## Accepted Manuscript

Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents

Jernej Iskra, S. Shaun Murphree

PII:	S0040-4039(17)30005-9
DOI:	http://dx.doi.org/10.1016/j.tetlet.2017.01.003
Reference:	TETL 48506
To appear in:	Tetrahedron Letters
Received Date:	2 December 2016
Revised Date:	21 December 2016
Accepted Date:	2 January 2017



Please cite this article as: Iskra, J., Shaun Murphree, S., Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.003

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

### Tetrahedron Letters

journal homepage: www.elsevier.com

# Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents

Jernej Iskra<sup>a,b,</sup> \* and S. Shaun Murphree<sup>c</sup>

<sup>a</sup> Laboratory for Organic and Bioorganic Chemistry, "Jožef Stefan" Institute, Jamova 39, 1000 Ljubljana, Slovenia

<sup>b</sup> Faculty of Chemistry and Chemical Technology, University of Ljubljana, Večna pot 113, 1000 Ljubljana, Slovenia

<sup>c</sup> Department of Chemistry, Allegheny College, 520 North Main Street, Meadville, PA, USA

#### ARTICLE INFO

#### ABSTRACT

Article history: Received Received in revised form Accepted Available online

Keywords: aromatic substitution hypervalent compounds iodination fluorinated solvents Arenes are rapidly converted to the corresponding iodides by aerobic oxidative iodination at room temperature by treatment with iodine and catalytic quantities of nitrous acid in a fluorinated solvent. Dichloroiodic acid is proposed as the actual iodination reagent.

2009 Elsevier Ltd. All rights reserved.

Iodoarenes<sup>1,2</sup> are valuable synthetic intermediates for the construction of complex organic targets, since they serve as convenient precursors for Grignard reagents<sup>3,4</sup> and as electrophilic various cross-coupling methodologies.<sup>5,6</sup> substrates for Consequently, the preparation of iodoarenes continues to command attention within the synthetic community.<sup>7</sup> Recently reported innovations include the use of N-iodosuccinimide activated by iron(III),<sup>8</sup> gold(I),<sup>9</sup> or rhodium(III)<sup>10</sup> catalysts; hydrogen iodide in DMSO,<sup>11</sup> and molecular iodine in the presence of a sulfated ceria-zirconia catalyst in ethylene glycol<sup>12</sup> or potassium 4-iodylbenzenesulfonate in acetonitrile.<sup>13</sup> With this backdrop, in connection with our ongoing program investigating the catalytic activation of iodine or iodide toward electrophilic aromatic substitution using environmentally benign terminal oxidants,<sup>14–18</sup> we wish to disclose our findings with respect to electrophilic aromatic iodination (Scheme 1) using elemental iodine in the presence of a substoichiometric amount of nitrous acid, which mediates the in situ generation of a hypervalent iodine reagent via aerobic oxidation.



**Scheme 1**. Electrophilic aromatic iodination catalyzed by nitrous acid generated in situ.

Prior work in our laboratory<sup>16</sup> had demonstrated the efficacy of nitrite catalysis in aromatic iodination, and there was evidence that fluorinated solvents could further facilitate the reaction.<sup>17</sup> Thus, we surveyed a variety of reaction media (Table 1) for the aerobic oxidative iodination of anisole using a sodium nitrite/hydrochloric acid system. After 90 min, the reaction did not show appreciable progress in seven solvents, including protic (ethanol), moderately polar (ether, ethyl acetate, dichloromethane, and acetone), and polar aprotic (DMF and DMSO) types. However, good to excellent results were observed in the fluorinated solvents hexafluoroisopropanol (HFIP), trifluoroacetic acid (TFA), and trifluoroethanol (TFE). Mixtures of fluorinated and non-fluorinated solvents were ineffective, as illustrated by the absence of reactivity in a 1:1 ethanol/TFE medium (entry 17).

<sup>\*</sup> Corresponding author. Tel.: +386-1-4773631; fax: +386-1-4773822; e-mail: jernej.iskra@ijs.si

#### Tetrahedron Letters

The pronounced effect of these solvents is interesting, as fluorinated alcohols are known to accelerate certain reactions (such as epoxidation) through template catalysis.<sup>19,20</sup> Inasmuch as TFE dissolves iodine better than HFIP, the effective activation is greater in TFE for this particular system. While somewhat more expensive than conventional reaction media, these fluorinated solvents can be easily recovered in larger-scale reactions.<sup>21</sup>

Table 1	Indination	of anisole in	various	solvents <sup>a)</sup>
Table 1.	Ioumation	of anisole in	various	sorvents.

Entry	Solvent	Conv. (%)
1	EtOH	0
2	$CH_2Cl_2$	0
3	acetone	0
4	$Et_2O$	0
5	DMF	1
6	DMSO	2
7	EtOAc	2
8	CHCl <sub>3</sub>	14
9	MeCN	20
10	$\mathrm{CCl}_4$	29
11	hexane	32
12	AcOH	56
13	$C_{6}F_{14}$	70
14	HFIP	75
15	TFA	86
16	TFE	99
17	EtOH/TFE (1:1)	0

<sup>a)</sup> Reactions were run using 0.5 eq  $I_2$ , 5 mol% NaNO<sub>2</sub>, and 15 mol% HCl. Conversion was determined by HPLC at 90 min.

Using TFE as a solvent, the loadings of hydrochloric acid and sodium nitrite were subsequently explored (Table 2). Nitrite is essential for the protocol—no discernible conversion is observed in its absence (entry 1). At a loading of 5 mol%, however, anisole is fully iodinated within 90 min (entry 3); reduced levels provide concomitantly lower conversions (entry 2). Examining the influence of hydrochloric acid (entries 5-9) reveals the need for two equivalents of acid vs. nitrite for satisfactory results (entry 6). The reaction is tolerant to a small excess of acid, but it responds negatively to stoichiometric quantities (entries 8 & 9).

Тa	able	2.	Influence	of	catal	ytic	parameters of	m	conversion.	a)
						-				

_				
	Entry	eq HCl	eq NaNO <sub>2</sub>	Conv. (%)
	1	0.15	0	0
	2	0.15	0.02	61
	3	0.15	0.05	99
	4	0.15	0.10	99
	5	0.05	0.05	70
	6	0.10	0.05	98
	7	0.20	0.05	97
	8	1.0	0.05	87
	9	2.0	0.05	78

<sup>a)</sup> Reactions were run using 0.5 eq  $I_2$ , 5 mol% NaNO<sub>2</sub>, and 15 mol% HCl. Conversion was determined by HPLC at 90 min.

A plausible mechanism for this reaction is shown in Scheme 2. Nitrosyl chloride is known to be produced by the reaction of sodium nitrite with hydrochloric acid.<sup>22</sup> When molecular iodine is present, these conditions lead to the subsequent formation of iodine chloride<sup>23</sup> through a process that likely liberates the byproduct nitrosyl iodide,<sup>24</sup> a transient species that is rapidly hydrolyzed to nitrous acid and hydroiodic acid.<sup>25</sup> In the closely related peroxide-iodine system, spectroscopic and kinetic studies pointed to dichloroiodic(I) acid (HICl<sub>2</sub>) as the relevant iodinating reagent responsible for the rapid conversions,<sup>17</sup> and comparable rates observed in the present study suggest a similar pathway. This would explain the need for excess hydrochloric acid (i.e., over and above the amount required to neutralize nitrite) to convert the initially formed iodine chloride to HICl<sub>2</sub> to maintain high conversions.

High atom economy is achieved by the *in situ* oxidation of HI to  $I_2$  mediated by a nitric oxide/nitrogen dioxide redox couple derived from the aqueous decomposition of nitrous acid.<sup>26</sup> The increased activity in trifluoroethanol is consistent with DFT studies suggesting coordination of the solvent with the active electrophile;<sup>27</sup> however, in this case there is no evidence of the concomitant oxidation of choride to  $Cl_2$ , since no organochlorine products are observed.



Scheme 2. Proposed mechanism for nitrous acidcatalyzed iodination.

To explore the scope of the reaction, several arenes were subjected to iodination under the optimized conditions of 5 mol% sodium nitrite and 15 mol% hydrochloric acid in TFE (Table 3). For comparison, each reaction was also carried out in two nonfluorinated solvents (acetonitrile and acetic acid), keeping the reaction time constant. Highest yields were observed with moderately nucleophilic arenes, such as durene, anisole, and mesitylene (entries 5, 7, and 8, respectively), which is in concord with a similar study conducted by Wang and co-workers.<sup>28</sup> In the case of anisole, iodination yielded a 95:5 mixture of para- and ortho-iodinated products. For slightly less electron-rich substrates, such as 4-bromoanisole (entry 3) and 4-tertbutyltoluene (entry 4), reactivity could be enhanced by shifting from trifluoroethanol to trifluoroacetic acid. However, the electron-poor arenes *p*-nitrotoluene (entry 1) and methyl *p*-toluate (entry 2) were resistant to iodination even in TFA for extended reaction times.

## ACCEPTED MANUSCRIPT Tetrahedron

4 **Table 3.** Nitrite-mediated aerobic iodination of arenes

Entry Substrate		rate Product So		Solvent Time	Yield <sup>a)</sup>	Conversion <sup>b)</sup> (%) in		
				(h)	(%)	MeCN	AcOH	
1	Me NO <sub>2</sub>		TFA	72	0	0	0	
2	Me CO <sub>2</sub> Me	Me CO <sub>2</sub> Me	TFA	65	< 1	< 1	<1	
3	BrOMe 1c	Br OMe	TFA	16	95	<1	<1	
4	t-Bu Me	t-Bu Me	TFA	4	94	< 1	< 1	
5		2e	TFE	3	93 <sup>c)</sup>	3	5	
6	t-Bu If	t-Bu OMe	TFE	3	92	33	65	
7	1g OMe	DOMe 2g	TFE	1.5	98 <sup>d)</sup>	56	69	
8		2h	TFE	1.5	92	38	84	
9	MeO- li OMe		TFE	1 <sup>e)</sup>	90	96	100	
10			TFE	1 <sup>e)</sup>	81	74	74	
11			TFE	1 <sup>e)</sup>	61	12	20	
12	MeO-OMe	MeO OMe	TFE	1 <sup>e)</sup>	12	< 1	< 1	

<sup>a</sup>isolated yield

<sup>b</sup>NMR conversion for the same reaction time

<sup>c</sup>used 5 mL of solvent

<sup>d</sup>isolated as an inseparable mixture of para- and ortho-isomers (95:5 ratio) <sup>e</sup>supplemental NaNO<sub>2</sub> (0.025 eq at a time) was added at 10 min intervals

At the other end of the nucleophilicity spectrum, highly electron-rich substrates required a slight modification to the Thus, when using di- and trimethoxybenzene conditions. derivatives as substrates (entries 9-12), it was necessary to add small aliquots of nitrite periodically throughout the iodination; otherwise, the reaction tended to stall. While dimethylresorcinol and 1,3,5-trimethoxybenzene (entries 9 and 10, respectively) gave excellent yields using this technique, the iodination of veratrole (entry 11) was somewhat sluggish and was accompanied by the formation of 4-nitro-1,2-dimethoxybenzene. An even more pronounced anomaly occurred in the case of *p*-dimethoxybenzene (entry 12), which provided the iodination product (2m) in only 12% yield. Moreover, NMR analysis of the crude reaction mixture indicated that 2-nitro-1,4-dimethoxybenzene was actually the major product (molar ratio of nitration to iodination = ca. 1.5:1).

It is noteworthy that the iodination efficiency of these highly electron-rich substrates correlates strongly with their oxidation potentials.29 Thus, dimethylresorcinol and 1.3.5trimethoxybenzene are well behaved and also have the highest redox potentials ( $E_{\frac{1}{2}} = 1.55$  and 1.54 V, respectively); veratrole  $(E_{\frac{1}{2}} = 1.42 \text{ V})$  provides moderate yield; and *p*-dimethoxybenzene  $(E_{\frac{1}{2}} = 1.28 \text{ V})$  gives the poorest iodination result. In the latter two cases, it appears that the arene substrate intercepts the nitrosonium cation in an SET process (as shown in Scheme 3) through a well-established pathway.<sup>30</sup> The formation of this byproduct has the collateral disadvantage of depleting the nitrosonium catalyst, essentially shutting down the iodination reaction. Notably, this competing nitration pathway for very electron-rich arenes was not reported by Wang et al.<sup>28</sup>



Scheme 3. Mechanism for the nitration of electron-rich arenes.

In summary, we have shown that molecular iodine in the presence of catalytic quantities of nitrite and hydrochloric acid in fluorinated solvent represents a convenient and efficient means for the aerobic oxidative iodination of moderately electron-rich aromatic substrates. We continue to study this interesting system with respect to mechanistic detail, as well as additional applications for halogenation.

#### Acknowledgments

The authors gratefully acknowledge the Fulbright Scholar Program (Grant No. 48131678), the Slovenian Research Agency (Program P1-0134 and Bilateral Project BI-US/15-16-083), and the Slovene Human Resources Development and Scholarship Fund for their financial support of this work.

#### **References and notes**

- Dohi, T.; Kita, Y.; in *Iodine Chem. Appl.* (Ed.: Kaiho, T.), John Wiley & Sons, Inc, Hoboken, NJ, **2015**, pp. 303–328.
- 2. Waldvogel, S.R. Sci. Synth. Knowl. Updat. 2010, 487-498.
- 3. Li, J.J.; in *Name React.*, Springer, **2014**, pp. 291–292.
- Cahiez, G.; Moyeux, A.; Cossy, J. Adv. Synth. Catal. 2015, 357, 1983–1989.
- Diederich, F.; Stang, P.J., Eds., Metal-Catalyzed Cross-Coupling Reaction, Wiley-VCH, 1998.
- 6. Suzuki, A. Angew. Chem. Int. Ed. Engl. 2011, 50, 6722-6737.
- 7. Hu, B.; Miller, W.H.; Neumann, K.D.; Linstad, E.J.; DiMagno,S.G. *Chemistry* **2015**, *21*, 6394–6398.
- Racys, D.T.; Warrilow, C.E.; Pimlott, S.L.; Sutherland, A. Org. Lett. 2015, 17, 4782–4785.
- Leboeuf, D.; Ciesielski, J.; Frontier, A. Synlett 2013, 25, 399–402.
  Schröder, N.; Wencel-Delord, J.; Glorius, F. J. Am. Chem. Soc.
- **2012**, *134*, 8298–8301. 11. Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. Org. Lett. **2015**, *17*, 2886–2889.
- 12. Kahandal, , S.S.; Kale, S.R.; Gawande, M.B.; Zboril, R.; Varma, R.S.; Jayaram, R.V. *RSC Adv.* **2014**, *4*, 6267–6274.
- Yusubov, M.S.; Yusubova, R.Y.; Nemykin, V.N.; Maskaev, A.V.; Geraskina, M.R.; Kirschning, A.; Zhdankin, V.V. European J. Org. Chem. 2012, 2012, 5935–5942.
- Iskra, J.; Stavber, S.; Zupan, M. Synthesis (Stuttg). 2004, 2004, 1869–1873.
- Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. Adv. Synth. Catal. 2008, 350, 2921–2929.
- Iskra, J.; Stavber, S.; Zupan, M. Tetrahedron Lett. 2008, 49, 893– 895.
- 17. Bedrač, L.; Iskra, J. Adv. Synth. Catal. 2013, 355, 1243-1248.
- Podgoršek, A.; Zupan, M.; Iskra, J. Angew. Chemie Int. Ed. 2009, 48, 8424–8450.
- Berkessel, A.; Adrio, J.A.; Hüttenhain, D.; Neudörfl, J.M. J. Am. Chem. Soc. 2006, 128, 8421–8426.
- Berkessel, A.; Adrio, J.A. J. Am. Chem. Soc. 2006, 128, 13412– 13420.
- 21. Možina, Š.; Stavber, S.; Iskra, J. J. Org. Chem. 2016, doi:10.1002/ejoc.201601339
- 22. Morton, J.R.; Wilcox, H.W. Inorg. Synth. 1953, 4, 48-52.
- 23. Horvitz, D.; Shaw, R.J.; Baugh, W.D. Manufacture of Interhalogen Compounds and Halogenoids, **1969**, 3,423,175.
- Bailleux, S.; Duflot, D.; Aiba, S.; Nakahama, S.; Ozeki, H. Chem. Phys. Lett. 2016, 650, 73–75.
- O'Driscoll, P.O.; Lang, K.; Minogue, N.; Sodeau, J. J. Phys. Chem. A 2006, 110, 4615–4618.
- 26. Park, J.Y.; Lee, Y.N. J. Phys. Chem. 1988, 92, 6294-6302.
- Ben-Daniel, R.; De Visser, S.P.; Shaik, S.; Neumann, R. J. Am. Chem. Soc. 2003, 125, 12116–12117.
- Wang, K.; Wang, X.; Zhang, G.; Liang, X. Jingxi Huagong 2009, 26, 715–719, 728.
- 29. Luo, P.; Feinberg, A.M.; Guirado, G.; Farid, S.; Dinnocenzo, J.P. J. Org. Chem. 2014, 79, 9297–9304.
- 30. Kim, E.K.; Kochi, J.K. J. Org. Chem. 1989, 54, 1692-1702.

Tetrahedron

## **Graphical Abstract**

To create your abstract, type over the instructions in the template box below.



6

**Rapid aerobic iodination of arenes mediated by hypervalent iodine in fluorinated solvents** Jernej Iskra and S. Shaun Murphree

## Highlights

- Moderately electron-rich arenes are the most suitable substrates for iodination.
- A catalytic mechanism involving dichloroiodic acid is proposed.
- Competitive formation of nitroarenes is observed in highly electron-rich substrates.