Regio- and Stereoselective Synthesis of α-Chiral 2-Substituted 4-Bromothiazoles from 2,4-Dibromothiazole by Bromine–Magnesium Exchange. Building Blocks for the Synthesis of Thiazolyl Peptides and Dolabellin

Alexandra Spieß, Golo Heckmann, Thorsten Bach*

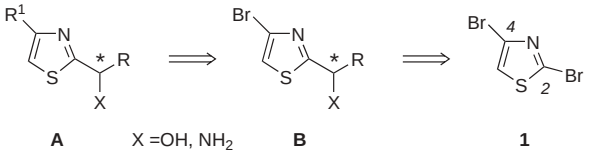
Lehrstuhl für Organische Chemie I, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany
Fax +49(89)28913315; E-mail: thorsten.bach@ch.tum.de

Received 9 September 2003

Abstract: Fragment **6** of thiazolyl peptide GE 2270 D2 and fragment **11** of dolabellin were synthesized stereoselectively from 2,4-dibromothiazole (**1**) in three (**6**, 44% overall yield) and five synthetic steps (**11**, 63% overall yield). Key to the success of the strategy was a bromine-magnesium exchange, which proceeds with excellent regio- and chemoselectivity at carbon atom C-2 of **1**.

Key words: asymmetric synthesis, magnesium, metalations, natural products, thiazoles

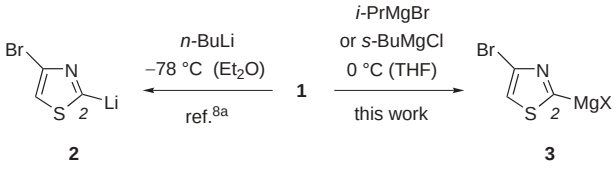
2,4-Disubstituted thiazoles are important subunits in a number of structurally varied natural products.[1] Besides the classic Hantzsch synthesis[2] several new methods for their preparation have been devised in recent years.[3] Research in our group has focussed on easily accessible 2,4-dibromothiazole[4] (**1**, Scheme 1) as a versatile building block, which can be used in sequential regioselective cross-coupling reactions.[5] Unfortunately, this approach has so far not been applicable[6] to the construction of 4-bromothiazoles **B**, which bear a stereogenic center at the α-carbon atom of the 2-substituent and are potential precursors for the synthesis of chiral thiazoles **A**.



Scheme 1 Retrosynthetic strategy for the preparation of 2,4-disubstituted thiazoles with a stereogenic center at the α-carbon atom of the 2-substituent

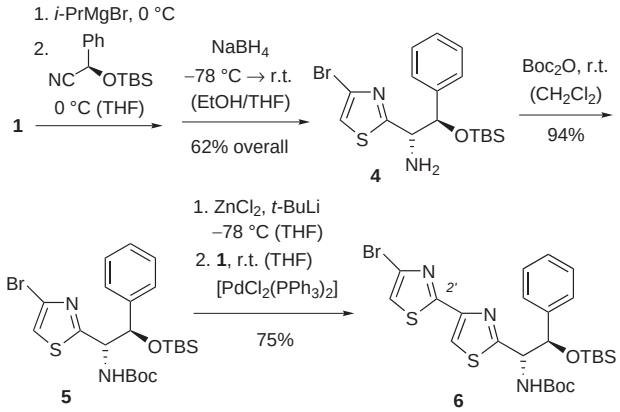
As a potential alternative approach to compounds **B** we envisaged an umpolung at carbon atom C-2 of compound **1** via bromine–metal exchange followed by an electrophilic quench. In this communication, we report the application of this strategy to the synthesis of two natural product fragments.

In order to access both amines of type **A** (X = NH_2) and alcohols of type **A** (X = OH) we planned to treat a 2-metalated 4-bromothiazole with nitriles. The intermediate imines can be reduced directly to amines or they can be hydrolyzed to the corresponding ketones, which are further reduced to alcohols. Since aryl lithium compounds have been reported to undergo double addition to activated nitriles[7] and since 2-thiazolyl lithium reagents proved to be unstable at Θ≥0 °C we did not employ the known[8] regioselective bromine–lithium exchange **1** → **2** (Scheme 2) to prepare a 2-metalated 4-bromothiazole. Instead, we attempted a regioselective bromine–magnesium exchange according to the protocol by Knochel et al.[9] It turned out that this reaction works well and with perfect regioselectivity to give the desired magnesium reagent **3**. We found the latter compound to be stable even at ambient temperature. It reacted nicely with nitriles at 0 °C to form a single addition product.



Scheme 2 Bromine–metal exchange of compound **1** under different conditions leading to lithium compound **2** and magnesium compound **3**

In a first application, we used intermediate **3** to prepare the enantiomerically pure bithiazole fragment **6** (Scheme 3) related to the thiazolyl peptides GE 2270.[10] The relative configuration of the 1,2-amino alcohol has been presumed to be *threo*.[11]



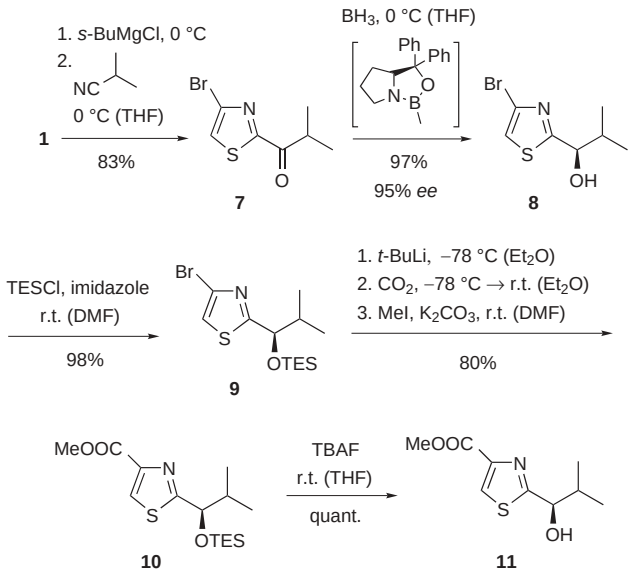
Scheme 3 Stereoselective synthesis of the thiazolyl peptide fragment **6** by nitrile addition/reduction and subsequent cross-coupling

SYNLETT 2004, No. 1, pp 0131–0133
Advanced online publication: 26.11.2003
DOI: 10.1055/s-2003-43361; Art ID: G23503ST.pdf

Following the approach described above, magnesium compound **3** was generated and treated with enantiomerically pure *tert*-butyldimethylsilyl- (TBS-) protected (*R*)-mandelonitrile[12] to yield an intermediate imine, which was directly reduced with $NaBH_4$ in EtOH/THF.[13,14] The reduction proceeded under Felkin–Anh control and the major product (dr = 79:21) was proven to be the desired *O*-TBS-protected *threo*-amino alcohol **4**.[15] The total yield of the sequence nitrile addition/reduction was 73% and the desired compound was isolated in 62% yield after separation from the minor *erythro*-product (11% yield). Subsequent *N*-*tert*-butyloxycarbonyl- (Boc-) protection of the free amino group yielded 4-bromothiazole **5**, which was converted by bromine-metal exchange into the corresponding zinc compound.[5c] Regioselective Negishi cross-coupling with another equivalent of 2,4-dibromothiazole proceeded as expected[5] and generated the desired bithiazole **6**.

The nitrile addition/reduction sequence can also be conducted enantioselectively. This was demonstrated in the synthesis of the α-chiral alcohol **11** whose enantiomer is found as a fragment in the cytotoxic bisthiazole metabolite dolabellin[16] (Scheme 4). The high yield achieved in the formation of ketone **7** underlines the excellent nucleophilicity of magnesium compound **3**. Alternative approaches gave lower chemical yields.[8] The enantioselective ketone reduction was best conducted using Corey's procedure,[17] which delivered the desired alcohol **8**[18] in excellent yield.

After triethylsilyl- (TES-) protection of the free alcohol the 4-lithium thiazole was formed by bromine–lithium exchange and trapped with carbon dioxide. Immediate methylation of the free acid yielded compound **10**, which was deprotected to the desired enantiomerically pure alcohol **11**.[19]



Scheme 4 Enantioselective synthesis of the dolabellin fragment **11** by nitrile addition/reduction and subsequent carboxylation

In summary, we have described a new route to α-chiral 2-substituted 4-bromothiazoles, which can be further used for the synthesis of naturally occurring 2,4-disubstituted thiazole fragments. Due to its brevity and due to the high stereoselectivities, which can be achieved, the method appears to be superior to known procedures. Further synthetic work directed towards the synthesis of α-chiral 2,4-disubstituted thiazoles is in progress and will be reported in due course.

Acknowledgment

This project was supported by the *Fonds der Chemischen Industrie*. The donation of chemicals by OMG AG (Hanau-Wolfgang) and by Wacker-Chemie (München) is gratefully acknowledged.

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(14) **Procedure for the Conversion 1→4:** At 0 °C, 6.60 mL (12.0 mmol) of a 1.80 M *i*-PrMgBr solution in Et_2O was added dropwise to a solution of 2.92 g (12.0 mmol) 2,4-dibromothiazole in 30 mL of THF and the solution was stirred for 15 min at 0 °C. Neat TBS-protected mandelonitrile[12] (2.47 g, 10.0 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C and for another 30 min at r.t. After adding 10 mL of EtOH the reaction mixture was cooled to –78 °C and $NaBH_4$ (0.76 g, 20.0 mmol) was added carefully in small portions. The mixture was stirred for 2 h at –78 °C and – after removing the cooling bath – over night at r.t. The reaction mixture was quenched with 25 mL of sat. aq NH_4Cl solution and diluted with 200 mL Et_2O. The organic layer was washed with 200 mL H_2O and 100 mL brine and it was subsequently dried over Na_2SO_4. GC analysis indicated a facial diastereoselectivity of 79:21. After filtration the solvent was removed and the residue was purified by flash chromatography (pentane/Et_2O: 75:25→50:50). Compound **4** (2.55 g, 6.18 mmol, 62%) was obtained as a yellow liquid. $[\alpha]_D^{20}$ –47.9 (*c* 1.5, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ = –0.21 (s, 3 H), –0.06 (s, 3 H), 0.82 (s, 9 H), 2.02 (br s, 2 H), 4.41 (d, ^3J = 5.9 Hz, 1 H), 5.04 (d, ^3J = 5.9 Hz, 1 H), 7.09 (s, 1 H), 7.19–7.26 (m, 5 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = –5.3, –4.8, 18.0, 25.7, 60.6, 78.2, 117.0, 124.3, 127.0, 128.0, 128.1, 140.1, 173.9. Anal. Calcd for $C_{17}H_{25}BrN_2OSSi$ (413.45): C, 49.39; H, 6.09; N, 6.78. Found: C, 49.45; H, 6.11; N, 6.71. The *erythro*-diastereoisomer (0.47g, 1.13 mmol, 11%) was obtained as a yellow liquid.

(15) The relative configuration was proven by converting the aminoalcohol **4** and its *erythro*-diastereoisomer into the corresponding cyclic *N*-Boc protected *N*,*O*-acetals which were studied independently by ^1H NMR spectroscopy. In addition, a known acetal[11] was prepared by carboxylation of product **5** at carbon atom C-4 (*t*-BuLi, CO_2 in Et_2O), transformation into the corresponding ester (EtI in DMF), TBS-deprotection (TBAF in THF) and acetal formation (2,2-dimethoxypropane, TsOH in CH_2Cl_2). The enantiomeric excess (95% ee) was determined by HPLC analysis of the N-Boc protected product **5** (column: Machery-Nagel, Nucleodex β-OH, 200 × 4.00 mm; eluent: H_2O/MeCN 20:80→0:100 over 30 min; flow rate: 1.0 mL/min).

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(18) Analytical data of compound **8**: $[\alpha]_D^{20}$ +27.5 (*c* 0.80, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ = 0.92 (d, ^3J = 6.8 Hz, 3 H), 1.02 (d, ^3J = 6.8 Hz, 3 H), 2.14–2.30 (m, 1 H), 2.60 (br s, 1 H), 4.80 (d, ^3J = 4.8 Hz, 1 H), 7.19 (s, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 16.2, 18.8, 34.9, 76.4, 116.7, 124.3, 175.6. Anal. Calcd for $C_7H_{10}BrNOS$ (236.13): C, 35.61; H, 4.27; N, 5.93. Found: C, 35.81; H, 4.38; N, 5.87.

(19) Analytical data of compound **11**: $[\alpha]_D^{20}$ +26.9 (*c* 1.15, $CHCl_3$). ^1H NMR (360 MHz, $CDCl_3$): δ = 0.93 (d, ^3J = 6.6 Hz, 3 H), 1.03 (d, ^3J = 7.0 Hz, 3 H), 2.08 (br s, 1 H), 2.20–2.35 (m, 1 H), 3.94 (s, 3 H), 4.82 (d, ^3J = 4.8 Hz, 1 H), 8.16 (s, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$): δ = 16.2, 18.9, 35.0, 52.4, 76.7, 127.6, 146.4, 161.9, 175.7. Anal. Calcd for $C_9H_{13}NO_3S$ (215.27): C, 50.21; H, 6.09; N, 6.51. Found: C, 49.91; H, 6.20; N, 6.29.