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A New Route to 2-Substituted Δ^2-Thiazolines: Stille Cross-Couplings of 2-Bromo-Δ^2-Thiazolines

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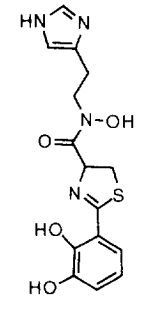
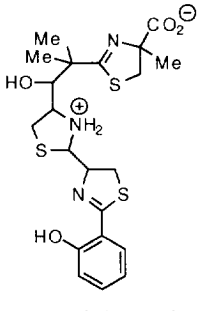
Abstract: 2-Substituted thiazolines are obtained by a Stille cross-coupling of 2-bromothiazolines and various tributylstannyl compounds. Copyright © 1996 Elsevier Science Ltd

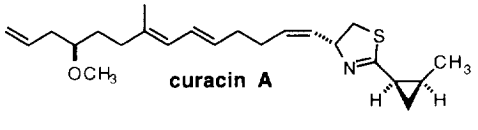
The thiazoline nucleus is present in several natural products, such as anguibactin[1] and yersiniabactin,[2] and is a common pharmacophore.[3] The recent isolation of the potent antimitotic agent curacin A[4] prompted us to study the possibility of obtaining 2-substituted thiazolines via Stille cross-couplings[5] of 2-trifloxy- or bromothiazolines with various stannanes. Stille couplings typically proceed under mild, neutral conditions, hence they could provide flexibility in syntheses of thiazoline containing natural products and structural derivatives. A previous attempt at palladium mediated coupling of 2-trimethylstannylthiazoline led only to decomposition of substrate.[6] Herein we describe an extension of the Stille coupling to the synthesis of 2-substituted-Δ^2-thiazolines employing the bromothiazoline **3** and proceeding under mild conditions. Thiazolines have typically been synthesized by cyclodehydration of amide precursors but, due to the harsh conditions employed or the sensitivity of the substrates, low yields of cyclized products are frequently obtained.[7]



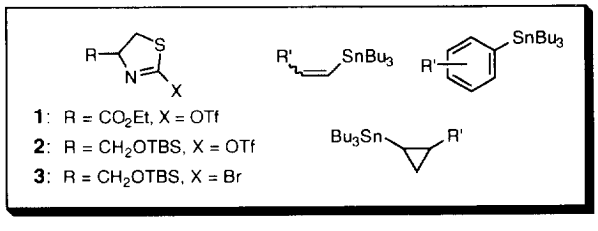
anguibactin



yersiniabactin



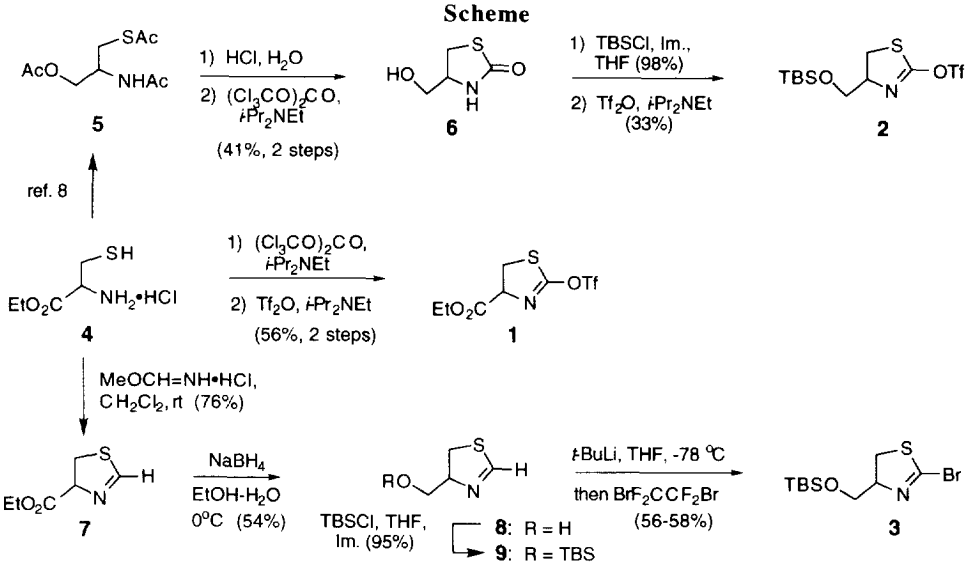
curacin A



Our initial efforts towards a cross-coupling route to thiazolines focused on the thiazoline triflates **1** and **2**. Triflate **1** was prepared in two steps from **4** by standard procedures (Scheme). The synthesis of triflate **2** began with the known triacetate **5** prepared from **4**.[8] Hydrolysis of triacetate **5** and direct treatment of the resulting crude aminohydroxythiol with triphosgene provided thiazolidinone **6** in 41% overall yield for the two steps.[9]

Notably, none of the corresponding oxazolidinone was formed in this two step sequence. Silylation of thiazolidinone **6** followed by treatment with triflic anhydride provided triflate **2**. These unoptimized routes provided sufficient quantities of triflates **1** and **2** to allow the study of their reactivities in various coupling reactions.[10] Several reaction conditions were explored for coupling to these triflates, including various cross-coupling procedures and cuprate additions, but most resulted in recovered starting material or decomposition of the triflates. Some success was obtained in the Stille coupling of triflate **1** and vinyltributylstannane employing $Pd_2(dba)_3$, trisfurylphosphine (tfp) (1:2, Pd:tfp), and 10 mol % copper (I) iodide as co-catalyst in *N*-methylpyrrolidinone as solvent.[11] However, the vinyl adduct was obtained in only low yield (~ 23%) after prolonged heating at 100° C accompanied by extensive decomposition of the substrate.

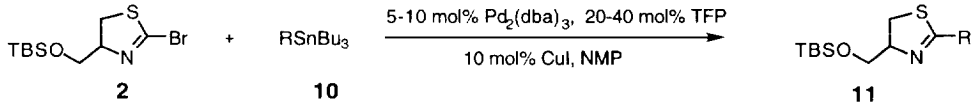
Scheme



In light of the low reactivity of triflates **1** and **2** in various coupling reactions, we turned our attention to the bromothiazoline **3**. This coupling substrate was prepared by metallation and bromination of the known thiazoline **9**[6] which was prepared by a modified literature procedure (Scheme).[12] The major byproducts of the metallation/bromination sequence are compounds derived from *t*-butyl addition to the thiazoline or the known ring opened isocyanide thiolate.[6, 13]

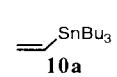
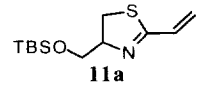
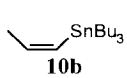
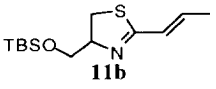
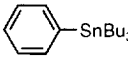
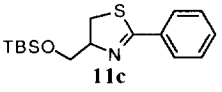
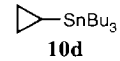
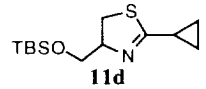
A series of reaction conditions were studied for the coupling of 2-bromothiazoline **3** and vinyltributylstannane and the best yields and reaction rates were obtained employing the conditions described above.[11] Separation of the products from tributylytin byproducts was simplified by use of the workup protocol (DBU/I_2) described by Curran and Chang.[14] Using these conditions, variable yields of the unstable vinyl adduct **11a** were obtained at ambient temperature depending on reaction time (Table).[15] *Cis*-propenyltributylstannane also coupled to the bromothiazoline at ambient temperature, however isomerization occurred to give a separable mixture of the *trans*-propenyl adduct **11b** and the corresponding *cis*-isomer (~4.5:1; *trans*/*cis*). Heating was required in the coupling with phenyltributylstannane but gave good yields of the 2-phenyl thiazoline **11c**.[16] Importantly, use of cyclopropyltributylstannane indeed provided the cyclopropyl adduct **11d**. However, this adduct was accompanied (~4:1) by an inseparable by-product which has tentatively been assigned a pyrroline

structure derived from a presumed iminocyclopropane rearrangement.[17] Less than 5% of dehalogenated starting material or butyl adduct was obtained in the reaction with cyclopropylstannane in contrast to previous reports.[18] Thus, as previously observed, copper (I) provides increased rates and high selectivity in the Sn → Cu transmetallation step leading to the cyclopropyl thiazoline **11d**.[11b]



2 **10** **11**

Table. Preparation of 2-Substituted Thiazolines **11** by Pd(0)/Cu(I) Co-catalysis.

entry	stannane	reaction conditions	product	% yield
1	 **10a**	25 °C, 128 h	 **11a**	38-64
2	 **10b**	25 °C, 144 h	 **11b**	41-44[a]
3	 **10c**	60°C, 132 h	 **11c**	74-76
4	 **10d**	80 °C, 8.5 h	 **11d**	37-49[b]

[a]Yield refers to the pure, isolated *trans*-olefin isomer. [b]Obtained as an inseparable ~4:1 mixture of cyclopropyl adduct and a presumed pyrroline (see text).

In summary, a new route to various 2-substituted thiazolines has been developed involving transition metal catalyzed cross-couplings between bromothiazolines and various tributylstannanes. This method provides a potentially general and mild route to thiazoline containing natural products and derivatives.

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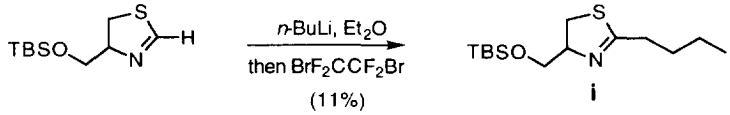
REFERENCES AND NOTES

1. Jalal, M. A.; Hossain, M. B.; Helm, D. V. D..; Snaders-Loehr, J.; Actis, L. A.; Crosa, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 292-296.
2. Drechsel, H.; Stephan, H.; Lotz, R.; Haag, H.; Zahner, H.; Hantke, K.; Jung, G. *Liebigs Ann.* **1995**, 1727-1733.
3. a) Hoveyda, H. R.; Karunaratne, V.; Orvig, C. *Tetrahedron* **1992**, *48*, 5219. b) Ragab, F. A.; Hussein, M. M.; Hanna, M. M.; Hassan, G. S.; Kewawy, S. A. *Pharmazie* **1993**, *48*, 808.
4. a) Isolation and two-dimensional structure: Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243-1245. b) Relative and absolute configuration determination: Nagle, D. G.; Geralds, R. S.; Yoo, H.-D.; Gerwick, W. H.; Kim, T.-S.; Nambu, M.; White, J. D. *Tetrahedron Lett.* **1995**, *36*, 1189-1192. Total syntheses: c) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612-5614. d) Hoemann, M. Z.; Agrios, K. A.; Aube, J. *Tetrahedron Lett.* **1996**, *37*, 953-956.
5. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.
6. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Heterocycles* **1993**, *36*, 473-484.
7. For example, in the two reported syntheses of curacin A (ref. 4c-d), 30 (two steps) and 50% yields

respectively, were obtained in the cyclodehydration step leading to the thiazoline. For some recently described cyclodehydration routes to thiazolines, see: a) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353-9372. b) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397-5400. c) Lafargue, P.; Guenot, P.; Lellouche, J.-P. *Synlett* **1995**, 171-172. d) Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett* **1995**, 417-419. e) Wipf, P,; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395-6398.

8. Ball, D. H.; Williams, J. M.; Long, L., Jr. *J. Org. Chem.* **1963**, *28*, 1589-1593.
9. All new compounds exhibited spectral data consistent with their assigned structures.
10. Evidence for O-triflation rather than N-triflation (*cf.* ref. 19) in the case of triflate **1** is provided by the fact that coupling product, albeit in low yield (23%), was indeed obtained. A trend was observed in the ^{13}C chemical shifts of the thiazolidinone carbonyl carbons (δ 174-175) and the enoltriflate carbon (δ 167-170) for a series of compounds which suggests O-triflation for triflate **2** since triflate **1** led to coupling product. These compounds and various derivatives did not provide crystals suitable for x-ray analysis.
11. For leading references, see: a) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434-5444. b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905-5911.
12. ***Synthesis of Thiazoline Bromide 3:*** Thiazoline **9** (925 mg, 4.0 mmol) was azeotropically dried with xylenes, dissolved in 40 mL of dry Et_2O and cooled to -78°C under N_2. To this solution was added 2.8 mL of *t*-BuLi (1.5 M in pentane, 1.05 equiv) over a period of 10 min down the side of the reaction flask. The resulting yellow solution was stirred at -78°C for 1hr then 478 μL of 1,2 dibromotetrafluoroethane (4.0 mmol, 1.0 equiv) was added. The reaction mixture was allowed to warm slowly to ambient temperature over 2 h and then quenched with 5-10 drops of pH 7 buffer. The mixture was dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane → 10% ethyl acetate /hexane by 2-3% increments) gave 716 mg (58%) of the bromothiazoline **3** as a light yellow oil. R_f 0.56 (20% ethyl acetate/hexane); ^1H NMR (200MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 3.50 (app d, *J*=7.64 Hz, 2H), 3.68 (d, *J*=10.2, 6.9 Hz, 1H), 3.86 (dd, *J*=10.25, 6.96 Hz, 1H), 4.45-4.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.4, 18.2, 25.8, 38.7, 63.5, 77.6, 140.6; IR (thin film): 2955, 2856, 1590, 1114 cm^{-1}; FAB HRMS calcd. for $C_{10}H_{20}BrNOSSi$ (M+H) 310.0297; Found 310.0294.
13. Interestingly, when *n*-BuLi was being studied as a base for the metallation/bromination sequence, the 2-butylthiazoline **i** was obtained as a byproduct along with the desired bromothiazoline.



i

14. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140-3157. The authors thank Professor P. Wipf (Univ. of Pittsburgh) for bringing this procedure to our attention.
15. Apparently, the vinyl adduct **11a** is unstable to the reaction conditions since lower yields were obtained with longer reaction times. Purified samples of this compound stored frozen in benzene at -18°C underwent extensive decomposition in a period of several days.
16. ***Representative Procedure for Stille Cross-Couplings as Described for Phenyl Thiazoline 8c:*** The thiazoline bromide **3** (99.6 mg, 0.321 mmol) was azeotropically dried with xylenes and dissolved in 1 mL of degassed (freeze thaw method) NMP. Tris-2-furyl phosphine (14.9 mg, 0.064 mmol), $Pd_2(dba)_3$ (14.7 mg, .016 mmol) and CuI (6.1 mg, .032 mmol) were added followed by introduction of 105 μL neat phenyltributylstannane (0.321 mmol, 1.0 equiv). The mixture was heated to 60 °C for 132 h then cooled, diluted with Et_2O and stirred while DBU (53 μL, 1.1 equiv, 0.353 mmol) and a 0.1 M solution of I_2 in Et_2O was added until the reddish-brown color persisted. This crude mixture was quickly filtered through SiO_2 with Et_2O, concentrated to a yellow-orange oil, and then purified by flash chromatography (hexane → 10% ethyl acetate/hexane by 2-3% increments) to give 74.6 mg (76%) of the phenyl adduct **11c** as a pale yellow oil: R_f 0.49 (12% ethyl acetate/hexane by 2% increments); ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s,9H), 3.42 (dd, *J* = 7.3, 11.1 Hz, 1H), 3.48 (dd, *J* = 8.0, 11.9 Hz, 1H), 3.67 (dd, *J* = 8.0, 10.0 Hz, 1H), 3.99 (dd, *J* = 4.3, 10.0 Hz, 1H), 7.33-7.46 (m, 3H), 7.77-7.85 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ -5.3, 18.3, 25.8, 35.4, 63.8, 79.6, 128.4, 130.9, 133.6, 168.5; IR (thin film) 2955, 1603, 1578, 1101 cm^{-1}; FAB HRMS (M+H) calcd. for $C_{16}H_{25}NOSi$ 308.1504; Found 308.1511; Anal. calcd. for $C_{16}H_{25}NOSSi$: C, 62.49; H 8.19; Found: C, 62.28; H, 8.17.
17. a) Stevens, R. V.; Fitzpatrick, J. M.; Kaplan, M.; Zimmerman, R. L. *J. Chem. Soc., Chem. Commun.* **1971**, 857-858. b) Boeckman, R. K., Jr.; Jackson, P. F.; Sabatucci, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 2191-2192.
18. For previous reports of palladium mediated couplings employing cyclopropylstannanes, see: a) Peters, D.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocyclic Chemistry* **1991**, *28*, 1629-1631. b) Turner, W. R.; Suto, M. J. *Tetrahedron Lett.* **1993**, *34*, 281-284.
19. Meyers, A. I.; Novachek, K. A. *Tetrahedron Lett.* **1996**, *37*, 1747.

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