The Ring Opening of Aziridine-2-carboxylate Esters with Organometallic Reagents

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The ring opening of aziridines with organocuprate reagents provides a new entry to amino acids.

The synthesis of non-proteinogenic amino acids continues to attract the attention of organic and medicinal chemists. One approach involves the elaboration of an existing amino acid to a more complex structure, for example the conversion of suitably functionalised serines to β-substituted alanines has been exploited.[1] Recently, we reported[2] the ring opening of *N*-acyl, *N*-trityl, and *N*-tosyl aziridine-(2*S*)-carboxylate methyl esters (**1**) with Wittig reagents to provide the stable phosphorus ylide (**2**), useful for the synthesis of unsaturated amino acids (Scheme 1). In this communication, we report the

Table 1. Examples of the reaction of (**3**) with organocuprates.[a]

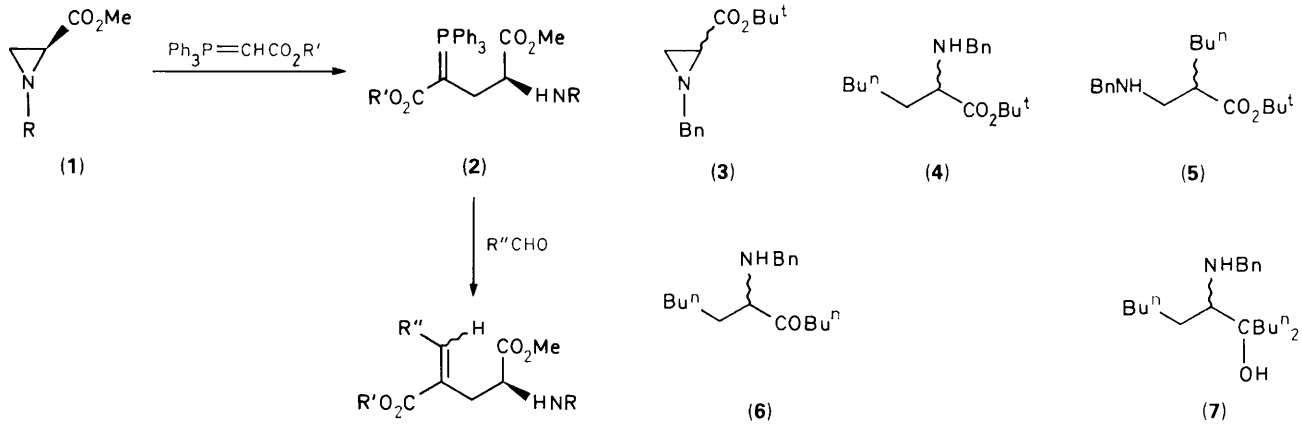
Entry	Reagent (equiv.)	*T*/°C	*t*/h	Product/% isolated yield (**3**)	(**4**)	(**5**)	(**6**)	(**7**)
1	$Bu^n_2Cu(CN)Li_2$ (1.1)	−78 to 20	6	>95	—	—	—	—
2	$Bu^n_2Cu(CN)Li_2{\cdot}BF_3{\cdot}Et_2O$ (3)	−78	0.3	20	30	8	—	—
3	$Bu^n_2Cu(CN)Li_2{\cdot}BF_3{\cdot}Et_2O$ (2)	−78	20	70	10	5	—	—
4	$Bu^n_2Cu(CN)Li_2{\cdot}BF_3{\cdot}Et_2O$ (3)	i, −78; ii, 20	20 22	20	25	25	—	—
5	$Bu^n_2Cu(CN)Li_2{\cdot}BF_3{\cdot}Et_2O$ (3)	i, −78 to 20; ii, reflux	1 2	—	—	—	50	20
6	Bu^nMgCl (5), $BF_3{\cdot}Et_2O$, (1.1) $CuBrSMe_2$ (0.2)	−25	2	<5	<5	<5	—	12

[a] Solvent = tetrahydrofuran (THF): hexane (1 : 1).

Table 2. Reaction of (**8**) with organocuprates.[a]

Entry	Reagent (equiv.)	*T*/°C	*t*/h	Product/% isolated yield (**8**)	(**9**)	(**10**)	(**11**)
1	Bu^nMgCl (3) (THF : HMPA[b] 6 : 1)	−12	1.0	—	47 (**9a**)	28 (**10a**)	21
2	Pr^iMgCl (5) (THF : HMPA 4 : 1)	−16	1.2	—	40 (**9b**)	—	25
3	EtMgCl (5) (THF : HMPA 4 : 1)	−20	1.0	—	32 (**9c**)	20 (**10c**)	21
4	Pr^nMgCl (5) (THF : HMPA 4 : 1)	−16	1.25	—	42 (**9d**)	21 (**10d**)	21
5	MeMgCl (5) (THF : SMe_2 20 : 1)	−25	2.0	—	10 (**9e**)	40 (**10e**)[c]	—
6	MeMgCl (2) (THF : SMe_2 10 : 1)	−20	2.0	—	30 (**9e**)	55 (**10e**)	—

[a] All reactions contained $CuBr{\cdot}SMe_2$ (0.2 equiv.), except entry 6, $CuBr{\cdot}SMe_2$ (0.8 equiv.), and were quenched with sat. aqueous NH_4Cl (0 °C). [b] HMPA = hexamethylphosphoramide. [c] The alcohol (**12**) (35%) and ketone (**13**) (10%) were also isolated.



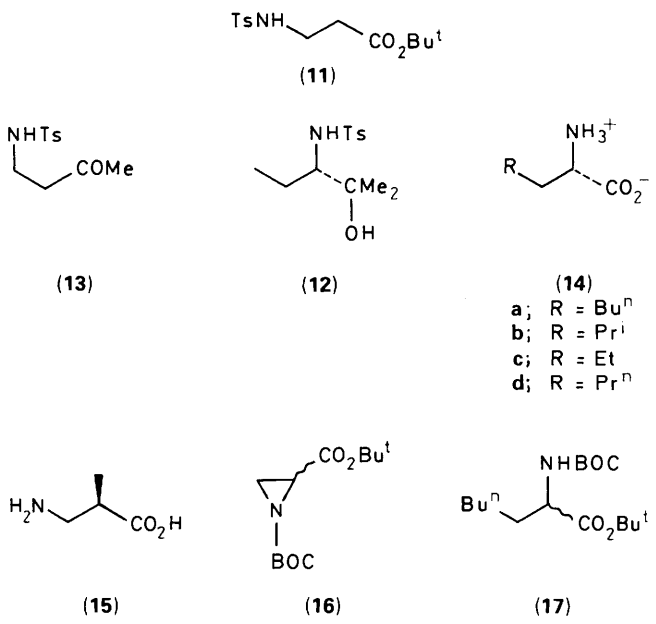
Scheme 1

further exploitation of aziridine carboxylate esters in amino acid synthesis.

Ganem[3] has described the ring opening of *N*-benzyl aziridine by organocuprates in high yield, thus we similarly attempted the reaction of (±)-*N*-benzyl aziridine carboxylate t-butyl ester (**3**)† with the 'higher order' di-n-butylcuprate[4,5] in the presence of $BF_3{\cdot}Et_2O$. The results, however, were unpromising: a mixture of products being observed (Table 1), resulting from reaction at the t-butyl ester as well as attack at C-2 and C-3 of (**3**).

† Synthesised from (±)-2,3-dibromopropanoic acid: i, $Cl_3CC(NH)O$-Bu^t (2 equiv.), $BF_3{\cdot}Et_2O$ (cat.)/CH_2Cl_2, cyclohexane/0 °C; ii, $PhCH_2NH_2$ (1 equiv.), Et_3N(2 equiv.), C_6H_6, reflux.

Bn = $PhCH_2$
Ts = $SO_2C_6H_4Me$-*p*



BOC = t-butoxycarbonyl

We reasoned that an electron withdrawing group bonded to the N should activate the aziridine to cleavage, hence we synthesised the (2*S*)-*N*-tosyl aziridine (**8**).‡ In the absence of $BF_3{\cdot}Et_2O$ we were able to eliminate products resulting from attack at the t-butyl ester (Table 2), and obtain ring opening to give (**10**) and (**9**) in much improved yields. Moreoever, we observed a new by-product, the reduced material (**11**), probably derived *via* a hydride transfer reaction.[6,7] For the butyl, ethyl, and isopropyl reagents the desired C-3–N cleavage was favoured over C-2–N cleavage (entries 1—4, Table 2), the reverse being true for the methyl cuprate reaction (entries 5 and 6).

The potential utility of the method was exemplified by the facile conversion of (**9a—d**) to the parent amino acids [i, 33% $HBr/MeCO_2H$)/phenol/25 °C/24 h;[8] ii, ion exchange chromatography] to give (**14a—d**) of high optical purity [>95% enantiomeric excess (e.e.)].§ The protected β-amino acid (**10e**), resulting from C-2–N cleavage by the methylcuprate (entries 5 and 6, Table 2), was deprotected in a similar fashion to give the naturally occurring β-amino acid, (2*R*)-3-amino-2-methylpropanoic acid (**15**),[9] {$[\alpha]_D^{20}$ −20° (*c* 0.45) *cf.* lit.[9] −21° (*c* 0.43)}. Very recently we have synthesised¶ and examined the ring cleavage of the racemic *N*-t-butoxycarbonyl aziridine t-butyl ester (**16**). Treatment with Bu^nMgCl (1.0 equiv.), $CuBr{\cdot}SMe_2$ (0.2 equiv.), toluene, −30 °C, gave the desired C-3–N cleavage product (**17**) (> 85% yield). The synthesis of chiral (**16**) and its reactivity are being currently explored.

In summary we have further demonstrated the synthetic potential of aziridine 2-carboxylates for the synthesis of amino acids of high optical purity. The optimisation of these ring openings is in progress.

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‡ Synthesised from methyl aziridine-(2*S*)-carboxylate[2] (**1**, R=H); i, *p*-$MeC_6H_4SO_2Cl/K_2CO_3/CH_2Cl_2$; ii, LiOH/dioxan, water/0 °C; iii, $Cl_3CC(NH)OBu^t$ (2 equiv.), $BF_3{\cdot}Et_2O$ (cat.)/CH_2Cl_2, cyclohexane/0 °C.

§ For (**14a**) $[\alpha]_D^{20}$ + 22.6° [*c* 0.45, HCl (6 M)], lit.[9] $[\alpha]_D^{27}$ + 23.9 [*c* 0.04, HCl (6 M)]; for (**14c**) $[\alpha]_D^{20}$ + 23.8° (*c* 0.75, 20% HCl), lit.[9] $[\alpha]_D^{20}$ + 23.6° (*c* 10, 20% HCl); for (**14b**) $[\alpha]_D^{20}$ + 21.0° (*c* 0.32, 20% HCl); for (**14d**) $[\alpha]_D^{20}$ + 22.8 [*c* 0.46, HCl (6 M)], lit.[9] $[\alpha]_D^{20}$ + 23.2° (HCl).

¶ Synthesised from t-butyl acrylate: i, Br_2, CCl_4; ii, NH_3; iii, t-butyl pyrocarbonate, *N,N*-dimethylaminopyridine, MeCN.