Biphasic Electrophilic Halogenation of Activated Aromatics and Heteroaromatics with *N*-Halosuccinimides Catalyzed by Perchloric Acid

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Catalytic amounts of 70% perchloric acid (0.1–10, mostly 0.1–1, mol %, based on substrate) initiate the regioselective halogenation of activated aromatics [mesitylene, 1,3-dimethoxybenzene, 2,3-dimethylanisole, *o*-xylene] and heteroaromatics [thiophene, its 2-methyl, 2-halo (chloro, bromo, iodo), and 3-bromo derivatives] with *N*-halosuccinimide (NXS, X = Cl or Br) in two-phase solid–liquid systems (NXS/hexane or NXS/CCl_4) at room temperature to give ring-halogenated products in high yields. For example, thiophene is transformed to 2-halo or 2,5-dihalo derivatives (yield 82–98%) using 1 or 2 equiv of NXS, respectively. Unsymmetrical 2,5-dihalothiophenes are obtained in 70–82% yield by reacting 2-halothiophenes with an appropriate NXS. The reaction of 3-bromothiophene with NBS affords 2,3-dibromothiophene in 93–99% yield. 1,3-Dimethoxybenzene and 2,3-dimethylanisole are halogenated regiospecifically at the 4 position to give the corresponding products in 81–94% yield.

Introduction

A two-phase catalytic method for the execution of various reactions involving anions, known as phase-transfer catalysis (PTC), is now a widely recognized and extremely useful tool for organic synthesis.[1] The first attempts at the application of PTC to cationic reactions were undertaken soon after the appearance of PTC.[2] In essence, formal antipodes of typical phase-transfer agents must be found. These are compounds containing a bulky lipophilic anion and a small hydrophilic cation capable of exchanging with the cation of the electrophilic reagent and thus transferring and solubilizing it in low polarity media as an ion pair with the catalyst anion. Sodium *p*-dodecylbenzene sulfonate (SDS) catalyzes the biphasic azo coupling of $4\text{-}O_2NC_6H_4N_2^+Cl^-$ with *N*-ethylcarbazole or Ph_2NH in a CH_2Cl_2/H_2O system.[3] Also, SDS accelerates the hydrogenation of C=C bonds catalyzed by $Co_2(CO)_8$ or $Co_2(PBu_3)_2(CO)_6$ in a C_6H_6/aqueous HBF_4 system.[4] Highly lipophilic sulfonic acids catalyze the biphasic saponification of $p\text{-}O_2NC_6H_4OCOCH_3$ with aqueous H_2SO_4,[5] as well as the condensation of styrene with aqueous formaldehyde (Prins reaction) in a C_6H_6/H_2O system.[6] The latter reaction is also smoothly catalyzed by solid acids, viz. strongly acidic cation exchangers with a sulfonic acid functionality.[7] Both strongly and weakly acidic cation-exchange resins are active catalysts for the hydroxymethylation of furan and some of its derivatives by aqueous formaldehyde in two-phase systems.[8] Acid-resistant sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate[9] was successfully used as a catalyst in biphasic azo coupling[10] and Friedel–Crafts alkylation.[11] Sodium picrate was reported to catalyzed the chlorination of furylsilanes and furylgermanes with chloramine T in a $CHCl_3/H_2O$ system.[12]

The application of *N*-halosuccinimides (NXS) for the electrophilic aromatic and heteroaromatics substitution is rather limited,[13] although NXS are known sources of positive halonium species.[14] The heterolysis of an N–X bond and aromatic nuclear halogenation can be achieved in solvents with high dielectric constants such as propylene carbonate,[15] sulfuric acid,[16] or dimethylformamide[17] or in the presence of Lewis acids. The activity of the latter is not catalytic since at least a stoichiometric amount of the Lewis acid is needed for halogenation to occur.[13a] The

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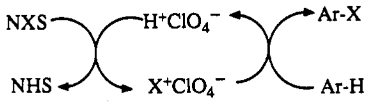
recent report by Fraser-Reid and co-workers[18] on the successful application of the NXS (X = I)/CF_3SO_3H pair for the generation of iodonium ion suggested to us that the protonation of NXS with strong, highly lipophilic acid, such as perchloric acid, could generate positive halonium species capable of halogenating aromatics in a *catalytic* manner in low polarity media according to the following scheme:



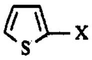
Herein, we report our results on the study of the biphasic halogenation of activated aromatics and heteroaromatics with NXS in solid/liquid catalytic systems using perchloric acid as a catalyst. The latter should act as a phase-transfer agent transferring in situ generated halonium species into the bulk of the organic phase.

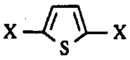
Results and Discussion

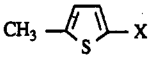
All reactions were carried out at room temperature in two-phase systems comprising a suspension of solid NXS (X = Cl or Br) in an organic solvent (hexane or carbon tetrachloride). Thiophene, its 2-methyl, 2-halo (chloro, bromo, and iodo) and 3-bromo derivatives, as well as methyl- and methoxy-substituted benzenes (mesitylene, 1,3-dimethoxybenzene, 2,3-dimethylanisole, *m*-xylene) were used as reactants. The concentration of the latter in the organic phase in all cases was 2 mmol/mL. The amount of catalyst ($HClO_4$) was varied from 0.1 to 10 mol % (based on substrate) depending on the reactivity of the substrate. The reaction course was monitored by GC and GC/MS analyses.

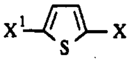
$$\mathrm{ArH} \xrightarrow[70\%\ \mathrm{HClO_4}\ (0.1\text{–}10\ \mathrm{mol}\ \%)]{\mathrm{NXS/solvent}} \underset{\mathbf{1}}{\mathrm{ArX}}$$

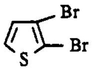
Halogenation of Thiophene and Its Derivatives. Prolonged stirring (24 h) of the heterogeneous mixture consisting of hexane (5 mL), NCS or NBS (10 mmol), and thiophene (10 mmol) at room temperature does not affect any transformations of the substrate. Only trace amounts of halogenated products were detected when the mixture was stirred at reflux temperature for several hours. Addition of catalytic quantities of 70% $HClO_4$ (0.1 mol % in the case of NBS and 0.5% in the case of NCS) to the reaction mixture initiates the halogenation which smoothly occurs at room temperature giving 2-chloro (**1a**) or 2-bromothiophenes (**1b**) in high yield. The formation of 2,5-substituted products is almost completely suppressed under the described conditions, their content in the reaction mixtures being less than 5%.[19] The dihalogenation reaction is one of the disadvantages of known procedures for the halogenation of thiophene.[20]


1a (X = Cl)
1b (X = Br)


1c (X = Cl)
1d (X = Br)


1e (X = Cl)
1f (X = Br)


1g (X = Cl, X^1 = Br)
1h (X = Br. X^1 = I)
1i (X = Cl, X^1 = I)


1j

The workup of the reaction mixtures is very simple, consisting of filtration of succinimide, evaporation of the solvent, and distillation of the residue. Monohalogenated thiophenes **1a** and **1b** were isolated in 85–90% yield. Similar results were obtained using CCl_4 as a solvent (Table I). The described method seems to be simpler and more convenient than those described previously.[20] The most recent procedure[21] affords 2-bromothiophene regioselectively and in high yield; however, the reaction protocol is rather complex involving an addition of a Br_2/48% HBr mixture to the solution of thiophene in an ether/48% HBr mixture at −20 °C or an addition of aqueous H_2O_2 to the mixture of thiophene, 48% HBr, and ether also at −20 °C. The workup is also much more laborious.

The halogenation of thiophene with NCS and NBS in hexane was also carried out in the presence of quaternary ammonium perchlorates ($Me_4N^+ClO_4^-$, $Et_4N^+ClO_4^-$, $Bu_4N^+ClO_4^-$) as well as by the use of hydrophilic inorganic (H_2SO_4) and lipophilic organic (picric) acids. Under identical conditions (1 mol % of catalyst, hexane as a solvent, room temperature), the activity of catalysts decreases in the following order: $HClO_4 \gg$ picric acid $\approx H_2SO_4 \gg (\mathrm{alkyl})_4N^+ClO_4^-$. Perchloric acid is the only catalyst among those studied where reaction proceeds to completion. Sulfuric and picric acid are much less active catalysts. For example, in the case of NBS, after 30 min reaction, the yield of 2-bromothiophene from thiophene was 100, 5, and 2% (GC data) in the presence of $HClO_4$, H_2SO_4, and $(NO_2)_3C_6H_2OH$, respectively. It is interesting to note that, despite low activity, tetraalkylammonium perchlorates do catalyze the halogenation of thiophene at room temperature (in the absence of catalyst the reaction does not occur at all) although the yield of 2-halothiophenes did not exceed 1–5% (reaction time, 24 h).

When 2 equiv of NXS are used for the biphasic halogenation of thiophene catalyzed by $HClO_4$, one can obtain the corresponding 2,5-dihalothiophenes (**1c** and **1d**) in high yield. The latter are also formed starting from 2-halo derivatives (**1a** or **1b**) and 1 equiv of NXS (Table I). Note that the transformation of **1a**,**b** to **1c**–**d** requires a larger concentration of the catalyst (1% for the reaction of **1b** with NBS and 10% (based on substrate) for the reaction of **1a** with NCS) as compared to that needed for the halogenation of thiophene (0.1–0.5%) due to the lower reactivity of 2-halothiophenes.

2-Methylthiophene under the same biphasic conditions is smoothly halogenated with NXS giving rise, as anticipated, to the corresponding 5-halo-2-methylthiophenes (**1e** and **1f**) as the major products in fair to good yields. In the case of chlorination, small amounts of isomeric 3-chloro-2-methylthiophene are also formed. Note that no side-chain halogenations occur using the NXS/$HClO_4$ system.

The biphasic catalytic halogenation of 2-halothiophenes with NXS is a simple, convenient and efficient route to

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Table I. Biphasic Halogenation of Thiophenes and Arenes with *N*-Halosuccinimides (NXS) in the Presence of Perchloric Acid[a]

starting material	NXS (mol equiv)	solvent	70% $HClO_4$ (mol %)	reactn time (h)	product	yield[b] (%)
thiophene	NCS (1)	hexane	0.5	12	2-chlorothiophene (**1a**)	88
	NCS (1)	CCl_4	0.5	12	**1a**	90
	NBS (1)	hexane	0.1	6 (0.5)[c]	2-bromothiophene (**1b**)	84 (90)[c]
	NBS (1)	CCl_4	0.1	5	**1b**	85
	NCS (2)	CCl_4	10.0	24	2,5-dichlorothiophene (**1c**)	82
	NBS (2)	hexane	1.0	24	2,5-dibromothiophene (**1d**)	95
	NBS (2)	CCl_4	1.0	4	**1d**	91
1a	NCS (1)	CCl_4	10.0	24	**1c**	82
1b	NBS (1)	CCl_4	1.0	24	**1d**	98
2-methylthiophene	NCS (1)	hexane	0.5	18	2-chloro-5-methylthiophene (**1e**)	91[d]
	NCS (1)	CCl_4	0.5	24	**1e**	94[d]
	NBS (1)	hexane	0.1	18	2-bromo-5-methylthiophene (**1f**)	80
	NBS (1)	CCl_4	0.1	20	**1f**	83
1a	NBS (1)	hexane	1.0	7	2-bromo-5-chlorothiophene (**1g**)	75
1a	NBS (1)	CCl_4	1.0	6	**1g**	82
2-iodothiophene	NCS (1)	hexane	3.0	24	2-chloro-5-iodothiophene (**1h**)	70
	NCS (1)	CCl_4	3.0	24	**1h**	74
	NBS (1)	hexane	1.0	24	2-bromo-5-iodothiophene (**1i**)	72
	NBS (1)	CCl_4	1.0	24	**1i**	70
3-bromothiophene	NBS (1)	hexane	5.0	24	2,3-dibromothiophene (**1j**)	93
	NBS (1)	CCl_4	5.0	24	**1j**	99
mesitylene	NCS (1)	hexane	1.0	48	2,4,6-trimethylchlorobenzene (**1k**)	81
	NCS (1)	CCl_4	1.0	48	**1k**	73
	NBS (1)	hexane	1.0	24	2,4,6-trimethylbromobenzene (**1l**)	94
	NBS (1)	CCl_4	1.0	22	**1l**	99
1,3-dimethoxybenzene	NCS (1)	hexane	1.0	20	2,4-dimethoxychlorobenzene (**1m**)	81
	NCS (1)	CCl_4	1.0	20	**1m**	88
	NBS (1)	hexane	1.0	4	2,4-dimethoxybromobenzene (**1n**)	83
	NBS (1)	CCl_4	1.0	1	**1n**	86
2,3-dimethylanisole	NCS (1)	hexane	1.0	24	4-chloro-2,3-dimethylanisole (**1o**)	90
	NCS (1)	CCl_4	1.0	15	**1o**	94
	NBS (1)	hexane	1.0	4	4-bromo-2,3-dimethylanisole (**1p**)	90
	NBS (1)	CCl_4	1.0	1	**1p**	85
m-xylene	NBS (1)	hexane	5.0	240	2,4-dimethylbromobenzene (**1q**)	72[e]

[a] Reaction conditions: substrate (10 mmol), NXS (1 or 2 mol equiv), solvent (5 mL), 70% $HClO_4$ (0.1–10 mol %), room temperature. [b] Isolated yield. [c] Reaction time and yield when using 1 mol % of 70% $HClO_4$. [d] Contains ca. 10% of isomeric 3-chloro-2-methylthiophene. [e] Conversion of starting material: 84%.

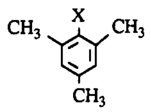
2,5-dihalothiophenes containing different halogen atoms (Table I). Thus, reaction of **1a** with NBS affords 2-bromo-5-chlorothiophene (**1g**) isolated in 25–82% yield. Alternatively, compound **1g** can be obtained by reacting **1b** and NCS under similar conditions. However, the latter route is somewhat less effective due to the competitive ipso-substitution[20e] of bromine resulting in parallel formation of the 2,5-dichloro derivative. Perchloric acid catalyzed two-phase halogenations of 2-iodothiophene with NCS and NBS afford 2-chloro-5-iodo- (**1h**) and 2-bromo-5-iodothiophene (**1i**), respectively, in good yield. In these cases, the ipso-substitution of iodine for more electronegative halogens[20e] also occurs. Nevertheless, compounds **1h** and **1i** are the major products which can be easily purified by distillation or using column chromatography on silica gel.

3-Bromothiophene smoothly reacts with NBS in hexane or CCl_4 in the presence of 5 mol % of $HClO_4$ to give 2,3-dibromothiophene regiospecifically and in quantitative yield[22] (Table I).

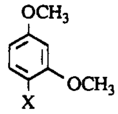
All halo-substituted thiophenes obtained are known compounds. They were identified by comparison of their physicochemical and spectral (^1H NMR, MS) data with those described in the literature.

It should also be noted that 2,5-dichloro- and 2,5-dibromothiophenes do not react with NCS and NBS, respectively, either in hexane or in CCl_4 in the presence of 5–10 mol % of $HClO_4$ (reaction time up to 48 h).

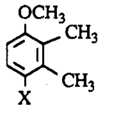
Halogenation of Activated Aromatics. As in the case of thiophene, in the absence of catalyst, mesitylene does not react with NCS or NBS in hexane or CCl_4 both at room temperature and under reflux. Catalytic amounts of 70% $HClO_4$ (1 mol %) initiate the halogenation and 2,4,6-trimethylhalobenzenes (**1k** and **1l**) are formed at room temperature in good to excellent yields (Table I).



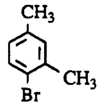
1k (X = Cl)
1l (X = Br)



1m (X = Cl)
1n (X = Br)



1o (X = Cl)
1p (X = Br)



1q

The most interesting results were obtained in the case of 1,3-dimethoxybenzene and 2,3-dimethylanisole which could give a mixture of isomeric halogenated derivatives. These compounds react with NXS regiospecifically (both in hexane and in CCl_4 in the presence of 1 mol % of 70% $HClO_4$) giving rise to 2,4-dimethoxyhalobenzenes (**1m** and **1n**) and 4-halo-2,3-dimethylanisoles (**1o** and **1p**) in high yields (Table I).

m-Xylene as one could anticipate, is much less reactive. Its reaction with NBS in hexane occurs very slowly (10 days) in the presence of 5 mol % of 70% $HClO_4$. The bromination also occurs mainly at position 4 to afford 2,4-dimethylbromobenzene (**1q**) in satisfactory yield.

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[22] Bromination of 3-bromothiophene with Br_2 in CCl_4 also gives 2,3-dibromothiophene: Gronowitz, S.; Dahlgren, K. *Arkiv Kemi* **1963**, *21*, 201.

However, in this case, an isomeric 2,6-dimethylbromobenzene is also formed as byproduct (ca. 10%). Under the same conditions, the reaction of *m*-xylene with NCS occurs even slower than that involving NBS and cannot be used for preparative purposes.

tert-Butylbenzene, toluene, and benzene also cannot be halogenated with NXS/$HClO_4$ under biphasic conditions. Therefore, *m*-xylene is obviously the limit of the applicability of the described two-phase method for the halogenation of aromatics.[23]

In conclusion, perchloric acid initiates the halogenation of heteroaromatics (thiophene, its methyl and halo derivatives) and activated aromatics and affords ring-halogenated products under mild conditions and in high yield and regioselectivity.

Experimental Section

All chemicals were purchased from commercial sources and were used as received. ^{1}H NMR spectra were obtained on a Gemini 200-MHz spectrometer using $CDCl_3$ as the solvent and Me_4Si as the internal standard. A VG 7070E spectrometer was used for mass spectral determinations. GC analyses were carried out on a Varian Vista 6000 instruments equipped by a column packed with 1.5% OV-17 + 1.95% OV-210 on chromosorb W-HP (100–120 mesh).

Representative Procedure for Biphasic Catalytic Halogenation. To a suspension of NBS (1.78 g, 10 mmol) in hexane (5 mL) were added 2-chlorothiophene (1.19 g, 10 mmol) and 70% $HClO_4$ (14 μL, 1 mol %), and the reaction mixture was stirred for 7 h at room temperature until disappearance of the starting material (GLC control). Potassium carbonate (ca. 20 mg) was added, the solids were filtered, the solvent was evaporated at room temperature, and the residue was distilled in vacuo to give 1.49 g (75%) of 2-bromo-5-chlorothiophene (1e), bp 45–46 °C/1 mm (lit.[24] bp 70 °C/18 mmHg). All other halogenations were carried out similarly using the same amounts of reagents. For the concentrations of perchloric acid, reaction times and product yields, see Table I. All products are known, and physical data (bp, IR, NMR, MS) were in accord with literature results.

Acknowledgment. We are grateful to British Petroleum and to the Natural Sciences and Engineering Research Council of Canada for support of this research.

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[23] It should be noted that sterically hindered 1,3,5-tri(*tert*-butyl)benzene also cannot be halogenated with NXS (X = Cl, Br)/$HClO_4$ in hexane or CCl_4.

[24] *CRC Handbook of Chemistry and Physics*, 68th ed.; CRC Press, Inc.; Boca Raton FL, 1987–1988; p C-512.