Direct Iodination of Aromatic Compounds with Iodine and Alumina-Supported Copper(II) Chloride or Sulfate

Mitsuo KODOMARI,* Natsuki AMANOKURA, Kiyoshi TAKEUCHI, and Suehiko YOSHITOMI
Department of Industrial Chemistry, Faculty of Engineering, Shibaura Institute of Technology, Shibaura, Minato-ku, Tokyo 108
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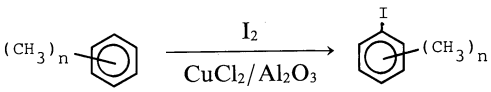
Synopsis. The iodination of aromatic compounds (polymethylbenzenes, alkyl phenyl ethers, and polynuclear aromatic hydrocarbons) with iodine in combination with copper(II) chloride or sulfate supported on alumina proceeds well under mild conditions to selectively give monoiodinated compounds in high yields.

Aryl iodides are usually more difficult to prepare than the other aryl halides, and synthetic methods leading to them are relative few.[1] The direct iodination of aromatic compounds with molecular iodine, which is the least reactive halogen in electrophilic substitution, is difficult in contrast to chlorination and bromination. Iodination requires HI removal as fast as it is formed because the reaction is reversible. Iodinations of aromtic compounds with iodine have thus been carried out in the presence of such oxidizing reagents as nitric acid, iodic acid and hydrogen peroxide.[2,3] Aryl iodides have also been synthesized by a reaction of aromatic compounds with iodine in combination with silver,[4] thallium,[5] and copper salts.[6] Baird et al. reported that iodination of aromatic compounds with iodine and copper(II) chloride produced the aryl iodides.[7] More recently, it was reported that the iodination of aromatic compounds with iodine supported on dehydrated alumina gave the corresponding aryl iodides.[8] We previously reported that the reactivity of copper(II) halides was remarkably increased when copper(II) halides were supported on neutral alumina.[9] In this paper we wish to report on the direct iodination of polymethylbenzenes, polynuclear aromatic hydrocarbons, and aromatic ethers with molecular iodine in combination with alumina-supported copper(II) chloride or copper(II) sulfate.

Results and Discussion

Iodination of Polymethylbenzenes. Iodination of *m*-xylene with iodine in the presence of neutral alumina in carbon tetrachloride at 80 °C for 4 h gave 6% yield of 4-iodo-*m*-xylene; with iodine in combination with copper(II) chloride under similar conditions it gave a 3% yield of the iodide. In contrast, when alumina-supported copper(II) chloride was used instead of copper(II) chloride, 4-iodo-*m*-xylene was obtained in 87% yield. A similar reaction was carried out without a solvent at 60 °C to give a 91% yield of the iodide after 4 h.



The iodination of polymethylbenzenes with iodine and alumina-supported copper(II) chloride without a solvent proceeded under milder conditions to give the monoiodo compounds in higher yields than in the reaction with a solvent (Table 1). The observed order of xylene reactivity (meta>ortho>para) is in accord with the basicity of xylene isomers toward electrophiles.[10] The degree of reactivity of the polymethylbenzenes increased with increasing number of methyl groups on the benzene ring. More reactive polymethylbenzenes, which contain three or more methyl groups, gave small amount of chlorinated products along with iodide. For example, in the case of pentamethylbenzene, besides iodopentamethylbenzene, chloropentamethylbenzene was formed in 4% yield. Chloropentamethylbenzene was produced in 59% yield from a similar reaction with alumina-supported copper(II) chloride alone, and in 20% yield from a halogen exchange of iodopentamethylbenzene with alumina-supported copper(II) chloride under the same conditions. These observations suggest that the chlorinated by-products result from chlorination of the substrate with copper(II) chloride, rather than a halogen exchange of the resulting iodide with copper(II) chloride. Although the iodination of aromatic compounds with

Table 1. Iodination of Polymethylbenzenes with Iodine and $CuCl_2/Al_2O_3$[a]

Polymethylbenzenes	°C/h	Product	Yield/%[b]
MeC_6H_5	120/14	I-MeC_6H_4[c]	75
1,2-$Me_2C_6H_4$	80/10	4-I-1,2-$Me_2C_6H_3$	96
1,3-$Me_2C_6H_4$	60/4	4-I-1,3-$Me_2C_6H_3$	91
1,4-$Me_2C_6H_4$	80/10	2-I-1,4-$Me_2C_6H_3$	87
1,3,5-$Me_3C_6H_3$	60/0.5	2-I-1,3,5-$Me_3C_6H_2$	96
1,2,4-$Me_3C_6H_3$	60/3	1-I-2,4,5-$Me_3C_6H_2$	97
1,2,4,5-$Me_4C_6H_2$	60/10	3-I-1,2,4,5-Me_4C_6H	84
1,3,4,5-$Me_4C_6H_2$	40/4	2-I-1,3,4,5-Me_4C_6H	96
1,2,3,4,5-Me_5C_6H	40/6	1-I-2,3,4,5,6-Me_5C_6	92

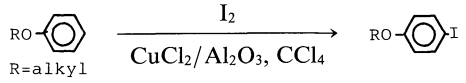
a) All reactions were carried out without solvent. When the substrate was solid, it was dissolved in a small amount of carbon tetrachloride. b) Determined by GLC. c) A mixture of *o*- and *p*-isomer.

iodine and copper(II) chloride is much improved by the addition of aluminum chloride, undesirable side-reactions occur when polymethylbenzenes serve as aromatic compounds.[11] In the present method, only nuclear iodination occurred and no by-products, such as biaryls, or disproportionation and polymeric materials were detected.

Iodination of Aromatic Ethers. Aromatic ethers were easily iodinated by iodine and alumina-supported copper(II) salts to give monoiodinated products in high yields. For example, while the reaction of 1-methoxy-3-methylbenzene with iodine and copper(II) chloride in carbon tetrachloride at 60 °C for 1 h produced only 4% of 4-iodo-1-methoxy-3-methylbenzene, a similar reaction with iodine and alumina-supported copper(II) chloride produced the monoiodide in 93% yield. The reaction proceeded even at 30 °C to give an 87% yield of the monoiodide after 4 h. In general, one-half of the molecule is discarded when molecular iodine is used as an iodinating agent. In the present iodination reaction, the added iodine was almost completely consumed, and two moles of aryl iodide were formed from one mole of iodine. Thus, the reaction appeared to occur in accord with the following stoichiometry.

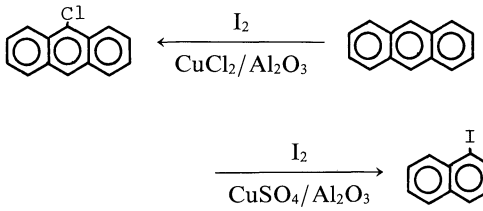
$$2ArH + I_2 + 2CuCl_2 \longrightarrow 2ArI + 2HCl + Cu_2Cl_2.$$

Iodinations of alkyl phenyl ethers such as anisole, butyl phenyl ether, and hexyl phenyl ether with iodine and alumina-supported copper(II) chloride gave the para isomer of the corresponding monoiodide selectively; the amount of the ortho isomer formed was negligible.



As the number of methoxyl groups attached to the benzene ring increased, the reactant was consumed more rapidly. The iodine and alumina-supported copper(II) chloride system could not be used to obtain monoiodide of more reactive substrates, such as 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene, but their monoiodide could be obtained in high yield by using iodine and alumina-supported copper(II) sulfate. In the case of 1,3-dimethoxybenzene, the reaction with iodine and alumina-supported copper(II) chloride produced a mixture of monoiodide, diiodide, monochloride, and iodochlorinated compounds. In contrast, a similar reaction with iodine and alumina-supported copper(II) sulfate afforded an 89% yield of 4-iodo-1,3-dimethoxybenzene and a trace amount of diiodide.

Iodination of Polynuclear Aromatic Hydrocarbons. Direct iodination of polynuclear aromatic hydrocarbons using alumina-supported copper(II) chloride failed, due to rapid chlorination with alumina-supported copper(II) chloride.[9] For example, the reaction of naphthalene with alumina-supported copper(II) chloride and iodine produced a 52% yield of 1-iodonaphthalene and a 15% yield of 1-chloronaphthalene; a similar reaction of anthracene afforded a 90% yield of 9-chloroanthracene, but no isolable iodoanthracene was obtained. Empirical testing of five copper(II) salts ($CuCl_2$, $CuBr_2$, CuF_2, and $Cu(OAc)_2$) revealed that copper(II) sulfate was the most effective for the iodination of polynuclear aromatic compounds.



The reaction of naphthalene with copper(II) chloride and iodine in chlorobenzene at 115 °C for 21 h afforded a 44% yield of 1-iodonaphthalene.[7] In contrast, an 84% yield of 1-iodonaphthalene was obtained from a reaction with alumina-supported copper(II) sulfate and iodine without a solvent at 80 °C for 4 h. 1-Methylnaphthalene, fluorene, and anthracene were also iodinated with alumina-supported copper(II) sulfate and iodine under similar conditions to produce monoiodinated compounds in high yields.

The present iodination reactions proceed under milder conditions in comparison with the method using copper(II) salts alone as the catalyst. The monoiodo compounds of polymethylbenzenes and alkyl phenyl ethers could be obtained by using alumina-supported copper(II) chloride; in the case of more reactive substrates, such as polynuclear aromatic hydrocarbons and polymethoxybenzenes, their monoiodo-derivatives

Table 2. Iodination of Aromatic Ethers with Iodine and Cu(II) Salt/Al_2O_3[a]

Aromatic ether	Cu(II)	°C/h	Product	Yield/%[b]
PhOMe	$CuCl_2$	80/3	4-IC_6H_4OMe	87
PhOEt	$CuCl_2$	60/5	4-IC_6H_4OEt	86
PhO-*n*-Bu	$CuCl_2$	60/2	4-IC_6H_4O-*n*-Bu	84
PhO-*n*-C_6H_{13}	$CuCl_2$	60/4	4-IC_6H_4O-*n*-C_6H_{13}	85
4-MeC_6H_4OMe	$CuCl_2$	80/4	2-I-4-MeC_6H_3OMe	89
3-MeC_6H_4OMe	$CuCl_2$	60/1	4-I-3-MeC_6H_3OMe	93
2-MeC_6H_4OMe	$CuCl_2$	60/3	4-I-2-MeC_6H_3OMe	96
1,3-$(MeO)_2C_6H_4$	$CuSO_4$	70/0.3	4-I-$C_6H_3(MeO)_2$-1,3	89
1,2-$(MeO)_2C_6H_4$	$CuSO_4$	90/3	4-I-$C_6H_3(MeO)_2$-1,2	80
1,3,5-$(MeO)_3C_6H_3$	$CuSO_4$	50/2	2-I-$C_6H_2(MeO)_3$-1,3,5	86

a) All reactions were carried out in carbon tetrachloride. b) Determined by GLC.

Table 3. Iodination of Polynuclear Aromatic Hydrocarbons with Iodine and Cu(II) Salt/Al_2O_3

Aromatics	Cu(II) salt	Method[a]	°C/h	Product	Yield/%[b]
Naphthalene	$CuCl_2$	A	80/5	1-I	52
				1-Cl	15
	$CuBr_2$	A	80/5	1-I	3
				1-Br	50
	$CuSO_4$	A[c]	130/8	1-I	62
	$CuSO_4$	B	80/4	1-I	84
1-Methylnaphthalene	$CuSO_4$	B	80/3	4-I	94
Fluorene	$CuSO_4$	B	80/2	2-I	76
Anthracene	$CuSO_4$	A	80/4	9-I	73
	$CuCl_2$	A	80/4	9-Cl	90

a) A: with solvent (benzene), B: without solvent. b) Determined by GLC. c) Chlorobenzene.

could be obtained by using alumina-supported copper (II) sulfate. The advantages of this procedure for monoiodination of aromatic compounds are its simple workup, mild reaction conditions, and higher selectivities.

Experimental

Excess iodine over that required for the monoiodination of polymethylbenzenes and polynuclear aromatic hydrocarbons resulted in an increased yield of iodide. For example, the iodination of *m*-xylene with 0.5 and 1.0 equiv mole of iodine gave 82 and 91% yield of monoiodide, respectively. Thus, all reactions of the polymethylbenzenes and polynuclear aromatic hydrocarbons were performed with 1.0 equiv mole of iodine.

Alumina-Supported Copper(II) Salt. The preparation of the reagent has been reported.[9] Alumina-supported copper(II) chloride and sulfate having 9 wt% copper(II) on alumina were used.

1-Iodo-2,4,5-Trimethylbenzene: Typical Procedure for Polymethylbenzenes. A mixture of 1,2,4-trimethylbenzene (0.48 g, 4 mmol) and iodine (1.03 g, 4 mmol) was added to alumina-supported copper(II) chloride (9.0 g, 6 mmol); the mixture was then stirred with a Teflon-coated magnetic stirring bar at 60 °C for 3 h. The products were removed from the mixture by stirring with carbon tetrachloride. The spent reagent was removed by filtration, and the filtrate was washed with 10% aqueous sodium thiosulfate to remove unreacted iodine and water; it was then dried over anhydrous sodium sulfate. The residual solid, after removal of the solvent, was recrystallized from methanol to give colorless needles of 1-iodo-2,4,5-trimethylbenzene (0.87 g, 88%); mp 35—36 °C (lit,[12] mp 36—37 °C).

Iodination of Polynuclear Aromatic Hydrocarbons. The iodination was carried out by two methods: (A) a solution method in which a solution of iodine and the substrate in benzene is stirred with alumina-supported copper(II) salt, and (B) a dry method in which iodine and the substrate are dissolved in a small amount of benzene; alumina-supported copper(II) salt is impregnated with the solution.

9-Iodoanthracene: General Procedure by Method A. To a mixture of iodine (0.51 g, 2 mmol) and anthracene (0.36 g, 2 mmol) in benzene (50 ml) was added alumina-supported copper(II) sulfate (10.6 g, 6 mmol); the mixture was stirred with a Teflon-coated magnetic stirring bar at 80 °C for 4 h. The mixture was then filtered and the spent reagent washed with benzene. The combined filtrate was washed with 10% aqueous sodium thiosulfate and water. The benzene solution was dried and the solvent was evaporated to afford a white solid, which is purified by recrystallization from benzene–methanol to give 0.37 g (60%) of 9-iodoanthracene; mp 78—80 °C (lit,[14] 79—81 °C).

1-Iodonaphthalene: General Procedure by Method B. To a solution of naphthalene (0.27 g, 2 mmol) in a test tube (20 cm^3) with a screw cap were added iodine (0.51 g, 2 mmol) and alumina-supported copper(II) sulfate (10.6 g, 6 mmol), and then thoroughly mixed. The mixture was heated at 80 °C for 3 h. The products were extracted from the mixture by stirring with benzene. The benzene solution was washed with 10% aqueous sodium thiosulfate and water, and then dried. The products were analyzed by GLC.

4-Iodo-1-methoxy-2-methylbenzene: General Procedure for Aromatic Ethers. A mixture of 1-methoxy-2-methylbenzene (0.37 g, 3 mmol), iodine (0.43 g, 1.7 mmol), and alumina-supported copper(II) chloride (9.0 g, 6 mmol) in carbon tetrachloride (30 ml) was stirred at 60 °C for 3 h. The mixture was filtered, and the spent reagent was washed with carbon tetrachloride. The combined filtrate was washed with 10% aqueous sodium thiosulfate and water, and then dried. The solvent was evaporated to afford a white solid, which was recrystallized from methanol to give 4-iodo-1-methoxy-2-methylbenzene (0.60 g (81%)); mp 77—78 °C (lit,[13] 77.5—78 °C).

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