A β-Lactam Framework as a β-Alanyl Dication Equivalent: New Synthesis of α-Amino Acid *N*-carboxy Anhydrides (NCAs) Derived from β-Substituted Alanines

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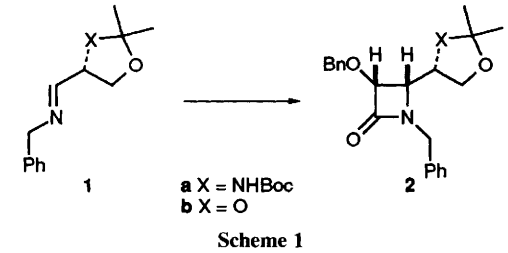
Optically pure 4-formyl-3-hydroxy β-lactams are transformed into 4-methylaryl and 4-(2-ethylaryl) derivatives and converted into β-substituted alanine-derived NCAs through oxidation and Baeyer–Villiger rearrangement of the resulting α-keto β-lactams.

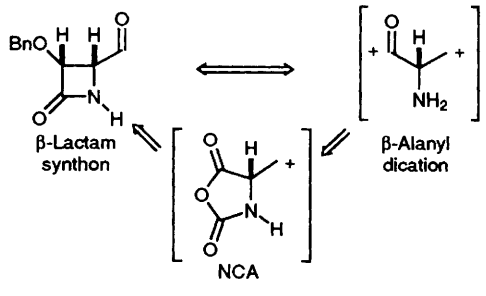
α-Amino acid *N*-carboxy anhydrides (NCAs) or Leuchs[1] anhydrides are of particular relevance as synthetic tools in the chemistry of α-amino acids, because they offer amino group protection and carboxylate activation simultaneously.[2] Recently, we undertook a study on a new synthesis of this particular class of mixed anhydrides, and found that oxidation of a 3-hydroxy β-lactam, followed by Baeyer–Villiger rearrangement of the resulting azetidine-2,3-dione, constituted an efficient alternative to the usual Leuchs procedure.[3]† The successful implementation of the approach was, however, based on the availability of the requisite starting α-hydroxy β-lactams *via* cycloaddition reaction of alkoxyketenes to either α-alkoxyimines or *N*-Boc-α-aminoimines,[4] Scheme 1. We report here our initial findings on the development of this approach into a general synthesis of β-substituted alanine-derived NCAs, whose significance as valuable precursors of dipeptide units, like those involved in macrocyclic compounds, could easily be anticipated.[5] The key to our approach is the use of an optically active 3-alkoxy-4-formyl β-lactam as a 1,3-alanyl dication equivalent, allowing either β-alkylation (or arylation) and carbonyl functionalization by suitable nucleophiles, Scheme 2.

Two examples were chosen to illustrate these concepts. First, the 4-formyl-β-lactam **3**,‡ obtained from **2a** as previously described,[6] was subjected to Wittig reaction, followed by hydrogenolysis under Pd/C of the resulting olefinic intermediates.§ As shown in Table 1, the resulting 4-alkyl-3-hydroxy β-lactams **4a–g** were obtained in excellent overall yields.[7] With the exception of **4g**,¶ no 1–4 β-lactam bond cleavage was observed.[8] For the oxidation of compounds **5** various reagents were tested, and the best results, in terms of chemical yield and large scale suitability, were obtained using dimethyl sulfoxide (DMSO), in combination with phosphorus pentoxide.[9] The α-keto β-lactams thus prepared were then allowed to react with MCPBA which had been previously dried over $MgSO_4$ in methylene chloride as solvent. The reaction temperature was found to be critical for the success of the transformation, the optimum results being recorded at −40 °C. Under these conditions, the reaction proceeded cleanly to give the desired homoarylalanine- and alkylglycine-derived NCAs **6** in almost quantitative yields. Nonetheless, at times some of the NCAs showed traces of MCPBA as the only by-product, but none of them showed loss of optical purity as judged by the amino acids formed, *vide infra*.

A further example confirming the versatility of **3** as a 1,3-alanyl dication equivalent is the formation of arylalanine-derived NCAs. The reaction of **3** with Grignard reagents (Scheme 4) was selected for development owing to the ample



Scheme 1

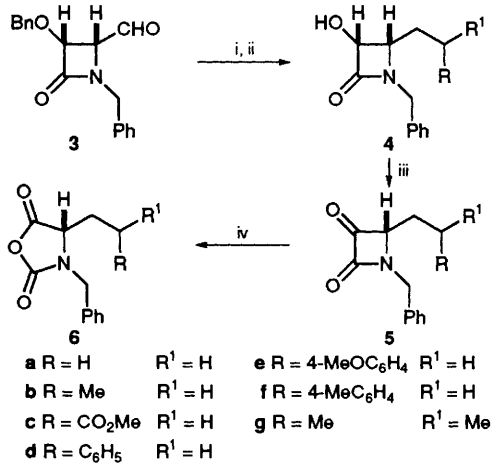


Scheme 2

Table 1 α-Hydroxy-3-alkyl β-lactams prepared[a]

Compound	Yield[b] (%)	Mp/°C[c]	$[\alpha]_D^{25}$ (*c* 1, CH_2Cl_2)
4a	86	86–87[d]	+59.6
4b	75	69–71[d]	+46.1
4c	74	48–50[d]	+46.4
4d	91	100–101[e]	+56.8
4e	80	140[f]	+54.4
4f	75	133–134[d]	+75.1
4g	70	[g]	+42.3
9h	90	91–93[f]	+13.3
9i	79	90–92[f]	+27.0
9j	71	95–96[f]	+23.3
9k	75	84–86[f]	+20.4

[a] Reactions conducted on a 10 mmol scale. [b] Yields of isolated pure products, after column chromatography or crystallization, for **3** → **4** and **7** → **9** overall transformations, respectively. [c] Crystallization solvents: [d] EtOAc–hexanes, [e] hexanes, [f] CH_2Cl_2–hexanes, [g] Isolated as an oil.



Scheme 3 *Reagents and conditions*: i, $Ph_3P{=}CR^1R$, THF, room temp., 2 h; ii, HCO_2NH_4, Pd/C, MeOH, reflux, 2 h; iii, P_2O_5, DMSO, CH_2Cl_2, room temp., 20 h; iv, MCPBA, CH_2Cl_2, −40 °C, 30 min

precedents for deoxygenation of hydroxy derivatives.[10]‖ Thus, treatment of **3** with arylmagnesium bromides at −40 °C in THF as solvent, produced the expected carbinols **7h–k** in 72–88% yields.** Simultaneous deoxygenation and debenzylation of alcohols **7** through their acetates **8** with HCO_2NH_4 and Pd/C in refluxing propan-2-ol gave the expected 4-arylmethyl-3-hydroxy β-lactams **9** in fairly good yields (Table 1). Finally, oxidation of each lactam **9** was followed by Baeyer–Villiger rearrangement of the resulting α-keto β-lactam, as above. By this means, NCAs **10h–k**, formally derived from arylalanines, were obtained in good overall yields. In every case (Scheme 3) the optical purity of the NCAs prepared was determined by their conversion into the α-amino esters **11** and **14**, followed by *N*-debenzylation and further treatment of the resulting free amino compounds **12** and **15** with Mosher[11] acid chloride and triethylamine. All of the resulting amide derivatives **13** and **16** showed a single set of signals in the ^1H, ^{13}C and ^{19}F NMR spectra, thus proving that the synthesis and reactions proceeded without detectable racemization. Some representative data are listed in Table 2 to illustrate that a 4-formyl-3-alkoxy β-lactam can indeed be regarded as a masked chiral 1,3-alanyl dication equivalent. In particular, formation of NCAs from non-α-amino acid precursors is the most essential feature of this approach when compared with the traditional Leuchs procedure and with the existing electrophilic β-alanyl equivalents.[12] Further work on the use of this chemistry for a stepwise peptide synthesis is currently under way.

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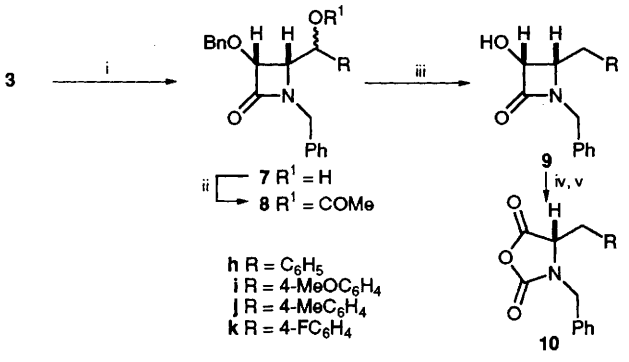
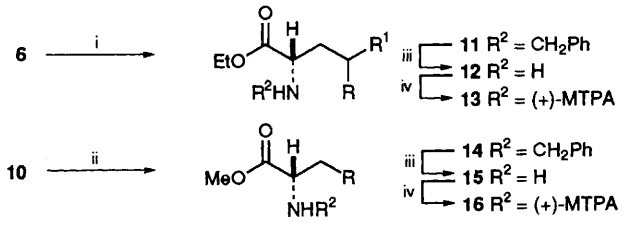


Scheme 4 *Reagents and conditions*: i, RMgBr, THF, −40 °C, 30 min; ii, MeCOCl, NEt_3, CH_2Cl_2, room temp., 2 h; iii, NH_4HCO_2, Pd/C, Pr^iOH, reflux, 1 h; iv, P_2O_5, DMSO, CH_2Cl_2, room temp., 20 h; v, MCPBA, CH_2Cl_2, −40 °C, 30 min



Scheme 5 *Reagents and conditions*: i, EtOH, reflux, 1 h, ii, MeOH, reflux, 1 h; iii, NH_4HCO_2, Pd/C, MeOH, reflux; iv, (+)-MTPA-Cl, NEt_3, CH_2Cl_2, room temp. [MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl]

Table 2 Synthesis of arylalanine, homoarylalanine and alkylglycine derivatives through α-amino acid-*N*-carboxyanhydrides **6** and **10**[a]

Compound	Yield[a] (%)	$[\alpha]_D^{25}$ (*c* 1)[b]
11b	81	−14.5(EtOH)
12b	85	+28.0(EtOH)
11d	75	−6.2(MeOH)
12d	90	+9.0(EtOH)
11e	90	−5.6(MeOH)
12e	90	+19.9(EtOH)
11f	76	−12.0(EtOH)
12f	85	+23.5(EtOH)
14i	89	−6.0(CH_2Cl_2)
15i	83	+5.4(CH_2Cl_2)

[a] Yields of isolated pure products for (α-oxo-β-lactam) → (α-*N*-benzylamino ester) **11**, **14** and (α-*N*-benzylamino ester) → (α-amino ester) **12**, **15** overall transformations. [b] All compounds isolated as oils, after preparative HPLC purification.

Footnotes

† During the course of this investigation a Smithkline Beecham group reported that ozonolysis of ethylidene azetidinones can give NCAs instead of α-keto β-lactams.[3c,d]

‡ Compound **3** could also be prepared using the corresponding D-glyceraldehyde-derived imine **1b** followed by chemical elaboration of the side chain at C(4): see D. R. Wagle, G. Garai, J. Chiang, M. G. Monteleone, A. E. Kurys, T. W. Strohmeyer, U. R. Hedge, M. S. Manhas and A. K. Bose, *J. Org. Chem.*, 1988, **53**, 4227. The enantiomer of **3** could also be obtained from the corresponding (*S*)-Boc-serinalacetonide-derived imine or by Hubschwerlen's method, see: C. Hubschwerlen and G. Schmid, *Helv. Chim. Acta*, 1983, **66**, 2206.

§ These compounds were usually formed as mixtures of *cis* and *trans* isomers around the double bond, which were not separated. The ylides were generated by using a deficiency of Bu^nLi to ensure complete absence of base in the subsequent step; otherwise, in some cases we observed partial racemization at C(4) of the β-lactam ring.

¶ **4g** could be obtained in two steps by reducing the alkene double bond using H_2 at 100 psi (1 psi = 6894.76 Pa) under Pd/C catalysis before the hydrogenolytic debenzylation at C(3) by means of HCO_2NH_4 and Pd/C in refluxing MeOH. Direct treatment of **3g** under ammonium formate conditions produced N–C(4) bond cleavage leading to the corresponding α-hydroxy carboxylic acid derivative as major product.

‖ We first examined the corresponding 4-methanesulfonyloxymethyl β-lactam, prepared by reduction of **3** and subsequent mesylation, as a 1,3-alanyl dication equivalent. However, reaction of this compound with organocuprates under different reaction conditions did not lead to the expected products. In a similar way, the corresponding triflate and iodomethyl derivatives were also found to be ineffective for this transformation. For a related problem, see: G. I. Georg and T. Durst, *J. Org. Chem.*, 1983, **48**, 2092.

** The diastereoisomeric mixtures of carbinols were acetylated with MeCOCl and Et_3N in dichloromethane, and the resulting acetates were used without separation in these reactions.

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