Pergamon

Tetrahedron Letters, Vol. 38, No. 4, pp. 587-590, 1997
Copyright © 1997 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02378-7

An Efficient Method for α-Monofluorination of Carbonyl Compounds with Molecular Fluorine: Use of α-Hydroxymethylene Substituent as Directing and Activating Groups

Hiroshi Kamaya, Masayuki Sato* and Chikara Kaneko

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

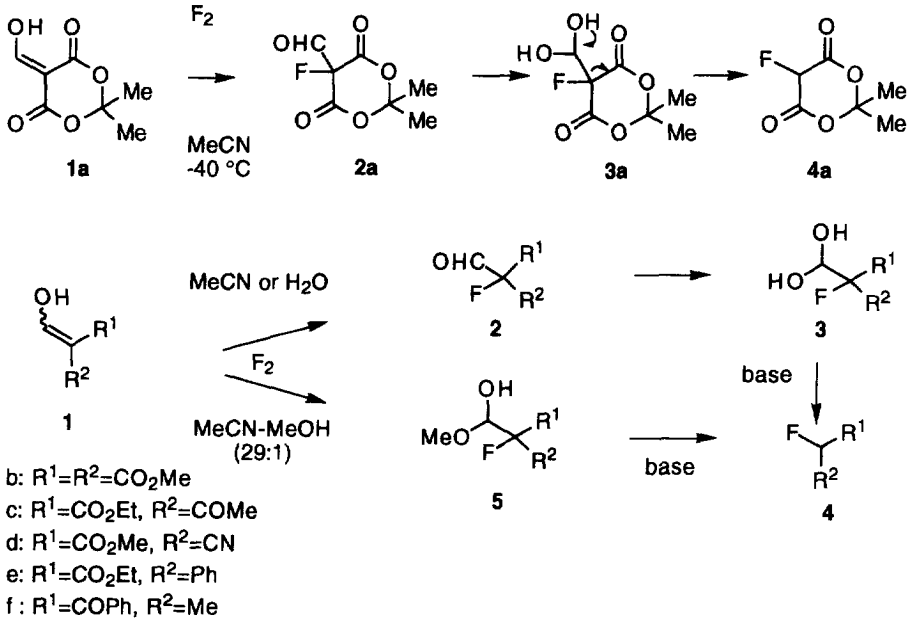
Abstract: Molecular fluorine efficiently reacts with α-hydroxymethylene carbonyl compounds to give α-fluoro-α-formyl compounds in a highly site-specific manner. The fluorinated compounds mostly isolated as their hemiacetals with methanol are readily deformylated just by treatment with weak bases affording α-monofluorinated carbonyl compounds. In this fluorination method, the hydroxymethylene group serves not only as a directing group but also as the activating group of carbonyl compounds for fluorination. By this method, a series of α-fluoro carbonyl compounds including esters was synthesized in high yields. © 1997, Elsevier Science Ltd. All rights reserved.

Introduction of fluorine atoms in specific site of molecules is a very important task from both chemical and pharmaceutical points of view.[1] Though molecular fluorine is the most economical as the electrophilic fluorinating reagent especially on a large scale, it is normally regarded as being too reactive for site-specific fluorination.[1,2] Thus, a range of modified fluorinating reagents (themselves made using molecular fluorine) has been developed in order to synthesize desirable fluorine-containing building blocks.[3] α-Fluoro carbonyl compounds have been synthesized by the fluorination of the parent carbonyl compounds[4] or their enolates[5] with modified fluorinating reagents. Recently, Umemoto *et al.*[6a] and Chambers *et al.*[6b] reported direct α-fluorination of β-diketones and β-keto esters with molecular fluorine in acidic solvents. However, the site selectivity was not very high and significant amounts of α,α-difluorinated products were also formed, particularly for cyclic β-diketones.[6b] In addition, diethyl malonate which is less acidic than β-diketones was not fluorinated by this method. Since α-fluoroketones and esters are of much interest from the synthetic and biological points of view,[1] our attention was focused on the site-specific monofluorination of carbonyl compounds. We report herein our successful result using an α-hydroxymethylene substituent as the directing and activating groups for the fluorination of carbonyl compounds with molecular fluorine.

Recently, we found that molecular fluorine adds to the carbon-carbon double bond of conjugated enone involved in heterocyclic systems such as 1,3-dioxin-4-one,[7] 4-chloro-2(1*H*)-quinolone, and 6-chlorouracil derivatives[8] in a highly selective manner. This fact strongly suggests that the hetero atom at the β-position of conjugated enone activates the double bond for molecular fluorine addition. Thus, we examined fluorination of α-formyl carbonyl compounds which mostly exist as the tautomeric β-hydroxy α,β-unsaturated carbonyl compounds and are readily available from the parent carbonyl compounds by standard formylation methods.

On treatment with 3% molecular fluorine (diluted to 3% in nitrogen, 1 mol equiv.) in acetonitrile at - 40 °C, hydoxymethylenated Meldrum's acid (**1a**)[9] was fluorinated quantitatively at the α-position to give **2a**, presumably by fluorine addition to the enone carbon-carbon double bond followed by spontaneous elimination of hydrogen fluoride. This reaction was so efficient that there is no need to use an excess amount of fluorine nor to use expensive trichlorofluoromethane usually required as the solvent for efficient fluorination with molecular fluorine.[10] Moreover, merely diluting this reaction solution with ether at room temperature resulted in the crystallization of pure monofluorinated Meldrum's acid (**4a**: 71% yield).[11] Apparently, the initial product **2a** is readily deformylated through the hydrate **3a** formed by the reaction with water contaminated in the solvents, due to the strongly electron-withdrawing character of the dioxanedione moiety.

Dimethyl hydroxymethylenemalonate (**1b**) was also fluorinated efficiently under this condition to give fluorinated formylmalonate **2b**. This product was not *in situ* deformylated and on treatment with water for extraction, it formed hydrate **3b**; however, extraction of the product from the water layer proved difficult. This problem was solved by converting **2b** to hemiacetal **5b** with methanol. Thus, use of a mixture of acetonitrile and methanol (29:1) as the fluorination solvent resulted in the formation of **5b**, which was readily isolated in a quantitative yield. On treatment with triethylamine (1 mol equiv.) in dichloromethane at room temperature, **5b** was transformed into fluoromalonate **4b**[5a] (84% overall yield). This fluorination could be also conducted in water under ice-cooling in the presence of an equimolar amount of sodium hydroxide, and addition of sodium bicarbonate (6.0 mol equiv.) to the reaction solution gave **4b** in 64% overall yield.



Other α-hydroxymethylene carbonyl compounds **1c-f** were likewise fluorinated in the mixture of acetonitrile and methanol to produce the fluorinated hemiacetals **5c-f** in almost quantitative yields.[12] Treatment of the dichloromethane solution of these hemiacetals with triethylamine or weakly basic solutions afforded α-fluoro carbonyl compounds **4c**,[5a] **d**,[13] **e**,[5b] and **f**[14] in satisfactory overall yields (Table 1, Entries 4-9).

Compound **1d** was transformed into **4d** in a comparable yield by fluorination in water followed by deformylation with sodium bicarbonate (Entry 7). In all cases, α,α-difluorinated products as well as polymeric products often formed due to the radical character of molecular fluorine[2] were never formed. This site-specific fluorination followed by clean deformylation enabled ready isolation of pure **4**.[15] The fluorination conditions, deformylation conditions, and isolated yields of α-fluoro carbonyl compounds are summarized in Table 1.

Table 1. Synthesis of α-Fluoro Carbonyl Compounds

Entry	Substrate	Solvent	Temp. (°C)	F_2 equiv.	Deformylation condition [a]	Yield of **4** (%)
1	**1a**	MeCN	-40	1	-	71
2	**1b**	MeCN:MeOH (29:1)	-40	1	A	84
3	**1b**	H_2O [b]	0	2	B	64
4	**1c**	MeCN[c]	-40	1	A	69
5	**1c**	MeCN:MeOH (29:1)	-40	1	A	49
6	**1d**	MeCN:MeOH (29:1)	-40	1	C	77
7	**1d**	H_2O [b]	0	2	B	71
8	**1e**	MeCN:MeOH (29:1)	-40	1	D	70
9	**1f**	MeCN:MeOH (1:1)	-40	1	D	71

a) A: Et_3N (1.0 mol equiv.) in dichloromethane. B: $NaHCO_3$ (6.0 mol equiv.). C: Phosphate buffer (pH 7.2). D: 5% NH_4OH. b) One mol equiv. of NaOH was used to dissolve **1** in water. c) Methanol was adeed after fluorination.

It should be noted that Meldrum's acid and dimethyl malonate themselves were not fluorinated under this condition even by use of 3 mol equiv. of molecular fluorine resulting in recovery of the starting materials. Thus, it is clear that the hydroxymethylene group employed in this study served not only as a directing group but also as a highly activating group of carbonyl compounds for α-fluorination with molecular fluorine which has been usually regarded as a nonselective reagent. The site specificity and high efficiency in this fluorination are attributable to the strongly nucleophilic character at the α-carbon of **1** due to the β-hydroxyl group in the enone system. Since the α-hydroxymethylene group is readily introduced into carbonyl compounds and readily eliminated as a formyl group after fluorination, this method should be equally applicable for site-specific introduction of fluorine atom to a wide range of carbonyl compounds.

Acknowledgment The gift of fluorine from Drs. Y. Morizawa and T. Asai of Asahi Glass Co. Ltd. is gratefully acknowledged.

REFERENCES AND NOTES

1. For recent reviews, see a) Mann, J. *Chem. Soc. Rev.* 1987, **16**, 381-436. b) Welch, J. T. *Tetrahedron*, 1987, **43**, 3123-3197. c) Resnati, G. *Tetrahedron* 1993, **49**, 9385-9445.

2. For reviews on fluorination with molecular fluorine, see a) Purrington, S. T.; Kagan, B. S. *Chem. Rev.*, 1986, **86**, 997-1018. b) Rozen, S. *Acc. Chem. Res.* 1988, **21**., 307-312.
3. For reviews, see a) Wilkinson, J. A. *Chem. Rev.* 1992, **92**, 505-519. b) Rozen, S. *Chem Rev.* 1996, **96**, 1717-1736. c) Lal, G. S.; Pez, G. P.; Syvret, R. G.*Chem. Rev.* 1996, **96**, 1737-1755.
4. Hara, S.; Sekiguchi, M.; Ohmori, A.; Fukuhara, T.; Yoneda, N. *J. Chem. Soc., Chem. Commun.* **1996**, 1899-1900. Stavber, S.; Zupan, M. *Tetrahedron Lett.* 1996, **37**, 3591-3594.
5. a) Lerman, O.; Rozen, S. *J. Org. Chem.* 1983, **48**, 724-727. b) Resnati, G.; Desmarteau, D. D. *J. Org. Chem.* 1991, **56**, 4925-4929. c) Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *J. Chem. Soc., Chem. Commun.* **1994**, 343-344. d) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* 1990, **112**, 8563-8575.
6. a) Umemoto, T.; Tomizawa, G. **PCT Int. Appl. WO 94** 10,120 (*Chem. Abstr.* 1994, **121**, 133536). b) Chambers, R. D.; Greenhall, M. P.; Hutchinson, J. *J. Chem. Soc., Chem. Commun.* **1995**, 21-22.
7. Sato, M.; Kaneko, C.; Iwaoka, T.; Kobayashi, Y.; Iida, T. *J. Chem. Soc., Chem. Commun.* **1991**, 699-700. Iwaoka, T. Murohashi, T.; Sato, M.; Kaneko, C. *Synthesis* **1992**, 977-981.
8. Sato, M.; Taniguchi, T.; Hirokawa, T.; Kaneko, C. *Tetrahedron Lett.* 1995, **36**, 6705-6708.
9. Bihlmayer, G. A.; Derflinger, G.; Derkosch, J.; Polansky, O. E. *Monatsh. Chem.* 1967, **98**, 564-578.
10. Merritt, R. *J. Am. Chem. Soc.* 1967, **89**, 609-612. Barton, D. H. R.; Lister-James, J.; Hesse, R. H.; Pechet, M. M.; Rozen, S. *J. Chem. Soc. Perkin I* **1982**, 1105-1110. Rozen, S.; Brand, M. *J. Org. Chem.* 1986, **51**, 3607-3611.
11. **4a**: Mp 177-179 °C (recrystallized from a mixture of dichloromethane and hexane). *Anal.* Calcd for $C_6H_7FO_4$: C, 44.45; H, 4.35. Found: C, 44.68; H, 4.60. ^1H NMR (300 MHz, $CDCl_3$): δ 1.835 and 1.845 (each 3H, broad s), 5.639 (1H, d, J = 45 Hz).^{13}C NMR (75 MHz, DMSO-d_6): 26.25, 27.75, 80.43, 83.03, 106.54, 106.57, 160.94, 161.21. IR ($CHCl_3$): 1818, 1777 cm^{-1}.
12. Compounds **5c-f** (1:1~2:3 diastereomixtures) were obtained as mixtures with **2c-d** (**5/2** = 3~10) in quantitative yields as shown by their ^1H NMR spectra.
13. **4d**: bp 70 °C (5 Torr). *Anal.* Calcd for $C_4H_4FNO_2$: C, 41.04; H, 3.44; N, 11.96. Found: C, 41.04; H, 3.55; N, 11.86. ^1H NMR (300 MHz): d 3.973 (3H, s), 5.533 (3H, d, J = 46 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 54.28, 73.05, 75.64, 111.55, 111.943, 161.30, 161.60. IR ($CHCl_3$): 2250, 1782 cm^{-1}.
14. Cousseau, J.; Albert, P. *J. Org. Chem.* 1989, **54**, 5380-5383.
15. Typical procedure: A stream of 3% molecular fluorine in nitrogen (3.0 mmol) was passed through a solution of **1b** (3.0 mmol) in a mixture of acetonitrile and methanol (29:1 v/v, 30 ml) under stirring at -40 °C. The solution was flushed with nitrogen, diluted with water, and extracted with dichloromethane. Triethylamine (3.0 mmol) was added to the organic layer. After 1 h at room temperature, the solution was washed with saturated NH_4Cl solution, dried over anhydrous magnesium sulfate, and evaporated. Distillation of the residue gave **4b** (378 mg, 84%) as a colorless oil of bp 76 °C (4 Torr).

(*Received in Japan* 14 *November* 1996; *accepted* 28 *November* 1996)