



# Direct and regioselective iodination and bromination of benzene, naphthalene and other activated aromatic compounds using iodine and bromine or their sodium salts in the presence of the $\text{Fe}(\text{NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4$ /charcoal system

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**Abstract**—Direct and regioselective iodination and bromination of benzene, naphthalene and other activated aromatic compounds with iodine and bromine or their sodium salts proceed well in the presence of  $\text{Fe}(\text{NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4$ /charcoal in  $\text{CH}_2\text{Cl}_2$  at room temperature.

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Aromatic halogenated compounds have been used for over a century as important chemicals or intermediates in organic synthesis.<sup>1</sup> Iodoarenes are valuable intermediates in the synthesis of a wide variety of organic compounds via reactions involving C–C bond formation by transition metals.<sup>2</sup> They have many applications in pharmacology, medicine and biochemistry.<sup>3</sup>

Since iodine is the least reactive halogen towards the electrophilic substitution, direct iodination of aromatic compounds with iodine is difficult.<sup>4</sup> A large diversity of methods for synthesis of aromatic iodides have been reported.<sup>1,3,4</sup> Some of the reported procedures need harsh conditions such as  $\text{HNO}_3/\text{H}_2\text{SO}_4$ ,<sup>5</sup>  $\text{HIO}_3$  or  $\text{HIO}_4/\text{H}_2\text{SO}_4$ ,<sup>6</sup>  $\text{KMnO}_4/\text{H}_2\text{SO}_4$ ,<sup>7</sup>  $\text{CrO}_3$  in acidic solution with  $\text{I}_2$ ,<sup>8</sup> vanadium salts/ $\text{CF}_3\text{SO}_3\text{H}$  at  $100^\circ\text{C}$ ,<sup>9</sup>  $\text{Pb}(\text{OAc})_4/\text{HOAc}$ .<sup>10</sup>  $\text{NIS}/\text{CF}_3\text{SO}_3\text{H}$  has also been reported for direct iodination of highly deactivated aromatics.<sup>3b</sup> The other reported protocols are:  $\text{I}_2/\text{HgX}_2$ ,<sup>11</sup>  $\text{ICl}/\text{Ag}_2\text{SO}_4/\text{H}_2\text{SO}_4$ ,<sup>12</sup>  $\text{NIS}/\text{CF}_3\text{CO}_2\text{H}$ ,<sup>13</sup>  $\text{I}_2/\text{Ag}_2\text{SO}_4$ ,<sup>14</sup>  $\text{I}_2/\text{F-TEDA-BF}_4$ ,<sup>15</sup>  $\text{NIS}/\text{CH}_3\text{CN}$ <sup>16a</sup> and  $(\text{CH}_3)_4\text{NCl}_2$ .<sup>16b</sup>

$\text{N}_2\text{O}_4$  gas is potentially useful and has been widely studied. During the last few years, we have been

involved in the study of the preparation and applications of  $\text{N}_2\text{O}_4$  complexes of metal nitrates<sup>17</sup> and crown ethers<sup>18</sup> in organic synthesis. We have also used  $\text{N}_2\text{O}_4$  supported on solids for this purpose.<sup>19</sup>

$\text{Fe}(\text{NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4$  is stable up to  $70^\circ\text{C}$  and thaws to a semi-liquid material at room temperature.<sup>20</sup> This compound is highly hygroscopic and its handling is not easy. We have found that this complex can be readily supported on active charcoal to produce a non-hygroscopic powder which is easy to handle and can be stored in a refrigerator in a capped bottle for months.<sup>21</sup>

Recently, the  $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}-\text{SiO}_2$  (Silfen)/ $\text{I}_2$ <sup>22</sup> and  $\text{NO}_2/\text{I}_2/\text{H}^+$ ,<sup>23</sup> systems have applied for iodination of active aromatic compounds at  $40-90^\circ\text{C}$  and at room temperature, respectively.

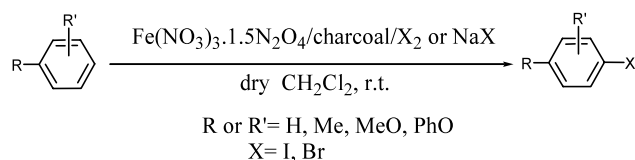
**Table 1.** *para*-Iodination of anisol with  $\text{I}_2$  in the presence of 0.25 molar ratio of metal nitrate complexes of  $\text{N}_2\text{O}_4$  in  $\text{CH}_2\text{Cl}_2$  at room temperature

Entry	Reagent	Time (h)	Yield (%) <sup>a</sup>
1	$\text{Fe}(\text{NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4$ complex/charcoal	2	98
2	$\text{Zn}(\text{NO}_3)_2 \cdot 2\text{N}_2\text{O}_4$ complex/charcoal	24	57
3	$\text{Cu}(\text{NO}_3)_2 \cdot \text{N}_2\text{O}_4$ complex/charcoal	24	Trace

<sup>a</sup> GC yields.

**Keywords:** arenes; iodination; bromination; dinitrogen tetraoxide; ferric nitrate.

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### Scheme 1.

These reports prompted us to investigate  $\text{N}_2\text{O}_4$  complexes of  $\text{Fe(NO}_3)_3$ ,  $\text{Zn(NO}_3)_2$  and  $\text{Cu(NO}_3)_2$  supported on active charcoal for the direct iodination of aromatic compounds. First, we studied iodination of anisole with  $\text{I}_2$  in  $\text{CH}_2\text{Cl}_2$  at room temperature (Table 1).<sup>24a</sup> We found that the  $\text{Fe(NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4/\text{charcoal}$  system was the most effective reagent for this purpose and 4-iodoanisole was produced in 98% yield (GC) after 2 h with high regioselectivity (Table 1, Scheme 1). Then we applied similar reaction conditions to other benzene and naphthalene derivatives substituted with electron-

releasing groups. The reactions proceeded with high yields and usually with high regioselectivity (Table 2, entries 1–3, 8, 9). Iodination of 4-methylanisole and toluene proceeded well with high yields and low regioselectivity with the formation of both regioisomers (Table 2, entries 4, 5).


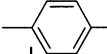

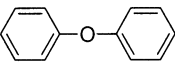
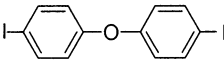


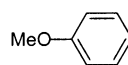
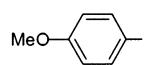
The strong feature of this procedure is the preparation of iodobenzene in 74% yield at room temperature (Table 2, entry 6) as a similar reaction in the presence of Silfen, did not proceed at all even after 48 h. Iodination of diphenyl ether (Table 2, entry 7)<sup>22</sup> with the same reagent produced 4,4'-diiododiphenyl ether in 80% isolated yield only after 28 h whereas, in the presence of the  $\text{Fe(NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4/\text{charcoal}$  system, this reaction proceeded in 2 h in 83% isolated yield. Direct iodination of naphthalene proceeded with high regioselectivity to produce 1-nitronaphthalene in 50% yield (Table 2, entry 8). Direct iodination of aromatic compounds with NaI is more economic and easier to carry

**Table 2.** Iodination of benzene, naphthalene and their activated derivatives with  $\text{I}_2$  and NaI in the presence of  $\text{Fe(NO}_3)_3 \cdot 1.5\text{N}_2\text{O}_4/\text{charcoal}$  in  $\text{CH}_2\text{Cl}_2$  at room temperature

Entry	Substrate	Product	Time(h)/Yield(%) <sup>a</sup>	Time(h)/Yield(%) <sup>b</sup>
1			2/96	1.45/94
2			3/93 <sup>c</sup>	8/94
3			2.5/88	2/86
4			7/63 <sup>d</sup>	24/20 <sup>d</sup>
			7/31 <sup>d</sup>	24/10 <sup>d</sup>
5			15/56 <sup>d</sup>	20/60 <sup>de</sup>
			15/37 <sup>d</sup>	20/40 <sup>d</sup>
6			24/74 <sup>e</sup>	24/0
7			2/83 <sup>f</sup>	24/15
8			24/50 <sup>g</sup>	24/0 <sup>h</sup>
9			2/70 <sup>i</sup>	2/0 <sup>h</sup>

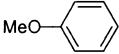
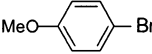
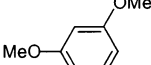
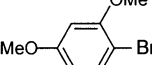
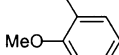
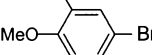
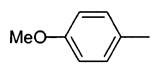
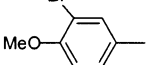

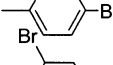
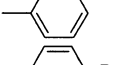


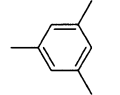
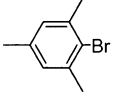
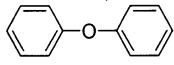
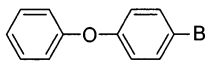
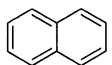

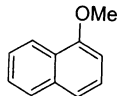
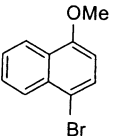
<sup>a</sup>  $\text{I}_2$  was used for iodination (isolated yields). <sup>b</sup> NaI was used for iodination (isolated yields). <sup>c</sup> The reaction was complete with 0.7 eq of  $\text{I}_2$ . <sup>d</sup> The ratio of isomers was determined by  $^1\text{H NMR}$ . <sup>e</sup> In these cases, the substrates were used as solvents. <sup>f</sup> 12% of the iodo by-product was isolated. <sup>g</sup> In this case 45% of 1-nitronaphthalene was isolated. <sup>h</sup> Only nitration reaction occurred. <sup>i</sup> 25% of 4-nitro-1-methoxynaphthalene was isolated.

**Table 3.** Comparison of the results obtained by NO<sub>2</sub>/I<sub>2</sub> and Silfen/I<sub>2</sub> for iodination of aromatic compounds with the Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub>/charcoal system/I<sub>2</sub>

Entry	Substrate	Product	Time(h)/Yield(%) /Temp°C		
			A	B	C
1			4/ 60/ 60	-/-	15/ 56/20
			4/ 40/ 60	-/-	15/37/20
2			10/90/ 40	28/80/20	2/83/20
3			-/-	48/0/20	24/74/20
4			6/95/70	3.5/95/20	2/96/20

A: NO<sub>2</sub> (GC yields) B: SiO<sub>2</sub>-Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (Silfen) (isolated yields). C: Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub>/charcoal system (isolated yields)

**Table 4.** Bromination of benzene, naphthalene and their activated derivatives with Br<sub>2</sub> and NaBr in the presence of Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub>/charcoal in CH<sub>2</sub>Cl<sub>2</sub> at room temperature

Entry	Substrate	Product	Time(h)/Yield (%) <sup>a</sup>	Time(h)/Yield(%) <sup>b</sup>
1			0.18/95	1.5/94
2			0.5/93	7/91
3			0.36/93	2.5/92
4			0.5/86	8/92
5			3/57 <sup>c</sup>	6/60 <sup>c,d</sup>
			3/38 <sup>c</sup>	6/40 <sup>c</sup>
6			2.5/85 <sup>d</sup>	8/80 <sup>d</sup>
7			0.36/96	1.5/93
8			0.18/85 <sup>e</sup>	1.45/80 <sup>f</sup>
9			0.5/89	5/70 <sup>g</sup>
10			0.18/87	0.5/85

<sup>a</sup> Br<sub>2</sub> was used for bromination (isolated yields). <sup>b</sup> NaBr was used for bromination (isolated yields). <sup>c</sup> The ratio of the isomers was determined by <sup>1</sup>H NMR. <sup>d</sup> In these cases substrates were used as solvents. <sup>e</sup> 4,4'-Dibromodiphenyl ether was produced in 91% yield after 1 h when a substrate/Br<sub>2</sub>/reagent (1/1.1/0.5) ratio was used. <sup>24a</sup> 4,4'-Dibromodiphenyl ether was produced in 86% yield after 3.5 h when substrate/NaBr/reagent (1/4/1.5) ratio was used. <sup>24b</sup> 1-Nitro naphthalene was also isolated in 20% yield.

out than using molecular iodine.<sup>24b</sup> Therefore, we studied iodination with NaI. Surprisingly iodination proceeded well with some of the substrates in excellent yields with high regioselectivity (Table 2, entries 1–3). Iodination of toluene proceeded in quantitative yield to give an isomer ratio (*para/ortho*) of 60/40 (Table 2, entry 5). This method was not effective for the iodination of benzene, diphenyl ether, naphthalene, or 1-methoxynaphthalene (Table 2, entries 6, 7, 8, 9).

We have compared some of the results obtained by our method for iodination of arenes with those reported using NO<sub>2</sub> gas and Silfen (Table 3).<sup>22,23</sup>

During the course of this study we applied this reagent system for the bromination of benzene, naphthalene and their activated derivatives with molecular bromine and NaBr (Scheme 1).<sup>24</sup> In comparison to the iodination reactions, bromination proceeded well, usually in excellent yields with faster reaction rates and higher regioselectivity. The features of this bromination method are: high yielding bromination of benzene, highly regioselective bromination of 4-methoxytoluene, diphenyl ether, naphthalene and 1-methoxynaphthalene (see Table 4). Substitution of Br<sub>2</sub> by NaBr makes the protocol much easier, more economical and environmentally favored.

In conclusion, we have provided a simple method for the direct, regioselective iodination and bromination of benzene, naphthalene and other activated aromatic compounds using molecular iodine and bromine and their sodium salts in the presence of the stable Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub>/charcoal system.

### Acknowledgements

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- Active charcoal (2.5 g) was added to a solution of Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub> (5 g) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C with stirring. After 2 h, the solvent was evaporated to give a stable powder of Fe(NO<sub>3</sub>)<sub>3</sub>·1.5N<sub>2</sub>O<sub>4</sub>/charcoal which was stored in a capped bottle in the refrigerator.
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- General procedure for iodination and bromination of arenes (a) with I<sub>2</sub> or Br<sub>2</sub> and (b) with NaI or NaBr.* (a) Arene (2 mmol) was added to the stirred mixture of Fe(NO<sub>3</sub>)<sub>3</sub>·1.5 N<sub>2</sub>O<sub>4</sub>/charcoal (0.5 mmol) and I<sub>2</sub> or Br<sub>2</sub> (1.1 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at room temperature. After the appropriate time, the reaction mixture was filtered. To the resulting filtrate, Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> solution (10%, 10 mL) was added and the mixture extracted with Et<sub>2</sub>O (3×10 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration and

evaporation of the solvent, crude liquid or crystalline compound was obtained. Solid products were recrystallized from *n*-hexane or ethanol and liquid purified by column chromatography.

(b) A mixture of  $\text{Fe}(\text{NO}_3)_3 \cdot 1.5 \text{N}_2\text{O}_4$ /charcoal (0.75 mmol) and NaI (3 mmol) or NaBr (4 mmol) in dry

$\text{CH}_2\text{Cl}_2$  (5 mL) was stirred for 0.5 h at room temperature. Another portion of  $\text{Fe}(\text{NO}_3)_3 \cdot 1.5 \text{N}_2\text{O}_4$ /charcoal (0.5 mmol) and arene (2 mmol) was added to the resulting reaction mixture. After the appropriate reaction time, isolation and purification of the halogenated arenes proceeded as outlined in the preceding procedure.