Syntheses of Physiologically Active Azaheterocycles by Electrophile-Induced Cyclisation Reactions

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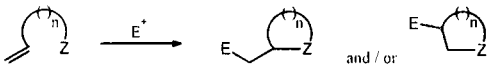
The electrophile-induced reaction of an olefin **1**, carrying a remote heteroatom Z, to produce heterocycles of type **2** or **3** is a well-established process in synthetic organic chemistry [1-4]. This process is well-known for oxygen derivatives (Z = O) but gives some problems with nitrogen compounds. If the *N*-substituent in an alkenylamine is equal to hydrogen or an alkyl group, in other words, if it concerns primary and secondary alkenylamines, then the reaction with electrophiles does not always lead to azaheterocycles because of several side reactions. The aminomercuration of alkenylamines offers sometimes an alternative but utilizes toxic organomercurials as intermediates. Therefore, a variety of *N*-protecting groups have been introduced already in alkenylamines in order to circumvent these problems. Protective groups such as alkoxycarbonyl, acyl, tosyl, *etc.*, have been used. In addition, various related protected alkenylamines, *e.g.* ureas, thioureas, imidates, thioimidates, *etc.*, have been evaluated with variable success.

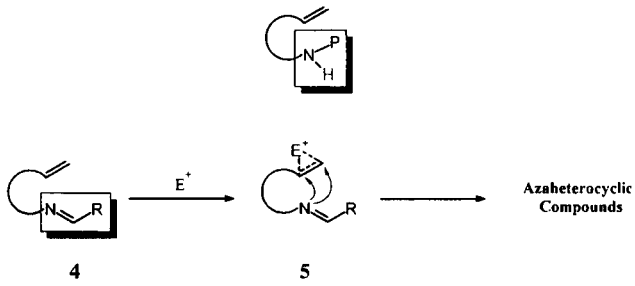
Scheme 1



1 **2** **3**

It is surprising to note that imines have never been used as protective group for the amino function in ω-alkenylamines. In the present investigation, it will be evaluated if *N*-(ω-alkenyl)imines **4** are substrates for the synthesis of azaheterocycles *via* electrophile-induced cyclisation reactions. It will be verified if the imino function in compounds **4** tolerates the presence of electrophiles (E^+) and if the imino function is nucleophilic enough to bring about cyclisation at the stage of the onium species **5**.

Scheme 2



4 **5**

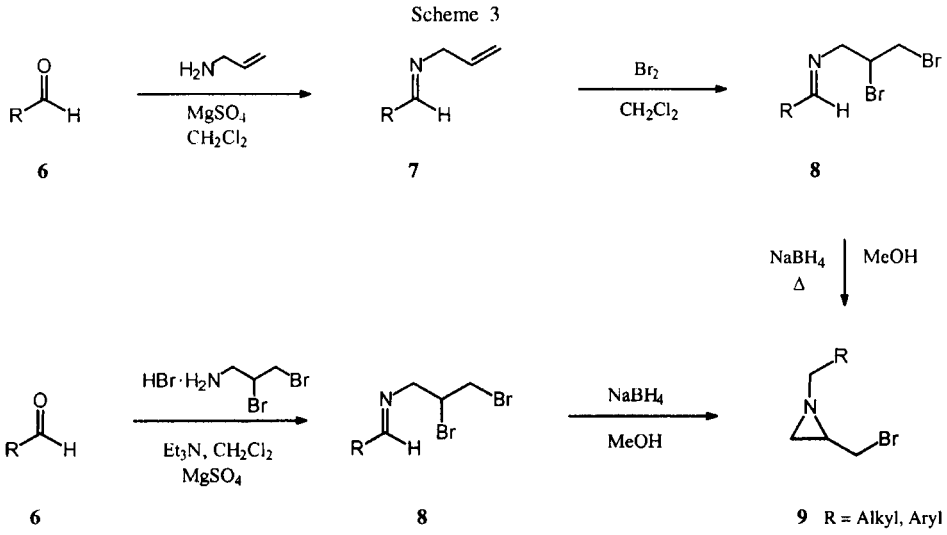
Some examples of *N*-allyl-, *N*-homoallyl- and *N*-bishomoallylimines will be worked out in the direction of a variety of *N*-heterocyles. Some of the resulting azaheterocycles have a potential use in the field of antiepileptics, antibiotics, pesticides and insect repellents. A final example of the synthetic potential of the title cyclisation reaction will be presented by the enantioselective total synthesis of the *Nitraria* alkaloid (-)-nitramine.

The first substrates studied are *N*-(allyl)imines **7** which react with bromine in dichloromethane to give rise to the dibromoimines **8**. Alternatively, dibromoimines **8** can be synthesized from aldehydes **6** and 2,3-dibromopropylamine hydrobromide in the presence of triethylamine. The reaction of *N*-(alkylidene or arylidene)-2,3-dibromopropylamines **8** with sodium borohydride in methanol under reflux gives rise to 2-(bromomethyl)aziridines **9**.

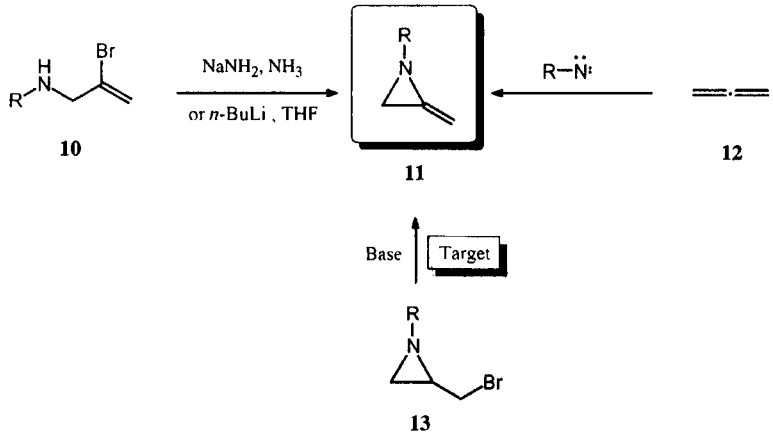
These 2-(bromomethyl)aziridines are suitable sources for the highly strained 2-methyleneaziridines **11** by base-induced 1,2-dehydrobromination. 2-Methyleneaziridines **11** are known to undergo valence tautomerism with isomeric 2-methyleneaziridines and cyclopropylideneamines, the nitrogen analogues of cyclopropanones. According to the literature, 2-methyleneaziridines are accessible from the cycloaddition of allenes with nitrenes or, preferably, by reaction of *N*-(2-bromo-2-propenyl)-amines with sodium amide in ammonia or *n*-butyllithium in tetrahydrofuran [5].

The 1,2-dehydrobromination of 2-(bromomethyl)aziridines **9** is limited to a few combinations of bases and solvents. Potassium *t*-butoxide in THF dehydrobrominates compounds **9** to afford 2-methyleneaziridines **14** in 40-48% yield, always accompanied by the substitution products **15**.

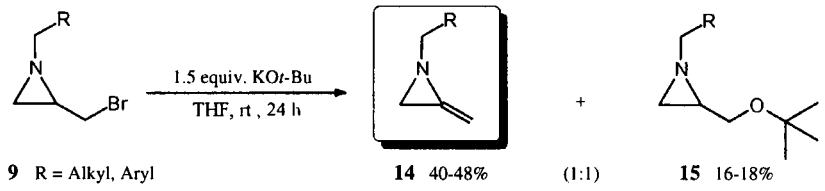
Scheme 3

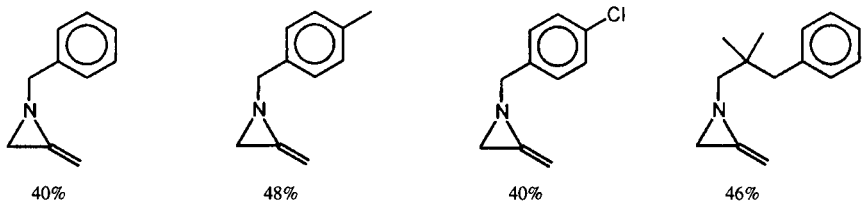


Scheme 4



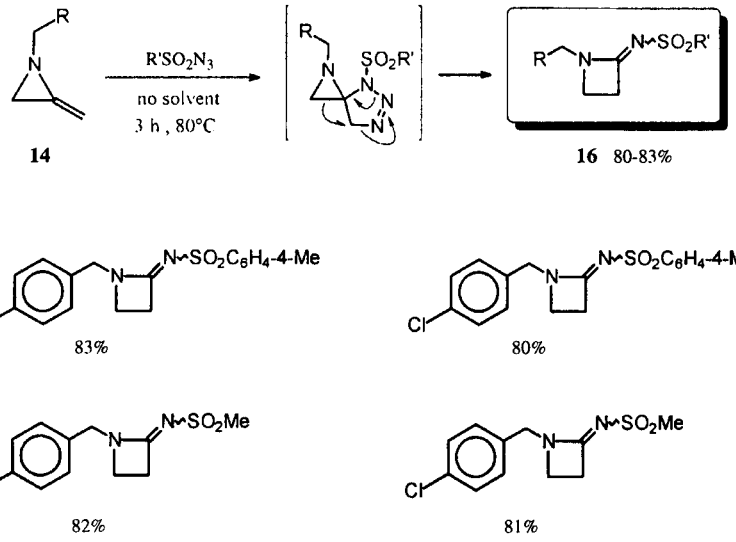
Scheme 5





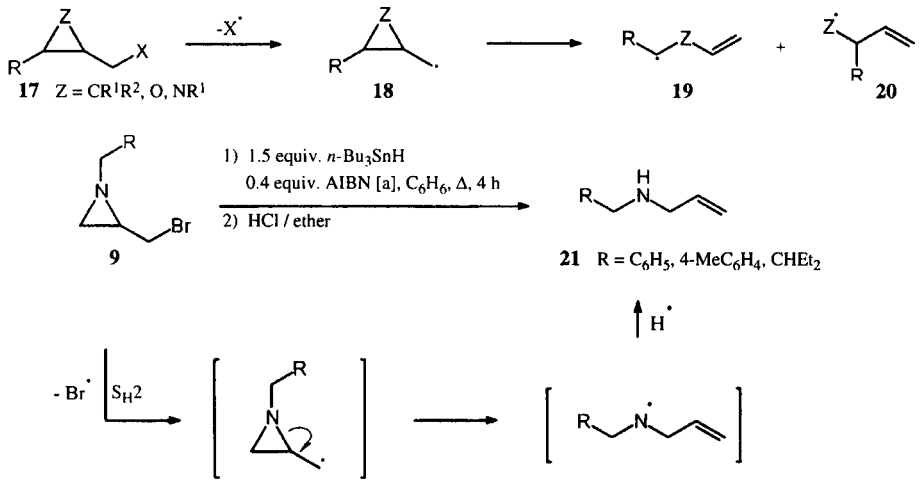
2-Methyleneaziridines **14** are suitable substrates for ring expansion with azides, carrying an electron-withdrawing group, to produce 2-iminoazetidines **16** *via* the intermediacy of spirotriazolines. Contrary to 2-methyleneazetidines, which react with sulfonylazides to give four-membered ring amidines by expulsion of diazomethane, 2-methyleneaziridines loose the elements of nitrogen during the ring expansion.

Scheme 6



Three-membered rings **17**, substituted with a CH_2X moiety by which X can easily be splitted off *via* a homolytic process, undergo a ring opening reaction, either leading to the Z-centered radical **20** or the carbon-centered radical **19**. This process is well-known for cyclopropanes **17** (Z = CR^1R^2) or oxiranes **17** (Z = O), but is rather unknown for aziridines **17** (Z = NR^1), apart from some exceptions. 2-(Bromomethyl)aziridines **9** undergo radical cleavage with tributyltin hydride in the presence of AIBN *via* the formation of a carbon-centered radical which rearranges to a ring-opened aminyl radical, finally affording *N*-allylamines **21**. This synthetically unattractive synthesis of *N*-allylamines **21** can be directed in a cascade of radical reactions if a radical intercepting olefinic double bond is positioned at the right place in the nitrogen substituent. The homolytic cleavage of the carbon-bromine bond in 1-alkenyl-2-(bromomethyl)aziridines **22** can generate radicals **23** and **24** as discussed above. The undesired capture of a hydrogen leading to **25** becomes less

Scheme 7



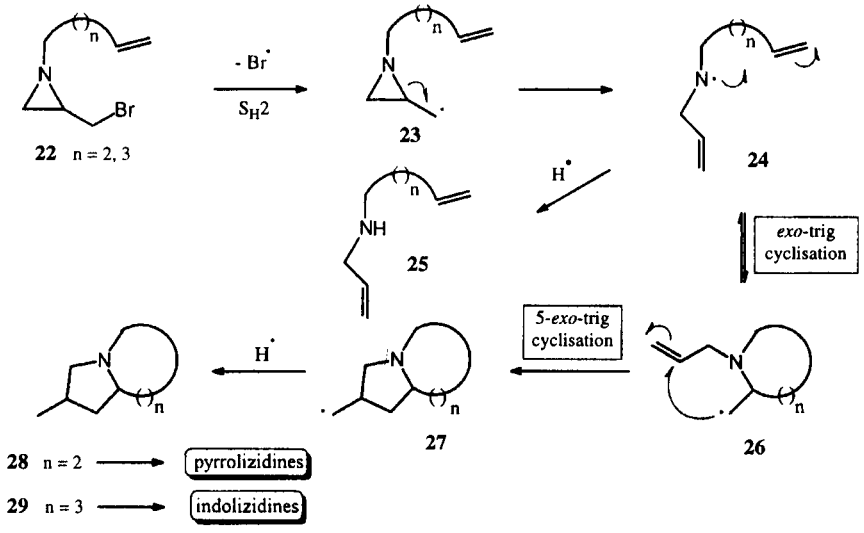
[a] AIBN: 2,2'-Azobisisobutyronitrile.

favourable if the aminyl radical **24** can cyclise according to an *exo*-trig process to azaheterocycle **26**, which holds a new carbon-centered radical. The latter radical can further give rise to a subsequent cyclisation onto the *N*-allyl substituent, generated *in situ* from the 2-(bromomethyl)aziridine moiety in the starting substrate. As such, the latter 5-*exo*-trig radical cyclization affords radical **27** which captures a hydrogen atom to afford bicyclic azaheterocycles **28** or **29**. This cascade of radical reactions offers the potential to synthesize pyrrolizidines **28** (n = 2) or indolizidines **29** (n = 3) according to an attractive set of domino reactions. Efforts were undertaken to verify if this construction of interesting bicyclic azaheterocycles **28** and **29** could be worked out in competition with undesired reactions leading to *N*-alkenyl-*N*-allylamines or *N*-allylazaheterocycles.

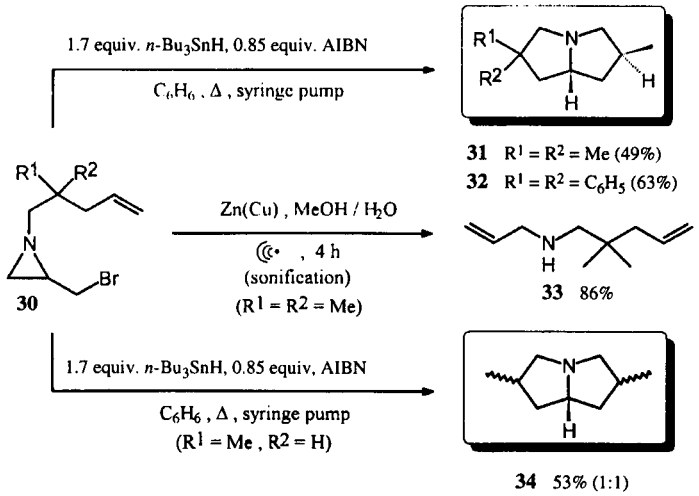
Preliminary results of the radical cascade cyclisation of 1-(4-alkenyl)-2-(bromomethyl)aziridines **30** with tributyltin hydride in the presence of AIBN in benzene under reflux indicate the pronounced synthetic potential by the synthesis of pyrrolizidines **31** and **32** in 49-63% isolated yield [6]. The process shows no stereoselection as found in the synthesis of pyrrolizidine **34** which was obtained as a 1:1 mixture of stereoisomers. Sonification of compounds **30** in aqueous methanol in the presence of an activated zinc/copper couple leads to opening of the aziridine ring but does not give rise to azaheterocyclic compounds. Only pyrrolizidines were synthesized and all attempts to synthesize indolizidines failed up to now.

The interest in this efficient domino reaction stems from the fact that a variety of pyrrolizidines and indolizidines are naturally occurring compounds, found in

Scheme 8

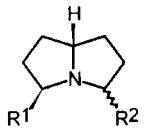


Scheme 9



poison frogs (*Dendrobates spp.* and *Melanophryniscus spp., e.g.* **35**), establishing a blocking activity of neuromuscular transmission.

Scheme 10



35 $R^1 = R^2 = n$-Bu
$R^1 = n$-Heptyl, R^2 = Me
$R^1 = n$-Bu, $R^2 = n$-Hexyl

With a suitable substitution pattern in the *N*-allyl substituent, imines **36** can easily be functionalized to **37** with *N*-bromosuccinimide in an alcohol to produce 3-alkoxyazetidines after a final hydride reduction. As such, it opens ready possibilities towards the synthesis of 3-oxygenated azetidines with anticonvulsant and antiepileptic properties.

compounds are suitable building blocks for further elaboration, as exemplified by the synthesis of 3-aminopyrrolidine **45** and 3-pyrroline **46**.

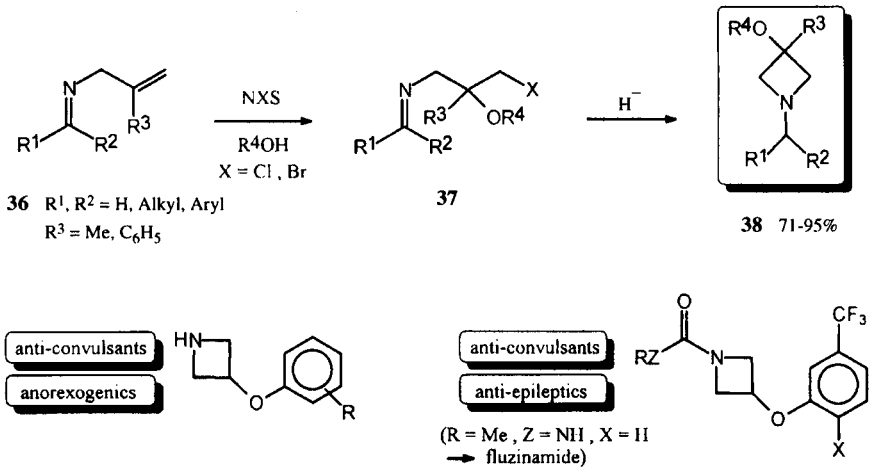
1-Benzyl-3-phenylpyrrolidine **52**, being the prototype of 3-arylpyrrolidines, was prepared by a set of reactions involving Claisen-rearrangement of cinnamyl alcohol **47**, modified Curtius-type rearrangement, carbamate cleavage, imination and electrophile-induced cyclisation, terminated by a reduction of the intermediate iminium salt and final radical removal of the bromo substituent in the stereoisomeric pyrrolidines **50** and **51**.

The isomeric 1-benzyl-2-phenylpyrrolidine **58** was prepared likewise from the homoallylic imine **54** *via* iminium salt formation **55**, reduction and radical reductive removal of the bromosubstituents in stereoisomers **56** and **57**.

All the pyrrolidines reported above are of interest from the viewpoint of the novel antibiotic quinolones **59** (Y = CH, CF, CBr, CCl) and naphthyridones **59** (Y = N), their use as potential agents for improvement of cognitive performances of Alzheimer's desease patients (*cf.* **60**) and their fungicidal activities (*cf.* **61**).

In order to prove the synthetic potential of the electrophile-induced cyclisation of *N*-(alkenyl)imines, the enantioselective synthesis of the *Nitraria* alkaloid

Scheme 11



36 R^1, R^2 = H, Alkyl, Aryl
R^3 = Me, C_6H_5

37

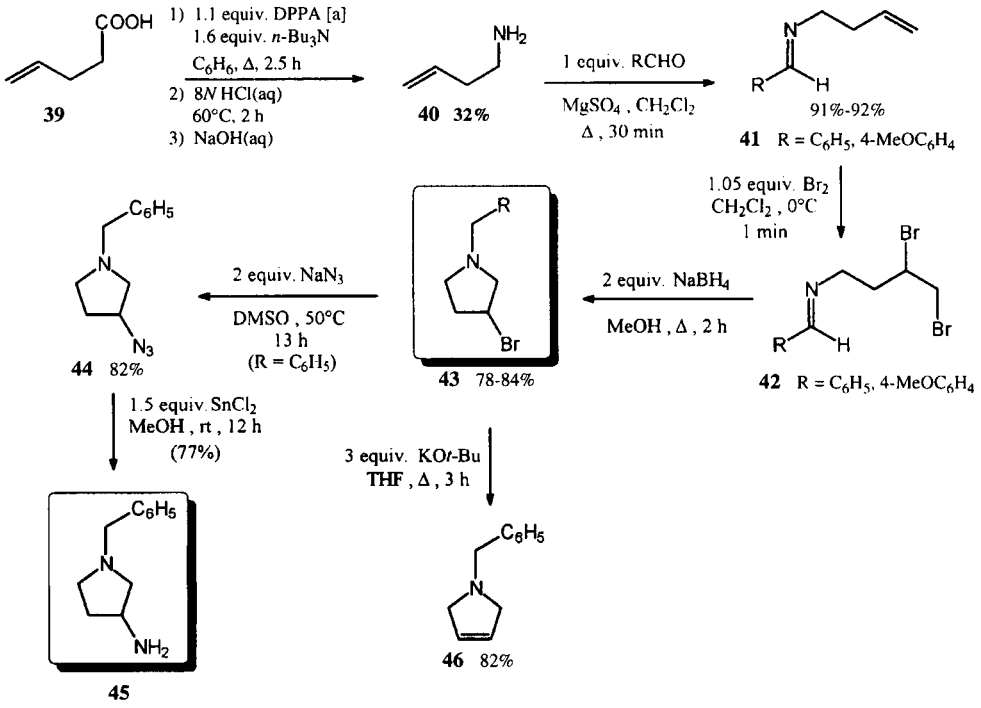
38 71-95%

N-(Homoallyl)imines **41** have the potential to react with electrophiles and nucleophiles in a subsequent fashion to afford either functionalized azetidines or functionalized pyrrolidines.

N-(Homoallyl)imines **41** are accessible from 4-pentenoic acid **39** *via* a modified Curtius rearrangement utilizing diphenylphosphorazidate and subsequent imination. The bromination of homoallylimines **41** gives rise to adducts **42** which cleanly react with sodium borohydride in methanol to give 3-bromopyrrolidines **43**. The latter

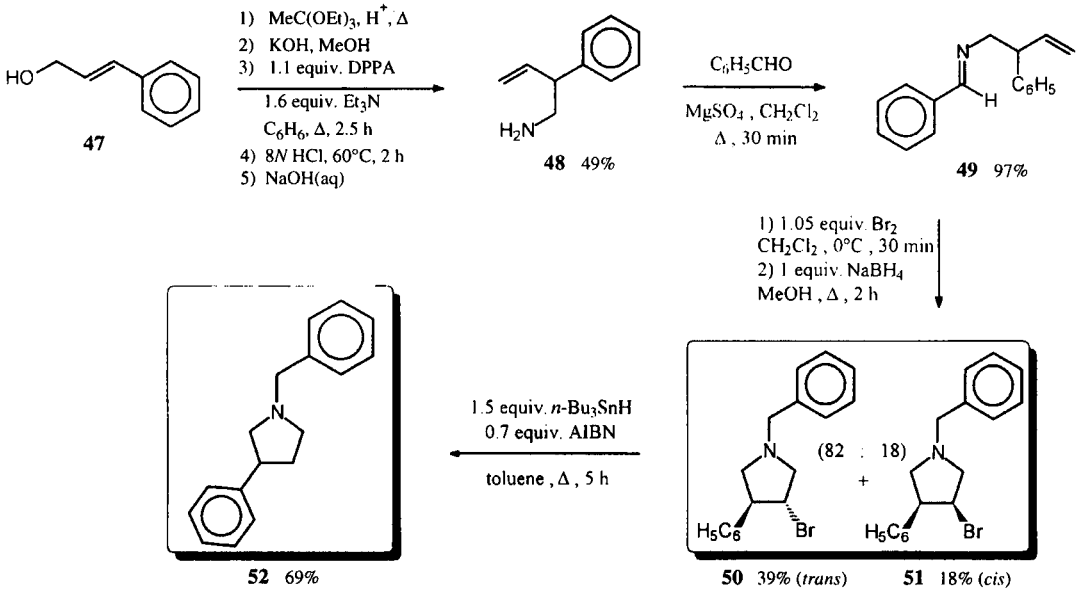
nitramine was worked out. The interest in 2-azaspiroalkaloids of *Nitraria* stems from their structural similarity with the neurotoxic histrionicotoxins **62** [7]. Retrosynthetically, the synthesis of (-)-nitramine **63** can be brought back to bishomoallyl imine **64**, which holds the right stereochemistry and *O*-protection. The required β-hydroxyester **65** was synthesised from reduction of ethyl cyclohexanone-2-carboxylate with *Saccharomyces cerevisiae*. By chelate-controlled α-allylation of (1*R*,1*S*)-β-hydroxyester, followed by *O*-protection, conversion of the ethyl ester unit

Scheme 12



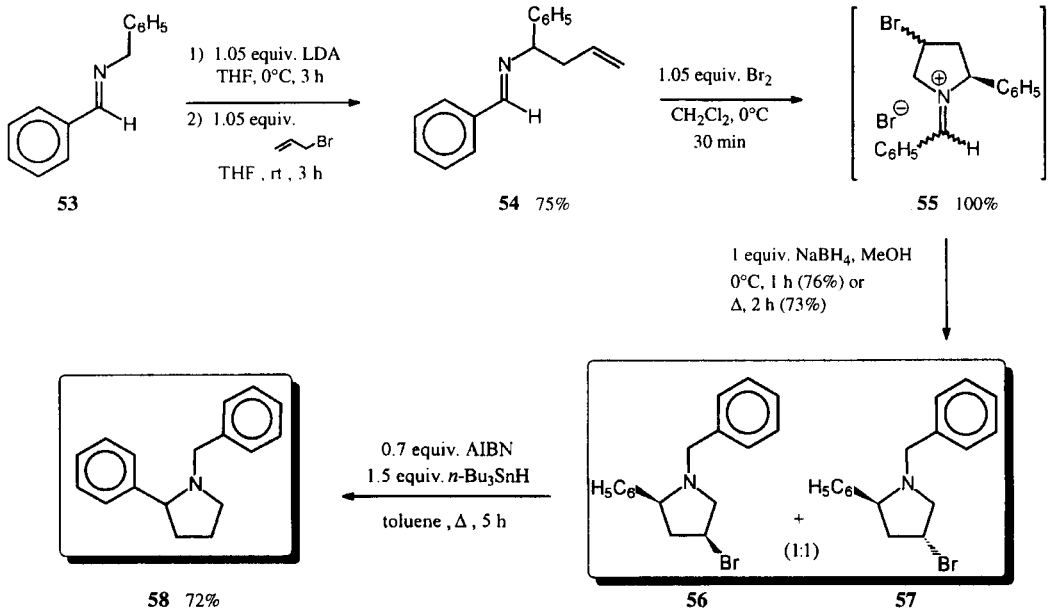
[a] DPPA: Diphenylphosphoryl azide.

Scheme 13



into an imidoyl moiety and final transamination, the target starting material **64** was prepared. However, the electrophile-induced cyclisation reaction, followed by reduction and hydrolysis, lead to a disappointingly low yield of the desired (-)-*N*-benzylnitramine **67** from which (-)-nitramine was obtained by hydrogenolysis. The relatively too high amount of 2-azaspiropyrrolidines **65** and **66** is probably due to stereoelectronic effects of the *O*-THP group, which influences the ring opening of the intermediate bicyclic aziridinium ion **68** in such a way that the ratio 2-azaspiropiperidine *vs.* 2-azaspiropyrrolidine lowers to 1:5.

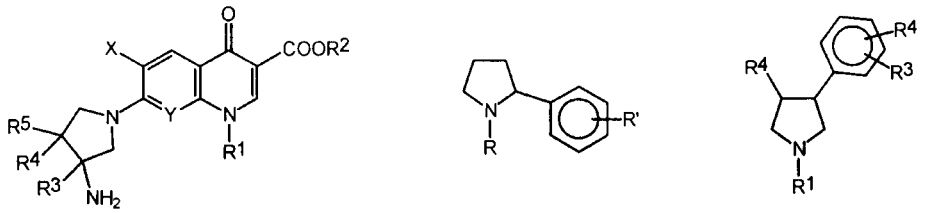
Scheme 14



53 **54** 75% **55** 100%

58 72% **56** **57**

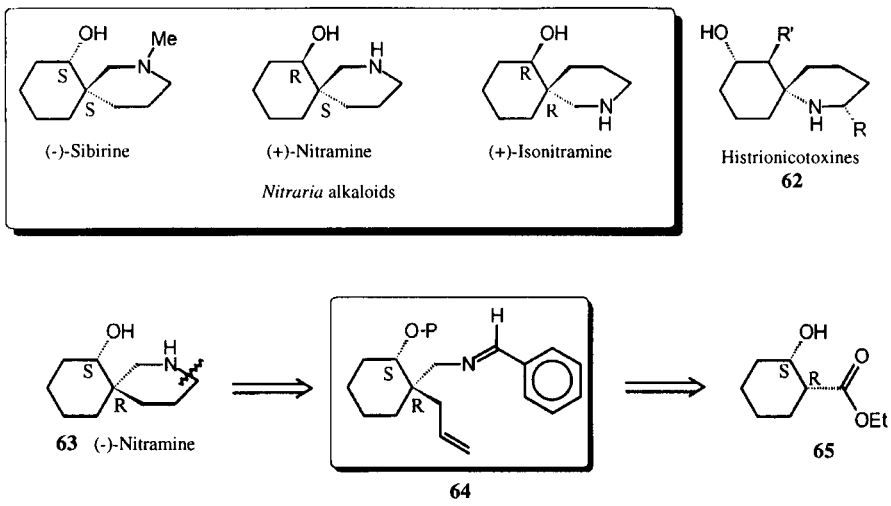
Scheme 15



59 R^1, R^2, R^3, R^4, R^5 = Alkyl, Cycloalkyl, Aryl, ...
X = Halogen
Y = CH, CF, CBr, CCl, ... (Quinolones)
Y = N (Naphthyridones)

60 **61**

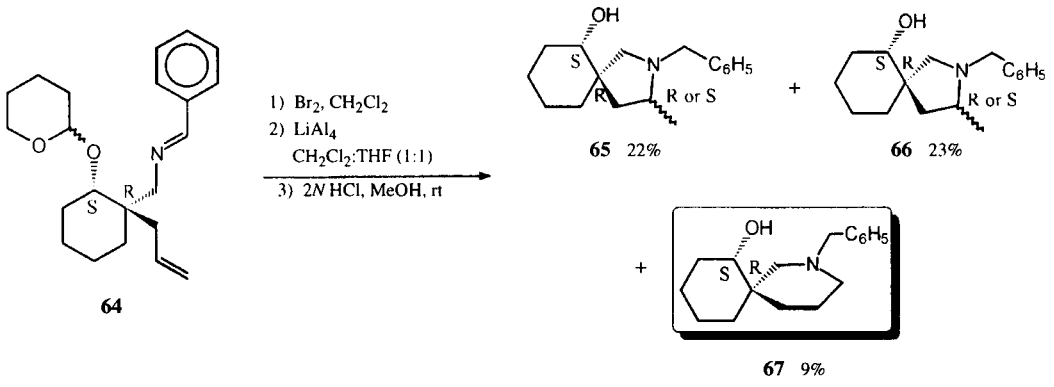
Scheme 16



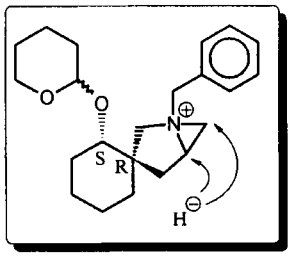
62

63 (-)-Nitramine **64** **65**

Scheme 17



Scheme 18



This unforseen low yield in the synthesis of (-)-nitramine *via* the electrophile-induced cyclisation of a suitable bishomoallylic imine forced us to follow an alternative route, in which (1*S*,2*S*)-ethyl-1-allyl-2-hydroxycyclohexanecarboxylate was converted into a (5*R*,6*S*)-spiropyrroline *via* cycloaddition of the azide moiety across the olefinic double bond and subsequent rearrangement with hydride shift and nitrogen expulsion.

The final ring transformation of the chiral spiropyrroline into (6*R*,7*S*)-7-benzyloxy-2-azabicyclo[5.5]undecane was accomplished *via* α,α,α-trichlorination with *N*-chlorosuccinimide and reaction with lithiumaluminium hydride. The latter rearrangement is explained *via* the intermediacy of a bicyclic dichloroaziridine, an azirinium chloride and an α-imidoylcarbenium ion. (-)-Nitramine **63** was obtained in good yield with an enantiomeric excess of 95% by hydrogenolysis of spirocompound thus obtained.

The present overview shows that the electrophile-induced cyclisation of *N*-alkenylimines and subsequent reductive treatment offers a great synthetic potential in the synthesis of functionalized aziridines, azetidines, pyrrolidines and piperidines.

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