

## Novel Synthesis of Fluoroalkylated $\alpha,\beta$ -Unsaturated Ketones by the Oxygenative Perfluoroalkylation of $\alpha$ -Chlorostyrenes

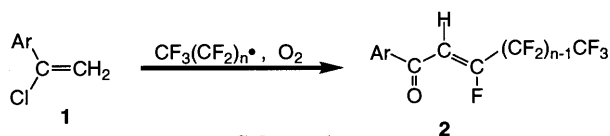
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The photochemical reaction of perfluoroalkyl iodide with  $\alpha$ -chlorostyrenes in the presence of hexabutyliditin under oxygen atmosphere produced fluoroalkylated  $\alpha,\beta$ -unsaturated ketones in moderate to good yields.

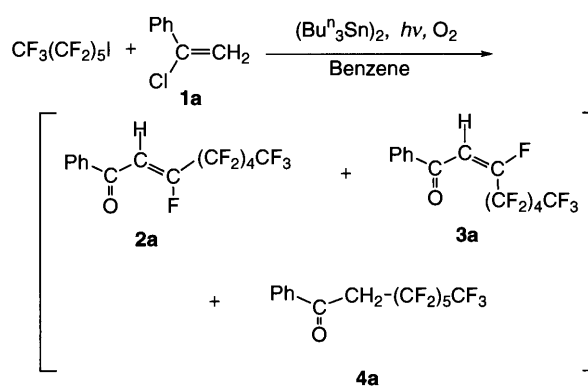
For the synthesis of perfluoroalkylated organic molecules, the building-block strategy has now become one of the most convenient approaches, and considerable efforts have been devoted to the development of the synthesis of the fluorine-containing building blocks. The perfluoroalkylated  $\alpha,\beta$ -unsaturated ketones **2** are expected to be important building blocks for various interesting fluoroalkylated heterocyclic compounds.<sup>1-3</sup> Now, we have found a novel synthesis of the ketones **2** starting from  $\alpha$ -chlorostyrenes **1** using perfluoroalkyl radicals and molecular oxygen (Scheme 1).



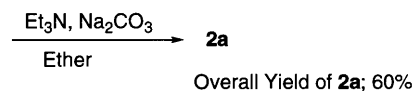
Previously, we found the photochemical reaction of perfluoroalkyl iodide with styrene in the presence of hexabutyliditin under oxygen atmosphere to produce the fluoroalkylated alcohol mainly and the ketone **2** as a side product.<sup>4</sup> In order to obtain the ketone **2** selectively, the reaction conditions and some olefins such as  $\alpha$ -halostyrenes and  $\alpha$ -trimethylsilylstyrenes were examined. Among the various attempts, in the reactions of  $\alpha$ -chlorostyrene **1a** with perfluoroalkyl iodide, fluoroalkylated ketones were obtained in good yield as a mixture of **2a**, **3a** and **4a** (Scheme 2).<sup>5,6</sup> Although three types of ketones (**2a–4a**) were produced in this reaction, the treatment of the reaction mixture consisting of **2a**, **3a** and **4a** with  $\text{NEt}_3$  and  $\text{NaHCO}_3$  in ether gave **2a** as the sole product in 60% overall yield. Thus, a practical one-pot procedure was carried out for the synthesis of **2a** directly from  $\alpha$ -chlorostyrene as shown in Scheme 2.

A solution of perfluoroalkyl iodide (0.40 mmol),  $\alpha$ -chlorostyrene **1a** (1.20 mmol), and  $(\text{Bu}_3\text{Sn})_2$  (0.44 mmol) in benzene (3 mL) was irradiated using a metal halide lamp (National Sky-beam MT-70) in a Pyrex tube under  $\text{O}_2$  atmosphere for 5 h. In order to consume the perfluoroalkyl iodide completely, 1.1 eq of  $(\text{Bu}_3\text{Sn})_2$  was required. The reaction mixture was evaporated and the residue was dissolved in ether (2 mL). After treatment of the solution with  $\text{Et}_3\text{N}$  (0.1 mL) and  $\text{NaHCO}_3$  (130 mg) for 2 h at room temperature, the ketone **2a** was isolated in 42% yield using a silica gel column chromatography, followed by gel permeation chromatography. Various  $\alpha$ -chlorostyrenes and related compounds were further examined

and the corresponding ketones (**2**) were obtained in moderate to good yields (Table 1). The length of the fluoroalkyl chains and the substituents on the benzene ring (*p*-Me and *p*-Cl) showed little effect on the yields of **2** (Table 1; entries 1–5). In 2-naphthyl, the ketones **2** were obtained in nearly the same yields with those in phenyl (Table 1; entries 9–11), but the yields in 1-naphthyl were slightly lower (Table 1; entries 6–8). The present



Yield; 69% (**2a** : **3a** : **4a** = 25 : 53 : 22)



**Scheme 2.**

**Table 1.** Synthesis of **2** from  $\alpha$ -chlorostyrenes

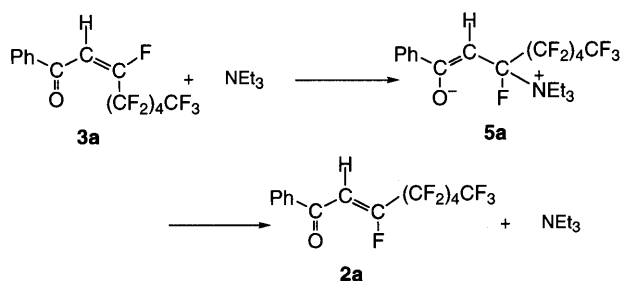
Entry	n of $\text{CF}_3(\text{CF}_2)_n\text{I}$	Ar of $\text{ArC}(\text{Cl})=\text{CH}_2$	Yield of <b>2</b> / % <sup>a</sup>
1	3	Ph	51
2	5	Ph	60
3	9 <sup>b</sup>	Ph	56
4	5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	50
5	5	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	53
6	3		49
7	5		51
8	9 <sup>b</sup>		44
9	3		61
10	5		66
11	9 <sup>b</sup>		65

<sup>a</sup>Yields were determined by <sup>19</sup>F-NMR based on  $\text{CF}_3(\text{CF}_2)_n\text{I}$  using  $\text{PhCF}_3$  as an internal standard. <sup>b</sup>Chlorobenzene was used as a solvent for the low solubility of  $\text{CF}_3(\text{CF}_2)_9\text{I}$  to benzene.

reaction was only applicable to the olefins possessing an aromatic ring at the  $\alpha$ -position; in the reaction with 2-chloro-1-octene, the desired fluoroalkylated ketone was not produced.

The oxyfluoroalkylation described here is a very unique example for the formation of fluoroalkylated ketones directly from olefins using a perfluoroalkyl radical and molecular oxygen; the use of molecular oxygen for the selective oxidation of organic substrate is very attractive and challenging.<sup>7-9</sup> As  $\alpha$ -chlorostyrenes were readily synthesized from styrenes with  $\text{PhSeCl}_3$  or acetophenones with  $\text{PCl}_5$ ,<sup>10,11</sup> this method is very convenient and practical for the synthesis of various perfluoroalkylated  $\alpha,\beta$ -unsaturated ketones.

Interestingly,  $\text{Et}_3\text{N}$  is an effective reagent for the conversion of **3a** to **2a** (Scheme 2). Since  $\text{Et}_3\text{N}$  easily added to **3a** to form the Michael adduct **5a**, the more thermodynamically stable isomer **2a** was formed almost quantitatively via addition-elimination reactions (Scheme 3). Further studies on the reactions of **2a** are now in progress.



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#### References and Notes

- 1 T. Umemoto, Y. Kuriu, S. Nakayama, and O. Miyano, *Tetrahedron Lett.*, **23**, 1471 (1982).
- 2 X.-Q. Tang and C.-M. Hu, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2161.
- 3 Q.-F. Wang, B. Hu, B.-H. Luo, and C.-M. Hu, *Tetrahedron Lett.*, **39**, 2377 (1998).
- 4 M. Yoshida, M. Ohkoshi, N. Aoki, Y. Ohnuma, and M. Iyoda, *Tetrahedron Lett.*, **40**, 5731 (1999).
- 5 In this reaction, the saturated ketone **4a** was produced at first, and then the elimination of HF from **4a** occurred to give the unsaturated ketone **2a**. The ketone **3a** should be produced by the photoisomerization of **2a**. When the isolated **2a** was irradiated in benzene under similar conditions, the isomerization from **2a** to **3a** was observed; the ratio of **2a** / **3a** in photostationary state was 1 / 4.
- 6 Spectral data. **2a**:  $^1\text{H-NMR}$  (500 MHz:  $\text{CDCl}_3$ )  $\delta$  6.73 (d, 1H,  $J_{\text{HF}} = 31.7$  Hz), 7.50 (m, 2H, Ph), 7.62 (m, 1H, Ph), 7.89 (m, 2H, Ph);  $^{13}\text{C-NMR}$  (125.7 MHz,  $\text{CDCl}_3$ )  $\delta$  110.67, 128.73, 129.00, 134.39, 136.23, 151.69 (d,  $J_{\text{CF}} = 284$  Hz), 186.29;  $^{19}\text{F-NMR}$  (470.4 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm down field from external  $\text{CF}_3\text{COOH}$ ) -5.92 (3F), -37.14 (1F), -43.43 (2F), -47.81 (4F), -51.32 (2F); HRMS, Found 418.0224. Calcd for  $\text{C}_{14}\text{H}_6\text{F}_{12}\text{O}$  418.0226. **3a**:  $^1\text{H-NMR}$  (500 MHz:  $\text{CDCl}_3$ )  $\delta$  6.85 (d, 1H,  $J_{\text{HF}} = 20.1$  Hz), 7.52 (m, 2H, Ph), 7.65 (m, 1H, Ph), 7.93 (m, 2H, Ph);  $^{13}\text{C-NMR}$  (125.7 MHz,  $\text{CDCl}_3$ )  $\delta$  116.24, 128.92, 129.14, 134.55, 135.76, 151.68 (d,  $J_{\text{CF}} = 302$  Hz), 186.43;  $^{19}\text{F-NMR}$  (470.4 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm down field from external  $\text{CF}_3\text{COOH}$ ) -5.92 (3F), -40.13 (2F), -41.36 (1F), -47.25 (2F), -47.99 (2F), -51.29 (2F). **4a**:  $^1\text{H-NMR}$  (500 MHz:  $\text{CDCl}_3$ )  $\delta$  3.78 (t, 2H,  $J_{\text{HF}} = 17.7$  Hz), 7.52 (m, 2H, Ph), 7.65 (m, 1H, Ph), 7.95 (m, 2H, Ph);  $^{13}\text{C-NMR}$  (100.4 MHz,  $\text{CDCl}_3$ )  $\delta$  38.69 (t,  $J_{\text{CCF}} = 21$  Hz), 128.60, 128.93, 134.19, 136.43, 189.58;  $^{19}\text{F-NMR}$  (470.4 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm down field from external  $\text{CF}_3\text{COOH}$ ) -5.92 (3F), -36.10 (2F), -46.86 (2F), -47.87 (4F), -51.26 (2F); HRMS, Found 438.0263. Calcd for  $\text{C}_{14}\text{H}_7\text{F}_{13}\text{O}$  438.0289.
- 7 T. Umemoto, Y. Kuriu, and S. Nakayama, *Tetrahedron Lett.*, **23**, 4101 (1981).
- 8 C.-M. Hu, Z.-Q. Xu, and F.-L. Quing, *Tetrahedron Lett.*, **30**, 6717 (1989).
- 9 Y. Sato, S. Watanabe, and K. Uneyama, *Bull. Chem. Soc. Jpn.*, **66**, 1840 (1993).
- 10 L. Engman, *J. Org. Chem.*, **52**, 4086 (1987).
- 11 T. L. Jacobs, *Org. Reactions*, **5**, 20 (1949).