

Regioselective Synthesis of γ -Lactones by Iron-Catalyzed Radical Annulation of Alkenes with α -Halocarboxylic Acids and Their Derivatives

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Supporting Information

ABSTRACT: An abundant and low toxicity iron catalyst has enabled regioselective annulation of alkenes with α -halocarboxylic acids and their derivatives. The reaction proceeds smoothly without any additional ligands, bases, and additives to afford a variety of γ -lactones in good yields. A proposed reaction pathway through radical annulation is supported by some mechanistic studies, involving radical clock and isotope labeling experiments. The present method was applied to the practical iron-powder-promoted synthesis of γ -lactones.



On the other hand, by applying iron catalysts, the most abundant transition metal on earth, to synthetic chemistry has remarkable advantages, owing to their inexpensive, low toxicity, and environmentally benign properties.⁷ Although iron is the most widely used transition-metal in atom-transfer radical polymerization,⁸ to the best of our knowledge, the ironcatalyzed annulation for preparation of γ -lactones is unprecedented. We previously revealed that a simple iron catalyst can promote the atom-transfer radical addition of sulfenyl chlorides to alkynes with high regio- and stereoselectivities.⁹ In continuation of our studies, we herein report the iron-catalyzed radical annulation of alkenes with α -halocarboxylic acids and their derivatives to synthesize γ -lactones in a perfectly regioselective fashion (Scheme 1b). In obvious contrast to the precedented procedures, the desired annulation proceeded efficiently, even though no ligand, base, or additive was added.





Scheme 1. γ -Lactone Synthesis by Annulation of Alkenes



(b) This work: Iron-catalyzed radical annulation



Moreover, α -halocarboxylic acids proved to serve as suitable substrates in addition to α -haloesters and amides. Very recently, the related iron-catalyzed alkenylation of α -bromoesters with alkenes has been reported, in which alkenylated products were exclusively obtained under basic reaction conditions, while no formation of γ -lactones was detected.¹⁰

Initially, the reaction of styrene (1a) with α -bromoisobutyric acid (2a) was selected as the model for screening the reaction



conditions (Table 1). In the absence of ligands and bases, γ -lactone 3aa was not obtained under copper, nickel, or

Table 1. Optimization for Annulation of Styrene (1a) with α -Bromoisobutyric Acid (2a)^{*a*}

Ph + Br OH O 1a 2a		catalyst (10 mol %)		
		DMF Pł 80 ºC, 16 h		Me Me 3aa
entry	catalyst	1a (mmol)	2a (mmol)	yield (%) ^b
1	CuI	0.4	1.6	0
2	$Ni(cod)_2$	0.4	1.6	0
3	$PdCl_2(PPh_3)_2$	0.4	1.6	0
4	FeCl ₂	0.4	1.6	34
5	Fe	0.4	1.6	48
6	$Fe_2(CO)_9$	0.4	1.6	69
7	$Fe_2(CO)_9$	0.8	0.4	77
8 ^c	$Fe_2(CO)_9$	0.8	0.4	97 (91)

^{*a*}Reaction conditions: **1a**, **2a**, catalyst (0.04 mmol), DMF (0.5 mL), 80 °C, 16 h. ^{*b*1}H NMR yield. An isolated yield is given in parentheses. ^{*c*}H₂O (2 equiv).

palladium catalysis (entries 1-3).^{4,5} When iron dichloride was employed as a catalyst, the desired annulation proceeded with perfect regioselectivity to give γ -lactone 3aa in 34% yield as a single product (entry 4).¹¹ After careful screening of other iron catalysts, iron powder showed the catalytic activity needed to drive the regioselective annulation (entry 5). Nonacarbonyldiiron was found to be the best catalyst, providing the product 3aa in 69% yield even without any ligands and bases (entry 6). A higher yield was obtained with an increased amount of 1a based on 2a (entry 7). The polarity of the solvent showed marked influences on the product yield; highly polar solvents gave better results.¹² The addition of deionized water significantly improved the yield, in which γ -lactone 3aa was isolated in 91% yield (entry 8). It should be noted that the present method can be scalable enough to be applied in practical syntheses. Indeed, γ -lactone 3aa (1.0 g, 66%) was obtained by simply performing the reaction on the 20 times scale, albeit in a slightly decreased yield.

We next explored the scope with respect to alkenes 1 in an iron-catalyzed annulation with 2a (Scheme 2). The reaction of styrenes 1b-1i having electron-rich and -deficient functional groups in either the para, meta, or ortho positions proceeded smoothly to give the corresponding γ -lactones 3ba-3ia. It is noteworthy that chloro and bromo groups were compatible during the reaction (3da, 3ea, and 3ia). In addition to 2vinylnaphthalene (1j), the sterically more demanding 1vinylnaphthalene (1k) participated in the reaction, affording the product 3ja and 3ka in 60% and 70% yields, respectively. Moreover, 1,1-disubstituted alkenes 11 and 1m underwent the reaction to give the tetrasubstituted γ -lactones 3la and 3ma. Furthermore, the regioselective annulation proceeded with even internal alkenes. The reaction of indene (1n) gave the tricyclic γ -lactone **3na** in 70% yield as a single product, which constructs the fundamental skeleton of the bioactive strigolactone derivatives.¹³ The structure of 3na was unambiguously confirmed by X-ray diffraction analysis (CCDC 1840890). The reaction of aliphatic alkenes such as allylbenzene and 1-decene only gave the products in modest yields,¹⁴ which is obviously complementary to the classical synthetic method by atom-transfer radical addition.³

Fe₂(CO)₉ (5 mol %) H₂O (2 equiv) DMF 80 °C, 16 h 1 2a 3 R = p-Me (**3ba**): 76% p-OMe (3ca): 67% p-CI (3da): 80% p-Br (3ea): 61% p-F (3fa): 52% m-OMe (3ga): 80% m-CF₃ (3ha): 56%^b o-Cl (3ia): 42% ме 3ka 3ja 60% 70% R = Ph (3la): 92% 3na Me (3ma): 52% 70%

Scheme 2. Iron-Catalyzed Annulation of Alkenes 1 with α -

Bromoisobutyric Acid $(2a)^a$

^aReaction conditions: 1 (0.8 mmol), 2a (0.4 mmol), Fe₂(CO)₉ (0.02 mmol), H₂O (0.8 mmol), DMF (0.5 mL), 80 $^{\circ}$ C, 16 h. b Fe₂(CO)₉ (0.04 mmol).

The representative α -halocarboxylic acid derivatives **2** were examined, shown in Table 2. α -Bromocarboxylic acids **2b** and **2c** were also applicable to the iron-catalyzed annulation, providing a 1:1 mixture of diastereomers **3ab** and **3ac** in 61% and 65% combined yields, respectively (entries 1 and 2). α -Bromoester **2d** was found to be a suitable substrate, and the corresponding γ -lactone **3aa** was obtained in 92% yield without further aqueous treatment, which demonstrates the step-economical method, compared with the previous procedures (entry 3).^{4,5a} The yield of γ -lactone **3aa** was slightly decreased with the corresponding iodide **2e** (entry 4). The reaction with α -bromoamide **2f** afforded γ -lactone **3aa** in 40% yield, though neither γ -iminolactone nor γ -lactam was obtained (entry 5).¹⁵

To gain mechanistic insight, some control experiments were performed, as shown in Scheme 3. The addition of well-known radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidine) and galvinoxyl, completely suppressed the formation of γ -lactone 3aa, which implies that the reaction proceeds through a radical process (Scheme 3a). However, the corresponding adducts of the radical scavengers were not detected. A radical clock experiment with α -cyclopropylstyrene (10) gave more direct evidence. As a result, the reaction provided the ring-opened product 30a in 28% yield (Scheme 3b).¹⁶ The results strongly suggest the formation of a benzyl radical intermediate. Incorporation of water to the product was investigated by the reaction with $H_2^{18}O$ (Scheme 3c). Unlabeled γ -lactone 3aa was obtained in the reaction with α -bromoisobutyric acid (2a). On the other hand, the reaction with α -bromoester 2d gave 3aa-18O in 67% yield, most of which was labeled by 18O,17 indicating that the carbonyl oxygen in the products originated from water. In addition, the reaction conducted in the dark also

Table 2. Iron-Catalyzed Annulation of Styrene (1a) with α -Halocarboxylic Acid Derivatives 2^{*a*}



^aReaction conditions: **1a** (0.8 mmol), **2** (0.4 mmol), Fe₂(CO)₉ (0.02 mmol), H₂O (0.8 mmol), DMF (0.5 mL), 80 °C, 16 h.

provided the product **3aa** in 65% yield, which can exclude excitation of the iron complex under visible light irradiation.

Based on the obtained results and previous reports, a reaction pathway through a radical process is proposed (Scheme 4). The reaction is initiated by single-electron transfer between an iron catalyst and α -bromoisobutyric acid (2a), affording an alkyl radical A stabilized by a carbonyl group.⁸ The following regioselective addition of A at the terminal carbon of styrene (1a) provides thermodynamically stable benzyl radical intermediate B. After single-electron oxidation of B by a high valent iron complex, the corresponding benzyl cation C^{18} or brominated intermediate D is generated.¹⁰ Finally, an intramolecular cyclization of C or D furnishes the desired γ -lactone 3aa, which might be accelerated by the addition of highly polar water. The results of the isotopic labeling experiment with α bromoester 2d (Scheme 3c) can be rationalized, as follows. After the formation of the corresponding benzyl cation or brominated intermediate, the intramolecular cyclization from the carbonyl moiety affords the oxonium intermediate,¹⁹ followed by hydrolysis to give γ -lactone 3aa.²⁰ However, the precise mechanism is not clear at this stage. As an alternative pathway, a radical chain reaction triggered by an iron complex as a radical initiator can also be conceivable.^{3,21} Further investigation is essential for clarification of the detailed mechanism.

Scheme 3. Control Experiments

(a) Reactions in the presence of radical scavengers



(b) Radical clock experiment



(c) Isotope labeling experiments



Scheme 4. Proposed Reaction Pathway



The practical synthesis has been achieved by a stoichiometric amount of the most inexpensive iron powder (Scheme 5). Under the slightly modified reaction conditions, styrene (1a) couples with α -bromocarboxylic acid (2a) in the presence of iron powder to afford the γ -lactone 3aa in 96% yield. It is noteworthy that the reaction with iron powder can also be conducted on gram scale.

Letter

Scheme 5. Iron-Powder-Promoted Radical Annulation



In summary, the iron-catalyzed radical annulation of alkenes with α -halocarboxylic acids and their derivatives has been developed for the construction of γ -lactone skeletons. The reaction can be conducted with only a catalytic amount of an abundant and low toxicity iron complex and does not require any additional ligands, bases, or additives. The preliminary mechanistic studies indicate that the reaction proceeds thorough a radical process. Further investigation of the mechanistic details and the development of a versatile synthetic method of heterocyclic compounds by iron-catalyzed radical annulation are underway in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01436.

More detailed results of iron-catalyzed reactions; ${}^{1}H$, ${}^{13}C{}^{1}H$, and ${}^{19}F{}^{1}H$ NMR spectra of the products (PDF)

Accession Codes

CCDC 1840890 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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ACKNOWLEDGMENTS

This work was partly supported by ACT-C, JST, as well as a Grant-in-Aid for Scientific Research (KAKENHI) (No. 16K17901) from JSPS. The authors gratefully thank Ms. Megumi Kosaka and Mr. Motonari Kobayashi (Department of Instrumental Analysis, Advanced Science Research Center, Okayama University) for performing elemental analyses, and the SC-NMR Laboratory (Okayama University) for the NMR spectral measurements.

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