

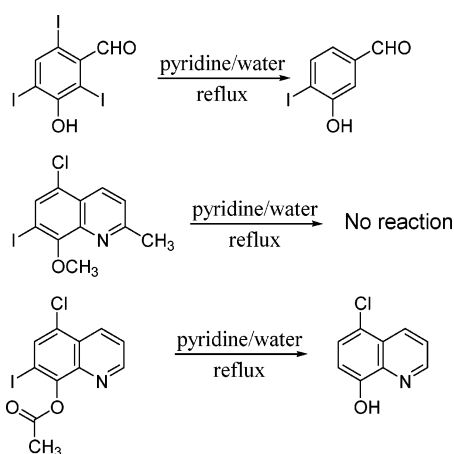
## Nonreductive Deiodination of *ortho*-Iodo-Hydroxylated Arenes Using Tertiary Amines

Rahul Subhash Talekar,<sup>†</sup> Grace Shiahuy Chen,<sup>‡</sup>  
Shin-Yu Lai,<sup>†</sup> and Ji-Wang Chern<sup>\*,†</sup>

School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan, ROC, and Department of Applied Chemistry, Providence University, 200 Chung-Chi Road, Shalu, Taichung, ROC

chern@jwc.mc.ntu.edu.tw

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A convenient and nonreductive deiodination is reported for the *ortho*-iodo-hydroxylated arenes including derivatives of quinolinol, phenol, and naphthol. Tertiary amines pyridine, triethylamine, and *N*-methylmorpholine in the presence of water initiated deiodination of *ortho*-iodo-hydroxylated arenes without affecting *para*-iodine and other reduction-susceptible groups. This reported method also works efficiently for polyiodinated systems. Simplicity, short reaction times, and absence of reducing catalyst are features of this method.

Halogenated arenes are very useful in substitution reaction. Recently, the bromine on aromatic system was considered as potential protecting group since the debromination could be achieved selectively and regioselectively by HBr.<sup>1</sup> In addition, the iodothyronine deiodinase enzymes catalyze the interconversion of active and inactive forms of thyroid hormones.<sup>2</sup> The enzyme causes deiodination of thyroxin to an inactive form of hormone. Some studies have attempted to study the deiodination by using derivatives of 2,4-diiodophenol to mimic the

action of the iodothyronine deiodinases.<sup>3,4</sup> In general, deiodination as well as debromination is achieved by various reducing agents such as catalytic hydrogenation,<sup>5</sup> metal hydrides,<sup>6</sup> and acidic conditions such as Pd/C–HCl,<sup>7</sup> Zn<sup>8</sup> or SnCl<sub>2</sub>/CH<sub>3</sub>CO<sub>2</sub>H,<sup>9</sup> Zn/HCl,<sup>10</sup> and CuCN/FeCl<sub>3</sub>.<sup>11</sup> Nevertheless, these methods are time-consuming or complicated or use expensive catalysts. Obviously, these methods also affect the reduction susceptibility of groups present in the structure.<sup>12</sup> Recently, debromination by HBr has been reported as the first case without affecting the reductive groups.<sup>1</sup>

Quinolines and their derivatives have attracted research in areas such as pharmaceuticals and are general synthetic building blocks due to their chemical and biological relevance.<sup>13</sup> 8-Hydroxyquinoline and its halo derivatives have attracted studies as analytical reagents and metal-extracting agents because of their ability to complex with metal ions.<sup>14</sup> They are also used as bactericides,<sup>15</sup> fungicides,<sup>16</sup> antimalarial agents,<sup>17</sup> and anticancer agents.<sup>18</sup> Recently, it was reported that antibiotic clioquinol (**1**, Table 1 where R = R' = H) was able to chelate and remove metal ions from the insoluble amyloid plaque deposited in the brains of patients with Alzheimer's disease.<sup>19</sup> In a study related to the derivatives of **1**, we found that the hydrolysis of the pivaloyl ester of quinolinols **2a–2c** in the presence of pyridine was associated with deiodination to yield quinolinols **4a–4c**.

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\* Author to whom correspondence should be addressed. Phone: 886-2-23939462. Fax: 886-2-23934221.

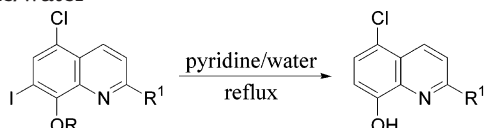
<sup>†</sup> National Taiwan University.

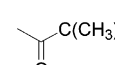
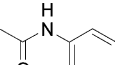
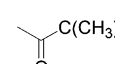
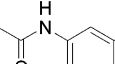
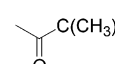
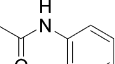


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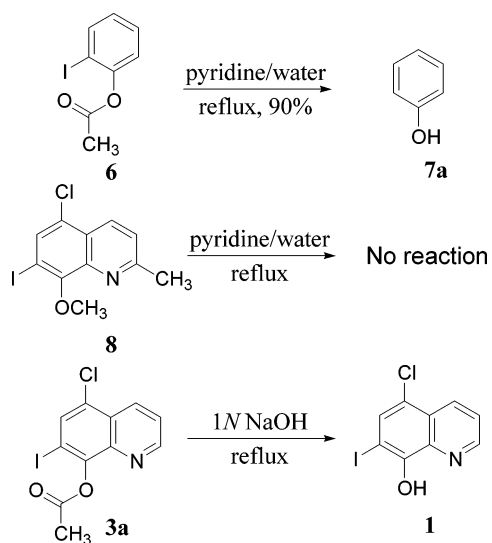
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**TABLE 1. Hydrolysis and Deiodination of *o*-Iodoquinolinyl Esters **2a–c** and **3a,b** in the Presence of Pyridine/Water**



substrate	R	R <sup>1</sup>	product	yield
<b>1</b>	—H	—H	—	—
<b>2a</b>			<b>4a</b>	89%
<b>2b</b>			<b>4b</b>	71%
<b>2c</b>			<b>4c</b>	84%
<b>3a</b>		—H	<b>5a</b>	92%
<b>3b</b>		—CH <sub>3</sub>	<b>5b</b>	81%

**SCHEME 1**



The same result was observed for the acetyl ester of quinolinols **3a** and **3b**.

Extended investigation into the phenol system, 2-iodophenyl acetate (**6**) in pyridine/water at reflux also resulted in both hydrolyzed and deiodinated product, phenol (**7a**, Scheme 1). It is suspected that the concurrent deiodination might be a result of the presence of pyridine after hydrolysis. For that reason, 2-methyl-5-chloro-7-iodo-8-methoxyquinoline (**8**) was examined in pyridine/water, and no deiodination occurred. To investigate the role of base, hydrolysis of **3a** using 1 N NaOH resulted in the hydrolyzed product **1** exclusively without deiodi-

nation. This leads us to assume that the prerequisite of *ortho*-OH group in aromatic derivatives is essential in deiodination by pyridine. Although deiodination has been mentioned in *N,N*-dimethylaniline for the preparations of chromene, 2,4-dihydroxy-6-methoxyphenyl methyl ketone,<sup>20a</sup> and benzopyran,<sup>20b</sup> the details have not been shown. On the basis of this observation, coupled with the use of the deiodination of 2,4-diiodophenols as templates to mimic the action of iodothyronine deiodinases,<sup>3,4</sup> we decided to further evaluate deiodination on a series of *ortho*-iodo-hydroxylated arenes.

To verify the necessity for the phenolic OH group and pyridine in *ortho*-deiodination, we carried out reactions for quinolinols, phenols, and naphthols containing an iodo substituent *ortho* to the hydroxy group as depicted in Table 2. In addition, we also investigated the role of pyridine in deiodination by other tertiary amines such as triethylamine and *N*-methylmorpholine. Tertiary amines were used without predrying. Halogenated hydroxyquinoline **9**, polyiodophenols **10**, and 1-iodo-2-naphthol (**11**) were prepared by iodination according to the reported methods.<sup>21,22</sup> All *o*-iodo-hydroxylated arenes **1** and **9–11** underwent deiodination by means of three tertiary amines in excellent yields, with the exception of **10c** with triethylamine due to the poor solubility. Generally speaking, iodophenols are more easily deiodinated than iodoquinolinol and iodonaphthols. In the presence of electron-withdrawing groups CN and CHO in the *o*-iodophenols **10e** and **10f**, respectively, deiodination required a longer reaction time.

The regioselectivity and halogen discrimination in the dehalogenation are considered as two major issues. Both the *ortho*-iodines of **10b** and **10c** were removed in the reaction to afford the corresponding phenols. The iodine *para* to the hydroxy group in the case of **9b** and **10c–e** was not removed in the present study. These results demonstrated the regioselective deiodination: only the *ortho*-iodines were selectively removed. A perusal of literature indicated that a treatment of 5,7-diiodo-8-hydroxyquinoline with pyridine hydrochloride led to both *ortho*- and *para*-deiodination.<sup>23</sup> Contrarily, a reductive dehalogenation of 2,4,6-triiodophenol (**10c**) by sulfite/bisulfate was reported to give only *para*-deiodinated product 2,6-diiodophenol.<sup>24</sup> To the best of our knowledge, the regioselective *ortho*-deiodination in the presence of *para*-iodine has never been reported. To investigate the prospect of different halogens, 2-bromo- and 2-chlorophenols, 1-bromo- and 1-chloro-2-naphthols, and 5,7-dibromo- and 5,7-dichloro-1-methyl-8-quinolinols were subjected to the analogous reaction. The dehalogenation did not occur even after prolonged reflux or at higher temperature. Furthermore, **10e** containing the reduction-susceptible cyano group underwent deiodination without detriment to the cyano group. 2,4,6-Triiodo-3-hydroxy-

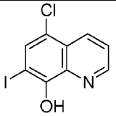
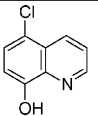
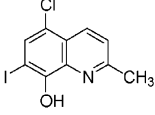
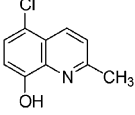
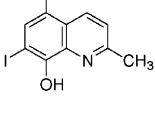
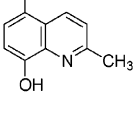




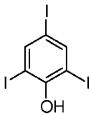
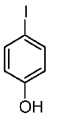
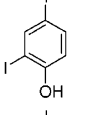
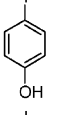
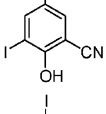
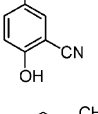
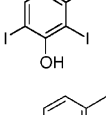
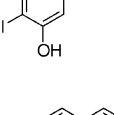
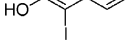
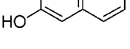
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TABLE 2. Deiodination of *o*-Iodo-Hydroxylated Arenes **1** and **9–11** in the Presence of Tertiary Amines

	reagent	amines <sup>a</sup>	time (h) <sup>b</sup>	product	yield (%) <sup>c</sup>
<b>1</b>		pyridine	4	<b>5a</b> 	94
		TEA	2.5		90
		NMM	2		92
<b>9a</b>		pyridine	4	<b>5b</b> 	85
		TEA	4		96
		NMM	3.5		91
<b>9b</b>		pyridine	5	<b>5c</b> 	92
		TEA	4		83
		NMM	4.5		90
<b>10a</b>		pyridine	0.75	<b>7a</b> 	98
		TEA	1		96
		NMM	0.5		90
<b>10b</b>		pyridine	1.5	<b>7a</b> 	90
		TEA	1		88
		NMM	1		92
<b>10c</b>		pyridine	2.5	<b>7c</b> 	78
		TEA	20		12 <sup>d</sup>
		NMM	4		72
<b>10d</b>		pyridine	1	<b>7c</b> 	88
		TEA	0.75		90
		NMM	0.75		86
<b>10e</b>		pyridine	6	<b>7e</b> 	83
		TEA	4.5		86
		NMM	5		92
<b>10f</b>		pyridine	7.5	<b>7g</b> 	91
		TEA	5.5		87
		NMM	6		92
<b>11</b>		pyridine	5.5	<b>12</b> 	93
		TEA	6		80
		NMM	5.5		82

<sup>a</sup> Amines were not dried before use. TEA = triethylamine, NMM = *N*-methylmorpholine. <sup>b</sup> At reflux. <sup>c</sup> Isolated yield. <sup>d</sup> Low yield due to poor solubility. 2,4-Diiodophenol was isolated in a trace amount.

benzaldehyde (**10f**) also gave a sole product. However, based on the <sup>1</sup>H NMR and the reported melting point the product could be either the expected 5-hydroxy-2-iodobenzaldehyde (**7f**)<sup>25</sup> or its isomer 3-hydroxy-4-iodobenzaldehyde (**7g**).<sup>26</sup> Therefore, 2D NMR experiments, HMQC and HMBC, were carried out to elucidate the structure. Surprisingly, the results showed that the product should be 3-hydroxy-4-iodobenzaldehyde (**7g**) instead of the expected **7f**. This result was different from all the other studied cases **9b** and **10c–e**. The reason might be due to the effect of the aldehyde group. The same strategy

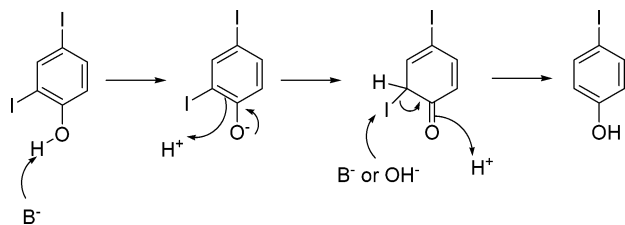
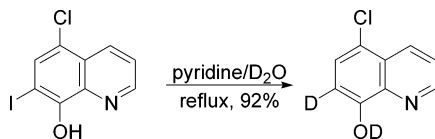
was extended to 1-iodo-2-naphthol (**11**) to afford 2-naphthol (**12**) in 6 h, more rapidly in comparison to that by KHSO<sub>4</sub>/Na<sub>2</sub>SO<sub>3</sub> reductive reaction.<sup>24</sup>

Phenols are present essentially in their deprotonated forms under basic conditions. A possible mechanism has been proposed for the dehalogenation.<sup>4,27</sup> The present deiodination might occur via initial deprotonation of the phenolic OH group by tertiary amines, and then the resulting anion abstracts a proton to form tautomeric dienone. Subsequently, nucleophilic attack on iodine atom by either hydroxide ion or base results in the deiodinated product (Scheme 2). Since all tertiary amines were used without predrying, we presumed that the

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**SCHEME 2. Plausible Mechanism for Deiodination Using Tertiary Amines**

**SCHEME 3**


proton source in this plausible mechanism came from water. To investigate the proton source, a predried pyridine was applied, leading to no deiodination at all. Further validation was performed in the presence of  $D_2O$ , which afforded a deuterium on the ortho position of phenol (Scheme 3). This ascertained the proton source. On the basis of the proposed mechanism, the debromination of *o*-bromophenol and *para*-deiodination of **9b** and **10c–e** would be hypothetically possible. In fact, the debromination was reported when thiol anion was used as a nucleophile.<sup>28</sup> However, debromination and *para*-deiodination did not occur in the present study. As a result, the exact mechanism is not clearly understood at this moment, and further exploitation is compulsory.

In conclusion, the present method is applicable for nonreductive deiodination of *ortho*-iodo-hydroxylated arenes without affecting *para*-iodine and reduction-susceptible groups. Simplicity, high yield, and absence of reducing catalyst are features of this method. This

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investigation demonstrated that deiodination of *o*-iodo-hydroxylated arenes by tertiary amines/water might provide a facile deprotecting reaction in which iodine can be used as a protective group.

**Experimental Section**

**General Procedure for Deiodination.** A mixture of 5-chloro-7-iodo-quinolin-8-ol (**1**, 0.2 g, 0.6 mmol) in *N*-methylmorpholine (12 mL, 1.2 mmol) was heated at reflux for 2 h. A strong fluorescent spot on TLC indicated the completion of reaction. The reaction mixture was concentrated and purified by flash column chromatography over silica gel (43–60  $\mu$ m, 2.5  $\times$  20 cm, 5% EtOAc/Hex,  $R_f$  0.28).

**5-Chloro-2-methylquinolin-8-ol (5b):** Yellowish solid. mp 65–68 °C (lit.<sup>29</sup> 68 °C); IR (KBr) 3378, 2924, 1503, 1257, 940, 824, 786  $cm^{-1}$ ;  $^1H$  NMR (200 MHz,  $CDCl_3$ )  $\delta$  8.29 (d,  $J$  = 8.6 Hz, 1H), 7.38 (d,  $J$  = 8.2 Hz, 1H), 7.33 (d,  $J$  = 8.6 Hz, 1H), 7.02 (d,  $J$  = 8.2 Hz, 1H), 2.69 (s, 3H);  $^{13}C$  NMR (50 MHz,  $CDCl_3$ )  $\delta$  157.5, 150.6, 137.8, 133.2, 126.2, 124.3, 123.3, 120.1, 109.7, 24.6; MS (ESI)  $m/z$  191.8 (M – H)<sup>–</sup>.

**2-Hydroxy-5-iodobenzonitrile (7e):** Yellowish solid. mp 115–117 °C; IR (KBr) 3332, 2229, 1454, 1186, 872, 674  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CD_3OD$ )  $\delta$  7.76 (s, 1H), 7.69 (d,  $J$  = 8.8 Hz, 1H), 6.73 (d,  $J$  = 8.8 Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CD_3OD$ )  $\delta$  142.9, 140.8, 133.0, 118.2, 115.1, 101.9, 78.2; MS (ESI)  $m/z$  243.7 (M – H)<sup>–</sup>; HRMS (FAB<sup>+</sup>) calcd for  $C_7H_5INO$  (M + H)<sup>+</sup> 245.9416, found 245.9411.

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**Supporting Information Available:** Experimental procedures and characterization for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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