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Preparation and synthetic application of methyl β,β-difluoro-α-trimethylsilyloxyacrylate: a fluoride ion-promoted desilylative-defluorination route

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Abstract—Catalytic amount of TBAT (0.2 mol %) promoted desilylation and subsequent defluorination of ketene silyl acetal of methyl *O*-trimethylsilyltrifluorolactate, affording methyl β,β-difluoro-α-trimethylsilyloxyacrylate in 95% yield of which reaction with electrophiles provided methyl β-substituted-β,β-difluoropyruvate in good yields.
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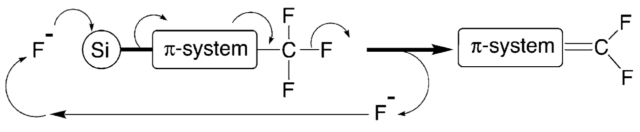
Desilylative-defluorination is a concept feasible for environmentally benign synthesis of difluorinated compounds. There have been several reported examples; difluorocyclopropanation by the use of trimethylsilyl fluorosulfonyldifluoroacetate, a versatile difluorocarbene source,[1] 1,6-desilylative-defluorination of (1′,1′,4′,4′,4′-pentafluoro-1′-trimethylsilyl)-1,4-xylene leading to 1′,1′,4′,4′-tetrafluoro-1,4-quinodimethane, a precursor of AF4 polymer[2] (intramolecular version),[3] and transformation of acylsilanes to β,β-difluoroenol silyl ethers[4] by trifluoromethylation with trifluoromethylsilane via Brook type rearrangement of α-silyl-α-trifluoromethyl-*tert*-alcoholates. In these desilylative-defluorination reaction system, a catalytic amount of fluoride ion catalyzes at first desilylation and subsequently induces defluorination from a trifluoromethyl group, leading to the formation of difluoromethylene moiety and at the same time regenerating fluoride ion which can be recycled (Scheme 1). An application of the concept to the synthesis of methyl β,β-difluoro-α-trimethylsilyloxyacrylate **3**, a promising precursor for β-substituted-β,β-difluoropyruvates, functionalized difluoromethyl building blocks is useful in particular since β,β-difluoroacrylates such as **3** are so base- and/or nucleophile-sensitive that they undergo further reactions in the presence of a large amount of base and/or nucleophile.



Scheme 1.

Because of the utility of difluoropyruvate derivatives, two syntheses have been reported. Shi et al. prepared **3** via three steps in total yields of 60% starting from methyl pyruvate; chloro-benzyloxylation, metal-Zn reductive dechloro-defluorination, and replacement of BnO group with $OSiMe_3$ group by the use of trimethylsilyl iodide.[5] Burger et al. prepared enol **6** via three steps process in total yields of 42–57% starting from methyl trifluorolactate **4** (Scheme 2).[6]

Designing the preparation of enol silyl ether **3** on the basis of the desilylative-defluorination concept (Scheme 1), we describe here a novel preparation of **3** and its transformation to methyl β-substituted-β,β-difluoropyruvates **8** (Scheme 3).

Ketene silyl acetal **7** was prepared in 82% yield by metal magnesium reduction of methyl pyruvate **1** in THF–TMSCl system.[7] After a systematic survey of the reaction conditions such as fluorides, solvents and reaction temperature, it has come to a conclusion that the use of a very trace amount of TBAT (tetrabutyl ammonium

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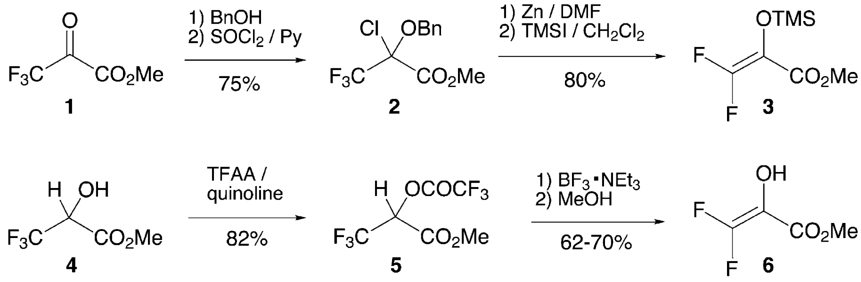
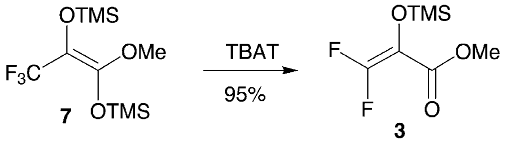


Scheme 2.



Scheme 3.

triphenyldifluorosilicate) in THF provided the desired compound **3** in an excellent yield (TBAT = 0.2 mol %, 1.0 M of **7** in THF, 0 °C for 10 min, 95% yield).[8,9] This experimental result clearly demonstrates the perfect recycle of fluoride ion in this desilylative-defluorination reaction. The use of a larger amount of TBAT made the products somewhat complicated presumably due to the attack of fluoride ion to β-position of **3** which is active to the nucleophilic attack.[10] Interestingly, desilylation occurs chemoselectively at the *O*-silyl group attached to the acetal site rather than that attached to the carbon-2 due to the facile formation of the more stable carbanion intermediate **A** than the formation of the less stable **B** (Fig. 1).[11]

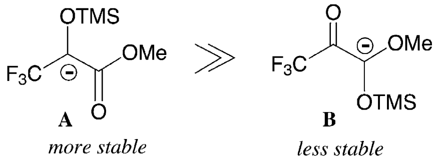


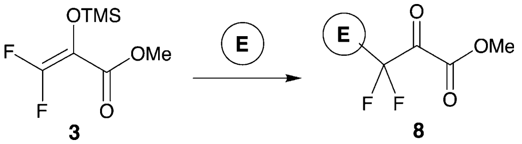
Figure 1. Relative stability of compounds **A** and **B**.

Difluoroenol silyl ether **3** reacts with a variety of electrophiles at the difluoromethylene site, affording the β-substituted-β,β-difluoropyruvates **8**, a new class of substituted difluoropyruvates. Thus, bromination, sulfenylation and selenenylation proceeded smoothly under the very mild conditions to give β-bromo, β-phenylsulfenyl, and β-phenylselenenyl-β,β-difluoropyruvates **8** in 64, 80, and 87% yields, respectively.

Carbon–carbon bond formation at the β-carbon of **3** is also possible. Carbocations from iminium cation, diphenylmethanol, and benzaldehyde dimethyl acetal were chosen for the purpose, since aldehydes and ketones were found to be less reactive electrophiles in the present electrophilic reactions of **3** due to the deactivation of β-position by carbomethoxyl group. *N*,*N*-Dimethyliminium chloride generated in situ from 1,1-bis(*N*,*N*-dimethylamino)-toluene reacted with **3**, affording **8d**, β,β-difluorinated-γ-amino ester in 73% yield.

Diphenylmethylation of **3** with diphenylmethyl alcohol under the solvolytic conditions provided the desired adduct **8e** in 54% yield. Lewis acid-catalyzed Friedel–Crafts reaction of **3** with benzaldehyde dimethyl acetal gave **8f** in 55% yield (Table 1).

Table 1. Products and yields of **8** in the reaction of **3** with electrophiles



Entry	Electrophile	Reaction conditions		Ⓔ[a]	Yield[b] (%)
1	Br_2	CH_2Cl_2, −30 °C, 3 h	**8a**	Br	64
2	PhSCl	DMF, RT, 3 h	**8b**	PhS	80
3	PhSeCl	DMF, RT, 3 h	**8c**	PhSe	87
4	$[PhCH{=}NMe_2]^+Cl^-$	DMF, 50 °C, 5 h	**8d**	$PhCH(NMe_2)$	73
5	$Ar_2CH(OH)$[c]	TMSOTf (0.2 mol equiv) CH_2Cl_2, 0 °C, 12 h	**8e**	Ar_2CH	54
6	$PhCH(OMe)_2$	BF_3–ether (1.0 mol equiv) CH_2Cl_2, RT, 7 h	**8f**	PhCH(OMe)	55

[a] Substituent E in product **8**.

[b] Isolated yields.

[c] Ar = 4-$MeOC_6H_4$.

Acknowledgements

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7. Takigawa, G.; Katagiri, T.; Uneyama, K. *J. Org. Chem.* **2005**, *70*, 8811–8816.
8. The use of KF (0.2 mol %) in THF was effective, but it required a rather higher temperature and a longer reaction time (50 °C for 10 h). The use of TBAF was useless for the purpose. The base provided mainly *O*-TMS trifluorolactate presumably due to the protonation of enolate intermediate from **7** with moisture involved in TBAF.
9. The spectroscopic data of **3** were consistent with those reported.[4]
10. For instance, the use of 10 mol % of TBAT made the reaction complete within 10 min and only 3% of **3** and a number of small peaks were observed in ^{19}F NMR: Some reactions of difluoroalkenes with nucleophiles: (a) Huang, X.-H.; He, P.-Y.; Shi, G.-Q. *J. Org. Chem.* **2000**, *65*, 627–629; (b) Ichikawa, J.; Kobayashi, M.; Yokota, N.; Noda, Y.; Minami, T. *Tetrahedron* **1994**, *40*, 11637–11646; (c) Shi, G.-Q.; Zhao, Z.-Y.; Zang, X.-Y. *J. Org. Chem.* **1995**, *60*, 6608–6611.
11. Carbanion **A** is more stable than **B**.