Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Fluorine Chemistry 125 (2004) 79–82
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/jfluchem

One step synthesis of 2-substituted 3-tri-(or di-)fluoromethyl-2-propenals in an ionic liquid

Tomoya Kitazume*, Hirokatsu Nagura, Shinichi Koguchi

Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku Yokohama 226-8501, Japan

Received 10 September 2003; received in revised form 24 October 2003; accepted 28 October 2003

Abstract

Investigation of one step synthesis of 2-substituted 3-tri-(or di-)fluoromethyl-2-propenals has been carried out using versatile aldehydes, tri- or di-fluoroacetaldehyde ethyl hemiacetal in the presence of diethylaminotrimethylsilane (DEATMS) in an ionic liquid, and it was demonstrated that this route enabled us to successfully construct 2-substituted 3-tri-(or di-)fluoromethyl-2-propenals with the high level selectivity of geometric isomers.

Keywords: 2-Substituted 3-tri-(or di-)fluoromethyl-2-propenals; Stereoselectivity; One step synthesis

1. Introduction

Several highly selective synthetic methods have been developed which allow the preparation of various types of materials with excellent regio-, stereo-, and chemoselectivity. In general, the usual synthetic procedure for the target materials is the stepwise formation of the individual bonds. While sequential syntheses that could form several bonds in one sequence without isolating the intermediates, changing the reaction conditions, or addition reagents have been recognized as being useful in organic synthesis [1], their synthetic value for tri- and/or di-fluoromethylated alkenes still appears to be grossly underestimated [2]. In nonfluorinated chemistry, the Wittig–Horner reactions and/or tandem vicinal difunctionalization reactions of alkynes are well-known as stereoselective synthetic methods for tri- and tetra-substituted alkenes. Further, fluorinated alkenes are prepared from the Horner–Wadsworth–Emmons reaction [3,4], trifluoromethylation using CF_3SiR_3–KF–Cu(I) system [5], and organometallics [6]. Clearly, one step selective and/or specific synthetic methods for introduction of the tri- and/or di-fluoromethyl group at an olefinic position remain an important synthetic challenge.

In this article, we have describe the one step synthesis to open a new avenue for the geometric selective construction of 2-substituted 3-tri-(or di-)fluoromethyl-2-propenals.

2. Results and discussions

Tri- and/or di-fluoroacetaldehyde ethyl hemiacetal **1** acts as a tri- or di-fluoroacetaldehyde equivalent in enamine-type reaction using the system of aldehyde and diethylaminotrimethylsilane (DEATMS) **2** in an ionic liquid to form 2-substituted 3-difluoromethyl-2-propenals. After a survey of conditions, the reaction of difluoroacetaldehyde ethyl hemiacetal with enamine-type reagent **3** generated from the reaction of hexanal with DEATMS in [emim][OTf] was found to afford 2-substituted 3-difluoromethyl-2-propenals. In the reaction path way, Hagiwara et al. have reported the generation of enamine as an intermediate [7]. Furthermore, on the bases of our reported reaction path way of difluoroacetaldehyde ethyl hemiacetal **1** with enol silyl ethers [8], we have revealed that the reaction could promote under forcing conditions such as ZnX_2 (X: Cl, I). In this reaction, the catalytic amount of DEATMS (20 mol%) was accelated the reaction, giving the corresponding alkene (entry 5) in 69%. From the above reported results, the reaction of hemiacetal **1** with enamine **3** generated by the reaction of DEATMS with aldehyde was proceeded to the intermediate **4**, producing 2-substituted 3-tri- (or di-) fluoromethyl-2-propenals **5** in moderate to good chemical yield as shown in Fig. 1.

In view of green chemistry, reuse of the solvent is preferable [9]. From the results shown in Table 1 (entries 8–10), successive reuse of the recovered ionic liquid in the same reaction yielded amounts of product and the geometric selectivity as high as in the first cycle.

* Corresponding author. Fax: +81-45-924-5780.
E-mail address: tkitazum@bio.titech.ac.jp (T. Kitazume).

0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2003.10.010

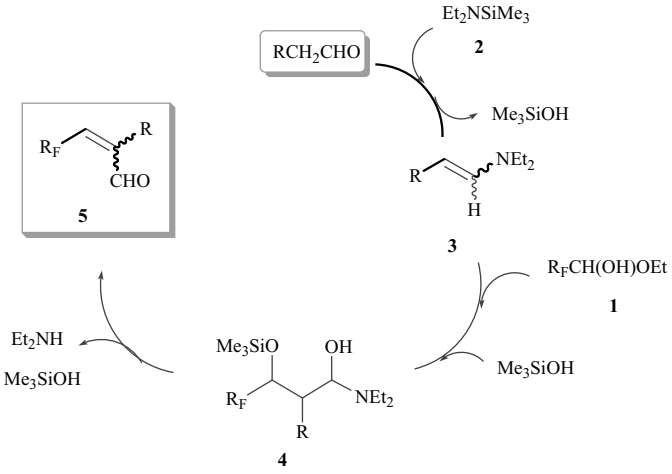


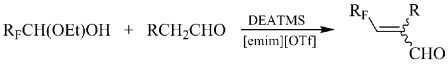
Fig. 1. Reaction mechanism.

In contrast, this stereoselective synthesis of alkenes was not proceede smoothly when trifluoroacetaldehyde ethyl hemiacetal **1b** was employed as acceptors. The yields of 2-substituted 3-trifluoromethyl-2-propenals are shown in Table 2. In Fig. 1, the tetrahedral form of hemiacetal **1b** (R_F: CF_3) was highly stable as a result of the strong electron-withdrawing effect of the trifluoromethyl group, so that transformation was not facile, giving the intermediate **4**.

The stereochemistry of products was confirmed by ^1H and ^{19}F NMR coupling constants and chemical shifts of the olefinic position. It is well-known that ^{19}F NMR chemical shift of the CHF_2 or CF_3 group of *E*-isomer on the olefinic position is upper area than that of *Z*-isomer [2]. Further, the signal of the olefinic proton for the case of the carbonyl group in the *trans* position (at δ, 5.5–6.5 ppm) is present upper area than that of *cis* position at δ, 6–7 ppm [10]. Obviously, the stereochemistry of the obtained main materials is that of the *E*-isomer on the basis of the signal area (δ, 6.5–6.6 ppm, down filed than that of *Z*-isomer) of the olefinic proton, and the coupling pattern of the aldehyde proton (t, $J = 0.8$ Hz) and fluorine atom (dd, $J_{\text{F-Hgem}} = 50-60$ Hz, $J_{\text{F-Hvic}} = 5-10$ Hz).

On the basis of these results, we have found that this proceeded was a convenient synthetic procedure for production of fluoromethylated trisubstituted alkenes.

Table 1
Synthesis of 3-fluoromethyl-2-substituted propenal



$R_F = CF_3$, CHF_2

Entry	R_F	R	Ionic liquid	Yield (%)	*E*/*Z* ratio
1	CHF_2	Ph	[emim][OTf]	23[a]	93:7
2		$PhCH_2$	[emim][OTf]	87[a]	92:8
3		$PhCH_2$	[bmim][BF_4]	72[a]	92:8
4		$PhCH_2$	MeCN	(75)[a]	91:9
5		$PhCH_2$	[emim][OTf]	69[b]	92:8
6		$CH_3(CH_2)_3$	[emim][OTf]	63[a]	95:5
7		$CH_3(CH_2)_4$	[emim][OTf]	46[a]	90:10
8		$CH_3(CH_2)_5$	[emim][OTf]	77[a]	95:5
9		$CH_3(CH_2)_7$	[emim][OTf]	55[c]	94:6
10				62[d]	94:6
11				56[e]	97:3
12	CF_3	$PhCH_2$	[emim][OTf]	24[f]	92:8
13		$CH_3(CH_2)_3$	[emim][OTf]	49[f]	96:4
14		$CH_3(CH_2)_5$	[emim][OTf]	50[f]	92:8
15		$CH_3(CH_2)_7$	[emim][OTf]	43[f]	96:4

[a] Isolated yield.
[b] DEATMS (20 mol%) was used.
[c] First cycle.
[d] Second cycle.
[e] Third cycle.
[f] Yields were determined by ^{19}F NMR.

3. Experimental

3.1. General

All commercially available reagents were used without further purification. Chemical shifts of ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ, 0.00) in $CDCl_3$. The ^{19}F (282 MHz) NMR spectra were recorded in ppm downfield from internal standard C_6F_6 in $CDCl_3$using a VXR 300 instrument.

Typical procedure is as follows:

3.2. 3-Difluoromethyl-2-phenylpropenal **5a**

In the 1-ethyl-3-methyl-1*H*-imidozolium trifluoromethanesulfonate ([emim][OTf], 2.0 g), benzylaldehyde (718 mg, 5.98 mmol), difluoroacetaldehyde ethyl hemiacetal (2.03 g, 16.1 mmol) and diethylaminotrimethylsilane (0.873 g, 6.01 mmol) were added, and then the whole was stirred at room temperature. After overnight of stirring, the product was extracted with diethyl ether (10 times × 20 ml). The organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed. Products were purified by column chromatography on silica gel using a mixture of hexane-ethyl acetate (10:1), giving 3-difluoromethyl-2-phenylpropenal **5a**. ^1H NMR ($CDCl_3$): δ, 6.25 (1 H, td, $J = 54.7$, 7.42 Hz), 6.62 (1 H, m), 7.21–7.47 (Ar–H), 9.78. ^{19}F NMR ($CDCl_3$): δ, 51.0 (dd, $J = 54.3$, 7.75 Hz); *Z*-isomer: 52.0 ((dd, $J = 54.9$, 10.5 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 111.792 (t, $J = 233.04$ Hz; *Z*-isomer: 110.164, t, $J = 233.32$ Hz), 128.458, 129.134, 129.444, 138.511 (t, $J = 27.48$ Hz), 147.259 (t, $J = 10.88$ Hz), 191.812. Anal. Cacld. for $C_{10}H_8F_2O$, C, 65.93, H, 4.43. Found. C, 65.55, H, 4.16. IR: 1702 (C=O) cm^{-1}.

3.3. 3-Difluoromethyl-2-benzylpropenal **5b**

E-isomer: ^1H NMR ($CDCl_3$): δ, 3.74, (2 H, s), 6.17 (1 H, tdt, $J = 11.2$, 6.11, 1.71 Hz), 6.56 (1 H, td, $J = 54.7$,

6.10 Hz), 7.15–7.29 (Ar–H), 9.56. ^{19}F NMR ($CDCl_3$): δ, 49.3 (dd, $J = 54.9$, 9.15 Hz); *Z*-isomer: 52.8 (dd, $J = 54.9$, 10.7 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 29.882, 111.204 (τ, $J = 234.47$ Hz), 126.580, 128.234, 128.518, 139.497 (t, $J = 26.34$ Hz), 146.500 (t, $J = 10.02$ Hz), 192.696. *Z*-isomer: δ, 35.804, 109.971 (t, $J = 234.18$ Hz), 126.762, 128.606, 128.985, 135.188 (t, $J = 26.63$ Hz), 136.557 (t, $J = 12.21$ Hz), 189.035. IR: 1700 (C=O) cm^{-1}.

3.4. 3-Difluoromethyl-2-butylpropenal **5c**

E-isomer: ^{1}H NMR ($CDCl_3$): δ, 0.89 (3 H, m), 1.27–1.41 (4 H, m), 2.35 (2 H, m), 6.37 (1 H, td, $J = 9.62$, 6.35 Hz), 6.55 (1 H, td, $J = 54.9$, 6.35 Hz), 9.51 (1 H). ^{19}F NMR ($CDCl_3$): δ, 48.6 (dd, $J = 54.9$, 9.47 Hz); *Z*-isomer: 52.8 (m) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 3.630, 22.621, 24.211, 31.203, 111.462 (t, $J = 233.04$ Hz), 139.038 (t, $J = 26.1$ Hz), 148.686 (t, $J = 10.0$ Hz), 193.554 (*Z*-isomer: 189.984).

3.5. 3-Difluoromethyl-2-pentylpropenal **5d**

E-isomer: ^{1}H NMR ($CDCl_3$): δ, 0.88 (3 H, $J = 6.84$ Hz), 1.27–1.41 (4 H, m), 2.34 (2 H, m), 6.36 (1 H, td, $J = 8.79$, 6.35 Hz), 6.55 (1 H, td, $J = 54.9$, 6.34 Hz), 9.51 (1 H). ^{19}F NMR ($CDCl_3$): δ, 48.6 (dd, $J = 54.9$, 9.15 Hz); *Z*-isomer: 52.8 (ddt, $J = 54.9$, 10.7, 3.05) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 13.941, 22.356, 24.522, 28.794, 31.669, 111.299 (t, $J = 234.18$ Hz), 139.905 (t, $J = 26.1$ Hz), 148.686 (t, $J = 10.0$ Hz), 193.273 (*Z*-isomer: 189.711). IR: 1703 (C=O) cm^{-1}.

3.6. 3-Difluoromethyl-2-hexylpropenal **5e**

E-isomer: ^{1}H NMR ($CDCl_3$): δ, 0.89 (3 H, t, $J = 8.08$ Hz), 1.26–1.57 (8 H, m), 2.34 (2 H, t, $J = 7.57$ Hz), 6.37 (td, $J = 9.03$, 6.35 Hz), 6.55 (td, $J = 54.9$, 6.34 Hz), 9.51 (t, $J = 0.8$ Hz). ^{19}F NMR ($CDCl_3$): δ, 48.6 (dd, $J = 54.9$, 7.63 Hz); *Z*-isomer: 52.8 (ddt, $J = 54.9$, 10.7, 3.05 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 13.801, 22.306, 24.302, 28.911, 28.983, 31.225, 111.113 (t, $J = 234.18$ Hz; *Z*-isomer: 109.785, t, $J = 233.60$ Hz), 138.613 (t, $J = 26.34$ Hz; *Z*-isomer: 133.780, t, $J = 26.63$ Hz), 148.473 (t, $J = 10.02$ Hz), 193.007 (*Z*-isomer: 189.453). IR: 1701 (C=O) cm^{-1}.

3.7. 3-Difluoromethyl-2-octylpropenal **5f**

E-isomer: ^{1}H NMR ($CDCl_3$): δ, 0.87 (3 H, t, $J = 7.14$ Hz), 1.27 (12 H, m), 2.35 (2 H, m), 6.56 (1 H, td, $J = 54.7$, 6.32 Hz), 6.36 (1 H, td, $J = 8.79$, 6.32 Hz), 9.51. ^{19}F NMR ($CDCl_3$): δ, 48.6 (dd, $J = 54.3$, 8.62 Hz); *Z*-isomer: 52.5 (ddt, $J = 55.2$, 10.3, 3.45 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 14.085, 22.697, 24.518, 29.150, 29.180, 29.230, 29.541, 31.821, 111.299 (t, $J = 234.18$ Hz; *Z*-isomer: 109.975, t, $J = 233.61$ Hz), 138.833 (t, $J = 26.05$ Hz), 148.674 (t, $J = 10.02$ Hz), 193.205 (*Z*-isomer: 189.658). IR: 1701 (C=O) cm^{-1}.

3.8. 3-Trifluoromethyl-2-benzylpropenal **5g**

In the 1-ethyl-3-methyl-1*H*-imidozolium trifluoromethanesulfonate ([emim][OTf], 2.04 g), 3-phenylpropanal (444 mg, 3.31 mmol), trifluoroacetaldehyde ethyl hemiacetal (1.43 g, 9.94 mmol) and diethylaminotrimethylsilane (0.479 g, 3.43 mmol) were added, and then the whole was stirred at room temperature. After overnight of stirring, the product was extracted with diethyl ether (10 times × 20 ml). The organic layer was dried over anhydrous $MgSO_4$, and then the solvent was removed. Products were purified by column chromatography on silica gel using a mixture of hexane-ethyl acetate (10:1), giving 3-difluoromethyl-2-benzylpropenal.

^{1}H NMR ($CDCl_3$): δ, 3.85 (2 H, s), 6.47 (1 H, q, $J = 7.82$ Hz: *Z*-isomer; 6.17, qt, $J = 9.28$, 1.71 Hz), 7.16–7.29 (Ar–H), 9.52. ^{19}F NMR ($CDCl_3$): δ, 103.04 (d, $J = 7.63$ Hz); *Z*-isomer: 108.38 (d, $J = 7.63$ Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 111.792 (t, $J = 233.04$ Hz; *Z*-isomer: 110.164, t.

3.9. 3-Trifluoromethyl-2-butylpropenal **5h**

^{1}H NMR ($CDCl_3$): δ, 0.90 (3 H), 1.25–1.40 (4 H, m), 2.45 (2 H, m), 6.34 (1 H, q, $J = 8.24$ Hz), 9.36. ^{19}F NMR ($CDCl_3$): δ, 102.30 (d, $J = 7.75$, 1.72 Hz); *Z*-isomer: 108.45 (m) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 14.040, 22.655, 24.499, 31.745, 122.79 (q, $J = 271.4$ Hz), 133.445 (q, $J = 35.2$ Hz), 150.856 (q, $J = 4.58$ Hz), 192.427.

3.10. 3-Trifluoromethyl-2-hexylpropenal **5i**

^{1}H NMR ($CDCl_3$): δ, 0.88 (3 H, t, $J = 6.87$ Hz), 1.29 (8 H, m), 2.44 (2 H, m), 6.33 (1 H, q, $J = 8.24$ Hz), 9.51. ^{19}F NMR ($CDCl_3$): δ, 102.32 (dt, $J = 7.75$, 1.72 Hz); *Z*-isomer: 108.46 (ddd, $J = 9.48$, 3.45, 1.72 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 14.017, 22.515, 24.920, 28.824, 29.404, 31.388, 122.790 (q, $J = 271.40$ Hz), 133.439 (q, $J = 35.5$ Hz), 150.875 (q, $J = 4.01$ Hz), 192.438. IR: 1706 (C=O) cm^{-1}.

3.11. 3-Trifluoromethyl-2-octylpropenal **5j**

E-isomer: ^{1}H NMR ($CDCl_3$): δ, 0.88 (3 H, t, $J = 6.86$ Hz), 1.18–1.60 (12 H, m), 2.43 (2 H, m), 6.33 (1 H, q, $J = 7.96$ Hz), 9.51. ^{19}F NMR ($CDCl_3$): δ, 102.33 (dt, $J = 7.81$, 1.72 Hz); *Z*-isomer: 108.46 (ddd, $J = 9.48$, 4.31, 1.73 Hz) ppm from internal C_6F_6. ^{13}C NMR ($CDCl_3$): δ, 14.093, 22.686, 24.928, 28.866, 29.150, 29.180, 29.750, 31.847, 122.790 (q, $J = 271.4$ Hz), 133.42 (q, $J = 35.5$ Hz), 150.880 (q, $J = 4.30$ Hz), 192.408.

References

[1] L.F. Tietze, Chem. Rev. 96 (1996) 115–136.

[2] (a) J.T. Welch, S. Eswarakrishnan (Eds.), Fluorine in Bioorganic Chemistry, Wiley, New York, 1991;
(b) I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, American Chemical Society, Washington, DC, 1996;
(c) R.D. Chambers, Topis in Current Chemistry, vol. 193, Springer, Berlin, Heidelberg, 1997;
(d) T. Kitazume, T. Yamazaki, Experimental Methods in Organic Fluorine Chemistry; Kodansha and Gordon and Breach Science, Tokyo, 1998

[3] D.J. Burton, Z.-Y. Yang, W. Qiu, Chem. Rev. 96 (1996) 1641–1715, and references cited therein.

[4] T. Kawasaki, T. Ichige, T. Kitazume, J. Org. Chem. 63 (1998) 7525–7528.

[5] H. Urata, T. Fuchikami, Tetrahedron Lett. 32 (1991) 91–94.

[6] (a) T. Ishihara, M. Kuroboshi, Chem. Lett. (1987) 1145–1148;
(b) M. Kuroboshi, N. Yamada, Y. Takebe, T. Hiyama, Tetrahedron Lett. 36 (1995) 6271–6274.

[7] (a) H. Hagiwara, N. Komatsubara, T. Hoshi, T. Suzuki, M. Ando, Tetrahedron Lett. 40 (1999) 1523–1526;
(b) H. Hagiwara, H. Ono, N. Komatsubara, T. Hoshi, T. Suzuki, M. Ando, Tetrahedron Lett. 40 (1999) 6627–6630;
(c) H. Hagiwara, N. Komatsubara, H. Ono, T. Okabe, T. Hoshi, T. Suzuki, M. Ando, M. Kato, J. Chem. Soc. Perkin Trans. I. (2001) 316–322;
(d) H. Hagiwara, S. Tsuji, T. Okabe, T. Hoshi, T. Suzuki, K. Shimizu, Y. Kitayama, Green Chem. (2002) 461–463;
(e) H. Hagiwara, T. Okabe, H. Ono, V. P. Kamat, T. Hoshi, T. Suzuki, M. Ando, J. Chem. Soc., Perkin Trans. I (2002) 895–900.

[8] S. Kaneko, T. Yamazaki, T. Kitazume, J. Org. Chem. 58 (1993) 2302–2312.

[9] P. Tundo, P. T. Anastas, Green Chemistry: Challenging Perspectives, Oxford Science, Oxford, 1999.

[10] (a) C. Pascual, J. Meier, W. Simon, Helv. Chim. Acta 49 (1966) 164;
(b) T.H. Instle, B.Y. Mandanas, Chem. Commun. (1968) 1699;
(c) K. Mori, M. Matsui, Tetrahedron 26 (1970) 2801;
(d) J.P. Gillet, R. Sauvétre, J. F. Normant, Synthesis (1982) 297.;
(e) L. Xiao, T. Kitazume, J. Fluorine Chem. 86 (1997) 99–104.