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Iodination with Potassium Permanganate/Hydroiodic Acid/Acetonitrile Reagent

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Iodination of various aromatic amines proceeds smoothly with a preformed homogeneous mixture of hydroiodic acid potassium permanganate in acetonitrile. *para*-Substituted products were obtained in high yields (71-78%) within twelve hours at room temperature.

With a slight modification of the permanganate, hydroiodic acid and substrate ratio, iodination of alkynes to *vic*-diiodoalkenes can be carried out at 60 °C in 65-87% yield.

INTRODUCTION

Aryl iodides are less readily accessible than the other aryl halides because there are fewer synthetic methods.[1-3] Direct iodination of aromatic compounds with molecular iodine, which is the least reactive halogen in electrophilic substitution, is difficult as compared to chlorination and bromination. Moreover, elemental iodine usually requires purification and careful grinding for good results.[1,4] Actually most of the synthetic effort has been placed in converting molecular iodine into a more active species, for example by employment of silver(I)[5,6] or copper(II)[7,8] ions to polarize the iodine molecule, making it more electrophilic and more reactive toward the aromatic substrates. Another approach requires the use of oxidizing agents,[1] which transform iodine or iodide into a stronger electrophilic species. Of the available methods for synthesizing aryl iodides, very few can be extended to free amines.[9,10] Primary aromatic amines are usually iodinated as *N*-acyl derivatives.[1]

While the use of a sodium hypochlorite and sodium iodide mixture offers an excellent method for preparing *para*-substituted phenols,[10] it is less satisfactory with aromatic amines. Recently Kajigaeshi and coworkers reported[9] the use of benzyltrimethylammonium dichloroiodate (BTMAICl$_2$) in the presence of calcium carbonate powder for the iodination of aromatic amines in CH$_2$Cl$_2$-CH$_3$OH. Yields were usually good, but the addition of methanol and powder calcium carbonate might cause problems for compounds sensitive to base or transesterification. Accordingly, a convenient, complementary and direct synthetic procedure is in need. In continuation of our recent work in halogenation[11] we have found that a proper combination of KMnO$_4$/HI/CH$_3$CN (*vide infra*) is an excellent iodinating agent for aromatic amines. Application of the cheap and non-toxic potassium permanganate as an *in situ* oxidizing agent, allowed the development of a one-pot synthesis of iodoaryl amines in high yields.

RESULTS AND DISCUSSION

Addition of hydroiodic acid to a solution of potassium permanganate in acetonitrile caused instantaneous discharge of the purple color of potassium permanganate, and rapid conversion to a homogeneous solution of manganese complex. Iodination of aromatic amines with this mixture proceeded smoothly at room temperture (ca. 20 °C) in high yields (Table 1). This reagent is highly selective for arylamines, but unsuitable for phenols, which undergo oxidative coupling[12] easily in the presence of electron transfer agent. The oxidative power of this reagent is relatively weak, as it does not affect benzylamine under normal reaction conditions. Oxidation to benzaldehyde (54%) occurred only after heating at 60 °C for 12 hours.

Two special features of the present procedure are: (1) Monoiodination was observed in all cases studied, (2) exclusive *para* iodination was observed with all monosubstituted anilines. 2-Methylaniline and 3-methylaniline yielded 4-iodo-2-methylaniline and 4-iodo-3-methylaniline, respectively. The only *ortho* iodination observed was with 3-methoxyaniline, which gave 2-iodo-5-methoxyaniline due to the combination effects of the powerful eletron donating amino and methoxy groups. The product was identified as 2-iodo-5-methoxyaniline instead of 4-iodo-3-methoxyaniline by nuclear Overhauser difference spectroscopy. In the NODS experiment, two *ortho* aromatic proton signals were observed when the methoxy group was irradiated.

Although the addition of iodine[13-15] to alkynes is a well documented process, only a few recent works[14,16,17] concerned with the stereochemistry and selectivity. We found that a slight modification of the permanganate, hydroiodic acid and substrate ratio can effect iodination of alkynes to

Table 1. Iodoanilines Obtained by Using KMnO$_4$/HI CH$_3$CN Reagent

Substrates	Products	Conditions (°C, h)	Yields (%)	m.p./ (b.p.)	Lit.m.p./ (b.p.)
aniline	4-iodoanilin	20, 6	76	66-68	67-68[9]
N-methylaniline	4-iodo-*N*-methylaniline	20, 6	74	30-31	31[19]
N,N-dimethylaniline	4-iodo-*N,N*-dimethylaniline	0, 12	77	76-78	78-79[19]
2-methylaniline	4-iodo-2-methylaniline	20, 12	71	86-87	86-88[9]
3-methylaniline	4-iodo-3-methylaniline	20, 12	74	45-47	46[9]
3-methoxyaniline	2-iodo-5-methoxyaniline	20, 12	75	43-44	
benzylamine	benzaldehyde	60, 12	54	(180)	(178-179)[19]

diiodoalkenes at 60 °C in 65-87% yield (Table 2). This reaction was highly stereoselective, depending on the steric environment of the triple bond. Only a single stereoisomer was obtained as checked by NMR spectra of the crude products. The products were purified by column chromatography and the structural confirmations were carried out by ^{1}H and ^{13}C NMR spectroscopy. The regiochemistry was determined based on the ^{13}C NMR chemical shift values of the vinylic carbons that bear the iodine atom. Namely, the ^{13}C NMR chemical shift values of the vinylic carbons can be estimated with the additivity rule reported by Hollins and Campos.[14,18] Comparison with literature values[14,19,20] confirmed the stereochemistry. Since configurational correction factor differs widely for (*E*) vs. (*Z*)-diiodoalkenes, it is quite easy to assign the correct stereochemistry (Table 3) by comparison with literature values of (*E*)-1,2-diiodo-1-hexene and (*Z*)-3,4-diiodo-3-hexene reported by Barluenga, Rodriguez and Campos.[20] Furthermore, we have also used the ^{1}H chemical shift of terminal alkenes[18] to obtain better agreement with configuration assignments (Table 4). These results gave affirmation to the assigned stereochemistry of the known compounds,[14,19,20] and provided reasonably con-

Table 2. Diiodoalkenes Obtained by Using KMnO$_4$/HI CH$_3$CN Reagent

Substrates	Products	Isolation yield (%)	^{13}C of I-attach (C2, C1)
1-nonyne	(*E*)-1,2-diiodo-1-nonene	78	104.4, 78.8
1-dodecyne	(*E*)-1,2-diiodo-1-dodecene	87	104.2, 78.6
cylohexylacetylene[a]	(*E*)-cyclohexyl-1,2-diiodoethene	75	114.4, 76.4
2-methyl-3-butyn-2-ol	(*E*)-3,4-diiodo-2-methyl-3-buten-2-ol	65	114.2, 76.0
phenylacetylene	(*E*)-α,β-diiodostyrene	71	96.2, 80.8[14]
1-phenyl-1-propyne[b]	(Z)-α,β-diiodo-α-methylstyrene	71	96.3, 95.6[19]
4-octyne	(Z)-4,5-diiodo-4-octene	76	102.2, 102.2
diphenylacetylene[b]	no reaction		

Reaction was carried out at 60 °C for 20 hours; except 24 hours for a and 48 hours for b.

Table 3. Observed and Calculated ^{13}C NMR Chemical Shifts of 1,2-Diiodoalkenes

Products	Observed C1, C2	Calcd. *Z* C1, C2	Calcd. *E* C1, C2	Assign
(*E*)-1,2-diiodo-1-nonene	104.4, 78.8	118.1, 94.6[18]	101, 77.5[18]	*E*
(*E*)-1,2-diiodo-1-dodecene	104.2, 78.6	118.1, 94.6[18]	101, 77.5[18]	*E*
(*E*)-cyclohexyl-1,2-diiodoethene	114.4, 76.4	126.2, 91.5[18]	109.1, 74.4[18]	*E*
(*E*)-3,4-diiodo-2-methyl-3-buten-2-ol	114.2, 76	126.2, 91.5[18]	109.1, 74.4[18]	*E*
(*E*)-α,β-diiodostyrene	96.2, 80.8	109, 85.5[14]	96.2, 80.9[14]	*E*[14]
(Z)-α,β-diiodo-α-methylstyrene	96.3, 95.6	100, 97.4[14]	84.5, 81.3[14]	*Z*[19]
(Z)-4,5-diiodo-4-octene	102.2, 102.2	102.3, 102.3[14]	86.4, 86.4[14]	*Z*
(*E*)-1,2-diiodo-1-hexene	105.4, 80.9[20]	118.1, 94.6[18]	101, 77.5[18]	*E*[20]
(Z)-3,4-diiodo-3-hexene	103.7, 103.7[20]	102.3, 102.3[14]	86.4, 86.4[14]	*Z*[20]

Table 4. Observed and Calculated ^{1}H NMR Chemical Shifts of 1,2-Diiodoalkenes[18]

Products	Observed	Calcd. *Z*[18]	Calcd. *E*[18]	Assign
(*E*)-1,2-diiodo-1-nonene	6.80	7.05	6.92	*E*
(*E*)-1,2-diiodo-1-dodecene	6.80	7.05	6.92	*E*
(*E*)-cyclohexyl-1,2-diiodo-ethene	6.80	7.05	6.92	*E*
(*E*)-3,4-diiodo-2-methyl-3-buten-2-ol	7.20	7.26	7.18	*E*
(*E*)-α,β-diiodostyrene	7.26	7.63	7.13	*E*[14]
(*E*)-1,2-diiodo-1-hexene	6.7[20]	7.05	6.92	*E*[20]

clusive assignments for new products. Based on comparison of their observed and calculated ^{1}H and ^{13}C NMR data, all terminal alkynes studied gave (*E*)-1,2-diiodoalkenes. For (*E*)-α,β-diiodostyrene, our calculated values are identical to that reported by Hollins and Campos.[14]

Terminal alkynes underwent anti-addition, while internal alkynes gave *syn*-adducts, although diphenylacetylene was unreactive. The stereochemistry depended on starting alkynes in concordance with the steric and electronic effects of the substitutents on the triple bond. The role of manganese was unclear, but a simple mixture of hydroiodic acid, iodine and manganese(II) bromide in acetonitrile is not effective. Iodination of 2-methyl-3-butyn-2-ol gave the simple addition product without affecting the hydroxyl group. Thus our method provides a direct route to 3,4-diiodo-2-methyl-3-buten-2-ol.

CONCLUSION

Starting from readily available and inexpensive potassium permanganate, hydroiodic acid and acetonitrile, the present procedure provides a convenient, simple regiospecific and high yielding method for preparing monoiodoanilines. With a slight modification in reagent/substrate ratio, this reagent converts alkynes to *vic*-diiodoalkenes in high yields and with high regio- and stereospecificity. Isolation procedures are simple because only one stereoisomer was obtained.

EXPERIMENTAL SECTION

IR spectra (neat or KBr pellet) were run on a JASCO-IR-700 spectrometer. ^{1}H and ^{13}C NMR were recorded on JEOL-JNM-EX-400 spectrometer; chemical shifts are reported in parts per million (δ) downfield from TMS. Mass spectra (EI) were recorded on either a JEOL-JMS-D 300 or a Finnigan TSQ-700 spectrometers, operating at an ionizing voltage of 70 eV. Melting points were recorded on a Mel-temp. instrument and were uncorrected. Elemental analyses were performed with Heraeus CHN-O RAPID and Tacussel Coulomax Instruments by National Cheng Kung University.

$KMnO_4$ and HI (E. Merck, analytical grade) were used without purification. Aromatic amines and alkynes (Aldrich, reagent grade) were purified by distillation or recrystallization before use.

General Procedure for Formation of Iodoanilines

To a mixture of $KMnO_4$ (0.395 g, 2.5 mmol) and CH_3CN (80 mL) in a round-bottomed flask under magnetic stirring was added HI (57%, 1.65 mL, 12.5 mmol). Stirring continued for 5 more min and followed by addition of the substrate (10 mmol). The reaction usually last 6 to 12 h at room temperature (ca. 20 °C). Which can be monitered by TLC (silica gel, CH_2Cl_2 as eluent). After the solvent was removed under vaccum, $CHCl_3$ (100 mL) was added to the mixture, the colloidal salts was then filtered. After concentration of the filtrate the product was purified by passing through a column of silica gel (2.5 cm × 10 cm, E. Merck 70-230 mesh) using CH_2Cl_2 as eluent. These products displayed satisfactory spectroscopic properties (^{1}H and ^{13}C NMR and MS). Bp or mp values are listed in Table 1.

2-Iodo-5-methoxyaniline

Yield: 1.88 g (75%); mp 43-45 °C. IR ν_{max} (KBr) 3456, 3336 (m, N-H), 1613 (s, N-H), 1596, 1487 (s, aromatic C=C), 1295 (s, C-N), 828, 774 (s, aromatic C-H) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J = 8.8 Hz aromatic H *meta* to NH_2), 6.31 (d, 1H, J = 2.5 Hz aromatic H *ortho* to NH_2), 6.26 (dd, 1H, J = 8.8, 2.5 Hz aromatic H *para* to NH_2), 4.06 (s, 2H, NH_2), 3.73 (s, 3H, OCH_3); MS *m/z*(%) 249 (M^+, 100); Anal. Calcd. for C_7H_8INO: C, 33.74; H, 3.24; N, 5.62; Found: C, 33.68; H, 3.26; N, 5.60.

General Procedure for the Formation of *vic*-Diiodoalkenes

The addition of alkyne (10 mmol) was carried out similarily to that described for iodoanilines, except that the $KMnO_4$/HI ratio is 3 mmol/25 mmol, for reaction of 10 mmol substrate. After the reaction mixture was stirred magnetically for 20-48 h at 60 °C, solvent was removed urlder vacuum. The residue was dissolved in $CHCl_3$ (100 mL), washed with 10% aqueous potassium iodide (3 × 50 mL) and dried ($MgSO_4$). After evaporation of $CHCl_3$ the residual oil was purified by passing through a alumium foil covered column of silica gel (2.5 cm × 10 cm, E. Merck 70~230 mesh) and eluted with $CHCl_3$/hexane = 1 : 1 to give the pure product.

(*E*)-1,2-Diiodo-1-nonene

Yield: 2.95 g (78%); thermally unstable and light sensitive. IR ν_{max} (neat) 3072 (m, =C-H), 1215 (m, =C-I), 1115 (m, =C-I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1H, =C-H), 2.50 (t, 2H, J = 7.3 Hz, $=C\text{-}CH_2$), 1.54 (m, 2H, $=C\text{-}CH_2\text{-}C\underline{H}_2$), 1.33 (m, 8H, $4CH_2$), 0.89 (t, 3H, J = 6.4 Hz, CH_3); MS *m/z* (%) 378 ($M^{+\cdot}$, 83); Anal. Calcd. for $C_9H_{16}I_2$: C, 28.59; H, 4.27; Found: C, 28.82; H, 4.23.

(*E*)-1,2-Diiodo-1-dodecene

Yield: 3.65 g (87%); thermally unstable and light sensitive. IR ν_{max} (neat) 3074 (m, =C-H), 1213 (m, =C-I), 1117 (m, =C-I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1H, =C-H), 2.50 (t, 2H, J = 7.3 Hz, $=C\text{-}CH_2$), 1.54 (t, 2H, J = 7.3 Hz, $=C\text{-}CH_2\text{-}C\underline{H}_2$), 1.32 (m, 14H, $7CH_2$), 0.88 (t, 3H, J = 6.3 Hz, CH_3); MS *m/z* (%) 420 ($M^{+\cdot}$, 90); Anal. Calcd. for $C_{12}H_{22}I_2$: C, 34.31; H, 5.28; Found: C, 34.34; H, 5.37.

(*E*)-1-Cyclohexyl-1,2-diiodoethene

Yield: 2.82 g (75%). IR ν_{max} (neat) 3060 (m, =C-H), 1218 (m, =C-I), 1058 (m, =C-I) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1H, =C-H), 2.08(tt, 1H, J = 12.7, 13.2 Hz, =C-CH), 1.8 (d, 2H, J = 12.7 Hz, $=C\text{-}CH\text{-}CH_{eq}$), 1.7 (d, 2H, J = 13.2 Hz, $=C\text{-}CH\text{-}CH_{ax}$), 1.1-1.6 (m, 6H, 3 CH_2); MS *m/z* (%) 362 ($M^{+\cdot}$, 67); Anal. Calcd. for $C_8H_{12}I_2$: C, 26.54; H, 3.34; Found: C, 26.71; H, 3.27.

(*E*)-3,4-Diiodo-2-methyl-3-buten-2-ol

Yield: 2.19 g (65%); mp 51 °C. IR ν_{max} (KBr) 3276 (s, OH), 3054 (m, =C-H), 1245 (m, =C-I), 1163 (m, =C-I) cm^{-1} ^1H NMR ($CDCl_3$) δ 7.20 (s, 1H, =C-H), 2.32 (s, 1H, OH), 1.62 (s, 6H, 2 CH_3); MS *m/z* (%) 338 ($M^{+\cdot}$, 100); Anal. Calcd. for $C_5H_8I_2O$: C, 17.77; H, 2.39; O, 4.73; Found: C, 17.78; H, 2.39; O, 4.79.

(*Z*)-4,5-Diiodo-4-octene

Yield: 2.76 g (76%); IR ν_{max} (neat) 1232, 1109 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (t, 4H, J = 7.5 Hz, 2 $=C\text{-}CH_2$), 1.60 (m, 4H, 2 $=C\text{-}CH_2\text{-}C\underline{H}_2$), 0.98 (t, 6H, J = 7.8 Hz, 2 $CH_2\text{-}C\underline{H}_3$); MS *m/z* (%) = 364 ($M^{+\cdot}$, 100); Anal. Calcd. for $C_8H_{14}I_2$: C, 26.40; H, 3.88, Found: C, 26.42; H, 3.85.

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Key Words

Iodination; *p*-Iodoanilines; Diiodoalkenes; Hydroiodic acid; Potassium permanganate.

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