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Oxidative Decarboxylation Enables Chemoselective, Racemization-Free Esterification: Coupling of α-Ketoacids and Alcohols Mediated by Hypervalent Iodine(III)

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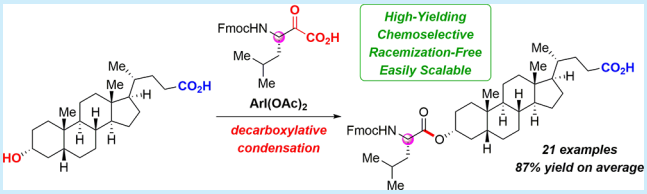
Supporting Information

ABSTRACT: An α-ketoacid could be converted into a reactive acylating agent by treatment with hypervalent iodine(III) species, and in so doing, we discovered a novel decarboxylative acylation of alcohols that affords a variety of esters in excellent yields. The esterification has been applied to a sterol bearing a free carboxylic acid and shows unique chemoselectivity. The procedure is racemization-free and operates under mild conditions.



The decarboxylative transformation of carboxylic acids has recently appeared in the field of organic chemistry and carries with it the potential advantage of releasing thermodynamically stable carbon dioxide (CO_2) gas from the reaction system to help drive the reaction to completion.[1] In biochemistry, α-ketoacids such as pyruvic acid can be converted to Breslow intermediates by the assistance of thiamine pyrophosphate (TPP) and following oxidative transformation provides acyl-CoAs, which are important acylating agents (Scheme 1a).[2] A palladium catalyst can also utilize an α-ketoacid as an acyl nucleophile through decarboxylation to afford an acylpalladium intermediate (Scheme 1b, eq 1).[1a] While α-ketoacids have been employed as acylanion equivalents as described above, oxidative condensation reactions of α-ketoacids with the appropriate oxidants have been recently developed.[1c,3−8] Among them, Lan and Lei and co-workers[3a] and Xu and co-workers[3b] have reported efficient decarboxylative amidations, which proceed at room temperature via a photo-induced radical pathway along with the release of CO_2 (eq 2). More importantly, ketoacid−hydroxylamine (KAHA) ligation developed by Bode and co-workers[4,5] merely needs mixing of an α-ketoacid and a hydroxylamine to afford the corresponding amide without any condensation agents. Despite the brilliant preceding studies on the amidation reactions, there are still only two reports on decarboxylative esterifications using alcohols due to their weak nucleophilicities.[8] In Beebe's and Ahmed's preceding works,[8a,b] oxidants such as *N*-iodosuccinimide (NIS) and Oxone were utilized to promote the decarboxylative esterifications, but these still need a large excess of alcohol to be used. We envisioned that α-ketoacids could be converted to a reactive acylating agent by the action of hypervalent iodine(III) reagents and that this would enable a wide range of oxidative transformations to be achieved (eq 3).[9−12] Herein, we describe a chemoselective, racemization-free coupling of alcohols and α-ketoacids mediated by (diacetoxy)iodoarenes.

First, we screened reaction conditions for the decarboxylative esterification of a representative α-ketoacid on the basis of the concept shown above (Table 1). 2-Phenylethanol **1** and commercially available α-ketoacid **2** were chosen as model substrates, and the treatment of **1** and **2** with iodosylbenzene (PhIO, **4a**) at room temperature for 4 h provided the corresponding ester **3** in 26% yield with a 73% recovery of alcohol **1** (entry 1).[13] Encouraged by the excellent combined mass balance of **1** and **3**, we screened different types of

Scheme 1. Decarboxylative Coupling of α-Ketoacids

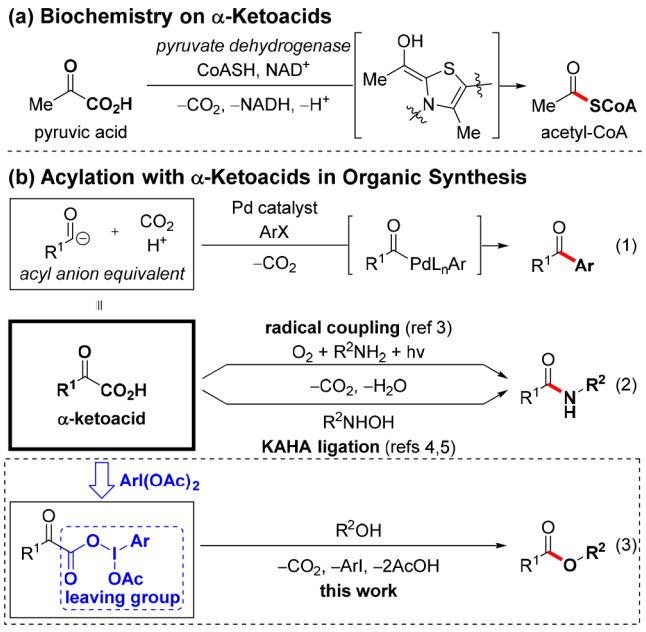


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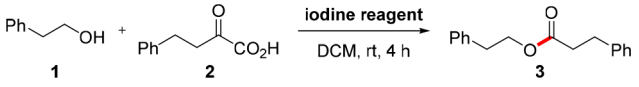
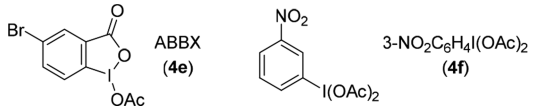
Table 1. Reaction Optimization[a]

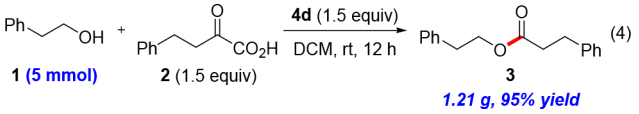


entry	iodine reagent	yield[b] (%)	rsm[b] (%)
1	PhIO (**4a**)	26	73
2	PhI(OH)OTs (**4b**)	46	34
3	$PhI(OCOCF_3)_2$ (**4c**)	30	44
4	$PhI(OAc)_2$ (**4d**)	65	35
5	ABBX (**4e**)	0	97
6	NIS	12	56
7	$3\text{-}NO_2C_6H_4I(OAc)_2$ (**4f**)	70	30
8[c]	$3\text{-}NO_2C_6H_4I(OAc)_2$ (**4f**)	92 (99)	6

[a]**1** (0.2 mmol), **2** (0.2 mmol), and iodine reagent (0.2 mmol) were employed in DCM (1 mL) at room temperature. [b]Determined by ^1H NMR spectra using dimethyl terephthalate as an internal standard; isolated yield in parentheses. [c]**2** (1.5 equiv) and **4f** (1.5 equiv) were used.

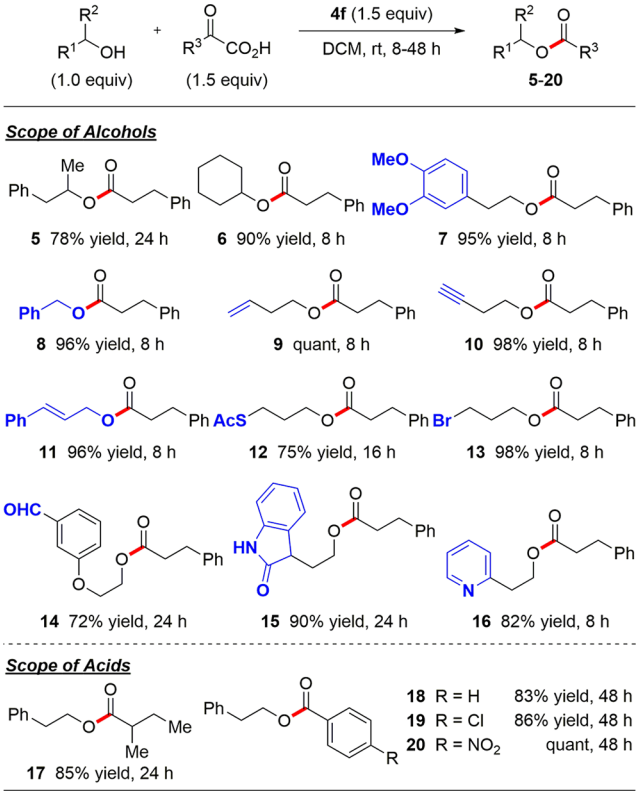


hypervalent iodine(III) species to further improve the extent of esterification (entries 2−5). While all acyclic reagents afforded the desired ester **3**, among them, (diacetoxy)iodobenzene ($PhI(OAc)_2$, **4d**) was the best for the transformation, and the yield of ester **3** improved to 65% (entry 4). Interestingly, only 1-acetoxy-5-bromo-1,2-benziodoxol-3(1*H*)-one (ABBX, **4e**), which is a cyclic hypervalent iodine(III) reagent used for the oxidation of alcohols,[14] provided almost perfect recovery of starting alcohol **1** (entry 5). NIS, which has previously been utilized for the decarboxylative esterification of α-ketoacids using a large excess of alcohols,[8a] afforded just 12% of the ester **3** (entry 6). More reactive (diacetoxy)iodoarene **4f** bearing a nitro group on the *meta* position[15,16] enabled a further increase of the conversion, with the desired ester being obtained in 70% yield (entry 7). Increasing the amount of α-ketoacid **2** and hypervalent iodine reagent **4f** provided almost a full conversion, and the desired ester **3** was isolated in 99% yield (entry 8). This reaction could be performed under air and easily applied on gram-scale without any precautions. By using commercially available $PhI(OAc)_2$ **4d**, 5 mmol of alcohol **1** was converted to 1.21 g of ester **3** in 95% yield with a longer reaction time (eq 4).



Having identified the optimal conditions for this reaction, we next investigated the substrate scope of the alcohols (Scheme 2, **5**−**16**). Secondary alcohols could be applied in this reaction and both acyclic and cyclic ones provided the corresponding esters **5** and **6** in 78% and 90% yields, respectively. Of note, the reaction rates were significantly influenced by the steric environments of the alcohols, with tertiary alcohols not giving the desired esters. Subsequently, we focused on evaluating the compatibility of different functional groups in the substrates, given the uniqueness of these oxidative acylation conditions. Electron-rich benzenes totally tolerated the reaction with the ester **7** being obtained in 95% yield. Benzyl alcohols also provided the corresponding ester **8** in excellent 96% yield without any

Scheme 2. Substrate Scope[a,b]



[a]Alcohol (0.2 mmol), α-ketoacid (0.3 mmol), and **4f** (0.3 mmol) were employed in DCM (1 mL) at room temperature. [b]Isolated yields were indicated.

benzylic oxidation products. While hypervalent iodine(III) species can potentially react with unsaturated bonds,[9,12] they did not damage the terminal olefin and alkyne fertures of **9** and **10** where the esterification successfully proceeded. Next, we applied the esterification to alcohols bearing electrophilic sites and revealed that allyl ester, thioester, alkyl halide, and aldehyde tolerated the mildly acidic reaction conditions with esters **11**−**14** being obtained without significant degradation of the compounds. Heterocycles were also applicable with oxindole and pyridine containing esters **15** and **16** being obtained in 90% and 82% yields, respectively. The scope of the α-ketoacids was also examined (**17**−**20**). Substitution adjacent to the carbonyl group did not have a significant influence on the yield of ester **17**. The reaction of benzoylformic acids afforded the benzoyl ester **18** in 83% yield. We also employed *para*-substituted substrates to test the electronic effect of the carbonyl group and electron-withdrawing substituents slightly improved the yield of esters **19** and **20**.

In addition to this basic analysis of the reaction as shown above, we attempted to determine the unique features of this decarboxylative esterification. Selective chemical modification by the introduction of amino acid or peptide structures would be a powerful tool in medicinal chemistry, and moreover, from the aspect of providing a practical coupling method, the preservation of stereochemical information would be critically important.[17] Decarboxylative esterification of Fmoc-Leu-CO_2H **21** successfully proceeded to afford the ester **22** in 91% yield with the perfect stereoretention (>99% ee) at a position adjacent to the carbonyl group (Scheme 3a). Importantly, amino acid derived α-ketoacids are easy to store and handle and Bode and

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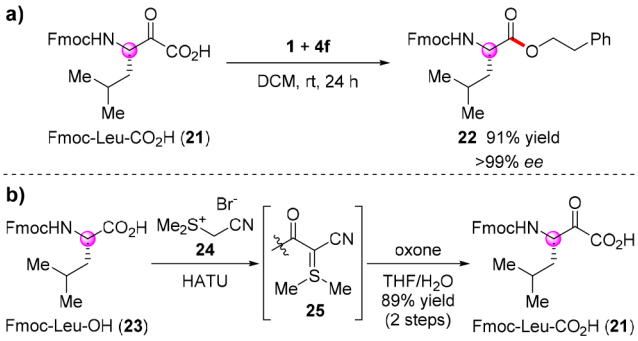
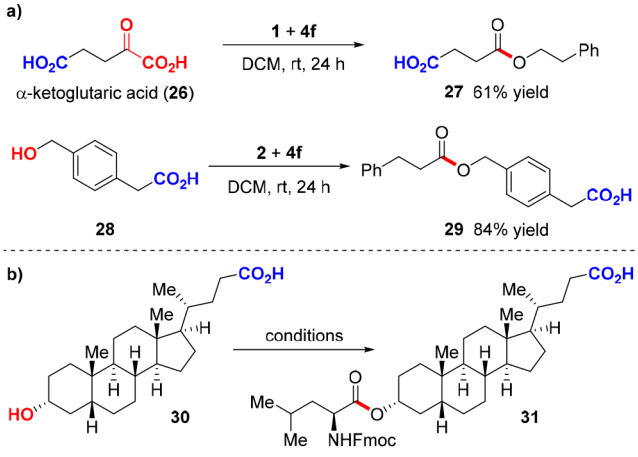
Scheme 3. Racemization-Free Esterification



co-workers previously reported a two-step prodecure to synthesize α-ketoacids from the corresponding amino acids through sulfur ylides of thiophene.[5c] It was revealed that a slightly modified sulfur ylide **24**[18] derived from dimethylsulfide is much easier to handle and maintains similar reactivity (Scheme 2b). Commercially available Fmoc-Leu-OH **23** reacted with HATU and the sulfur ylide **24** to afford an intermediate **25** and the following oxidation with Oxone provided Fmoc-Leu-CO_2H **21** in optically pure form in 89% yield over two steps.

Significantly, it was found that our decarboxylative esterification method could differentiate between carboxy groups in the molecules. We revealed that the reaction conditions predominantly accelerate the decomposition of α-ketoacids in the presence of unprotected "normal" carboxy groups (Scheme 4a). Specifically, we demonstrated chemoselective esterification of α-ketoglutaric acid **26** bearing both α-ketocarboxy and simple carboxy groups to afford ester **27** in 61% yield, preserving the terminal carboxy group. This feature enabled the selective esterification of hydroxyacid **28**, with the corresponding ester **29** being obtained in 84% yield without touching the unprotected carboxy group.

Scheme 4. α-Ketoacid-Specific Esterification

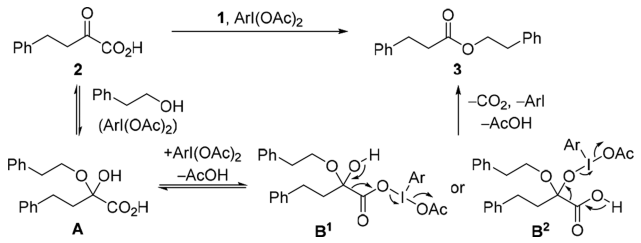


entry	conditions	yield (%)
1	Fmoc-Leu-CO_2H (**21**), **4f**	78
2	Fmoc-Leu-OH (**23**), HATU, DIPEA	<5
3	Fmoc-Leu-OH (**23**), COMU, DIPEA	<5
4	Fmoc-Leu-OH (**23**), PyBOP, DIPEA	<5

Based on the uniqueness of this decarboxylative esterification, we next demonstrated the chemoselective acylation of complex molecules (Scheme 4b). Lithocholic acid **30**, which is a cholane sterol containing an unprotected carboxy group,[19] was successfully acylated to afford the corresponding ester **31** in 78% yield (entry 1). A variety of sterol esters are known,[20] and this result reasserts that the decarboxylative esterification enables the introduction of an amino acid residue without any loss of stereochemical information in the presence of an unprotected carboxy group. This transformation is known to be hard to achieve with the commonly used dehydrative condensation protocol and the combination of Fmoc-Leu-OH **23** and condensation reagents such as HATU, COMU, and PyBOP did not provide a traceable amount of the ester **31** (entries 2–4).

Finally, we propose a plausible mechanism for this decarboxylative esterification (Scheme 5).[13] At first, alcohol **1** and α-ketoacid **2** react to afford hemiacetal **A**, which interacts with the hypervalent iodine on the oxygen atom of the tertiary hydroxy or carboxy groups.[21] The resulting reactive intermediate $\mathbf{B^1}$ or $\mathbf{B^2}$ would promote the oxidative decarboxylation to provide the desired ester **3**.[22] Although it appears difficult to determine which is most likely to be a true reactive intermediate between $\mathbf{B^1}$ or $\mathbf{B^2}$; more importantly, the esterification would not go through any reactive acyl intermediates such as acyl halides or carboxylic anhydrides in which racemization or azlactone formation frequently occurs with amino acids.[17] Therefore, the novel decarboxylative esterification could avoid the problem of racemization in a fundamental way.

Scheme 5. Proposed Mechanism



In summary, we have demonstrated a new decarboxylative esterification that employs α-ketoacids, which are reactive, yet storable acylating agents that are easy to prepare and handle. The esterification proceeds under mild, racemization-free conditions and possesses unique chemoselectivity in contrast to a general acylation reaction. In general, esterification of a hydroxy group can dramatically change not only the bioactivity but also the physical properties of organic compounds.[23] Thus, we envision that this chemoselective, racemization-free method will offer a new choice for the acylation of complex alcohols containing a variety of functional groups. We are currently exploring this decarboxylative condensation and studying its mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02466.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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