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Communications

A New Method for The Preparation of α -Fluorinated and α -Perfluoroalkylated Ketones

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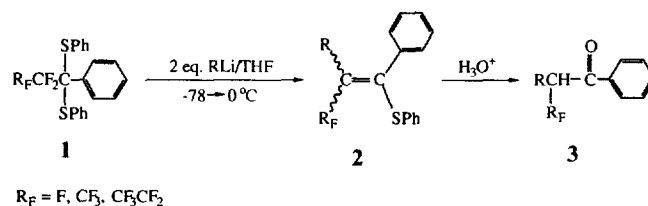
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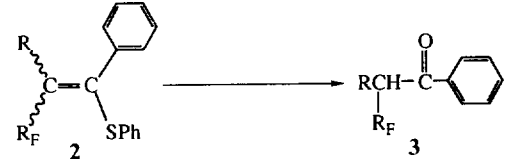
Fluorocarbonyl derivatives have been known to be one of the most important bioactive fluoroorganic compounds because of remarkable enzyme inhibitory effect.¹ In particular, α -fluorinated ketones which show a very strong tendency to bind with enzyme have been employed as inhibitors of hydrolytic enzyme² such as acetylcholinesterase, angiotensin and carboxypeptidase A, and α -trifluoromethyl ketones have also been successfully explored as inhibitor of aldolase.³ A number of methods for the preparation of α -fluorinated ketones has been previously reviewed⁴ and these methods involve the substitution reaction of α -haloketones with fluoride ion, reaction of enolates with positive fluorine and hydrolysis of fluoroolefins. In contrast, there are only limited reports on the synthesis of α -perfluoroalkylated ketones which can be achieved *via* radical addition reaction of enamine^{5,6} or enol silyl ether⁷ with perfluoroalkyl iodide, reaction of enamine or enolate with bromochlorodifluoromethane⁸ and reaction of enolates with (trifluoromethyl)dibenzothio- and (trifluoromethyl) dibenzoselenonium salt.⁹ Although there are numerous methods for the synthesis of either α -fluorinated or α -perfluoroalkylated ketones, however, no methodology for the synthesis of both α -fluorinated and α -perfluoroalkylated ketones has been reported.

As a part of our continuing studies on the chemistry and application of perfluoroalkylated dithioketals **1**,¹⁰⁻¹² we found that hydrolysis of β -fluorovinyl and β -perfluoroalkylvinyl sulfides **2**, which were obtained from the reaction of **1** with

organolithium compounds such as alkyl lithium and phenyllithium,¹² afforded corresponding α -fluoroketones and α -perfluoroalkylketones **3**. In this communication, we wish to describe our preliminary results on the synthesis of **3**.

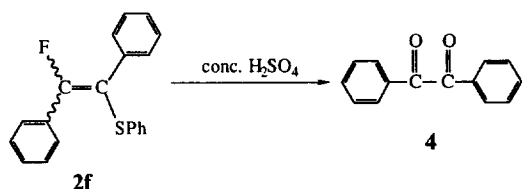


It has been well known that nonfluorinated vinyl sulfides are enolate equivalents and thus hydrolysis of these compounds afforded the corresponding ketones.^{13,14} Therefore, we began our studies by examining the hydrolysis of **2b** under several conditions which have been employed in the hydrolysis of nonfluorinated vinyl sulfides. When the compound **2b** was reacted with $HgCl_2$ in CH_3CN and H_2O cosolvent at $80^\circ C$ for 30 hours, the reaction did not proceed at all. Alternatively, treatment of **2b** with $TiCl_4$ and copper (II) chloride in CH_3CO_2H and H_2O cosolvent at $50^\circ C$ for 52 hours afforded α -fluoroketone **3b** in 39% yield based on the 40% conversion of starting material, though the result was not satisfied. When the compound **2b** was reacted with only conc. H_2SO_4 at $-5^\circ C$ followed by slow warming to room temperature, however, α -fluorinated ketone **3b** was obtained in 61% isolated yield. Further studies on the reaction of **3b** with dilute H_2SO_4 did not give improved results. The use of conc. H_2SO_4 in other β -alkylsubstituted β -fluorovinyl sulfide derivatives also provided the similar results which are summarized in Table 1. In contrast, the reaction of β -acetylenic β -fluorovinyl sulfide **2e** with conc. H_2SO_4 under the same reaction condition resulted in the formation of messy reaction mixture in which no isolable product was obtained. Interestingly, the reaction of **2f** with conc. H_2SO_4 under the same reaction condition afforded the unexpected product **4**, diphenyl 1,2-diketone, in 45% yield instead of the formation of the corresponding α -fluoroketone **3f**. This unexpected result provides a nice methodology for the synthesis of substituted diphenyl 1,2-diketones which are very useful synthetic intermediate in natural product synthesis.¹⁵

Table 1. Preparation of α -Fluoroketones and α -Perfluoroalkylketones


Product	R _F	R	Reaction Condition	Yield(%)
3a	F	CH ₃	conc. H ₂ SO ₄ (-5°C → 25°C, 2 h)	40
3b	F	n-C ₄ H ₉	∞	61
3c	F	s-C ₄ H ₉	∞	61 ^b
3d	F	t-C ₄ H ₉	∞	64
3e	F	C ₆ H ₅ C≡C	∞	0 ^c
3f	F	C ₆ H ₅	∞	0 ^d
3g	CF ₃	C ₆ H ₅	∞	72 ^e
3h	CF ₃ CF ₂	C ₆ H ₅	∞	70 ^f
3i	CF ₃	C ₆ H ₅ C≡C	∞	0 ^c
3j	CF ₃	n-C ₄ H ₉	∞	65 ^g
3j	CF ₃	n-C ₄ H ₉	90% H ₂ SO ₄ (75°C, 1.5 h)	70
3k	CF ₃	s-C ₄ H ₉	∞	67
3l	CF ₃ CF ₂	n-C ₄ H ₉	∞	67
3g	CF ₃	C ₆ H ₅	∞	39 ^h

^a Isolated yield. ^b Diastereomeric mixture (60 : 40). ^c Decomposition reaction occurred. ^d Diphenyl 1,2-diketone as a sole product was obtained in 54% yield. ^e Starting material (60%) was recovered. ^f Starting material (56%) was recovered. ^g Starting material (36%) was recovered. ^h Starting material (37%) was recovered.



Generally, reactions of β -perfluoroalkyl substituted vinyl sulfides with H₂SO₄ were more sluggish than those of β -fluoro-vinyl sulfides. For example, when the reaction of **2j** with conc. H₂SO₄ at -5°C followed by slow warming to room temperature for 2 hours, the corresponding product **3j** was obtained in 67% yield based on the 64% conversion of starting material. However, heating of **2j** with 90% H₂SO₄ at 75°C for 1.5 hours caused to complete this reaction and product **3j** was obtained in 70% yield which was shown in Table 1. The prolong heating time of **2j** with 90% H₂SO₄ caused to decompose the product **3j**. Similar results were obtained from the reactions of **2k** and **2l** with 90% H₂SO₄ at 75°C for 1.5 hours, in which products **3k** and **3l** were isolated in 67% yields, respectively. In the case of the reaction of β -trifluoromethylated vinyl sulfide **2g** with conc. H₂SO₄ at -5°C followed by slow warming to room temperature for 2 hours, the corresponding ketone **3g** was isolated in 72% yield, although 60% of starting material was recovered. Similarly, the reaction of β -pentafluoroethylated vinyl sulfide **2i** with conc. H₂SO₄ under the same reaction condition afforded

the corresponding ketone **3i** in 70% yield based on the 44% conversion of starting material. This result indicated that substitution of phenyl group at β -position in the β -trifluoromethylated vinyl sulfides made the reaction to be more sluggish than substitution of alkyl group in that system. Every effort to complete reaction of β -phenyl substituted β -trifluoromethylated vinyl sulfide **2g** with H₂SO₄ under the more vigorous condition than previously employed one has been resulted in the formation of corresponding α -trifluoromethylated ketone **3g** in relatively low yield. As in the case of reaction of **2e** with conc. H₂SO₄, the treatment of **3i** with conc. H₂SO₄ also resulted in the formation of messy reaction mixture.

In a typical experiment, a 100 ml two-neck flask equipped with a magnetic stir bar, glass stopper and a nitrogen tee connected to a source of argon was charged with 30 ml conc. H₂SO₄. The flask was cooled to -5°C and 2-fluoro-2-(1-methylpropyl)-1-phenylthiostyrene 1.43 g (5.0 mmol) was added at -5°C. After the reaction mixture was slowly warmed to room temperature, it was stirred at room temperature for 2 hours. The reaction mixture was slowly poured into a separatory funnel containing 50 ml H₂O, neutralized with 5 N NaOH solution, and extracted with 50 ml ether three times. After the ether layer was dried with anhydrous MgSO₄, column chromatography (hexane) provided 0.59 g (61% yield) of 1-fluoro-2-methylbutyl phenyl ketone **3c**: oil; ¹H-NMR (300 MHz, CDCl₃) δ 7.99-7.92 (m, 2H), 7.61-7.47 (m, 3H), 5.61 (dd, $J=49.8$ Hz, 3.3 Hz, one diastereoisomer), 5.34 (dd, $J=50.2$ Hz, 5.3 Hz, other diastereoisomer), 2.14-2.10 (m, 1H), 1.67-1.56 (m, 1H), 1.49-1.25 (m, 1H), 1.05-0.99 (t, 3H), 0.94-0.90 (m, 3H); ¹⁹F-NMR (80 MHz, CDCl₃) δ -42.88 (d, $J=49.0$ Hz, one diastereomer), -43.00 (d, $J=50.0$ Hz, other diastereomer); IR (neat) ν 2970, 2934, 2877, 1701 (C=O), 1597, 1454 (aromatic C=C), 1277, 1227 (C-F), 1134, 1011, 979, 964, 907, 853, 756, 698 cm⁻¹; MS, m/e (relative intensity) 194 (M⁺, 8), 167 (52), 149 (100), 105 (85), 77 (33), 57 (28), 43 (22).

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Synthesis and Characterization of the Superconducting Compound $\text{HgBa}_2\text{CuO}_{4+x}$

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Recently Schilling *et al.*¹ reported the rise of the superconducting critical temperature up to 134 K in the Hg-Ba-Ca-Cu-O system, shortly after the discovery of superconductivity at 94 K in $\text{HgBa}_2\text{CuO}_{4+x}$ by Putlin *et al.*² The observation of superconductivity on the novel mercury-based cuprate oxides has generated great interests in the fields of superconductivity³⁻⁵. In addition to their remarkable high critical transition temperature, the mercury compounds are attractive because of the structural similarity with the thallium based compounds such as $\text{TlBa}_2\text{Ca}_{n-1}\text{Cu}_n\text{O}_{2n+2+x}$. The possible homologous series of single HgO layered $\text{HgBa}_2\text{Ca}_{n-1}\text{Cu}_n\text{O}_{2n+2+x}$ ($n=1, 2, 3$) compounds were thus expected to be synthesized with use of analogous preparative techniques. Due to decomposition of HgO at 500°C and sensitiveness to the moisture in the product, isolation of single phasic mercury based cuprate is difficult. In this communication we report the successful isolation of pure superconducting $\text{HgBa}_2\text{CuO}_{4+x}$ by using precursor method.

The bulk samples were prepared by solid state reaction between yellow HgO (Janssen Chimica, 99%) and precursor powders of $\text{Ba}_2\text{CuO}_{3+x}$. A precursor material $\text{Ba}_2\text{CuO}_{3+x}$ was obtained from the reaction of stoichiometric mixtures of BaO_2 (Kanto Chemical Co., 90%) and CuO (Aldrich, 99%) in an oxygen atmosphere for 20 h at 900°C. Immediately after sintering, the pellets of the $\text{Ba}_2\text{CuO}_{3+x}$ were brought into the argon-filled dry box to avoid the decomposition of the compound in air. The precursor powder was mixed with slight excess (1.1 to 1.2 fold) of HgO, compacted into pellets, and finally sealed in evacuated quartz tubes. All these operations were performed in the dry box. The sealed quartz tube was placed inside a steel container which was kept in a bottom

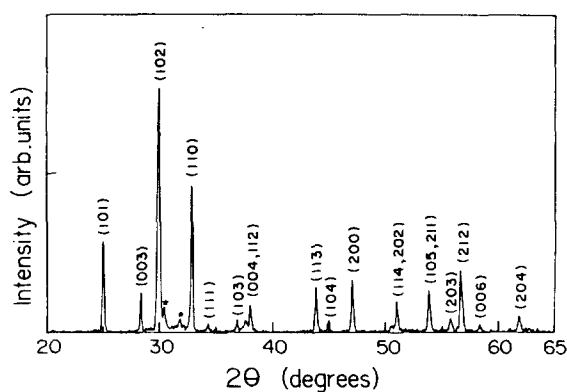


Figure 1. X-ray powder diffraction pattern of $\text{HgBa}_2\text{CuO}_{4+x}$ compound.

loading furnace to prevent contamination of mercury by exploding the silica tubes during the reaction period. The samples were heated slowly to 800°C in 6 h, sintered at the temperature for 5 h, and then slowly cooled to room temperature in 10 h. During the reaction period the quartz tube remained intact. The black pellets were obtained along with a drop of mercury inside the tube.

Attempts to synthesize the $\text{HgBa}_2\text{CuO}_{4+x}$ compound with use of individual metal oxides led to non-superconducting product. This suggests that the reaction between the individual oxides requires higher temperature to form the superconducting phases. In order to make the $\text{HgBa}_2\text{CuO}_{4+x}$ compound, we used $\text{Ba}_2\text{CuO}_{3+x}$ as a precursor material and slight excess amount of HgO to compensate evaporation of mercury in this study. Synthesis of pure $\text{HgBa}_2\text{CuO}_{4+x}$ was strongly dependent on experimental conditions such as reaction rate, sintering temperature, and moisture. The products prepared by similar preparative conditions often gave non-superconducting compounds. Minimum exposure in air and fully dried starting materials could avoid the formation of undesirable side products. $\text{HgBa}_2\text{CuO}_{4+x}$ phase was revealed by X-ray powder diffraction as shown in Figure 1. All the diffraction lines are well indexed on a tetragonal cell ($P4/mmm$) with lattice parameters, a and c with the value of 3.8868 (2) Å and 9.4886 (1) Å, respectively. Trace amounts of unreacted HgO peaks were identified, which were marked asterisks. Pure single phasic $\text{HgBa}_2\text{CuO}_{4+x}$ was obtained by controlling HgO amount, where optimum amount of HgO in this reaction is about 1.1 fold excess. The finely ground powder samples used for X-ray measurement were stable in air for one day but appeared to decompose slowly into greenish black powders. The structure of $\text{HgBa}_2\text{CuO}_{4+x}$ is very similar with the known $\text{TlBa}_2\text{CuO}_{5-x}$ ⁶ besides the oxygen contents in rock-salt layers of HgO_x and TlO_{1-x} . While the oxygen in the HgO layer is largely depleted (x is about 0.10)¹, corresponding TlO layer shows very small amount of oxygen-deficiency.

Magnetic susceptibility data of the $\text{HgBa}_2\text{CuO}_{4+x}$ are shown in Figure 2, which were obtained by using a SQUID magnetometer (Quantum Design) with an applied field $H_a=20$ G. The data clearly demonstrate a normal to superconducting transition with a T_c of about 92 K. If we assume an average density is about 6 g/cm³, the shield volume fraction (ZFC) amounts to about 70% and the flux expulsion fraction (FC)