Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2008

Supporting Information

Facile and Highly Efficient Synthesis of Fluorinated Heterocycles via Prins Cyclization in Ionic Liquid Hydrogen Fluoride Salts

*Yuichiro Kishi, Hirokatsu Nagura, Shinsuke Inagi and Toshio Fuchigami**

Department of Electronic Chemistry, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8502, Japan
E-mail: fuchi@echem.titech.ac.jp

General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on JEOL JNM EX-270 (^{1}H: 270 MHz, ^{13}C: 67.8 MHz, ^{19}F: 254 MHz) spectrometer in $CDCl_3$. The chemical shifts for ^{1}H, ^{13}C, and ^{19}F NMR spectra were given in δ (ppm) from internal TMS, $CDCl_3$, and monofluorobenzene (-36.5 ppm), respectively. EI mass spectra were recorded on Shimadzu GCMS-QP5050A mass spectrometer. HR mass spectra were recorded on JEOL The MStation JMS-700.

Materials

1-Octanal (**1a**), cyclohexanecarboxaldehyde (**1b**), benzaldehyde (**1c**), 4-nitrobenzaldehyde (**1d**), *p*-tolualdehyde (**1e**), cyclohexanone (**1f**), 3-buten-1-ol (**2a**), 1-phenyl-3-buten-1-ol (**2c**), and 3-buten-1-amine (**15a**) were purchased and used without purification. 1-Undecen-4-ol (**2b**),[1] 3-buten-1-thiol (**11a**),[2] and *N*-(3-butenyl)-*p*-toluenesulfonamide (**15b**)[3] were synthesized according to the literature. Et_3N-3HF, Et_3N-4HF, Et_3N-5HF, Et_4NF-4HF, and Et_4NF-5HF were kindly supplied by Morita Chemical Industries Co. Ltd. (Japan). Ionic liquid HF salts are toxic and may cause serious burns if they come in contact with unprotected skin.

General procedure for Prins cyclization

Prins cyclization of various aldehydes or ketones (0.2 mmol) and homoallylic alcohols, thiols or amines (0.2 mmol) was carried out in Et_4NF-5HF (3 ml) using a plastic cell at room temperature. The conversion of starting materials was monitored by TLC. After the stating materials were consumed, the reaction mixture was passed through a short column of silica gel eluting with ethyl acetate to remove the fluoride salt. The eluent was evaporated under vacuum. Then, the almost pure product was obtained. In case of thia- or aza-Prins cyclization, the products were obtained as stereoisomeric mixtures of cis and trans

forms. Then the diastereomeric ratio was calculated by means of ^{19}F NMR by using monofluorobenzene as an internal standard. Next, after the products were purified by silica gel column chromatography eluting with hexane and ethyl acetate, the total isolated yields of both stereoisomeric mixtures were calculated.

Spectroscopic data of fluorinated products ***5-8, 10, 12-14, 17-19***

cis-4-Fluoro-2-phenyltetrahydropyran (5)

Obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 4.95-4.65 (m, J_{H-F} = 49.1 Hz, 1H), 4.33-4.27 (m, 1H), 4.24-4.15 (m, 1H), 3.60-3.49 (m, 1H), 2.38-2.28 (m, 1H), 2.15-2.06 (m, 1H), 1.94-1.68 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.1 (d, J = 1.7 Hz), 128.3, 127.7, 125.7, 89.3 (d, J = 176.1 Hz), 77.8 (d, J = 11.2 Hz), 65.4 (d, J = 12.1 Hz), 40.5 (d, J = 17.2 Hz), 33.0 (d, J = 17.3 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ -93.1 (m); MS (m/z) 180 (M^+), 179 ($M-H^+$), 105, 91, 77, 51; HRMS Calcd for $C_{11}H_{13}FO$: 180.0950. Found: 180.0949.

cis-4-Fluoro-2-(4-nitrophenyl)tetrahydropyran (6)

Obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 8.21 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 5.00-4.70 (m, J_{H-F} = 49.0 Hz, 1H), 4.46-4.42 (m, 1H), 4.29-4.20 (m, 1H), 3.65-3.54 (m, 1H), 2.42-2.34 (m, 1H), 2.20-2.12 (m, 1H), 1.95-1.58 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 148.4 (d, J = 1.7 Hz), 147.2, 126.3, 123.6, 88,7 (d, J = 176.8 Hz), 76.5 (d, J = 11.4 Hz), 65.4 (d, J = 12.1 Hz), 40.5 (d, J = 17.9 Hz), 32.8 (d, J = 17.7 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ -93.7 (m); MS (m/z) 224 ($M-H^+$), 208, 178, 150, 107, 77, 59; HRMS Calcd for $C_{11}H_{12}FNO_3$: 225.0801. Found: 225.0803.

cis-4-Fluoro-2-_p_-tolyltetrahydropyran (7)

Obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.22 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.92-4.62 (m, J_{H-F} = 49.1 Hz, 1H), 4.28-4.12 (m, 2H), 3.57-3.47 (m, 1H), 2.32 (s, 3H), 2.30-2.24 (m, 1H), 2.12-2.04 (m, 1H), 1.92-1.66 (m, 2H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.1 (d, J = 1.7 Hz), 137.3, 128.9, 125.7, 89.3 (d, J = 175.9 Hz), 77.6 (d, J = 11.2 Hz), 65.3 (d, J = 12.1 Hz), 40.5 (d, J = 16.7 Hz), 33.0 (d, J = 17.3 Hz), 21.1; ^{19}F NMR (254 MHz, $CDCl_3$) δ -93.0 (m); MS (m/z) 194 (M^+), 179, 119, 105, 91, 77, 65, 55; HRMS Calcd for $C_{12}H_{15}FO$: 194.1107. Found: 194.1107.

cis-4-Fluoro-2,6-diheptyltetrahydropyran (8)

Obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 4.80-4.50 (m, J_{H-F} = 49.4 Hz, 1H), 3.22 (m, 2H), 2.10-2.03 (m, 2H), 1.64-1.27 (m, 26H), 0.88 (t, J = 6.4 Hz, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 89.8 (d, J = 174.0 Hz), 74.9 (d, J = 11.2 Hz), 38.7 (d, J = 16.2 Hz), 36.1 (d, J = 1.7 Hz), 31.9, 29.6, 29.3, 25.7, 22.7, 14.2; ^{19}F NMR (254 MHz, $CDCl_3$) δ -93.1 (m); MS (m/z) 300 (M^+), 201, 181, 163, 127, 113, 95, 81, 69, 55; HRMS Calcd for $C_{19}H_{37}FO$: 300.2828. Found: 300.2823.

4-Fluoro-1-oxa-spiro[5.5]undecane (10)

Obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ 5.01-4.73 (m, J_{H-F} = 49.3 Hz, 1H), 3.91-3.82 (m, 1H), 3.64-3.54 (m, 1H), 2.04-1.25 (m, 14H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 87.3 (d, J = 171.3 Hz), 73.2 (d, J = 7.3 Hz), 57.5 (d, J = 7.8 Hz), 41.6 (d, J = 17.2 Hz), 37.3 (d, J = 2.2 Hz), 33.7, 32.5 (d, J = 18.4 Hz), 25.9, 21.7, 21.4; ^{19}F NMR (254 MHz, $CDCl_3$) δ -99.1 (m); MS (m/z) 172 (M^+), 129, 116, 55; HRMS Calcd for $C_{10}H_{17}FO$: 172.1263. Found: 172.1262.

4-Fluoro-2-heptylthiacyclohexane (12)

Obtained as a clear oil.

cis-**12**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.54-4.25 (m, J_{H-F} = 46.9 Hz, 1H), 2.83-2.60 (m, 3H), 2.42-2.33 (m, 2H), 1.83-1.27 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 91.6 (d, J = 170.6 Hz), 42.1 (d, J = 12.3 Hz), 41.2 (d, J = 18.8 Hz), 35.8, 34.0 (d, J = 20.1 Hz), 31.8, 29.5, 29.2, 26.9, 26.6 (d, J = 13.4 Hz), 22.7, 14.2; ^{19}F NMR (254 MHz, $CDCl_3$) δ -90.4 (m), MS (m/z) 218 (M^+), 161, 143, 119, 101, 99, 73, 67, 55; HRMS Calcd for $C_{12}H_{23}FS$: 218.1504. Found: 218.1507.

trans-**12**: ^{19}F NMR (254 MHz, $CDCl_3$) δ -108.7 (m)

2-Cyclohexyl-4-fluorothiacyclohexane (13)

Obtained as a white silid, mp. 39-40 ^{o}C.

cis-**13**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.52-4.23 (m, J_{H-F} = 46.8 Hz, 1H), 2.79-2.57 (m, 3H), 2.43-2.33 (m, 2H), 1.83-1.05 (m, 13H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 92.3 (d, J = 170.1 Hz), 48.4 (d, J = 11.7 Hz), 42.5, 38.3 (d, J = 19.0 Hz), 34.2 (d, J = 20.1 Hz), 30.4, 30.3, 26.6 (d, J = 13.9 Hz), 26.4; ^{19}F NMR (254

MHz, $CDCl_3$) δ -89.5 (m); MS (m/z) 202 (M^+), 119, 99, 85, 73, 55; HRMS Calcd for $C_{11}H_{19}FS$: 202.1191. Found: 202.1189.

trans-**13**: ^{19}F NMR (254 MHz, $CDCl_3$) δ -108.8 (m)

4-Fluoro-2-phenylthiacyclohexane (14)

Obtained as a white silid, mp. 54-55 ^oC.

cis-**14**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.37-7.23 (m, 5H), 4.66-4.37 (m, J_{H-F} = 46.6 Hz, 1H), 3.96-3.90 (m, 1H), 2.93-2.73 (m, 2H), 2.61-2.43 (m, 2H), 2.18-2.03 (m, 1H), 1.94-1.76 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 140.4, 128.6, 127.6, 127.3, 91.8 (d, *J* = 171.2 Hz), 46.2 (d, *J* = 13.4 Hz), 41.5 (d, *J* = 19.4 Hz), 33.6 (d, *J* = 20.1 Hz), 28.1 (d, *J* = 14.4 Hz); ^{19}F NMR (254 MHz, $CDCl_3$) δ -90.2 (m); MS (m/z) 196 (M^+), 176, 161, 147, 135, 121, 105, 91, 77, 65, 51; HRMS Calcd for $C_{11}H_{13}FS$: 196.0722. Found: 196.0718.

trans-**14**: ^{19}F NMR (254 MHz, $CDCl_3$) δ -110.2 (m)

4-Fluoro-2-heptyl-*N*-tosylpiperidine (17)

Obtained as a clear oil.

cis-**17**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.86-4.57 (m, J_{H-F} = 48.5 Hz, 1H), 4.18-4.16 (m, 1H), 3.97-3.92 (m, 1H), 3.08-2.98 (m, 1H), 2.42 (s, 3H), 1.96-1.90 (m, 2H), 1.52-1.23 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.1, 138.1, 129.6, 126.7, 87.0 (d, *J* = 172.4 Hz), 53.6 (d, *J* = 12.8 Hz), 38.8 (d, *J* = 12.8 Hz), 34.2 (d, *J* = 18.3 Hz), 31.8, 31.3 (d, *J* = 18.8 Hz), 31.1, 29.2, 29.1, 26.5, 22.7, 21.6, 14.1; ^{19}F NMR (254 MHz, $CDCl_3$) δ -99.9 (m); MS (m/z) 256, 236, 155, 91, 55; HRMS Calcd for $C_{19}H_{30}FNO_2S$: 355.1981. Found: 355.1989.

trans-**17**: ^{19}F NMR (254 MHz, $CDCl_3$) δ -104.2 (m)

2-Cyclohexyl-4-fluoro-*N*-tosylpiperidine (18)

Obtained as a clear oil.

cis-**18**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.81-4.51 (m, J_{H-F} = 48.7 Hz, 1H), 3.98-3.92 (m, 1H), 3.82 (m, 1H), 3.03-2.93 (m, 1H), 2.42 (s, 3H), 2.17-2.10 (m, 1H), 1.87-0.88 (m, 14H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.1, 138.3, 129.7, 126.7, 86.8 (d, *J* = 172.3 Hz), 58.8 (d, *J* = 12.8 Hz), 39.2 (d, *J* = 12.8 Hz), 36.6, 31.0 (d, *J* = 13.9 Hz), 30.7 (d, *J* = 14.5 Hz), 30.3, 30.1,

26.1, 26.0, 25.9, 21.5; ^{19}F NMR (254 MHz, $CDCl_3$) δ -98.5 (m); MS (m/z) 256, 236, 155, 91, 55; HRMS Calcd for $C_{18}H_{26}FNO_2S$: 339.1668. Found: 339.1671.

trans-**18**: ^{19}F NMR (254 MHz, $CDCl_3$) δ -106.0 (m)

4-Fluoro-2-phenyl-*N*-tosylpiperidine (19)

Obtained as a clear oil.

cis-**19**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78-7.75 (m, 2H), 7.35-7.22 (m, 7H), 5.43 (m, 1H), 4.73-4.44 (m, J_{H-F} = 48.6 Hz, 1H), 4.02-3.95 (m, 1H), 3.07-2.96 (m, 1H), 2.70-2.60 (m, 1H), 2.44 (s, 3H), 1.87-1.82 (m, 1H), 1.76-1.62 (m, 1H), 1.52-1.33 (m, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.4, 137.7, 137.5, 129.8, 128.7, 127.2, 126.8, 126.3, 86.6 (d, J = 173.1 Hz), 55.5 (d, J = 12.6 Hz), 39.9 (d, J = 12.3 Hz), 33.5 (d, J = 19.1 Hz), 31.1 (d, J = 19.0 Hz), 21.6; ^{19}F NMR (254 MHz, $CDCl_3$) δ -99.4 (m); MS (m/z) 333 (M^+), 256, 178, 155, 144, 130, 115, 104, 91, 77, 65, 51; HRMS Calcd for $C_{18}H_{20}FNO_2S$: 333.1199. Found: 333.1199.

trans-**19**: ^{19}F NMR (254 MHz,$CDCl_3$) δ -105.4 (m)

References

(1) J. Yoshida, M. Sugawara, M. Tastumi, N. Kise, *J. Org. Chem.* **1998**, *63*, 5950-5961.

(2) M. Minozzi, D. Nanni, J. C. Walton, *Org. Lett.* **2003**, *5*, 901-904.

(3) S. Handa, M. S. Kachala, S. R. Lowe, *Tetrahedron Lett.* **2004**, *45*, 253-256.