JOC*Note*

Selective Formal Transesterification of Fluorinated 2-(Trimethylsilyl)ethyl α-Imino Esters Mediated by TBAF

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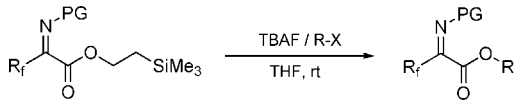
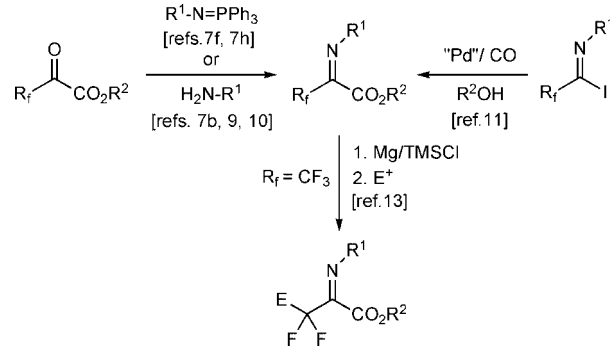
Received March 12, 2008



The scope of the transesterification reaction between β-fluorinated α-imino esters and various electrophiles in the presence of TBAF as fluorine source is described. The reaction is highly selective for alkyl iodides, bromides, and mesylates, while alkyl chlorides react at a significantly slower rate and tosylates do not react under the reaction conditions. This methodology represents a simple and useful alternative for the preparation of a wide variety of fluorinated α-imino esters.

Fluorinated α-imino esters (FαIE) are important building blocks in fluorine chemistry. They are synthetic intermediates for the preparation of β-fluorinated α-amino acids,[1] compounds that are witnessing a growing interest in medicinal, agricultural, and material sciences. Thus, starting from fluorinated α-imino esters, the synthesis of several synthetic analogues of naturally occurring amino acids has been devised, such as trifluoroalaninates,[2] trifluoromethyl aspartic acids,[3] difluoro and trifluoromethyl ornithine,[4] difluoroglutamic acids and difluoroprolines,[5]

SCHEME 1. Methods for Preparing Fluorinated α-Imino Esters



and difluoroserine or difluorocysteine derivatives.[6] Furthermore, FαIE have also been used as substrates for the preparation of other non-natural fluorinated nitrogen derivatives, such as cyclic and acyclic fluorinated quaternary α-amino acids[7] and difluoromethyl aziridines.[8]

Few different methodologies that gain access to fluorinated α-imino esters have been described in the literature, namely aza-Wittig reactions,[7f,h] condensation of carbamates[9] or amines[7b,10] with trifluoropyruvates, and palladium-catalyzed alkoxycarbonylation of fluorinated imidoyl iodides[11] (Scheme 1). The scope of both, the aza-Wittig protocol and the reaction with amines or carbamates, is limited since they involve the condensation with a fluorinated α-keto ester (it is noteworthy that only ethyl and methyl trifluoropyruvates are commercially available). In addition, the condensation reaction is highly dependent on the nature of the amine.[12] On the other hand, the alkoxycarbonylation reaction offers more possibilities in the substitution pattern of the final products, due to the easy preparation of the starting imidoyl iodides. However, this reaction usually requires relatively long reaction times and it is also sensitive to the steric hindrance of the alcohol nucleophiles. Thus, in general, primary alcohols react faster and give higher chemical yields than secondary or tertiary ones.[11]

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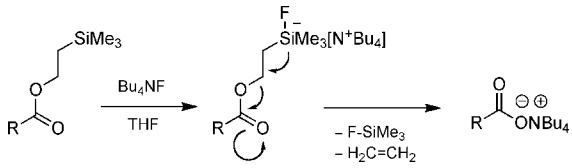
10.1021/jo800567a CCC: $40.75
Published on Web 06/21/2008

SCHEME 2. Deprotection of TMSE-Esters



Additionally, as an extension of the methods described, it is possible to perform a magnesium metal promoted activation of the C−F bonds followed by addition of electrophiles, which allows further functionalizations in the trifluoromethyl-derived imino esters[13] (Scheme 1).

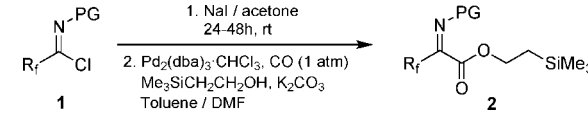
Stability, selectivity, and cost will usually dictate how an imino ester is to be prepared. However, although a great number of methodologies exist to accomplish this task,[14] in particular cases, a mild, generally applicable protocol is still missing. The transesterification reaction is one of most useful synthetic methods for the preparation of esters.[15] Often, transesterifications are more advantageous than the direct ester synthesis from carboxylic acids (or their derivatives, such as alkanoyl halides or carboxylic acid anhydrides) and alcohols. Thus, the ester-to-ester transformation is particularly useful when the parent carboxylic acids are labile and/or difficult to isolate. Fluorinated α-imino esters are included in this category, and the corresponding α-imino acids are not stable under the conditions needed to release the acid functionality.

Gerlach[16] and Sieber[17] independently developed 2-(trimethylsilyl)ethyl (TMSE) esters as a protecting group of the carboxylic moiety, which can be selectively unmasked in the presence of other esters under mild conditions. Since their introduction, TMSE esters have been appreciated for the ease and selectivity of their deprotection.[18] Upon treatment with TBAF, these esters undergo a fragmentation reaction to afford ethylene, trimethylsilyl fluoride (TMSF), and the tetra-*n*-butylammonium salt of the carboxylic acid, which can be obtained in free form through acidification (Scheme 2).

We have found that fluorinated 2-(trimethylsilyl)ethyl imino esters can undergo a mild transesterification process when the deprotection of the TMSE ester moiety is carried out in the presence of an appropriate electrophile, which in situ reacts with the deprotected carboxylate under mild conditions to afford the corresponding ester in moderate to excellent yields. Herein, we report a new and selective transesterification protocol, which constitutes an alternative method to the alkoxycarbonylation process for the preparation of FαIE, dramatically reducing the reaction times once the starting TMSE ester is prepared.

Following the methodology described by Uneyama and coworkers,[11] we obtained chiral and achiral TMSE-derived fluorinated α-imino esters **2** in moderate to good isolated yields (Table 1) from imidoyl chlorides **1**,[19] via their imidoyl iodides, which in turn underwent an alkoxycarbonylation reaction with trimethylsilyl ethanol in the presence of a palladium catalyst.

TABLE 1. Preparation of Fluorinated TMSE-α-Imino Esters 2

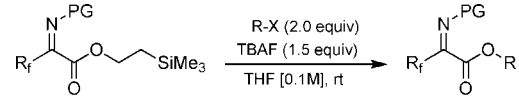


1 **2**

entry	**1**	R_f	PG	**2**	yield (%)[a]
1	**1a**	CF_3	PMP[b]	**2a**	88
2	**1b**	CF_3	(*S*)-PhCH(Me)	**2b**	66
3	**1c**	$CF_2CH_2CH{=}CH_2$	PMP	**2c**	52
4	**1d**	$CF_2CH_2CH{=}CH_2$	(*S*)-phegly-OMe[c]	**2d**	51
5	**1e**	CF_2CF_3	PMP[b]	**2e**	78
6	**1f**	CF_2Cl	PMP[b]	**2f**	40
7	**1g**	(*E*)-$CF_2CH{=}CHPh$	(*R*)-phegly-OMe[c]	**2g**	54

[a] Isolated yields. [b] PMP = *p*-$MeOC_6H_4$. [c] phegly-OMe = PhCH-(CH_2OMe).

TABLE 2. Transesterification Reaction of Fluorinated TMSE-Imino Esters 2



2 **3**

entry	**2**	R-X	**3**	*t* (h)	yield (%)[a]
1	**2a**	Bn-Br	**3a**	1	95
2	**2a**	Bn-OH	**3a**		N.R.
3	**2a**	Allyl-Br	**3b**	1	75
4	**2a**	homoallyl-Br	**3c**	3	95
5	**2a**	*i*Pr-I	**3d**	4	95
6	**2a**	*t*Bu-I	**3e**	24	40
7	**2c**	allyl-Br	**3f**	1	85
8	**2c**	Bn-Br	**3g**	1	94
9	**2c**	Bn-Cl	**3g**	5	20
10	**2c**	Bn-OMs	**3g**	2	77
11	**2c**	Bn-OTs	**3g**		N.R.
12	**2c**	*i*Pr-OMs	**3h**	24	48
13	**2b**	Bn-Br	**3i**	1	79
14	**2d**	Bn-Br	**3j**	1	94
15	**2e**	Bn-Br	**3k**	1	89
16	**2f**	Bn-Br	**3l**	1	95
17	**2g**	Bn-Br	**3m**	1	80

[a] Isolated yields.

When we attempted the standard TMSE ester deprotection with TBAF on compounds **2**, we realized that the resulting carboxylic acids were too sensitive to withstand the reaction conditions. Thus, the corresponding carboxylic acids could not be isolated, probably due to the presence of the labile imine moiety. At that point, instead of trying to isolate the carboxylic acid, we decided to attempt an in situ alkylation of the carboxylate as a convenient means to avoid this problem. To our delight, we found out that when imino ester **2a** was treated with TBAF, in the presence of benzyl bromide, a smooth transesterification process took place to afford benzyl ester **3a** with excellent yield (Table 2, entry 1). In contrast, when benzyl alcohol was used instead of benzyl bromide, in the presence of a coupling reagent such as DIC, no benzyl ester was formed (Table 2, entry 2). At this point, we tried to extend this simple transesterification protocol to other electrophiles to prepare a wide variety of fluorinated α-imino esters.

We were able to determine that our method was also effective for the preparation of allylic, homoallylic, secondary, and even tertiary esters **3** from TMSE esters **2** (Table 2, entries 3−7).

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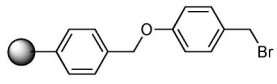
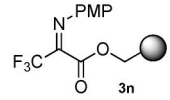
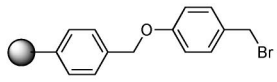
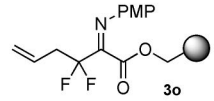
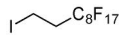
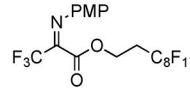
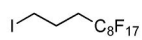
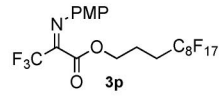
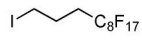
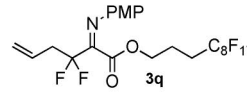
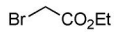
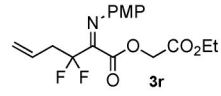
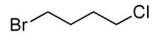
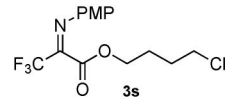
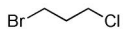
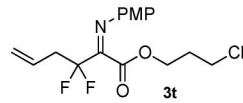
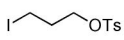
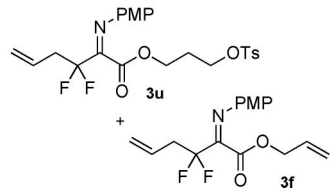
TABLE 3. Further Transesterification Reactions of TMSE-Esters 2[b]

Entry	2	R-X	3	t (h)	Yield (%)[a]
1	**2a**		 **3n**	15	-
2	**2c**		 **3o**	15	-
3	**2a**			-	N.R. [b]
4	**2a**		 **3p**	2	95
5	**2c**		 **3q**	2	90
6	**2c**		 **3r**	1	95
7	**2a**		 **3s**	2	95
8	**2c**		 **3t**	2	75
9	**2c**		 **3u** + **3f**	2	**3u** (50%) **3f** (43%)

[a] Isolated yields. [b] Imino ester **2a** did not react with $CF_3(CF_2)_7(CH_2)_2I$ in the presence of TBAF, probably due to a competitive β-elimination reaction.

With regard to the electrophile leaving group (X), we found that bromides and iodides (Table 2, entries 3−8 and 13−17), as well as primary mesylates[20] (Table 2, entry 10), worked adequately in this reaction. On the other hand, chlorides (Table 2, entry 9) and secondary mesylates (Table 2, entry 12) reacted slower, while tosylates (Table 2, entry 11) completely failed to react under the same reaction conditions.[21]

From these results it became apparent that our transesterification protocol was selective for alkyl iodides, bromides, and primary mesylates. Therefore, we decided to study the scope and utility of this new synthetic methodology by employing differently functionalized electrophiles (Table 3).

In an ongoing project in our laboratory directed toward the asymmetric synthesis of fluorinated cyclic quaternary α-amino acids,[7c] we are attempting to prepare these kinds of compounds on solid- and fluorous-phase techniques,[22] due to their usefulness for the preparation of novel compound libraries in the drug discovery process.[23] One of the key steps in solid-phase as well as fluorous-phase synthesis is the development of new procedures to anchor substrates to either the resin or the perfluoroalkyl chain. We thought that our transesterification protocol might be a useful method for the linking of TMSE imino esters **2** to a modified Wang resin bearing bromobenzylic groups (Table 3, entries 1 and 2). In a similar way, when imino esters **2a** and **2c** were treated with TBAF in the presence of a perfluoroalkylated iodo compound, the attachment of the fluorous tag occurred after 2 h of reaction time in excellent yields (Table 3, entries 4 and 5).[24]

After having shown that tosylates are unreactive as alkylating agents and alkyl chlorides are significatively less reactive than bromides and iodides, we subjected imino esters **2** to our standard transesterification conditions in the presence of dielec-

trophiles, such as 1-bromo-4-chlorobutane and 1-bromo-3-chloropropane. We found that these reactions were completely regio- and/or chemoselective, affording the corresponding chloroesters **3s**,**t** in excellent yields (Table 3, entries 7 and 8). In the same fashion, when the reaction was performed with 1-iodo-3-tosylpropane, the alkylation took place exclusively at the iodide terminus to afford **3u**, together with the allylic ester **3f** derived from tosyl β-elimination (Table 3, entry 9).

Finally, the reaction with ethyl bromoacetate gave the corresponding functionalized imino ester **3r** in excellent yield (Table 3, entry 6).

In conclusion, we have shown that fluorinated α-imino esters derived from 2-(trimethylsilyl)ethanol undergo a selective transesterification process with alkyl halides and mesylates in the presence of TBAF. This simple methodology allows for the preparation of a wide variety of fluorinated α-imino esters and it is also compatible with solid-phase and fluorous syntheses. Other applications of this methodology are currently underway.

Experimental Section

General Procedure for the TBAF-Mediated Transesterification Reaction. To a stirred solution of silylated α-imino ester **2** (1.0 equiv) in THF (0.1M) were added TBAF (1 M in THF, 1.5 equiv) and the corresponding electrophile R-X (2.0 equiv). The reaction mixture was stirred at room temperature until TLC indicated the total disappearance of the starting material. The solvents were then removed under reduced pressure and the residue was purified by means of flash chromatography.

Synthesis of 3r. Following the general procedure described above, **3r** was obtained as a yellow oil in 95% yield from **2c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 3.09 (dt, J_1 = 7.1, J_2 = 16.7 Hz, 2H), 3.81 (s, 3H), 4.21 (q, J = 7.2, 2H), 4.64 (s, 2H), 5.27−5.35 (m, 2H), 5.82−5.96 (m, 1H), 6.87 (d, J = 9.0 Hz, 2H), 7.03 (d, J = 8.9 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 39.5 (t, $^2J_{CF}$ = 24.4 Hz), 55.4, 61.5, 61.7, 114.3, 118.5 (t, $^1J_{CF}$=245.5 Hz), 121.3, 122.1, 127.9 (t, $^3J_{CF}$ = 4.9 Hz), 139.8, 152.9 (t, $^2J_{CF}$ = 33.6 Hz), 158.9, 161.5, 166.3; ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −99.97 (t, J_{FH} = 16.4 Hz, 2F). HRMS calcd for $C_{17}H_{19}F_2NO_5$ (M^+) 355.1231, found 355.1221.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (CTQ2007-61462) of Spain for their financial support. V.R., A.G., and S.C. express their thanks for predoctoral fellowships, M.S.-R. for a postdoctoral contract, and C.P. for a Ramón y Cajal contract.

Supporting Information Available: Experimental procedures and characterization data for compounds **1g**, **2a**,**b**, **2e**−**g**, **3b**,**c**, **3f**, and **3h**−**u** and copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800567A

(20) For a similar transesterification process with a mesylate in an intramolecular macrolactonization reaction, see: Vedejs, E. J.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030–3032.

(21) (a) Other fluoride sources were also tested in the reaction of **2a** with benzyl bromide: CsF did not work, while TBAT and TASF afforded the expected product **3a** although in lower yields (67% and 72%, respectively) and longer reaction times (6 h) than TBAF (Table 2, entry 1). (b) An analogue example of this protocol with *n*-BuBr promoted by NaH was previously reported: Serrano-Wu, M. H.; Regueiro-Ren, A.; Carroll, T. M.; Balasubramanian, B. N.; St. Laurent, D. R. *Tetrahedron Lett.* **2001**, *42*, 8593–8595. In our case, the reaction with NaH turned out to be a complex mixture in which only 8% of the desired product could be detected after 6 h by GC-MS.

(22) (a) Studer, A.; Hadida, S.; Ferrito, S. Y.; Kim, P. Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823–826. (b) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174–1196. (c) Curran, D. P. *Med. Res. Rev.* **1999**, *19*, 432–438.

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(24) The alkoxycarbonylation reaction of the corresponding imidoyl iodide in the presence of 3-(perfluorooctyl)propanol also gave the desired α-imino ester **3q** but it took place slowly (5 days) and in low yield (<30%).