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Use of (*S*)-*N*-*tert*-Butoxycarbonylaziridine-2-carboxylate Derivatives for α-Amino Acid Synthesis

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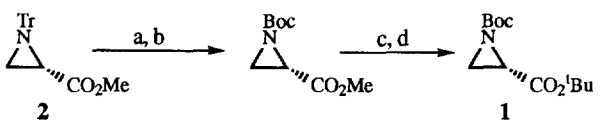
Abstract: (*S*)-*tert*-Butyl-*N*-*tert*-butoxycarbonylaziridine-2-carboxylate and (*S*)-*tert*-butyl-*N*-*tert*-butoxycarbonylaziridine-2-carboxamide were synthesised and found to react with copper 'catalysed' Grignard reagents to give protected α-amino acids in moderate to good yields.

One approach to the synthesis of β-substituted α-amino acids involves the side chain 'activation' of a readily available β-functionalised α-amino acid, followed by subsequent reaction with a nucleophile. For example various protected serine and threonine derivatives have been activated either by conversion of the β-alcohol to a leaving group[1,2] or more usefully by formation of a β-lactone[3]. The ring opening of serine derived aziridines by reaction with nucleophiles has also been reported[4]. Heteroatomic nucleophiles[5], indoles[6], Wittig reagents[7] and organometallic reagents[8] have been successfully reacted with *N*-activated aziridine-2-carboxylates. However, yields of the desired ring-opened products are often compromised by competing reaction of nucleophiles both at the aziridine C-2 and at the ester carbonyl. Until now, *N*-sulphonamide activation, with its concomitant deprotection problems, has been necessary for successful reactions between aziridine-2-carboxylate esters and organometallic reagents. An approach using *N*-diphenylphosphinoyl activation, though successful for simple aziridines, failed when applied to aziridine-2-carboxylate esters[9]. Although the problems of regioselectivity and deprotection have recently been circumvented by use of the corresponding free acids with activation by an acid-labile sulphonamide[10], the main drawback associated with the use of aziridines for amino acid synthesis is the lack of efficient synthetic routes to them. We envisaged that a short synthesis of (*S*)-*tert*-butyl-*N*-*tert*-butoxycarbonylaziridine-2-carboxylate **1** could be developed and that this compound might react selectively at the 3-position of the aziridine whilst also facilitating acidic deprotection to the desired α–amino acids after ring-opening.

We initially synthesised **1** from aziridine **2** (available in 61% over 3 steps from serine methyl ester hydrochloride[11]) as in Scheme 1. Although this route provided enough material for initial investigations, it is too lengthy and low yielding for efficient preparative work.



2 **1**

Scheme 1: a) CF_3CO_2H, MeOH, -10°C, quant. b) Boc_2O, NEt_3, cat. 4-*N*,*N*-dimethylaminopyridine, 12hrs, 73% c) LiOH, dioxane, H_2O, 96%, d) $Cl_3CC(=NH)O^tBu$, $BF_3{\cdot}Et_2O$, cyclohexane, acetone, 12hrs, 19%

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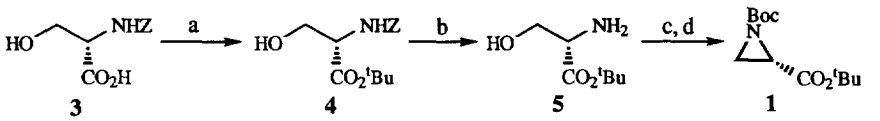
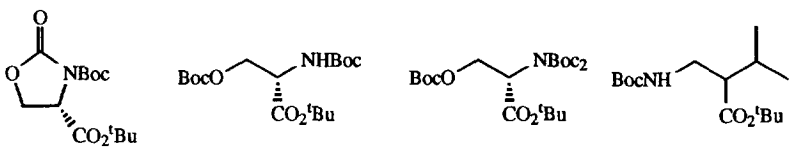
A more direct route (Scheme 2) was developed in which aziridine **1** was synthesized in 4 steps from *N*-Z-(*S*)-serine **3**. The first step required chemoselective esterification of **3**. It is known[12] that selective esterification of acids in the presence of phenols may be effected by *N,N*-dimethylformamide dineopentyl acetal[13] and that *N,N*-dimethylformamide di-*tert*-butyl acetal[14] may be used to make *tert*-butyl esters. We found that slow addition of *N,N*-dimethylformamide dineopentyl acetal to a solution of **3** in benzene: *tert*-butanol 2:1, gave **4** in good yield. This reaction compares favourably in terms of convenience, especially for large-scale preparations, with the *tert*-butyl esterification of *N*-Boc-serine using ^{t}BuBr/BnEt$_3$NCl/K$_2$CO$_3$[15], although it is slightly lower yielding. The utility of this procedure for the preparation of other *tert*-butyl esters was also explored. Thus, *N*-acetyl-(*R*)-cysteine, *N*-Z-(*S*)-threonine and *N*-Boc-(*S*)-proline were converted to their respective *tert*-butyl esters in 90, 76 and 88% (unoptimized) yields respectively. Similarly the *tert*-butyl esters of 3,4-dimethoxycinnamic acid and 3,4-dimethoxybenzoic acid were prepared in high yields (86 and 93%, respectively).

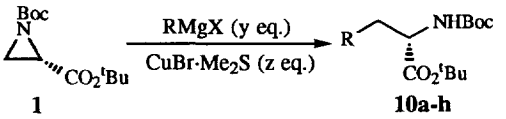


Scheme 2: a) *N,N*-Dimethylformamide dineopentyl acetal, *tert*-butanol, benzene, 3hrs reflux, 83%. b) 1 atm. H_2, 10% Pd/C, 4hrs 20°C, quant. c) DTPP, toluene, 20-40°C, 24hrs. d) Boc_2O, DMAP, MeCN, 25-69% over 2 steps.

Hydrogenolysis of the Z group from **4** smoothly afforded serine *tert*-butyl ester **5**. Ring closure to the aziridine **1** was effected using diethoxytriphenylphosphorane (DTPP)[16], a method previously applied to the formation of an aziridine from serine benzyl ester[17]. *In situ* protection as the *N*-Boc derivative followed by chromatography gave **1**, which could be readily distilled and was stable at room temperature. A drawback to the use of this synthesis is that the yield of the ring closure reaction was dependent upon the batch of DTPP used[18]. Although different batches of DTPP appeared identical by ^{1}H, ^{13}C and ^{31}P NMR spectroscopic analyses, the yield of the ring-closure reaction varied between 25 and 69% dependent on the batch employed. When the yield of **1** was low, the other isolated products were oxazolidinone **6** and derivatized serines **7** and **8**.



Investigations into ring-opening with copper catalysed Grignard reagents (Scheme 3, Table 1) demonstrated that *N*-Boc 'activated' aziridine **3** reacted with better regioselectivity with copper catalysed Grignard reagents than with the corresponding *N*-sulphonamide activated aziridines[8]. In each case the major, usually exclusive product, was the desired product resulting from ring opening of the aziridine at C-3. However, if the temperature of the reaction mixture was allowed to increase from that shown in Table 1, C-2 attack became detectable, *e.g.* in the case of the isopropyl Grignard (entry 2) at -20 °C, it was possible to isolate the product **9** (18%) arising from C-2 attack, whilst the isolated yield of the product of C-3 attack, **10b**, decreased to 52%. Deprotection of the products was effected using trifluoroacetic acid. Subsequent ion exchange chromatography (Amberlite IR-45) afforded the amino acids. The optical rotations of these amino acids closely correlated with literature values implying that no significant racemization occurred either in the synthesis of **1** or in its ring-opening reactions[19].



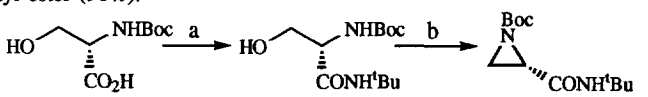
1 **10a-h**

Scheme 3

Entry	R	X	y	z	Temp. /°C	reaction time /hrs	Solvent	Yield of **10a-h**
1	Ph	Br	2.3	0.28	-20	1	PhMe	83%
2	^{i}Pr	Cl	2.0	0.27	-40	4	PhMe	71%
3	^{i}Bu	Cl	1.4	0.21	-20	2	PhMe	75%
4	^{n}Hex	Br	3.0	0.29	-30	2	THF	85%
5	^{n}Bu	Cl	2.0	0.19	-40	16	PhMe	79%
6	vinyl	Br	2.1	0.16	-40	4	THF	50%*
7	^{n}Pr	Cl	2.9	0.22	-50	4	PhMe	50%†
8	Me	Br	3.2	0.15	-30	18	THF	71%

Table 1: Reactions of aziridine **1** with copper catalysed Grignard reagents.
*11% Starting material also isolated. †23% Starting material also isolated.

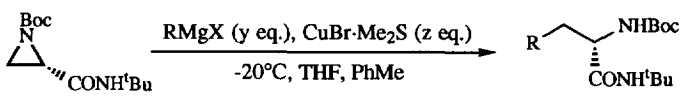
It was found that the *tert*-butyl amide **11** could be synthesized by a more concise and high yielding route than that used for the corresponding *tert*-butyl ester **1** (Scheme 4) and thus its reactivity was also investigated. The success of the ring-closure of *N*-Boc serine *tert*-butyl amide to aziridine **11** contrasted with the attempted Mitsunobu ring-closure of *N*-Boc serine *tert*-butyl ester to **1** which resulted in the isolation of *N*-Boc dehydroalanine *tert*-butyl ester (96%).



11

Scheme 4: a) ^{t}BuNH$_2$, 1-hydroxybenzotriazole, dicyclohexylcarbodiimide, THF, 0°C, 73%, b) PPh$_3$, diethylazodicarboxylate, THF, 0°C, 74%

Aziridine **11** was also successfully reacted with copper catalysed Grignard reagents to produce protected α-amino acids, although the reactions were less efficient than in the case of aziridine **1** (Scheme 5, Table 2). Deprotection of the products (CF_3CO_2H then 6N HCl), followed by ion exchange chromatography as before, gave the desired free amino acids, with optical rotation values closely correlating with reported values.



11 **12a-d**

Scheme 5

Entry	R	X	y	z	time /hrs	Yield of **12a-d**
1	Ph	Cl	3.5	0.14	16	82%
2	^{i}Pr	Cl	10.1	0.10	18	53%
3	^{n}Bu	Cl	4.3	0.19	18	29%
4	Me	Br	4.1	0.16	16	33%

Table 2: Reactions of aziridine **11** with copper catalysed Grignard reagents

In summary, concise syntheses of the chiral aziridines **1** and **11** have been developed, and it has been demonstrated that both can be ring-opened by copper catalysed Grignard reagents to form protected amino acids without significant loss of optical purity.

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5. For example, see: (a) Nakajima, K.; Oda, H.; Okawa, K. *Bull. Chem. Soc. Jpn.*, **1983**, *56*, 1565. (b) Parry, R.J.; Naidu, M.V. *Tetrahedron Lett.*, **1983**, *24*, 1133.
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17. Kuyl-Yeheskiely, E.; Lodder, M.; van der Marel, G.A.; van Boom, J.H. *Tetrahedron Lett.*, **1992**, *30*, 3013 This report suggested that an aziridine could not be formed from (*S*)-threonine benzyl ester using DTPP. However, we successfully used DTTP to ring close and subsequently *N*-Boc derivatize the resultant aziridine derived from threonine *tert*-butyl ester in an unoptimized 34% yield.
18. DTPP was synthesized according to the procedure of Chang *et al*[16a], rather than by the potentially hazardous reaction between diethyl peroxide and triphenylphosphine as used by Robinson *et al*[16b].
19. For entries 3 and 5, Table 1, derivatization of the product amino acids with α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher's reagent[20]) gave e.e. values of >90% and >95%, respectively.
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