A New Access to 3-Halo-3,3-difluoropropanoic Acid Derivatives via Fluorine–Halogen Exchange Reaction of Silyl Enolates of 3,3,3-Trifluoropropanoic Acid Derivatives

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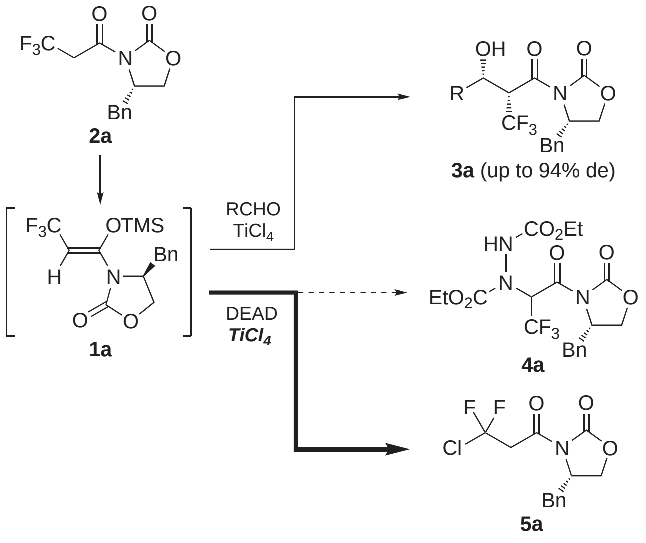
On the treatment of silyl enolates derived from *N*-(3,3,3-trifluoropropanoyl)oxazolidinones with 2.0 equiv. of titanium(IV) halide at −20 °C for 2 h, a novel fluorine–halogen exchange reaction occurred efficiently to give 3-halo-3,3-difluoropropanoic imides in high yields.

The development of the reaction with silyl enolates derived from 3,3,3-trifluoropropanoic acid derivatives has been recognized as one of the most challenging fields in the fluorine chemistry because of its significant low reactivity imparted by a strongly electron-withdrawing CF_3 group at a reactive carbon.[1]

Quite recently, we reported on the Mukaiyama aldol reaction of the silyl enolate **1a**, generated readily from *N*-(3,3,3-trifluoropropanoyl)oxazolidinone **2a**, with aldehydes in the presence of titanium(IV) chloride ($TiCl_4$), which provided the corresponding α-trifluoromethyl-β-hydroxypropanoic imide derivatives **3a** in high yields with excellent syn selectivity.[2] In continuing investigations on further synthetic applications of **1a**, for instance, the α-amination of **1a** using a diethyl azodicarboxylate (DEAD)–$TiCl_4$ system,[3] we have made intriguing observations that the reaction between **1a** and DEAD in the presence of $TiCl_4$ did not give any trace of the desired aminated product **4a** but a large quantity of the unexpected halogen-exchanged product, 3-chloro-3,3-difluoropropanoic imide **5a**[4,5] (Scheme 1). Herein, we wish to disclose the results of this unprecedented fluorine–halogen exchange reaction[6] of the silyl enolate **1a** and related enolate species with metal halides, leading to 3-halo-3,3-difluoropropanoic acid derivatives.

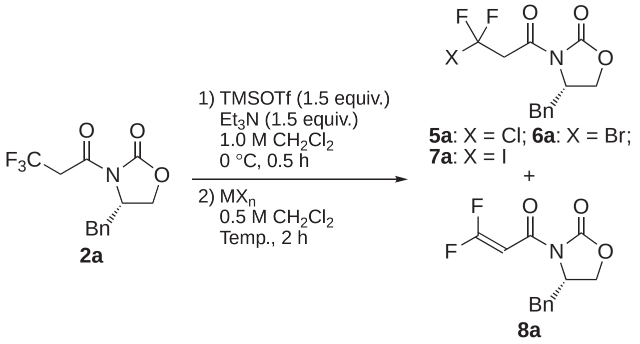


Scheme 1.

Initially, when the reaction between **1a** generated in situ and 1.2 equiv. of $TiCl_4$ was conducted at room temperature for 2 h, the halogen-exchanged product, 3-chloro-3,3-difluoropropanoic imide **5a** was given in very low yield (18%, Table 1, Entry 1). Lowering the reaction temperature to 0 °C led to an appreciable increase in the yield of **5a** (Entry 2). On employing 2.0 equiv. of $TiCl_4$ and the temperature of −20 °C, the reaction proceeded cleanly to afford **5a** in 87% yield (Entry 4). The use of $TiBr_4$ and TiI_4 in place of $TiCl_4$ was also found to be effective, providing the corresponding 3-bromo- and 3-iodo-3,3-difluoropropanoic imides **6a** and **7a** in 89 and 31% yields, respectively (Entries 7 and 8).

In addition, other metal chlorides (MCl_n) than TiX_4 were examined for the halogen-exchange reaction. As shown in Entries 9–11 of Table 1, zirconium(IV) chloride or

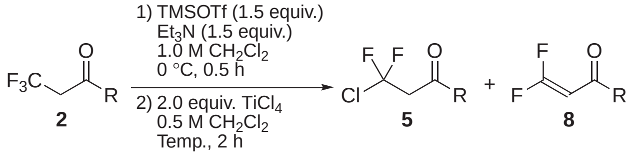
Table 1. Fluorine–halogen exchange reaction using various titanium(IV) halides

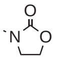
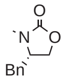


Entry	MX_n/equiv.	Temp./°C	Yield[a]/% of **5a**, **6a**, or **7a**	Yield[a]/% of **8a**	Recovery[a] /% of **2a**
1	$TiCl_4$ (1.2)	r.t.	18	0	6
2	$TiCl_4$ (1.2)	0	42	0	7
3	$TiCl_4$ (2.0)	0	65	0	1
4	$TiCl_4$ (2.0)	−20	87 (81)	0	trace
5[b]	$TiCl_4$ (2.0)	−20	83	0	13
6[b]	$TiCl_4$ (2.0)	−45	36	0	59
7	$TiBr_4$ (2.0)	−20	89 (85)	0	trace
8	TiI_4 (2.0)	−20	31	0	18
9	$ZrCl_4$ (2.0)	−20	6	0	87
10	$AlCl_3$ (2.0)	−20	16	7	53
11	$AlCl_3$ (2.0)	0	20	12	32
12	$SnCl_4$ (2.0)	r.t.	0	83	13
13	$ZnCl_2$ (2.0)	−20	0	0	quant.

[a]Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [b]Stirred for 10 h.

Table 2. Fluorine–halogen exchange reaction using various substrates **2**

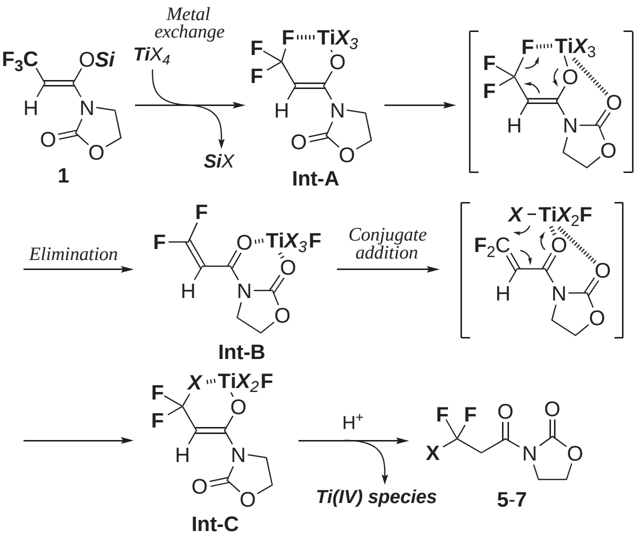


Entry	R	Temp./°C	Yield[a]/% of **5**	Yield[a]/% of **8**	Recovery[a] /% of **2**
1	OPh	−20	0	32	5
2	OBn	−20	0	27	21
3	SPh	−20	0	31	0
4	SPh	−40	0	78	0
5	NBu$_2$	−20	0	0	26
6		−20	72 (72)	trace	trace
7		−20	87 (81)	trace	trace

[a]Determined by ^{19}F NMR. Values in parentheses are of isolated yield.

aluminium(III) chloride (AlCl$_3$) allowed the reaction to proceed, but the yields of the product **5a** were extremely low. In the case of AlCl$_3$, 3,3-difluoropropenoic imide **8a** was formed as a byproduct along with **5a**. The use of tin(IV) chloride (SnCl$_4$) or zinc(II) chloride led to no formation of the halogen-exchanged product at all (Entries 12 and 13). Particularly, the reaction with SnCl$_4$ gave rise to 3,3-difluoropropenoic imide **8a** exclusively (Entry 12). To be noted is that a molar concentration employed is crucial for the halogen-exchange reaction, the concentration of 0.5 M being strongly recommended.[7]

We next examined the halogen-exchange reaction of silyl enolates generated from various 3,3,3-trifluoropropanoic acid derivatives **2**[8] with TiCl$_4$ under similar conditions. The results are summarized in Table 2. The silyl enolates from phenyl ester, benzyl ester, and phenyl thioester did not give the halogen-exchanged products **5** at all, the corresponding 3,3-difluoropropenoic acid esters **8** being produced in around 30% yields (Entries 1–4). In the case of the silyl enolate from *N*,*N*-dibutylamide, neither formation of **5** nor **8** was observed in the reaction (Entry 5). In contrast, the silyl enolates from imides were found to participate efficiently in the halogen-exchange reaction to give rise to the corresponding 3-chloro-3,3-difluoropropanoic imides **5** in good yields (72 and 87%), as shown in Entries 6 and 7.



Scheme 2. A possible reaction mechanism.

The following mechanism for the present halogen exchange reaction is proposed as shown in Scheme 2. Thus, the silyl enolate **1** undergoes metal exchange with TiX$_4$ to give a titanium(IV) enolate intermediate[9] (**Int-A**). The titanium(IV) enolate **Int-A** would be susceptible to the intramolecular abstraction of a fluorine atom through interaction with Lewis acidic titanium(IV) metal, resulting in the formation of 3,3-difluoropropenoic imide coordinated with titanium(IV) halide (**Int-B**). The resultant **Int-B** may be subject to the intramolecular conjugate addition of another halogen atom X on the titanium moiety,[10] leading to a halogen-exchanged titanium(IV) enolate (**Int-C**). Taking into account the results that the silyl enolates from imides **2** only react effectively with TiX$_4$, as shown in Table 2, the oxazolidinone moiety is strongly suggested to take an important part in the conjugate addition. Thus, a halogen atom on the titanium metal of **Int-B** becomes nucleophilic by coordination with the carbonyl oxygen of oxazolidinone, so that the conjugate addition of the halogen atom may be facilitated to afford the titanium(IV) enolate **Int-C**. Finally, this enolate **Int-C** is converted by a hydrolytic workup to the products, 3-halo-3,3-difluoropropanoic imides **5**–**7**.

In short, we have developed a novel efficient method for the preparation of 3-halo-3,3-difluoropropanoic acid derivatives **5**–**7** starting from 3,3,3-trifluoropropanoic imides **2** through the fluorine–halogen exchange reaction.

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[6] Many examples for the halogen-exchange reactions are reported. For instance, see: *Chemistry of Organic Fluorine Compounds II. A Critical Review*, ed. by M. Hudlicky, A. E. Pavlath, American Chemical Society, Washington, DC, **1995**; G. K. S. Prakash, J. Hu, J. Simon, D. R. Bellew, G. A. Olah, *J. Fluorine Chem.* **2004**, *125*, 595; J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh, N. Kambe, *Chem. Commun.* **2007**, 855.
[7] The experimental procedure is given in Supporting Information, which is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
[8] The silyl enolates of 3,3,3-trifluoropropanoic esters, thioester, and amide were confirmed to be prepared under the same reaction conditions as employed for the imide enolates **1**.
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[10] It was confirmed that the treatment of **8a** with TiCl$_4$ (2.0 equiv.) at −20 °C for 2 h, followed by hydrolysis, gave **5a** in 60% yield.

Published on the web (Advance View) April 7, 2007; doi:10.1246/cl.2007.636