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β-Lactams

Reactivity of 3-Oxo-β-lactams with Respect to Primary Amines—An Experimental and Computational Approach

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Abstract: The reactivity of 3-oxo-β-lactams with respect to primary amines was investigated in depth. Depending on the specific azetidin-2-one C4 substituent, this reaction was shown to selectively produce 3-imino-β-lactams (through dehydration), α-aminoamides (through CO elimination), or ethanediamides (through an unprecedented C3–C4 ring opening). In addition to the experimental results, the mechanisms and factors governing these peculiar transformations were also examined and elucidated by means of DFT calculations.

Introduction

Through the development of the β-lactam synthon method by the group of Ojima in the 1980s and 1990s,[1] azetidin-2-ones have acquired a prominent position in organic chemistry as building blocks for further elaboration. Indeed, by exploiting the inherent reactivity associated with this strained four-membered ring system, several β-lactam classes have been deployed as important intermediates in the synthesis of a wide variety of acyclic and heterocyclic nitrogen compounds by selective bond-cleavage and ring-rearrangement protocols.[2]

One of those classes, the highly reactive 3-oxo-β-lactams, have a long tradition as key scaffolds in the stereocontrolled synthesis of a broad diversity of functionalized azetidin-2-ones and other scaffolds of pharmaceutical interest.[3] In 1972, Sheehan and Lo reported the preparation of benzyl 6-oxopenicillanate as a source of new antibacterials, for example, by means of its further transformation to oxygen and carbon analogues of penicillin V.[4] Interesting examples concerning the use of monocyclic 3-oxo-β-lactams en route to biological applications comprise the total synthesis of the antifungal lipopeptide echinocandin B,[5] serotonin reuptake inhibitor dapoxetine,[6] and potent anticancer agent haouamine B.[7] Furthermore, azetidine-2,3-diones are useful precursors for α-hydroxy-β-amino acids, such as *N*-benzoyl-(2*R*,3*S*)-phenylisoserine methyl ester, which is the renowned side chain of the antitumor agent Taxol.[8] In the framework of our interest in the use of functionalized β-lactams as building blocks in heterocyclic chemistry,[2g,j] we pursued the strategy to treat 3-oxo-β-lactams with primary alkylamines as a possible entry to the synthetically useful class of 3-alkylimino-β-lactams. Subsequent imine reduction could then afford the corresponding 3-amino-β-lactams, which represent important structural entities present in many β-lactam antibiotics and β-lactamase inhibitors.[9]

Although the transformation of azetidine-2,3-diones into 3-iminoazetidin-2-ones seems easy to achieve, at first sight, by applying (standard) imination conditions, only one single example of the use of free amines has been described in the literature so far. In 1996, Cainelli and co-workers treated 1-(4-methoxyphenyl)-4-phenylazetidine-2,3-dione (**1a**) with benzhydrylamine in dichloromethane in the presence of magnesium sulfate as a drying agent, affording 3-benzhydrylimino-1-(4-methoxyphenyl)-4-phenylazetidin-2-one (**2a**) in 76% yield after trituration with pentane (Scheme 1 A).[10] Other examples in the literature concerning the imination of 3-oxo-β-lactams fall outside the scope of this comparison because they all employ hydroxylamine hydrochloride or methoxyamine hydrochloride, instead of a primary alkylamine.[11]

In 2000, Alcaide and co-workers described the unexpected formation of α-aminoamides **3a**–**p** in 42–77% yield upon treating azetidine-2,3-diones **1a**–**e** with a selection of primary amines in THF, with or without the addition of magnesium sulfate (Scheme 1 B).[12a] Mechanistically, this transformation was explained by nucleophilic addition of the amine across the 3-oxo group, followed by C2–C3 ring opening, and carbon mon-

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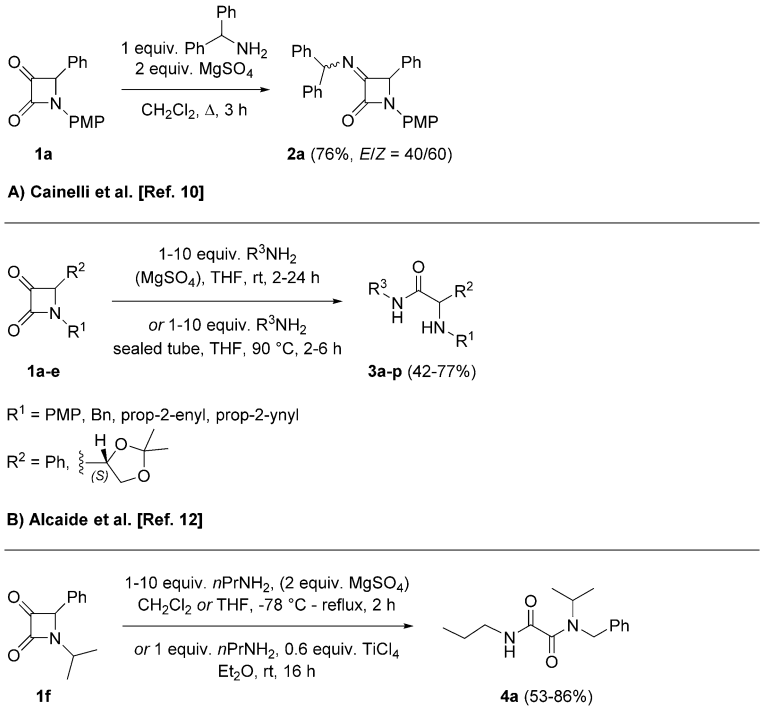
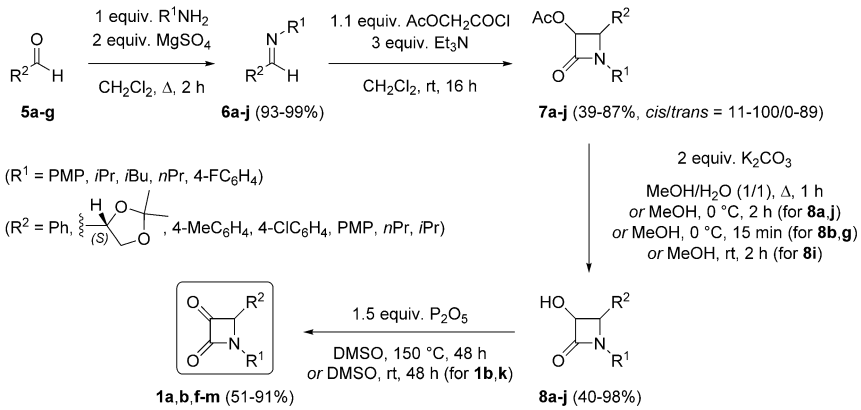


Scheme 1. Treatment of 3-oxo-β-lactams **1** with primary amines: information reported in the literature and preliminary in-house results. PMP = *p*-methoxyphenyl, Bn = benzyl.

oxide elimination.[12b] However, upon applying similar reaction conditions to azetidine-2,3-dione **1f** in a preliminary experiment, we observed the formation of the novel ethanediamide **4a** (Scheme 1C) through an unprecedented C3–C4 ring opening (see below). This remarkable new reactivity persuaded us to perform a thorough and comprehensive study, both experimentally and computationally, on different factors that govern the reactivity of 3-oxo-β-lactams with respect to primary alkylamines.

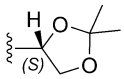
Results and Discussion

The synthesis of the starting 3-oxo-β-lactams **1** was performed by means of four consecutive steps (Scheme 2 and Table 1), with respect to literature precedents (see the Supporting Information). First, aldehydes **5a–g** were condensed with different primary amines in dichloromethane in the presence of magnesium sulfate, and the resulting imines **6a–j** were used as such in the Staudinger synthesis of 3-acetoxy-β-lactams **7a–j**. To that end, imines **6a–j** were treated with acetoxyacetyl chloride in dichloromethane in the presence of triethylamine to afford the corresponding azetidin-2-ones **7a–j** in 39–87% yield with varying diastereoselectivities. This relative *cis* or *trans* stereochemistry could be easily deduced from the ^{1}H NMR spectra ($CDCl_3$) of β-lactams **7** because the vicinal coupling constants between the 3H and 4H protons on the β-lactam ring varied between 4.4 and 5.6 Hz for the obtained *cis* isomers and had a value of 1.6 Hz for the *trans* isomers; this corresponds well



Scheme 2. Synthesis of 3-oxo-β-lactams **1**.

Table 1. Synthesis of imines **6**, 3-acetoxy-β-lactams **7**, 3-hydroxy-β-lactams **8**, and 3-oxo-β-lactams **1**.

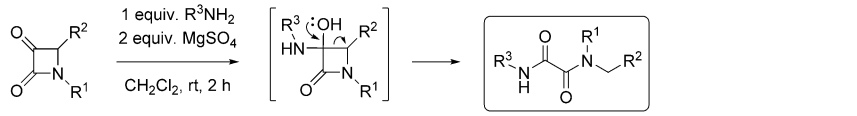
Entry	R^1	R^2	**6**	Product (yield [%]) **7**[a] *cis*/*trans*[b]	**8**	**1**[d]
1	PMP	Ph	**6a** (99)	**7a** (87) 21/79	**8a** (98)	**1a** (91)
2	PMP		**6b** (99)	**7b** (70) 100/0	**8b** (85)[a]	**1b** (72)
3	*i*Pr	Ph	**6c** (98)	**7c** (83) 100/0	**8c** (92)	**1f** (91)
4	*i*Bu	4-MeC_6H_4	**6d** (96)	**7d** (87) 100/0	**8d** (97)	**1g** (86)
5	*i*Pr	4-ClC_6H_4	**6e** (97)	**7e** (81) 100/0	**8e** (95)	**1h** (51)
6	*n*Pr	PMP	**6f** (97)	**7f** (69) 100/0	**8f** (63)[a]	**1i** (67)
7	4-FC_6H_4	Ph	**6g** (93)	**7g** (67) 11/89	**8g** (73)[a]	**1j** (58)[a]
8	*i*Pr	*n*Pr	**6h** (99)	**7h**[c] 100/0	**8h** (40)[d]	**1k** (51)
9	PMP	*i*Pr	**6i** (99)	**7i** (44)[d] 100/0	**8i** (78)[a]	**1l** (73)
10	4-FC_6H_4	*i*Pr	**6j** (96)	**7j** (39)[d] 100/0	**8j** (61)[a]	**1m** (84)

[a] After purification by recrystallization from absolute EtOH or EtOAc/hexane (30/1), unless stated otherwise. [b] Based on ^{1}H NMR spectroscopic ($CDCl_3$) analysis of the crude reaction mixture. [c] Separation of β-lactam **7h** and the corresponding N-acyl enamine proved to be impossible at this stage. [d] After purification by column chromatography (SiO_2).

with reported literature values.[13] Subsequently, azetidin-2-ones **7a–j** were converted into the corresponding 3-hydroxy-β-lactams **8a–j** through a potassium carbonate mediated acetate hydrolysis in methanol or in a mixture of methanol/water (1:1). No attempts were made toward the separation of *cis*/*trans* isomers for compounds **7** and **8**; this is not relevant with respect to the synthesis of the target structures **1**. It should be noted that the low isolated yields of β-lactams **7i**, **7j**, and **8h** can be explained by the formation of the corresponding N-acyl enamines during the Staudinger synthesis, which appears to be difficult to avoid if using N-(alkylidene)amines as substrates.[14] Finally, an Albright–Onodera oxidation protocol with phosphorus pentoxide as a DMSO activator was applied on azetidin-2-ones **8a–j**, affording azetidine-2,3-diones **1a**, **b**, and **f–m** in 51–91% yield after purification by column chromatography on silica gel. For azetidine-2,3-diones **1**, representatives **1f–m** (as well as β-lactam precursors **7c–j** and **8c–j**) have not been reported before.

In the next stage, the reactivity of 3-oxo-β-lactams **1** with respect to primary alkylamines was investigated as a potential entry into the synthetically useful and virtually unexplored class of 3-alkylimino-β-lactams. To that end, 1-isopropyl-4-phenylazetidine-2,3-dione (**1f**) was dissolved in anhydrous dichloromethane and treated with *n*-propylamine (1 equiv) at room temperature for 2 h (Scheme 1C). Surprisingly, although the formation of either the corresponding 3-imino-β-lactam[10] or α-aminoamide[12] was expected, spectroscopic analysis revealed the molecular structure of the obtained product to be exclusively N^1-benzyl-N^1-isopropyl-N^2-propylethanediamide (**4a**). Additional experiments were carried out with an excess of the volatile amine (10 equiv), THF as the solvent, the presence of magnesium sulfate or titanium tetrachloride (in diethyl ether) as drying agents, and temperatures varying from −78 °C to reflux; all afforded a full and selective substrate conversion toward the same product, **4a** (Scheme 1C).

Subsequently, azetidine-2,3-diones **1a,f–j** were smoothly converted into novel ethanediamides **4b–l** under similar reaction conditions in 76–95% yield (Scheme 3). For the specific substitution pattern of substrates **1**, see Table 1. These ethanediamides **4** were present as 1:1 (**4a–g,k**) or 9:1 (**4h–j,l**) mixtures of two rotamers, which could be explained by hindered rotation about the amide bond. For compounds **4h–j** and **l** (R^1 = aryl), the crude reaction mixture was contaminated with several unidentified side products, although in a combined yield of a maximum of 10%, which made an additional purification step by preparative TLC necessary to obtain analytical purity. The application of aniline as a primary amine (cf. aromatic amines, R^3 = Ar) in these experiments led to complex reaction mixtures. In addition to their main application as substitutes for urea in fertilizers,[15] ethanediamides (also known as



1a,f-j

(R^1 = *i*Pr, *i*Bu, PMP, *n*Pr, 4-FC_6H_4)

(R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, PMP)

(R^3 = *n*Pr, *i*Pr, Bn, $Cl(CH_2)_2$)

9

4a (R^1 = *i*Pr, R^2 = Ph, R^3 = *n*Pr, 86%)
4b (R^1 = *i*Pr, R^2 = Ph, R^3 = *i*Pr, 80%)
4c (R^1 = *i*Bu, R^2 = 4-MeC_6H_4, R^3 = *n*Pr, 89%)
4d (R^1 = *i*Bu, R^2 = 4-MeC_6H_4, R^3 = Bn, 90%)
4e (R^1 = *i*Pr, R^2 = 4-ClC_6H_4, R^3 = *n*Pr, 92%)
4f (R^1 = *i*Pr, R^2 = 4-ClC_6H_4, R^3 = *i*Pr, 85%)
4g (R^1 = *i*Pr, R^2 = 4-ClC_6H_4, R^3 = $Cl(CH_2)_2$, 88%)
4h (R^1 = PMP, R^2 = Ph, R^3 = *n*Pr, 95%)
4i (R^1 = PMP, R^2 = Ph, R^3 = *i*Pr, 90%)
4j (R^1 = PMP, R^2 = Ph, R^3 = Bn, 91%)
4k (R^1 = *n*Pr, R^2 = PMP, R^3 = *i*Pr, 76%)
4l (R^1 = 4-FC_6H_4, R^2 = Ph, R^3 = *i*Pr, 89%)

Scheme 3. Synthesis of ethanediamides **4**.

oxamides) represent important structural motifs that show diverse bioactivities,[16] which explains interest in new and better strategies for their construction.

From a mechanistic point of view, the formation of ethanediamides **4** can be rationalized by considering the initial nucleophilic addition of the primary amine across the 3-oxo group of azetidine-2,3-diones **1**, followed by a C3–C4 ring opening of the intermediate hemiaminals **9** (Scheme 3). This unprecedented C3–C4 ring opening of 3-oxo-β-lactams is clearly provoked by the presence of an aromatic C4 substituent (R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, PMP). Indeed, the availability of a benzylic position at the β-lactam C4 facilitates C3–C4 bond fission through benzylic stabilization of the forming carbanion.

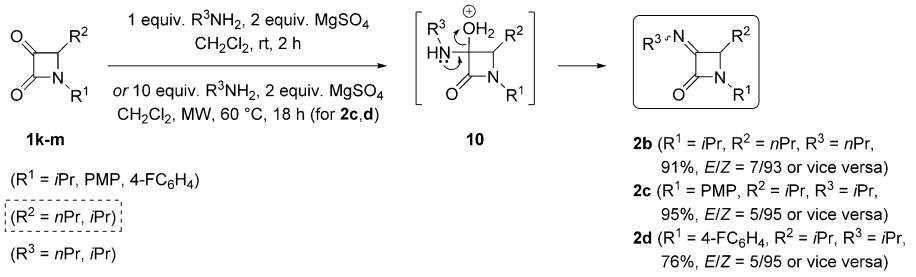
As seen in Scheme 3, the introduction of an electron-donating aromatic C4 substituent (such as R^2 = PMP), which could destabilize the developing carbanion to a certain extent, proved to be ineffective to switch the reactivity of 3-oxo-β-lactam **1i** toward the formation of the corresponding 3-imino-β-lactam; this supports the importance of the proposed benzylic stabilization hypothesis. This line of reasoning was further corroborated by the transformation of 3-oxo-β-lactam **1j** into ethanediamide **4l**, in which an electron-withdrawing aromatic N1 substituent (R^1 = 4-FC_6H_4) could not induce the formation of the corresponding α-aminoamide by carbon monoxide elimination through additional stabilization of the developing nitrogen anion.

To further investigate the role of the specific β-lactam substituents on the reactivity of 3-oxo-β-lactams with respect to primary alkylamines, azetidine-2,3-dione **1k**, with an alkyl group at both positions N1 and C4 (R^1 = *i*Pr, R^2 = *n*Pr), was subjected to standard imination conditions. The absence of a benzylic position at the β-lactam C4 might prevent C3–C4 ring opening in favor of the formation of the desired 3-imino-β-lactam. Indeed, the treatment of 1-isopropyl-4-propylazetidine-2,3-dione (**1k**) with *n*-propylamine (1 equiv) in anhydrous dichloromethane in the presence of magnesium sulfate (2 equiv) at room temperature for 2 h afforded 1-isopropyl-4-propyl-3-(propylimino)azetidin-2-one (**2b**) in 91% yield, with an *E*/*Z* ratio (based on ^{1}H NMR spectroscopy in $CDCl_3$) of 7:93 or vice versa (Scheme 4). Also, 4-isopropylazetidine-2,3-diones **1l**,**m**, with aromatic N1 substituents (R^1 = PMP, 4-FC_6H_4), could be selectively converted toward the corresponding new 3-imino-β-lactams **2c** and **2d** under MW irradiation, which indicated the suitability of 4-alkylazetidine-2,3-diones as eligible substrates for the preparation of 3-(alkylimino)azetidin-2-ones. Imines **2c** and **2d** proved to be both base and acid stable upon washing with 1 M sodium hydroxide and column chromatography on silica gel, respectively.

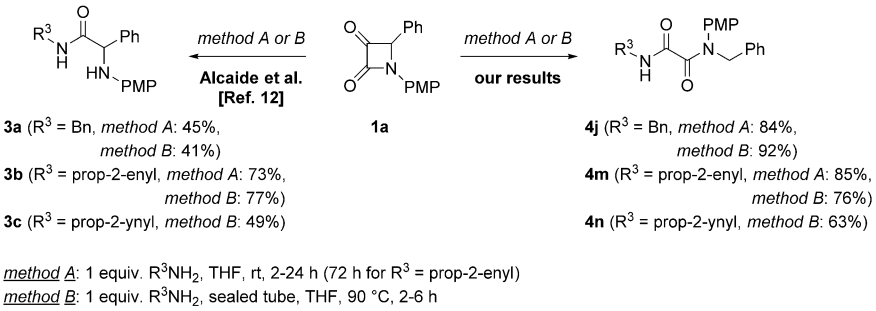
Taking the above-described results into account, it can be concluded that the presence of an aromatic C4 substituent is the main prerequisite for the formation of ethanediamides upon treatment of azetidine-2,3-diones with primary amines. This unprecedented reactivity of 3-oxo-β-lactams stands in sharp contrast to the previously described formation of **2a**[10] (Scheme 1 A) or **3a**–**d**[12] (R^2 = Ph, Scheme 1 B) from **1a** under similar reaction conditions. To scrutinize this discrepancy, we decided to repeat these procedures reported in the literature with full respect to reaction scale and dilution. Unfortunately, all our attempts to reproduce the experimental result described by Cainelli et al.[10] led to complex reaction mixtures, in which no significant amounts of 3-imino-β-lactams, α-aminoamides, or ethanediamides were detected.

In addition, when conscientiously repeating the procedures described by Alcaide et al.,[12] N^1-benzyl-N^1-(4-methoxyphenyl)-ethanediamides **4j**, **m**, and **n** were isolated as major compounds instead of the 2-[(4-methoxyphenyl)amino]-2-phenylacetamides **3a**–**c** reported in the literature (Scheme 5). This result confirms our benzylic stabilization hypothesis. It should be stressed that, for compounds **4j**, **m**, and **n**, the crude reaction mixtures were contaminated with multiple unidentified side products, although in a combined yield of maximum 15%, in which the occurrence of α-aminoamides **3a**–**c** (< 5%) was confirmed by ^{1}H NMR spectroscopy ($CDCl_3$). Furthermore, a detailed spectroscopic analysis revealed that the ^{13}C NMR ($CDCl_3$) spectral data of ethanediamide **4m** obtained by us were identical to the reported data for compound **3b** (except for an extra carbonyl signal at $\delta \approx 160$ ppm), which could indicate an incorrect assignment of compound **3b** in the literature. To ensure that ethanediamides **4** could not be further transformed into the corresponding α-aminoamides **3** through CO elimination, N^1,N^2-dibenzyl-N^1-(4-methoxyphenyl)ethanediamide (**4j**) was heated under reflux in THF for several days (with or without the addition of benzylamine), resulting in full recuperation of the starting compound **4j**. It should be noted that, when comparing the synthesis of ethanediamide **4j** in Schemes 3 and 5, it seems that both CH_2Cl_2 and THF are suitable solvents for the transformation of azetidine-2,3-diones **1** into ethanediamides **4**.

Finally, azetidine-2,3-dione **1b** was treated with a few primary amines to verify the claimed formation of α-aminoamides

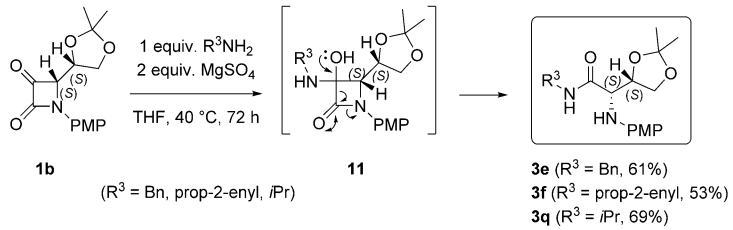


Scheme 4. Synthesis of 3-imino-β-lactams **2**. MW = microwave.



Scheme 5. Treatment of **1a** with primary amines: a comparison of our results with those reported in the literature.

3 (Scheme 1B).[12] To that end, azetidine-2,3-dione **1b** was dissolved in THF, after which a solution of benzylamine, allylamine, or isopropylamine in THF was added. After stirring for 2–24 h at room temperature, the selective conversion of 15–50% toward the corresponding acetamides **3e**, **f**, and **q** was observed. This reaction could be driven to completion by stirring for 72 h at 40 °C, giving rise to α-aminoamides **3e**, **f**, and **q** in 53–69% yield after purification by preparative TLC (Scheme 6).



Scheme 6. Synthesis of α-aminoamides **3**.

Mechanistically, this transformation was explained by the nucleophilic addition of the amine across the 3-oxo group of azetidine-2,3-dione **1b**, followed by C2–C3 ring opening, and carbon monoxide elimination.[12b] Irrefutable proof of the formation of α-aminoamides **3** was eventually established by single-crystal X-ray analysis of (*S*)-*N*-benzyl-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[(4-methoxyphenyl)amino]acetamide (**3e**) (Figure 1). In other words, azetidine-2,3-dione **1b** was confirmed to be an eligible substrate for the selective synthesis of α-aminoamides **3** upon treatment with primary amines as reported;[12] this pointed to the peculiar effect of the C4 dioxolane substituent on the overall reactivity.

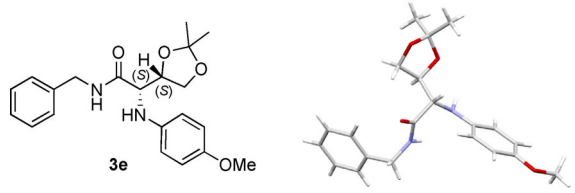


Figure 1. Molecular structure of **3e**.

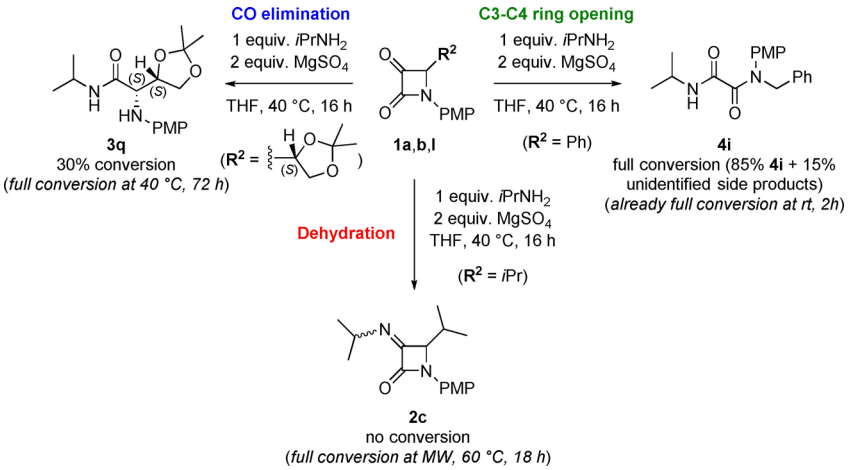
Upon summarizing all experimental results obtained herein, it is clear that the specific reactivity of 3-oxo-β-lactams **1** with respect to primary amines can be completely controlled by the choice of the C4 substituent, affording the selective preparation of 3-imino-β-lactams **2** (dehydration products), α-aminoamides **3** (CO-elimination products), or unprecedented ethanediamides **4** (C3–C4 ring-opening products). This interesting behavior is exemplified in Scheme 7, which presents an overview of the reactivity of azetidine-2,3-diones **1a**, **b**, and **l** (only different with respect to their C4 (R^2) substituent) upon treatment with isopropylamine in THF. The selective formation of either 3-imino-β-lactams or ethanediamides from 4-alkyl- or 4-aryl-3-oxo-β-lactams, respectively, is certainly of relevance from a synthetic chemistry point of view, whereas the production of α-aminoamides from 3-oxo-β-lactams seems to be a peculiarity related to the presence of a specific C4 substituent (i.e., the (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl group).

To further investigate the proposed mechanistic rationalizations governing this intriguing reactivity profile, DFT calculations were performed. Because the formation of α-aminoamides **3** has only been observed in the case of very specific substituents (i.e., R^1 = PMP and R^2 = (*S*)-2,2-dimethyl-1,3-dioxolan-4-yl), combined with the possible incorrect assignment of compound **3b** in the literature (see above), further in-depth experimental studies are necessary to elucidate the exact reaction parameters inducing CO elimination. Thus, illustrative DFT calculations were primarily focused on the difference in reactivity for 3-oxo-β-lactams with an aromatic C4 substituent (i.e., R^2 = Ph; Scheme 7) versus a simple alkyl C4 substituent (i.e., R^2 = *i*Pr; Scheme 7).

Theoretical Rationalization

Computational methodology

The M06-2X functional,[17] which accounts for dispersion effects, was used for geometry optimizations with the 6-31+G(d,p) basis set. This level of theory yields reliable results for reactions involving small N-heterocycles.[18] Minima (ground states) and first-order saddle points (transition states (TSs)) were characterized by normal-mode analysis. Reactant and product complexes were verified by intrinsic reaction coordi-



Scheme 7. Treatment of 1-(4-methoxyphenyl)azetidine-2,3-diones **1a**, **b**, and **l** with isopropylamine.

nate (IRC) calculations,[19] followed by full geometry optimizations. A continuum model was used to account for the solvent environment.[20] D3 dispersion corrections were added by calculating the electronic energies at the B3LYP-D3/6-311+G(d,p) level of theory,[21] by using the geometries and thermal free energy corrections obtained with M06-2X/6-31+G(d,p) at 1 atm and 298 K. These corrections, proposed by Grimme et al., account for the dispersion effects in complex systems and at long range.[22] All computations were carried out with the Gaussian 09 package.[23]

Amination of 3-oxo-β-lactams 1

Nucleophilic addition of primary amines across the 3-oxo group of azetidine-2,3-diones **1** leads, in the first step, to intermediate hemiaminals **9**–**11** (Schemes 3, 4, and 6). Whereas an unrealistic Gibbs free activation barrier of 115.4 kJ mol^{-1} was found for the reaction of 3-oxo-β-lactam **1** ($R^1=R^2=$Me) with $MeNH_2$ (M06-2X/6-31+G(d,p)), the assistance of a second amine molecule substantially lowered this activation barrier to a plausible value of 62.1 kJ mol^{-1} (Figure 2). Thus, during nucleophilic attack of the amine nitrogen atom across the carbonyl carbon atom, a proton is transferred from the nitrogen atom

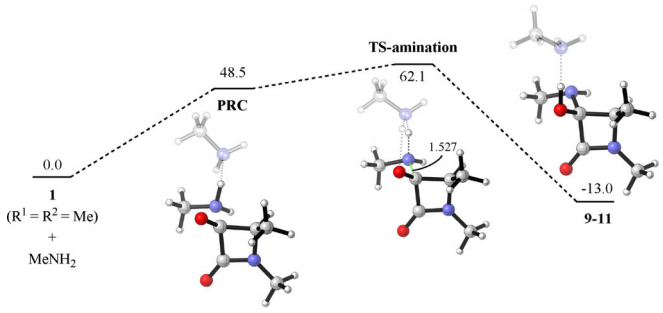


Figure 2. Gibbs free energy profile for the amination of 3-oxo-β-lactams **1** into 3-amino-3-hydroxy-β-lactams **9**–**11** with the assistance of a second amine molecule (polarizable continuum model (PCM; $\varepsilon=7.43$) M06-2X/6-31+G(d,p), kJ mol^{-1}). PRC denotes the prereactive complex. Critical distance is given in Å. Energies relative to the separate reactants.

to the carbonyl oxygen atom through a second amine molecule, which acts as a proton bridge.

Dehydration, CO elimination, and C3–C4 ring opening of 3-amino-3-hydroxy-β-lactams 9–11

These intermediate hemiaminals **9**–**11** can subsequently undergo dehydration, CO elimination, or C3–C4 ring opening, leading to 3-imino-β-lactams **2**, α-aminoamides **3**, or ethanediamides **4**, respectively. Initially, all three reactions were thoroughly investigated for $R^1=R^2=R^3=$Me, which clearly showed that the barriers for all three reactions without any assisting molecules were unrealistically high (>200 kJ mol^{-1}, M06-2X/6-31+G(d,p)). Therefore, an extra β-lactam molecule **9**–**11** was added to assist the reactions under study. Indeed, the amino and hydroxyl groups of these additional β-lactams **9**–**11** can act as proton-accepting and/or -donating sites to facilitate the reactions under study. Various possibilities have been examined: assistance of one or two groups and stepwise or concerted pathways. Assistance by an extra β-lactam molecule was shown to lower the reaction barriers tremendously. For the three reactions under study (i.e., dehydration, C3–C4 ring opening, and CO elimination of β-lactams **9**–**11** with $R^1=R^2=R^3=$Me), the reaction barriers for all of these possible pathways were compared (see Table S1 in the Supporting Information).

Subsequently, for the pathways with the lowest reaction barriers and those with a reaction barrier of less than 20 kJ mol^{-1} higher, the methyl group on the β-lactam C4 carbon atom (R^2) was replaced by isopropyl and phenyl groups because these substituents selectively lead to 3-imino-β-lactams **2** (i.e., dehydration products; Scheme 4) and ethanediamides **4** (i.e., C3–C4 ring-opening products; Scheme 3), respectively (see Table S2 in the Supporting Information). The Gibbs free energy profiles for the pathways with the lowest reaction barrier for the three reactions under study are shown in Figures 3 and 4.

For $R^2=i$Pr (Figure 3), the dehydration reaction is clearly preferred over the CO elimination reaction and the C3–C4 ring-opening reaction ($\Delta G^{\ddagger}=93.6$, 128.8, and 149.2 kJ mol^{-1}, re-

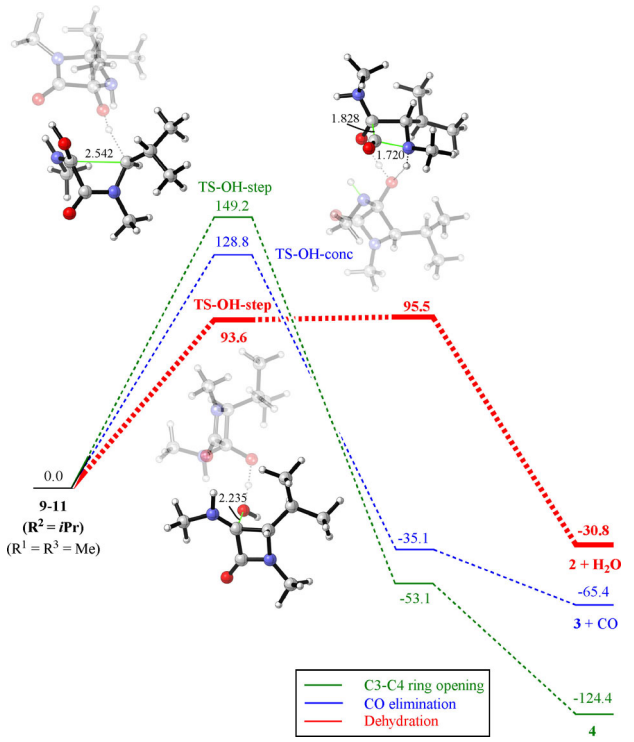


Figure 3. Gibbs free energy profiles for the dehydration, CO elimination, and C3–C4 ring opening of β-lactams **9**–**11** ($R^2 = i$Pr) with the assistance of a second β-lactam molecule (PCM ($\varepsilon = 7.43$) B3LYP-D3/6-311 + G(d,p)//PCM ($\varepsilon = 7.43$) M06-2X/6-31 + G(d,p), kJ mol^{-1}). OH denotes assistance by the hydroxyl group of the assisting molecule, step denotes stepwise, and conc denotes concerted. Some critical distances are given in Å. Energies are given relative to separate reactants.

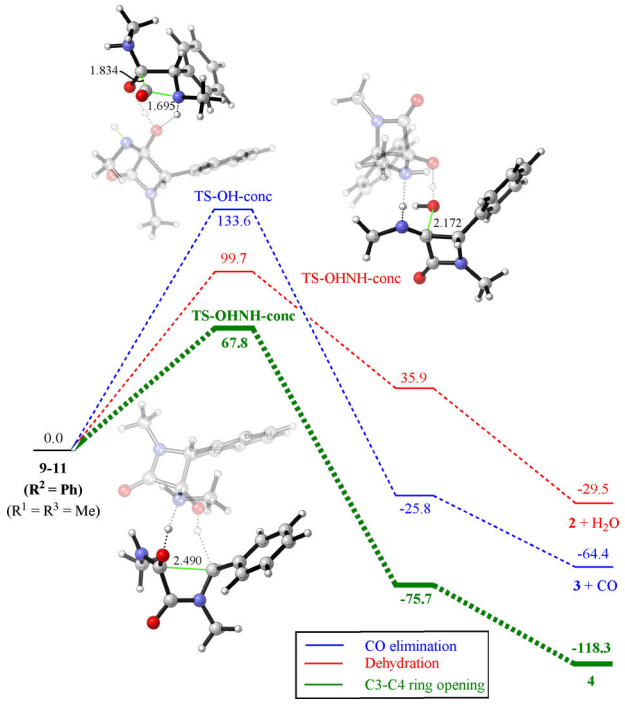


Figure 4. Gibbs free energy profiles for the dehydration, CO elimination, and C3–C4 ring opening of β-lactams **9**–**11** ($R^2 = $Ph) with the assistance of a second β-lactam molecule (PCM ($\varepsilon = 7.43$) B3LYP-D3/6-311 + G(d,p)//PCM ($\varepsilon = 7.43$) M06-2X/6-31 + G(d,p), kJ mol^{-1}). OH denotes assistance by the hydroxyl group of the assisting molecule, NH denotes assistance by the amino group of the assisting molecule, step denotes stepwise, and conc denotes concerted. Some critical distances are given in Å. Energies are given relative to separate reactants.

spectively), as found experimentally. Dehydration occurs through a stepwise pathway, in which the hydroxyl group of the assisting molecule donates a proton to the hydroxyl group of the reacting molecule with the formation of water. In the second step, the amino group of the reacting molecule readily donates its proton to the negatively charged oxygen atom of the assisting molecule by a simple proton transfer.

For $R^2 = $Ph (Figure 4), comparable reaction barriers to those for $R^2 = i$Pr are found for the dehydration reaction ($\Delta G^{\ddagger} = 93.6$ and 99.7 kJ mol^{-1} for $R^2 = i$Pr and Ph, respectively) and the CO elimination reaction ($\Delta G^{\ddagger} = 128.8$ and 133.6 kJ mol^{-1} for $R^2 = i$Pr and Ph, respectively). However, a remarkably lower reaction barrier is found for the C3–C4 ring-opening reaction ($\Delta G^{\ddagger} = 149.2$ and 67.8 kJ mol^{-1} for $R^2 = i$Pr and Ph, respectively), leading to a clear preference for C3–C4 ring opening. The C3–C4 ring opening occurs through a concerted pathway, in which the amino group of the assisting molecule accepts a proton from the hydroxyl group of the reacting molecule, and the hydroxyl group of the assisting molecule donates a proton to the C4 atom of the reacting molecule. Stabilization of the TS for C3–C4 ring opening can be explained by stabilization of the carbanion in the TS by the phenyl group (atomic charge, calculated with natural population analysis (NPA),[24] of the C4 atom is −0.397).

Conclusion

The reactivity profile of azetidine-2,3-diones with regard to primary amines was explored in depth, both experimentally and computationally. By changing the specific β-lactam C4 substituent, the selective preparation of 3-imino-β-lactams (dehydration products), α-aminoamides (CO-elimination products), or ethanediamides (C3–C4 ring-opening products) could be achieved; thus revisiting preceding literature reports. This work also comprises the first report on the direct transformation of β-lactam scaffolds into biologically interesting oxamides (ethanediamides) through an unprecedented C3–C4 ring-opening pathway. Computationally, a clear preference was found for the dehydration reaction (imination) if $R^2 = i$Pr and for the C3–C4 ring-opening reaction if $R^2 = $Ph, which was in full correspondence with the experimental results.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: density functional calculations · lactams · natural products · reaction mechanisms · structure elucidation

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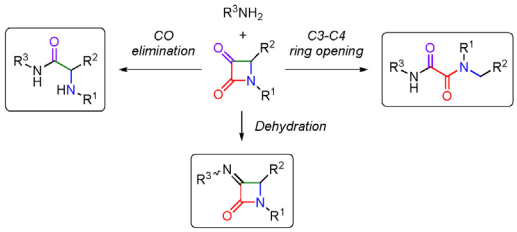

Profiling reactivity: 3-Oxo-β-lactams selectively produce 3-imino-β-lactams (dehydration products), α-aminoamides (CO-elimination products), or unprecedented ethanediamides (C3–C4 ring-opening products) upon reaction with primary amines (see scheme). In particular, the specific β-lactam C4 substituent is responsible for this intriguing reactivity; an observation that is supported by DFT calculations.

β-Lactams

N. Piens, H. Goossens, D. Hertsen, S. Deketelaere, L. Crul, L. Demeurisse, J. De Moor, E. Van den Broeck, K. Mollet, K. Van Hecke, V. Van Speybroeck, M. D'hooghe**

■■ – ■■

Reactivity of 3-Oxo-β-lactams with Respect to Primary Amines—An Experimental and Computational Approach