

Difluorinated Malonaldehyde Derivatives as Useful Difluoromethylene-containing Building Blocks

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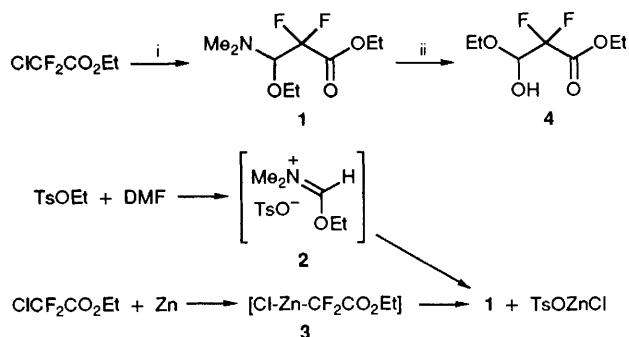
New CF₂-containing building blocks, ethyl 3-ethoxy-2,2-difluoro-3-hydroxy-propionate and -propioamide, were prepared *via* formylation of α,α -difluorinated Reformatsky reagents, and reacted with active methylene compounds, nitromethane or phosphonoacetate to afford α,α -difluoro-functionalized esters and amides.

Organic molecules possessing a difluoromethylene group are of considerable interest, since this moiety has a steric profile similar to that of the methylene group but has a very different polarity and a drastically altered reactivity.¹ The Reformatsky reaction of halodifluoroacetates with various electrophiles has been one of the most common methods for the introduction of this moiety,²⁻⁸ and has been applied to the synthesis of *gem*-difluorinated analogues of natural products, such as deoxy sugars,⁴ β -lactams,⁶ malic acid⁷ and pepstatin.⁸ In contrast, few reports have appeared on the reaction of difluoromethylene-containing aldehydes with nucleophiles,⁹ mainly owing to the difficulty in obtaining such species. In this communication, we describe the facile preparation of difluori-

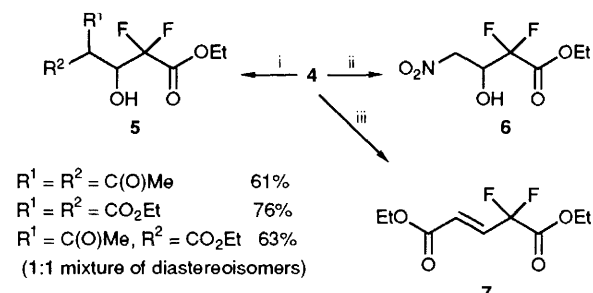
nated malonaldehyde derivatives **4** and **9** starting from the ethyl ester or *N,N*-diethylamide of chlorodifluoroacetic acid, and their reactions with some nucleophiles.

When a mixture of ethyl toluene-*p*-sulfonate (15 mmol), activated zinc (30 mmol) and ethyl chlorodifluoroacetate (10 mmol) was stirred in dimethylformamide (DMF) (5 ml) at 80 °C for 5 h, the dimethylaminopropionate **1** was obtained in 64% yield after aqueous work-up followed by distillation. From the mechanistic point of view, this reaction seems similar to the Vilsmeier reaction reported by Lang,¹⁰ involving initial generation of ethyl *N,N*-dimethylformimidate **2** which is eventually attacked by the difluorinated Reformatsky reagent **3**. The ester **1** was readily converted into the corresponding ethyl hemiacetal in quantitative yield.

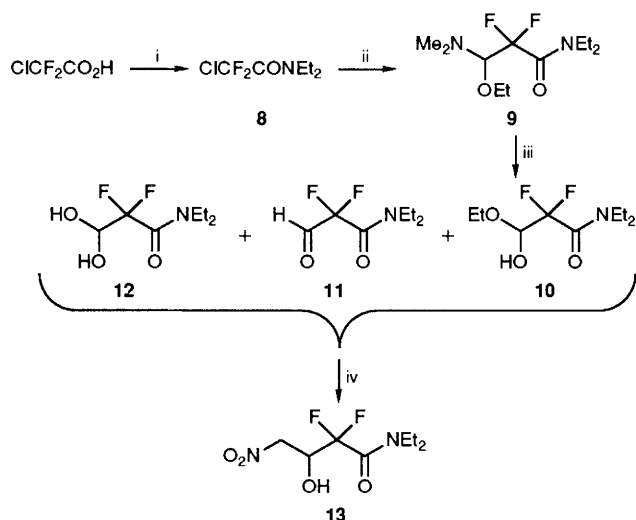
To demonstrate the synthetic utility of **4**, its reactions with nucleophiles were examined. Since α,α -difluorinated esters



Scheme 1 Reagents and conditions: i, ethyl toluene-*p*-sulfonate, Zn, DMF, 80 °C, 5 h; ii, H₂SO₄, EtOH, room temp., 10 min (Ts = *p*-MeC₆H₄SO₂)



Scheme 2 Reagents and conditions: i, R¹CH₂R², ZnI₂, dioxane, reflux, 4–8 h; ii, MeNO₂, K₂CO₃, THF, 3 h, reflux; iii, (EtO)₂POCH₂CO₂Et, Et₃N, LiBr, THF, room temp., 2 h (THF = tetrahydrofuran)



Scheme 3 Reagents and conditions: i, *N,N*-diethylcarbamoyl chloride, Et_3N , room temp., 2 h, then distillation (90 °C; 28 mmHg); ii, ethyl toluene-*p*-sulfonate, Zn, DMF, 90 °C, 6 h; iii, H_2SO_4 , EtOH, 10 min, then distillation; iv, MeNO_2 , K_2CO_3 , THF, room temp., 2 h

are sensitive to strong bases, undergoing hydrolysis even under carefully anhydrous conditions, the reactions with nucleophiles were performed using a Lewis acid or relatively weak bases. As shown in Scheme 2, in the presence of zinc iodide, **4** reacts with 1,3-dicarbonyl compounds to give α,α -difluoro- β -hydroxy esters **5** in 61–76% yields. The γ -nitro-substituted hydroxy ester **6** was obtained in 73% yield on treatment of **4** with nitromethane under basic conditions. Because of concomitant hydrolysis, Horner–Wadsworth–Emmons reactions using common bases (*n*-butyllithium or sodium hydride) resulted in low yields of the product; however, **4** was successfully converted into the difluorinated glutaconate **7** in 83% yield using triethylamine in the presence of lithium bromide.¹¹

Formylation with the chlorodifluoroacetamide **8** was also effective, giving the ethoxy-dimethylamino compound **9**. Unlike **1**, compound **9** was unstable to aqueous work-up, and a mixture of the corresponding hemiacetal **10**, aldehyde **11** and diol **12** was obtained after treatment with ethanol followed by distillation. Interestingly, in the reaction with nitromethane, the mixture of **10–12** was more reactive than **4** and even at room temperature the reaction afforded **13** in 85% yield. This fact indicates that the reactivity of the hemiacetals towards nucleophiles largely depends on their equilibration with the corresponding aldehydes.

In conclusion, the hemiacetal **4** and the mixture of **10–12** are useful difluorinated aldehyde equivalents in reactions with nucleophiles, and provide an alternative route to α,α -difluoro-functionalized esters or amides that cannot be obtained *via* Reformatsky reaction of halodifluoroacetates with electrophiles.

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