Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 37-40, 1996
Published by Elsevier Science Ltd
Printed in Great Britain
0957-4166/96 $15.00 + 0.00

0957-4166(95)00415-7

Enantioselective Synthesis of 2-Fluoro Carboxylic Acids from Trichloromethyl Carbinols: an Efficient Approach to Chiral Fluorine Introduction into Insect Sex Pheromones

Achot P. Khrimian,*† James E. Oliver,‡ Rolland M. Waters,‡ Sini Panicker,† Jesse M. Nicholson,† and Jerome A. Klun‡

†Department of Chemistry, Howard University, Washington, D.C. 20059. *Mailing address: B.007, ICEL, BARC-W, Beltsville, MD 20705-2350. ‡USDA-ARS, Insect Chemical Ecology Laboratory, Beltsville, MD 20705;

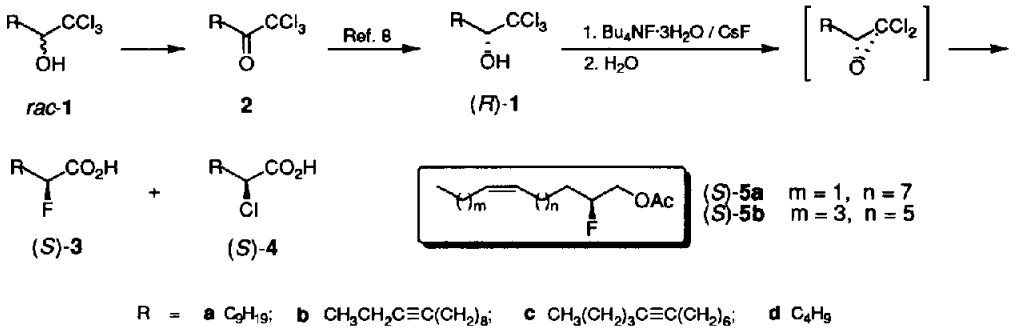
Abstract : Chiral syntheses of 2-fluoro carboxylic acids were achieved (ee ≥ 92 %, yield 50-60 %) by stereoselective conversion (with inversion of configuration) of optically active trichloromethyl carbinols to fluoroacids with tetrabutylammonium fluoride. Fluorinated pheromone analogs of the European corn borer, *Ostrinia nubilalis* , and of the beet armyworm, *Spodoptera exigua*, were synthesized.

We recently reported a convenient synthesis of racemic 2-fluoro carboxylic acids and the utilization of these products in the syntheses of fluorinated insect pheromone analogs.[1] Preliminary results with the fluorinated pheromone analogs, both in behavioral[2] and catabolic[3] studies, stimulated a need for these materials as individual enantiomers, and we investigated modifications of the earlier synthetic conditions that would permit syntheses of chiral 2-fluoroacids. Optically active 2-fluoro carboxylic acids have previously been synthesized by deamination of corresponding aminoacids with HF·Py with little[4a] or no racemization,[4b] asymmetric hydrogenation of 2-fluoro-2-alkenoic acids (ee ≤ 90%),[5] through diastereoselective electrophilic fluorination of chiral imide enolates with subsequent hydrolysis of corresponding 2-fluoro amides (ee ≤ 90%)[6], and by nucleophilic displacement (KF / formamide) of chiral 2-sulfonyloxy esters followed by transesterification of 2-fluoro methyl esters by formic acid and liberation of free acid (ee ≤ 92 %).[7] Herein we report facile chiral syntheses of 2-fluoro carboxylic acids with ee ≥ 92 % and 50-60 % yield from readily available optically active trichloromethyl alcohols.[8] The utility of the method is demonstrated by the preparation of individual enantiomers of 2-fluoro analogs of two insect sex pheromones.

The racemic trichloromethyl alcohols **1**[9] (Scheme 1) were converted to the respective ketones **2** *via* Swern oxidation.[10] Enantioselective reduction of the ketones **2** by catecholborane in the presence of (*S*) and (*R*) oxazaborolidine catalysts, respectively, provided (*R*)- and (*S*)- carbinols **1**.[11] Treatment of (*R*)-**1a** with 1M $Bu_4NF{\cdot}3H_2O$ in THF + CsF[1], afforded a 73:27 mixture of **3a** and **4a** (Scheme 1), with **3a** consisting of 72:28 (*S*) : (*R*) and **4a** consisting of 59:41 (*S*) : (*R*). The ratios did not change with time, and from various controls we concluded that the products, once formed, were neither racemizing nor interconverting under the conditions. Although no recognizable pattern emerged, we found that the ratios of fluoroacid to chloroacid, as well as the enantiomeric proportions, varied with solvent and temperature (see Table 1). The best results for enantioselective conversion of (trichloromethyl)carbinol **1** to fluoroacid **3** were achieved with excess $Bu_4NF{\cdot}3H_2O$ plus CsF in

dichloromethane at 0-5 °C[12]. Curiously, chloroacids were in all cases formed with lower enantioselectivity than the corresponding fluoroacids.

Scheme 1



R = **a** C_9H_{19}; **b** $CH_3CH_2C{\equiv}C(CH_2)_8$; **c** $CH_3(CH_2)_3C{\equiv}C(CH_2)_6$; **d** C_4H_9

The fact that (*R*)-**1d** was converted to (*S*)-(-)-2-fluorohexanoic acid (**3d**)[14] of known absolute configuration is consistent with the mechanism outlined in Scheme 1. The clean inversion of configuration in CH_2Cl_2 is indicative of an S_N2 opening of the dichlorooxirane by fluoride, consistent with the stereochemistry of *gem*-dichlorooxirane ring opening by other nucleophiles.[8] The moderate stereoselectivity of chloroacid formation may be attributable to the occurrence of both intermolecular[15] or intramolecular[16] chloride transfer, with the latter possibly involving different mechanisms. From a practical standpoint, the use of $Bu_4NF{\cdot}3H_2O$, which presumably acts as both base and nucleophile, is crucial for the fluorine introduction (no conversions of carbinols **1** to fluoroacids have been successful in the absence of Bu_4NF). "Partially dehydrated" (40-45 °C / 0.25 mm, 5 h.) tetrabutylammonium fluoride (Table 1, entry 8) seemed to favor fluorination over chlorination (**3/4** - 87:13), most likely as a result of increased nucleophilicity of fluoride.[17] However, probably due to its high basicity, this reagent also promoted retrocondensation of the (trichloromethyl)carbinol **1**, thus lowering the yield of fluoroacid. In contrast to the dried reagent, the use of exposed-to-air tetrabutylammonium fluoride (entry 9) significantly decreased fluorination in favor of chlorination.

We next turned our attention to chiral synthesis of two unsaturated 2-fluoro acetates (Scheme 1), the analogs of the European corn borer, *Ostrinia nubilalis* (**5a**), and beet armyworm, *Spodoptera exigua* (**5b**) sex pheromones. Fluoroacid (*R*)-**3b** was reduced with LAH (1.2 eq., THF, -20 °C, yield 70-75 %), the resulting alcohol was acetylated (Ac_2O, Py, 20 °C) and then semi-hydrogenated (H_2, Pb-poisoned $Pd/CaCO_3$, cyclohexene) to provide (*R*)-2-fluoro-(*Z*)-11-tetradecen-1-ol acetate (**5a**) (yield 65 % from (*S*)-**3b**), $[\alpha]^{25}_D$ - 4.58 (c 0.94, $CHCl_3$). The enantiomeric purity of the intermediate acetylenic fluoroalcohol, determined by GC analysis of the corresponding Mosher ester,[18] was 92 %. Analogously, (*S*)-**3b** was converted to (*S*)-**5a** (62 %, $[\alpha]^{25}_D$ + 3.68 (c 1.58, $CHCl_3$), ee 90 %), and (*S*)-**3c** to (*S*)-**5b** (60 %, ee 92 %, $[\alpha]^{25}_D$ + 4.40 (c 1.01, $CHCl_3$).[19]

From preliminary assays (*S*)-**5a** and (*R*)-**5a** displayed remarkably different behavior eliciting properties against the European corn borer. The (*R*)-enantiomer mimicked the natural pheromone, while *S* was behaviorally inert. Complete bioassay data will be reported elsewhere.

Table 1: Synthesis of optically active fluoroacids **3** and chloroacids **4** from trichloromethyl alcohols **1**

Entry	Starting alcohol	Reaction conditions	**3** / **4**[a]	Fluoroacid **3** yield[b], %	Fluoroacid **3** ee[c], % (*R*/*S*)	Chloroacid **4** ee[c], %
1	(*R*)-**1a**	CH_2Cl_2, 0-20 °C	67 : 33	51[d]	94 (*S*)	33
2	(*R*)-**1a**	DMSO, 0-20 °C	86 : 14	-	66 (*S*)	40
3	(*R*)-**1a**	THF, 0-20 °C	73 : 23	-	44 (*S*)	18
4	(*R*)-**1b**	CH_2Cl_2, 0-5 °C	70 : 30	53[e]	90 (*S*)	42
5	(*S*)-**1b**	CH_2Cl_2, 0-5 °C	75 :35	60[f]	92 (*R*)	46
6	(*R*)-**1b**	CH_2Cl_2, 20 °C	60 : 40	35	86 (*S*)	30
7	(*R*)-**1c**	CH_2Cl_2, 0-5 °C	72 : 28	53[g]	94 (*S*)	50
8	(*R*)-**1c**	TBAF:H_2O (>1:3) CH_2Cl_2, 0-5 °C	87 : 13	42	94 (*S*)	-
9	(*S*)-**1b**	TBAF:H_2O (<1:3) CH_2Cl_2, 0-5 °C	45 : 55	28	90 (*R*)	-
10	(*R*)-**1d**	CH_2Cl_2, 0-5 °C	80 : 20	50	90 (*S*)[h]	-

[a] Determined by GC analysis of methyl esters. [b] Isolated yield after flash chromatography. All new compounds gave satisfactory C, H analyses. [c] GC of corresponding (*S*)-α- methylbenzylamides (Ref. 13) [d] Racemic fluoroacid was characterized in Ref. 1. [e] $[\alpha]^{25}_D$ - 6.5 (c 0.56, $CHCl_3$); spectral data of rac. acid are presented in Ref. 1. [f] $[\alpha]^{25}_D$ + 6.7 (c 0.57, $CHCl_3$). [g] $[\alpha]^{25}_D$ - 6.6 (c 1.15, $CHCl_3$); ^1H NMR of methyl ester (300 MHz, $CDCL_3$): 0.91 (t, 3H, J = 6.3 Hz), 1.44 (m, 12H), 1.80 - 1.98 (m, 2H, H-3), 2.14 (t, 4H, J = 6.3 Hz), 3.80 (s, 3H, OCH_3), 4.91 (dt, 1H, $^3J_{HH}$ = 5.8, $^2J_{HF}$ = 49.0 Hz, CHF); ^{19}F NMR (283 MHz, $CDCl_3$ / CCl_3F): - 192.6 (dt, $^3J_{HF}$ = 26,3 Hz). [h] $[\alpha]^{25}_D$ - 11.4 (c 1.25, $CHCl_3$); Lit.[14] ee 68.5 %, $[\alpha]^{25}_D$ - 8.68 (c 1.3, $CHCl_3$).

REFERENCES AND NOTES

1. Oliver, J. E.; Waters, R. M.; Lusby, W. R. *Synthesis* **1994**, 273-274.
2. Klun, J. A.; Schwarz, M.; Wakabayashi, N.; Waters, R. M. *J. Chem. Ecol.* **1994**, *20*, 2705-2719.
3. Klun, J. A.; Oliver, J. E. *207th ACS National Meeting*, San Diego, 1994; Book of Abstracts, part 1, Division of Agrochemicals, paper 120.
4. (a) Lowe, G.; Potter, B. V. L.; *J. Chem. Soc., Perkin Trans. I* **1980**, 2029-2032. (b) Faustini, F.; De Munari, S.; Panzeri, A.; Villa, V.; Gandolfi, C. A. *Tetrahedron Lett.* **1981**, *22*, 4533-4536.
5. Saburi, M.; Shao, L.; Sakurai, T.; Uchida, Y. *Tetrahedron Lett.* **1992**, *33*, 7877-7880.
6. Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153-1156.
7. Fritz-Langhals, E. *Tetrahedron: Asymmetry* **1994**, *5*, 981-986.
8. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906-1908.
9. (±)-**1** were prepared according to Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435-3438. (see also Ref. 1 for **1a** and **1b**). *1,1,1-trichloro-9-tetradecyn-2-ol* (**1c**): ^1H NMR ($CDCl_3$, 300 MHz): 0.91 (t, 3H), 1.30-1.55 (m, 11H), 1.56-1.65 (m, 2H), 2.05 (m, 1H), 2.15 (m, 4H), 4.00 (dd, 1H, J = 9.3 and 1.8 Hz, CHOH). *1,1,1-trichloro-2-hexanol* (**1d**): ^1H NMR: 0.95 (t, 3H), 1.41 (m, 3H), 1.63 (m, 2H), 2.06 (m, 1H), 4.01 (dd, 1H, J = 9.6 and 2.0 Hz, CHOH).

10. Oxidation of the racemic alcohols **1** using 2.2 eq. of $(COCl)_2$ and 4.8 eq. of DMSO, as described by Mancuso, A. J.; Huang, S.-L; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482, and subsequent flash chromatography on SiO_2 with hexane-ethyl acetate, 98:2 provided ketones **2** with 70-80% yield. *1,1,1-trichloro-11-tetradecyn-2-one* (**2b**). ^1H NMR: 1.11 (t, 3H, J = 7.5 Hz), 1.25-1.50 (m, 10H), 1.73 (tt, 2H, $J_1 = J_2 = 6.1$ Hz), 2.13 (m, 4H), 2.97 (t, 2H, J = 7.2 Hz, $CH_2C{=}O$). *1,1,1-trichloro-9-tetradecyn-2-one* (**2c**). ^1H NMR: 0.91 (t, 3H, J = 7.2 Hz), 1.32-1.55 (m, 10H), 1.76 (tt, 2H, $J_1 = J_2 = 6.9$ Hz), 2.15 (m, 4H), 2.99 (t, 2H, J = 7.5 Hz, $CH_2C{=}O$).
11. Reductions of ketones **2** were conducted at -78 °C for 24 h as described in Ref. 8. (*R*) and (*S*)-trichloromethyl alcohols **1** were isolated by flash chromatography on silica gel with hexane-ethyl acetate, 10:1. Enantiomeric excess of **1** was determined by GC analysis on Cyclodex-B capillary column, and the absolute configuration was assigned on the basis that (*S*)-oxazaborolidine catalyst led to (*R*) alcohols.[8] (*R*)-**1a**: yield 95%, ee 96%, $[\alpha]^{22}_D$ + 24.2 (c 1.49 $CHCl_3$); (*R*)-**1b**: 90%, ee 94%, $[\alpha]^{25}_D$ + 22.2 (c 0.54 $CHCl_3$); (*S*)-**1b**: 88%, ee 92%, $[\alpha]^{24}_D$ - 19.9 (c 1.35 $CHCl_3$); (*R*)-**1c**: 90%, ee 94%, $[\alpha]^{25}_D$ + 22.2 (c 0.54 $CHCl_3$); (*R*)-**1d**: 86%, $[\alpha]^{25}_D$ + 31.7 (c 1.80 $CHCl_3$);
12. A mixture of CsF (3 mmol) and $Bu_4NF{\cdot}3H_2O$ (3 mmol, Aldrich) was stirred under nitrogen in dry CH_2Cl_2 (5 mL) at 25 °C 15 min., then cooled to 0 °C and a solution of (*R*) or (*S*)-**1** (0.3 mmol) in triethylamine (0.2 mL) was added at 0-5 °C. After stirring for 1 h at 0-5 °C, then 1 h at r.t., and concentration *in vacuo*, the product was partitioned between 10% HCl and ether / hexane (1:1). Acid-base partitioning with 15% NaOH and 10% HCl, extraction of the acidic products with 1:1 ether / hexane, and flash chromatography on silica gel with hexane / ethyl acetate (5:1) containing 0.3% CF_3COOH, afforded fluoroacids **3** and chloroacids **4** (Table 1). A small amount (3-5%) of a byproduct, which we believe to be the corresponding 2-hydroxyacid, was also found in the acidic extract.
13. Acid **3/4** (ca. 1 mg, either in a pure form or as a mixture) was treated with oxalyl chloride (3 μL) and a cat. amount of DMF in CH_2Cl_2 for 3-4 h. After evaporation *in vacuo*, the residue was treated with (S)-α methylbenzylamine (3 μL) in benzene for 3 h, and the resulting amides were analyzed by GC on a SPB-1 capillary column (60 m x 0.25 mm, film 0.25 μm, Suppelco).
14. Kalaritis, P.; Regenye, R. W.; Partridge, J. J.; Coffen, D. L. *J. Org. Chem.* **1990**, *55*, 812-815.
15. Elimination of hydrogen chloride from the alcohol **1** provided external source of chloride which can compete with fluoride in the epoxide ring opening.
16. Reeve, W.; McKee, J. R.; Brown, R.; Lakshmanan, S.; McKee, G. A. *Can. J. Chem.* **1980**, *58*, 485-493.
17. Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1989**, *54*, 328. Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *549*, 3216.
18. Mosher esters were prepared from (+)-MTPA according to Sreinz, L.; Valterova, I.; Wimmer, Z.; Budesinsky, M.; Saman, D.; Kohoutova, J.; Romanuk, M.; Vrkoc, J. *Collect. Czech. Chem. Cummun.* **1986**, *51*, 2207, and analyzed by GC on a SPB-1 column.
19. ^1H NMR ($CDCl_3$): 0.90 (t, 3H), 1.32 (m, 12H), 1.40-1.77 (m, 2H, CH_2CHF), 2.02 (m, 4H), 2.11 (s, 3H), 4.05-4.30 (m, 2H, OCH_2), 4.67 (dm, 1H, $^2J_{HF}$ = 49.5 Hz, CHF), 5.35 (m, 2H, CH=CH). ^{19}F NMR ($CDCl_3/CFCl_3$): - 187.7.

Mention of a proprietary product does not imply endorsement by the U.S. Department of Agriculture.

(*Received in USA* 16 *October* 1995)