Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 81–83
Tetrahedron Letters

A mild and simple regioselective iodination of activated aromatics with iodine and catalytic ceric ammonium nitrate☆

Biswanath Das,* Maddeboina Krishnaiah, Katta Venkateswarlu and V. Saidi Reddy

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 28 August 2006; revised 23 October 2006; accepted 1 November 2006
Available online 21 November 2006

Abstract—Molecular iodine in the presence of a catalytic amount of CAN has been utilized efficiently for regioselective iodination of activated aromatic compounds under mild reaction conditions.
© 2006 Elsevier Ltd. All rights reserved.

Aromatic iodo compounds are important intermediates for the synthesis of various pharmaceutical and bioactive compounds.[1] They are also useful in metal-catalyzed cross coupling reactions, such as Heck, Stille and Negishi reactions which are utilized in C–C and C–N bond formation.[2] However, direct iodination of aromatic compounds is difficult due to the low electrophilicity of molecular iodine compared to that of molecular chlorine and bromine. Generally, arenes are iodinated by iodine in the presence of a Lewis acid or an oxidizing agent. Direct iodination methods have been reported using various iodonium donating systems, such as NIS–CF_3SO_3H,[3a] iodine–Ag_2SO_4,[3b] iodine–HgO,[3c] NIS,[3d] iodine–tetrabutylammonium peroxydisulfate,[3e] *n*-BuLi–CF_3CH_2I,[3f] and ICl.[3g] However, most of these methods require toxic and costly reagents, high temperatures and long reaction times. Thus it is desirable to apply a simple, inexpensive and non-toxic reagent system for iodination of aromatic compounds.

In continuation of our work[4] on the development of useful synthetic methodologies, we have observed that iodine in the presence of a catalytic amount of ceric ammonium nitrate (CAN) is an effective reagent system for iodination of activated aromatic compounds. CAN is a valuable reagent for various chemical transformations.[5] Here, a series of activated aromatic compounds have been iodinated using iodine–CAN at room temperature to form the corresponding iodo compounds (Table 1). The I^+ electrophile generated in situ by the reaction of iodine and CAN causes nuclear iodination of the electron rich aromatic compounds and Ce(III) is re-oxidized to Ce(IV) in the presence of aerial oxygen. Under nitrogen, the yields of aryl iodides were very low. Electron deficient aromatic compounds, such as nitrobenzene and benzoic acid, did not undergo iodination. Though CAN is acidic, aniline (Table 1, entry e) could be iodinated smoothly. The phenolic hydroxyl groups (entries g–k) were not affected.

The iodination of the substrates took place with high regioselectivity and only mono-iodination was found to occur. When an alkoxy or an amine group was present on the aromatic ring (entries a, e and n), iodination proceeded with high *para*-selectivity while *ortho*-iodination occurred when the *para*-position was blocked with a substituent other than a hydroxyl group (entries m and o). However, with the phenolic compounds (entries d and j) the *ortho*-iodo compounds were the major products. The structures of the aryl iodides were established from their ^1H NMR and mass spectral data.

In conclusion, we have developed a very simple, mild and regioselective method for nuclear iodination of activated aromatic compounds using the iodine–CAN reagent system which is readily available, inexpensive and non-toxic.

General experimental procedure: To a mixture of an activated arene (0.5 mmol) and molecular iodine (0.5 mmol), CAN (10 mol %) was added. The mixture

---

Keywords: Activated aromatic; Aryl iodide; Iodine; CAN; Regioselectivity.

☆Part 113 in the series, 'Studies on novel synthetic methodologies.' IICT Communication No. 061022.

*Corresponding author. Tel./fax: +91 40 7160512; e-mail: biswanathdas@yahoo.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.009

Table 1. Iodination of aromatic compounds using CAN and I_2[a]

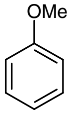
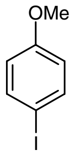
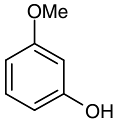
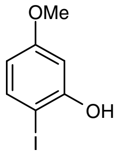
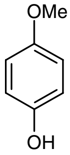
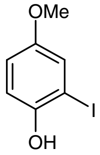
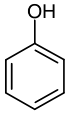
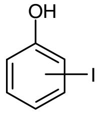
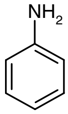
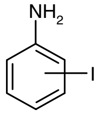
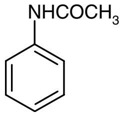
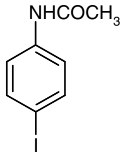
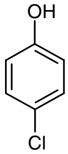
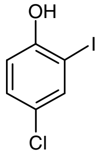
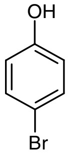
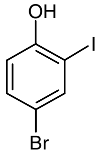
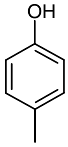
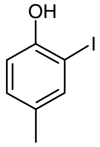
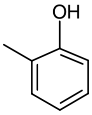
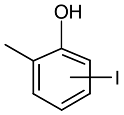
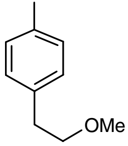
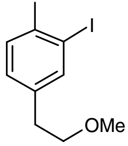
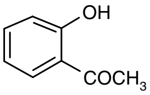
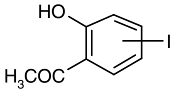
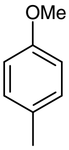
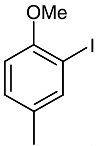
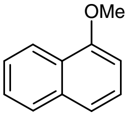
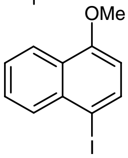
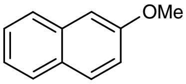
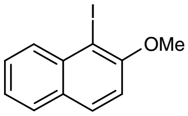
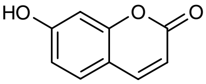
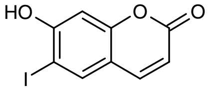
Entry	Substrate	Product	Reaction time (h)	Isolated yield (%)
a			3	94
b			3	85
c			4	90
d		 (7:3)[b]	3.5	70
e		 (2:8)[b]	4	78
f			6	75
g			3.5	87
h			4	85
i			4	82
j		 (7:3)[b]	4	70
k			5	92

Table 1 (*continued*)

Entry	Substrate	Product	Reaction time (h)	Isolated yield (%)
l		 (7:3)[b]	4	70
m			3.5	89
n			4.5	95
o			5	93
p			5	78

[a] The structures of the products were established from their spectral (^{1}H NMR and MS) data.

[b] Ratio of *ortho*/*para*-iodinated products.

was stirred at room temperature and the reaction was monitored by TLC. After completion, the mixture was treated with aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with EtOAc (3 × 10 mL). The extract was concentrated and the residue was purified over silica gel to obtain pure aryl iodides(s).

Acknowledgement

The authors thank CSIR and UGC, New Delhi for financial assistance.

References and notes

1. (a) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575–590; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009–4091.
2. (a) Merkushev, E. B. *Synthesis* **1988**, 923–927; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
3. (a) Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* **1993**, *58*, 3194–3195; (b) Sy, W. W. *Tetrahedron Lett.* **1993**, *34*, 6223–6224; (c) Orito, K.; Hatakeyama, T.; Takeo, M.; Suginoma, H. *Synthesis* **1995**, 1273–1277; (d) Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081–4084; (e) Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1999**, *40*, 6051–6054; (f) Blackmore, I. J.; Boa, A. N.; Murray, E. J.; Dennis, M.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 6671–6672; (g) Johnson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11656–11657.
4. (a) Das, B.; Ramu, R.; Ravikanth, B.; Reddy, K. R. *Tetrahedron Lett.* **2006**, *47*, 779–782; (b) Das, B.; Thirupathi, P.; Reddy, V. S.; Rao, Y. K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 233–239; (c) Das, B.; Krishnaiah, M.; Venkateswarlu, K. *Tetrahedron Lett.* **2006**, *47*, 4457–4460; (d) Das, B.; Ravikanth, B.; Thirupathi, P.; Rao, B. V. *Tetrahedron Lett.* **2006**, *47*, 5041–5044.
5. Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731–6747.