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USE OF DEOXO-FLUOR FOR DOUBLE CYCLIZATION TO BIS-THIAZOLINES. LIMITATIONS OF THIS AGENT FOR THE SYNTHESIS OF OXAZOLINES

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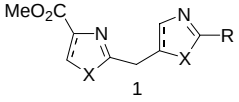
Abstract – Double cyclizations to bis-thiazolines have been performed using the Deoxo-Fluor cyclodehydration agent. Some limitations of the use of Deoxo-Fluor for the synthesis of oxazolines are described.

Bis-thiazoles, bis-oxazoles and oxazole-thiazole systems are found in numerous interesting biologically active natural products such: cystothiazoles, myxothiazoles, diazonamide and bengazoles.[1]
Enantiomerically pure bis-oxazolines are also extensively used as chiral auxiliaries and as ligands in asymmetric synthesis.[2]

There have been many efforts,[3] devoted to the preparation of [2,4'] bisthiazoles or [2,4'] bisoxazoles and to the synthesis of two oxazolines separated by a methylene backbone. However, data for the synthesis of [2,5'] bisthiazoles or bisoxazoles are less frequent reported in the literature.[4]

As part of a search for clinically effective compounds with anthelmintic or cytotoxic activity,[5] we are interesting in the synthesis of [2,5'] bisheterocycles of type (**1**), Figure **I**, where two heterocycles are connected by a single methylene unit.



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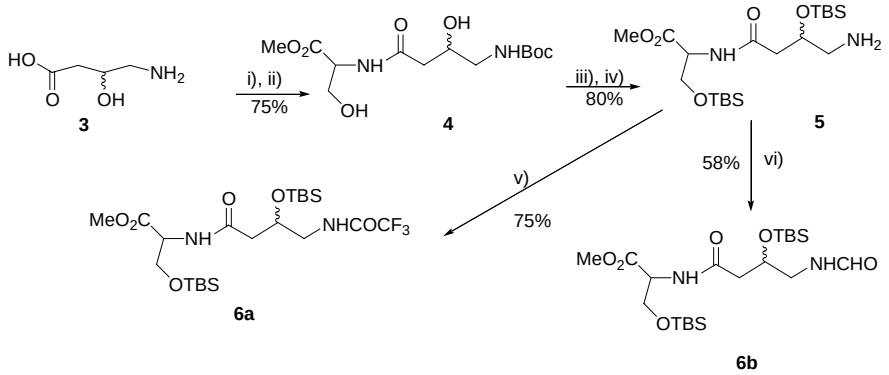
X= O or S
R = H or CF_3

Figure I

A variety of methods have been reported for the synthesis of oxazolines or thiazolines, and the cyclodehydration protocol is perhaps the most popular.[6] Bis(2-methoxyethyl)aminosulfurtrifluoride (Deoxo-Fluor) has been used as the cyclodehydration agent for β–hydroxy amides or -thioamides in the synthesis of oxazolines and thiazolines, respectively.[5f, 6j] Recently, this reagent has been used in the preparation of the complex natural product (-)-hennoxazole A,[7a] in the assembly of ligands for catalytic asymmetric synthesis,[7b] and in the synthesis of analogues of curacin A.[7c]

In the present study, we explore the scope of Deoxo-Fluor to perform double cyclizations in the synthesis of bis-heterocyclic scaffolds.

First, we obtained the amides (**6a**) and (**6b**) as shown in Scheme **I**. After protection of 4-amino-3-hydroxybutyric with a Boc group and coupling to serine methyl ester, the resulting amide (**4**) was deprotected under TFA conditions. The hydroxy groups of this compound were silylated with TBS-OTf, and the amine group was acylated with trifluoroacetic anhydride or the formic-acetic acid mixed anhydride to obtain products (**6a**) and (**6b**).



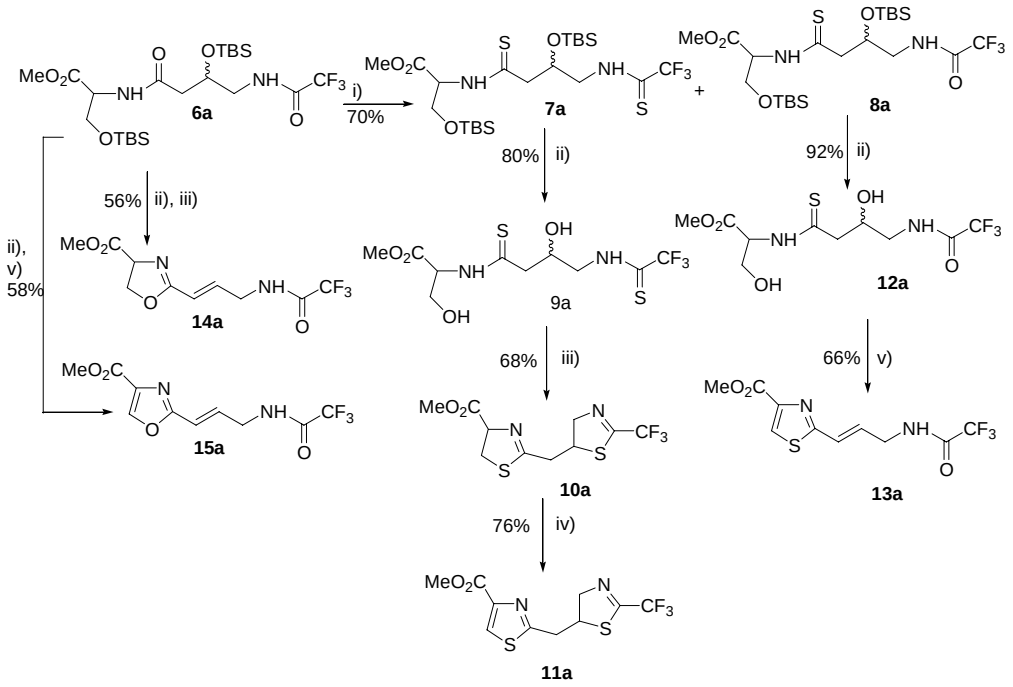
i) Boc_2O, Et_3N, Dioxane/H_2O, rt; ii) (*S*) Ser-OMe.HCl, CH_2Cl_2, Et_3N, DMPA, DCC, rt; iii) TFA, CH_2Cl_2, 0 ºC, 2 h; iv) TBS-OTf, CH_2Cl_2, Et_3N, 0 ºC, 5 h; v) $(CF_3CO)_2O$, Et_3N, DMPA, CH_2Cl_2, rt, 5 h; Formic-Acetic Acid mixed anhydride, Et_3N, CH_2Cl_2, rt, 0.5 h.

Scheme I

The linear precursors (**6a**) and (**6b**) were used as intermediates for further analog preparations and subjected to the reaction conditions as outlined in Scheme **II** and Scheme **III**, respectively. A solution of Lawesson reagent in benzene was used to obtain the desired thioamides.[5d] Under these conditions, a mixture of **7a** and **8a** (80:20) was obtained from **6a**. Flash column chromatography has been used to obtain the purified products (**7a**) and (**8a**). After deprotection of **7a**, **9a** was subjected to cyclodehydration with Deoxo-Fluor reagent to obtain the bis-thiazoline (**10a**).[8]

In order to perform the subsequent oxidation of this bis-thiazoline to the aromatic heterocycles, we used 2.2 eq. of $BrCCl_3$ in the presence of DBU. Under these conditions the corresponding bis-thiazoles were not formed. In contrast, the thiazole-thiazoline (**11a**) was obtained in good yield according to the protocol of Williams and co-workers.[6j] As suggested in the literature report, a C-4-acyl substituted thiazoline or

oxazoline was found to be necessary to allow the oxidation reaction to the corresponding thiazoles or oxazoles to proceed under the $BrCCl_3$/DBU conditions.



i) Lawesson reagent, C_6H_6, reflux, 5 h, Flash column chromatography; ii) TBAF, THF; iii) Deoxo-Fluor, CH_2Cl_2, -20 ºC, 2 h; iv) $CBrCl_3$, DBU, CH_2Cl_2, 2 h; v) Deoxo-Fluor, CH_2Cl_2, -20 ºC, 1 h, $CBrCl_3$, DBU, 0 ºC, 3 h.

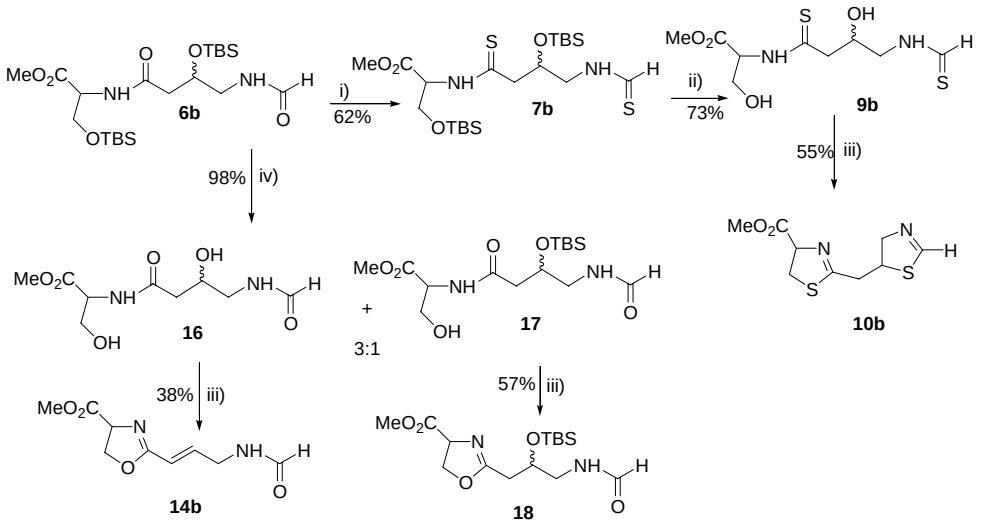
Scheme II

Product (**12a**) was obtained from **8a** using TBAF. It was not possible to convert **12a** to the corresponding mixed thiazole-oxazole bis-heterocycle using Deoxo-Fluor and $BrCCl_3$. Rather, the elimination product (**13a**) (as an (*E*)-alkene), was obtained under these conditions.

Starting from intermediate (**6a**), deprotection and analogous cyclodehydration or cyclodehydration-oxidation conditions afforded the (*E*)-alkenes (**14a**) and (**15a**).

Using a similar strategy, the conversions shown in Scheme **III** were realized. The formamide group proved to be labile toward nucleophilic attack and limited the range of transformations that could be accomplished. When **6b** was used as starting material, the reaction with Lawesson reagent only provided the product (**7b**). Subsequently , deprotection and cyclodehydration afforded the bis-thiazoline (**10b**).

In order to obtain the corresponding oxazolines analogs, we studied a range of conditions for cleavage of the OTBS group in **6b**: TBAF in THF, HF-pyridine in THF, HF in CH_3CN, Dowex 50W-X8 in MeOH and AcOH:THF:H_2O (2:1:1). The best results were obtained using the last set of conditions which provided a mixture of **16** and **17** (3:1). After chromatographic separation the purified products (**16** and **17**) were obtained in 74 and 24% yield, respectively.



i) Lawesson reagent, C_6H_6, reflux, 1 h; ii) TBAF,THF,rt, 3 h; iii) Deoxo-Fluor, THF:CH_2Cl_2 (1:1), -20 ºC, 1 h; iv) AcOH: THF: H_2O, rt, 4 h, chromatographic separation.

Scheme III

As we have observed for R = CF_3 (products **12a** and **6a**), it was not possible to obtain the corresponding bis-oxazoline when R = H. Starting from **16**, cyclodehydration conditions using Deoxo-Fluor afforded the (*E*)-alkene (**14b**). In contrast, when the secondary alcohol was protected (**17**), the elimination did not occur and the oxazoline (**18**) was obtained in 57% yield.

Lellouche and co-workers have reported an attempted cyclization of Boc-Phe-Thr-OMe with DAST,[9] which resulted only in elimination to give a dehydropeptide. In addition, in a recent publication, Shioiri *et al*.[10] reported that Deoxo-Fluor/Et_3N and DAST/Et_3N mediated a stereospecific dehydrative elimination of *N*-acylthreonine esters.

The stereospecific formations of (*E*)-alkenes (**13a**, **14a**, **14b** and **15a**) using Deoxo-Fluor,[11] are in agreement with an E_2-elimination process as described by Shanzer *et al*.,[12] under DAST/pyridine conditions.

In conclusion, several oxazoline, oxazole, thiazoline, thiazole and bis-thiazoline or thiazoline-thiazole scaffolds have been prepared. Deoxo-Fluor can be used to obtain [2,5'] bisthiazolines, but this reagent failed in the [2,5'] bisoxazoline system.

Our results also indicate a limitation of the use of Deoxo-Fluor for obtaining 5-substituted oxazolines. The presence of a secondary hydroxy group and the relative low nucleophilicity of the amido group are very important factors that can lead to a failure of the cyclodehydration reaction and a preference for E_2-elimination (as shown in the formation of **13a**, **14a** and **14b**). In contrast, when the amido function is replaced by a more nucleophilic thioamido group (such as shown for **9a** and **9b**), Deoxo-Fluor is suitable

for performing the cyclodehydration reaction leading to the corresponding bisthiazolines (**10a**) or (**10b**), respectively.

The study of alternative cyclization strategies for the preparation of a series of [2,5'] bis-oxazolines is currently in progress in our laboratory.

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8. Typical procedure: 2-(2-Trifluoromethyl-4,5-dihydro-thiazol-5-ylmethyl)-4,5-dihydrothiazole-4-carboxylic acid methyl ester (**10a**): To a stirred solution of **9a** (21 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) cooled to –20 ºC (bath temperature) was added dropwise Deoxo–Fluor reagent (22 μL, 0.12 mmol). The reaction mixture was stirred until monitoring by TLC indicated that all starting material had been consumed. The mixture was quenched with saturated aqueous sodium bicarbonate at –20 ºC. After warming to rt, 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 (SiO_2, AcOEt/*n*-hexane, 3:2) afforded the bis-thiazoline (**10a**) (13 mg, 68%) as an oil; R_f = 0.56 (AcOEt/*n*-hexane, 3:2); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.87 (m, 2H), 3.57 (dd, *J*= 9.6, 11.2 Hz, 1H), 3.65 (dd, *J*= 8.2, 11.2 Hz, 1H), 3.83 (s, 3H); 4.38 (m, 2H); 4.53 (m, 1H); 5.13 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 36.4, 40.6, 50.2, 53.2, 69.4, 78.1, 118.8 (q, $J_{C\text{-}F}$= 274 Hz), 160.4, 171.1, 171.3. EIMS (70 eV), *m/z* (%) 312 (M^+, 4.07), 295 ([M-Me]$^+$, 1.3), 253 ([M-CO_2Me]$^+$, 9.1), 159 (100.0), 154 (13.1), 100 (88.0), 86 (16.3).
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