Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6225-6228, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01431-7

An Efficient and Regioselective Direct Aromatic Iodination Using Iodine and Nitrogen Dioxide

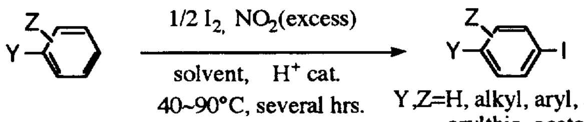
Yumiki Noda* and Mikito Kashima

Corporate Research and Development, UBE Industries, Ltd., 8-1, Goiminamikaigan,
Ichihara City, Chiba 290, Japan

Abstract: Direct iodination of a variety of aromatic compounds is achieved by using nitrogen dioxide as an oxidant in addition to iodine. The reaction affords aromatic monoidodides in high yields with high para-regioselectivity. 4,4'- Diiodo binuclear compounds are also obtained effectively by controlling the stoichiometry. © 1997 Elsevier Science Ltd.

Aromatic iodides have long been utilized in organic synthesis. Recent progress in organotransition metal chemistry has renewed the importance of iodoarenes; thus, the chemistry of transformations of iodoarenes to a variety of functional compounds by transition metal catalysis has been a popular and fruitful area of investigation.[1] Unlike chlorine and bromine, iodine is unreactive towards most aromatic substrates; thus, a more powerful iodinating species than iodine is required in direct aromatic iodination.[2] This has been usually accomplished by adding an oxidizing reagent such as iodic acid,[3] periodic acid,[3] peracetic acid[4] or silver(I) salts[5] to the iodine source.[6] However, these methods are not quite suitable, especially in large-scale, due to the use of costly and hazardous reagents and production of a large amount of waste. Although a mixture of nitric acid and sulfuric acid[7] is one of the most practical and useful oxidants, considerable nitration of the substrates tends to occur.

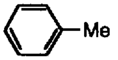
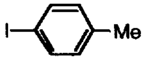
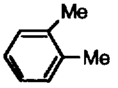
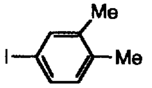
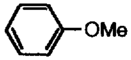
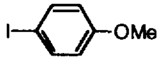
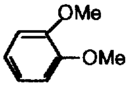
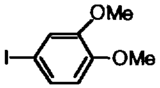
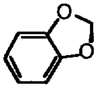
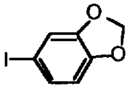
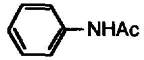
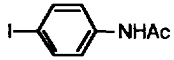
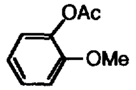
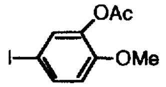
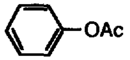
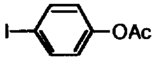
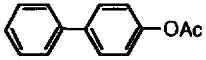
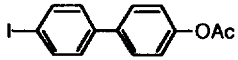
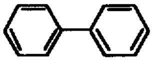
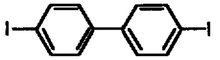
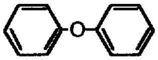
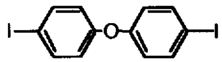
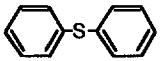
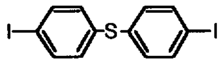
We have discovered an efficient and selective method of direct aromatic iodination. Our method is based on the *in situ* oxidation of iodine by nitrogen dioxide.[8] The reaction is carried out simply by bubbling nitrogen dioxide, or adding a solution of it, into a mixture of the substrate and an equivalent amount of iodine in an appropriate solvent with a catalytic amount of an acid (Eq.1). Some representative results are shown in Table 1.[9]



(Eq. 1)

Y,Z=H, alkyl, aryl, alkoxy, aryloxy, arylthio, acetoxy, and acetylamino groups.
Y>Z (electron donating ability)

Table 1. Direct Aromatic Iodination Using Iodine and Nitrogen Dioxide

Entry	Substrate[a]	NO_2[b] (mmol)	Solvent[c]	Catalyst[d]	Temp. (°C)	Time (h)	Product	Yield[e] (%)
1		55	A	D	60	4		60[f]
2		60	B	D	90	6		75[g]
3		55	B	D	70	6		95
4		50	B	D	70	5		89
5		123	B	E	80	5		92
6		60	B	D	90	4		87
7		95	A	F	60	2		88
8		130	A	F	60	5		81
9		185	A	F	60	3		62[h]
10[i]		115	C	D	40	6		90
11[i]		120	B	D	40	10		95
12[i]		120	B	D	90	10		77[j]

a) A 50 mmol of substrate was used in each experiment. b) NO_2 was bubbled into the reaction mixture for 2 to 6 h. c) A: $CHCl_3$, B: $AcOH/H_2O/CHCl_3$ =3:1:1, C: CH_2Cl_2. d) D: H_2SO_4 (5 mol%), E: Amberlite IR-200C™(150 wt% to iodine), F: 5%$H_3(PW_{12}O_{40})/SiO_2$(30 wt% to iodine). e) Yields were determined by GLC using adequate internal standards. f) 2-Iodotoluene was formed in 40% yield. g) 3-Iodo-1,2-dimethylbenzene was formed in 18% yield. h) 36% of the starting material was recovered. i) 2 equiv of iodine were used. j) Monoiodide was formed in 12% yield.

In our earlier attempts, there was substantial formation of the nitro compounds in some cases. However, we found that slow introduction of nitrogen dioxide reduced the amount of the nitro compounds. And more significantly, use of a mixture of acetic acid, chloroform and water in the ratio of 3:1:1 as a solvent has been found to be very effective to suppress the nitration of the reactive substrates. This method has been applied successfully to the substrates having electron-donating substituents such as alkyl, aryl, alkoxy, and aryloxy. Although phenols and anilines suffered from low yields, because of over-oxidation to form tarry material, their acetyl derivatives also gave the corresponding iodides in high yields (Entries 6, 7, 8, and 9). This method requires an acid catalyst to obtain a practical reaction rate. For this purpose, we utilized sulfuric acid, a strongly acidic cation exchange resin, or silica gel supported 12 tungusto(IV) phosphoric acid.[10] Use of the ion exchange resin or silica gel supported heteropoly acid is advantageous in view of its recovery and reuse. In addition, the latter in chloroform was compatible with the acetoxy function, which rendered acetoxy derivatives applicable to this method. On the other hand, the present method was not applicable to substrates having electron-withdrawing substituents such as nitro, cyano, or carbonyl groups.

One of the most important features of this method is its regioselectivity. The iodination proceeded highly para-selective to the substituent, especially to alkoxy and aryloxy groups, even though in the cases of toluene and xylene the selectivities were moderate (Entries 1 and 2). This character was strongly reflected in the result of Entry 7, where the iodination occurred exclusively at the para-position to the methoxy group. After the hydrolysis of the product of Entry 7, one can obtain 5-iodo-2-methoxyphenol in high yield, which is not easily accessible by the conventional iodination reactions. Regioselective diiodination of binuclear aromatics has also been achieved by controlling the stoichiometry. Adding two equivalents of iodine afforded 4,4'-diiodides in good to excellent yields. These compounds are potentially useful intermediates for functional materials.

We have described a selective and high-yield method for the direct aromatic iodination, which is operationally simple and produces far less amount of waste materials compared with that from conventional methods. Nitrogen monoxide, which is formed during the reaction, is readily oxidized to nitrogen dioxide by mixing with air(oxygen); thus, it is recyclable. These facts have ensured a wide application of the method in laboratory and industrial use.

Acknowledgment: We wish to thank UBE Scientific Analysis Laboratory, Inc. for all the spectral data.

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8. In this paper, an equilibrium mixture of nitrogen dioxide and dinitrogen tetroxide is referred to as nitrogen dioxide, which is a commercially available gas (mp.-9.3°C, bp.21.3°C).
9. The following procedure of Entry 7 is representative. Into a mixture of 2-acetoxyanisole (3.32 g, 20.0 mmol), iodine (2.53 g, 10 mmol) and 5% $H_3(PW_{12}O_{40})$ on silica gel (0.80 g) in 20 mL of $CHCl_3$ was bubbled nitrogen dioxide at 60 °C over a period of 2 h. The total amount of supplied nitrogen dioxide was 1.75 g (38 mmol). After an additional 2 h, the solid catalyst was filtered and the filtrate was analyzed by GLC using tetradecane as an internal standard which showed the formation of 4-iodo-2-acetoxyanisole in 88% yield. After extractive workup, the crude product was recrystallized from ethanol to afford 4.67 g of the product (80% yield): IR(KBr) 1765 (s), 1205 (s), 1195 (m), 1010 (m), 800 (m) cm^{-1}; ^1H NMR ($CDCl_3$, $SiMe_4$) δ 2.30(s, 3H), 3.80(s, 3H), 6.72(d, J = 8Hz, 1H), 7.34(d, J =2Hz, 1H), 7.49(dd, J = 2 and 8Hz, 1H); ^{13}C NMR ($CDCl_3$, $SiMe_4$) δ 20.54, 55.96, 81.31, 114.28, 131.62, 135.70, 140.45, 151.35, 168.60; MS(m/z) 292(M^+). Anal Calcd for $C_9H_9O_3I$: C,37.01; H,3.11. Found: C, 37.05, H, 3.05.
10. 5% $H_3(PW_{12}O_{40})$ on silica gel was prepared as follows: A solution of 12 tungusto(IV) phosphoric acid (1.25 g) in water (5 mL) was added to silica sol (Cataloid-S-30L^{RM}, Shokubai Kasei Co., Ltd., SiO_2 content 30wt%) and mixed thoroughly. Then the mixture was evaporated to dryness at 120 °C. The obtained solid was ground to a powder and calcined at 300°C for 4 h. It can be stored under N_2 atmosphere without loss of activity for several months.

(*Received in Japan* 29 *May* 1997; *revised* 4 *July* 1997; *accepted* 11 *July* 1997)