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Short Effective Synthesis of α-Fluoroketones by Palladium-Catalyzed Decarboxylation Reactions of Allyl α-Fluoro-β-keto Carboxylates

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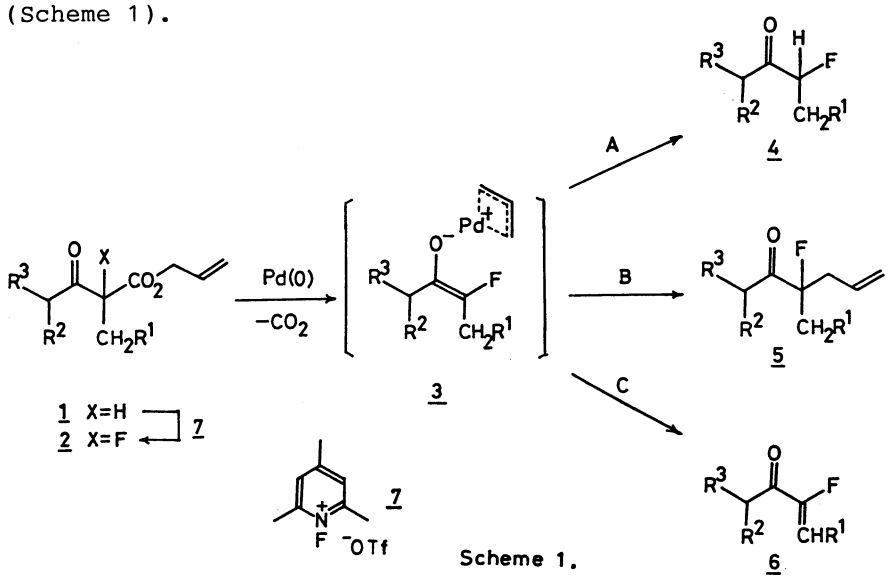
α-Fluoroketones, α-fluoro-α-allylketones, and α-fluoro-α,β-unsaturated ketones are synthesized by palladium-catalyzed decarboxylation reactions of allyl α-fluoro-β-keto carboxylates.

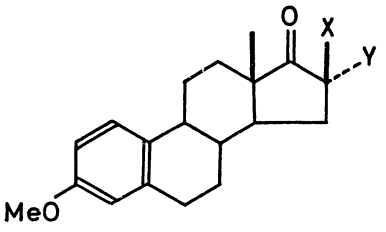
Although α-fluoroketones occupy an important position for synthesis of various fluorinated compounds, only a few practical synthetic methods for α-fluoroketones have been reported.[1] Recently, Umemoto has developed N-fluoropyridinium triflates as mild fluorinating agents of active hydrogen compounds, such as β-keto esters.[2] However, decarboxylation of α-fluoro-β-keto esters to the corresponding ketones are difficult owing to acyl fission reaction (retro-Claisen condensation) during hydrolysis. We have reported that allylic β-keto esters are decarboxylated easily using palladium catalysts to give ketones by decarboxylation-hydrogenolysis,[3] α-allylketones by decarboxylation-allylation,[4] and α,β-unsaturated ketones by decarboxylation-dehydrogenation.[5] We wish to report here facile synthetic methods for the preparation of α-fluoroketones,[1b] α-fluoro-α-allylketones,[1c] and α-fluoro-α,β-unsaturated ketones[1d] from allyl α-fluoro-β-keto carboxylates based on the palladium-catalyzed decarboxylation reactions (Scheme 1).



Scheme 1.

Decarboxylation of allyl 2-fluorocyclododecanone carboxylate (**2a**)[6] to 2-fluorocyclododecanone (**4a**) was carried out using formic acid in the presence of palladium catalyst (Method A). A mixture of HCO_2H (88%, 0.14 ml) and Et_3N (0.21 ml) in dioxane (5 ml) was added to a mixture of $Pd_2(dba)_3CHCl_3$ (0.019 mmol) and PPh_3 (0.019 mmol) in dioxane (10 ml) at room temperature under argon. To the mixture was added a solution of **2a** (0.75 mmol) in dioxane (5 ml). The reaction mixture was stirred for 24 hr at room temperature, poured into saturated $NaHCO_3$, and extracted with ether. The usual workup and purification by column chromatography on SiO_2 gave **4a** in 80% yield: **4a** ^{1}H NMR ($CDCl_3$, 90.0 MHz) δ 1.61-2.16 (m, 3H), 2.43-2.79 (m, 1H), 4.86 (ddd, J=49.0, 7.0, and 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 34.3, 95.5 (d, J_{CF}=184.5 Hz), 208.5 (d, J_{CCF}=21.4 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -188.67--189.74 (m); IR (neat) 1721 cm^{-1}; HRMS Found 200.1558, Calcd for $C_{12}H_{21}OF$ 200.1577.

This decarboxylation method was successfully applied to the synthesis of 16β-fluoroestrone methyl ether (**12**).[8] The allyl α-fluoro-β-keto ester **11** was prepared from estrone methyl ether (**8**) in three steps and decarboxylated using HCO_2H with Pd catalyst under reflux to give **12** in 93% yield. The stereochemistry at C-16 of **12** was determined by ^{1}H and ^{19}F NMR spectra.[8b,10] Formation of the α-fluoro epimer at C-16 was not detected in this reaction. The selectivity is easily explained by the preferential α-side protonation of the enolate of the 17-keto steroid.



8. X,Y=H
9. X,Y=H,CO_2Me — a (78%)
10. X,Y=H,$CO_2CH_2CH{=}CH_2$ — b (94%)
11. X,Y=F,$CO_2CH_2CH{=}CH_2$ — c (78%)
12. X=F,Y=H — d (93%)

a) $(MeO)_2CO$, KH in THF reflux. b) $Cl(n\text{-}Bu)_2Sn\text{-}O\text{-}Sn(n\text{-}Bu)_2OH$ (1mol%), $HO\text{-}CH_2\text{-}CH{=}CH_2$ in toluene reflux.[9] c) NaH, **7** in THF at 0 °C. d) HCO_2H, Et_3N, $\frac{1}{2}Pd_2(dba)_3CHCl_3$ (5 mol%), PPh_3 (2.5 mol%), in dioxane reflux.

When the reaction of **2a** was carried out without using formic acid, decarboxylation-allylation took place to give the α-allyl-α-fluoroketone **5a** (Method B). Thus, a solution of **2a** (0.56 mmol) in dry THF (10 ml) was added to a refluxing mixture of $Pd_2(dba)_3CHCl_3$ (0.014 mmol) and 1,2-bis(diphenylphosphino)-ethane (dppe) (0.056 mmol) in dry THF (10 ml) under argon. The mixture was refluxed for 1 h. The usual workup and purification by chromatography on SiO_2 to give **5a** in 73% yield: **5a** ^{1}H NMR (CCl_4, 60.0 MHz) δ 4.83-5.05 (m, 1H), 5.13 (s, 1H), 5.37-6.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 34.5, 39.8 (d, J_{CCF}=22.1 Hz), 102.4 (d, J_{CF}=185.2 Hz), 118.8, 130.8 (d, J_{CCCF}=3.6 Hz), 210.0 (d, J_{CCF}=26.3 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -160.72--161.68 (m); IR (neat) 1719, 1472, 992, and 917 cm^{-1}; HRMS Found 240.1906, Calcd for $C_{15}H_{25}OF$ 240.1890.

Decarboxylation-dehydrogenation of **2a** to the α,β-unsaturated ketone **6a** was

also carried out in CH_3CN (Method C). A solution of **2a** (0.75 mmol) in dry CH_3CN (4 ml) was added to a refluxing mixture of $Pd_2(dba)_3CHCl_3$ (0.038 mmol) and PPh_3 (0.038 mmol) in dry CH_3CN (3.5 ml) under argon, and the mixture was refluxed for 2 hr to give **6a** in 74% yield: **6a** ^{1}H NMR ($CDCl_3$, 90.0 MHz) δ 2.16-2.72 (m, 4H), 6.02 (dt, J=35.5 and 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 37.2 (d, J_{CCCF}=1.4 Hz), 119.6 (d, J_{CCF}=12.4 Hz), 156.3 (d, J_{CF}=262.5 Hz), 196.6 (d, J_{CCF}=31.1 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -127.20 (d, J=35.5 Hz); IR (neat) 1703, 1650, 1467, and 1445 cm^{-1}; HRMS Found 198.1408, Calcd for $C_{12}H_{19}OF$ 198.1420.

The conversion of **2a** to **4a**, **5a**, and **6a** are considered to occur via the π-allylpalladium enolates of the α-fluoroketones **3** which generate after oxidative addition of the ester **2** and subsequent decarboxylation. Similarly as shown in Table 1, α-fluorocyclohexanones **5b** and **5c**, and α-fluorocyclohexenones **6b** and **6c** were obtained from the corresponding esters **2b** and **2c** with high regioselectivity.[10]

Table 1. Palladium-Catalyzed Decarboxylation Reactions of Allyl α-Fluoro-β-Keto Carboxylates to α-Fluoroketones

Run	Ester	R^1, R^2	R^3	Method	Product	Yield/%[a]
1	**2a**	$-(CH_2)_8-$	H	A	2-Fluorocyclododecanone (**4a**)	80
2		$-(CH_2)_8-$	H	B	2-Allyl-2-fluorocyclododecanone (**5a**)	73
3		$-(CH_2)_8-$	H	C	(E)-2-Fluoro-2-cyclododecenone (**6a**)	74
4	**2b**	$-(CH_2)_2-$	H	B	2-Allyl-2-fluorocyclohexanone (**5b**)	45
5		$-(CH_2)_2-$	H	C	2-Fluoro-2-cyclohexenone (**6b**)	56
6	**2c**	$-(CH_2)_2-$	Me	B[b]	2-Allyl-2-fluoro-6-methylcyclohexanone (**5c**)	66
7		$-(CH_2)_2-$	Me	C	1-Fluoro-6-methyl-2-cyclohexenone (**6c**)	61

a) Isolated yield. b) PPh_3 (20 mol%) was used instead of dppe.

Since the reaction proceeds under mild conditions, the present methods would provide a useful synthetic method for the synthesis of fluorinated compounds. Further application of these methods to synthesis of biologically active compounds is in progress.

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6) The α-fluoro ester **2a** was prepared in 84% yield from allyl cyclododecanone carboxylate (**1a**) by fluorination using **7**:[2,7] **2a** ^{1}H NMR (CCl_4, 60.0 MHz) δ 1.10-2.87 (m, 20H), 4.58 (d, J=5.5 Hz, 2H), 5.04-5.45 (m, 2H), 5.54-6.23 (m, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) -166.29 (d, J=26.2 Hz); IR (neat) 1758 and 1731 cm^{-1}; HRMS Found 284.1801, Calcd for $C_{16}H_{25}O_3F$ 284.1788.
7) The reagent **7** is commercially available from Wako Pure Chemical Industries, Ltd.
8) a) T. B. Patric and R. Mortezania, J. Org. Chem., 53, 5153 (1988); b) D. O. Kiesewetter, J. A. Katzenellenbogen, M. R. Kilbourn, and M. J. Welch, ibid., 49, 4900 (1984).
9) J. Otera, T. Yano, A. Kawabata, and H. Nozaki, Tetrahedron Lett., 27, 2383 (1986).
10) Spectral data. **5b** ^{1}H NMR (CCl_4, 60.0 MHz) δ 4.83-5.04 (m, 1H), 5.15 (s, 1H), 5.43-6.11 (m, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -157.61--158.51 (m); IR (neat) 1728, 1432, 1127, and 923 cm^{-1}; HRMS Found 156.0958, Calcd for $C_9H_{13}OF$ 156.0951. **6b** ^{1}H NMR (CCl_4, 60.0 MHz) δ 6.31 (dt, J=14.8 and 4.0 Hz, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -130.40 (d, J=14.8 Hz); IR (neat) 1693, 1180, 1146, 1112, and 893 cm^{-1}. **5c** ^{1}H NMR (CCl_4, 60.0 MHz) δ 1.01 (d, J=6.5 Hz, 3H), 4.85-5.06 (m, 1H), 5.16 (s, 1H), 5.40-6.05 (m, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -153.96--154.69 (m); IR (neat) 1726, 1453, 1128, and 981 cm^{-1}; HRMS Found 170.1135, Calcd for $C_{10}H_{15}OF$ 170.1107. **6c** ^{1}H NMR (CCl_4, 60.0 MHz) δ 1.14 (d, J=6.5 Hz, 3H), 6.21 (dt, J=15.0 and 4.0 Hz, 1H); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -130.66 (d, J=15.0 Hz); IR (neat) 1691, 1453, 1346, 1195, 1180, 1005, 926, and 910 cm^{-1}; HRMS Found 128.0604, Calcd for C_7H_9OF 128.0637. **11** ^{1}H NMR (CCl_4, 60.0 MHz) δ 1.09 (s, 3H), 1.22-3.04 (m, 13H), 3.69 (s, 3H), 4.66 (d, J=5.5 Hz, 2H), 5.06-5.49 (m, 2H), 5.56-6.25 (m, 1H), 6.64 (d, J=7.0 Hz, 1H), 6.66 (d, J=9.5 Hz, 1H), 7.14 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 55.11, 66.60, 95.28 (d, J_{CF}=201.1 Hz), 111.58, 113.80, 119.20, 126.09, 130.75, 131.24, 137.28, 157.58, 167.37 (d, J_{CCF}=26.3 Hz), 207.88 (d, J_{CCF}=15.9 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -161.23 (t, J=16.2 Hz); HRMS Found 386.1896, Calcd for $C_{23}H_{27}O_4F$ 386.1894. **12** ^{1}H NMR (CCl_4, 60.0 MHz) δ 1.02 (s, 3H), 1.17-3.12 (m, 13H), 3.75 (s, 3H), 4.73 (dt, J=49.9 and 7.5 Hz, 1H), 6.66 (d, J=7.0 Hz, 1H), 6.68 (d, J=9.5 Hz, 1H), 7.16 (d, J=9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 54.94, 91.40 (d, J_{CF}=194.8 Hz), 111.43, 113.66, 125.92, 131.30, 137.22,157.46, 212.63 (d, J_{CCF}=11.6 Hz); ^{19}F NMR ($CDCl_3$, 84.7 MHz, internal $CFCl_3$) δ -184.86 (dd, J=49.9 and 21.4 Hz).

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