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An Efficient Synthesis of Perfluoroalkyl Ketones Using Perfluoroalkyllithiums

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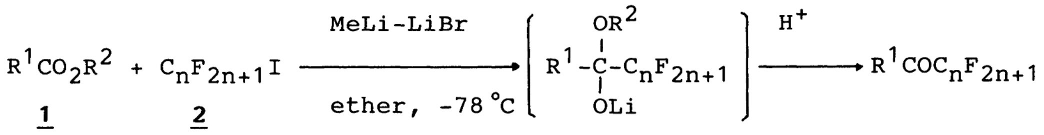
Perfluoroalkylation of esters with perfluoroalkyllithiums occurs smoothly in ether at -78 °C, giving the corresponding perfluoroalkyl ketones in good yields.

Considerable efforts have been concentrated upon developing a method to introduce perfluoroalkyl groups into organic materials.[1)] The method using organometallic reagents of perfluoroalkyl compounds is counted to be a powerful candidate for such purposes. Although successful results have been reported,[2)] perfluoroalkylmetallic reagents are still of limited use mainly because of their instability and low reactivity.[3)] For example, perfluoroalkyl Grignard reagents react with aldehydes or ketones to give carbinols but hardly react with non-activated esters. Perfluoroalkyllithiums, more reactive than the corresponding Grignard reagents, are generally taken to be unsuitable for the preparation of perfluoroalkyl-containing compounds, because they are very unstable and easily decompose into lithium fluoride and perfluoroalkenes even at low temperatures.[4)]



$$\underset{\mathbf{1}}{R^1CO_2R^2} + \underset{\mathbf{2}}{C_nF_{2n+1}I} \xrightarrow[\text{ether, }-78\ ^\circ\text{C}]{\text{MeLi-LiBr}} \left[R^1-\overset{OR^2}{\underset{OLi}{C}}-C_nF_{2n+1} \right] \xrightarrow{H^+} R^1COC_nF_{2n+1} \qquad (1)$$

However, we have found that the addition of perfluoroalkyllithium reagents to non-activated esters occur far more smoothly than their decomposition to produce perfluoroalkanoyl compounds in excellent yields (Eq. 1). Our method is based on in situ generation of perfluoroalkyllithiums recently reported by Gassman and his co-worker.5)

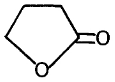
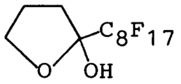
A general procedure of the reaction with an ester is as follows: To an ethereal solution of an ester **1** (1 mmol) and a perfluoroalkyl iodide **2** (1.2 mmol) is added an ethereal solution of methyllithium-lithium bromide (1.1 mol/L; 1 mL, 1.1 mmol) at -78 °C during 5 min and the mixture is stirred for 1 h at the same temperature. Then, the reaction mixture is quenched by addition of an NH_4Cl solution and extracted with ethyl acetate or ethyl ether. The organic phase is washed with brine and dried. After the solvent is removed, distillation and/or chromatographic purification of the residue give a perfluoroalkylated ketone in good yields shown in Table 1. In this reaction, quantities of methyllithium are crucial. If more excess amounts of methyllithium toward an ester were used, addition of both perfluoroalkyl and methyl groups to the ester carbonyl group occurs to give the corresponding carbinol, even in the presence of excess amounts of perfluoroalkyl iodide. Unfortunately, the present method cannot be applied for the preparation of perfluoroisopropyl ketones and vinyl perfluoroalkyl ketones (entries 7 and 17). It is interesting that perfluoroalkyllithium reagents complement perfluoroalkylzinc reagents in the preparation of perfluoroalkanoyl compounds.6) Perfluoroalkyllithiums did not react with benzonitrile and styrene oxide but decomposed mainly into dimeric perfluoroalkenes.

$$\underset{\mathbf{1b}}{\mathrm{PhCH{=}CHCO_2Me}} + \underset{\mathbf{2}}{\mathrm{C_nF_{2n+1}I}} \xrightarrow[\text{ether, }-78\,^\circ\mathrm{C}\rightarrow\text{r.t.}]{\text{MeCu, MeLi}} \mathrm{PhCH(Me)CH_2COC_nF_{2n+1}} \qquad (2)$$

15a (n=8) 75%
b (n=6) 52%
c (n=4) 37%

$$\underset{\mathbf{1b}}{\mathrm{PhCH{=}CHCO_2Me}} + \underset{\mathbf{2a}}{\mathrm{C_8F_{17}I}} \xrightarrow[\text{2) PhMgBr, }-78\,^\circ\mathrm{C}\rightarrow\text{r.t.}]{\text{1) CuI(cat.), MeLi, }-78\,^\circ\mathrm{C}} \underset{\mathbf{16}\quad 65\%}{\mathrm{Ph_2CHCH_2COC_8F_{17}}} \qquad (3)$$

Table 1. Preparation of perfluoroalkyl ketones

Entry	Ester **1**	Perfluoroalkyl iodide **2**	Product[a)]	Yield/%[b)]	Bp/°C(mmHg)[c)] [Mp/°C]
1	$PhCO_2Me$ (**1a**)	$C_8F_{17}I$ (**2a**)	$PhCOC_8F_{17}$ (**3**)	86	140(22)
2	**1a**	**2a**	**3**	79[d)]	
3	$PhCH{=}CHCO_2Me$ (**1b**)[e)]	**2a**	$PhCH{=}CHCOC_8F_{17}$ (**4**)[e)]	86	[61-62]
4	**1b**[e)]	**2a**	**4**[e)]	93[d)]	
5	**1b**[e)]	$C_6F_{13}I$ (**2b**)	$PhCH{=}CHCOC_6F_{13}$ (**5**)[e),f)]	83	[47-48]
6	**1b**[e)]	C_4F_9I (**2c**)	$PhCH{=}CHCOC_4F_9$ (**6**)[e)]	85	[29]
7	**1b**[e)]	$i\text{-}C_3F_7I$ (**2d**)	—[g)]	—	
8	$PhCH{=}CHCO_2Et$ (**1c**)[e)]	**2a**	**4**[e)]	83	
9	$PhC{\equiv}CCO_2Me$ (**1d**)	**2a**	$PhC{\equiv}CCOC_8F_{17}$ (**7**)	95	[25]
10	$PhCH_2CH_2CO_2Me$ (**1e**)	**2a**	$PhCH_2CH_2COC_8F_{17}$ (**8**)	86	[38]
11	$(CH_3)_2CHCO_2Me$ (**1f**)	**2a**	$(CH_3)_2CHCOC_8F_{17}$ (**9**)	72	125(760)
12	$(CH_3)_3CCO_2Me$ (**1g**)	**2a**	$(CH_3)_3CCOC_8F_{17}$ (**10**)	60	125(760)
13	$BrCH_2CO_2Me$ (**1h**)	**2a**	$BrCH_2COC_8F_{17}$ (**11**)	68	[39]
14	**1h**	**2a**	**11**	86[d)]	
15	$CH_3CH{=}CHCO_2Me$ (**1i**)[e)]	**2a**	$CH_3CH{=}CHCOC_8F_{17}$ (**12**)[e)]	58	120(760)
16	$CH_3CH{=}C(CH_3)CO_2Me$ (**1j**)[e)]	**2a**	$CH_3CH{=}C(CH_3)COC_8F_{17}$ (**13**)[e)]	74	145(760)
17	$CH_2{=}CHCO_2Me$ (**1k**)	**2a**	—[h)]	—	
18	 (**1l**)	**2a**	 (**14**)	99	[80]

a) All new compounds gave satisfactory elemental analyses (C, H; ±0.3) and/or mass spectral data. b) Isolated yield. c) Kugelrohr oven temperatures. d) The reaction was undertaken on a 10 mmol scale. e) E isomer. f) T. Ishihara, T. Maekawa, and T. Ando, Tetrahedron Lett., 24, 4229 (1983). g) Starting compound **1b** was recovered. h) Complex mixture.

Perfluoroalkyllithium reagents can coexist with an alkylcopper reagent. Thus, in the presence of methylcopper, 1,2-addition of a perfluoroalkyl group followed by 1,4-addition of a methyl group to methyl cinnamate (**1b**) occurred to give **15** in moderate to good yields (Eq. 2).[7] A phenyl group could be also introduced by sequential addition of methyllithium-lithium bromide and a phenyl Grignard reagent in the presence of a catalytic amount of CuI (Eq. 3). In these reactions, conjugate addition of a perfluoroalkyl group was never observed.[8]

References

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4) P. Johncock, J. Organomet. Chem., 19, 257 (1968); O. R. Pierce, E. T. McBee, and G. F. Judd, J. Am. Chem. Soc., 76, 474 (1954).

5) P. G. Gassman and N. J. O'Reilly, Tetrahedron Lett., 26, 5243 (1985).

6) A. Sekiya and N. Ishikawa, Chem. Lett., 1977, 81.

7) A general procedure: To a mixture of **1b** (1 mmol), perfluoroalkyl iodide **2** (2 mmol), methylcopper (1 mmol; prepared in situ) in ether is added methyllithium-lithium bromide (3 mmol) at -78 °C. After addition, the reaction mixture is allowed to warm with stirring and stood for 30 min at room temperature. Then aqueous NH_4Cl solution is added to the reaction mixture. The organic phase is separated and the aqueous phase is extracted twice with ethyl acetate. The combined organic phase is dried (Na_2SO_4) and the solvent is removed. The residue is chromatographed on silica-gel (hexane as eluent).

8) In the presence of a copper salt, perfluoroalkyl Grignard reagents react with α,β-unsaturated aldehydes, see: N. Thoai, J. Fluorine Chem., 5, 115 (1975).

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