New reactions involving addition to and substitution at carbon-carbon π bonds†

Novas reacções envolvendo adição a e substituição em ligações π carbono-carbono

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The work involving addition to and substitution at carbon-carbon π bonds, conducted in the authors' laboratory, during the last five years, is reviewed. The first part refers to the synthesis of various heterocycles, obtained through a reaction which involves a formal [3,3]-sigmatropic rearrangement, in which a nitrogen-oxygen bond is cleaved. The second part describes a new aziridinating agent derived from hydroxamic acids. The third part refers to an aryl arly coupling through the use of radical reactions, which was applied in the synthesis of various *Amaryllidaceae* alkaloids.

Este artigo passa em revista o trabalho realizado no laboratório dos autores nos últimos cinco anos, relacionado com a adição e a substituição em ligações carbono-carbono π. A primeira parte refere a síntese de vários heterociclos, obtidos através de uma reacção envolvendo um rearranjo formal 3,3]-sigmatrópico, em que se quebra uma ligação azoto-oxigénio. A segunda parte trata de um novo agente de aziridinação derivado de ácidos hidroxâmicos. A terceira parte refere a formação através de reacções radicalares de acoplamento aril-aril, aplicado na síntese de vários alcaloides da família das *Amaryllidaceae*.

Carbon-carbon π bonds have always been of paramount importance in organic synthesis for the functionality that can be added to them or for the substitution reactions in which they can intervene.

Of particular interest in the last decade has been the drive to invent new chemical reactions which use very mild conditions, whereby a high regio, stereo and chemoselectivity of bond formation is achieved.

The present article summarizes the work conducted in our laboratory in the past few years in the development of new reactions involving addition to and substitution at carbon - carbon π bonds. These reactions have proved useful in the synthesis of a variety of heterocycles, such as imidazolinones, oxindoles, phenanthridines, benzo(c)phenanthridines, aziridines and imidazoles — substances of actual or potential use in the pharmaceutical, agrochemical and micro-electronics industries.

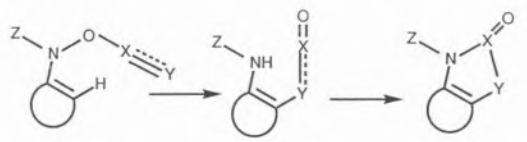


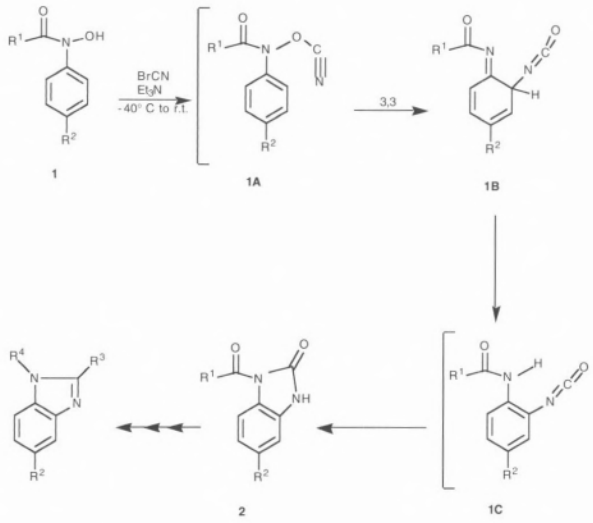
Figure 1. 3,3 - Sigmatropic rearrangement of ene-hydroxylamine derivatives

† This review is dedicated to Professor Sir Derek Barton on the occasion of his 75th birthday

1. Substitutions at Carbon-Carbon π Bonds Triggered by Nitrogen-Oxygen Cleavage. Synthesis of Benzimidazolinones, Oxindoles, Imidazoles, N-Iminocarboxybenzimidazoles and Amidines

Let us consider the general rearrangement depicted in Figure 1, where Z is an acyl or aroyl group, X is a carbon atom and Y a nitrogen atom. This rearrangement which can formally be placed under the more-general heading of 3,3 - sigmatropic rearrangement [1] draws its driving force at least in part from the cleavage of the weak N—O bond (*ca.* 50 Kcal mol $^{-1}$) [2] and in the formation of a strong carbonyl group. Thus, when equimolecular quantities of N - phenyl benzohydroxamic acid (**1a**) (Scheme I) and cyanogen bromide were treated with a base such as triethylamine, under mild conditions (-40°C to room temperature), a fast and clean reaction occurred to give rise to N - benzoyl benzimidazolinone (**2a**) in 65% yield.[3] .Variation in the electronic character of either the hydroxylamine moiety or the acyl portion of the hydroxamic acids **1** (*cf.* Table 1 and Scheme II) did not significantly alter either the yield or the regiospecificity of the reaction. We therefore believe that, in the light of exclusive formation of benzimidazolinones and the

Scheme I



a: $R^1 = C_6H_5$ $R^2 = H$

b: $R^1 = C_2H_5O$ $R^2 = H$

c: $R^1 = C_6H_5$ $R^2 = CH_3$

d: $R^1 = C_2H_5O$ $R^2 = CH_3$

e: $R^1 = C_6H_5$ $R^2 = Br$

f: $R^1 = C_2H_5O$ $R^2 = Br$

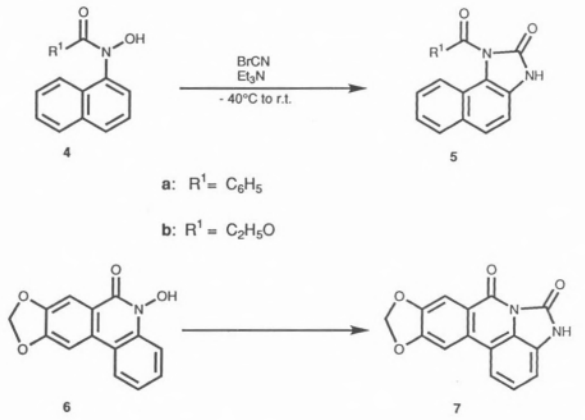
g: $R^1 = CF_3$ $R^2 = H$

Table I

Starting material	Product	Yield
1a	**2a**	65%
1b	**2b**	59%
1c	**2c**	52%
1d	**2d**	72%
1e	**2e**	81%
1f	**2f**	77%
1g	**3**[a]	64%
4a	**5a**	69%
4b	**5b**	63%
6	**7**	99%

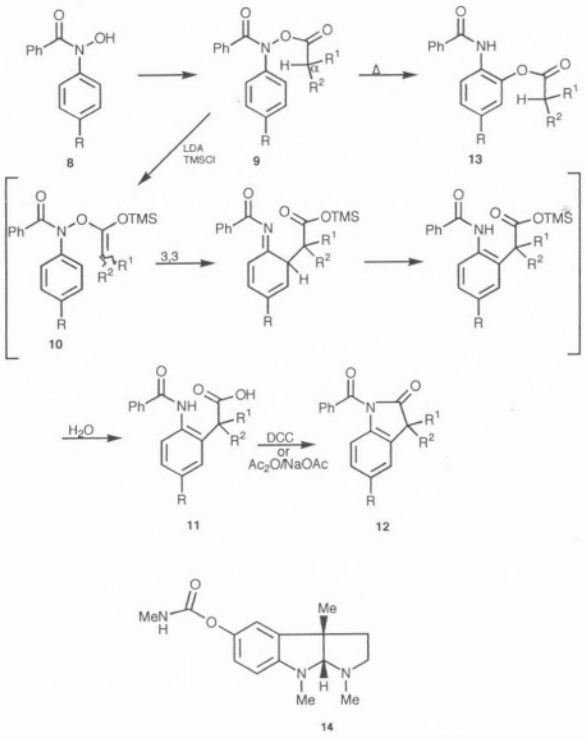
[a] After hydrolysis of **2g**.

Scheme II



Scheme III

Synthesis of 3 - Substituted N - Benzoyl Oxindoles



high yields obtained in all cases, the rearrangements are intramolecular and most probably concerted in nature as shown in Scheme I. The 2-substituted benzimidazoles, many of them known to possess useful properties,[4] are, in principle, accessible from these benzimidazolones by standard chemical reactions.

Considering again Figure 1, an analogous reaction can be envisioned if the system X=Y constitutes part of an olefinic system, i.e. X=Y=C. This system can be generated *in situ* [5] if compounds **9**, easily obtained from benzohydroxamic acids **8** (*cf.* Scheme III) by acylation with an acid chloride or with an acid in the presence of dicyclohexylcarbodiimide (DCC), are treated with a strong base such as lithium di-isopropyl amide (LDA)

at low temperature in the presence of trimethylsilyl chloride (TMSCl) . The resulting silyl enol ethers **10** thus formed underwent a spontaneous 3,3-sigmatropic rearrangement to yield, after aqueous work-up, the *o* - aminobenzoyl - phenyl acetic acids **11** (Table II). These substances can be cyclised smoothly (DCC or NaOAc-Ac_2O) to the corresponding oxindoles **12** (Table III) of obvious utility as starting material for the synthesis of a biologically active alkaloid such as physostigmine (**14**) and related molecules.

The results show that the presence of carbanion stabilizing groups (SPh, Ph or olefin) α to the carbonyl function in the acetyl fragment of **9** is necessary to prevent a rapid reversion to the parent hydroxamic acid **8** (*cf.* behaviour of **9**, R=R^1=R^2=H in Table II) and to favour the rearrangement. [6] Functional groups such as *p*-OMe, *p*-Cl and *p*-CO_2Me in the aniline moiety of **9** do not seriously interfere with the reaction. Of particular synthetic interest is the ready access the method provides for phenylthio-oxindoles, with the nitrogen already suitably protected, thus permitting further useful chemical transformations to be performed at C-3 by radical and/or carbanion chemistry.

It is also interesting to note that the esters **9** are thermally unstable and rearrange[6] to the corresponding *o* -acyloxybenzanilides **13**. However, in the presence of base a radically different chemical reactivity is manifested.

We have previously shown that aroyl and acyl cyanides tend predominantly to *O*-acylate N-aryl hydroxylamines.[8] It was thus of interest to study the chemistry of alkoxycarbonyl cyanide **15** in which the electronic character of the carbonyl group has been slightly modified. With this substance as electrophile, the reaction with hydroxylamines took a different course.[9] The products obtained were the addition compounds **16** (Scheme IV) arising from the attack of the nitrogen atom of the hydroxylamines at the *sp* carbon of the cyanide group. The structure of one (**16a**) of these highly functionalised molecules, containing a number of adjacent functional groups, was shown to possess unambiguously the nitrone structure by X-ray crystallography (Figure 2). Further evidence for predominance of the nitrone form for these compounds in solution came from the comparative study of the UV spectra of **17** in Scheme V and **16a-16f**.[9]

Table II

Synthesis of N-Aryl-O-acyl Hydroxamic Acids and Products of Rearrangement

9			9, Yield	11, Yield
R	R^1	R^2		
H	H	H	92%	8%[a]
H	H	Ph	72%	68%[b]
H	Ph	Ph	73%	25%[b,c]
H	H	SPh	76%	50%[b]
Cl	H	SPh	69%	50%[b]
CO_2Me	H	SPh	89%	54%[b]
Me	H	SPh	72%	71%[b]

[a] Recovered starting material 90%.
[b] Characterised as methyl esters.
[c] The corresponding benzanilide isolated in *ca.* 40%.

Table III

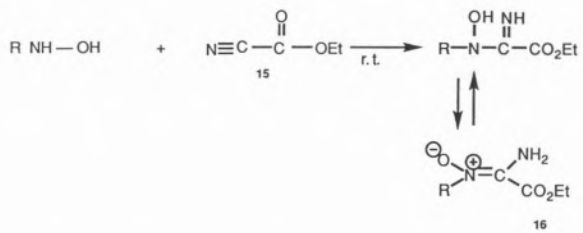
3-Substituted N-Benzoyl Oxindoles

12			Yield
R	R^1	R^2	
H	H	Ph	65%
H	Ph	Ph	25%[a]
H	H	SPh	46%
Cl	H	SPh	49%
CO_2Me	H	SPh	51%
Me	H	SPh	53%
OMe	H	SPh	34%

[a] The corresponding benzanilide was isolated in *ca.* 40%.

Scheme IV

Synthesis of α-Aminonitrones



Product	R	Yield
16a	Me	65%
16b	^{i}Pr	73%
16c	Ph	79%
16d	4 - MeC_6H_4	72%
16e	3 - MeC_6H_4	62%
16f	4 - BrC_6H_4	67%

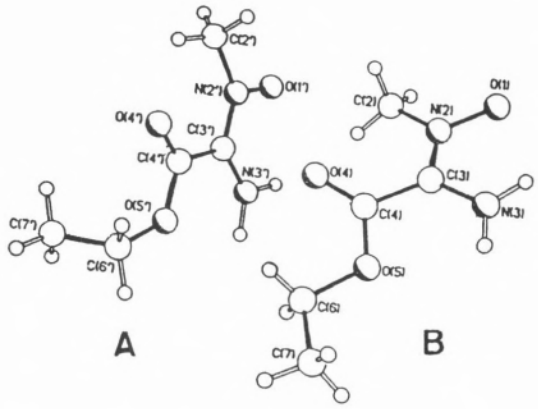
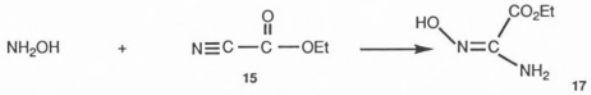


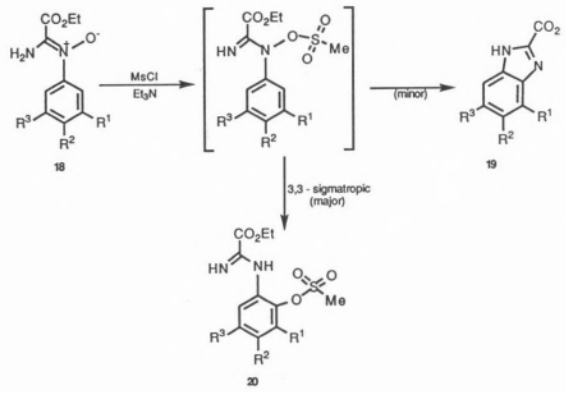
Figure 2. X-Ray structure of compound **16a**, showing the presence of two crystallographically independent molecules **A** and **B**.

Scheme V



Scheme VI

α-Aminonitrones and Mesylchloride



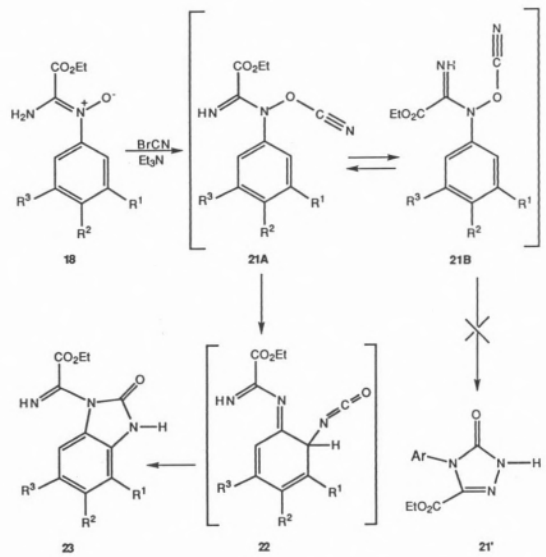
Starting material	Product	R^1	R^2	R^3	Yield
18a	20a	H	H	H	60%
18b	20b	H	Me	H	56%
18c	20c	H	H	Me	50%
	20c'	Me	H	H	15%
18d	20d	H	Br	H	40%

Reaction of **18** with mesyl chloride[9] (Scheme VI) yielded as the major product, the mesyloxy amidine **20** — the hoped for benzimidazole-2-carboxylate **19** being formed only in 7% yield.

Similarly, reaction with bromocyanogen and **18** (Scheme VII) afforded the N - substituted benzimidazolones **23**. The intermediate **21A** formed from **18** undergoes a rapid 3,3-sigmatropic rearrangement to give **22**. Rearomatisation results in the formation of the benzimidazolones **23**. It is interesting to note that in none of the compounds studied the alternative 3,3-hetero-oxy-Cope rearrangement involving the conformer **21B** leading to the triazolone **21'** was observed. A

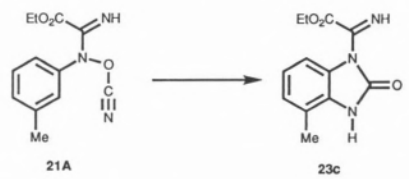
Scheme VII

α-Aminonitrones and Bromocyanogen



Starting Material	Product	R^1	R^2	R^3	Yield
18a	23a	H	H	H	66%
18b	23b	H	Me	H	82%
18c	23c	Me	H	H	87%
18d	23d	H	Br	H	75%

Scheme VIII



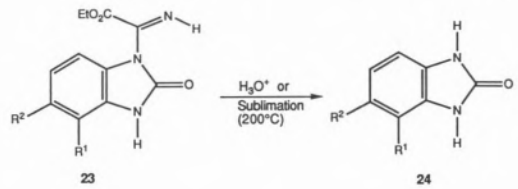
possible reason, other than one conformational in origin, could be due to considerable weakening of the N—O bond with significant positive charge already developed in the aromatic ring in the intermediate **21A**. Also intriguing is the exclusive formation of the benzimidazolone **23c** resulting from attack *ortho* to the methyl group. Obviously the conformation of the intermediate **21A** depicted in Scheme VIII is preferred, the reason for such preference, however, remains obscure.

The N-imidoylbenzimidazolones **23** (Scheme IX) were all sensitive to acid and to heat, the action of both of them leading to the formation of the corresponding benzimidazolones **24** in excellent yields.

The failure of the aminonitrones **16a** and **16b** (Scheme IV) to give any useful products with cyanogen bromide led us to employ the less powerful electrophile, the propiolate esters. Indeed, when **16a** (Scheme X) was treated at room temperature for an hour with methyl propiolate in the presence of triethylamine, and then boiled for 15 min, an excellent yield of an imidazole dicarboxylic ester was obtained. *A priori*, the product formed could be either the 2,4-disubstituted imidazole **26** or its 2,5-regioisomer **27**, depending on the nature of the rearrangement, namely 3,3 or 1,3, suffered by the intermediate **25** (Scheme X). Since the spectral characteristics (^{13}C and ^{1}H NMR) and the m.p. of the known 2,5-dimethyl ester [10] **27** (R=Me) were significantly different from those found for our product it follows that the latter is to be represented by structure **26**.

Scheme IX

Benzimidazolones from N-imidoylbenzimidazolones



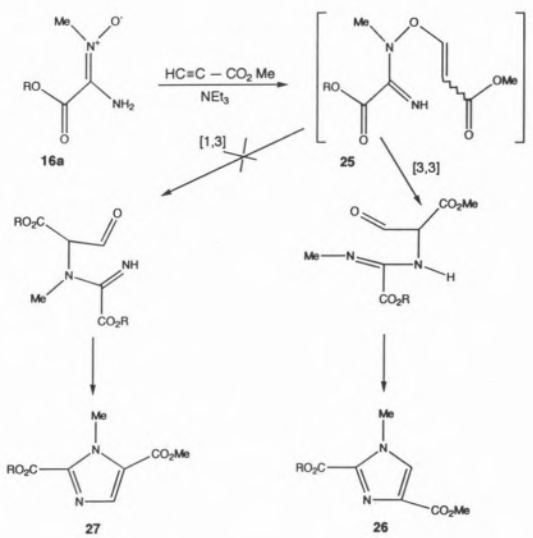
23 **24**

Starting material	Product	R^1	R^2	Yield
23a	**24a**[a]	H	H	95%
23b	**24b**[b]	H	Me	93%
23c	**24c**[c]	Me	H	95%
23d	**24d**[c]	H	Br	92%

[a] Hershenson, F. ; Bauer, L.; King. K. *J. Org. Chem.*, *33* (1968) 2543.
[b] Staab, H. *Ann.*, *609* (1957) 75.
[c] Robert, L. ; Arsenio, A. *J. Am. Chem. Soc.*, *80* (1958) 1657.

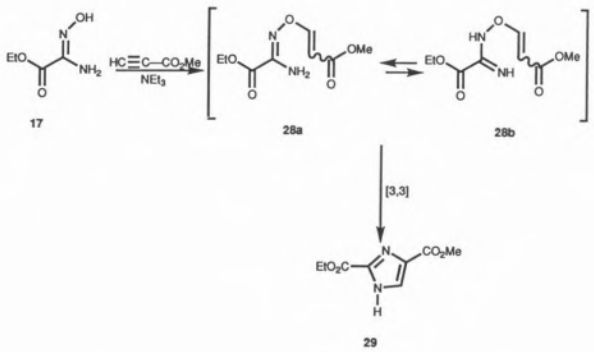
Scheme X

Imidazoles from α-Aminonitrones



16a **25** **27** **26**

Scheme XI



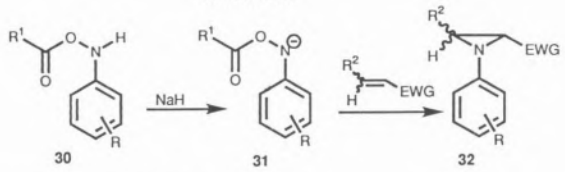
17 **28a** **28b** **29**

In the case of the oxime **17** (Scheme XI) it was possible to isolate the initial Michael adduct **28a** or **28b** consisting of the *trans* isomer (80%) and the *cis* isomer (20%). On thermolysis the mixture was cleanly converted into the imidazole derivative **29** in a sequence of reactions involving a 3,3-sigmatropic rearrangement and a 1,3-prototropic shift followed by dehydration.

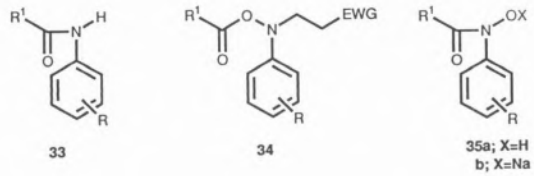
2. Addition to Carbon-Carbon π Bonds — A New Aziridination Triggered by Nitrogen-Oxygen Cleavage

The discovery by our group that a variety of acylating agents[11] can specifically O-acylate N-aryl hydroxylamines to yield **30** (R=H, R^1=Ph,Me, *t* -Bu) (Scheme XII) has enabled the examination of reactivity towards carbon—carbon π bonds of these substances hitherto accessible only with difficulty. It was anticipated that the anion **31** (R=H, R^1=Ph), generated from **30** (R=H, R^1=Ph) would react with a carbon—carbon π bond of a Michael acceptor by an AE (addition-elimination) mechanism[12] and provide a new method for 2-substituted aziridines **32**. In the event, **31** (R=H, R^1=Ph) with ethyl acrylate yielded azoxybenzene, azobenzene, the amide **33** (R=H, R^1=Ph), benzoic acid and the aziridine **32** (R=H, R^2=H, EWG=CO_2Et, 27%).[13] The use of *tert* - butyl ester **31** (R=H, R^1= *t* -Bu) with ethyl acrylate or phenyl vinyl sulfoxide did not significantly improve the yield of **32** , the former affording in addition to the aziridine **32** (R=R^2=H, EWG=CO_2Et) the Michael adduct **34** (EWG= CO_2Et, 19%), and the latter affording **32** (R=R^2=H, EWG=SOPh, 32%) as a mixture of two diastereoisomers. However with the sodium hydroxamate **35b** (X=Na, R^1=*t* -Bu) generated *in situ* from the corresponding hydroxamic acid **35a** with sodium hydride in the presence of the same electrophile, phenyl vinyl sulfoxide, yielded the aziridine **32** (R=H, R^2=Ph, EWG=SOPh) in 65% at room temperature in 30 min. The results (Table IV) 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,[13] which can be used for further useful chemical transformations.[14] While a single ß - alkyl substituent (*cf.* entries 6 and 7) in the electrophile tends to reduce the yield, the presence of ß,ß - disubstitution (*cf.* entries 16 and 17) inhibits the reaction completely. Also noteworthy is the complete stereospecificity observed for this aziridination. Thus

Scheme XII



EWG = electron-withdrawing group



33 34 35a; X=H b; X=Na

Table IV

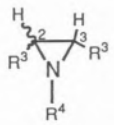
Aziridines 32 prepared from Hydroxamic Acids 35a

Entry	Starting material R	Olefin R^2	Olefin EWG	Aziridine 32 R^2	Aziridine 32 EWG	Aziridine 32 R	Yield (%)[a]
1	4-Br	H	SOPh	H	SOPh	4-Br	77 (2:1)
2	4-Cl	H	SOPh	H	SOPh	4-Cl	68 (2:1)
3	3-Me	H	SOPh	H	SOPh	3-Me	70 (1:1)
4	4-Me	H	SOPh	H	SOPh	4-Me	77 (1:1)
5	4-NO_2	H	SOPh	H	SOPh	4-NO_2	43 (11:1)
6	H	H	CO_2Me	H	CO_2Me	H	67
7	H	Me *(trans)*	CO_2Me	H	CO_2Me	Me *(trans)*	48
8	4-Br	H	CO_2Me	H	CO_2Me	4-Br	62
9	4-Cl	H	CO_2Me	H	CO_2Me	4-Cl	60
10	4-Cl	H	CO_2Et	H	CO_2Et	4-Cl	95
11	3-Me	H	CO_2Et	H	CO_2Et	3-Me	93
12	4-Me	H	CO_2Et	H	CO_2Et	4-Me	90
13	3-Br	H	CO_2Me	H	CO_2Me	3-Br	62
14	4-NO_2	H	CO_2Me	H	CO_2Me	4-NO_2	67
15	4-OMe	H	CO_2Me	H	CO_2Me	4-OMe	9
16	H	H	COMe	H	COMe	H	80
17	H	Δ^4-Cholestenone		—	—	—	0
18	H	CO_2Me *(trans)*	CO_2Me	CO_2Me *(trans)*	CO_2Me	H	41
19	H	CO_2Me *(cis)*	CO_2Me	CO_2Me *(cis)*	CO_2Me	H	41

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

Table V

^{1}H NMR Data for C_2-H and C_3-H of Aziridines



Compound R_3	Compound R_4	δ_{cis}	δ_{trans}
COPh	cyclohexyl	3.38[a]	4.07[a]
COPh	Me	3.25[a]	3.92[a]
COPh	CH_2Ph	3.38[a]	4.10[a]
CO_2Me	4-MeOC_6H_4	2.86[b]	3.31[b]
		3.05[c]	3.44[c]
CO_2Me	Ph	3.31[d]	3.85[d]
CO_2Me	3-MeC_6H_4	3.11[d]	3.47[d]

[a] Turner, A.B.; Heine, H.W.; Irving, J.; Bush, J.B. *J. Am. Chem. Soc.*, *87* (1965) 1050.
[b] Huisgen, R.; Scheer; W.; Huber, H. *J. Am. Chem. Soc.*, *89* (1967) 1753.
[c] Huisgen, R.; Szeimies, G., *Chem. Ber.*, *99* (1966) 491.
[d] Reference 19.

dimethyl maleate afforded exclusively the *cis* aziridine (entry 19) with no traces of the *trans* isomer being formed (within the limits of detection by thin layer chromatography). Likewise the fumarate yielded solely the *trans* compound (entry 18). The stereochemical assignments were based on the chemical shifts of the two equivalent methine protons at C-2 and C-3, of the corresponding *cis* and *trans* aziridines. It is known that in a series of N-substituted aziridines bearing two identical electron withdrawing groups at C-2 and C-3, the methine proton of the *trans* isomer invariably resonates at *lower field* than the corresponding proton of the *cis* isomer (Table V).

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 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:

a) the N-pivaloyl hydroxamic acids consistently give better yields of aziridines than the corresponding benzoyl analogs;

b) the Michael adduct **34** (R=H, R^1= *t* -Bu, EWG = CO_2Me) does not yield the aziridine on treatment with a variety of bases, showing that *it is not the precursor of the aziridine* **32**;

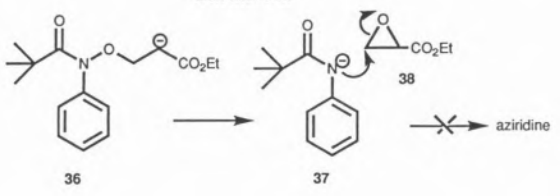
c) no aziridination occurs with N-acyloxy hydroxylamine in the absence of base;

d) slow addition of **30** to an excess of methyl acrylate in the presence of base causes a significant increase in the yield of the aziridine (75%);

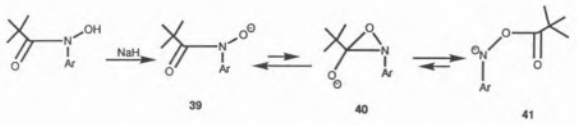
e) change of solvent from THF to cyclohexane does not significantly decrease the yield of the product, thus precluding the involvement of a solvent stabilized singlet aryl nitrene[15] as the reactive nucleophilic species;

f) the anion of N-pivaloylaniline (**37**) (Scheme XIII) and ethyl glycidate (**38**), which in principle could be formed by the initial Michael adduct **36** 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.

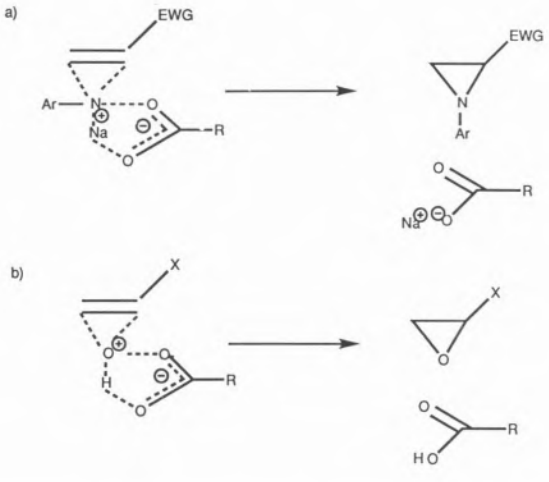
Scheme XIII



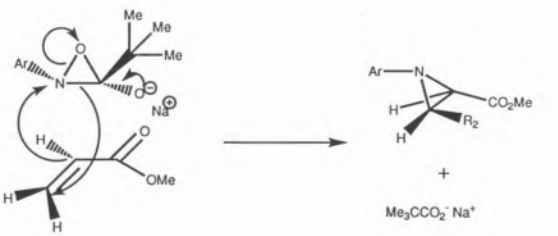
Scheme XIV



Scheme XV



Scheme XVI



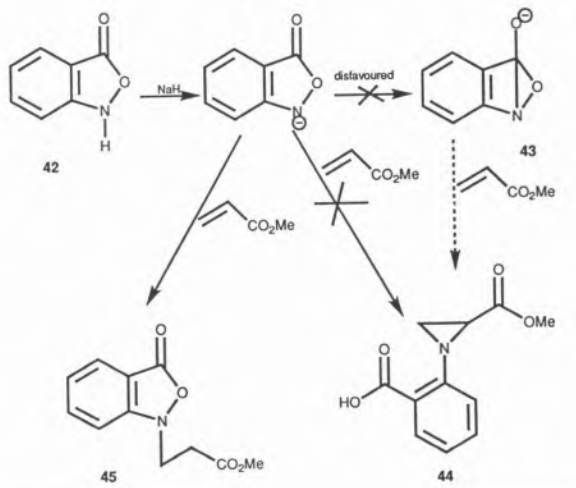
On the basis of this evidence two possible mechanisms could be written for this novel reaction. The formation of the Michael adduct **34** implied a thermodynamically driven isomerisation[16] of the hydroxamate anion **39** (Scheme XIV) to the N-acyloxyaniline anion **41** through the oxaziridine intermediate **40**. Both of these latter two species, **40** and **41**, could, in principle, act as the aziridinating agent (see Schemes XV and XVI), provided it is assumed that an equilibrium exists between them with the former having a sufficient half-life to permit its reaction with external electrophiles. In Scheme XV-a) is depicted a concerted aziridination

mechanism which draws its analogy from the epoxidation of olefins by peracids[17] (*cf.* Scheme XV-b) and also the mechanism proposed by Atkinson[18] and coworkers in their aziridination reactions utilising hydrazine derivatives. Scheme XVI on the other hand shows the concerted attack of the oxaziridine anion on the electron deficient carbon-carbon π bond of the olefin.

Although a definite choice between the two mechanisms is difficult to make in the absence of kinetic data, an attempt nevertheless was made to clarify the situation by utilizing the benz-5-oxo-2,5-dihydro-1,2-oxazole (**42**) with the tacit assumption that geometric constraints would disfavour the formation of the strained tricyclic system **43** (*cf.* Scheme XVII). Reaction of the cyclic N-acyl compound **42** in the presence of NaH with methyl acrylate *did not yield the aziridine* **44**; instead the principal product, formed in 55% yield, was the Michael adduct **45** — a result that strongly suggests the involvement of the oxaziridine as the effective nitrogen transfer reagent.[19]

As can be easily seen, the above reaction of aziridination has obvious advantages over the common azide method in that it is simple to perform, occurs at or below room temperature, and does not require thermolysis of the potentially explosive azides used as starting materials. Furthermore the reaction (in the cases studied so far) occurs with complete stereospecificity.

Scheme XVII

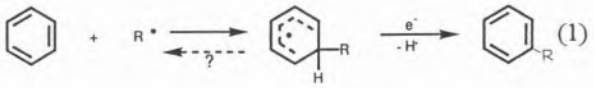


3. Aryl-Aryl Bond Formation via Radical Reactions

The use of radical reactions to effect carbon-carbon bond reactions of synthetic use is a relatively new field.[20] This stemmed from the lack of knowledge concerning the predictability and selectivity of free radical chemistry, for until the late sixties organic chemists tended to consider free radical reactions as erratic, capricious, and prone to give intractable mixtures of products. During the past decade this view has changed profoundly and it is now widely recognized that radical reactions, even with very complex and heavily substituted substrates, can be conducted in a highly selective and efficient manner, and often display advantages over alternative ionic processes.[21,22] A review [23] describes the uses of free radical methodology in the synthesis of natural products, and a recent book [24] offers a highly interesting account of the incidence of radical chemistry in a variety of topics such as the pyrolysis of chlorinated hydrocarbons, the synthesis of aldosterone and the generation of disciplined radicals.

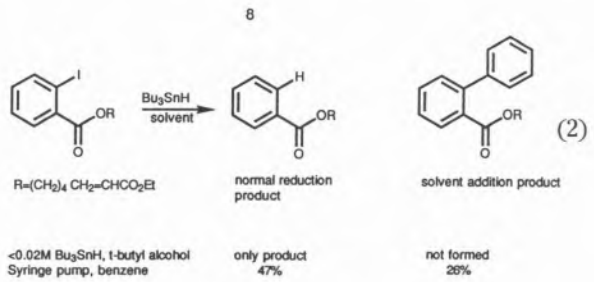
3.1. A New Phenanthridine Synthesis

Most known addition reactions of radicals to aromatic rings involve net substitution for a hydrogen atom by the general mechanism outlined in (eq. 1).



(1)

The addition reactions of alkyl and substituted alkyl radicals to simple aromatic rings are very slow.[25] The addition of aryl radicals to aromatic rings are considerably faster[26] but their preparative utility has been hampered by low regio- and chemoselectivity. However, the addition of an aryl radical to benzene, used as the solvent, can become a limiting side reaction when techniques like slow syringe pump addition of tin hydride are used and there is no good trap for the aryl radical[27] (*cf.*eq.2.)

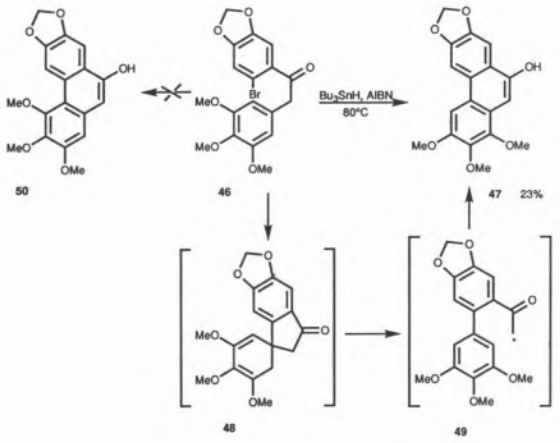


(2)

Applications of radical aryl-aryl coupling reactions in synthesis are scare. A literature survey showed that an aryl-aryl coupling reaction involving the use of stannyl compounds occurred when the aryl bromide **46** (Scheme XVIII) was treated with tributyltin hydride under standard conditions, to yield the phenanthrene **47**, presumably *via* radicals **48** and **49** and *not* the anticipated isomeric product **50**.[28]

Our interest in the synthesis of *Amaryllidaceae* alkaloids, such as lycoricidine **51**, from a fully aromatic precursor, led us to investigate the chemistry of aryl radicals formed by *n*-tributyl stannyl hydride (*n*-Bu_3SnH) and 1,1'-azobisisobutyronitrile (AIBN) treatment of

Scheme XVIII



Scheme XIX

Radical Aryl - Aryl Coupling

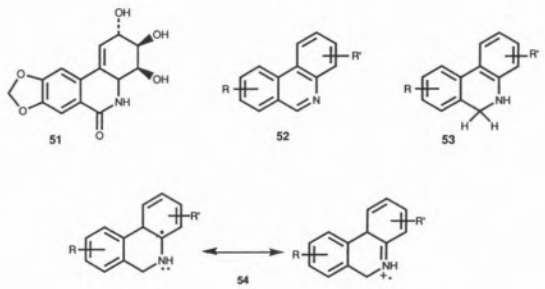
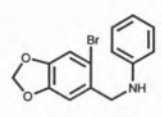
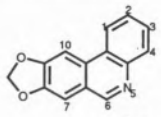
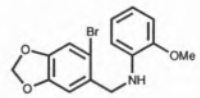
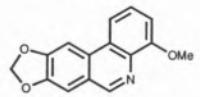
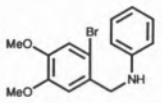
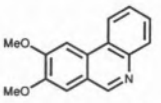
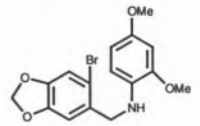
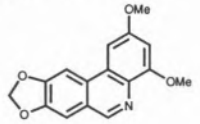
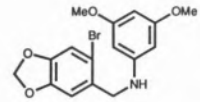
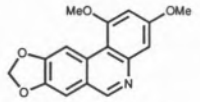
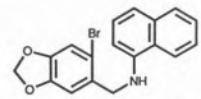
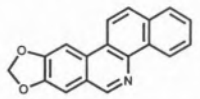


Table VI

Polyalkoxyphenanthridines by Radical Aryl-Aryl Coupling

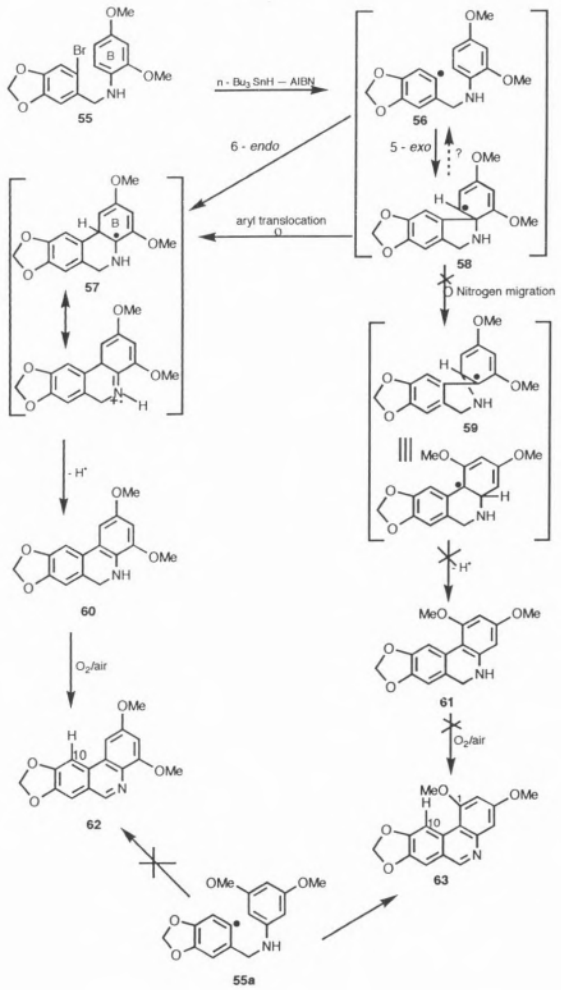
Entry	$ArCH_2NHAr'$	Phenanthridine	Yield[a] (%)
1			66
2			63
3			68
4			67
5			62
6			70

[a] Represents yields of products obtained after evaporation of the solvent, washing the residue with cold *n*-pentane, followed by chromatography on SiO_2 to separate small amounts of unreacted starting material and debrominated product (total 15%).

N-(*o*-bromobenzyl) anilines. The expectation that the cyclisation would be facilitated by the additional stabilization of the putative intermediate radical **54** was fully realized (*cf.* Scheme XIX).[29] A variety of polyalkoxyphenanthridines[30] **52**, by radical aryl-aryl coupling and subsequent aerial oxidation of the initially formed 5,6-dihydrophenantridines **53**, was obtained in synthetically useful yields (Table VI).

Taking the example (entry 4; Table VI) the addition of the *sigma* aryl radical formed **56** (Scheme XX) to the vicinal aromatic ring B, can, in principle, operate via a 6-*endo* cyclisation to yield the radical **57** or alternatively via a 5-*exo* mode to generate radical **58** (*ipso* substitution). The latter can suffer an aryl translocation to generate species **57** or rearrange, involving the nitrogen atom to produce a new cyclohexadienyl radical **59**. Both these radicals **57** and **59**, on loss of a hydrogen atom would lead to the dihydrophenanthridines **60** and/or **61** and thence, by aerial oxidation, to the heterocycles **62** and/or **63**. A careful analysis of the ^1H NMR spectra of the two isomeric phenantridines **62** and **63** (entries 4 and 5 respectively, in Table VI) provided a definitive answer to the question as to which of the two possible mechanisms was operating. It is well known that a methoxy substituent at C-1 in a phenantrene molecule[31] causes a pronounced diamagnetic deshielding of the proximate C-10 hydrogen. Whereas in the phenanthridine **63** (entry 5) the C-10 hydrogen resonates at Δ 8.81 as a sharp one proton singlet, in the isomeric phenanthridine **62** (entry 4) the same hydrogen possessed a normal chemical shift value (Δ 7.61, 1 H , singlet). Thus the absence, among the products isolated in the cyclisation of **55** (Scheme XX) of product **63**, strongly suggests that radical **57** is in the reaction pathway, and may originate directly from **56** or indirectly from **58**, via an aryl translocation. Similarly **55a** (Scheme XX, bottom) gave solely the phenanthridine **63**. This observation shows convincingly that the formation of phenanthridines is regiospecific and *does not involve a nitrogen to carbon migration in the initially formed spirocyclohexadienyl radicals,* if indeed they are formed.

Scheme XX



3.2. Applications in the Synthesis of Amaryllidaceae *Alkaloids*

Amaryllidaceae alkaloids represent a family of alkaloids of wide structural variety, and many of these have interesting biological properties.[32]

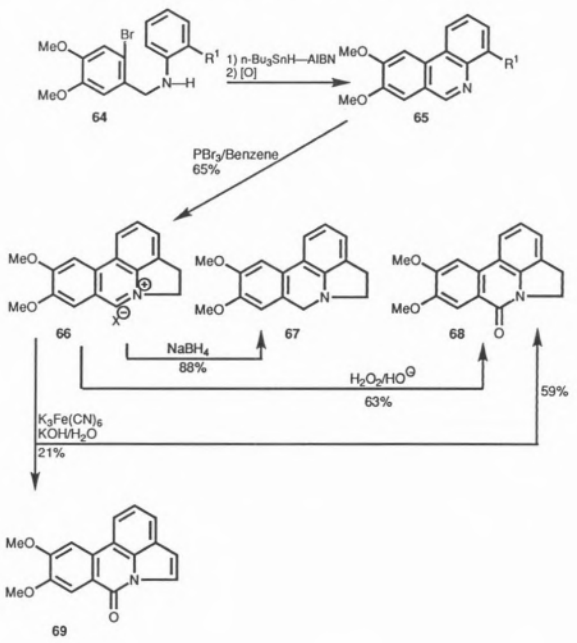
Application of the radical reaction previously described to **64** (R^1=CH_2CH_2OH) (*cf.* Scheme XXI) led to the synthesis of the functionalised phenanthridine **65**. With the use of appropriate reagents[33] , the intermediate **65** (R^1=CH_2CH_2OH) could be made to yield vasconine[34] (**66**), assoanine[35] (**67**), oxoassoanine[35] (**68**) and pratosine[36] (**69**). Extension of the method to the benzyl phenyl ether **70** (cf. Scheme XXII) yielded as the sole isolable product the benzopyran **71** (48%), probably arising from a *6-endo* ring closure. However, the aminobenzyl ether **72** (Scheme XXIII) easily prepared in excellent yield from simple starting materials, afforded in one step N-*nor*ismine **74** (26%), accompanied by the phenanthridine **75** (8%), the debromo compound **76** (10%) and the benzopyran **77** (10%).

The significant preponderance of products derived from the *5-exo* process (Scheme XXIII) at the expense of the *6-endo* mode in the cyclisation of **72** lends weight to our contention that a carbon centered radical adjacent to an amino group such as in **73** is indeed substantially stabilized.

Since we had earlier[37] devised an efficient method to convert N-*nor*ismine to the interesting alkaloid ismine **78** , this method provides an alternative and shorter synthesis of this natural product.

Scheme XXI

Synthesis of Amaryllidaceae Alkaloids



Scheme XXII