Metal-free generation of halogen radicals using NXS/TBHP: Application in *site*-selective halogenation of quinoxalin-2(1H)-ones and synthesis of *gem*-dihaloketones

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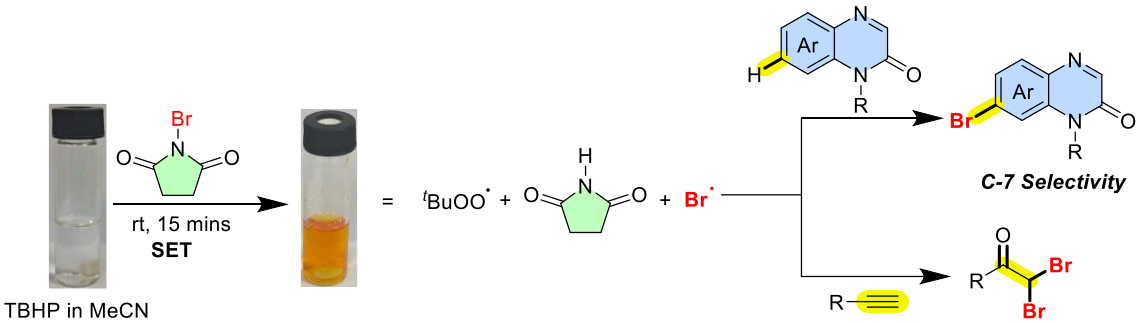
GRAPHIC FOR TOC



ABSTRACT:

Here we report an efficient and practical protocol for the generation of halo radicals (Br and Cl) using inexpensive and readily available NXS/TBHP reagent system at rt. The halo radicals were further utilized for the *site*-selective C-H bromination and chlorination of the unexplored benzo-core of quinoxalinones. This protocol offers excellent regioselectivity towards C7 position of benzo-core over readily functionalized C3 position in hetero-core of quinoxalinones under mild reaction conditions. Notably, this transformation showed good functional group compatibility and a wide substrate scope. Further, selective synthesis of *gem*-dihaloketones from alkynes has been accomplished using the same reagent system.

INTRODUCTION

Organohalides are explicitly acknowledged as a highly important class of organic compounds due to their excellent reactivity and convenient accessibility.[1] In particular, brominated and chlorinated compounds, due to their unique role in numerous pharmaceuticals, materials, and agrochemicals, are of great significance (Figure 1).[2] They play inimitable roles in transition-metal-facilitated cross-coupling reactions such as Heck, Suzuki, Sonogashira, etc. and are also used as precursors for organometallic reagents, including Grignard and organolithium reagents.[3] They are key intermediates for late-stage functionalization (LSF) to redesign drug

molecules and derivatization of biologically active organohalides are crucial to get insight in the structure–activity relationship (SAR) studies.[4]

Among various heteroarenes, quinoxalin-2(1H)-ones are explicitly acknowledged as a highly important and privileged class due to its immense significance in several bioactive natural products, agrochemicals, material science and various pharmaceutical compounds.[5] Therefore, much interest prevails in the development of simple and convenient methods for the functionalization of quinoxalin-2(1H)-ones, which include alkylation, arylation, sulfenylation, phosphorylation, amination, trifluoromethylation, etc. (Scheme 1a).[6] The reported synthetic methodologies have largely focused on the functionalization of heterocyclic core of quinoxalin-2(1H)-ones, precisely at the C3 position.[6] The functionalization of benzo-core of quinoxalin-2(1H)-one is very much unexplored.[7] In fact, the functionalization of the benzo ring in quinoxalin-2(1H)-one may lead to modification of the overall properties of heteroarenes rather than just the benzo-core. Therefore, halogenated heteroarenes are ideal substrates for structural modifications.[8]

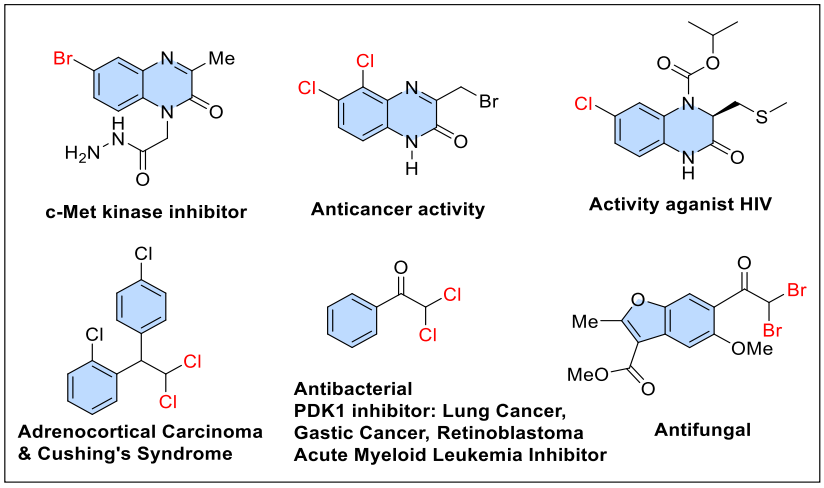
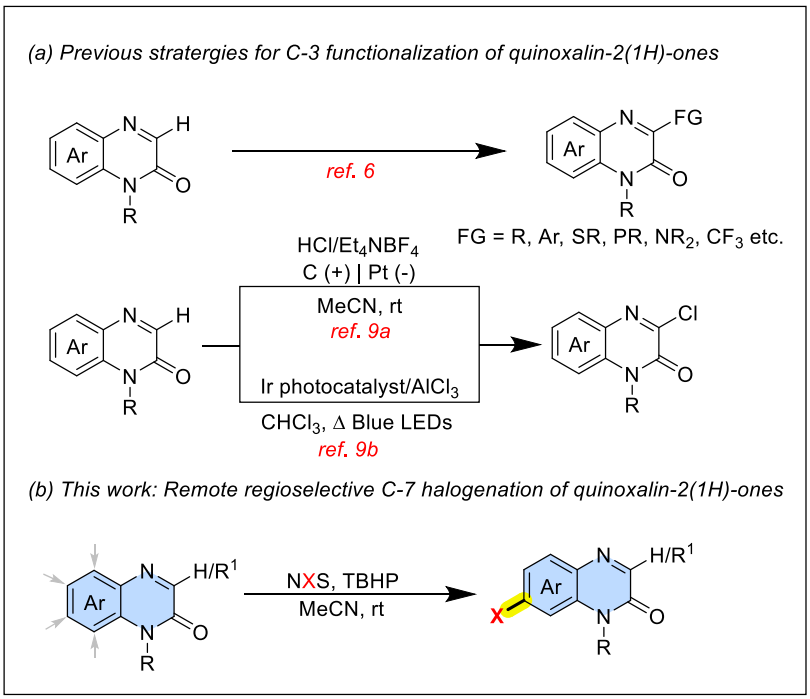


Figure 1. Representative Examples of Biologically Active Halogenated Compounds.

It is noteworthy to mention the electrochemical and photochemical approach by Liu's and Yang's group, respectively, for regioselective C-3 chlorination of quinoxaline-2(1H)-ones (Scheme 1a).[9] However, halogenation of benzo-core of quinoxaline-2(1H)-ones still remains unexplored.[7a] This spurred our curiosity to develop a methodology for the introduction of halogen groups at distal sites on privileged heterocyclic moiety such as quinoxalinones, which are found ubiquitously in many pharmaceutical compounds.

Bromination is normally carried out through two major pathways i.e., electrophilic or radical pathway.[10] The scope of radical bromination is often limited to benzylic and allylic position

and aromatic bromination often encounters regioselective issues.[10] Thus, developing efficient method to generate bromo radical in a controlled manner is very important. Herein, we disclosed a metal free protocol for the generation of halo radicals (Br and Cl) in a controlled manner using NXS/TBHP reagent system at rt and further employed it for *site*-selfective halogenation of benzo-core of quinoxalinones (Scheme 1b).

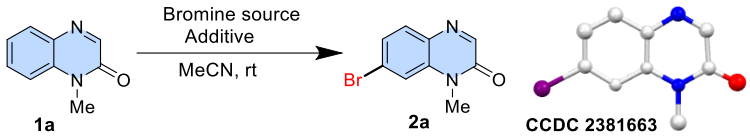


Scheme 1. (a) Previous Strategies for C-3 Functionalization of Quinoxalin-2(1H)-ones. (b) Remote Regioselective C-7 Halogenation of Quinoxalin-2(1H)-ones.

RESULTS AND DISCUSSION

To verify our hypothesis, 1-methylquinoxalin-2(1H)-one (1a) was chosen as the model substrate to test the bromination. Treatment of 1-methylquinoxalin-2(1H)-one (**1a**) with $CuBr_2$ (1.0 equiv) and TBHP (3.0 equiv) in acetonitrile at rt for 12 h, surprisingly produced exclusively 80% of the single product i.e., 7-Bromo-1-methylquinoxalin-2(1H)-one (**2a**) (entry 1, Table 1). No C-3 brominated product was detected nor were any other regioisomers formed. This encouraging results further prompted us to replace $CuBr_2$ with other non-metallic brominating agents. When the reaction was performed using NaBr and TBAB as a bromine source with TBHP, product formation was not observed and starting material was recovered (entries 2-3, Table 1). Under common bromination conditions such as CBr_4/^{t}BuONa, NBS, or NBS/TFA product formation was not observed (entries 4-6, Table 1). Employment of 1.0 equiv of NBS with l.0 equiv of TBHP gave the desired product in excellent isolated yield of 92% (entry 7, Table 1).

Table 1. Optimization of the Reaction Conditions for the Synthesis of 7-Bromo-1-methylquinoxalin-2(1H)-one.[a]



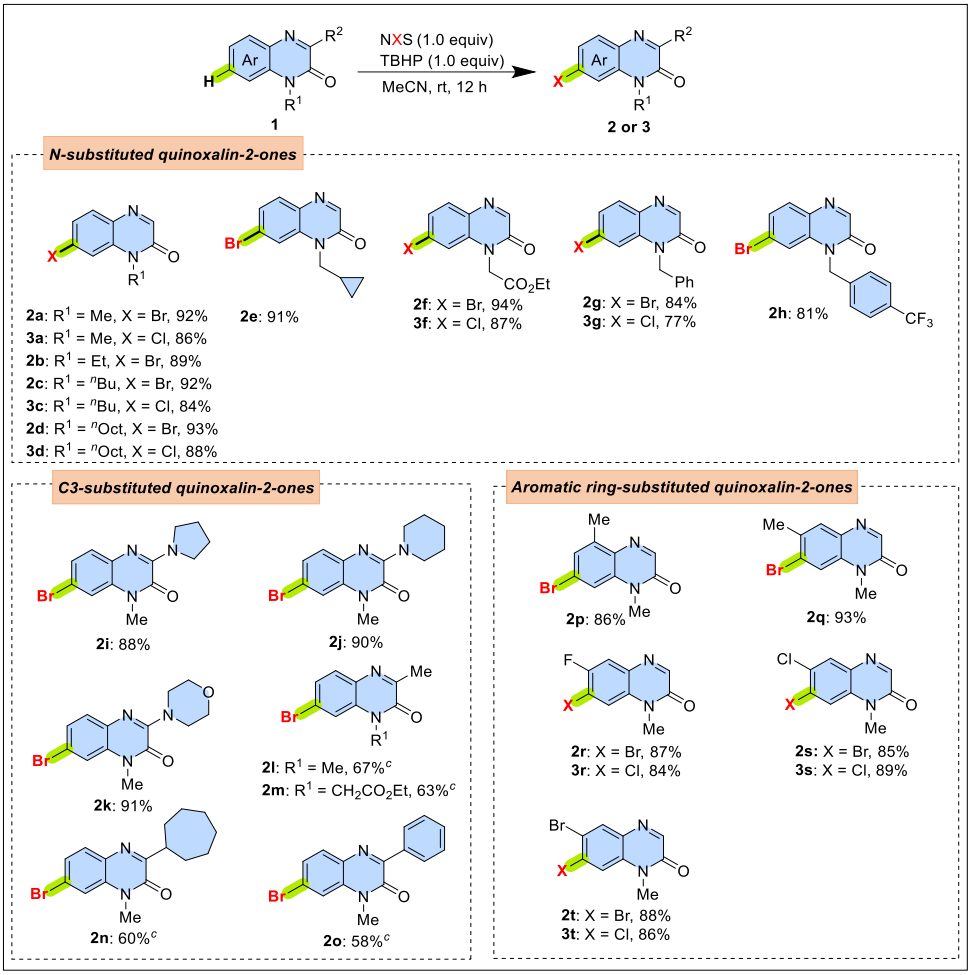
Entry No.	Bromine source (equiv)	Additive (equiv)	Yield (%)[b]
1	$CuBr_2$ (1.0)	TBHP (3.0)	80
2	NaBr (1.0)	TBHP (3.0)	-
3	TBAB (1.0)	TBHP (3.0)	-
4	NBS (1.0)	-	-
5	NBS (1.0)	TFA (1.0)	-
6	**NBS (1.0)**	**TBHP (1.0)**	**92**
7	CBr_4 (1.0)	^{t}BuONa (0.5)	-

[a]Unless mentioned otherwise, all reactions were conducted by employing **1a** (0.5 mmol) in MeCN (5 mL) at rt. [b]Isolated yield based on **1a**.

After getting the optimized reaction condition, we sought to evaluate the scope of various quinoxalin-2-one derivatives with this *site*-selective bromination reaction protocol (Scheme 2). To our delight the desired brominated product **2a**–**2t** was formed in good to excellent yield under standard reaction conditions with excellent regioselectivity. The reactions were observed to occur in a facile manner for various *N*-alkylated quinoxalin-2-one (Me, Et, *n*-butyl, *n*-octyl and isopropyl methyl) to furnish the corresponding brominated product **2a**–**2e** in excellent isolated yields 85-91%. Furthermore, quinoxalin-2-one bearing electron-withdrawing group (CH_2CO_2Et) and benzylic groups (CH_2Ph and *p*-CF_3CH_2Ph) at N1 position was well tolerated to produce the desired product **2f** and **2g**–**2h** in very good isolated yield of 94, 84 and 81%, respectively. Additionally, this methodology is compatible with 3-aminoquinoxalin-2-one derivatives **2i**–**2k** and delivered the desired brominated product in excellent yields 88-91%. However, relatively lower yield was obtained in case of 3-alkylquinoxalin-2-one **2l**–**2n** and 3-arylquinoxalin-2-one **2o** derivatives 60-63% and 58%, respectively. Gratifyingly, quinoxalin-2-one substituted with both electron-donating group (5-Me and 6-Me) as well as electron-withdrawing substituents (6-F, 6-Cl and 6-Br) on the aromatic ring had no effect on the reaction and produced the corresponding product **2p**–**2t** in excellent isolated yields 85-93%. Furthermore, replacing NBS with NCS under the optimized

reaction conditions delivered the corresponding C-7 chlorinated quinoxalinones **3a**, **3c**–**3d**, **3f**, **3g**, and **3r**–**3t** in very good, isolated yield of 77-89%.

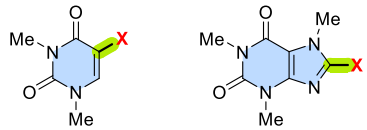
Scheme 2. Substrate Scope in the Synthesis of 7-Haloquinoxalin-2(1H)-ones.[a,b]



[a]Standard reaction conditions: **1** (0.5 mmol), NXS (0.5 mmol), and TBHP (0.5 mmol) in MeCN (5.0 mL) for 6 h at rt. [b]Isolated yield based on **1**. [c]Starting material was recovered.

To our gratification, 1,3-dimethyluracil, which is a nucleobase and caffeine, a central nervous system stimulant can be halogenated in a regioselective manner under the optimized reaction condition (Scheme 3).

Scheme 3. Halogenation of Natural Products

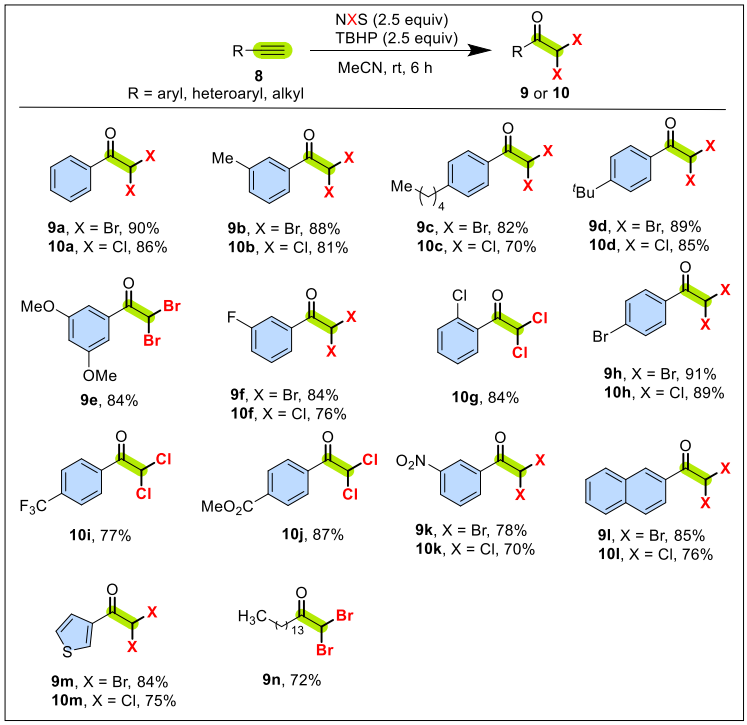


4a, X = Br, 95%
5a, X = Cl, 90%

6a, X = Br, 55%
7a, X = Cl, xx%

The generality of this protocol was thoroughly tested for the oxybromination and oxychlorination of various alkynes (Scheme 4). The *geminal* dihalo compounds are among the biogenic halogenated molecules that are found in numerous agrochemicals and pharmaceuticals.[11] Phenylacetylene and various aromatic acetylenes substituted with electron-donating groups, such as methyl, *n*-butyl, *tert*-butyl, and methoxy, underwent the reaction in a facile manner, affording the corresponding *gem*-dibromoacetophenones (**9a**–**9e**) in very good isolated yields of 82-90% (Scheme 4). Moreover, terminal aromatic alkynes bearing electron-withdrawing substituents such as F, Br, and NO_2 reacted smoothly to give desired *gem*-dibromoacetophenones **9f**, **9h**, and **9k** in very good yields of 78-91%, respectively. Notably, 2-ethynylnaphthalene, heteroaromatic alkyne (3-ethynylthiophene) and aliphatic alkyne (1-hexadecyne) were also found to be compatible with this methodology, furnishing the corresponding products **9l-9n** in 85, 84 and 72% yields, respectively. Under standard reaction conditions, replacing NBS with NCS, various terminal alkynes followed a similar reactivity trend and afforded a diverse range of *gem*-dichloroketones **10a-10d** and **10f-10m** in very good isolated yields, as shown in Scheme 4.

Scheme 4. Substrate Scope of Oxyhalogenation of Alkynes[a,b]



[a]Standard reaction conditions: **8** (0.5 mmol), NXS (1.25 mmol), and TBHP (1.25 mmol) in MeCN (3.0 mL) for 6 h at rt. [b]Isolated yields based on **1**.

When 1-(prop-2-yn-1-yl)quinoxalin-2(1H)-one **1l**, which possess two reactive sites was treated with NBS/TBHP, we exclusively obtained *gem*-dibromoketone product **12** (Figure 2).

The C-7 bromination of quinoxalinone was not observed. Thus, the developed protocol is highly chemoselective towards alkynes.

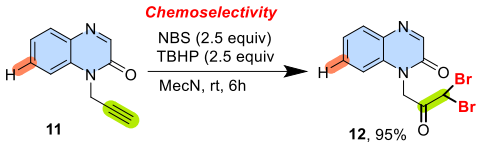
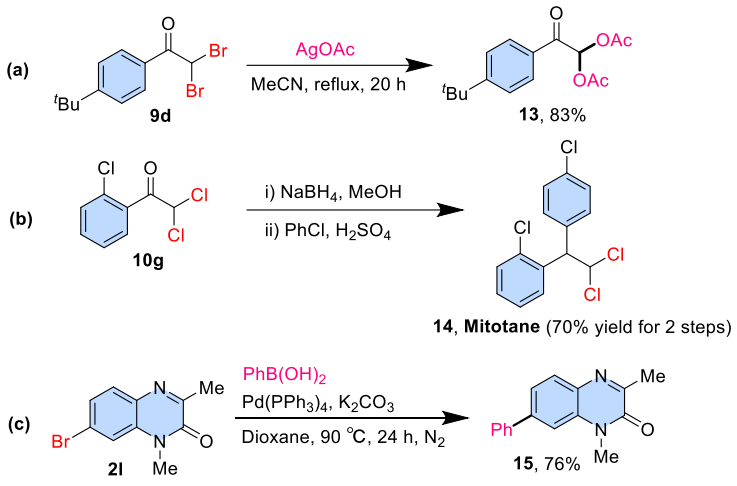


Figure 2. Chemoselectivity.

The late-stage functionalization of the products of established protocols, i.e., *gem*-dihaloacetophenones and 7-bromoquinoxaliones, is displayed in Scheme 5. The treatment of 2,2-dibromo-1-(4-(*tert*-butyl)phenyl)ethan-1-one **9d** with silver acetate in acetonitrile under refluxing conditions for 20 h leads to the formation of a yellow liquid, which was characterized as 2-(4-(*tert*-butyl)phenyl)-2-oxoethane-1,1-diyl diacetate **13** in 84% yield (Scheme 5a). Further, we demonstrated a 2-step synthesis of a very important *geminal* dichloro-drug, Mitotan, which is used for the treatment of Cushing's syndrome and adrenocortical carcinoma, starting from 2,2-dichloro-1-(2-chlorophenyl)ethan-1-one **10g**, as shown in Scheme 5b. Moreover, the brominated product i.e., 7-bromo-1,3-dimethylquinoxalin-2(1H)-one **2l** was subjected to Suzuki coupling with phenylboronic acid to afford the 1,3-dimethyl-7-phenylquinoxalin-2(1H)-one **15** in 76% yield (Scheme 5c).

Scheme 5. Late-Stage Functionalization



To understand the excellent regioselectivity observed in the halogenation reactions of various quinoxalin-2(1H)-ones in Figure 3, charge densities at different positions of the quinoxalin-2(1H)-one core scaffold were computed by density functional theory (DFT) calculations. The optimization of the molecule **1a** was carried out using b3LYP functional and 6-31++g(d, p)

basis set. The charge densities thus computed for various atoms of the benzene core of the quinoxalin-2(1H)-one along with that at C3 position are shown in Figure 3. The results clearly show that C7 position has the highest electron density.

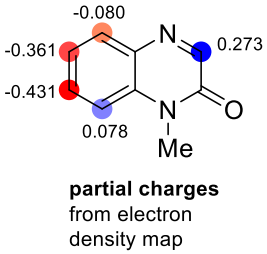
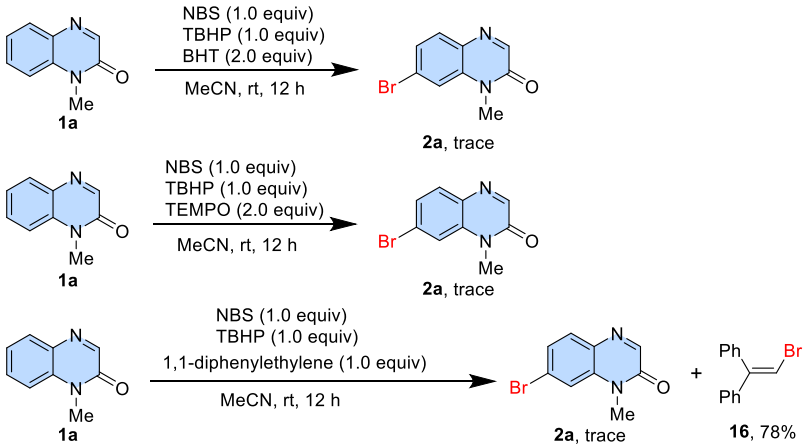


Figure 3. Computational Experiment Predicts Regioselectivity

To get insights about the mechanism of halogenations, a few control experiments were performed. When the reaction of 1-methylquinoxalin-2(1H)-one **1a** with NBS/TBHP in acetonitrile was conducted in the presence of a radical scavenger such as butylated hydroxytoluene (BHT) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the reaction was found to be significantly retarded, and only a trace amount of the product **2a** was produced (Scheme 6a and Scheme 6b). When the reaction was run in the presence of 1.0 equiv of 1,1-diphenylethylene (Scheme 6c) under standard reaction conditions, the formation of **2a** was found to be suppressed with only a trace amount being formed. However, the addition product, namely (2-bromoethene-1,1-diyl)dibenzene was isolated in 78% yield.

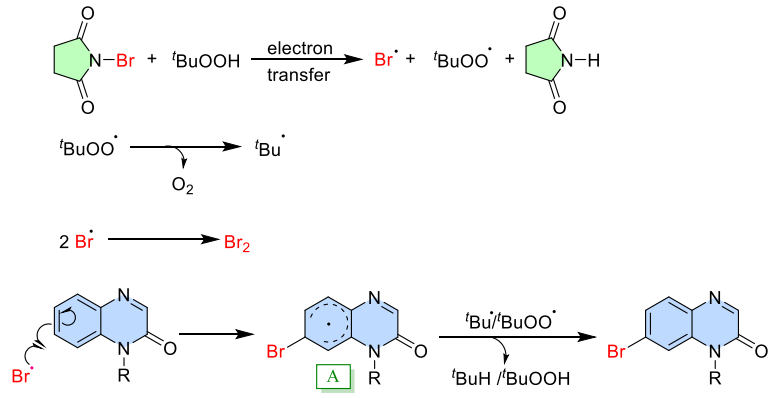
Scheme 6. Control Experiments.



Based on these results, a plausible mechanism for bromination of quinoxalin-2(1H)-ones with NBS/TBHP is shown in Scheme 7. Accordingly, a single electron transfer (SET) from TBHP to *N*-bromosuccinimide (NBS) may lead to the formation of succinimide, and bromo as well as *tert*-butylperoxy (^{t}BuOO$^{\bullet}$) radicals. The formation of succinimide was confirmed by ^{1}H

NMR analysis. Moreover, the redox potentials of TBHP (E_{ox} = 0.75 V *vs* SCE) and NBS (E_{red} = −0.70 V *vs* SCE), cf. Figure S1, Supporting Information, further confirms that single electron transfer (SET) from TBHP to the NBS is thermodynamically facile. The ^{t}BuOO radical may lose oxygen to produce ^{t}Bu radical, while the bromo radical may attack quinoxalin-2(1H)-one. Evidently, the electrophilic bromo radical selectively attacks the most electron-rich C7 position, as implicated by DFT analysis, leading to the radical intermediate **[A]**, which may suffer hydrogen atom loss to ^{t}Bu/^{t}BuOO radical, producing the target bromination product.

Scheme 7. Proposed Mechanism for Regioselective Bromination of Quinoxalinones.



CONCLUSION

An efficient and expedient protocol for the regioselective halogenation of the benzene core of quinoxalin-2(1H)-ones has been developed using NXS/TBHP as the reagent system. This protocol, without the need of any directing group, provides a facile access to diverse C7-brominated/chlorinated quinoxalin-2(1H)-ones. The methodology permits access to a broad range of quinoxaline-2(1H)-ones containing a variety of functional groups. The mild operation may permit late-stage functionalization of quinoxalin-2(1H)-one derivatives. Using the same reagent system, we further demonstrated the selective transformation of alkynes into *gem*-dihaloketones and synthesis of Mitotan, a pharmaceutical drug used for the treatment of Cushing's syndrome and adrenocortical carcinoma by post-synthetic modification.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPORTING INFORMATION

Details of the experimental setup, cyclic voltammetry experiments, general synthetic procedure of product, characterization data, control experiments, NMR spectral reproductions for all products (PDF) and crystal structure data are available in the supporting information.

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