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Diastereoselective synthesis of a bicyclic β-lactam with penicillin G-like spectrum of activity by carboxylation 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. In 1913 Staudinger described the thermal decarbonylation of ketenes, together with an analysis of the follow-up products of the resulting transient carbenes. The decomposition of the parent ketene $H_2C=CH_2$ to CO and $CH_2$ is one of the most extensively studied reactions in physical chemistry. Conversely, a classic method for the detection of transient carbenes is their trapping by carbonylation.

The advent of isolable N-heterocyclic carbenes in 1991 triggered the development of these and related persistent dianimocarbenes from laboratory curiosities to reliable workhorses in synthesis and catalysis. Such carbenes are usually inert towards CO, but exceptions occur with particularly electrophilic representatives such as, for example, acyclic dianimocarbenes (ADACs). In 1996 as the first ADAC to be isolated and structurally characterised. We found that its primary carboxylation product ($iPr_2N_iC$) undergoes a remarkable intramolecular follow-up reaction (Scheme 1).

A retro-Wolff rearrangement leads to the (amino)carboxamido carbene, which subsequently affords the β-lactam as a C–H insertion. Bona fide examples of this reaction type are rare. Previously studied cases exhibit considerably higher calculated activation barriers ($\geq 37$ kcal mol$^{-1}$). The process $1a + CO \rightarrow 4a$ represents a new entry to the important β-lactam ring system and proceeds with 100% atom efficiency. 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.

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.

Diisopropylamino-cis-2,6-dimethylpiperidinocarbene ($iPr_2N_iC(PipMe)_2$) is the only ADAC known to which which meets the requirements for this investigation. Just like $1a$, it is very bulky. In addition, it contains a cyclic amino group ($PipMe_2$), 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. Indeed, we have found such a chemical similarity also in their carboxylation. 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 $PipMe_2$ unit undergoes the rearrangement and concomitant C–H insertion. The monocyclic β-lactam $4c$, which contains an intact $PipMe_2$ unit, is not observed. Equally remarkable is the diastereoselectivity of the reaction. The diastereomer of $4b$ which exhibits a trans orientation of the $iPr_2N$ group with respect to the methyl substituents (trans-$4b$), is not observed.

Scheme 1

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

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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 $\Delta G^\circ_{298}$ values (kcal mol$^{-1}$) are given in parentheses.
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).†‡

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 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 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 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 1bax 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 PipMe₂ or the iPr₂N group. For the dominant conformer 2bax 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 3bax. The corresponding process which involves the iPr₂N group and would finally lead to 4c has a
significantly higher barrier (ΔG² = 25.6 kcal mol⁻¹, see ESI for details).† In the case of the less abundant conformer 2b,‡ the retro-Wolff rearrangement involving the PiPMε₂ unit is kinetically favoured over the alternative process involving the iprN group (ΔG² = 20.1 vs. 23.7 kcal mol⁻¹). For both ketene conformers the activation energy differences (ΔΔG² = 4.3 kcal mol⁻¹ and 3.6 kcal mol⁻¹ for 2ba and 2b, 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 carboxylation. A comprehensive study will be required to develop a rationale for the reactivity of the primary carboxylation 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 antibacterial 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 are we currently developing.

We thank the DFG for generous funding (grant SI 429/19-1). T. S. is grateful to the Studienstiftung des deutschen Volkes for a doctoral fellowship. J. E. B. and P. P. are financially supported by a grant from the German federal state of North Rhine-Westphalia and the European Union (European Regional Development Fund. 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

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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/