Pergamon

Tetrahedron Letters 40 (1999) 2243–2246

TETRAHEDRON LETTERS

Palladium-Catalyzed Stereospecific Carboalkoxylation of 1,2-Difluoro-1-iodoalkenes and α,β-Difluoro-β-iodostyrenes

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Received 17 November 1998; revised 12 January 1999; accepted 14 January 1999

Abstract: *(E)- and (Z)-1,2-Difluoro-1-iodoalkenes and (E)- and (Z)-α, β-difluoro-β-iodostyrenes give the corresponding esters in the presence of catalytic $Cl_2Pd(PPh_3)_2$, alcohol, trialkylamine, and carbon monoxide (80-180 psi) under mild conditions in excellent yields with retention of configuration.* © 1999 Elsevier Science Ltd. All rights reserved.

It is well established that the Van der Waals radii of fluorine (r_F~1.35 Å) and hydrogen (r_H~1.10 Å) are quite similar, thereby rendering fluorine the only element that can replace hydrogen in biological systems without changing steric demands.[1] However, the strong electronegative nature of fluorine, relative to that of hydrogen, imparts a strong electron-withdrawing inductive effect causing substantial differences in the reactivity of neighboring functional groups. Consequently, site-specific fluorination of organic molecules has attracted interest for applications in polymer, medicinal, and agricultural chemistry.[2]

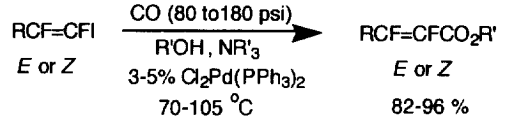
Fluorinated acrylic esters, in particular, are interesting sythons due to their prolific chemistry and potential for further elaboration into fluorinated analogs of natural products. For example, fluoroacrylic esters are excellent Michael acceptors and have been employed as such in the synthesis of γ-fluoroglutamic acid derivatives,[3] angiotensin II derivatives,[3] and a fluorinated analog of Captopril, an angiotensin converting enzyme inhibitor.[4] α-Trifluoromethylacrylic acid has found utility in the preparation of trifluoromethyluracil derivatives *via* an annulation process.[5] Furthermore, fluoroacrylic esters are suitable dienophiles for Diels-Alder cycloadditions, and have been employed as dienophiles in the synthesis 6-trifluoromethylshikimic acid[6] and a fluorinated analog of retinal.[7]

Fluoroacrylic esters of the type $CFH{=}CHCO_2R$,[8] $CH_2{=}CFCO_2R$,[9] $CF_2{=}CHCO_2R$,[10] $CH_2{=}C(CF_3)CO_2R$,[11] (*E*)-$CF_3CH{=}CHCO_2R$,[12] and (*Z*)-$CF_3CH{=}CHCO_2R$[6] have been prepared by multistep sequences in which the α,β-unsaturated double bonds were introduced late in the synthesis by β-elimination reactions. Other approaches to fluorinated acrylates involved the quenching of fluorovinyllithium reagents with CO_2 at low temperatures,[10b,11b,13] condensation reactions with hexafluoroacetone for the synthesis of $(CF_3)_2C{=}CHCO_2R$,[14] Ojima's synthesis of $CH_2{=}C(CF_3)CO_2H$ *via* palladium-catalyzed carbonylation of $CH_2{=}C(CF_3)Br$,[5] and palladium-catalyzed cross-coupling of (*Z*)-RCF=CFZnCl with ethyl chloroformate.[15] However, in our hands, (*Z*)-PhCF=CFZnI coupled with $ClCO_2Et$ under palladium catalysis to give only low yields of the corresponding ester.[16] The lack of general and convenient methodology for the stereospecific synthesis of (*E*)- and (*Z*)-α,β-difluoroacrylate ester derivatives and α,β-difluorocinnamate esters has impeded the investigation of this interesting class of compounds.

Recent publications from this laboratory have described strategies for the stereospecific introduction of

PII: S0040-4039(99)00216-6

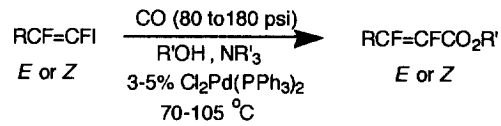
cis - and *trans* -1,2-difluoroethylene units into organic molecules.[17] Given the available methodology for the stereospecific preparation of *cis* - and *trans* -1,2-difluoro-1-iodoalkenes and α,β-difluoro-β-iodostyrenes developed by our group[17,18] and others,[19] we anticipated that these may be ideal precursors for the synthesis of (*E*)- and (*Z*)-α,β-difluoroacrylate ester derivatives and α,β-difluorocinnamate esters. Herein we wish to report the stereospecific palladium-catalyzed carboalkoxylation of 2-substituted-1,2-difluorovinyl iodides to form the corresponding fluorinated esters.



The palladium catalyzed carboalkoxylation of non-fluorinated alkenyl and aryl halides has been previously explored by Heck[20] and Stille.[21] However, Heck and coworkers found that the carboalkoxylation of terminal vinylic halides suffers from isomerization under the reaction conditions.[20] For example, *cis* -$CH_3(CH_2)_3CH$=CHI yields *cis* -$CH_3(CH_2)_3CH$=$CHCO_2Bu$ and *trans* -$CH_3(CH_2)_3CH$=$CHCO_2Bu$ in 79% and 6% yield, respectively. When the steric bulk of the substituent on the double bond increased from butyl to phenyl, the severity of isomerization is even more pronounced, with *cis* -PhCH=CHBr affording *cis* - and *trans* -PhCH=$CHCO_2Bu$ in 52% and 30% yield, respectively. In contrast to their hydrocarbon counterparts, *no isomerization was observed* in the carboalkoxylation of 2-substituted-1,2-difluoro-1-iodoalkenes or α,β-difluoro-β-iodostyrenes. The results are summarized in Table 1. Alt hough palladium-catalyzed carbobutoxylation of non-fluorinated vinyl halides proceeds readily under 1 atm of carbon monoxide, the fluorinated substrates required elevated carbon monoxide pressure (80 to 180 psi) to react at reasonable rates (entries 5 and 6). Effective conditions for rapid carboalkoxylation of the various fluorinated substrates investigated are the reaction of fluoroorganic halide (1.0 eq), trialkylamine (1.2 eq), CO (80 to 180 psi), 3-5% $Cl_2Pd(PPh_3)_2$, and excess alcohol as solvent at 80-125 °C for 12-24 hours, and the reaction progress is conveniently monitored by noting the carbon monoxide pressure throughout the course of the reaction.

In a typical experiment, (*Z*)-*p* -cyano-α,β-difluoro-β-iodostyrene (0.50 g, 1.72 mmol), tri-*n* -butylamine (0.42 g, 2.24 mmol), 3-5% dichlorobis(triphenylphosphine) palladium(II) and 5 ml of 1-butanol were added to a 100 mL Fischer-Porter glass pressure reactor.[22] (*Caution: All reactions should be carried out behind a safety shield.*) The reactor was pressurized to 100 psi with carbon monoxide, and the pressure was released. This was repeated for four cycles to rid the system of air. Finally, the reactor was filled to 100 psi and heated at 80 °C for 12 hours, or until carbon moxoxide consumption ceases. The reactor was allowed to cool, and the pressure was carefully released. The reaction mixture was transferred to a separatory funnel containing 40 mL of ethyl acetate. The organic layer was washed successively with aqueous 10% hydrochloric acid (2 x 15 mL), 15 mL of saturated aqueous sodium bicarbonate, and 15 mL of brine. After drying the organic layer over anhydrous magnesium sulfate, the mixture was concentrated by rotary evaporation. The crude ester was chromatographed on a silica gel column, eluting with 10% ethyl acetate in hexanes (10% ethyl acetate in hexanes, R_f 0.33) to yield 0.44 g (96%) of butyl (*E*)-*p* -cyano-α,β-difluorocinnamate as a clear, colorless oil which crystallized to a white solid on

Table 1. Palladium-Catalyzed Carboalkoxylation Reactions of Fluoroorganic Halides



Entry	Fluoroorganic Halide	Products	CO Pressure (psi)	Temperature (°C)	Yield (%)[a]
1	(*Z*)-*t*-BuCF=CFI	(*E*)-*t*-BuCF=CFCO$_2$Bu	80	105	85
2	(*Z*)-*t*-BuCF=CFI	------	80	85	N.R.
3	(*Z*)-*sec*-BuCF=CFI	(*E*)-*sec*-BuCF=CFCO$_2$Bu	80	105	92
4	(*Z*)-PhCF=CFI	(*E*)-PhCF=CFCO$_2$Bu	80	105	89
5	(*E*)-*n*-BuCF=CFI	(*Z*)-*n*-BuCF=CFCO$_2$Et	1 atm	85	33[b]
6	(*E*)-*n*-BuCF=CFI	(*Z*)-*n*-BuCF=CFCO$_2$Et	50	95	82
7	(*E*)-*t*-BuCF=CFI	(*Z*)-*t*-BuCF=CFCO$_2$Bu	180	80	83
8	(*Z*)-*p*-CH$_3$OC$_6$H$_4$CF=CFI	(*E*)-*p*-CH$_3$OC$_6$H$_4$CF=CFCO$_2$Bu	80	80	86
9	(*Z*)-*p*-CNC$_6$H$_4$CF=CFI	(*E*)-*p*-CNC$_6$H$_4$CF=CFCO$_2$Bu	100	80	96
10	(*Z*)-*m*-CF$_3$C$_6$H$_4$CF=CFI	(*E*)-*m*-CF$_3$C$_6$H$_4$CF=CFCO$_2$Bu	80	80	89
11	(*Z, Z*)-*p*-C$_6$H$_4$(-CF=CFI)$_2$	(*E, E*)-*p*-C$_6$H$_4$(-CF=CFCO$_2$Bu)$_2$	100	80	95
12	(*E*)-*p*-CH$_3$OC$_6$H$_4$CF=CFI	(*Z*)-*p*-CH$_3$OC$_6$H$_4$CF=CFCO$_2$Bu	180	70	88

a) Isolated Yields. All products gave satisfactory ^{19}F, ^{1}H, ^{13}C NMR and HRMS data. b) 32% of unreacted starting material was recovered.

standing: mp 42-43 °C; ^{19}F NMR ($CDCl_3$) δ -137.4 (d, $^3J_{FF(trans)}$ = 128.5 Hz, 1 F), -156.9 (d, $^3J_{FF(trans)}$ = 128.5 Hz, 1 F); ^{1}H NMR ($CDCl_3$) δ 7.90 (dm, J = 8.7 Hz, 2 H), 7.79 (d, J = 8.5 Hz, 2 H), 4.37 (t, J = 6.6 Hz, 2 H), 1.76 (quintet, J = 6.7 Hz, 2 H), 1.47 (sextet, J = 7.6 Hz, 2 H), 0.98 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.5 (dd, $^2J_{CF}$ = 30.8 Hz, $^3J_{CF}$ = 5.9 Hz), 153.4 (dd, $^1J_{CF}$ = 259.3 Hz, $^2J_{CF}$ = 39.7 Hz), 141.0 (dd, $^1J_{CF}$ = 250.6 Hz, $^2J_{CF}$ = 43.3 Hz), 132.5 (d, $^4J_{CF}$ = 1.654 Hz), 132.5 (dd, $^2J_{CF}$ = 23.3 Hz, $^3J_{CF}$ = 6.7 Hz), 127.5 (dd, $^3J_{CF}$ = 10.6 Hz, $^4J_{CF}$ = 8.0 Hz), 117.9, 114.6 (d, $^5J_{CF}$ = 2.7 Hz), 66.1, 30.5, 19.1, 13.7; GC-MS, *m / z* (relative intensity) 265 (M^+, 7), 245 (5), 223 (4), 209 (M^+ - C_4H_8, 55), 192 (M^+ - OC_4H_9, 44), 164 (M^+ - $CO_2C_4H_9$, 12), 144 (30), 130 (23), 124 (9), 57 ($C_4H_9^+$, 20), 56 ($C_4H_8^+$, 100); HRMS calc for $C_{14}H_{13}F_2NO_2$ 265.0914, obs 265.0939.

In conclusion, we have described a stereospecific, high yielding method for the synthesis of α,β-difluoroacrylate ester derivatives and α,β-difluorocinnamate esters. These unique classes of compounds should find important applications in medicinal and agricultural chemistry due to their potential for further elaboration into biologically active products. Future reports will describe the details of this and related work.

Acknowledgment

We gratefully acknowledge the National Science Foundation for financial support of this research.

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22. For reactions conducted at CO pressures greater than 100 psi, a 120 mL Hastelloy Parr pressure reactor was employed rather than the Fischer-Porter glass apparatus.