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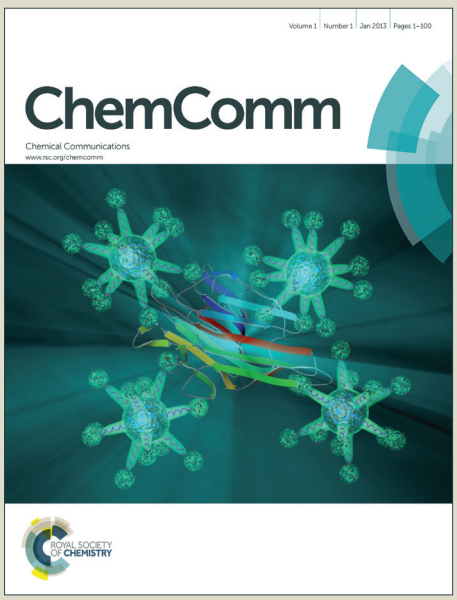

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ARTICLE TYPE

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

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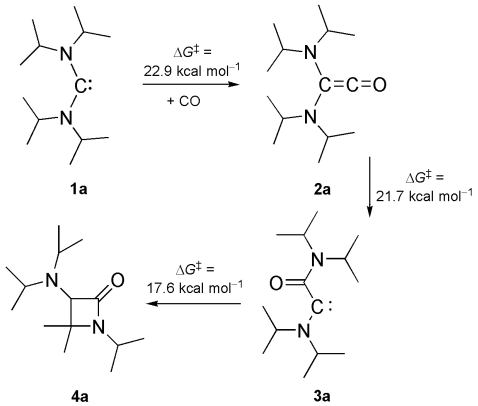
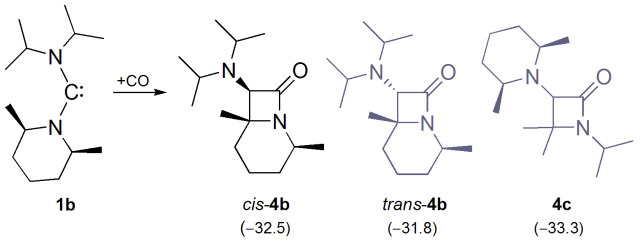
Diisopropylamino-*cis*-2,6-dimethylpiperidinocarbene reacts regio- and diastereoselectively with CO to afford with 100% atom efficiency a bicyclic β-lactam, whose spectrum of activity resembles that of penicillin G or amoxicillin.

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 $H_2C{=}C{=}O$ 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 1991[5] 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] ($i\mathrm{Pr_2N})_2$C (**1a**) was reported in 1996 as the first ADAC to be isolated and structurally characterised.[9] We found that its primary carbonylation product ($i\mathrm{Pr_2N})_2$C=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



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



Scheme 2 Carbonylation of **1b**, leading to the bicyclic β-lactam *cis*-**4b** as final product. The isomers *trans*-**4b** and **4c** shown in grey are not observed. Only one enantiomer is shown in each case. Calculated ΔG_{298} values (kcal mol^{-1}) are given in parentheses.

type are rare. Previously studied cases exhibit considerably higher calculated activation barriers (≥ 37 kcal mol^{-1}).[10] The process **1a** + CO → **4a** represents a new entry to the important β-lactam ring system[11] 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 ($i\mathrm{Pr_2N}$)C($\mathrm{PipMe_2}$) (**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 ($\mathrm{PipMe_2}$), which incidentally may be viewed as a conformationally constrained version of the $i\mathrm{Pr_2N}$ 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 bicyclic β-lactam derivative *cis*-**4b** (Scheme 2). This process is regioselective, since only the $\mathrm{PipMe_2}$ unit undergoes the rearrangement and concomitant C–H insertion. The monocyclic β-lactam **4c**, which contains an intact $\mathrm{PipMe_2}$ unit, is not observed. Equally remarkable is the diastereoselectivity of the reaction. The diastereomer of **4b** which exhibits a *trans* orientation of the $i\mathrm{Pr_2N}$ group with respect to the methyl substituents (*trans*-**4b**), is not observed.

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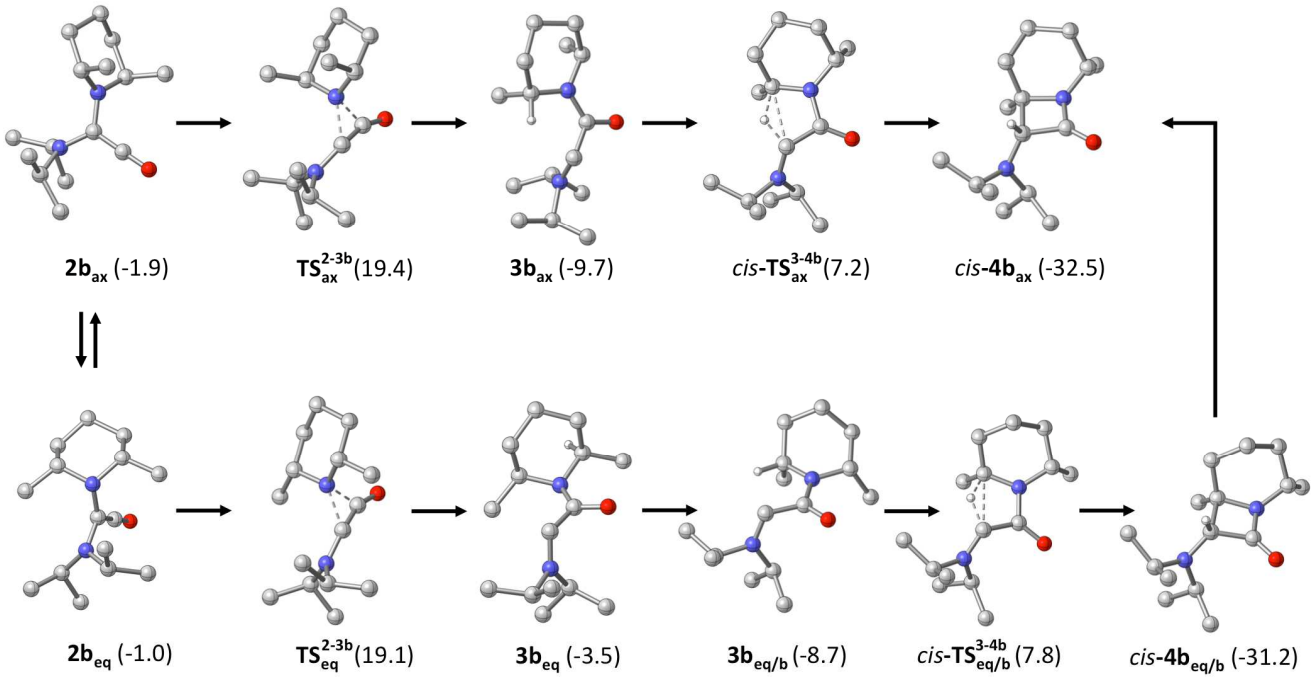

Fig. 2 Computed kinetically favourable reaction pathways for diaminoketene **2b** (shown for one enantiomer only). Pathways potentially leading to *trans*-**4b** and **4c** (Scheme 2) are kinetically less favourable and have been omitted for clarity (see ESI for details).†‡

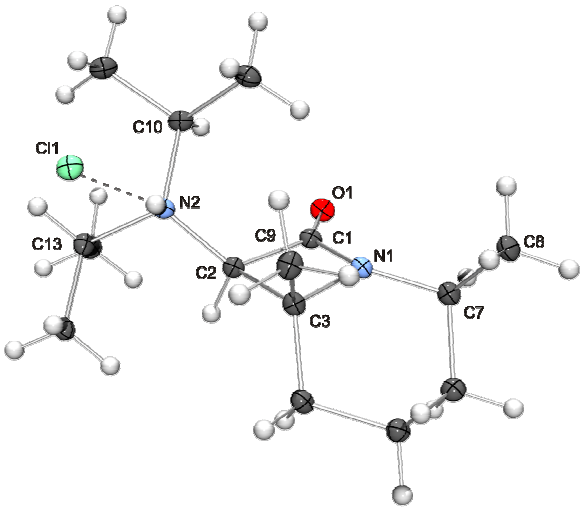

Fig. 1 Molecular structure of [*cis*-**4b**H]Cl in the crystal (ellipsoids drawn at the 30% probability level). The broken line indicates a hydrogen bond between the chloride anion and the cationic iPr$_2$HN substituent.

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*-**4b**H]Cl, which we were able to determine by single-crystal X-ray diffraction (Fig. 1).

We have investigated the formation of *cis*-**4b** by 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 conformation (eq) of the PipMe$_2$ 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 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 contrasteric 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 PipMe$_2$ or the iPr$_2$N 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 PipMe$_2$ group, leading to the transient carbene **3b**$_{ax}$. The corresponding process which involves the iPr$_2$N group and would finally lead to **4c** has a

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significantly higher barrier ($\Delta G^{\ddagger}$ = 25.6 kcal mol^{-1}, see ESI for details).† In the case of the less abundant conformer $\mathbf{2b}_{eq}$, too, the *retro*-Wolff rearrangement involving the $PipMe_2$ unit is kinetically favoured over the alternative process involving the iPr_2N group ($\Delta G^{\ddagger}$ = 20.1 *vs.* 23.7 kcal mol^{-1}). For both ketene conformers the activation energy differences ($\Delta\Delta G^{\ddagger}$ = 4.3 kcal mol^{-1} and 3.6 kcal mol^{-1} for $\mathbf{2b}_{ax}$ and $\mathbf{2b}_{eq}$, 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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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental, crystallographic and computational details, Fig. S1 – S3, Table S1. CCDC 951678. See DOI: 10.1039/b000000x/

‡ In the same vein, the nucleophilic addition of **1b** to **2b**, affording the oxyallyl species $(\mathbf{1b})_2CO$, turned out to be kinetically unfavourable and has therefore not been incorporated in Fig. 2 (see ESI for details).†

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