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α-Allylation of α-amino acids *via* 1,5-hydrogen atom transfer

Muhammad I. Chowdhry, Peter N. Horton, Michael B. Hursthouse and Mark E. Wood*

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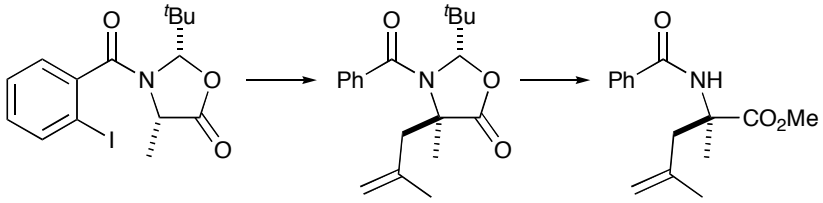
1,5-Hydrogen atom transfer in *N*-(2-iodobenzoyl)oxazolidin-5-ones facilitates the α-allylation of proteinogenic amino acids.



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α-Allylation of α-amino acids *via* 1,5-hydrogen atom transfer

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Abstract—A straightforward method for the radical-based α-allylation of proteinogenic α-amino acids is described in which the key step involves 1,5-hydrogen atom transfer from the C-4 position of an oxazolidin-5-one.

The development of general synthetic methodologies for the preparation of highly substituted, in particular, α,α-disubstituted α-amino acids still represents a formidable synthetic challenge. The majority of approaches reported to date involve the alkylation, often asymmetric, of enolate derivatives of existing proteinogenic amino acids.[1] The inherent limitations of using such methodology for the generation of quaternary centres in systems containing reactive functional groups however, often results in alanine being the most complex amino acid that can be further functionalised. We have recently shown that the use of a radical-based methodology facilitates the stereocontrolled generation of quaternary centres α-to nitrogen in β-amino alcohols, leading to a short synthetic route to protected α,α-disubstituted, α-amino acids.[2] The need to oxidise the functionalised β-amino alcohols to amino acids however, still limits the applicability of this approach and hence, related methods for the direct α-functionalisation of proteinogenic amino acids were investigated. Radical 1,5-hydrogen atom transfer represents a powerful method for carbon-centred radical generation at remote sites and prior to our studies described below, Giraud and Renaud[3] showed that pendant glycine and alanine derivatives, built into oxazolidin-4-ones containing a C-2 2-bromobenzyl protecting-radical-translocating (PRT) group,[4] could be stereoselectively α-allylated. The introduction of the amino acid functionality into this system *via* an α-bromoester, however, still restricted the scope of this process and so our attention turned to the direct allylation of a variety of α-amino acids incorporated into the ring of oxazolidin-5-ones **1** bearing an *N*-(2-iodobenzoyl) PRT group (Figure 1).

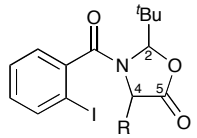

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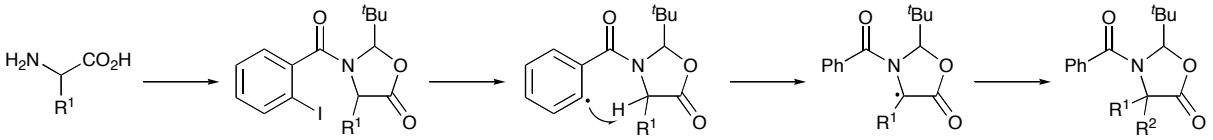
Figure 1. General structure of *N*-(2-iodobenzoyl)oxazolidin-5-ones.



2 **1** **3** **4** **5**

Scheme 1. General scheme for radical-based α-functionalisation of α-amino acids *via* 1,5-hydrogen atom transfer.

In forming these substrates **1**, it was expected that the α-stereocentre in the original amino acid **2** would exert some control over the C-2 stereochemistry. Aryl radical **3** generation from the iodide would then be followed by hydrogen atom transfer from the C-4 position of the oxazolidin-5-ones to generate the key α-aminoalkyl radical

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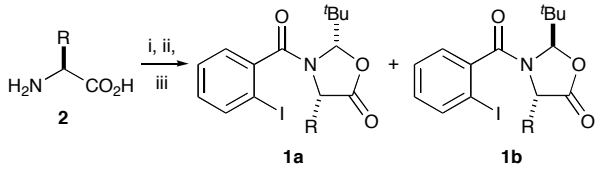
intermediate **4** which would subsequently be trapped to give the required quaternary centre in product **5** with stereoselectivity being controlled by the C-2 stereocentre, following Seebach's principle of "self-regeneration of stereocentres"[5] (Scheme 1). From previous studies,[2] it was anticipated that there would not be a problem with regioselectivity in the hydrogen atom transfer step.

The required oxazolidin-5-ones **1** were prepared by treatment of the sodium salts of the pivaldehyde-derived imines of the appropriate amino acids **2** with 2-iodobenzoyl chloride (Scheme 2), a modification of an existing literature procedure for the preparation of such compounds.[6]



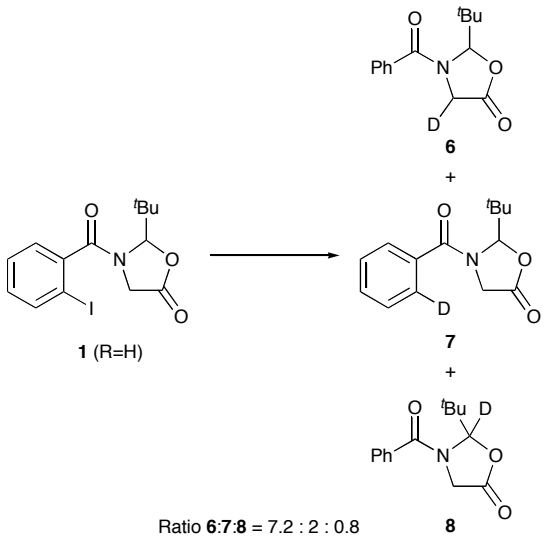
Scheme 2. Reagents and conditions: i. NaOH, H_2O, EtOH; ii. ^{t}BuCHO, pentane, reflux; iii. 2-iodobenzoyl chloride, $CHCl_3$, reflux.

Table 1. Results of the preparation of *N*-(2-iodobenzoyl)oxazolidin-5-ones

Entry	R	Ratio **1a**:**1b**	% Yield
1	H	-	48
2	Me	1.2:1	50
3	^{i}Pr	1:0	53
4	Bn	6:1	34

Table 1 summarises the results obtained using glycine, L-alanine, L-valine and L-phenylalanine (entries 1 to 4, respectively). In all cases where appropriate, it was assumed that the stereochemistry of the original amino acid (C-4 in the products **1**) remained intact and the major diastereoisomer of the product **1** was the one in which the C-2 and C-4 substituents were in a *cis*-relationship, in line with previous reports for similar systems.[5] The degree of stereocontrol for the heterocycle synthesis followed, as expected, the steric bulk of the amino acid **2** side-chain, with only a single diastereoisomer being produced with L-valine (entry 3). The diastereoisomeric products (entries 2 and 4) proved to be inseparable using conventional silica gel chromatography and they were therefore, used as a mixture in subsequent experiments.[7] (Note: No further experiments were attempted with the L-phenylalanine derived oxazolidin-5-one **1**, R=Bn.)

As for our previously reported radical experiments using 1,3-oxazolidines,[8,9] the efficiency of 1,5-hydrogen atom transfer from C-4 was examined by reduction of the glycine-derived oxazolidin-5-one (**1**, R=H) with tributyltin deuteride (Scheme 3). The expected mixture of deuterated reduction products was obtained in an overall yield of 94%, the predominant product being the required C-4 deuterated material **6**. Direct reduction accounted for only 20% of the product mixture (compound **7**) and only a very small level of hydrogen atom transfer from C-2 (compound **8**) was observed, suggesting that generation of the required C-4 α-aminoalkyl radical intermediate **4** (R=H) was the major reaction pathway.

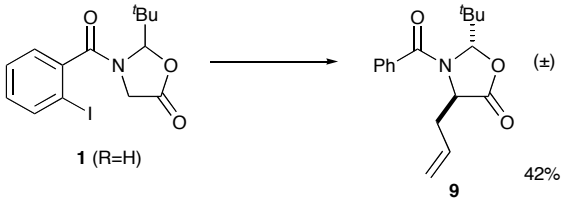


Scheme 3. Reagents and conditions: Bu_3SnD (1.5 equiv), AIBN, C_6H_6, reflux; overall yield 74%.

Attempts to trap the same glycine-derived C-4 α-aminoalkyl radical intermediate **4** (R=H) using methyl acrylate and acrylonitrile in the presence of tributyltin hydride and AIBN failed to give any of the desired C-4 alkylated oxazolidin-5-one product with the reduced starting material being the major product obtained in each case. Given the more electrophilic nature of amino acid α-radicals compared with those obtained from amino alcohols[10] and the electrophilic nature of these radicalphiles, these results were not surprising and subsequent experiments focussed on the use of electron-rich allyltin reagents as nucleophilic radicalphiles.

Photochemical radical generating conditions at room temperature (using a standard medium pressure mercury vapour lamp) were found to give the best results for the C-4 allylation of the glycine-derived oxazolidin-5-one **1** (R=H) with an equimolar quantity of allyltributyltin, at a relatively high substrate concentration of 130 mM in benzene (Scheme 4). It was found to be necessary to use an equimolar quantity of AIBN, although slow addition of allyltributyltin proved to be unnecessary, the reaction being complete in 8 h.[11] The desired, racemic allylated product **9** was obtained in a single disatereoisomeric form in 42% yield, the *trans*-relative stereochemistry between the C-2 *tert*-butyl and C-4 allyl substituents being established by X-ray crystallography (Figure 2).[12] This stereochemical outcome is consistent with those obtained in enolate alkylations using related oxazolidin-5-one substrates[5,6] and suggests that the bulky C-2 *tert*-butyl substituent confers

facial selectivity on trapping of the intermediate α-aminoalkyl radical **4** (R=H).



Scheme 4. Reagents and conditions: allyltributyltin (1 equiv), AIBN (1 equiv), C_6H_6, hν, rt, 8 h.

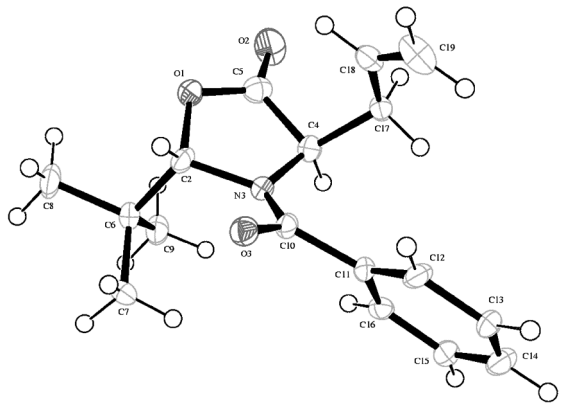
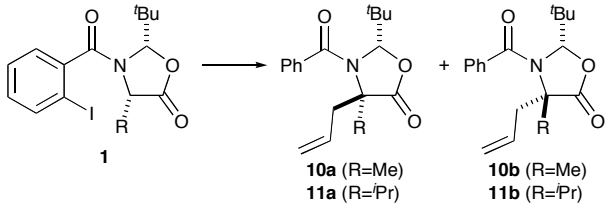


Figure 2. ORTEP representation of **9**; ellipsoids drawn at 30% probability level.

Identical radical allylations were carried out with the L-alanine **1** (R=CH_3) and L-valine **1** (R=^{i}Pr) derived oxazolidin-5-ones. The expected products **10a**/**b** and **11a** were obtained in 64% and 5% yields, respectively, a 4:1 ratio of inseparable diastereoisomers (presumed by analogy to **9** to be *trans*:*cis* with respect to the C-4 allyl and C-2 *tert*-butyl substituents, **10a**:**10b**) being obtained in the former case and only a single diastereoisomer (presumed to be *trans*, **11a**) in the latter (Scheme 5 - only the major diastereoisomer of **1**, R=CH_3 shown, Table 2). Clearly, the yield of product **11a** was disappointingly low but this result does demonstrate the fact that remarkably hindered quaternary centres can be constructed using this radical-based methodology.

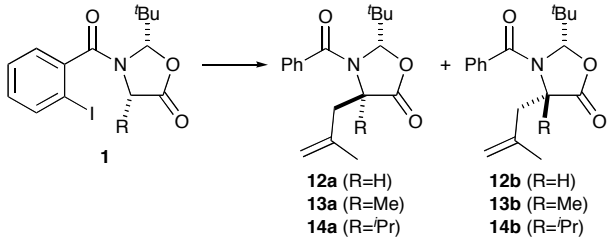


Scheme 5. Reagents and conditions: allyltributyltin (1 equiv), AIBN (1 equiv), C_6H_6, hν, rt, 8 h.

Table 2. Results of the radical allylation of C-4 alkyl *N*-(2-iodobenzoyl)oxazolidin-5-ones.

Entry	R	Product ratio	% Yield
1	Me	**10a**:**10b** 4:1	64
2	^{i}Pr	**11a**:**11b** 1:0	5

The introduction of more highly functionalised allylic substituents was also investigated using (2-methylallyl)tributyltin (Scheme 6 - only the major diastereoisomer of **1** shown where appropriate), which is known to show high reactivity towards electrophilic radicals.[13] The results, summarised in Table 3, show that comparable yields and diastereoisomer ratios were obtained in comparison with the previous results found using allyltributyltin. Again, the L-valine derived oxazolidin-5-one **1** (R=^{i}Pr) gave a disappointingly low yield of products **14a** and **14b**, and as before, the relative stereochemistry between the C-2 *tert*-butyl and C-4 2-methylallyl substituents was presumed to be *trans* in the major products. Significantly, the 2-methylallyl functionality in the radical allylation products has the potential for conversion into a range of biologically important heterocycles,[14] expanding the scope of highly substituted amino acids that can be accessed using this methodology.



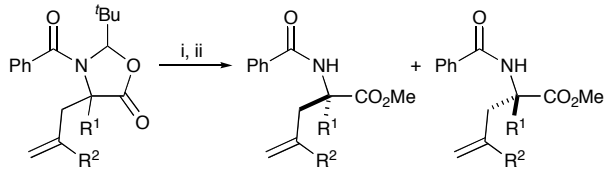
Scheme 6. Reagents and conditions: (2-methylallyl)tributyltin (1 equiv), AIBN (1 equiv), C_6H_6, hν, rt, 8 h.

Table 3. Results of the radical 2-methylallylation of *N*-(2-iodobenzoyl)oxazolidin-5-ones

Entry	R	Product ratio	% Yield
1	H	**12a**:**12b** 1:0 (±)	43
2	Me	**13a**:**13b** 1.6:1	39
3	^{i}Pr	**14a**:**14b** 1.6:1	3

In contrast to the harsh acidic conditions required to hydrolyse the *N*-benzoyl-1,3-oxazolidines prepared in previous studies,[2] the C-4 allylated oxazolidin-5-ones were readily cleaved by alkaline hydrolysis with lithium hydroxide. In order to facilitate the isolation of the *N*-benzoylated amino acid products, the free acids thus obtained were converted into their methyl esters using

(trimethylsilyl)diazomethane and excellent yields of the desired, fully protected amino acids were obtained after the two reaction steps. Scheme 7 and Table 4[15] illustrate and summarise the results.



9 (R^1=H, R^2=H) **15a** (R^1=H, R^2=H) **15b** (R^1=H, R^2=H)
12a/b (R^1=H, R^2=Me) **16a** (R^1=H, R^2=Me) **16b** (R^1=H, R^2=Me)
13a/b (R^1=Me, R^2=Me) **17a** (R^1=Me, R^2=Me) **17b** (R^1=Me, R^2=Me)

Scheme 7. Reagents and conditions: i. LiOH (3 equiv), H_2O, MeOH, 40 °C, 20 h; ii. Me_3SiCHN_2, hexane:C_6H_6:MeOH (1:3:1 v/v), rt.

Table 4. Results of the oxazolidin-5-one hydrolysis/amino acid esterification.

Entry	R^1	R^2	Product ratio	ee/%	Yield/%
1	H	H	**15a**:**15b** 1:1	0	98
2	H	Me	**16a**:**16b** 1:1	0	98
3	Me	Me	**17a**:**17b** 1.6:1	23	92

In summary, we have shown through these preliminary studies, that it is possible to α-allylate proteinogenic α-amino acids directly *via* 1,5-hydrogen atom transfer using allyltributylstannanes. This leads to the construction of highly substituted α,α-disubstituted (quaternary) amino acids in a minimal number of steps. Further work is required in order to improve and optimise the allylation step, however, the methodology should be applicable to a wide range of amino acid substrates.

Acknowledgments

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11. Typical procedure: Allyltributyltin (440 mg, 1.33 mmol) and 2,2'-azobisisobutyronitrile (220 mg, 1.34 mmol) were added to a degassed solution of *N*-(2-iodobenzoyl)-2-*tert*-butyl-1,3,-oxazolidine (500 mg, 1.34 mmol) in benzene (10 cm^3) in a quartz tube. The reaction mixture was stirred at room temperature and irradiated with a medium pressure mercury vapour lamp for 8 h. The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether, the resulting solution being vigorously stirred with a 10% w/v aqueous solution of potassium fluoride for 1 h. The separated organic phase was evaporated *in vacuo* and the residue obtained was purified by column chromatography on silica gel containing 10% w/w potassium fluoride,[16] eluting with 75% petroleum ether (bp 40-60 °C): 15% ethyl acetate. This gave **9** (160 mg, 42%) as a white, crystalline solid (found MH^+ (ES^+) 288.1596, $C_{17}H_{22}NO_3$ requires 288.1594); ν_{max}(thin film)/cm^{-1} 3040-2765 (m) (C-H), 1788 (s) (oxazolidin-5-one C=O), 1634 (s) (amide C=O), 1445 (m), 1338 (s), 1240 (m), 1189 (m), 1148 (m), 1045 (m), 1015 (m), 928 (m), 871 (w), 794 (w), 722 (m) and 651 (m); δ_H (400 MHz; $CDCl_3$) 1.03 (9H, s, $(CH_3)_3C$), 1.99 (1H, br m, $CH_aH_bCH=CH_2$), 2.47 (1H, br m, $CH_aH_bCH=CH_2$), 4.50 (1H, dd, J = 1.2 and 5.1 Hz, CNHC=O), 4.96 (1H, d, J = 17.8 Hz, CH=CH_aH_b *trans*), 5.15 (1H, d, J = 10.2 Hz, CH=CH_aH_b *cis*), 5.46 (1H, br m, CH=CH_2), 6.16 (1H, br s, NCHO), 7.50 (2H, *ca* q, J = 7.5 Hz, phenylCH), 7.57 (1H, *ca* t, J = 7.5 Hz, phenylCH) and 7.64 (2H, d, J = 7.0 Hz, phenylCH); δ_C (100 MHz; $CDCl_3$; some resonances not resolved through line broadening) 24.7 ($(CH_3)_3C$)), 39.8 ($(CH_3)_3C$), 95.0 (NCHO), 121.7 ($CH=CH_2$), 127.7, 129.0, 132.1 (phenylCH and $CH=CH_2$) and 172.6 (oxazolidin-5-one C=O); *m/z* (EI) 230 ((M-^{t}Bu)$^+$, 8%), 105 (100), 77 (54), 57 (48), 51 (13) and 41 (49); *m/z* (CI) 305 ($M+NH_4^+$, 13%), 289 (19), 288 ($M+H^+$, 100), 105 (15), 96 (8), 86 (10) and 79 (4).
12. Crystal data for **9**: $C_{17}H_{21}NO_3$, M = 287.35, monoclinic, space group $P2_1$, a = 5.9385(8) Å, b = 13.0338(19) Å, c = 10.4518 (16) Å, β = 104.583(6)°, U = 782.9(2) Å^3, D_c = 1.219 Mg m^{-3}, Z = 2, Mo-Kα radiation (λ = 0.71073 Å), μ = 0.083 mm^{-1} T = 120(2) K, 1880 observed reflections (R_{int} = 0.1014) R_1 = 0.0579 [$I>2\sigma(I)$], wR_2 = 0.1537 (all data). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number no. CCDC 716085. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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