Aldol Reactions of Acylsilanes and Difluoroenoxysilanes. Application to the Synthesis of 2-Fluoro-1,3-diketones[1]

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Received 1 December 1998

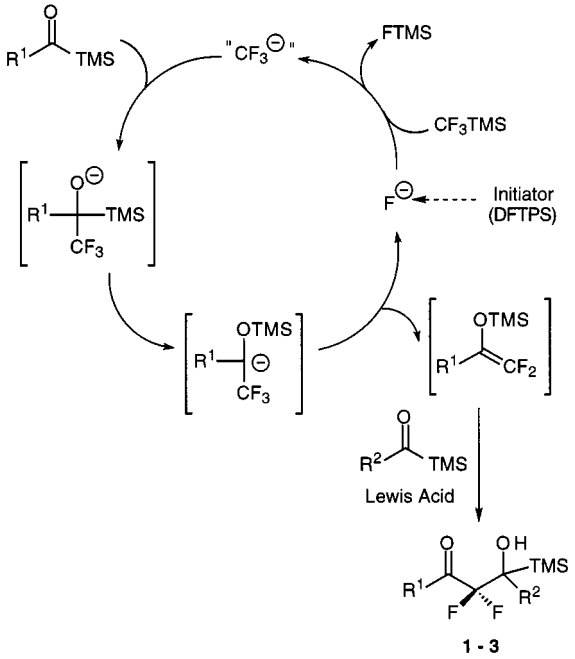
Abstract: We describe the synthesis of new *gem*-difluoro-C-silylated aldols from acylsilanes and trifluoromethyltrimethylsilane via an aldol reaction. Their defluorosilylation gives aliphatic and alicyclic 2-fluoro-1,3-diketones. The overall reaction sequence can be considered as a new complementary method giving access to a wide variety of such fluorinated 1,3-diketones.

Key words: acylsilane, difluoroenoxysilane, aldol reaction, 1,3-diketone

The trifluoromethyltrimethylsilane (TFMTMS)-acylsilane system is a convenient source of difluoroenoxysilanes.[2,3] These enoxysilanes may be trapped *in situ* with various types of electrophilic substrates to give *gem*-difluoro compounds. In our preliminary account[2a] we mentioned the trapping of an enoxysilane with benzaldehyde in a Mukaiyama aldol reaction. This paper is devoted to the aldol reaction of difluoro-enoxysilanes with acylsilanes and the transformation of the corresponding C-silylated aldols into 2-fluoro-1,3-diketones. Extension of these reactions to 1,5-bis-acylsilanes and then to cyclic 2-fluoro-1,3-diketones is also reported.

The general one-pot methodology depicted in Scheme 1 was applied.[4] In a first experiment, two equivalents of benzoylsilane were reacted in dichloromethane with TFMTMS and a catalytic amount of tetrabutyl-ammonium difluorotriphenylstannate (DFTPS) as the initiator.[2] To the difluoroenoxysilane generated *in situ* was added boron trifluoride etherate in order to activate the benzoylsilane in excess and to induce the aldol reaction. The expected aldol **1** was isolated in 57 % yield (Scheme 1, Table 1: entry 1).

The same one-pot methodology[4] was successfully applied to one equivalent of acylsilane with, in the second step, addition of a second different acylsilane. Among several Lewis acids tested, good results were obtained with boron trifluoride (excess) or bismuth trichloride (catalytic amount) (Table 1). It is important to notice that the yields refer to the overal one-pot process and are determined from the starting acylsilane. As pointed out previously,[2a] the choice of DFTPS as fluoride initiator is crucial to avoid self-condensation of the difluoroenoxysilane, which was observed with TBAF and can sometimes occur as a minor side reaction with DFTPS especially after a long storage of the reagent.



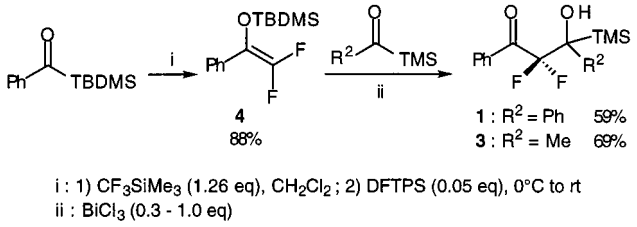
Scheme 1

Table 1. Reactions of difluoroenoxysilanes with acylsilanes.

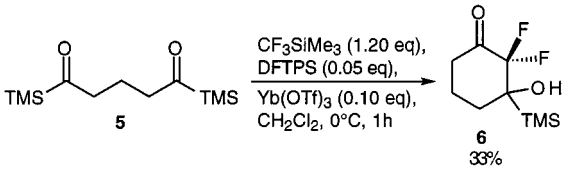
Entry	R^1	R^2	Lewis Acid (eq)	Aldols	Yield (%)
1	Ph	Ph	$BF_3.OEt_2$ (2.8)	**1**	57
2	Me	Ph	$BF_3.OEt_2$ (1.4)	**2**	58
3	Ph	Me	$BiCl_3$ (0.3)	**3**[5]	41

In order to evaluate the effectiveness of the aldol step, we carried out the reaction on the isolated 1-*tert*-butyldimethylsilyloxy-1-phenyldifluoroethene **4**,[2a] whose preparation was optimized (88% yield). This difluoroenoxysilane was then treated with benzoyl- or acetyl-trimethysilane under bismuth trichloride activation, leading to the corresponding C-silyl aldols **1** and **3** in 59% and 69% yields, respectively (Scheme 2). Hence the one-pot process is a valuable methodology for the syntheses of such aldols.

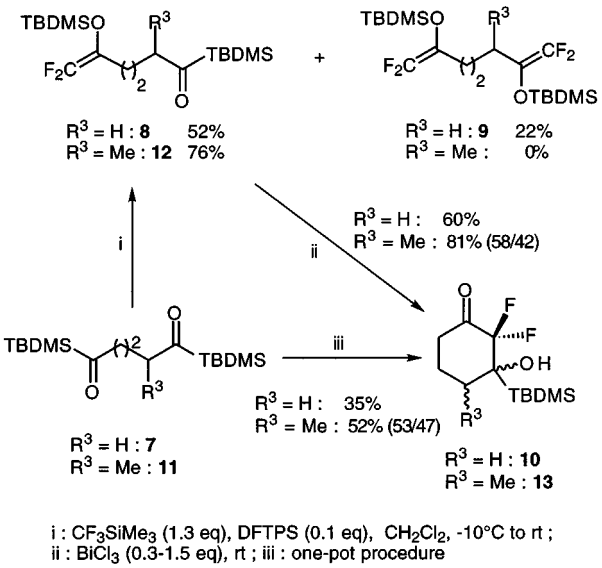
It was interesting to extend these reactions to 1,5-bis-acylsilanes.[6] Our aim was to build a difluoroenoxysilane from one acylsilane function and to induce an intramolecular aldol reaction in a second step. The first experiment was carried out with the bis-acylsilane **5**.[6] Application of a one-pot methodology allowed the isolation of the expected cyclic aldol **6** in 33 % yield (Scheme 3). The latter was



Scheme 2



Scheme 3



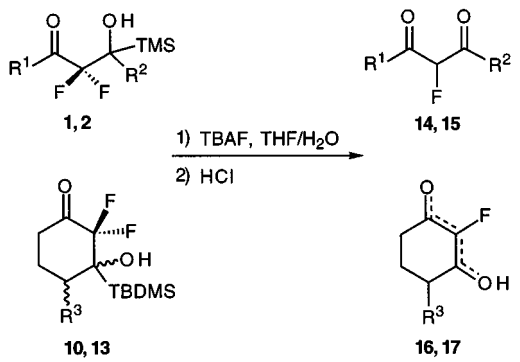
Scheme 4

separated from several other products among which was identified the 2,6-bis-trimethylsilyl-4H-pyrane coming from the cyclodehydration of the starting bis-acylsilane.[6] Obviously some other by-products came from double addition in the first step.

A two-step procedure would make the intramolecular aldol reaction more effective (Scheme 4). The *tert*-butylated bis-acylsilane **7**[6] was treated under fluoride initiation with 1.3 equivalents of TFMTMS to give the expected mono difluoroenoxysilane **8** as the major product (52%) and the bis difluoroenoxysilane **9** (22%) which were separated by silica gel chromatography. Bismuth trichloride was added to a dichloromethane solution of compound **8** and the mixture was stirred overnight at room temperature. After the usual work-up,[4] the C-silyl cycloaldol **10**[7] was isolated in 60 % yield. The same compound was obtained in 35% yield using the one-pot procedure (Scheme 4). We felt that the modification of one of the two carbonyl groups should allow a higher selectivity for monoaddition in the first step. The 2-methyl-1,5-bis-acylsilane **11**[6] was submitted to the same one-pot or two-step procedure (Scheme 4). The addition of the trifluoromethyl group proved to be completely regioselective on the less hindered carbonyl group, leading to a single difluoroenoxysilane **12** (76%) besides the unreacted starting material **11** (11%). The bismuth trichloride activation gave the cycloaldol **13** in 81% yield (mixture of diastereomers 58/42).

The structure of the minor diastereomer of **13** was determined by X-ray diffraction analysis[8] and presented the TBDMS and the methyl groups in a cis relationship. Owing to the higher selectivity of the first step, the one-pot procedure allowed to directly synthesize the compound **13** in fairly good yield (52%) (Scheme 4).

These inter- or intramolecular aldol reactions constitute an original route towards *gem*-difluoro functionalized compounds including vicinal silicon and fluorine. We then anticipated that an elimination of fluoro-trialkylsilane should be a thermodynamically favorable transformation owing to the formation of both a silicon-fluorine bond and a 1,3-diketone system. Such an elimination might be induced either by an initial deprotonation of the hydroxyl group followed by silicon migration and fluoride β-elimination, or by an initial nucleophilic attack on silicon. The aldols **1** and **2** were treated with tetrabutylammonium fluoride (TBAF) in a THF/H_2O mixture to yield the corresponding 2-fluoro-1,3-diketones[9] **14**[10] and **15**[10] (Scheme 5, Table 2). The cyclic aldols **10** and **13** were also converted into 2-fluoro-3-hydroxy-cyclohexen-2-ones **16**[11] and **17** in 68% and 80% yields. The acyclic 2-fluoro-1,3-diketones **14** and **15** exist mainly as the keto tautomers, while the cyclic derivatives **16** and **17** are almost completely enolic. This phenomenon has already been observed and discussed in the literature.[10] Whether fluoride acts as a base or a nucleophile in this reaction remain undetermined. We did not observe any O-silylated compound derived from a Brook rearrangement of a possible aldolate intermediate, which do not exclude its occurrence owing to the expected easy β-elimination of fluoride.



Scheme 5

Table 2. Preparation of 2-fluoro-1,3-diketones.

Entry	Aldols	R^1	R^2	R^3	Diketones or enols	Yield (%)
1	**1**	Ph	Ph	-	**14**	56
2	**2**	Me	Ph	-	**15**	50
3	**10**	-	-	H	**16**	68
4	**13**	-	-	Me	**17**	80

Some 2-fluoro-1,3-diketones have already been reported. In general, they have been prepared by electrophilic fluorination of diketones or silyl enol ethers, using molecular fluorine[10-12] or electrophilic fluorine donor reagents.[13]

In conclusion, the synthesis of a new class of *gem*-difluoro-C-silylated aldols, in both aliphatic and alicyclic series, is described. They can be defluoro-silylated under fluoride treatment. The overall reaction sequence can be considered as a complementary method giving access to a variety of 2-fluoro-1,3-diketones, a type of compounds so far prepared by demanding procedures and expensive reagents.

Acknowledgement

The authors thank Dr. B. Tinant and J. -P. Declercq for X-ray diffraction analysis and Bayer A.G. for a generous gift of CF_3SiMe_3.

References and Notes

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(4) *Typical one-pot procedure for the synthesis of aldol* **3:** To a solution of benzoyltrimethylsilane (1.50 mmol) and trifluoromethyltrimethylsilane (0.30 mL, 1.89 mmol) in CH_2Cl_2 (5 mL) under argon, at 0°C, was added a catalytic amount of tetrabutyl-ammonium difluorotriphenylstannate (DFTPS, 54 mg, 0.075 mmol). After 5 min at 0°C, the reaction mixture was stirred for 30 min at room temperature. The formation of the difluoroenoxysilane was monitored by GC. Acetyltrimethylsilane (0.26 mL, 1.80 mmol) and $BiCl_3$ (142 mg, 0.45 mmol) were then added and the reaction mixture was stirred until total conversion (GC). The reaction was quenched by addition of a saturated $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: ether/petroleum ether).

(5) Spectral data for aldol **3**: IR (film, cm^{-1}): 3488, 1680. ^{19}F-NMR ($CDCl_3/CFCl_3$, 235.4 MHz, *J* / Hz) δ -101.4 (d, $^2J_{FF}$ 288, 1F), -103.5 (d, $^2J_{FF}$ 288, 1F). ^{1}H-NMR ($CDCl_3$, 250 MHz, *J* / Hz) δ 0.20 (s, 9H, $SiMe_3$), 1.43 (m, 3H, CH_3), 2.63 (s, 1H, OH), 7.45 (t, 2H, $^3J_{HH}$ 7.3, aromatic), 7.61 (t, 1H, $^3J_{HH}$ 7.3, aromatic), 8.11 (d, 2H, $^3J_{HH}$ 7.3, aromatic). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, *J* / Hz) δ -2.8 (s, $SiMe_3$), 19.4 (dd, $^3J_{CF}$ 7.5, $^3J_{CF}$ 3.8, CH_3), 69.7 (t, $^2J_{CF}$ 31.6, C_4), 120.3 (t, $^1J_{CF}$ 257.6, CF_2), 128.5, 130.3, 133.5, 134.2, 192.0 (t, $^2J_{CF}$ 33.4, CO).

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(7) Spectral data for aldol **10**: IR (KBr, cm^{-1}): 3470, 1751. ^{19}F-NMR ($CDCl_3/CFCl_3$, 235.4 MHz, *J* / Hz) δ -106.7 (d, $^2J_{FF}$ 252, 1F), -123.2 (d, $^2J_{FF}$ 252, 1F). ^{1}H-NMR ($CDCl_3$, 250 MHz, *J* / Hz) δ 0.15 (s, 6H, $SiMe_2$), 1.01 (s, 9H, Si^{t}Bu), 1.67 (s, 1H, OH), 1.8-2.4 (m, 4H, $CH_2CH_2CH_2CO$), 2.7 (m, 2H, $CH_2CH_2CH_2CO$). ^{13}C-NMR ($CDCl_3$, 62.9 MHz, *J* / Hz) δ -6.6 (s, SiMe), -6.5 (s, SiMe), 18.1 (s, C_4), 20.6 (s, CH_2), 27.3 (s, ^{t}Bu), 31.0 (d, $^3J_{CF}$ 6.9, CH_2), 38.6 (s, CH_2), 75.2 (t, $^2J_{CF}$ 33.5, C_4), 117.1 (t, $^1J_{CF}$ 256.0, CF_2), 199.5 (t, $^2J_{CF}$ 27.6, CO).

(8) Selected data for X-ray diffraction analysis of the minor diastereomer of **13**: $C_{13}H_{24}F_2O_2Si$, M = 278.41, monoclinic, space group P21/c, a = 12.132(4) Å, b = 9.182(3) Å, c = 14.022(4) Å, β = 99.76(3)°, V = 1539.4(8) Å^3, Z = 4. Atomic coordinates, bond lengths and bond angles were deposited at the Cambridge Crystallographic Data Centre.

(9) *Typical procedure for the preparation of 2-fluoro-1,3-diketones* **14 - 17:** To a solution of aldol (2.0 mmol) in THF (25 mL) was added tetrabutylammonium fluoride (TBAF) (631 mg, 2.0 mmol). After stirring at room temperature until total conversion, the reaction was quenched by addition of HCl (1M, 10 mL) for the aliphatic diketones **14** and **15** or by addition of a saturated HCl/THF solution (50 ml) for the alicyclic diketones **16** and **17**. After extraction with ether (4 x 15 mL) and drying over $MgSO_4$ (for **14** and **15**), the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silicagel (eluent: AcOEt/petroleum ether).

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