Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Fluorine Chemistry 127 (2006) 545–547
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Asymmetric synthesis of β-hydroxy-β-trifluoromethylated ketones via in situ generation of trifluoroacetaldehyde and its asymmetric carbon–carbon bond formation reaction with chiral imines in aqueous media

Kazumasa Funabiki *, Kazutoshi Hasegawa, Yoshihiro Murase, Hideyuki Nagaya, Masaki Matsui

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1, Yanagido, Gifu 501-1193, Japan

Received 28 December 2005; accepted 29 December 2005
Available online 21 February 2006

Abstract

Asymmetric synthesis of β-hydroxy-β-trifluoromethylated ketones via in situ generation of trifluoroacetaldehyde from its hemiacetal as well as the simultaneous asymmetric carbon–carbon bond formation reaction in aqueous media is described.

Keywords: Fluorine and compounds; Asymmetric synthesis

1. Introduction

Much attention has been addressed to the synthesis of trifluoromethylated compounds, because the introduction of the trifluoromethyl group often improve the chemical, physical and biological properties of the organic molecules [1]. Recently, although various types of asymmetric synthesis of these compounds have been reported [2], there is only few literatures concerning with asymmetric synthesis of trifluoromethylated compounds in aqueous media [3]. In our continuing studies on the in situ generation of trifluoroacetaldehyde from its hemiacetal or hydrate as well as successive carbon–carbon bond formation reaction with imines or enamines [4], we have found that in situ generation of trifluoroacetaldehyde and its simultaneous *asymmetric* carbon–carbon bond formation reaction with chiral imines occurred *in aqueous media*. Herein we wish to describe asymmetric synthesis of β-hydroxy-β-trifluoromethylated ketones by the reaction of trifluoroacetaldehyde ethyl hemiacetal with chiral imines in aqueous media.

2. Results and discussion

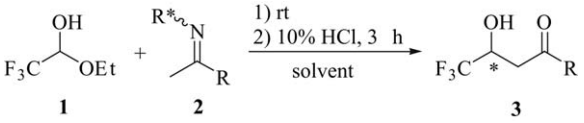
Chiral imines **2** were prepared according to our previous report [5]. That is, treatment of acetophenone with chiral amine in the presence of a catalytic amount of *p*-toluenesulfonic acid for overnight or 2 days gave the corresponding chiral imine **2** in good yields via distillation or recrystallization.

When trifluoroacetaldehyde ethyl hemiacetal **1** was treated with an equimolar amount of chiral imine **2a**, derived from (*S*)-1-phenylethylamine, at ambient temperature in a buffer solution (pH 4.01), after hydrolysis of the reaction mixture, β-hydroxy-β-trifluoromethylated ketone **3a** was obtained in 45% yield with 49.6% *ee* (Table 1, entry 3). The absolute configuration of **3a** could be determined as *R* by the comparison with the reported optical rotation value [6]. The results of the reaction between trifluoroacetaldehyde ethyl hemiacetal **1** and an equimolar amount of chiral imine **2a** in various aqueous media are summarized in Table 1. Using other buffer solutions (pH 9.18 and 6.86) gave similar yields as well as the enantioselectivities (entries 1 and 2). The use of distilled water resulted in slight reduction of the yield (entry 4). Enantiomer ratios of the aldol product **3a** are equally good to high in every instance under different pH conditions, when compared with the reported results by other reactions in aqueous media [3].

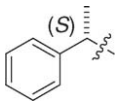
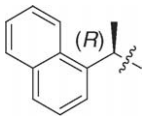
* Corresponding author. Fax: +81 58 293 2599.
E-mail address: kfunabik@apchem.gifu-u.ac.jp (K. Funabiki).

0022-1139/$ – see front matter
doi:10.1016/j.jfluchem.2005.12.020

Table 1
Asymmetric synthesis of (3-hydroxy-(3-trifluoromethylated) ketones via in situ generation of CF_3CHO and its asymmetric reaction with chiral imines in aqueous media



1 2 3

Entry[a]	2	R^*	R	pH of a buffer solution	Time (h)	3	Yield of 3[b] (%)	Isomer ratio (S:R)[c]
1	**2a**		Ph	9.18	24	**3a**	39	25.0:75.0
2				6.86	24		41	25.3:74.7
3				4.01	24		45	25.2:74.8
4				Distilled water	24		35	25.0:75.0
5				4.01	48		62	25.0:75.0
6	**2b**		4-ClC_6H_4	4.01	48	**3b**	12	81.4:18.6

[a] All the reaction was conducted with trifluoroacetaldehyde ethyl hemiacetal **1** (0.5 mmol) and imine **2** (0.5 mmol) in solvent (2 ml).
[b] Yields of isolated products.
[c] Determined by HPLC analysis with CHIRALCEL OD-H (hexane:*i*-PrOH = 95/5).

Interestingly, although the reaction of hemiacetal **1** with chiral imine **2a** in aqueous media proceeded more slowly than those in organic solvents, such as hexane, toluene, dichloromethane (CH_2Cl_2) and acetonitrile (MeCN), the enanitoselectivities of **3a** in aqueous media are slightly better than those in MeCN (S:R = 71.9:28.1) and CH_2Cl_2 (S:R = 71.3:28.7) [4a]. Prolonged reaction time (48 h) resulted in the increase of the product **3a** (entry 5). The reaction of hemiacetal **1** with other chiral imine **2b**, derived from 4-chloroacetophenone and (*R*)-1-(1-naphthyl)ethylamine, was sluggish to produce the product **3b** in only 12% yield, due to the low solubility of the solid chiral imine **2b** (entry 6). However, the enantioselectivity (S:R = 81.4:18.6) of the aldol adduct **3b** was much higher than that of **3a**, because the 1-(1-naphthyl)ethyl group is much bulkier than the 1-phenylethyl one.

3. Conclusion

In summary, we have demonstrated the first example of the in situ generation of trifluoroacetaldehyde from its hemiacetal as well as the simultaneous asymmetric carbon–carbon bond formation reaction in aqueous media, affording a novel asymmetric synthetic route to β-hydroxy-β-trifluoromethylated ketones.

4. Experimental

4.1. Measurements

^1H (400 MHz) or ^{13}C (100 MHz) NMR spectra were measured with a JEOL α-400 FT-NMR spectrometers in $CDCl_3$ solutions with TMS as the internal standard. ^{19}F NMR (376 MHz) spectra were recorded on a JEOL α-400 FT-NMR in $CDCl_3$ solutions using TFA as the external standard. Optical rotations were measured on a HORIBA SEPA-300 in Uvasol grade $CHCl_3$ (Merck). HPLC was achieved using a Daicel CHIRALCEL OD (Daicel, 0.46 cm × 25 cm) column on a SHIMADZU LC-4A using *n*-hexane:*i*-PrOH = 95:5 as an eluent with the flowing rate of 0.8 ml/min and detected at 254 nm. Melting points were obtained on a Yanagimoto MP-S2 micro melting point apparatus and were uncorrected. The IR spectra were recorded on a SHIMADZU FT-IR 8100A spectrometer.

4.2. Reaction of trifluoroacetaldehyde ethyl hemiacetal with chiral imines in aqueous media

Trifluoroacetaldehyde ethyl hemiacetal **1** (0.074 g, 0.500 mmol) was added to a mixture of chiral imine **2a** (0.112 g, 0.500 mmol) in a buffer solution was added at room temperature. After being stirred at the same temperature for 48 h, the reaction mixture was hydrolyzed with 10% HCl aq. (2 ml) for 3 h, followed by extraction with Et_2O (30 ml × 3), dried over Na_2SO_4, and concentration under vacuum. The residue was chromatographed on silica gel using hexane–EtOAc, giving **3a** in 62% yield (0.067 g, 50.0% *ee*). The *ee* of the product was determined by chiral HPLC analysis.

4.2.1. (R)-4,4,4-trifluoro-3-hydroxy-1-phenyl-1-butanone ((R)-3a)

Chiral HPLC (Daicel, CHIRALCEL OD, *n*-hexane:*i*-PrOH = 95:5, 0.8 ml/min, 254 nm, t_R = 15.0 min (*S*), 17.5 min (*R*)); 41.0–42.0 °C (92.8% *ee* (*S*), hexane), IR (KBr) 1686.5 (C=O), 3390.3 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (dd, J = 17.93, 3.17 Hz, 1H), 3.39 (dd, J = 17.93, 8.79 Hz, 1H), 3.47 (d, J = 2.92 Hz, 1H), 4.65–4.74 (m, 1H), 7.49–7.53 (m, 2H), 7.62–7.66 (m, 1H), 7.97–7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 38.22 (s), 67.03 (q, J = 31.98 Hz), 124.69 (q,

J = 280.37 Hz), 128.21 (s), 128.88 (s), 134.18 (s), 135.96 (s), 197.56 (s); ^{19}F NMR ($CDCl_3$) δ 1.80 (d, J = 6.87 Hz, 3F); MS (EI) m/z (rel intensity) 218 (M^+; 11.7), 200 (4.0), 198 (12.2), 162 (3.8), 106 (7.9), 105 (100.0), 78 (4.1), 77 (38.9). HRMS (EI) Calcd for $C_{10}H_9F_3O_2$: M, 218.0555. Found: m/z 218.0533. Anal. Calcd for: C, 55.05; H, 4.21. Found: C, 54.99; H, 4.21.

*4.2.2. (S)-1-(4-chlorophenyl)-4,4,4-trifluoro-3-hydroxy-1-butanone ((S)-**3b**)*

Chiral HPLC (t_R = 14.5 min (S), 15.5 min (R)); mp 57.0–58.0 °C (>99.9% *ee* (S), hexane); IR (KBr) 1688.3 (C=O), 3383.7 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.27 (dd, J = 17.63, 2.56 Hz, 1H), 3.37 (dd, J = 17.63, 9.27 Hz, 1H), 3.40 (d, J = 4.63 Hz, 1H), 4.65–4.74 (m, 1H), 7.49 and 7.92 (AB quartet, J = 8.79 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 38.28 (s), 66.90 (q, J = 33.08 Hz), 124.70 (q, J = 281.19 Hz), 129.24 (s), 129.60 (s), 134.29 (s), 140.76 (s), 196.18 (s); ^{19}F NMR ($CDCl_3$) δ 1.50 (d, J = 6.86 Hz, 3F). MS (EI) m/z (rel intensity) 254 (M^+ + 2; 1.3), 252 (M^+; 4.0), 236 (13.0), 235 (3.7), 234 (34.2), 232 (7.8), 142 (3.3), 141 (40.6), 140 (10.0), 139 (100.0), 123 (4.5), 113 (14.8), 112 (4.4), 111 (33.8), 76 (4.1), 75 (14.0), 74 (3.7); HRMS (EI) Calcd for $C_{11}H_{11}{}^{37}ClF_3O_3$: M, 254.0135. Found: m/z 254.0138. Calcd for $C_{11}H_{11}{}^{35}ClF_3O_3$: M, 252.0165. Found: m/z 252.0162. Anal. Calcd for: C, 47.55; H, 3.19. Found: C, 47.54; H, 3.30.

Acknowledgments

This work was partially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the OGAWA Science and Technology Foundation and Gifu University. We are grateful to the Central Glass Co. Ltd., for the gift of trifluoroacetaldehyde ethyl hemiacetal as well as financial support. We thank Professors H. Yamanaka and T. Ishihara as well as Dr T. Konno of the Kyoto Institute of Technology for the HRMS measurements.

References

[1] T. Hiyama (Ed.), Organofluroine Compounds: Chemistry and Applications, Springer, Berlin, 2000.
[2] (a) K. Iseki, Tetrahedron 54 (1998) 13887–13914;
(b) V. Soloshonok (Ed.), Enantiocontrolled Synthesis of Fluoro-organic Compounds, John Wiley & Sons, Chichester, 1999;
(c) P.V. Ramachandran (Ed.), Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions, American Chemical Society, Washington, DC, 1999;
(d) K. Mikami, Y. Itoh, M. Yamanaka, Chem. Rev. 141 (2004) 1–16.
[3] (a) T.-P. Loh, X.-R. Li, Angew. Chem. Int. Eng. 36 (1997) 980–982;
(b) T.-P. Loh, Tetrahedron 55 (1999) 5611–5622.
[4] (a) K. Funabiki, W. Hashimoto, M. Matsui, Chem. Commun. (2004) 2056–2057;
(b) K. Funabiki, K. Matsunaga, M. Nojiri, W. Hashimoto, H. Yamamoto, K. Shibata, M. Matsui, J. Org. Chem. 68 (2003) 2853–2860;
(c) K. Funabiki, K. Matsunaga, M. Matsui, K. Shibata, Synlett (1999) 1477–1479;
(d) K. Funabiki, M. Nojiri, M. Matsui, K. Shibata, Chem. Commun. (1998) 2051–2052.
[5] K. Funabiki, N. Honma, W. Hashimoto, M. Matsui, Org. Lett. 5 (2003) 2059–2061.
[6] J.T. Lin, T. Yamazaki, T. Kitazume, J. Org. Chem. 52 (1987) 3211–3217.