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SYNTHESIS OF 2,2-DIFLUOROESTERS BY IODODIFLUOROACETATE-COPPER WITH ORGANIC HALIDES

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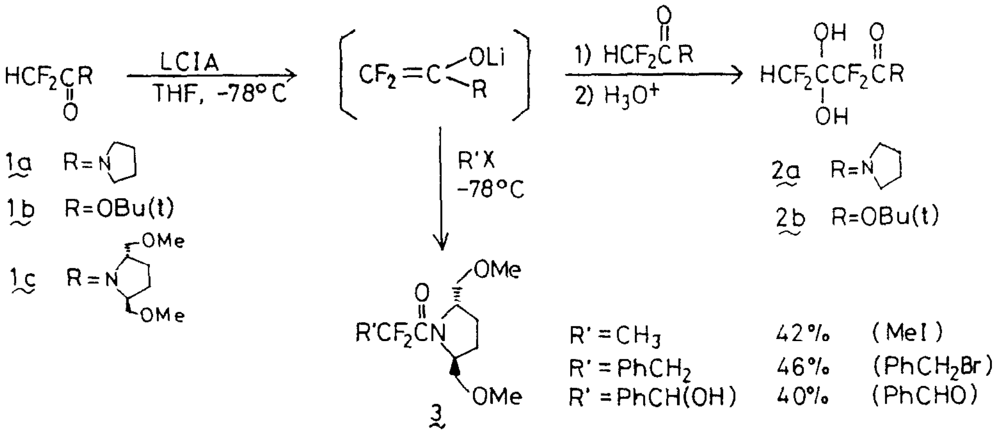
Summary: C-C bond formation through reactions of iododifluoroacetate-copper with various organic halides in aprotic solvent proceeds effectively to give 2,2-difluoroesters in good yield. With alkenyl iodides, these reactions are stereospecific.

Fluorinated organic compounds are attracting interest owing to the characteristic features of fluorine atom, particularly for the synthesis of biologically active compounds.1) Utilization of difluoroacetate derivatives for the preparation of 2,2-difluoroesters2) presents a major problem due to differences in the characteristics of difluoroacetate and monofluoroacetate3) or acetate. In this paper we report an efficient method for the preparation of various 2,2-difluoroesters(6) through the reactions of iododifluoroacetate-copper system with organic halides.

$$\underset{4a}{ICF_2COOMe} + Cu + \underset{5}{RX} \longrightarrow \underset{6}{RCF_2COOMe}$$

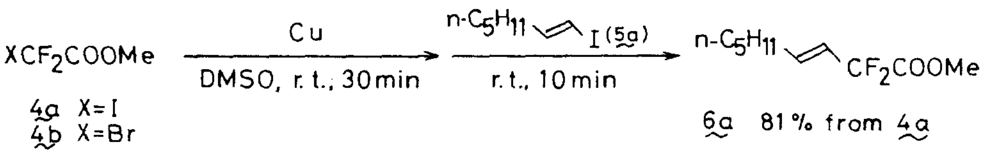
Generation of lithium enolates from difluoroacetic acid derivatives(1) by deprotonation and their reactions with electrophiles are considerably limited due to the enhanced reactivity of the ester carbonyl group, instability and relatively low nucleophilicity of the enolate.4) For example, the addition of pyrrolidide(1a) or t-butyl ester(1b) to a THF solution of LCIA followed by the addition of electrophiles(BnBr, PhCHO e.g.) gave the keto amide(2a) or keto ester(2b) as the major product. Using the sterically hindered amide(1c) we succeeded in generating and trapping lithium enolate with electrophiles to give 3 in moderate yields. The lithium enolate derived from 1c was found to decompose above ca -30°C in THF into a messy mass. Reformatsky reaction of bromodifluoroacetate reported by Fried is one effective method for extending the carbon chain of difluoroacetate derivative.5)

In need of a procedure for the stereospecific preparation of 2-alkenyl-2,2-difluoroesters, a new general method involving the reactions of iododifluoroacetae-copper with alkenyl halides has been developed. Furthermore,



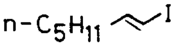
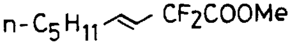
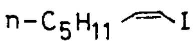
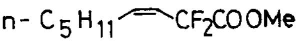
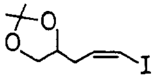
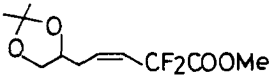
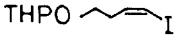
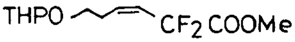
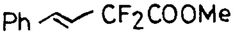
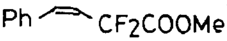
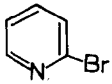
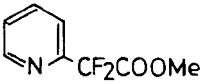
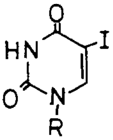
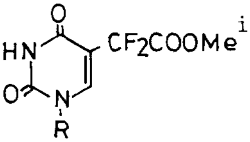
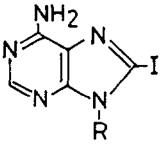
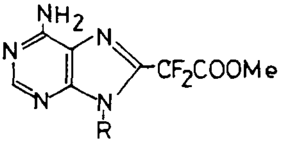
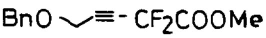
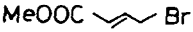
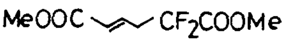
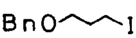
this method makes possible the conversion of aryl, alkynyl, allyl as well as alkyl halides to the corresponding difluoroesters in good yield.

First, we examined the reaction conditions for generation of reactive species from iododifluoroacetate(4a)6) and copper7) through the reaction with (E)-1-iodoheptene(5a) monitering by glc. A mixture of copper(4 mg-atom), methyl iodifluoroacetate(2 mmol) and 5a(0.67 mmol) in DMSO(5 ml) was stirred at 60°C for 30min and the subsequent extractive work-up afforded the coupling product(6a) in 43% yield(Method A). The reaction of iodoester(4a) with copper in DMSO was found to complete within 30-45min at room temperature (in DMF this requires about 4h) to form reactive species which reacted with 5a at room temperature within 10min to give 6a in 81% yield(Method B). In both cases, small amount of dimethyl difluorofumarate probably formed by the decomposition of reactive species into the carbene(:CFCOOMe) was isolated. Although THF and CH_3CN were ineffective solvents, HMPA(Method A, 60°C, 10h, 6a, 67%) and DMF(Method A, 60°C, 20h, 6a, 58%) were found suitable.



Compared with iodoester(4a), bromo difluoroester(4b) was much less usable for the copper mediated reaction. Bromoester(4b) did not react with copper at room temperature in either HMPA or DMSO. After the reaction with copper in HMPA(80°C, 20h) was almost complete, 5a was added but failed to produce any coupling product(6a). This suggests instability of the reactive species under the reaction conditions. When the three components(4b, Cu and 5a) in HMPA were heated at 60°C for 12h, 6a was isolated only in moderate yield(30%) along with the formation of 1-bromoheptene which is less reactive in this

Table. Preparation of 2,2-Difluoroesters (6)

Entry	R-X (5)	Conditions[c]			RCF_2COOMe (6)	Yield (%)
			Temp (°C)	Time		
1		B[b]	r.t.	10 min		81
2		B	r.t.	30 min		84
3		A[a,d]	55~60	15 h		64
4		A	55~60	45 min		37
5	 [e]	A	40	30 min	 [f]	43
6	 [g]	A	40	30 min	 [h]	50
7		B	r.t.	10 h		81
8	 [i]	B	r.t.	30 min	 [i]	88
9	 [i]	B	r.t.	25 min	 [i]	60
10	C_6H_5I	A	r.t.	4 h	$C_6H_5-CF_2COOMe$	80
11		B	r.t.	10 min		21
12	BnBr	B	r.t.	20 min	$BnCF_2COOMe$	79
13		B	r.t.	30 min		84
14		B[d]	70	3 h		38

a. A mixture of 4a, Cu and 5 was stirred. b. Following completion of the reaction of 4a and Cu in DMSO at room temperature (for 30-45 min), 5 was added. c. solvent: DMSO d. In this case HMPA was used as the solvent. e. E:Z=13:1 f. E:Z=13:1 g. E:Z=1:35 h. E:Z=1:4.4 i. R=2',3',5'-tri-O-acetylribofuranosyl reaction. At this moment, reaction of iodoester(4a)-copper system with organic halides in DMSO is suitable for the preparation of 2,2-difluoroesters (6) and the results are summarized in Table. From the present results followings are noteworthy. With sp^2 halides iodide gave the coupling product in satisfactory yield and the reaction is completely stereospecific in retention manner except for (Z)-bromostyrene(entry 6). Aromatic halides including the 5-iodouridine and 8-iodoadenosine derivatives gave the coupling products in good yield. The reaction with alkynyl iodide resulted in a complex mixture, giving the 3-alkynylester in low yield(entry 11). Although reaction with alkyl iodide in HMPA required relatively high temperature to give the coupling product in moderate yield(entry 14), reactive allylic bromides gave satisfactory results(entry 12, 13).

Further investigation of the properties of reactive species$^{8)}$ and application of the present reaction is being carried out.

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