Diastereoselective Radical Addition to Methyleneoxazolidinones: an Enantioselective Route to α-Amino Acids

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The diastereoselectivity of radical addition to methyleneoxazolidinones depends on the nature of the addend radical and of the *N*-protecting group; the reaction provides a convenient enantioselective route to α-amino acids.

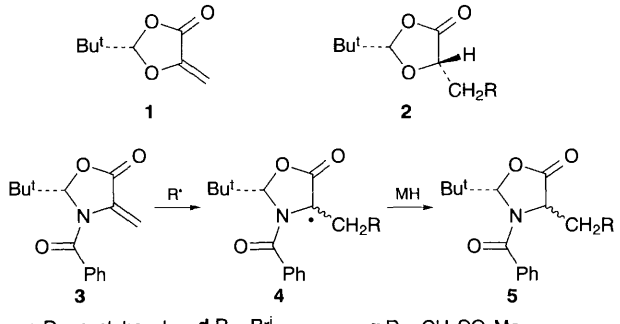
With the aim of developing highly diastereoselective routes to important synthetic targets, considerable effort has recently been directed towards delineating the factors that control the diastereoselectivity of organic free radical reactions.[1] One such study of reactions potentially capable of affording highly enantiomerically enriched α-amino or α-hydroxy acids[2] showed that radical addition to the methylene compounds **1** and **3** proceeds with moderate to good diastereoselectivity. When treated with an alkyl halide/tributylstannane or an alkylmercury hydride the dioxolanone **1** gives mainly the *cis* product **2** while the oxazolidinone **3** gives mainly the *trans* isomer of **5**. In the present study we have found that both the direction and the degree of diastereoselectivity of radical addition to methyleneoxazolidinones depends on the nature of the addend radical and the *N*-acyl group. The utility of the method is illustrated by the synthesis of one enantiomer of the new glucosylalanine **15** and its galactose analogue **16**.

In the first series of reactions the pure (2*S*)-*N*-benzoyl methyleneoxazolidinone **3**, prepared from (*S*)-alanine as previously described,[3] was treated with an iodo compound, azobisisobutyronitrile (AIBN) and tributylstannane (method A);[4] with an alkylmercuric halide and sodium cyanoborohydride (method B);[5] or with an iodo compound, tributyltin chloride (10 mol%) and sodium cyanoborohydride (method C).[6] The reaction (Scheme 1) involves addition of the radical to the double bond of **3** to give **4** which then undergoes diastereoselective hydrogen-atom transfer from the metal hydride.

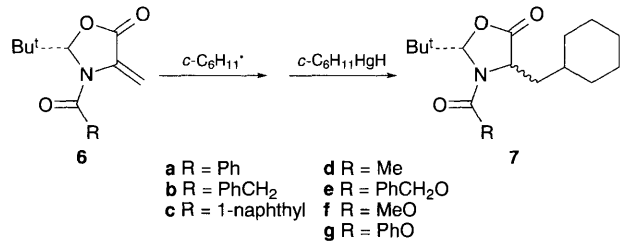
In most cases the reaction afforded a mixture of diastereoisomers from which the pure components† could be isolated by chromatography. The assignment of structure and stereochemistry to the products was based mainly on NMR evidence, but in the cases of *trans*-**5a** and *trans*-**5i** X-ray crystal structures were obtained. The diastereoisomeric ratio of products in the crude mixture was determined by integration of the resonances in the regions δ 6.0–6.22 and 4.0–4.45 of the ^{1}H NMR spectra; generally the *trans* adducts have signals at lower field than their *cis* isomers.

The results (Table 1) indicate that in every case the *trans* diastereoisomer is the major product; *i.e.* the transfer of a hydrogen atom from the metal hydride occurs preferentially on the face of the intermediate radical **4** *syn* to the *tert*-butyl substituent. However, the degree of diastereoselectivity depends on the nature of both the addend radical and the metal hydride. Reactions with tributylstannane always gave a higher diastereoisomeric ratio than those with mercury hydrides, but the latter reagent gave better yields. The diastereoselectivity also reflects the size of the addend, being smallest for the methyl radical and other simple primary radicals and greatest for the bulky adamantyl and *tert*-butyl radicals. In the last case the *cis* isomer could not be detected. These experiments also showed that the reaction proceeds with both nucleophilic (methoxymethyl) and electrophilic (*e.g.* perfluorobutyl) radicals.

In a second series of experiments (Scheme 2), methyleneoxazolidinones **6** bearing various *N*-protecting groups were treated with cyclohexylmercuric chloride and sodium cyanoborohydride in THF. As in the first series of experiments, the assignment of stereochemistry to the products rests mainly on the relative intensities of the ^{1}H NMR signals for the protons at the 2- and 4-positions, but in some cases (the *cis* isomers of **7d**, **7e** and **7f**) the structures were confirmed by X-ray diffraction. These results show that the nature of the protecting group determines not only the degree of diastereoselectivity but also its direction. The compound **6c** like the *N*-benzoyl compound **6a** gave mainly the *trans* product. The benzylacetamide **6b**, the acetamide **6d** and the carbamates **6e–g**, however, unexpectedly gave *cis* products with very high diastereoselectivity.



Scheme 1



Scheme 2

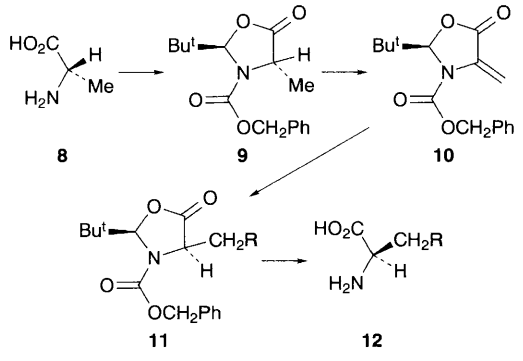
Table 1 Radical addition to (2*S*)-methyleneoxazolidinone **3**

Product	Method[a]	*trans*:*cis*	Yield (%)	Product	Method[a]	*trans*:*cis*	Yield (%)
5a	A	91:9	52	**5e**	A	>98:2	70
	B	84:16	89	**5f**	A	73:27	24
5b	A	95:5	66	**5g**	A	72:28	20
	B	92:8	>95	**5h**	A	80:20	56
5c	C	78:22	58	**5i**	A	85:15	54
5d	A	92:8	63				

[a] See text.

The reasons for this remarkable reversal of diastereoselectivity when the *N*-protecting group is changed from aryl to phenylacetyl, acetyl or alkoxycarbonyl have not yet been fully elucidated. The X-ray structures of starting materials and of products show no changes in geometry that consistently reflect the direction or degree of diastereoselectivity. Nor do these reactions necessarily give the more thermodyanamically stable diastereoisomer as determined by molecular mechanics calculations. It appears that a full rationalisation of the stereochemistry of these reactions awaits a theoretical study of the type recently conducted on reactions of dioxolanones.[7]

The observation that radical addition to suitable methylene oxazolidinones can be conducted with high diastereoselectivity and reasonable yield opens the way to a practicable enantioselective synthesis of amino acids (Scheme 3). Only four operational steps are required: (*i*) conversion of (*S*)-alanine into a mixture of the (2*R*,4*S*) and (2*S*,4*S*) *N*-benzyloxycarbonyl oxazolidinones from which one, *e.g.* the former **9**, is separated; (*ii*) preparation of the (2*R*)-methyleneoxazolidinone **10** from **9**; (*iii*) treatment of **10** with an alkyl iodide, a catalytic amount of tributyltin chloride and sodium cyanoborohydride to give the *cis* adduct **11**; (*iv*) hydrogenolysis in high yield of **11** over palladium on carbon in ethyl acetate[8] to give the free (*R*) amino acid **12**. The same sequence of reactions gives (*S*) amino acids when the *cis* (2*S*,4*S*) isomer of **9** is used as starting material. Application of the method to the formation of (*S*)-cyclohexylalanine and (*S*)-leucine identical with the authentic compounds[9] showed that the hydrogenolysis proceeds without any detectable racemisation.



Scheme 3

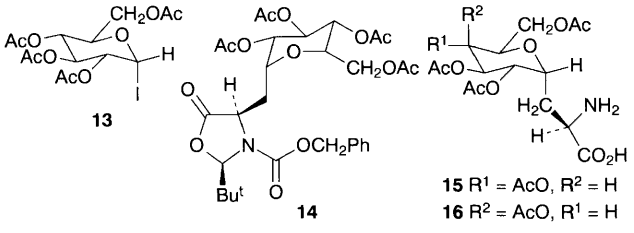


Table 2 Cyclohexyl radical addition[a] to (2*S*)-methyleneoxazolidinone **6**

Product	*cis*:*trans*	Yield (%)	Product	*cis*:*trans*	Yield (%)
7a	16:84	89	**7d**	>98:2	69
7b	94:6	86	**7e**	98:2	60
7c	16:84	77	**7f**	>95:5	63
			7g	>98:2	47

[a] By method B (see text).

The efficiency of the method has been tested by the preparation of the α-D-glucosyl-(*R*)-alanine **15**. Treatment of **10** with the iodide **13**, sodium cyanoborohydride and tributyltin chloride (10 mol%) in *tert*-butanol gave exclusively the diastereoisomer **14** (88%) arising from addition of the glucosyl radical on its α-face followed by hydrogen-atom transfer to the intermediate oxazolidinonyl radical *anti* to the *tert*-butyl group. Subsequent hydrogenolysis of **14** proceeded quantitatively to afford the amino acid **15**. Similar treatment of **10** with tetraacetyl galactosyl iodide gave the galactose analogue of **14** (73%) as a single diastereoisomer from which the amino acid **16** (92%) was obtained. The propensity of the glucosyl radical and related species to form a new bond in the α-orientation has been previously noted.[10]

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Footnote

† All new compounds gave satisfactory ^{1}H and ^{13}C NMR spectra, and microanalytical data.

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