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Microwave Promoted Halogenation of Quinines, Heteroarenes, Natural Products and Drugs Using Aqueous Halogen Donors and NCS

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Abstract:
Late-stage C–H chlorination and bromination of bioactive scaffolds is significant for drug discovery, as carbon–halogen bonds can effectively modulate biological activity, metabolic stability, and physicochemical profiles. Here, we develop an atom-economical, radical-mediated protocol that synthesizes high-value chlorinated or brominated quinones and (hetero)arenes. The system employs inexpensive, low-molecular-weight HCl or HBr as the halogen source, commercially available NCS in ionic liquid as ethyl ammonium nitrate, without any photocatalyst or metal catalyst. The mild reaction conditions, ready availability of reagents, excellent functional-group tolerance, high regioselectivity, and facile scalability under continuous-flow operation collectively render this approach a practical and efficient protocol for the late-stage aromatic C(sp^2)–H chlorination and bromination of complex drugs and natural products. Mechanistic investigations reveal that nitrosyl halides, generated in situ by reaction of NCS and aqueous HCl or HBr, undergo homolysis to produce the corresponding halogen radicals that selectively initiate the radical halogenation of quinones and (hetero) arenes and natural products and drugs.

Keywords: Ionic liquid,N-chlorosuccinsimide,aq.HCl/ HBr,Neproxen.

Introduction:

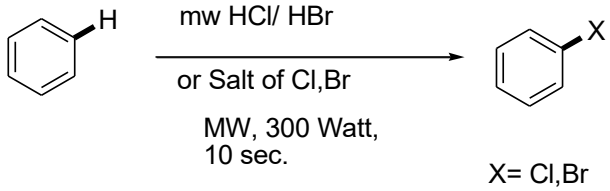
Late-stage C–H functionalization of bioactive molecules is a powerful strategy for creating a diverse molecule library to explore structure-activity relationships and optimize druggability.1-6 Among the various reported late-stage functionalization reactions, C–H chlorination and bromination have proven to be particularly useful, due to the unique properties of carbon-halogen bond (C–Cl and C–Br) on modulating biological activity, metabolic stability, and physicochemical properties of drugs and natural products.7-14 Additionally, aromatic C(sp^2)–Cl and C(sp^2)–Br bonds are prevalent in a wide range of high-value compounds, including fine chemicals,15-17 approved pharmaceuticals,18-20 natural products,21 agrochemicals,22,23 and functional materials (Figure 1A). These bonds are also extensively utilized in coupling reactions, highlighting their significance in synthetic chemistry.24-26 Therefore, developing aromatic C(sp2)–H halogenation methods with better reactivity, selectivity and biocompatibility are necessary. Traditional electrophilic aromatic substitution (SEAr) methods for aromatic C(sp^2)–H chlorination or bromination typically employ highly reactive halogenating reagents (such as Cl_2, Br_2, or $SOCl_2$), Lewis acids (such as $FeCl_3$, $FeBr_3$, or $AlCl_3$), and harsh reaction conditions. These approaches often suffer from low chemoselectivity and regioselectivity, as well as poor

compatibility with functional groups (Figure 1B).27,28 To address these limitations, various alternative halogenating reagents have been developed in recent years.29-38 Although these new reagents have significantly improved the efficiency and regioselectivity of aromatic halogenation reactions, some of them exhibit lower atom economy, are prepared through complex synthetic processes, or suffer from instability issues (Figure 1B).29-38 Given these challenges, the development of selective aromatic C(sp^2)–H halogenation methods that employ practical, commercially available, and inexpensive halogenating reagents—such as aqueous HX (X = Cl, Br), halogen-containing inorganic salts, or halogenated solvents—is urgently needed, as this would improve atom economy and reduce reaction costs. With the recent advances in photochemistry,39-49 photo-promoted aromatic C(sp^2)–H halogenation reactions have developed rapidly (Figure 1C).7-14,50-63 To date, visible-light-promoted C(sp^2)–H halogenation of (hetero)arenes has been dominated by two paradigms. The first relies on N–Cl or N–Br reagents (such as NCS, NBS, PhthN–Cl, PhthN–Br, NCSacc, TCCA, DCDMH and Palau'chlor reagent) in combination with a photocatalyst to deliver selective aromatic C(sp^2)–H chlorinated or brominated products. This manifold requires a photocatalyst and inevitably generates stoichiometric by-products, thereby compromising the atom economy. The second manifold employs aqueous HCl or HBr, or inorganic halide salts as the halogen source; a strong chemical oxidant or strongly oxidizing photocatalyst is then required to generate the corresponding halogen radical that adds to the (hetero)arene. These strongly oxidative conditions erode functional-group tolerance and restrict substrate scope, rendering late-stage C(sp2)–H halogenation of complex natural products or drug scaffolds difficult. For example, The Fukuzumi group reported the first visible-light-induced bromination of MeO-substituted aromatic hydrocarbons and thiophenes using 9-mesityl-10-methylacridinium perchlorate as a photocatalyst and aqueous HBr as the brominating reagent under an oxygen atmosphere.54 Subsequently, they also developed a visible-light-promoted chlorination protocol for MeO-substituted arenes and phenols, utilizing HCl as the chlorine source.55 Similarly, the König group introduced a method that integrates aqueous HCl into photocatalysis to achieve selective chlorination of simple electron-rich arenes under visible light irradiation.57,58 Despite significant advances in visible-light-induced aromatic C–H halogenation using HX as the halogen source, most protocols still require harsh illumination conditions, exogenous photosensitizers and are largely limited to simple, low-molecular-weight substrates with narrow functional-group tolerance. To the best of our knowledge, there is still a lack of practical approaches for late-stage chlorination and bromination of natural products and drugs using a commercially accessible aqueous HCl or HBr as halogen source. Based on these prior studies and our own work on visible-light-promoted reactions,64-70 we herein report a $NaNO_2$/HCl-mediated radical strategy for the selective C(sp^2)–H chlorination and bromination of quinones, (hetero)arenes, natural products, drugs, and active pharmaceutical ingredients. This strategy operates under visible-light irradiation at room temperature without the need for a photo- or metal-catalyst. Furthermore, by simply replacing aqueous HCl with aqueous HBr, this system can be conveniently modulated to achieve late-stage C(sp^2)–H bromination of complex substrates. Moreover, these halogenated reactions can be readily scaled up via continuous-flow technology .

Results and Discussion

Screening conditions. Our research in radical C–H late-stage halogenation chemistry is motivated by our interest in the synthesis and biological activity studies of drugs. To this end, we initiated our investigation of selective C(sp^2)–H chlorination using the challenging drug molecule naproxen (1s) as

the substrate and inexpensive, readily available aqueous HCl and N-chlorosuccinimide as the chlorine donor under microwaveoven at 300 watt for 10 sec.irradiation. We were pleased to find that the reaction of naproxen (1s) (0.1 mmol) with 37% aqueous HCl (12 µL) and 0.2 equivalents of ionic liquid (IL) 15% yield of the selective C(sp²)–H chlorination product (1) (Table 1, entry 1). Moreover, while keeping the equivalent ratio of aqueous HCl and NCS constant, increasing the equivalents of aq. HCl led to a further increase in the yield of chlorinated naproxen (compare entries 1, 2, and 3). product 1 (30% yield based on crude ^{1}H-NMR spectroscopy) (entry 3). Furthermore, reducing the amount of aqueous HCl to 50 µL maintained the yield at a similar level (entry 4). However, further reduction in the amount of aqueous HCl led to a decrease in the chlorination yield (entries 5 and 6). When we used 2.0 equivalents of NCS and 50 µL of aqueous HCl, both chlorinated product 1 (51% yield) and nitrated product 1′ (40% yield) were obtained (entry 7). Moreover, under MW irradiation, substituting aqueous HCl and NCS with alternative chlorinating reagents—such as NCS, DSDMH, $PhICl_2$ or Palau'chlor—afforded the target chlorinated products only in moderate to low yields (entries 9-11). As anticipated, this system can be further modulated to form selective C(sp2)–H brominated product 2 in a nearly quantitative yield by replacing aqueous HCl with aqueous HBr (entry 12,14).

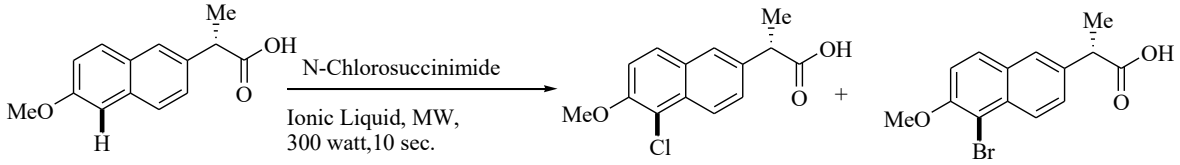


Entry	Reagent (eq.) HCl(36%) or HBr (40%aq.) (uL)	Yield (%)
1	NCS (0.1),HCl(12 uL,1.4)	15%
2	NCS (0.5),HCl(30 uL,3.6)	25%
3	NCS (0.1),HCl(60 uL,7.2)	30%
4	NCS (0.1),HCl(50 uL,6.0)	28%
5	NCS (2),HCl(30 uL,3.6)	50%
6	NCS (2),HCl(10 uL,1.2)	40%
7	NCS (1),HCl(50uL,6.0)	40%
8	NCS (1),HCl(50uL,3.0)	30%
9	DCDMH (5.0)	40%
10	$PhICl_2$	55%
11	Palauchlor (5.0)	50%
12	NCS (1),HBr(50uL,3.0)	70% 2
13	NCS (1), HCl(50uL),IL(10uL,3.0)	90%
14	NCS (1),HBr(50uL),IL(10uL,3.0)	85% 2

With two optimized sets of reaction conditions in hand (Table 1, entries 4 and 14), we evaluated the substrate scope of the selective C(sp2)–H chlorination and bromination reactions. Visible-light-promoted late-stage chlorination of quinones, (hetero)arenes, natural products and drugs. As shown in Scheme 1, a diverse array of quinolones, arenes, and heteroarenes underwent NCS/HCl-mediated chlorination under MW light irradiation at 300 watt , affording the corresponding C(sp²)–H chlorination products (2-33) with excellent regioselectivity. A variety of functional groups, including halogen atoms

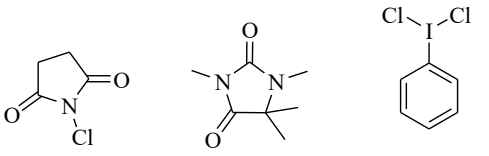
(F, Cl, Br), ethers, esters, amides, tertiary amines, carboxylic acids, cyano groups, and sulfonyl groups, were well tolerated under these conditions. Specifically, 1,4-benzoquinone delivered 56% of mono-chlorinated and 32% of di-chlorinated products (3 and 3') under the standard chlorination conditions. However, upon precisely reducing the aqueous HCl loading to 3.0 equivalents, mono-chlorinated benzoquinone (3) is obtained as the sole isolable product in 87% isolated yield. 1,4-Benzoquinones containing electron-withdrawing chloride substituents or electron-donating groups (Me- and MeO-) all gave corresponding mono-chlorinated products in high yields (4-10). Among the tested naphthoquinones, increased steric hindrance of the naphthoquinones has a negative effect on the reaction yield (11 vs 12). Moreover, the electronegativity of substituents on naphthoquinones also has a slight impact on the yield of the chlorination, as evidenced by the contrasting results between 2-Chloro-1,4-naphthoquinone (12) and Menadione (13). 1,4-Anthraquinone also worked under the standard chlorination conditions, but resulted in relatively low yield of the corresponding dichlorination product (14). Likewise, by adjusting the aqueous HCl to 3.0 equiv we sought to obtain the mono-chlorinated 1,4-anthraquinone; regrettably, 1,4-anthraquinone afforded only a trace amount of the desired mono-chloro product (~3%), with 90% of the starting material being recovered. Additionally, various substituted electron-rich arenes can all be smoothly chlorinated with moderate to good yields and excellent regioselectivities (15-24). Notably, C–H chlorination of ethoxybenzene exclusively affords the para-substituted chlorination product (16), with no ortho-chlorinated product observed, as a consequence of steric hindrance. Moreover, the tertiary amine of 1-phenylpiperidine remains intact, despite its oxidant sensitivity, likely due to protection by protonation under the acidic condition (25). Furthermore, heteroarenes such as pyrazole, indole, imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine, and thiophene derivatives were all efficiently chlorinated with high regioselectivity (26-32). Significantly, the electron-deficient heteroarene 2,6-dimethoxypyridine also performed in the chlorination system, although with a lower isolated yield, e.g., 33. Regrettably, other electron-deficient (hetero)aromatic compounds—including quinoline, benzoic acid, methyl benzoate, and nitrobenzene—proved entirely unreactive under the optimized conditions (see the Supporting Information for details, Scheme S7). The mild reaction conditions and excellent functional group compatibility enable this selective chlorination protocol to be readily applied to the late-stage chlorination of pharmaceuticals and natural products (Scheme 1, compounds 1 and 34-42). Remarkably, a diverse range of drugs and drug fragments, including naproxen (1), leflunomide (34), apremilast (35), alogliptin derivative (36), and acetaminophen derivative (37), successfully underwent the selective aromatic C(sp^2)–H chlorination reaction, affording the desired chlorinated products in moderate to good yields. Moreover, the chlorinated analogs of caffeine (38), xanthotoxin (39), coumarin (40-41), and uracil (42) were each efficiently accessed in a single step using this protocol. Visible-light-promoted late-stage bromination of quinolones, (hetero)arenes, natural products and drugs. As shown in Scheme 2, the visible-light-promoted C(sp2)–H bromination reactions of quinones, arenes, and heteroarenes with NaNO2 and aqueous HBr as the bromine donor also demonstrated excellent efficiency, site-selectivity and functional group tolerance (43-67). Notably, in the bromination of 1,4-dimethoxybenzene and 1,3-dimethoxybenzene, our standard conditions afforded the dibrominated products 51 and 52 in excellent yields. However, by precisely reducing the aqueous HBr loading to 1.7 equivalents, both substrates provided the monobrominated product in 90 % yield. As expected, the NaNO2/HBr mediated bromination system was successfully employed for the late-stage bromination of pharmaceuticals and natural products (Scheme 2, 2 and 68-79). Particularly, the system exhibited excellent tolerance towards acid-sensitive groups (e.g., ether, alkene), base-sensitive groups

(e.g., amide, ester, carboxylic acid), and oxidant-sensitive groups (e.g., tertiary amine, N-heterocycle, aldehyde). Specifically, a range of drugs and drug fragments, such as naproxen, leflunomide, apremilast, an alogliptin derivative, and an acetaminophen derivative, underwent bromination under our optimized conditions, affording the desired products 2 and 68-71 in 48-91% yield with high regioselectivity. Moreover, the bromination of several natural products, including xanthotoxin (72), coumarin (73 and 74), uracil (76), veratrole (76), and vanillin (77), afforded the corresponding brominated products in moderate to high yields (56-90%). Given the importance of tyrosine and tryptophan in proteins and peptide drugs such as alarelin and oxytocin, we explored the late-stage bromination of these amino acids. Encouragingly, the C(sp^2)–H bromination of N-benzoyl tyrosine methyl ester and N-phthaloyl tryptophan pentenyl ester under standard visible-light-promoted conditions afforded the corresponding brominated products with good yields and excellent region-selectivity (78 and 79). The simplicity, generality, and low cost of this NCS/HX system suggest its potential utility for the derivatization of specialty chemicals and the development of novel bioactive compounds.



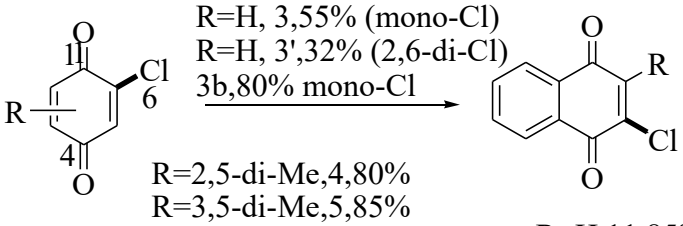
naproxen (0.1 mmol) 1 2

Chlorinating reagent:: HCl (37% aq.)



NCS DCDMH $PHICl_2$

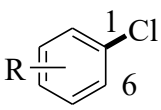
Quinones chlorination:



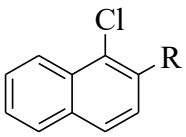
R=2,5-di-Me,4,80%
R=3,5-di-Me,5,85%
R=2,5-di-Cl,6,90%
R=3,5-di-Cl,7,92%
R=2,5-di-Ph8,88%
R=2,3,5-tri-Me 9,80%
R=2,3-di-OMe-5-Me-10,90%

R=H,11,85%,R=Me,12,75%,R=Cl,13,90%
14,45% (di-chlo)

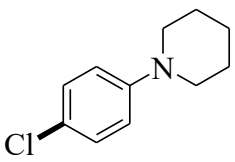
Arenes chlorination:



R=2-NHC(O)Ph,15,50%
R=4-OEt,16,72%
R=3-Me-4-OMe,17,85%
R=3,4-di-OMe,18,80%
R=2,4-di-OMe,19,85%
R=2,5-di-OMe,20,65%
R=2,4,6-tri-OMe,21,80%
R=2-Me-4,6-di-OMe,22,65%(2,6-di-Cl)

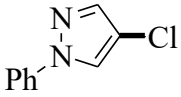


R=OMe,23,85%
R=NHHC(O)Ph,24 75%

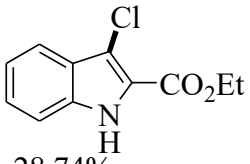


25,65%

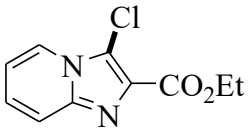
Heteroarenes chlorination:



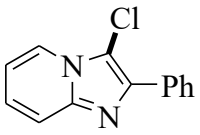
27, 70%



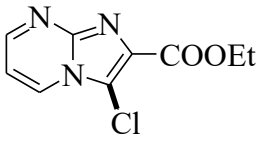
28,74%



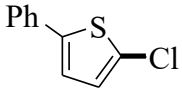
29,85%



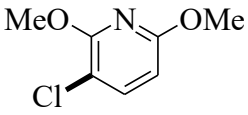
30,80%



31,63 %

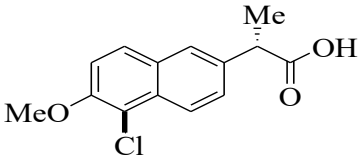


32%, 80%

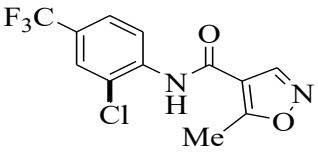


33,35%

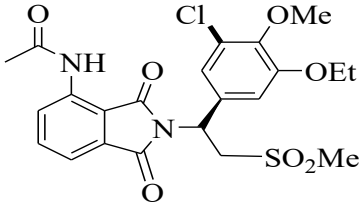
Natural product and drug derivatives:



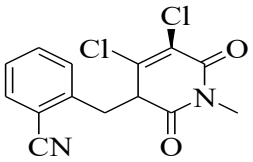
Naproxen 1,79%



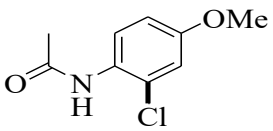
Leflunomide,34,65%



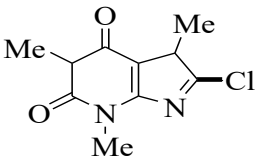
Apremilast,35,70%



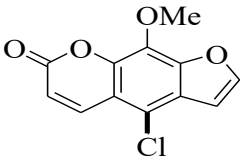
Alogliptin derivatives,3 6,70%



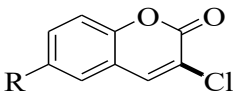
Paracetamol derivatives,37,82%



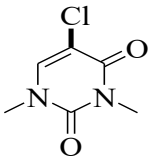
Caffeine,38,86%



Xanthotoxin 39,85%



Coumarin
R=H,40,70%
R=Me,41, 65%



Dimethyl uracil 42,85%

Conclusion:

In summary, we have developed a microwave promoted, versatile, tunable, and radical-mediated strategy for the selective C(sp^2)–H chlorination and halogenation of quinones, (hetero)arenes, natural products and drugs. This practical method is enabled by the in situ generation of the reactive chlorinating reagent, nitrosyl halide, from NCS and aqueous HX. Significantly, the use of commercially available and inexpensive reagents, combined with the mild reaction conditions, broad substrate scope, scalability, and excellent functional group tolerance, renders this protocol particularly useful for the

rapid and direct construction of halogenated new drug candidates and highly competitive for the late-stage halogenation of complex bioactive molecules.

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