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Hypervalent Iodine(III)-Mediated Oxidative Decarboxylation of β,γ-Unsaturated Carboxylic Acids

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Supporting Information

ABSTRACT: A novel oxidative decarboxylation of β,γ-unsaturated carboxylic acids mediated by hypervalent iodine(III) reagents is described. The decarboxylative C−O bond forming reaction proceeded in the presence of $PhI(OAc)_2$ to give the corresponding allylic acetates. In addition, decarboxylative C−N bond formation was achieved by utilizing hypervalent iodine(III) reagents containing an I−N bond. Mechanistic studies suggest the unique reactivity of hypervalent iodine reagents in this ionic oxidative decarboxylation.

The decarboxylative functionalization of carboxylic acids is one of the most attractive transformations in organic synthesis. However, oxidative decarboxylation that involves C−heteroatom bond forming reactions, particularly C−O and C−N bond formation, has received considerably less attention.[1] A classic method for oxidative decarboxylation involving C−O bond formation employs heavy metal oxidants under high-temperature conditions.[2,3] Mosher and Kehr reported on the decomposition of aliphatic carboxylic acids in the presence of $Pb(OAc)_4$, in which oxidative decarboxylation occurred and gave the corresponding carbocation intermediate, which was trapped by carboxylate anions to provide esters.[4,5] In a subsequent study, Kochi et al. demonstrated that oxidative decarboxylation mediated by $Pb(OAc)_4$ proceeded via a free-radical chain mechanism,[6] and they also reported on the decarboxylative acetoxylation of phenyl acetic acids and β,γ-unsaturated carboxylic acids in a benzene/AcOH mixed solvent in the presence of $Pb(OAc)_4$ and $Cu(OAc)_2$.[7] In contrast, a metal-free protocol employing a combination of $PhI(OAc)_2$ and I_2 was developed by Suárez et al., and the method enabled radical decarboxylation involving C−O and C−N bond forming reactions of uronic acids and α-amino acids.[8,9] Despite this progress, we consider that the development of decarboxylative oxy- and nitrogenation of carboxylic acids remains a challenging task.

Recently, hypervalent iodine reagents, which have a low toxicity and can be handled easily, have been recognized as an alternative to toxic heavy-metal oxidants.[10] In particular, taking advantage of their ability to activate a C−C multiple bond, significant advances have been made in the oxidative functionalization of alkenes and alkynes.[11] Inspired by this unique reactivity, we envisaged that hypervalent iodine reagents would enable the oxidative decarboxylation of carboxylic acids containing a C−C multiple bond at a suitable position. Herein, we report on the decarboxylative oxygenation and nitrogenation of β,γ-unsaturated carboxylic acids by hypervalent iodine reagents (Figure 1).

We began our investigation on decarboxylative acetoxylation using 3-phenylbut-3-enoic acid (**1a**) as a model substrate in the presence of $PhI(OAc)_2$. Although the reaction proceeded effectively in 1,2-dichloroethane (DCE) at 80 °C, the corresponding allylic acetate **2a** and ester **3a** were obtained in 54% and 42% yields, respectively. Thus, we examined the use of AcOH in order to suppress the formation of **3a**, and then a DCE/AcOH (2:1 v/v) mixed solvent was found to be optimal, achieving both a high yield and selectivity (Scheme 1a).[12] In contrast, Wirth et al. recently reported on the oxidative cyclization and rearrangement of β,γ-unsaturated carboxylic acids using highly electrophilic hypervalent iodine reagent $PhI(OTf)_2$ to give furanones.[13] Indeed, the reaction of **1a** with $PhI(OTf)_2$, prepared by the reaction of $PhI(OAc)_2$ and trimethylsilyl triflate (TMSOTf),[14] led to oxidative cyclization, with **4** being produced and no detectible decarboxylative product being produced (Scheme 1b).

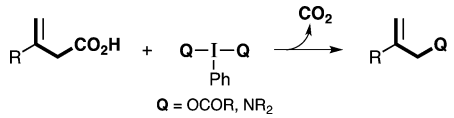
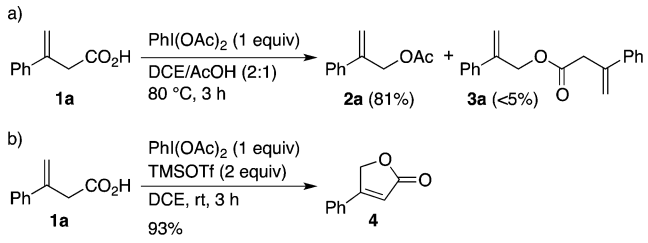


Figure 1. Oxidative decarboxylation of β,γ-unsaturated carboxylic acids.

Scheme 1. Reactions of 1a with Hypervalent Iodine Reagents



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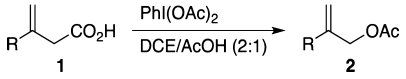
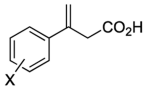
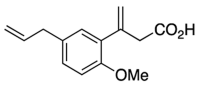
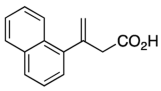
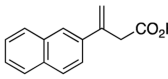
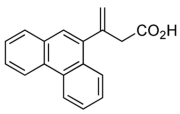
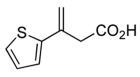
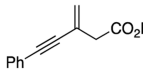
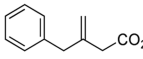
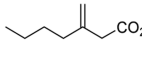
Employing $PhI(OAc)_2$ in a DCE/AcOH (2:1 v/v) mixed solvent, the decarboxylative acetoxylation reactions of various β-substituted β,γ-unsaturated carboxylic acids **1** were examined (Table 1).[15] Carboxylic acids bearing electron-rich aryl substituents at the β-position showed high reactivity (Table 1, entries 1–4). However, in reactions of highly electron-rich **1b** and **1c**, products **2** and/or starting acids **1** appear to have been partially decomposed during the reaction. Acetoxylation using substrates bearing electron-withdrawing groups on the phenyl ring proceeded well under reflux conditions (Table 1, entries 5–8). Unfortunately, the highly electron-deficient **2j** gave a low yield, even when the reaction time was extended (Table 1, entry 9). While a substituent at the *ortho* position decreases the reactivity, the reaction of **1k** using 1.5 equiv of $PhI(OAc)_2$ under reflux improved the yield (Table 1, entry 10). An allyl group on the phenyl ring was well tolerated under the reaction conditions used (Table 1, entry 12). Other β-aromatic substrates including naphthyl, phenanthryl, and thienyl groups also underwent decarboxylative acetoxylation (Table 1, entries 13–16). An alkynyl group was also tolerated under the oxidative conditions, while the product yield was moderate (Table 1, entry 17). Moreover, the reaction could also be expanded to substrates with β-aliphatic substituents (Table 1, entries 18 and 19). Disappointingly, no product was obtained when a β-nonsubstituted acid, but-3-enoic acid, was used as a substrate.

Table 1. Substrate Scope for Decarboxylative Acetoxylation

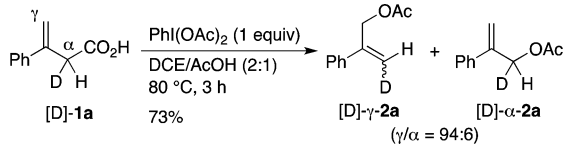


entry	1	conditions[a]	2, yield (%)[b]
			
1	**1b**, X = 3,4-$(MeO)_2$	80 °C, 1 h	**2b**, 68
2	**1c**, X = 4-MeO	80 °C, 1 h	**2c**, 75
3	**1d**, X = 4-Me	80 °C, 3 h	**2d**, 70
4	**1e**, X = 4-^{t}Bu	80 °C, 3 h	**2e**, 81
5	**1f**, X = 4-F	reflux, 3 h	**2f**, 76
6	**1g**, X = 4-Cl	reflux, 6 h	**2g**, 79
7	**1h**, X = 4-Br	reflux, 3 h	**2h**, 76
8	**1i**, X = 4-CF_3	reflux, 20 h	**2i**, 73
9	**1j**, X = 3,5-$(CF_3)_2$	reflux, 24 h	**2j**, 31
10	**1k**, X = 2-Me	reflux, 7 h	**2k**, 61 (90)[c,d]
11	**1l**, X = 3-Me	80 °C, 3 h	**2l**, 76
12[c,e]	 **1m**	80 °C, 3 h	**2m**, 72
13[c]	 **1n**	reflux, 20 h	**2n**, 79
14	 **1o**	80 °C, 3 h	**2o**, 82
15[c]	 **1p**	reflux, 20 h	**2p**, 69
16	 **1q**	80 °C, 3 h	**2q**, 71
17[c]	 **1r**	reflux, 3 h	**2r**, 62
18	 **1s**	reflux, 20 h	**2s**, 78
19	 **1t**	reflux, 20 h	**2t**, 60

[a]Reactions under reflux conditions were conducted at 95 °C (thermostat temperature). [b]Isolated yields. [c]$PhI(OAc)_2$ (1.5 equiv) was used. [d]The reaction was run for 16 h. [e]0.1 mmol scale.

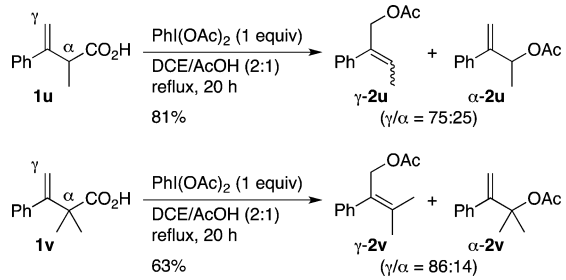
In an attempt to confirm the site of incorporation of the acetoxy group (α- vs γ-position), the reaction of α-monodeuterated carboxylic acid [D]-**1a** was examined. Under the standard conditions, the reaction predominantly afforded [D]-γ-**2a**, which contained a deuterium atom at the vinylic position, over the α-product [D]-α-**2a** (γ/α = 94:6) (Scheme 2). No deuterium atom exchange of the starting acid [D]-**1a** in DCE/AcOH at 80 °C was observed. Moreover, no isomerization between products was observed under identical conditions. These results clearly demonstrate that the acetoxylation is inherently γ-selective.

Scheme 2. Deuterium-Labeling Experiment



We conducted the reactions by using β,γ-unsaturated carboxylic acids bearing α-substituents (Scheme 3). The decarboxylative acetoxylation of **1u** smoothly proceeded, but the resulting product was a mixture of regioisomers, γ-**2u** and α-**2u** (γ/α = 75:25, *E*/*Z* of the γ-product = 15:85).[16] Similarly, an α,α-dimethyl substrate **1v** also gave a mixture of regioisomers (γ/α = 86:14).[17] These results indicate that substituents at the α-position affect the reaction mechanism, increasing the α-product being produced (vide infra).

Scheme 3. Reactions Using α-Substituted Substrates



To gain additional insights into the mechanism, the following experiments were carried out. When the reaction of the

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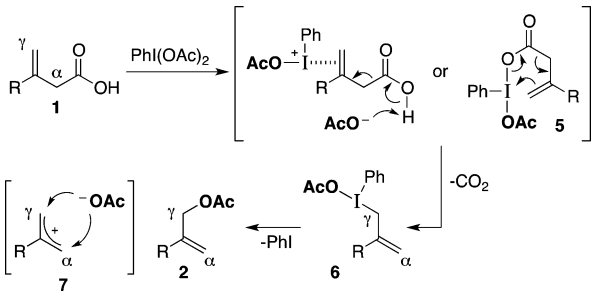
corresponding ester, ethyl 3-phenylbut-3-enoate, with $PhI(OAc)_2$ was conducted under the standard conditions, no reaction was observed, and the alkene moiety remained unreacted.[18] This result suggests that a pathway that involves direct attack of the acetoxy anion at the γ-carbon of the alkene moiety is less likely in the decarboxylative acetoxylation of **1**. Futhermore, when a radical inhibitor was added to the reaction, the yield of product remained essentially the same, indicating that the mechanism including a radical pathway is also not likely.[18] The proposed reaction mechanism based on the experimental results is shown in Scheme 4. The reaction is

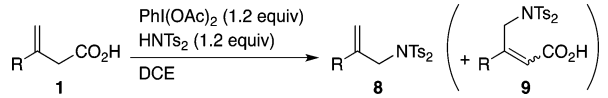
Scheme 4. Plausible Reaction Mechanism for Decarboxylative Acetoxylation

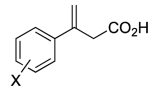
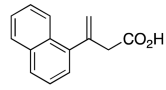
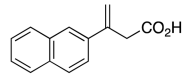
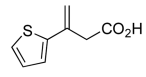
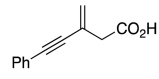
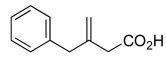
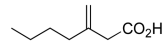


initiated through the activation of **1** by $PhI(OAc)_2$ with the spontaneous dissociation of the acetoxy anion from the iodine center. The abstraction of a proton from **1** leads to decarboxylation, affording the allyl-λ^3-iodane intermediate **6**. Moreover, an alternative pathway including generation of **5** by ligand exchange, followed by an intramolecular rearrangement with decarboxylation, is also a reasonable pathway for the formation of **6**. The subsequent S_N2 displacement by an acetoxy anion in conjunction with the reductive elimination of PhI results in the formation of the product **2** in a γ-selective manner.[19] When the acetoxy anion is dissociated from **6**, the subsequent reductive elimination of PhI provides the allylic cation intermediate **7**, which would lead to the formation of a mixtutre of α- and γ-products.[20] In the case of reactions using α-substituted substrates such as **1u** and **1v**, larger amounts of α-products were produced, probably through the formation of highly stable secondary and tertiary allylic cation intermediates, respectively.

We next envisaged that the use of hypervalent iodine reagents containing an I–N bond would allow the decarboxylative amination of β,γ-unsaturated carboxylic acids in a similar manner. We initially chose $HNTs_2$ as a nitrogen source in these attempts.[11a] After a brief screening of reaction conditions,[18] we found that the decarboxylative imidation of **1a** proceeded effectively by simply using a combination of $PhI(OAc)_2$ and $HNTs_2$ in DCE at 80 °C, with **8a** being produced in 73% isolated yield (Table 2, entry 1). The reaction of $PhI(OAc)_2$ with an equimolar amount of $HNTs_2$ in dichloromethane at room temperature provided a mixture of $PhI(OAc)_2$, $PhI(OAc)(NTs_2)$, and $PhI(NTs_2)_2$ in a ratio of 27:64:9, as determined by ^1H NMR analysis, indicating that hypervalent iodine reagents with imide ligands participate in the reaction.[18] The trend for the reactivity of the decarboxylative imidation was similar to that for the acetoxylation (Table 2). Although substrates bearing electron-rich aryl-substituents showed a higher reactivity than electron-deficient substrates, the product yields were somewhat low, because the reactions of **1c**, **1d**, **1e**, and **1q** yielded γ-amino-α,β-unsaturated carboxylic acids **9** as side products, which are probably formed through the formation of stable benzylic cation intermediates (Table 2, entries 2–4 and 13).[21]

Table 2. Substrate Scope for Decarboxylative Imidation



entry	1	conditions[a]	yield (%)[b]
			
1	**1a**, X = H	80 °C, 3 h	**8a**, 73
2	**1c**, X = 4-MeO	rt, 0.5 h	**8c**, 34
3	**1d**, X = 4-Me	70 °C, 3 h	**8d**, 60
4	**1e**, X = 4-^{t}Bu	80 °C, 3 h	**8e**, 57
5	**1f**, X = 4-F	80 °C, 3 h	**8f**, 69
6	**1g**, X = 4-Cl	80 °C, 3 h	**8g**, 70
7	**1h**, X = 4-Br	80 °C, 3 h	**8h**, 64
8	**1i**, X = 4-CF_3	reflux, 8 h	**8i**, 70
9	**1k**, X = 2-Me	reflux, 9 h	**8k**, 73
10	**1l**, X = 3-Me	80 °C, 3 h	**8l**, 66
11	 **1n**	reflux, 9 h	**8n**, 63
12	 **1o**	80 °C, 3 h	**8o**, 70
13	 **1q**	rt, 1 h	**8q**, 34
14	 **1r**	reflux, 7 h	**8r**, 52
15	 **1s**	reflux, 9 h	**8s**, 73
16	 **1t**	reflux, 3 h	**8t**, 62

[a]Reactions under reflux conditions were conducted at 95 °C (thermostat temperature). [b]Isolated yields.

The use of saccharin instead of $HNTs_2$ also afforded the corresponding product **10** (Scheme 5a). In contrast, attempts to introduce a phthalimide moiety by simply utilizing phthalimide and $PhI(OAc)_2$ were unsuccessful, and only the allylic acetate **2a** was obtained, indicating that an iodine(III) reagent containing an I–N bond is not generated in situ by ligand exchange because of the lower acidity of the phthalimide compared to acetic acid. Thus, we examined the use of $PhI(NPhth)_2$ (Phth = phthaloyl) that was separately prepared by reacting $PhI(OCOCF_3)_2$ with potassium phthalimide,[22] and to our delight, decarboxylative imidation proceeded using this reagent, to afford **11** with a slight modification in the reaction conditions (Scheme 5b).

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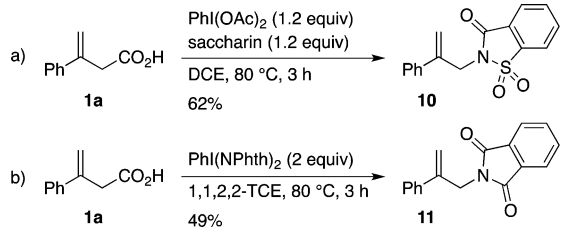
Scheme 5. Synthesis of Saccharin and Phthalimide Derivatives



In conclusion, we report the development of decarboxylative oxygenation and nitrogenation of β,γ-unsaturated carboxylic acids mediated by hypervalent iodine reagents. Based on mechanistic investigations, hypervalent iodine reagents appear to be unique for use in ionic oxidative decarboxylation. Further investigation focused on expanding the scope of substrates of this method is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Most of the reactions gave **2** as products, with a small amount of homocoupling product **3**. Detailed results were described in the Supporting Information.

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(17) When the reaction using **1v** was carried out for a shorter reaction time (3 h), a 51% yield was obtained with a γ/α ratio of 69:31. The change in the γ/α ratio indicates that the isomerization of α-**2v** to the thermodynamically more stable γ-**2v** occurred under the reaction conditions. The acid-catalyzed isomerization of allylic acetates has been reported; see: (a) Young, W. G.; Webb, I. D. *J. Am. Chem. Soc.* **1951**, *73*, 780. (b) Young, W. G.; Green, H. E.; Diaz, A. F. *J. Am. Chem. Soc.* **1971**, *93*, 4782.

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(21) The detailed results of reactions and a plausible reaction mechanism are shown in the Supporting Information.

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