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A new sequential defluorination route to α-fluoro-α,β-unsaturated ketones from trifluoromethyl ketones

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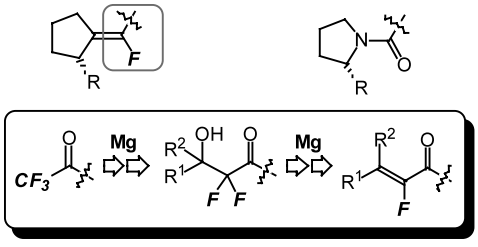
Abstract—α-Fluoro-α,β-unsaturated ketones were prepared from trifluoromethyl ketones via a sequence involving Mg metal promoted successive double defluorination. Trifluoromethyl ketones were transformed to β,β-difluoroenol silyl ethers which were then coupled with aldehydes and ketones to β-hydroxy-α,α-difluoroketones. A second Mg-promoted defluorination of the hydroxyketones followed by acid-catalyzed hydrolysis of γ-hydroxy-β-fluoroenol silyl ethers provided α-fluoro-α,β-unsaturated ketones as a final product.

Peptides have been modified to improve their biological activities by changing the backbone structure.[1] Replacement of the amide bond with a monofluorinated carbon–carbon double bond (CF=C) has been recognized to provide conformationally fixed peptide bond isosteres (Scheme 1).[2,3] Physical data such as bond length, dipole moment, and charge distribution of fluoroolefins also suggest the similarity between an amide moiety and a fluoroolefin.[4] On this basis, several peptide mimetics possessing monofluoroolefinic skeletons have been prepared.[2,3,5] α-Fluoro-α,β-unsaturated carbonyl compounds are promising precursors for fluoroalkene oligopeptide isosteres, and have been prepared by a variety of approaches such as aldol reaction of α-fluoro-α-silylacetates with ketones followed by Peterson olefination,[3b] alkylation of 1,1,1,2-tetrafluoroethane with aldehydes followed by acid-catalyzed hydrolysis,[6] Grignard reaction of β-fluorovinamidium salt,[7] Wittig–Horner reaction with diethylphosphono-2-fluoroacetate,[8] Pd-catalyzed carbonylation of 1-fluorovinyl-stannanes,[9] and so on.[10]



Scheme 1.

To further define the biological utility of the peptide mimetics, it is necessary to develop a more effective route for the synthesis of α-fluoro-α,β-unsaturated carbonyl compounds, promising intermediates for fluoroalkene oligopeptide isosteres. Recently, we reported Mg(0)-promoted defluorinative silylenolization of trifluoromethyl ketones,[11] which might be applicable to the construction of β-hydroxy-α,α-difluorocarbonyl compounds due to the readily reducibility of multifluoromethyl carbonyl compounds with metallic magnesium. This communication describes a double defluorination pathway leading to an efficient synthesis of α-fluoro-α,β-unsaturated carbonyl compounds.

The first C–F bond cleavage in the sequence for monofluoroolefins is Mg(0)-promoted selective defluorinative silylation of trifluoromethylketones **1** to afford 2,2-difluoroenol silyl ethers **2**.[11] Without further purification, the crude enols **2** were employed directly in the next aldol reaction. The $TiCl_4$-catalyzed aldol reaction of **2** with various aldehydes and ketones gave **3** in good overall yields (from **1**). The results of transformation of **1** to **3** are summarized in Scheme 2.

The second C–F bond cleavage for the synthesis of the monofluoroolefins requires defluorinative silylation of the difluoroaldols **3** to give monofluoroenol silyl ethers

Keywords: fluorine and compounds; magnesium; cleavage reaction; aldols; enones.

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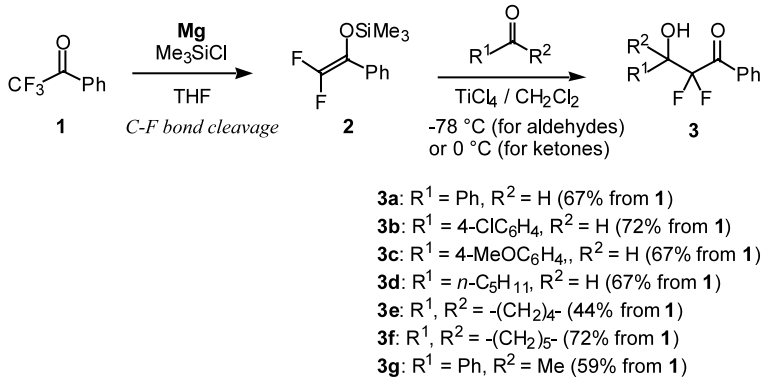


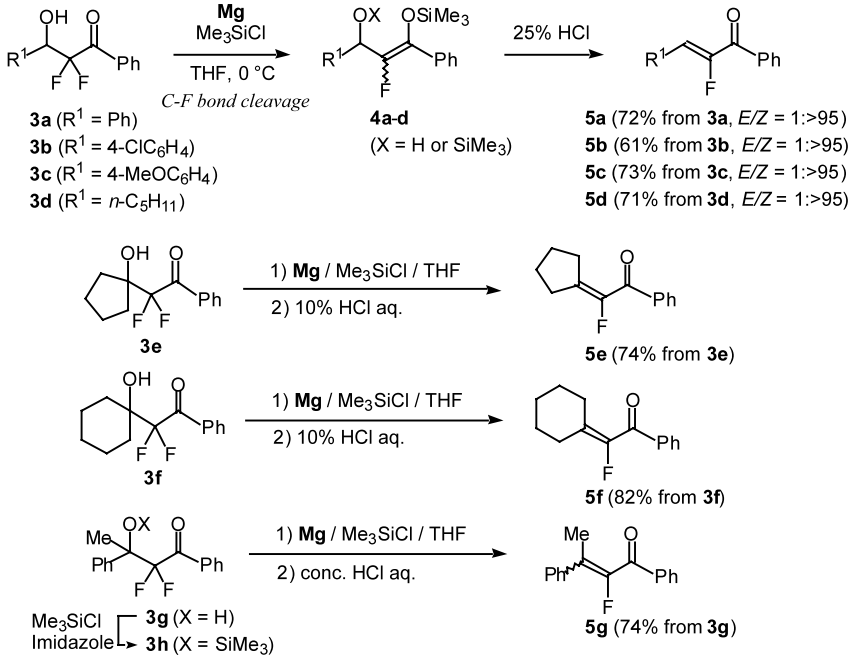
Scheme 2.

4. Upon treatment of **3a** with Mg metal (8 equiv.) and Me_3SiCl (4 equiv.) in THF at 0°C, the defluorinative silylation completed within 30 min affording monofluoroenol silyl ether **4a**. It is noted that the defluorination reaction proceeded smoothly with no need for precautionary protection of the hydroxyl group in **3a**. After simple filtration and treatment of the crude enol **4a** with aq. HCl, α-fluoro-α,β-unsaturated ketone **5a** was obtained in 72% yield from **3a**.

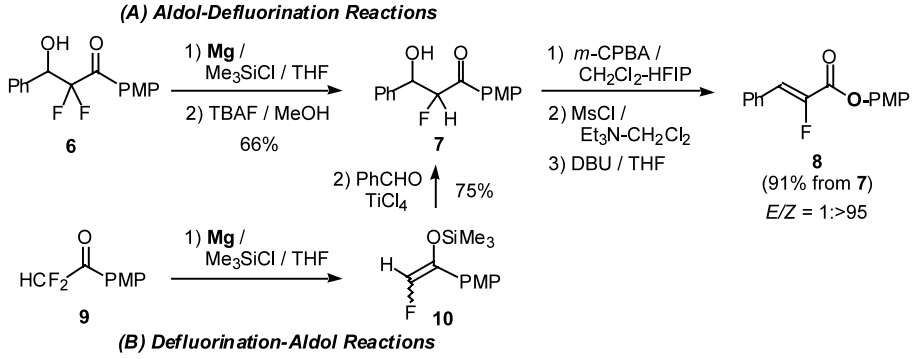
In light of operational simplicity and high efficiency, Mg-promoted selective defluorination of **3** and subsequent hydrolysis of **4** gave a reliable route for preparing monofluoro enones **5**.[12]

As shown in Scheme 3, this procedure worked well for other β-hydroxyketones **3b–d** derived from aldehydes to provide **5b–d** in good yields. Interestingly, in both the case of **3a–c** (from aromatic aldehydes; $R^1 = Ar$) and **3d** (from an aliphatic aldehyde; $R^1 = C_5H_{11}$), the reactions led to exclusive formation of (*Z*)-**5a–d**.[13] β-Hydroxyketones **3e** and **3f** from cyclic ketones underwent defluorination cleanly, affording *exo*-fluoromethylene cyclic compounds **5e** and **5f** in 74% and 82% yields, respectively. However, the reaction of **3g** (obtained from acetophenone) provided a complex mixture under the same experimental conditions. When *O*-silylated derivative **3h** was subjected to the Mg-promoted defluorination and subsequent hydrolysis, the desired enone **5g** was formed as a mixture ($E/Z = 1{:}4$) of stereoisomers in 74% yield.[13]

Furthermore, α-fluoro-α,β-unsaturated ester **8** was obtained by the following Baeyer–Villiger oxidation procedures (Scheme 4). α-Fluoro-β-hydroxy-β-phenyl (*p*-methoxyphenyl) ketone (**7**) which was prepared from **6** by Mg-promoted defluorination followed by a basic hydrolysis (route A), and which was also prepared from difluoromethyl ketone **9** by Mg-promoted C–F bond cleavage[14] followed by aldol reaction with benzaldehyde (route B), could be transformed to (*Z*)-α-fluorocinnamate **8** in reasonable yield.



Scheme 3.



Scheme 4.

Compared with published methods, the present defluorination route to α-fluoro-α,β-unsaturated ketones has several advantages. The procedure for selective defluorination is very simple; Mg metal as a reducing agent is inexpensive and easily handled.[14] Simple repetition of the defluorination procedures allowed selective formation of the monofluorinated enones, with high stereoselectivities in some cases. Trifluoromethyl ketones were successfully transformed to α-fluoro-α,β-unsaturated esters without the necessity to employ toxic monofluoroacetates as a starting material. Thus, the design of the reaction sequences involving C–F bond cleavage enables the development of various practical transformations, with potential biological and chemical utility.

Acknowledgements

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References

1. Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedicinal Frontiers of Fluorine Chemistry*; ACS Symposium Series 639, ACS: Washington, DC, 1996.
2. Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett*. **1990**, *31*, 7297.
3. (a) Boros, L. G.; Corte, B. D.; Gimi, R. H.; Welch, J. T.; Wu, Y.; Handschumacher, R. E. *Tetrahedron Lett*. **1994**, *35*, 6033; (b) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291; (c) Lin, J.; Welch, J. T. *Tetrahedron Lett*. **1998**, *39*, 9613; (d) Welch, J. T.; Allmendinger, T. In *Peptidomimetic Protocols*; Kazmierski, W. M., Ed. Fluoroolefin peptide isosteres; Humana Press: New Jersey, 1999; pp. 375–384.
4. Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101.
5. (a) Otaka, A.; Mitsuyama, E.; Watanabe, H.; Tamamura, H.; Fujii, N. *Chem. Commun*. **2000**, 1081; (b) Otaka, A.; Watanabe, H.; Yukimasa, A.; Oishi, S.; Tamamura, H.; Fujii, H. *Tetrahedron Lett*. **2001**, *42*, 5443.
6. Kanai, M.; Percy, J. M. *Tetrahedron Lett*. **2000**, *41*, 2453.
7. Yamanaka, H.; Odani, Y.; Ishihara, T.; Gupton, J. T. *Tetrahedron Lett*. **1998**, *39*, 6947.
8. (a) Kim, B. T.; Min, Y. K.; Asami, T.; Park, N. K.; Kwon, O. Y.; Cho, K. Y.; Yoshida, S. *Tetrahedron Lett*. **1997**, *38*, 1797; (b) Komatsu, Y.; Kitazume, T. *J. Fluorine Chem*. **1998**, *87*, 101.
9. Chen, C.; Wilcoxen, K.; Kim, K.-I.; MaCarthy, J. R. *Tetrahedron Lett*. **1997**, *38*, 7677.
10. (a) Ring-opening of α,β-epoxyketone with Et_3N/3HF: Todoroki, Y.; Hirai, N.; Ohigashi, H. *Tetrahedron* **1995**, *51*, 6911; (b) Fluoroolefination of β-ketoesters with DAST: Bildstein, S.; Ducep, J.-B.; Jacobi, D.; Zimmermann, P. *Tetrahedron Lett*. **1995**, *36*, 5007; (c) *O*-Acetylation of α-fluoromalonaldehyde: Funabiki, K.; Fukushima, Y.; Matsui, M.; Shibata, K. *J. Org. Chem*. **2000**, *65*, 606; (d) Electrochemical fluorination of β-phenylsulfenyl-α,β-unsaturated ketones: Andres, D. F.; Dietrich, U.; Laurent, E. G.; Marquet, B. S. *Tetrahedron* **1997**, *53*, 647.
11. Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun*. **1999**, 1323.
12. A typical procedure: preparation and characterization of monofluoroenones **5a**. Chlorotrimethylsilane (0.26 g, 24 mmol) in freshly distilled THF (2.5 mL) and Mg (0.12 g, 4.8 mmol) cooled down to 0°C under argon atmosphere, **3a** (160 mg, 0.6 mmol) was added dropwise and then stirred for additional 30 min. After evaporation of most of THF, hexane (20 mL) was added to the residue, and the resulting salt was filtered and the filtrate concentrated to give the crude product **4a**. Hydrochloric acid was added dropwise to the crude **4a** in Et_2O and the mixture was stirred at room temperature for 30 min. Purification of the products by chromatography on silica gel (hexane/ether = 25/1) provided **5a** (98 mg, 72% from **3a**) as a colorless solid. Mp 57°C; IR (Nujol) 1658 cm^{-1} (ν_{CO}); ^1H NMR ($CDCl_3$, 200 MHz) δ 6.87 (d, $^3J_{FH}$ = 36.4 Hz, 1H), 7.4–7.8 (m, 8H),

7.90 (d, $J=6.1$ Hz, 2H); ^{19}F NMR ($CDCl_3$, 188 MHz, C_6F_6 as an internal standard) δ 42.3 (d, $^3J_{FH}=36.4$ Hz, 1F). Anal. calcd for $C_{15}H_{11}FO$: C, 79.63; H, 4.90. Found: C, 79.55; H, 5.13.

13. Stereochemistries of the products ((*Z*)-**5a**–**d**, (*E*)- and (*Z*)-**5g**) were determined by NOE difference NMR spectroscopy of their 1,2-reduction alcohols ($NaBH_4$/$CeCl_3$).
14. An application of the Mg-promoted defluorination to difluoromethyl ketones leading to monofluoromethyl ketones has recently been reported; Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2001**, *112*, 357.