

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

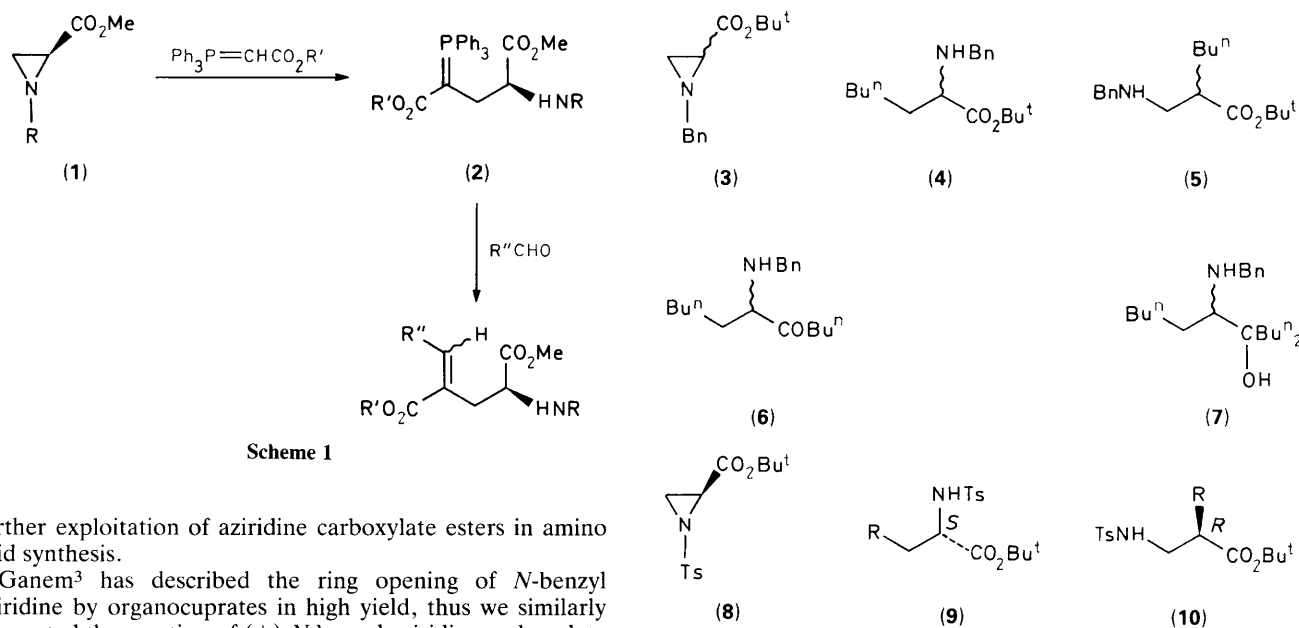
been exploited.¹ Recently, we reported² the ring opening of *N*-acyl, *N*-trityl, and *N*-tosyl aziridine-(2*S*)-carboxylate methyl esters (**1**) with Wittig reagents to provide the stable phosphorus ylide (**2**), useful for the synthesis of unsaturated amino acids (Scheme 1). In this communication, we report the

Table 1. Examples of the reaction of (3) with organocuprates.^a

Entry	Reagent (equiv.)	<i>T</i> /°C	<i>t</i> /h	Product/% isolated yield				
				(3)	(4)	(5)	(6)	(7)
1	Bu ₂ Cu(CN)Li ₂ (1.1)	-78 to 20	6	>95	—	—	—	—
2	Bu ₂ Cu(CN)Li ₂ ·BF ₃ ·Et ₂ O (3)	-78	0.3	20	30	8	—	—
3	Bu ₂ Cu(CN)Li ₂ ·BF ₃ ·Et ₂ O (2)	-78	20	70	10	5	—	—
4	Bu ₂ Cu(CN)Li ₂ ·BF ₃ ·Et ₂ O (3)	i, -78; ii, 20	20	20	25	25	—	—
5	Bu ₂ Cu(CN)Li ₂ ·BF ₃ ·Et ₂ O (3)	i, -78 to 20; ii, reflux	1	—	—	—	50	20
6	Bu ⁿ MgCl (5), BF ₃ ·Et ₂ O, (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.)	<i>T</i> /°C	<i>t</i> /h	Product/% isolated yield			
				(8)	(9)	(10)	(11)
1	Bu ⁿ MgCl (3) (THF: HMPA ^b 6:1)	-12	1.0	—	47 (9a)	28 (10a)	21
2	Pr ⁱ MgCl (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 ⁿ MgCl (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)	—

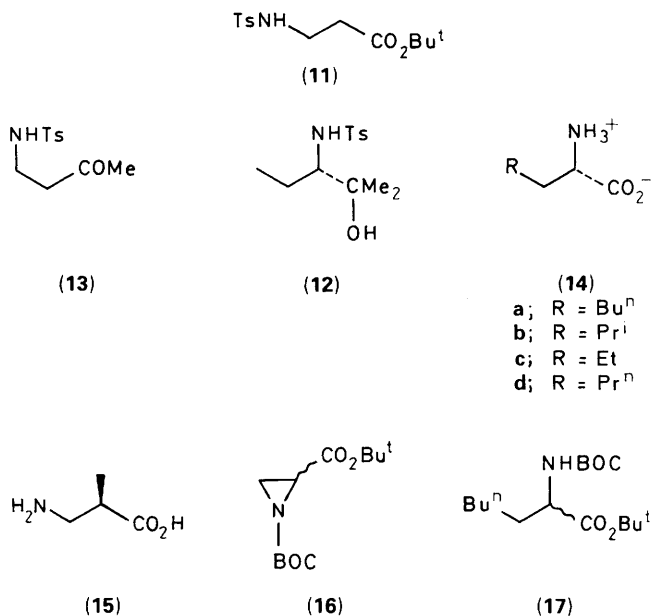
^a All reactions contained CuBr·SMe₂ (0.2 equiv.), except entry 6, CuBr·SMe₂ (0.8 equiv.), and were quenched with sat. aqueous NH₄Cl (0 °C). ^b HMPA = hexamethylphosphoramide. ^c The alcohol (12) (35%) and ketone (13) (10%) were also isolated.

further exploitation of aziridine carboxylate esters in amino acid synthesis.

Ganem³ 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 BF₃·Et₂O. 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, Cl₃CC(NH)O-Bu^t (2 equiv.), BF₃·Et₂O (cat.)/CH₂Cl₂, cyclohexane/0 °C; ii, PhCH₂NH₂ (1 equiv.), Et₃N (2 equiv.), C₆H₆, reflux.

Bn = PhCH₂
Ts = SO₂C₆H₄Me-*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 $\text{BF}_3\cdot\text{Et}_2\text{O}$ 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. Moreover, 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% $\text{HBr/MeCO}_2\text{H}$ /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 $\{[\alpha]_D^{20} - 20^\circ$ (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.), $\text{CuBr}\cdot\text{SMe}_2$ (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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[§] For (**14a**) $[\alpha]_D^{20} + 22.6^\circ$ [c 0.45, HCl (6 M)], lit.⁹ $[\alpha]_D^{27} + 23.9^\circ$ [c 0.04, HCl (6 M)]; for (**14c**) $[\alpha]_D^{20} + 23.8^\circ$ (c 0.75, 20% HCl), lit.⁹ $[\alpha]_D^{20} + 23.6^\circ$ (c 10, 20% HCl); for (**14b**) $[\alpha]_D^{20} + 21.0^\circ$ (c 0.32, 20% HCl); for (**14d**) $[\alpha]_D^{20} + 22.8^\circ$ [c 0.46, HCl (6 M)], lit.⁹ $[\alpha]_D^{20} + 23.2^\circ$ (HCl).

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

[‡] Synthesised from methyl aziridine-(2*S*)-carboxylate² (**1**, R=H); i, $p\text{-MeC}_6\text{H}_4\text{SO}_2\text{Cl/K}_2\text{CO}_3/\text{CH}_2\text{Cl}_2$; ii, LiOH/dioxan , water/0 °C; iii, $\text{Cl}_3\text{CC(NH)OBu}^t$ (2 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (cat.)/ CH_2Cl_2 , cyclohexane/0 °C.