A New Synthesis of α-Fluoro-α,β-unsaturated Ketones and Esters based on Organoselenium Methodology

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Fluoroselenenylation of α-diazoketones and α-diazoesters using a phenylselenenyl fluoride equivalent, generated *in situ* from phenylselenenyl bromide and AgF, followed by oxidation with hydrogen peroxide, provided α-fluoro-α,β-unsaturated ketones and ester, respectively, in moderate yields.

Modification of biological activity of organic compounds by introducing a fluorine substituent has attracted growing interest in the area of synthetic chemistry and numerous endeavours have been made to search for new fluorination methodologies.[1] However, there have been only few selective and generally applicable methods[2] available for the preparation of α-fluoro-α,β-unsaturated ketones and esters, which have been employed as important intermediates in the synthesis of biologically active materials.[3] As an extension of our work on organoselenium-based methodology for fluorination of organic substrates,[4] we describe the reaction of α-diazoketones and α-diazoesters by the use of a phenylselenenyl fluoride equivalent [eqns. (1)–(3)].

The phenylselenenyl fluoride equivalent was prepared *in situ* by the reaction of silver(I) fluoride with phenylselenenyl

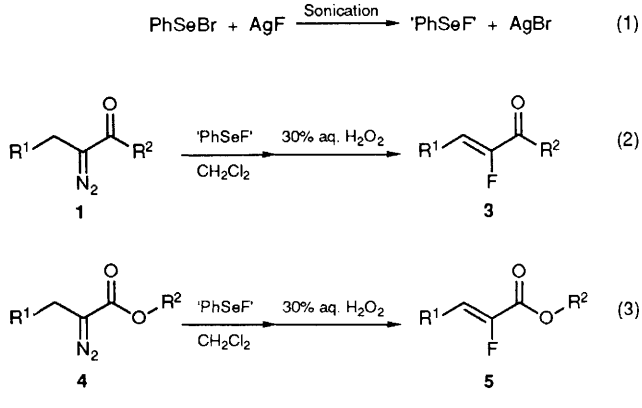
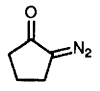
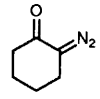
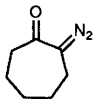
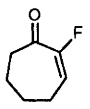
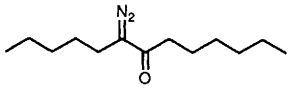
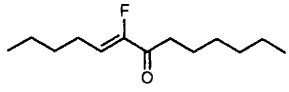
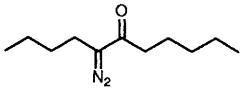
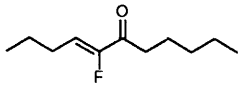
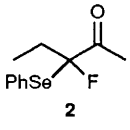


Table 1 Preparation of α-fluoro-α,β-unsaturated ketones

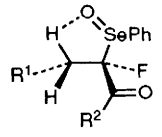
Entry	α-Diazoketones **1**	Product **3**	Yield (%)	^{19}F NMR[a]
a			55.9	−139.9
b			51.7	−130.6
c			68.7	−119.4
d			72.0	−129.1
e			54.3	−129.0

[a] Obtained at 84.26 MHz in [^{2}H]chloroform with trichlorofluoromethane as an internal standard.

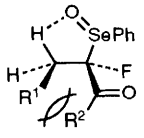


2

bromide in dichloromethane under ultrasound irradiation.† Subsequent addition of α-diazoketones **1**[5] to the reaction mixture caused immediate evolution of nitrogen gas. Considering the analogous reactions of phenylselenenyl derivatives PdSeX (X = Cl, Br, OCOMe,[6a] SCN and SeCN[6b]) with **1** and α-fluorination of thioacetals with mercury(II) fluoride,[7] we assume that the primary products would be the corresponding α-fluoro-α-phenylseleno ketones **2**. Since the α-fluoro selenides **2** thus obtained could not be isolated, they were oxidized without further purification by immediate addition of 30% aqueous hydrogen peroxide to the reaction mixture to obtain α-fluoro-α,β-unsaturated ketones **3** in moderate yields.‡ The



A



B

results are summarized in Table 1.§ Acyclic α-diazoketones **1d** and **1e** were transformed only to the corresponding (*Z*)-α-fluoro-α,β-enones.¶ The complete preference for formation of the (*Z*)-enones may be attributed to the difference in the relative stability between the two conformations **A** and **B**, the latter of which would be sterically less favourable to undergo selenoxide *syn*-elimination.

The same procedure was applicable to α-diazoesters **4**, which were prepared by diazotization of α-amino esters with isopentyl nitrite.[8] As shown in Table 2,§ various α-diazoesters reacted with the phenylselenenyl fluoride equivalent to afford α-fluoro-α,β-unsaturated esters **5** in moderate yields after oxidative *syn*-elimination with 30% aqueous hydrogen peroxide [eqn. (2)]. Similarly to the reaction with **1**, only the products with (*Z*)-configuration were obtained (entries **a–c** in Table 2).¶

The new method described herein, which requires only simple and safe operations, should provide a wide range of α-fluoro-α, β-unsaturated ketones and esters, which are quite useful synthons for various fluorinated compounds. Of much significance is that these reactions are completely stereoselective and afford exclusively the (*Z*)-isomers.

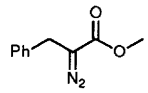
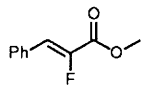
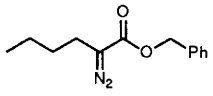
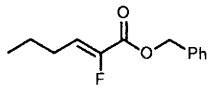
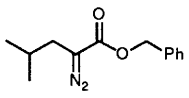
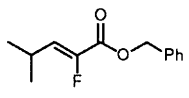
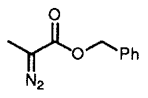
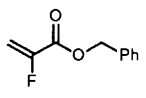
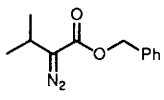
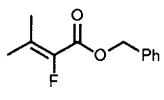
† Ultrasound irradiation is essential to obtain satisfactory yields of desired fluorinated products presumably because of the insolubility of silver(I) fluoride in dichloromethane. The thermally unstable phenylselenenyl fluoride equivalent was immediately used for the subsequent reactions in one-pot with continuous sonicative stirring.

‡ A typical procedure for the synthesis of **2** is as follows: a suspension of finely powdered AgF (140 mg, 1.1 mmol) and phenylselenenyl bromide (241 mg, 1.0 mmol) in dry dichloromethane (2.5 ml, freshly distilled from calcium hydride) was irradiated with ultrasound at 5–10 °C for 10 min under nitrogen atmosphere. A pale-yellow precipitate was formed and the dichloromethane solution turned pale yellow. To the mixture was added a solution of 2-diazocyclohexanone (124 mg) in dry dichloromethane (3.5 ml), and the whole mixture was irradiated with ultrasound for 1.5 h at the same temperature. After addition of 30% aqueous hydrogen peroxide (1.2 ml), the mixture was further sonicated for 30 min. The residual oil, obtained by usual extractive workup with chloroform, was purified by bulb-to-bulb distilation (b.p. 60 °C) to afford 2-fluorocyclohex-2-enone **2b** as a pale-yellow oil (59 mg, 51.7%): IR(neat) ν/cm^{-1} 2927, 1690, 1647, 1358, 1107; ^{1}H NMR (90 MHz, $CDCl_3$–Me_4Si) δ 1.85–2.23 (m, 2 H), 2.23–2.65 (m, 2 H), 6.46 (dt, 1 H *J* 4.5 and 14.7 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$–Me_4Si) δ 22.6, 23.8 (d, *J* 5.5 Hz), 38.3 (d, *J* 3.3 Hz), 125.5 (d, *J* 13.2 Hz), 154.0 (d, *J* 260.4 Hz), 191.5 (d, *J* 19.8 Hz); ^{19}F NMR (89.26 MHz, $CDCl_3$–$CFCl_3$) δ −130.6 (d, *J* 14.7 Hz). LRMS 114 (M^+).

§ All new compounds (**2a**, **2d**, **4b–e**) had IR, HRMS, ^{1}H, ^{13}C and ^{19}F NMR consistent with assigned structures. The structures of literature compounds (**2b**, **2c**, **2e** and **4a**) were confirmed by IR, LRMS, ^{1}H, ^{13}C and ^{19}F NMR. Each methyl ester derivative of **4b–e** has already been described in the literature.[2a,c,d]

¶ The stereochemical assignments were based on the coupling constant between a vinylic hydrogen and fluorine (for example $^3J_{HF}$ 34 Hz for **2d**).

Table 2 Preparation of α-fluoro-α,β-unsaturated esters

Entry	α-Diazoesters **4**	Product **5**	Yield (%)	^{19}F NMR[a]
a			85.0	−126.1
b			81.4	−131.0
c			58.5	−130.3
d			57.7	−117.4
e			51.4	−151.1

[a] Obtained at 84.26 MHz in [^{2}H]chloroform with trichlorofluoromethane as an internal standard.

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