Journal of Fluorine Chemistry, *38* (1988) 249–256

Received: June 30, 1987; accepted: September 29, 1987

A NOVEL SYNTHESIS OF PERFLUOROALKYL ALKYL KETONES

WEIMING QIU and YANCHANG SHEN*

Shanghai Institute of Organic Chemistry, Academia Sinica
345 Lingling Lu, Shanghai (China)

SUMMARY

A novel synthesis of perfluoroalkyl alkyl ketones via the hydrolysis of fluorinated β-ketophosphonium salts is described. In view of the fact that a one-pot reaction without isolation of intermediates and the total yield in 2 steps reaches 37-78%, the present method provides a convenient synthesis of the title compounds.

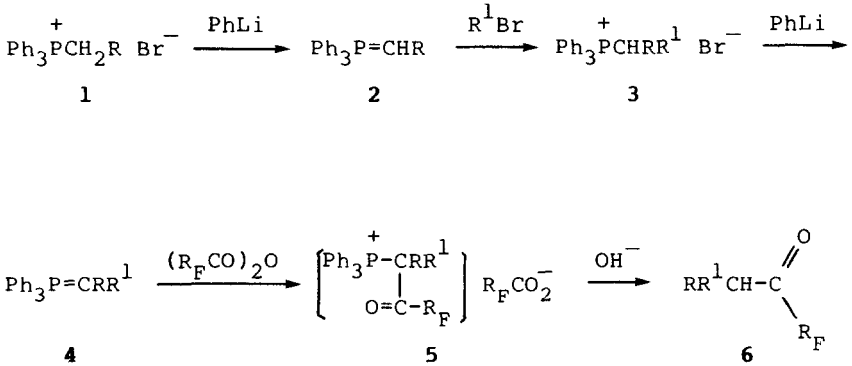
INTRODUCTION

Fluorinated ketones are useful intermediates for the synthesis of fluorine-containing compounds [1]. Perfluoroalkyl alkyl ketones, particularly trifluoromethyl ketones, have attracted much attention because of their biochemical activity. These fluorinated ketones are selectively employed as inhibitors for certain esterases or bovine trypsin [2]. Therefore, it is of much value to develop an effective and convenient method for the synthesis of perfluoroalkyl alkyl ketones.

0022-1139/88/$3.50

RESULTS AND DISCUSSION

We wish to report a novel synthesis of perfluoroalkyl alkyl ketones via the hydrolysis of fluorinated β-keto-phosphonium salts. The reaction sequence is as follows: alkylidenetriphenylphosphoranes **4** are generated from alkyl-triphenylphosphonium bromide **3** and phenyllithium in ether, and submitted to reaction with perfluoroacidic anhydrides to give fluorinated phosphonium salts **5**, which are hydrolyzed at room temperature to afford the products **6**.



1 **2** **3** **4** **5** **6**

a R=Me; R^1=$PhCH_2$; R_F=CF_3 b R=Me; R^1=$PhCH_2$; R_F=C_2F_5
c R=Me; R^1=$PhCH_2$; R_F=C_3F_7 d R=Et; R^1=$PhCH_2$; R_F=CF_3
e R=n-Pr; R^1=$PhCH_2$; R_F=CF_3 f R=n-Bu; R^1=$PhCH_2$; R_F=CF_3
g R=Ph; R^1=Me; R_F=CF_3 h R=i-Hep; R^1=Me; R_F=CF_3
i R=$PhCH{=}CHCH_2$; R^1=Me; R_F=CF_3

The results are summarized in Table 1.

TABLE 1

Perfluoroalkyl alkyl ketones prepared.

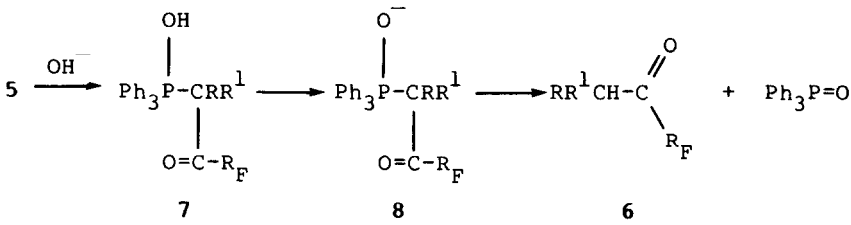
Compound	Method[a]	b.p.[b] (°C/mmHg)	Yield[c] (%)
6a	A	110/10	78
6b	A	116/10	67
6c	A	120/10	75
6d	A	114/10	66
6e	A	120/10	70
6f	A	125/10	70
6g	B	105/10	40
6h	A	105/15	54
6i	A	95/1	37

[a] Method A: compounds **1** used as starting material; method B: compound **3** used as starting material.

[b] Bath temperature.

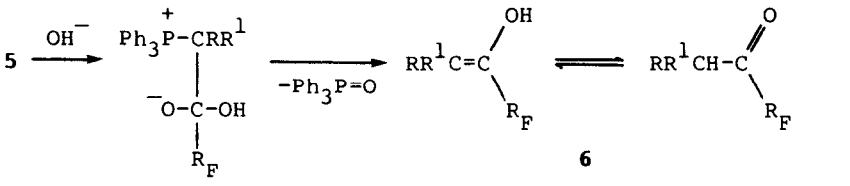
[c] Total yields in 2 steps from compounds **4** to **6**.

This hydrolysis may proceed via the following sequence which is somewhat like that suggested by Aksnes [3]. The hydroxyl ion attacks the phosphorus atom in the phosphonium salts **5**, then **6** result via **7** and **8**.



7 8 6

We previously reported that a nucleophile could attack the carbon atom of carbonyl groups in phosphonium salts **5**, with elimination of triphenylphosphine oxide to form olefins [4]. There is, however, another possibility, that a hydroxyl ion as a nucleophile attacks the carbon atom of the carbonyl group in the phosphonium salts **5** , then the products **6** result through **9**.



9 6

It is noteworthy that the characteristic feature of the reaction is a one-pot synthesis leading to the formation of perfluoroalkyl alkyl ketones by union of two or three fragments under mild conditions. The present method provides a more convenient synthesis of the title compounds than that reported previously [5].

EXPERIMENTAL

All boiling points were uncorrected. Infrared spectra of liquid products were determined as films on a Shimadzu RI-440 Spectrometer. NMR spectra (chemical shifts in ppm from TMS for ^{1}H NMR and from external TFA for ^{19}F NMR positive for upfield shifts) were obtained on a EM-360 Spectrometer at 60 MHz. Mass spectra were recorded on a Finnigan GC-MC 4021 Mass Spectrometer.

General procedure for preparation of ketones **6**:

Method A: A solution of phosphoranes **2** generated from phosphonium bromides **1** (3.5mmol) and phenyllithium(3.5mmol) in absolute ether (30ml) was stirred at 20°C under nitrogen while alkyl bromide (3mmol) was added. After stirring at 20°C for 0.5 h, a second portion of phenyllithium (3mmol) was added. The mixture was again stirred for further 1 h, cooled to -78°C and perfluoroacidic anhydride (3mmol) was slowly added. After addition, the mixture was allowed to warm to room temperature. Then, the aqueous solution of sodium hydroxide (5%,10ml) was added. The mixture was stirred for 2 h at 25°C. After standing overnight, the ethereal layer was washed with water until neutral and dried. Evaporation of the solvent gave the residue which purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (30:1) to afford the products **6**.

Method B: The similar procedure was used as in method A, but tne first two operations were omitted as the intermediate 3 was available.

6a: 78% yield; b.p. 110°C/10mmHg; IR(film): 1760(s),1605(w) cm^{-1}; ^{1}H NMR(CCl_4): δ 1.13(d,3H,J=7Hz);2.30-3.36(m,3H); 6.78-7.45(m,5H); ^{19}F NMR (CCl_4): δ -0.6(s)ppm; MS m/e: 216(M^+), 147(M^+-CF_3). Analysis: Calcd for $C_{11}H_{11}F_3O$: C,61.11, H,5.13, Found: C,61.14, H,5.42.

6b: 67% yield; b.p. 116°C/10mmHg; IR(film); 1755(s),1605(w) cm^{-1}; ^{1}H NMR(CCl_4): δ 1.17(d,3H,J=7Hz);2.45-3.39(m,3H); 7.01-7.25(m,5H); ^{19}F NMR (CCl_4): δ 3.4(s,3F);44.2(s,2F); MS m/e: 266(M^+), 147($M^+-C_2F_5$). Analysis: Calcd for $C_{12}H_{11}F_5O$: C,54.14, H,4.17, Found: C,53.93, H,4.13.

6c: 75% yield; b.p. 120°C/10mmHg; IR(film): 1755(s),1600(w) cm^{-1}; ^{1}H NMR(CCl_4): δ 1.13(d,3H,J=7Hz);2.39-3.33(m,3H); 6.98-7.28(m,5H); ^{19}F NMR (CCl_4): δ 2.2(t,3F,J=10Hz);42.0 (q,2F,J=10Hz);47.8(s,2F); MS m/e: 316(M^+); Analysis: Calcd for $C_{13}H_{11}F_7O$: C,49.38, H,3.51, Found: C,49.56, H,3.43.

6d: 66% yield; b.p. 114°C/10mmHg; IR(film): 1755(s),1605(w) cm^{-1}; ^{1}H NMR (CCl_4): δ 0.87(t,3H,J=7Hz);1.33-1.84(m,2H); 2.53-3.26(m,3H);6.98-7.34(m,5H);^{19}F NMR(CCl_4): δ 0.5(s); MS m/e: 230(M^+); Analysis: Calcd for $C_{12}H_{13}F_3O$: C,62.60, H,5.69, Found: C,63.01, H,6.10.

6e: 70% yield; b.p. 120°C/10mmHg; IR(film): 1755(s),1605(w) cm^{-1}; ^{1}H NMR (CCl_4): δ 0.62-1.75(m,7H); 2.49-3.24(m,3H); 6.95-7.30(m,5H); ^{19}F NMR(CCl_4): δ 0.5(s);MS m/e: 244(M^+); Analysis: Calcd for $C_{13}H_{15}F_3O$: C,63.93, H,6.19, Found: C,64.32, H,6.46.

6f: 70% yield; b.p. 125°C/10mmHg; IR(film): 1755(s), 1605(w) cm^{-1}; ^{1}H NMR (CCl_4): δ 0.66-1.79(m,9H); 2.54-3.29(m,3H); 7.06-7.37(m,5H); ^{19}F NMR(CCl_4): δ 0.4(s);MS m/e: 258(M^+); Analysis: Calcd for $C_{14}H_{17}F_3O$: C,65.10, H,6.63, Found: C,65.15, H,6.51.

6g: 40% yield; b.p. 105°C/10mmHg; IR(film): 1755(s),1605(w) cm^{-1}; ^{1}H NMR(CCl_4): δ 1.50(d,3H,J=7Hz);4.11(q,1H,J=7Hz); 7.08-7.30(m,5H); ^{19}F NMR(CCl_4): δ -2.0(s); MS m/e: 202 (M^+),133(M^+-CF_3); Analysis:Calcd for $C_{10}H_9F_3O$;C,59.41, H,4.49, Found: C,59.79, H,4.49.

6h: 54% yield; b.p. 105°C/15mmHg; IR(film): 1755(s)cm^{-1}; ^{1}H NMR(CCl_4): δ 0.88(d,6H,J=6Hz);0.95(d,3H,J=6Hz);1.13-1.78 (m,9H);2.79-3.19(m,1H); ^{19}F NMR (CCl_4): δ-0.4(s);MS m/e 224(M^+), 155(M^+-CF_3); Analysis: Calcd for $C_{11}H_{19}F_3O$: C,58.91, H,8.54, Found: C,59.12, H,8.82.

6i: 37% yield; b.p. 95°C/1mmHg; IR(film): 1755(s), 1600(w), 985(s)cm^{-1}; ^{1}H NMR (CCl_4): δ 1,29(d,3H,J=7Hz); 2.20-3.31 (m,3H);5.77-6.64(m,2H);7.17-7.33(m,5H); ^{19}F NMR (CCl_4): δ-0.5(s); MS m/e: 242(M^+), 173(M^+-CF_3); Analysis: Calcd for $C_{13}H_{13}F_3O$: C,64,46, H,5.41, Found:C,64.94, H,5.89.

ACKNOWLEDGEMENT

The authors wish to thank the National Science Foundation of China for the financial support.

REFERENCES

1 A.V. Fokin, Yu.N. Studnev, A.I. Rapkin, K.I. Pasevina, O.V. Verenikin and A.F. Kolomiets, Izv. Akad. Nauk SSSR, Ser. Khim., (1981) 1655; C.A. 95 (1981) 149875; T.B. Zapevalova, A.Ya. Zapevalov, V.P. Sass, I.P. Kolenko, V.S.Plashkin and S.V.Sokolov, Zh.Org.Khim.,14 (1978) 487; C.A. 89 (1978) 42318.

2 U.Brodbeck, K.Schweikert, R. Gentinetta and M. Rottenberg Biochim. Biophys. Acta, 567 (1979) 357; B.D. Hammock, K.D. Wing, J. McLaughlin, V.M. Lovell and T.C. Sparks, Pestic. Biochem. Physiol., 17 (1982) 76.

3 G.Aksnes, F.Y. Khalil and P.J. Majewski, Phosphorus and Sulfur, 3 (1977) 157.

4 Yanchang Shen and Weiming Qiu, Tetrahedron Lett.,28 (1987) 449; Yanchang Shen and Weiming Qiu, J. Chem. Soc., Chem. Commun., (1987) 703.

5 M. Hudlicky, 'Chemistry of Organic Fluorine Compounds: Laboratory Manual', 2rd Ed., Ellis Horwood, Sussex, England, (1976); pp 360-361, 380.