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Unusual reaction of azetidine-2,3-diones with primary amines. Straightforward asymmetric synthesis of α-amino acid and peptide derivatives

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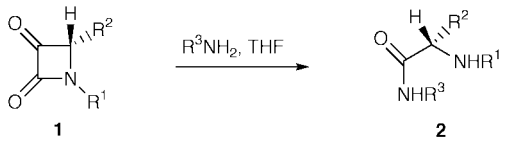
An unprecedented one-step synthesis of unnatural α-amino acid and peptide derivatives, in both the racemic and optically pure forms, using azetidine-2,3-diones as building blocks has been developed by treatment with primary amines.

As the defining subunit of peptides and proteins, α-amino acids play a central role in chemistry and biology, and the development of new stereoselective strategies for the synthesis of α-amino acids has evolved in a very active field in recent years.[1] In addition to the need for large-scale preparation of the 20 common proteinogenic α-amino acids, there is an ever increasing demand for the much rarer nonproteinogenic α-amino acids. Peptides containing α-amino acids that are not naturally occurring can also be used in biological studies, either to provide information on the active conformation of related peptides,[2] or as enzyme inhibitors.[3] On the other hand, while the chemistry of 6-oxopenicillanates and 7-oxocephalosporanates has been the focus of intense effort,[4] little was known about the synthesis and application of monocyclic azetidine-2,3-diones[5] and even less on their optically active derivatives,[6] until Palomo *et al.* elegantly merged into this field.[7] In our ongoing project directed toward the asymmetric synthesis and synthetic applications of functionalised 2-azetidinones,[8] we have recently described both the allylation and the stereoselective Baylis–Hillman reaction of enantiopure azetidine-2,3-diones.[9] In connection with this work, we report here, the unexpected manner in which azetidine-2,3-diones **1** and a variety of primary amines undergo reaction to give novel α-amino acid and peptide derivatives **2** (Scheme 1). The concise and convergent approach described herein presents a practical opportunity to connect the rapidly expanding fields of β-lactam chemistry and α-amino acid and peptides.[10]

Starting substrates, azetidine-2,3-diones **1**, were prepared both in racemic and in optically pure forms following our previously reported methods. Racemic compound **1a** was obtained from 3-methylidene-4-phenyl-2-azetidinone by dihydroxylation followed by oxidative cleavage with $NaIO_4$.[11] Enantiopure azetidine-2,3-diones (+)-**1b** and (−)-**1c** were available in high yield by Swern oxidation of the corresponding 3-hydroxy-β-lactam.[9] We sought to explore the reactivity of azetidine-2,3-diones **1** with various primary amines. To our surprise, under the usual conditions utilized for imine formation,† α-amino acid derivatives **2** can be smoothly prepared in both the racemic and enantiopure forms, instead of the expected imino-β-lactams (Table 1).‡ This result is in sharp contrast with the smooth reaction of related indoline-2,3-diones with primary amines to afford imino-γ-lactams.[12] Of particular interest was the reaction of azetidine-2,3-diones **1** with α-amino esters such as methyl glycinate or methyl alaninate, showing the utility of this approach in the rapid synthesis of optically pure peptides (Table 1, entries 4, 8 and 9).§ Treatment of azetidine-2,3-dione (+)-**1b** with (*S*)-alanine methyl ester forms in 55% yield the peptide **(–)-2i**, bearing three chiral centers.¶ Compound (−)-**2i** showed a single set of signals in ^{1}H NMR spectrum, thus proving that this transformation proceeded without detectable racemization.



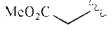
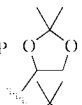
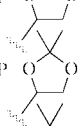
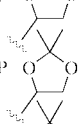
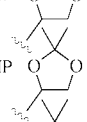
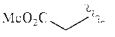
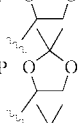
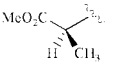
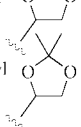
1 **2**

Scheme 1

Palomo *et al.* have reported the synthesis of some α-amino acid derivatives from *N*-carboxy anhydrides (NCA), with NCAs being obtained through Baeyer–Villiger oxidation of azetidine-2,3-diones.[7] However, our one-step flask synthesis of α-amino acid derivatives starting from azetidine-2,3-diones is significant and should have application in organic synthesis.

This process could be rationalized through an initial nucleophilic addition of the amine to the ketone moiety of the azetidine-2,3-dione **1**, forming an intermediate carbinolamine **3**. This intermediate **3** may react through two different pathways to give the expected 3-imino-β-lactam **4** or the intermediate **5**, but presumably evolves to the fused aziridine-β-lactam **5**. We believe that the N1–C2 bond of intermediate **5** should be very labile, evolving to aziridinone **6**. Compound **6** under the reaction conditions furnish *N*-formylamide **7**. Intermediate **7** appears as the final, not isolable product, in the reaction. It is well known that *N*-formylamides, related to **7** smoothly lose CO under basic conditions to give the corresponding NH-amides.[13] Furthermore, heating in a sealed tube at 90 °C may well favour

Table 1 Synthesis of *α*-amino acid and dipeptide derivatives **2**

Entry	Substrate	R^1	R^2	R^3	Product	Yield(%)[b]	$[\alpha]_D$[c]
1	(±)-**1a**	PMP[a]	Ph	$PhCH_2$	(±)-**2a**	45	-
2	(±)-**1a**	PMP	Ph	allyl	(±)-**2b**	77	-
3	(±)-**1a**	PMP	Ph	propargyl	(±)-**2c**	49	-
4	(±)-**1a**	PMP	Ph		(±)-**2d**	60	-
5	(+)-**1b**	PMP		$PhCH_2$	(+)-**2e**	50	41.7
6	(+)-**1b**	PMP		allyl	(+)-**2f**	45	17.0
7	(+)-**1b**	PMP		propargyl	(+)-**2g**	48	8.5
8	(+)-**1b**	PMP			(−)-**2h**	50	−2.4
9	(+)-**1b**	PMP			(+)-**2i**	55	18.7
10	(−)-**1c**	Allyl		$PhCH_2$	(−)-**2j**	58	−34.0

[a] PMP = 4-$MeOC_6H_4$. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] Specific rotation is given in degrees dm^{-1} at 20 °C (*c* 1.0, $HCCl_3$).

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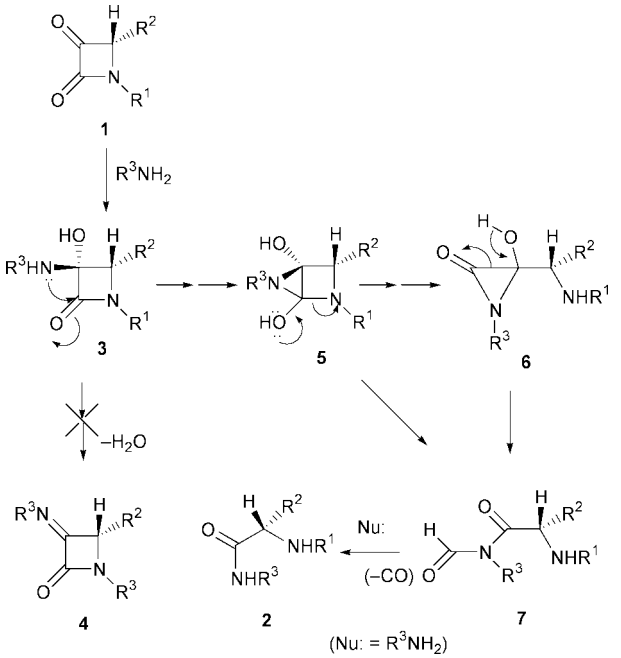

Scheme 2

the suggested CO extrusion and hence the shorter time needed for the thermal process in comparison with the reaction at room temperature (Scheme 2).

The suggestion that the reactive species involved in the reaction is the aziridine **5**, is presently made to explain the formation of α-amino acid derivatives rather that of the expected 3-imino-β-lactams. The different behaviour of azetidine-2,3-diones and pyrroline-2,3-diones may be due to differences in the carbinolamine presumably involved in the reaction, perhaps in the easier opening tendecy of the more strained four-membered ring.

In conclusion, a rapid one-step synthesis of unnatural α-amino acid and peptide derivatives both in racemic and in optically pure forms, starting from azetidine-2,3-diones has been developed. Furthermore, as far as we know, this unusual reaction of azetidine-2,3-diones with primary amines to afford α-amino acid derivatives is unprecedented, allowing structure variability and facile incorporation of functional groups. Studies concerning the scope and generality of this methodology are underway in our laboratory, and further details will be reported in due course.

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Notes and references

† Preliminary experiments were carried out under the usual anhydrous conditions utilized for the formation of imines, using $MgSO_4$, but we then realised that this was not necessary. Also, initial experiments with the most volatile amines were carried out in large excess (10 equiv.), however we later performed the reaction using equimolecular amounts of amine/substrate obtaining the same results as previously. Besides, we have carried out the experiments either with or without argon and with or without rigurously dry and degassed THF, obtaining similar results in all cases.

‡ No loss of optical purity was evident by ^{1}H NMR spectroscopy in presence of a chiral shift reagent of europium(III).

§ *Representative experimental procedures* for the synthesis of α-amino acid and dipeptide derivatives **2**: *method A* [Compounds **2a**–**c**, (−)-**2f**–**g**]: A solution of the appropriate amine (0.5 mmol) in tetrahydrofuran (1 mL) was added to a solution of the azetidine-2,3-dione **1** (0.5 mmol) in tetrahydrofuran (5 mL) and the solution was heated in a sealed tube at 90 °C for 2–6 h. The reaction mixture was allowed to cool to room temperature, the solvent removed under reduced pressure and after flash chromatography eluting with hexanes–ethyl acetate or dichloromethane–ethyl acetate, compounds **2** were obtained in analytically pure form.

Method B [Compounds **2a**, (−)-**2d**–**e**, (−)-**2h**–**j**]: a solution of the appropriate amine (0.5 mmol) in tetrahydrofuran (0.1 mL) was added to a solution of the azetidine-2,3-dione **1** (0.5 mmol) in tetrahydrofuran (5 mL) and the solution stirred at room temperature for 2–24 h. Compound (−)-**2j** required more prolonged reaction time (4 days). The solvent was removed under reduced pressure and after flash chromatography eluting with hexanes–ethyl acetate or dichloromethane–ethyl acetate, compounds **2** were obtained in analytically pure form.

¶ All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

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