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Tetrahedron Letters

Tetrahedron Letters 46 (2005) 5257–5261

Chromium mediated stereoselective synthesis of (*Z*)-1-fluoro-2-alkenyl alkyl and trialkylsilyl ethers from dibromofluoromethylcarbinyl ethers

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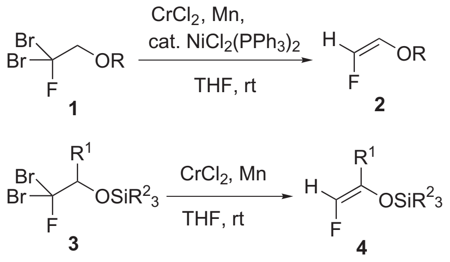
Received 24 May 2005; revised 9 June 2005; accepted 13 June 2005

Abstract—Reactions of 2,2-dibromo-2-fluoroethyl alkyl ethers and dibromofluoromethylcarbinyl silyl ethers with $CrCl_2$ and Mn powder provided 2-fluorovinyl alkyl ethers and 1-fluoro-2-alkenyl enol silyl ethers in high yields and in *Z* selective manner.

Due to the importance of fluorinated olefins in synthetic chemistry, medicinal chemistry and material science, development of efficient synthetic methods for fluorinated olefins has been extensively investigated.[1–3] For example, fluorine-bearing alkenyl ether derivatives, in particular enol silyl ethers, are used as versatile building blocks in a variety of carbon–carbon bond forming reactions. Among such molecules, although stereochemically unilateral *gem*-difluorovinyl derivatives have been well documented,[4–6] stereoselective preparation of monofluorovinyl or monofluoroalkenyl ethers involving silyl derivatives is a remaining subject to be solved.[7,8] Towards this subject, recent advances in chromium chemistry attracted our attention to develop a new synthetic method for monofluoroalkenyl ether derivatives.[9,10] In particular, Mioskowski and co-workers demonstrated that 2,2,2-trichloroethyl alkyl ethers can be converted to the corresponding (*Z*)-2-chlorovinyl alkyl ethers upon treating with $CrCl_2$.[11] When we started the chromium chemistry to develop synthetic methods for fluorinated olefinic compounds, there had been reported very few examples on the reaction of dihalofluoromethyl derivatives with $CrCl_2$[12,13] and thus, we examined the $CrCl_2$ mediated reactions using a variety type of dibromofluoromethyl and 1-bromo-1-fluoroalkene compounds to accumulate basic knowledge on the reactivities.[14] In this letter, we report $CrCl_2$ mediated *Z* selective preparation of 2-fluorovinyl alkyl ethers **2** from 2,2-dibromo-2-fluoroethyl ether derivatives **1**, and regio- and *Z* selective preparation of enol silyl ethers of fluoromethyl ketone **4** from dibromofluoromethylcarbinyl silyl ethers **3** (Scheme 1).



Scheme 1.

Preparative procedure for the starting ethers **1** and **3** is shown in Scheme 2. Etherification of 2,2-dibromo-2-fluoroethanol **6a**, obtained by $LiBH_4$ reduction of the ester **5** in the presence of trimethylborate,[15] provided the starting ethers **1**. Due to the low nucleophilicity of dibromofluoro alcohol **6a** and its relatively labile nature under the strong basic conditions, although reactive benzylic, allylic and propargylic bromide gave the ether compounds (**1a–m** except for **1g**) in good yields using phase-transfer catalyzed conditions (6% NaOH and TBAI in CH_2Cl_2 and H_2O at 0 °C to rt), alkyl (4-phenylbutyl) derivative **1g** was prepared in moderate yield (55%) using NaH as a base and the triflate instead of the bromide or iodide. On the other hand, silylation

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Keywords: Chromium salt; Fluoroalkene; Fluoroenol ether; Dibromofluoromethylcarbinol.

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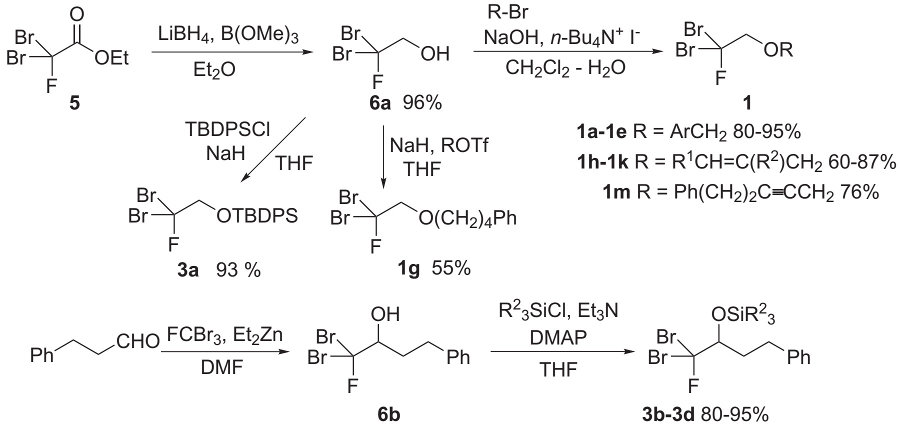
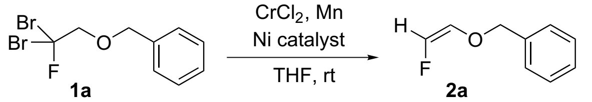
doi:10.1016/j.tetlet.2005.06.035



Scheme 2.

Table 1. Additive effect on reaction of **1a** with $CrCl_2$



Entry	$CrCl_2$ (equiv)	Mn (equiv)	Ni (equiv)	Time (h)	**2a**[a] (%)	**1a**[a] (%)
1	4	0	—	21	41	29
2	3	2	—	26	32	15
3[b]	2	3	0.3[b]	6	27 (45)[d]	0
4	2	3	0.1[c]	3	59 (72)[d]	0
5	3	2	0.1[c]	2	76 (90)[d]	0

[a] Isolated yield.

[b] $NiCl_2$ was used.

[c] $NiCl_2(PPh_3)_2$ was used.

[d] Yield in parenthesis was determined by 300 MHz ^1H NMR.

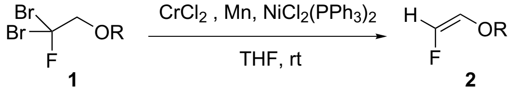
reaction of these dibromofluoro alcohols **6a** and **b**[16] smoothly proceeded using the corresponding silyl chloride and NaH for the primary alcohol **6a** or tertiary amine for the secondary alcohol **6b** to give silyl ethers **3a–d** in high yields.

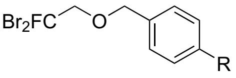
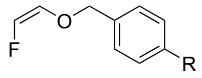
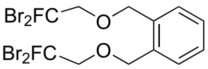
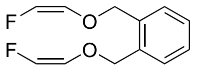
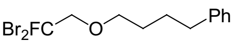
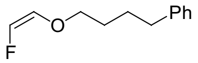
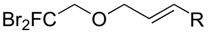
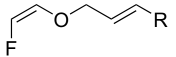
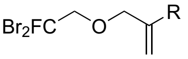
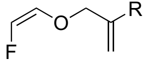
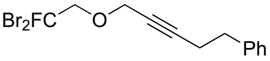
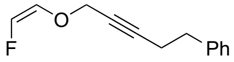
Reaction of 2,2-dibromo-2-fluoroethyl benzyl ether **1a** with $CrCl_2$ was conducted under various conditions to obtain 2-fluorovinyl ether **2a** (Table 1). As shown in entries 1 and 2, reaction of **1a** with $CrCl_2$ or $CrCl_2$ and Mn powder in THF proceeded rather slowly. On the other hand, as shown in entries 3–5, addition of a catalytic amount of Ni was found to remarkably accelerate the reaction and $NiCl_2(PPh_3)_2$ rather than $NiCl_2$ was more effective to give **2a** in excellent yield (entry 5). Addition of Mn powder was sometimes effective to reduce the amount of $CrCl_2$.[17] The stereoselectivity was also excellent obtaining only *Z* isomer.

Next, we examined the fluorovinyl ether synthesis using various 2,2-dibromo-2-fluoroethyl ethers (Table 2). Under the similar reaction conditions (3 equiv $CrCl_2$, 2 equiv Mn powder, 0.1 equiv $NiCl_2(PPPh_3)_2$, THF, rt) benzylic as well as alkyl ethers afforded (*Z*)-2-fluorovinyl ethers **2a–g** in stereoselective manner (entries 1–7). Existence of arylbromide[18] and ester group in the substrate can be tolerated as in the cases of **1d** and **e** (entries 4 and 5). On the other hand, with allylic and propargylic ethers, this chromium mediated olefination reaction did not always work well. For example, allylic ether having vicinally disubstituted pattern **1h–i** gave only trace amount of 2-fluorovinyl ether compounds **2h–i**, and in the case of **1i** cyclized tetrahydrofuran derivative **7** was isolated in 63% yield (entries 8 and 9). As shown in Scheme 3, formation of this tetrahydrofuran derivative **7** should involve the 5-exo addition reaction of the radical species **9** leading to the cyclized intermediate **10** prior to the second electron transfer reaction to the radical species **9** to form the carbenoid intermediate structurally similar to **11**.[12a,19] When the allylic ether has geminally disubstituted pattern as in the case of the substrates **1j–k**, such 5-exo cyclization can be clearly retarded due to the sterically crowded reaction site in the radical species **9′** in Scheme 3, and thus the desired fluorovinyl ether **2j–k** possibly formed through the carbenoid intermediate **11** was obtained in moderate yields (39% and 44% yield, respectively, entries 10 and 11). Likewise, with propargyl derivative **1m**, 5-exo cyclization was a major reaction pathway to give furan compound **8** in 40% yield along with the isolation of 2-fluorovinyl ether **2m** in 10% yield (entry 12, see also Scheme 3). Similar furan formation through chromium mediated radical cyclization of trichloro derivatives was reported by Mioskowski and co-workers.[20]

Chromium mediated reaction of dibromofluoromethylcarbinyl silyl ethers **3** also proceeded smoothly to provide (*Z*)-fluoroalkenyl enol silyl ethers **4** in high yield and with complete stereoselectivity (Table 3). Thus, reaction of trimethylsilyl (TMS) ether **3b** with $CrCl_2$ and Mn powder in THF smoothly proceeded to give enol TMS ether **4b** in excellent yield (93%), while in the presence of Ni catalyst yield of **4b** significantly dropped to 35% since the enol silyl ether **4b** thus formed further reacted with Ni catalyst giving rise to a complex mixture (entry 2 vs entry 3). As shown in Table 3, present $CrCl_2$–Mn powder mediated preparation of fluoromethyl ketone enol silyl ethers **4** is applicable to a

Table 2. Synthesis of (*Z*)-2-fluorovinyl ethers **2**[a]



Entry		1		Time (h)		2	Yield[b] (%)
1		**1a**	R = H	2		**2a**	76
2		**1b**	R = OMe	1		**2b**	98
3		**1c**	R = Me	2		**2c**	56
4		**1d**	R = Br	1		**2d**	47
5		**1e**	R = AcOCH$_2$	6		**2e**	60
6[c]		**1f**		7		**2f**	75
7		**1g**		2		**2g**	66
8[d]		**1h**	R = Ph	4		**2h**	4
9[d]		**1i**	R = PhCH$_2$CH$_2$	4		**2i**	—[e]
10[d]		**1j**	R = Ph	4		**2j**	39
11[d]		**1k**	R = PhCH$_2$CH$_2$	6		**2k**	44
12[d]		**1m**		6		**2m**	10[f]

[a] 3 equiv of CrCl$_2$, 2 equiv of Mn and 0.1 equiv of NiCl$_2$(PPh$_3$)$_2$ were used, unless otherwise stated.

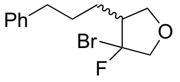
[b] Isolated yield.

[c] 6 equiv of CrCl$_2$, 4 equiv of Mn and 0.1 equiv of NiCl$_2$(PPh$_3$)$_2$ were used.

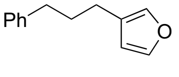
[d] 4 equiv of CrCl$_2$ and 4 equiv of Mn were used.

[e] Cyclized product **7** was obtained in 63% yield.

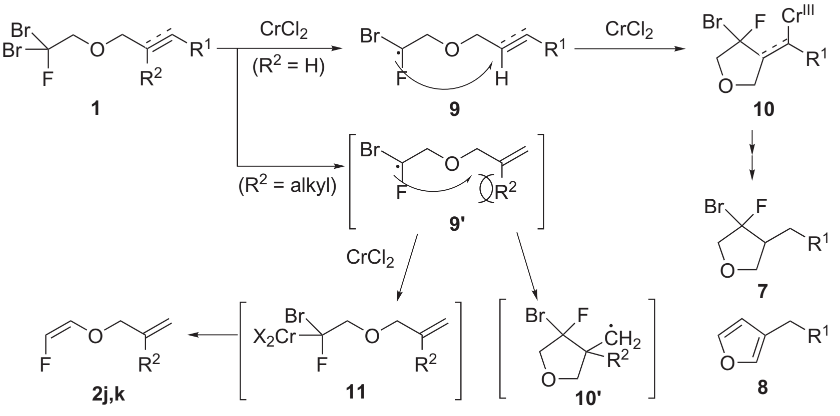
[f] Furan **8** was obtained in 40% yield.



7



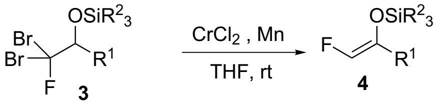
8

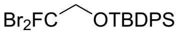
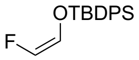
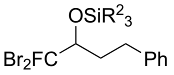
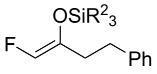
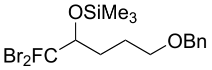
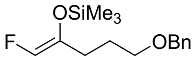


Scheme 3.

variety type of substrates with respect to the substituents on both fluorovinyl and silyl parts. Steric effect of silyl group on the reaction rate was obvious, that is, reaction period was 2 h for TMS ether **3b**, 6 h for triethylsilyl (TES) ether **3c**, and 13 h for *tert*-butyldimethylsilyl (TBDMS) ether **3d**, respectively (entries 2, 4 and 5). Regarding the substituent on fluorovinyl part, both alkyl and hydrogen derivatives can be prepared in good yield. Furthermore, reaction proceeded in a completely regio- and stereoselective manner to give *Z* isomer. Although Takai reported that elimination of trimethylsilyloxy group is a major pathway in the reaction of trichloromethylcarbinyl TMS ether with CrCl$_2$ pretreated with DMF in THF or with CrCl$_2$ in DMF,[21] under the similar conditions dibromofluoro derivative **3b** gave the enol silyl ether **4b** as a main product.

Table 3. Synthesis of (*Z*)-fluoroalkenyl silyl enol ethers **4**[a]

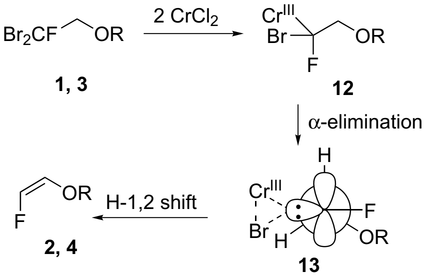


Entry		3		Time (h)		4	Yield[b] (%)
1		**3a**		12		**4a**	68
2		**3b**	R^2_3Si = TMS	2		**4b**	93
3[c]		**3b**	R^2_3Si = TMS	2		**4b**	35
4		**3c**	R^2_3Si = TES	6		**4c**	91
5		**3d**	R^2_3Si = TBDMS	13		**4d**[7c]	68
6		**3e**		3		**4e**	70

[a] 4 equiv of $CrCl_2$ and 4 equiv of Mn were used, unless otherwise stated.

[b] Isolated yield.

[c] 0.1 equiv of $NiCl_2(PPh_3)_2$ was added.



Scheme 4.

It would be likely that the present reaction involves carbene mechanism for the fluorovinyl ether formation. Thus, the carbenoid intermediate **12** is formed by the reaction of dibromide with two equimolar amount of $CrCl_2$ and then α-elimination and simultaneous hydrogen-1,2-shift occurs to give the fluorovinyl ether **2** or **4** (Scheme 4).[11b,22,23]

In summary, a high yield and *Z* selective formation of 2-fluorovinyl alkyl ethers and 1-fluoro-2-alkenyl enolsilyl ethers was achieved through chromium mediated alkenylation reaction of 2,2-dibromo-2-fluoroethyl ethers and dibromofluoromethylcarbinyl silyl ethers.

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