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PRELIMINARY NOTE

Copper Catalyzed Addition Reaction of Iododifluoroacetates to Olefins

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SUMMARY

The addition of iododifluoroacetates to alkenes is catalyzed by copper powder (10-20 mol %) at 50° to $60^{\circ}C$. The reaction can be carried out neat or in hexane or benzene as solvent. Both terminal and internal alkenes gave good yields (65-83%). Reduction of the adduct with tributyltin hydride provides the α,α-difluoroacetate.

Bioactive compounds that contain the difluoromethylene group have been the subject of increased research efforts in recent years [1]. The most widely utilized method to introduce this group into organic molecules has been the Reformatsky reaction of halodifluoroacetates [2]. More recently, difluoroketene silyl acetals have also been employed for the preparation of functionalized difluoromethylene compounds [3], and the zinc catalyzed addition reaction of 3-bromo-3,3-difluoropropene to aldehydes and ketones has been used as a route to gem-difluorohomoallylic alcohols [4]. In 1986, Kobayashi reported the preparation of [$CuCF_2CO_2R$] from iododifluoroacetate and copper in aprotic solvents [5]. Although reactions of aryl

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iodides, alkenyl iodides and allyl halides with this organocopper reagent gave good yields of the coupled product, the reaction with an alkyl halide required a relatively high temperature in HMPA, and only a modest yield of the alkylated product was obtained [5]. Consequently, in our continuing efforts to explore new synthetic methods for the introduction of the difluoromethylene group into organic compounds, we sought alternative methodology for this alkylation approach.

Previous reports by Coe and Milner [6] and Chen *et al*. [7,8,9] documented that the addition of *F*-alkyl iodides to alkenes can be catalyzed by copper. The reactive species in these reactions depends on the solvent employed [7,9]. In coordinating solvents, such as DMSO or HMPA, the *F*-alkylcopper was proposed as the reactive intermediate. However, in less coordinating solvents, such as hexane or benzene, a free radical was suggested as the reactive intermediate.

Consequently, it appeared that addition of iodohaloacetates to alkenes might be catalyzed by copper in poorly coordinating solvents. Subsequent reductive removal of the iodide would give

$$ICF_2CO_2R^1 \quad + \quad H_2C = CHR \xrightarrow{Cu} RCHICH_2CF_2CO_2R^1$$

$$RCHICH_2CF_2CO_2R^1 \xrightarrow{Bu_3SnH} RCH_2CH_2CF_2CO_2R^1$$

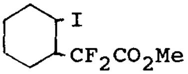
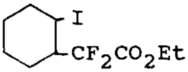
the α,α-difluoroester. Thus, the initial focus of this work was to test the generality of the copper catalyzed addition of iododifluoroacetates to olefins.

We have found that this addition reaction proceeds readily under mild conditions (50° - 60°C) in the presence of a catalytic amount of copper powder (10-20 mol %). Although non-coordinating solvents, such as hexane or benzene, gave excellent results, the reactions proceeded equally well in the absence of a solvent.

TABLE I

Copper catalyzed addition reaction of iododifluoroacetates to alkenes

$$ICF_2CO_2R \quad + \quad R^1CH = CHR^2 \xrightarrow[50 - 60^oC]{Cu} R^1CHICH(R^2)CF_2CO_2R$$

R	R^1	R^2	Product[a]	Yield[b]
Me	H	n-Bu	$n\text{-}BuCHICH_2CF_2CO_2Me$	75
Me	H	$n\text{-}C_5H_{11}$	$n\text{-}C_5H_{11}CHICH_2CF_2CO_2Me$	65
Me	H	$SiMe_3$	$Me_3SiCHICH_2CF_2CO_2Me$	83
Me	$-(CH_2)_4-$			78
Et	H	n-Bu	$n\text{-}BuCHICH_2CF_2CO_2Et$	65
Et	H	$n\text{-}C_5H_{11}$	$n\text{-}C_5H_{11}CHICH_2CF_2CO_2Et$	76
Et	H	Me_3Si	$Me_3SiCHICH_2CF_2CO_2Et$	70
Et	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	$n\text{-}C_3H_7CHICH(n\text{-}C_3H_7)CF_2CO_2Et$	72
Et	$-(CH_2)_4-$			75
^iPr	H	Me_3Si	$Me_3SiCHICH_2CF_2CO_2{}^iPr$	72
^iPr	H	$n\text{-}C_6H_{13}$	$n\text{-}C_6H_{13}CHICH_2CF_2CO_2{}^iPr$	76
^iPr	H	$n\text{-}C_6H_{13}$	$n\text{-}C_6H_{13}CHICH_2CF_2CO_2{}^iPr$	80[c]
^iPr	H	$n\text{-}C_6H_{13}$	$n\text{-}C_6H_{13}CHICH_2CF_2CO_2{}^iPr$	73[d]

[a] all products gave satisfactory ^{19}F, ^1H NMR, IR and GC/MS data.

[b] isolated yields.

[c] carried out in benzene.

[d] carried out in hexane.

Terminal, internal, and cyclic alkenes gave similar results and vinyl silanes also worked well. The results of this exploratory study are summarized in Table I.

The adduct can be reduced to the α,α-difluoroester with tributyltin hydride[10].

A typical experimental procedure is as follows: A two-necked flask fitted with a Teflon coated magnetic stir bar and a condenser topped with a nitrogen inlet was charged with 0.1 g (1.6 mmol) of copper powder [11], 1.6 g (20 mmol) of 1-hexene and 2.6 g (10 mmol) of methyl iodofluoroacetate. The reaction mixture was stirred at 50°C under nitrogen for 6 hours. The excess hexene was removed by rotary evaporation, and the residue was distilled to give 2.6 g (75%) of methyl-2,2-difluoro-4-iodooctanoate, bp 95-96°C/3.4 mm Hg.

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10 Work in progress with Dr. Zhen-Yu Yang; the results with Bu_3SnH and other reducing agents will be published elsewhere.

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