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Deoxo-Fluor-mediated cyclodehydration of β-hydroxy thioamides to the corresponding thiazolines

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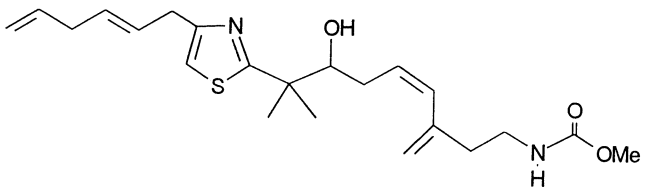
Abstract—An efficient method for thiazoline synthesis via β-hydroxy thioamide cyclodehydration using Deoxo-Fluor reagent is described.

In the past two decades a great number of 2,4-disubstituted thiazoline- and thiazole-containing rings have been isolated from natural sources. Many of these compounds, such as Curacin A,[1] Thiangazole,[2] Mirabazole B,[3] Mycothiazole,[4] Patelazoles A–C[5] and Pateamine,[6] have attracted considerable interest because of their biological activity. Different methodologies have been reported in the literature for the construction of the thiazoline ring. $TiCl_4$-mediated cyclodehydration of cysteine amide derivatives,[7] and the cyclodehydration of β-hydroxy thioamide derivatives using Burgess reagent,[8] or $SOCl_2$,[9] or Mitsunobu conditions[10] are perhaps the most used. However, high yields are not always obtained using these sequences and, thus, the search for new methodologies aiming at the synthesis of the thiazoline ring is justified.

As part of our work in the search for compounds with anthelmintic activity,[11] our group has been very interested in the synthesis and biological evaluation of natural products containing thiazole rings. We have selected Mycothiazole (Fig. 1) as a target, and we have obtained promising preliminary results in developing synthetic methodologies toward precursors of new analogs of this natural product. We explored the synthesis of 2,4-disubstituted thiazoline rings using two methodologies,[12] i.e. the cyclodehydration of cysteine amides with $TiCl_4$ and the cyclodehydration of β-hydroxy thioamides with PEG-Burgess reagent.[13]



Mycothiazole (1)

Figure 1.

In a previous study, Lellouche and co-workers obtained 2,4-disubstituted oxazolines[14] and thiazolines[15] from the corresponding β-hydroxy amides and thioamides, using (diethyl amino)sulfur trifluoride (DAST). Recently, the use of this reagent in the synthesis of complex natural products like Hennoxazole A,[16] Trunkamide A,[17] and Phorborxazole A[18] has been reported.

Prozonic and co-workers reported that [bis(2-metoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor) reagent is closely related to DAST,[19] but is more thermally stable than DAST. Wipf, Williams and co-workers extended the DAST cyclodehydration protocol to this new reagent to obtain oxazolines. They concluded that Deoxo-Fluor is able to convert β-hydroxy amides into oxazolines with high yields under mild conditions.[20]

In the present work, we explored the synthesis of 2,4-disubstituted thiazoline by cyclodehydration of β-hydroxy thioamide using Deoxo-Fluor reagent.

The β-hydroxy thioamides shown in Table 1 were obtained using Lawesson's procedure upon the corre-

Keywords: thiazoline; Deoxo-Fluor; cyclodehydration; β-hydroxy thioamide.

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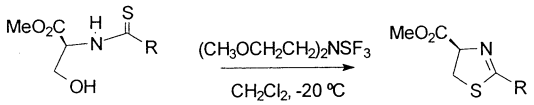
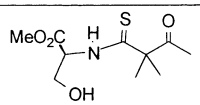
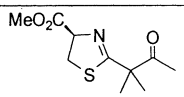
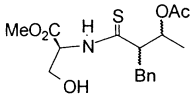
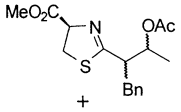
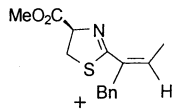
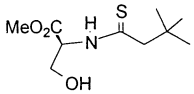
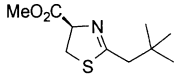
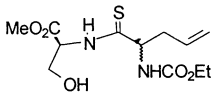
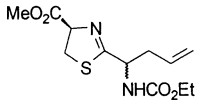
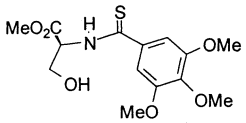
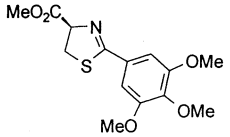
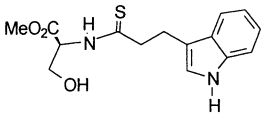
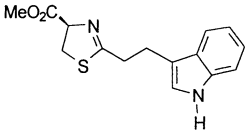
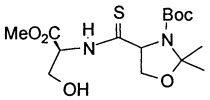
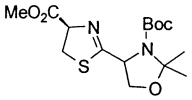
Table 1. Conversion of β-hydroxy thioamides to thiazolines[a]



Entry	Reagent	Product	Yield (%)[b] Deoxo-Fluor/ Burgess	Reaction time (h) Deoxo-Fluor/ Burgess
1			80/64	1/3
2		 +  + Reagent	90[c]/0[c] 2/40 0/30	0.5/8
3			85[d]/71	2/2
4			85[c]/nt	0.5/nt
5			93/nt	1/nt
6			70/nt	1/nt
7			97/nt	0.5/nt

a The typical procedure was used in all cases. b Yields are for purified compounds. All new compounds were fully characterized by NMR, MS and Elem. *Anal.* c The diastereomeric mixture of thioamides was used as starting material. d 96% ee determined by chiral GLC, on a 2,3-di-O-ethyl-6-O-TBDMS-β-cyclodextrin column.
nt not tested

sponding amides.[21] These compounds were treated with a slight excess (1.1 equiv.) of Deoxo-Fluor at –20°C in CH_2Cl_2 to obtain the thiazolines.[22] The reactions took place rapidly and cleanly within 30–120 min.

In entries 1–3, the yields were higher and the reaction times were shorter than those obtained using PEG-Burgess reagent.[23]

In all cases tried, Deoxo-Fluor was an effective cyclization reagent with very good yields (70–97%).

For entry 3, Deoxo-Fluor afforded the expected thiazoline in 85% yield and 96% ee, determined using chiral GLC. For entry 2, the desired thiazoline was obtained in 90% yield together with 2% of the product resulting from acetic acid elimination from the obtained thiazoline. Conversely, the conditions using PEG-Burgess reagent promoted complete acetic acid elimination of the thiazoline and an important percentage of the starting material was recovered. This result constituted the most important difference between the two methodologies studied by us.

It is possible to dehydrogenate the thiazoline ring to thiazole using different methodologies reported in the literature.[24] For entry 2, we proved the one-pot methodology described by Williams and co-workers for oxazoline oxidation,[20] using $BrCCl_3$ and DBU. The thiazole was obtained from the corresponding thioamide in 75% yield.

Even though more examples are needed to extend the methodology, it is noteworthy that the procedure is compatible with various structural patterns. Cyclization occurs without any formation of the corresponding dehydrothioamide ester.[14] Sterically hindered groups (see entries 1, 5 and 7), ethyl and *tert*-butylcarbamate (see entries 4 and 7), acetyl alcohol (entry 2) and acetonide (entry 7) groups are well tolerated.

In summary, we described a novel, convenient, and high-yielding methodology to obtain thiazolines using Deoxo-Fluor reagent.

Acknowledgements

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22. **Typical procedure** (Table 1, entry 3): to a stirred solution of methyl (2*S*)-2-[(3′,3′-dimethylthiobutanoyl)amino]propanoate (50 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) cooled to −20°C (bath temperature) was added dropwise Deoxo-Fluor reagent (43 μL, 0.23 mmol). The mixture was stirred until monitoring of the reaction by TLC indicated that all the starting material had been consumed (ca. 2 h). The mixture was quenched with saturated aqueous sodium bicarbonate at −20°C. After warming to room temperature, the mixture was further diluted with saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash-column chromatography (silica gel, AcOEt/*n*-hexane 1:4) afforded the desired thiazoline (38 mg, 85%) as an oil; $R_f = 0.54$ (silica gel, EtOAc/*n*-hexane, 1:2); IR (film): ν_{max} 1748, 1616, 1119 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H), 2.50 (s, 2H), 3.52 (dd, $J = 11.1$, 9.6 Hz, 1H), 3.60 (dd, $J = 11.1$, 8.4 Hz, 1H), 3.81 (s, 3H), 5.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.16, 31.80, 36.57, 48.16, 52.99, 78.21, 171.85, 172.93; EIMS (70 eV) *m*/*z* (%): 200 ($M^+ - CH_3$, 8.9), 159 (74.6), 100 (100.0), 86 (40.0), 71 (16.4). Anal. calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51; S, 14.89. Found: C, 56.45; H, 8.36; N, 6.84; S, 14.87%.
23. **Typical procedure** (Table 1, entry 3): To a stirred solution of thioamide (350 mg, 1.5 mmol) in dry THF (4 mL) was added a solution of PEG-Burgess reagent (3.1 g, 3.2 mmol) in dry dioxane (4 mL). The reaction mixture was heated to 85°C. The solvent was removed in vacuo and the residue partitioned between Et_2O and aqueous $NaHCO_3$. The aqueous layer was extracted five times

with Et_2O and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (silica gel, AcOEt/*n*-hexane 1:2) afforded 230 mg (71%) of the desired thiazoline.

24. (a) For activated MnO_2, see: North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267–8290; (b) For $BrCCl_3$ oxidation, see: Williams, D. R.; Lowder, P. D.; Gu, Y. D.; Brooks, D. A. *Tetrahedron Lett*. **1997**, *38*, 331–334; (c) For CuBr, $Cu(OAc)_2$, see: Meyers, A. I.; Tavares, F. X. *J. Org. Chem*. **1996**, *61*, 8207–8215.