DOI: 10.1002/ejoc.201000948

Fluoroalkylated α,β-Unsaturated Imines: Efficient and Versatile Substrates for the Synthesis of Fluorinated Vinylogous β-Amino Esters and 3,4-Dihydropyridin-2-ones

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Dedicated to Professor Dr. Jose Barluenga on the occasion of his 70th birthday

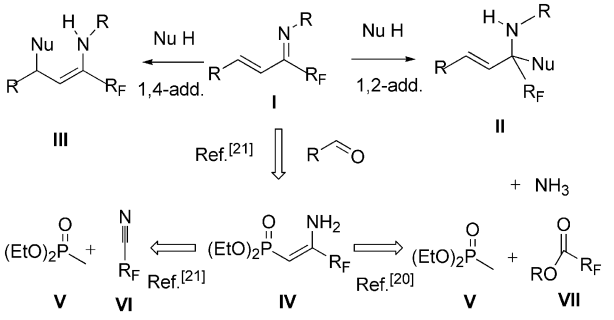
Keywords: Amino acids / Fluorine / Nitrogen heterocycles / Lactams / Spiro compounds

A simple and efficient synthesis of vinylogous fluoroalkylated β-amino mono- (**4**) and diester (**9**) derivatives by the regioselective 1,2-addition of enolates derived from alkyl acetates or diethyl malonate to fluoroalkylated α,β-unsaturated imines (**1**) is described. These fluorinated imines (**1**) were used as intermediates in the regioselective synthesis of fluorine-containing *trans*-3,4-dihydropyridin-2-ones (**6**, **8a**, **8b**, **10**) and 3,3-spiro-3,4-dihydropyridin-2-ones (**8c**–**h**) by conjugate (1,4-) addition of enolates derived from α-mono- and α,α-disubstituted esters. Fluoroalkylated β-amino esters (**4**, **9**) and 3,4-dihydropyridin-2-ones (**6**, **8**, **10**) were also prepared by the olefination of enaminophosphonate **2** with BuLi, addition of aldehydes and subsequent addition of the enolates derived from esters **3**.

Introduction

Fluoroorganic compounds have received much attention because the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical and biological properties.[1] Special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks as they can be used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[2] The development of new methods for the preparation of fluorine-substituted heterocycles is an interesting goal in synthetic organic chemistry, not only because of their use in medicinal chemistry,[3] but also for the development of active ingredients for crop protection.[4] Likewise, the preparation of fluorinated analogues of amino acids has recently been used to stabilize proteins for their application in protein-based biotechnologies such as protein therapeutics and biosensors[5] and in the preparation of fluorinated peptidomimetics.[6]

Furthermore, α,β-unsaturated imines (**I**, Scheme 1), also called 1-azadienes, are a versatile family of compounds with a wide range of applications in preparative organic chemistry.[7] Besides the well-known aza-Diels–Alder reaction[8] for the preparation of six-membered heterocycles and [4+1] cycloaddition reactions for the synthesis of pyrroles,[9] 1-azadienes have been extensively used in the synthesis of several natural products.[10] Moreover, owing to their ambident electrophilic character, α,β-unsaturated imines can either undergo 1,2-[11] or conjugate (1,4-)[12] nucleophilic addition processes (compounds **II** and **III**, Scheme 1). However, control of the regioselectivity is generally difficult, and very often double nucleophilic addition products are obtained.[13]



Scheme 1. Fluorinated α,β-unsaturated imines (**I**): synthetic strategies for their preparation and nucleophilic reactions (1,2 vs. 1,4).

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000948.

The simplest method for the synthesis of α,β-unsaturated imines or 1-azadienes involves the condensation of α,β-unsaturated carbonyl compounds (1,2-addition) with primary amines.[14] However, this method is often complicated by a Michael addition reaction (1,4-addition), especially in the case of α,β-unsaturated ketones, but can be avoided by using the aza-Wittig reaction[15,16] of phosphazenes, and it has recently been applied to the construction of α,β-unsaturated imines derived from α-amino esters[17a] and α-aminophosphonates.[17b] Likewise, the olefination of α-phosphorated imines or enamines with aldehydes to generate the conjugated C=C bond of 1-azadienes is usually a good alternative.[18]

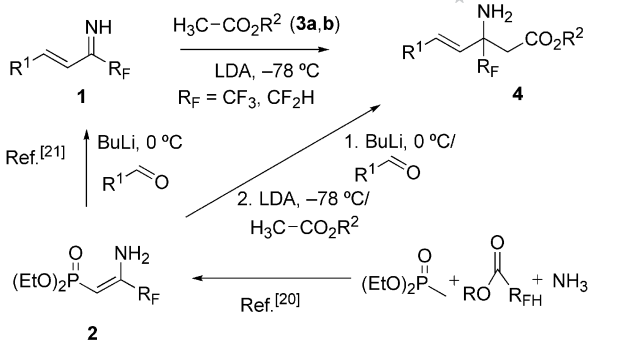
In this context we have reported the preparation of fluorine-substituted aminophosphonates from fluorinated aziridines[19] and enamines[20] and applied this strategy to the preparation of the first stable *N*-unsubstituted α,β-unsaturated imines[21] **I** (R = H) by means of an olefination reaction (Wadsworth–Emmons reaction, WER) with aldehydes of primary enaminophosphonates[22] **IV** obtained either from alkylphosphonates **V** and fluorinated nitriles[21] **VI** or from alkylphosphonates **V**, fluorinated esters **VII** and ammonia[20] (see Scheme 1).

A recent paper[23] reporting the multicomponent synthesis of dihydropyridin-3-ones from methylphosphonate, nitriles, aldehydes, with the initial formation of an unsaturated imine intermediate, and isocyanoacetates (Michael addition–lactamization sequence) prompted us to report our own results concerning the preparation of the previously unknown fluorinated 3,4-dihydropyridin-2-ones from carboxylates and fluorinated imines **1** as well as the first synthesis of vinylogous fluorinated β-amino acid derivatives.

Results and Discussion

Synthesis of Fluoroalkylated β-Amino Esters 4

Unsaturated imines **1** were prepared in good yields by the olefination of primary enamines **2** with butyllithium followed by the addition of aldehydes in a stereoselective fashion.[21] Azadienes **1** are unstable, but they can be isolated and kept in a refrigerator for 2–3 d. However, for synthetic purposes they can be used without isolation. Addition of the enolate derived from methyl acetate (**3a**) (R^2 = Me) at –78 °C to the fluorinated azadienes **1** (R_F = CF_3, CHF_2) and warming of the reaction mixture to room temperature gave vinylogous fluoroalkylated β-amino esters **4** in good yields with the (*E*) configuration of the C=C double bond retained (Scheme 2, Table 1, Entries 1–4, 6 and 7). Similar behaviour was observed when the enolate derived from isopropyl acetate (**3b**) (R^2 = *i*Pr) was used and β-amino ester **4e** (Scheme 2, Table 1, Entry 5) was obtained. The formation of fluoroalkylated β-amino esters **4** can be explained by the regioselective 1,2-addition of the enolate derived from alkyl acetates **3a**,**b** to α,β-unsaturated imine **1** (see Scheme 2).



Scheme 2. Synthesis of vinylogous fluoroalkylated β-amino esters **4**.

Table 1. Synthesis of vinylogous fluoroalkylated β-amino esters **4**.

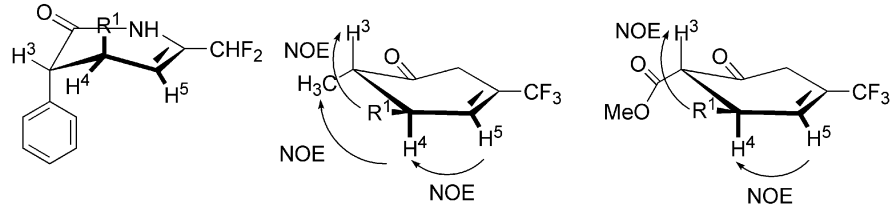
Entry	Compound	R^1	R^2	R_F	Yield (%)[a]
1	**4a**	*p*Tol	CH_3	CF_3	61
2	**4b**	*p*-$O_2NC_6H_4$	CH_3	CF_3	66 (72)[b]
3	**4c**	2-thienyl	CH_3	CF_3	52 (57)[b]
4	**4d**	C_6H_5	CH_3	CF_3	68 (71)[b]
5	**4e**	*p*Tol	*i*Pr	CF_3	65 (70)[b]
6	**4f**	*p*Tol	CH_3	CHF_2	59 (64)[b]
7	**4g**	*p*-FC_6H_4	CH_3	CHF_2	54

[a] Yield of the isolated purified compound obtained from **1**. [b] Yield obtained from **2**.

β-Amino esters **4** can also be prepared by treatment of enaminophosphonate[24] **2** with BuLi, addition of aldehyde and subsequent addition of the enolate derived from methyl acetate (**3a**) or isopropyl acetate (**3b**) (Scheme 2, Table 1, Entries 2–6). The scope of the process is very wide, because different alkyl acetates (R^2 = Me, *i*Pr) can be used, wide variation of the aldehyde (R^1) proved to be possible (aromatic, heteroaromatic or cinnamaldehyde) and the fluoroalkyl group (R_F) was not restricted to trifluoromethyl (R_F = CF_3) (Table 1, Entries 2, 4, 6 and 7), because difluoromethyl-substituted derivatives (R_F = CHF_2) (Table 1, Entries 6 and 7) can also be prepared. As far as we know, this is the first time that vinylogous fluoroalkylated β-amino esters **4** have been obtained.

Synthesis of Fluoroalkylated 3,4-Dihydropyridin-2-ones 6 and 8

The versatility of α,β-unsaturated imines **1** as starting materials for the preparation of acyclic compounds being known, the synthetic applications of α,β-unsaturated imines **1** as intermediates in the preparation of heterocyclic compounds was explored. 3,4-Dihydropyridin-2-ones (3,4-DHP-ones) are important substrates in medicinal chemistry[25] and as intermediates in the preparation of natural products.[26] Addition of the enolate derived from methyl 2-phenylacetate (**3c**; R^2 = C_6H_5) at –78 °C to the azadiene **1** (R^1 = *p*-Tol, R_F = CF_3), after the reaction mixture had been warmed to room temperature, gave 3,4-dihydropyridin-2-one **6a** (Scheme 3, Table 2, Entry 1) in a regioselective fash-



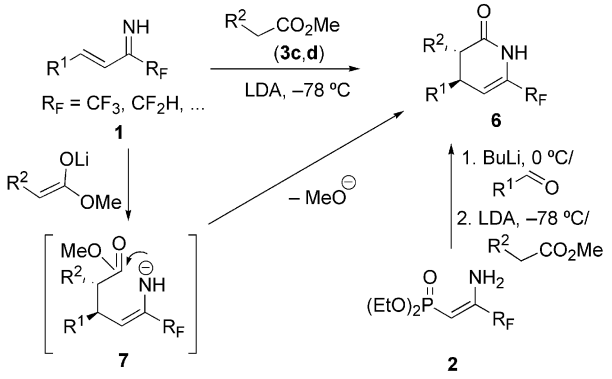
6b (R^1 = *p*Tol) **6c** (R^1 = *p*Tol) **10b** (R^1 = *p*-O_2N-C_6H_4)

$^3J_{H3H4}$ = 7.9 Hz $^3J_{H3H4}$ = 10.8 Hz $^3J_{H3H4}$ = 9.9 Hz

$^3J_{H4H5}$ = 2.9 Hz $^3J_{H4H5}$ = 3.2 Hz $^3J_{H4H5}$ = 2.9 Hz

Figure 1. NOE correlations for **6c** and **10b** and some H,H coupling constants (3-H,4-H and 4-H,5-H) observed for *trans*-3,4-dihydropyridin-2-ones **6b**, **6c** and **10b**.

ion, which was isolated as the *trans* isomer. The process was also extended to difluoromethyl-substituted imine **1** (R^1 = *p*-Tol, R_F = CHF_2), and *trans*-3,4-dihydropyridin-2-one **6b** was obtained (Scheme 3, Table 2, Entry 2). The *trans* stereochemical configuration was assigned on the basis of the 3-H,4-H (7.9 Hz) and 4-H,5-H (2.9 Hz) coupling constants observed for dihydropyridine **6b** (Figure 1). These values are consistent with those reported in the literature.[27] X-ray crystal structure analysis of 3,4-dihydropyridin-2-one **6b** confirmed the *trans* relationship between the two phenyl groups (R^1 = *p*-Tol and R^2 = C_6H_5; Figure 2).[28]



Scheme 3. Synthesis of vinylogous fluoroalkylated β-amino esters **4**.

Table 2. Synthesis of fluoroalkylated *trans*-3,4-dihydropyridin-2-ones **6**.

Entry	Compound	R^1	R^2	R_F	Yield [%][a]
1	**6a**	*p*-Tol	C_6H_5	CF_3	52 (57)[b]
2	**6b**	*p*-Tol	C_6H_5	CHF_2	60
3	**6c**	*p*-Tol	CH_3	CF_3	60 (69)[b]
4	**6d**	2-furyl	CH_3	CF_3	68

[a] Yield of the isolated purified compound obtained from **1**. [b] Yield obtained from **2**.

The formation of heterocycle **6** can be explained by a selective conjugative addition (1,4-addition) of the enolate of ester **3c** to α,β-unsaturated imine **1** with the formation

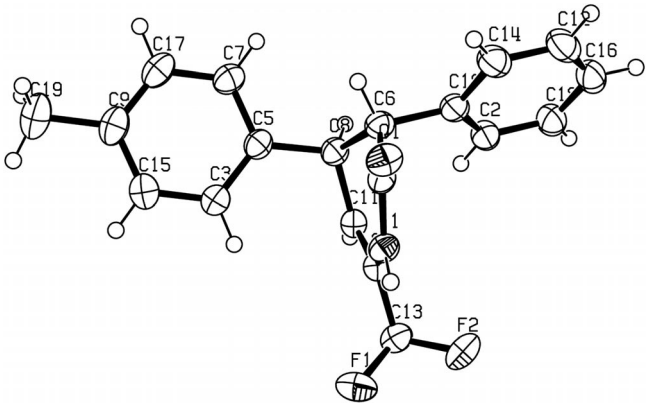
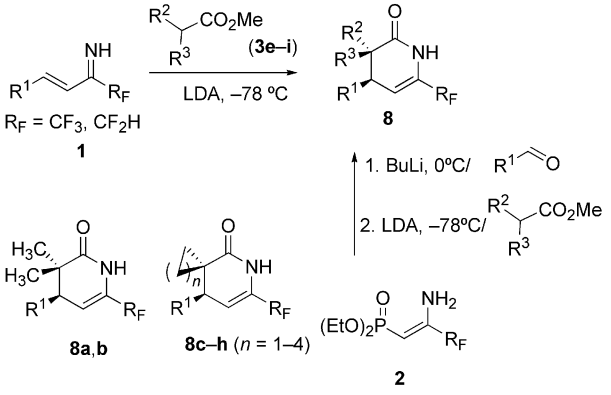


Figure 2. X-ray structure of **6b**.

of adduct **7**, followed by intramolecular cyclocondensation of the terminal nitrogen atom of the enamine to the carbonyl group of the ester moiety with the loss of methanol (see Scheme 3).

The chemical diversity can be increased, because not only 2-arylacetate **3c** but also the aryl group can be substituted by an alkyl group. Addition of the enolate derived from methyl propionate (**3d**; R^2 = CH_3) at –78 °C to fluoroalkylated unsaturated imines **1** gave the corresponding fluorinated *trans*-3,4-dihydropyridin-2-ones **6c**,**d** (Scheme 3, Table 2, Entries 3 and 4) in a selective fashion. The *trans* stereochemical configuration was assigned by nuclear Overhauser measurements (1D NOESY experiments). Irradiation of 3-H (δ = 2.66 ppm) of dihydropyridine **6c** showed an interaction with aromatic protons from the tolyl group (R^1 = *p*-Tol) at the 4-position. Similarly, interactions between the methyl group at C-3 and 4-H and between 4-H and 5-H were observed (see Figure 1). The coupling constants for 3-H,4-H (10.8 Hz) and 4-H,5-H (3.2 Hz) observed for dihydropyridine **6c** are consistent with the *trans* isomer.[27] The pyridine derivatives **6** may also be prepared by treatment of enaminophosphonate[24]**2** with BuLi, the addition of aldehydes and subsequent addition of the enolates derived from α-monosubstituted esters **3c**,**d** (Scheme 3, Table 2, Entries 1,3).

The chemical complexity and diversity of this new family of fluoroalkylated *trans*-3,4-dihydropyridin-2-ones can be increased by using alkyl α,α-disubstituted acetates instead of alkyl acetates or α-monosubstituted esters such as 2-phenylacetate **3c** or methyl propionate (**3d**; see above). Conjugate (1,4-) addition of the enolate derived from methyl 2-methylpropionate (**3e**) ($R^2 = R^3 = CH_3$) at low temperature (–78 °C) to trifluoromethyl ($R_F = CF_3$) and difluoromethyl unsaturated imines **1** ($R_F = CHF_2$) gave 3,4-dihydropyridin-2-ones **8a**,**b** (Scheme 4, Table 3, Entries 1 and 2).



Scheme 4. Synthesis of fluoroalkylated 3,3-disubstituted 3,4-dihydropyridin-2-ones **8a**,**b** and 3,3-spiro-3,4-dihydropyridin-2-ones **8c**–**h**.

Table 3. Synthesis of fluoroalkylated 3,3-disubstituted 3,4-dihydropyridin-2-ones **8a**,**b** and 3,3-spiro-3,4-dihydropyridin-2-ones **8c**–**h**.

Entry	Compound	R^1	R^2	R^3	R_F	Yield [%][a]
1	**8a**	*p*-Tol	CH_3	CH_3	CF_3	61 (65)[b]
2	**8b**	*p*-Tol	CH_3	CH_3	CHF_2	63
3	**8c**	*p*-Tol	$–(CH_2)_2–$		CF_3	55 (62)[b]
4	**8d**	*p*-Tol	$–(CH_2)_3–$		CHF_2	64 (71)[b]
5	**8e**	*p*-Tol	$–(CH_2)_4–$		CF_3	68 (72)[b]
6	**8f**	*p*-Tol	$–(CH_2)_4–$		CHF_2	56 (61)[b]
7	**8g**	*p*-Tol	$–(CH_2)_5–$		CF_3	69 (75)[b]
8	**8h**	2-furyl	$–(CH_2)_5–$		CF_3	69

[a] Yield of the isolated purified compound obtained from **1**. [b] Yield obtained from **2**.

This strategy is not restricted to ester **3e** ($R^2 = R^3 = CH_3$), given that cycloalkanecarboxylates **3f**–**i** [R^2–R^3 = $–(CH_2)_n–$, n = 2–5] can also be used. Conjugate (1,4-) addition of the enolates derived from methyl cyclopropanecarboxylate [**3f**; R^2–R^3 = $–(CH_2)_2–$], methyl cyclobutanecarboxylate [**3g**; R^2–R^3 = $–(CH_2)_3–$], methyl cyclopentanecarboxylate [**3h**; R^2–R^3 = $–(CH_2)_4–$] and methyl cyclohexanecarboxylate [**3i**; R^2–R^3 = $–(CH_2)_5–$] at low temperature to the fluorinated unsaturated imines **1** gave 3,3-spiro-3,4-dihydropyridin-2-ones **8c**–**h** (Scheme 4, Table 3, Entries 3–8). The 3,3-dimethyl- and 3,3-spiro-3,4-dihydropyridin-2-ones **8** can also be prepared by treatment of enaminophosphonate[24] **2** with BuLi, the addition of aldehydes and addition of the enolates derived from esters **3e**–**i** (Scheme 4, Table 3, Entries 1 and 3–7).

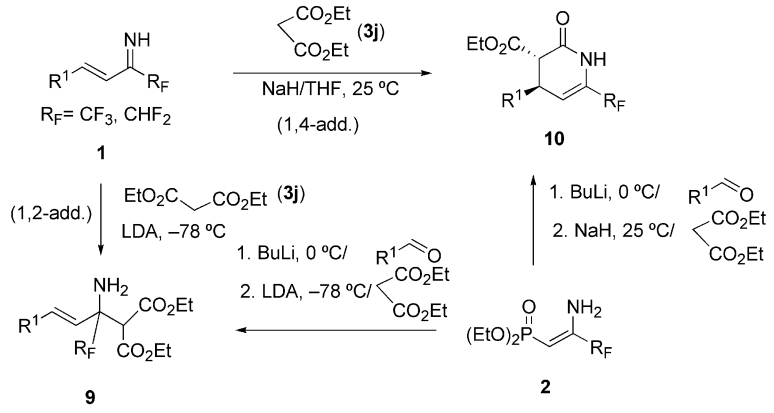
Methods for the preparation of 3,4-dihydropyridin-2-ones by the aza-annulation of imines[29] or enamines[25,30] and α,β-unsaturated carboxylic acid derivatives, as well as the addition of enolates from esters[23,31] or from oxazolones[32] to α,β-unsaturated imines have been described. In addition, a hetero-Diels–Alder reaction[14c,33] of 1-azadienes has also been used. However, the process reported here allows for considerable diversity. The scope of the process is very wide, because R^1 can be aromatic or heteroaromatic, and the fluoroalkyl group (R_F) was not restricted to trifluoromethyl ($R_F = CF_3$) as difluoromethyl ($R_F = CHF_2$) can also be used. Additional diversity can be introduced by using alkyl-substituted acetates ($R^2 = CH_3$, *i*Pr) as well as α-aryl- ($R^2 = C_6H_5$), α-alkyl- ($R^2 = CH_3$), α,α-dialkyl- ($R^2 = R^3 = CH_3$), or cycloalkanecarboxylates [R^2–R^3 = $–(CH_2)_n–$; n = 2–5]. Therefore, this strategy is an example of "diversity-oriented synthesis" (DOS).[34] In addition, as far as we know, this is the first time that fluorinated 3,4-dihydropyridin-2-ones **6** and **8** have been obtained, and this strategy also represents the first example of the preparation of fluorinated 3,3-spiro-3,4-dihydropyridin-2-ones.

Synthesis of Fluoroalkylated β-Amino Diesters 9 and *trans*-3,4-Dihydropyridin-2-ones 10

Taking into account the observed versatility of α,β-unsaturated imines **1** as starting materials for the preparation of acyclic compounds such as β-amino esters by using enolates derived from alkyl acetates and as intermediates in the preparation of heterocycles such as 3,4-dihydropyridin-2-ones from enolates derived from α-mono- and α,α-disubstituted esters (see above), we extended the study to enolates derived from diesters. The addition of the enolate derived from diethyl malonate generated with sodium hydride at –20 °C was explored. Thus, the treatment of fluorinated azadiene **1** (R^1 = *p*-Tol, $R_F = CF_3$) with diethyl malonate (**3j**) in the presence of NaH (–20 °C) gave a 55:45 mixture of vinylogous fluoroalkylated β-amino diesters **9a** with retention of the (*E*) configuration of the C=C double bond and 3,4-dihydropyridin-2-one **10a** (Scheme 5).

The formation of the fluoroalkylated β-amino diester **9a** can be explained by regioselective 1,2-addition of the enolate derived from diethyl malonate (**3j**) to α,β-unsaturated imine **1**, whereas the formation of 3,4-dihydropyridin-2-one **10a** can be explained by the conjugative (1,4-) addition of the enolate of ester **3j** to α,β-unsaturated imine **1** followed by intramolecular cyclocondensation of the terminal nitrogen atom of the enamine to the carbonyl group of the ester with the loss of ethanol, in a similar way to that reported in Scheme 3.

Given these results, we studied whether the reaction conditions could be controlled for the regioselective preparation of fluoroalkylated β-amino diesters **9** and/or 3,4-dihydropyridin-2-ones **10**. The selective 1,2-addition of the enolate derived from diethyl malonate (**3j**) to the fluorinated azadienes **1** ($R_F = CF_3$, CHF_2) was achieved at –78 °C to give vinylogous fluoroalkylated β-amino diesters **9** in good yields with retention of the (*E*) configuration of the C=C double bond (Scheme 5, Table 4, Entries 1–3). The process



Scheme 5. Synthesis of fluoroalkylated β-amino diesters **9** and *trans*-3,3-disubstituted 3,4-dihydropyridin-2-ones **10**.

is not restricted to trifluoromethyl (R_F = CF_3) given that difluoromethyl (R_F = CHF_2) amino esters can also be prepared. The β-amino diesters **9** can also be prepared by treatment of enaminophosphonate **2** with BuLi, the addition of aldehyde and subsequent addition of the enolate derived from malonate **3j** (Scheme 5, Table 3, Entry 2). As far as we know, this is the first time that vinylogous fluoroalkylated β-amino diesters **9** have been obtained.

Table 4. Synthesis of vinylogous fluoroalkylated β-amino diesters **9** and *trans*-3,3-disubstituted 3,4-dihydropyridin-2-ones **10**.

Entry	Compound	R^1	R_F	Yield [%][a]
1	**9a**	*p*-Tol	CF_3	54
2	**9b**	*p*-$O_2NC_6H_4$	CF_3	58 (64)[b]
3	**9c**	*p*-Tol	CHF_2	52
4	**10a**	*p*-Tol	CF_3	41(46)[b]
5	**10b**	*p*-$O_2NC_6H_4$	CF_3	45 (51)[b]
6	**10c**	*o*-$O_2NC_6H_4$	CF_3	41
7	**10d**	*p*-$O_2NC_6H_4$	CHF_2	41(48)[b]

[a] Yield of the isolated purified compound obtained from **1**. [b] Yield obtained from **3**.

Conversely, when the enolate derived from diethyl malonate (**3j**) was generated with NaH (0 °C), added to the azadienes **1** and the reaction mixture was warmed to room temperature, new fluorinated *trans*-3,4-dihydropyridin-2-ones **10** were obtained (Scheme 5, Table 3, Entries 4–7) in a regioselective fashion. The *trans* stereochemical configuration was assigned by nuclear Overhauser measurements (NOESY 1D experiments). Irradiation of 3-H (δ = 3.64 ppm) of the dihydropyridine **10b** showed an interaction with the aromatic protons of the *p*-nitrophenyl group (R^1 = *p*-$O_2NC_6H_4$). Similarly, an interaction between 4-H and 5-H was observed (see Figure 1). The coupling constants for 3-H,4-H (9.9 Hz) and 4-H,5-H (2.9 Hz) observed for dihydropyridine **10b** are consistent with the *trans* isomer.[27] X-ray crystal structure analysis of 3,4-dihydropyridin-2-one **10b** confirmed the *trans* relationship between the *p*-nitrophenyl and carboxylate groups (Figure 3).[35] As before, heterocycles **10** can also be prepared by reaction of enaminophosphonate[24] **2** with BuLi, the addition of aldehydes and subsequent addition of the enolate derived from diethyl malonate (**3j**; Scheme 5, Table 3, Entries 4, 5 and 7).

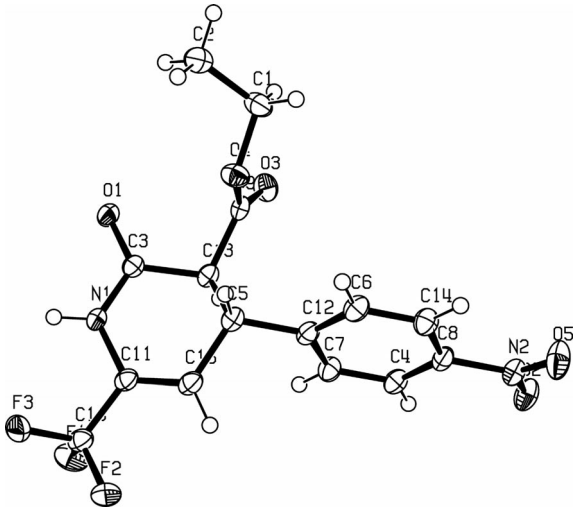
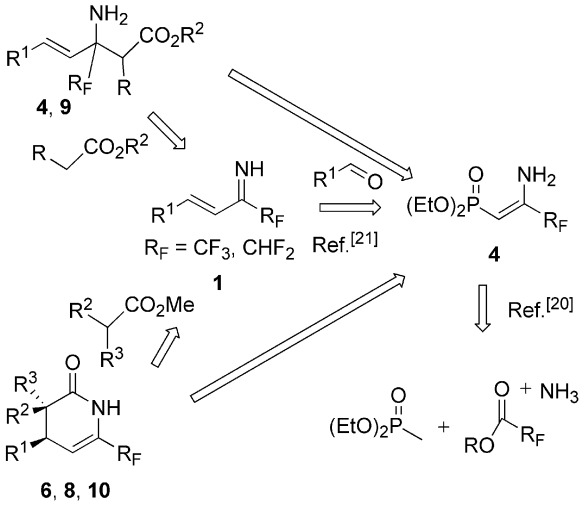


Figure 3. X-ray structure of **10b**.

Conclusions

This account describes a simple, mild and convenient strategy for the preparation of vinylogous β-trifluoromethyl- and β-difluoromethyl-substituted β-amino mono- and diester derivatives by the simple regioselective 1,2-addition of alkyl acetates or diethyl malonate enolates to fluoroalkylated α,β-unsaturated imines **1**. These new fluorinated vinylogous amino esters could be very interesting starting materials for the preparation of new fluorine-containing peptidomimetics in which the fluoroalkyl substituents could stabilize the corresponding biologically active peptides or proteins.[3,5] Likewise, the regioselective synthesis of fluorine-containing *trans*-3,4-dihydropyridin-2-ones and 3,3-spiro-3,4-dihydropyridin-2-ones by the conjugate (1,4-) addition of enolates derived from α-mono- and α,α-disubstituted esters to fluoroalkylated α,β-unsaturated imines **1** has also been described. Fluoroalkylated β-amino esters and 3,4-dihydropyridin-2-ones can also be prepared by the olefination of enaminophosphonate **2** with base (BuLi), addition of aldehydes and subsequent addition of the enolates derived from esters (see Scheme 6). High chemical diversity can be achieved, because variation of the aldehyde

(R^1), fluoroalkyl group (R_F) and esters (R, R^2, R^3) proved to be possible. Substituted fluorinated dihydropyridine derivatives[2] as well as vinylogous β-amino ester derivatives[3,5] are important building blocks in organic synthesis and in the preparation of biologically active compounds of interest in medicinal chemistry.



Scheme 6. Synthetic strategy for the regioselective preparation of fluoroalkylated β-amino esters **4** and **9**, *trans*-3,3-disubstituted 3,4-dihydropyridin-2-ones **6**, **8a** and **10** and 3,3-spiro-3,4-dihydropyridin-2-ones **8b**–**e**.

Experimental Section

General Procedure for the Synthesis of Fluoroalkylated β-Amino Esters 4 from Imines 1: A solution of fluorinated azadiene **1** (1 mmol) in dry THF (6 mL) was added to a solution of the enolate derived from alkyl acetate **3a** or **3b** (1.5 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) at –78 °C under nitrogen. The mixture was stirred at the same temperature for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then it was allowed to reach room temperature, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of Fluoroalkylated β-Amino Esters 4 from Enaminophosphonates 2: Butyllithium (1.6 M in hexanes, 0.65 mL, 1 mmol) was added to a solution of fluorinated enaminophosphonate **2** (1 mmol) in THF (6 mL) at 0 °C under N_2. The mixture was stirred at the same temperature for 1 h. Then a solution of the corresponding aldehyde (1 mmol) in THF (6 mL) was added, and the reaction mixture was stirred at room temperature, until TLC showed the disappearance of **2**. Then a solution of the enolate derived from methyl acetate **3a** or **3b** (1 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) was added. The mixture was stirred at the same temperature for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then it was allowed to reach room temperature, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

Methyl 3-Amino-5-(*p*-tolyl)-3-trifluoromethylpent-4-enoate (4a): Yield: 175 mg, 61%; obtained as a pale-yellow oil from imine **1** as described in the general procedure. R_f = 0.32 (hexane/ethyl acetate, 7:3). ^{1}H NMR (CD_3OD): δ = 2.14 (s, 2 H, NH_2), 2.34 (s, 3 H, CH_3), 2.77 (s, 2 H, CH_2), 3.64 (s, 3 H, OCH_3), 6.20 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, =CH), 6.82 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, =CH), 7.14 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, H_{Ar}), 7.29 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (CD_3OD): δ = 20.9, 34.9, 51.6, 59.3 (q, $^2J_{F,C}$ = 27.2 Hz), 124.5, 126.0 (q, $^1J_{F,C}$ = 285.0 Hz), 126.5, 129.1, 132.6, 132.7, 138.0, 169.6 ppm. ^{19}F NMR (CD_3OD): δ = –80.8 ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3402, 3324, 1739, 1161 cm^{-1}. MS (EI): *m*/*z* (%) = 287 (23) $[M]^+$. $C_{14}H_{16}F_3NO_2$ (287.28): calcd. C 58.53, H 5.61, N 4.88; found C 58.69, H 5.55, N 4.79.

General Procedure for the Synthesis of Fluoroalkylated 3,4-Dihydropyridin-2-ones 6 and 8 from Imines 1: A solution of the fluorinated azadiene **1** (1 mmol) in dry THF (6 mL) was added to a solution of the enolate derived from the corresponding ester **3c**–**i** (1 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) at –78 °C under nitrogen. Then the mixture was stirred for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1** at –78 °C, except in the case of the compound **6a** or **6b**, which were allowed to reach room temperature slowly, and the mixture was stirred at the same temperature. Then a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of Fluoroalkylated 3,4-Dihydropyridin-2-ones 6 and 8 from Enaminophosphonates 2: Butyllithium (1.6 M in hexanes; 0.65 mL, 1 mmol) was added to a solution of the fluorinated enaminophosphonate **2** (1 mmol) in THF (6 mL) at 0 °C under N_2. The mixture was stirred at the same temperature for 1 h. Then a solution of the corresponding aldehyde (1 mmol) in THF (6 mL) was added, and the reaction mixture was stirred at room temperature, until TLC showed the disappearance of **2**. Then a solution of the enolate derived from the corresponding ester **3c**–**i** (1 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) was added at –78 °C under nitrogen. Then the mixture was stirred for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1** at –78 °C, except in the case of the compound **6a** or **6b**, which were allowed to reach room temperature slowly, and the mixture was stirred at the same temperature. Then, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

6-(Difluoromethyl)-3-phenyl-4-(*p*-tolyl)-3,4-dihydropyridin-2(1*H*)-one (6b): Yield: 188 mg, 60%; obtained as a white solid from imine **1** as described in the general procedure. R_f = 0.62 (hexane/ethyl acetate, 7:3); m.p. 139–142 °C. ^{1}H NMR (CD_3OD): δ = 2.29 (s, 3 H, CH_3), 3.82 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, =CH), 3.87–3.94 (m, 1 H, =CH), 5.58 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, =CH), 6.16 (t, $^2J_{FH}$ = 53.9 Hz, 1 H, CHF_2), 6.95–7.24 (m, 9 H, H_{Ar}), 7.28 (s, 1 H, NH) ppm. ^{13}C NMR (CD_3OD): δ = 20.9, 45.9, 55.0, 111.1 (t, $^3J_{F,C}$ = 7.7 Hz), 119.0 (t, $^1J_{F,C}$ = 238.4 Hz), 127.2, 127.4, 128.2, 128.7, 129.5, 130.7 (t, $^2J_{F,C}$ = 22.1 Hz), 137.1, 137.8, 170.0 ppm. ^{19}F NMR (CD_3OD): δ = –119.5 (d, $^2J_{F,H}$ = 53.4 Hz) ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3395, 3211, 1679, 1188 cm^{-1}. HRMS (EI$^+$): calcd. for $C_{19}H_{17}F_2NO$ $[M]^+$ 313.1278; found 313.1281.

X-ray Analysis of 6-(Difluoromethyl)-3-phenyl-4-(*p*-tolyl)-3,4-dihydropiridin-2(1*H*)-one (6b): A colourless prismatic crystal having approximate dimensions of 0.33 × 0.33 × 0.12 mm was mounted on

a MicroMount. All measurements were carried out by using a STOE IPDS 2T diffractometer with graphite-monochromated Mo-K_α radiation. Crystal data: $C_{19}H_{17}F_2NO$, T = 100 K, monoclinic, space group $P2_1/n$, a = 11.303(1), b = 10.578(1), c = 13.442(1) Å, β = 95.654(4)°, V = 1599.3(2) Å^3, Z = 4 ($d_{calcd.}$ = 1.301 g cm^{-3}), μ(Mo-K_α) = 0.096 mm^{-1}, multiscan absorption correction, 3416 unique reflections and all of them were used in refinement, R = 5.3%, R_w = 10.6% for all reflections [R = 3.8% for reflections with $F_o > 4\sigma(F_o)$].[28]

Synthesis of 9a and 10a: A solution of the fluorinated azadiene **1** (1 mmol) in dry THF (6 mL) was added to a solution of the enolate derived from diethyl malonate (**3j**; 1 mmol; NaH, –20 °C, for 1 h) in dry DMF (15 mL) at –20 °C under nitrogen. The mixture was stirred at the same temperature for 1 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then it was allowed to reach room temperature, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with Et_2O (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum to give a 55:45 mixture of vinylogous fluoroalkylated β-amino diesters **9a**, with retention of the (*E*) configuration of the C=C double bond, and *trans*-3,4-dihydropyridin-2-one **10a**. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of Vinylogous Fluoroalkylated β-Amino Diesters 9 from Imines 1: A solution of the fluorinated azadiene **1** (1 mmol) in dry THF (6 mL) was added to a solution of the enolate derived from diethyl malonate (**3j**; 1 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) at –78 °C under nitrogen. The mixture was stirred at the same temperature for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then it was allowed to reach room temperature, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of Fluoroalkylated β-Amino Diesters 9 from Enaminophosphonates 2: Butyllithium (1.6 M in hexanes; 0.65 mL, 1 mmol) was added to a solution of fluorinated enaminophosphonate **2** (2 mmol) in THF (6 mL) at 0 °C under N_2. The mixture was stirred at the same temperature for 1 h. Then a solution of the corresponding aldehyde (1 mmol) in THF (6 mL) was added, and the reaction mixture was stirred at room temperature, until TLC showed the disappearance of **2**. Then a solution of the enolate derived from diethyl malonate (**3j**; 1 mmol; LDA, –78 °C, for 1 h) in dry THF (15 mL) was added at –78 °C under nitrogen. The mixture was stirred at the same temperature for 16 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then it was allowed to reach room temperature, a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of *trans*-Fluoroalkylated 3,4-Dihydropyridin-2-ones 10 from Imines 1: A solution of the fluorinated azadiene **1** (1 mmol) in dry THF (6 mL) was added to a solution of the enolate derived from diethyl malonate (**3j**; 1 mmol; NaH, 25 °C, for 1 h) in dry THF (15 mL) under nitrogen. The mixture was stirred at the same temperature for 1 h, until TLC showed the disappearance of the fluorinated azadiene **1**. Then a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with Et_2O (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

General Procedure for the Synthesis of *trans*-Fluoroalkylated 3,4-Dihydropyridin-2-ones 10 from Enaminophosphonates 2: Butyllithium (1.6 M in hexanes; 1.25 mL, 1 mmol) was added to a solution of fluorinated enaminophosphonate **2** (1 mmol) in THF (6 mL) at 0 °C under N_2. The mixture was stirred at the same temperature for 1 h. Then a solution of the corresponding aldehyde (2 mmol) in THF (6 mL) was added, and the reaction mixture was stirred at room temperature, until TLC showed the disappearance of **2**. Then a solution of the enolate derived from diethyl malonate (**3j**; 1 mmol; NaH, 25 °C, for 1 h) in dry THF (15 mL) was added under nitrogen. The mixture was stirred at the same temperature for 1 h. Then a saturated solution of NH_4Cl (10 mL) was added, and the organic layer was extracted with Et_2O (3× 25 mL), dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under vacuum. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate).

Ethyl 3-Amino-3-ethoxycarbonyl-5-(*p*-tolyl)-3-trifluoromethylpent-4-enoate (9a): Yield: 202 mg, 54%; obtained as a colourless oil from imine **1** as described in the general procedure. R_f = 0.46 (hexane/ethyl acetate, 7:3). ^{1}H NMR (CD_3OD): δ = 0.99 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.14 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 2.36 (s, 2 H, NH_2), 3.80 (s, 1 H, =CH), 3.96 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2), 4.03–4.13 (m, 2 H, OCH_2), 6.00 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, =CH), 6.73 (d, $^3J_{H,H}$ = 16.0 Hz, 1 H, =CH), 6.99 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H_{Ar}), 7.14 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (CD_3OD): δ = 13.5, 13.6, 20.9, 52.4, 61.5 (q, $^2J_{F,C}$ = 29.5 Hz), 61.6, 61.8, 125.2 (q, $^1J_{F,C}$ = 285.5 Hz), 122.7, 126.5, 129.1, 133.6, 138.2, 165.0, 166.0 ppm. ^{19}F NMR (CD_3OD): δ = –78.1 ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3400, 3339, 1754, 1143 cm^{-1}. MS (EI): *m/z* (%) = 374 (5) [M + 1]$^+$. $C_{18}H_{22}F_3NO_4$ (373.37): calcd. C 57.90, H 5.94, N 3.75; found C 58.09, H 5.88, N 3.88.

Ethyl 2-Oxo-4-(*p*-tolyl)-6-(trifluoromethyl)-1,2,3,4-tetrahydropyridine-3-carboxylate (10a): Yield: Obtained as a white solid as from imine **1** in a yield of 134 mg, 41%, and from enaminophosphonate **2** in a yield of 150 mg, 46%, as described in the general procedure. R_f = 0.40 (hexane/ethyl acetate, 7:3); m.p. 121–122 °C. ^{1}H NMR (CD_3OD): δ = 1.13 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 3.58 (d, $^3J_{H,H}$ = 9.8 Hz, 1 H, =CH), 4.02–4.28 (m, 3 H, CH_2, CH), 5.77 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, =CH), 7.04 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H_{Ar}), 7.09 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H_{Ar}), 8.15 (s, 1 H, NH) ppm. ^{13}C NMR (CD_3OD): δ = 13.9, 21.0, 40.7, 54.6, 61.9, 111.1 (q, $^3J_{F,C}$ = 4.0 Hz), 119.7 (q, $^1J_{F,C}$ = 271.9 Hz), 127.2, 129.8, 135.7, 137.7, 166.1, 167.9 ppm. ^{19}F NMR (CD_3OD): δ = –70.6 ppm. IR (NaCl): $\tilde{\nu}_{max}$ = 3313, 2990, 1734, 1693 cm^{-1}. MS (EI): *m/z* (%) = 255 (70) [M – 72]$^+$. $C_{16}H_{16}F_3NO_3$ (327.30): calcd. C 58.72, H 4.93, N 4.28; found C 58.60, H 4.97, N 4.15.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures and characterization data (^{1}H, ^{13}C, ^{31}P and ^{19}F NMR, IR and elemental analysis) for compounds **4b**–**4g**, **6a**, **6c**, **6d**, **8a**–**8h**, **9b**, **9c** and **10b**–**10d**, NOE correlations for **6c** and **10b**.

Acknowledgments

The authors thank the University of the Basque Country (UPV/EHU, GIU09/56), the Education and Research Department of the Gobierno Vasco (GV, Vitoria) (IT-422-10) and the Dirección General de Investigación del Ministerio de Ciencia y Tecnología

(MICIN, Madrid DGI) (CTQ2009-12156) for supporting this work. G. F. T. thanks the University of the Basque Country for a formation contract. UPV/EHU-SGIKer technical support (MICINN, GV/EJ, European Social Fund) is gratefully acknowledged.

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Received: July 6, 2010
Published Online: October 15, 2010

