Br bond.

Difunctionalization[35-40] of bioactive compounds such as quinoxalin-2(1H)-one is of significant interest to chemists, particularly when it allows one building block to be transformed into two distinct functionalized molecules in one pot using a radical pathway. Over the past two decades, C-3 functionalization[41-46] has been well investigated and documented for quinoxalin-2(1H)-ones. On the other hand, there are only a few reports available on the C-7 functionalization of quinoxalin-2(1H)-ones.[47-48] However, there are not one single article that describes the functionalization of C-3 versus C-7 in one single pot. So, there are a lot of opportunities for improvement in that area. Our group recently published two articles on the C-3 functionalization of quinoxalin-2(1H)-ones: one is an oxygenation reaction[49] at C-3 using fukuzumi photocatalyst in blue LEDs, and the other is an atom transfer radical addition reaction (ATRA) at C-3 using the same photocatalyst and light source. Since our previous study, we have been eager to directly add a halogen atom to quinoxalin-2(1H)-ones but we were unable to achieve our goal.[2] Though we did report interesting atom transfer radical addition reactions. In the past, our group also published a series of C-X[50-51] and C-N[52-53] bond formation reaction,

which are extremely intriguing in the field of organic chemistry, particularly in the methodological area. Using palladium salt, ligand and PIDA Hartwig group reported one imidation reaction of benzene.[54] Here in this work, we have first investigated the temperature dependent one pot divergent product employing 1,1-dioxide, 2-Bromobenzo[d]isothiazol-3(2H)-one and 1-Methylquinoxalin-2(1H)-one in acetonitrile as optimized solvent.

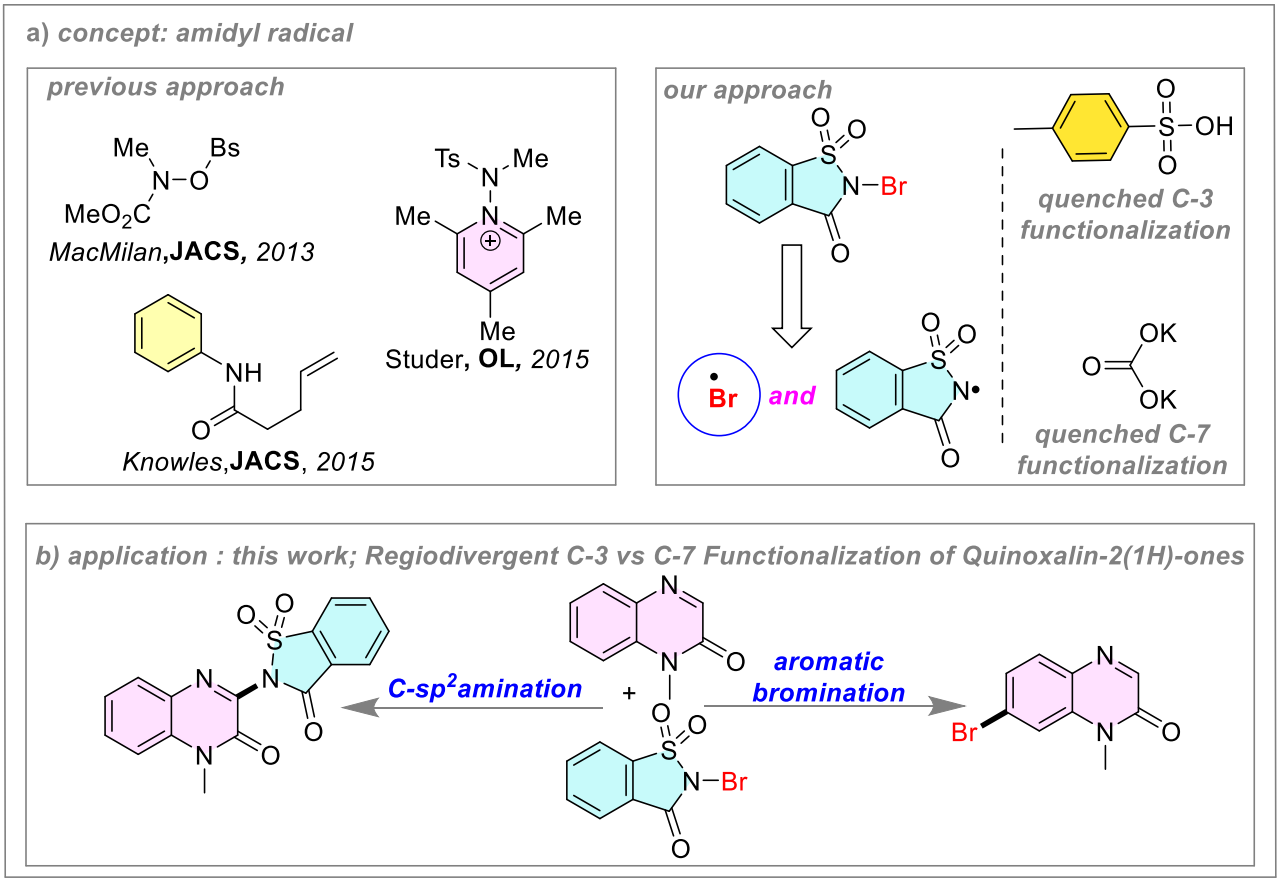


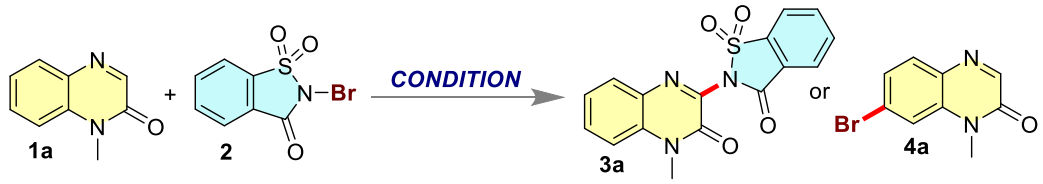
Figure 1. a) Concept behind the reaction b) Application: this work; Additive controlled selectivity and regiodivergent C-3 vs C-7 Functionalization of Quinoxalin-2(1H)-ones.

RESULTS AND DISCUSSION

The reaction conditions were optimized using quinoxalin-2(1H)-one 1a (0.3 mmol, 1.0 equiv) as the model substrate with N-bromosaccharin 2 (0.5 mmol, 1.5 equiv) in acetonitrile for 3 h to synthesize the C_3 aminated product **3a** and the C_7 brominated product **4a** (Table 1). The

temperature was adjusted to either -10 ºC or 35 ºC. In the absence of additives, **3a** and **4a** were obtained with yields of 35% and 65%, respectively (entry 1). At +35 ºC and with *p*-toluene sulfonic acid (*p*TSA) as an additive, **4a** was exclusively isolated with an 80% yield (entry 2). With *p*-toluic acid, only product **4a** was isolated in a 75% yield (entry 3). The reaction did not proceed in the absence of additives when using solvents such as DCE (entry 4), DCM (entry 5), acetone (entry 6), and HFIP (entry 9). In solvents like 1,4-dioxane (entry 7) and DMF (entry 8), a mixture of products was obtained with poor yields. At -10 ºC, the yields for **3a** and **4a** were 76% and 23%, respectively (entry 10). Notably, **3a** was exclusively obtained in the presence of the base K_2CO_3 with a yield of 88% (entry 11). The optimized conditions for the C_3 aminated product **3a** and the C_7 brominated product **4a**, are shown in the entries 2 and 11, respectively.

Table 1. Reaction condition optimization.



Entry	Solvent	Temperature (ºC)	Additive	**3a** (%)	**4a** (%)
1	CH_3CN	+35	-	35	63
2	**CH_3CN**	**+35**	***p*TSA**	**-**	**80**
3	CH_3CN	+35	*p*-Toluic acid	-	75
4	DCE	+35	-	trace	trace
5	DCM	+35	-	trace	trace
6	Acetone	+35	-	0	trace
7	1,4-Dioxane	+35	-	10	52
8	DMF	+35	-	15	42

9	HFIP	+35	-	0	0
10	CH_3CN	-10	-	76	23
11	**CH_3CN**	**-10**	**K_2CO_3**	**88**	**-**

Reaction Conditions: **1a** (0.3 mmol, 1 equiv), NBSA **2** (0.5 mmol, 1.5 equiv) at varying temp.

Quinoxalin-2(1*H*)-one scaffold is a significant N-heterocyclic compound that finds application in the pharmacological and industrial domains[27, 55]. For C-3 and C-7 functionalized bromination and imidation, substrate scope for the synthesis of derivatives **3a**, **4a**, and **5a** is displayed in Figure **2**, **3**, and **4**. X-ray crystallography, alongside with mass and NMR studies, established the formation of both functionalized products. Here, we are able to combine two distinct key products with two separate conditions. Initially, we investigated the cooling conditions within the substrate scopes. Figure 1 shows that the electro donating (EDG) and withdrawing (EWG) groups both produced excellent yields. Benzylic group yield 90% (**3b**) of the corresponding C-3 nitrogenated product while *N*-methyl quinazoline yields 88% (**3a**). A reasonable yield also obtained from the benzylic group containing methyl (**3c**, 95%), isopropyl (**3d**, 90%), and tertbutyl (**3e**, 93%) groups at para position, but less than the electron-withdrawing substrate. The presence of electron withdrawing groups in benzylic rings, such as -NO_2 (**3f**), -CF_3 (**3g**), and -CN (**3h**), yields good results of 95%, 93% and 96% respectively. Additionally, halogen-containing substrates have good yields for **3i** (95%), **3j** (92%) and **3k** (93%) respectively. Apart from the *N*-benzylic group, numerous *N*-protected quinazolines were well tolerated for both C-3 and C-7 functionalization. In addition, **3l** to **3p** were successfully produced during this synthesis, achieving the intended yield of 81% to 91%.

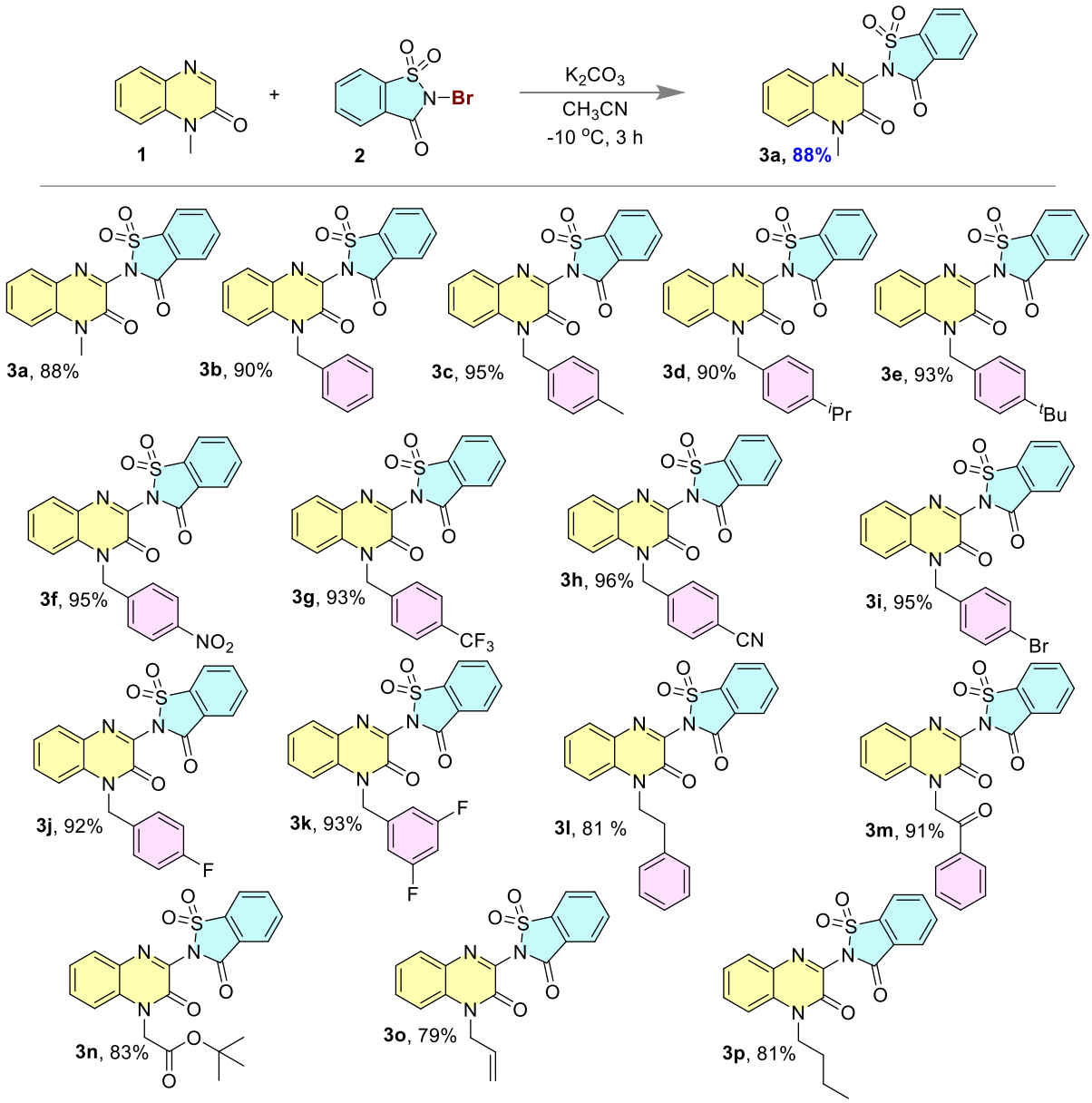


Figure 2. Substrate scope for 1-methylquinoxalin-2(1*H*)-one **1** with 2-Bromobenzo[d]isothiazol-3(2H)-one 1,1-dioxide **2** under cooling condition.

The substrate scope for the desired C-7 bromination product was then expanded (Figure 3). By changing the benzylic group at position *N*-1, we were able to lengthen the substrate here as well. First, we obtained methyl protected quinoxalin-2(1H)-one (**4a**) yielded 80% and benzyl protected quinoxalin-2(1H)-one (**4b**) yielded 79%. In an optimal condition, both EDG and

EWG produce acceptable results. We obtained the anticipated yields of 81%, 83%, and 70% accordingly by substituting the methyl (**4c**), isopropyl (**4d**) and tertbutyl (**4e**) groups at the para position of the benzylic group. likewise, EWG at the para position of the *N*-benzylic groups were well tolerated. The targeted yields for the nitro (**4f**), nitrile (**4g**), and trifluoromethyl (**4h**) groups were 83%, 92% and 88%, respectively. The halogen groups likewise showed good tolerance, yielded 79% (**4i**), 84% (**4j**), and 80% (**4k**) respectively. The desired brominated product achieved excellent outcomes (77% to 87%) for **4l** to **4p**.

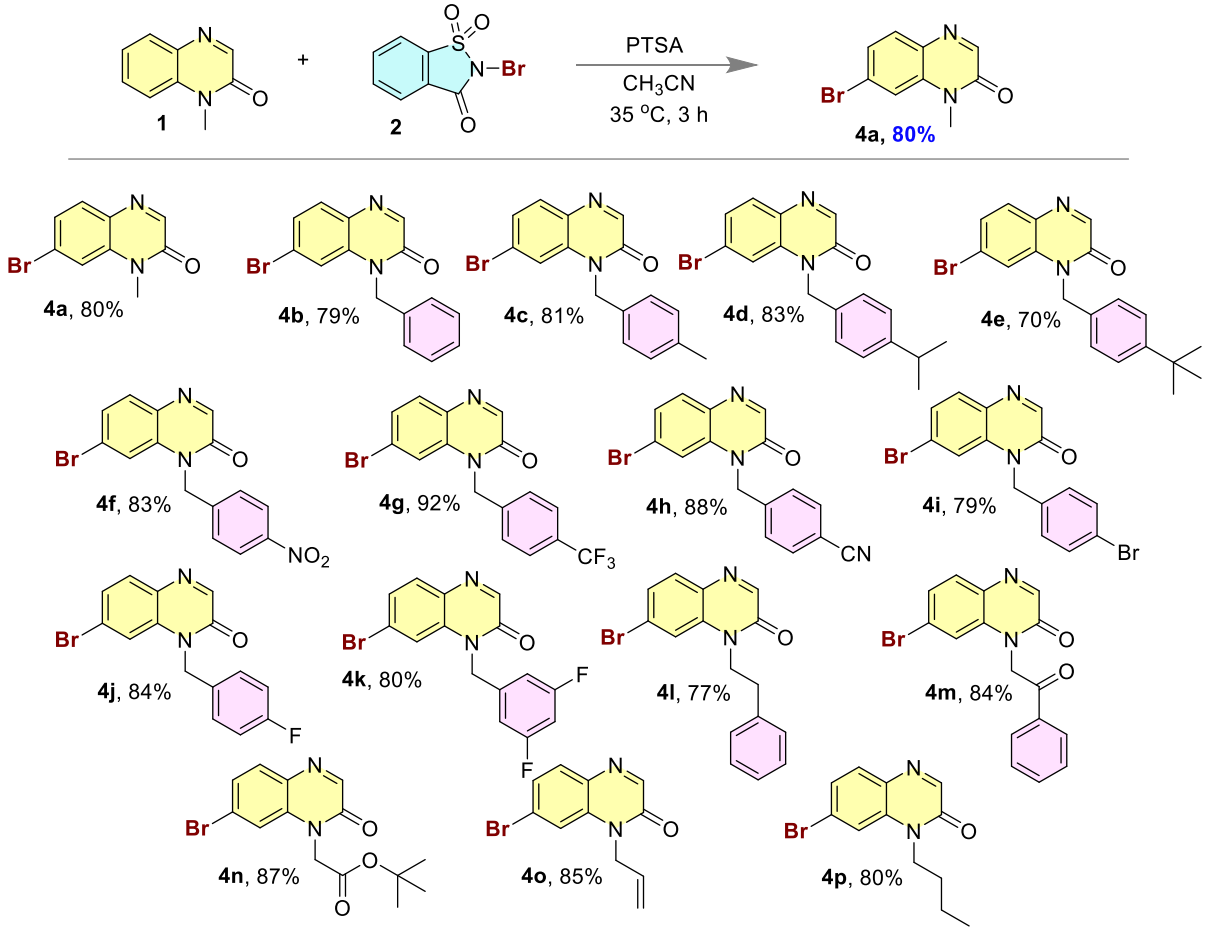


Figure 3. Substrate scope for 1-methylquinoxalin-2(1*H*)-one **1** with 2-Bromobenzo[d]isothiazol-3(2H)-one 1,1-dioxide **2** under room temperature.

By blocking the C-7 position we perform the same reaction with 1,6,7-trimethylquinoxalin-2(1H)-one as model substrate and we observe the full conversion of the single C-7 functionalized product (Figure 4). First, we got 92% (**5a**) of yield using benzylic protection in quinoxaline. The benzylic group containing methyl, tert-butyl and halo group gives 90-97% yield for **5b**-**6** (Figure 4).

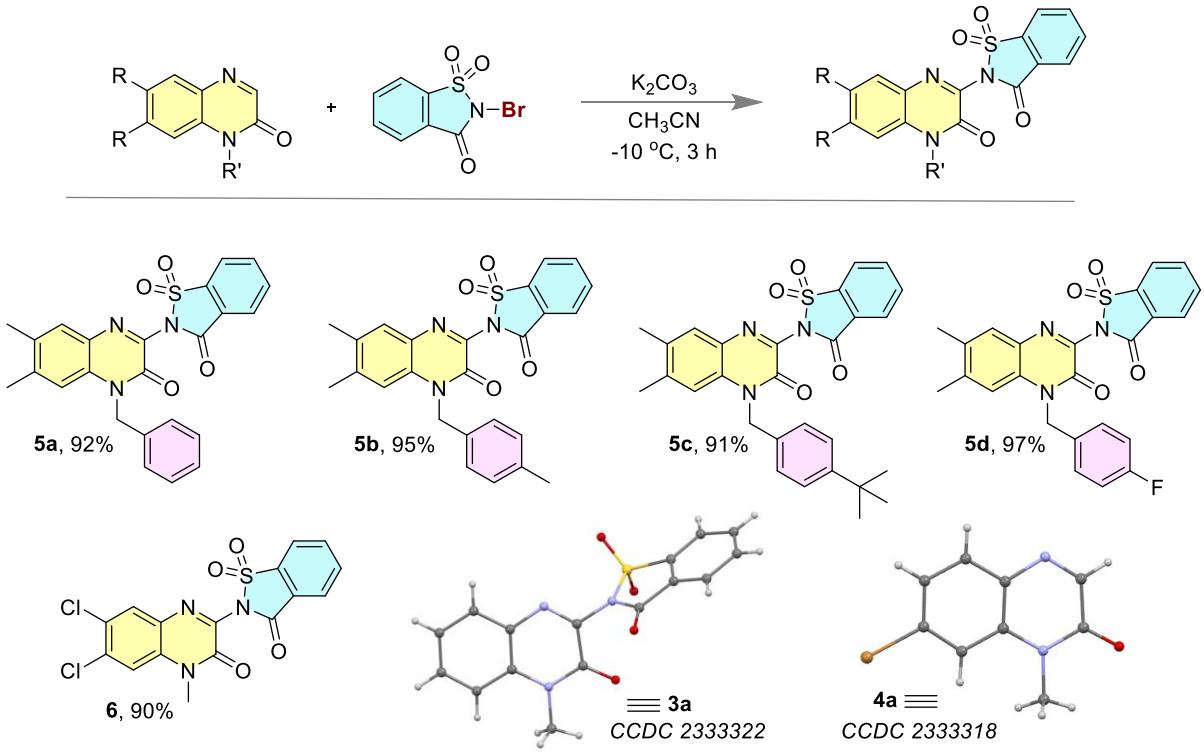


Figure 4. Substrate scope with different substitution at *N*-1 position and different *o*-phenylenediamine and crystal structure of **3a** and **4a**.

In the presence of radical inhibitors, that support the radical process, such as 1,1-diphenylethylene, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), and BHT (butylated hydroxytoluene), no desirable product was formed. Nonetheless, using the normal reaction conditions in the presence of excess 1,1-diphenylethylene, we are able to isolate 2-(2-bromo-1,1-diphenylethyl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide. To determine if the reaction

conditions are relevant or not in industrial scale, gram-scale synthesis was carried out; in that instance, the yield of the two products (**3a)** and 7-Bromo-1-methylquinoxalin-2(1H)-one (**4a**) under two distinct conditions was fulfilled. In EPR[56] study we perform two experiments; first we set up one reaction in standard reaction condition and check the EPR but no peak was observed (shown in black colour), next we perform the same reaction by adding DMPO under standard condition and one sharp peak was observed (red colour peak) which suggest our reaction goes via homolytic cleavage of *N*-Br bond via imidyl radical intermediate. The intended product could not be produced by 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (DBHT) and 1,3,5-tribromo-1,3,5-triazinane-2,4,6-trione (TBIA), 1-Bromopyrrolidine-2,5-dione (NBS), and 2-Bromoisoindoline-1,3-dione (PNBS). However, the yields of 7-Bromo-1-methylquinoxalin-2(1H)-one was 40% and 7% for *N*-Bromoacetamide (NBA), and 1,3-Dibromo-1,3,5-triazinane-2,4,6-trione (DBIA) respectively.

Quinoxalin-2(1H)-one derivatives are fluorescent and bromo derivatives also fluorescent in nature; however, the C-3 functionalized derivatives (**3d**) are intense fluorescent due to their longer conjugations and present of SO_2 group in the molecule. Therefore, we perform the UV analysis for the C-3 functionalized derivative and its corresponding starting material, and different absorption spectra was observed. The C-3 functionalized compound (**3d**) exhibited a greater red shift in comparison to its corresponding starting material. Additionally, compound **3d** showed an emissions peak at 433 nm. Future research by biologists will be able to examine the various biological features of this highly fluorescent C-3 functionalized derivatives, as quinoxalin-2(1H)-one derivatives are among the most interesting bioactive molecules in nature.

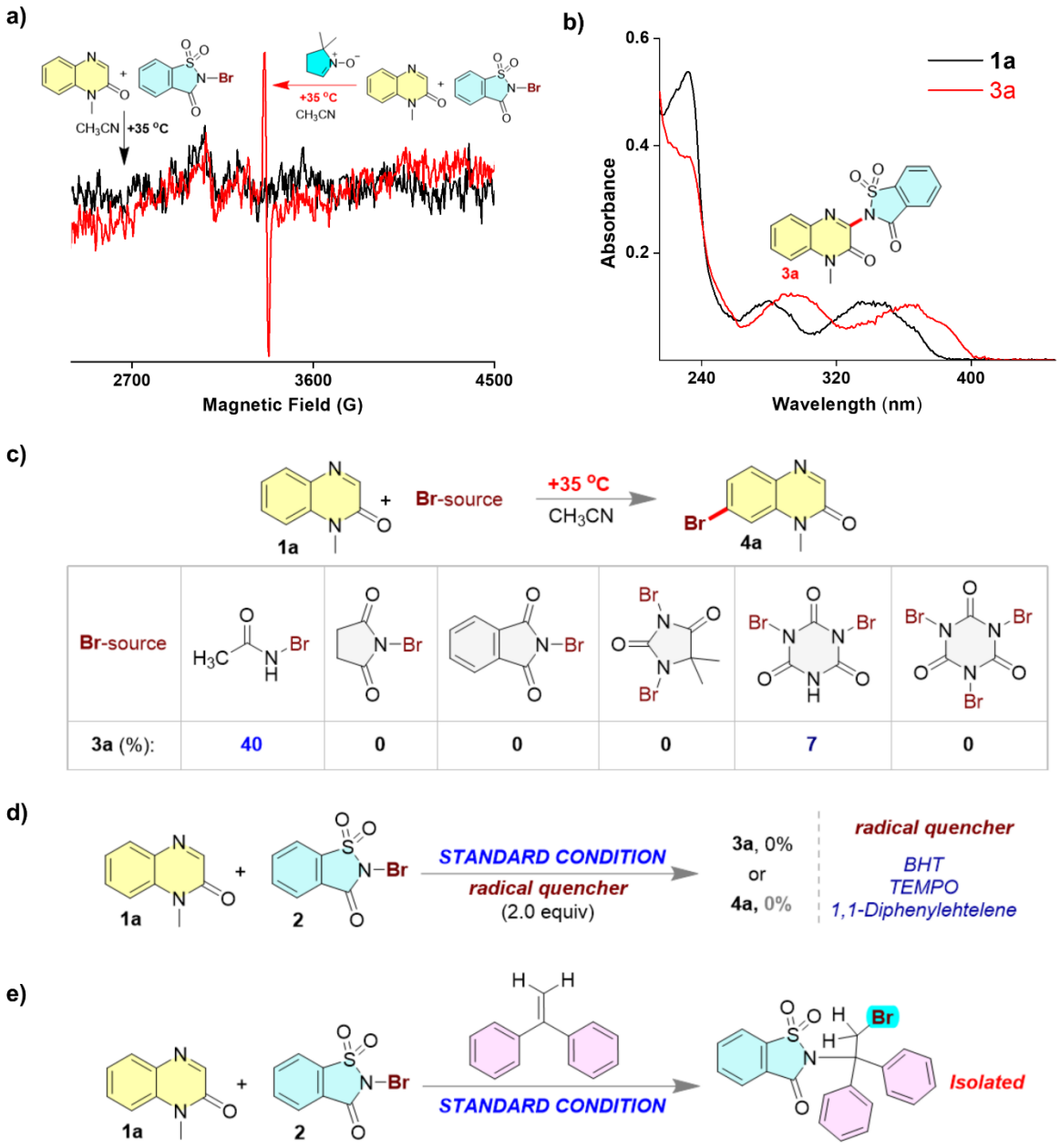


Figure 5. a) EPR Experiment. b) Absorption and Emission spectra. c) Standard reaction condition by varying different bromine source d) Radical trapping experiments using TEMPO, BHT and diphenylethylene. e) Diphenylethylene functionalised isolated compound.

We present a plausible mechanism of the reaction based on control experiments and literature reports (Figure 6a). During optimization, we also tested the reaction with PNBS, but the yield of **4a** in that case was not satisfied, suggesting that the reaction was speed up by replacing CO with SO_2. The sulfonyl group (-SO_2) group attached to the nitrogen centre directly support the dissociation of the *N*-Br bond by sharing the unpaired electron density, that SO_2 functional group assist to stabilize the radical species when present close to a nitrogen centre radical. This stabilization influencing its behaviour in various chemical reactions. The bromination and imidation reaction in this case depend on the *N*-Br bond breaking. Thus, in both situations, intermediate **2'** and bromine radical is generated during the initial breaking of *N*-Br in the present of acetonitrile solvent. And in the presence of quinoxalin-2(1*H*)-one (**1**), radical intermediate **4a'** is formed after the removal of Benzo[d]isothiazol-3(2H)-one 1,1-dioxide and by deprotonation 7-bromo-1-methylquinoxalin-2(1H)-one (**4a**) is formed. Likewise for the C-3 functionalized imidation path, intermediate **2'** is formed and **2'** acts as a nucleophile to generate intermediate **3a'** and removal of HBr to generate 2-(4-methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**3a)**.

The compound **4a**, as depicted in Figure 7b, served as the starting material for a synthetic application. A Suzuki coupling reaction was carried out using 7-bromo-1-methylquinoxalin-2(1H)-one (**4a**) and phenylboronic acid in the presence of $Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (1.5 equiv), and a mixed solvent of DMF : EtOH : H_2O (1.5 : 1.5 : 1) at 100 °C for 24 h under inert atmosphere. Also one Sonogashira cross coupling reaction was performed using 7-bromo-1-methylquinoxalin-2(1H)-one (**4a**) and phenylacetylene in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (20 mol %), and a mixed solvent of DMF : NEt_3 (2 : 1) at 80 °C for 24 h under inert atmosphere.

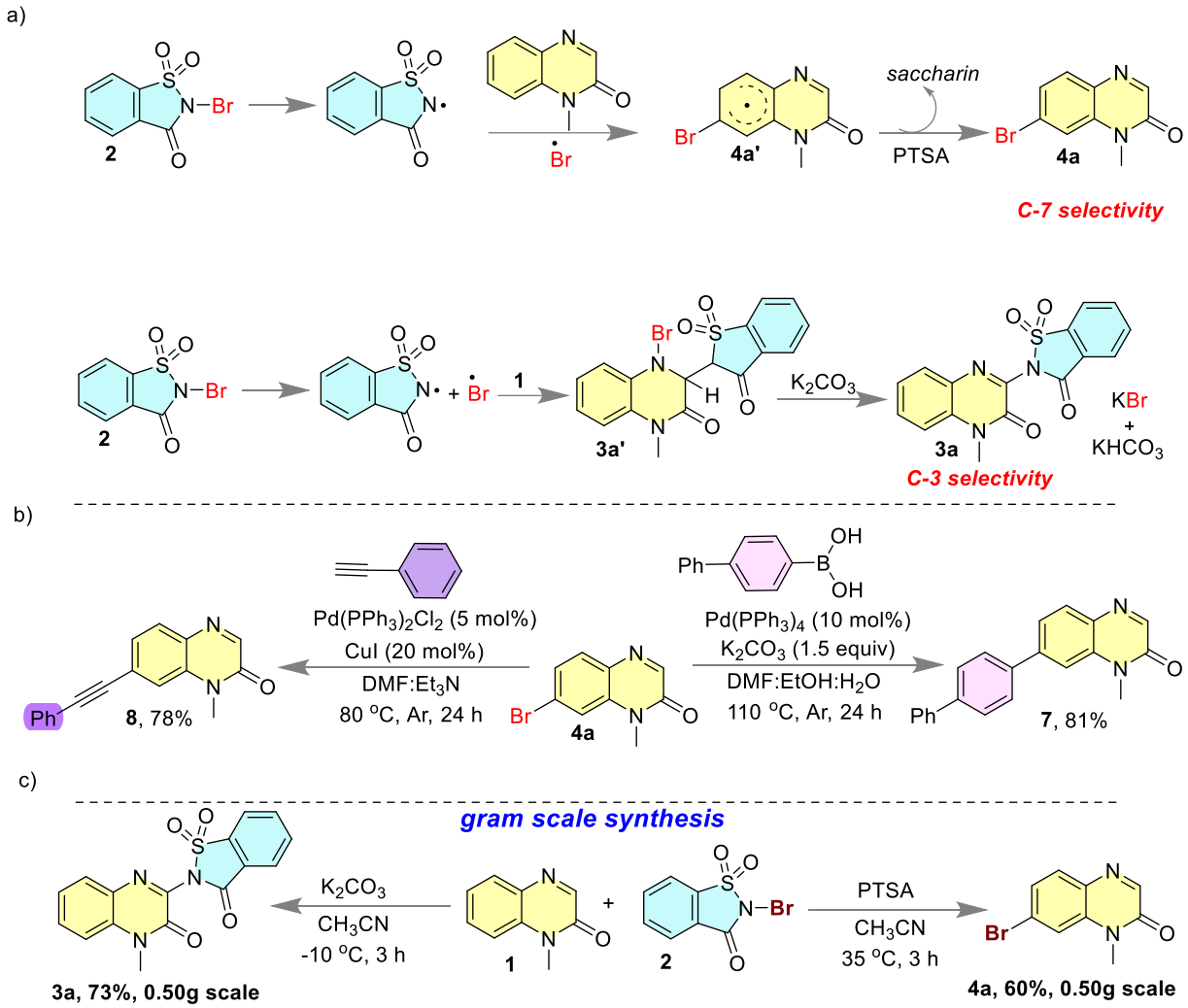


Figure 6. a) Plausible mechanism b) Chemical modification of **4a** *via* Suzuki coupling (right) and Sonogashira coupling (left). c) Gram scale synthesis of 2-(4-Methyl-3-oxo-3,4-dihydroquinoxalin-2-yl)benzo[d]isothiazol-3(2H)-one 1,1-dioxide (**3a**) and 7-Bromo-1-methylquinoxalin-2(1H)-one (**4a**).

To summarize, we demonstrate temperature-controlled C-3 versus C-7 regioselectivity for quinoxalin-2(1H)-one by utilizing 2-Bromobenzo[d]isothiazol-3(2H)-one 1,1-dioxide in acetonitrile solvent. Breaking the *N*-Br bond is key stage in the reaction that produces the

bromo and imidyl radicals, which allow us to obtain distinct selective products under various conditions. Through a radical cascade procedure, this reaction was carried out in a two-component, one-pot setup. This strategy unites the various fields of organic chemistry and has the potential to greatly advance the field of chemistry.

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