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Organocatalytic Ring Expansion of β-Lactams to γ-Lactams through a Novel N1–C4 Bond Cleavage. Direct Synthesis of Enantiopure Succinimide Derivatives

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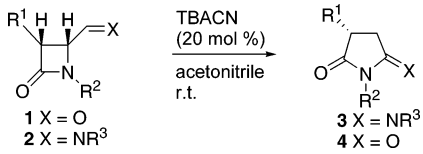
ABSTRACT



Tetrabutylammonium cyanide (20 mol %) catalyzes ring expansion of 4-(arylimino)methylazetidin-2-ones 2 to 5-aryliminopyrrolidin-2-ones 3 through a novel N1–C4 bond cleavage of the β-lactam nucleus. New, efficient one-pot protocols to enantiopure succinimide derivatives 3 and 4 from β-lactam aldehydes 1 have also been developed.

Due to ring strain, azetidin-2-ones are susceptible to ring-cleavage reactions. We and others have successfully exploited this property, demonstrating the usefulness of β-lactams as building blocks in the stereocontrolled synthesis of a wide variety of compounds.[1] Opening of the β-lactam ring can occur through cleavage of one or more of its bonds.[2] Cleavage of the amide bond by nucleophilic attack at the N1−C2 bond is the most common and has been the subject of many investigations to give β-amino acids,[1d] taxoids,[3] pyrrolizidines and indolizidines,[4] macrocyclic alkaloids,[5] and complex natural products. *N*-Carboxy anhydrides, α-amino acids, and peptides have been obtained by breakage of the C2−C3 bond.[6] Pyrazines, oxazines, and eight-membered lactams can be prepared through cleavage of the C3−C4 bond on the β-lactam nucleus.[7] Cleavage of the N1−C4 bond of 4-arylazetidin-2-ones by hydrogenolysis is a very well-known methodology developed by Ojima for the synthesis of α-amino acids and peptidomimetics.[8] Furthermore, McMurray et al. have reported the N1−C4 ring opening of 4-(4′-hydroxyphenyl)-2-azetidinones, leading to 4-hydroxyhydro-

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cinnamides or glutarimides, after treatment with base; "tyrosyl" peptidomimetics were also obtained under acidic conditions.[9] Also, we recently described the synthesis of α-alkoxy-γ-keto acid derivatives via N1−C4 bond cleavage when we reacted 2-(trimethylsilyl)thiazole with azetidin-2-ones lacking an aryl moiety at C4.[10]

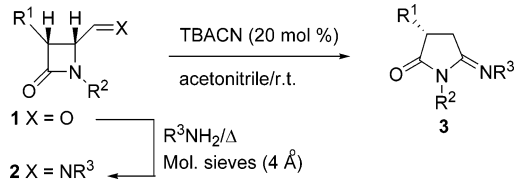
As part of a program aimed at exploring new reactivity patterns for the β-lactam nucleus and subsequent synthetic applications,[11] we now document the catalytic synthesis of enantiopure 5-aryliminopyrrolidin-2-ones **3** as well as pyrrolidine-2,5-diones (succinimides) **4** from 4-(arylimino)-methylazetidin-2-ones **2**. In addition to providing a new method for the preparation of these important compounds from readily available starting materials, our chemistry unveils the first organocatalytic N1−C4 bond breakage of the β-lactam skeleton.

Succinimides are an important class of heterocyclic compounds with numerous pharmacological applications in different fields[12] such as irreversible protease inhibitors.[13] Succinimide-based pseudopeptides have been shown to stabilize β-turn conformations.[14] Also, succinimides have been used as valuable reagents and intermediates in the synthesis of natural and unnatural compounds.[15] Due to the many uses of 3-heterosubstituted succinimides and related pyrrolidin-2-one derivatives in organic and medicinal chemistry, the development of new synthetic routes to these versatile compounds is an important endeavor.[16]

Our enantiopure cis-disubstituted 4-oxoazetidinecarbaldehyde starting substrates **1a**−**d** were prepared from the [2 + 2]-cycloaddition reactions of (*R*)-2,3-*O*-isopropylidene-glyceraldehyde imines with methoxy- or benzyloxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[4,17] Treatment of aldehydes **1** with aromatic amines in the presence of molecular sieves (4 Å), in refluxing benzene for 4−6 h, provided the corresponding imines **2** (Table 1) in nearly quantitative yields, which were used without further purification.

The use of tetrabutylammonium cyanide (TBACN) as catalyst for the cyanosilylation of carbonyl compounds with

Table 1. Catalytic Expansion of 4-Oxoazetidine-2-carbaldehydes **1** and 4-Imino-β-lactams **2** into 5-Iminopyrrolidin-2-ones **3**



compd	R^1	$R^{2\,a}$	R^3	*t* (h)	product	yield[b] (%)
(+)-**2a**	MeO	PMP	PMP	2	(+)-**3a**	64
(+)-**2b**	MeO	Bn	PMP	1.5	(+)-**3b**	45
(+)-**2c**	MeO	allyl	PMP	1.5	(+)-**3c**	44
(+)-**2d**	MeO	PMP	*p*-MeC_6H_4	2.5	(+)-**3d**	63
(+)-**2e**	MeO	PMP	*p*-ClC_6H_4	2	(+)-**3e**	44
(+)-**2f**	MeO	PMP	*p*-$Me_2NC_6H_4$	24	(+)-**3f**[c]	53
(+)-**1a**	MeO	PMP	PMP	6	(+)-**3a**[d]	70
(+)-**1c**	MeO	allyl	PMP	5.5	(+)-**3c**[d]	50
(+)-**1d**	BnO	PMP	PMP	24	(+)-**3g**[d]	67

[a] PMP = 4-$MeOC_6H_4$. [b] Yields are from aldehydes **1**, for pure isolated products with correct analytical and spectroscopic data. [c] 50 mol % of TBACN was used in this case. [d] One-pot synthesis in acetonitrile; *t* is overall time.

trialkylsilyl cyanides has been scarcely studied,[18] and as far as we know its use is unprecedented for the Strecker reaction of imino derivatives. However, other applications of this reagent both as nucleophile or base have been reported.[19] In this context, we began this work by investigating the cyanosilylation of *cis*-4-imino-β-lactam (+)-**2a** with *tert*-butyldimethylsilyl cyanide (1.2 equiv) catalyzed by TBACN (20 mol %) in dry acetonitrile at room temperature. The reaction provided the enantiomerically pure 5-aryliminopyrrolidin-2-one (+)-**3a** in a reasonable 48% isolated yield after 24 h. The expected α-amino nitrile was not detected in the crude reaction mixture.

Importantly, we were pleased to find that use of catalytic amounts (from 50 to 10 mol %) of TBACN efficiently promoted ring expansion to pyrrolidine-2,5-dione (+)-**3a** without *tert*-butyldimethylsilyl cyanide being necessary for the reaction to occur. Optimal conditions were found when 20 mol % of TBACN was used as catalyst. Encouraged by these results, we decided to extend the process to a variety of imino-β-lactams **2b**−**f**, bearing benzyl, allyl, or *p*-methoxyphenyl substituents at the lactam nitrogen (Table 1, entries 2−6). The influence of the nature of different R^3 groups bonded to the imine nitrogen was studied next. This revealed that introducing one methyl group at the 4-position of the aromatic ring was not detrimental, although the NMe_2 and chlorine substituents were (Table 1, entries 4−6). To

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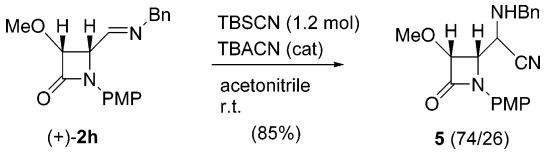
develop a more simple and convenient experimental procedure, we decided to explore a one-pot procedure for accessing **3** from aldehyde **1**, without imine **2** isolation. In this regard, a solution of compound (+)-**1a**, or (+)-**1c**, in acetonitrile was treated with *p*-anisidine and heated at reflux for 4 h in the presence of molecular sieves (4 Å). After the reaction mixture was cooled, a catalytic (20 mol %) amount of TBACN was added to the resulting imine solution, and the reactants were maintained at room temperature for 2 h. Formation of compounds (+)-**3a** or (+)-**3c** took place smoothly (Table 1, entries 7 and 8). The procedure was extended to a direct synthesis of 5-iminopyrrolidine-2-one (+)-**3g** from aldehyde (+)-**1d** (Table 1, entry 9). The presence of a bulkier R^1 group decreased the rate of ring expansion. A dramatic effect on the reactivity was observed with imines derived from aliphatic amines, as exemplified by the *N*-benzylimine (+)-**2h** (Scheme 1). Its reaction with

Scheme 1. Synthesis of α-Amino Nitrile **5** from *N*-Benzylimino-*β*-lactam (+)-**2h**



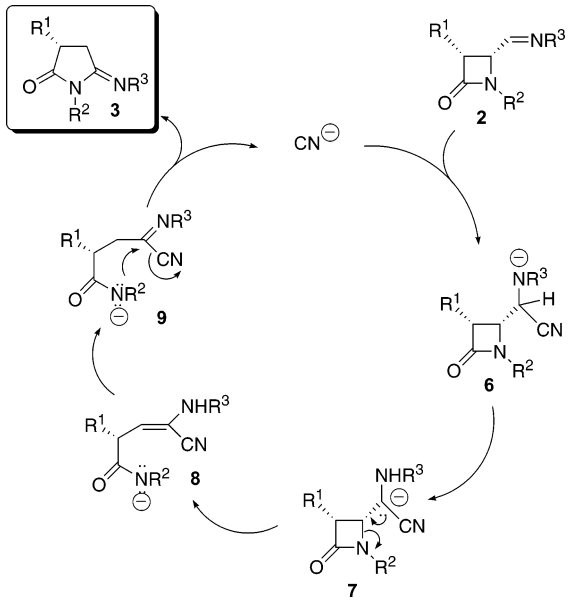
(+)-**2h** **5** (74/26)

TBACN under the above experimental conditions was troublesome.[20] α-Amino nitrile **5** was obtained as an easily separable mixture of diastereomers (74/26), by using 1.2 equiv of TBDMSCN in the presence of 10 mol % of TBACN, after 4.5 h (Scheme 2). From these results, we have concluded that an aromatic group bonded to the imine nitrogen is needed for an effective ring expansion to occur.

We propose the catalytic cycle shown in Scheme 2 to account for our new ring expansion. Under the reaction conditions, nucleophilic addition of cyanide to the imino group will form species **6** which will evolve into the corresponding α-cyano carbanion **7**. Intermediate **7** is then converted into the imino nitrile amide **9** via the corresponding enamino nitrile **8** formed by N1−C4 *β*-lactam bond breakage. This process should be favored for aromatic R^3 groups. Finally, anionic cyclization on the imino group with concurrent cyanide elimination should afford the iminopyrrolidin-2-one **3**.

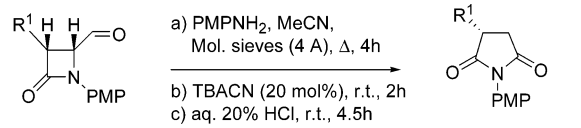
We have also investigated hydrolysis of the imino group of compounds **3** to provide enantiopure pyrrolidin-2,5-diones **4**.[21] Thus, iminopyrrolidin-2-one (+)-**3a** was treated with aqueous 20% HCl in acetonitrile at room temperature for

Scheme 2. Proposed Catalytic Cycle for the Formation of Succinimide Derivatives **3** from Imino-*β*-lactams **2**



4.5 h, to give pure succinimide (+)-**4a** in 64% yield. As a consequence, we decided to explore a new one-pot procedure for obtaining (+)-**4a** from aldehyde (+)-**1a**. Thus, the reaction mixture obtained by sequential treatment of compound (+)-**1a** with *p*-anisidine and a catalytic (20 mol %) amount of TBACN in acetonitrile was hydrolyzed in situ with aqueous HCl. The overall reaction yield for the one-pot method (55%) was improved when compared to the step-by-step procedure (41%). This yield represents a one-pot, three step process involving imine formation, catalytic ring expansion and selective imine hydrolysis (Scheme 3).

Scheme 3. One-Pot Synthesis of Succinimides **4** from *β*-Lactam Aldehydes **1**



(+)-**1a**: R^1 = OMe (+)-**4a** (55%)

(+)-**1d**: R^1 = OBn (+)-**4b** (50%)

Analogous results were observed in the preparation of succinimide (+)-**4b** (50%) from aldehyde (+)-**1d** (Scheme 3).

In conclusion, the first organocatalytic N1−C4 bond breakage of the *β*-lactam skeleton has been uncovered, and this relies upon appropriate substitution at C4. In addition, a new, direct method for the preparation of enantiopure 5-aryliminopyrrolidin-2-ones **3** as well as pyrrolidin-2,5-diones (succinimides) **4** from 4-(arylimino)methylazetidin-2-ones **2** is described. Studies concerning the scope and generality of this methodology as well as mechanistic

(20) No conversion was observed under catalytic conditions (20 mol % of TBACN, 142 h). A complex reaction mixture containing α-amino nitrile **5** was obtained when an equimolar amount of the reagent was used after prolonged reaction time (2 days).

(21) The overall transformation occurs without loss of the stereochemical integrity of the starting material. The optical purity was checked by ^{1}H NMR using tris[3-heptafluoropropylhydroxymethylene)-*d*-camphorate]-europium(III), Eu(hfc)$_3$, as the chiral shift reagent, both in the racemic and optically pure compounds.

implications are underway in our laboratory, and further details will be reported in due course.

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Supporting Information Available: General experimental procedures as well as spectroscopic and analytical data for compounds **2b**,**d**−**h**, **3a**−**g**, **4a**,**b**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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