Journal of Fluorine Chemistry, *59* (1992) 179–183

One-pot reaction for the synthesis of fluorinated β-diketones[†]

Wei-yuan Huang and Yong-ming Wu
Shanghai Institute of Organic Chemistry, Academia Sinica, Shanghai 200032 (China)

(Received September 3, 1991; accepted April 1, 1992)

Abstract

Fluorinated β-diketones have been synthesized in high yield from the one-pot reaction of silyl enol ethers with perfluoroalkyl iodides initiates with $Na_2S_2O_4/NaHCO_3$, followed by treatment with diethylamine and acid hydrolysis.

Introduction

As a class of useful chelating agents [2–4] and synthetic intermediates [5, 6], the chemistry of β-diketones have been studied extensively [7, 8]. The most commonly used synthetic method for these compounds is the Claisen condensation using a variety of different condensing agents such as sodium alkoxide [8, 9], sodium amide [10], sodium hydride [11], Grignard reagents [12], etc. However, because of the strongly basic conditions employed, this method does not give satisfactory yields in the synthesis of fluorinated β-diketones [8, 13, 14]. In the course of our studies of the reaction of silyl enol ethers with perfluoroalkyl iodides we have obtained α-perfluoroalkyl ketones and their dehydrofluorinated products [1]. Applying the method of Portella and Iznaden [15–17] for the conversion of 2-*H*-perfluoro-esters into 2-*H*-perfluoro-β-keto esters, we have developed a simple one-pot reaction for the synthesis of fluorinated β-diketones starting from silyl enol ethers and perfluoroalkyl iodides. The results are reported herein.

Results and discussion

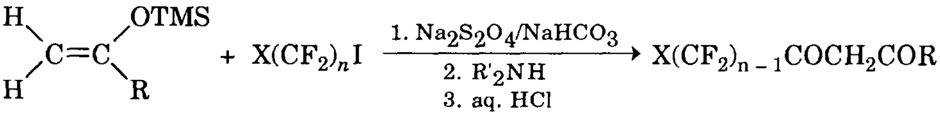
The α-perfluoroalkyl ketone (**1**), obtained from the reaction between a perfluoroalkyl iodide and the corresponding silyl enol ether [1], when treated with a secondary amine in methylene chloride followed by acid hydrolysis gave the β-diketone (**2**) in excellent yield.

$$\underset{\textbf{(1)}}{Cl(CF_2)_6CH_2COBu^t} \longrightarrow \underset{\textbf{(2bd)}}{Cl(CF_2)_5COCH_2COBu^t}$$

[†] Studies on the reactions of silyl enol ether with perfluoro-organic compounds. II. For part I, see ref. 1(b).

0022-1139/92/$5.00

Tandem reactions of the silyl enol ether **3**, first with perfluoroalkyl iodide **4** in the presence of $Na_2S_2O_4$ and $NaHCO_3$, followed by treatment of the resulting product with a secondary amine directly followed by acidic hydrolysis with dilute aqueous mineral acid, gave the expected β-diketone in a one-pot synthesis in high yield. The various β-diketones thus synthesized may be summarized by the following equation.



(3) **(4)** **(2)**

a: R = Me
b: R = Bu^t

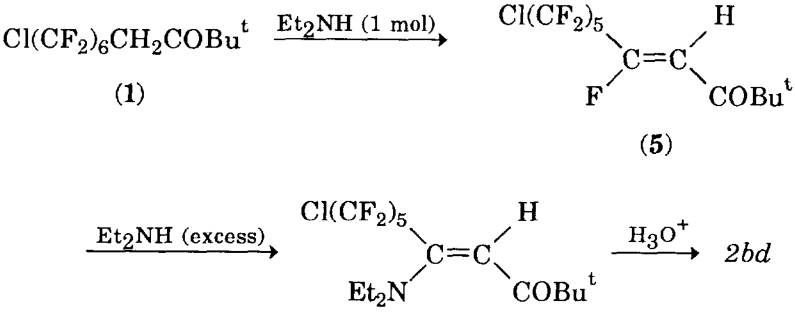
c: X = Cl, *n* = 4
d: X = Cl, *n* = 6
e: X = Cl, *n* = 8
f: X = F, *n* = 6
g: X = F, *n* = 8

ac—ag
bc—bg

Scheme 1.

It was found that different aliphatic secondary amines gave similar results, for example the tandem reaction between silyl enol ether **3b** with perfluoroalkyl iodide (**4d**) using diethyl amine or piperidine gave the β-diketone **2bd** in 87% or 85% yield, respectively.

When equimolar amounts of β-perfluoroalkyl ketone (**1**) and the secondary amine were allowed to react, the product was the α, β-unsaturated fluorinated ketone **5**. However, if **1** was reacted with excess secondary amine (3 mol), then the immediate product was the β-aminofluorinated enone **6** which could undergo acidic hydrolysis.



(1) **(5)** **(6)**

Scheme 2.

All new compounds were characterized through their elemental analyses, IR, ^1H NMR, ^{19}F NMR and MS spectra.

Experimental

^1H NMR spectra were recorded on a Varian XL-200 (200 MHz) or Varian EM-360A (60 MHz) spectrometer. TMS was used as the external standard. ^{19}F NMR spectra were recorded on a Varian EM-360 (56.4 MHz) spectrometer. Chemical shifts in ppm were positive upfield using TFA as the external standard. IR spectra were recorded on a Carl Zeiss Specord 75 IR or a Schimadzu IR-440 spectrometer. MS were recorded on a Finnigan-4021 instrument. Silyl enol ethers were prepared by the usual method [18].

General procedure for the synthesis of fluorinated β-diketones (2)

From silyl enol ether (3)

Into a 50 ml round-bottomed flask fitted with a condenser and a magnetic stirrer, the reactants were added in the following order: 5.5 mmol silyl enol ether, 5 mmol perfluoroalkyl iodide, 6 mmol sodium dithionite, 6 mmol sodium bicarbonate, 10 ml MeCN and 1 ml H_2O. The mixture was stirred at 40 °C and the progress of the reaction was monitored using ^{19}F NMR spectroscopy until the chemical shift corresponding to ICF_2 — disappeared. Then 20 mmol Et_2NH was added to the mixture which was stirred at room temperature for another 2 h. Solid was removed by filtration, 10 ml 4 N aqueous HCl solution was added to the filtrate and the resulting mixture stirred for 0.5 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ether (3×20 ml). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ solution (1×30 ml) and saturated aqueous NaCl solution (30 ml) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column with petroleum ether as eluent.

2ac (1 g, 74% yield): Analysis: Found: C, 31.05; H, 1.78; F, 42.37; Cl, 13.13%. $C_7H_5O_2F_6Cl$ requires: C, 31.08; H, 1.86; F, 42.13; Cl, 13.10%. ^1H NMR CCl_4 δ: 14 (1H, s, $O-H\cdots O=C$); 5.73 (1H, s, $H-C=$); 2.0 (3H, s, Me) ppm. ^{19}F NMR CCl_4 δ: -9 (2F, t, $ClCF_2-$); 45–46 (4F, m, $2CF_2$) ppm. IR (cm^{-1}) 1600; 1180; 1130. MS m/z 271 (M^+); 272 (M+1); 235 (M−Cl); 86, 43 (Me−C=O).

2ad (1.5 g, 81% yield): Analysis: Found: C, 28.90; H, 1.28; F, 51.54; Cl, 9.80%. $C_9H_5O_2F_{10}Cl$ requires: C, 29.17; H, 1.36; F, 51.27; Cl, 9.57. ^1H NMR CCl_4 δ: 14 (1H, s, $O-H\cdots O=C$); 5.78 (1H, s, $H-C=$); 1.98 (3H, s, Me) ppm. ^{19}F NMR CCl_4 δ: -8.7 (2F, t, $ClCF_2-$); 44.5, 46 (8F, m, $4CF_2$) ppm. IR (cm^{-1}): 1600; 1420; 1200; 1140. MS m/z: 371 (M^+); 86, 43 (Me−C=O).

2ae (2.0 g 85% yield): Analysis: Found: C, 27.98; H, 0.98: F, 57.01; C, 17.52%. $C_{11}H_5O_2F_{14}Cl$ requires: C, 28.08; H, 1.07; F, 56.52; Cl, 7.53%. ^1H NMR CCl_4 δ: 14 (1H, s, $O-H\cdots O=C$); 6.1 (1H, s, $H-C=$); 1.1 (3H, s, Me) ppm. ^{19}F NMR CCl_4 δ: -9 (2F, t, $ClCF_2-$); 44, 45, 45,7 (12F, m, $6CF_2$) ppm. IR (cm^{-1}): 1600; 1200; 1140. MS m/z: 471 (M^+); 86, 43 (Me−C=O).

2af (1.4 g, 84% yield): Analysis: Found: C, 30.40; H, 1.37; F, 60.21%. $C_9H_5O_2F_{11}$ requires: C, 30.53; H, 1.42; F, 59.01%. ^{1}H NMR CCl_4 δ: 14 (1H, s, $O-H\cdots O=C$); 5.9 (1H, s, $H-C=$); 1.1 (3H, s, Me) ppm. ^{19}F NMR CCl_4 δ: 4.7 (3F, t, CF_3-); 50 (2F, m, CF_3-CF_2-) 45, 46.5 (6F, m, $3CF_2$) ppm. IR (cm^{-1}) 1600; 1240; 1200; 1140. MS *m/z*: 354 (M^+); 86, 43 ($Me-C=O$).

2ag (2.0 g, 88% yield): Analysis: Found: C, 28.89; H, 1.07; F, 62.20%. $C_{11}H_5O_2F_{15}$ requires: C, 29.09; H, 1.11; F, 62.75%. ^{1}H NMR CCl_4 δ: 14 (1H, s, $O-H\cdots O=C$); 5.8 (1H, s, $H-C=$); 1.0 (3H, s, Me) ppm. ^{19}F NMR CCl_4 δ: 5 (3F, t, CF_3); 50 (2F, m, CF_3-CF_2-); 45–46 (10F, m, $5CF_2$) ppm. IR (cm^{-1}) 1600; 1240; 1200; 1140. MS *m/z* 454 (M^+); 86, 43 ($Me-C=O$).

2bc (1.4 g, 90% yield): Analysis: Found: C, 37.96; H, 3.37; F, 36.30. Cl, 11.33%. $C_{10}H_{11}O_2Cl$ requires: C, 38.42; H, 3.55; F, 36.46; Cl, 11.34%. ^{1}H NMR CCl_4 δ: 14.1 (1H, s, $O-H\cdots O=C$); 5.7 (1H, s, $H-C=$); 0.9 (9H, s, Bu^t) ppm. ^{19}F NMR CCl_4 δ: -9.5 (2F, t, $ClCF_2-$); 43.2–44 (4F, m, $2CF_2$) ppm. IR (cm^{-1}) 2950; 1600; 1360; 1200; 1140. MS *m/z* 313 (M^+); 127 ($Bu^t-CO-CH_2-CO$); 85 ($Bu^t-C=O$); 57(Bu^t).

2bd (1.8 g, 87% yield): Analysis; Found: C, 34.7; H, 2.6; F, 46.4; Cl, 8.7%. $C_{12}H_{11}O_2F_{10}Cl$ requires: C, 34.9; H, 2.7; F, 46.0; Cl, 8.6%. ^{1}H NMR CCl_4 δ: 14.2 (1H, s, $O-H\cdots O=C$); 6.0 (1H, s, $H-C=$); 0.8 (9H, s, Bu^t) ppm. ^{19}F NMR CCl_4 δ: -9 (2F, t, $ClCF_2-$); 44, 46 (8F, m, $4CF_2$) ppm. IR (cm^{-1}) 2900; 1600; 1360; 1200; 1140. MS *m/z* 413 (M^+); 414 ($M+1$); 127, 85, 57.

2be (2.2 g, 86% yield): Analysis: Found: C, 32.5; H, 2.0; F, 5.21; Cl, 6.8%. $C_{14}H_{11}O_2F_{14}Cl$ requires: C, 32.8; H, 2.3; F, 51.9; Cl, 6.9%. ^{1}H NMR CCl_4 δ: 14.1 (1H, s, $O-H\cdots O=C$); 6.0 (1H, s, $H-C=$); 0.8 (9H, s, Bu^t) ppm. ^{19}F NMR CCl_4 δ: -9 (2F, t, $ClCF_2$); 44, 45, 46 (12F, m, $6CF_2$) ppm. IR (cm^{-1}) 2920; 1600; 1380; 1200; 1140. MS *m/z*: 513 (M^+); 127, 85, 57.

2bf (1.6 g, (81% yield): Analysis: Found: C, 36.2; H, 2.6; F, 52.4%. $C_{12}H_{11}O_2F_{11}$ requires: C, 36.4; H, 2.8; F, 52.75%. ^{1}H NMR CCl_4 δ: 14.2 (1H, s, $O-H\cdots O=C$); 6.0 (1H, s, $H-C=$); 0.9 (9H, s, Bu^t) ppm. ^{19}F NMR CCl_4 δ: 5 (3F, t, CF_3-); 50 (2F, m); 44, 46 (6F, m, $3CF_2$) ppm. IR (cm^{-1}) 2900; 1600; 1240; 1200; 1140. MS *m/z*: 397 (M^+); 127, 85, 57.

2bg (2.1 g, 83% yield): Analysis: Found: C, 33.95; H, 2.29; F, 57.71%. $C_{14}H_{11}O_2F_{15}$ requires; C, 33.95; H, 2.23; F, 57.43%. ^{1}H NMR CCl_4 δ: 14.3 (1H, s, $O-H\cdots O=C$); 6.0 (1H, s, $H-C=$); 0.9 (9H, s, Bu^t) ppm. ^{19}F NMR CCl_4 δ: 5.2 (3F, t, CF_3-); 51 (2F, m, CF_3-CF_2-); 45, 46 (10F, m, $5CF_2$) ppm. IR (cm^{-1}): 2900; 1600; 1240; 1200; 1140. MS *m/z* 497 (M^+); 127, 85, 57.

From α-perfluoroalkyl ketones

A mixture of α-perfluoroalkyl ketone (3 mmol) and diethylamine (10 mmol) in 5 ml dichloromethane was stirred at room temperature for 2 h. Then 4 N aqueous HCl solution (5 ml) was added and the stirring continued at r.t. for another 0.5 h. Addition of 5 ml H_2O to the mixture, followed by the usual work-up gave the expected β-diketones.

*Preparation of **6***

Into a 25 ml round-bottomed flask fitted with a condenser and a magnetic stirrer, the reactants were added in the following order: 0.52 g **3b** (3 mmol), 1.16 g **4d** (2.5 mmol), 0.8 g $NaHCO_3$, 0.8 g $Na_2S_2O_4$, 5 ml MeCN and 0.5 ml H_2O. The mixture was stirred at 40 °C, the progress of the reaction being monitored by ^{19}F NMR spectroscopy until the peak corresponding to ICF_2- disappeared (*c.* 1 h). Then diethylamine (1.2 ml) was added, the mixture stirred at r.t. for 2 h and worked-up in the usual way. The crude product was purified by chromatography on a silica gel column with petroleum ether as the eluent to give **6** (1.05 g, 90% yield). Analysis: Found: C, 40.83; H, 4.12; N, 2.87; F, 41.01; Cl, 7.47%. $C_{16}H_{20}ONF_{10}Cl$ requires: C, 41.08; H, 4.31; N, 2.99; F, 41.08; Cl, 7.58%. ^1H NMR CCl_4 δ: 5.85 (1H, H−C=); 2.9 (6H, q, CH_3-CH_2-); 0.95 (13H, s, m) ppm. ^{19}F NMR CCl_4 δ: −9 (2F, t, $ClCF_2-$); 31 (2F, t, $CF_2-C=$); 44, 46 (6F, t, $3CF_2$) ppm. IR (cm^{-1}) 2920; 1680; 1200; 1140. MS *m/z* 468 (M^+); 469 (M+1); 411 (M-Bu^t); 57 (Bu^t).

References

1 (a) W. Y. Huang and L. Q. Zhang, *Youji Huaxue, 9* (1989) 38; (b) W. Y. Huang, Y. M. Wu and W. Z. Ge, *Chin. J. Chem., 9* (1991) 528.

2 W. Y. Huang and L. Q. Zhang, *Acta Chimica Sinica, 45* (1987) 324; *ibid 43* (1985) 173.

3 A. E. Pedler, R. C. Smith and J. C. Tatlow, *J. Fluorine Chem., 1* (1971/1972) 433.

4 K. C. Joshi, A. K. Sharma and B. S. Joshi, *J. Fluorine Chem., 47* (1990) 1.

5 M. Lipp, F. Dallacke and S. Munner, *Justus Liebigs Ann. Chem., 618* (1958) 110.

6 (a) Y. Kobayashi, I. Kumadaki, A. Ohsawa, S. Murakami and T. Nakano, *Chem. Pharm. Bull., 26* (1978) 1247; (b) H. Ogoshi, M. Homma, K. Yokota, H. Toi and Y. Anyama, *Tetrahedron Lett., 24* (1983) 929.

7 P. Mushak, M. T. Glern and J. Savory, *Fluorine Chem. Rev., 6* (1973) 43.

8 A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, *Chem. Rev., 73* (1973) 551.

9 W. G. Scribener, B. H. Smith, R. W. Mosher and R. E. Sievers, *J. Org. Chem., 35* (1970) 1696.

10 K. C. Joshi and B. S. Joshi, *J. Fluorine Chem., 32* (1986) 229.

11 E. D. Bergmann, S. Cohen and I. Shohak, *J. Chem. Soc.,* (1961) 3278.

12 W. Y. Huang and L. Q. Zhang, *Acta Chimica Sinica, 44* (1986) 642.

13 A. E. Tipping and V. J. Davis, *Fluorocarbon and Related Chemistry*, Vol. 3, Chem. Soc., London, 1976, p. 141.

14 E. Bergan, *J. Org. Chem., 23* (1958) 476.

15 M. Iznaden and C. Portella, *J. Fluorine Chem., 43* (1989) 105.

16 M. Iznaden and C. Portella, *Tetrahedron Lett., 29* (1988) 3683.

17 C. Portella and M. Iznaden, *Tetrahedron Lett., 28* (1987) 1655.

18 (a) H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem., 34* (1969) 2324; (b) P. Cazeau, F. Duboudin, F. Moulines, O. Babot and J. Dunogues, *Tetrahedron, 43* (1987) 2075 (part I); 2089 (part II).