Tetrahedron Letters,Vol.24,No.42,pp 4503-4506,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

1. BORON TRIFLUORIDE ACTIVATED 3-THIAZOLINES. AN EFFICIENT PREPARATION OF FUNCTIONALIZED THIAZOLIDINES.

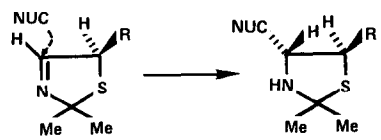
Clifford N. Meltz and Robert A. Volkmann*

Central Research, Pfizer Inc.

Groton, Connecticut 06340

Summary: Boron trifluoride activated 2,2,5-trialkyl-3-thiazolines react with a wide range of organometallic reagents to generate substituted thiazolidines.

In the course of our studies related to the biological cofactor, d-biotin,[1] we required a method for generating stereospecifically threo-substituted 2-aminothiols. We focused our attention on a straightforward approach involving the addition of organometallic reagents to 3-thiazolines 1[1,2] in the hope that this reaction would provide directly masked 2-aminothiols in the form of substituted thiazolidines 2.

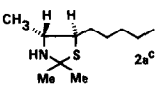
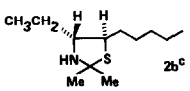
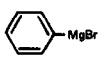
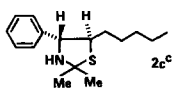
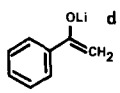
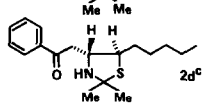
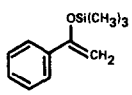
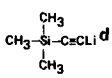
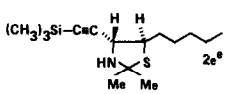
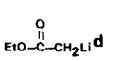
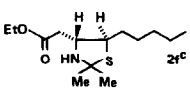
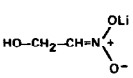
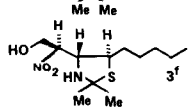
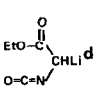
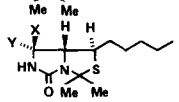
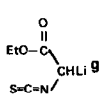
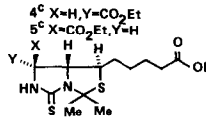


1 2

The imine moiety in 1 proved inert to organometallic attack.[3] This result was not completely unexpected since most aldimines or ketimines bearing hydrogen atoms undergo rapid proton abstraction.[4] Furthermore, imine additions are subject to steric constraints.[5] On occasion, reductive dimerization competes with the desired condensation.[6] While methods exist for circumventing some of these problems,[7] the imine addition reaction[8] has inherent limitations and typically involves substrates incapable of enolization which are activated (as acylimines or immonium salts).[9] Our efforts to solve the thiazoline reactivity problem resulted in the discovery that 3-thiazolines 1, activated with an equivalent of boron trifluoride, react readily with a wide range of organometallic reagents to generate a variety of trans-4,5-disubstituted thiazolidines 2.

Solutions of the organometallic reagents shown in Table I were cooled (preferably -78°) and added rapidly to the Lewis acid-imine solutions (-78°) which were generated by BF_3 OEt_2 (1 equiv.) treatment of the 2,2-dimethyl-5-alkyl-3-thiazolines I[1] (1 equiv., THF, 0°, 1 hr). The reaction mixtures were stirred at -78° (1-2 hr), quenched (AcOH) and worked up using standard procedures[10] to give the corresponding thiazolidines 2-7.[11] As indicated in Table I, alkyl lithiums, Grignards, lithium acetylides, nitronates, ester and ketone enolates add equally well to I. While enol ether additions are possible (entry 5), the corresponding ketone enolate condensations are superior (entry 4). In all the examples as best we can tell only the trans ring substituted thiazolidines are formed as a result of preferential attack at the more accessible face of the thiazolines.

THIAZOLIDINE SYNTHESIS

Entry	Reagent	3-Thiazoline 1[a]	Product(s)	Yield[b] (product ratio)
1	CH_3Li	R = $(CH_2)_4CH_3$	 2a[c]	48%
2	CH_3CH_2MgBr	R = $(CH_2)_4CH_3$	 2b[c]	53%
3		R = $(CH_2)_4CH_3$	 2c[c]	42%
4		R = $(CH_2)_4CH_3$	 2d[c]	70%
5		R = $(CH_2)_4CH_3$	2d[c]	20%
6		R = $(CH_2)_4CH_3$	 2e[e]	85%
7		R = $(CH_2)_4CH_3$	 2f[c]	54%
8		R = $(CH_2)_4CH_3$	 3[f]	47%
9		R = $(CH_2)_4CH_3$	 4[c] X=H,Y=CO_2Et 5[c] X=CO_2Et,Y=H	50% (50(4):50(5))
10		R = $(CH_2)_4CO_2Et$	 6[c] X=H, Y=CO_2Et 7[c] X=CO_2Et, Y=H	75% (70(6):30(7))

a) References 1 and 2.

b) Yields are reported for isolated products and have not been optimized.

c) Chromatographed on silica gel.

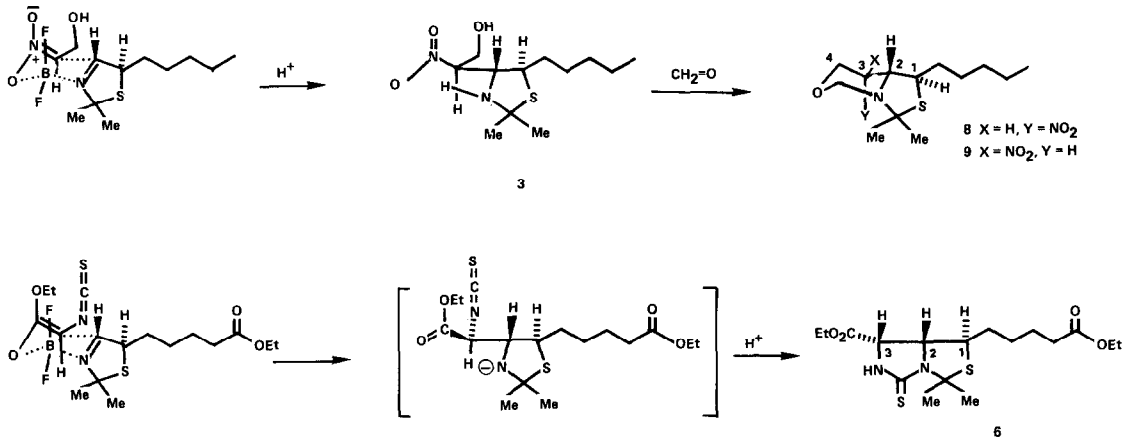
d) Formed by treatment of the corresponding starting material with LDA (THF, -78°)

e) Chromatographed on pH 9 buffered silica gel

f) Product was precipitated from the crude reaction mixture with hexane

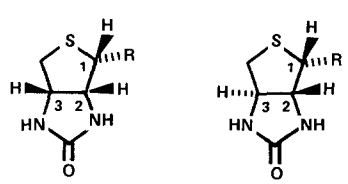
g) Formed by ester treatment (THF, -78°) with LiO^tBu

The methodology is particularly attractive in the generation of thiazolidines bearing three contiguous asymmetric centers.[1] Analogous to the aldol condensation,[12] the stereochemistry about the newly formed carbon-carbon bonds of 3[13] and 6 (the major products of entries 8 and 10) can be rationalized by a pericyclic process in which steric interactions involved in nitronate (enolate[14])-3-thiazoline transition state play a dominant role (Scheme 1). While the formation of 3 could well be a thermodynamic consequence, bicyclic products 4-7 are likely formed under kinetically controlled conditions.



SCHEME 1

Our stereochemical assignments for the products bearing three contiguous asymmetric centers were based on spectral (^{1}H and ^{13}C NMR) as well as chemical evidence. The stereochemistry of nitroethanol adduct 3, mp 97-98°, was best determined by aqueous formaldehyde conversion (80% yield) of 3 to tetrahydro-1,3-oxazine derivative 8, mp 86-88°, ^{1}H NMR ($CDCl_3$) 3.33 (dd, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 3.7 Hz, 2-H), 4.80 (m, $J_{3,4\ ax}$ = 2.5 Hz, $J_{3,4\ eq.}$ = 2.2 Hz, 3-H). Treatment of 8 with potassium t-butoxide (1 equiv.) followed by AcOH furnished quantitatively the equatorial nitro isomer 9, mp 68-69°, ^{1}H NMR ($CDCl_3$) 3.96 (dd, $J_{1,2}$ = 2 Hz, $J_{2,3}$ = 9.5 Hz, 2-H), 4.88 (m, $J_{3,4\ ax}$ = 10 Hz, $J_{3,4\ eq}$ = 4 Hz, 3-H). In addition, the relative stereochemistry of 3 as well as bicyclic adducts 4-7 were established by the conversion of 4 and 6 to the biotin ring nucleus (10) and the conversion of 3, 5 and 7 to the allobiotin framework (11).[1,15]



10 11

The methodology provides an excellent opportunity for obtaining a variety of masked threo-substituted 2-aminothiols, which were heretofore unknown. An application of this technology is the subject of the following communication.

References and Notes

1. R. A. Volkmann, J. T. Davis and C. N. Meltz, submitted for publication in J. Am. Chem. Soc.
2. 3-Thiazolines are obtained in high yield by treatment of the corresponding bromoaldehydes with NaHS, a ketone or aldehyde, and NH_3. See M. Thiel, F. Asinger, K. Schmiedel, Liebigs Ann. Chem. 611, 121 (1958); F. Asinger, H. Offermanns, Angew. Chem. Int. Ed. Engl. 6, 907 (1967).
3. Several additions to unactivated 2,2,5,5-tetrasubstituted-3-thiazolines have been reported. See (a) I. Ugi and E. Wischhöfer, Chem. Ber. 95, 136 (1962); (b) F. Asinger, W. Schäfer, and E.-C. Witte, Ang. Chem. 3, 313 (1964); (c) A. K. Bose, G. Spiegelman and M. S. Manhas, Chem. Comm. 321 (1968).
4. The generation of imine anions has been elegantly exploited in the enantioselective alkylation of optically active cyclohexanone derived imines. See J. K. Whitesell and M. A. Whitesell, J. Org. Chem. 42, 377 (1977).
5. B. L. Emling, R. J. Horvath, A. J. Saraceno, E. F. Ellermeyer, L. Haile, and L. D. Hudac, J. Org. Chem. 24, 657 (1959).
6. H. Thies and H. Schönenberger, Arch. Pharm., 289, 408 (1956); H. Thies and H. Schönenberger, Chem. Ber., 89, 1918 (1956).
7. F. A. Davis and P. A. Mancinelli, J. Org. Chem. 42, 398 (1977).
8. "The Chemistry of the Carbon-Nitrogen Double Bond", ed. S. Patai, Interscience, New York, 1970, Chapter 6, pp 255-298; R. W. Layer, Chem. Rev. 63 489 (1963); D. Barton and W. D. Ollis, "Comprehensive Organic Chemistry", ed. I. O. Sutherland, Pergamon, New York, 1979, Chapter 8, pp 385-590.
9. A. I. Meyers and E. W. Collington, J. Am. Chem. Soc. 92, 6678 (1970); K. Akiba, K. Araki, M. Nakatani and M. Wada, Tetrahedron Lett. 4961 (1981).
10. Typically, the reaction mixtures were concentrated, dissolved in ethyl acetate and extracted with dilute bicarbonate and brine. The organic extracts were dried ($MgSO_4$), conc. in vacuo and, in most cases, chromatographed on silica gel to remove unreacted I. Product decomposition on silica gel can be minimized by using Na_2HPO_4 buffered silica gel (see entry 6).
11. Yields are reported for isolated chromatographically pure products and have not been optimized. NMR and IR spectra were entirely consistent with the assigned structures and satisfactory combustion analyses were obtained.
12. (a) See D. A. Evans, J. V. Nelson, T. R. Taber, "Topics in Stereochemistry", Vol. 13, N. L. Allinger, E. L. Eliel and S. H. Wilen, Eds., John Wiley and Sons, 1982, Chapter I; (b) C. H. Heathcock, "Stereoselective Aldol Condensations", in Comprehensive Carbanion Chemistry, Vol. II, T. Durst and E. Buncel, Eds., Elsevier, 1981, Chapter 4.
13. In this case, the BF_3 imine solution (CH_2Cl_2, -78°) was added to the lithium nitronate solution (Et_2O, -78°) and the reaction was gradually allowed to warm to 0°.
14. We assume lithium isothiocyanatoacetate has the Z configuration based on its structural similarity to known lithiopropionates (see C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, J. Org. Chem. 45, 1066 (1980).
15. J. T. Davis, R. B. Drolet, C. N. Meltz and R. A. Volkmann unpublished results.

(Received in USA 20 June 1983)