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Synthesis of α-Amino Acids by Ring Opening of Aziridine-2-carboxylates with Carbon Nucleophiles

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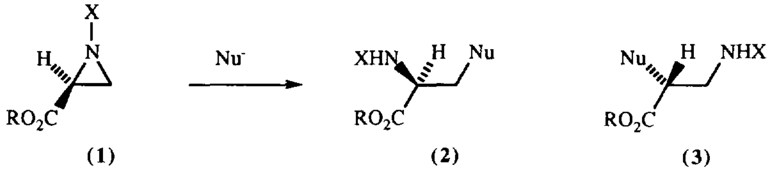
Abstract : Excellent regiospecificity has been achieved in the reaction of carbon nucleophiles with N-*para*-toluenesulfonylaziridine-2-carboxylic acid (**6, R = H**) protected as the anion. This has been developed into a general and high yielding synthesis of optically pure α-amino acids containing one chiral centre. When the aziridine (**20**) containing a second chiral centre was used, only lithium trimethylsilylacetylide gave the desired α-amino acid. Reaction with higher order cuprates gave lower yields, the principal products being the protected β-amino acids (**22**) and (**23**).

Synthesis of α-amino acids has become an increasingly important field of research in recent years and this has led to the development of a large variety of new synthetic methods.[1] A useful general synthetic entry to chiral amino acids would be to react a suitably substituted optically pure aziridine-2-carboxylate (**1**) with a variety of nucleophiles as in Scheme 1. Reaction at the β-carbon atom would give the desired protected α-amino acids (**2**), whereas reaction at the α-carbon atom would yield the β-amino acids (**3**). Regiospecific ring opening at the β-carbon atom of such aziridine esters to yield the more useful products (**2**) has been successfully achieved using heteronucleophiles such as sulfur nucleophiles,[2-7] oxygen nucleophiles,[7-16] nitrogen nucleophiles,[17-20] and halides.[7,21,22] The method would be truly general if it could be successfully extended to carbon nucleophiles.

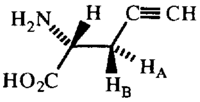


Scheme 1

There has been considerable effort spent in studying the ring opening of aziridines with carbon nucleophiles but, apart from some work using indoles as nucleophiles,[23,24] only the elegant studies of Baldwin *et al.* have addressed this question using aziridine-2-carboxylates relevant to the synthesis of optically pure amino acids.[25-27] They found that carbonyl stabilised Wittig reagents would react with suitably N-activated aziridines *via* C-3—N-1 cleavage to provide optically pure ylides, suitable for modification to the 4-alkylidene-(2S)-glutamic acid family of natural products.[25] When organometallic reagents such as organolithium or Grignard reagents were used as nucleophiles then the ester group of N-*para*-toluenesulfonylaziridine-2-carboxylate esters was attacked.[27] With higher order organocuprates or Grignard reagents in the presence of $CuBr.Me_2S$, nucleophilic attack was at the aziridine carbon rather than the carbonyl group but it occurred at *both* C-2 *and* C-3.[26,27]

Because of our interest in the mechanism of action of enzyme inhibitors, we wished to synthesise samples of D-propargylglycine (**4**) stereospecifically labelled at C-3 with deuterium. We had already prepared the labelled aziridines (**5, H_A or H_B = ^2H**)[7] and so an attractive synthetic route to our target was to ring open these using a protected acetylene anion. This should occur with inversion of stereochemistry at the labelled atom

C-3. Using the N-*para*-toluenesulfonylaziridine esters (**6, R = Me**) and (**6, R = ^{t}Bu**), we found,[28] like Baldwin,[27] that the ester group reacted in preference to the aziridine functionality. Arguing that the carboxylate anion would prevent attack at the carbonyl, and encourage regiospecific attack at C-3 of the aziridine, we reacted the aziridine free acid (**6, R = H**)[28] with an excess of lithium trimethylsilylacetylide and obtained a mixture of the free acetylene (**7, R = H**) (30%) and the trimethylsilyl derivative (**7, R = SiMe$_3$**) (49%).[28] Although we found it necessary to change the activating group on the aziridine nitrogen to Ramage's 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) protecting group[28] before we could deprotect the product successfully, it was evident that we had achieved our objective of regiospecific ring opening at C-3. This suggested that we might have overcome the problem of regiospecificity in the synthesis of optically pure α-amino acids by ring opening of N-activated aziridine-2-carboxylates with carbon nucleophiles by the simple expedient of using the carboxylate anion. We therefore resolved to examine the generality of the method.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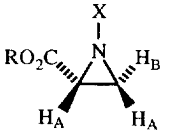
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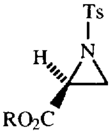
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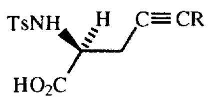
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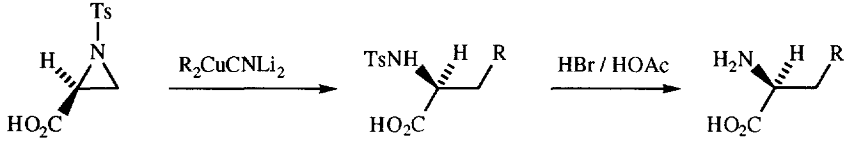
On reacting the aziridine-2-carboxylic acid (**6, R = H**) with 2.5 mole equivalents of higher order cuprates, we found that Me$_2$CuCNLi$_2$, ^{n}Bu$_2$CuCNLi$_2$ and ^{t}Bu$_2$CuCNLi$_2$ gave the products (**8**)†, (**9**)† and (**10**)† in 68%, 56% and 60% yields respectively. Only the crude product from the reaction yielding the protected 2-aminobutyrate (**8**) appeared to contain a very small amount of the regioisomer. This contrasted with the previous work[27] where reaction of the aziridine ester (**6, R = ^{t}Bu**) (a) with Me$_2$CuCNLi$_2$, gave the corresponding ester of (**8**) in 20% yield together with a 20% yield of the regioisomer obtained from attack at C-2 of the aziridine and (b) with ^{n}Bu$_2$CuCNLi$_2$ gave the corresponding ester of (**9**) in *ca.* 30% yield together with a smaller amount of the product of α-attack. Use of the free acid had thus overcome the regiospecificity problem and had put the method on a sound synthetic footing.



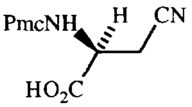
(**6, R = H**)

R = Me, (**8**), 68%
R = ^{n}Bu, (**9**), 56%
R = ^{t}Bu, (**10**), 60%
R = Ph, (**11**), 57%
R = CH=CH$_2$, (**12**), 54%

R = Me, (**16**) 50 %
R = ^{n}Bu, (**17**) 50 %
R = Ph, (**18**) 42 %

Scheme 2

Reaction of the acid (**6, R = H**) with Ph$_2$CuCNLi$_2$, (H$_2$C=CH)$_2$CuCNLi$_2$, and (Me$_3$SiC≡C)$_2$CuCNLi$_2$ gave the single products (**11**)†, (**12**)† and (**7, R = H**) in 57%, 54% and 18% yields respectively. Apart from the product (**7, R = H**) which had lost the trimethylsilyl protecting group and which we had already obtained in good yield from reaction of the lithium acetylide, these reactions showed that the method was a useful, general and high yielding route to α-amino acids. When KCN was used as nucleophile with the Pmc protected aziridine, the protected β-cyanoalanine (**13**)† was obtained in 56% yield. On using the stereospecifically labelled aziridines, (**5, X = Pmc, R = H, H$_A$ = ^{2}H**) and (**5, X = Pmc, R = H, H$_B$ = ^{2}H**) in this reaction however, the deuterium label was washed out due to the enhanced acidity of the β-hydrogens in the product. The method was, therefore, not appropriate for preparation of stereospecifically labelled samples of the enzyme inhibitor β-cyanoalanine. When the aziridine (**6, R = H**) was reacted with indolyl lithium then the ^{1}H-NMR spectrum of the product indicated *ca.* 20% of the protected tryptophan (**14**) had been formed but purification for full characterisation proved difficult. Further, although malonate anion and cyanoacetate anion had been used successfully as carbon nucleophiles with simpler activated aziridines,[29,30] the cyclic products (**15, X = CO$_2$R**) and **(15, X = CN)** proved difficult to isolate in characterisable form when the aziridine **(6, R = H)** was reacted with these nucleophiles.



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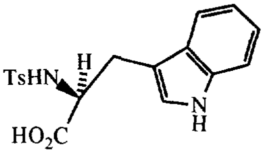

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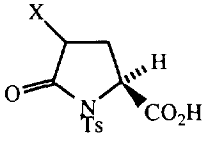
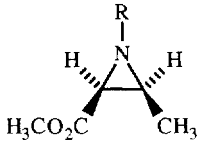


(15)

The protected amino acids **(8)**, **(9)** and **(11)** were deprotected by treatment with 30% HBr in acetic acid to yield the free amino acids L-2-aminobutyric acid, **(16)**, $[\alpha]_D$ +21.7° (c 0.38, 6N HCl) (lit.[31(i)] $[\alpha]_D$ +20.7°); L-norleucine, **(17)**, $[\alpha]_D$ +27.3° (c 0.34, 6N HCl) (lit. [31(ii)] $[\alpha]_D$ +23.2°); and L-phenylalanine, **(18)**, $[\alpha]_D$ -30.1° (c 0.4, H_2O) (lit.[31(iii)] $[\alpha]_D$ -34.5°). These were spectroscopically identical with authentic samples and so the reactions had proceeded both regiospecifically and stereospecifically.

Having developed a successful general synthesis of optically pure α-amino acids, it was of interest to see if the method could be extended to the preparation of amino acids with two chiral centres. We therefore prepared the tritylaziridine **(19, R = Ph_3C)**† from L-threonine by adaptation of the method of Wakamiya *et al.*[3] and, on deprotection using trifluoroacetic acid in $CHCl_3$: MeOH at 0 °C for 5 hours and reaction of the unstable product **(19, R = H)** with toluene-*para*-sulfonyl chloride under Schotten Baumann conditions for 20 hours at room temperature, obtained the tosyl ester **(19, R = Ts)**† in 67% overall yield. This was converted into the free acid **(20)**† in quantitative yield by hydrolysis with 1N aqueus sodium hydroxide in THF at room temperature for 3 hours.



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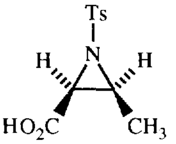

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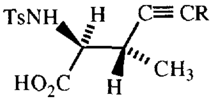

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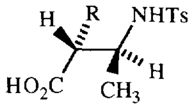

(22), R = CH_3
(23), R = ^{n}Bu

When the tosyl acid **(20)** was reacted with lithium trimethylsilylacetylide, a 70% yield of a mixture of the protected and unprotected products **(21, R = $SiMe_3$)** and **(21, R = H)** was obtained. Regiospecific attack at C-3 was evident from the fact that the quartet at δ 3.86 ppm for H-2 in the ^1H NMR spectrum was reduced to a doublet on exchange of the NH proton in ^2H_2O. The synthesis was therefore valid for preparation of α-amino acids with two chiral centres when this nucleophile was used.

Reaction with higher order cuprates with the aziridine **(20)**, was less satisfactory than had been the case with the reaction using the aziridine **(6, R = H)**. Thus reaction with $Me_2CuCNLi_2$, gave but a 30% yield of a product which consisted of a mixture of the two regioisomers in a ratio of 3.5 : 1. The major isomer was the protected β-aminoacid **(22)** as shown by a double irradiation experiment in the ^1H NMR spectrum. Irradiation of one methyl doublet at δ 0.89 ppm caused decoupling of the multiplet at δ 3.4 ppm due to C*H*N, whereas irradiation of the other methyl doublet at δ 1.09 ppm caused decoupling of the multiplet at δ 2.3 ppm due to C*H*CO_2H. Reaction with $^nBu_2CuCNLi_2$ also gave a 34% yield of a mixture of the regioisomers in a ratio of 3 : 1 with the β-amino acid as the major isomer as shown by decoupling experiments in which the two one-proton multiplets for H-2 and H-3 each coupled separately to the resonances due to the CH_3 group and a CH_2 group.

Use of the aziridine carboxylic acid **(6, R = H)** has allowed regiospecific attack of carbon nucleophiles at C-3 of the aziridine resulting in a high yielding and general synthesis of optically pure α-amino acids. The synthesis could only be extrapolated to the aziridine **(20)** containing two chiral centres when the sterically undemanding nucleophile lithium trimethylsilylacetylide was used. With higher order cuprates, yields were low and the principal products were the β-amino acids.

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References

1. Williams, R. M., *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989.
2. Bernstein, Z.; Ben-Ishai, D., *Tetrahedron*, 1977, **33**, 881 - 883.
3. Wakamiya, T.; Shimbo, K.; Shiba, T.; Nakajima, K.; Neya, M.; Okawa, K., *Bull. Chem. Soc. Japan*, 1982, **55**, 3878 - 3881.
4. Nakajima, K.; Oda, H.; Okawa, K., *Bull. Chem. Soc. Japan*, 1983, **56**, 520 - 522.
5. Parry, R. J.; Naidu, M. V., *Tetrahedron Lett.*, 1983, **24**, 1133 - 1134.
6. Baldwin, J. E.; Adlington, R. M.; Moss, N.; Robinson, N. G., *J. Chem. Soc., Chem. Commun.*, 1987, 1664 - 1667.
7. Axelsson, B. S.; O'Toole, K. J.; Spencer, P. A.; Young, D. W., *J. Chem. Soc., Chem. Commun.*, 1991, 1085 - 1086: *ibid, J. Chem. Soc., Perkin Trans. 1*, 1994, 807 - 816.
8. Harada, K.; Nakamura, I., *J. Chem. Soc., Chem. Commun.*, 1978, 522 - 523.
9. Nakamura, I.; Harada, K., *Chem. Lett.*, 1979, 313 - 314.
10. Tanaka, T.; Nakajima, K.; Maeda, T.; Nakamura, A.; Hayashi, N.; Okawa, K., *Bull. Chem. Soc. Japan*, 1979, **52**, 3579 - 3581.
11. Okawa, K.; Yuki, M.; Tanaka, T., *Chem. Lett.*, 1979, 1085 - 1086.
12. Tanaka, T.; Nakajima, K.; Okawa, K., *Bull. Chem. Soc. Japan*, 1980, **53**, 1352 - 1355.
13. Okawa, K.; Nakajima, K.; Tanaka, T., *J. Heterocyclic Chem.*, 1980, **17**, 1815 - 1816.
14. Nakajima, K.; Neya, M.; Yamada, S.; Okawa, K., *Bull. Chem. Soc. Japan*, 1982, **55**, 3049 - 3050.
15. Nakajima, K.; Tanaka, T. Neya, M.; Okawa, K., *Bull. Chem. Soc. Japan*, 1982, **55**, 3237 - 3241.
16. Bodenan, J.; Chanet-Ray, J.; Vessiere, R., *Synthesis*, 1992, 288 - 292.
17. Shiba, T.; Ukita, T.; Mizuno, K.; Teshima, T.; Wakamiya, T., *Tetrahedron Lett.*, 1977, 2681 - 2684.
18. Wakamiya, T.; Mizuno, K.; Ukita, T.; Teshima, T.; Shiba, T., *Bull. Chem. Soc. Japan*, 1978, **51**, 850 - 854.
19. Nakajima, K.; Tanaka, T.; Morita, K.; Okawa, K., *Bull. Chem. Soc. Japan*, 1980, **53**, 283 - 284.
20. Shigematsu, N.; Setoi, H.; Uchida, I.; Shibata, T.; Terano, H.; Hashimoto, M., *Tetrahedron Lett.*, 1988, **29**, 5147 - 5150.
21. Wade, T. N.; Gaymard, F.; Guedj, R., *Tetrahedron Lett.*, 1979, 2681 - 2682.
22. Wade, T. N.; Kheribet, R., *J. Chem. Res. (S)*, 1980, 210 - 211.
23. Sato, K.; Kozikowski, A. P., *Tetrahedron Lett.*, 1989, **30**, 4073 - 4076.
24. Shima, I.; Shimazaki, N.; Imai, K.; Hemmi, K.; Hashimoto, M., *Chem. Pharm. Bull.*, 1990, **38**, 564 - 566.
25. Baldwin, J. E.; Adlington, R. M.; Robinson, N. G., *J. Chem. Soc., Chem. Commun.*, 1987, 153 - 155.
26. Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B., *J. Chem. Soc., Chem. Commun.*, 1989, 1852 - 1854.
27. Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B., *Tetrahedron*, 1993, **49**, 6309 - 6330.
28. Church, N. J.; Young, D. W., *J. Chem. Soc., Chem. Commun.*, 1994, 943 - 944.
29. Buchholz, B.; Stamm, H., *Chem. Ber.*, 1987, **120**, 1239 - 1244.
30. Onistschenko, A.; Buchholz, B.; Stamm, H., *Chem. Ber.*, 1986, **119**, 2678 - 2680.
31. Buckingham, J. (Ed.), *Dictionary of Organic Compounds*, 5th Edn., Chapman and Hall, London,1982, (i) p 163 [sign incorrect, see *Merck Index*, **11**, 439]; (ii) p 222; (iii) p 4592; (iv) p 5681.

† These compounds had the expected analytical and spectroscopic data and an acceptable specific rotation.

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