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Diversity oriented synthesis of benzoxazoles and benzothiazoles

Julia H. Spatz,[a,b,*] Thorsten Bach,[b] Michael Umkehrer,[a] Julien Bardin,[a] Günther Ross,[a] Christoph Burdack[a] and Jürgen Kolb[a]

[a]*Priaton GmbH, Gmunder Strasse 37-37a, D-81739 München, Germany*
[b]*Technical University Munich, Lichtenbergstrasse 4, D-85747 Garching, Germany*

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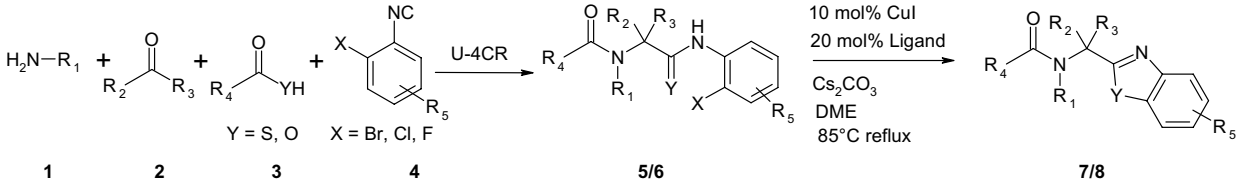
Abstract—A combinatorial synthetic route yielding benzoxazoles and benzothiazoles is described. The use of *o*-halophenylisocyanides in the Ugi reaction (U-4CR) followed by a copper-catalyzed cyclization affords the benzoxazole as well as the benzothiazole moiety in good yield and high diversity.

Benzoxazoles and benzothiazoles belong to an important class of molecules and are common heterocyclic scaffolds in biologically active and pharmaceutically significant compounds. Benzoxazoles are found in a variety of natural products[1] and are important scaffolds in drug discovery.[2,3] Therefore several classical synthetic procedures were developed,[4,5] but with a lack of diversity, which is required for an effective lead discovery and optimization. In contrast to the classical organic synthesis, the combinatorial synthesis of 'drug-like' compounds permits the fast preparation of compound libraries suitable for lead finding and optimization.[6–16] Thus multi-component reactions (MCRs) represent a powerful tool for high-throughput screening strategy.[17,18] Especially the Ugi-reaction has generated much interest due to its synthetic potential, and its capacity to generate molecular diversity. In the Ugi-four component reaction,[19] amine **1**, aldehyde **2**, carboxylic acid **3** and isocyanide **4** react simultaneously to afford peptide-like structure **5/6** (Scheme 1). In order to reach a maximum of diversity, several research groups have successfully joined different classical methods with multi-component reactions.[20–25] For further progress in molecular diversity we combined the Ugi-4CR with a copper-catalyzed cyclization. The reaction involves an intramolecular C–O or C–S cross-coupling of the *ortho*-halophenylamide originating from the isocyanide and is believed to proceed via an oxidative insertion/reductive elimination pathway through a Cu(I)/Cu(III) manifold in analogy with other Cu- and Pd-catalyzed C–X bond formations[3,26–29] (Scheme 2). Herein the first step of the reaction involves the coordination of the amide group **5/6** with catalyst **9** to give intermediate **10**, then followed by an oxidative insertion to **11** and finally a reductive elimination to release product **7/8** with simultaneous regeneration of catalyst **9**.

The Ugi-reaction is generally initiated by the condensation of amine **1** with aldehyde **2** leading to an intermediate imine, which subsequently reacts with carboxylic



Scheme 1. Combinatorial synthesis of benzoxazoles and benzothiazoles via U-4CR and copper-catalyzed cross-coupling strategy.

Keywords: Ugi-reaction; Multi-component reaction; Benzoxazoles; Benzothiazoles; Copper-catalyzed cyclization; Cross-coupling.
* Corresponding author. Tel.: +49 89 45213080; e-mail: spatz@priaton.de

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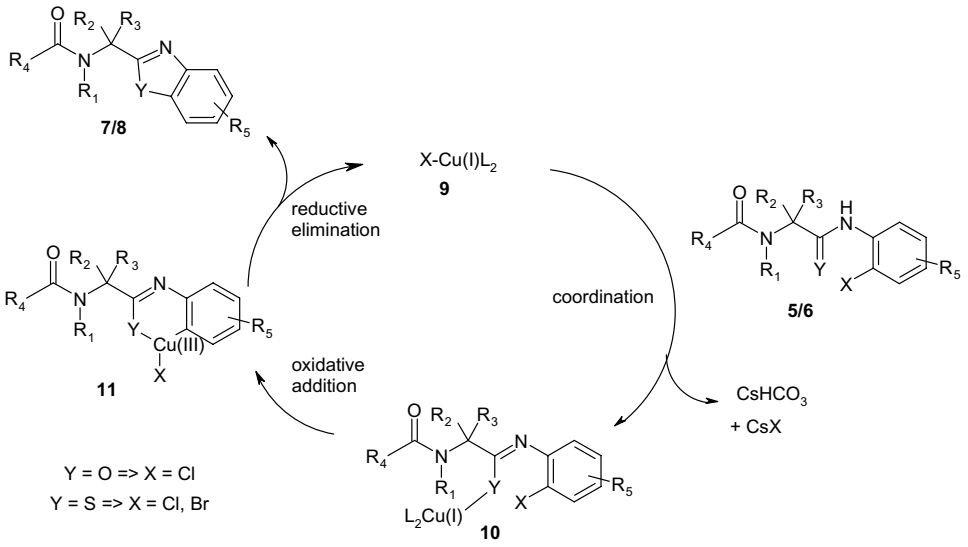
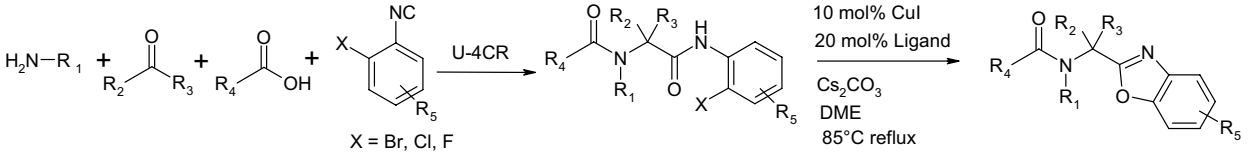
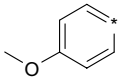
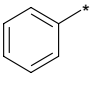
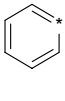
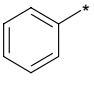
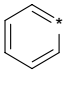


Scheme 2. Mechanistic proposal for the copper-catalyzed formation of benzoxazoles and benzothiazoles.

Table 1. Synthesized benzoxazoles



1 **2** **3** **4** **5** **7**

Entry	R_1	R_2	R_3	R_4	X	R_5	Y_1 (%)	MCR	Y_2 (%)	Final product
1		H			Br	H	99	**5a**	31	**7a**
2		H			Br	4-F, 6-Br	87	**5b**	42	**7b**
3		H		CH_3	Br	H	62	**5c**	99	**7c**
4		H		H	Br	H	99	**5d**	65	**7d**
5		H		CH_3	Cl	3-CF_3	99	**5e**	0	**7e**
6		H		CH_3	F	H	90	**5f**	0	**7f**
7		H		CH_3	Br	H	32	**5g**	65	**7g**
8		H	H		Br	H	99	**5h**	37	**7h**
9		CH_3	CH_3		Br	H	68	**5i**	68	**7i**

(*continued on next page*)