N-Hydroxy-*N*-pivaloylanilines: a New Aziridinating Agent

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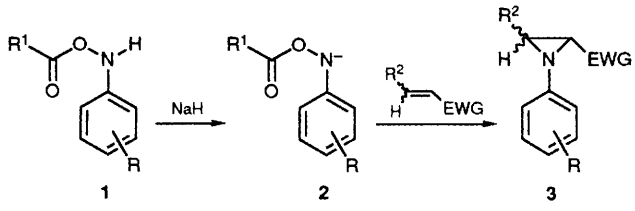
An efficient synthesis of 2-functionalised *N*-arylaziridines from hydroxamic acids and electron deficient olefins is described.

The presence of two adjacent and reactive functional groups and a weak but powerfully nucleophilic N–OH bond in hydroxamic acids has endowed these molecules with rich chemistry.[1] This feature has permitted the use of these substances in the synthesis of important heterocyclic compounds such as phenanthridines,[2] pyrroloindoles[3] and oxindoles.[4]

The occurrence of the three-membered heterocyclic ring in bioactive molecules has prompted the development of new routes for the synthesis of functionalised aziridines. The methods available to date for the preparation of *N*-arylaziridines carrying a substituent such as CN, CO_2R and SOPh, at C-2 generally involve: (*i*) reaction of a primary amine with appropriately 2-substituted acrylic derivatives,[5] (*ii*) addition of a carbanion derived from α-halomethyl sulfoxide to an arylimine, followed by ring closure,[6] and (*iii*) thermolysis of triazoles derived from aryl azides and olefins.[7] The recently developed simple method utilising acyl cyanides[8] and 2-acylthiazolium salts[9] for specific *O*-acylation of *N*-arylhydroxylamines has now enabled the examination of the synthetic potential of these substances **1** hitherto accessible only with difficulty (R = H; R^1 = Ph, Me, Bu^t).

It was anticipated that the anion **2** (R = H, R^1 = Ph), generated from **1** (R = H, R^1 = Ph) would react with Michael acceptors by an AE (addition–elimination) mechanism[10] and provide a new method for 2-substituted aziridines **3** (Scheme 1). In the event, **2** (R = H, R^1 = Ph) with ethyl acrylate yielded azoxybenzene, azobenzene, the amide **4** (R = H, R^1 = Ph), benzoic acid and the aziridine **3** (R = H, R^2 = H, EWG = CO_2Et, 27%). The use of the *tert*-butyl ester **2** (R = H, R^1 = Bu^t) with ethyl acrylate or phenyl vinyl sulfoxide did not significantly improve the yield of **3**, the former affording in addition to the aziridine **3** (R = R^2 = H, EWG = CO_2Et) the Michael adduct **5** (EWG = CO_2Et, 19%), and the latter



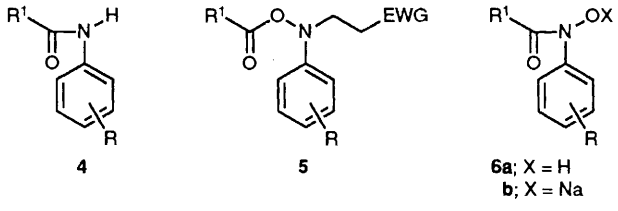
1 2 3

Scheme 1 EWG = electron-withdrawing group

Table 1 Aziridines **3** prepared from hydroxamic acids **6a**

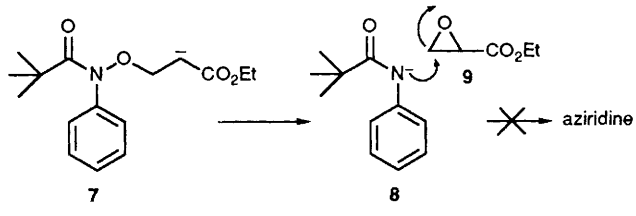
	Starting material	Olefin		Aziridine **3**					
Entry	R	R^2	EWG	R^2	EWG	R	Yield (%)[a]	M.p./°C	*t*/h
1	4-Br	H	SOPh	H	SOPh	4-Br	77 (2:1)	160–168	0.3
2	4-Cl	H	SOPh	H	SOPh	4-Cl	68 (2:1)	117–151	0.3
3	3-Me	H	SOPh	H	SOPh	3-Me	70 (1:1)	77–106	0.3
4	4-Me	H	SOPh	H	SOPh	4-Me	77 (1:1)	82–110	1
5	4-NO_2	H	SOPh	H	SOPh	4-NO_2	43 (1:1)	122–150	0.3
6	H	H	CO_2Me	H	CO_2Me	H	67	Oil	18
7	H	Me(*trans*)	CO_2Me	H	CO_2Me	Me(*trans*)	48	Oil	18
8	4-Br	H	CO_2Me	H	CO_2Me	4-Br	62	Oil	18
9	4-Cl	H	CO_2Me	H	CO_2Me	4-Cl	60	Oil	18
10	4-Cl	H	CO_2Et	H	CO_2Et	4-Cl	95	47–48	18
11	3-Me	H	CO_2Et	H	CO_2Et	3-Me	93	Oil	18
12	4-Me	H	CO_2Et	H	CO_2Et	4-Me	90	Oil	18
13	3-Br	H	CO_2Me	H	CO_2Me	3-Br	62	Oil	18
14	4-NO_2	H	CO_2Me	H	CO_2Me	4-NO_2	67	54–55	18
15	4-OMe	H	CO_2Me	H	CO_2Me	4-OMe	9	Oil	18
16	H	H	COMe	H	COMe	H	80	Oil	18
17	H	Δ^4-Cholestenone		—	—	—	0	—	18
18	H	CO_2Me(*trans*)	CO_2Me	CO_2Me(*trans*)	CO_2Me	H	41	Oil	120
19	H	CO_2Me(*cis*)	CO_2Me	CO_2Me(*cis*)	CO_2Me	H	41	Oil	120

[a] Isomeric ratio by ^1H NMR in brackets.



affording **3** (R = R^2 = H, EWG = SOPh, 32%) as a mixture of two diastereoisomers. However with sodium hydroxamate **6b** (R = Na, R^1 = Bu^t), generated *in situ* from the corresponding hydroxamic acid **6a** with sodium hydride (1 equiv.), in the presence of the same electrophile phenyl vinyl sulfoxide (2–3 equiv.) in tetrahydrofuran (THF) at room temperature, yielded the aziridine **3** (R = H, R^2 = Ph, EWG = SOPh) in 65% in 30 min. The results (Table 1) clearly demonstrate that a variety of hydroxamic acids bearing different ring substituents (except entry 15; *p*-MeO) afford in good to excellent yields the corresponding aziridines, which can be used for further useful chemical transformations.[11] While a single β-alkyl substituent (*cf.* entries 6 and 7) in the electrophile tends to reduce the yield, the presence of β,β-disubstitution (*cf.* entries 16 and 17) inhibits the reaction completely. Also noteworthy is the complete stereospecificity observed for this aziridination reaction. Thus, dimethyl maleate afforded exclusively the *cis* aziridine (entry 19) with no traces of the *trans* isomer being formed (within the limits of detection by TLC). Likewise the fumarate yielded solely the *trans* compound (entry 18).†

The essentially nucleophilic but not the nitrenic nature of the aziridinating agent was demonstrated by its total incapacity to produce the corresponding aziridines (or products resulting therefrom) with cyclohexene, styrene or dihydropyran. In each case the products were azobenzene (*cis* and *trans*, 80%), azoxybenzene and *N*-pivaloylaniline, the latter



Scheme 2

two constituting *ca.* 10%, virtually the same percentage distribution observed when the hydroxamate alone was left to decompose in solution.‡

Germane to the discussion of any possible mechanism are the following observations: (*i*) the Michael adduct **5** (R = H, R^1 = Bu^t, EWG = CO_2Me) obtained from the known methyl 3-(*N*-hydroxy-*N*-phenyl)aminopropionate[15] by *O*-acylation (Bu^tCOCl, dimethylaminopyridine, CH_2Cl_2) does not yield the aziridine on treatment with bases (KH–THF, NaH–dimethylformamide or lithium diisopropylamide–THF, −80 to +15 °C) showing that it *is not* the precursor of the aziridine **3**; (*ii*) change of solvent from THF to cyclohexane does not significantly decrease the yield of the product, thus precluding the involvement of a solvent stabilised singlet aryl nitrene[17] as the reactive nucleophilic species; (*iii*) the anion of *N*-pivaloylaniline **8** and epoxide **9**, which in principle could be formed by the initial Michael adduct **7** suffering a 3-*exo*-*Tet* ring closure, do not react by ring opening of the epoxide, followed by *N*- to *O*-transacylation and subsequent ring closure to afford the aziridine (Scheme 2); (*iv*) no aziridination occurs with *N*-acyloxyamine *in the absence of base*; (*v*) slow addition§ of **1** to an excess of methyl acrylate (3 or 10 equiv.) and NaH (1 equiv.) in THF causes a significant increase in the yield of the

† Assignment of *cis*/*trans* stereochemistry was based on the chemical shift differences observed for pairs of geometrical isomers.[12–14]

‡ The mechanism of the decomposition of *N*-arylhydroxamate anions in aprotic solvent into azoarenes, azoxyarenes, amides and carboxylic acids will be published elsewhere.

§ We thank a referee for this suggestion.

aziridine (75%). On the basis of this evidence it is likely that aziridination is the result of a thermodynamically driven isomerisation[18] of the hydroxamate ion *via* the isomeric oxaziridine to the *N*-acyloxyaniline anion, followed by a concerted attack on the electron-deficient olefin.¶

Model experiments of relevance to C-8 *N*-arylation of guanosine,[19] a process believed to be implicated in the induction of cancer by aromatic hydroxylamines, involving imines as Michael acceptors, are under study.

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¶ However, Atkinson[16] has found that *N*-acetoxyaminoquinazolinones, in the absence of base, are good aziridinating agents of *both* electron-deficient and electron-rich olefins.