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ENANTIORETENTIVE ALKYLATION OF ACYCLIC AMINO ACIDS

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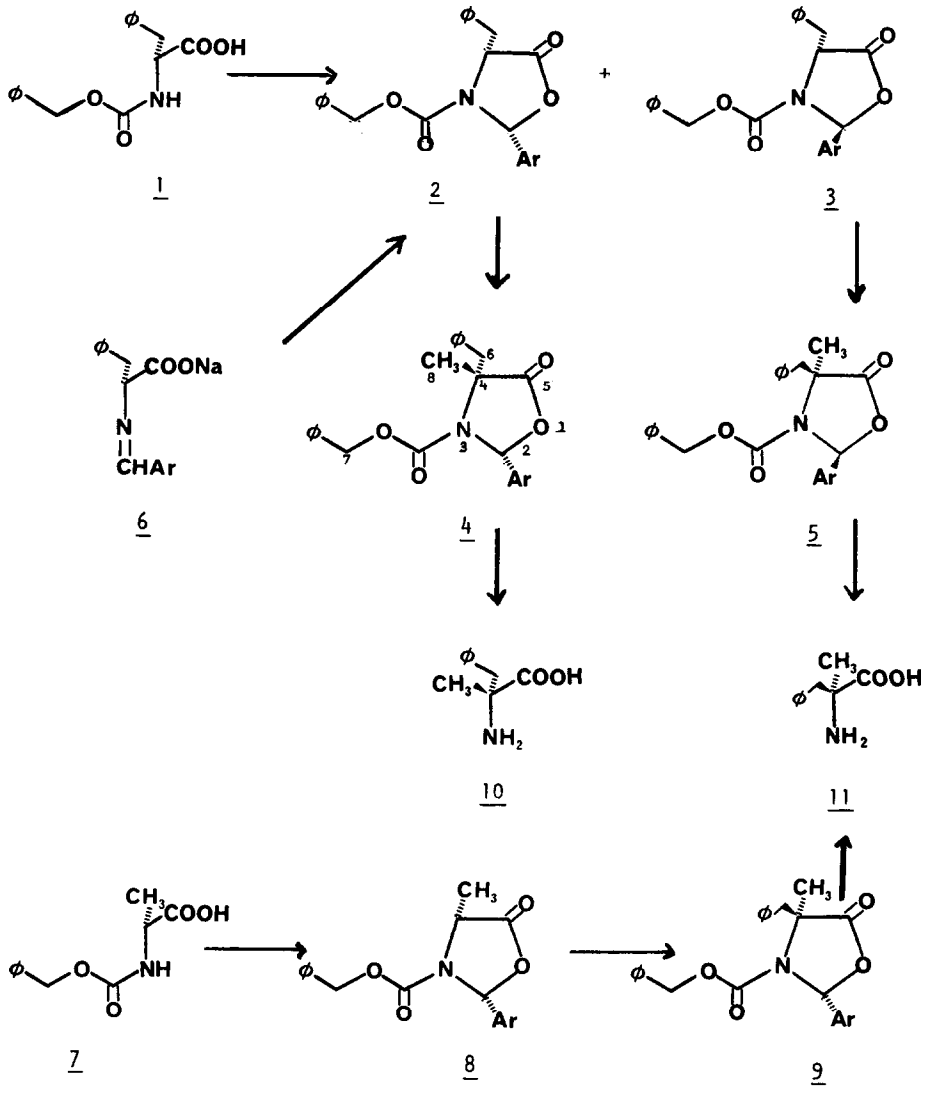
Abstract

A stereospecific method is described for the alkylation of acyclic amino acids (alanine and phenylalanine) which proceeds with retention of configuration. The method involves a) conversion of the amino acid to the predominantly cis 2-aryl-3-carbobenzyloxy oxazolidinones (2 and 8), b) alkylation of the potassium enolate with CH_3I or $PhCH_2Br$, c) Base hydrolysis and hydrogenolysis to afford the alkylated amino acid.

Many optically active α-alkyl amino acids bearing configurations corresponding to the natural product are important enzyme inhibitors and other pharmaceuticals[1]. A method which permits replacement of the α-hydrogen while retaining the original stereochemistry, i.e. an enantio-retentive process, has been the goal of previous workers[2]. Following the α-alkylation of α-hydroxy acids with retention of configuration by Frater[3] and by Seebach[4] via dioxalone derivatives, Seebach and coworkers have also reported on the alkylation of proline oxazolidinone derivatives and proposed the elegant concept of "self reproduction of chirality". In this extensive work, it was mentioned that "neither . . . nor acyclic amino acids could be condensed with pivaldehyde, in spite of numerous attempts under a variety of conditions". In this paper a procedure for the enantioretentive alkylation of acyclic amino acids is described which involves conversion of the amino acid to the cis-oxazolidinone derived from an aromatic aldehyde followed by alkylation of the potassium enolate, oxazolidinone hydrolysis and deprotection to the α-alkylated amino acid. It is exemplified by the conversion of S-phenylalanine 1 and S-alanine 7 to S- and R-α-methylphenylalanine (10 and 11 respectively).

Oxazolidinone derivatives of acyclic amino acids have been known since 1904[5] but their stereochemistry has not been investigated in detail[6]. It was rewarding to observe that the two methods of synthesis that we examined yielded predominantly cis oxazolidinones. Thus, condensation of CBZO-phenylalanine with benzaldehyde or 2,4-dichlorobenzaldehyde (2 eq



a) Ar = Ph

b) Ar = 2,4-dichlorophenyl

aldehyde, 1 eq toluenesulfonic acid in 1,1,1-trichloroethane, with azeotropic removal of water, for 18 hrs)[5] afforded a 9:1 mixture of oxazolidinones 2 and 3 in 40% yield[7]. Similarly alanine was converted to a 4:1 mixture of 8b[8] and its trans isomer. The diastereomers, readily separated by chromatography and crystallization, were correlated based on their ^{13}C NMR spectra[7,8]. The cis assignment of the major diastereomer was confirmed by single crystal X-ray analysis on 2a. An alternative method[9], starting from the Schiff's base 6b (stirred the slurry of 6b overnight in CH_2Cl_2 with 1.5 eq of CBZCl) yielded 2b and 3b in the ratio of 2.5:1 in 46% yield[7].

Alkylation of the potassium enolates of the oxazolidinones of 2, 3 and 8 (K-hexamethyldisilazide[10], THF, -78°C, 5 min, CH_3I or $PhCH_2Br$, slow warming to room temperature) took place completely stereospecifically, yielding a single diastereomer in ~80% yield. In each case the alkyl groups entered from the side opposite the aryl function. This resulted in retention of the original configuration for the cis isomers (2—>4 and 8b—>9b) and inversion for the trans oxazolidinone (3b—>5b)[11]. The relative stereochemistry of 4a and 5b was established by single crystal X-ray analysis. As expected, the two alkylation products 4b and 5b were antipodes, exhibiting equal but opposite rotation[11].

Deuteration of the potassium enolate followed a parallel pathway. Thus 2b was deuterated (K enolate in THF at -78°C, quenched with excess of CH_3COOD, slowly warmed to room temperature) with retention of stereochemistry[12], in 70% yield.

The alkylated amino acids were generated from the oxazolidinones by the following two step procedure: hydrolysis with an excess of NaOH (1 N NaOH, MeOH, room temperature overnight, extractive isolation with EtOAc) followed by hydrogenolysis (MeOH, 10% Pd/C, H_2, 40 psi, room temperature, 2 hrs). In this manner 4a was converted to S-α-methylphenylalanine 10[13,14] and 5 and 9 to the corresponding R-antipode 11[13].

The conversion of alanine and phenylalanine to the opposite antipodes of α-methylphenylalanines demonstrates the power of the oxazolidinone method for the enantioretentive alkylation of acyclic amino acids.

Acknowledgements

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(7) The major byproduct of this reaction is the benzyl ester of the CBZ-amino acid. 2a: mp 109-112°; $[\alpha]_D^{25}$ + 92.0° (C 1; CH_2Cl_2); IR ($CHCl_3$) 1800, 1725 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 36.59 (C6) 58.25 (C4), 67.90 (C7), 89.21 (C2) 153.89 (CON) 171.00 (C5). 2b mp: 209-211°; $[\alpha]_D^{25}$ + 101° (C 1, CH_2Cl_2); essentially the same NMR spectrum as 2a except: ^{13}C NMR δ 35.76 (C6), 85.05 (C2) 3b: was purified by chromatography and obtained as a viscous oil. IR ($CHCl_3$) 1700, 1800 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 34.25 (br, C6), 58.16 (C4), 67.69 (C7), 87.1 (br, C2), 151.36 (CON), 170.68 (C5); the broadness of C2 and C6 signals are caused by hindered rotation. At 70° (in CH_3CN) the signals become sharper and at 5° they separated to two lines.
(8) The cis/trans ratio was estimated from the peak heights of the C2 ^{13}C NMR signals. 8b: mp 92-94°; ^{13}C NMR ($CDCl_3$) δ 17.95 (C6); 52.35 (C4), 68.05 (C7), 86.22 (C2), 153.31 (CON), 171.66 (C5).
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(10) Purchased from Callery Chem. Co., Callery PA, as a stable toluene solution.
(11) 4a $[\alpha]_D^{25}$ + 85° (C 1, CH_2Cl_2); IR ($CDCl_3$) 1800, 1725 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 22.41 (br,C8), 41.83 (C7), 61.71 (C4) 66.89 (C7), 88.52 (C2), 153.20 (CON), 173.67 (C5). 4b: mp 85-88°; $[\alpha]_D^{25}$ + 102° (C 1, CH_2Cl_2); ^{13}C NMR ($CDCl_3$) substantially identical with 4a, except: δ 83.39 (C2). 5b: mp 82-84°, $[\alpha]_D^{25}$ - 99.2° (C 1, CH_2Cl_2); ^{13}C NMR superimposible with that of 4b. 9b: mp 86-88°; $[\alpha]_D^{25}$ - 149° (C 1, CH_2Cl_2); ^{13}C NMR ($CDCl_3$) δ 23.78 (br, C8), 40.85 (C6), 64.85 (C4) 67.37 (C7), 85.11 (C2), 151.67 (CON), 173.86 (C5). At 37°C, signals of C8, C7, C6 and CON were broad and showed small satelite peaks. At 60° these coalesced into one peak, indicating hindered rotation.
(12) $[\alpha]_D^{25}$ + 94.3° (C 1, CH_2Cl_2); ^{13}C NMR spectrum was superimposible with that of 2b except that the signal of δ 58.25 (C4) was reduced to a trace. ^1H NMR spectrum also indicated a trace of protio compound left.
(13) 10: mp 307-310° dec; $[\alpha]_D^{25}$ - 20.0°; $[\alpha]_{578}^{25}$ + 22.0° (C 0.1, MeOH); Cu complex $[\alpha]_{546}^{25}$ + 180; Lit data[4]: mp 306.5° dec, $[\alpha]_{578}^{24}$ - 22.8° (C 1, H_2O). The ^1H NMR spectrum was identical with that of an authentic sample. 11: $[\alpha]_D^{25}$ + 19.00° (C 0.1, MeOH).
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