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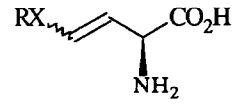
A NEW CLASS OF UNUSUAL α-AMINOACIDS : α-AMINOACID β,γ-ENOL THIOETHERS

P. Meffre*, H. Lhermitte, L. Vo-Quang, Y. Vo-Quang, F. Le Goffic
Laboratoire de Bioorganique et Biotechnologies, associé au CNRS
Ecole Nationale Supérieure de Chimie de Paris
11 rue Pierre et Marie Curie, 75231 Paris CEDEX 05, France

Summary : Two representative α-aminoacid β,γ-enol thioethers have been synthesized starting from the corresponding easily available saturated α-aminoacids by a Pummerer-like reaction.

In the course of our investigations in the field of potential enzyme inhibitors, we decided to synthesize α-aminoacids bearing unusual side chain functions from easily available starting material[1].

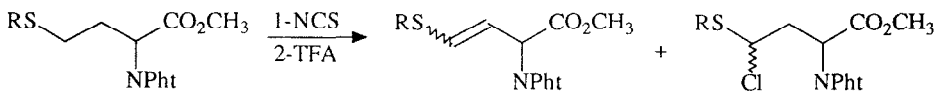
α-Aminoacid β,γ-enol thioethers **1** are a new class of exotic α-aminoacids to study since only one example : 2S-2-amino-4-methylthio-but-3E-enoic acid ("3,4-dehydro-L-methionine" **1**, R=CH_3, E) is described in the literature[2]. Furthermore, none of its biological properties have been reported to date despite its potential antimetabolic activities. The oxygen-analogues, the α-aminoacid β,γ-enol ethers **2** are a well-known class of naturally occuring unusual α-aminoacids of biological interest[3] : 2S-2-amino-4-methoxy-but-3E-enoic acid (L-trans-AMB) **2** (R=CH_3, E), Rhizobitoxine **2** (R=(R)-$CH_2CH(CH_2OH)NH_2$, E), 2S-2-amino-4-(2-aminoethoxy)-but-3E-enoic acid (AVG) **2** (R=$CH_2CH_2NH_2$, E) are potent inhibitors of enzymes involved in methionine metabolism. Moreover, synthetic 2S-2-amino-4-methoxy-but-3Z-enoic acid (L-cis-AMB) **2** (R=CH_3, Z) is a potent methionine analogue inhibitor of S-adenosylmethionine synthetase [4]. The thioethers **1** might have similar biological properties and could among others act as plant growth regulators by inhibition of ethylene biosynthesis in plants[3c]. As methionine analogues, they are also potential anticancer agents[4].



1 : X=S
2 : X=O

"3,4-Dehydro-L-methionine" **1** (R=CH_3, E) and L-trans-AMB **2** (R=CH_3, E) have been synthesized in a similar way starting from diethyl acetamidomalonate[2,5]. Racemic fully protected "dehydromethionine" was thus obtained by a six step procedure in 10% overall yield, alkaline hydrolysis and enzymatic resolution leading to optically active aminoacid.

The present paper deals with a general and straightforward synthesis of β,γ-dehydrohomocysteine derivatives **1** starting from the corresponding saturated derivatives **3** based on a Pummerer-like reaction using N-chlorosuccinimide (NCS)[6] to afford the transient chlorinated derivatives **4**, followed by an acid catalyzed dehydrochlorination[7] (scheme 1).

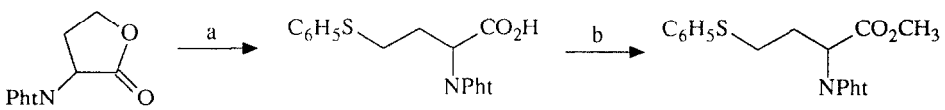


R=CH_3, 2S : **3a** **1a,b** **4a,b**

R=C_6H_5 , 2RS : **3b**

scheme 1 (NPht=NPhthaloyl)

The phthaloyl moiety was chosen as amino protecting group to avoid any internal amine participation[8]. N-Phthaloyl-L-methionine methyl ester **3a** was readily obtained by classical amino protection[9] of L-methionine methyl ester hydrochloride using phthalic anhydride / triethylamine in toluene. N-Phthaloyl-S-phenyl-DL-homocysteine methyl ester **3b** was synthesized as outlined in scheme 2[10] : after usual protection, lactone **5** was opened using sodium thiophenolate in refluxed THF / HMPA to obtain N-Phthaloyl-S-phenyl-DL-homocysteine **6**. Esterification using anhydrous sulfuric methanol yielded **3b**.



5 **6** **3b**

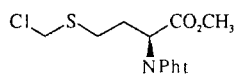
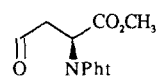
scheme 2

a-C_6H_5SH : 2 eq., NaH : 2.2 eq., HMPA : 2.4 eq., THF, reflux, 24h, yield : 70% b-H_2SO_4, CH_3OH, rt, 18h, yield : 80%

α-Chlorination was chosen because of its regioselectivity towards branched carbon compared with methyl group[11a,b]. Thus the fully protected homocysteine derivatives **3a,b** were subjected to Pummerer-like reaction using NCS in carbon tetrachloride or diethyl ether / benzene[11c] (table 1).

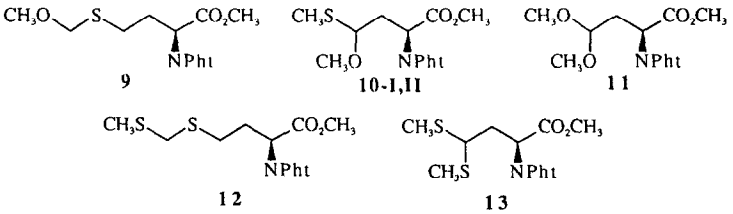
sulfide	reaction conditions 1	reaction conditions 2	% crude reaction products [a] 1 E	1 Z	4	7 [c]	8 [c]	entry
3a	NCS : 1.04 eq.,CCl_4 0°C-reflux , 4 days	–	30	9	39	16	8	1
	NCS : 1.04eq. , Et_2O/C_6H_6: 1/2 rt , 24h	–	14	2	66	15	2	2
		cat. TFA, CCl_4 reflux , 2h	36	9	32	17	7	3
3b	NCS : 1.04 eq. CCl_4 rt , 16h	–	0	0	100[b]	–	0	4
		cat. TFA, CCl_4 rt : 17h	20	5	60	–	15	5
		-20°C, 1 month	37	5	53	–	5	6

table 1

a-estimated by NMR ^1H in $CDCl_3$[13]; b-pure **4b** is obtained; c- **7** :  **8** : 

Initial attempts to perform dehydrochlorination in basic conditions (Et_3N, DBU) failed, but spontaneous[7b] (entry 6) or thermal acid catalyzed elimination occured (entries 1,3,5). All attempts to isolate these products by silica gel chromatography led to decomposition[6b]. Therefore purification by HPLC using methanol was performed[12] and **1a-Z**, **1a-E**, **1b-Z** were isolated and characterized[13].

In a typical experiment (entry 3), a mixture of **3a** (2.93 g, 10 mmoles) and N-chlorosuccinimide (1.39 g, 10.4 mmoles) in 50 ml of benzene and 25 ml of diethyl ether was stirred at room temperature for 24 h. After filtration and solvent evaporation, the residue was triturated with CCl_4 and filtered again. The solvent was removed to give 3.3 g of crude product. To 1.04 g of this material in 15 ml of dry CCl_4 were added 3 drops of TFA and the mixture was refluxed for 2 h and evaporated to give 0.97 g of an oily residue. HPLC was performed[12] to give pure methyl 2S-2-(2-phthalimido)-4-methylthio-but-3Z-enoate **1a-Z** (32 mg, 4% from **3a**) and a mixture (66 mg) with 60% of methyl 2S-2-(2-phthalimido)-4-methylthio-but-3E-enoate **1a-E** and 40% of one diastereomer of methyl 2S-2-(2-phthalimido)-4-methylthio-4-methoxy-butanoate **10-I**. Also recovered : **9** (41 mg, 4%), pure **10-I** (66 mg, 7%), **10-II** (169 mg, 17%), **11** (94 mg, 10%), **12** (30 mg, 3%), **13** (42 mg, 4%). Those compounds may result from methanolyses of α-chlorosulfides **4a** or enol thioethers **1a**[11b] during HPLC purification and subsequent trans thioacetalizations.



This Pummerer-like reaction on suitable homocysteine derivatives is therefore a general and straightforward way to synthesize the corresponding optically active β,γ-unsaturated derivatives. Improvements and biological evaluations are under investigations.

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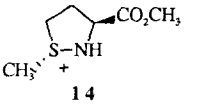
8- S-methylisothiazolidine-3-carboxylate **14** (another "dehydro-methionine"), has been also synthesized by oxidizing methionine (I_2/ CH_3ONa / CH_3OH, N-Chlorosuccinimide / CH_3OH, ...) due to internal amine participation : (a) D. C. Billington, B. T. Golding, *J.Chem. Soc., Perkin Trans. 1*, 1982, 1283-1290 and reference 3 therein.



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12-HPLC conditions : Delta pak column Waters C18, 100 Å, 15 µ, flow rate : 10 ml/mn, eluent : CH_3OH/H_2O : 60/40 (**1a**) ; 70/30 (**1b**). In the case of **1b**, HPLC analysis is less efficient than for **1a**. The stereochemistry of the stereoisomers **10-I, 10-II** has not been determined.
13-α-Aminoacid β,γ-enol thioethers :
NMR ($CDCl_3$, δ ppm vs TMS). **1a-E** : ^1H, 200MHz, 2.26 (s, 3H, CH_3S) ; 3.75 (s, 3H, CO_2CH_3) ; 5.43 (d, 1H, 8.6Hz, CHN) ; 5.85 (dd, 1H, 15Hz, 8.6Hz, SCH=C**H**) ; 6.47 (dd, 1H, 15Hz, 0.8Hz, SC**H**=CH) ; 7.65-7.9 (m, 4H, NPht). ^{13}C, 50.3MHz, 14.2 (CH_3S) ; 53, 53.7 (CHN, $CO_2\underline{C}H_3$) ; 115.6 (SCH=**C**H) ; 132.9 (S**C**H=CH) ; 123.5, 131.7, 134.2 (C arom.) ; 166.8, 168.6 (CO). **1a-Z** : ^1H, 200MHz, 2.29 (s, 3H, CH_3S) ; 3.77 (s, 3H, CO_2CH_3) ; 5.77 (dd, 1H, 7.8Hz, 0.9Hz, CHN) ; 6.17 (dd, 1H, 7.8Hz, 9.4Hz, SCH=C**H**) ; 6.35 (dd, 1H, 9.4Hz, 0.9Hz, SC**H**=CH) ; 7.65-7.90 (m, 4H, NPht). ^{13}C, 50.3 MHz, 17.2 (CH_3S) ; 49.7, 53 (CHN, CO_2CH_3) ; 119.4 (SCH=**C**H); 123.5, 131.7, 134.1 (Carom.) ; 134.2 (S**C**H=CH) ; 166.8, 168.6 (CO). **1b-E** : ^1H, 250MHz, 5.48 (dd, 1H, 8Hz, 0.8Hz,CHN) ; 6.28 (dd, 1H, 15Hz, 8Hz, SCH=C**H**) ; 6.55 (dd, 1H, 15Hz, 0.8Hz, SC**H**=CH). **1b-Z** : ^1H, 200MHz, 5.94 (d, 1H, 8Hz, CHN) ; 6.39 (dd, 1H, 8Hz, 9.3Hz, SCH=C**H**) ; 6.62 (dd, 1H, 9.3Hz, 0.8Hz, SC**H**=CH).
MS : (CI in NH_3): **1a-Z** 309 $(M+NH_4)^+$, 292 $(M+H)^+$; **1a-E** +**8-I** 341, 324, 309, 292, 276.
Optical rotation : **1a-Z** $[\alpha]D^{25}$=-32 (c=3.6, $CHCl_3$).

For the following compounds, only characteristic analytic data are indicated :
3a : m.p. 40-41°C (diethyl ether/petroleum ether) ; $[\alpha]D^{25}$=-42 (c=1.49, $CHCl_3$). **4a** : ^1H NMR, 200MHz, δ 5.15, 4.95 (2m, SCHCl, CHN). **4b** : ^1H NMR, 250MHz, δ 5.2 (dd, 1H, 5.5Hz, 8.9Hz, CHN) ; 5.25-5.4 (m, 1H, SCHCl). **5** : m.p. 178-179°C (chloroform/petroleum ether). **6** : m.p. 153-154°C (methylene chloride/petroleum ether). **7** : ^1H NMR, 200MHz, δ 4.65 (s, $ClCH_2S$). **8** : ^1H NMR, 200MHz, δ 9.75 (t, 1H, 0.8Hz) ; $[\alpha]D^{25}$=-9 (c=2.76, CCl_4). **9** : ^1H NMR, 200MHz, δ 4.60 (s, 2H, SCH_2O); $[\alpha]D^{25}$=-31 (c=4.9, $CHCl_3$). **10-I** : ^1H NMR, 200MHz, δ 4.41 (m, 1H, OCHS) ; 5.14 (m, 1H, CHN) ; $[\alpha]D^{25}$=+59 (c=6.3, $CHCl_3$). **10-II** : ^1H NMR, 250MHz, δ 4.14 (dd, 1H, 3.6Hz, 9.9Hz, OCHS) ; 5.13 (dd, 1H, 3.9Hz, 10.4Hz, CHN) ; $[\alpha]D^{25}$=-70 (c=17.9, $CHCl_3$). **11** : ^1H NMR, 200MHz, δ 4.40 (t, 1H, 5.7Hz, OCHO) ; 5.00 (dd, 1H, 4.9Hz, 9.7Hz, CHN) ; $[\alpha]D^{25}$=-20 (c=9.1, $CHCl_3$). **12** : ^1H NMR, 200MHz, δ 3.64 (s, 2H, SCH_2S) ; $[\alpha]D^{25}$=-23 (c=3.2, $CHCl_3$). **13** : ^1H NMR, 200MHz, δ 3.68 (dd, 1H, 6.4Hz, 8.5Hz, SCHS) ; 5.37 (dd, 1H, 5.5Hz, 8.9Hz, CHN) ; $[\alpha]D^{25}$=-29 (c=4.5, $CHCl_3$).

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