Direct organocatalytic synthesis of enantiopure succinimides from β-lactam aldehydes through ring expansion promoted by azolium salt precatalysts†

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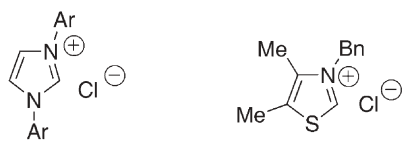
A single-step catalytic ring expansion approach from 4-oxoazetidine-2-carbaldehydes to enantiopure succinimides has been achieved by the use of a base (DBU) and a thiazolium salt precatalyst.

Succinimides constitute an important compound class due to their wide profile of biological activity.[1] Besides, the succinimide nucleus is a useful building block for the synthesis of natural as well as unnatural products,[2] and succinimide-based pseudopeptides have been shown to stabilize β-turn conformations.[3] On the other hand, in addition to the key role that β-lactams have played in the fight against pathogenic bacteria, the use of 2-azetidinones as chiral building blocks in organic synthesis is now well established.[4] Although many efforts have been made in these fields, the preparation of the succinimide ring from the β-lactam nucleus has remained unexplored, with the only exception being our one-flask three-step process from β-lactam aldehydes involving imine formation, TBACN-promoted ring expansion and selective imine hydrolysis.[5] One aspect of the above transformation is the prerequisite of preparing the imino-β-lactam in a separate step coupled with the necessity of a final hydrolysis step. Herein, we present an alternative single-step approach starting directly from 4-oxoazetidine-2-carbaldehydes by the use of a thiazolium salt precatalyst, thus further enhancing the applicability of this unconventional transformation. The inspiration comes from our previous report on the addition reaction of 2-(trimethylsilyl)-thiazole to 4-oxoazetidine-2-carbaldehydes to give enantiopure α-alkoxy-γ-keto acid derivatives *via* a novel N1–C4 bond breakage of the β-lactam nucleus,[6] in conjunction with the fact that thiazolium salts have been reacted with an aziridinylcarbaldehyde to afford a β-aminoester.[7]

Precursors for succinimide formation, enantiopure 2-azetidinones **1a–e**, were prepared using standard methodology as single *cis*-enantiomers from aryl imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with the corresponding acetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[8] Enantiopure spiranic or 3-substituted 3-alkoxy-β-lactam aldehydes **1f** and **1g** were prepared from (*S*)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(4-methoxyphenyl)azetidine-2,3-dione *via* metal-mediated Barbier-type carbonyl–addition reactions in aqueous media followed by functionalization reactions, as we recently described.[9] First, the general reactivity of 4-oxoazetidine-2-carbaldehydes toward the ring expansion reaction was tested with substrate **1a** by the use of commercially available imidazolium salt **2** as well as readily prepared thiazolium chloride **3** (Fig. 1).[10] The combination of an amine base and azolium salts **2** or **3** should produce the necessary nucleophilic zwitterionic catalyst *in situ* which promotes the β-lactam to succinimide conversion.[11] At the outset, reaction of β-lactam aldehyde **1a** was studied by using different loadings (1–10 mol%) of both azolium precatalysts and bases (Table 1). While Hünig's base or triethylamine afforded poor (imidazolium chloride **2**) or moderate (thiazolium chloride **3**) yields of succinimide **4a**, the chemical yields were good when DBU was used. The activity of the azolium salt precatalyst was similar in the presence of DBU, but a superior yield (88% *vs.* 57%) was obtained by the use of thiazolium chloride **3** in comparison with imidazolium salt **2** (Table 1, entries 5 and 10). Optimization of solvent revealed that acetonitrile was superior to chlorinated or aromatic solvents. Optimal reactivity was obtained at 80 °C when 5 mol% of thiazolium chloride **3** and 10 mol% of DBU were employed in boiling acetonitrile. With the best succinimide formation conditions identified, the scope of this transformation was examined (Table 2).‡ No advantage accrues from changing the methoxy group at C1 to a benzyloxy (Table 2, entry 1) in the starting 4-oxoazetidine-2-carbaldehyde **1**. Interestingly, nitrogenated substituents can be incorporated onto the β-lactam scaffold to afford good yield of succinimide **4c** (Table 2, entry 2).[12] Both placing a less electron-donating substituent in the *para* position of the *N*-aryl ring (Table 2, entry 3) as well as the introduction of one halogen atom at the 4-position of the aromatic ring (Table 2, entry 4) slightly decreased the efficiency of the process. β-Lactams bearing a benzyl or an allyl substituent at nitrogen failed to give the ring expansion; partial epimerization together with some unreacted aldehyde was observed.



2 Ar = 2,4,6-MeC_6H_2 **3**

Fig. 1 Structure of azolium salt precatalysts **2** and **3**.

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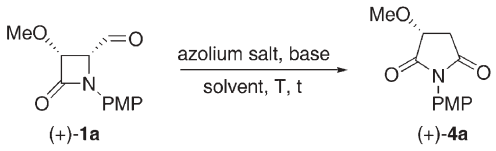
† Electronic supplementary information (ESI) available: Compound characterization data and experimental procedures for all new compounds. See DOI: 10.1039/b711473g

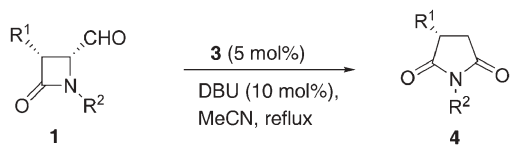
Table 1 Optimization of β-lactam ring expansion reaction conditions[a]



Entry	Precatalyst (mol%)	Base (mol%)	Solvent	*T*/°C	*t*/h	Yield (%)[b]
1	**2** (10)	$(i\text{Pr})_2\text{EtN}$ (10)	CH_2Cl_2	40	23	[c]
2	**2** (10)	$(i\text{Pr})_2\text{EtN}$ (10)	MeCN	80	22	[d,e]
3	**2** (10)	Et_3N (10)	MeCN	80	22	[d,f]
4	**2** (10)	DBU (10)	MeCN	80	0.75	53
5	**2** (5)	DBU (10)	MeCN	80	0.33	57
6	**2** (1)	DBU (10)	MeCN	80	21	[d,g]
7	**2** (1)	DBU (5)	MeCN	80	18	[d,h]
8	**3** (5)	$(i\text{Pr})_2\text{EtN}$ (10)	MeCN	80	22	54
9	**3** (5)	Et_3N (10)	MeCN	80	21	[d,i]
10	**3** (5)	DBU (10)	MeCN	80	0.33	88
11	**3** (5)	DBU (5)	MeCN	80	18	[d,j]
12	**3** (2)	DBU (10)	MeCN	80	0.33	67
13	**3** (1)	DBU (10)	MeCN	80	0.33	64

[a] PMP = 4-$MeOC_6H_4$. [b] Yields are for pure isolated products with correct analytical and spectroscopic data. [c] A complex mixture of uncharacterized products was obtained. [d] A mixture of compounds **1/4** was obtained as determined by ^{1}H NMR analysis of the crude reaction mixture before purification. In addition, some epimerization of the starting aldehyde was detected. [e] Ratio **1a** : **4a** = 79 : 9; 12% epimerization of **1a**. [f] Ratio **1a** : **4a** = 79 : 14; 7% epimerization of **1a**. [g] Ratio **1a** : **4a** = 24 : 54; 22% epimerization of **1a**. [h] Ratio **1a** : **4a** = 36 : 35; 29% epimerization of **1a**. [i] Ratio **1a** : **4a** = 27 : 63; 10% epimerization of **1a**. [j] Ratio **1a** : **4a** = 18 : 76; 6% epimerization of **1a**.

Table 2 Scope of β-lactam ring expansion reaction[a]

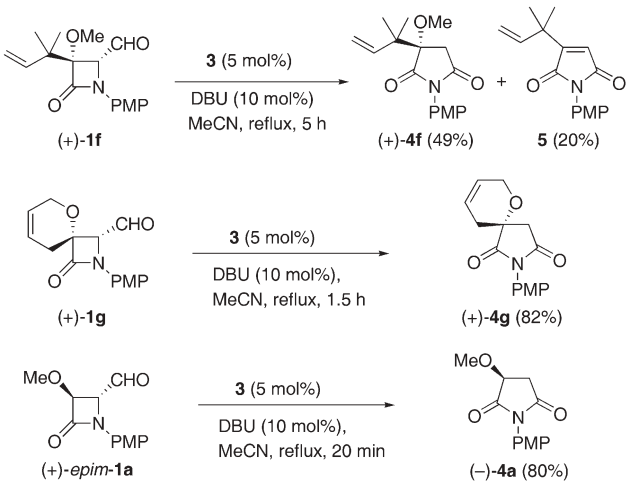


Entry	Aldehyde	R^1	R^2	*t*/h	Product	Yield (%)[a]
1	(+)-**1b**	BnO	PMP[b]	1	(+)-**4b**	62
2	(+)-**1c**	Pht[c]	PMP	0.3	(+)-**4c**	87
3	(+)-**1d**	MeO	PMeP[d]	2	(+)-**4d**	78
4	(+)-**1e**	MeO	PCP[e]	2	(+)-**4e**	76

[a] Yields are for pure isolated products with correct analytical and spectroscopic data. [b] PMP = 4-$MeOC_6H_4$. [c] Pht = phthalimidoyl. [d] PMeP = 4-MeC_6H_4. [e] PCP = 4-ClC_6H_4.

Gratifyingly, the reaction of sterically encumbered 4-oxoazetidine-2-carbaldehydes **1f** and **1g** afforded in reasonable yields enantiopure tertiary and spiranic succinimide derivatives **4f** and **4g** (Scheme 1).[13] Next, the response of the ring expansion reaction to the stereochemically different *trans*-β-lactam aldehyde *epim*-**1a** was explored.[14] Happily, the enantiopure succinimide *enant*-**4a** was obtained in good yield (Scheme 1), matching the absolute configuration of the succinimide product to that of the corresponding β-lactam aldehyde. Therefore, a synthesis of both enantiomers of succinimide derivatives could be achieved.

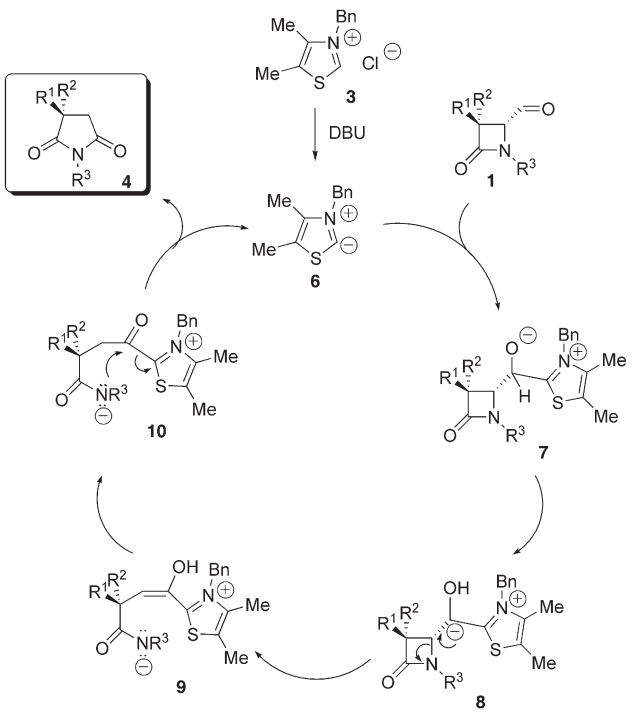
Our proposed working catalytic cycle to account for the new ring expansion is shown in Scheme 2. It involves the nucleophilic



Scheme 1 Preparation of conformationally constrained enantiopure succinimides **4f** and **4g** and succinimide *enant*-**4a**.

addition of a zwitterionic species **6**, generated *in situ* from the exposure of the azolium salt **3** to DBU, to a 4-oxoazetidine-2-carbaldehyde **1**. This addition product, alkoxide **7**, initiates a 1,2-hydrogen group migration and produces intermediate **8**. Due to ring strain, species **8** would suffer a N1–C4 β-lactam bond breakage to afford the enolamide intermediate **9** and reforms the carbonyl to species **10**, which produces the succinimide compound **4** with concomitant liberation of the catalyst.

In conclusion, this is the first single-step catalytic approach to the succinimide core *via* the thiazolium-catalyzed ring expansion reaction of the β-lactam nucleus. This mild protocol uses a neutral organic molecule as the catalyst, can install polysubstitution at the



Scheme 2 Proposed reaction course for the formation of succinimides **4** from 4-oxoazetidine-2-carbaldehydes **1**.

succinimide ring, and can provide both enantiomers of the final product. Studies concerning the scope and generality of this methodology are underway in our laboratory, and further details will be reported in due course.

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Notes and references

‡ *Representative experimental procedure* for the β-lactam ring expansion reaction: synthesis of succinimides **4**. DBU (15 mg, 0.10 mmol, 15 μL) was added to a stirred solution of thiazolium chloride **3** (12 mg, 0.05 mmol) and the appropriate 4-oxoazetidine-2-carbaldehyde **1** (1.0 mmol) in acetonitrile (10 mL). The reaction mixture was heated at 80 °C until complete disappearance (TLC) of starting material. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and analytically pure adducts **4** were obtained after purification by flash chromatography on silica gel using hexanes–ethyl acetate mixtures.

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10 Precatalyst **3** was prepared from 4,5-dimethylthiazole and benzyl chloride as reported in ref. 7.

11 No succinimides were produced in the absence of the catalyst or in the presence of azolium salt or base on their own.

12 No loss of enantiomeric purity of succinimides **4** was evident by the ^{1}H NMR spectra in presence of a chiral shift reagent of europium(III), except for phthalimidoyl succinimide **4c** which was obtained in 50% ee. It is well known that the structurally related thalidomide may suffer racemization even at physiological conditions. See: (*a*) T. Yamada, T. Okada, K. Sakaguchi, Y. Ohfune, H. Ueki and V. A. Soloshonok, *Org. Lett.*, 2006, **8**, 5625; (*b*) T. Eriksson, S. Bjorkman, B. Roth, A. Fyge and P. Hoglund, *Chirality*, 1998, **10**, 223; (*c*) M. Reist, P. A. Carrupt, E. Francotte and B. Testa, *Chem. Res. Toxicol.*, 1998, **11**, 1521; (*d*) B. Knoche and G. Blaschke, *J. Chromatogr., A*, 1994, **666**, 235.

13 It was observed that the organocatalyzed reaction of β-lactam aldehyde **1f** yielded as main product succinimide **4f**, together with maleimide **5** (Scheme 1). The formation of compound **5** involves methanol elimination under the reaction conditions to relieve the strain.

14 Optically pure *trans*-4-oxoazetidine-2-carbaldehyde (+)-*epim*-**1a** was prepared as reported, see: D. R. Wagle, C. Garai, J. Chiang, M. G. Monteleone, B. E. Kurys, T. W. Strohmeyer, V. R. Hedge, M. S. Manhas and A. K. Bose, *J. Org. Chem.*, 1988, **53**, 4227.

