

Tris(pentafluorophenyl)silyl enol ethers: synthesis and aldol reactions

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Received 20 January 2004; revised 5 March 2004; accepted 16 March 2004

Abstract—Silyl enol ethers bearing three pentafluorophenyl groups at the silicon atom are described. These compounds undergo uncatalyzed aldol reactions with aliphatic, α,β -unsaturated, and aromatic aldehydes. The observed reactivity is analyzed in terms of the Lewis acidity of the silyl fragment.

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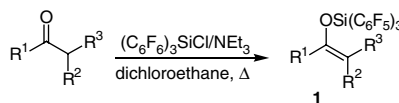
Silyl enol ethers have become popular reagents acting as the equivalents of enolate anions in a variety of processes.¹ However, the nucleophilicity of trialkylsilyl derivatives is not very high,² and for their efficient coupling with electrophiles, the employment of either a Lewis acid³ or fluoride anion⁴ is required.

Significant increase in reactivity can be achieved by using compounds containing a silicon atom capable of expanding its valence shell.⁵ In this case the Lewis acidic silyl group of a reagent may serve as a template bringing together nucleophilic (e.g., enol ether) and electrophilic (e.g., aldehyde) fragments. Such behavior is usually observed when the silicon is either confined within a

small ring⁶ or substituted by heteroatomic substituents (e.g., halogen, alkoxy).^{5,7} At the same time, it would be interesting to consider such species in which the enhanced Lewis acidity is determined by electron-withdrawing carbon-centered functions. In this respect, we decided to investigate the chemistry of silyl enol ethers bearing three pentafluorophenyl groups.⁸ Herein we report their synthesis and application as nucleophiles in aldol reactions.

Silylation of carbonyl compounds with chlorotris(pentafluorophenyl)silane⁹ in the presence of triethylamine occurred in refluxing dichloroethane (Table 1). The desired products **1** were isolated by vacuum distillation.¹⁰

Table 1. Synthesis of tris(pentafluorophenyl)silyl enol ethers



Entry	R ¹	R ²	R ³	Time, h	Product	Yield, %	Bp, °C/Torr	Mp, °C
1	Me	H	H	3	1a	55	127–131/0.4	112–114
2	Ph	H	H	5	1b	77	185–193/0.9	—
3		(CH ₂) ₃	H	4	1c	72	157–163/0.5	77–82
4		(CH ₂) ₄	H	3	1d	42	135–140/0.2	—
5	H	Me	Me	2	1e	73	137–142/0.45	55–60

Keywords: Silyl enol ethers; Silicon Lewis acidity; Aldol reaction.

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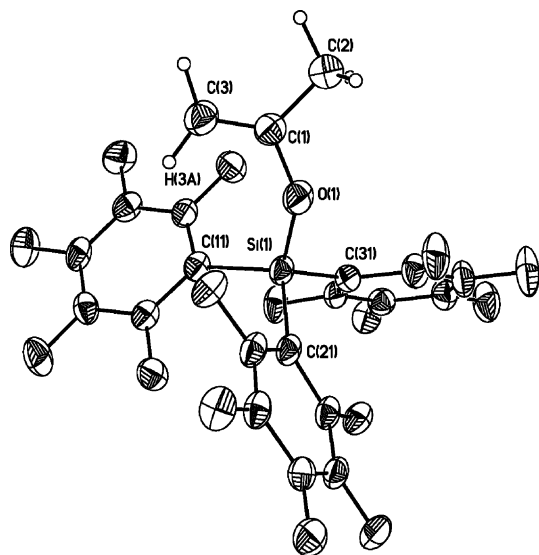


Figure 1. The molecular structure of **1a**. Nonhydrogen atoms are presented by thermal ellipsoids at 50% probability. Selected bonds (Å): Si(1)–O(1) 1.614(2), Si–C (averaged) 1.866 Å, O(1)–C(1) 1.347(3) Å, C(1)–C(2) 1.482(3) Å, C(1)–C(3) 1.314(3) Å; bond angles: O(1)Si(1)C(2) 105.84(9), O(1)Si(1)C(1) 111.92(8), O(1)Si(1)C(3) 107.88(9), C(1)O(1)Si(1) 138.9(1).

The crystal and molecular structure of **1a** was investigated by X-ray diffraction analysis.¹¹ The presence of bulky C₆F₅ substituents did not lead to significant distortion of the tetrahedral configuration of the silicon atom. Si–C bonds as well as O–Si–C and C–Si–C bond angles were close to their standard values.¹² On the other hand, the Si–O bond (1.614 Å) was considerably shorter than that in the structures of conventional trialkylsilyl enol ethers (Si–O bond 1.65–1.67 Å)¹³ a fact, which can be attributed to the influence of the electron-withdrawing C₆F₅ groups. Another feature, originating from the proximity of one of the C₆F₅ groups and the methylene

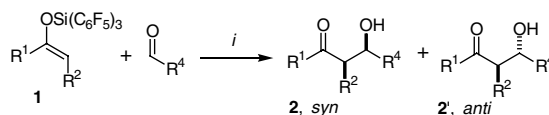
moiety, corresponds to the weak intramolecular C–H π -contact between atoms C(11) and H(3A) with the interatomic distance of 2.85 Å (Fig. 1).^{12b}

It was found that enol ethers **1** were extremely moisture sensitive species, undergoing rapid hydrolysis back to the parent ketones. The ease of hydrolysis may be associated with facile nucleophilic attack of water at the silicon atom. Hence, it can be proposed that the tris(pentafluorophenyl)silyl moiety may have stronger Lewis acidic character in comparison with trialkylsilyl analogues.

Indeed, ethers **1a–d** react with aliphatic, α,β -unsaturated, and aromatic aldehydes at room temperature in dichloromethane without catalyst leading after work-up to β -hydroxy ketones **2** (Table 2).¹⁴ When substrates **1c,d** were employed the aldols were produced as mixtures of *syn* and *anti* isomers with the diastereoselectivities up to 25:1 (entries 8–11). However, under standard conditions no reaction was observed between enol ether **1e** and benzaldehyde. Apparently, in the latter case, the steric hindrance at the nucleophilic terminus prevents the reaction.

It is quite likely that the Lewis acidity of the silicon plays a crucial role in determining the reactivity of ethers **1**. Thus, the mechanism of the aldol coupling may involve complexation between the silicon atom and the carbonyl group followed by carbon–carbon bond formation proceeding either intramolecularly (path **a**) or intermolecularly (path **b**), Scheme 1. Path **a** implies a cyclic six-membered transition state, and from a general point of view is preferable. In addition, the cyclic model is usually encountered in uncatalyzed aldol reactions of silyl enol ethers of other types.^{6b,7b} Nevertheless, the low diastereoselectivities observed in the reactions of **1c,d** with benzaldehyde (Table 2, entries 8 and 10) cast some doubt on the validity of path **a**.¹⁶

Table 2. Reaction of silyl enol ethers **1** with aldehydes

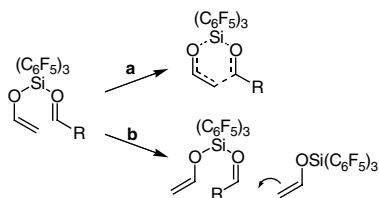


i. (a) CH₂Cl₂, r.t., 72 h, (b) NH₄F/AcOH

Entry	1	R ¹	R ²	R ⁴	Product	Yield, ^a %	<i>syn:anti</i> ^b
1	1a	Me	H	Ph	2a	88	
2	1a	Me	H	<i>p</i> -ClOC ₆ H ₄	2b	86	
3	1a	Me	H	<i>p</i> -MeOC ₆ H ₄	2c	82	
4	1a	Me	H	<i>E</i> -MeCH=CH	2d	88	
5	1a	Me	H	<i>E</i> -PhCH=CH	2e	92	
6	1b	Ph	H	Ph	2f	71	
7	1b	Ph	H	<i>i</i> -Pr	2g	93	
8	1c	(CH ₂) ₃	Ph	Ph	2h	91	1:1.6
9	1c	(CH ₂) ₃	<i>i</i> -Pr	Ph	2i	83	1:25
10	1d	(CH ₂) ₄	Ph	Ph	2j	72	1.8:1
11	1d	(CH ₂) ₄	<i>i</i> -Pr	Ph	2k	71	1:3.4

^a Isolated yield.

^b Determined by NMR analysis of crude reaction mixtures. Assignment of configuration was made by comparison with literature data.¹⁵



Scheme 1. Possible mechanisms of the aldol reaction.

In summary, enol ethers with new silyl fragments have been prepared. The presence of three electron-withdrawing pentafluorophenyl substituents imparts Lewis acidity to these species that is reflected in their reactivity toward aldehydes. Our further investigations will be aimed at understanding the exact mechanism of the observed aldol reaction, as well as at elaboration of the chemistry of other tris(pentafluorophenyl)silyl derivatives.

Acknowledgements

This work was performed at the Scientific educational center for young chemists and supported by the Ministry of Science (project MK-2352.2003.03), Russian Foundation for Basic Research (project # 00-15-97359), and INTAS (project # 2003-55-1185). We also thank Prof. S. L. Ioffe for start-up funding and Prof. Yu. I. Baukov and Dr. V. M. Danilenko for helpful discussions.

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10. General procedure: Under an argon atmosphere to solid chlorotris(pentafluorophenyl)silane⁹ (6.7 mmol) were successively added dichloroethane (6.4 mL), triethylamine (1.25 mL, 9.0 mmol), and the carbonyl compound (6.4 mmol). The mixture was heated under reflux for the time indicated in Table 1, concentrated under vacuum, diluted with 20 mL of dry hexane, filtered under argon, and the solid residue washed with 5 mL of hexane. The combined hexane solution was concentrated, and the residue was fractionally distilled.

1a: ¹H NMR (CDCl₃), δ: 1.89 (s, 3H, Me), 4.05 (s, 1H), 4.20 (s, 1H) (CH₂). ¹³C, δ: 21.2 (Me), 93.6 (CH₂), 104.5 (t, ²J_{C-F} = 27.4, C_i-C₆F₅), 137.5 (dm, ¹J_{C-F} = 255, CF), 144.1 (dm, ¹J_{C-F} = 259, CF), 149.2 (dm, ¹J_{C-F} = 244, CF), 153.8 (CO). ¹⁹F, δ: -161.3 (m, *meta*), -147.9 (tt, J_{F-F} = 6.8, 18.1, *para*), -128.5 (d, J_{F-F} = 18.1, *ortho*). ²⁹Si, INEPT from H, δ: -37.44. Anal. Calcd for C₂₁H₅F₁₅OSi: C, 43.02; H, 0.86. Found: C, 42.95; H, 0.92.

1b: ¹H NMR (CDCl₃), δ: 4.61 (d, 1H, J = 2.8), 5.14 (d, 1H, J = 2.8) (CH₂), 7.37–7.46 (m, 3H), 7.67–7.77 (m, 2H) (Ph). ¹³C, δ: 93.4 (CH₂), 104.7 (t, ²J_{C-F} = 26.9, C_i-C₆F₅), 125.4, 128.2 (*o*-, *m*-CH_{Ph}), 128.6 (*p*-CH_{Ph}), 135.8 (C_i-Ph), 138.0 (dm, ¹J_{C-F} = 255, CF), 144.7 (dm, ¹J_{C-F} = 259, CF), 149.7 (dm, ¹J_{C-F} = 246, CF), 154.9 (CO). ¹⁹F, δ: -161.3 (m, *meta*), -147.8 (tt, J_{F-F} = 4.5, 20.4, *para*), -128.0 (d, J_{F-F} = 20.4, *ortho*). ²⁹Si, INEPT from H, δ: -34.40. The compound was contaminated with 5% of ((C₆F₅)₃Si)₂O, which is only visible in the ¹⁹F spectra (-161.0, *meta*; -146.7, *para*, -127.9 *ortho*).

1c: ¹H NMR (CDCl₃), δ: 1.82–1.96 (m, 2H), 2.18–2.29 (m, 2H), 2.31–2.41 (m, 2H) (CH₂)₃, 4.66 (br s, 1H, CH). ¹³C, δ: 21.3, 28.5, 32.5 (CH₂)₃, 104.6 (t, ²J_{C-F} = 27.4, C_i-C₆F₅), 105.7 (CH=), 137.7 (dm, ¹J_{C-F} = 255, CF), 144.4 (dm, ¹J_{C-F} = 259, CF), 149.5 (dm, ¹J_{C-F} = 248, CF), 152.3 (CO). ¹⁹F, δ: -161.1 (m, *meta*), -147.7 (t, J_{F-F} = 20.0, *para*), -128.4 (d, J_{F-F} = 20.0, *ortho*). Anal. Calcd for C₂₃H₇F₁₅OSi: C, 45.11; H, 1.15. Found: C, 44.88; H, 1.11.

1d: ¹H NMR (CDCl₃), δ: 1.43–1.56 (m, 2H), 1.61–1.75 (m, 2H), 1.90–2.01 (m, 2H), 2.05–2.17 (m, 2H) (CH₂)₄, 4.90 (t, 1H, J = 3.9, CH), ¹³C, δ: 21.9, 22.9, 23.7, 28.8 (CH₂)₄, 105.1 (t, ²J_{C-F} = 28.3, C_i-C₆F₅), 106.8 (CH=), 137.7 (dm, ¹J_{C-F} = 255, CF), 144.2 (dm, ¹J_{C-F} = 259, CF), 149.3 (CO), 149.7 (dm, ¹J_{C-F} = 247, CF). ¹⁹F, δ: -161.7 (m, *meta*), -148.4 (tt, J_{F-F} = 4.5, 20.0, *para*), -128.4 (d, J_{F-F} = 20.0, *ortho*). ²⁹Si, INEPT from H, δ: -37.93. The compound contained 10% of ((C₆F₅)₃Si)₂O along with ca. 7% of other unidentified impurities.

1e: ¹H NMR (CDCl₃), δ: 1.59 (s, 3H, Me), 1.69 (s, 3H, Me), 6.12 (s, 1H, CH). ¹³C, δ: 14.7, 18.8 (CMe₂), 104.5 (t, ²J_{C-F} = 28.4, C_i-C₆F₅), 118.8 (CMe₂), 120.1 (CH), 137.9 (dm, ¹J_{C-F} = 254, CF), 144.7 (dm, ¹J_{C-F} = 260, CF), 149.5 (dm, ¹J_{C-F} = 247, CF). ¹⁹F, δ: -161.3 (m, *meta*), -147.8 (tt, J_{F-F} = 4.5, 20.4, *para*), -128.6 (d, J_{F-F} = 20.4, *ortho*). ²⁹Si, INEPT from H, δ: -34.42. Anal. Calcd for C₂₂H₇F₁₅OSi: C, 44.01; H, 1.18. Found: C, 44.15; H, 1.03.

- Crystallographic data for **1a**: Crystals of C₂₁H₅F₁₅OSi at 120 K are monoclinic, space group C2/c, a = 18.6179(16) Å, b = 11.5282(9) Å, c = 20.9796(18) Å, V = 4158.4(6) Å³, Z = 8, M = 586.34, d_{calc} = 1.873 g cm⁻³, μ(MoKα) = 2.62 cm⁻¹, F(000) = 2304; 23474 reflections were collected; 5980 reflections were unique. R₁ = 0.0497 was calculated for 3256 observed reflections with I > 2σ(I). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 229201) and are available free of charge at CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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14. General procedure: The aldehyde (1.05 mmol) was added to a solution of **1** (1 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred for 72 h at room temperature, cooled with an ice/water bath, and quenched with a solution of NH₄F (56 mg, 1.5 mmol) and AcOH (114 μL, 2 mmol) in MeOH/water (1 mL/0.2 mL). The cooling bath was removed, the mixture stirred at room temperature for 30 min, diluted with excess ether, filtered through a glass filter, concentrated under vacuum, and purified by flash chromatography on silica gel using hexane/ethyl acetate.
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