I_2-Catalyzed enantioselective ring expansion of β-lactams to γ-lactams through a novel C3–C4 bond cleavage. Direct entry to protected 3,4-dihydroxypyrrolidin-2-one derivatives†

Benito Alcaide,*[a] Pedro Almendros,[b] Gema Cabrero[a] and M. Pilar Ruiz[a]

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Molecular iodine (10 mol%) efficiently catalyzes the ring expansion of 4-oxoazetidine-2-carbaldehydes 1 in the presence of *tert*-butyldimethyl cyanide to afford protected 5-cyano-3,4-dihydroxypyrrolidin-2-ones 2 with good yield and high diastereoselectivity, through a novel C3–C4 bond cleavage of the β-lactam nucleus.

The pyrrolidine ring is a ubiquitous structural feature of many natural products and pharmacologically active compounds.[1] Enantiopure pyrrolidines are versatile chiral building blocks for the synthesis of more complex derivatives,[1] as well as valuable organocatalysts, chiral auxiliaries and ligands for asymmetric syntheses.[2] In recent years, polyhydroxylated pyrrolidines, dihydroxylated pyrrolidin-2-ones and their synthetic analogues have attracted a great deal of attention due to the range of biological activities they exhibit,[3] including action as glycosidase inhibitors,[4] and anti-HIV candidates.[5] In addition, pyroglutamic acid derivatives are structural units of widespread chemical importance.[6,7] Although many methods have been reported for the synthesis of functionalized pyrrolidines, a great challenge is to design more direct asymmetric methods allowing access to functionalized rings which can provide complex compounds.[8]

Besides 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.[9] Due to ring strain, 2-azetidinones are susceptible to ring cleavage reactions with a broad range of reagents with high or often complete regio- and stereoselectivity.[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, enantioselective synthesis of protected 5-cyano-3,4-dihydroxypyrrolidin-2-ones **2** from 4-formylazetidin-2-ones **1**. In addition to providing a new method for the stereoselective preparation of these important compounds from readily available starting materials, our chemistry unveils a novel iodo-catalyzed C3–C4 bond breakage of the β-lactam skeleton.[12,13]

The starting substrates, enantiopure *cis*-4-oxoazetidine-2-carbaldehydes **1a–i**, were prepared from the [2 + 2]-cycloaddition reactions of (*R*)-2,3-*O*-isopropylideneglyceraldehyde imines with the appropriate substituted acetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis, and oxidative cleavage.[14]

The use of molecular iodine as a mild catalyst to promote various transformations is well documented in the literature.[15] In particular, iodine has been found to catalyze efficiently the addition of trimethylsilyl cyanide (TMSCN) to ketones[16] as well as the three-component condensation of aldehydes or ketones, amines and TMSCN for the synthesis of α-aminonitriles.[17] Our interest in the use of 4-oxoazetidine-2-carbaldehydes **1** as substrates for addition reactions,[14] prompted us to evaluate their cyanosilylation reaction with *tert*-butyldimethylsilyl cyanide (TBSCN) using iodine as the catalyst. In this context, we began this work by investigating the reaction of *cis*-4-formyl-β-lactam **1a** with TBSCN catalyzed by iodine in dry acetonitrile at room temperature. To our surprise, the reaction provided the 5-cyanopyrrolidin-2-one **2a** in a good 78% isolated yield after 1.5 h, with total diastereoselectivity (Table 1, entry 1). The expected addition product, **3a**, was not detected in the crude reaction mixture. Optimal conditions were found when 10 mol% of iodine was used as catalyst at room temperature.‡ Switching solvents (dichloromethane, THF, methanol) had no beneficial effects. Encouraged by these results, we decided to extend the process to a variety of 4-formyl-β-lactams **1a–i**, bearing different substitution patterns both at the lactam nitrogen and in position C3 (Table 1). The presence of a bulkier R^1 group decreased the rate of ring expansion while resulting in a totally diastereoselective process (Table 1, entry 2). β-Lactams bearing aliphatic substituents at nitrogen also give in a totally chemoselective process the corresponding expansion products **2** with good yields, but with decreased diastereoselectivity. To ensure the success of the reaction, a larger excess (2.5–5 equiv.) of the reagent was necessary in all these cases (Table 1, entries 5–7).

A dramatic effect on the reactivity was observed with formyl-β-lactams having R^1 groups different from alkoxy substituents at the C3 position, such as *p*-methoxybenzoyloxy, **1h**, and phthalimido, **1i**. No reaction took place under the reaction conditions used for compound **1a**. However, when 5 equiv. of TBSCN in the presence of 10 mol% of iodine were used, the corresponding *O*-silylated cyanohydrins **3h** and **3i** were obtained in reasonable yield as easily separable mixtures of *syn–anti*-diastereomers (Table 1, entries 8 and 9). The change in reactivity for compounds **1h** and **1i** supports the decisive role of the alkoxy groups at C3 in promoting the rearrangement to compounds **2**.

Next, the response of the iodo-catalyzed ring expansion reaction to the sterically encumbered 4-oxoazetidine-2-carbaldehydes **4a**

[a]*Departamento de Química Orgánica, Facultad de Química, Universidad Complutense de Madrid, 28040-Madrid, Spain. E-mail: alcaideb@quim.ucm.es; Fax: +34 91-3944103*
[b]*Instituto de Química Orgánica General, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain. E-mail: iqoa392@iqog.csic.es; Fax: +34 91-5644853*

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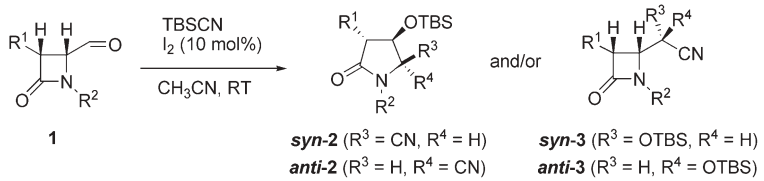
Table 1 Iodine mediated TBSCN addition to β-lactam aldehydes **1**. Catalytic expansion to 5-cyanopyrrolidin-2-ones **2** *vs.* *O*-silylated cyanohydrins **3**



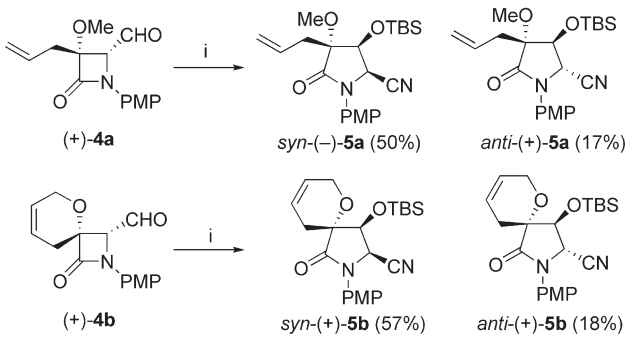
Entry	Aldehyde	R^1	R^{2a}	TBSCN (equiv.)	*t*/h	Product	*syn* : *anti* ratio	Yield (%)[b]
1	(+)-**1a**	MeO	PMP	1.5	1.5	(+)-**2a**	100 : 0	78
2	(+)-**1b**	BnO	PMP	2	3	(+)-**2b**	100 : 0	54[c]
3	(+)-**1c**	MeO	Bn	1.5	1.5	**2c**	90 : 10	70
4	(+)-**1d**	MeO	PMB	1.5	1.5	**2d**	90 : 10	80
5	(+)-**1e**	MeO	allyl	2.5	1.5	**2e**	86 : 14	65
6	(+)-**1f**	MeO	propargyl	4	1	**2f**	87 : 13	57
7	(+)-**1g**	BnO	PMB	2.5	2.5	**2g**	88 : 12	62
8	(+)-**1h**	PMBzO	PMP	5	1.5	**3h**	46 : 54	59
9	(+)-**1i**	Ft	PMP	5	1	**3i**	75 : 25	64

[a] PMP = 4-$MeOC_6H_4$; PMB = 4-$MeOC_6H_4CH_2$; PMBz = 4-$MeOC_6H_4CO$. [b] Combined yield of pure, isolated products **2** or **3** after silica gel chromatography with correct analytical and spectral data. [c] In addition, a further 15% yield of a *syn*–*anti* mixture (73 : 27) of *O*-silylated cyanohydrin **3b** was obtained.

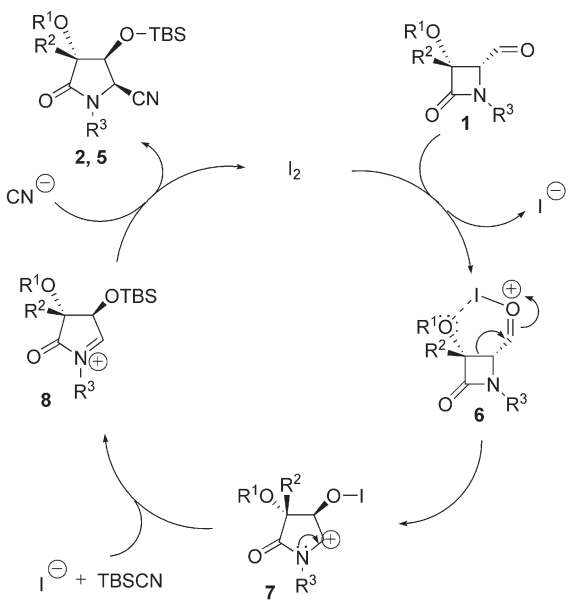
and **4b** was explored.[18] Gratifyingly, the reaction afforded in reasonable yields the corresponding 3,3-disubstituted and spiranic pyrrolidinone derivatives **5a** and **5b**, although with some lower selectivity (Scheme 1). Finally, the susceptibility of the process to the stereochemically different *trans*-β-lactam aldehyde (epimerized at C3), *epim*-**1a**, was studied.[19] However, no reaction was produced under different reaction conditions, the starting aldehyde being recovered as the main component and only traces of the mixture of *O*-silylated cyanohydrins was detected. From all these results we can conclude that a *cis*-alkoxy group at position C3 is a necessary condition for the ring expansion to occur.

The cyclic structures and the stereochemistry of 5-cyano-lactams **2** and **5** were established by one- and two- dimensional NMR techniques and NOE experiments. The values for vicinal coupling constants (see ESI for data†) show unequivocally an *anti*–*syn* orientation for protons H3–H4/H4–H5 in compounds *syn*-**2** and *anti*–*anti* in compounds *anti*-**2**, in agreement with that reported in the literature for related products.[7b]

Our proposed working catalytic cycle to account for the new ring expansion is shown in Scheme 2. It involves previous activation of the carbonyl aldehyde by coordination with iodine to form intermediate **6**, probably as a six-membered chelate with the alkoxy group at C3. This coordination should promote the C3–C4 bond breakage to form *N*-acyliminium intermediate **7** through a process which would be favoured by both the ring strain, the enhanced reactivity of the carbonyl carbon atom and the ability of the nitrogen atom to stabilize the emerging positive charge at C4 (at the former β-lactam). Finally, cyanation of the *N*-acylpyrrolidinium intermediate **8**, formed from cation **7** by iodo–silicon exchange, produces compounds **2** and **5** with concomitant liberation of the catalyst. According to the proposed reaction course, the presence of a *cis*-alkoxy group attached at C3 should facilitate the ring expansion to give 5-cyanopyrrolidin-2-one derivatives **2** and **5**.



Scheme 1 Preparation of sterically hindered pyrrolidin-2-ones **5a** and **5b**. Reagents and conditions: (i) TBSCN (5 equiv.), I_2 (10 mol%), CH_3CN, RT, 1 h.



Scheme 2 Proposed catalytic cycle for the formation of pyrrolidin-2-one derivatives **2** and **5** from 4-formyl-β-lactams **1**.

From the stereochemical point of view two new stereogenic centers, C4 and C5, are generated sequentially from the starting 4-formyl-β-lactam. Stereocenter C4 is formed first as a result of the expansion process of the β-lactam nucleus involving cleavage of the C3–C4 bond. The fact that compounds **2** and **5** have the same *anti*-C3–C4 relative stereochemistry points to a concerted mechanism for this process. Intermediate chelate **6** would be responsible for the observed stereochemistry at C4. Regarding the C5 stereocenter, its generation cannot be accounted for by taking into consideration steric effects. In agreement with previous reports on the Lewis acid-promoted *syn*-addition of tin and silicon nucleophiles to *N*-acyliminium ions controlled by an adjacent OTBS group,[20] the stereochemical outcome may be ruled by the Cieplak-type stereoelectronic effect.[21]

In conclusion, a novel iodo-catalyzed C3–C4 bond breakage of the β-lactam skeleton in 4-oxoazetidine-2-carbaldehydes **1** has been uncovered and this relies upon appropriate substitution and stereochemistry at C3. In addition, a new, direct method for the diastereoselective preparation of optically pure protected 5-cyano-3,4-dihydroxypyrrolidin-2-ones **2** and **5** is described. Studies concerning the scope and generality of this methodology, as well as mechanistic implications 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 the pyrrolidin-2-one derivative **2a**. A solution of TBSCN (271 mg, 1.92 mmol) in acetonitrile (4.3 mL) was added dropwise to a stirred solution of the 4-oxoazetidine-2-carbaldehyde **1a** (300 mg, 1.28 mmol) and molecular iodine (32 mg, 0.13 mmol) in acetonitrile (4.3 mL) at RT and under argon. The reaction mixture was stirred until disappearance of starting material (TLC). Then, brine was added and the resulting mixture was extracted with DCM. The organic layer was dried and the solvent was removed under reduced pressure. Analytically pure adduct **2a** (375 mg, 78%) was obtained after purification by flash chromatography on silica gel using a hexanes–ethyl acetate (5 : 1) mixture.

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