Practical and Metal-Free Electrophilic Aromatic Halogenation by Interhalogen Compounds Generated In Situ from *N*-Halosuccinimide and Catalytic TMSCl

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Abstract: Halomonochloride compounds (ClCl, BrCl, ICl) generated in situ from *N*-halosuccinimide and catalytic chlorotrimethylsilane (TMSCl, 0.1 equiv) can efficiently halogenate aromatic compounds to give halogenated products in good to excellent yields and selectivities. The reaction can be carried out at room temperature or at lower temperatures, requires only one hour, is practical to apply to a wide range of substrates, and provides a simple access to a variety of haloarene compounds.

Key words: interhalogens, electrophilic aromatic halogenation, isocryptolepine, chlorotrimethylsilane, *N*-halosuccinimide

Halogen-substituted aromatic compounds are of major interest because they find many applications as important building blocks for the preparation of organometallic reagents[1] and as substrates for various cross-coupling reactions.[2] In addition, halogenated aromatic compounds display properties which may find various uses in the pharmaceutical, agrochemical, and medicinal industries.[3] In fact, several well-known and important drugs contain halogen atoms as the crucial part of their structures (Figure 1).

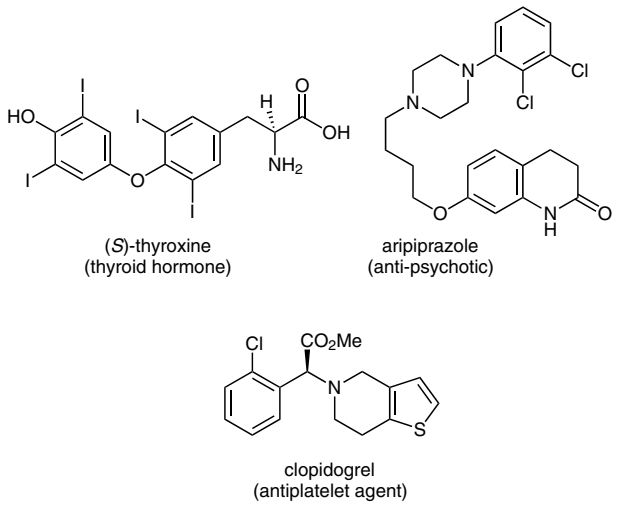

Figure 1 Examples of halogen-containing drugs

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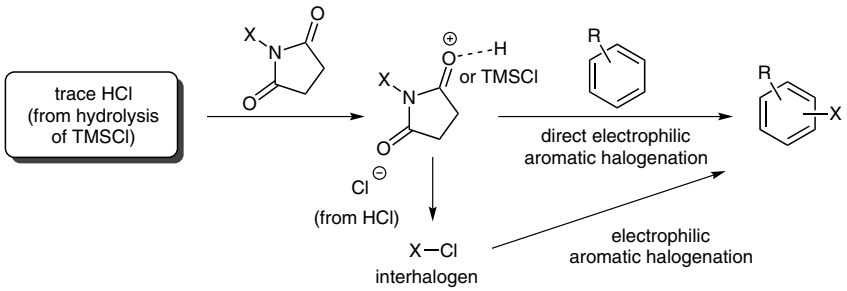
A number of examples have shown the utility of the classical electrophilic aromatic halogenation for the installation of a halogen atom. Several procedures employ Cl_2, Br_2, I_2, and interhalogen compounds (ICl and IBr) as the electrophilic halogenating reagents. However, *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), and *N*-iodosuccinimide (NIS) have become more common and convenient alternatives, especially to Cl_2, Br_2, and interhalogens, which are toxic and more difficult to handle. For some unreactive substrates, the employment of catalysts is necessary to promote the halogenation reaction. These catalysts include Lewis acids, such as $AlCl_3$,[4] $ZrCl_4$,[5] $AuCl_3$,[6] and $FeCl_3$[7] and protic acids, namely TFA,[8] AcOH,[9] *p*-TsOH,[10] and $HClO_4$.[11] Moreover, heat and/or stoichiometric amounts of promoters may be needed under certain conditions.[12] For reactions utilizing metal Lewis acids, trace amounts of metal may remain in the product, which can be an important concern especially in the pharmaceutical industry where final products with the complete absence of trace metal are extremely important. Due to these restrictions and limitations, a mild, practical, and metal-free electrophilic aromatic halogenation is still actively investigated and remain a highly desirable protocol.

As mentioned previously, protic acids are known to activate *N*-halosuccinimides (NXSs) in aromatic halogenations. Recently, Shi[13] and Mahajan[14] have shown that halide ions from metal halide salts (LiBr and NaCl) can react with NBS or NCS to generate Br_2 or Cl_2 in situ. Inspired by our recent work using a chlorotrimethylsilane (TMSCl)–LiBr combination in wet MeCN for the in situ production of HBr,[15] we envisioned that TMSCl in wet solvent could provide protons and chloride ions (as HCl), which in the presence of NXS may generate interhalogen XCl in situ for electrophilic aromatic halogenations as shown in Scheme 1.

To examine the possibility of the proposed reaction, 4-bromoanisole (**1a**) was selected as the substrate for screening with NCS as the halogenating agent(Table 1).

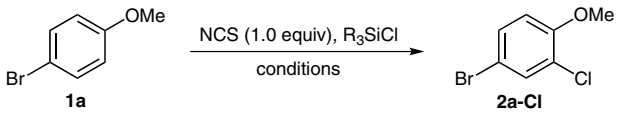
As seen in Table 1, we found that indeed the electrophilic aromatic chlorination could be effected using TMSCl and NCS. Both CH_2Cl_2 and DCE were found inefficient for the chlorination (entries 1 and 2). The reaction was less ef-



Scheme 1 Proposed generation of interhalogens from TMSCl

ficient when conducted in ethereal solvents, including diethyl ether and THF (entries 3 and 4). When a non-polar solvent such as hexane was employed, the reaction gave no conversion at all (entry 5). The reaction became more efficient when conducted in EtOH (entry 6), which provided a 56% conversion. The reaction could be improved further when performed in solvents such as $MeNO_2$ and MeCN which provided a range of noticeably better conversions (entries 7–11). In these solvents, the reactions proceeded well even at 0 °C using one equivalent of NCS with conversions up to 97% in as little as 30 minutes. In addition, the amount of TMSCl could be reduced to only 0.1 equivalent, resulting in up to 96% conversion when conducting the reaction in MeCN at room temperature for one hour (entry 11). When anhydrous MeCN was used, the conversion was lower (47%), indicating that the presence of water was crucial for an efficient reaction (entry 12). In the absence of TMSCl, no conversion was observed (entry 13), which proved that it was necessary for the reaction. In addition to TMSCl, *tert*-butyldimethylsilyl chloride (TBSCl) was also attempted and found to effect a lower conversion (entry 14), which may be attributed to the slower rate of hydrolysis due to steric hindrance, hence lowering the effective concentration of HCl. We next attempted the reaction with 0.1 equivalent of concd HCl which was found to give 73% conversion (entry 15). This result seemed to confirm the necessary role of HCl (Scheme 1) in our halogenation with NCS. Other protic acids were also attempted for comparison (entry 16) and their efficiency was found to be inferior to TMSCl, giving conversions ranging from 4% to 29%.

Table 1 Optimization of Chlorination of 4-Bromoanisole



Entry	Solvent[a]	Acid (Equiv)	Temp (°C)	Time (min)	Conversion[b] (%)
1	CH_2Cl_2	TMSCl (1.0)	0	30	20
2	DCE	TMSCl (1.0)	0	30	12
3	Et_2O	TMSCl (1.0)	0	30	0
4	THF	TMSCl (1.0)	0	30	9
5	hexane	TMSCl (1.0)	0	30	0
6	EtOH	TMSCl (1.0)	0	30	56
7	$MeNO_2$	TMSCl (1.0)	0	30	80
8	**$MeNO_2$**	**TMSCl (1.0)**	**r.t.**	**30**	**97**
9	MeCN	TMSCl (1.0)	0	30	75
10	MeCN	TMSCl (1.0)	r.t.	30	95
11	**MeCN**	**TMSCl (0.1)**	**r.t.**	**60**	**96**
12	MeCN[c]	TMSCl (0.1)	r.t.	60	47
13	MeCN	–	r.t.	60	0
14	MeCN	TBSCl (0.1)	r.t.	60	53
15	MeCN[c]	HCl (0.1)[d]	r.t.	60	73
16	MeCN	protic acids[e] (0.1)	r.t.	60	4–29

[a] Analytical reagent grade solvents were used except where indicated.
[b] Determined by ^1H NMR.
[c] Anhyd MeCN was used.
[d] Concd HCl was used.
[e] Protic acids were employed: Si-TsOH (conversion 15%), *p*-TsOH (conversion 10%), TfOH (conversion 29%) and TFA (conversion 4%).

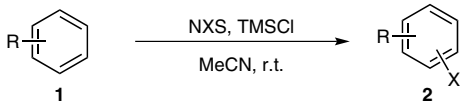
In general, the reaction was equally efficient in both $MeNO_2$ and MeCN, however the latter is preferred for being more easily removable, promoting the practicality of the reaction. Therefore, MeCN was chosen as the solvent for our optimized conditions with 0.1 equivalent of TMSCl and 1.0 equivalent of halogenating agent (NCS, NBS or NIS) at room temperature for one hour.

We next investigated the scope of the reaction, and the results are summarized in Table 2. Several substrates could be easily and effectively halogenated with NCS, NBS, and NIS under the general and optimized conditions. In all cases, the reactions were conducted at room temperature and in most cases they were complete within one hour. For 4-bromoanisole, the reaction proceeded readily to give **2a-Cl** or **2a-Br** in excellent yields (entry 1). For anisole, the reaction proceeded readily with NCS or NBS to give the desired products in excellent yields as regioisomeric mixtures with preference for the *p*-halogenated products (entry 2). Propargylic ether **1c** could be halogenated with NCS or NBS to give the desired products in excellent yields and regioselectivities (entry 3). It is espe-

cially noteworthy that no addition of the interhalogen to the alkyne was observed with NCS or NBS. However, for 4-iodoanisole (**1d**), only NBS provided the desired product in 77% yield, whereas no conversion was observed with NCS. As for multiply oxygenated substrates, the reactions generally proceeded smoothly and provided the expected products in good to excellent yields and excellent regioselectivities (entries 5–11). It is worth to mention that for the highly electron-rich 1,3,5-trimethoxybenzene (**1j**), we also conducted the reaction without TMSCl for comparison. We found that the reaction with TMSCl proceeded to a full conversion within one hour to give the monochlorinated and dichlorinated products in 93% and 4% yields (Table 2, entry 10), while for the reaction without TMSCl we observed 88% conversion within the same amount of time. These results demonstrated the effect of TMSCl in accelerating the reaction to a full conversion. For toluene, the reaction proceeded uneventfully to give the desired products in moderate yields as regioisomeric mixtures with some remaining starting material (entry 12).

For aniline derivatives (entries 13–15), the reactions proceeded as expected to give the desired products in all cases. For the unprotected *N*-methylaniline, the reaction with NCS gave only 21% of the expected *p*-chloro product (**2m-Cl**) along with other unidentified by-products, possibly a mixture of overchlorinated compounds. For the reaction with NBS, *p*-bromo product **2m-Br** was obtained in 66% yield as well as 6% of dibrominated product **2m-diBr** and other inseparable unidentified by-products (entry 13). For anilines **1n** and **1o**, the reactions proceeded smoothly to furnish the desired halogenated products in excellent overall yields as regioisomeric mixtures (entries 14 and 15). For both *N*-protected homoveratrylamine derivatives **1p** and **1q**, the reactions were smooth to give the corresponding chloro- and iodo products in good to excellent yields for **1p** (entry 16) and good yields of the corresponding chloro- and bromo products for **1q** (entry 17). It should be noted that the acid-labile Boc group could withstand our conditions, and we observed very clean conversions in the crude reaction mixtures.

Table 2 Scope of TMSCl-Catalyzed Halogenation



1 **2**

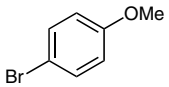
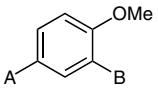
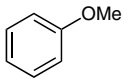
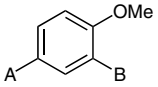
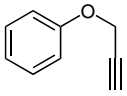
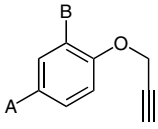
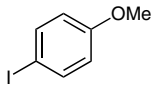
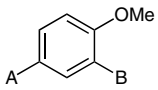
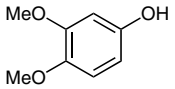
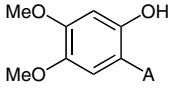
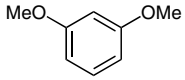
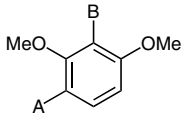
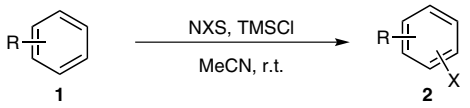
Entry	Substrates (**1**)	Products (**2**)/Yields[a]
1	 **1a**	 X = Cl: **2a-Cl**; A = Br, B = Cl; 88% **2a-diCl**; A = B = Cl; 11% X = Br: **2a-Br**; A = B = Br; 95%
2	 **1b**	 X = Cl: **2b-*p*-Cl**; A = Cl, B = H; 86% **2b-*o*-Cl**; A = H, B = Cl; 11% X = Br: **2b-*p*-Br**; A = Br, B = H; 81% **2b-*o*-Br**; A = H, B = Br; 2% **2b-diBr**; A = B = Br; 9%
3	 **1c**	 X = Cl: **2c-*p*-Cl**; A = Cl, B = H; 88% **2c-*o*-Cl**; A = H, B = Cl; 7% X = Br: **2c-*p*-Br**; A = Br, B = H; 91% **2c-*o*-Br**; A = H, B = Br; 4%
4	 **1d**	 X = Cl: **2d-Cl**; A = I, B = Cl; NR X = Br: **2d-Br**; A = I, B = Br; 77% **2d-diBr**; A = B = Br; 8%
5	 **1e**	 X = Cl: **2e-Cl**; A = Cl; 91% X = Br: **2e-Br**; A = Br; 70%
6	 **1f**	 X = Cl: **2f-Cl**; A = Cl, B = H; 64% **2f-diCl**; A = B = Cl; 5% X = Br: **2f-Br**; A = Br, B = H; 77%

Table 2 Scope of TMSCl-Catalyzed Halogenation (continued)



1 2

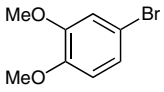
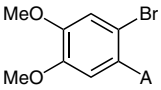
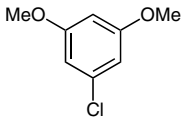
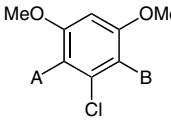
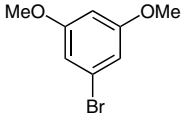
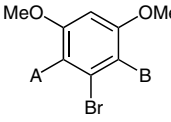
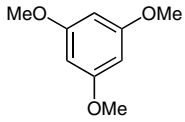
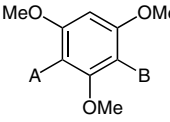
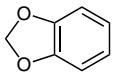
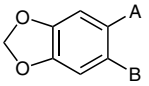
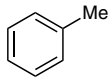
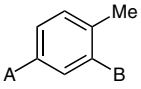
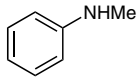
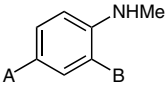
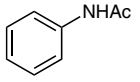
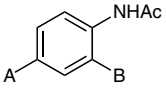
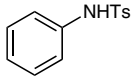
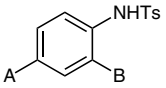
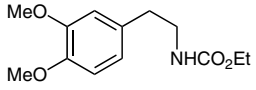
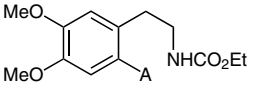
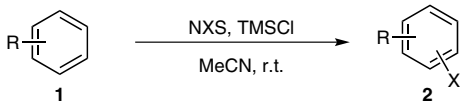
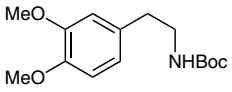
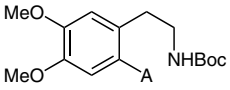
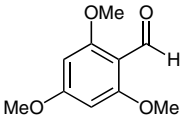
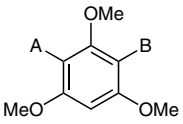
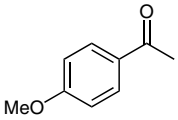
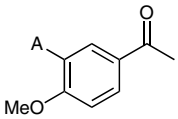
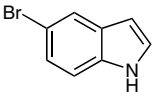
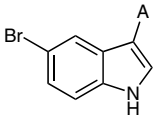
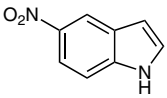
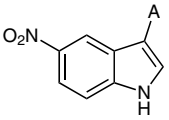
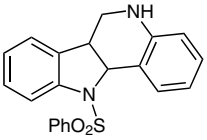
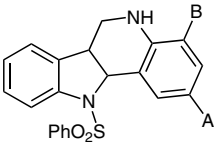
Entry	Substrates (**1**)	Products (**2**)/Yields[a]
7	 **1g**	 X = Cl: **2g-Cl**; A = Cl; 99% X = Br: **2g-Br**; A = Br; ≤99% X = I: **2g-I**; A = I; 86% **1g**; 9%
8	 **1h**	 X = Cl: **2h-Cl**; A = Cl, B = H; 73% X = Br: **2h-Br**; A = Br, B = H; 82% X = I: **2h-I**; A = I, B = H; 62% **2h-diI**; A = B = I; 7%
9	 **1i**	 X = Cl: **2i-Cl**; A = Cl, B = H; 75% X = Br: **2i-Br**; A = Br, B = H; 89% X = I: **2i-I**; A = I, B = H; 59% **2i-diI**; A = B = I; 6%
10	 **1j**	 X = Cl: **2j-Cl**; A = Cl, B = H; 93% **2j-diCl**; A = B = Cl; 4% X = Br: **2j-Br**; A = Br, B = H; 58% **2j-diBr**; A = B = Br; 6%
11	 **1k**	 X = Cl: **2k-Cl**; A = Cl, B = H; 73% **2k-diCl**; A = B = Cl; 15% **1k**; 2% X = Br: **2k-Br**; A = Br, B = H; 76% **2k-diBr**; A = B = Br; 16%
12[b]	 **1l**	 X = Cl: **2l-*p*-Cl**; A = Cl, B = H; 33% **2l-*o*-Cl**; A = H, B = Cl; 22% **1l**; 43% X = Br: **2l-*p*-Br**; A = Br, B = H; 57% **2l-*o*-Br**; A = H, B = Br; 24% **1l**; 11%
13	 **1m**	 X = Cl: **2m-Cl**; A = Cl, B = H; 21% X = Br: **2m-Br**; A = Br, B = H; 66% **2m-diBr**; A = B = Br; 6%
14	 **1n**	 X = Cl: **2n-*p*-Cl**; A = Cl, B = H; 75% **2n-*o*-Cl**; A = H, B = Cl; 24% X = Br: **2n-*p*-Br**; A = Br, B = H; 94% **2n-*o*-Br**; A = H, B = Br; 4%
15	 **1o**	 X = Cl: **2o-*p*-Cl**; A = Cl, B = H; 79% **2o-*o*-Cl**; A = H, B = Cl; 14% X = Br: **2o-*p*-Br**; A = Br, B = H; 79% **1o**; 12%
16	 **1p**	 X = Cl: **2p-Cl**; A = Cl; 76% X = I: **2p-I**; A = I; 91%

Table 2 Scope of TMSCl-Catalyzed Halogenation (continued)



Entry	Substrates (**1**)	Products (**2**)/Yields[a]
17	 **1q**	 X = Cl: **2q-Cl**; A = Cl; 74% X = Br: **2q-Br**; A = Br; 75%
18	 **1r**	 X = Cl: **2r-Cl**; A = Cl, B = CHO; 87% **2r-diCl**; A = B = Cl; 2% X = Br: **2r-Br**; A = Br, B = CHO; 99%
19	 **1s**	 X = Cl: **2s-Cl**; A = Cl; complex mixture X = Br: **2s-Br**; A = Br; 87% **1s**; 7%
20	 **1t**	 X = Cl: **2t-Cl**; A = Cl; 98% X = Br: **2t-Br**; A = Br; complex mixture
21	 **1u**	 X = Cl: **2u-Cl**; A = Cl; 83% X = Br: **2u-Br**; A = Br; complex mixture
22	 **1v**	 X = Cl: **2v-*p*-Cl**; A = Cl, B = H; 56% **2v-*o*-Cl**; A = H, B = Cl; 16% X = Br: **2v-*p*-Br**; A = Br, B = H; 79% **2v-diBr**; A = B = Br; 15% X = I: **2v-*p*-I**; A = I, B = H; 90%

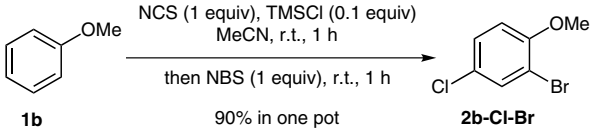
[a] Isolated yield.
[b] Regioselectivities and yields were determined by GC using *p*-anisaldehyde as the internal standard.

For compound **1r** (2,4,6-trimethoxybenzaldehyde, entry 18), we found the reaction to proceed cleanly to give both chloro- and bromo products in excellent efficiencies. For the reaction with NCS, however, a trace amount (ca. 2%) of chlorodeformylation product, which is the same compound as **2j-diCl**, was also obtained. As for compound **1s**, the reaction with NCS afforded a complex mixture, while the reaction with NBS gave 95% yield of the desired product **2s-Br** (entry 19). Our halogenation conditions could be applied to heterocycles as shown in entries 20 and 21. For indole **1t**, we found the reactions proceeded normally with NCS to give indole **2t-Cl** in 98% yield (entry 20). However, the reaction with NBS only showed decomposition. The same was also observed with indole **1u**, where we could obtain the desired indole **2u-Cl** in excellent yield while decomposition was observed with NBS (entry 21).

Finally, we attempted our halogenation with compound **1v** which has been used as a synthetic precursor to isocryptolepine analogues,[16] compounds possessing antimalarial and anticancer activities[17] (entry 22). As seen in Table 2, the chlorination of **1v** with NCS afforded two isomeric products **2v-*p*-Cl** (56%) and **2v-*o*-Cl** (16%). The reaction of **1v** with NBS afforded the desired **2v-*p*-Br** in good yield (79%) along with dibrominated product **2v-diBr** in 15% yield. The reaction of compound **1v** with NIS proceeded smoothly to provide only **2v-*p*-I** as the single product in 90% yield. These examples highlight the convenience and efficiency of our halogenation procedure in installing halogen atoms onto compounds of advanced structures, which will be useful in preparing compounds for biological activity studies. Specifically, isocryptolepine analogues containing halogen atoms at various positions in the structures have been evaluated for their

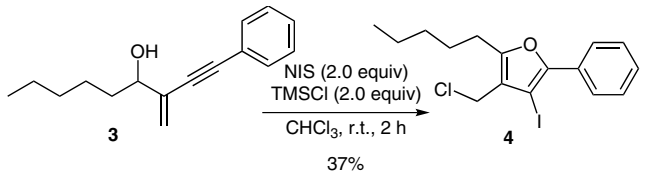
activities against both drug-sensitive and drug-resistant strains recently.[17e]

Further practicality of this procedure is shown in Scheme 2; anisole could be halogenated sequentially in one pot by controlling the order of addition of NXS to give the desired dihalogenated **2b-Cl-Br** with high regiocontrol in 90% yield based on ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.



Scheme 2 Sequential halogenation of anisole

As proposed in Scheme 1, we set out to prove the existence of interhalogen compounds (XCl) generated in situ from NXS and TMSCl by performing a reaction with alcohol **3**, which we have shown previously that it could be converted into furan **4** using ICl.[18] In the current reaction, we subjected compound **3** to ICl generated from NIS (2.0 equiv) and TMSCl (2.0 equiv) in $CHCl_3$ at room temperature, and we obtained the expected iodofuran **4** in 37% yield unoptimized (Scheme 3).



Scheme 3 ICl-promoted cyclization of **3** with NIS and TMSCl

Additionally in the beginning of the reaction, the solution of alcohol **3** and NIS appeared light orange. Once TMSCl was added to the reaction, it immediately turned dark brown. Upon completion, the reaction was quenched with aqueous sodium metabisulfite ($Na_2S_2O_5$), causing the color to disappear and indicating that the interhalogen species was reduced. All of these observations support our proposal that interhalogen species are generated during the reaction.

In conclusion, we have demonstrated that TMSCl could be used as a universal and powerful catalyst which in combination with *N*-halosuccinimide (NXS) leads to the formation of interhalogen compounds (XCl) in MeCN.[19] The interhalogens generated by this innovative combination can be used to efficiently halogenate aromatic compounds to give the desired haloarenes free of metal contaminant in good to excellent efficiencies. The current procedure presents a significant improvement for electrophilic aromatic halogenations, which is highlighted by the practicality in conducting the reaction, the widely available reagents (NCS, NBS, NIS) and catalyst (TMSCl), and the applicability to a wide range of substrates, all of which make this procedure a very robust and attractive method for halogenating aromatic compounds.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(19) **General Procedure for the Electrophilic Aromatic Halogenation; 4-Bromo-2-chloro-1-methoxybenzene (2a-Cl) and 2,4-Dichloro-1-methoxybenzene (2a-diCl; Ref 20)**: To a solution of 4-bromoanisole (**1a**; 200.8 mg, 1.09 mmol, 1.0 equiv) in MeCN (2 mL) was added *N*-chlorosuccinimide (NCS; 158.3 mg, 1.19 mmol, 1.1 equiv) at r.t. to give a slightly cloudy mixture. Chlorotrimethylsilane (TMSCl; 14 μL, 0.11 mmol, 0.1 equiv) was then added dropwise to the reaction mixture. Within a few minutes, the reaction mixture became clear pale yellow solution. The mixture was stirred continuously at r.t. for 1 h and H_2O was added to it. The separated aqueous layer was extracted with EtOAc. The combined organic phases were washed with sat. aq NaCl, dried over Na_2SO_4 and concentrated. The crude material was purified by flash SiO_2 column eluted with 5–10% EtOAc–hexane to give a mixture of 4-bromo-2-chloro-1-methoxybenzene (**2a-Cl**) and 2,4-dichloro-1-methoxybenzene (**2a-diCl**): 237.0 mg yield (88% of **2a-Cl** and 11% of **2a-diCl**, based on NMR ratio **2a-Cl/2a-diCl** = 7.1:1.0; as a pale yellow solid). IR (neat): 2854, 1288, 1222, 1028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 2.4 Hz, 1 H), 7.36 (d, *J* = 2.4 Hz, 0.15 H, minor), 7.32 (dd, *J* = 8.7, 2.4 Hz, 1 H), 7.19 (dd, *J* = 9.0, 2.7 Hz, 0.14 H, minor), 6.84 (d, *J* = 8.7 Hz, 0.15 H, minor), 6.79 (d, *J* = 8.7 Hz, 1 H), 3.87 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 132.6, 130.5, 129.9 (minor), 127.6 (minor), 123.6, 113.3, 112.8 (minor), 112.5, 56.34, 56.28 (minor).

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