2,4,5-Trisubstituted Thiazole Building Blocks by a Novel Multi-Component Reaction

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Abstract: A novel multi-component reaction (MCR) of oxo-components, primary amines, thiocarboxylic acids and 3-bromo-2-isocyanoacrylates yielding 2,4,5-trisubstituted thiazole building blocks is described.

Key words: combinatorial chemistry, multicomponent reaction, one-pot synthesis, 3-substituted 3-bromo-2-isocyanoacrylates, 2,4,5-trisubstituted thiazoles

Thiazole containing peptides are a well known class of compounds with a high structural diversity and a high pharmaceutical potential.[1–7] Thiazole containing peptides, especially those obtained from microbial and marine origins, exhibit important biological effects such as antitumor, antifungal, antibiotic and antiviral activities.[8–11] Examples of some prominent thiazole containing natural products are the lissoclinum class of cyclic peptides,[12,13] such as bistratamide D (**1**),[11] ascidiacylamide (**2**)[14] and the group of thiostrepton antibiotics (**3**).[15] The high pharmaceutical potential of these thiazole-containing natural products led to the development of several multi-step synthetic protocols for their total synthesis[16–18] and to different combinatorial modifications.[19–26]

Dömling et al. developed the first true multicomponent single step reaction towards 2,4-disubstituted thiazoles using β-dimethylamino-isocyanoacrylates.[27] This isocyanide was first described by Schöllkopf et al. It contains a dimethylamino leaving group in the β-position suitable for one-pot, four-component thiazole synthesis.[28]

For further progress in molecular diversity we developed a novel four-component reaction using 3-substituted 3-bromo-2-isocyanoacrylates **4**,[29,30] which allows general access to the class of 2,4,5-trisubstituted thiazoles. In comparison to the formerly used β-dimethylamino-isocyanoacrylates, it is now possible to introduce a new substituent in 5-position of the thiazole system.

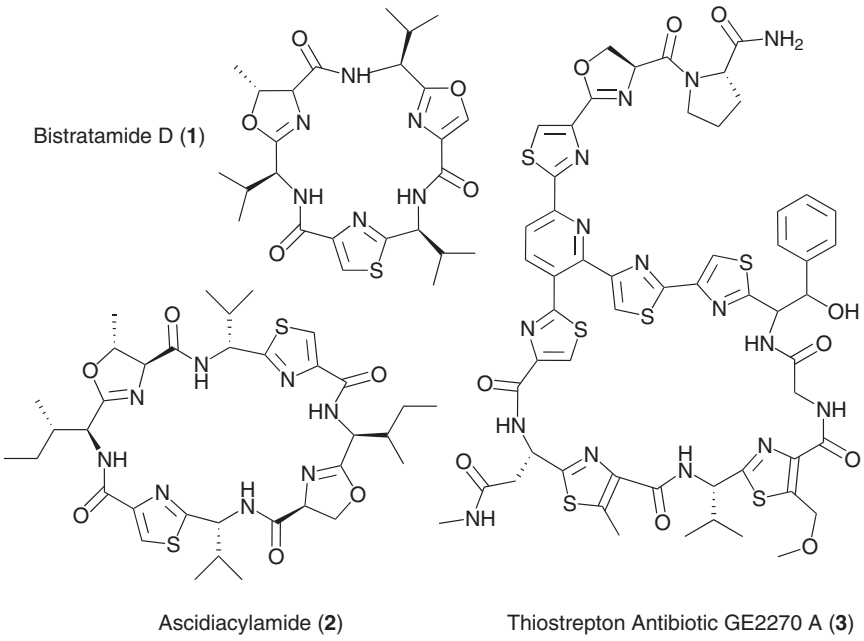

Figure 1 Bioactive and natural products incorporating the thiazole motif

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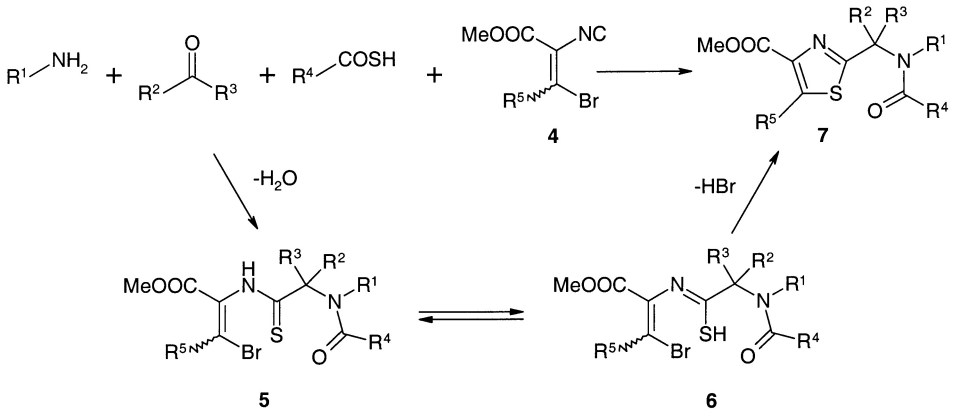
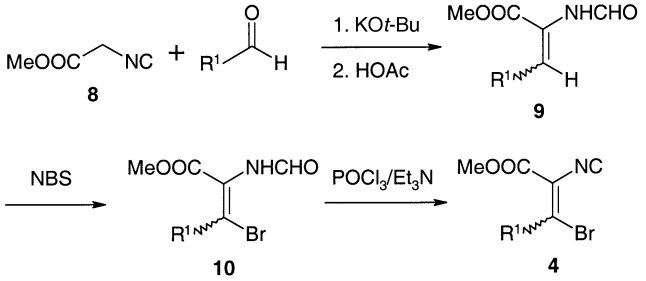


Scheme 1 Proposed mechanism for the synthesis of 2,4,5-trisubstituted thiazoles **7**

A possible mechanism is proposed in Scheme 1. During the reaction, the isocyanide, the Schiff base and the thiocarboxylic acid react regioselectively according to the mechanism of a Ugi reaction. The intermediate Ugi product **5**, which cannot be isolated, is in equilibrium with its mercaptoimine tautomer **6**. The following Michael addition and final hydrogen bromide abstraction lead to the expected 2,4,5-trisubstituted thiazole **7**.

In this communication we show an efficient synthesis of various types of 2,4,5-trisubstituted thiazoles **7** (Table 1) using 3-substituted 3-bromo-2-iscyanoacrylates **4**, which can be synthesized in 3 steps from commercially available methyl-isocyanoacetate **8** via 3-substituted 2-(formylamino)acrylates **9**[31] (Scheme 2).



Scheme 2 Synthesis of 3-substituted 3-bromo-2-isocyanoacrylates

The main advantage of 3-substituted 3-bromo-2-isocyanoacrylates is the great variability of substitution at the 3-position, which allows the easy addition of various substituents at the 5-position of the thiazole system. Therefore, this novel four-component reaction represents a powerful tool for the total synthesis of natural products and for the combinatorial synthesis of interesting pharmacological templates incorporating the thiazole motif.

The reaction of 3-substituted 3-bromo-2-isocyanoacrylates together with Schiff bases and thiocarboxylic acids leads to the desired 2,4,5-trisubstituted thiazoles **7a–k** in a one-pot procedure (Table 1) with moderate yields. In reaction **7j–k** chiral amines were used and in the case of compound **7j** it was possible to determine a diastereomeric excess of 71%. The diastereomeric ratio was determined by separation of the major and minor diastereomer whereby the relative configuration was not assigned. In this new four-component reaction the primary amines, the oxo-components, the isocyanides[29,30] and the thiocarboxylic acids[32] can be varied broadly, producing products with four potential diversity points. The use of unsymmetrical ketones can even lead to molecules with five points of diversity.

The reaction conditions of this novel thiazole MCR are mild: stirring for 1 day at room temperature, basic and acid extraction, evaporation of the solvent and column chromatography on silica gel.[33]

In summary, a novel one-pot solution-phase procedure for the preparation of 2,4,5-trisubstituted thiazole building-blocks has been reported.[34] This reaction is suitable for the total synthesis of certain naturally occurring thiazoles as well as for the combinatorial chemistry. With final products containing five points of potential diversity and a facile and rapid production protocol, access to thousands of diverse analogues with the aforementioned core structure is now feasible.

Table 1 Synthesized 2,4,5-Trisubstituted Thiazoles

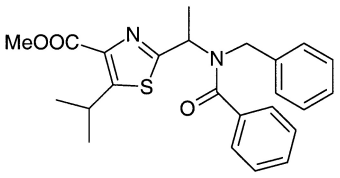
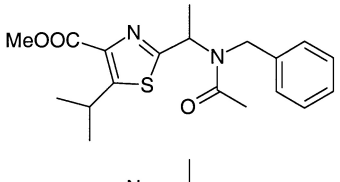
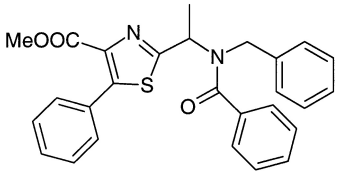
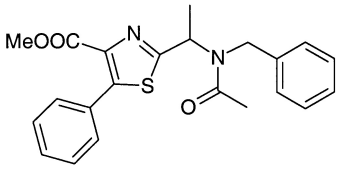
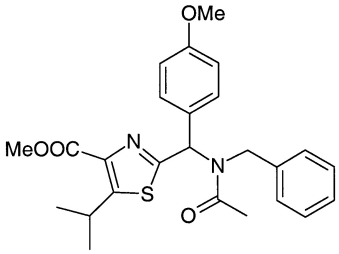
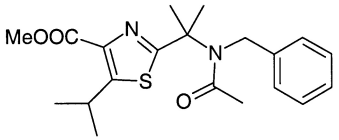
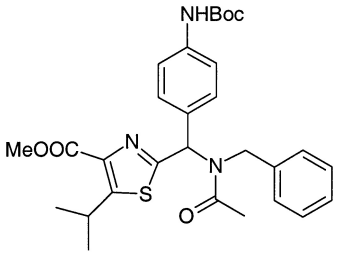
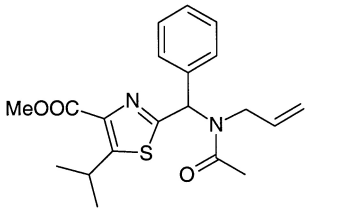
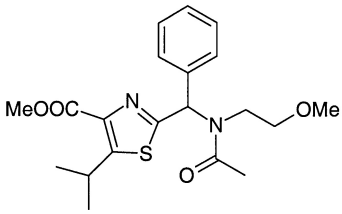
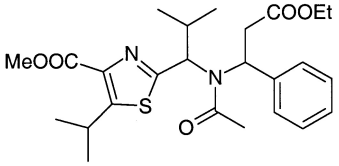
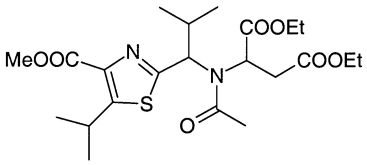
Product	Thiazole	Yield (%)
7a		42
7b		43
7c		32

Table 1 Synthesized 2,4,5-Trisubstituted Thiazoles (continued)

Product	Thiazole	Yield (%)
7d		41
7e		34
7f		25
7g		45
7h		57
7i		35
7j		35 (71% de)
7k		31

Current efforts are now focusing on the development of an enantioselective one-pot synthesis of 2,4,5-trisubstituted thiazoles.

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(33) **Typical Procedure:**
Aldehyde or ketone (1 mmol), amine and $MgSO_4$ are stirred under inert and water-free conditions in 2 mL dry MeOH at 0 °C. The imine is precondensed for 2 h and the solution is cooled to –10 °C: 1 mmol of the thiocarboxylic acid and

isocyanide are added and the reaction volume is increased to 4 mL. The reaction mixture is allowed to warm up to r.t. and stirred for 24 h until the reaction is completed (indication by TLC). Then the reaction mixture is diluted with 25 mL CH_2Cl_2. The organic layer is washed with sat. $NaHCO_3$ solution, 3% HCl and sat. NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The resulting oil is purified by column chromatography on silica gel (hexane–EtOAc).

(34) Compound **7b** was isolated in 43% yield as a yellow oil. HPLC-MS spectra (Varian 1200); RP OmniSpher C18 column, 3 mm × 150 mm, 5 µm; ProStar 320 (254 nm); 0.3 mL/min, 10 min, MeCN–H_2O = 70:30 coupled with a Quadrupol MS/MS mass spectrometer using electrospray ionisation (ESI): t_R(254nm) = 5.37 min; *m/z* = 361.1 [M + H]$^+$, 383.1 [M + Na]$^+$. ^{1}H NMR (270.17 MHz, $CDCl_3$): δ = 1.30 [d, 6 H, *J* = 7.01 Hz, $CH(CH_3)_2$], 1.61 (d, 3 H, *J* = 7.01 Hz, H_3C-CH), 2.12 (s, 3 H, H_3C-CO), 3.91 (s, 3 H, CH_3OOC), 4.07 [h, 1 H, *J* = 7.01 Hz, $CH(CH_3)_2$], 4.57 (s, 1 H, CH_2-C_6H_5), 4.60 (s, 1 H, CH_2-C_6H_5), 6.18 (q, 1 H, *J* = 7.01 Hz, CH-CH_3), 7.14–7.31 (m, 5 H, C_6H_5). ^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 17.13 (H_3C-CH), 22.26 (H_3C-CO), 24.96 [$(CH(CH_3)_2$], 24.99 [$CH(CH_3)_2$], 27.89 [$CH(CH_3)_2$], 48.85 (CH_2-C_6H_5), 51.56 (CH-CH_3), 51.94 (CH_3OOC-), 125.79, 127.17, 128.58, 137.30 (Cq), 138.60 (Cq), 159.71 (Cq), 162.71 (Cq), 166.35 (CON), 171.85 (COOMe).

Compound **7d** was isolated in 41% yield as a yellow oil. HPLC-MS spectra (Varian 1200); RP OmniSpher C18 column, 3 mm × 150 mm, 5 µm; ProStar 320 (254 nm); 0.3 mL/min, 10 min, MeCN–H_2O = 80:20 coupled with a Quadrupol MS/MS mass spectrometer using electrospray ionisation (ESI): t_R (254 nm) = 5.08 min; *m/z* = 395.4 [M + H]$^+$, 417.2 [M + Na]$^+$. ^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 1.66 (d, 3 H, *J* = 7.26 Hz, H_3C-CH), 2.13 (s, 3 H, H_3C-CO), 3.79 (s, 3 H, CH_3O-), 4.67 (s, 2 H, CH_2-C_6H_5), 6.04 (q, 1 H, *J* = 7.26 Hz, CH-CH_3), 7.19–7.41 (m, 10 H, C_6H_5). ^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 17.23 (H_3C-CH), 22.34 (H_3C-CO), 49.19 (CH_2-C_6H_5), 51.85 (CH-CH_3), 52.07 (CH_3OOC-), 125.94, 127.31, 128.11, 128.70, 129.09, 129.73, 130.27, 137.34 (Cq), 139.27 (Cq), 147.29 (Cq), 162.53 (Cq), 168.86 (CON), 171.83 (COOMe).