Sodium hydroxide-promoted reaction of 1-substituted 2,3,3-trifluoro-prop-1-enyl toluene-*p*-sulfonates with alcohols. First efficient and convenient access to α-fluoro-β,β-dialkoxy ketones

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2,3,3-Trifluoro-1-aryl- or -1-alkyl-prop-1-enyl toluene-*p*-sulfonates **1**, readily available from 2,2,3,3-tetrafluoropropanol, react smoothly with alcohols in the presence of sodium hydroxide at ambient temperature for 1 h to afford the corresponding α-fluoro-β,β-dialkoxy ketones **2** in good to excellent yields.

There has been considerable interest in fluorinated compounds, which often confer unique biological and physical properties. Fluorinated aldehydes,[1] ketones[2] and acetals[3] are among the most important and versatile intermediates for various fluorine-containing molecules. Fluorinated ketones have also been used as hydrolytic enzyme inhibitors.[4] Although it is of great significance to develop effective and facile methods for the synthesis of these compounds, little is known about the preparation of fluorinated molecules bearing both ketone and acetal moieties,[5] and the methods that have been used previously have some serious disadvantages, such as variable yields of products, difficulties in accessibility or handling of the reagent because of toxicity, and low applicability of the reaction.

In our continuing studies on the chemistry and synthetic utilization of fluorinated enol toluene-*p*-sulfonates (tosylates),[6] we have found that a 1-substituted fluorinated enol tosylate smoothly reacted with alkoxide *via* the cleavage of the enol oxygen–sulfur bond leading to α-fluoro-β,β-dialkoxy ketones. This communication describes a new reaction of 1-substituted enol tosylate **1** with alcohols in the presence of sodium hydroxide, which offers a novel, promising and efficient method for the synthesis of α-fluoro-β,β-dialkoxy ketones **2** in good to excellent yields.

Scheme 1
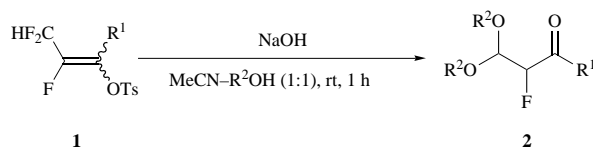
Treatment of **1a** (R¹ = *p*-MeOC₆H₄) with 1.1 equiv. of sodium hydroxide (NaOH) in a mixed solvent of acetonitrile (MeCN)–methanol (MeOH) (1 : 1) at ambient temperature for 3 h gave the α-fluoro-β,β-dialkoxy ketone **2a** in 40% yield and the starting tosylate **1a** was recovered in 47% yield. The use of 2.2 equiv. of NaOH was found to provide an 86% yield of the product **2a**, together with methyl tosylate in 73% yield (Table 1, entry 1). Triethylamine and tetrabutylammonium fluoride were undesirable for the reaction, whereas *n*-butyllithium, sodium hydride, potassium *tert*-butoxide efficiently provided **2a** in

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Table 1 Synthesis of α-fluoro-β,β-dialkoxyketones **2**

Entry	Tosylate	R¹	R²OH	Product	Yield[a] (%) of **2**
1	**1a**	*p*-MeOC₆H₄	MeOH	**2a**	86
2	**1a**	*p*-MeOC₆H₄	EtOH	**2b**	78
3	**1a**	*p*-MeOC₆H₄	PrOH	**2c**	77
4	**1a**	*p*-MeOC₆H₄	PrⁱOH	**2d**	Trace
5	**1b**	*m*-MeOC₆H₄	MeOH	**2e**	95
6	**1c**	*p*-NO₂C₆H₄	MeOH	**2f**	87
7	**1d**	*p*-EtOCOC₆H₄	EtOH	**2g**	82
8	**1e**	Me	MeOH	**2h**	65

[a] Isolated yields.

69–85% yields. Tetrahydrofuran and toluene as solvent gave **2a** in 77% and 68% yields, respectively. Table 1 summarizes the results of the reaction of **1** with various alcohols in the presence of NaOH.

Ethanol (EtOH) and propan-1-ol (PrOH) also gave good results in this reaction to provide the corresponding α-fluoro-β,β-dialkoxy ketones **2** in good to excellent yields (entries 2 and 3). The reaction of propan-2-ol (PrⁱOH) was extremely sluggish, providing only a trace amount of product **2d**, and the starting tosylate **1a** was recovered in 81% yield (entry 4). The recovery of **1a** could be attributed to the undesirable cleavage of the enol sulfur–oxygen bond by the bulky isopropoxide ion. Other enol tosylates **1b–e** reacted smoothly with MeOH or EtOH in the presence of 2.2 equiv. of NaOH under the same conditions to afford the products **2e–h** (entries 5, 6, 7 and 8).

It should be noted that alkyl tosylates were obtained in similar yields to the α-fluoro-β,β-dialkoxy ketones **2** in all cases. Although exact elucidation of the reaction mechanism awaits further investigation, the reaction seems to occur *via* the cleavage of the enol oxygen–sulfur bond with alkoxide followed by elimination of a fluoride ion to generate α,β-difluoro-α,β-unsaturated ketones, which are simultaneously attacked by alcohol or alkoxide to give α-fluoro-β,β-dialkoxy ketones **2**.[7]

In summary, the reaction of 1-substituted enol tosylate **1** with alcohols in the presence of NaOH efficiently proceeds to give the α-fluoro-β,β-dialkoxy ketone **2**, which is difficult to prepare by other methods.

Experimental

Preparation of 2-fluoro-3,3-dimethoxy-1-(4-methoxyphenyl)-propan-1-one 2a

To a methanol (2 ml) solution of NaOH (88 mg, 2.2 mmol) was added dropwise to an acetonitrile (2 ml) solution of the tosylate **1a** (370 mg, 0.99 mmol) at 0 °C. After being stirred at room temperature for 1 h under an argon atmosphere, the reaction mixture was quenched with cold brine (30 ml), followed by

extraction with diethyl ether (30 ml × 3), drying over Na_2SO_4 and concentration under vacuum. Column chromatography of the residual oil on silica gel using 1,2-dichloroethane as an eluent afforded analytically pure **2a** (206 mg, 86%) as a colourless oil, ν_{max}(neat)/cm^{-1} 1682 (CO); δ_H(400 MHz; CDCl$_3$; Me$_4$Si; J/Hz) 3.41 (3H, s, CH$_3$), 3.52 (3H, s, CH$_3$), 3.89 (3H, s, CH$_3$), 4.74 [1H, dd, J 9.76 and 5.37, (CH$_3$O)$_2$CH], 5.47 (1H, dd, J 49.03 and 5.37, CFH), 6.95 and 8.01 (4H, AB q, J 9.03); δ_F(376 MHz; CDCl$_3$; ext. CF$_3$COOH; J/Hz) −119.14 (1F, dd, J 49.03 and 9.76); m/z (EI) 242.0948 (M$^+$, 1.5%, C$_{12}$H$_{15}$FO$_4$ requires 242.0955), 222 (3), 205 (6), 135 (100), 107 (8), 96 (3), 75 (77), 64 (5).

Acknowledgements

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