3-Aminoacetylthiazolidine-4-carboxylate Esters and their 1-Thia-4-azaspiro[4.5]decane-3-carboxylate Derivatives. Synthesis and Stereochemical Properties

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Dimethyl thiazolidine-2,4-dicarboxylate **2** and ethyl 1-thia-4-azaspiro[4.5]decane-3-carboxylates **3-5** were obtained as a diastereoisomeric mixture while their 3-aminoacetyl derivatives were isolated in only one isomeric form. These reactions of *N*-acylation were stereoselective, which can be explained by an interconversion of the diastereoisomers *via* a seco intermediate. The ^{1}H nmr analysis of amides **6** and **11** exhibited the presence of both *cis* and *trans* amide bond conformations, whereas only one *cis* conformation was observed for spiro amides **8-10** and **13-15**.

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Recently [1], the synthesis and behaviour in solution of thiazolidine-2,4-dicarboxylic acid and its esters have been described. The present study reports the synthesis and the stereochemical properties of 3-aminoacetylthiazolidine-4-carboxylate esters and their 1-thia-4-azaspiro[4.5]decane-3-carboxylate. Although *N*-acetylthiazolidine-4-carboxylic acid and its 2-substituted derivatives have been known for some time [2,3] their formation was usually performed by *N*-acetylation using acetic anhydride or acetyl chloride [4]. It is only recently [5,6,7] that the mechanism of stereochemical properties have been reported. It has been demonstrated that *N*-acetylation of 2-substituted thiazolidine-4-carboxylic acids involves the inversion of C2 with a high degree of stereoselecitivity [2,8]. The presence of a *cis/trans* isomerism around the amide bond involving nitrogen of proline or thiazolidine has been suggested by Thomas and Deber [9,10].

This paper discusses the mechanism involved in the formation of two diastereoisomers of spiroderivatives and a detailed stereochemical and conformational analysis of the amides prepared is described. *Cis/trans* isomerism around the amide bond was investigated using 200 MHz nmr for the above compounds and the stereochemistry of isomeric forms.

Chemistry.

Thiazolidine-4-carboxylic acids and their esters have been reported for several decades [11,12], methyl thiazolidine-4-carboxylate **1** and dimethyl thiazolidine-2,4-dicarboxylate **2** were obtained by esterification of the corresponding acids with thionyl chloride in methanol. The starting ethyl 1-thia-4-azaspiro[4.5]decane-3-carboxylates were **3-5** prepared by condensation of cyclanones with the ethyl ester of (-)-*L*-(*R*)-cysteine by the procedure in the literature [13,14].

Good yields of compounds **11-15** were obtained by *N*-acylation of esters **1-5** by chloroacetyl chloride followed by the reaction of cyclic secondary amines as shown in Figure 1.

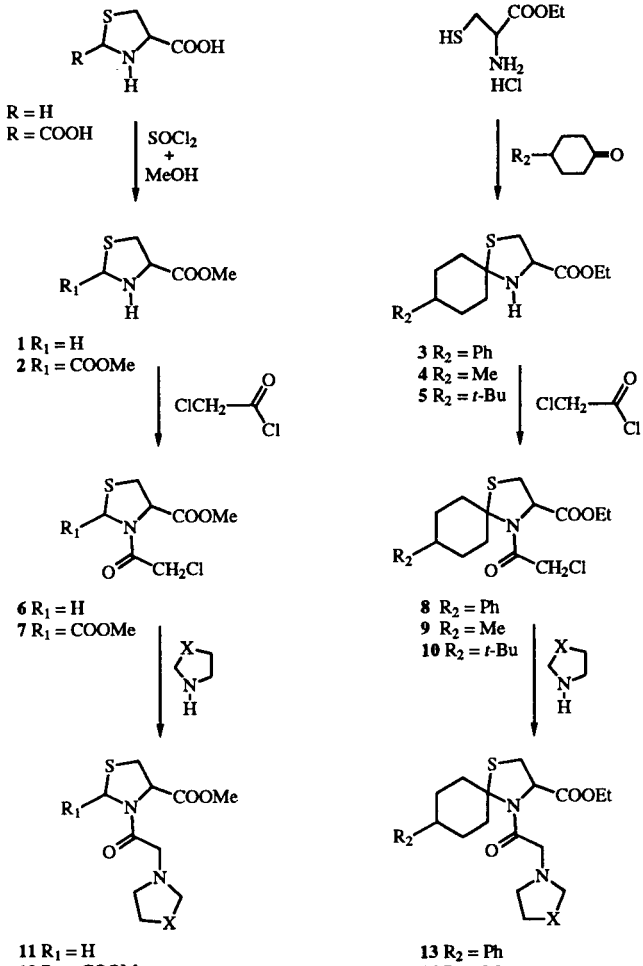


Figure 1.

Results and Discussion.

Methyl thiazolidine-4-carboxylate **1** was isolated in only one isomeric form (4*R*), while dimethyl thiazolidine-2,4-dicarboxylate **2** was obtained with a 9 to 1 predominance for the 2*S*,4*R* isomer as indicated by the ^{1}H nmr analysis [1].

Ethyl 1-thia-4-azaspiro[4.5]decane-3-carboxylates **3-5** were obtained in a mixture of two diastereoisomers, arising from a *cis/trans* ring forming isomerism.

The ^{1}H nmr spectra of these compounds were investigated at different temperatures and no changes were observed.

These diastereoisomeric mixtures **2-5** yielded pure products **7-10** by *N*-acetylation under specific conditions. The stereoselectivity of this acylation could be explained by interconversion of two diastereoisomers, through a ring opening mechanism involving Schiff base intermediates (Figure 2). A similar mechanism has been suggested [2,3] to account for mutarotation and selective acylation of C2 substituted thiazolidines.

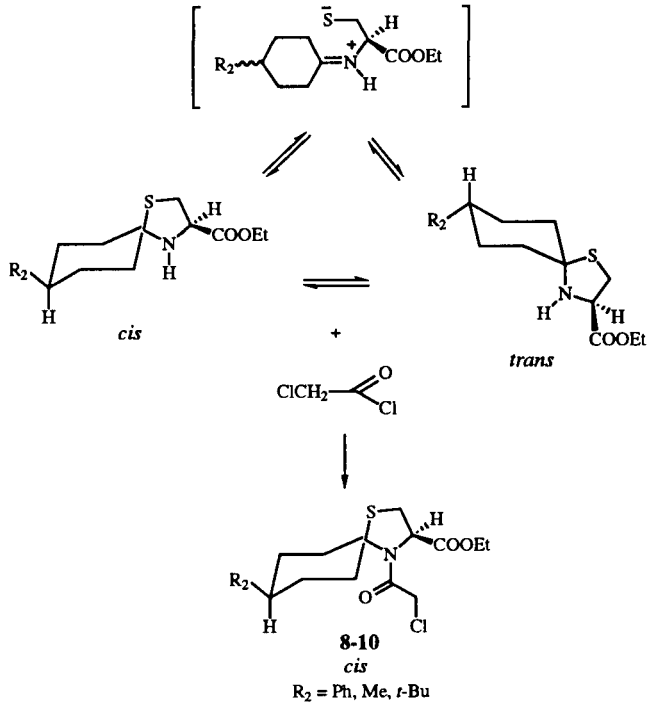


Figure 2.

The stereochemistry of the C2 of compounds **7** and **12** with respect to C4 can be resolved by high field ^{1}H nmr analysis. This analysis is based on the difference of assignments between H_5 and $H_{5'}$ protons for *cis* and *trans* diastereoisomers of dimethyl thiazolidine-2,4-dicarboxylate **2** ($\Delta\delta_{H5,H5'}$ *cis* isomer = 0.2 ppm and $\Delta\delta_{H5,H5'}$ *trans* isomer = 0.6 ppm) [1]. Thus, the difference of assignments between 0.15 ppm and 0.35 ppm observed for **7** and **12** should fit the structure of *cis* isomer *2R, 4R* for these compounds. A *cis* position for both methyl esters can be compatible with a conformational pseudoequatorial equatorial position when the thiazolidine ring takes the same half chair conformation as the tetrahydrothiophene [15,16] (Figure 3).

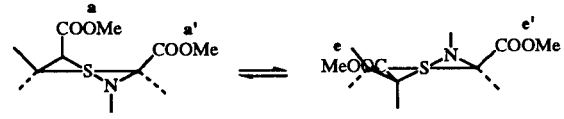


Figure 3.

The *N*-acylation of 1-thia-4-azaspiro[4.5]decane-3-carboxylate derivatives **3-5** gave a specific *cis* isomer from the *cis/trans* diastereoisomeric mixture (Figure 2). This result was determined by X-ray crystallography on compound **8** crystallized from ethanol. The crystals are quadratic, there are two independent molecules in the asymmetric unit of the crystal and eight molecules in the unit cell. The phenyl groups have different rotation angles about C8-C9 (Figure 4). A stereoview of the molecules is

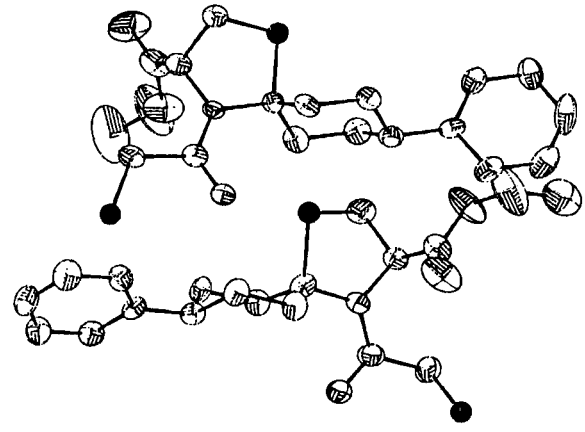


Figure 4. A stereo view of the molecule **8**.

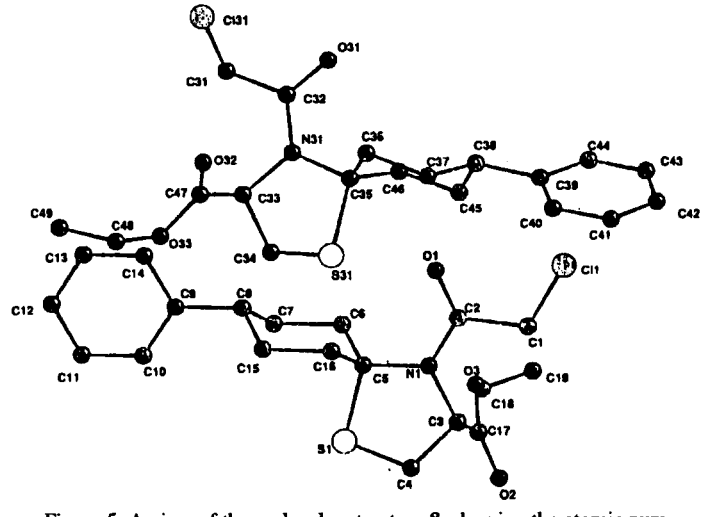
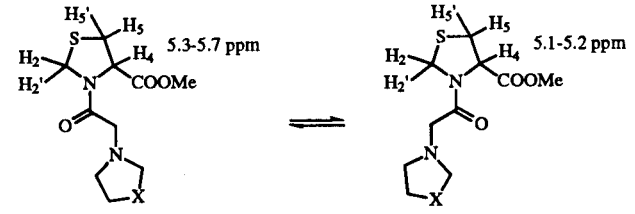
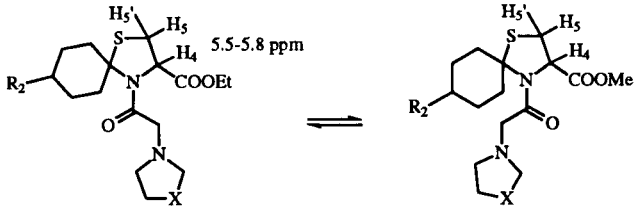


Figure 5. A view of the molecular structure **8**, showing the atomic numbering.

given in Figure 4. Numbering of the atoms is shown in Figure 5. Crystal data conditions of measurement and refinement are listed in Table 1. Table 2 contains positional parameters and equivalent isotropic temperature factors. Table 3 shows the geometric parameters: bond lengths and bond angles.



Compounds **11-12**



Compounds **13-15**

Figure 6.

Table 1

Crystal Data and Structure Refinement for **8**

Empirical formula	$C_{19}H_{23}N_1O_3ClS$
M_r	761.83
Temperature	292(2) K
Wavelengh	1.54180 Å
Crystal system	quadratic
Space group	$P4_1$
Unit cell dimensions	a = 10.126(4) Å alpha= 90 deg
	b = 10.126(4) Å beta= 90 deg
	c = 38.141(8) Å gamma = 90 deg
Volume	3910.825(10) $Å^3$
Z	8
Density (calculated)	1.294 g/cm^3
Absorption coefficient	2.87 mm^{-1}
F (000)	1608
Crystal size	0.65x0.25x0.18 mm
Theta range for data collection	2.0 to 119.98 deg
Index ranges	0<=h<=11, 0<=k<11, 0<=1<=35
Reflections collected	2801
Independent reflections	1890
Refinement method	Full-matrix least-squares on F
Data/ restraints/ parameter	1890/1/474
Goodness-of-fit on F	2.0(5)
R indice	4.74
Rw indice	4.72
Largest diff. peak and hole	0.311 and -0.207 $e.Å^{-3}$

The ^1H nmr analysis of amides **6** and **11** exhibited two sets of resonances for each of the H_2, $H_{2'}$ and H_4 protons and the ^1H nmr spectrum was changed when samples were heated. These results, which can not be explained by an optical isomerism, suggest the presence of both *cis* and *trans* amide bond conformations [17,18,19] (Figure 6). Similar results were found for diester derivatives **7** and **12**.

Table 2

Fractional Atomic Coordinates and Equivalent Isotropic Displacement Paramaters, with their E. S. D.'s in parentheses

	x/a	y/b	z/c	U(eq)
Cl(1)	0.8096(2)	0.0850(3)	0.44123(8)	0.0696
C(1)	0.6604(9)	0.166(1)	0.4493(3)	0.0635
C(2)	0.5448(8)	0.0671(9)	0.4562(2)	0.0512
N(1)	0.4269(6)	0.1252(6)	0.4592(2)	0.0410
C(3)	0.4052(9)	0.2681(9)	0.4557(2)	0.0565
C(4)	0.2674(9)	0.2814(9)	0.4408(3)	0.0560
S(1)	0.1708(2)	0.1693(3)	0.46628(8)	0.0620
C(5)	0.3056(8)	0.0454(8)	0.4665(2)	0.0434
C(6)	0.3065(9)	-0.026(1)	0.5011(2)	0.0486
C(7)	0.182(1)	-0.109(1)	0.5072(2)	0.0593
C(8)	0.1598(8)	-0.2080(9)	0.4777(2)	0.0541
C(9)	0.0375(9)	-0.2907(8)	0.4829(2)	0.0441
C(10)	-0.086(1)	-0.2367(9)	0.4836(2)	0.0594
C(11)	-0.198(1)	-0.314(1)	0.4878(3)	0.0671
C(12)	-0.186(1)	-0.449(1)	0.4901(3)	0.0724
C(13)	-0.062(1)	-0.504(1)	0.4902(3)	0.0737
C(14)	0.048(1)	-0.4264(9)	0.4865(3)	0.0643
C(15)	0.1576(8)	-0.1366(9)	0.4423(2)	0.0517
C(16)	0.2803(8)	-0.0507(9)	0.4365(2)	0.0507
C(17)	0.414(1)	0.348(1)	0.4898(3)	0.0738
O(2)	0.3904(9)	0.4626(8)	0.4905(2)	0.1059
O(3)	0.4609(9)	0.2768(8)	0.5161(2)	0.0842
C(18)	0.449(2)	0.329(2)	0.5535(5)	0.1415
C(19)	0.561(2)	0.366(2)	0.5610(5)	0.1398
O(1)	0.5662(6)	-0.0514(6)	0.4590(2)	0.0623
Cl(31)	.3984(4)	-0.6554(3)	0.6516(1)	0.1150
C(31)	0.361(1)	-0.500(1)	0.6708(3)	0.0783
C(32)	0.4456(9)	-0.394(1)	0.6531 (3)	0.0636
N(31)	0.3850(7)	-0.2897(7)	0.6385(2)	0.0504
C(33)	0.2411(8)	-0.2719(9)	0.6381(2)	0.0497
C(34)	0.216(1)	-0.128(1)	0.6343(3)	0.0652
S(31)	0.3343(3)	-0.0760(3)	0.60157(8)	0.0678
C(35)	0.4623(9)	-0.1843(9)	0.6204(2)	0.0499
C(36)	0.539(1)	-0.241(1)	0.5894(2)	0.0619
C(37)	0.6276(9)	-0.1358(9)	0.5718(2)	0.0518
C(38)	0.7190(9)	-0.0727(8)	0.59832(2)	0.0481
C(39)	0.8208(9)	0.0220(8)	0.5838(2)	0.0474
C(40)	0.8180(9)	0.064(1)	0.5491(2)	0.0593
C(41)	0.914(1)	0.147(1)	0.5360(2)	0.0675
C(42)	1.012(1)	0.192(1)	0.5570(3)	0.0656
C(43)	1.018(1)	0.152(1)	0.5913(3)	0.0722
C(44)	0.9224(9)	0.0696(9)	0.6039(2)	0.0576
C(45)	0.6372(9)	-0.0090(8)	0.6276(2)	0.0497
C(46)	0.5490(9)	-0.1096(9)	0.6454(2)	0.0533
C(47)	0.176(1)	-.356(1)	0.6088(3)	0.0653
O(32)	0.2324(8)	-0.4305(9)	0.5913(2)	0.0960
O(33)	0.0492(7)	-0.327(1)	0.6069(2)	0.0882
C(48)	-0.026(2)	-0.400(2)	0.5802(3)	0.1151
C(49)	-0.118(2)	-0.482(2)	0.5982(5)	0.1225
O(31)	0.5653(6)	-0.4076(7)	0.6537(2)	0.0731

Table 3

Bond Lengths (Å) and Angles (deg), with their E. S. D.'s in parentheses

Cl(1) - C(1)	1.75(9)	C(31) - C(32)	1.53(1)
C(1) - C(2)	1.56(1)	C(32) - N(31)	1.35(1)
C(2) - N(1)	1.34(1)	C(32) - O(31)	1.22(1)
C(2) - O(1)	1.22(1)	N(31) - C(33)	1.47(1)
N(1) - C(3)	1.50(1)	N(31) - C(35)	1.49(1)
C(3) - C(4)	1.51(1)	C(33) - C(34)	1.49(1)
C(3) - C(1)	1.53(1)	C(33) - C(47)	1.55(1)
C(4) - S(1)	1.79(1)	C(34) - S(31)	1.81(1)
S(1) - C(5)	1.85(8)	S(31) - C(35)	1.84(9)
C(5) - C(6)	1.50(1)	C(35) - C(36)	1.53(1)
C(5) - C(16)	1.52(1)	C(35) - C(46)	1.50(1)
C(6) - C(7)	1.53(1)	C(36) - C(37)	1.55(1)
C(7) - C(8)	1.53(1)	C(37) - C(38)	1.51(1)
C(8) - C(9)	1.51(1)	C(38) - C(39)	1.51(1)
C(8) - C(15)	1.53(1)	C(38) - C(45)	1.53(1)
C(9) - C(10)	1.36(1)	C(39) - C(40)	1.39(1)
C(9) - C(14)	1.38(1)	C(39) - C(44)	1.37(1)
C(10) - C(11)	1.39(1)	C(40) - C(41)	1.38(1)
C(11) - C(12)	1.38(2)	C(41) - C(42)	1.35(1)
C(12) - C(13)	1.36(2)	C(42) - C(43)	1.37(1)
C(13) - C(14)	1.37(1)	C(43) - C(44)	1.37(1)
C(15) - C(16)	1.53(1)	C(45) - C(46)	1.52(1)
C(17) - O(2)	1.19(1)	C(47) - O(32)	1.16(1)
C(17) - O(3)	1.32(1)	C(47) - O(33)	1.32(1)
O(3) - C(18)	1.53(2)	O(33) - C(48)	1.47(1)
C(18) - C(19)	1.22(2)	C(48) - C(49)	1.42(2)
Cl(31)- C(31)	1.78(1)		
Cl(1) - C(1) - C(2)	112.2(7)	Cl(31)- C(31) - C(32)	108.5(8)
C(1) - C(2) - N(1)	113.7(8)	C(31) - C(32) - N(31)	118.5(9)
C(1) - C(2) - O(1)	120.7(8)	C(31) - C(32) - O(31)	118.2(9)
N(1) - C(2) - O(1)	125.6(8)	N(31) - C(32) - O(31)	123.2(9)
C(2) - N(1) - C(3)	124.0(7)	C(32) - N(31) - C(33)	123.6(8)
C(2) - N(1) - C(5)	120.8(7)	C(32) - N(31) - C(35)	121.0(7)
C(3) - N(1) - C(5)	115.2(6)	C(33) - N(31) - C(35)	115.4(7)
N(1) - C(3) - C(4)	105.0(7)	N(31) - C(33) - C(34)	106.9(7)
N(1) - C(3) - C(17)	115.7(8)	N(31) - C(33) - C(47)	111.0(7)
C(4) - C(3) - C(17)	109.1(8)	C(34) - C(33) - C(47)	113.1(8)
C(3) - C(4) - S(1)	104.1(6)	C(33) - C(34) - S(31)	103.8(6)
C(4) - S(1) - C(5)	91.7(4)	C(34) - S(31) - C(35)	91.4(4)
N(1) - C(5) - S(1)	103.8(5)	N(31) - C(35) - S(31)	103.7(6)
N(1) - C(5) - C(6)	114.7(7)	N(31) - C(35) - C(36)	110.8(7)
S(1) - C(5) - C(6)	109.4(6)	S(31) - C(35) - C(36)	106.5(6)
N(1) - C(5) - C(16)	110.0(7)	N(31) - C(35) - C(46)	111.8(7)
S(1) - C(5) - C(16)	107.8(6)	S(31) - C(35) - C(46)	111.0(6)
C(6) - C(5) - C(16)	110.8(7)	C(36) - C(35) - C(46)	112.6(8)
C(5) - C(6) - C(7)	113.0(7)	C(35) - C(36) - C(37)	111.7(8)
C(6) - C(7) - C(8)	111.9(8)	C(36) - C(37) - C(38)	110.7(7)
C(7) - C(8) - C(9)	113.2(8)	C(37) - C(38) - C(39)	116.1(8)
C(7) - C(8) - C(15)	109.9(7)	C(37) - C(38) - C(45)	109.5(7)
C(9) - C(8) - C(15)	111.4(7)	C(39) - C(38) - C(45)	111.6(7)
C(8) - C(9) - C(10)	122.1(8)	C(38) - C(39) - C(40)	121.9(8)
C(8) - C(9) - C(14)	120.1(8)	C(38) - C(39) - C(44)	122.0(8)
C(10) - C(9) - C(14)	117.8(9)	C(40) - C(39) - C(44)	116.0(8)
C(9) - C(10) - C(11)	121.5(9)	C(39) - C(40) - C(41)	121.1(9)
C(10) - C(11) - C(12)	119.8(10)	C(40) - C(41) - C(42)	120.6(9)
C(11) - C(12) - C(13)	118.9(10)	C(41) - C(42) - C(43)	119.8(9)
C(12) - C(13) - C(14)	121.0(10)	C(42) - C(43) - C(44)	119.0(10)
C(9) - C(14) - C(13)	120.9(10)	C(39) - C(44) - C(43)	123.5(9)
C(8) - C(15) - C(16)	112.5(7)	C(38) - C(45) - C(46)	111.3(7)
C(5) - C(16) - C(15)	113.0(7)	C(35) - C(46) - C(45)	113.4(8)
C(3) - C(17) - O(2)	121.6(11)	C(33) - C(47) - O(32)	124.5(10)
C(3) - C(17) - O(3)	112.4(9)	C(33) - C(47) - O(33)	109.3(8)
O(2) - C(17) - O(3)	125.8(11)	O(32) - C(47) - O(33)	126.2(10)
C(17) - O(3) - C(18)	119.7(11)	C(47) - O(33) - C(48)	115.6(10)
O(3) - C(18) - C(19)	104.7(15)	O(33) - C(48) - C(49)	107.3(11)

For amides **8-10** and **13-15**, spectral data leads to the conclusion that the amide bond was present in only one conformation, the latter having a *Z* conformation which presents minimal steric interaction (Figure 6).

The major conformer of compounds **11-12** exhibited a multiplet at 5.1-5.2 ppm for the C4 methine proton while the minor conformer of compounds **11-12** exhibited a multiplet at 5.3-5.7 ppm (Table 4b). Comparing the assignments of the C4 methine proton of the only **13-15** spiro conformer (*Z*), it may have inferred that the major conformer was an *E* conformation and the minor conformer was a *Z* conformation for compounds **11-12** (Figure 6).

EXPERIMENTAL

Melting points were determined on a Buchi No. 510 apparatus and were uncorrected. Infrared spectra were taken in potassium bromide pellets on a Bruker IFS 45 spectrometer. The ^{1}H nmr spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz using tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million and signals are quoted as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Elemental analyses were carried out at the Service Central d'Analyses, Centre National de la Recherche Scientifique, 69390 Vernaison, France. The crystal structure was determined by X-ray diffraction. Data were collected on a Philips PW1100 diffractometer with CuK_α radiation. Crystal data conditions of measurement and of refinement are listed in Table 1. The structure was solved using Sir 92 [20] and refined using CRYSTALS [21]. The data were corrected for absorption using Difabs.

Methyl Thiazolidine-4-carboxylate (1).

To a stirred and ice cooled solution of thiazolidine-4-carboxylic acid (3.99 g, 0.03 mole) in 200 ml of methanol thionyl chloride (9 g, 0.06 mole) was added dropwise. The reaction mixture was stirred for 12 hours at room temperature and heated at reflux for 1 hour. The crystals obtained were collected by filtration, washed with ethyl ether and recrytallized from methanol. This product was dissolved in 50 ml of water, the aqueous solution was made basic by the addition of sodium carbonate, and extracted with ethyl ether. The organic layers were dried over sodium sulfate, filtered and evaporated, colorless oil, yield 87%; ir (potassium bromide): ν 3300 (NH), 3000 (CH), 1740 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.6 (s, 1H), δ 2.9 (dd, 1H), δ 3.25 (dd, 1H), δ 3.8 (s, 3H), δ 3.9 (t, 1H), δ 4.1 (d, 2H).

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.82; H, 6.12; N, 9.52; S, 21.77. Found: C, 40.53; H, 6.27; N, 9.62; S, 22.08.

Dimethyl Thiazolidine-2,4-dicarboxylate (2).

This product was prepared in the same manner as described for 1 using thiazolidine-2,4-dicarboxylic acid [12], colorless powder, yield 89%, mp 70°; ir (potassium bromide): ν 3290 (NH), 2990 (CH), 1740 (CO) cm^{-1}. ^{1}H nmr (deuteriochloroform): major diastereoisomer (90%): δ 2.8 (dd, 1H), δ 3.1 (s, 1H), δ 3.3 (dd, 1H), δ 3.85 (s, 6H), δ 3.95 (m, 1H), δ 5.0 (s, 1H); minor diastereoisomer (10%): δ 3.0 (dd, 1H), δ 3.1 (s, 1H), δ 3.2 (dd, 1H), δ 3.85 (s, 6H), δ 4.0 (m, 1H), δ 5.0 (s, 1H).

Table 4a

Physical Constants for 3-(Aminoacetyl)thiazolidine-4-carboxylate Esters

Compounds	R_1	X	yield %	mp°C	Formula (MW)	Anal. Calcd./Found C %	H %	N %	S %
11a	H	CH_2	71	[a]	$C_{11}H_{18}N_2O_3S$	51.16/51.03	6.98/6.77	10.85/11.05	12.40/12.28
11b	H	CH_2CH_2	76	[a]	$C_{12}H_{20}N_2O_3S$	52.94/53.02	7.35/7.26	10.29/10.13	11.76/11.58
11c	H	CH_2O	75	[a]	$C_{11}H_{18}N_2O_4S$	48.18/48.41	6.57/6.39	10.22/10.14	11.68/11.85
12a	COOMe	CH_2	66	89	$C_{13}H_{20}N_2O_5S$	49.37/49.50	6.33/6.39	8.86/8.69	10.13/9.96
12b	COOMe	CH_2CH_2	72	115	$C_{14}H_{22}N_2O_5S$	50.91/51.15	6.67/6.52	8.48/8.29	9.70/9.91
12c	COOMe	CH_2O	75	138	$C_{13}H_{20}N_2O_6S$	46.99/47.25	6.02/6.19	8.43/8.26	9.64/9.49

[a] Oils.

Table 4b

Spectral Data for 3-(Aminoacetyl)thiazolidine-4-carboxylate Esters

Compounds	IR (cm^{-1})	H_5	$H_{5'}$	H_4	H_2	R_1	CH_2N	COOMe	NC_3H_6X	Ratio of *cis/trans* conformers
11a	1740, 1660	3.35 (m)	3.35 (m)	5.1 (dd)	4.9 (d)	4.75 (dd)	3.1 (m)	3.75 (s)	1.6 (m), 2.5 (m)	60
		"	"	5.3 (dd)	4.95 (d)	4.45 (dd)	"	"	"	40
11b	1740, 1660	3.25 (m)	3.25 (m)	5.1 (dd)	4.95 (d)	4.75 (dd)	3.1 (m)	3.75 (s)	1.5 (m), 2.5 (m)	55
		"	"	5.55 (dd)	4.9 (d)	4.45 (dd)	"	"	"	45
11c	1740, 1660	3.35 (m)	3.35 (m)	5.1 (dd)	4.85 (d)	4.75 (dd)	3.2 (m)	3.75 (s)	2.5 (m), 3 8 (m)	65
		"	"	5.3 (dd)	4.9 (d)	4.45 (dd)	"	"	"	35
12a	1740, 1660	3.2 (t)	3.55 (t)	5.7 (d)	5.4 (s)	3.8 (s)	3 3 (d)	3.75 (s)	1.6 (m), 2.5 (m)	60
		3.3 (t)	3.65 (t)	5.1 (d)	5.6 (s)	"	3.15 (d)	"	"	40
12b	1740, 1660	3.25 (t)	3.4 (t)	5.7 (d)	5.3 (s)	3.8 (s)	3.3 (d)	3.75 (s)	1.5 (m), 2.5 (m)	60
		3.3 (t)	3.45 (t)	5.1 (d)	5.4 (s)	"	3.1 (d)	"	"	40
12c	1740, 1660	3.2 (t)	3.5 (t)	5 7 (d)	5.3 (s)	3.8 (s)	3.3 (d)	3.75 (s)	2.5 (m), 3.8 (m)	65
		3.3 (t)	3.6 (t)	5.2 (d)	5.6 (s)	"	3.15 (d)	"	"	35

Table 5a

Physical Constants for Ethyl 4-(Aminoacetyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylates

Compounds	R_2	X	yield %	mp°C	Formula (MW)	Anal. Calcd./Found C %	H %	N %	S %
13a	Ph	CH_2	62	123	$C_{23}H_{32}N_2O_3S$	66.35/66.56	7.69/7.58	6.73/6.61	7.69/7.52
13b	Ph	CH_2CH_2	71	111	$C_{24}H_{34}N_2O_3S$	66.98/67.16	7.91/7.72	6.51/6.59	7.44/7.28
13c	Ph	CH_2O	72	129	$C_{23}H_{32}N_2O_4S$	63.89/63.64	7.41/7.22	6.48/6.63	7.41/7.54
14a	Me	CH_2	71	[a]	$C_{18}H_{30}N_2O_3S$	61.02/61.28	8.47/8.62	7.91/7.75	9.04/8.81
14b	Me	CH_2CH_2	68	[a]	$C_{19}H_{32}N_2O_3S$	61.96/61.71	8.66/8.51	7.61/7.82	8.70/8.83
14c	Me	CH_2O	73	[a]	$C_{18}H_{30}N_2O_4S$	58.38/58.57	8.11/7.95	7.57/7.38	8.65/8.75
15a	*t*-Bu	CH_2	59	58	$C_{21}H_{36}N_2O_3S$	63.64/63.40	9.09/9.21	7.07/7.17	8.08/8.00
15b	*t*-Bu	CH_2CH_2	64	69	$C_{22}H_{38}N_2O_3S$	64.39/64.15	9.27/9.41	6.83/6.97	7.80/7.60
15c	*t*-Bu	CH_2O	66	82	$C_{21}H_{36}N_2O_4S$	61.17/60.92	8.74/8.91	6.80/6.95	7.77/7.82

[a] Oils.

Table 5b

Spectral Data for 4-(Aminoacetyl)-1-thia-4-azaspiro[4.5]decane-3-carboxylates

Compounds	IR (cm^{-1})	H_5	$H_{5'}$	H_4	C_6H_8	R_2	CH_2N	COOEt	NC_3H_6x	ratio of *cis/trans* conformers
13a	1740, 1660	3.2 (m)	3.2 (m)	5.5 (d)	1.6-2.2 (m), 7.3 (m)	3.1 (d)	1.25 (t), 4.3 (q)	1.6 (m), 2.5 (m)	100	
13b	1740, 1660	3.2 (m)	3.2 (m)	5.8 (d)	1.6-2.2 (m), 7.3 (m)	3.0 (d)	1.25 (t), 4.3 (q)	1.5 (m), 2.5 (m)	100	
13c	1740, 1660	3.2 (m)	3.2 (m)	5.5 (d)	1.6-2.2 (m), 7.3 (m)	3.05 (d)	1.25 (t), 4.3 (q)	2.5 (m), 3.8 (m)	100	
14a	1740, 1665	3.1 (m)	3.1 (m)	5.6 (d)	1.6-2.2 (m), 0.9 (d)	3.05 (d)	1.25 (t), 4.25 (q)	1.6 (m), 2.5 (m)	100	
14b	1740, 1665	3.0 (m)	3.0 (m)	5.8 (d)	1.6-2.2 (m), 0.9 (d)	2.9 (d)	1.25 (t), 425 (q)	1.5 (m), 2.5 (m)	100	
14c	1740, 1665	3.1 (m)	3.1 (m)	5.5 (d)	1.6-2.2 (m), 0.9 (d)	3.0 (d)	1.25 (t), 4.2 (q)	2.5 (m), 3.8 (m)	100	
15a	1745, 1660	3.1 (m)	3.1 (m)	5.6 (d)	1.5-2.1 (m), 0.8 (s)	3.0 (d)	1.3 (t), 4.3 (q)	1.6 (m), 2.5 (m)	100	
15b	1745, 1660	3.1 (m)	3.1 (m)	5.8 (d)	1.5-2.1 (m), 0.8 (s)	2.9 (d)	1.3 (t), 4.3 (q)	1.5 (m), 2.5 (m)	100	
15c	1745, 1660	3.1 (m)	3.1 (m)	5.5 (d)	1.5-2.1 (m), 0.8 (s)	3.0 (d)	1.3 (t), 4.3 (q)	2.5 (m), 3.8 (m)	100	

Anal. Calcd. for $C_7H_{11}NO_4S$: C, 40.98; H, 5.37; N, 6.83; S, 15.61. Found: C, 41.23; H, 5.42; N, 6.80; S, 15.68.

Ethyl 8-Phenyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**3**).

To a stirred solution of (-)-*L*-(*R*)-cysteine ethyl ester hydrochloride (5.6 g, 0.03 mole) in 50 ml of ethanol, phenylcyclohexanone (5.22 g, 0.03 mole) was added. The mixture was stirred for 30 minutes at room temperature and then at 70° for 30 minutes. The reaction mixture was concentrated and the crystals obtained were washed with ethyl ether, collected by filtration, and recrystallized from ethanol. This product is dissolved in 50 ml of water and ethyl ether was added. The aqueous solution was made basic by the addition of sodium carbonate. The combined organic layers were dried over sodium sulfate, filtered and evaporated, colorless powder, yield 81%, mp 104°; ir (potassium bromide): ν 3300 (NH), 2950 (CH), 1740 (CO) cm^{-1}. ^1H nmr (deuteriochloroform): major diastereoisomer (65%): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), δ 2.5 (m, 1H), δ 2.5 (s, 1H), δ 2.9 (t, 1H), δ 3.35 (dd, 1H), δ 4.0 (dd, 1H), δ 4.3 (q, 2H), δ 7.3 (m, 5H); minor diasteroisomer (35%): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), 2.5 (m, 1H), δ 2.5 (s, 1H), δ 2.9 (t, 1H), δ 3.4 (dd, 1H), δ 4.1 (dd, 1H), δ 4.3 (q, 2H), δ 7.3 (m, 5H).

Anal. Calcd. for $C_{17}H_{23}NO_2S$: C, 66.89; H, 7.54; N, 4.59; S, 10.49. Found: C, 66.75; H, 7.64; N, 4.37; S, 10.72.

Ethyl 8-Methyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**4**).

This product was prepared in the same manner as described for **3** using 4-methylcyclohexanone, colorless liquid, yield 71%; ir (potassium bromide): ν 3300 (NH), 3000 (CH), 1740 (CO) cm^{-1}. ^1H nmr (deuteriochloroform): major diastereoisomer (60%): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), δ 2.4 (m, 1H), δ 2.5 (s, 1H), δ 2.85 (dd, 1H), δ 3.25 (dd, 1H), δ 4.05 (dd, 1H), δ 4.25 (q, 2H), δ 0.9 (d, 3H), minor diastereoisomer (40%): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), δ 2.4 (m, 1H), δ 2.5 (s, 1H), δ 2.9 (dd, 1H), δ 3.3 (dd, 1H), δ 3.95 (dd, 1H), δ 4.2 (q, 2H), δ 0.9 (d, 3H).

Anal. Calcd. for $C_{12}H_{21}NO_2S$: C, 59.26; H, 8.64; N, 5.76; S, 13.17. Found: C, 58.92; H, 8.72; N, 5.95; S, 13.33.

Ethyl 8-*tert*-butyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**5**).

This product was prepared in the same manner as described for **3** using *tert*-butylcyclohexanone, colorless powder, yield 68%, mp 72°; ir (potassium bromide): ν 3290 (NH), 3000 (CH), 1745 (CO) cm^{-1}. ^1H nmr (deuteriochloroform): major diastereoisomer (70%): δ 1.3 (t, 3H), δ 1.5-2.3 (m, 8H), δ 2.1 (m, 1H), δ 2.4 (s, 1H), δ 2.85 (dd, 1H), δ 3.3 (dd, 1H), δ 4.05 (dd, 1H), δ 4.25 (q, 2H), δ 0.85 (s, 9H), minor diasteroisomer (30%): δ 1.3 (t, 3H), δ 1.5-2.3 (m, 8H), δ 2.1 (m, 1H), δ 2.4 (s, 1H), δ 2.9 (dd, 1H), δ 3.35 (dd, 1H), δ 3.95 (dd, 1H), δ 4.25 (q, 2H), δ 0.85 (s, 9H).

Anal. Calcd. for $C_{15}H_{27}NO_2S$: C, 63.16; H, 9.47; N, 4.91; S, 11.23. Found: C, 63.42; H, 9.38; N, 5.08; S, 11.08.

Methyl 3-Chloroacetylthiazolidine-4-carboxylate (**6**).

To a stirred and ice cooled solution of methyl thiazolidine-4-carboxylate **1** (2.94 g, 0.02 mole) and sodium carbonate (2.12 g, 0.02 mole) in 100 ml of dichloromethane was added dropwise chloroacetyl chloride (3.39 g, 0.03 mole). The reaction mixture was stirred for 24 hours at room temperature, then filtered and concentrated. After cooling, the product crystallized. This product was obtained in a mixture of conformers, colorless powder, yield 60%, mp 60°; ir (potassium bromide): ν 3000 (CH), 1740 (CO ester), 1660 (CO amide) cm^{-1}. ^1H nmr (deuteriochloroform): major conformer (70%): δ 3.3 (dd, 2H), δ 3.8 (s, 3H), δ 4.15 (s, 2H), δ 4.65 (d, 1H), δ 4.75 (d, 1H), δ 5.1 (dd, 1H); minor conformer (30%): δ 3.4 (dd, 2H), δ 3.85 (s, 3H), δ 4.05 (s, 2H), δ 4.55 (d, 1H), δ 4.8 (d, 1H), δ 5.0 (dd, 1H).

Anal. Calcd. for $C_7H_{10}ClNO_3S$: C, 37.58; H, 4.47; N, 6.26; S, 14.32; Cl, 15.88. Found: C, 37.35; H, 4.32; N, 6.39; S, 14.48; Cl, 15.71.

Dimethyl 3-Chloroacetylthiazolidine-2,4-dicarboxylate (**7**).

This product was prepared in the same manner as described for **6** from **2**. This compound was obtained in a mixture of conformers, colorless powder, yield 68%, mp 121°; ir (potassium bromide): ν 2950 (CH), 1740 (CO ester), 1660 (CO amide) cm^{-1}. ^1H nmr (deuteriochloroform): major conformer (60%): 3.45 (m, 1H), δ 3.7 (m, 1H), δ 3.75 (d, 6H), δ 4.1 (d, 2H), 5.1 (m, 1H), δ 5.7 (s, 1H); minor conformer (40%): δ 3.45 (m, 1H), 3.7 (d, 1H), δ 3.9 (d, 6H), δ 4.3 (d, 2H), δ 5.1 (m, 1H), 65.6 (s, 1H).

Anal. Calcd. for $C_9H_{12}ClNO_5S$: C, 38.36; H, 4.26; N, 4.97; S, 11.37; Cl, 12.61. Found: C, 38.16; H, 4.19; N, 4.89; S, 11.17; Cl, 12.80.

Ethyl 4-Chloroacetyl-8-phenyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**8**).

This compound was prepared in the same manner as described for **6** from **3**, colorless powder, yield 59%, mp 116°; ir (potassium bromide): ν 3000 (CH), 1740 (CO ester), 1660 (CO amide) cm^{-1}. ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), δ 2.4 (m, 1H), δ 3.25 (dd, 1H), δ 3.4 (d, 1H), δ 4.0 (s, 2H), δ 4.3 (q, 2H), δ 5.1 (d, 1H), δ 7.3 (m, 5H).

Anal. Calcd. for $C_{19}H_{24}ClNO_3S$: C, 59.76; H, 6.29; N, 3.67; S, 8.39; Cl, 9.31. Found: C, 59.58; H, 6.46; N, 3.75; S, 8.27; Cl, 9.53.

Ethyl 4-Chloroacetyl-8-methyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**9**).

This compound was prepared in the same manner as described for **6** from **4**, colorless oil, yield 46%; ir (potassium bromide): ν 3000 (CH), 1740 (CO ester), 1665 (CO amide) cm^{-1}. ^1H nmr (deuteriochloroform): δ 1.25 (t, 3H), δ 1.6-2.2 (m, 8H), δ 2.4 (m, 1H), δ 3.15 (dd, 1H), δ 3.3 (d, 1H), δ 3.9 (s, 2H), δ 4.25 (q, 2H), δ 5.05 (d, 1H), δ 0.9 (d, 3H).

Anal. Calcd. for $C_{14}H_{22}ClNO_3S$: C, 52.58; H, 6.89; N, 4.38; S, 10.02; Cl, 11.11. Found: C, 52.72; H, 7.05; N, 4.34; S, 9.88; Cl, 11.14.

Ethyl 4-Chloroacetyl-8-*tert*-butyl-1-thia-4-azaspiro[4.5]decane-3-carboxylate (**10**).

This compound was prepared in the same manner as described for **6** from **5**, colorless powder, yield 48%, mp 104°; ir (potassium bromide): ν 2990 (CH); 1745 (CO ester); 1660 (CO amide) cm^{-1}. ^1H nrnr (deuteriochloroform): δ 1.3 (t, 3H), δ 1.5-2.1 (m, 8H), δ 2.1 (m, 1H), δ 3.15 (dd, 1H), δ 3.35 (d, 1H), δ 3.9 (s, 2H), δ 4.25 (q, 2H), δ 5.0 (d, 1H), δ 0.85 (s, 9H).

Anal. Calcd. for $C_{17}H_{28}ClNO_3S$: C, 56.43; H, 7.74; N, 3.87; S, 8.85; Cl, 9.82. Found: 56.24; H, 7.82; N, 4.01; S, 8.99; Cl, 9.88.

General Preparation Procedure for (Aminoacetyl)thiazolidine-4-carboxylate Esters **11-15**.

To a stirred solution of **6-10** (0.01 mole) and sodium carbonate (0.015 mole) in 30 ml of methanol, 0.015 mole of a cyclic secondary amine was added. The mixture was heated for 20

hours at reflux, filtered and then evaporated. The crude product was taken up in chloroform, washed with water, dried over sodium sulfate and filtered. Afrer evaporation of the solvent, the crude product was purified by column chromatography.

See Tables 4a,b and 5a,b for physical constants and spectral data.

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