



Research article

General and sustainable synthesis of benzoimidazopyrimidinones and –thiones

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ABSTRACT

N-Heterocyclic compounds play a key role in chemistry and the life sciences and their (sustainable) synthesis is of great general interest. We report here on the synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and –thiones. Our reaction is a consecutive three-component reaction using simple and readily available starting materials, such as benzene-1,2-diamines, 3-aminopropan-1-ols and 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole. The reaction is mediated by a well-defined 3d-metal catalyst that is a manganese pincer complex and hydrogen is liberated during the reaction. All benzoimidazopyrimidinone and –thione examples synthesised haven't been reported in literature yet.

1. Introduction

N-Heterocyclic compounds are of fundamental importance in chemistry and the life sciences [1] and the synthesis of classes of *N*-heterocyclic compounds that are less explored regarding their synthesis or even unknown is of great general interest. 3,4-Dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and –thiones are examples of classes of *N*-heterocycles that are pharmaceutically important (Fig. 1, A) [2–5] but less explored regarding their synthesis. Existing syntheses start from 2-β-aminoethylbenzimidazole (ABI) synthesised from amino acids, such as β-alanine and *ortho*-phenylenediamine (PDA) first described in 1949. [6] Davies and Dickerson were the first to report the synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-one outgoing from ABI hydrochloride, sodium and diethyl carbonate by melting the resulting carbamate intermediate (Fig. 1, B). [7] Bocion *et al.* and Shafik *et al.* described further syntheses of the carbamate intermediate using chloroformates and ABI to receive the benzoimidazopyrimidinone after their thermal cyclisation. [2,3] Buschauer *et al.* reported another synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-one by melting the ABI with 1,1'-carbonyldiimidazole (CDI) and also synthesised the 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-thione by using 1,1'-thiocarbonyldiimidazole (TCDI). [8] The syntheses of benzoimidazopyrimidinethiones is often described by the cyclisation of ABI with carbon disulfide and a base such as sodium hydroxide or trimethylamine [2,9–11].

We [12] and others [13–18] recently reported a variety of

dehydrogenation reactions mediated by molecular manganese (Mn) catalysts. What is especially interesting conceptually about this work is the rational design of *N*-heterocyclic compound classes via regenerative cyclisation of diamines [19] and the ring-closing of diamines by methanol via Mn-catalysed dehydrogenation catalysis [20]. We report here on the synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and –thiones. Our reaction is a consecutive three-component reaction using simple and readily available starting materials, such as benzene-1,2-diamines, 3-aminopropan-1-ols and 1,1'-CDI or 1,1'-TCDI. The reaction is mediated by a well-defined 3d-metal catalyst that is an Mn pincer complex and hydrogen is liberated during the reaction. By using amino alcohols, which can also be synthesised in sustainable ways, [21] instead of amino acids, we were able to significantly expand the product spectrum regarding the substituents R¹ to R³ (compare Fig. 1 B) and C)). All benzoimidazopyrimidinone and –thione examples synthesised haven't been reported in literature yet.

2. Results

2.1. Optimisation of the reaction conditions

We optimised the reaction conditions for the consecutive reaction of PDA with 3-amino-2,2-dimethyl-propanol in the first step and with 1,1'-CDI in the second step to preserve the product 4,4-dimethyl-3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-one A1 (Fig. 2). We used Mn(I) PN₅Ppincer complexes to generate the reactive amino aldehyde *in*

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situ from amino alcohols via the liberation of hydrogen for the catalytic formation of intermediate **ABI** (Fig. 2). The primary amino group introduced from the amino alcohol and the secondary amine generated by the cyclisation are in proximity, enabling further cyclisation. The cyclisation between these two amino groups with **CDI** or 1,1'-**TCDI** as C1 building blocks in the second step leads to the formation of benzo[4,5]imidazo[1,2-*c*]pyrimidinones (**A1-A12**, Fig. 2 and **A15-A22**, Fig. 3) and -thiones (**A13-A14**, Fig. 2 and **A23-A26**, Fig. 3). We investigated Mn(I) complexes stabilised by different pincer ligands as precatalysts for the dehydrogenation of the amino alcohol. The precatalyst **[Mn-II]** (Fig. 2) stabilised by a PN₃P-pincer ligand showed the highest activity, whilst a cobalt(II) PN₃P-pincer complex (**[Co-I]**), which is only stable to 90 °C, [22] showed no activity. A Mn(I) complex stabilised by a PN₃P-pincer ligand (**[Mn-VI]**) showed a significantly lower activity since there are no pockets in the ligand backbone for potassium binding [23] (Supplementary Table 1). The catalyst works best in combination with an alkali metal base, with KO^tBu proving to give the best results

(Supplementary Table 2). Corresponding sodium and lithium bases bind stronger to the catalyst since they fit better in the pockets of the ligand backbone. [23] Their removal from the catalyst during hydride transfer (charge compensation) steps is more energy intensive and therefore such reaction are significantly slower. [23] KOH is not soluble enough under the reaction conditions applied. For KHMDS, we see a bit of reactivity, but the acidity of the amine is lower, and the hydrogen liberation is usually slower than (Fig. 4). A volume of 200 mol% KO^tBu related to the amount of **PDA** are necessary for a complete consumption of the **PDA**. The other reaction parameters, such as solvent, temperature, precatalyst loading, equivalents of amino alcohol and **CDI**, were also optimised, and details are shown in Supplementary Tables 1-8. The optimised reaction parameters for the first step of the synthesis of **A1** were 200 mol% KO^tBu, 3 mol% precatalyst **[Mn-II]**, 1.2 equivalents of amino alcohol, 8 mL 1,4-dioxane, at 110 °C under argon counterflow for 21 h. The volume of 8 mL of dioxane were used to guarantee a good solubility of all components and to still have enough solvent left, if we lose some during

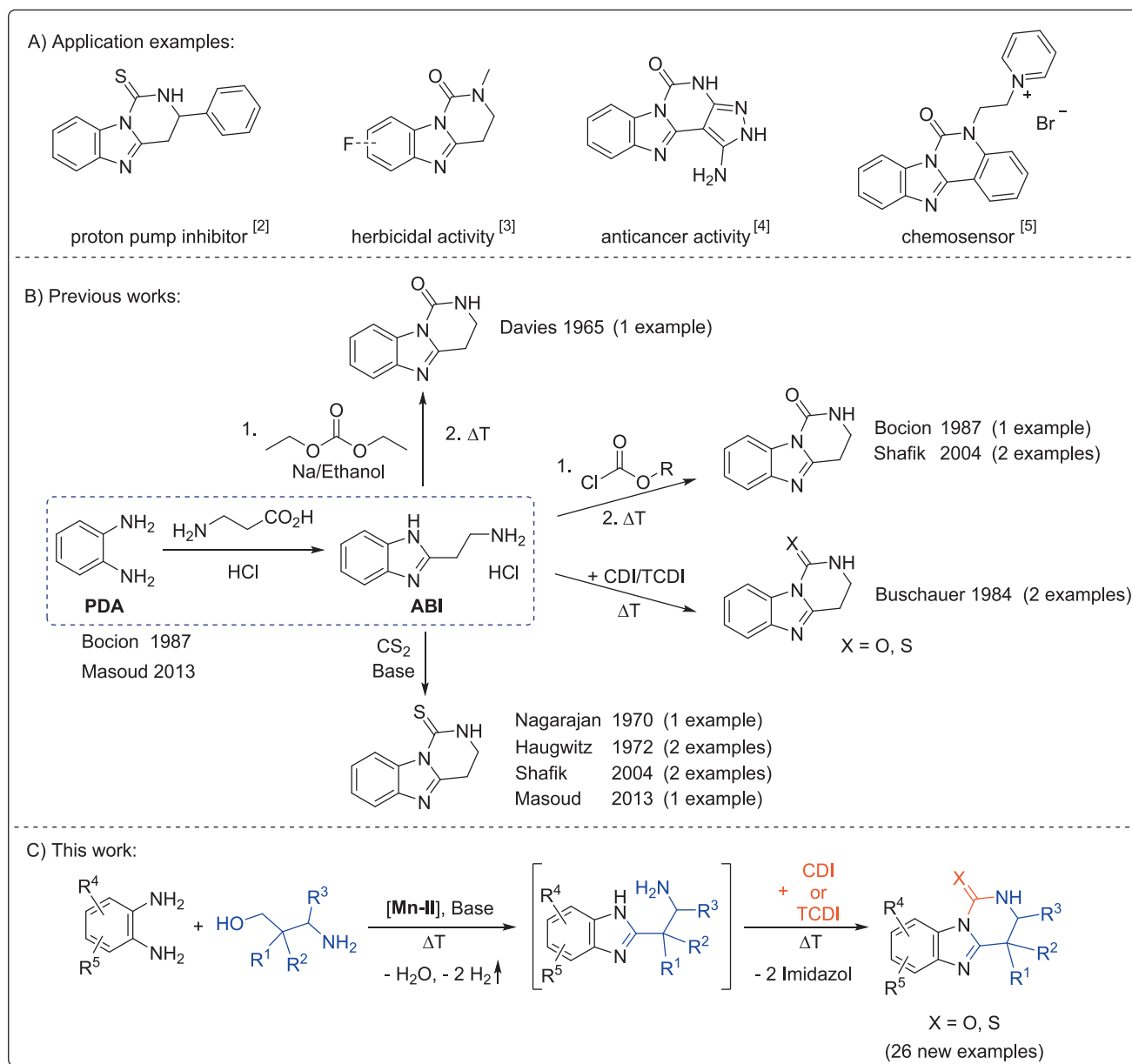


Fig. 1. A) Examples of applications and properties of benzoimidazopyrimidinones and -thiones. B) Previous methods for the synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and -thiones outgoing from 2- β -aminoethylbenzimidazole (**ABI**). C) Synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and -thiones via manganese catalysis.

the 21 h of dehydrogenation catalysis under argon counterflow. The addition of a solution of 1.25 equivalents of **CDI** in 2 mL dioxane and a reaction time of 2 h at 110 °C resulted in the best yield of **A1** in the consecutive second step. The hydrogen released during the dehydrogenation and aromatisation was liberated by a bubble counter.

2.2. Substrate scope

We used twelve aliphatic 1,3-amino alcohol derivatives which we partially synthesised via hydrogenation from the corresponding amino acids, for the examination of the substrate scope of the 3,4-dihydrobenzo[4,5]-imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones (Supplementary Fig. 3). The optimised conditions for the reaction to form **A1** resulted in a yield of 95% of isolated product. We obtained single crystals after recrystallisation from ethyl acetate at -24 °C and confirmed the molecular structure of **A1** via X-ray single crystal diffraction analysis (Fig. 2, for more details, see Supporting Information). Regarding **A1**, **CDI** was used as a

C1 building block for the second step of the consecutive reaction to get the products **A2-A12**. A methyl group on the β - or γ -position on the 1,3-amino alcohol led to isolated yields of 80% for **A2** and 87% for **A3**. A larger steric aliphatic substituent, such as an isobutyl group, was also tolerated, and resulted in the product **A4** with a yield of 72%. 1,3-Amino alcohols with cyclic aliphatic substituents, such as cyclopropyl and cyclohexyl, were successfully introduced, giving the products **A5** and **A6** with 70% yield each. The products **A1-A6** represent the tolerance towards electron-donating groups at the β - or γ -positions of the 1,3-amino alcohol, especially aliphatic groups. In addition to the aliphatic substituents, we investigated aromatic substituents at the γ -position of the 1,3-amino alcohols, such as the *p*-tolyl substituent, which resulted in **A7** with an isolated yield of 65%. A methoxy group at the *meta*-position on a phenyl substituent led to a yield of 64% for **A8**. We have succeeded in incorporating an aromatic heterocycle, more precisely, a pyridinyl substituent – **A9** – with an isolated yield of 42%. We were able to demonstrate the feasibility of introducing halides into the benzo[4,5]

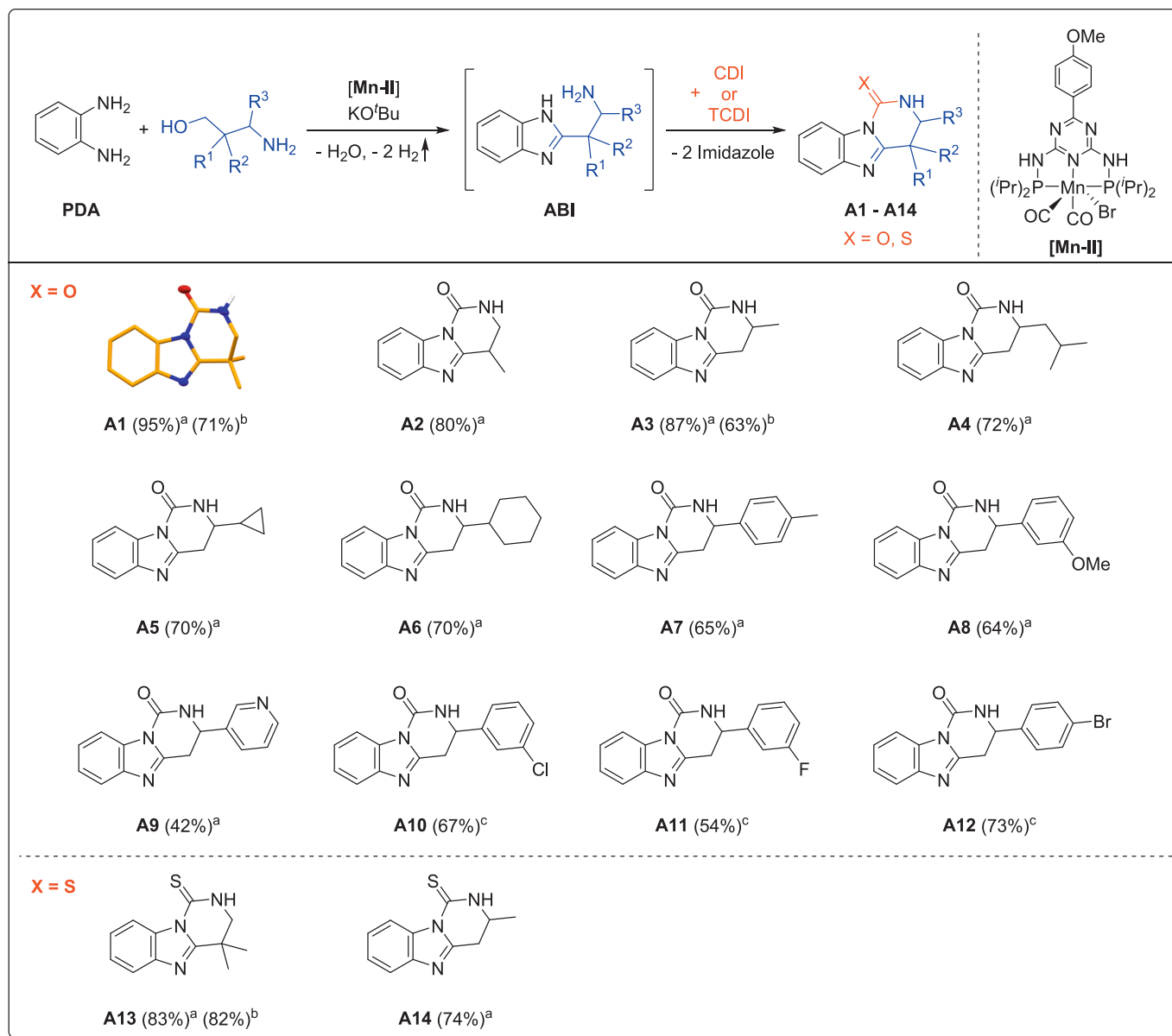


Fig. 2. Synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones **A1-A12** and -thiones **A13-A14**. Variation of 1,3-amino alcohols. Isolated yields in brackets. a: Reaction conditions: 1. Step: 1 mmol **PDA**, 1.2 mmol amino alcohol, 2 mmol **KO^tBu**, 3 mol% **[Mn-II]** (0.03 mmol), 8 mL dioxane, 110 °C (oil bath), argon atmosphere, 21 h. 2. Step: Addition of 1.25 mmol **CDI/TCDI** in 2 mL dioxane, 110 °C (oil bath), argon atmosphere, 2 h. b: Scale up experiments (10 mmol). c: 100 °C (oil bath) and 18 h.

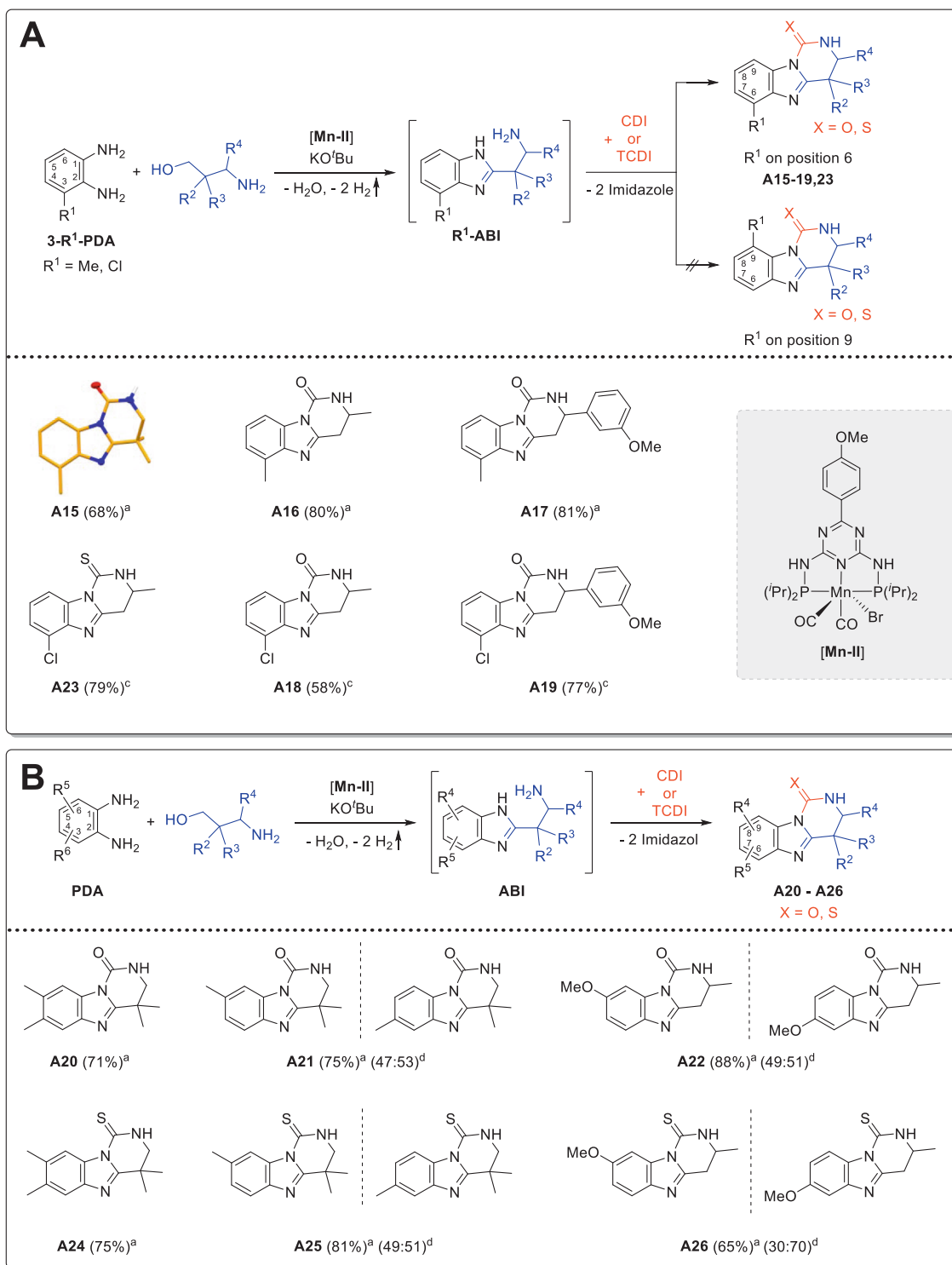


Fig. 3. A) Selective synthesis of constitutional isomers of the benzo[4,5]imidazo[1,2-*c*]-pyrimidinones or -thiones **A15-A19** by using mono-substituted PDAs at position 3. B) Synthesis of 3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones and -thiones **A20-A26** by using substituted PDAs at position 4 and/or 5. Isolated yields in brackets. a: Reaction conditions: 1. Step: 1 mmol PDA derivatives, 1.2 mmol amino alcohol, 2 mmol KO^tBu, 3 mol% [Mn-II] (0.03 mmol), 8 mL dioxane, 110 °C (oil bath), argon atmosphere, 21 h. 2. Step: Addition of 1.25 mmol CDI in 2 mL dioxane, 110 °C, argon atmosphere, 2 h. c: 100 °C (oil bath) and 18 h. d: Isomeric ratios.

imidazo[1,2-*c*]-pyrimidinones with the products **A10-A12**. A partial dehalogenation occurs during the reaction under optimised conditions. To reduce the dehalogenation, the reaction parameters have been modified to milder conditions with 100 °C and a shorter overall time of 18 h. The 3-amino-3-(3-chlorophenyl)propan-1-ol was used for **A10** and

led to the corresponding product in a 67% yield without any dehalogenation being observed. The 1,3-amino alcohol with a fluoro instead of the chloro substituent led to the product **A11** with a yield of 54%. As an example of a bromo derivative, 3-amino-3-(4-bromophenyl)propan-1-ol was successfully converted to the corresponding benzo[4,5]imidazo

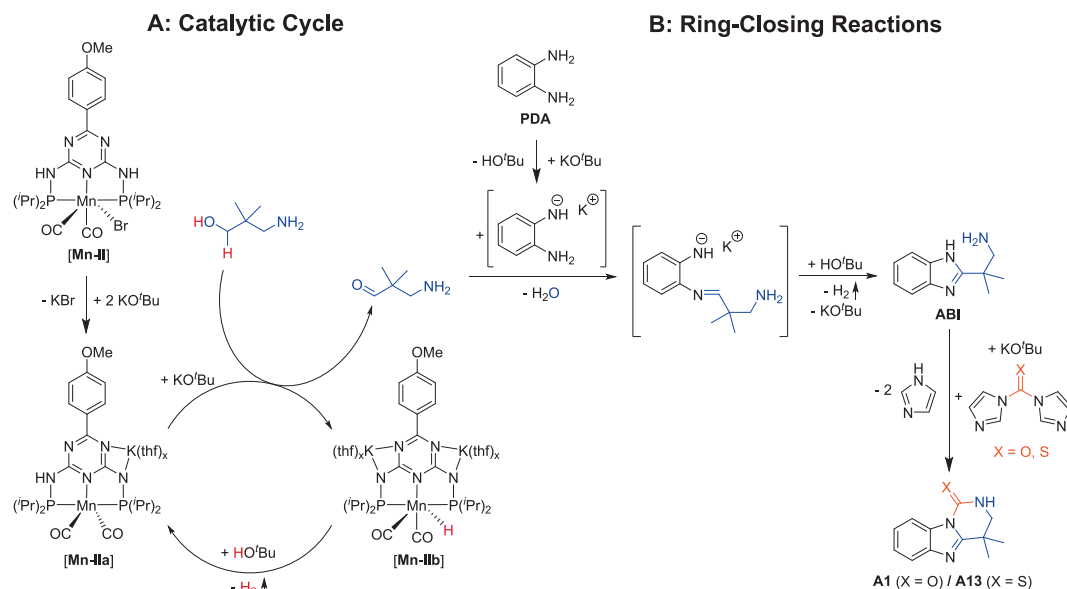


Fig. 4. Proposed mechanism for the catalytic dehydrogenation of amino alcohols and the succeeding ring-closing reactions. **A:** Proposed catalytic cycle. **B:** Proposed ring-closing reactions.

[1,2-*c*]-pyrimidinone **A12** with a yield of 73%.

Besides the use of **CDI** as a C1 building block, we used the thio-pendant **TCDI** to achieve the corresponding benzo[4,5]imidazo[1,2-*c*]pyrimidinethiones **A13** and **A14** (Fig. 2). Firstly, we carried out the optimised model reaction of **A1** with **TCDI** instead of **CDI** to obtain the 4,4-dimethyl-3,4-dihydrobenzo[4,5]imidazo[1,2-*c*]pyrimidin-1(2*H*)-thione **A13** with an isolated yield of 83% (Fig. 2). In another example, the 3-amino-3-methylpropan-1-ol was successfully converted to the corresponding product **A14** by using **TCDI** in the second step and a yield of 74% was obtained. We examined scale up experiments with a tenfold batch size to achieve multigram scales of the products **A1** (71%), **A3** (63%) and **A13** (82%) (Fig. 2, details shown in Supporting Information).

After the variation of the 1,3-amino alcohol (Fig. 2), we investigated the variation of **PDA** (Fig. 3). Two constitutional isomers of the resulting products are possible with mono-substituted **PDA**. Exemplarily, the corresponding products can be substituted at position 6 or 9 by converting a at position 3-substituted **PDA** (**3-R¹-PDA**) (Fig. 3, A). These isomers are possible because the C-N double bond and the proton from the secondary amine group of the intermediate **ABI** can shift between the nitrogen atoms of the benzimidazole part. The products **A15**–**A19** of the converted 3-substituted PDAs were selective in constitutional isomerism, where only the at position 6-substituted isomers were received.

A methyl group in the 3-position on the **PDA** was used as an example of an electron-donating group and the reaction with 3-amino-2,2-dimethyl-1-propanol resulted in the corresponding product **A15** with a yield of 68% (Fig. 3, A). Regarding **A15**, we obtained single crystals after recrystallisation from ethyl acetate at -24°C , and confirmed the molecular structure via X-ray diffraction analysis (Fig. 3, A, for more details, see Supporting Information). The reaction of 3-methyl-substituted **PDA** with 3-amino-3-methyl-1-propanol led to the product **A16** with an isolated yield of 80%. The consecutive one-pot reaction of 3-methyl-*ortho*-**PDA** with 3-amino-3-(*m*-methoxy-phenyl)-1-propanol yielded **A17** in an isolated yield of 81%. 3-Chloro-*ortho*-**PDA** was used as an example of an electron-withdrawing group and converted with 3-amino-3-methyl-1-propanol to the corresponding product **A18** with a yield of 58% (Fig. 3, A). **A19** was received with the 3-chloro-derivate and the 3-amino-3-(*m*-methoxy-phenyl)-1-propanol with a yield of 77%. The 3-chloro-*ortho*-**PDA** also resulted in the selective constitutional isomer **A23**, even if **TCDI** was used during the reaction and was obtained with a yield of 79%. The same milder reaction conditions were successfully

applied as those for **A10**–**A12** for the synthesis of the chlorine substrates, and no dehalogenation was observed.

A symmetrical 4,5-dimethyl-substituted **PDA** derivate was also successfully converted to the product **A20** and resulted in a yield of 71% (Fig. 3, B). The constitutional selectivity for mono-substituted **PDA** derivatives on the 4-position was not observed and resulted in a mixture with the substituent on the position 7 or 8 of the 3,4-dihydrobenzo[4,5]-imidazo[1,2-*c*]pyrimidin-1(2*H*)-ones **A21** and **A22** (Fig. 3, B). 4-Methyl-*ortho*-**PDA** led to the corresponding isomer mixture **A21** with a yield of 75% and an isomeric ratio of 47:53. A **PDA** with a methoxy group on the 4-position was converted to the respective product as isomer mixture **A22** with a yield of 88% and an isomeric ratio of 49:51. We next synthesised benzo[4,5]imidazo[1,2-*c*]pyrimidinethiones **A24**–**A26**, whereby different PDAs were used (Fig. 3, B). The reaction of 4,5-dimethyl-*ortho*-**PDA** with 3-amino-2,2-dimethyl-propanol led to the product **A24** after conversion with **TCDI** with a yield of 75%. The two 4-substituted **PDA** derivatives previously used were also tested for the synthesis of the thiones and again resulted in isomeric mixtures. **A25** starting from 4-methyl-*ortho*-**PDA** resulted in a yield of 81% with an isomeric ratio of 49:51. The 4-methoxy-substituted diamine was converted to the corresponding product **A26** with a yield of 65% and an isomeric ratio of 30:70.

2.3. Mechanistic studies

The mechanism proposed for the catalytic dehydrogenation of the amino alcohol to the corresponding amino aldehyde and the succeeding ring-closing reactions is shown in Fig. 4. Firstly, the activated catalyst **[Mn-IIa]** was formed *in situ* by the reaction of KO^tBu with the precatalyst **[Mn-II]**.^[15,23] The pincer ligand is deprotonated by the strong base and potassiation takes place. The Mn catalyst **[Mn-IIa]** dehydrogenates the amino alcohol to the amino aldehyde under the formation of the species **[Mn-IIb]** (Fig. 4, A). The catalyst **[Mn-IIa]** is regenerated under the liberation of hydrogen in combination with the *tert*-butanol proton and the hydride from **[Mn-IIb]**. We propose that the 1,3-amino aldehyde formed *in situ* then condensates with **PDA**, activated by KO^tBu , to an imine which undergoes an intramolecular ring closure. The **ABI** is generated by the liberation of hydrogen to achieve the aromaticity (Fig. 4, B). According to these, two equivalents of hydrogen were released during the consecutive one-pot synthesis, which we analysed qualitatively and quantitatively with gas chromatography analysis

(Supplementary Fig. 9). The second ring-closing reaction occurs base-mediated by adding the C1 building block CDI or TCDI to form the products benzo[4,5]-imidazo[1,2-*c*]pyrimidinones or –thiones with a release of two equivalents of imidazole as leaving groups.

We have isolated the intermediate **ABI** to confirm that the intermediate 2- β -amino-1,1-dimethylethylbenzimidazole **ABI** is formed *in situ* from the reaction of **PDA** and 1,3-amino aldehyde. We used the **PDA** and 3-amino-2,2-dimethyl-propanol to react under the optimised conditions with KO^tBu and the precatalyst [Mn-II]. After a reaction time of 21 h at 110 °C, the reaction was stopped by cooling to room temperature and quenched with water. After work up and isolation we obtained the postulated intermediate **ABI** with a yield of 85% (see Supporting Information for more details).

3. Conclusion

We have developed a sustainable (hydrogen liberation and molecular earth-abundant metal catalyst) synthesis protocol for substituted 3,4-dihydrobenzo[4,5]imidazo-[1,2-*c*]pyrimidin-1(2*H*)-ones and –thiones via a catalytic consecutive one-pot, three-component reaction employing readily available starting materials. All benzoimidazopyrimidinone and –thione examples synthesised haven't been reported in literature yet.

4. Data availability

Crystallographic data for compounds **A1** and **A15** are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 2535185 (**A1**) and CCDC 2535183 (**A15**), respectively. Materials and methods, experimental procedures, mechanistic studies, characterisation data and spectral data are available in the Supplementary Information. Correspondence and requests for materials should be addressed to R.K.

Authors contributions

F.L.-K., T.I. and R.K. jointly devised the experimental programme. R. K. conceived the concept. T.I. supervised the experimental programme. F.L.-K. carried out the experimental programme. All authors jointly wrote the manuscript.

CRediT authorship contribution statement

Felix Leowsky-Künstler: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Torsten Irrgang:** Writing – review & editing, Supervision. **Rhett Kempe:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualisation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcat.2026.117045>.

Data availability

Data will be made available on request.

Crystallographic data for compounds **A1** and **A15** are available free of charge from the Cambridge Crystallographic Data Centre under references CCDC 2535185 (**A1**) and CCDC 2535183 (**A15**), respectively. Materials and methods, experimental procedures, mechanistic studies, characterisation data and spectral data are available in the Supplementary Information. Correspondence and requests for materials should be addressed to R.K.

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