Tetrahedron Letters, Vol. 34, No. 22, pp. 3621-3624, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Transamination of Fluorinated ß-Keto Carboxylic Esters. A Biomimetic Approach to ß-Polyfluoroalkyl-ß-amino Acids.

Vadim A. Soloshonok*, Alexander G. Kirilenko, and Valery P. Kukhar'

Institute of Bioorganic Chemistry and Petrol Chemistry, Ukrainian Academy of Sciences, Kiev, 253160, Kharkovskoe Shausse 50, Ukraine.

Giuseppe Resnati

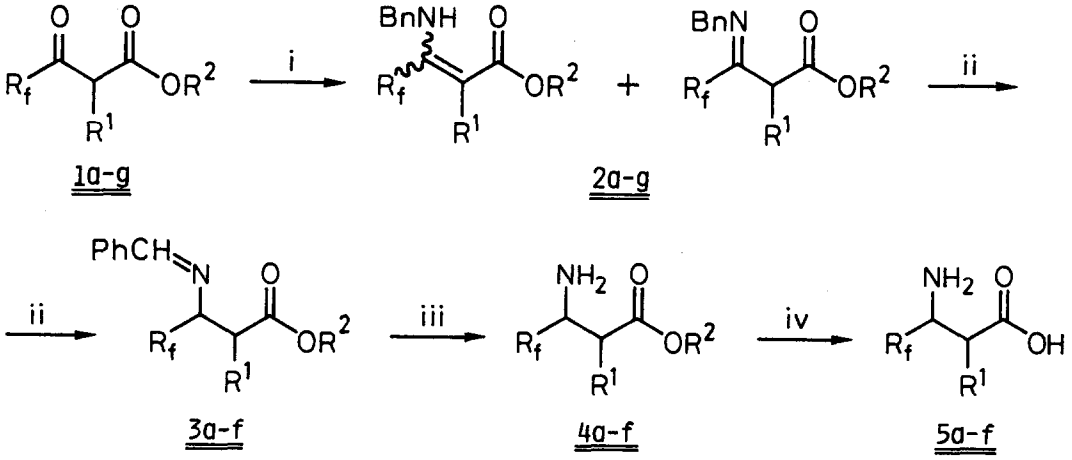
CNR-Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica, Politecnico, via Mancinelli 7, 20131 Milano, Italy.

ABSTRACT: The base-catalyzed isomerization of N-benzylimines (or enamines) of β-polyfluoroalkyl-β-ketocarboxylic esters cleanly affords the N-benzylidene derivatives of β-polyfluoro-β-aminocarboxylic esters which are hydrolyzed to corresponding amino acids in high overall yields.

Fluorine containing amino acids have found a wide range of applications in enzymology and pharmaceutical, medicinal, agricultural chemistry as a consequence of their usefulness in studying biochemical processes and modifying biological activity.[1] Whereas the literature is rich in methodologies for the preparation of fluorinated α-amino acids, examples of synthetic procedures for β-amino acids are notably rare.[2] In living organisms α-keto acids are routinely transformed into α-amino acids.[3] The key-step of the process is a 1,3-proton shift which allows the interconversion of two isomeric imines. Chemical syntheses which mimic these biochemical transformations usually require severe reaction conditions[4] and this problem has to be overcome in order to have preparatively useful processes. No satisfactory results are reported in the literature for the synthesis of β-amino acids from corresponding β-ketoacids.

Our interest in studying the chemistry of fluorinated β-amino acids[5] and in proving the usefulness of fluorinated β-ketoesters as versatile synthons[6] prompted us to develop the efficient synthesis of β-fluoroalkyl-β-amino acids here described.

SCHEME: i, benzylamine, benzene, Dowex-50 (H^+-form), reflux; ii, base, see Table; iii, 2N HCl, Et_2O, 25-30 °C, 2h: iv, 6N HCl, 100 °C, 6h.



	a	b	c	d	e	f	g
R_f	C_3F_7	C_2F_5	CF_3	CF_3	CF_3	CHF_2	CH_3
R^1	H	H	H	CH_3	C_2H_5	H	H
R^2	C_2H_5	C_2H_5	CH_3	CH_3	CH_3	C_2H_5	C_2H_5

Specifically, we have found that β-perfluoroalkyl-β-ketoesters **1a-g** gave corresponding enamines **2a-g** in 50-87% yields by treatment with benzylamine under acid catalysis.[7,8] Unexpectedly we have found that in the presence of triethylamine perfluoropropyl- and perfluoroethyl-enamines **2a,b** easily underwent two 1,3-proton shifts at room temperature and gave corresponding Schiff bases of β-amino acids **3a,b** (Table, entries 1-4). About 98% convertion of **2a,b** was achieved in 35h and 42h, respectively, at 22 °C. The heating of the reaction mixture greatly accelerated isomerization. The trifluoromethyl containing enamine **1c** required elevated temperature for complete conversion to occur within a convenient time span.[9] Similary α-alkyl substituted compounds **2d,e** were isomerized into the Schiff bases **3d,e** (Table, entries 5-7). The reaction proceeded with low diastereoselectivity affording an approximate 2:1 mixture of diastereoisomers at the adjacent carbon stereocentres.

1,8-Diazabicyclo[5.4.O]undec-7-ene (DBU) and 1,3-diazabicyclo[2.2.2] octane (Dabco) were more effective in catalyzing the isomerization. However, higher yields and cleaner reaction mixtures generally resulted from the use of triethylamine.

Table

Entry	R_f	R^1	R^2	1,3-Proton shift[a]			Yields (%)[b]	
				Base[c]	temp./(°C)	time/(h)	3a-f	5a-f
1	C_3F_7	H	C_2H_5	Et_3N	r.t.	35	72	83
2	C_3F_7	H	C_2H_5	Et_3N[d]	70	6	70	-
3	C_2F_5	H	C_2H_5	Et_3N	r.t.	42	87	70
4	C_2F_5	H	C_2H_5	Et_3N[d]	70	8	74	-
5	CF_3	H	CH_3	Et_3N	90	12	76	84
6	CF_3	CH_3	CH_3	Et_3N	r.t.	40	94	75
7	CF_3	C_2H_5	CH_3	Et_3N	r.t.	38	86	78
8	CHF_2	H	C_2H_5	Et_3N	90	24	no reac.	-
9	CHF_2	H	C_2H_5	DBU[e]	110	21	61	67
10	CH_3	H	C_2H_5	DBU[f]	150	24	no reac.	-

[a]Conversion of starting material >95%. [b]Yields are based on isolated, analytically pure products. [c]Except where noted, reactions were done in Et_3N solution. [d]1:1 mixture of Et_3N/hexane. [e]Enamine/DBU ratio 1:0,1. [f]Enamine/DBU ratio 1:1.

The reaction was more difficult with enamine **2f** bearing less electron withdrawing difluoromethyl group. Thus, triethylamine was ineffective to catalyze isomerisation of **2f** to **3f**. Howewer, a complete conversion was observed when DBU was used (Table, entries 8, 9).

In contrast to fluorine-containing enamines **2a-f**, hydrocarbon enamine **2g** could not be transformed into corresponding Schiff base, even in the presence of more than 1 equivalent of DBU at 150 °C (Table, entry 10).

It is possible to conclude that there is a qualitative correlation between the behaviour of the enamines **2a-g** and the electron-withdrawing effets (σ_m) of substituent in the β-position,[10] the order of reactivity in fact parallels σ_m values: **2a>2b**(σ_m=0,47)> **2c,d,e**(0.44)>>**2f**(0,29).

β-Fluoroalkyl-β-aminoacids **5a-f** can be produced by one step hydrolysis of Schiff bases **3a-f** in 6N HCl. Howewer, yields were higher when 2N HCl was used for splitting off the benzylidene groups followed by ester hydrolyses with 6N HCl. Purification of the intermediated amino esters **4a-f** was not necessary. The free amino acids **5a-f** were purified by chromatography on ion-exchange column (Dowex-50).

In conclusion, we have reported a versatile and efficient method for the preparation of β-fluoroalkyl-β-amino acids via transamination of fluorinated β-ketocarboxylic esters with

benzylamine. In view of the ready availability of starting compounds and the simplicity of the synthetic procedure, this protocol represents a useful,new entry to fluorine-containing β-amino acids.

The overall transformation here described is a reductive amination. It is performed resorting to prototropic shifts while the unique reported procedure for the reductive amination of trifluoromethyl ketones employs hydride reagents.[11] The two procedure can therefore be considered complementary.

Acknowledgments. We are obliged to Prof. Pierfrancesco Bravo (Dipartimento di Chimica, Politecnico di Milano, Italy) for providing us with a starting fluorinated material.

References and notes

1. Welch, J. T.; Eswarakrischnan, S., *Fluorine in Bioorganic Chemistry*, J. Wiley and Sons, New York, 1991. Bravo, P.; Resnati, G., *Tetrahedron Asymm.*, **1990**, *1*, 661. Welch, J. T., *Tetrahedron*, **1987**, *43*, 3123. Sieler, M.; Jung, M. J.; Koch-Waser, *Enzyme-Activated Irreversible Inhibitors*, Elsevier, Amsterdam, 1988, p. 396.
2. Kukhar', V. P.; Yagupolskii, Yu. L.; Soloshonok, V., A., *Russ. Chem. Rev.*, **1990**, *59*, 89. Kukhar', V. P.; Soloshonok, V. A., ibid., 1991, 60, 850.
3. Dunathan, H. C.; Davis, L.; Kury, P. G.; Kaplan, M., *Biochemistry*, **1968**, *7*, 4532. Kochetkov, K. A.; Belikov, V. M., *Russ. Chem. Rev.*, **1987**, *56*, 1832. Staunton, J., *Primary metabolism, a mechanistic approach*, Clarendon Press, Oxford, 1978.
4. Guthrie, R. D.; Jaeger, D. A.; Meister, W.; Cram, D. J., *J. Am. Chem. Soc.*, **1971**, *93*, 5137. Jaeger, D. A.; Cram, D. J., *ibid.*, **1971**, *93*, 5153.
5. Soloshonok, K.; Svedas, V. K.; Kukhar', V. P.; Kirilenko, A. G.; Rybakova, A. V.; Solodenko, V. A.; Galaev, I. Yu.; Kozlova, E. V.; Shishkina, I. P.; Galushko, S. V., *SYNLETT*, **1993**, in press.
6. Bravo, P.; Diliddo, D.; Resnati, G., *Heterocycles*, **1992**, *34*, 1703.
7. α-Unsubstituted-β-ketocarboxylic esters **1a-c,f,g** afforded exclusively (Z)-enamines **2a-c,f,g** probably as a consequence of a stabilizing intramolecular hydrogen bond. α-Substituted-β-ketocarboxylic esters **1d,e** gave a mixture of imine, (Z)- and (E)-enamines in approximate 3.5:1.2:1.0 ratio. Ahlbrecht, H.; Henk, H., *Chem. Ber.*, **1976**, *109*, 1516. Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K., *J. Am. Chem. Soc.*, **1984**, *106*, 2718.
8. All isolated compounds showed expected ^{1}H, ^{19}F NMRs, IR, mass spectra. Correct microanalyses (C, H) were obtained for new compounds.
9. A typical procedure is as follows. A solution of (Z)-enamine **2c** (91g, 0.35 mol) in triethylamine (150 mL) was refluxed for 12h. Triethylamine was evaporated in vacuum (40-50 °C, 10-15 mmHg) and distillation of the residue (136-139 °C, 10 mmHg) yielded 70g (76%) of the Shiff base **3c**. δ_H ($DMSO_{d\text{-}6}$): 2.78, 2.92 (ABX system, 2H, J=16.5, 9.6, 3.3 Hz, CH_2), 3.52 (m, 3H, CH_3), 4.29 (ddq, 1H, J=9.6, 3.3, 7.5 Hz, CH), 7.35-7.45 (m, 5H, CH_{ar}), 8.47 (s, 1H, CH=N). The described synthetic sequence allowed the preparation of more than 50g of β-trifluoromethyl-β-alanine **5c** in one experiment, thus proving the efficiency and reliability of the methodology.
10. Yagupolskii, L. M.; Il'chenko, A, Y.; Kondratenko, N. V., *Russ. Chem. Rev.*, **1974**, *43*, 64.
11. Barney, C. L.; Huber, E. W.; McCarthy, J. R., *Tetrahedron Lett.*, **1990**, *31*, 5547.

(Received in UK 10 February 1993)