A Novel and Practical Method for the Preparation of α,α-Difluoro Functionalized Esters

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α,α-Difluoro functionalized esters can be readily prepared in good yields from the reaction of iododifluoroacetates with alkenes and zinc in the presence of catalytic amounts of nickel dichloride hexahydrate.

Recent reports have demonstrated the importance of α,α-difluoro esters in the synthesis of bioactive compounds that contain the difluoromethylene group.[1] However, the lack of a general synthetic methodology for the preparation of α,α-difluoro functionalized esters has hampered development along these lines. Recently, we reported a new approach to α,α-difluoroesters *via* a copper-initiated addition of iododifluoroacetates to alkenes, followed by reduction with zinc in the presence of nickel chloride.[2] A mechanistic investigation revealed that the addition reaction proceeded through a single electron transfer (SET) process. The catalyst in the reduction step is most likely to be Ni^0 generated from the reaction of zinc with nickel dichloride. We anticipated that Ni^0 could not only catalyse reduction of the adduct but also initiate addition of the iododifluoroacetate to the alkene. Therefore, the two-step sequence could potentially be conducted in one pot with zinc in the presence of nickel chloride [eqn. (1)]. Herein we report the preliminary results of this new method for the preparation of α,α-difluoro functionalized esters.

$$\underset{\mathbf{1}}{CH_2{=}CHR + ICF_2CO_2R'} \xrightarrow[THF]{Zn\text{–}NiCl_2\cdot 6H_2O} RCH_2CH_2CF_2CO_2R' \quad (1)$$

In a typical procedure, isopropyl iododifluoroacetate (1.3 g, 5 mmol) and oct-1-ene (1.1 g, 10 mmol) were added to a stirred mixture of zinc (0.65 g, 10 mmol), $NiCl_2\cdot 6H_2O$ (0.1 g, 0.42 mmol) and 1 drop of water in tetrahydrofuran (THF: 10 cm^3) at room temperature under nitrogen. The resultant reaction mixture was stirred for several hours at room temperature and then poured into an aqueous NH_4Cl solution (40 cm^3) and extracted with diethyl ether (2 × 40 cm^3). The

Table 1 Preparation of α,α-difluoroesters from **1** and alkenes[a]

Entry	R	R′	Yield(%)[b,c]
1	n-C_3H_7	$CHMe_2$	83
2	n-C_4H_9	$CHMe_2$	71
3	n-C_6H_{13}	$CHMe_2$	80
4	n-$C_{12}H_{25}$	Et	64
5	Me_3Si	$CHMe_2$	65
6	$MeCO(CH_2)_2$	Me	76
7	$EtO_2CC(Me)CH_2$	Et	73
8	$HO(CH_2)_8$	$CHMe_2$	76

[a] The reactions were carried out at room temperature. [b] Isolated yields based on **1** by distillation at reduced pressure. [c] All compounds gave satisfactory ^{19}F, ^1H, ^{13}C NMR, FTIR and GC–MS data.

combined diethyl ether layers were washed with water and dried over $MgSO_4$. After evaporation of the diethyl ether, the residue was distilled at reduced pressure to give 1.0 g (80%) of isopropyl α,α-difluorodecanoate, 97.3% GLPC purity, b.p. 96–98 °C (1.4 mmHg). ^{19}F NMR($CDCl_3$): δ −106.5 (t, $^3J_{FH}$ 17.1 Hz); ^1H NMR($CDCl_3$): δ 5.14 (spt, $^3J_{HH}$ 6.2 Hz, 1H), 2.10–1.96 (m, 2H), 1.45–1.38 (m, 2H), 1.32–1.01 (m, 16H) and 0.88 (t, $^3J_{HH}$ 7.1 Hz, 3H); ^{13}C NMR($CDCl_3$): δ 164.05 (t, $^2J_{FC}$ 33.0 Hz), 116.47 (t, $^1J_{FC}$ 250.0 Hz), 70.90, 34.59 (t, $^2J_{FC}$ 23.2 Hz), 31.88, 29.30, 29.17, 28.79, 22.72, 21.63, 21.55 and 14.10; FTIR (CCl_4): ν/cm^{-1} 2984s, 1769s, 1377s, 1182s and 1082s; GC–MS: *m/z* 207(0.62), 119(1.33), 69(8.46), 57(43.75), 43(100) and 41(36.40%).

Representative examples are summarized in Table 1. The nickel-catalysed reaction proved to be quite general for various alkenes. When non-functionalized alkenes were utilized as substrates, good yields of α,α-difluoresters were obtained independent of chain length with alkenes such as pent-1-ene and tetradec-1-ene. Alkenes substituted with a number of functional gorups, including trimethylsilyl, hydroxy, ketone and ester, also gave the α,α-difluoro functionalized esters in high yields. In addition, variation of the ester portion of the iododifluoroacetates had little effect on the reaction.

Although the mechanism of this new reaction has not been investigated in detail, we propose that Ni^0, produced from the reaction of zinc and nickel dichloride, initiated the addition of iododifluoroacetate to the alkene to afford an adduct (*cf.* Raney-Ni catalysed addition of perfluoroalkyl iodides to alkenes[3]) followed by reduction of the adduct with Ni^0 in moist THF to give the corresponding α,α-difluoro functionalized ester.

In conclusion, a new, useful and practical reaction of iododifluoroacetates with functionalized alkenes has been discovered. The ready availability of catalysts and alkene precursors, the simplicity of the experimental procedure, and the high yields obtained make this approach a useful route to a variety of α,α-difluoro functionalized esters.

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References

1 E. A. Hallinan and J. Fried, *Tetrahedron Lett.*, 1984, **25** 2301; M. H. Gelb, J. P. Svaren and R. H. Abeles, *Biochemistry*, 1985, **24**, 1813; S. Thaisrivongs, D. T. Pals, W. M. Kati, S. R. Turner and L. M. Thomasco, *J. Med. Chem.*, 1985, **28**, 1553; S. Thaisrivongs, D. T. Pals, W. M. Kati, S. R. Turner, L. M. Thomasco and W. Watt, *J. Med. Chem.*, 1986, **29**, 2080; D. J. Burton and J. C. Easdon, *J. Fluorine Chem.*, 1988, **38**, 125; R. W. Lang and B. Schaub, *Tetrahedron Lett.*, 1988, **29**, 2943; L. W. Hertel, J. S. Kroin, J. W. Misner and J. M. Tustin, *J. Org. Chem.*, 1988, **53**, 2406; L. H. Takahashi, R. Radhakrishnan, R. E. Rosenfield, Jr., E. F. Meyer Jr. and D. A. Trainor, *J. Am. Chem. Soc.*, 1989, **111**, 3368; O. Kitagawa, T. Taguchi and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 1803; T. Taguchi, O. Kitagawa, Y. Suda, S. Ohkawa, A. Hashimoto, Y. Iitaka and Y. Kobayashi, *Tetrahedron Lett.*, 1988, **29**, 5291.

2 Z. Y. Yang and D. J. Burton, *J. Fluorine Chem.*, 1989, **45**, 435; Z. Y. Yang and D. J. Burton, *J. Org. Chem.*, 1991, **56**, 5125.

3 Q. Y. Chen and Z. Y. Yang, *J. Chem. Soc., Chem. Commun.*, 1986, 498.