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/CCl4) 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 70-92% 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 regioselectively 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 anionic, 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 cation and a small hydrophilic anion 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-O2NC6H4N2Cl- with N-ethylnitrobenzene or Ph2NH in a CH2Cl2/H2O system.3 Also, SDS accelerates the hydrogenation of C=C bonds catalyzed by Co2(CO)8 or Co3-(PBu3)2(CO)8 in a C6H6/aqueous HBF4 system.4 Highly lipophilic sulfonic acids catalyze the biphasic saponification of p-O2NC6H4OCOC6H5 with aqueous H2SO4 as well as the condensation of styrene with aqueous formaldehyde (Prins reaction) in a C6H6/H2O system.5 The latter reaction is also smoothly catalyzed by solid acids, viz. strongly acidic cation exchangers with a sulfonic acid functionality.6 Both strongly and weakly acidic cation-exchange resins are active catalysts for the hydroxymethylolation of furan and some of its derivatives by aqueous formaldehyde in two-phase systems.8 Acid-resistant sodium tetrasil[5,5-bis(trifluoromethyl)phenyl]borate was successfully used as a catalyst in biphasic azo coupling9 and Friedel-Crafts alkylation.10 Sodium picrate was reported to catalyze the chlorination of furylilanes and furylgermanes with chloramine T in a CHCl3/H2O system.11

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 dimethylformamide17 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.18a

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References

(2) It has been reported that the acidic hydrolysis of p-nitrophenyl acetate in a cyclohexane/aqueous HCl system is smoothly catalyzed by sodium tetroxafulborate: Armstrong, D. W.; Godart, M. J. J. Am. Chem. Soc. 1979, 101, 2428. However, these data were later disputed: Sainpes, S.; Herriott, A. W. J. Am. Chem. Soc. 1979, 101, 6441.
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recent report by Fraser-Reid and co-workers on the successful application of the NXS (X = I)/CF$_3$SO$_3$H 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.

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%. The dihalogenation reaction is one of the disadvantages of known procedures for the halogenation of thiophene.

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.

The workup of the reaction mixtures of thiophene with NCS and NBS in hexane was also carried out in the presence of quaternary ammonium perchlorates (Me$_4$N$^+$ClO$_4^-$, Et$_4$N$^+$ClO$_4^-$, Bu$_4$N$^+$ClO$_4^-$) as well as by the use of hydrophilic inorganic (H$_2$SO$_4$) 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$_4$ >> picric acid = H$_2$SO$_4$ >> (alkyl)$_4$N$^+$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$_2$SO$_4$, and (NOz)$_2$C$_6$H$_4$OH, 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 mol % 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
Table I. Biphasic Halogenation of Thiophenes and Aromatics with N-Halosuccinimides (NXS) in the Presence of Perchloric Acid*  

<table>
<thead>
<tr>
<th>starting material</th>
<th>NXS (mol equiv)</th>
<th>solvent (vol ml)</th>
<th>70% HClO₄ (mol %)</th>
<th>reactn time (h)</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>thiophene</td>
<td>NCS (1)</td>
<td>hexane 0.5</td>
<td>12</td>
<td>2-chlorothiophene (la)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCS (1)</td>
<td>CCl₄ 0.5</td>
<td>12</td>
<td>la</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (1)</td>
<td>hexane 0.1</td>
<td>6 (0.5)</td>
<td>2-bromothiophene (lb)</td>
<td>84 (90)</td>
<td></td>
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<tr>
<td></td>
<td>NBS (1)</td>
<td>CCl₄ 0.1</td>
<td>5</td>
<td>lb</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCS (2)</td>
<td>CCl₄ 10.0</td>
<td>24</td>
<td>2,5-dichlorothiophene (le)</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (2)</td>
<td>hexane 1.0</td>
<td>24</td>
<td>2,5-dibromothiophene (ld)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (2)</td>
<td>CCl₄ 1.0</td>
<td>4</td>
<td>le</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>NCS (1)</td>
<td>CCl₄ 10.0</td>
<td>24</td>
<td>2-chlorothiophiene (lg)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>NBS (1)</td>
<td>CCl₄ 1.0</td>
<td>6</td>
<td>lg</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>2-methylthiophene</td>
<td>NCS (1)</td>
<td>hexane 0.5</td>
<td>18</td>
<td>2-chloro-5-methylthiophene (le)</td>
<td>91 (e)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCS (1)</td>
<td>CCl₄ 0.5</td>
<td>24</td>
<td>le</td>
<td>94 (e)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (1)</td>
<td>hexane 0.1</td>
<td>24</td>
<td>2-bromo-5-methylthiophene (lf)</td>
<td>80</td>
<td></td>
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<tr>
<td></td>
<td>NBS (1)</td>
<td>CCl₄ 0.1</td>
<td>20</td>
<td>lf</td>
<td>85</td>
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<td>3-bromothiophene</td>
<td>NBS (1)</td>
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<td>7</td>
<td>2-bromo-5-chlorothiophene (lg)</td>
<td>75</td>
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<tr>
<td>mesitylene</td>
<td>NCS (1)</td>
<td>hexane 1.0</td>
<td>48</td>
<td>2,4,6-trimethylchlorobenzene (lk)</td>
<td>81</td>
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<tr>
<td></td>
<td>NCS (1)</td>
<td>CCl₄ 1.0</td>
<td>48</td>
<td>1k</td>
<td>73</td>
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<td>NBS (1)</td>
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<td>24</td>
<td>2,4,6-trimethylbromobenzene (ll)</td>
<td>94</td>
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<tr>
<td></td>
<td>NBS (1)</td>
<td>CCl₄ 1.0</td>
<td>22</td>
<td>ll</td>
<td>99</td>
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<td>1,3-dimethoxybenzene</td>
<td>NCS (1)</td>
<td>hexane 1.0</td>
<td>20</td>
<td>2,4-dimethoxychlorobenzene (lm)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCS (1)</td>
<td>CCl₄ 1.0</td>
<td>20</td>
<td>1m</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (1)</td>
<td>hexane 1.0</td>
<td>4</td>
<td>2,4-dimethoxybromobenzene (ln)</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (1)</td>
<td>CCl₄ 1.0</td>
<td>1</td>
<td>ln</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>2,3-dimethylanisole</td>
<td>NCS (1)</td>
<td>hexane 1.0</td>
<td>24</td>
<td>4-chloro-2,3-dimethylanisole (lo)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NCS (1)</td>
<td>CCl₄ 1.0</td>
<td>15</td>
<td>lo</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NBS (1)</td>
<td>hexane 1.0</td>
<td>4</td>
<td>4-bromo-2,3-dimethylanisole (lp)</td>
<td>90</td>
<td></td>
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<tr>
<td></td>
<td>NBS (1)</td>
<td>CCl₄ 1.0</td>
<td>1</td>
<td>lp</td>
<td>85</td>
<td></td>
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<tr>
<td>m-xylene</td>
<td>NBS (1)</td>
<td>hexane 5.0</td>
<td>240</td>
<td>2,4-dimethylbromobenzene (1q)</td>
<td>72 (q)</td>
<td></td>
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</tbody>
</table>

* Reaction conditions: substrate (10 mmol), NXS (1 or 2 mol equiv), solvent (5 mL), 70% HClO₄ (0.1–10 mol %), room temperature.  

Isolated yield. See reaction and yield when using 1 mol % of 70% HClO₄.  

Contains ca. 10% of isomeric 3-chloro-2-methylthiophene.  

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 (la) isolated in 25–82% yield. Alternatively, compound lg can be obtained by reacting lb and NCS under similar conditions. However, the latter route is somewhat less effective due to the competitive ipso-substitution 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-iodothiophene (le) in 82% yield.  

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 CCl₄ in the presence of 5–10 mol % of HClO₄ (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 CCl₄ both at room temperature and under reflux. Catalytic amounts of 70% HClO₄ (1 mol %) initiate the halogenation and 2,4,6-trimethoxybenzenes (lk and ll) are formed at room temperature in good to excellent yields (Table I).  

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 regioselectively (both in hexane and in CCl₄ in the presence of 1 mol % of 70% HClO₄) giving rise to 2,4-dimethoxybenzenes (lm and ln) and 4-halo-2,3-dimethylanisolos (lo and lp) 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% HClO₄. The bromination also occurs mainly at position 4 to afford 2,4-dimethylbromobenzene (1q) in satisfactory yield.  

(22) Bromination of 3-bromothiophene with Br₃ in CCl₄ 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.

*t*-/ Butylbenzene, toluene, and benzene also cannot be halogenated with NXS/HClO₄ 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. ¹H NMR spectra were obtained on a Gemini 200-MHz spectrometer using CDCl₃ as the solvent and MeSi as the internal standard. A VG 7070E spectrometer was used for mass spectral determinations. GC analyses were carried out on a Varian Vista 6000 instrument 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% HClO₄ (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 (le), 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.

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²³ It should be noted that sterically hindered 1,3,5-tri(t- butyl)benzene also cannot be halogenated with NXS (X = Cl, Br)/HClO₄ in hexane or CCl₄.