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Free-Radical Functionalisation of β-Amino Alcohols *via* 1,5-Hydrogen Atom Abstraction in 1,3-Oxazolidines

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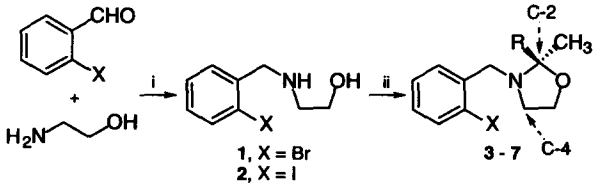
Abstract: *Functionalisation of ethanolamine at the carbon atom α- to nitrogen can be achieved in a diastereoselective C-4 alkylation of 1,3-oxazolidines using free-radical methodology.*

α-Aminoalkyl and α-amidoalkyl radicals represent important intermediates in the synthesis of α-amino acids and other amine derivatives.[1] Of the methods available for the generation of such carbon-centred radicals, 1,5-hydrogen atom transfer has the significant advantage that prior α-functionalisation of the amine derivative (*e.g.* halogenation) is not necessary. Undheim has used 2-halobenzyl protecting-radical translocating (PRT) groups to facilitate the functionalisation of aliphatic amines in addition to pyrrolidine and morpholine derivatives α-to the nitrogen atom.[2] Snieckus has also demonstrated excellent levels of 1,3-asymmetric induction in such an amine α-derivatisation as the key step in an enantioselective synthesis of β-substituted β-amino acids.[3]

Baldwin has shown that primary alkyl radicals (generated from 2-bromomethylpyrrolidine amides of *N*-Z-glycine and *N*-Z-alanine) can be used to generate α-amidoalkyl radicals from amino acids[4] and importantly, Renaud has demonstrated that a related methodology can be used in stereocontrolled intermolecular carbon-carbon bond formation at the α-position of amino acid derivatives already possessing an α-substituent.[5]

We report our preliminary studies into a new method for the remote functionalisation of β-amino alcohols *via* free-radical 1,5-hydrogen atom abstraction which has the potential to be extended into a versatile method for the asymmetric synthesis of highly substituted amines and amino acids. The experiments described herein concentrate on functionalisation at the carbon atom α- to nitrogen using 2-halobenzyl PRT groups.[6]



Scheme 1 *Reagents and conditions*: i, $NaBH_4$, EtOH (**1**, 89%; **2**, 91%); ii, $RCOCH_3$ (-H_2O) (see Table 1)

Table 1 *Results for step* ii

β-Amino Alcohol	X	R	Method	Product	Yield (%)
1	Br	Ph-	*a*	3	83
1	Br	4-NO_2Ph-	*a*	4	100
1	Br	4-pyridyl-	*a*	5	71
2	I	4-pyridyl-	*a*	6	62
2	I	EtO_2C-	*b*	7	65

a, $RCOCH_3$, TsOH (cat.), C_6H_6, Δ (-H_2O)
b, EtO_2CCOCH_3, 4Å mol. sieves, THF, RT

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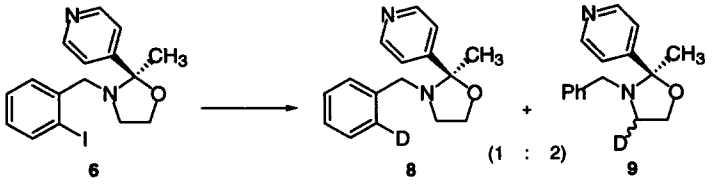
Ethanolamine was chosen as our initial β-amino alcohol from which *N*-2-halobenzyl derivatives **1** and **2** were prepared using 2-bromobenzaldehyde and 2-iodobenzaldehyde (prepared by PDC oxidation of 2-iodobenzyl alcohol) respectively in a standard reductive amination procedure. The resulting β-amino alcohols **1** and **2** were cyclised to 1,3-oxazolidines **3-7** using a range of aryl methyl ketones and ethyl pyruvate under appropriate dehydrating conditions as summarised in Scheme 1[7] and Table 1.

1,3-Oxazolidine **3** prepared using acetophenone proved to be unstable towards silica gel chromatography and was hence deemed unsuitable for further experiments. The significantly increased stability towards silica gel observed in 1,3-oxazolidine **4** confirmed the desirability of having an electron withdrawing group at C-2 although as expected, the nitro- group proved to be incompatible with tin hydride mediated radical processes. Condensations using 4-acetylpyridine and ethyl pyruvate however, were found to be efficient, the resulting heterocycles **5-7** being sufficiently stable towards silica gel chromatography and standard free-radical generating conditions.

The viability of 1,5-hydrogen atom abstraction from C-4 in this heterocyclic system was investigated in free-radical reduction reactions of 1,3-oxazolidines **5** and **6** using tributyltin deuteride / AIBN. To gain a qualitative insight into the efficiency of the required radical translocation step, the tributyltin deuteride / AIBN mixture was added in one portion at the start of the experiment rather than by slow addition. Unsurprisingly, it was found that the reduction of iodo-derivative **6** was more efficient than that of the bromo-derivative **5**. The results of reduction of oxazolidine **6** are summarised in Scheme 2.[7]



6 **8** **9**

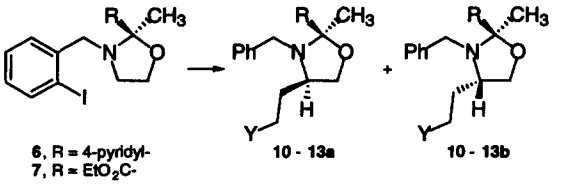
Scheme 2 *Reagents and conditions*: Bu_3SnD (1.5eq.), AIBN, C_6H_6 (concentration of **6** = 40mM), Δ (92% overall)

The mixture of reduced products **8** and **9** was obtained in good overall yield (92%), the ratio of **8** : **9** of 1 : 2 (determined by ^2H NMR) suggesting that the radical translocation step was occurring efficiently. ^2H NMR spectroscopy indicated that **9** was formed as a 1 : 1 ratio of diastereoisomers and mass spectrometry provided additional support for the position and level of deuterium incorporation into the two products. (Note: The yield obtained under identical conditions using brominated substrate **5** was 74% with identical product / diastereoisomer ratios).

Trapping of intermediate α-aminoalkyl radicals with other radicalphiles was therefore attempted using 1,3-oxazolidines **6** and **7** and a variety of radical initiation methods. The results obtained are summarised in Scheme 3[7] and Table 2. (It should be noted that in all cases, there was no evidence of initial aryl radical trapping with either radicalphile, the major by-products for the reactions in each table entry being recovered starting material, reduced starting material or a mixture of both).

Starting with C-2 4-pyridyl derivative **6** and *tert*-butyl acrylate (3 eq.), slow addition of tributyltin hydride (4 eq.) and AIBN (over 8 hours) gave the required product **10a/b** in 50% isolated yield as a 2 : 1 mixture of diastereoisomers[8] using thermal homolysis of the initiator. Photolytic AIBN cleavage allowed the reaction to be carried out at room temperature in comparable yield (using 5 eq. of *tert*-butyl acrylate) with the same diastereoisomeric mixture of products[8] but with a significant reduction in the number of minor by-products as evidenced by thin layer chromatographic analysis of the crude reaction products. Likewise, the use of triethylborane / O_2 as initiator with 2 eq. of *tert*-butyl acrylate, at room temperature[9] gave a very "clean" reaction, the optimum yield for this process being obtained without slow addition of tributyltin hydride and the initiator. The use of acrylonitrile (2 eq.) as the radicalphile gave similar results, **11a/b** being obtained in 51% yield and 2 : 1 diastereoisomer ratio[8] with triethylborane / O_2 as the initiator. Unambiguous assignment

of the relative stereochemistry of the 2 stereocentres in the racemic major and minor diastereoisomers of **10a/b** and **11a/b** proved difficult as attempts at chromatographic separation proved unsuccessful.



Scheme 3 *Reagents and conditions:* CH_2=CH-Y, Bu_3SnH, initiator, C_6H_6 (see Table 2)

Table 2 *α-Aminoalkyl radical trapping with unsaturated radicalphiles*

1,3-Oxazolidine	[6 or 7] / mM	R	Radicalphile Y (eq.)	Bu_3SnH (eq.)	Conditions	Product	Isolated Yield (%)	Diastereoisomer ratio[8]
6	60	4-pyridyl-	$-CO_2{}^tBu$ (3.0)	4.0	*a*	**10a/b**	50	2 : 1
6	50	4-pyridyl-	$-CO_2{}^tBu$ (5.0)	3.0	*b*	**10a/b**	54	2 : 1
6	50	4-pyridyl-	$-CO_2{}^tBu$ (2.0)	2.0	*c*	**10a/b**	42	2 : 1
6	50	4-pyridyl-	-CN (2.0)	2.5	*c*	**11a/b**	51	2 : 1
7	30	EtO_2C-	$-CO_2{}^tBu$ (3.0)	3.5	*c*	**12a/b**	41	3 : 1
7	30	EtO_2C-	-CN (3.0)	3.5	*c*	**13a/b**	26	3 : 1

a, AIBN, Δ (Note: Maximum possible substrate concentration after slow addition = 40mM)
b, AIBN, hν, RT
c, Et_3B, O_2, RT

Identical trapping experiments conducted with the 1,3-oxazolidine **7** again revealed triethylborane / O_2 to be the initiation method of choice with 3 eq. of both radicalphiles proving optimal. Functionalised 1,3-oxazolidines **12a/b** and **13a/b** were obtained in yields comparable with those obtained for the corresponding 4-pyridyl derivatives **10a/b** and **11a/b** but with an improved diastereoisomer ratio of 3 : 1 in each case.[8] The diastereoisomers of **13** proved to be separable by silica gel chromatography and NOESY experiments indicated the major diastereoisomer to be that in which the C-2 ethyl ester and the C-4 substituent were *cis*-**13a**. This result suggests a possible structure for the intermediate α-aminoalkyl radical **14** in which the ethyl ester substituent at C-2 preferentially adopts a pseudoequatorial position with the pseudoaxial C-2 methyl group effectively blocking approach of the radicalphile from the lower face (as drawn) of the radical **14** (Figure 1).[7] NOESY experiments conducted on the diastereoisomeric mixture **12a/b** also suggested that the major diastereoisomer was that in which the C-4 substituent was *cis*- to the C-2 ethyl ester, *i.e.* **12a**.

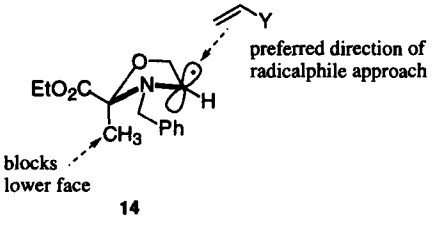
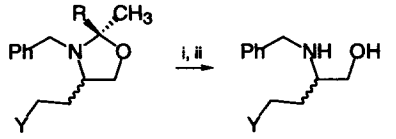


Figure 1 *Preferred approach of radicalphile to α-aminoalkyl radical* **14**

Efficient hydrolytic cleavage of the stereoisomeric mixtures of 1,3-oxazolidines **10a/b**, **11a/b** and **12a/b** to the corresponding *N*- benzyl β-amino alcohols could be effected under mild conditions, the racemic

free amines **15** and **16** being obtained on treatment of the hydrochloride salts with neutral alumina[10] (Scheme 4[7] and Table 3).



10a/b, 11a/b, 12a/b 13a, 13b **15, 16**

Scheme 4 *Reagents and conditions*: i, HCl, H_2O, THF, RT; ii, neutral alumina

Table 3 *Hydrolysis of C-4 functionalised 1,3-oxazolidines*

1,3-Oxazolidine	R	Y	Product	Yield (%)
10a/b	4-pyridyl-	$-CO_2{}^tBu$	**15**	100
11a/b	4-pyridyl-	-CN	**16**	100
12a/b	EtO_2C-	$-CO_2{}^tBu$	**15**	85

In summary, we have shown that it is possible to functionalise a β-amino alcohol at the carbon atom α- to nitrogen using a free-radical methodology involving, as the key step, 1,5-hydrogen atom transfer. The incorporation of the β-amino alcohol into a 1,3-oxazolidine structure provides the possibility of stereocontrol in such a process and we are currently examining the use of this methodology for further functionalising β-amino alcohols already possessing a substituent at the carbon atom α-to the nitrogen, with stereocontrol following Seebach's principle of "self-reproduction of chirality."[11] Such a methodology should be applicable to the stereocontrolled synthesis of highly substituted amine derivatives.

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