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CONVENIENT SYNTHESIS OF 1-AZA-3-THIABICYCLO[3.1.0]HEXANES FROM L-CYSTEINE

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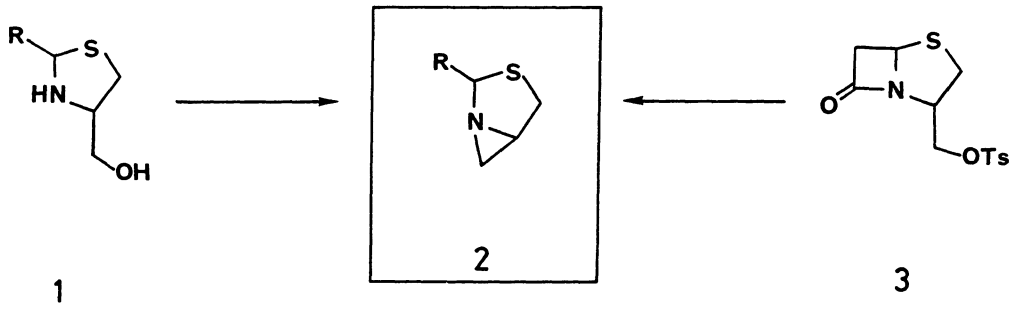
Synthesis of optically active 2-substituted and unsubstituted 1-aza-3-thiabicyclo[3.1.0]hexanes are accomplished by intramolecular cyclization of 4-hydroxymethylthiazolidines which are prepared by the reaction of L-cysteine methyl ester with appropriate aldehydes followed by reduction of ester function.

Aziridine chemistry has still received particular attention due to the useful biological activity based on the strained structure.[1] One of the important and reliable synthesis of aziridines utilizing intramolecular cyclization is the derivation from amino alcohol by a variety of reagents. Among these, recent development utilizes reagents formed from triphenylphosphine and halogen, carbon tetrachloride or azodicarbonyl compound, where the driving force is furnished by the strength of the phosphorus - oxygen bond.[1] Meanwhile, Bell et al. reported a transformation of penicillanyl p-toluenesulfonate (parent skelton 3) into fused aziridine (parent skelton 2) by base-catalyzed methanolysis.[2] Since no synthesis of the fused aziridine system 2 has been reported other than Bell's derivation, we have studied the convenient synthesis from 4-hydroxymethylthiazolidine 1 in connection with our recent investigation on the chemistry of thiazolidines.[3] In this communication, synthesis of optically active bicyclic aziridines, i.e. 1-aza-3-thiabicyclo[3.1.0]hexanes 2 (R= H, isobutyl, phenyl) from L-cysteine, is described.



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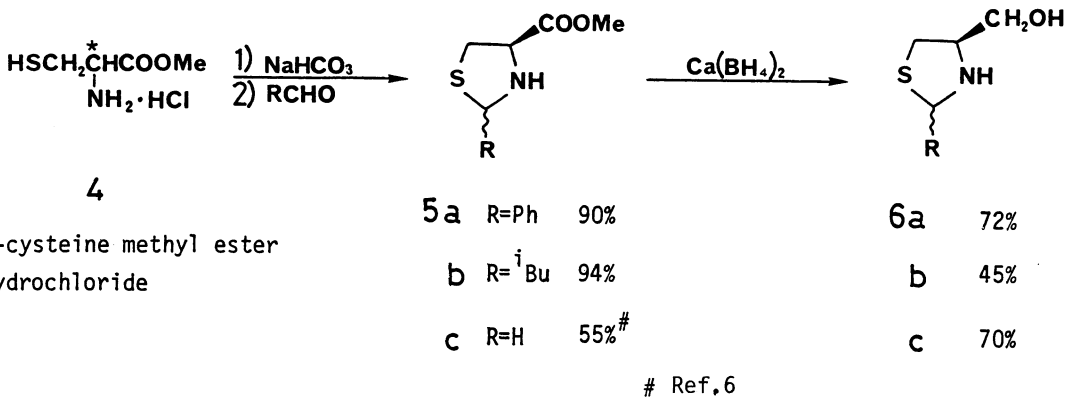

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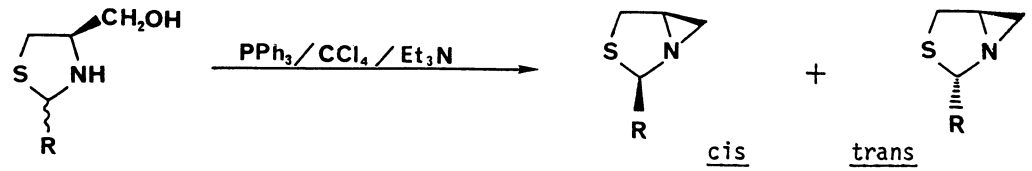
L-cysteine methyl ester hydrochloride

5a	R=Ph	90%	6a	72%
b	R=^{i}Bu	94%	b	45%
c	R=H	55%#	c	70%

Ref.6

In a typical procedure (R= Ph), L-cysteine methyl ester hydrochloride 4 (0.34 mol, 58.4 g) was neutralized with sodium bicarbonate (0.34 mol, 28.6 g) and then was treated with an equimolar amount of benzaldehyde (0.34 mol, 36.8 g) for 2 h at room temperature. Colorless oil (68.2 g) obtained in 90% yield was used without further purification because of decomposition of 5a even under high vacuum distillation. According to Habermehl's modified method,[4] reduction of the ester 5a was carried out with $Ca(BH_4)_2$ prepared *in situ* by $CaCl_2 \cdot 2H_2O$ (11 mmol, 1.62 g) and $NaBH_4$ (20 mmol, 0.75 g) at -30 °C. To a suspension of $Ca(BH_4)_2$ thus obtained an ethanol solution of 5a (26 mmol, 5.8 g) was added dropwise at -30 °C. As colorless crystals recrystallized from dichloromethane - hexane, 6a was collected (3.68 g, 72%).

Aziridine ring was built by the method of literature.[5] Mixture of 6a (5.0 mmol, 0.98 g), triphenylphosphine (5.7 mmol, 1.5 g), triethylamine (5.0 mmol, 0.51 g) and carbon tetrachloride (5.0 mmol, 0.77 g) was stirred at 4 °C (ice - water bath) in dry acetonitrile overnight (16 h). Removal of triphenylphosphine oxide by filtration after addition of excess hexane and chromatographic purification (siilca gel/ether) of the filtrate afforded colorless oil (2a, 0.6 g, 67%; overall yield from 4, 43%). ^{1}H and ^{13}C NMR of the product indicated presence of two diastereomers (1:1 ratio), as well as TLC. In ^{1}H NMR high field shifted protons of aziridine ring appeared at a region of 2.95 - 1.50 ppm. Mass spectrum with molecular ion peak at m/e 177 and elemental analysis supported the structure of 2a, while IR spectrum showed no charateristic absorption except for those of phenyl ring.



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		cis		trans
2a	67%	(1	:	1)
b	58%	(1	:	1)
c	19%#			

Ref.7

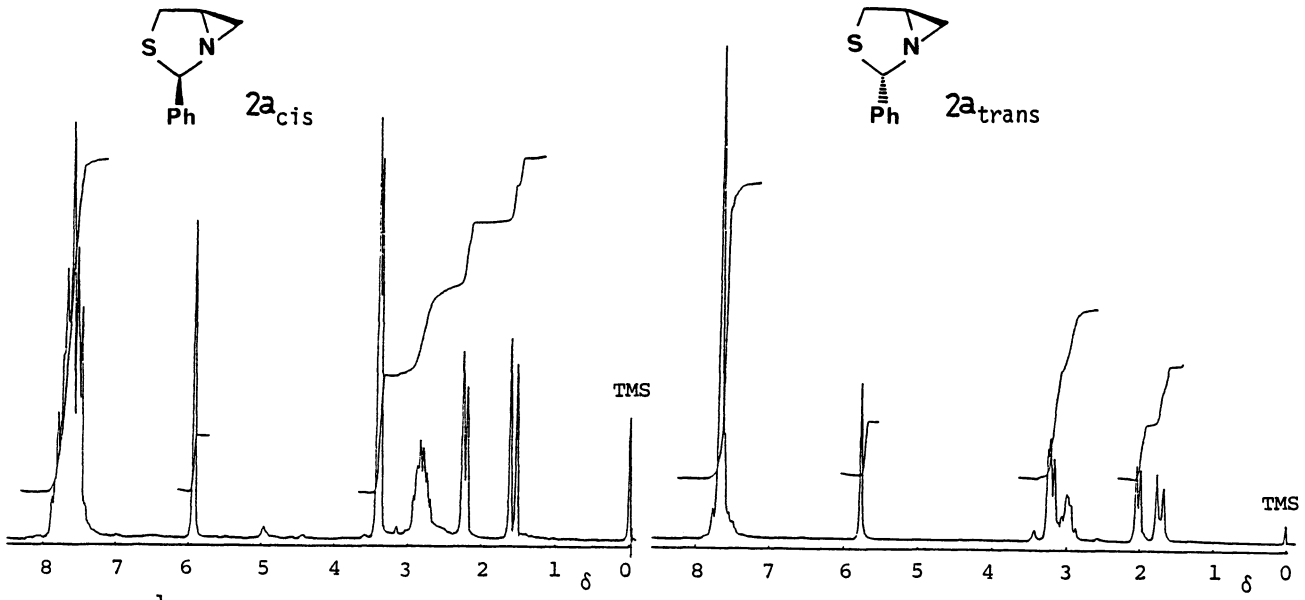

Fig. 1. ^{1}H NMR spectra of 2a$_{cis}$ and 2a$_{trans}$ at 60 MHz in $CDCl_3$. Chemical Shifts in ppm from tetramethylsilane (TMS) as an internal standard.

By the similar procedure, parent compound 1-aza-3-thiabicyclo[3.1.0]hexane 2c[8] and 2-isobutyl derivative 2b were obtained in satisfactory yields (overall yields: 25% for 2b from 4 and 7.3%[7] for 2c from thiazolidine-4-carboxylic acid[6]). Both structures were assigned by spectroscopic (^{1}H and ^{13}C NMR and IR) and analytical data.[8,10]

Fortunately, careful column chromatography over silica gel (eluenet: ether) of the each diastereomer mixture gave two pure diastereomers (cis and trans) separately.[9,10] ^{1}H NMR spectra of the two diastereomers of 2a are revealed in Fig. 1. These isomers are clearly differentiated by large difference between the chemical shifts and signal patterns of both ^{1}H and ^{13}C NMR spectra.[9] Referring to structure determination by ^{1}H NMR of 1-aza and 1,3-diazabicyclo[3.1.0]hexane systems having presumably similar structures,[11] more down field shifted signal of 2-methine proton is that of cis form (5.87 ppm) which is far from trans one (5.72 ppm) which was eluted earlier than cis isomer. In both cases absence of geminal coupling between protons at 6-position is consistent with reported data[12] in which very small coupling constants (0 - 2 Hz) are obtained for 1,2-substituted aziridines, in contrast to unsubstituted ones. Furthermore, ring fusion to aziridine ring makes the geminal coupling smaller.[12]

Thus, optically active 1-aza-3-thiabicyclo[3.1.0]hexane and its alkyl and aryl derivatives were conveniently prepared from L-cysteine in good yields. By this method compounds having a variety of substituents at 2-position are to be obtained by the use of appropriate aldehydes.

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6) The compound 5c was obtained in 55% yield by esterification followed by neutralization of thiazolidine-4-carboxylic acid hydrochloride prepared from L-cysteine and formaldehyde.
7) Unfortunately, 2c was too volatile to be pure enough to measure correct yield and specific rotation by the present time.
8) Physical data of 2c: colorless oil; ^{1}H NMR(δ,$CDCl_3$) 4.12(s,2H), 3.37 - 2.78 (m,2H), 2.68 - 2.41(m,1H), 1.81(d,1H,J=3.5 Hz), 1.42(d,1H,J=5.0 Hz); ^{13}C NMR (δ,$CDCl_3$) 59.9(t), 42.3(d), 32.3(t), 22.7(t).
9) Physical data of 2a(cis): mp 214 - 216 °C; ^{1}H NMR(δ,$CDCl_3$) 7.52(m,5H), 5.87(s, 1H), 3.35(d,2H,J=2.2 Hz), 2.79(m,1H), 2.27(d,1H,J=3.7 Hz), 1.53(d,1H,J=5.6 Hz); ^{13}C NMR(δ,$CDCl_3$) 137.1(s), 128.0(d), 127.6(d), 127.0(d), 75.9(d), 41.8(d), 33.9(t), 20.0(t); $[\alpha]_D^{24}$ -158°(c 1.14,$CHCl_3$); Anal.($C_{10}H_{11}NS$) C, H, N.
Physical data of 2a(trans): colorless oil; ^{1}H NMR(δ,$CDCl_3$) 7.59(s,5H), 5.72(s, 1H), 3.44 - 2.79(m,3H), 1.99(d,1H,J=3.5 Hz), 1.69(d,1H,J=5.8 Hz); ^{13}C NMR(δ, $CDCl_3$) 143.6(s), 127.2(d), 126.4(d), 125.2(d), 75.5(d), 43.6(d), 31.1(t), 23.6 (t); $[\alpha]_D^{24}$ +1.11°(c 1.13,$CHCl_3$).
10) Physical data of 2b(cis): mp 227 - 229 °C; ^{1}H NMR(δ,$CDCl_3$) 4.83(t,1H,J=6.9 Hz), 3.27(d,2H,J=2.0 Hz), 2.71(m,1H), 2.02(d,1H,J=3.6 Hz), 1.88 - 1.56(m,2H), 1.46 (d,1H,J=5.6 Hz), 0.99(d,6H,J=5.7 Hz); Anal.($C_7H_{15}NS$) C, H, N.
Physical data of 2b(trans): colorless oil; ^{1}H NMR(δ,$CDCl_3$) 4.80 - 4.48(doublet of doublet,1H,J=6.8 and 8.0 Hz), 3.48 - 2.97(m,2H), 2.80(m,1H), 2.22 - 1.23(m, 4H), 1.00(d,3H,J=6.2 Hz); Anal.($C_7H_{15}NS$) C, H, N.
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