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A One Step Synthesis of Thiazolines from Esters

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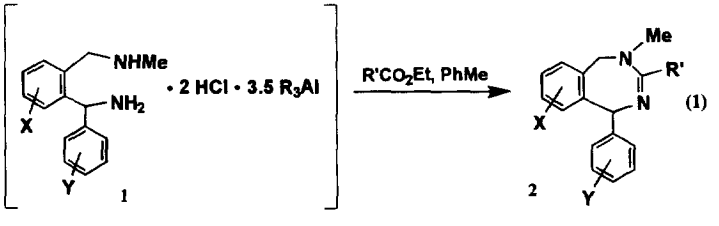
Abstract: *Condensation of the triisobutylaluminum complex of cysteamine HCl with a variety of carboxylic esters furnishes thiazolines in one step. This new method has been applied to chiral α-aminoesters to give α-amino thiazolines of high optical purity, yet N-benzyl protection of the amine is required.* Copyright © 1996 Elsevier Science Ltd

Thiazoline rings are found in a large number of biologically active natural products. These include the tantazoles such as thiangazole, which possesses anti HIV-1 activity,[1] curacin A which inhibits cell division *via* tubulin binding,[2] and the large class of lissoclinamides[3,4] which are antineoplastic agents and likely metal ion chelators. Considerable interest in the total synthesis of these species has thus been generated. Some methods for construction of the thiazoline ring include condensation of 2-aminoethanethiol (cysteamine) with nitriles[1] or iminoethers,[3] and multistep conversions from oxazolines[5] or oxazolidines.[2] Synthesis of 2-phenylthiazoline from benzoic acid has been reported,[6] but the product formed as part of a three component mixture. Thiazoline itself has been prepared from thermal condensation of cysteamine with methyl formate.[7]

We desired a more facile synthesis of thiazolines from a readily available carbonyl species. The synthesis of 1-phenyl-2,4-benzodiazepines **2** *via* condensation of the triorganoaluminum-diamine complex **1** with carboxylic esters has been reported (eq. 1).[8] Wide tolerance of functional groups was observed. This



synthesis was in turn predicated on the earlier work of Neef[9] in which trimethylaluminum complexes of 1,2-diamines and 2-mercaptoaniline with esters provided imidazolines and a benzimidazole, respectively.

We have found that addition of esters to a triisobutylaluminum/cysteamine HCl complex leads directly to 2-substituted thiazolines[10] as shown (eq. 2). Our initial results are summarized in Table 1. Aryl, heteroaryl

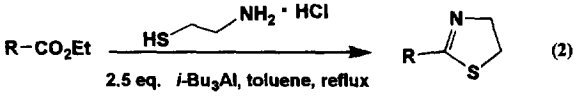
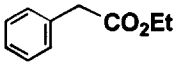
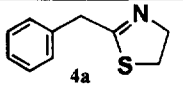
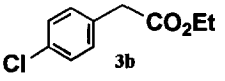
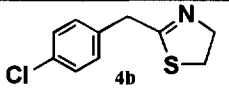
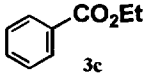
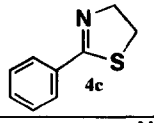
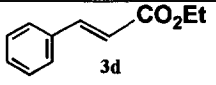
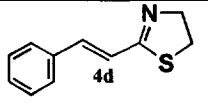
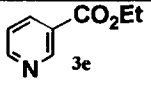
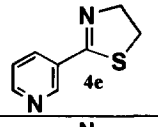
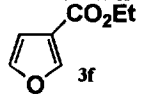
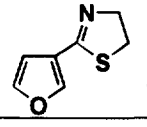
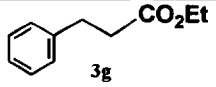
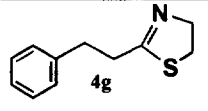
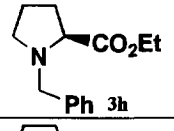
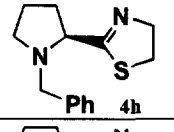
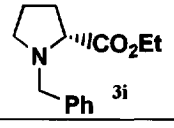
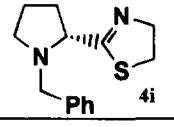
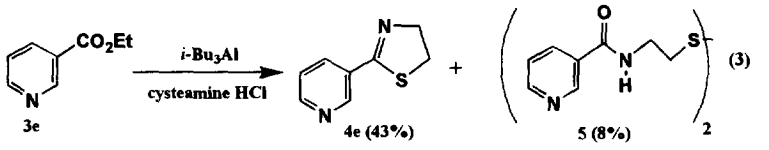


Table 1. Synthesis of Thiazolines.

Entry	Carboxylic ester	Thiazoline Product	Yield
1	 3a	 4a	71%
2	 3b	 4b	73%
3	 3c	 4c	61%
4	 3d	 4d	21%
5	 3e	 4e	43%
6	 3f	 4f	50%
7	 3g	 4g	75%
8	 3h	 4h	77%
9	 3i	 4i	75%

and alkyl esters were found to be successful, and reaction times are brief (1-2 hours). Ethyl cinnamate (entry 4) provided the lowest observed yield, likely due to competing Michael addition and conjugate addition pathways. Some insight into the mechanism of ring formation was gained in the reaction of pyridyl ester **3e** (entry 5). Polar disulfide **5** was isolated in 8% yield, suggesting initial attack at the ester carbonyl may be by nitrogen, followed by thiol attack to furnish the cyclized product (eq. 3).

Of paricular interest to us was the use of α-aminoesters. Our initial results were disappointing in that



N-BOC and N-CBZ protected α-aminoesters led only to decomposition products. Reaction of the N-benzyl proline esters (entries 8,9) however, gave the desired thiazolines in good yield. The novelty of this transformation required us to investigate the optical purity of these products. Chiral capillary electrophoresis[12] using γ-cyclodextrin readily separated the two enantiomers. Figure 1 shows electropherograms of **4h** (Fig. 1A) and **4h** spiked with its enantiomer **4i** (Fib. 1B). Both thiazolines were determined to be greater than 95% ee. We found that the use of new bottles of *i*-Bu_3Al was required for obtaining products with high optical purity. This is likely due to the formation of *i*-Bu_2AlH on standing,[13] leading to racemization. Prolonged exposure of **4i** to Na_2CO_3 solutions (pH 10.5, 24h rt) caused no racemization.

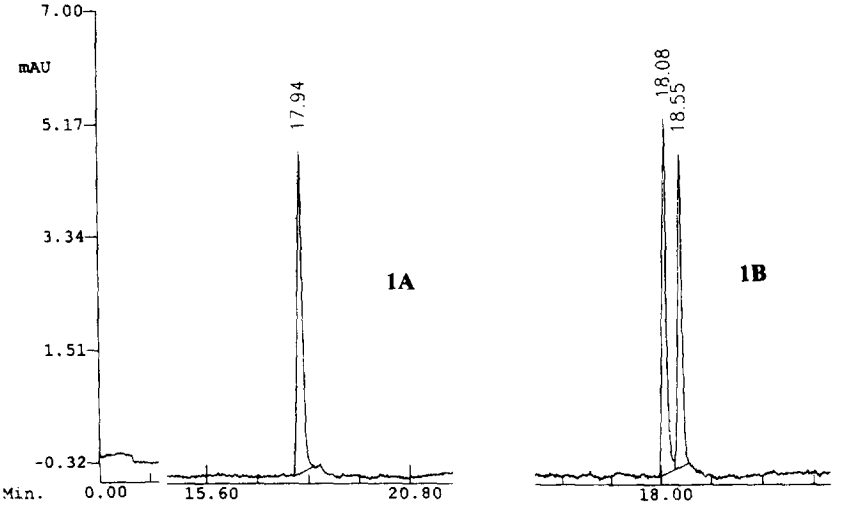


Figure 1. Electropherograms of thiazoline **4h (1A)** and **4h + 4i (1B)**.

In summary, we have described a new one step synthesis of 2-substituted thiazolines from carboxylic esters. The reaction appears to be fairly general, and is applicable to α-aminoesters as well, with the proviso that the amine nitrogen contain alkyl substitution. Significantly, the use of optically active α-aminoesters leads to α-aminothiazolines with high optical purity, a finding which may allow application of this methodology to chiral targets.

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(10) **General procedure for condensation.** To a dry 250mL 3 neck RB flask fitted with a Graham style reflux condenser under N_2 was added 0.676g cysteamine HCl (5.95 mmol, 1 eq) and 25mL PhMe. To this suspension stirring at 23°C was cautiously added 14.9mL 1M *i*-Bu_3Al (14.9 mmol, 2.5 eq) *via* syringe through the condenser inlet in several portions. The ensuing exotherm and gas evolution led rapidly to the formation of a clear, colorless solution. The solution was refluxed 30 min , then 1.46mL α-aminoester **3i** (6.55 mmol, 1.1 eq) was added via syringe in four portions. After 2.0 h at reflux, TLC analysis indicated reaction completion to a polar product which stained orange with Dragendorff's reagent.[11] The reaction mixture was then diluted with 25mL PhMe, cooled to 23°C , and quenched by the dropwise addition of 4mL MeOH. This mixture was stirred at 23°C for 5 min , and then 20mL sat'd Rochelle's salt solution, 20mL sat'd Na_2CO_3, and 20 mL sat'd NaCl were added in the order given. To this mixture was added 50mL EtOAc, and the mixture stirred vigorously for 15 min. The mixture was poured into a separatory funnel, and after 20 min the organic phase was separated, and the aq. phase was reextracted with EtOAc (3 X 50mL). The combined organic phases were dried ($MgSO_4$), and the solvents removed in vacuo to give a yellow oil which was then chromatographed on silica gel eluting with 3:1 hexane:EtOAc to give 1.1g of **4i** (75%) as a viscous, pale yellow oil which crystallized on standing. m.p. 47-48 °C. $[\alpha]^{23}_D$ = +22° (CH_3CN, c 0.01g ml^{-1}). Chiral capillary electrophoresis determination[12] : ee >95%. ^1H NMR (270 MHz, $CDCl_3$): δ 7.46-7.20 (m, 5H), 4.35-4.14 (m, 2H), 4.03 (d, *J*=14.6 Hz, 1H), 3.53 (m, 1H), 3.25 (d, *J*=14.6 Hz, 1H), 3.24-3.10 (m, 2H), 3.00 (m, 1H), 2.23-1.70 (m, 5H). ^{13}C NMR (68 MHz, $CDCl_3$): δ 178.3 (s), 138.8 (s), 128.7 (d), 128.0 (d), 126.8 (d), 66.1 (d), 64.6 (t), 58.5 (t), 53.0 (t), 31.5 (t), 30.9 (t), 23.0 (t). Anal. Calc'd for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37; S, 13.01. Found: C, 68.30; H, 7.42; N, 11.51; S, 12.94.
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(12) **Chiral Capillary Electrophoresis Method.** A Biorad Biofocus 3000 CE System was used with a 36cm x 50μm capillary column at 20°C. The run buffer was 100mM γ cyclodextrin in 100mM pH 2.5 phosphate buffer, utilizing UV detection at 200nm. See also Figure 1.
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