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A Convenient Procedure for Iodination of Electron-rich Aromatic Compounds using Iodine-Copper(II) Acetate

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Synopsis. The iodination of some electron-rich aromatic compounds, namely, three polymethylbenzenes, aniline, phenol, anisole, and phenetole, using iodine–copper(II) acetate in acetic acid, afforded the corresponding iodo compound in high yield.

Much work has been reported on the bromination and chlorination of aromatic compounds. However, since it is known that iodination is usually difficult accomplish due to the reducing effect of the hydrogen iodide produced, the iodination of aromatic compounds has been carried out in the presence of an oxidizing reagent such as nitric acid, iodic acid, sulfur trioxide, or hydrogen peroxide.[1] Many procedures are available for the iodination of activated aryl compounds by iodine–thallium(I) acetate,[2] iodine–mercury(II) acetate,[3] iodine–silver(I) acetate,[4] iodine-ammonium hexanitratocerate(IV),[5] and alkali metal iodide-ammonium hexanitratocerate(IV).[5] Moreover, Bird and Surridge recently reported[6] that the iodination of aromatic compounds with iodine and copper(II) halide gave the aryl iodides. Still more recently, it was reported the iodination of the less reactive substrates with iodine–aluminum(III) and copper(II) chloride[7] gave the corresponding aryl halide.

We have been investigating a novel iodination using iodine–copper(II) acetate; and as a first step in this research project, we reported earlier the α-iodination of ketones,[8] and the regioselective iodination of estradiol, estriol, and estrone.[9] In the work described in these reports, we demonstrated that iodine–copper(II) acetate in acetic acid is a useful reagent for the syntheses of some iodo compounds.

In the present paper, we report the iodination of some activated aryl compounds, namely, three polymethylbenzenes, aniline, phenol, anisole, and phenetole.

The reactions of the polymethylbenzenes, mesitylene (**1**), durene (**2**), and pentamethylbenzene (**3**) with iodine and copper(II) acetate in acetic acid under refluxing for 5—9 h yielded in all cases the iodo compound (**8**—**10**) (70—89%). All products were characterized by comparisons of their NMR and IR spectra and their melting points with those of authentic samples. Similarly, the reaction of aniline (**4**) afforded 4-iodoaniline (**11**) in a good yield. In the cases of anisole (**5**) and phenetole (**6**), *para*-substituted products (**12** and **13**) were obtained. This result is in agreement with the fact that the iodination of anisole using thallium(I) acetate[2] or copper(II) chloride[6] occurs at the *para*-position. The method used in the present work gave a better yield than Cambie's one. In the case of phenol (**7**), it was found that *ortho*-attacked products, namely, 2-iodo- (**15**) (64%) and 2,6-diiodo-phenol (**14**) (11%), and 4-iodo derivative (**16**) (5%) were obtained. This agrees with the result of the iodination using thallium(I) acetate or silver(I) acetate; and both of these results are also supported by our earlier finding that the iodination using the iodine-copper(II) acetate of the 3-hydroxy-estrogen derivative occurred at the *ortho*-position,[9] while the reaction of 3-methoxyestrogen derivative resulted in the recovery of the starting material. Thus, it was found that the iodine and copper(II) acetate used in these reactions were efficient and selective iodinating agents for electron-rich aromatic compounds.

Experimental

All the melting points are uncorrected. The IR and NMR spectra were measured using a Hitachi model 215 grating infrared spectrometer and a nuclear magnetic resonance spectrometer, Hitachi-Perkin Elmer R-20A, in carbon tetrachloride with TMS as an internal standard.

General Procedure. A mixture of a substrate (1.1×10^{-2} M), iodine (1.0 mol. equiv), and copper(II) acetate (1.0 mol. equiv) in acetic acid (50 ml) was stirred under refluxing for 6—9 h. The precipitated copper(I) iodide was removed by filtration, and the filtrate was poured into water and extracted with ether. The ethereal solution was washed with sodium hydrogencarbonate solution and with water, then

Table 1. Products and isolated yields (%) in the iodination of electron-rich aromatic compounds (**1**—**7**)

Materials	Time/h	Products	Isolated yield/%	Mp θ_m/°C	Lit. Mp θ_m/°C
Mesitylene (**1**)	5	Iodomesitylene (**8**)	80	30—31	32—34[10]
Durene (**2**)	6	Iododurene (**9**)	89	79—80	80—81[11]
Pentamethylbenzene (**3**)	9	Iodopentamethylbenzene (**10**)	70	139—140	141—142[11]
Aniline (**4**)	2	4-Iodoaniline (**11**)	90	61—62	59—62[2]
Anisole (**5**)	10	4-Iodoanisole (**12**)	69	48—49	48—50.5[2]
Phenetole (**6**)	10	4-Iodophenetole (**13**)	80	29—30	29[12]
Phenol (**7**)	4	2,6-Diiodophenol (**14**)	11	66—67	65.5—67.5[2]
		2-Iodophenol (**15**)	64	43—44	42—43[2]
		4-Iodophenol (**16**)	5	92—93	92—94[10]

dried with anhydrous sodium sulfate. After removal of the desiccant, evaporation of the solvent left a solid, which was recrystallized from hexane to give the corresponding aryl iodide.

Iodination of Phenol (**7**). A mixture of phenol (**7**) (1.021 g), iodine (2.753 g), and copper(II) acetate (2.167 g) in acetic acid was treated according to the general procedure. After the usual work-up, the resultant oil was chromatographed on silica gel (50 g). Elution with hexane (50 ml) and benzene (70 ml) gave plates of **14** (420 mg) from hexane, mp 66—67 °C. The next fraction, eluted by the same solvent (70 ml), on crystallization from hexane gave plates of **15** (1.529 g), mp 43—44 °C, while the last fraction, eluted with the same solvent (30 ml), on crystallization from hexane gave plates of **16** (115 mg), mp 92—93 °C.

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