

Diastereoselective synthesis of a bicyclic β -lactam with penicillin G-like spectrum of activity by carbonylation of an acyclic diaminocarbene†

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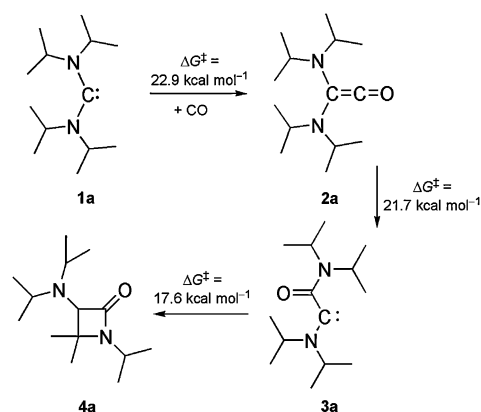
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Diisopropylamino-*cis*-2,6-dimethylpiperidinocarbene reacts regio- and diastereoselectively with CO to afford a bicyclic β -lactam with 100% atom efficiency, whose spectrum of activity resembles that of penicillin G or amoxicillin.

The chemistry of carbenes and ketenes has been intertwined for a century now.¹ In 1913 Staudinger described the thermal decarbonylation of ketenes, together with an analysis of the follow-up products of the resulting transient carbenes.² The decomposition of the parent ketene $\text{H}_2\text{C}=\text{C}=\text{O}$ to CO and CH_2 is one of the most extensively studied reactions in physical chemistry.³ Conversely, a classic method for the detection of transient carbenes is their trapping by carbonylation.⁴

The advent of isolable N-heterocyclic carbenes in 1991⁵ triggered the development of these and related persistent diaminocarbenes from laboratory curiosities to reliable workhorses in synthesis and catalysis.⁶ Such carbenes are usually inert towards CO,⁷ but exceptions occur with particularly electrophilic representatives such as, for example, acyclic diaminocarbenes (ADACs) **1**.⁸ (iPr_2N)₂C (**1a**) was reported in 1996 as the first ADAC to be isolated and structurally characterised.⁹ We found that its primary carbonylation product (iPr_2N)₂C=C=O (**2a**) undergoes a remarkable intramolecular follow-up reaction (Scheme 1).^{8b,e} A *retro*-Wolff rearrangement leads to the (amino)(carboxamido)carbene **3a**, which subsequently affords the β -lactam **4a** by a C–H insertion. *Bona fide* examples of this reaction type are rare. Previously studied



Scheme 1 Carbonylation of **1a**, leading to β -lactam **4a** (racemic mixture) as the final product. ΔG_{298}^\ddagger values were calculated by DFT methods.

cases exhibit considerably higher calculated activation barriers (≥ 37 kcal mol⁻¹).¹⁰ The reaction **1a** + CO \rightarrow **4a** represents a new entry to the important β -lactam ring system¹¹ and proceeds with 100% atom efficiency.¹² As a first milestone of a systematic study to probe the limitations of this new synthetic method, we have shown that β -lactam formation requires very bulky ADACs.^{8b} We here address the question whether this reaction can be applied to the synthesis of bicyclic β -lactams, using bulky ADACs with cyclic amino groups. This is important in view of the bicyclic nature of the penicillins and cephalosporins, which are the most widely used β -lactam antibiotics.¹³ Diisopropylamino-*cis*-2,6-dimethylpiperidinocarbene (iPr_2N)C(PipMe₂) (**1b**)¹⁴ is the only ADAC known to date which meets the requirements for this investigation. Just like **1a**, it is very bulky. In addition, it contains a cyclic amino group (PipMe₂), which incidentally may be viewed as a conformationally constrained version of the iPr_2N group.

We have shown previously that **1a** and **1b** are very similar in terms of stability, both undergoing a slow β -fragmentation reaction in solution.¹⁵ Indeed, we have found such a chemical similarity also in their carbonylation. The reaction of **1b** with CO proceeds smoothly and swiftly at room temperature, cleanly affording the

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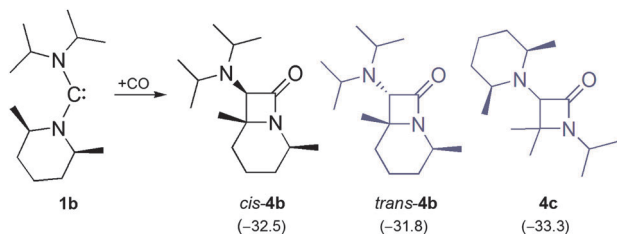
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Scheme 2 Carbonylation of **1b**, leading to the bicyclic β-lactam *cis*-**4b** as the final product. The isomers *trans*-**4b** and **4c** shown in grey are not observed. Only one enantiomer is shown in each case. Calculated ΔG₂₉₈ values (kcal mol⁻¹) are given in parentheses.

bicyclic β-lactam derivative *cis*-**4b** (Scheme 2). This process is regioselective, since only the PipMe₂ unit undergoes the rearrangement and concomitant C–H insertion. The monocyclic β-lactam **4c**, which contains an intact PipMe₂ unit, is not observed. Equally remarkable is the diastereoselectivity of the reaction. The diastereomer of **4b**, which exhibits a *trans* orientation of the iPr₂N group with respect to the methyl substituents (*trans*-**4b**), is not observed.

The all-*cis* arrangement of the substituents at the bicyclic core of the final product is unequivocally demonstrated by the structure of the hydrochloride [*cis*-**4bH**]Cl, which we were able to determine by single-crystal X-ray diffraction (Fig. 1).

We have investigated the formation of *cis*-**4b** using high-level DFT calculations (B2GP-PLYP-D/def2-QZVP//B97-D/SVP, see ESI[†] for details), with special attention to the axial (ax) and the equatorial (eq) conformation (eq) of the PipMe₂ group, including in our analysis also possible boat (b) conformations of the six-membered ring (Fig. 2). First of all, we address thermodynamic aspects concerning the final carbonylation product. The energy of the experimentally observed bicyclic β-lactam *cis*-**4b** is 0.7 kcal mol⁻¹ lower than that of its diastereomer *trans*-**4b** and 0.8 kcal mol⁻¹ higher than that of the monocyclic β-lactam **4c** (Scheme 2). These small

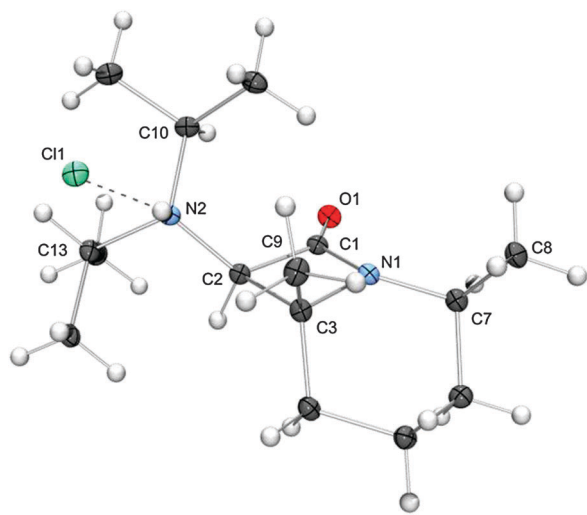


Fig. 1 Molecular structure of [*cis*-**4bH**]Cl in the crystal (ellipsoids drawn at the 30% probability level). The broken line indicates a hydrogen bond between the chloride anion and the cationic iPr₂NH substituent.

energy differences indicate that the intramolecular follow-up reaction of **2b**, which exclusively gives rise to *cis*-**4b**, is governed by kinetic, rather than thermodynamic, factors. Therefore, we now turn our attention to the course of the reaction. The axial carbene conformer **1b**_{ax} is more stable than the equatorial one (**1b**_{eq}) by 6.8 kcal mol⁻¹ (not shown in Fig. 2; see ESI[†]). This significant contrastreric bias is due to the anomeric effect.¹⁶ It is less pronounced for the ketene **2b**, whose axial conformer is only 0.9 kcal mol⁻¹ lower in energy than the equatorial one, which corresponds to a value of the equilibrium constant of *ca.* 5 at room temperature. For each calculated reaction pathway, the first step, *viz.* the *retro*-Wolff rearrangement, is rate-determining. This rearrangement can involve either the PipMe₂ or the iPr₂N group. For the dominant conformer **2b**_{ax} the activation barrier has a value of 21.3 kcal mol⁻¹ for the process which involves the PipMe₂ group, leading to the transient carbene **3b**_{ax}. The corresponding process which involves the iPr₂N group and would finally lead to **4c** has a significantly higher barrier (ΔG[‡] = 25.6 kcal mol⁻¹, see ESI[†] for details). In the case of the less abundant conformer **2b**_{eq} too, the *retro*-Wolff rearrangement involving the PipMe₂ unit is kinetically favoured over the alternative process involving the iPr₂N group (ΔG[‡] = 20.1 *vs.* 23.7 kcal mol⁻¹). For both ketene conformers the activation energy differences (ΔΔG[‡] = 4.3 kcal mol⁻¹ and 3.6 kcal mol⁻¹ for **2b**_{ax} and **2b**_{eq}, respectively) are sufficiently large to be compatible with an essentially exclusive formation of *cis*-**4b** *via* the kinetically favoured carbene **3b**. At the same time, the energy barrier differences for the various calculated pathways are small enough to suggest that subtle changes in the periphery of a bulky ADAC may have a dramatic influence on the outcome of its carbonylation. A comprehensive study will be required to develop a rationale for the reactivity of the primary carbonylation product, *viz.* the diaminoketene **2**.

We have investigated the antimicrobial activity of the monocyclic β-lactam **4a** and its bicyclic relative *cis*-**4b** against Gram-positive and Gram-negative bacteria by determining their minimal inhibitory concentrations (MICs) (see ESI[†]). The bicyclic β-lactam *cis*-**4b** exhibits significant activity against the Gram-positive bacteria *B. subtilis* and *S. aureus*. MIC values are 64–128 μg mL⁻¹ for the *S. aureus* type strain and 128 μg mL⁻¹ for *B. subtilis* 168 and a methicillin-resistant *S. aureus* (MRSA) strain. The antibiotic activity of **4a** is lower by a factor of 2 (MIC = 256 μg mL⁻¹ in all cases). Both compounds are inactive against Gram-negative bacteria. Their spectrum of activity resembles that of penicillin G or amoxicillin, whose activities, however, are higher than that of *cis*-**4b** by *ca.* two orders of magnitude.

In conclusion, the efficient and highly selective synthesis of *cis*-**4b** from **1b** and CO under mild conditions opens up new possibilities to access unprecedented bicyclic β-lactams with useful antibiotic properties. We will continue our study with new ADACs containing bulky cyclic amino substituents, which we are currently developing.

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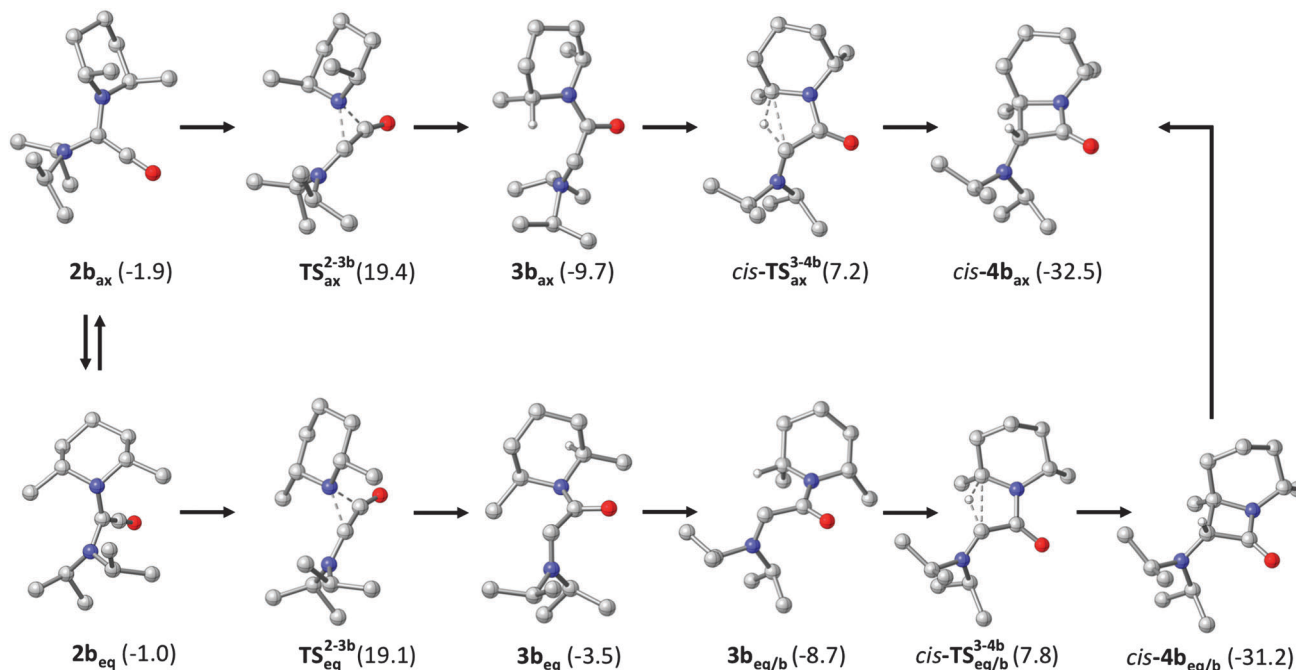


Fig. 2 Computed kinetically favourable reaction pathways for diaminoketene **2b** (shown for one enantiomer only). Pathways potentially leading to *trans*-**4b** and **4c** (Scheme 2) are kinetically less favourable and have been omitted for clarity (see ESI† for details).‡

Investing in your future). Quantum-chemical calculations were performed at the Center for Scientific Computing (CSC) Frankfurt on the LOEWE-CSC high-performance computing cluster.

Notes and references

‡ In the same vein, the nucleophilic addition of **1b** to **2b**, affording the oxallyl species (**1b**)₂CO, turned out to be kinetically unfavourable and has therefore not been incorporated in Fig. S2 (see ESI† for details).

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