



Mild and regioselective iodination of electron-rich aromatics with *N*-iodosuccinimide and catalytic trifluoroacetic acid

Anne-Sophie Castanet, Françoise Colobert* and Pierre-Emmanuel Broutin

Laboratoire de stéréochimie associé au CNRS, URA 7008, Université Louis Pasteur, ECPM, 25 rue Becquerel,
67087 Strasbourg Cedex 2, France

Received 24 May 2002; accepted 27 May 2002

Abstract—A variety of aromatics compounds substituted with methoxy or methyl groups were regioselectively iodinated with *N*-iodosuccinimide and catalytic trifluoroacetic acid with excellent yields under mild conditions and short reaction times. © 2002 Elsevier Science Ltd. All rights reserved.

In recent years, iodoarenes have assumed increasing importance in organic synthesis because they can be easily functionalized through metal catalyzed cross-coupling reactions.¹ Due to their potential ability as intermediates in organic syntheses and also as bioactive materials,² iodination of aromatic compounds have been the subject of numerous studies. The moderate reactivity of iodine with aromatic substrates implies the addition of activating agents and recently direct iodination methods have been developed by using iodonium donating reagents: iodine-tetrabutylammoniumperoxydisulfate,³ BuLi-F₃CCH₂I,⁴ iodine-nitrogendioxide,⁵ iodine-F-TEDA-BF₄,⁶ NIS,⁷ iodine-diiodine pentoxide,⁸ bis(symcollidine)iodine(I)hexafluorophosphate,⁹ iodine-monochloride,¹⁰ bis(pyridine)iodonium(I)tetrafluoroborate-CF₃SO₃H,¹¹ NIS-CF₃SO₃H,¹² iodine-silversulfate,¹³ iodine-mercury salts,¹⁴ NaOCl-NaI.¹⁵

However, most of these methods require hazardous or toxic reagents or high reaction temperature for a long reaction time. A combination of *N*-iodosuccinimide and trifluoromethane sulfonic acid (2–5 equiv.)¹² has been used for the iodination of deactivated aromatics compounds. Iodination of activated aromatic ethers with only *N*-iodosuccinimide in acetonitrile has been reported more recently.⁷ Nevertheless long reaction times (6–24 h) and high reaction temperature (reflux of acetonitrile) are generally needed with this reaction.

Furthermore we have noticed an influence of the amount of starting aromatic compound on the reaction time. For example iodination of 750 mg of 2-methoxynaphtalene with NIS was completed after 30 h whereas iodination of a few grams required 4 days at reflux of acetonitrile.

We have discovered that a combination of *N*-iodosuccinimide (1.1 equiv.) and catalytic trifluoroacetic acid (0.3 equiv.) is an excellent reagent (in term of reaction time and reaction temperature) for the regioselective iodination of activated aromatic compounds. A variety of commercially available methoxy and methyl aromatic derivatives were submitted to the reaction with NIS and cat. CF₃COOH and our results are collected in Table 1. Iodination of methoxy aromatic derivatives took place with high yield at room temperature with short reaction times, between several minutes (entries 1, 2 and 7) and 1–4 h (entries 3, 5 and 6). Surprisingly, iodination of mesitylene proceeded at room temperature in 4.5 h (entry 4) whereas reaction of 2-methylnaphtalene (entry 9), *meta*-xylene (entry 8) and diphenylether (entry 10) required refluxing acetonitrile to be completed in 2.5–6 h.

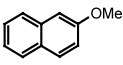
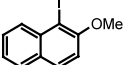



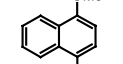
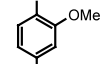
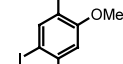

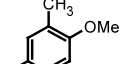
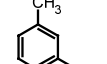
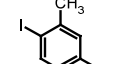
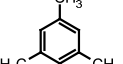
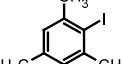
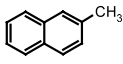
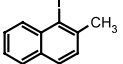

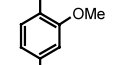
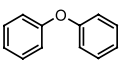
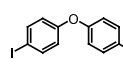
Iodination was *para*-directed when possible, otherwise it occurred in the *ortho*-position.

From a mechanistic point of view, we think that the active species for this iodination is probably the 'in situ formed' iodine trifluoroacetate who can act as a very reactive electrophile, allowing iodination in short reaction times at 20°C (Scheme 1).

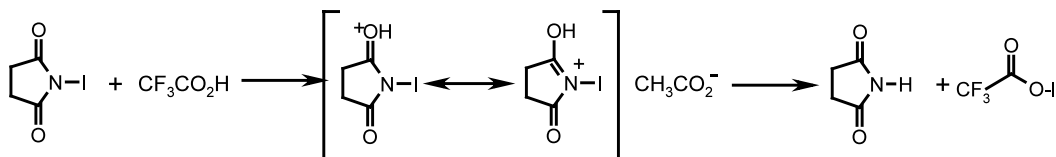
Keywords: aromatic iodination; *N*-iodosuccinimide; trifluoroacetic acid.

* Corresponding author. Tel.: +0-33-390-242-744; fax: +0-33-390-242-742; e-mail: fcolober@chimie.u-strasbg.fr

Table 1. Iodination of methoxy and methyl aromatic derivatives with NIS and CF₃CO₂H

Entry	Substrate	T (°C)	Time (h)	Product	Crude yield %	Entry	Substrate	T (°C)	Time(h)	Product	Crude yield %
1		20	0.5		99	6		20	4		92
2		20	0.15		>99	7		20	0.1		99
3		20	1.6		81	8		80	4.25		94
4		20	4.5		95	9		80	2.5		86
5		20	4.5		99	10		80	6		96

Reaction conditions : aromatic compound (1 mmol), CH₃CN 4ml, NIS (1.1 equiv), CF₃CO₂H (0.3 equiv)

**Scheme 1.** Active species for the iodination.

In conclusion, we report an efficient new method for the electrophilic iodination of activated aromatic compounds using *N*-iodosuccinimide and catalytic trifluoroacetic acid.

Acknowledgements

Financial support from Rhodia Chimie is gratefully acknowledged.

References

- Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.
- (a) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575; (b) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377.
- Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 6051.
- Blackmore, I. J.; Boa, A. N.; Murray, E. J.; Dennis, M.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 6671.
- Noda, Y.; Kashima, M. *Tetrahedron Lett.* **1997**, *38*, 6225.
- Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron Lett.* **1997**, *38*, 6305.
- Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081.
- Bradzil, L. C.; Cutler, C. J. *J. Org. Chem.* **1994**, *59*, 6233.
- Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *45*, 8217.
- Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 6233.
- Barluenga, J.; Gonzalez, J. M.; Garcia-Martin, M. A.; Campos, P. J.; Asensio, G. *J. Org. Chem.* **1993**, *58*, 2058.
- Olah, G. A.; Qi, W.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194.
- Sy, W.-W. *Tetrahedron Lett.* **1993**, *34*, 6223.
- Bachky, A.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5139.
- Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287.