Diastereoselective Radical Addition to Derivatives of Dehydroalanine and of Dehydrolactic Acid

Athelstan L. J. Beckwith* and Christina L. L. Chai

Research School of Chemistry, Australian National University, Canberra, Australia, 2601

The cyclic methylene compounds (**1**)—(**3**) undergo diastereoselective free radical addition when treated with alkylmercury hydride or alkyl iodide/tributylstannane to give products useful for the enantioselective synthesis of α-amino and α-hydroxy acids.

Radical addition to alkenes, both inter- and intra-molecular, is a significant method for the formation of carbon–carbon bonds, especially when the acceptor is activated by an electron withdrawing substituent.[1] The evidence concerning addition to alkenes bearing both an electron donating and an electron accepting substituent at the same site ('captodative' alkenes)[2] is less clear cut. The addition of cyanoisopropyl radicals to captodative alkenes exhibits the predicted enhanced reactivity of the substrates,[3] but no significant effect was detected in some other kinetic studies of inter- and intra-molecular radical additions.[4] Recently, it was reported that peptides containing the captodative dehydroalanine residue would not undergo radical additions when the radicals were generated from Barton esters or alkyl halides/tributylstannane.[5] The addition of alkylmercury hydrides proceeded satisfactorily but exhibited little stereoselectivity.[5] We now describe improved routes to the cyclic derivatives (**1**) of dehydrolactic acid and, (**2**) and (**3**), of dehydroalanine, and show that they do undergo radical addition[6] sometimes with relatively high diastereoselectivity.

UV irradiation of the Barton ester (**5**) prepared in the usual way[7] from the *cis*-(2*S*,5*S*)-dioxolanone (**4**)[8] in $BrCCl_3$ afforded the expected bromo compound (**7**) (85% by NMR), addition to which of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the (2*S*)-enantiomer of 2-t-butyl-5-methylene-1,3-dioxolan-4-one (**1**), $[\alpha]_D^{23}$ −14.8° (*c* 1.2, $CHCl_3$) (lit.[9] −14.9°), in 54% yield from (**4**). Alternatively the same product could be obtained more directly in 68% overall yield by DBU-induced decarboxylative dehydrobromination of the single bromide [probably diastereoisomer (**6**)] formed by bromination of (**4**) with *N*-bromosuccinimide (NBS). The (2*R*)-enantiomer of (**1**) was similarly obtained from the *trans*-(2*R*, 5*S*)-isomer of (**4**).

Bromination of the oxazolidinone (**8**)[6] derived from (*S*)-alanine with NBS (2 mol equiv.) in CCl_4 gave an unstable dibromide, which was converted directly into the (2*S*)-enantiomer of *N*-benzoyl-2-t-butyl-4-methylene-1,3-oxazolidin-5-one (**2**) (56% overall), $[\alpha]_D^{23}$ −186.3° (*c* 1.5, $CHCl_3$) (lit.[9] −148.6°), by treatment with sodium iodide in acetone. 2-t-Butyl-5-methylene-1,3-imidazolidin-4-one (**3**) can be similarly prepared from the diastereoisomers of the imidazolidinone (**9**).

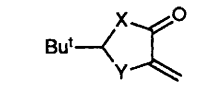
In a typical radical addition a solution of the oxazolidinone (**2**) and cyclohexyl iodide in benzene was irradiated with UV light at room temperature while tributylstannane and azoisobutyronitrile (AIBN) in benzene were added during 1 h from a syringe pump (method A). Chromatography of the crude product gave a mixture of the diastereoisomers of the addition product (**11**), the relative yields of which were determined by ^1H NMR spectroscopy. The results are given in Table 1 together with those for the corresponding reactions of the dioxolanone (**1**) and the imidazolidinone (**3**).†

In a second series of experiments each of the substrates was stirred with cyclohexylmercury chloride in dichloromethane while an aqueous solution of sodium borohydride was added dropwise (method B).[5,10] The isolated yields of products and

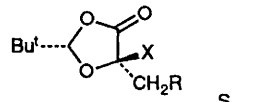
Table 1. Radical addition to captodative alkenes.

Alkene	Product	Major isomer	Method A[a] %Yield[b]	Method A[a] %D.e.[c]	Method B[a] %Yield[b]	Method B[a] %D.e.[c]
(**1**)	(**10**)	*cis*	26	>70[e]	33	>75[d]
(**2**)	(**11**)	*trans*	73	>75[d]	68	60[d]
(**3**)	(**12**)	*trans*	44	>75[e]	25	68[d]

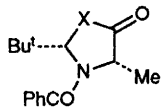
[a] Method A: cyclohexyl iodide/tributylstannane; method B: cyclohexylmercury chloride/sodium borohydride. [b] Isolated yields. [c] Diastereoisomeric excess. [d] Determined by ^1H NMR. [e] Estimated by ^{13}C NMR.



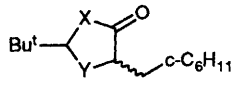
(**1**) X = Y = O
(**2**) X = O, Y = NCOPh
(**3**) X = NMe, Y = NCOPh



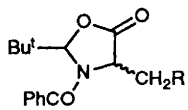
(**4**) R = CO_2H, X = H
(**5**) X = H, R = CO_2-N
(**6**) R = CO_2H, X = Br
(**7**) R = Br, X = H



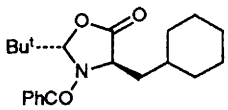
(**8**) X = O
(**9**) X = NMe



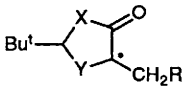
(**10**) X = Y = O
(**11**) X = O, Y = NCOPh
(**12**) X = NMe, Y = NCOPh



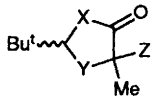
(**13**) R = Me
(**14**) R = CH_2Ph
(**15**) R = Bu^t



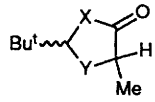
(**16**)



(**17**)



(**18**)



(**19**)

a; X = NMe, Y = NCOPh, Z = SPh
b; X = Y = O, Z = Br

† Satisfactory microanalytical and spectral (IR, ^1H, and ^{13}C NMR) data were obtained for all new compounds.

Table 2. Reactions of (**2**) with alkyl iodide/tributylstannane.

Alkyl iodide	Product	Major isomer	% Yield	D.e.
MeI	(**13**)	*trans*	60	42[b]
$PhCH_2I$	(**14**)	*trans*	71	46[a]
c-$C_6H_{11}I$	(**11**)	*trans*	73	>75[a]
Bu^tI	(**15**)	*trans*	70	>75[b]

[a] Determined by ^1H NMR. [b] Estimated by ^{13}C NMR.

the diastereoisomeric excesses are given in Table 1. The results show that both methods A and B for free radical addition are applicable to these substrates, and that the stannane method is marginally the better of the two. However, the yields were sufficiently high to be synthetically useful only in the case of the oxazolidinone (**2**); in the other cases considerable amounts of starting material were recovered.

In a further series of experiments the oxazolidinone (**2**) was treated with various alkyl iodides and tributylstannane to afford the addition products (**11**) and (**13**)—(**15**). The isolated yields and diastereoisomeric excesses are listed in Table 2. Finally, each of the methods A and B was used to convert the pure (2*S*)-enantiomer of (**2**) into the pure *trans*-(2*S*, 4*R*)-product (**16**), $[\alpha]_D^{23}$ −94.9° (*c* 0.9, $CHCl_3$) in 60—70% yield when isolated by flash chromatography.

The stereochemistry of the products given in Tables 1 and 2 was assigned on the basis of NOE and NOESY experiments, and by analogy with that similarly determined for the products from other radical reactions of similar substrates. If, as expected, the formation of the final addition products involves the transfer of hydrogen atoms from either tributylstannane or cyclohexylmercury hydride to radicals of the general type (**17**), the diastereoselectivities exhibited by these reactions should be similar to those observed when radicals (**17**) are generated from different precursors. In the event, treatment of the imidazolidinone sulphide (**18a**) with tributylstannane gave mainly the *trans*-isomer of the substitution product (**19a**), while similar treatment of the bromodioxolanone (**18b**) gave mainly the *cis*-isomer of the product (**19b**).‡ The results clearly show that the diastereoselectivity depends both on the nature of the ring heteroatoms and on the bulk of the group R in the adduct radical (**17**). The rationalisation of these trends will be presented later.

Since the addition products such as (**10**)—(**15**) can be readily hydrolysed, the radical addition reactions adumbrated above provide a potentially useful new method for the synthesis of enantiomerically pure α-amino- and α-hydroxy-acids.

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‡ Assignment of stereochemistry in these 5-membered heterocycles is difficult. The assignments given here are based on NOE and NOESY experiments, and are self-consistent. Further *X*-ray crystallographic studies are in hand.