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Tandem Alkylation-Defluorination Reaction: Synthesis of 2-(*N*-Alkyl-*N*-aryl)amino-3,3-difluoropropenoates from 2-(*N*-Aryl)imino-3,3,3-trifluoropropanoates

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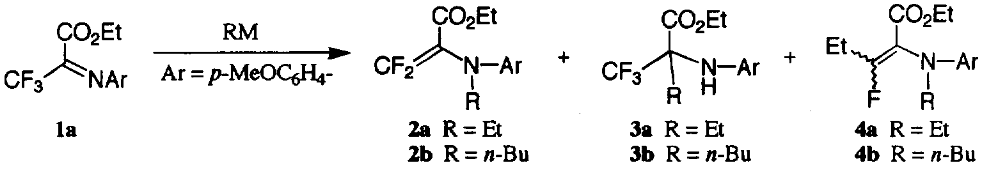
***Abstract*:** A novel synthesis of fluoroolefins from trifluoromethylated compounds with organometallic reagents was developed. The reaction seems to proceed *via* 1,4-alkylation on imino nitrogen followed by defluorination of the trifluoromethyl group. Diethylzinc was found to be an efficient reagent for the preparation of 2-(*N*-aryl-*N*-ethyl)amino-3,3-difluoropropenoates in excellent yield. A similar synthesis of monofluoroolefin with Grignard reagent was also developed.

Fluoroolefins have gained considerable attention not only because of their bioactivity, but also their usefulness in further synthesis of organofluorine compounds.[1] A large number of studies has been published on fluoroolefin synthesis, especially on difluoroolefin synthesis[2] such as difluoromethylenation of the carbonyl moiety,[3] thermal decarboxylation of 2,2-difluoro-β-lactones,[4] Reformatsky reaction of 4-chloro-4,4-difluorocrotonate,[5] and reaction of chlorodifluoromethyl epoxyethers with butyllithium.[6] Recently, defluorination of the trifluoromethyl group[7] has been receiving a growing interest because it could be employed in preparation of fluoroolefins starting from commercially available compounds with lithium amides,[8a-f] Zn-CuI,[8g] 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU),[8h] and Grignard reagent.[8i] Herein, we wish to report a novel method for syntheses of difluoroolefins and monofluoroolefin by reaction of 2-(*N*-aryl)imino-3,3,3-trifluoropropanoates **1**[9] with diethylzinc and Grignard reagent.

Reactions of imino ester **1a** with various ethyl or *n*-butyl organometallic reagents were examined; results are summarized in Table 1.[10] The reactions of both *n*-butyllithium (entry 1)[11] and Reformatsky reagent (EtZnBr, entry 5) gave normal imino *C*-addition products **3b** and **3a**, respectively. Meanwhile, to our surprise, when an equimolar amount of 'EtMgBr' was allowed to react with imino ester **1a** in ethyl ether at room temperature (entry 2), an *N*-addition product, ethyl 2-[*N*-ethyl-*N*-(*p*-methoxyphenyl)]amino-3,3-difluoropropenoate **2a**[12] (50%) and monofluoroolefin **4a**[12] (15%) were produced, and 30% of the starting substrate **1a** was recovered.[13,14] In this reaction, none of the normal *C*-addition product was obtained. Under the conditions examined so far, the concomitant production of mono-fluoroolefin inhibited higher yield of **2a**. Monofluoroolefin **4a** was produced in 61% yield by the use of a large excess amount of 'EtMgBr'(entry 3).

We found the reaction of diethylzinc produced up to 88% difluoroolefin **2a** (entry 6).[10] Diethylzinc reacted completely within 30 seconds under the mild conditions, and product **2a** can be easily isolated by silica gel column chromatography.[15] Diethylmagnesium was less reactive toward our imino ester (entry 4).

Table 1. Reactions of imino ester **1a** with organometallic reagents



1a

2a R = Et
2b R = *n*-Bu

3a R = Et
3b R = *n*-Bu

4a R = Et
4b R = *n*-Bu

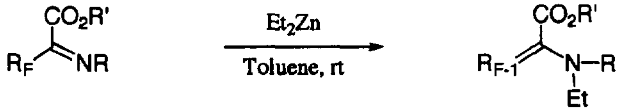
Entry	RM		Solvent	Temp. (°C)	Yield (%)			Recovery of **1a** (%)
					2	**3**	**4**	
1	*n*-BuLi	(1.1 eq)	toluene	-80	0	80	0	0
2	EtMgBr	(1.1 eq)	ether	rt	50	0	15	30[a]
3	EtMgBr	(2.5 eq)	ether	rt	0	0	61	0
4	Et$_2$Mg[b]	(1.1 eq)	ether	rt	0	1	0	>90
5	EtZnBr[c]	(1.1 eq)	ether	rt	0	>90	0	0
6	Et$_2$Zn	(1.1 eq)	toluene	rt	88	1	0	0

[a] 'EtMgBr' was completely consumed by monofluoroolefin formation. [b] Diethylmagnesium was prepared from 'EtMgBr' by precipitation of MgBr$_2$ with 1,4-dioxane. [c] Ethylzinc bromide was prepared from diethylzinc and ZnBr$_2$.

The effect of substituents of imino esters **1** on the reaction of diethylzinc is summarized in Table 2. The good yield of **2** was not affected by the *para*-substituent on *N*-aryl (entry 1-3) or even the alkyl substituent on nitrogen (entry 6). Meanwhile, the *o*-substitution on the *N*-phenyl ring lowered the reaction rate considerably. In the reaction of *o*-ethylphenyl compound **1e**, yield of *N*-addition product **2e** decreased to 65 % and 12% of the starting material **1e** was recovered (entry 4). In this reaction, 3,3,3-trifluoroalanine derivative (reduction product) was produced in 12 % yield. The reaction of the more hindered imine ester (Ar = 2,6-dimethylphenyl group, **1f**) resulted in recovery of the starting material and the formation of the desired difluoroolefin **2f** (entry 5) was negligible.

Fortunately, an imine-bearing perfluoroalkyl group (C$_3$F$_7$, **1h**) similarly underwent the same addition-defluorination reaction and resulted in the production of the corresponding perfluoroalkene compound **2h** in 77% yield (as a mixture of *E* / *Z* isomers, entry 7), but the reaction must be carried out at 100 °C for completion of the reaction.

Table 2. Addition-defluorination of imino esters **1** with diethylzinc



1a, c-h **2a, c-h**

Entry		R_F	R	R'	Yield of **2** (%)[a]		Recovery of **1** (%)
1	**1a**	CF_3	p-$MeOC_6H_4$-	Et	**2a**	88	0
2	**1c**	CF_3	C_6H_5-	Et	**2c**	80	0
3	**1d**	CF_3	p-ClC_6H_4-	Et	**2d**	84	0
4[b]	**1e**	CF_3	o-EtC_6H_4-	Et	**2e**	65	12
5	**1f**	CF_3	2,6-$Me_2C_6H_4$-	Et	**2f**	1	>90
6	**1g**	CF_3	$PhCH(CH_3)$-	Bn	**2g**	85	0
7[c]	**1h**	C_3F_7	p-$MeOC_6H_4$-	Et	**2h**	77	0

[a] Isolated yields. [b] By-product of reduction of the imine moiety was also obtained in 12 % yield. [c] The reaction was conducted at 100 °C for 2 min.

Further study on the reaction mechanism[14] and the transformation of difluoroolefins **2** into 3,3-difluoro-2-amino acids and its derivatives is in progress.

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(10) A typical defluorination of **1a**: To a solution of imino ester **1a** (55 mg, 0.20 mmol) in toluene (1 ml) at room temperature was added diethylzinc (1.00 M in hexane, 0.22 ml, 0.22 mmol) under argon. After being stirred for 30 seconds, the reaction was immediately quenched by addition of water and the organic layer was extracted with ethyl acetate . Usual workup followed by purification by silica gel column gave **2a** (50.2 mg, 88 % yield).

(11) Butyl, methyl, and phenyl lithiums attack to the imino carbon of **1**, see ref. 9.

(12) Difluoroolefin **2a**: IR (neat) 1744, 1696 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.19 (t, $J = 7.0$ Hz, 3H, $NCH_2\underline{CH_3}$), 1.21 (td, $J_1 = 7.2$ Hz, $J_2 = 1.0$ Hz, 3H, $OCH_2\underline{CH_3}$), 3.44 (q, $J = 7.2$ Hz, 2H, NCH_2), 3.75 (s, 3H, OCH_3), 4.18 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.67 (d, $J = 9.2$ Hz, 2H, C_6H_4), 6.81 (d, $J = 9.3$ Hz, 2H, C_6H_4); ^{13}C NMR (50 MHz, CDCl$_3$) δ 12.92, 14.06, 45.44, 55.64, 61.27, 98.89 (dd, $J_{C\text{-}C\text{-}F} = 16.9, 16.8$ Hz), 114.66 (4C), 141.29, 152.70, 163.07 (dd, $J_{C\text{-}F} = 299.7, 229.5$ Hz), 163.76; ^{19}F NMR (188 MHz, CDCl$_3$) δ 86.88 (d, $J = 13.2$ Hz, 1F), 88.45 (d, $J = 13.5$ Hz, 1F); Anal. Calcd for $C_{14}H_{17}F_2NO_3$: C, 58.94; H, 6.01; N, 4.91. Found: C, 59.09; H, 5.71; N, 4.99. Monofluoroolefin **4a**: IR (neat) 1726, 1658 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.08-1.25 (m, 9H, $3CH_3$), 2.46 (qd, $J_1 = 7.6$ Hz, $J_2 = 21.8$ Hz, 2H, $CF\underline{CH_2}CH_3$), 3.41 (q, $J = 7.2$ Hz, 2H, NCH_2), 3.74 (s, 3H, OCH_3), 4.14 (q, $J = 7.1$ Hz, 2H, OCH_2), 6.65 (d, $J = 9.2$ Hz, 2H, C_6H_4), 6.80 (d, $J = 9.3$ Hz, 2H, C_6H_4); ^{19}F NMR (188 MHz, CDCl$_3$) δ 63.92 (t, $J = 21$ Hz, 1F).

(13) 1,4-Addition of Grignard reagent to 2-trifluoromethylacrylate produces 2-alkyl-3,3-difluoroacrylate, see ref. 8(i).

(14) Several studies have shown abnormal 1,4-addition of nucleophile at heteroatom (N or O) in the reaction of organometallic reagents with 1,2-diketones, 1,2-diimines, 1,2-ketimines. One of the present authors had reported production of both α-ethylbenzoin (usual 1,2-addition product) and benzoin ethyl ether or ethylbenzoate (abnormal 1,4-oxygen addition product) in the reaction of 'EtMgBr' with benzil: (a) Maruyama, K.; Katagiri, T. *J. Am. Chem. Soc.* **1986**, *108*, 6263. (b) Maruyama, K.; Katagiri, T. *J. Phys. Org. Chem.* **1989**, *2*, 205. (c) Holm, T. *Acta Chem. Scand. Ser. B* **1987**, *41*, 278. (d) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, 44, 5415. (e) van der Steen, F. H.; Kleijn, H.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1991**, *56*, 5147.

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