Ethyl 2-Benzyloxy-3,3-difluoropropenoate as a Novel Synthon of β-Fluoro-α-keto Acid Derivatives, Preparation and Reactions with Nucleophiles

Guo-qiang Shi* and Zhi-yao Cao

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Academia Sinica, 354 Fenglin Lu, 200032 Shanghai, China

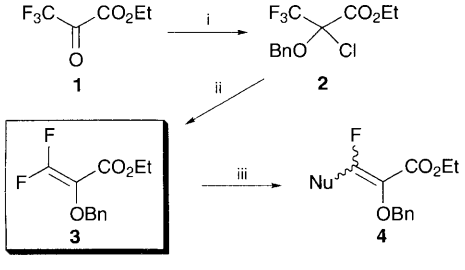
Ethyl 2-benzyloxy-3,3-difluoropropenoate **3**, prepared from the readily obtainable ethyl trifluoropyruvate, reacts with a variety of nucleophiles to give β-fluoro-α-keto acid derivatives in high yield.

In view of the prominent features that fluorine may confer to biologically active molecules[1] and the central importance of α-keto acid in the studies of various biological processes and in the development of enzyme inhibitors,[2] the introduction of a fluorine atom into the β-position of α-keto acid derivatives may bring about significant biological consequences. Moreover, from a synthetic point of view, β-fluoro-α-keto acids are particularly valuable precursors of the corresponding β-fluoro-α-amino acids that are currently of great interest in the design of potential enzyme inhibitors and therapeutic agents.[1b,3]

Only two methods are known for the synthesis of β-fluoro-α-keto acid derivatives. The first involves direct fluorination of enol-type α-keto esters with molecular fluorine, which is only applicable to a very limited number of substrates due to the extraordinarily high reactivity of molecular fluorine.[4] The alternative method of preparing β-fluoro-α-hydroxy esters by the ring opening of glycidic esters with HF–pyridine and their subsequent oxidation to β-fluoro-α-keto esters has also been of limited utility because of the low regioselectivity of the ring opening reaction and the necessity to use a strong oxidant for the oxidation step.[5] In a search for a more efficient and convenient method for the synthesis of β-fluoro-α-keto acid derivatives, we have sought to develop a building block approach involving the use of readily available fluorinated starting materials as a source of fluorine. Herein we report a convenient preparation of the title compound and demonstrate its utility as a novel synthon of β-fluoro-α-keto acid derivatives *via* its reactions with various nucleophiles.

For the first time, we have found that treatment of the hemiketal formed between ethyl trifluoropyruvate[6] **1** and benzyl alcohol† with $SOCl_2$ (1.5 equiv.) and pyridine (3.0 equiv.) readily afforded the α-chloro ether **2**.‡ Owing to the strong electron-withdrawing property of the CF_3 and ester groups, compound **2** was found to be fairly stable, capable of being isolated from aqueous workup and distilled under reduced pressure. Subsequent reductive dechlorofluorination of **2** with zinc powder (5.0 equiv.) in DMF proceeded smoothly to provide **3** in 85% yield.§

Having established a convenient preparation of compound **3**, we then explored the feasibility of using **3** as a synthon of β-fluoro-α-keto acid derivatives. Being rendered electron deficient by the substitution of two fluorine atoms as well as the carbonyl group, compound **3** was envisaged to be a quite reactive Michael acceptor which can react with nucleophiles in a 1,4-fashion followed by the elimination of a fluoride ion.[8]

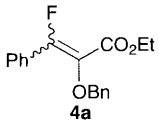
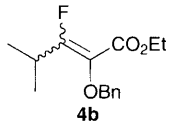
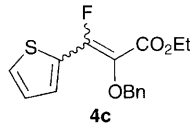
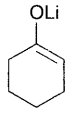
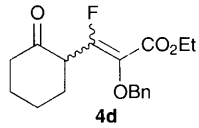
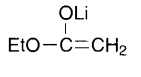
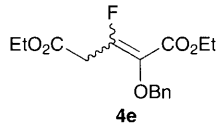
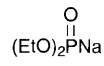
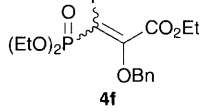
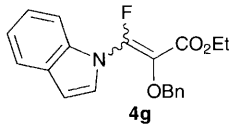


Scheme 1 *Reagents and conditions*: i, benzyl alcohol (1.0 equiv.), benzene; then $SOCl_2$ (1.5 equiv.), pyridine (3.0 equiv.), 0 °C, 76% overall yield; ii, activated zinc dust (5.0 equiv.), DMF, 85% yield; iii, nucleophile

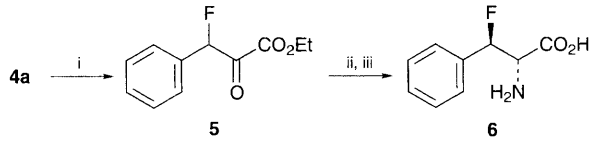
Indeed, addition of a variety of nucleophiles to **3** proceeded very smoothly affording the expected enol ether of β-fluorinated α-keto acid derivative **4** in high yield (Table 1).¶

The results are summarized in Table 1. As can been seen from the table, organolithium and Grignard reagents reacted well with **3** in the presence of CuI to give overall substitution products. With 2-thiophenylmagnesium bromide as the nucleophile (entry 3), the reaction was best performed in the absence of the copper salt. Simple ketone and ester enolates also effectively underwent this type of nucleophilic substitution reaction to furnish highly functionalised products **4d** and **4e**. Heteroatom nucleophiles, such as sodium diethylphosphite (entry 6) and 1-indolyllithium (entry 7), also react with **3** to furnish the corresponding phophonic acid derivative **4f** and

Table 1 Reaction of nucleophiles with ethyl 2-benzyloxy-3,3-difluoropropenoate **3**[a]

Entry	Nucleophile	Product[b]	Yield (%) (*Z*: *E*)[c]
1	Ph_2CuLi	 **4a**	90 (10 : 90)
2	Pr^iMgBr, CuI	 **4b**	90 (12 : 88)
3		 **4c**	84 (84 : 16)
4		 **4d**	76 (15 : 85)
5		 **4e**	80 (22 : 78)
6		 **4f**	93 (11 : 89)
7	1-indolyllithium	 **4g**	82 (25 : 75)

[a] All reactions were performed in THF at −78 °C using 1.1–1.2 equiv. of the nucleophile for 1.0 equiv. of **3**. [b] All products were characterized by ^1H and ^{19}F NMR, MS and elemental analysis. [c] Yield of isolated product. Numbers in parentheses indicate the ratio of two isomers determined by ^{19}F and/or ^1H NMR. The configuration was tentatively assigned by ^{19}F NMR measurement. See footnote ‖.



Scheme 2 *Reagents and conditions*: i, H_2 (1 atm.), 10% Pd on charcoal (cat.), EtOH, 1 h, 95% yield; ii, $NaHCO_3$ (3.0 equiv.), 50% (*v*/*v*) aqueous isopropanol, 25 °C, 24 h; iii, conc. aqueous NH_3, 35 °C, 4 h, then $NaBH_4$ (5 equiv.), 10–25 °C 1 h, 43% yield

1-alkylated indole compound **4g** in high yields. In all cases, the products were obtained as a mixture of *Z*- and *E*-isomers‖ which can equally serve as precursors of β-fluoro-α-keto acid derivatives (*vide infra*).

It is worth noting that, unlike simple β,β-difluoro-α,β-unsaturated carbonyl compounds whose reactions with nucleophiles are generally complicated by the consecutive addition of 2 equiv. of the nucleophile to give a fluorine free product and therefore are not of great synthetic value,[8] compound **3** shows the capacity to react with only one equivalent of nucleophile even though the latter was employed in excess. This property, which ensured a high yield of the desired monosubstituted product, is apparently imparted by the synthetically desirable benzyloxy group at the α-position which rendered the initially formed product unreactive towards further nucleophilic reactions.

Finally, the feasibility of converting **4** to unprotected β-fluoro-α-keto esters and the use of the latter as procursors of β-fluoro-α-amino acid has been examined using **4a** as the representative compound. Thus, removal of the benzyl group from **4a** (mixture of two isomers) was readily achieved by hydrogenation on Pd–C to give β-fluoro-α-keto ester **5** in nearly quantitative yield. Following a protocol described by Tsushima, compound **5** was stereoselectively converted to the known β-fluorophenylalanine **6** (Scheme 2).[4b]

This work was supported by grants from the National Natural Science Foundation of China and Shanghai Municipal Scientific Committee.

Received, 14th June 1995; Com. 5/03842A

Footnotes

† A few other primary alcohols have also been found to undergo similar transformations.

‡ This reaction was believed to proceed through a mechanism similar to that commonly proposed for the reaction of an ordinary alcohol with $SOCl_2$–pyridine, *i.e* a S_Ni2 displacement of $OSON^+C_5H_5$ by the weak chloride nucleophile. A similar transformation starting from a hemiketal derived from dimethyl oxomalonate has been reported, see ref. 7.

§ *Procedure and selected data* for **3**: A mixture of compound **2** (14.8 g, 50 mmol) and freshly activated zinc dust (12.8 g) in dry DMF (100 ml) was vigorously stirred at room temp. until heat evolution ceased. After removal of the precipitate by filtration, the reaction mixture was diluted with diethyl ether (200 ml), washed with water (2 × 100 ml) and dried over Na_2SO_4. Distillation through a Vigreux column afforded **3** (10.3 g, 85%). Bp 85 °C (0.1 mmHg); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.21 (s, 5 H), 4.82 (s, 2 H), 4.25 (q, *J* 7.1 Hz, 2 H), 1.30 (t, *J* 7.1 Hz, 3 H); ^{19}F NMR ($CDCl_3$, 60 MHz TFA) 4.1 (d, *J* 9.0 Hz), 9.4 (d, *J* 9.0 Hz); MS (EI) *m*/*z* 242 (5, M^+), 197 (8), 169 (15).

¶ *Typical procedure*: compound **3** (0.24 g, 1.0 mmol) was added to a solution of a nucleophile (1.2 mmol) in THF (5 ml) at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was warmed to 0 °C during 1 h and quenched with saturated aqueous NH_4Cl solution. The product was isolated by flash column chromatography.

‖ In all cases, the two *Z*- and *E*-isomers showed a relatively large difference of ^{19}F NMR chemical shifts (Δ ppm ≥ 13). The configuration was assigned by assuming a downfield shift of the fluorine *cis* to the ester group.[8e,f]

References

1 (*a*) *Biomedicinal Aspects of Fluorine Chemistry*, ed. R. Filler and Y. Kobayashi, Elsevier Science, Amsterdam, 1982; (*b*) J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1990; (*c*) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolski, Elsevier Science, Amsterdam, 1993.

2 For a review on the syntheses and properties of α-keto acid derivatives, see: A. J. L. Cooper, J. Z. Ginos and A. Meister, *Chem. Rev.*, 1983, **83**, 321.

3 *Fluorine-containing Amino Acids: Synthesis and Application*, ed. V. P. Kukhar and V. A. Soloshonok, Wiley, New York, 1994.

4 (*a*) T. Tsushima, K. Kawada and T. Tsuji, *J. Org. Chem.*, 1982, **47**, 1107; (*b*) T. Tsushima, K. Kawada, J. Nishikawa, T. Sato, K. Tori and T. Tsuji, *J. Org. Chem.*, 1984, **49**, 1163.

5 A. I. Ayi, M. R. Remli, R. Condom and R. Geudj, *J. Fluorine Chem.*, 1981, **17**, 565; M. Remli, A. I. Ayi and R. Guedj, *J. Fluorine Chem.*, 1982, **20**, 677.

6 Ethyl trifluoropyruvate is commercially available. It can also be readily prepared by two convenient methods: D. Sianesi, A. Pasetti and F. Tarli, *J. Org. Chem.*, 1966, **31**, 2312; C. Francese, M. Toxdeux and C. Wakselman, *Tetrahedron Lett.*, 1988, **29**, 1029; see also G.-q. Shi and Y.-y. Xu, *J. Chem. Soc., Chem. Commun.*, 1989, 617.

7 D. A. McGowan and G. A. Berchtold, *J. Am. Chem. Soc.*, 1982, **104**, 7036.

8 For related examples of the Michael addition to β,β-difluoro-α,β-unsaturated carbonyl compounds bearing no alkoxy group at the α-position, see (*a*) M. Suda, *Tetrahedron Lett.*, 1981, **22**, 1421; (*b*) J. P. Gillet, R. Sauvetre and J. F. Normant, *Synthesis*, 1982, 297; (*c*) T. Fuchikami, Y. Shibata and Y. Suzuki, *Tetrahedron Lett.*, 1986, **27**, 3173; (*d*) T. G. Archibald and K. Baum, *J. Org. Chem.*, 1990, **55**, 3562; (*e*) J. Ichikawa, N. Yokota, M. Kobayashi and T. Minami, *Synlett*, 1993, 186; (*f*) J. Ichikawa, M. Kobayashi, N. Yokota, Y. Noda and T. Minami, *Tetrahedron*, 1994, **50**, 11637.