Pergamon

Tetrahedron Letters, Vol. 38, No. 38, pp. 6771-6774, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01549-9

N-Substituted β-Enamino Acid Derivatives: A New Approach to Fluorinated β-Enamino Esters

Santos Fustero,* Belén Pina, and Antonio Simón-Fuentes

Departamento de Química Orgánica, Facultad de Farmacia, Avda. Vicente Andrés Estellés s/n,
46100 Burjassot, Valencia, Spain.

Abstract: Reaction of fluorinated imidoyl chlorides **1** with lithium ester enolates **2** gave *N*-substituted γ-fluorinated β-enamino and/or β-imino esters **4** in good to excellent yields. β-Enamino esters were obtained exclusively as *Z* isomers. © 1997 Published by Elsevier Science Ltd.

β-Enamino acid derivatives, particularly β-enamino esters, represent a class of highly reactive difunctionalized compounds, which have often been shown to be useful and versatile in the preparation of numerous biologically active compounds, especially in the asymmetric synthesis of naturally occurring alkaloids[1] and β-amino acids.[1,2] Although several routes for the synthesis of these derivatives have been reported, most are limited, usually due to their low chemical yield and general applicability.[3]

In contrast to the non-fluorinated derivatives, γ-fluorinated-β-enamino esters have received far less attention. A survey of the literature reveals that few methods have been developed for the preparation of γ-fluorinated-β-enamino esters. They usually require the use of either alkyl α-H-perfluoro esters[4a] or fluoroalkynes,[4b,c] or alternatively fluorinated β-ketocarboxylic esters[4d] and ammonia or amines. More recently, a new approach that involves iminophosphoranes and organozinc compounds has also been described.[5] However, in all cases, the chemical yield, nature and stereochemistry of the obtained products depend strongly both on the nature of the starting amine and the method used. Thus, while on some occasions the reaction only works well with primary aromatic amines,[5] on others the starting materials either are not easily accessible[4b,c] or can only be use to prepare *N*-alkyl-β-enamino ester analogs.[4a]

Due to their unique properties, organo-fluorine compounds have found numerous industrial and pharmaceutical applications.[6] Although most applications refer to fluorinated oxygen derivatives, fluorine-containing amino compounds have received increasing interest in recent years.[6b] Among these, fluorinated imidoyl halides, recently synthesized by Uneyama,[7] are some of the most promising fluorine electrophilic synthons, and have been successfully used as building blocks in a wide variety of synthetic processes.[8]

Based on a study of their reactivity, we recently reported a simple route to *N*-substituted β-enamino acid derivatives by reacting 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines with perfluorinated imidoyl chlorides.[9] *N*-Alkyl- and *N*-aryl-substituted γ-fluorinated-β-enamino acid derivatives can be easily synthesized via the same strategy. We report here a new, simple and general method for preparing γ-fluorinated-β-enamino esters starting from lithium ester enolates of **2** and imidoyl chlorides **1**.

When a solution of lithium enolates of alkyl esters, conveniently prepared by reacting alkyl ester derivatives **2** with 2.0 equiv of LDA, was cooled to -78 °C in dry tetrahydrofuran solvent, and subsequently treated with the corresponding imidoyl chloride **1** (1.0 equiv),[7] γ-fluorinated-β-enamino esters (**4β**) and/or β-imino tautomers (**4α**) were formed as the only products (Scheme I). The reactions were complete in 2-5 h (TLC). The described procedure provides a simple, high-yielding route to this class of derivatives **4** (see Table). As previously indicated,[3e,9] two equivalents of LDA should be used to ensure the presence of the intermediate **3**, which results in a remarkable improvement in the chemical yield (Table, entries 1,4) and also in the stereochemical outcome of the resulting products (see below).

Scheme I

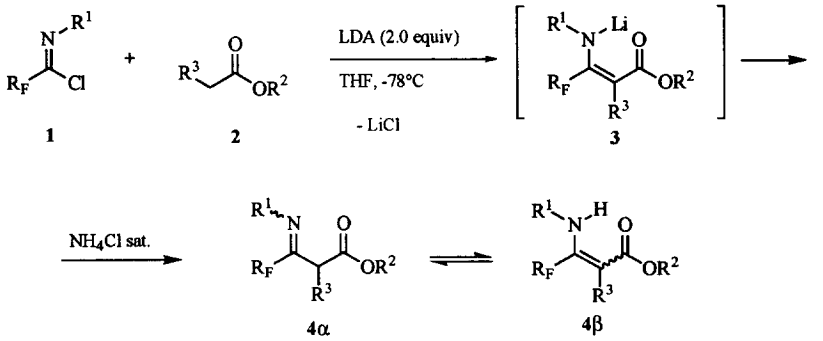


Table. Fluorinated *N*-substituted β-enamino esters **4** obtained from imidoyl chlorides **1** and esters **2**.

Entry	R_F	R^1	R^2	R^3	Product	Yield (%)[a,b]	ratio[c] 4α/4β
1	CF_3	*p*-$MeOC_6H_4$	$C(CH_3)_3$	H	**4a**	90 (47)[d]	30:70
2	CF_3	*p*-$MeOC_6H_4$	$CH(CH_3)_2$	H	**4b**	85	20:80
3	CF_3	*p*-$MeOC_6H_4$	(1*R*)-(-)-Menthyl	H	**4c**[e]	95	10:90
4	CF_3	(*S*)-(+)-*c*-C_6H_{11}(Me)CH	$C(CH_3)_3$	H	**4d**[e]	81(51)[d]	10:90
5	CF_3	(*R*)-(+)-C_6H_5(Me)CH	(1*R*)-(-)-Menthyl	H	**4e**[e]	90	0:100
6	CF_3CF_2	*p*-$MeOC_6H_4$	$C(CH_3)_3$	H	**4f**	75	80:20
7	$CF_3(CF_2)_7$	*p*-$MeOC_6H_4$	$CH(CH_3)_2$	H	**4g**	78	75:25
8	CF_2Cl	*p*-$MeOC_6H_4$	— $(CH_2)_2$ —		**4h**	81	0:100

[a] Isolated yields. [b] Purified by flash chromatography. [c] Tautomer ratio estimated by analysis of the 250MHz ^1H NMR and 235 MHz ^{19}F NMR spectra of the crude reaction mixtures. [d] Yield using 1.0 equiv of LDA. [e] **4c**: $[\alpha]^{25}_D$ -45.9° (*c* 1.60, $HCCl_3$); **4d**: $[\alpha]^{25}_D$ +245.5° (*c* 0.50, $HCCl_3$); **4e**: $[\alpha]^{25}_D$ +318.0° (*c* 1.50, $HCCl_3$).

It should be emphasized that this process, in contrast to others described previously,[4,5] works well independent of the nature of the starting materials **1** and **2**. Thus, imidoyl halides derived from alkyl and aryl amines can be used without a decrease in the chemical yield and with the same stereochemical outcome. Indeed, lactones, for example γ-butyrolactone, react in the same manner to give the cyclic fluorinated β-enamino ester **4h** (see Table, entry 8).

The Table shows that the resulting compounds **4** were isolated, in general, as a mixture of the imino **4α** and enamino **4β** tautomeric forms. The **4α** /**4β** ratio is influenced mainly by the length of the perfluoroalkyl chain. Thus, while in the case of trifluoro- or difluoromethyl derivatives the enamino tautomer **4β** clearly predominates (Table, entries 1-5, 8), in other perfluoroalkyl derivatives ($R_F \neq CF_3$) (Table, entries 6,7) the β-imino ester **4α** appears as the major tautomer.[10] Moreover, we have observed that, although fluorinated β-enamino esters **4β** may exist as *E*- and *Z*-geometric isomers (Scheme II), **4β** appears exclusively as the *Z*-tautomer (chelated configuration) both for *N*-aliphatic and *N*-aromatic derivatives.

Scheme II

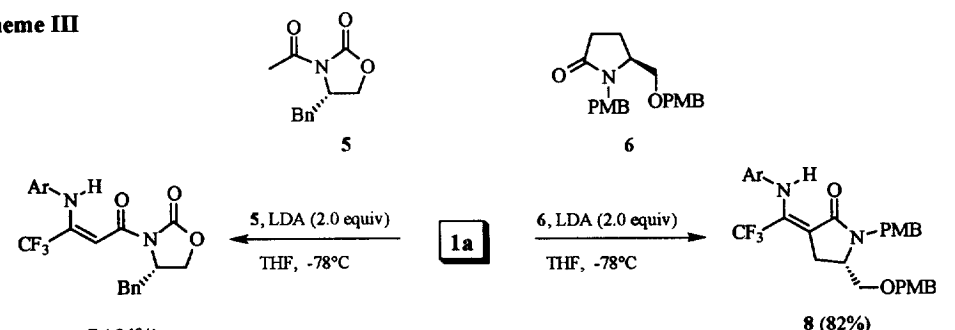
4β (*Z*) 4β (*E*)

Stereochemical assignments for the enamino tautomer **4β** were based on 2D HOESY NMR 1H-19F experiments using ^{1}H-^{19}F long correlations. The results showed, for example, for **4b** (Table, entry 2), that the vinylic hydrogen at δ 5.28 ppm (^{1}H NMR) have cross peaks with the fluorine atoms at δ -63.8 ppm in the ^{19}F NMR spectrum. The signal connecting the fluorine atoms with the hydrogens of the *p*-anisidine ring at δ 7.15 ppm unequivocally corroborates the *Z* configuration of the enamino tautomer **4β**.

However, this result is not consistent with other reports in the literature. Several authors[4b,5] have indicated that fluorinated *N*-aryl derivatives **4** appear exclusively in the *E*-configuration. A plausible explanation for these contradictory results is that the stereochemistry of the fluorinated β-enamino esters is sensitive to the method used for their preparation.[11] In our case, the lithium intermediate **3** could be responsible for stabilization of the resulting *Z*-enamino tautomer.

This approach has also been successfully applied to the synthesis of other β-enamino carbonyl substrates, such as fluorinated β-enamino amides derived from chiral non-racemic acyclic and cyclic amides **5** and **6** (Scheme III).

Scheme III



7 (94%) **8** (82%)

Thus, for example, imidoyl chloride **1a** (R_F=CF_3, R^1=*p*-$MeOC_6H_4$) reacts with commercially available *N*-acyloxazolidinone **5** under the same reaction conditions described for the esters to exclusively give compound **7** {$[\alpha]^{25}_D$ +60.2° (*c* 1.36, $HCCl_3$)} in almost quantitative yield. Similarly, treatment of **1a** with the γ-lactam **6** (PMB= *p*-methoxybenzyl), obtained in three steps from *L*-pyroglutamic acid, resulted in the formation of the fluorinated 2-pyrrolidinone derivative **8** {$[\alpha]^{25}_D$ +261.4° (*c* 1.08, $HCCl_3$)} in 82% yield (Scheme III). Both derivatives **7** and **8**, along with the possibility of introducing chirality at the R^1 and R^2 positions of the γ-fluorinated-β-enamino esters **4** (Table, entries 3-5) make these systems valuable for the asymmetric synthesis of compounds of biological interest, especially fluorinated β-amino acids.[4c,d]

In summary, we have provided a new and remarkably simple route for the synthesis of fluorinated β-enamino and/or imino esters **4**[12] starting from imidoyl chlorides **1**. In addition, β-enamino amides **7** and **8** were obtained following the same strategy.[12] Further studies of the utility of these systems are in progress.

Acknowledgments

We are grateful to the Dirección General de Investigación Científica y Técnica (DGICYT, PB93-0360, PB94-1313-C02-02 and PB96-0760-C02-01) and for a fellowship from the Generalitat Valenciana to B.P. We also thank Bruker Española, S.A. for conducting the HOESY experiments.

References and Notes

1. Beholz, L.G.; Benovsky, P.; Ward, D.L.; Barta, N.S.; Stille, J.R. *J. Org. Chem.* **1997**, *62*, 1033 and references cited therein.
2. (a) Lubell, W.D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543. (b) Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557.
3. (a) Ferraz, H.M.C.; Oliveira, E.O.; Payret-Arrua, M.E.; Brandt, C.A. *J. Org. Chem.* **1995**, *60*, 7357. (b) Lee, A. S-Y.; Cheng, R-Y.; Pan, O-G. *Tetrahedron Lett.*, **1997**, *38*, 443 and references cited therein. (c) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*, Baldwin, J.E., Magnus, P.D., Eds.; Pergamon Press; Oxford U.K., 1992, Chapter 7, p 352. (d) Fustero, S.; Díaz, D.; Pérez Carlón, R. *Tetrahedron Lett.*, **1993**, *34*, 725. (e) Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, *51*, 8613. (f) Fustero, S.; Díaz, D.; Barluenga, J.; Aguilar, E. *Tetrahedron Lett.*, **1992**, *33*, 3801.
4. (a) Iznaden, M.; Portella, C. *Tetrahedron Lett.*, **1988**, *29*, 3683. (b) Froissard, J.; Greiner, J.; Pastor, R.; Cambon, A. *J. Fluorine Chem.*, **1981**, *17*, 249. (c) Cen, W.; Ni, Y.; Shen, Y. *J. Fluorine Chem.*, **1995**, *73*, 161. (d) Soloshonok, V.A.; Kukhar, V. *Tetrahedron* **1996**, *52*, 6953.
5. Shen, Y.; Gao, S. *J. Fluorine Chem.*, **1996**, 76, 37.
6. (a) Welch, J.T.; Eswarakrishnan, S. In *Fluorine in Bioorganic Chemistry*; John Wiley Inc.: New York, 1991. (b) Kukhar, V.; Soloshonok, V.A. In *Fluorine-Containing Amino Acids: Synthesis and Properties*, John Wiley Inc.: New York, 1995.
7. Takamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32.
8. (a) Kobayashi, M.; Sadamune, K.; Mizukami, H.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 1909. See also: (b) Ref. 6b, p. 129. (c) Huang, W.S.; Yuan, C.Y. *J. Chem. Soc. Perkin Trans. 1* **1995**, 741.
9. Fustero, S.; Navarro, A.; Díaz, D.; G. de la Torre, M.; Asensio, A.; Sanz, F.; Liu, M. *J. Org. Chem.* **1996**, *61*, 8849.
10. These results agree with others previously reported. See refs. 4 and 5.
11. A similar behaviour has been observed for non-fluorinated derivatives. See ref. 3c.
12. Compounds **4**, **7**, and **8** all exhibited ^1H, ^{13}C, ^{19}F NMR and mass spectra consistent with their assigned structures.

(*Received in UK* 24 *June* 1997; *revised* 24 *July* 1997; *accepted* 25 *July* 1997)