

Hypervalent Iodine(III)–LiX Combination in Fluoroalcohol Solvent for Aromatic Halogenation of Electron-Rich Arenecarboxylic Acids

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Abstract: The novel reagent system, $\text{PhI}(\text{OAc})_2$ –LiX combination in fluoroalcohol solvents, was found to be effective for halodecarboxylation of electron-rich arenecarboxylic acids. The method provided an efficient route to halogenated phenol ether derivatives.

Key words: carboxylic acids, hypervalent iodine, halogenation, fluoroalcohol, decarboxylation

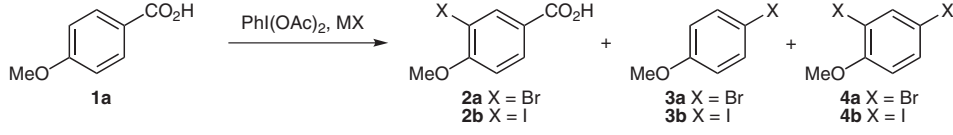
For many years, the use of arenecarboxylic acids as building blocks in chemical synthesis has received considerable attention due to their wide availability and low price.¹ A great deal of effort has been invested to provide the synthetic strategies starting from arenecarboxylic acids. Decarboxylative transformations of arenecarboxylic acids under the catalysis of late transition metals have generated much interest in the past few years.^{1,2} On the other hand, halodecarboxylation of carboxylic acids into halogenated compounds, known as the Hunsdiecker-type reaction, is another powerful alternative to offer the useful synthetic applications of arenecarboxylic acids.^{3,4} Despite its importance, the Hunsdiecker reaction is generally inefficient for the conversion of arenecarboxylic acids relative to the halodecarboxylation of aliphatic and alicyclic carboxylic acids. Moreover, the conversion of arenecarboxylic acids to the corresponding iodobenzene is quite difficult. Therefore, these facts indicate the need for the creation of new strategy for halodecarboxylation of arenecarboxylic acids.

Over the past two decades, hypervalent iodine reagents have gained much attention owing to their attractive features such as low toxicity, high stability, and reactivity similar to those of highly toxic heavy metal salts.^{5–7} It is well known that upon irradiation trivalent iodine reagents, $\text{PhI}(\text{OAc})_2$, undergo decarboxylative decomposition and generate radical species.⁸ On the basis of this procedure, Camps reported Hunsdiecker-type bromodecarboxylation of aliphatic carboxylic acids and nitro-substituted benzoic acids to the corresponding brominated compounds.^{8d} Further, several groups also reported the devising methodology of hypervalent iodine mediated Hunsdiecker-type decarboxylations. Although such heavy metal salt free approaches constitute an important method in this chemistry, their utility is limited for the reaction of aliphatic and

α,β -unsaturated carboxylic acids in many cases and they are undesirable for the reaction of electron-rich arenecarboxylic acids. In this communication, we report the use of novel reactivity of hypervalent iodine(III)–LiX combination in fluoroalcohol media for the effective iodination of arenecarboxylic acids.

In the course of our synthetic studies on the use of indolecarboxylic acid as building blocks for bioactive compounds via decarboxylative strategies, we have found the novel ability of hypervalent iodine(III)–LiX combination in halodecarboxylation.⁹ When we attempted to apply our previous conditions,^{9b} $\text{PhI}(\text{OAc})_2$ –LiBr combination in THF, for the purpose of bromodecarboxylation of electron-rich arenecarboxylic acids such as *p*-anisic acid, the ring-halogenation product,¹⁰ 3-bromo-*p*-anisic acid (**2a**), was obtained but the halodecarboxylation product was not detected (Table 1, entry 1). Additionally, no reaction occurred in iododecarboxylation under our previous conditions (Table 1, entry 2).

The reluctant result prompted us to design new reaction conditions utilizing hypervalent iodine reagent. We focused our attention on the use of the unique reactivity of hypervalent iodine reagents in fluoroalcohol.^{11,12} Since the pioneer work reported by Kita, this reactivity was widely investigated in hypervalent iodine chemistry, and many remarkable advantages appeared in the reaction with phenol or phenol ether type substrates.¹¹ In hope of developing new reaction conditions to achieve the halodecarboxylation of electron-rich arenecarboxylic acids, we tried to use the fluoroalcohol solvents with the combination of $\text{PhI}(\text{OAc})_2$ and LiX. Gratifyingly, the bromodecarboxylation along with ring bromination proceeded cleanly to provide a dibrominated product **4a** when the reaction was carried out in trifluoroethanol (TFE, $\text{CF}_3\text{CH}_2\text{OH}$) or 1,1,1,3,3,3-hexafluoroisopropanol [HFIP, $\text{CF}_3\text{CH}(\text{OH})\text{CF}_3$] (Table 1, entries 3 and 4). In addition, the iododecarboxylation was successfully achieved by utilizing a combination of $\text{PhI}(\text{OAc})_2$ and LiI in fluoroalcohol solvents, and diiodinated product **4b** was smoothly obtained in HFIP, while 4-iodoanisole (**3b**) was obtained in TFE as major product (Table 1, entries 5 and 6). To our knowledge, this is first example of high-yielding iododecarboxylation of electron-rich arenecarboxylic acids. After tuning of equivalence of the reagent system (Table 1, entries 7–9), iododecarboxylation could be performed on 3 equivalents of $\text{PhI}(\text{OAc})_2$ with 2 equivalents of LiI in HFIP (Table 1, entry 9).

Table 1 Iododecarboxylation of *p*-Anisic Acid


Reaction scheme showing the iododecarboxylation of *p*-anisic acid (**1a**) using $\text{PhI}(\text{OAc})_2$ and MX to yield products **2a** (X = Br), **3a** (X = Br), and **4a** (X = Br). The structures of **2b** (X = I), **3b** (X = I), and **4b** (X = I) are also shown.

Entry	Oxidant (equiv)	MX (equiv)	Solvent	Temp (°C)	Time (h)	Yield of 2 (%) ^a	Yield of 3 (%) ^a	Yield of 4 (%) ^a
1	$\text{PhI}(\text{OAc})_2$ (6)	LiBr (6)	THF	50	12	59	–	–
2	$\text{PhI}(\text{OAc})_2$ (6)	LiI (6)	THF	50	12	–	–	–
3	$\text{PhI}(\text{OAc})_2$ (6)	LiBr (6)	TFE	50	12	–	–	75
4	$\text{PhI}(\text{OAc})_2$ (6)	LiBr (6)	HFIP	r.t.	12	–	–	85
5	$\text{PhI}(\text{OAc})_2$ (6)	LiI (6)	TFE	50	3	11	83	–
6	$\text{PhI}(\text{OAc})_2$ (6)	LiI (6)	HFIP	r.t.	3	–	–	92
7	$\text{PhI}(\text{OAc})_2$ (4)	LiI (4)	HFIP	r.t.	3	4	–	90
8	$\text{PhI}(\text{OAc})_2$ (1)	LiI (1)	HFIP	r.t.	3	2	60	6
9	$\text{PhI}(\text{OAc})_2$ (3)	LiI (2)	HFIP	r.t.	3	7	–	88
10	$\text{PhI}(\text{OAc})_2$ (3)	KI (2)	HFIP	r.t.	3	7	–	83
11	$\text{PhI}(\text{OAc})_2$ (3)	NaI (2)	HFIP	r.t.	3	5	–	85
12	$\text{PhI}(\text{OAc})_2$ (3)	TBAI (2) ^b	HFIP	r.t.	3	9	4	75
13	$\text{PhI}(\text{OCOCF}_3)_2$ (3)	LiI (2)	HFIP	r.t.	3	75	–	–
14	PhIO (3)	LiI (2)	HFIP	r.t.	24	–	–	–
15	DMP (3) ^c	LiI (2)	HFIP	r.t.	24	–	–	–
16	HgO [red] (3)	LiI (2)	HFIP	r.t.	24	–	–	–
17	$\text{Ti}(\text{OCOCF}_3)_2$ (3)	LiI (2)	HFIP	r.t.	3	84	–	4
18	VOCl_3 (3)	LiI (2)	HFIP	r.t.	24	36	–	–

^a Yield of isolated product.^b TBAI = tetrabutylammonium iodide.^c DMP = Dess–Martin periodinate [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one].

Additionally, other iodine salts, such as KI, NaI, or TBAI (Bu_4NI), could also be applicable for this reaction instead of LiI (Table 1, entries 10–12). In order to find the best iododecarboxylation method, the reaction was also carried out with various oxidants in HFIP (Table 1, entries 13–18).⁷ Although ring-iodination product **2b** was obtained in some cases, no other conditions gave the iododecarboxylation products sufficiently. These results clearly indicate

that a reagent system of $\text{PhI}(\text{OAc})_2$ and LiI in HFIP is the best condition for the iododecarboxylation of electron-rich arenecarboxylic acids.

The exciting result obtained with the reaction of *p*-anisic acid (**1a**) prompted us to extend our procedure to various electron-rich arenecarboxylic acids (Table 2). The reaction of arenecarboxylic acid possessing *p*-methoxy or *o*-methoxy substituents gave the corresponding iododecar-

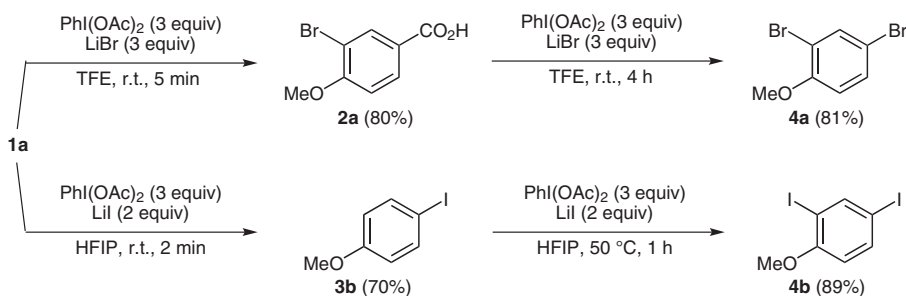
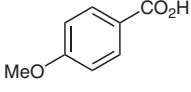
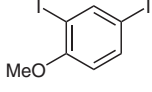
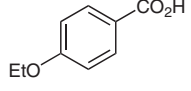
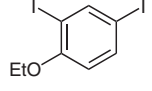
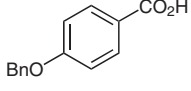
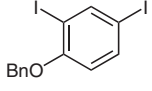
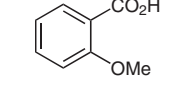
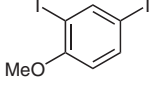
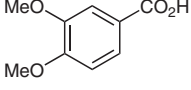
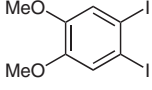
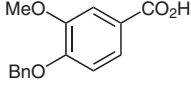
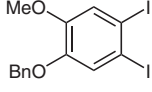
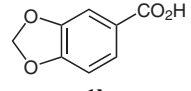
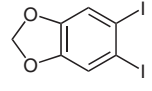
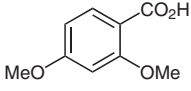
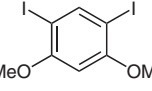
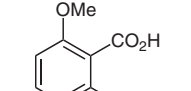
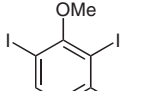
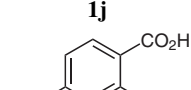
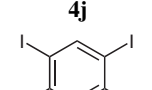
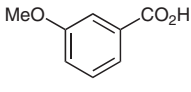
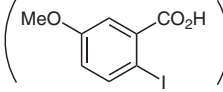
**Scheme 1** Sequence for dibromination and diiodination

Table 2 Iododecarboxylation of Arenecarboxylic Acids

Ar ¹ CO ₂ H		PhI(OAc) ₂ (3 equiv), LiI (2 equiv), HFIP		Ar ² I		Yield (%) ^a	
1		r.t., 1–6 h		4			
Entry	Ar ¹ CO ₂ H		Ar ² I				
1					88		
2					90		
3					89		
4					74		
5					90		
6					80		
7					88		
8					91		
9					83		
10					81		
11					65 ^b		
12	4-nitrobenzoic acid 1m		no reaction		–		
13	4-methylbenzoic acid 1n		no reaction		–		

^a Yield of isolated product.^b Yield of **2l**.

boxylation products in good yields, where ring iodination also occurred on *para* position of methoxy substituent (Table 2, entries 1–10).¹³ In addition, the benzyl ether moiety was not cleaved during the reaction (Table 2, entries 3 and 6). When the reaction was performed with *m*-anisic acid, the decarboxylation does not occur and the ring-iodination product was obtained (Table 2, entry 11). It is interesting to note that the reaction with the electron-deficient arenecarboxylic acid such as *p*-nitrobenzoic acid did not occur at all contrary to the previous hypervalent iodine mediated procedures under irradiation (Table 2, entries 12 and 13).^{8b,d} This result suggests that our iododecarboxylation procedure would not involve the carboxy radical pathway, but possibly involves the radical-cation intermediate through an ionic path.^{8,12} When the reaction was stopped in the early stages (after 2–15 min), compound **2a** was obtained as major product in the bromination of **1a**, while **3b** was obtained as major product in the iodination of **1a**.¹⁴ Therefore, ring bromination was faster than bromodecarboxylation, while ring iodination was slower than iododecarboxylation (Scheme 1).

In summary, we have developed an efficient decarboxylation method of electron-rich arenecarboxylic acids utilizing a PhI(OAc)₂–LiX combination in fluoroalcohol solvents. This new method provided an efficient route to various iodinated phenol ether syntheses. Further application of this method in organic synthesis and detailed investigation on the reaction mechanism are in progress.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (14) Compound **3b** was also obtained as minor product into the iodination of **1a** where **3b** was not converted to **4b** smoothly (<10%) in further iodination reaction [$\text{PhI}(\text{OAc})_2/\text{LiI}$ combination in HFIP].