Regio- and stereoselective synthesis of benzothiazolo-pyrimidinones via an NHC-catalyzed Mannich/lactamization domino reaction†

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An NHC-catalyzed regio- and stereoselective Mannich/lactamization domino reaction of N-(benzothiazolyl)imines with α-chloroaldehydes has been developed. This new protocol provides a facile approach for the asymmetric synthesis of benzothiazolo-pyrimidinones and a pyrrolo[1,2-α]indolone in moderate to good yields (34–78%) and excellent stereoselectivities (87–99% ee, up to >20:1 d.r.).

The tricyclic pyrimido[2,1-b]benzothiazole core prevails in a wide range of bioactive molecules with remarkable biological properties, such as the inhibition of c-AMP phosphodiesterase, antineoplastic and antimalarial activity. Moreover, the isothiourea-based HBTM is used as an efficient organocatalyst and received great attention in the field of asymmetric catalysis (Fig. 1). Although various approaches for the synthesis of the pyrimido[2,1-b]benzothiazole motif have been developed, most of them are non-stereoselective and/or need relatively harsh conditions. In the past decade, great advances have been achieved in the development of N-heterocyclic carbene (NHC) catalyzed organocatalytic reactions via the umpolung of aldehydes. Especially since the seminal studies concerning the NHC-catalyzed conjugate umpolung reactions reported by the groups of Glorius and Bode in 2004, NHC organocatalysis has been extended for the activation of the β-carbon (homoenolate intermediate) and α-carbon (enolate intermediate) of enals. These two kinds of intermediates used as nucleophiles reacted with a variety of reactive electrophiles to afford heterocyclic compounds such as lactones, lactams or cyclopentenes. It is noteworthy that aldimines behaved as excellent electrophiles in the reactions of enolate intermediates, providing the corresponding β-lactams (Scheme 1, eqn (1)). Smith et al. and Ye et al. reported an NHC-catalyzed [2+2] cycloaddition of ketenes with N-tosyl imines and N-Boc imines, respectively. Very recently, the Ye group was able to carry out Staudinger reactions of ketenes with isatin-derived ketimines, yielding spirocyclic oxindolo-β-lactams. We envisioned that 2-benzothiazolimine 1a in combination with an azolium enolate could not only produce the β-lactam 4, but also provide access to benzothiazolo-pyrimidinone 3 through a formal [4+2] annulation (Scheme 1, eqn (2)). Obviously, influencing the regioselectivity of the reaction site of the intermediate ambident anions is the greatest challenge in order to improve the ratio of 3/4 in the Mannich/lactamization domino reaction.

To test our hypothesis, we initially checked several triazolium precatalysts A–C in the model reaction of 2-benzothiazolimine 1a with 2-chloro-3-phenylpropanal (2a) at room temperature.

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We found that the chiral triazolium salt B resulted in an excellent stereoselectivity for ent-3a (97% ee, >20:1 d.r.), albeit with a low yield (19%) and regioselectivity (Table 1, entry 2). Attempting to improve the regioselectivity and the yield of ent-3a, we next tested a series of bases, but no satisfying improvement was achieved (Table 1, entries 4–9). Solvent screening led to no improvement in yield and selectivity (Table 1, entries 10–14). After the screening of the base and solvent, DABCO in combination with toluene turned out to give the highest yield of ent-3a (31%), maintaining the excellent stereoselectivity and the low regioselectivity as well (Table 1, entry 6). Notably, the triazolium salt A provided rac-3a in 43% yield exclusively, even though with a drastically decreased d.r. (Table 1, entry 1). Therefore we further screened a series of pyrrolidinone-derived triazolium salts D–G. To our delight, a dramatic improvement in both yield and regioselectivity was obtained (Table 1, entries 15–18). The NHC-catalyzed reaction based on the triazolium salt F afforded cycloadduct 3a in a better yield but with relatively low regioselectivity (Table 1, entry 17). After using 4 Å MS as an additive, the yield (69%) and regioselectivity (14:1) improved further, but the enantioselectivity (93% ee) decreased slightly (Table 1, entry 19).

Next we investigated the substrate scope of this protocol on a 0.5 mmol scale. As shown in Table 2, a wide range of 2-benzothiazolinones 1 with diverse electronic and steric properties were first explored. The use of 2-benzothiazolinones 1a afforded the desired 3a in 63% yield with >20:1 d.r. and 90% ee (Table 2, 3a). Electron-donating substituents such as 4-Me and 4-OMe on the Ar group reduced the electrophilicity of the imine carbon, which led to lower yields and even the diastereomeric ratio (d.r.) decreased (Table 2, 3b–3e). In the case of electron- withdrawing groups such as 4-Br, 4-Cl and 2-Cl, the reactions gave the desired cycloadducts 3d–f in good yields and with good to excellent diastereomeric and enantioselectivities. The introduction of a heterocyclic furyl group on the Ar position gave comparable results, affording the corresponding product 3g in 69% yield, 11:1 d.r. and 93% ee under an elevated temperature. Several electron-donating and electron-withdrawing substituents such as R1 were also investigated, yielding the cycloadducts 3h–k in good yields and excellent stereoselectivities. We then varied the 2-chloroaldehyde moiety. An aliphatic linear 2-chloroaldehyde moiety. An aliphatic linear α-chloroaldehyde reacted smoothly with a slight loss of yield and with a reasonable ee value (Table 2, 3l). When a para-nitrophenyl group instead of Ph as R2 was used, a better result in terms of yield and ee was obtained (Table 2, 3m).

The relative configuration of the major diastereomer 3a was determined by NOE measurements (see ESI†), which is in accordance with the absolute configuration of compound 3e determined by X-ray crystal structure analysis (Fig. 2).
addition of NHC to \( \text{x} \)-chloroaldehyde gives rise to the intermediate I, followed by base assisted HCl-elimination to provide the enolate species II. This azolium-enolate then reacts on its \( \text{Re} \)-face with 2-benzothiazolimine 1 via a Mannich reaction to afford the adduct III with \( \text{cis} \) selectivity. Finally, the benzothiazole N-anion then cyclizes with the acylazolium intermediate liberating the NHC catalyst and producing the desired benzothiazolopyrimidinone 3 in \( \text{cis} \) configuration.

In conclusion, we have developed an asymmetric NHC-organocatalyzed annulation of 2-benzothiazolimines with \( \text{x} \)-chloroaldehydes, producing the desired benzothiazolopyrimidinones in moderate to good yields with excellent regio- and stereoselectivities. Particularly noteworthy is the reaction of indolyl-bound 2-benzothiazolimine with 2-chloro-3-phenylpropanal. This version of the protocol leads to the formation of pyrrolo-[1,2-\( \text{a} \)]indolone with high regioselectivity and excellent stereo-selectivity. Further applications of this protocol in the scope and application are ongoing in our laboratory.

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Notes and references


10 CCDC 1029497 contains the supplementary crystallographic data for compound 3e reported in this communication.