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Application of the Evans Aziridination Procedure to 2-Substituted Acrylates and Cinnamates : An Expedient Route to α-Substituted α- and β-Amino Acids

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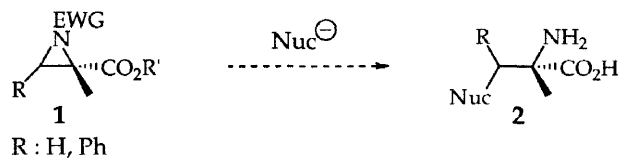
Abstract : Reaction of the title compounds with PhI=NSO$_2$Ar (Ar = p-tolyl or p-nitrophenyl) in the presence of catalytic copper (II) triflate in acetonitrile gave the corresponding 2 and/or 3-substituted aziridine-2-carboxylates in generally good yields. The latter, on reaction with nucleophiles, gave α-substituted α- or β-amino acids depending on the pattern of substitution on the aziridine ring.

There has been a considerable interest in the synthesis of α,α-disubstituted amino acids and this for many reasons. Such molecules can, for instance, impart biological and conformational stability to the peptides they are incorporated in.[1] They can also display biological activities in their own right, for instance, as enzyme inhibitors[2] or as receptor ligands.[3] Moreover, they have served as building blocks for the total synthesis of a variety of natural products.[4] Both racemic and chiral α,α-disubstituted amino acids have been prepared by a wide variety of methods which have been reviewed.[5]

More recently the value of aziridines for the preparation of α,α-disubstituted amino acids has been demonstrated by the chiral syntheses of α-methylserine,[6] α-methylphenylalanine[7,8] and α-methylcysteine.[9] The synthetic routes to these compounds (general formula **2**) all rely on the preparation of a 2-methylaziridine-2-carboxylate **1** (or its reduced 2-hydroxymethyl precursor) followed by nucleophilic ring opening of the aziridine ring at C-3 (Scheme 1).



Scheme 1

In all these examples, the starting chiral aziridines were prepared in multistep fashion from the corresponding chiral epoxides or sulfinimes. Surprisingly, whereas the Evans procedure[10] for the direct aziridination of double bonds using (N-(p-tolylsulfonyl)imino)phenyliodinane (PhI = NTs) and copper salts currently represents a viable alternative to other synthetic methods[11] both in terms of overall yields and chiral induction (*via* the adjunct of chiral ligands),[12] this methodology has never been applied to the synthesis of 2-substituted aziridine-2-carboxylates of type **1**. In fact, the Evans aziridination procedure, while giving reasonable yields of aziridine carboxylates from acrylate and cinnamate, has never been applied to more complex examples of these substrates, in particular, to 2-substituted acrylates and cinnamates. We report herein the preparation of 2-substituted and 2,3-disubstituted aziridine-2-carboxylates using Evans's general aziridination conditions and

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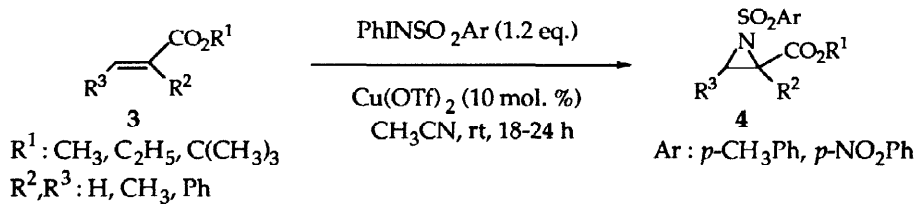
some preliminary results concerning the nucleophilic ring opening of some of these aziridines to give α-substituted α- and β-amino acids.

The aziridinations of the acrylates and cinnamates and their substituted derivatives were conducted under conditions shown to be generally optimal,[13] that is, in acetonitrile at rt in the presence of 10 mol% of copper (II) triflate as catalyst and a slight excess of PhI =NTs as nitrene source (Scheme 2).[14] In some cases, results were compared with those using the p-nitrobenzenesulfonyl (nosyl) analogue of PhI = NTs (i.e. PhI = NNs). The nosyl derivative has been shown to provide better yields of aziridines from olefins, including methyl cinnamate and has the added advantage of being more easily cleaved than the N-tosyl group to provide the free amino function.[13,15,16]



Scheme 2

Results of aziridination of the various methyl acrylates used in this study are shown in Table 1. As expected, aziridination of the model substrate, methyl acrylate itself, proceeded in higher yield with PhI = NNs (entry 1b) than with PhI = NTs (entry 1a). However, both these yields (< 30%) were modest.[17] Considerably higher yields, particularly for the nosyl derivative, were obtained for aziridination of methyl methacrylate (entries 2a and 2b).[18] On the other hand, methyl crotonate (entry 3) provided only low yields of *trans* N-Ts aziridinated product (8%) but again, the beneficial effect of a 2-methyl substituent was demonstrated by the significantly higher product yield obtained from methyl tiglate (42%, entry 4). Good yields of aziridinated product were also obtained when the 2-methyl group was replaced by a phenyl group (entries 5 and 6a,b). Moreover, the steric bulk presented by a tert-butyl ester (entries 6a,b) produced only a modest decrease in product yield. Finally, acrylonitriles (entries 7, 8) gave lower yields than the corresponding acrylates but again, a 2-methyl substituent had a favorable effect on yield.

In Table 2 are shown the results of aziridination reactions using various cinnamates as substrates. Aziridination of the model cinnamate substrates (entries 1 and 2a,b) proceeded in yields comparable to published results,[13] the N-nosyl aziridine being again obtained in higher yield (70%) than the equivalent tosyl analogue (40%). In contrast to the results with acrylate derivatives, however, introduction of a methyl group at C-2 (entries 3a,b) led to considerably lower isolated yields of *trans* aziridine, though in terms of consumed starting material, the yields may be considered as excellent (~ 95%). The additional 2-methyl group thus apparently results in sluggish, incomplete reaction. No attempts were made to drive these reactions to completion by addition of an excess of nitrene source (of limited lifetime in solution in the presence of copper salts).

We next conducted a preliminary investigation concerning the regioselectivity of attack of the 2,2-disubstituted aziridines by several nucleophiles (Table 3). In cases where a phenyl group is attached to the aziridine ring, attack is apparently directed toward the benzylic carbon. Thus, reductive ring opening of N-tosyl-2-phenylaziridine-2-carboxylate using sodium borohydride and nickel chloride in methanol[19] gave exclusively the product of hydride attack at C-2 (entry 1), despite the considerable steric hindrance present at this position. By comparison, the same reaction conditions applied to the 3-phenyl derivative (entry 2) gave phenylalanine as a result of hydride attack at C-3. However, the 2-methyl-3-phenyl-aziridine-2-carboxylate (entry 3) unexpectedly provided a 1:1 mixture of products of C-2 and C-3 attack. Finally, tert-butyl N-nosyl-2-phenylaziridine-2-carboxylate was submitted to either acid hydrolysis (catalytic trifluoroacetic acid in aqueous dioxane at 100°C ; entry 4) or to amination (α-methylbenzylamine and triethylamine in THF ; entry 5). In both cases, the quaternary benzylic position, i.e. C-2, was the preferred site of nucleophilic attack. The decisive influence of the phenyl group is again indicated by the fact that in analogous reactions with 2-methylaziridine-2-carboxylates, both these reagents gave exclusively the products of C-3 attack.[7,8]

Table 1. Copper-Catalyzed Aziridination of Acrylate Derivatives

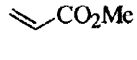
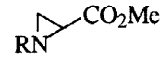
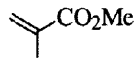
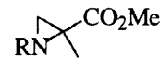
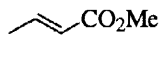
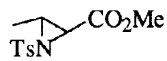
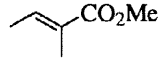
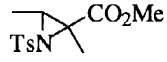
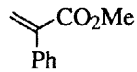
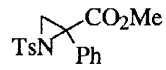
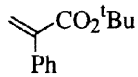
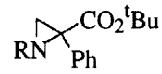
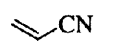
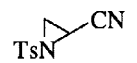
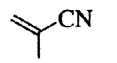
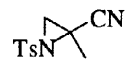
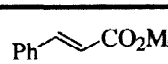
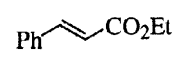
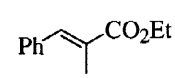
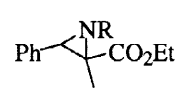
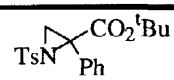
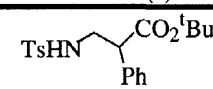
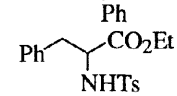
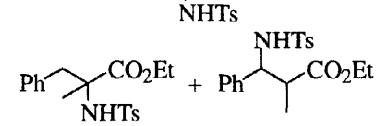
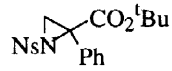
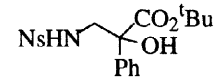
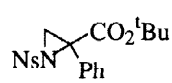
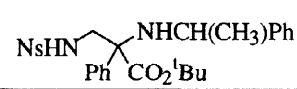
Entry	Substrate	Product		% Yield[a]
1			**1a** : R = Ts **1b** : R = Ns	18 28
2			**2a** : R = Ts **2b** : R = Ns	58 75
3				8[b]
4				42[b]
5				72
6			**6a** : R = Ts **6b** : R = Ns	50 60
7				10
8				34

Table 2. Copper-Catalyzed Aziridination of Cinnamate Derivatives

Entry	Substrate	Product		% Yield[a,c]
1				42
2			**2a** : R = Ts **2b** : R = Ns	40 70
3			**3a** : R = Ts **3b** : R = Ns	21 (96)[b,d] 39 (95)[b]

[a] Isolated yield after flash chromatography. [b] Only *trans* aziridine was observed by ^{1}H-NMR.
[c] Value in parentheses for yield based on consumed starting olefin. [d] Average of two runs.

Table 3. Nucleophilic Ring Opening of Representative Substituted Aziridine 2-Carboxylates.

Entry	Substrate	Reaction conditions[a]	Product(s)	% Yield
1		A		90
2		A		95
3		A		90 (1/1)
4		B		70
5		C		78

[a] **A** : $NaBH_4$, $NiCl_2.6H_2O$, MeOH, O°C ; **B** : catalytic trifluoroacetic acid, 50% aqueous dioxane, 100°C, 4h ; **C** : α-methylbenzylamine, triethylamine, THF, rt.

In conclusion, we have shown that the Evans aziridination procedure can effectively be applied to 2- and/or 3-substituted acrylates as well as to 2-substituted cinnamates to give the correspondingly substituted aziridine-2-carboxylates. The possibility of using these substrates for the preparation of α,α-disubstituted amino acids as well as novel α-substituted β-amino acids has also been demonstrated, both here and elsewhere.[6-9] The extension of these studies to the preparation of enantiopure amino acid derivatives *via* the addition of chiral ligands to the reaction is presently being pursued.

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14. A typical procedure was as follows : to a stirring solution of 4 Å molecular sieves (~ 600 mg) and $Cu(OTf)_2$ (72 mg, 10 mol %) in dry acetonitrile (4 mL) was successively added methyl methacrylate (200 mg, 2 mmol) and, in small portions, PhI = NTs[20] (900 mg, 2.4 mmol). The reaction mixture was stirred at rt for 24 h and then filtered on silica gel. The filtrate was evaporated to dryness under reduced pressure and the oily residue was purified by flash chromatography on silica gel (heptane-ethyl acetate 3:1) affording the corresponding aziridine (310 mg, 58% ; Table 1, entry 2a) as a white solid.
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17. The lower yield of aziridine obtained with methyl acrylate and PhI=NTs (18%) compared to the results reported by Evans and coworkers (40%) (ref. 10) may be attributed to the fact that these authors used a large excess of acrylate (5 eq) with the nitrene source being the limiting reagent (1 eq). Yields were based on the latter.
18. All new compounds gave satisfactory analytical and spectroscopic data.
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