

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2017, 4, 565

Silver-catalyzed radical carbofluorination of unactivated alkenes with acetic acid in aqueous solution†

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Accepted 17th January 2017

DOI: 10.1039/c6qo00854b

rsc.li/frontiers-organic

The AgNO₃-catalyzed reactions of unactivated alkenes with acetic acid and Selectfluor reagent in aqueous solution afforded the corresponding γ -fluorinated carboxylic acids under mild conditions. Carbofluorination was not only efficient and regioselective, but also enjoyed a wide functional group compatibility.

Introduction

Fluorinated molecules have found increasingly important roles in pharmaceuticals and agrochemicals.¹ The introduction of fluorine atoms into pharmaceuticals can make them more lipophilic and metabolically stable, and increase the strength of their interactions with target proteins.^{1a} As a consequence, significant efforts have been devoted to the development of new methods for C–F bond formations under mild conditions in the past decade.² In this aspect, γ -fluorinated aliphatic carboxylates are a class of compounds with important biological properties.³ They have also found applications as fluorinated probes in membrane topology and protein studies.⁴ In addition, they serve as useful building blocks for more complex molecules such as a fluorinated erythromycin antibiotic.⁵ However, these compounds required multistep syntheses, and the overall efficiencies were low. It is thus desirable to develop convenient and efficient methods for the synthesis of γ -fluorinated aliphatic carboxylic acids.

We recently reported the silver-catalyzed oxidative decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor⁶ reagent (1-chloromethyl-4-fluorodiazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) in aqueous solution.⁷ However, during our extension of this method,⁸ we observed that the decarboxylation of acetic acid was so sluggish that it could be used as a co-solvent in Selectfluor-mediated oxidative

radical fluorination reactions.^{8b,d} Meanwhile, it is well documented that Mn(OAc)₃-mediated oxidative radical addition of acetic acid to alkenes leads to γ -lactones.⁹ In light of these phenomena, we envisioned that acetic acid might be able to participate in the 1,2-carbofluorination of alkenes. It should be pointed out that only a few examples of intermolecular carbofluorination were reported and they mainly dealt with activated alkenes such as styrenes or enamines.^{8d,10} Herein we report the silver-catalyzed carbofluorination of unactivated alkenes by condensation with acetic acid and Selectfluor in aqueous solution, providing an efficient and general entry to various γ -fluorinated aliphatic carboxylic acids in one step.

Results and discussion

N-(Pent-4-en-1-yl)phthalimide (**1a**) was thus chosen as the model substrate for the optimization of reaction conditions (Table 1). In a preliminary test, alkene **1a** was treated with Selectfluor (3 equiv.) and AgNO₃ (20 mol%) in mixed solvents of H₂O/dichloromethane(DCM)/AcOH at 50 °C for 24 h, a condition similar to the carbofluorination of alkenes with β -ketoesters.^{8d} Gratifyingly, the expected carbofluorination product **2a** was obtained in 57% yield (entry 1, Table 1). Both water and DCM were required as solvents, as evidenced by control experiments (entries 2 and 3, Table 1). Switching the catalyst AgNO₃ to AgBF₄, AgPF₆ or AgOTf did not show any improvement (entries 4–6, Table 1). Next, several additives were screened in an attempt to increase the product yield. The addition of a base such as NaOAc inhibited the reaction (entry 7, Table 1). On the other hand, the addition of an acid such as trifluoroacetic acid (TFA) or nitric acid slightly increased the product yield (entries 8 and 9, Table 1). We then chose phosphoric acid as the co-solvent, and we were delighted to find that the carbofluorination product **2a** was isolated in

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† Electronic supplementary information (ESI) available: Experimental details, characterization of products and copies of ¹H, ¹³C and ¹⁹F NMR spectra. See DOI: 10.1039/c6qo00854b



Table 1 Optimization of reaction conditions

Entry ^a	Solvent	Additive (equiv.)	Yield ^b (%)
1	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	—	57
2	H ₂ O/AcOH (1 : 1)	—	Trace
3	DCM/AcOH (1 : 1)	—	Trace
4 ^c	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	—	56
5 ^d	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	—	53
6 ^e	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	—	47
7	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	NaOAc (3)	28
8	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	TFA (3)	58
9	H ₂ O/DCM/AcOH (1 : 0.5 : 0.5)	HNO ₃ (3)	64
10	H ₂ O/DCM/AcOH/H ₃ PO ₄ (1 : 0.5 : 0.5 : 0.6)	—	82
11	H ₂ O/DCM/AcOH/H ₃ PO ₄ (1 : 0.5 : 0.5 : 0.8)	—	84
12 ^f	H ₂ O/DCM/H ₃ PO ₄ (1 : 0.5 : 0.8)	—	17
13 ^g	H ₂ O/DCM/AcOH/H ₃ PO ₄ (1 : 0.5 : 0.5 : 0.8)	—	0

^a Conditions: **1a** (0.2 mmol), AgNO₃ (0.04 mmol), Selectfluor (0.6 mmol), solvent (2 mL), additive, 50 °C, 24 h. ^b Isolated yield based on **1a**. ^c AgBF₄ rather than AgNO₃ was used. ^d AgPF₆ rather than AgNO₃ was used. ^e AgOTf rather than AgNO₃ was used. ^f AcOH (3 equiv.) was used. ^g No AgNO₃ was used.

84% yield (entry 11, Table 1). In the above cases, acetic acid was used as both the reagent and the co-solvent. Lowering the amount of AcOH to 3 equivalents significantly decreased the yield of **2a** (entry 12, Table 1). Finally, the role of AgNO₃ as a catalyst was proved by the control experiment (entry 13, Table 1).

With the optimized conditions (entry 11, Table 1) in hand, we set out to explore the scope and limitation of this method. The results are summarized in Scheme 1. The reactions of mono-substituted alkenes proceeded smoothly to afford the corresponding products **2a–2i** in satisfactory yields. Disubstituted alkenes underwent efficient carbofluorination under slightly milder conditions (2 equivalents of Selectfluor and less H₃PO₄), leading to the synthesis of γ -fluorinated carboxylic acids **2j–2p**. A number of functional groups, including amide, tosylate, alkyl bromide or chloride, ester, nitrile, aryl and ketone, were well tolerated. All the reactions were carried out in aqueous solution and thus were very easy to operate. Nevertheless, the reaction was not applicable to activated alkenes such as styrene, in which a hydroxyfluorination product (2-fluoro-2-phenylethan-1-ol) was observed in about 40% yield.¹¹ The extension of this method to propanoic acid or butanoic acid also failed because decarboxylative fluorination became competitive. These results clearly reveal the unique property of acetic acid from other alkanolic acids in silver-catalyzed radical fluorination reactions.^{7,8}

The above results indicate that the reaction may proceed *via* a radical fluorination mechanism. To provide further evidence, 1,6-diene **3** as a radical probe was prepared and subjected to the above optimized reaction conditions. Cyclopentane **4** was achieved in 38% yield as a mixture of two stereoisomers in an 83 : 17 ratio



Scheme 1 Carbofluorination of unactivated alkenes. ^a Reaction conditions: **1** (0.2 mmol), Selectfluor (0.6 mmol), AgNO₃ (0.04 mmol), DCM (0.5 mL), H₂O (1 mL), AcOH (0.5 mL), H₃PO₄ (0.8 mL), 50 °C, 24 h. ^b Isolated yield based on **1**. ^c Selectfluor (0.4 mmol) and H₃PO₄ (0.4 mL) were used. ^d Reaction time: 12 h.

(eqn (1)).^{8b,e} This addition–cyclization–fluorination sequence strongly supports the radical mechanism of carbofluorination.

On the basis of the above results and literature reports,^{7,8} a plausible mechanism is proposed as shown in Fig. 1. The interaction of AgNO₃ with Selectfluor generates the Ag(III)–F intermediate presumably *via* oxidative addition. The single electron transfer between acetic acid and Ag(III)–F leads to the formation of α -carbonyl radical **A** and Ag(II)–F. The electrophilic radical **A** then adds to an electron-rich alkene to give adduct radical **B**. Finally, the nucleophilic alkyl radical **B** abstracts a fluorine atom from Ag(II)–F to afford the carbofluorination product along with the regeneration of Ag(I). Thus, this reaction further expands the scope of radical fluorination.¹²



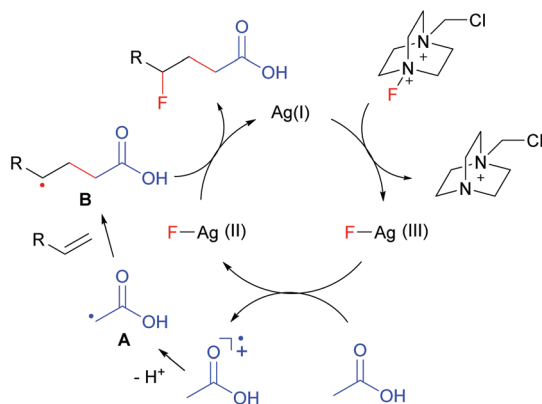
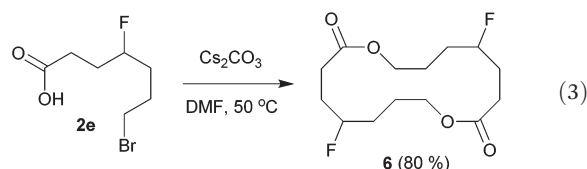


Fig. 1 Proposed mechanism of carbofluorination.

The above carbofluorination offers a convenient route to γ -fluorinated aliphatic carboxylic acids. The remarkable functional group compatibility also enables the carbofluorination products to be versatile building blocks for the synthesis of more complex fluorinated molecules. For example, upon treatment with Cs_2CO_3 , the carbofluorination product **2b** could be easily converted to γ -fluorocaprolactone **5** in 71% yield (eqn (2)). The reaction of analogous γ -fluoroacid **2e** with Cs_2CO_3 in DMF did not offer the expected cyclization product γ -fluoroheptanolactone. Instead, the 16-membered cyclic dimer **6** was obtained exclusively in 80% yield as the mixture of two stereoisomers in a 1:1 ratio (eqn (3)). It is worth mentioning that the reaction of 6-bromohexanoic acid under almost identical conditions produced the corresponding cyclic dimer (similar to **6**) rather than **5**.¹³ Thus, the formation of **5** from **2b** might be attributed to the fluorine effect on substrate conformations.



Conclusion

In summary, we have successfully developed the silver-catalyzed radical carbofluorination of unactivated alkenes with

acetic acid and Selectfluor in aqueous solution. This three-component condensation proceeds under mild conditions, providing a convenient and efficient entry into various γ -fluorinated aliphatic carboxylic acids with wide functional group compatibility.

Experimental section

Typical procedure for silver-catalyzed carbofluorination of unactivated alkenes with acetic acid

N-(Pent-4-en-1-yl)phthalimide (**1a**, 43.1 mg, 0.2 mmol), AgNO_3 (6.8 mg, 0.04 mmol) and Selectfluor (212.6 mg, 0.6 mmol) were placed in a Schlenk tube under a nitrogen atmosphere. Dichloromethane (0.5 mL), water (1 mL), acetic acid (0.5 mL) and 85% phosphoric acid (0.8 mL) were added successively at room temperature. The reaction mixture was then stirred at 50 °C for 24 h. The resulting mixture was cooled down to room temperature and extracted with CH_2Cl_2 (3×10 mL). The organic phases were combined and dried over anhydrous Na_2SO_4 . After the removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with dichloromethane/methanol (60:1, v:v) as the eluent to give the pure product **2a** as a white solid. Mp: 86–88 °C. Yield: 49.1 mg (84%). ^1H NMR (400 MHz, CDCl_3): δ 7.83–7.85 (m, 2H), 7.70–7.72 (m, 2H), 4.48–4.64 (m, 1H), 3.69–3.76 (m, 2H), 2.46–2.57 (m, 2H), 1.55–1.96 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 178.6, 168.4, 133.9, 132.0, 123.2, 92.4 (d, $J = 169.0$ Hz), 37.5, 32.2 (d, $J = 20.6$ Hz), 29.9 (d, $J = 21.0$ Hz), 29.5 (d, $J = 4.3$ Hz), 24.3 (d, $J = 3.9$ Hz); ^{19}F NMR (282 MHz, CDCl_3): δ -183.8 (m, 1F); IR (KBr): ν (cm^{-1}) 2942, 1772, 1719, 1713, 1707, 1440, 1400, 1367, 1051, 721; ESI-MS: (m/z) 316.1 (M + Na); HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{FNNaO}_4$ (M + Na): 316.0956, found 316.0966.

Acknowledgements

This project was supported by the National Basic Research Program of China (973 Program) (Grant 2015CB931900), by the National Natural Science Foundation of China (Grants 21272259, 21290180, 21421002, 21472220, 21502210, 21532008, 21602239, and 21361140377), and by the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB20020000).

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