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Methyl 3,3-difluoro-2-trimethylsilyloxyacrylate: preparation and Mukaiyama-type aldol condensation as a novel route to β,β-difluoro-α-keto ester derivatives

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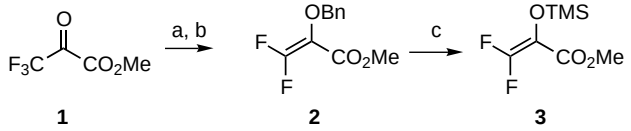
Abstract—Mukaiyama-type aldol condensation of arylaldehyde acetals occurs smoothly with methyl 3,3-difluoro-2-trimethylsilyloxyacrylate (derived from ethyl 3,3-difluoro-2-benzoylacrylate) when catalyzed by a Lewis acid, allowing preparation of 4-alkyloxy-3,3-difluoro-2-keto esters in high yields. © 2002 Elsevier Science Ltd. All rights reserved.

The introduction of a fluorine atom into organic compounds may bring about significant biological consequences.[1] In the amino acid and peptide fields, particular interest has been attracted by fluorinated amino acids, which can function as highly selective and potent inhibitors of pyridoxyl phosphate-dependent enzymes via a suicide-type mechanism.[2] Therefore, they have received considerable attention from both mechanistic and synthetic viewpoints.

β,β-Difluoro-α-keto acids are particularly valuable precursors of the corresponding β,β-difluoro-α-amino acids, which are of great interest in the design of potential enzyme inhibitors and therapeutic agents. There are only two methods known for the synthesis of β,β-difluoro-α-keto acids. The first involves the direct fluorination of di-*tert*-butyl oxaloacetate with $FClO_3$ for the preparation of di-*tert*-butyl difluorooxaloacetate.[3] The alternative method of preparing unsaturated β,β-difluoro-α-keto acids by the Claisen rearrangement of allyl-substituted difluoroenol pyruvyl ethers has also been of limited utility due to the fact that the reaction cannot be tolerated by many functional groups.[4]

Therefore, it is important to develop more effective and efficient methods for preparing β,β-difluoro-α-keto acids. To accomplish this goal, we focused our attention on the development of a reagent that uses readily available fluorinated starting materials as the fluorine source.[5] Here we report the use of a novel β,β-difluoro-α-keto acid synthon (methyl β,β-difluoro-α-trimethylsiloxyacrylate) and a Lewis acid to catalyse the Mukaiyama-type aldol condensation of arylaldehyde acetals for the preparation of β,β-difluoro-α-keto acid derivatives.

In a previous paper we reported the development of an efficient method for the synthesis of 2-benzyloxy-3,3-difluoropropenoate by means of dechlorofluorination of an α-chloro-β,β,β-trifluoroacetyl ester, which is easily prepared from the readily obtainable methyl trifluoropyruvate **1**.[6] A strategy based on the utilization of this difluoropropenoate for the preparation of β,β-difluoro-α-trimethylsiloxyacrylates was initiated. We found that heating methyl 2-benzyloxy-3,3-difluoropropenate **2** with 1 equiv. of trimethylsilyl iodide in dichloromethane resulted in the production of methyl 3,3-difluoro-2-trimethyl siloxyacrylate **3** (bp 52–54°C) in 92% yield.[7] It is worth noting that **3** can be stored without decomposition at room temperature (Scheme 1).



1 **2** **3**

Scheme 1. *Reagents and conditions*: (a) benzyl alcohol/$SOCl_2$/pyridine, 0°C, 75%; (b) Zn/DMF, 87%; (c) TMSI/CH_2Cl_2, reflux, 92%.

Keywords: Mukaiyama-type aldol condensation; Lewis acid; fluorosiloxyacrylate; fluoro-keto-ester.

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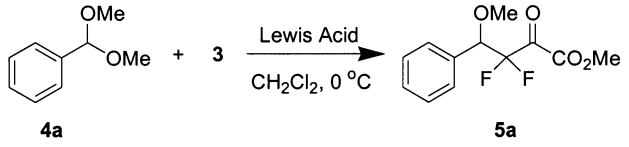
Mukaiyama-type aldol condensation is probably the most important reaction of silyl enol ethers for the formation of carbon–carbon bonds.[8] A preliminary study of the reaction was aimed at determining the capacity of **3** for the Mukaiyama-type condensation with aldehydes, promoted by a Lewis acid. Unfortunately, when **3** was treated with an aldehyde in the presence of various Lewis acids, the aldol condensation failed. We then tested the reaction with acetals instead of aldehydes. When benzaldehyde dimethylacetal **4a** was treated with **3** in the presence of $BF_3{\cdot}Et_2O$ as the catalyst at 0°C, a facile Mukaiyama-type aldol condensation occurred, resulting in the expected β,β-difluoro-α-keto ester **5a** (Scheme 2).

The Mukaiyama-type aldol condensation of the silyl enol **3** with acetal **4a** was studied under the influence of Lewis acids in dichloromethane (Table 1). Conventional Lewis acids such as $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}OEt$ were effective and afforded the adduct **5a** in high yields, however, equimolar amounts of the Lewis acid were required. For example, the Mukaiyama-type aldol condensation of **3** with **4a** under the influence of 0.5 equiv. of $BF_3{\cdot}Et_2O$ afforded **5a** in only 35% yield. It has been reported that trimethylsilyl triflate (TMSOTf) mediates many aldol-type condensations of silyl enol ethers and acetals, especially reactions of relatively non-nucleophilic enol derivatives with carbonyl compounds.[9] Trimethylsilyl triflate efficiently promoted the aldol-type reaction of **4a** in high yield, and only required 0.02 equiv. of the catalyst and gave the same yield of adduct as with an equimolar amount of $BF_3{\cdot}Et_2O$.



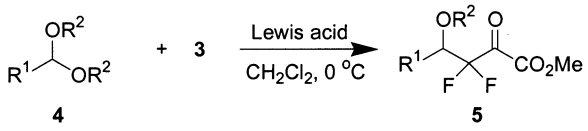
Scheme 2.

Table 1. Effect of Lewis acid

Entry	Lewis acid	Equiv.	Yields (%)
1	$TiCl_4$	0.5	10
2	$TiCl_4$	1.0	61
3	$BF_3{\cdot}OEt_2$	0.5	35
4	$BF_3{\cdot}OEt_2$	1.0	85
5	TMSOTf	0.02	85
6	$SnCl_4$	1.0	67

The Mukaiyama-type aldol reactions of **4a**–**h** with other acetals were studied, and the results are summarised in Table 2. Only acetals derived from aromatic aldehydes gave satisfactory yields. All reactions using 0.02 equiv. TMSOTf as the promoter were completed within 4–6 h, and resulted in the conversion of **4** to **5** in high yields (entries 1–6), except in the case of *p*-nitrobenzylaldehyde (entry 9).[10] Aryl rings bearing an electron donating group gave higher yields than those possessing an electron withdrawing group. The reaction of *p*-methoxybenzaldehyde dimethyl acetal using 1 equiv. of $BF_3{\cdot}Et_2O$ afforded the corresponding adduct in 90% yield, whilst the dimethyl acetal of *p*-nitrobenzylaldehyde gave the product in only 23% yield (0.02 equiv. TMSOTf). Unfortunately, treatment of aliphatic aldehyde acetals in this case led to complicated product mixtures (Scheme 3).

In conclusion, methyl 3,3-difluoro-2-trimethylsilylacrylate **3** was conveniently prepared from methyl 3,3-difluoro-2-benzyloxyacrylate. The Lewis acid catalysed aldol reaction of this difluorinated silyl enol synthon with arylaldehyde acetals provides an efficient method for the preparation of β,β-difluoro-α-keto derivatives under mild conditions.



Scheme 3.

Table 2. Mukaiyama-type aldol condensation of **3** with acetals[a]

Entry	**4**	R^1	R^2	Lewis acid	Eq. (mol)	**5**[b]	Yield (%)[c]
1	**4a**	Ph	Me	TMSOTf	0.02	**5a**	85
2	**4b**	*p*-F-C_6H_4	Et	TMSOTf	0.02	**5b**	80
3	**4b**	*p*-F-C_6H_4	Et	$BF_3{\cdot}OEt_2$	1.0	**5b**	78
4	**4c**	*p*-Cl-C_6H_4	Me	TMSOTf	0.02	**5c**	70
5	**4c**	*p*-Cl-C_6H_4	Me	$BF_3{\cdot}OEt_2$	1.0	**5c**	66
6	**4d**	*p*-MeO-C_6H_4	Me	TMSOTf	0.02	**5d**	91
7	**4d**	*p*-MeO-C_6H_4	Me	$BF_3{\cdot}OEt_2$	1.0	**5d**	90
8	**4d**	*p*-MeO-C_6H_4	Me	$TiCl_4$	1.0	**5d**	71
9	**4e**	*p*-NO_2-C_6H_4	Me	TMSOTf	0.02	**5e**	23
10	**4f**	Et	Me	$BF_3{\cdot}OEt_2$	1.0	**5f**	0
11	**4g**	PhCH=CH	Me	$BF_3{\cdot}OEt_2$	1.0	**5g**	0
12	**4h**	CH_2=CH	Et	$BF_3{\cdot}OEt_2$	1.0	**5h**	0

[a] All reactions were performed in CH_2Cl_2 at 0°C under N_2.
[b] All products were characterized by ^1H, ^{19}F NMR and MS spectroscopy, and by elemental analysis.
[c] Yield of isolated product.

Acknowledgements

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7. Procedure and selected data for **3**: $(CH_3)_3SiI$ (8.42 g, 42 mmol) was added to a solution of methyl 3,3-difluoro-2-benzyloxyacrylate (9.12 g, 40 mmol) in CH_2Cl_2 (50 mL) at room temperature. Then the mixture was refluxed for 2 h. After removal of the solvent, the residue was subjected to distillation under reduced pressure to give **3** (7.74 g, 92%). Bp 52–54°C/9 mmHg; δ_H ($CDCl_3$) 0.2 (s, 9H), 3.6 (s, 3H); δ_F ($CDCl_3$) 9.2 (d, *J* 24 Hz, 1F), 16.3 (d, *J* 24 Hz, 1F); *m*/*z*: 211 (M^+1, 1.03), 195 (100), 165 (12.8), 89 (71.7), 73 (53.9), 59 (18.6); HRMS calcd for $C_7H_{12}F_2O_3Si$: 210.0523. Found: 210.0539.
8. For a review of the Mukaiyama aldol reaction, see: (a) Mukaiyama, T.; Murakami, M. *Croat. Chim. Acta* **1986**, *59*, 221; (b) Ellis, W. W.; Bosnich, B. *Proceedings of the Fifth Symposium of the Organic Synthesis of Organometallics* (1996); Helmchen, G. V., Ed.; Wiesbaden, 1997, p. 209; (c) Nicolas, G.; Pierre, V. D. W.; Mohamed, M.; Jacqueline, C. *Tetrahedron* **1998**, *54*, 13129.
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10. **Typical procedure for Mukaiyama-type aldol condensation of methyl 3,3-difluoro-2-trimethylsilyloxyacrylate with acetals**: the Lewis acid or TMSOTf was added to a solution of methyl 3,3-difluoro-2-trimethylsilyloxyacrylate **3** (0.21 g, 1 mmol) and the acetal **4** (1 mmol) in CH_2Cl_2 (2 mL) at 0°C under a nitrogen atmosphere. After stirring for 6 h at 0°C, the reaction mixture was poured into 10% sodium bicarbonate (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with brine and dried. After removing the solvent, the residue was crystallized from petroleum/diethyl ether to afford **5**. Satisfactory spectroscopic data and elemental analyses were obtained for compounds **5a**–**5e**. Selected data for **5a**: Mp 92–94.5°C; δ_H ($CDCl_3$) 3.35 (s, 3H), 3.90 (s, 3H), 4.92 (dd, *J* 3.1 Hz, *J* 21.3 Hz, 1H), 7.4 (m, 5H); δ_F ($CDCl_3$) 38.5 (dd, *J* 3.1 Hz, *J* 28.8 Hz, 1F), 48.7 (dd, *J* 21.3 Hz, *J* 28.8 Hz, 1F). For **5b**: mp 76.1–77.2°C; δ_H ($CDCl_3$) 1.22 (t, *J* 7.1 Hz, 3H), 3.49 (q, *J* 7.1 Hz, 2H), 3.90 (s, 3H), 5.01 (dd, *J* 3.1 Hz, *J* 21.3 Hz, 1H), 7.08 (t, *J* 8.7 Hz, 2H), 7.40 (dd, *J* 5.6 Hz, *J* 8.4 Hz, 2H); δ_F ($CDCl_3$) 38.9 (dd, *J* 3.1 Hz, *J* 28.8 Hz, 1F), 50.4 (dd, *J* 21.3 Hz, *J* 28.8 Hz, 1F). For **5c**: mp 92.5–93.7°C; δ_H ($CDCl_3$) 3.34 (s, 3H), 3.91 (s, 3H), 4.91 (dd, *J* 3 Hz, *J* 20.8 Hz, 1H), 7.38 (d, *J* 2.8 Hz, 4H); δ_F ($CDCl_3$) 39.0 (dd, *J* 3 Hz, *J* 28.5 Hz, 1F), 47.0 (dd, *J* 20.8 Hz, *J* 28.5 Hz, 1F). For **5d**: mp 104.2–105.6°C; δ_H ($CDCl_3$) 3.23 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 4.88 (dd, *J* 5 Hz, *J* 21.4 Hz, 1H), 6.95 (d, *J* 8.4 Hz, 2H), 7.33 (d, *J* 8.4 Hz, 2H); δ_F ($CDCl_3$) 32.0 (dd, *J* 5 Hz, *J* 28.0 Hz, 1F), 48.5 (dd, *J* 21.4 Hz, *J* 28.0 Hz, 1F). For **5e**: mp 95–97°C; δ_H ($CDCl_3$) 3.39 (s, 3H), 3.92 (s, 3H), 5.03 (dd, *J* 2.9 Hz, *J* 17.6 Hz, 1H), 7.64 (d, *J* 7.9 Hz, 2H), 8.29 (d, *J* 7.9 Hz, 2H); δ_F ($CDCl_3$) 47.0 (dd, *J* 2.9 Hz, *J* 36.0 Hz, 1F), 52.80 (dd, *J* 17.6 Hz, *J* 36.0 Hz, 1F).