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Facile Multicomponent Synthesis of Oxazolidinones from Primary Amines and Cesium (Hydrogen)Carbonate

Lorenz Fehr,[a] Leonard Sewald,[a] Robert Huber,[a, b, c] and Markus Kaiser*[a]

A facile multicomponent, catalyst-free oxazolidinone synthesis from primary aliphatic or aromatic amines, dibromoethane (DBE), and the usage of either cesium carbonate or cesium hydrogencarbonate as the simultaneous base and C1 source is reported. The applicability of this technically simple reaction was demonstrated by a broad scope with generally high yields, enabling concise late-stage functionalization of amino groups into N-substituted oxazolidinones. The proposed operating reaction mechanism consists of a first-step nucleophilic substitution reaction between DBE and the primary amine, followed by the formation of a carbamate or carbonate intermediate and subsequent cyclization. Additional versatility of the herein-developed protocol has been showcased in a medicinal chemistry approach by the generation of an oxazolidinone-modified dipeptidyl peptidase 8 (DPP8) inhibitor.

Introduction

Oxazolidinones are important chemical entities and are frequently used in chemistry and drug discovery, for example as chiral auxiliaries for asymmetric organic syntheses[1] or as pharmacophores of biologically active compounds.[2] For example, several antibiotics, with the bacterial translation inhibitor linezolid as the most prominent member, are based on oxazolidinone scaffolds.[3] Besides their established antibiotic properties, oxazolidinones have also been explored in anticonvulsant,[4] anti-inflammatory,[5] or antiviral[6] compounds. Indeed, the conversion of a primary aliphatic or aromatic amine into an oxazolidinone residue is an established medicinal chemistry practice for investigating and optimizing the pharmacological properties of bioactive compounds.

Two emerging potential targets for the development of anticancer, anti-inflammatory, or even anti-Covid19 drugs are the intracellular dipeptidyl peptidases 8 (DPP8) and 9 (DPP9).[7] Both proteases share highly similar active site architectures, thereby turning the development of DPP8 versus DPP9 selective inhibitors into a challenge.[8] We recently reported a 4-oxo-β-lactam compound (**1**) as a promising DPP8 and DPP9 inhibitor (Figure 1).[9] This compound inhibited both proteases with K_i values in the submicromolar range, however with a limited, only 7-fold DPP8 vs. DPP9 selectivity. The subsequent structure-guided rational design suggested that the introduction of an oxazolidinone scaffold at the *meta*-position of the central phenyl ring should result in inhibitors with improved selectivity (Figure 1). Therefore, we sought potential synthetic routes for incorporating this moiety into the compound structure to test this hypothesis.

The synthesis of oxazolidinones has been an active line of research for several decades and was commonly performed from 1,2-aminoalcohols and phosgene, a C1 source that was replaced by other reagents such as carbon dioxide or 1,1′-carbonyldiimidazole in ensuing synthesis protocols.[10] Yet, we searched for synthetic routes allowing us to straightforwardly build the desired oxazolidinones from primary amines. Such procedures are also available, besides the usage of the harsh reagent 2-chloroethyl chloroformate[11] for example from aromatic amines and ethylene carbonate in presence of 1-ethyl-3-methylimidazolium acetate ([Bmim]OAc) as an ionic liquid catalyst (Scheme 1A).[12] However, most procedures rely on the application of additional C1 sources. Hence, the ionic liquid-catalyzed reaction above was modified to incorporate carbon dioxide with aromatic amines and ethylene oxide as starting materials.[13] A more mild procedure for the conversion of aromatic amines into oxazolidinones was achieved in another multicomponent cyclization reaction with the usage of 1 atm carbon dioxide as a C1 source, dichloroethane (DCE), cesium carbonate as a base and also [Bmim]OAc as a catalyst.[14] A related synthesis protocol with 1 atm carbon dioxide, DBE, again cesium carbonate as a base and a guanidine base catalyst was also reported.[15] Quite recently, an analog approach was published for the first time for aliphatic amines. In this procedure, 10 atm of carbon dioxide, DCE, cesium carbonate as a base, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst were used.[16] Finally, aliphatic amines were converted

[a] L. Fehr, L. Sewald, Prof. Dr. R. Huber, Prof. Dr. M. Kaiser
Fakultät für Biologie
Zentrum für Medizinische Biotechnologie
Universität Duisburg-Essen
45117 Essen (Germany)
E-mail: markus.kaiser@uni-due.de
[b] Prof. Dr. R. Huber
Max-Planck-Institut für Biochemie
82152 Planegg Martinsried (Germany)
[c] Prof. Dr. R. Huber
Fakultät für Chemie
Technische Universität München
85747 Garching (Germany)

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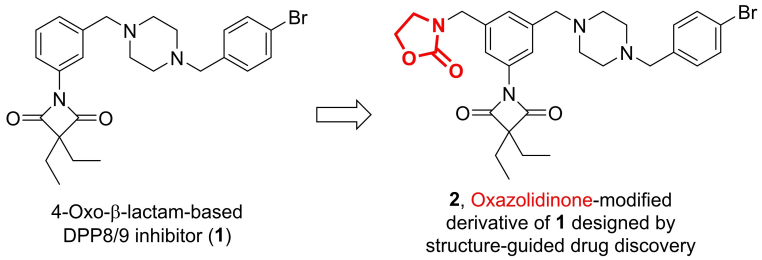
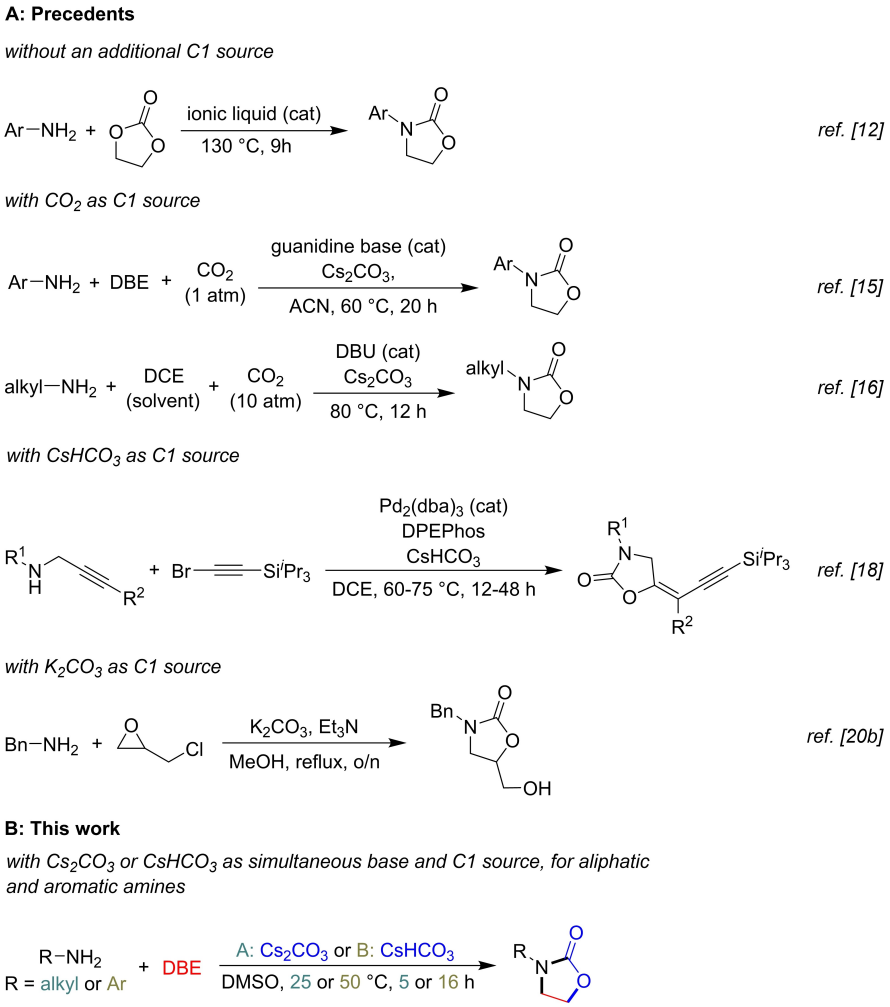


Figure 1. Chemical structures of the established 4-oxo-β-lactam-based DPP8/9 inhibitor (**1**) and the target structure of an oxazolidinone derivative (**2**) obtained from structure-guided rational design.



Scheme 1. A: Overview of previously reported oxazolidinone syntheses from primary amines. B: A simplified catalyst- and carbon dioxide-free approach to oxazolidinones.

into oxazolidinones based on the usage of 10 atm of carbon dioxide, DCE, and a ruthenium complex catalyst.[17] Carbonate salts as C1 feedstock instead of carbon dioxide are known for a long time but have so far only rarely been applied to the synthesis of oxazolidinones. For example, propargyl amines and silyl alkynyl bromides have been used as starting materials in a palladium-catalyzed protocol with cesium hydrogencarbonate replacing carbon dioxide.[18] Furthermore, potassium hydrogencarbonate as a C1 source was used in a copper-catalyzed oxazolidinone formation starting with *N*-(2-bromoallyl)amines.[19] The conversion of an aliphatic primary amine into oxazolidinones with haloalkyl oxiranes reagents and base treatment was also reported using cesium or potassium carbonates.[20]

Serendipitously, we found that oxazolidinones can be directly obtained from aromatic or aliphatic amines and DBE in

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a mild and non-catalytic fashion with cesium carbonate or cesium hydrogencarbonate as the simultaneous base and C1 source (Scheme 1B). We here report our efforts to optimize reaction conditions for this convenient synthetic approach and to define the scope of the reaction. We then showcase the applicability of this methodology by the synthesis of the envisaged DPP8 inhibitor motif.

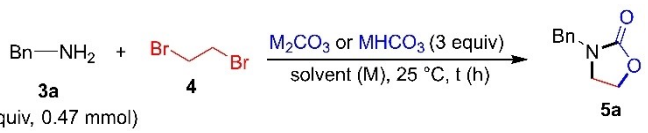
Results and Discussion

Our investigations started with the discovery that benzylamine (**3a**) in presence of 5 equivalents of DBE (**4**) and three equivalents of cesium carbonate at a reaction temperature of 60 °C formed oxazolidinone **5a** (Table 1, entry 1). Since this finding is an example of an oxazolidinone synthesis from an aliphatic amine by a non-catalyzed and carbon dioxide-free multicomponent cyclization, we decided to further examine and optimize the reaction. Table 1, entries 2–16 and Supporting Information Table S1 show the individually changed parameters in chronological order. We found that the reaction already proceeded at 25 °C, resulting in a 67% yield of oxazolidinone **5a** (Table 1, entry 2). Lowering the equivalents of **4** from 5 to 2 or 1.5 also improved the yields (Table 1, entries 3–4). Next, we tested the impact of the concentrations of the reaction partners, showing that more diluted **3a** concentrations led to a higher isolated yield (83%, Table 1, entries 5–6). Testing of different solvents revealed that non-protic and polar solvents like DMSO, or to a lower extent DMF, were a prerequisite for an efficient reaction as methanol or THF did not furnish any product (Table 1, entries 7–9). Cesium carbonate was found as the optimal reagent for this reaction as usage of cesium hydrogencarbonate or other carbonate salts such as sodium or potassium carbonate led to lower yields (Table 1, entries 10–12) while the omission of any (hydrogen)carbonate salt did not deliver any product at all (Table 1, entry 13). Finally, evaluation of the reaction time showed that shorter periods were also feasible (Table 1, entries 14–16), in particular, if a five-hour reaction time was used. These conditions, from now on named as 'conditions A' were subsequently used for the synthesis of oxazolidinones from primary aliphatic amines (conditions A, Table 1, entry 16).

To test whether the optimized conditions were also applicable to primary aromatic amines, aniline **3b** was next submitted to the established 'conditions A', with the exception of an elongated reaction time of 16 h. These conditions led to the respective oxazolidinone **5b** in a yield of only 11% (Table 2, entry 1). Therefore, a second optimization of the reaction conditions for aromatic amines was performed, initiated by screening different carbonate salts (Table 2, entries 2–5, Supporting Information Table S2). We found that usage of cesium hydrogencarbonate led to an improved isolated yield of 41%. Variation of the reaction temperature also had an impact on the reaction outcome and revealed that a temperature of 50 °C led to higher yields (Table 2, entries 6–9). Finally, the effect of the reaction time was investigated but confirmed that 16 h were most beneficial (Table 2, entries 10–11). Overall, this led to the optimized 'conditions B' for the synthesis of oxazolidinones from aromatic amines (Table 2, entry 8).

With the optimized reaction conditions A and B in hand, we set out to explore the corresponding reaction scope (Scheme 2). To this end, we first tested the suitability of condition A to convert various aliphatic amines into oxazolidinones. 4-Chloro-, 4-cyano-, 4-methoxybenzylamine, and ethyl 4-(aminomethyl)benzoate (**3c–3f**) as well as 4-bromo- and 3-methoxyphenethylamine (**3g** and **3h**) formed the corresponding oxazolidinones **5c–5h** in high yields, comparable to the previously observed outcome for benzylamine (**3a**). In contrast,

Table 1. Optimization of the reaction conditions for generating oxazolidinone **5a** from benzylamine (**3a**) and DBE (**4**) as starting material.



Entry	Equiv of **4**	M_2CO_3 or $MHCO_3$	Solvent [M]	t [h]	Yield of **5a** [%][a]
1[b]	5	Cs_2CO_3	DMSO (0.243)	16	60
2	5	Cs_2CO_3	DMSO (0.243)	16	67
3	2	Cs_2CO_3	DMSO (0.243)	16	77
4	1.5	Cs_2CO_3	DMSO (0.243)	16	73
5	2	Cs_2CO_3	DMSO (0.122)	16	86 (83)
6	2	Cs_2CO_3	DMSO (0.097)	16	83
7	2	Cs_2CO_3	DMF (0.122)	16	50
8	2	Cs_2CO_3	MeOH (0.122)	16	0
9	2	Cs_2CO_3	THF (0.122)	16	0
10	2	$CsHCO_3$	DMSO (0.122)	16	20
11	2	Na_2CO_3	DMSO (0.122)	16	34
12	2	K_2CO_3	DMSO (0.122)	16	62
13	2	–	DMSO (0.122)	16	0
14	2	Cs_2CO_3	DMSO (0.122)	2	53
15	2	Cs_2CO_3	DMSO (0.122)	4	79
16	**2**	**Cs_2CO_3**	**DMSO (0.122)**	**5**	**84 (82)**

[a] Yield determined by ^{1}H NMR spectroscopy using 1,1,2-trichloroethane as the internal standard. In brackets: isolated yield after column chromatography. [b] Reaction was conducted at 60 °C.

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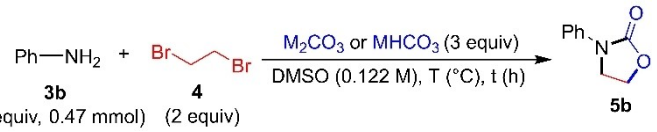
Table 2. Optimization of the reaction conditions for the conversion of aniline (**3b**) and DBE (**4**) into oxazolidinone **5b**.



3b (1 equiv, 0.47 mmol) **4** (2 equiv) **5b**

Entry	M_2CO_3 or $MHCO_3$	T [°C]	t [h]	Yield of **5b** [%][a]
1	Cs_2CO_3	25	16	11
2	Na_2CO_3	25	16	4
3	K_2CO_3	25	16	14
4	$KHCO_3$	25	16	10
5	$CsHCO_3$	25	16	42 (41)
6	$CsHCO_3$	75	16	64
7	$CsHCO_3$	60	16	71
8	**$CsHCO_3$**	**50**	**16**	**71 (74)**
9	$CsHCO_3$	40	16	55
10	$CsHCO_3$	50	4	37
11	$CsHCO_3$	50	8	47

[a] Yield determined by ^{1}H NMR spectroscopy using 1,1,2-trichloroethane as the internal standard. In brackets: isolated yield after column chromatography.

4-(aminomethyl)-*N*-methylbenzamide and 4-(aminomethyl)benzamide (**3i** and **3j**) delivered oxazolidinones **5i** and **5j** only in rather low yields. But the heterocyclic compound tryptamine (**3k**) was transformed into the desired product (**5k**) in a high yield. Interestingly, we also found that benzylamine (**3a**) and dibromopropane (DBP, **6**) formed oxazinanone **7** in a moderate yield, indicating the feasibility to extend the scope of the reaction also towards six-membered rings. To test the tolerance of further functional groups, starting materials with a terminal alkyne (**3l**), a terminal ethene (**3m**), as well as a phosphonate group (**3n**), were submitted to the standard conditions A, producing the oxazolidinones **5l**–**5n** in high to moderate yields. **3o** as a starting material for the envisaged synthesis of the oxazolidinone-modified DPP8 inhibitor was synthesized in six steps and formed the desired oxazolidinone **5o** in an excellent yield. This result demonstrates that the oxazolidinone synthesis route can also be applied to more complex starting materials and at a later stage of organic synthesis. We next evaluated the reaction scope of conditions B for the oxazolidinone synthesis from primary aromatic amines. For all tested *para*-substituted anilines (**3p**–**3t**), overall high yield conversions were observed (**5p**–**5t**), comparable to those obtained with aniline (**3b**) as starting material. Surprisingly, even a free phenol group (**3s**) was tolerated, as demonstrated by the production of oxazolidinone **5s**. 4-Methoxyaniline (**3t**) was also efficiently converted as well as the heterocyclic pyrazole amine starting material (**3u**). Finally, we tested 'conditions B' for more complex starting materials by converting them into the corresponding oxazolidinone **5v** as well as by the synthesis of the known antibiotic drug furazolidone (**5w**) by a straightforward two-step sequence. Of note, the synthesis of **5w** was achieved by the usage of a hydrazone instead of an amine starting material, indicating that the reaction scope extends beyond amines.

A mechanistic proposal for the oxazolidinone synthesis from aliphatic amines is given in Scheme 3. First, intermediate **I** is formed by a base-promoted nucleophilic substitution at DBE and the following steps could occur via two possible pathways. The reaction could proceed as depicted by route A leading to intermediate **II**, a carbamate built from cesium hydrogencarbonate or in situ formed carbon dioxide as a C1 source, followed by the final, irreversible cyclization step. Alternatively, route B could be followed, consisting of a nucleophilic attack of cesium hydrogencarbonate at the alkyl bromide moiety of **I**, thereby forming intermediate **III**, followed by the final cyclization step.

Control experiments were conducted to gather evidence for the proposed reaction mechanism (Supporting Information Scheme S1). To this end, we synthesized some potential reaction intermediates and submitted them to the established reaction conditions. This approach allowed us to exclude the formation of aziridine, ethylene carbonate, and amino alcohol intermediates. An oxazolidinone product was however obtained if *N*-benzyl-2-bromoethan-1-aminium bromide, corresponding to intermediate **I**, was used as a starting material, which could support the first step of the reaction mechanism (Supporting Information Scheme S1EF). If the reaction continues via route A or B remains elusive. In our hands, DBE and cesium carbonate did not form ethylene carbonate at the employed reaction conditions (Supporting Information Scheme S1G), this however does not exclude route B.

Although we have made control experiments for the reaction with aliphatic amines as starting material, it seems probable that the same reaction mechanism is also underlying the oxazolidinone synthesis with aromatic amines. The finding that different cesium salts, i.e. cesium carbonate for aliphatic amines (conditions A) and cesium hydrogencarbonate for aromatic amines (conditions B), deliver better yields might be explained by a different rate-determining step in the reaction sequence: in reactions with aliphatic amines, intermediate **I** was not detected during LC–MS-based reaction controls, thus indicating a fast transformation of **I** into the corresponding oxazolidinone and the generation of intermediate **I** as the rate-determining step. In the case of aromatic amines such as aniline, intermediate **I** was however robustly detected in LC–MS reaction control runs, particularly if cesium carbonate instead of

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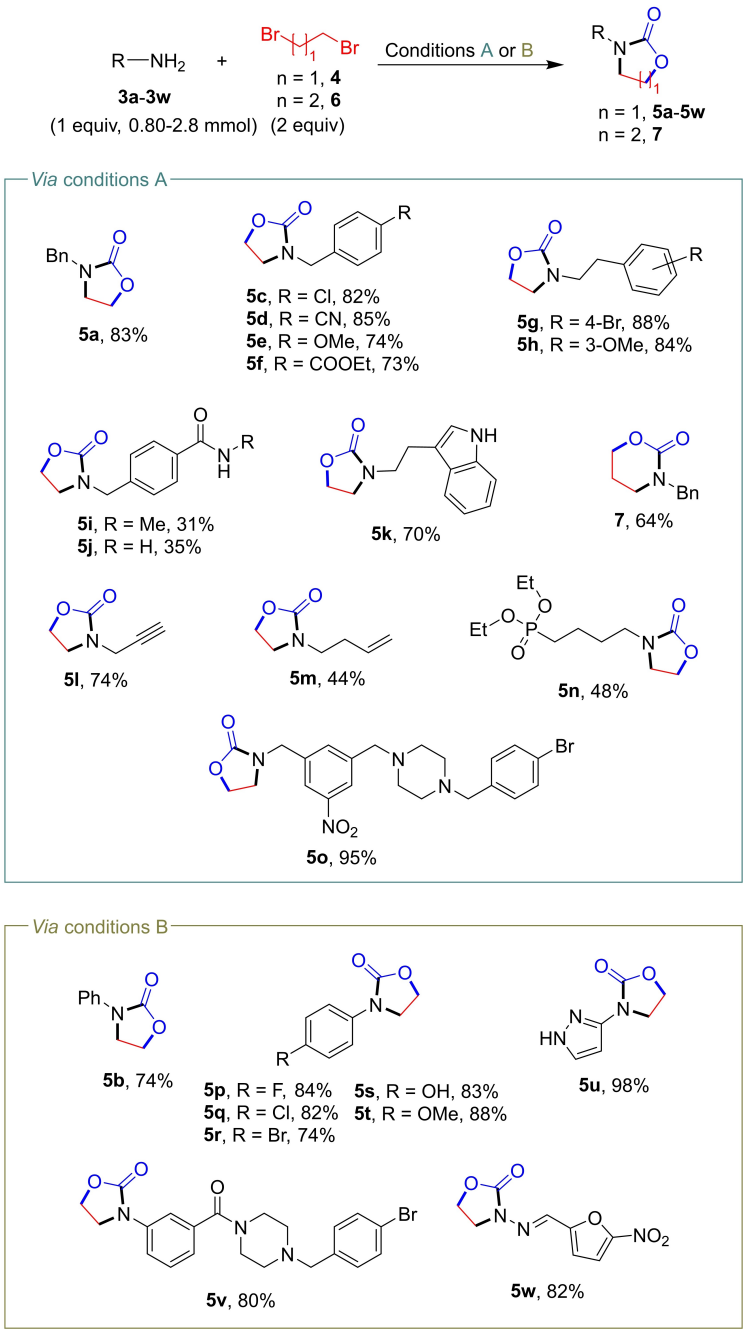

Scheme 2. Exemplary applications of the developed oxazolidinone multicomponent synthesis. Reported are the isolated yields after column chromatography. Conditions A: Cs_2CO_3 (3 equiv), DMSO (0.122 M), 25 °C, 5 h. Conditions B: $CsHCO_3$ (3 equiv), DMSO (0.122 M), 50 °C, 16 h.

cesium hydrogencarbonate was used as a base and C1 source (Supporting Information Figures S1–3). This finding additionally supports the proposed reaction mechanism via intermediate **I** but also seems to indicate that the subsequent steps are less rapid for aromatic amines and thus now appear rate-determining.

After the establishment of the oxazolidinone synthesis route, we continued with the envisaged synthesis of the oxazolidinone-modified 4-oxo-β-lactam derivative (**2**). To this end, we used oxazolidinone **5o** as a precursor and continued the synthesis with a reduction of the nitro-group by stannous chloride, thereby forming precursor **8** that was directly converted into the desired oxazolidinone-4-oxo-β-lactam **2** by a reaction with diethylmalonyl dichloride (Scheme 4).

The synthesized inhibitor **2** was then tested in biochemical DPP8 and DPP9 inhibition assays (Figure 2). In these assays, **2** inhibited DPP8 with an IC_{50} of 26.0 ± 11.9 μM while for DPP9, due to insufficient inhibition, no IC_{50} could be determined. In contrast, the parent, non-oxazolidinone-modified compound **1** inhibited both proteases in these assay conditions with an IC_{50}

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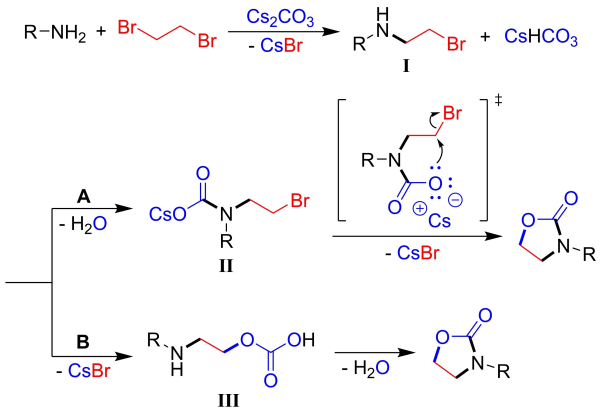
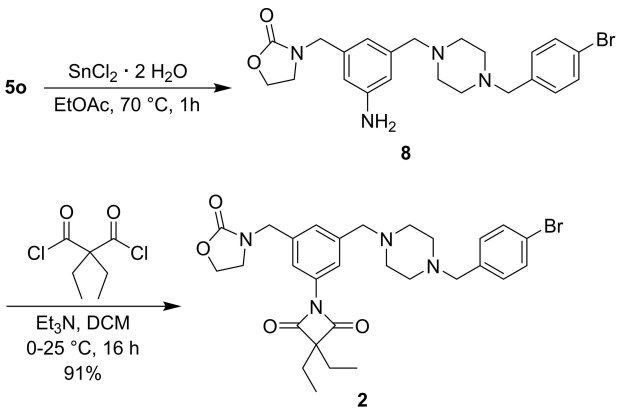


Scheme 3. Proposed reaction mechanism for the formation of aliphatic oxazolidinones. The reaction starts with an initial nucleophilic substitution step leading to the secondary amine intermediate **I**. The next steps can occur either via route A which is the formation of a carbamate intermediate **II**, followed by cyclization, or route B, in which a carbonate intermediate **III** is formed before the final cyclization step takes place.



Scheme 4. Synthesis of the envisaged oxazolidinone-modified 4-oxo-β-lactam-based DPP8 and DPP9 inhibitor (**2**).

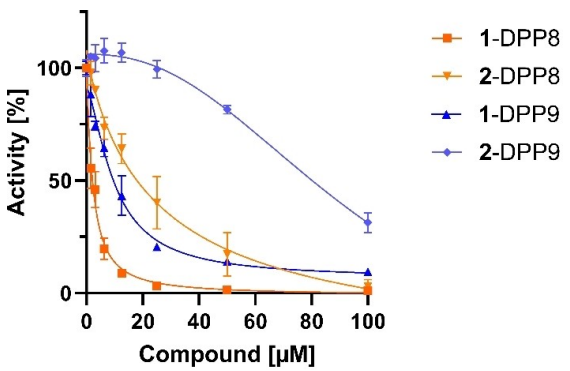


Figure 2. DPP8 and DPP9 inhibition curves of the parent unmodified 4-oxo-β-lactam **1** and the oxazolidinone-modified inhibitor **2**. Compound **2** is a less potent inhibitor than **1** but more DPP8 selective due to the oxazolidinone scaffold.

of 2.33 ± 2.06 μM (DPP8) and an IC_{50} of 9.99 ± 1.45 μM (DPP9) (Figure 2). Accordingly, compound **2** displays a promising DPP8 versus DPP9 selectivity, particularly in the low micromolar range (< 10 μM) in which no inhibition of DPP9 has yet been observed.

Conclusions

Oxazolidinones are pharmacologically and chemically important compounds. Here, we showed that N-substituted oxazolidinones can be straightforwardly generated in a technically simple and mild multicomponent approach from primary aliphatic or aromatic amines, DBE and cesium carbonate or cesium hydrogencarbonate, respectively, serving both as a base and C1 source. In contrast to many other reported methodologies, this approach works without the addition of carbon dioxide gas and thus specialized technical equipment. We demonstrated a promising reaction scope with a broad functional group tolerance, thereby allowing a facile synthesis of a variety of oxazolidinones from easily accessible primary amines. The applicability of the established reaction sequence for late-stage modifications was also demonstrated by the conversion of structurally more complex substrates. We then proposed a potential operating reaction mechanism that was supported by test reactions and LC–MS reaction controls. Finally, we used this methodology to generate an oxazolidinone-modified 4-oxo-β-lactam inhibitor of DPP8 with promising target selectivity. Overall, we believe that the developed methodology with its technical simplicity and robustness represents a valuable addition to the established oxazolidinone synthesis repertoire and may find wide application, particularly in the medicinal chemistry field to probe structure-activity relationships of chemical inhibitors.

Experimental Section

Reaction conditions A: oxazolidinone synthesis from aliphatic primary amines, DBE or DBP, and cesium carbonate: The corresponding amine (1 equiv) and dibromoalkyl reagent (2 equiv) were dissolved in DMSO (0.122 M with respect to the limiting reagent) and Cs_2CO_3 (3 equiv) was subsequently added at 25 °C. The resulting mixture was stirred at 25 °C under Ar for 5 h until it was quenched by the addition of H_2O and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (silica gel, EtOAc:cyclohexane, or MeOH:DCM) affording the corresponding oxazolidinone in pure form.

Reaction conditions B: oxazolidinone synthesis from primary aromatic amines, DBE, and cesium hydrogencarbonate: The corresponding amine (1 equiv) and DBE (2 equiv) were dissolved in DMSO (0.122 M with respect to the limiting reagent) and $CsHCO_3$ (3 equiv) was subsequently added at 25 °C. The resulting mixture was heated to 50 °C and stirred at this temperature under Ar for 16 h. After the mixture was allowed to cool to 25 °C, it was quenched by the addition of H_2O and diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo. The crude

product was purified by flash column chromatography (silica gel, EtOAc:cyclohexane, or MeOH:DCM) affording the corresponding oxazolidinone in pure form.

Biochemical inhibition assays: Enzyme activity of DPP4, DPP8, and DPP9 was determined by measuring the initial velocity of AMC release from the substrate GP-AMC using a Tecan Spark® 10 M multimode microplate reader in activity buffer (20 mM HEPES/KOH pH 7.3, 110 mM potassium acetate, 2 mM Mg acetate, 0.5 mM EGTA, 0.02% Tween 20, supplemented with 1 mM DTT) and a final volume of 20 μL for 15 min at 30 °C. Before the activity measurement, 10 nM enzyme was incubated for 45 min at 30 °C and gentle shaking with the inhibitor compounds in concentrations ranging from 0 to 100 μM. The test compounds were dissolved in DMSO and diluted in activity buffer (final DMSO concentration: 0.295%). To the inhibitor-enzyme mixture, GP-AMC was added to a final concentration of 250 μM. Afterward, enzyme activity was determined by calculating the slope (fluorescence release over time) and plotted against the concentrations of the inhibitor. IC_{50} values were calculated using the Graph-Pad software using the equation: [Inhibitor] vs. response-variable slope. All measurements were performed in triplicates and error bars represent standard errors of the fit.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

All raw data produced in this study will be made available upon reasonable request.

Keywords: annulation · carbonate C1 source · DPP8 and DPP9 inhibitors · multicomponent reactions · oxazolidinones

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