Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 5403–5406
Tetrahedron Letters

Lewis acid promoted aldol reaction of fluorinated silyl enol ethers from new fluoroacetylsilane derivatives ☆

Woo Jin Chung, Silvana C. Ngo, Seiichiro Higashiya and John T. Welch*

Department of Chemistry, University at Albany, State University of New York, 1400 Washington Ave., Albany, NY 12222, USA

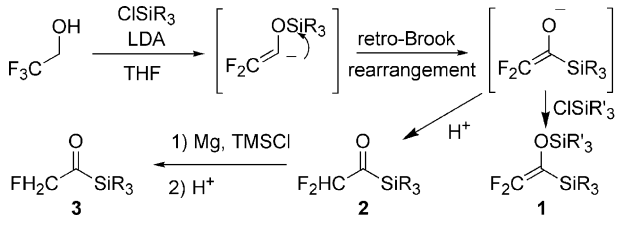
Received 8 January 2004; accepted 13 May 2004

Abstract—New fluorinated silyl enol ethers with various trialkylsilyl groups were synthesized. Various fluorinated β-hydroxy ketones were synthesized by Lewis acid promoted aldol reaction of silyl enol ethers with diverse aldehydes. Reactivity of various trialkylsilyloxy groups toward Lewis acid was also studied.
© 2004 Elsevier Ltd. All rights reserved.

The introduction of fluorine into organic molecules has been a subject of interest in organic and medicinal chemistry due to the improved or unexpected properties imparted by fluorine.[1] For example, fluorinated ketones that contain fluorinated carbons alpha to the carbonyl group and promote the formation of stable hydrates may act as inhibitors of proteases and esterases. These stable hydrates mimic the transition state involved in amide and ester hydrolysis.[2] Silyl enol ethers, widely used in carbon–carbon bond formation because of their high reactivity and ready availability can also be recognized as precursors for the formation of α-fluorinated ketones.[3] Various aldol reactions have been effected with difluoroenol ethers prepared from ethyl α-chloro-α,α-difluoroacetate,[4] difluoroketene silyl acetals,[5] and difluorosilyl enol ethers.[6–9] Precedence for the preparation of difluorosilyl enol ethers has been reported. Several of the known preparative methods for the synthesis of these compounds involve reductive trimethylsilylation using metals such as zinc with chlorodifluoroketones[6] or magnesium with trifluoroketones[7] in the presence of chlorotrimethylsilane. Alternative approaches require the electrophilic reaction of silylketones with trifluoromethyltrimethylsilane[8] or nucleophilic addition of organometallic reagents to trifluoroacetylsilanes.[9]

Recently, we reported the facile preparation of mono- and difluorinated acetyltrialkylsilanes **2**, **3**, and the silyl enol ethers **1** from 2,2,2-trifluoroethanol in the presence of chlorotrialkylsilanes and LDA (Scheme 1).[10] These fluorinated acetylsilane derivatives, synthetic equivalents of hindered aldehydes, react with nucleophiles under basic conditions to give Brook isomerized products, which are normally not obtainable from the corresponding aldehydes (Scheme 2).[11] Furthermore, reactions with electrophiles give α-substituted products preserving the fluoroacylsilanes functionality. Exploration of the reactions of this class of compounds can be expected to expand organofluorosilicon chemistry and open pathways to the preparation of various materials with medicinal and materials applications.

In this letter, we wish to present the results of our continuing studies on the development of new fluorinated building blocks and their synthetic utility, including nucleophilic modification on the α-carbons.



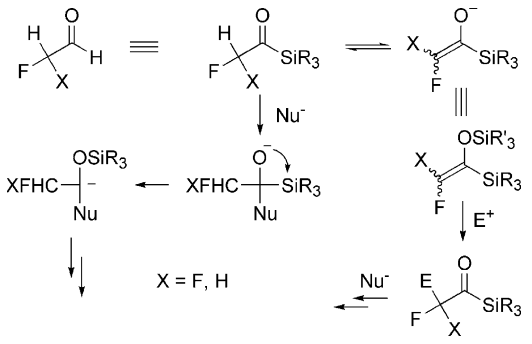
Scheme 1.

Keywords: Fluorinated ketone; Aldol reaction; Lewis acid; Fluorinated silyl enol ether.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.05.055

* Corresponding author. Tel.: +1-518-442-4455; fax: +1-518-442-3462; e-mail: jwelch@uamail.albany.edu

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.05.055

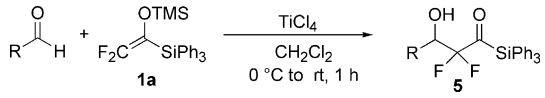


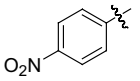
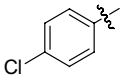
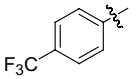
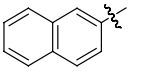
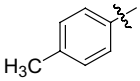
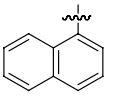
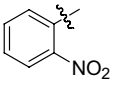
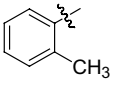
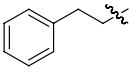
Scheme 2.

Initially the utility of these compounds in the aldol condensation was demonstrated with compound **1** employing benzaldehyde as substrate. The $TiCl_4$ promoted aldol condensation reaction of **1e** at room temperature gave the desired product (either little or no aldol product was obtained at lower temperatures, −78 and 0 °C). Under optimized reaction conditions, various β-hydroxy-α,α-difluorotrialkylsilylketones **4** were synthesized in good yields. The influence of substituents on the 2-trialkylsilyl groups (R) was seemingly limited. In contrast, variation of the substituents on the 2-trialkylsilyloxyl groups (R′) dramatically affected the reactivity. For example, reactions of triphenylsilylenol ether **1f** with $TiCl_4$ and BCl_3 did not give the desired aldol product **4a** even with longer reaction times at room temperature, while the $InCl_3$ promoted reactions of **1f** and **1g** proceeded more slowly than the corresponding trimethylsilylenol ethers but did form **4a** and **4f**, respectively, in good yields (Table 1).

The generality of the reaction of compound **1a** was explored further with various aldehydes. As summarized in Table 2, the desired β-hydroxy-α,α-difluorotriphenylsilylketones **5** were obtained in good yields. As expected, aromatic aldehydes **5a**–**h** gave better yields than aliphatic aldehydes **5i**–**j**. The presence of electron withdrawing groups on the aromatic rings generally resulted in higher yields in contrast to those aromatic moieties with electron donating groups. Aldehydes with

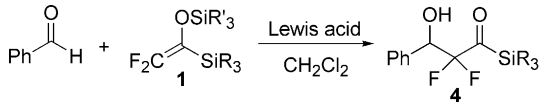
Table 2. Formation of β-hydroxy-α,α-difluorotriphenylsilylketones **5** from **1a** and various aldehydes[12]



5	R	Yield (%)[a]	^{19}F NMR of **5**
5a		84	−109.5 (dd), −119.4 (dd)
5b		80	−110.5 (dd), −119.3 (dd)
5c		82	63.2 (s) −109.8 (dd), −119.6 (dd)
5d		72	−110.3 (dd), −118.5 (dd)
5e		74	−110.0 (dd), −120.2 (dd)
5f		58	107.2 (dd), −121.5 (dd)
5g		68	−106.1(dd), −122.0 (dd)
5h		59	−107.6 (dd), −121.8 (dd)
5i		45	−111.5 (dd), −120.0 (dd)
5j	Et	42	−111.3 (dd), −122.4 (dd)

[a] Isolated yield and characterized by ^{1}H, ^{13}C, and ^{19}F NMR.

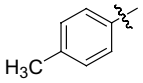
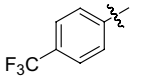
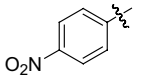
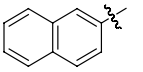
Table 1. Formation of β-hydroxy-α,α-difluorotrialkylsilylketones **4**



1	SiR_3	SiR'_3	Lewis acid	Conditions	4	Yield (%)[a]	^{19}F NMR of **4**
1a	TPS (triphenylsilyl)	TMS	$TiCl_4$	0 °C to rt, 1 h	**4a**	82	−109.6 (dd), −120.4 (dd)
1b	TES (triethylsilyl)	TMS	$TiCl_4$	0 °C to rt, 1 h	**4b**	71	−112.2 (dd), −122.8 (dd)
1c	TBDMS (*t*-butyldimethylsilyl)	TMS	$TiCl_4$	0 °C to rt, 1 h	**4c**	78	−112.4 (dd), −121.2 (dd)
1d	TBDPS (*t*-butyldiphenylsilyl)	TMS	$TiCl_4$	0 °C to rt, 1 h	**4d**	76	−109.6 (dd), −121.2 (dd)
1e	TIPS (triisopropyl)	TMS	$TiCl_4$	0 °C to rt, 1 h	**4e**	75	−110.5 (dd), −123.6 (dd)
1f	TPS	TPS	$InCl_3$	rt, 2 d	**4a**	73	−109.6 (dd), −120.4 (dd)
1g	TMS (trimethylsilyl)	TPS	$InCl_3$	rt, 2 d	**4f**	63	−112.3 (dd), −121.3 (dd)

[a] Isolated yield and characterized by ^{1}H, ^{13}C, and ^{19}F NMR.

Table 3. Aldol reaction of mono-and difluorinated silyl enol ethers **6**, **7**[13]

6, 7	SiR_3	R^2	Lewis acid	Conditions	Yield of 8+9 (%)[a]	^{19}F NMR of 8	^{19}F NMR of 9
6a	TES	Ph	BCl_3	rt, 2 h	44 (**8a+9a**)	−128.0 (dd)	−126.6 (d)
6a	TES		BCl_3	rt, 2 h	37 (**8b+9b**)	−128.0 (dd)	−126.5 (d)
6a	TES		BCl_3	rt, 2 h	41 (**8c+9c**)	−63.3 (s), −128.0 (dd)	−63.6 (s) −126.6 (d)
6a	TES		BCl_3	rt, 2 h	48 (**8d**)	−127.8 (dd)	—
6a	TES		BCl_3	rt, 2 h	66 (**8e+9e**)	−127.9 (dd)	−126.5 (d)
7b	TIPS	Ph	$TiCl_4$	rt, 24 h	57 (**8f+9f**)	−228.4 (t)	−229.2 (t)
7c	TBDPS	Ph	$TiCl_4$	rt, 24 h	47 (**8f+9f**)	−228.4 (t)	−229.2 (t)

[a] Isolated yield and characterized by ^1H, ^{13}C, and ^{19}F NMR.

hetero atom-bearing substituents such as anisaldehyde and dimethylaminobenzaldehyde are not compatible with Lewis acids promoted reaction and gave no aldol product. Products obtained from aromatic aldehydes were solids easily purified by recrystallization in hexane, while aldol products from aliphatic aldehydes were purified by silica gel column chromatography.

The Mukaiyama aldol reaction of di and mono-fluorosilyl enol ethers **6** and **7**,[11] prepared from the corresponding fluoroacetyltrialkylsilanes **2** and **3**, respectively, with dimethylsulfoxonium methylide by means of Brook isomerization, was explored. Results with $TiCl_4$ as Lewis acid (Table 3) showed that those molecules with sterically demanding silyl substituents are remarkably unreactive. Similar results were observed with other Lewis acids such as $TaCl_5$, SbF_5, $BF_3{\cdot}Et_2O$, and TMSOTf. Use of BCl_3 with **6a** gave β-hydroxy ketones **8** as the major products with small amounts of α,β-unsaturated ketones **9**. However, spontaneous dehydration occurred on chromatographic purification forming **9** as the major products. For the mono-fluorinated silyl enol ethers **7**, $TiCl_4$ promoted the aldol reaction. As in the difluoro cases, concomitant dehydration occurred on purification.

In summary, Lewis acid promoted aldol reactions of two different fluorinated silyl enol ethers were studied. Reactions with 1,1-difluoro-2-trialkylsilyl-2-trialkylsilyloxyethenes **1** gave various β-hydroxy-α,α-difluorotrialkylsilylketones **4** and **5** in good to moderate yields. Aldol reactions of compounds **6** and **7** gave β-hydroxy ketones **8** as the major products but dehydration during purification resulted in the formation of α,β-unsaturated ketones **9** except for the nitro-substituted aromatic aldehydes, which gave the aldol product exclusively. Effects of substituents on silyl group showed that reactions with sterically hindered silyl substituents required longer reaction times and careful choice of Lewis acid.

Acknowledgements

Financial support of this work by National Institutes of Health Grant Number AI40972 is gratefully acknowledged.

References and notes

1. (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; (b) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; John Wiley and Sons: New York, 1991; (c) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619; (d) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131.
2. Altenburger, J. M.; Schirlin, D. *Tetrahedron Lett.* **1991**, *32*, 7255.
3. (a) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1; (b) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 2.5.
4. Kodama, Y.; Yamane, H.; Okumura, M.; Shiro, M.; Taguchi, T. *Tetrahedron* **1995**, *51*, 12217.
5. Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271.
6. Yamana, M.; Ishihara, T.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 507.
7. (a) Amii, H.; Kobayashi, T.; Hatamoto, T.; Uneyama, K. *J. Chem. Soc., Chem. Commun.* **1999**, 1323; (b) Uneyama, K.; Amii, H. *J. Fluorine Chem.* **2002**, *114*, 127.

8. (a) Brigaud, T.; Doussot, P.; Portella, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2117; (b) Lefebvre, O.; Brigaud, T.; Portella, C. *J. Org. Chem.* **2001**, *66*, 1941.
9. (a) Jin, F.; Jiang, B.; Hu, Y. *Tetrahedron Lett.* **1992**, *33*, 1221; (b) Jin, F.; Hu, Y.; Huang, W. *J. Chem. Soc., Chem. Commun.* **1993**, 814; (c) Jin, F.; Hu, Y.; Huang, W. *J. Chem. Soc., Perkin Trans.* **1993**, 795.
10. Higashiya, S.; Lim, D. S.; Ngo, S. C.; Toscano, P. J.; Welch, J. T. *Abstract of Paper*, 222nd National Meeting of the American Chemical Society, Chicago, IL, 2001; American Chemical Society: Washington, DC, ORGN 41.
11. Ngo, S. C.; Chung, W. C.; Lim, D. S.; Higashiya, S.; Welch, J. T. *J. Fluorine Chem.* **2002**, *117*, 207.
12. Typical procedure for **4** and **5**: To a mixture of aldehyde (0.8 mmol) and $TiCl_4$ (1 mmol, 189 mg) in 3 mL of dichloromethane was added a solution of compound **1a** (1 mmol, 410 mg) in 2 mL of dichloromethane at 0 °C. The resulting mixture was stirred at room temperature for 1 h. Reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution, and then extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Product **5** was purified by recrystallization in hexane or silica gel column chromatography using a mixture of hexane and ethyl acetate (30:1 v/v).
13. Typical procedure for **8** and **9**: Lewis acid (2 equiv) was added to a solution of the aldehyde in dichloromethane at 0 °C. The silyl enol ethers **6** or **7** were added and the mixture allowed to warm to room temperature. After 2–3 h, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic portions were dried over $MgSO_4$, filtered, and concentrated. Purification via silica gel column chromatography afforded the spectroscopically pure products **8** and **9**.