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INTRAMOLECULAR REACTIONS OF N-ACYLIMINIUM INTERMEDIATES

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1.1 1.2

Scheme 1.

A. INTRODUCTION

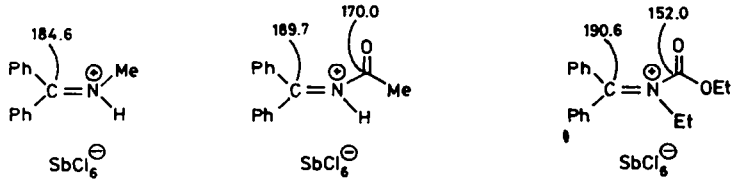
Progress in the art of organic synthesis in the last decades has been achieved by marked advances in chemo-, regio- and stereoselectivity of classical and newly developed reagents. Well known in the former respect are the Mannich reagent (**1.1**) and the amidoalkylating reagent (**1.2**) of which the latter—also called N-acyliminium ion—had been designed primarily to allow Mannich-type condensations with primary amines.[1] It soon appeared however, that the N-acyliminium ion has highly versatile reaction characteristics in a much broader sense, which is now reflected in an impressive number of synthetic applications. Most of these reactions are of the *intermolecular* type and have been reviewed comprehensively.[2,3] A new dimension in the reactivity and selectivity pattern of amidoalkylative reagents emerged from the study of intramolecular processes. In this Report emphasis will be given on the *intramolecular carbon–carbon bond forming* reactions of N-acyliminium ions **1.2**. Quite remarkably, this type of process has not been reviewed before and consequently several older references are also included. Moreover, the recognition of the reaction principle in a few of the seemingly unrelated areas will help to assess the scope of the intramolecular process. Finally, since novel pathways have been developed for the synthesis of precursors for **1.2** a separate section on the preparation of the N-acyliminium intermediate is also included.

For substituents R^1, R^2 and R^3 only aryl, alkyl and hydrogen will be considered while R^4 may be a carbon- or heterosubstituent.

B. GENERAL

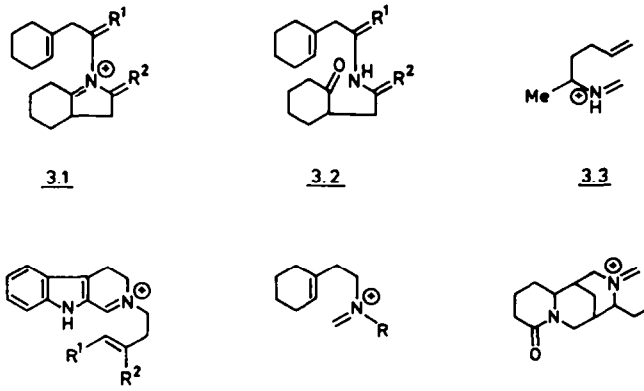
B.a. *Reactivity of* N-*Acyliminium vs Iminium Ions*

The presence of a strongly electron withdrawing carbonyl group leads one to expect that the imino carbon atom in the amidoalkylating reagent **1.2** is more electron-poor than in the Mannich reagent **1.1**. Recently, this expectation was borne out for iminium salts **2.1** and **2.2** by comparison of their ^{13}C-NMR spectra.[4a,b] Substitution of an N-methyl by an N-acetyl group leads to a down-field shift of the imino carbon absorption of about 5 ppm. The carbamate derived N-acyliminium ion **2.3** exhibits its imino carbon absorption also around 190 ppm.[4c] Thus, one may anticipate that N-acyliminium ions are more electrophilic, i.e. more reactive than iminium ions.[5] However, quantitative data, i.e. mechanistic and/or kinetic investigations with intentional comparison of reactivities of the two types of reagents have not been published as far as we know. Qualitatively, it is known, that in intermolecular arylation, Mannich reagents only react with strongly activated aromatics (e.g. phenols)[6] whereas amidoalkylation even succeeds with extremely poor nucleophiles like nitrobenzene.[2] A nice illustration of the difference in reactivity in intramolecular reactions is the result on olefin cyclizations obtained in Erythrina alkaloid synthesis. Both N-acyliminium ions **3.1** (R^1 = O, R^2 = H_2[7] and R^1 = H_2, R^2 = O)[8] generated from the respective keto amides **3.2** gave the expected cyclization product. In contrast, attempted ring



2.1 2.2 2.3

Scheme 2.



3.1 3.2 3.3

3.4 a $R^1 = H$ $R^2 = H$
b $R^1 = Me$ $R^2 = H$
c $R^1 = H$ $R^2 = Me$

3.5 3.6

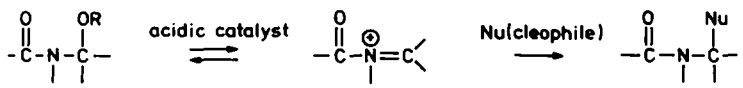
Scheme 3.

closure of the iminium salt **3.1** ($R^1 = R^2 = H_2$) led to unidentifiable products.[8] Other iminium systems such as **3.3**,[9] **3.4a**[10] and **3.4b**[10] also failed to undergo cyclization. Comparable N-acyliminium systems are expected to readily cyclize as will become apparent in Section D. Care must be taken, however, not to overestimate the reactivity difference between **1.1** and **1.2**, since cyclization of **3.4c**[10] and **3.5**,[11] where tertiary carbenium ions occur as intermediates, proceed smoothly. Even **3.6**[12] has been reported to cyclize in good yield, despite the low nucleophilicity of a monosubstituted double bond. Therefore, the actual differences in reactivity between iminium and N-acyliminium ions are not always obvious. One should realize here that these olefin cyclization reactions are in principle reversible processes, the reverse reaction being a Grob fragmentation.[13] The product of an N-acyliminium–olefin cyclization, being an amide, is much less susceptible to fragmentation, than the product of an iminium–olefin cyclization, which is an amine. Therefore, the greater usefulness of N-acyliminium ion cyclizations in organic synthesis may primarily be attributed to their irreversibility.

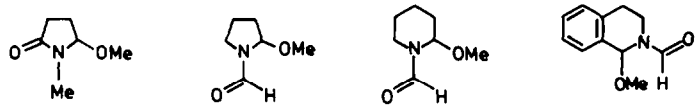
B.b. *Mechanistic Aspects; Structure vs Reactivity of* N-*Acyliminium Ions*

For application in elaborate organic syntheses, N-acyliminium ions are almost always generated *in situ*, in view of their limited stability and high reactivity. The various ways for their preparation will be treated in a systematic fashion in Section C. Some general features of the chemistry of N-acyliminium ions are discussed here.

The mechanistic scheme which applies to most amidoalkylation reactions is shown in Scheme 4. A precursor is in equilibrium with an N-acyliminium ion through the influence of an acidic catalyst. The nucleophile then reacts in an irreversible process with the N-acyliminium ion to yield the product. This scheme closely resembles the S_N1 process. Zaugg and Martin distinguish two extreme kinetic situations, namely (i) the formation of the N-acyliminium ion is rate-limiting and (ii) the reaction with the nucleophile is rate-limiting.[2a] The former case implies that a more stable N-acyliminium ion leads to a faster reaction, whereas in the latter case the opposite is true. It has been found, that this latter case applies to reactions of α-hydroxymethyl amides with relatively unreactive aromatic nucleophiles carried out in strongly acidic media like concentrated sulfuric acid.[2a] With more reactive nucleophiles, however, mildly acidic conditions will suffice to induce reaction. This situation, with the formation of the N-acyliminium ions as the rate-limiting step, probably pertains to much more elaborate synthetic



Scheme 4.



5.1 5.2 5.3 5.4

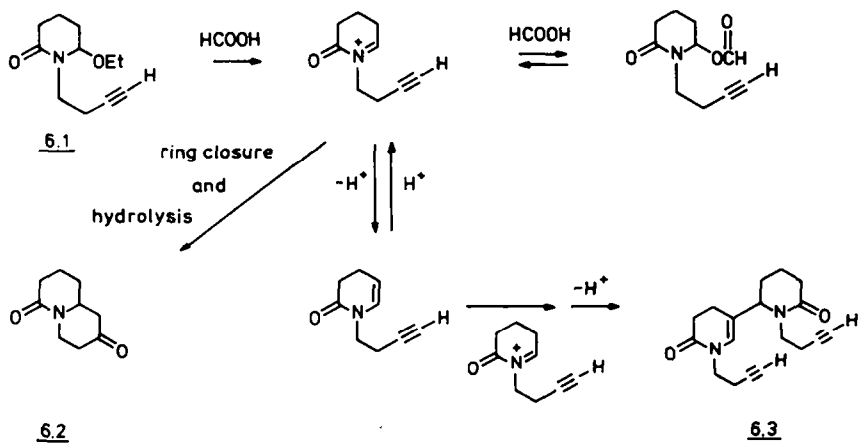
Scheme 5.

applications, especially the intramolecular variant. However, absolute kinetic information pertinent to this type of amidoalkylation is unavailable, as far as we know.

Some data on relative reaction rates depending on structural variations were recently published by Malmberg and Nyberg.[14] They determined by way of competition experiments the relative reactivities of methoxy amides **5.1**–**5.4** toward arylation with 1,3,5-trimethoxybenzene, catalyzed by $AlCl_3$. The order of reactivity appeared to be **5.1** : **5.2** : **5.3** : **5.4** = 30 : 4.5 : 1 : 200. The most stable ion might well be the one derived from **5.4** due to the favourable conjugation with the aromatic ring. The ion derived from **5.1** is probably more stable than the one from **5.2**, since in the former conjugation with the carbonyl is always present, whereas in the latter this is only the case in two carbonyl conformers. The ion derived from **5.2** is likely to be more stable than the one from **5.3**, because the presence of a double bond is energetically more favourable in a five-membered than in a six-membered ring. Thus, it seems that the order of reaction rates corresponds with the order of stability of N-acyliminium ions. This means that generation of these species is rate-limiting in the arylation reaction of **5.1**–**5.4**. More extensive kinetic experiments are needed to prove this conclusion.

The ease of formation of N-acyliminium ions by way of heterolysis of α-substituted amides depends, of course, also on the nature of the leaving group. The only more or less systematic study has been conducted for 4-substituted azetidinones. The following order of reactivity Cl > RCOO > RSO_2 > N_3 > R—O > R—S, was found for substitution reactions carried out under non-acidic conditions.[15] In an acidic medium this order will likely be different. The nature of the solvent and the structure of the acidic catalyst are also of great influence on the outcome of the amidoalkylation. For intramolecular reactions with olefins and acetylenes formic acid has been shown to be the best choice for serving both as acid and solvent.

An important side reaction in N-acyliminium ion chemistry is the formation of an enamide via loss of a proton. This reaction may be reversible in an acidic medium, but this is not always the case. Enamides may further react as a nucleophile with the N-acyliminium ions still present, to give dimeric structures.[16] These problems of enamide formation and subsequent side reactions arise, if the N-acyliminium ion is not trapped fast enough by a nucleophile. This may occur if the nucleophile is not very reactive, if there is too much steric hindrance, or in the case of intramolecular reactions, if stereoelectronic factors are unfavourable (anti-Baldwin processes) or if a medium-sized or large ring is to be formed. An example is the ring closure of acetylene **6.1**.[17] A 5 : 1 mixture of the desired product **6.2** and dimer **6.3** is obtained if the reaction of 0.5 mmol of **6.1** is carried out in 3 ml of formic acid. In a more



6.1 6.2 6.3

Scheme 6.

dilute solution (40 ml of formic acid) formation of **6.3** was not observed and only **6.2** was isolated in high yield. Thus, it appears that in this system enamide formation is reversible. It has further been found that the proclivity of N-acyliminium ions to form enamides depends on the nature of acidic catalyst and solvent.[16]

C. GENERATION OF N-ACYLIMINIUM IONS AND SYNTHESIS OF THEIR PRECURSORS

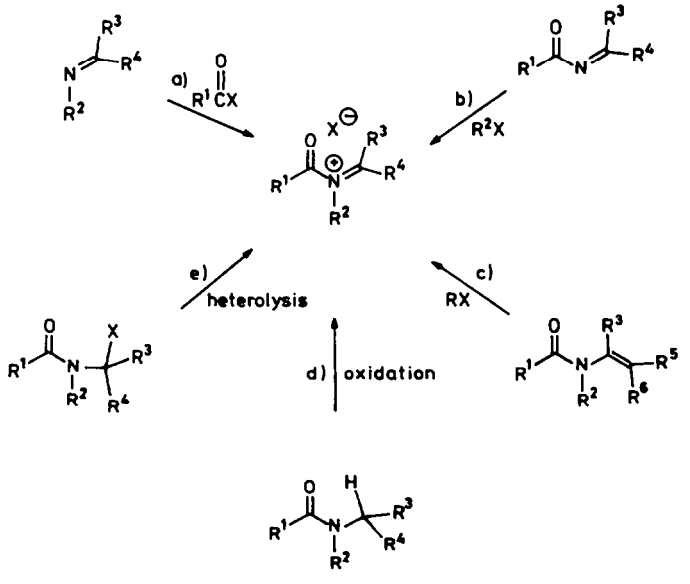
In 1965 Zaugg and Martin provided a detailed account on the generation of N-acyliminium ions and the synthesis of their precursors.[2a] In subsequent years some of these methods have been refined and new ones have been added. In this review we attempt to give an overview of the methods that now exist to arrive at N-acyliminium ions. This review is not intended to be exhaustive and only selective references are given.

There are five major synthetic pathways to N-acyliminium ions as shown in Scheme 7. In the sequel these various methods will be discussed. Aspects such as synthesis of the precursors and direct synthetic applications will receive appropriate attention.

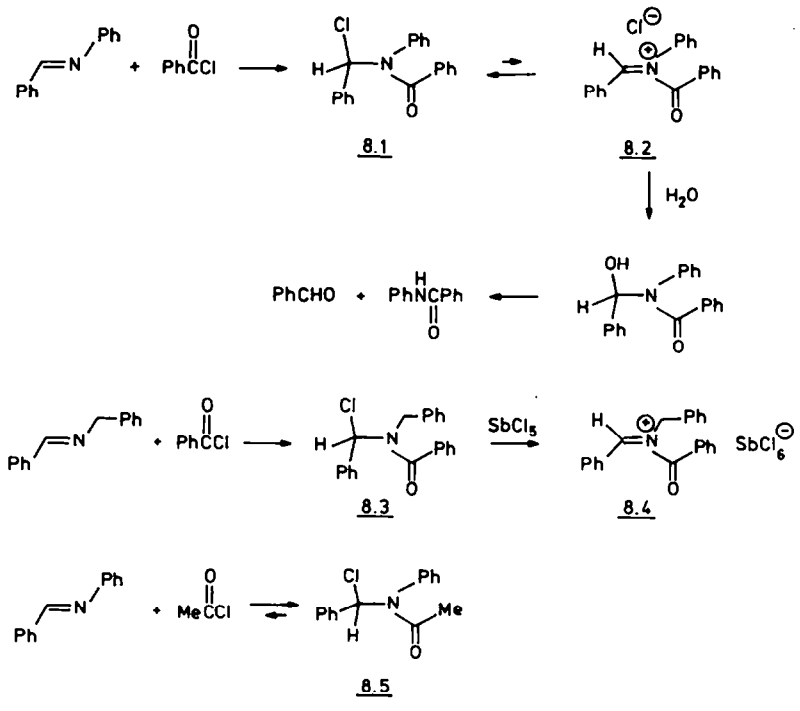
C.a. N-*Acylation of Imines* (*Schiff Bases*)

Imines are easily available in high yield by condensation of aldehydes or ketones with primary amines.[18] Their acylation with reactive carboxylic acid derivatives like acid chlorides or anhydrides was first reported in 1914, when James and Judd reacted benzalaniline with benzoyl chloride.[19] The crystalline product **8.1** was readily hydrolyzed in water to give benzaldehyde and benzanilide. The lability of the carbon–chlorine bond illustrates the propensity to N-acyliminium ion (**8.2**) formation in this system. The structure of the imine adduct is best represented, though, by the covalent structure **8.1**.[20,21] The really ionic structure (**8.4**) can be obtained from the adduct **8.3** by addition of antimony pentachloride.[4,22] The acylation of imines has been shown to be an equilibrium,[20,22] which shifts to the side of the adduct when the temperature is lowered. With ^{1}H-NMR it was determined[20] that in the reaction between equimolar amounts of benzalaniline and acetylchloride at 40°, 95% of the acetylchloride had been converted to the adduct **8.5**; at 65° the corresponding proportion was reduced to 90%. The position of the equilibrium will naturally be highly dependent on the structure of the imine and the reactive acid derivative, but no systematic study has been directed to this point.

The fate of the adduct, which is highly reactive, but has been isolated in some cases,[23] depends heavily on the structure of the starting imine. The most important applications are: (1) enamide formation, (2) synthesis of β-lactams and (3) trapping reactions with carbon and heteroatom nucleophiles.[24]



Scheme 7.



Scheme 8.

C.a.1. *Enamide formation*

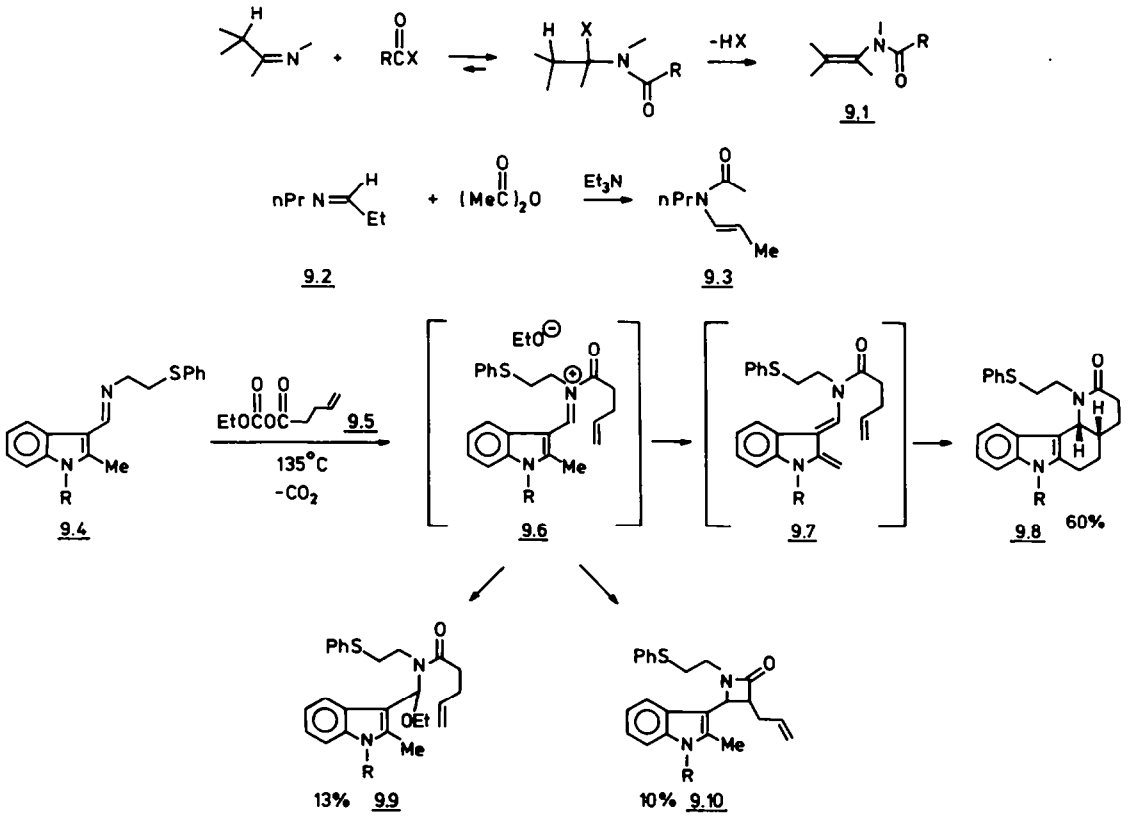
The acylation product of an imine transforms into an enamide **9.1** via elimination of HX. Breederveld[25a] showed, in 1960, that reaction of imine **9.2** with acetic anhydride in the presence of 1 equiv. of triethylamine in benzene at room temperature affords the enamide **9.3** in 75% yield. Using acetyl chloride the same product is obtained in a comparable yield.[25b] A review on the synthesis of enamides via acylation of imines has appeared in 1978.[26] Enamides themselves are useful precursors for N-acyliminium ions (Section C.c.).

In recent years Magnus *et al.* have made elegant use of a vinylogous variant of the enamide formation reaction for the synthesis of indole alkaloids.[27] Reaction of imine **9.4** with mixed carbonic anhydride **9.5** yields the N-acyliminium ion **9.6** which *in situ* is deprotonated by the basic ethoxide anion to diene amide **9.7**. This diene is an indole-2,3-quinodimethane and readily undergoes an intramolecular Diels–Alder reaction to tetracycle **9.8** in 60% yield from **9.4**.[28] In addition to **9.8** are obtained ethoxy derivative **9.9** and β-lactam **9.10**. The formation of **9.9** is the result of a rejoining of the ions in salt **9.6**. β-Lactam **9.10** can be envisaged to arise from a deprotonation α to the carbonyl group to give a zwitterion, followed by cyclization. This β-lactam formation is the subject of the next section.

C.a.2. *β-Lactam formation*

A general method for the synthesis of β-lactams is the reaction of imines with acid chlorides in the presence of triethylamine.[29,30] Although the mechanism of this process is still a matter of debate there is now ample evidence that zwitterion **10.1** is the crucial intermediate. Conrotatory electrocyclic ring closure leads to the β-lactam.[31–33] The zwitterion **10.1** can be formed via two different ways from the starting materials. The acid chloride can either be converted to the corresponding ketene before combining with the imine, or the acid chloride can first react with the imine to form an N-acyliminium ion, which is then deprotonated (Scheme 10). Which mechanism is operative, probably depends to a certain extent on the sequence with which the three reagents are combined. The way of performance of the reaction indeed has a great influence on the stereochemistry of the process.[20,34–36] It is beyond the scope of this report to discuss these various aspects of β-lactam formation. Suffice it to note that it is the most simple intramolecular reaction of N-acyliminium ions.

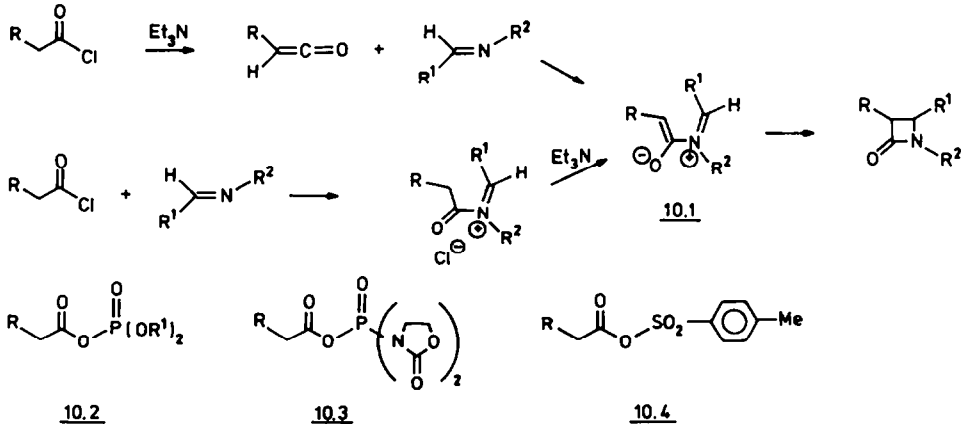
Recently, various other reactive acid derivatives have been used in β-lactam formation, namely **10.2**,[37,38] **10.3**,[39] and **10.4**.[40] These compounds are made *in situ* and sometimes have advantages over simple acid chlorides.



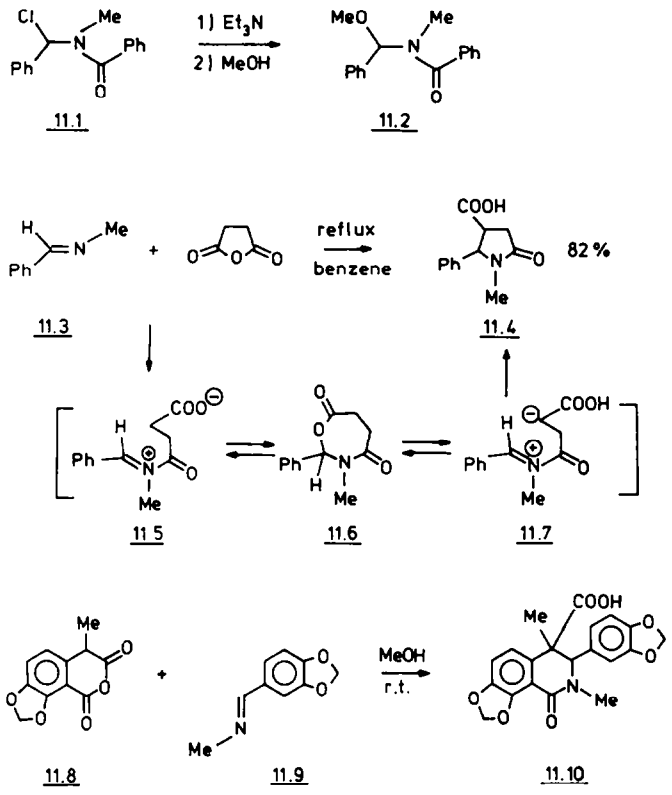
Scheme 9.

C.a.3. *Trapping reactions with carbon and heteroatom nucleophiles*

The acylation products of imines with acid chlorides have already a distinct N-acyliminium ion character, in view of their ready hydrolysis (Scheme 8). Böhme and Hartke[23] showed that **11.1** can be converted to the more stable methoxy amide **11.2** in high yield with methanol in the presence of triethylamine. Various intermolecular reactions with carbon nucleophiles have been reviewed elsewhere.[2] In the sequel of this section a special intramolecular alkylation reaction is discussed of an N-acyliminium ion which is generated by acylation of an imine with a cyclic anhydride. Castagnoli and co-workers[41,42] discovered that refluxing an equimolar mixture of benzylidenemethylamine (**11.3**) and succinic anhydride in benzene afforded a *cis–trans* mixture of pyrrolidones **11.4** in good yield. The probable mechanism consists of initial formation of the N-acyliminium ion **11.5** which mainly exists in



Scheme 10.



Scheme 11.

its closed form **11.6**. Ring closure via the acid enolate anion **11.7** furnishes the stable product **11.4**. This methodology was later applied to more complex imines and anhydrides by Cushman and co-workers[43–45] and Haimova *et al.*[46] To mention one example, the reaction between homophthalic anhydride **11.8** and imine **11.9**, furnishing **11.10** in excellent yield, is the key step in a synthesis of corynoline.[44]

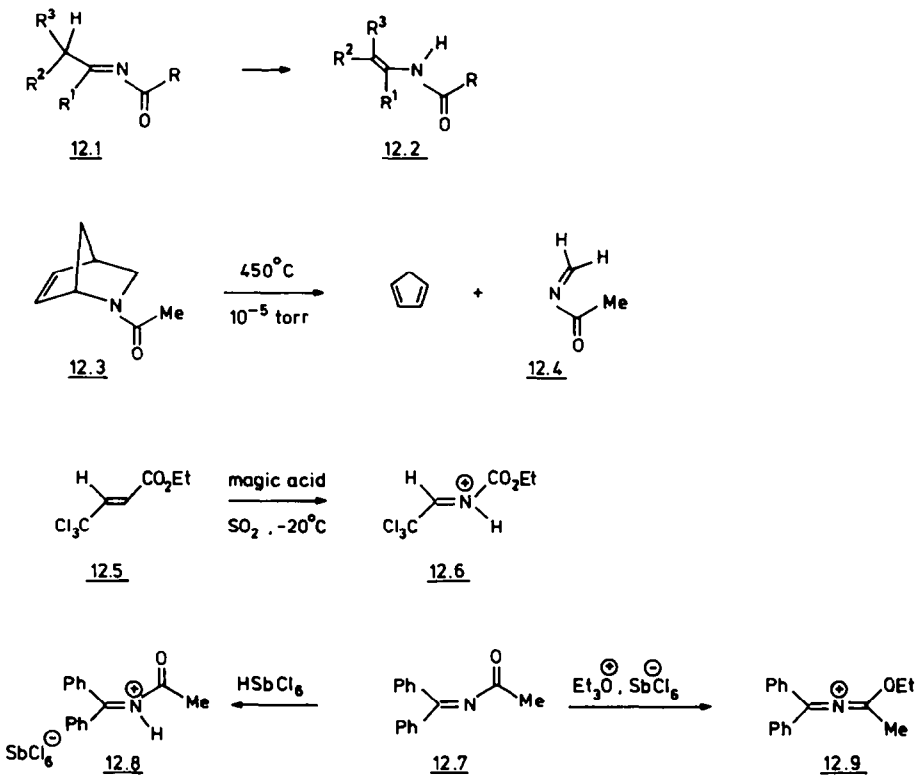
C.b. N-*Protonation of* N-*Acylimines*

This method for the preparation of N-acyliminium ions is more of mechanistic than of synthetic interest, since N-acylimines (**12.1**) themselves are rather unstable. If possible, they tautomerize rapidly into the corresponding enamides (**12.2**). Only those acylimines bearing, on the imino carbon atom, electron-withdrawing substituents[47,48] or tetra-substituted groups[49] have been isolated. Recently Lasne *et al.*[50] succeeded in preparing the parent compound **12.4** via flash vacuum pyrolysis of **12.3**. N-methyleneacetamide **12.4** slowly decomposes in solution even at $-100°$, while in the pure state polymerization already occurs at $-150°$.

Krow *et al.*[51] studied the protonation of acylimines, e.g. **12.5** with fluorosulfonic acid–antimony pentafluoride and inferred from the ^{1}H-NMR spectrum that the N-acyliminium ion (**12.6**) formed, has the *trans* configuration. Würthwein *et al.*[4a] investigated the protonation of imine **12.7** and presented convincing evidence for the N-acyliminium ion structure of the product (**12.8**). On the other hand, alkylation of **12.7** with triethyloxonium hexachloro-antimonate occurs at oxygen, leading to the 1-ethoxy-2-azaallenium structure **12.9**.[4a]

C.c. *Electrophilic Addition to Enamides*

Enamides are easily obtainable via acylation of an imine with an acid chloride or anhydride followed by elimination, as was described in Section C.a1.[26] Other methods[26] for the preparation of enamides are the reaction of ketoximes with refluxing acetic anhydride in pyridine, followed by



Scheme 12.

chromatography over alumina (e.g. **13.1** → **13.2**),[52] the elimination of methanol from α-methoxy amides,[53,54] and the transition metal induced double bond isomerization in N-allylamides.[55]

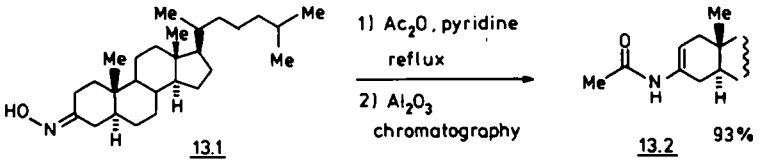
Enamides are stable compounds under neutral or basic conditions. With Brönsted acids they give rate determining protonation at carbon, which leads to hydrolysis in aqueous medium.[56] The intermediate after protonation is the N-acyliminium ion (e.g. **13.3**). An interesting illustration of the use of enamides in synthesis is the conversion of **13.4** to **13.5**, reported by Brossi *et al.*[57]

Other electrophilic addition reactions to enamides have recently been reported by several groups.[54,58–60] Friedel–Crafts type reaction of **13.6** with acetyl chloride in the presence of tin tetrachloride affords **13.7** in moderate yield. A Vilsmeier reaction furnished **13.8** in excellent yield.[54] Enamide addition to the sulfonium salt obtained from **13.9** by way of Pummerer reaction, gives after proton loss and double bond isomerization **13.10**.[58] Reaction of enecarbamate **13.11** with ethoxycarbonyl isocyanate smoothly leads to the acylated product **13.12**.[59] In all of these reactions an N-acyliminium ion acts as an intermediate which subsequently loses a proton with formation of the product, a new enamide.

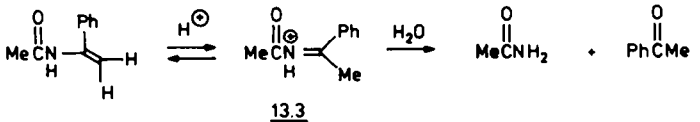
Whereas protonation and acylation of enamides lead to the intermediacy of N-acyliminium ions, alkylation occurs only at the amide moiety of the enamide functionality. The main reason is that amide protonation and acylation reactions are reversible, which is mostly not the case with amide alkylation reactions. To illustrate this point enamide **14.1** reacts with alkylhalides only after prior formation of the amide anion and then the product is exclusively the N-alkyl enamide **14.2**.[52] A much more reactive alkylation reagent triethyloxonium tetrafluoroborate furnishes the O-alkylated product **14.3**.[52]

C.d. *Oxidation of Amides*

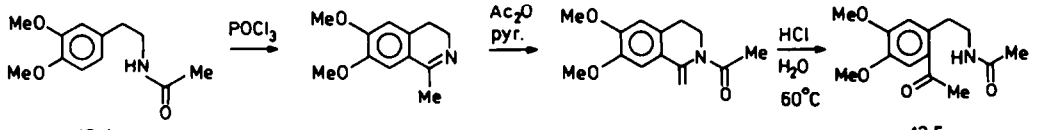
Removal of a hydride from the α-carbon of an amide formally leads to an N-acyliminium ion. The most important way to effect this transformation is the electrochemical method, developed by several research groups.[61–65] The mechanism involves initial removal of an electron from the lone pair on nitrogen followed by a proton and another electron (Scheme 15). This electrochemical oxidation is conducted in the presence of a nucleophile, mostly methanol, so that the N-acyliminium ion is trapped



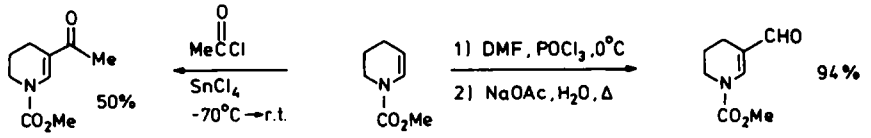
13.1 13.2



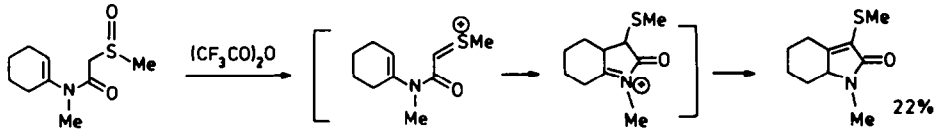
13.3



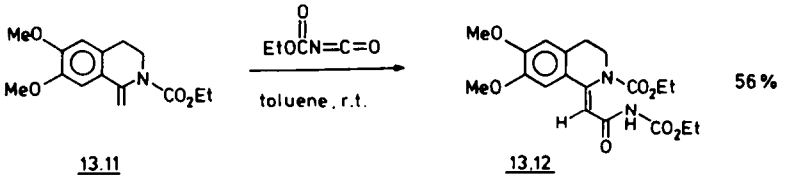
13.4 13.5



13.7 13.6 13.8

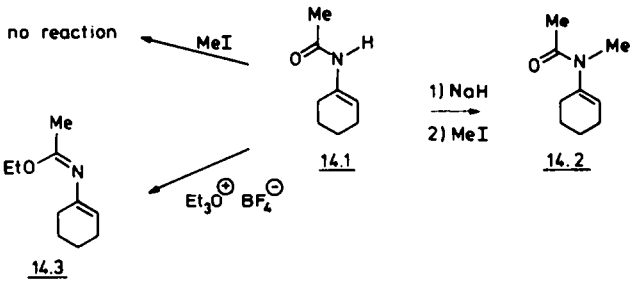


13.9 13.10



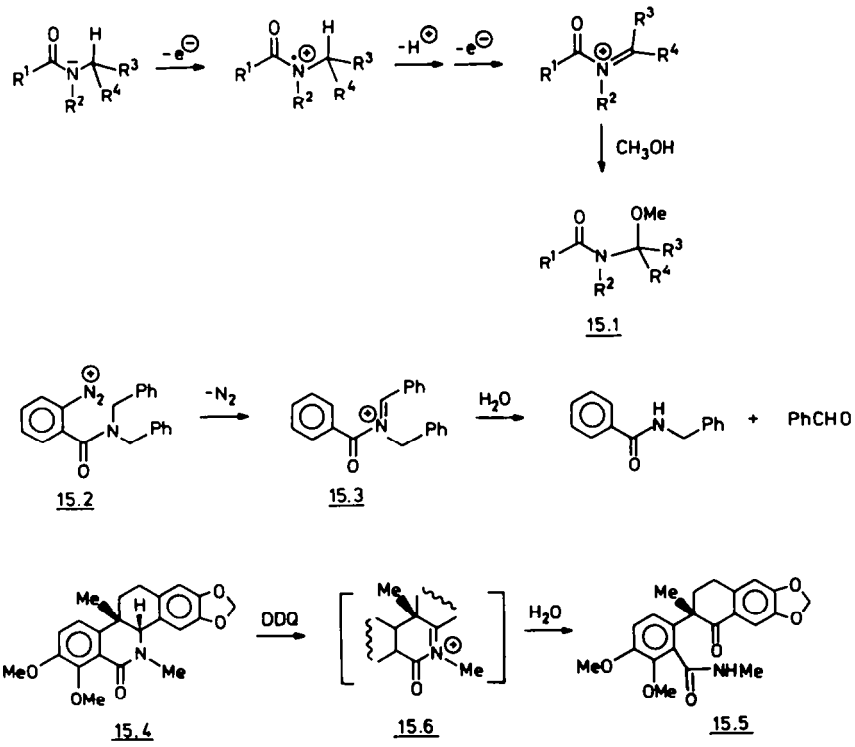
13.11 13.12

Scheme 13.



14.1 14.2 14.3

Scheme 14.



Scheme 15.

as soon as it is generated to give α-methoxyalkyl amide **15.1**. The reaction works well for a large structural variety of amides and carbamates and has recently been reviewed comprehensively.[66]

There are a few reports of other methods for generation of N-acyliminium ions from amides by a formal hydride abstraction. Thermal decomposition of diazonium ion **15.2** produces among other products benzaldehyde and N-benzylbenzamide, arising from hydrolysis of N-acyliminium ion **15.3**. This latter ion is the result of a hydride shift to the phenyl ring.[22] Amide **15.4** gives on oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) ketone **15.5**. The intermediate in this process is presumed to be N-acyliminium ion **15.6**.[67]

C.e. *Heterolysis of Amides, Bearing a Leaving Group* X *on the α-Carbon (with Respect to Nitrogen)*

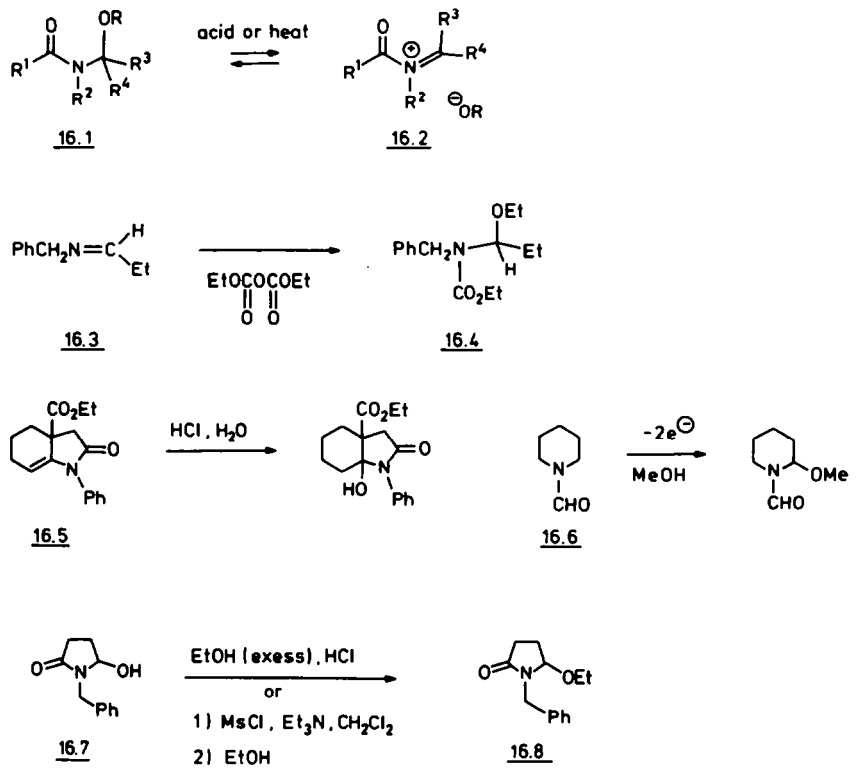
Heterolysis of α-substituted amides is the most often employed method for the generation of synthetically useful N-acyliminium ions. In more than 90% of the examples X is an oxygen substituent. But X may also be a halogen, a nitrogen, a sulfur or a phosphorus substituent (see Scheme 7, method e).

C.e.1. X = OR

Generally, Brönsted or Lewis acids are used to generate the corresponding N-acyliminium ions **16.2** from α-oxyalkyl amides **16.1** if R is alkyl or hydrogen. If R is acetyl[68] or methanesulfonyl[69] no acidic catalyst is necessary.

There are several methods for the preparation of α-oxyalkyl amides **16.1**, the most important of which are discussed below.

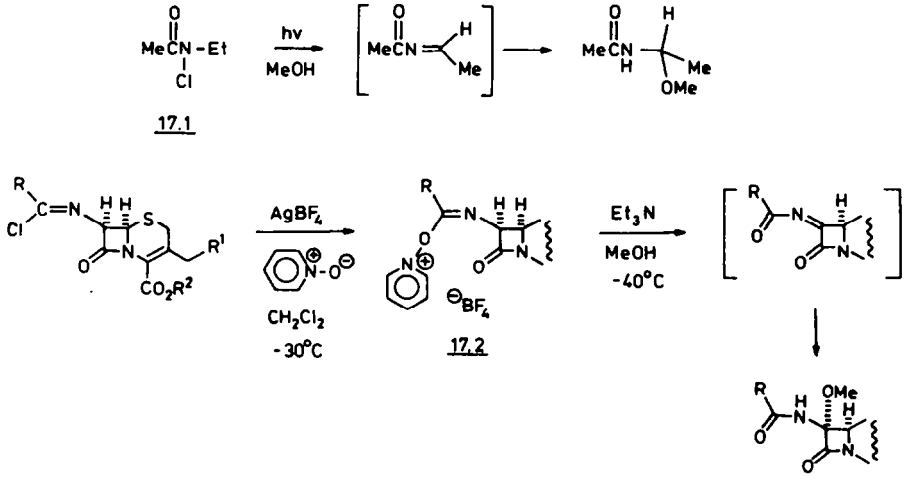
C.e.1.a. *Addition of oxygen nucleophiles to* N-*acyliminium ions or* N-*acylimines.* N-acyliminium ions generated by either of the ways shown in Scheme 7 react with water, alcohols and other oxygen nucleophiles to yield more or less stable α-oxyalkyl amides (or carbamates). Some examples are the addition of diethylpyrocarbonate to aldimine **16.3**, affording α-ethoxy carbamate **16.4** (cf. Section C.a),[70] the acid catalyzed addition of water to enamide **16.5**[71] (cf. Section C.c), the anodic methoxylation of formamide **16.6**[61] (cf. Section C.d), and the conversion of hydroxylactam **16.7** into ethoxy lactams **16.8**, either under acidic conditions with an excess of ethanol[72] or under almost neutral conditions via a mesylate using a stoichiometric amount of ethanol[73] (cf. Section C.e.1).



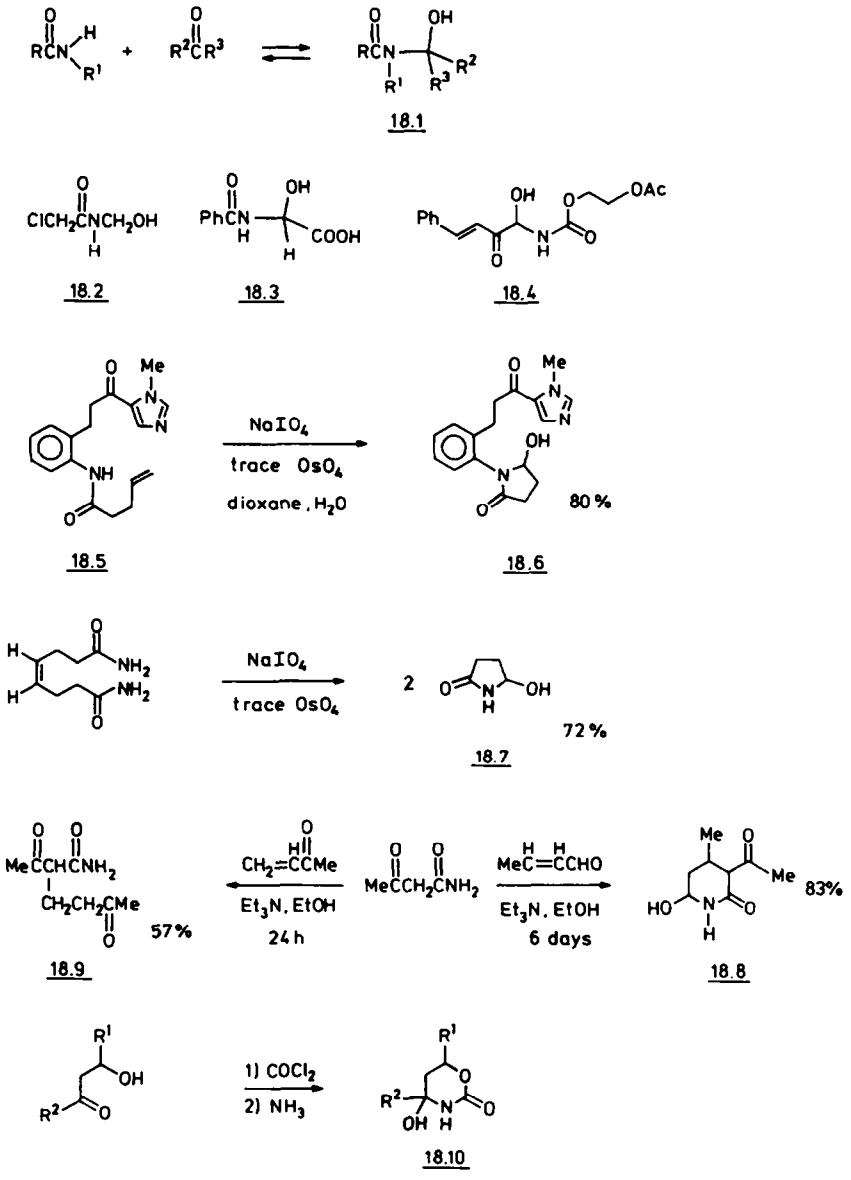
Scheme 16.

Another method occasionally used for the preparation of α-methoxy amides involves the generation of an N-acylimine in the presence of an excess of methanol (cf. Section C.b). N-Acylimines used for this purpose have been obtained through photolytic[74] or base catalyzed elimination[75,76] of HCl from N-chloroamide **17.1** or through a base catalyzed elimination of imidate **17.2**.[77]

C.e.1.b. *Reaction of primary or secondary amides with aldehydes or ketones.* Addition of primary or secondary amides to aldehydes or ketones leads to α-hydroxyalkyl amides (**18.1**) in an equilibrium process. Only if the equilibrium lies far to the right can stable products be isolated. This is the case with very reactive carbonyl compounds like formaldehyde, trichloroacetaldehyde, glyoxylic acid and other α-dicarbonyl compounds. Some examples of stable adducts are **18.2**,[78] **18.3**[79] and **18.4**.[80] The reaction between primary or secondary amides and aldehydes or ketones can also be a favourable process, if a



Scheme 17.



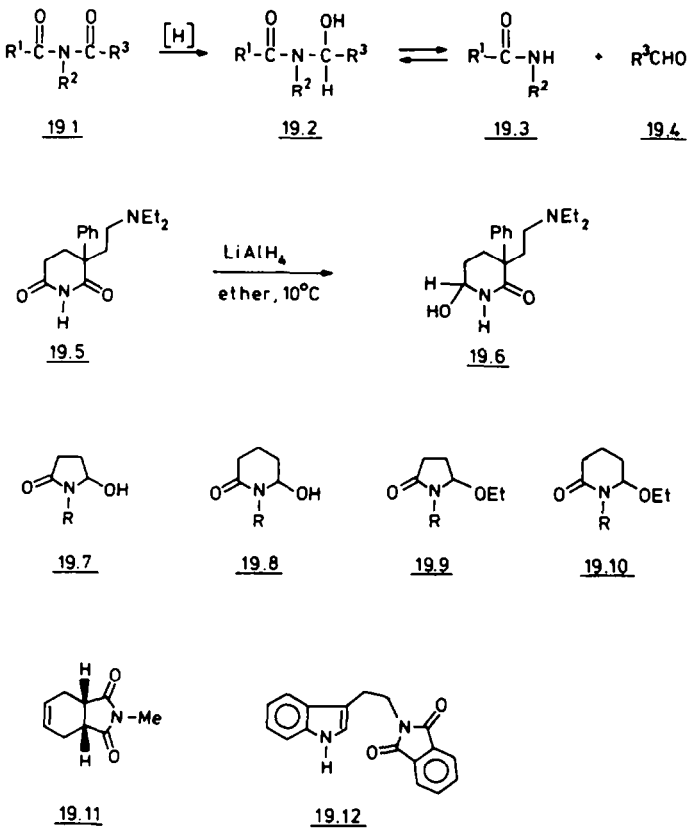
Scheme 18.

five- or six-membered ring is formed. Oxidation of **18.5** with sodium periodate and a catalytic amount of osmium tetroxide affords hydroxy lactam **18.6** which is the natural product isolongistrobine.[81] This oxidation procedure has later been applied to the synthesis of the parent hydroxy lactam **18.7**.[82] Michael addition of acetoacetamide to crotonaldehyde gives a product which cyclized under the reaction conditions to six-membered hydroxy lactam **18.8** in 83%.[83] However, this reaction sequence is sensitive to the presence and location of substituents since a similar reaction with methyl vinyl ketone leads to 57% of **18.9** which does not cyclize.[83]

The cyclic hydroxy carbamate moiety **18.10** occurs in the maytansinoids, a group of natural products with potent antitumour activity. Its synthesis has received considerable attention. The most simple and straightforward approach is the reaction of a β-hydroxy ketone with phosgene, followed by ammonia.[84,85]

Although many α-hydroxyalkyl amides are not stable enough for isolation, they can still be synthetically employed. To this end oxo-amides are treated with (strong) acid, so that the equilibrium amount of α-hydroxyalkyl amide *in situ* is converted into the N-acyliminium ion. This principle is often utilized in intramolecular N-acyliminium ion reactions as will be reviewed in Section D.

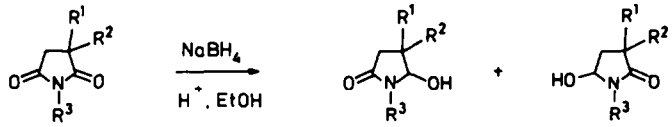
C.e.1.c. *Partial reduction of cyclic imides.* When reducing the amide functionality (**19.1**) the first



Scheme 19.

product to be expected is the α-hydroalkyl amide (**19.2**). As was discussed before this product is in equilibrium with amide **19.3** and aldehyde **19.4** (which would easily be further reduced), unless the aldehyde has a very reactive carbonyl group or the labile C—N bond of **19.2** is contained in a five- or six-membered ring. This latter principle is the basis of a simple and synthetically very useful method for the synthesis of five- and six-membered hydroxy lactams. Already in 1954, it was shown that mild $LiAlH_4$ reduction of **19.5** leads to hydroxy piperidone **19.6**.[86] Speckamp and co-workers have developed this partial reduction of cyclic imides to a high yielding procedure by using excess sodium borohydride in ethanol.[72,87–89] During the reaction a dilute solution of hydrochloric acid in ethanol is slowly added in order to stop the medium from becoming too basic, causing ring opening of the product. Ring opening is furthermore prevented by conducting the reduction of succinimides at temperatures below 5° and reduction of glutarimides below −10°. In this way hydroxy lactams **19.7** and **19.8** (R = H, alkyl or aryl) can be obtained from succinimide and glutarimide, respectively, in good to excellent yields. The corresponding ethoxy lactams **19.9** and **19.10** are isolated, if the reaction medium is made (strongly) acidic before work-up. More complex imides such as **19.11**[90] and **19.12**[91] are also reduced in excellent yields to their corresponding hydroxy lactams. It has been reported that addition of acid is not necessary for obtaining a good yield of hydroxy lactams, if the reduction is carried out at −4° in *methanol* as solvent.[69] Metal salts have also been used as catalysts.[92] Four- and seven-membered hydroxy lactams cannot be obtained due to their tautomeric instability.[93]

Asymmetrically substituted cyclic imides pose the problem of regiochemistry of reduction. In the case of geminally disubstituted succinimides it has been found that the carbonyl group adjacent to the quaternary centre, i.e. the more sterically hindered one, is preferentially reduced.[89,94] The regioselectivity varies from a 79/21 ratio for the dimethyl derivative **20.1** to > 95/ < 5 for the diphenyl case **20.2**.[94] The regioselectivity of reduction of monosubstituted succinimides (e.g. **20.3**, **20.4**) is low,[94] unless the substituent is an acetoxy group (**20.5**).[95,96] The phenomenon of preferential reduction of the sterically more hindered carbonyl group of succinimides bears close resemblance to the behaviour of succinic anhydrides toward reducing agents. Various explanations have been advanced[97–99] but the matter is very complicated and it is unlikely that one soon will be able to make reliable predictions on



20.1	$R^1 = R^2 = R^3 = Me$	79 %	21 %
20.2	$R^1 = R^2 = Ph$ $R^3 = Me$	>95 %	< 5 %
20.3	$R^1 = R^3 = Me$ $R^2 = H$	59 %	41 %
20.4	$R^1 = Ph$ $R^2 = H$ $R^3 = Me$	40 %	60 %
20.5	$R^1 = OAc$ $R^2 = H$ $R^3 = alkyl$	>95 %	< 5 %

Scheme 20.

the regiochemical outcome of reductions of more complex imide systems. Glutarimides seem to be preferentially reduced at the less hindered carbonyl group.[86,89]

The use of diisobutylaluminium hydride (DIBAH) for the partial reduction of cyclic imides was first reported by Winterfeldt.[100] Although less convenient than $NaBH_4$ an important aspect of the use of DIBAH is the fact that the regiochemical outcome seems to be the opposite. Imide **21.1** gives on reduction with DIBAH 52% isolated yield of hydroxy lactam **21.2**,[101] whereas $NaBH_4$ reduction yields the other regioisomer (cf. Scheme 20). A similar effect is apparent from the behaviour of imide **21.3** towards the two reducing agents.[102]

A stereochemically interesting reaction is the reduction of imide **21.4** to **21.5**.[103a] The best stereoselectivity is attained by using an aluminium hydride reagent containing two active hydrides. Presumably, the first hydride connects the aluminium to the oxygen of the hydroxy group, so that the reduction of the carbonyl by the second hydride occurs in an intramolecular fashion enhancing the chance of high asymmetric induction. Ring opening and further reduction of **21.5** is achieved by using $NaBH_4$ in 60% ethanol at 50°. Amide hydrolysis and lactone ring closure complete the asymmetric synthesis of bicyclic lactones **21.6**.[103a] $NaBH_4$ reductions of optically active imides have also been reported by Wakabayashi and Saito.[103b]

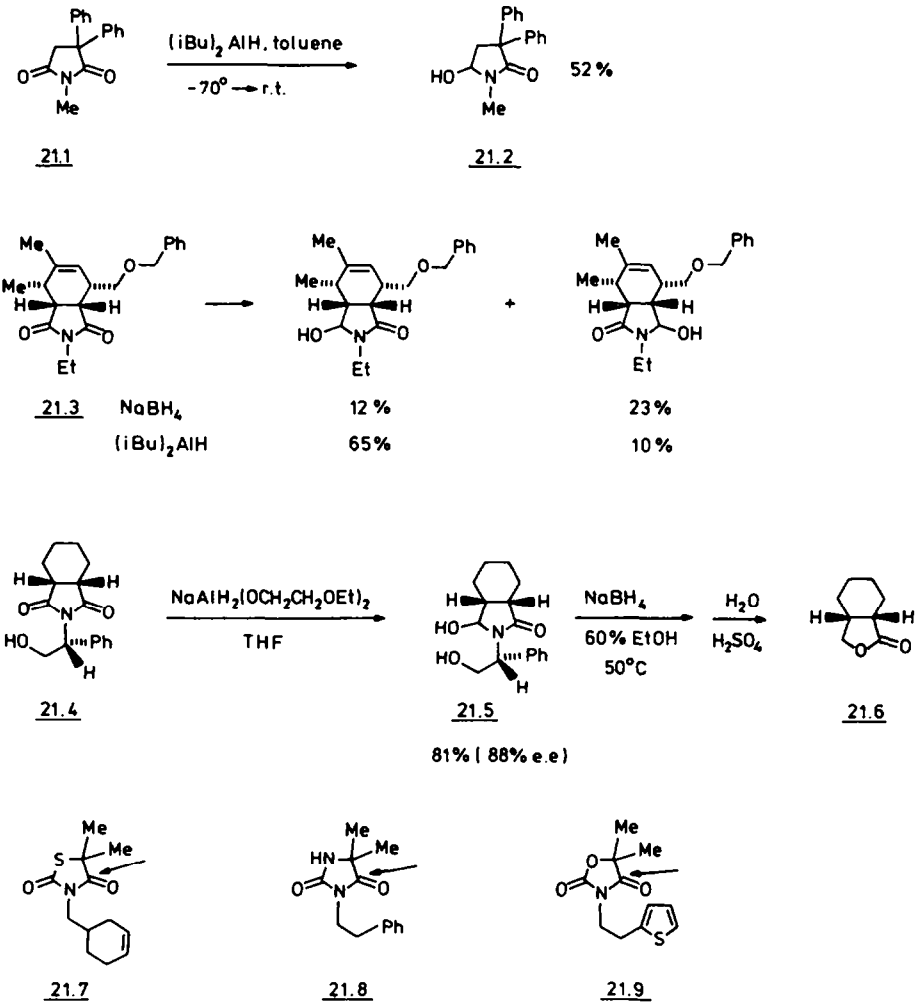
Cyclic "imides", containing another heteratom in the ring can also be reduced to their corresponding hydroxy analogues using $NaBH_4$ in ethanol plus acid or DIBAH. Examples of such systems are **21.7**,[104] **21.8**[105] and **21.9**.[106] Reduction occurs with complete regioselectivity at the carbonyl group indicated with an arrow.

C.e.1.d. *Reduction of* N-*acylimidates.* Cyclic N-acylimidates can be prepared from cyclic imides by alkylation of their silver salt with ethyl iodide.[107] Acyclic N-acylimidates are most conveniently prepared by reaction of an acid chloride with an imidate in the presence of triethylamine.[108] Examples are the synthesis of N-acylimidates **22.1** and **22.2**. Reduction of these compounds with $NaBH_4$ occurs in high yield to afford alkoxyalkyl amides **22.3** and **22.4**, respectively. This method was applied in the total synthesis of insect poison pederine.[109]

C.e.1.e. *Grignard addition to cyclic imides.* Addition of Grignard reagents to five- or six-membered ring imides lead to hydroxy lactams with a tertiary hydroxy group.[110–113] This reaction is occasionally complicated by an undesired ring opening of the initially formed magnesium alkoxide (**23.1**) to afford the magnesium salt of an amide and a ketone (**23.2**), to which further Grignard addition can occur. Moreover, the tertiary hydroxy lactam is very susceptible to dehydration, making isolation and/or purification sometimes difficult. Whether the hydroxy lactam can be obtained in good yields strongly depends on the substitution pattern of the imide and the structure of the Grignard reagent. In principle, N-unsubstituted imides require two equivalents of Grignard reagent and N-substituted ones only one, but it has been reported that in the latter case also the use of two equivalents provides better yields.[114] Recently, Evans *et al.* reported that, if dichloromethane is used as solvent instead of diethyl ether, the addition of Grignard reagent **23.3** to salt **23.4** can be improved to afford hydroxy lactam **23.5** in almost quantitative yield, uncontaminated with ring-opened products.[115]

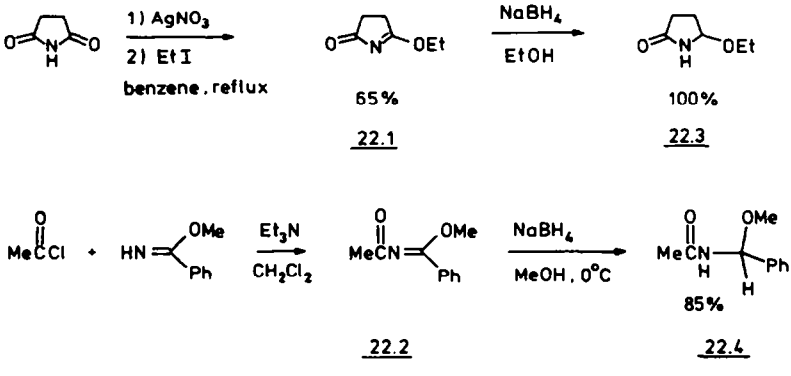
The Grignard addition to unsymmetrical cyclic imides is attended with high regioselectivity, with preferential addition to the least hindered carbonyl group.[111–113] Some examples are the preparation of **23.6**[111] and **23.7**.[113]

C.e.1.f. *Miscellaneous.* Oxidation at the double bond of enamides may lead to α-oxyalkyl amides.

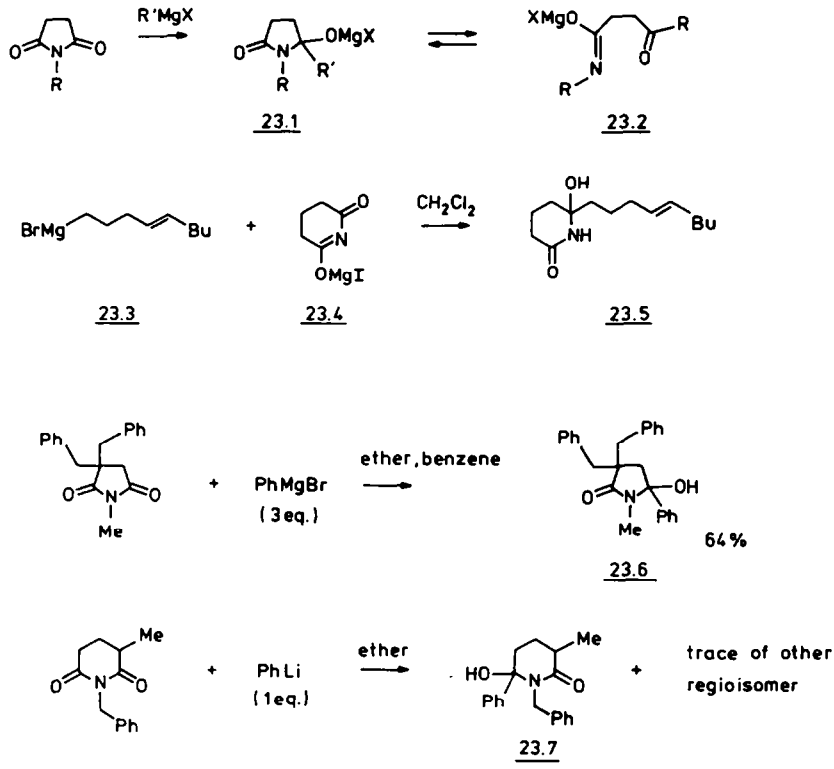


Scheme 21.

Among the oxidizing agents that have been used are osmium tetroxide,[116] lead tetraacetate,[117] peracids,[118–120] thallium(III) nitrate[118] and benzene seleninic anhydride.[120] Often the primary oxidation product is not stable, due to easy formation of an N-acyliminium ion, which is subject to further reaction. An exception is OsO_4, which cleanly gives the expected diol, exemplified with the formation of **24.1**,[116] an intermediate in the total synthesis of velbanamine. An interesting example is the oxidation of **24.2** with *m*-chloroperbenzoic acid.[119] One equivalent of peracid in methylene chloride



Scheme 22.



Scheme 23.

leads to a 1 : 1 mixture of starting material and imide **24.3**, whereas performance of the reaction in methanol affords the α-methoxy compound **24.4** in high yield.

Another oxidative procedure, the Baeyer–Villiger oxidation, converts azetidinone **24.5** into acetoxy lactam **24.6** in quantitative yield, with complete stereospecificity.[121] Curtius rearrangement of α-oxycarbonylazides gives rise to the formation of α-oxyalkyl carbamates, as was shown by two reports in connection with the total synthesis of maytansinoids.[122,123] Thus, refluxing **24.7** in benzene in the presence of sodium acetate, followed by treatment with tetra-n-butylammonium fluoride leads to **24.8**.[123]

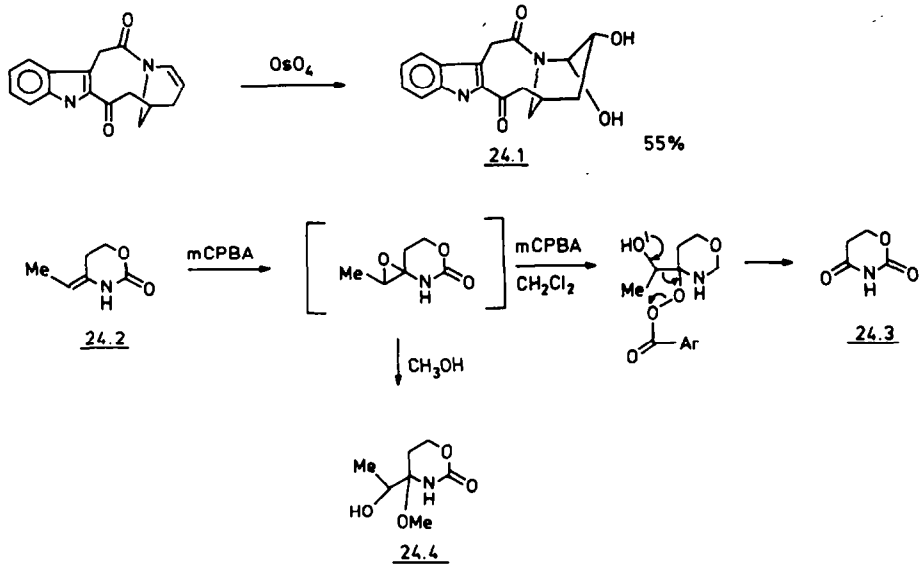
Cycloaddition can also lead to α-oxyalkyl amides. Photocycloaddition of acylimidate **25.1** with cyclohexene yields the [2+2] cycloadduct **25.2** as a single product. Hydrolysis with dilute HCl gives tricycle **25.3** in quantitative yield.[124,125] 4-(Acyloxy)azetidin-2-one (**25.4**) is an important starting material in β-lactam chemistry. It is obtained through cycloaddition of vinyl acetate with chlorosulfonyl isocyanate, followed by mild reductive hydrolysis.[15] Ethoxyazetidinone **25.7** is obtained by way of reaction of acid chloride **25.5** with imidate **25.6** in the presence of triethylamine.[35]

C.e.2. $X = NR_2$

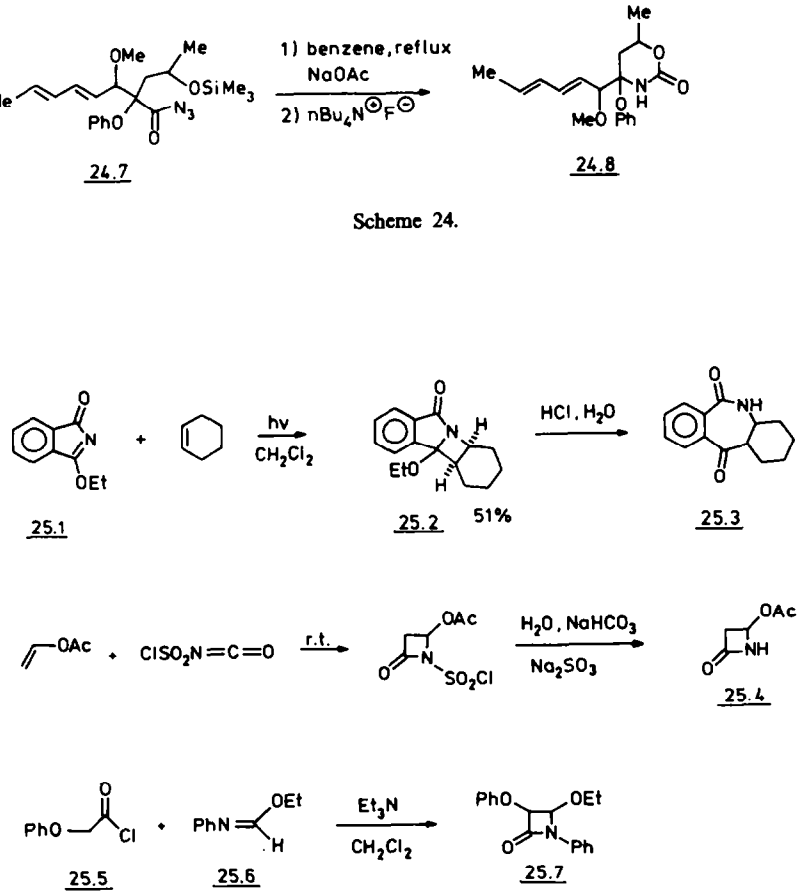
Bisamides (or biscarbamates) of general type **26.1** are easily obtainable from an aldehyde and two equivalents of a primary amide. Bisamides frequently serve as precursors for N-acyliminium ions[2,47] into which they are converted on heating, often in the presence of acid. This method is not applicable, if R^1 bears an α-hydrogen atom, in which case enamide formation occurs. The chemistry of bisamides requires rather harsh conditions, so that its usefulness in elaborate natural product synthesis is limited.

N,N-Dialkylaminomethyl amides (or N-acyl aminals, **26.2**) are obtained through condensation of a primary amide, a secondary amine and formaldehyde.[126] It is interesting to note that **26.2** on acylation with benzoyl chloride can afford either the N-acyliminium ion **26.4** or the iminium ion **26.3** depending on the size of the substituents R^1 and R^2. The reactive **26.4** is trapped as soon as it is formed by **26.2** to afford salt **26.5**.[126] A simpler synthesis of quaternary aminoalkyl amides has also been published recently.[127]

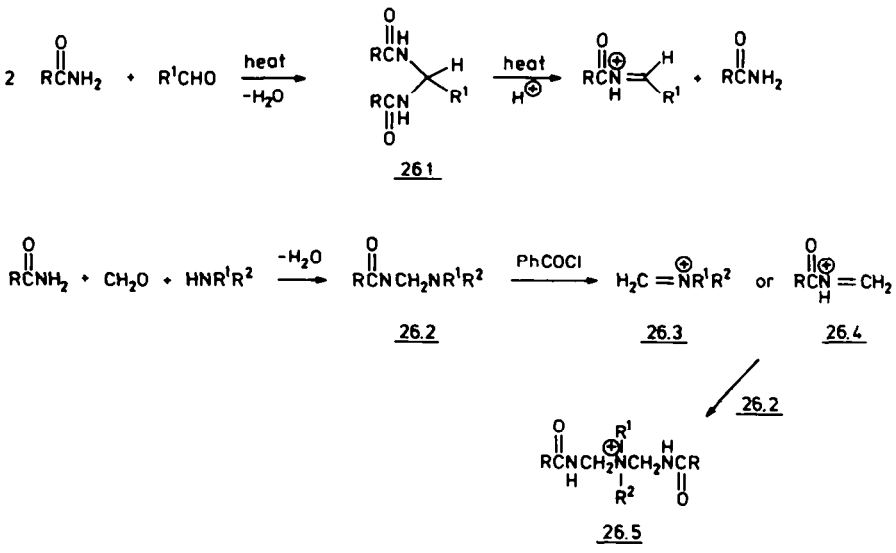
A milder method for the synthesis of bisamides **26.1** utilizes the Curtius rearrangement, starting from amino acid derivatives.[128–130] As applied to proline, azide **27.1** on refluxing in t-butanol affords



Scheme 24.



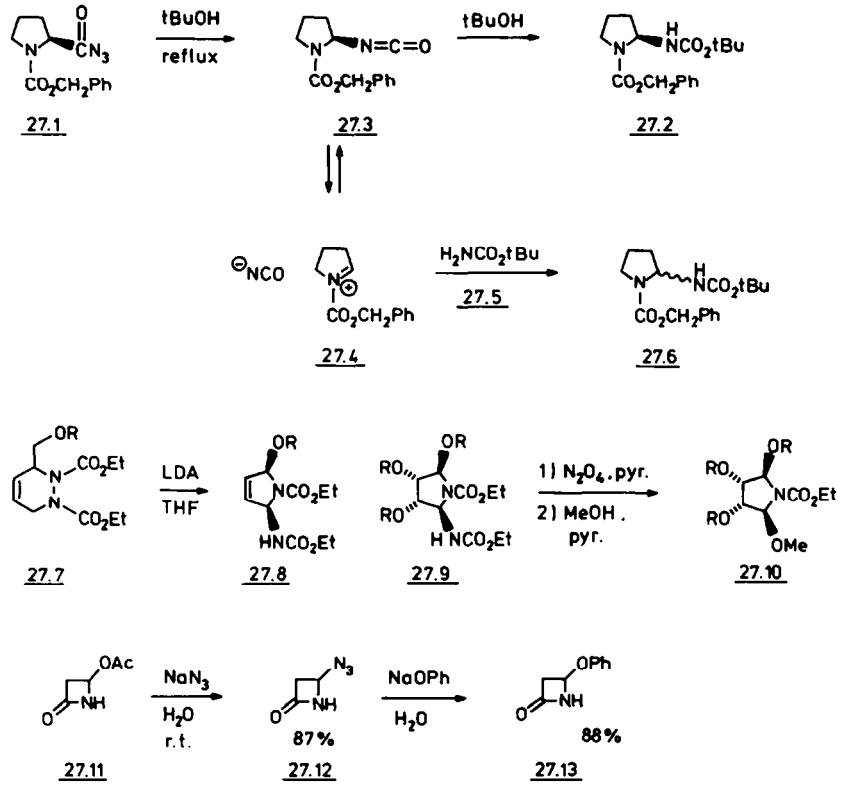
Scheme 25.



Scheme 26.

optically active biscarbamate **27.2** in only 5% yield, due to the low rate of addition of t-BuOH to isocyanate **27.3** in comparison with its heterolysis into N-acyliminium ion **27.4** and further reactions thereof. If, however, the Curtius reaction is carried out in the presence of 2.5 equiv. of carbamate **27.5** racemic **27.6** is obtained in 66% yield.[128] The Curtius rearrangement of amino acid derivatives has found use in peptide chemistry.[129,130]

A recent synthesis of biscarbamates involves the strong base induced ring contraction of **27.7**, synthesized by way of a Diels–Alder reaction using diethyl azodicarboxylate.[131] Compound **27.9** synthesized from **27.8** is activated for N-acyliminium ion formation through N-nitrosation. Refluxing



Scheme 27.

the N-nitroso compound with methanol in the presence of pyridine affords methoxy derivative **27.10**.[131]

Other α-azaalkylamides are known in the β-lactam field.[15] For example, azetidin-2-one **27.11** is converted in excellent yield to azido compound **27.12**. The azido group in turn can be replaced by a phenoxy group to yield **27.13**.

C.e.3. X = Cl

α-Chloroalkyl amides are most straightforwardly prepared through acylation of an imine with an acyl chloride as has been described in Section C.a. They are very susceptible to hydrolysis[21,23] and, if possible, easily eliminate HCl to give the corresponding enamide.[25] As already indicated by their instability, α-chloroalkyl amides often do not require an acidic catalyst in order to serve as an N-acyliminium ion source. With less reactive nucleophiles Lewis acids are used as catalysts.

Other synthetic methods for synthesis of α-chloroalkyl amides involved classical substitution of the hydroxy group in stable α-hydroxyalkyl amides using reagents like $SOCl_2$ and PCl_5[2a] and substitution of the thioether functionality, which was first applied in the penicillin field. This reaction will be treated in the next section on sulfur chemistry.

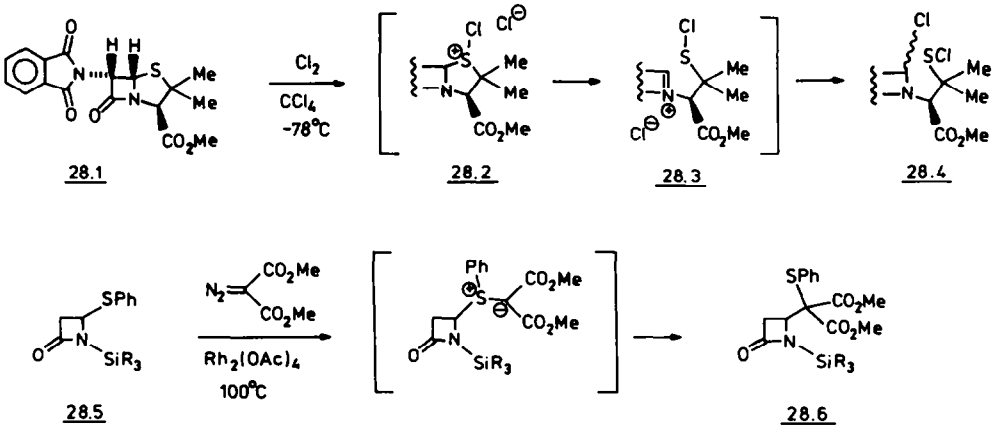
C.e.4. X = S

α-Thioalkyl amides are easily available through substitution of other heterosubstituents like acyloxy, alkoxy and sulfonyl, thanks to the high nucleophilicity of the sulfur atom. The reaction can be carried out under acidic[132] or non-acidic[15,101,133] conditions, and yields are usually high. The reaction has been mostly applied in the β-lactam field. It is noteworthy that penicillins and cephalosporins themselves are α-(alkylthio)alkyl amides.

The thioester function in itself is not a good leaving group to give the N-acyliminium ion, but it can be activated for heterolysis in various ways, all involving intermediates with a positive sulfur atom.[134,135] This was first shown in 1971 when Kukolja reacted penicillin esters (**28.1**) with chlorine gas.[136] A mixture of two 4-chloroazetidinones (**28.4**) was obtained. Sulfonium salt **28.2** and N-acyliminium salt **28.3** are assumed as intermediates. Later, various other reagents were used to generate N-acyliminium ions via thioether cleavage, such as mercury(II) acetate in acetic acid[137] and chloramine-T.[138] A special case of the activation of the sulfur atom is the reaction with diazo compounds.[139,140] Treatment of azetidinone **28.5** with dimethyl diazomalonate in the presence of rhodium(II) acetate gives alkylation product **28.6**.[139]

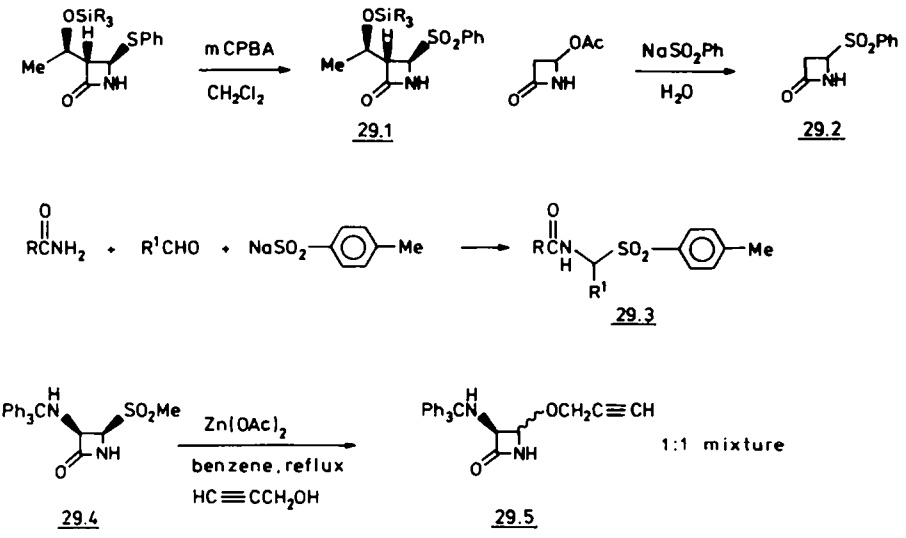
Sulfones are obtained from the corresponding sulfides by simple oxidation.[15,141,142] They can also be prepared by substitution of the acyloxy group using sodium sulfinate.[15] Examples are the syntheses of **29.1** and **29.2**. A Mannich-type route to acyclic α-sulfonylalkyl amides (**29.3**) involves the condensation of primary amides with aldehydes and sodium *p*-toluenesulfinate.[143]

α-Sulfonylalkyl amides have been reported to undergo displacement reactions with azide, alkoxide, thiolate, amine and carbon nucleophiles.[15,141–143] Reactions are mostly conducted under non-acidic conditions, but Lewis acids can also be used to effect heterolysis of the sulfonyl substituent. This is



28.1 28.2 28.3 28.4 28.5 28.6

Scheme 28.



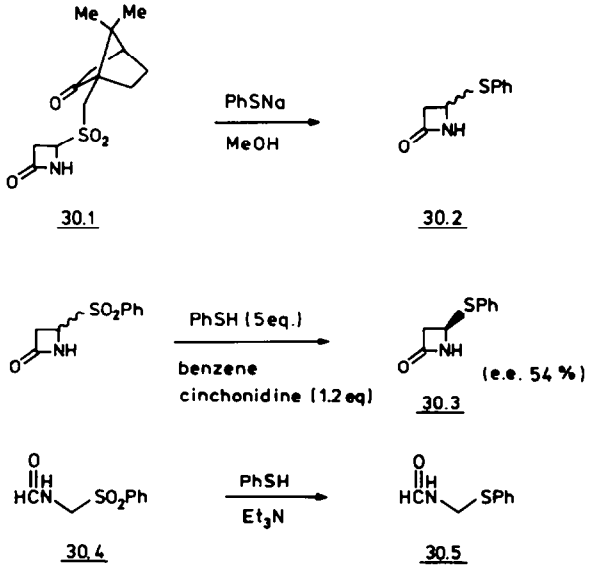
Scheme 29.

exemplified by the zinc acetate catalyzed formation of a 1 : 1 mixture of isomers **29.5** from isomerically pure **29.4**.[144]

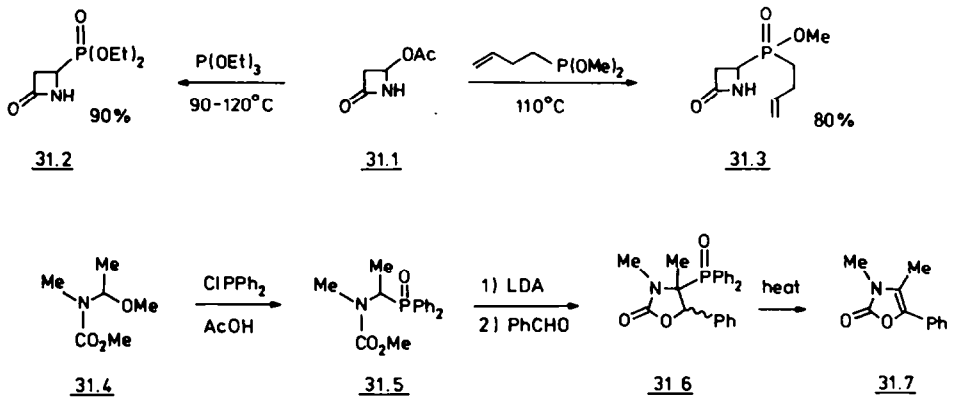
The stereochemical course of sulfinate displacement has received some special attention. Reaction of a single enantiomer of azetidinone **30.1** with sodium thiophenolate in methanol furnished racemic **30.2** in 82% yield.[15] This result points to an S_N1 process, thus the intermediacy of an N-acyliminium ion (or an N-acylimine). This mechanism was elegantly confirmed by a recent paper describing the displacement of phenylsulfonyl by phenylthio in the presence of the chiral base cinchonidine. Optically active **30.3** was obtained in 54% enantiomeric excess and 96% chemical yield.[141,142] On the other hand, a similar reaction in the open chain system **30.4** to yield **30.5** is argued to be a direct S_N2 sulfinate displacement.[143]

C.e.5. X = P

A few reports have appeared on the introduction of a phosphorus substituent at the α-position of an amide using the Arbuzov reaction. Campbell *et al.* used as starting material acetoxyazetidinone **31.1** and obtained phosphanates like **31.2** and **31.3** in good yield.[145,146] Shono *et al.* reacted methoxy amide



Scheme 30.



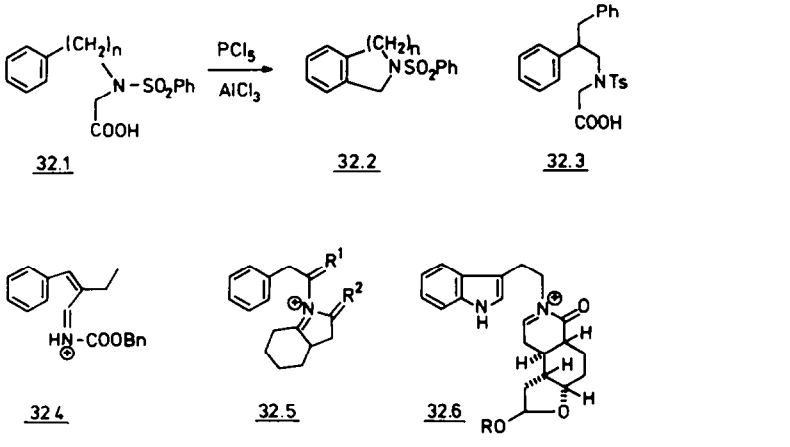
Scheme 31.

31.4 with chlorodiphenylphosphine to give **31.5**.[147] On deprotonation and condensation with benzaldehyde oxazolidone **31.6** was obtained, which was subjected to thermal elimination to yield oxazolone **31.7**.

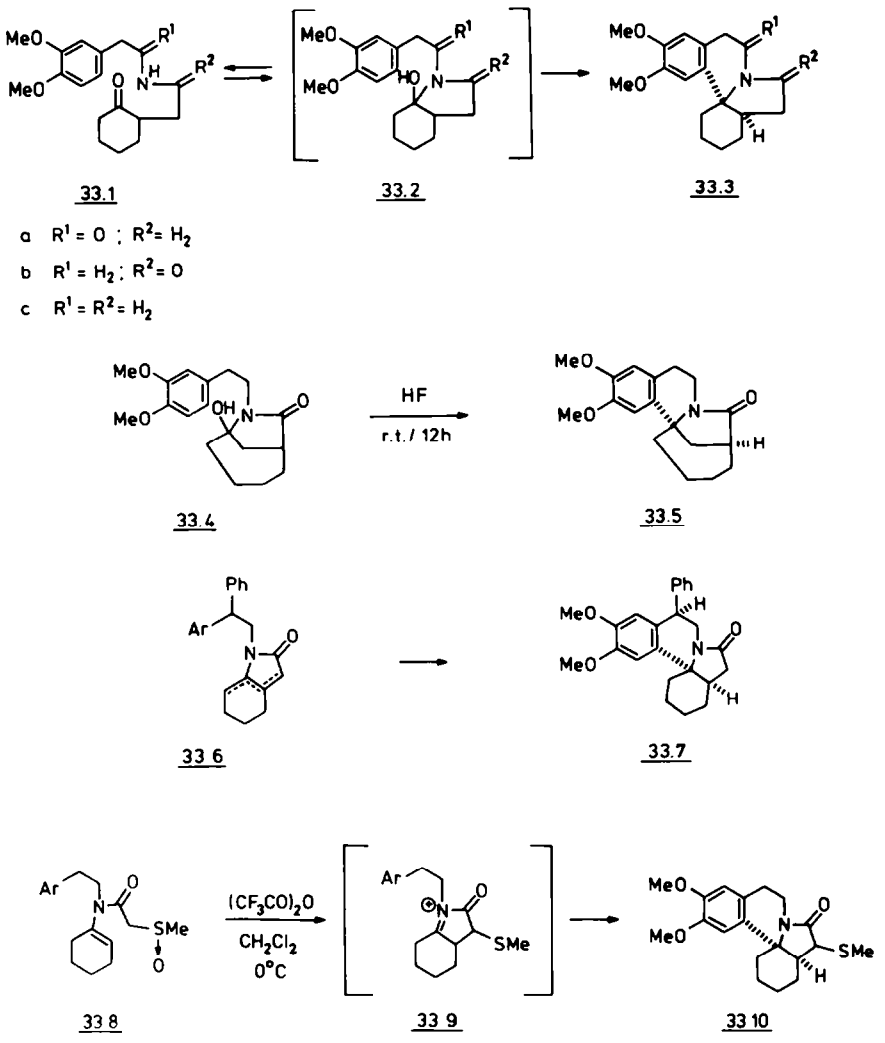
D. INTRAMOLECULAR AMIDOALKYLATIONS WITH AROMATIC π-NUCLEOPHILES

More than 20 years after the first report on the intermolecular amidoalkylation by Tscherniac[148a] and Einhorn[148b] the intramolecular counterpart was described by von Braun *et al.*[149] while investigating the ring closure of sulfonamide glycine derivatives **32.1** by $AlCl_3$-catalyzed decarbonylation of the corresponding acid chloride. Six- ($n = 2$), seven- ($n = 3$) and even eight- ($n = 4$) membered[150] rings **32.2** were formed. The reaction failed for **32.1** ($n = 1$) already representing a case of an unfavourable 5-endo-trig ring closure[151] of an N-phenylsulfonyliminium ion. Preferential formation of six- vs seven-membered rings was demonstrated in the reaction of **32.3**.[150] Interestingly, the more facile 5-exo-trig process has also been reported albeit many years later and starting with a different N-acyliminium precursor.[152] Thus, reaction of α-(*Z*)-ethyl cinnamic aldehyde with benzyl urethane under the influence of $POCl_3$ in refluxing xylene and subsequent hydrolysis gave 2-ethyl indanone via cyclization of **32.4**.

After these isolated examples a major breakthrough in the synthetic applications of the intramolecular amidoalkylation occurred in the early 1950s when the reaction was applied in alkaloid syntheses. Both the pioneering work by Belleau[153] and Mondon[154] on the synthesis of Erythrina alkaloids by ring closure of N-acyliminium ions **32.5a** ($R^1 = O$, $R^2 = H_2$) and **32.5b** ($R^1 = H_2$, $R^2 = O$), respectively, as well as the synthesis of yohimbine by van Tamelen *et al.*[155] via a route in which the essential step is the acid-catalyzed ring closure of the N-acyliminium ion **32.6** can be con-



Scheme 32.



Scheme 33.

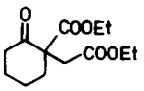
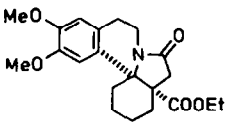
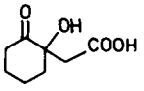
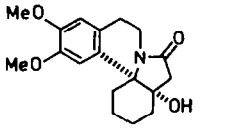
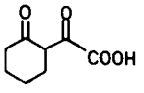
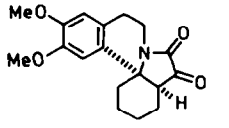
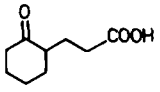
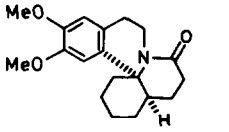
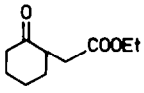
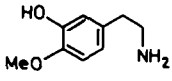
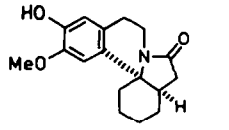
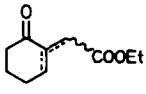
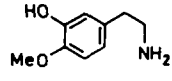
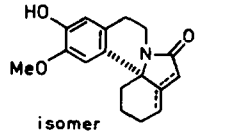
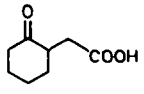
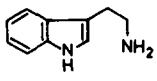
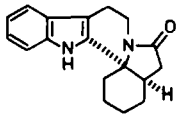
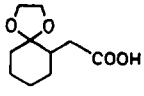
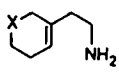
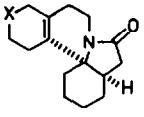
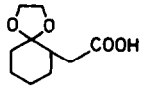
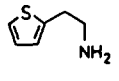
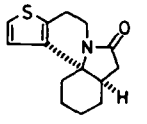
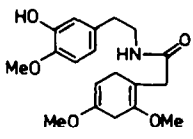
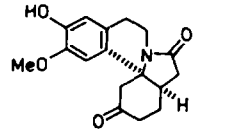
sidered as initiating studies in this field. Particularly in the latter case, the reaction proceeded remarkably easily indicating the high reactivity of an electron-rich aromatic ring as a nucleophile in such cyclizations. In the following, the reactions will be discussed with regard to the specific type of aromatic product obtained.

D.a. *Erythrina Type Cyclizations*

An interesting difference in reactivity between ketoamides **33.1a**, and **33.1b** is manifested upon reaction with acid. Whereas the former **33.1a** needs a reaction time of 3 h at 100° in PPA affording[156] **33.3a** in 71% yield, for the ring closure of **33.1b** 2 days standing at r.t. in 1 N HCl/EtOH aq suffices to obtain a yield of 75% of **33.3b**.[7,157–159] The experimental data therefore point to a higher reactivity of the endocyclic N-acyliminium ion **32.5b** as compared to the exocyclic form **32.5a**. In simple systems these differences in reactivity have also been established (cf. Section B.b). It must be kept in mind, that no separate data are available on the rates of formation of the intermediary tertiary hydroxylactams **33.2a** and **33.2b**. Since the ring closure is more facile in relation to the degree of nucleophilic character of the aromatic ring,[157] the reactivities of the electrophilic N-acyliminium ions are likely to be involved.

As can be expected for steric reasons only the *cis* products **33.3** are formed. Because of the more flexible synthesis of the starting ketolactams **33.1** by condensing homoveratryl amine with an appropriate keto or aldehyde carboxylic acid most work in this area follows the Mondon procedure. A survey is given in Table 1. The apparent connection between the degree of nucleophilic character of the

Table 1. Synthesis of erythnria type compounds

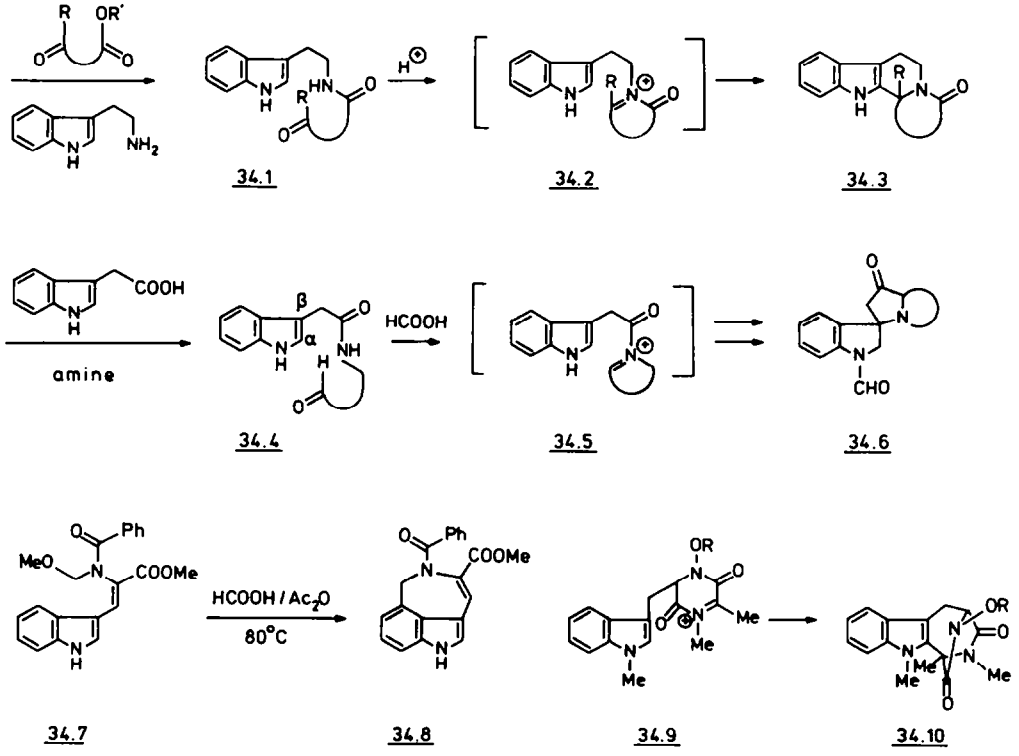
Entry	Keto acid	Amine[a]	Conditions	Products	Yield	Reference
1		HVA	H_3PO_4 ΔT		93 %	70
2		HVA 2 eq.	H_3PO_4-MeOH 1 : 1 100°C / 2h		84 %	163
3		HVA 2 eq.	H_3PO_4 (30%) MeOH-H_2O 100°C		90 %	164
4		HVA	PPA 100°C/1.5h		29.3 %	165
5			EtOH ΔT / 3h		[b]	166, 167
6	 isomer mixture		EtOH ΔT / 12 h	 isomer mixture	[b]	166, 168
7			xylene ΔT / 5h		77 %	169
8		 X = CH_2 , O	various		X = CH_2 X = O	7, 236 170
9			EtOH-HCl dil r.t. / 6d		30.8 %	165
10	 obtained by Birch reduction		HCOOH reflux / 16 h		65 %	171

[a] HVA = homoveratryl amine.
[b] Yield not specified.

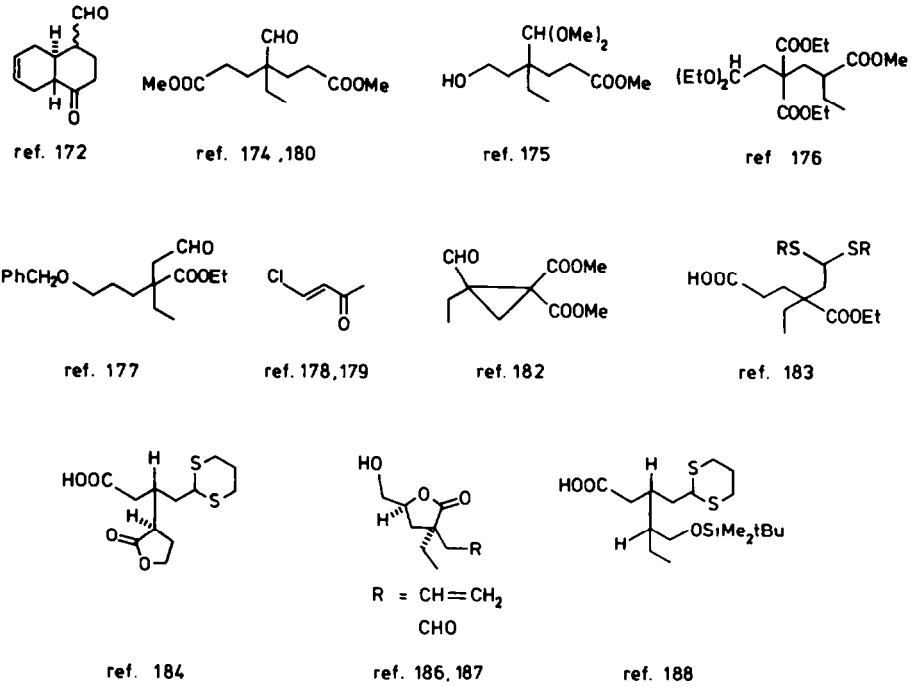
aromatic ring and the ease of ring closure is to some extent manifested from the data of Table 1 (cf. entries 5 and 6). A notable result is obtained in the cyclization of a heptanone carboxylic acid via the carbinol amide **33.4** to the azabicyclo[4.2.1]nonane **33.5**. In HF the intermediacy of a bridgehead carbenium ion has to be postulated which raises the question to what extent stabilization by an amide nitrogen is really necessary.[160,161] Substituted erythrina derivatives have also been obtained by starting from cyclohexanone-2-acetic ester and the appropriate amine which upon ring closure affords the enamide **33.6**. EtOH–HCl cyclization then yields **33.7**.[162] Generation of the N-acyliminium intermediate **33.9** via a Pummerer reaction of thioether **33.8** was recently described to afford the erythrinone **33.10**.[58]

D.b. *Indole Type Cyclizations*

The versatility of the N-acyliminium cyclization in the total synthesis of various indole alkaloids is reflected in the work of many research groups. Because of the highly reactive nature of the indole π-nucleophile this category stands out as a unique collection of illustrative examples. As the first of these van Tamelen *et al.*'s syntheses of yohimbine[172] and strychnine-type alkaloids[173] were followed by many others among which Kuehne with vincamine,[174] Harley-Mason and co-workers with aspidospermidine[175] and catharanthine,[176] Kutney with Vinca alkaloids,[177] Büchi and co-workers with vindorosine[178] and vindoline[179] Laronze *et al.* with vincadifformine,[180] Winterfeldt and co-workers with roxburghin D[181] and Vinca alkaloids,[182] Takano *et al.* with Aspidosperma alkaloids[183] and antirhine[184] and finally Kaluns *et al.* with different Vinca compounds[185] are well known. Very recently, enantioselective syntheses of (+)- and (−)-quebrachamine[186,187] were reported by Takano *et al.* while (+)-dihydroantirhine was synthesized by Kametani *et al.*[188] In the latter cases chiral precursors were used. In almost all of these cyclizations the essential step is the coupling of an oxo carboxylic acid derivative with tryptamine and acid catalyzed ring closure of the so-formed oxo amide **34.1** into the desired skeleton **34.3** via the N-acyliminium ion **34.2**. Since many of these syntheses have been reviewed elsewhere[189] and fall outside the scope of this report only a selection of the precursors used is given (Scheme 35). As can be expected in cases where different stereoisomers may be formed, mixtures of both CH—N diastereomers are obtained the composition of which depend on the location of additional substituents in the N-acyliminium part.



Scheme 34.



ref. 172 ref. 174, 180 ref. 175 ref 176

ref. 177 ref. 178, 179 ref. 182 ref. 183

ref. 184 ref. 186, 187 ref. 188

Scheme 35.

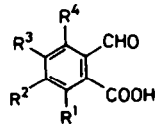
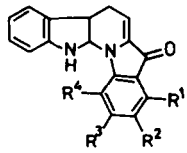
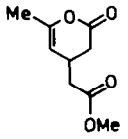
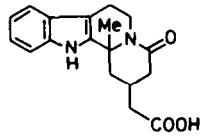
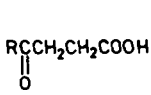
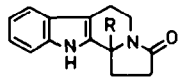
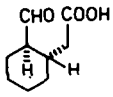
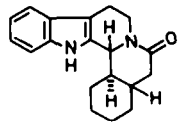
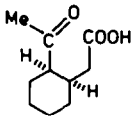
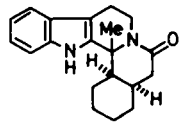
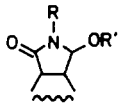
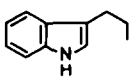
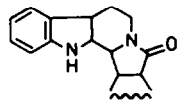
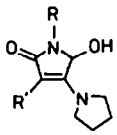
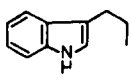
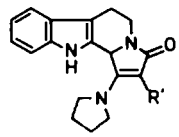
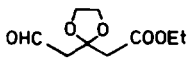
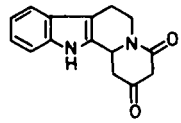
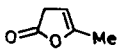
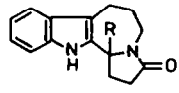
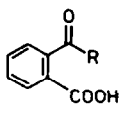
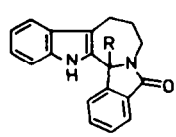
Indole alkaloids have also been synthesized by van Tamelen *et al.*[173,190] and Wenkert *et al.*[191] starting from indole-3-acetic acid and an amine to form the amide precursor **34.4** which is cyclized by acid-catalyzed formation of the N-acyliminium intermediate **34.5** and subsequent ring closure to **34.6**. Whereas so far in reactions of N-acyliminium species **34.2** only bond formation at C_α of the indole ring is observed in the latter examples due to the greater stability of the λ-lactam the more stable reaction product of the cyclization of **34.5** is the spiro structure **34.6**. This result is most likely accounted for by assuming initial C_α attack followed by a $C_\alpha \rightarrow C_\beta$ rearrangement[192] and reduction of the indolenin to **34.6** by formic acid as is extensively discussed by van Tamelen *et al.*[190] Such a distinct difference in behaviour between the ions **34.2** and **34.5** is highly useful for exerting regiocontrol in this type of bond formation.

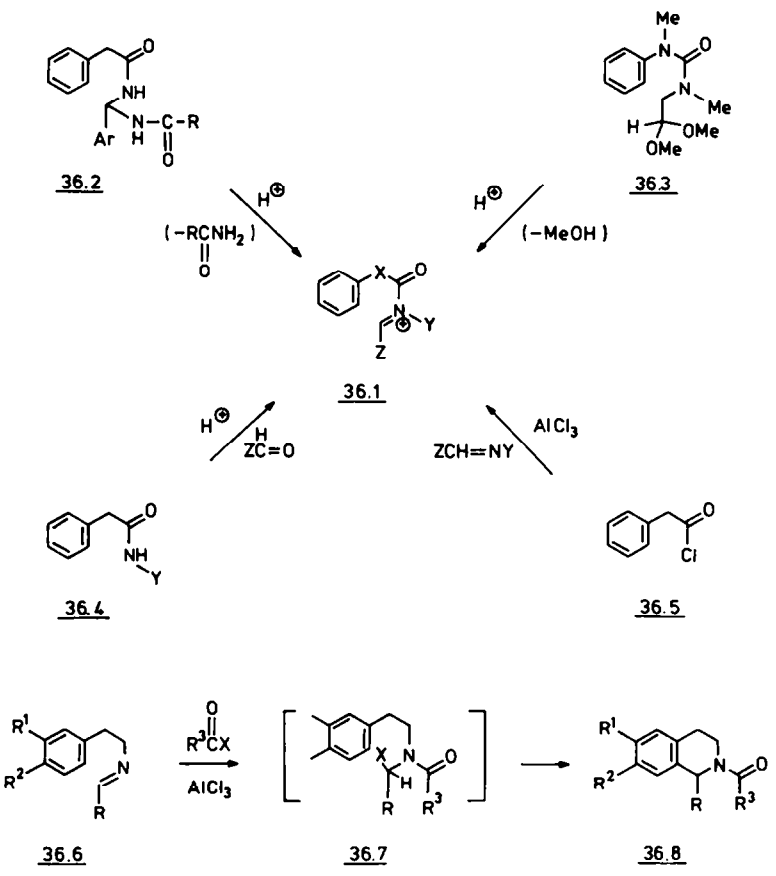
The success of this type of heterocyclization initiated a number of investigations not directly coupled with the synthesis of a particular alkaloid. Some results of these studies are summarized in Table 2. Since the method used in essence is the condensation of a suitable form of an oxo acid with tryptamine itself or a derivative only a few comments will be given. With regard to the stereochemistry of the starting carbonyl compound the *trans* aldehyde ester (entry 4) leads mainly to the thermodynamically more stable *trans-anti* isomer while the *cis* keto ester (entry 5) gives the *cis-anti* product which upon treatment with CF_3COOH is converted to the *cis-syn* isomer. A second point of interest is the formation of condensation products by prior formation and isolation of a hydroxy lactam starting from a cyclic imide and consecutive cyclization (entries 6 and 7). The imide itself is prepared by condensing the carboxylic anhydride with tryptamine or with a substituted tryptamine. Other interesting uses of indole as a π-nucleophile in N-acyliminium cyclizations are found in the cyclization of **34.7** to **34.8** which takes place at the C-4 position and not at C-2[201] and in work on the synthesis of neoechinulin[202] represented by the ring closure of **34.9** to **34.10** which is formed as a side product.

D.c. *Other Aromatic Nucleophiles*

Considering the lower reactivity of benzene as a π-nucleophile the intramolecular amidoalkylation requires more strenuous conditions as compared to indole cyclizations. Therefore, the mild aldehyde or keto-acid method is preferably applied to activated aromatic rings. In effecting ring closures on benzene, intermediates of type **36.1** are useful which can be prepared through HX elimination from a suitable $-CONCH_2X$ precursor under acid catalysis, e.g. bisamides or biscarbamates **36.2**[203–205] or

Table 2. Synthesis of indole type compounds.

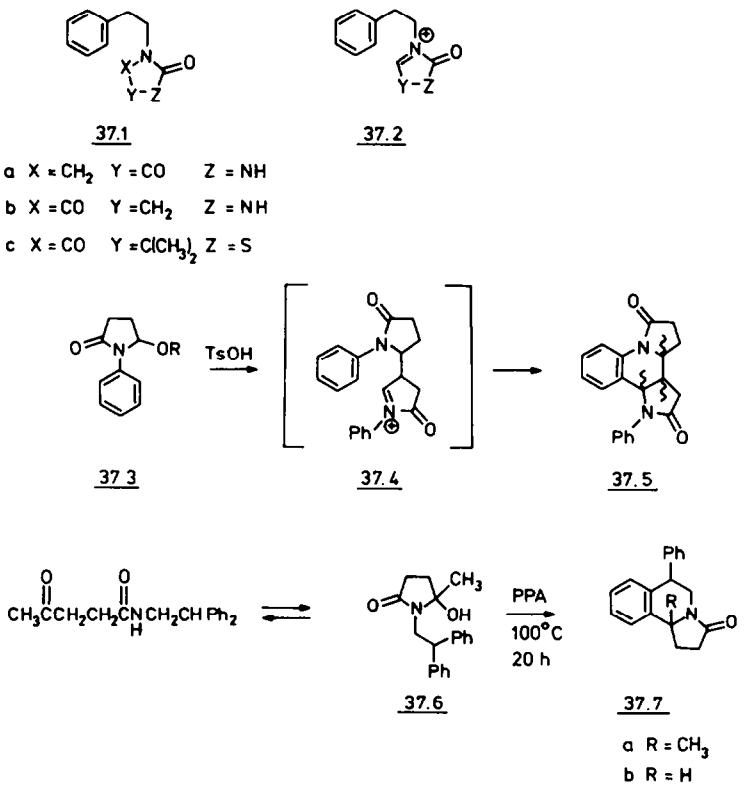
Entry	Aldehyde-or keto-acid	Condition	Product	Yield	Ref
1		EtOH / H_2O / H_2SO_4 40h -100°C		24.9-42.6 %	193
2		1) CH_2Cl_2 / ΔT 2) MeOH / HCl		95 %	194
3		xylene / ΔT / 4h		69.7 % R = Me	181, 195,196
4		AcOH / ΔT / 2 h	 + other stereoisomers	61 %	197
5		CF_3COOH / dioxane r t / 24 h (from enamide)		70 %	181
6	 R = 	5% HCl ΔT / 1h		78 - 91 %	91
7	 R = 	Ac_2O / pyridine AcOH		R'=Cl 84 % R'=H 72 %	198
8		1) AcOH / ΔT / 2h 2) H_2SO_4 (10%) ΔT		35 %	199
9		HCl / EtOH r.t. / 20h		R =Me 32 %	200
10		ΔT / xylene 24 h		R =Me 24 %	200



Scheme 36.

N-aryl-α-ureidoacetals **36.3**[206] by reaction of amides or nitriles of arylacetic acid **36.4** and aldehydes in acid[203,207,208] or by reaction of arylacetyl halides **36.5** with Schiff bases.[209] Alternatively the latter addition can be carried out by addition of acyl halides to imines **36.6** giving rise to isoquinolines **36.8** via the intermediates **36.7**.[210,211] In these types of cyclization usually 1-substituted isoquinoline derivatives are obtained (see for R = H, Ref. 212) since only the intermediates containing a secondary N-acyliminium structure give satisfactory results.

Methods for preparing cyclic intermediates are a bromination of a hydantoin **37.1a** followed by Lewis acid treatment to give **37.2a** and LAH reduction followed by reaction with acid of a imidazolindione **37.1b** to yield **37.2b**.[105,106,213] Similarly, sulfur containing N-acyliminium ions can be prepared by the latter method of which **37.2c** cyclizes by reflux in CH_2Cl_2–*p*-TsOH for 112 h.[214] A dimer **37.5** (mixture of stereoisomers) is obtained upon *p*-TsOH/C_6H_6 reflux of alkoxy lactam **37.3** which arises via the intermediate **37.4**.[16] The amide of 4-acetylbutyric acid and 2,2-diphenylethylamine cyclizes by intermediacy of the tertiary hydroxy lactam **37.6**[160] and produces the lactam **37.7a**. Reaction via the secondary hydroxy lactam obtained by $NaBH_4/H^+$ reduction of the corresponding imide gave tricyclic lactam **37.7b**. The failure to observe intramolecular ring closure upon reaction of adducts of glyoxylic acid was explained on the basis of a difference in energy between s-*cis* **38.1** and s-*trans* **38.2** forms.[205] In benzene as a solvent high yields of intermolecular reaction products were obtained pointing to an unfavourable equilibrium between **38.1** and **38.2** as non-stabilized (R = H, COOH, CCl_3) N-acyliminium ions. On the other hand the nature of Y and the choice of the solvent and/or acid can influence the course of the reaction to a great extent as for instance is shown by the easy formation of **38.3**.[208] From this result it follows that the use of strong acid and high temperatures are not prerequisites for effecting C—C bond formation. This is clearly indicated by the results obtained with cyclic ω-alkoxy lactams, which serve as versatile precursors for synthesizing lactams of type **38.5** under relatively mild conditions. For instance **38.4a** cyclizes to **38.5a** in formic acid at r.t. for 16 h[215] while the amide isomer **38.4b** affords **38.5b** in H_2SO_4 (conc) at r.t.[216] Even the phenylcyclopropane

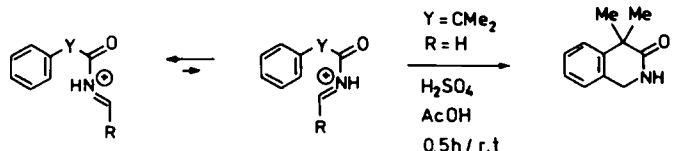


Scheme 37.

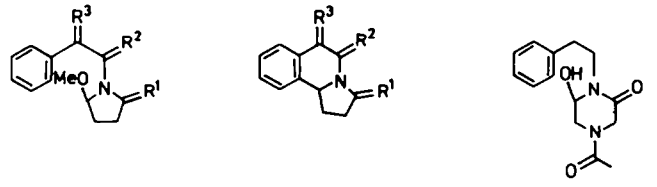
38.4c can be reacted to **38.5c** albeit that the resulting product is rather unstable.[217] Similarly, **38.6** gives the tricyclic compounds in high yield under influence of 12 N HCl at 0° for 16 h.[218] As can be expected for electronic reasons the choice of experimental conditions is widened upon the use of more nucleophilic aromatic substrates. Thus the oxo acid method can be applied to homoveratryl amine or derivatives as starting materials.[160,219] Moreover, reaction of a highly activated phenolic amine with levulinic acid directly gives the tricyclic **38.7** (R = CH_3, n = 1) upon fusion at 150–200° or upon reflux in isopropanol without the use of acid catalyst. Via the same technique other derivatives **38.7** have been prepared.[220] A highly activated aromatic ring has been used to construct **38.8** an intermediate in the total synthesis of renierone.[221]

Another possibility for obtaining the intermediate is the protonation of an enamide of which examples can be found in the syntheses of berberine alkaloids[222] and of lycopodine.[223] In the former case a disadvantage of this method is illustrated by the failure to cyclize **38.9**. Protonation of the amide carbonyl is favoured due to the presence of an electron-releasing OMe group, thus effectively blocking the generation of the intermediate for subsequent ring closure. As discussed before ω-alkoxy lactams obtained by reduction of cyclic imides can serve as efficient precursors for N-acyliminium species. In this manner a number of alkaloids have been synthesized. Work on the total synthesis of emetine alkaloids by cyclization of **38.10a**[224] and of **38.10b**[225] and on the construction of the corynoline skeleton via $NaBH_4$-reduction of **38.11**[226] is noteworthy in this respect. A useful variant of the cyclization method is demonstrated in the synthesis of saframycin B[227a] in which the aldehyde amide **38.12** is obtained by ozonolysis of an alkene precursor. Upon reaction of **38.12** in HCOOH (60°, 20 min) ring closure takes place to **38.13**. The N-acyliminium ion **38.15** generated by an acid-catalyzed isomerization of **38.14** leads to tricyclic lactam **38.16**. The latter structure is formally derived from ring closure of a monosubstituted imide precursor in which the N-acyliminium intermediate is formed with complete regiocontrol.[227b]

Seven-membered rings can also be prepared by similar techniques albeit that depending on the type of aldehyde used inter- and intramolecular amidoalkylation may compete. Thus, for R = H the formation of **39.1a** in PPA–AcOH at r.t. is less efficient (36%) than for R = Ph (64%) ($R^1 = R^2$ = Me). Even more pronounced is the difference in **39.1b**. For R = veratryl the yield is 84% while for R = H only

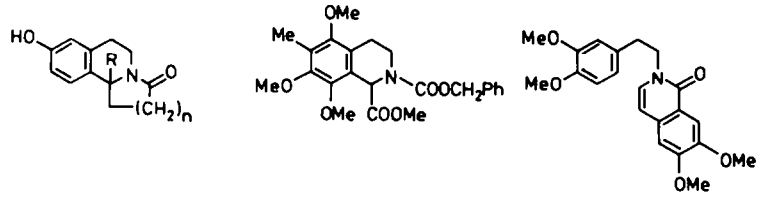


38.1 38.2 38.3

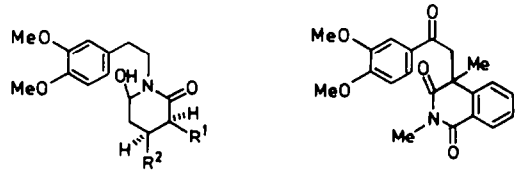


38.4 38.5 38.6

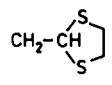
a $R^1 = O$ $R^2 = H_2$ $R^3 = H$
b $R^1 = H_2$ $R^2 = O$ $R^3 = H$
c $R^1 = O$ $R^2 = H_2$ $R^3 = c\text{-}CH_2CH_2$

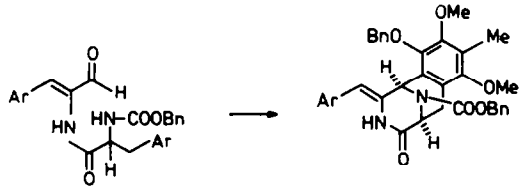


38.7 38.8 38.9

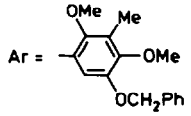


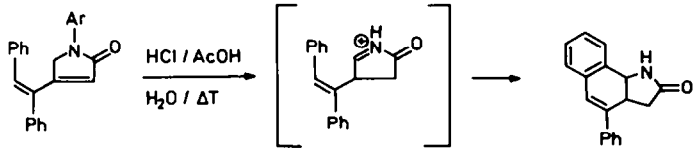
38.10 38.11

a $R^1 = R^2 = H$
b $R^1 = Et$ $R^2 =$ 



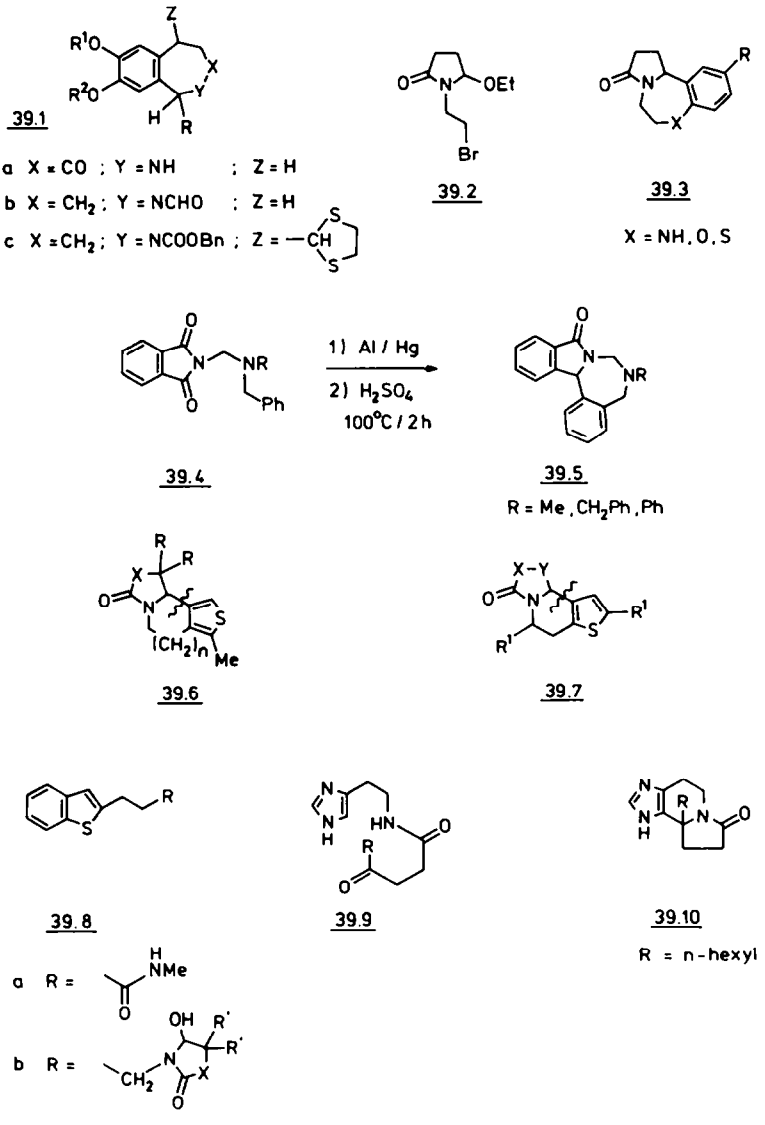
38.12 38.13





38.14 38.15 38.16

Scheme 38.



Scheme 39.

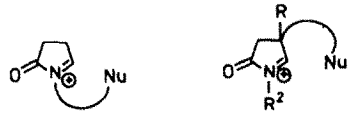
intermolecular coupling is observed[228] ($R^1 = R^2 = Me$). A recent application of seven-membered ring formation is found in the synthesis of the elwesine precursor **39.1c** ($R = H$; R^1, $R^2 = CH_2$).[229] Benzodiazepines **39.3** are formed in the reaction of ethoxylactam **39.2** with substituted aromatics ArXH and ensuing ring closure.[230] For X = NH the liberated $ArNH_3 \cdot Br$ serves as a catalyst, for X = O, S the use of Lewis acid is necessary. Benzodiazepines-2,4 **39.5** have been obtained from phthalimides **39.4** in the manner indicated.[231]

Heteroaromatic rings can also serve as π-nucleophiles. Cyclization may start from appropriate alkoxy lactams or linear amides which are subjected to similar types of condensation as discussed before. Upon reaction of thiophenes compounds of type **39.6** and **39.7** have been prepared. Thus, via the alkoxy lactam (X = NH, O and S; R = H, CH_3; $n = 1$) cyclization to **39.6** occurs in HCOOH at 60° while for $n = 2$ upon use of the stronger acid CF_3COOH at 60° the seven-membered **39.6** is formed.[232] Thienopyrazines **39.7** (X—Y = CH_2—NCOR—CH_2; R^1 = H) have been prepared[233] via cyclization of the alkoxy lactam (12 N HCl, 0°) as isosteres of praziquantel.[218] By the same technique other thieno derivatives **39.7**, e.g. (X—Y = O—CMe_2; R^1 = H, Me) or (X—Y = O—CHPh; R^1 = Me) have been obtained.[106] Upon use of benzthiophenes **39.8** the corresponding thienoazepines have been obtained either by condensation with formaldehyde from **39.8a** ($(CH_2O)_n$/HCOOH/60°/14 h) or by ring closure of the hydroxy lactam **39.8b** ($CF_3COOH/\Delta T$/3 h).[234] The imidazole moiety is also well known to

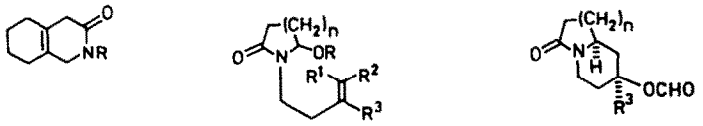
function as an activated aromatic π-nucleophile. Thus cyclization of **39.9** to **39.10** occurs readily upon boiling in 10% AcOH.[235]

E. REACTIONS OF NON-AROMATIC π-NUCLEOPHILES

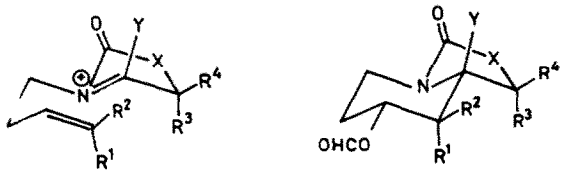
While the first major improvement in the experimental N-acyliminium chemistry consisted of the preparation of stable precursors an equally important contribution was made when the particular reactivity towards olefins was discovered. Although the principle had been described already by



40.A 40.B 40.C



40.1 40.2 40.3



40.4 40.5

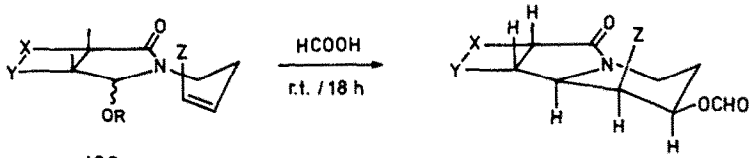
a $R^1 = R^2 = R^3 = R^4 = H$

b $R^1 = Et$; $R^2 = H$; $R^3 = R^4 = H$

c $R^1 = H$; $R^2 = Me$; $R^3 = R^4 = H$

d $R^1 = Et$; $R^2 = H$, $R^3 = H$; $R^4 = OMe$

e $R^1 = Et$; $R^2 = H$; $R^3 = Ph$; $R^4 = Me$



40.6 40.7

a X-Y = c-$(CH_2)_2$ Z = H, Et

b X-Y = c-$(CH_2)_4$ Z = H, Et

c X-Y =  Z = H, Et

d X-Y =  Z = H, Et

Scheme 40.

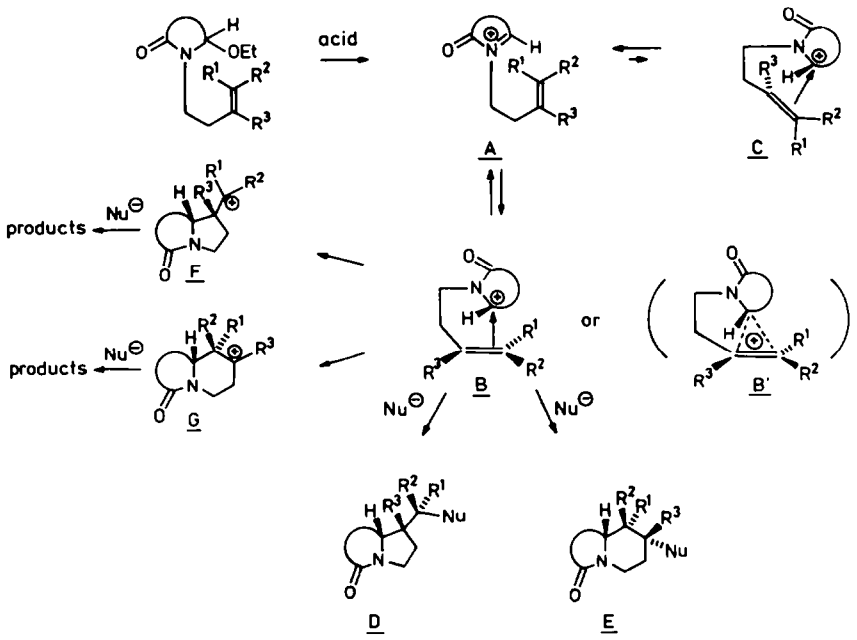


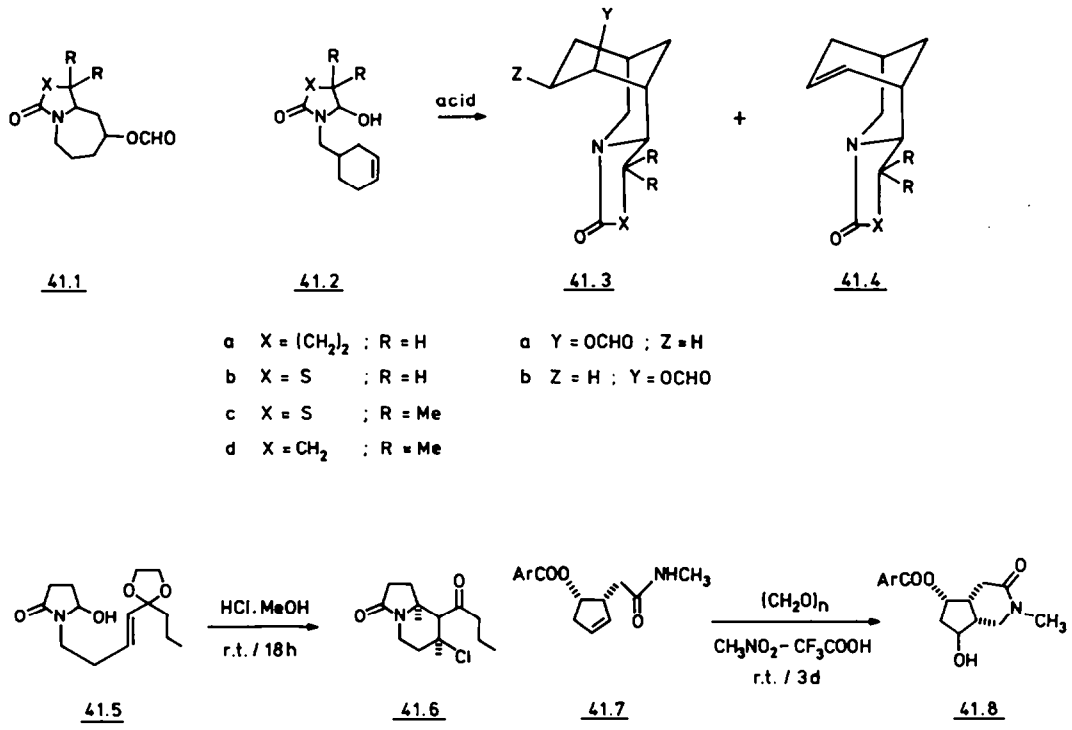
Fig. 1. Mechanism of cyclization.

Belleau[236] in the synthesis of **40.1** the harsh experimental conditions to form the intermediate prevented general use. The synthesis of alkoxy lactams **40.2** provided a first opportunity for testing the real electrophilic nature of N-acyliminium ions toward olefins. The high reactivity of these ions was evident from their behaviour in formic acid at r.t. For $R_1 = R_2 = R_3 = H$ a high yield of the single stereoisomer **40.3** was obtained, which constituted the basis of a great number of applications.[237,238] Before discussing these in more detail, some general comments on the reaction of N-acyliminium ions with olefins are appropriate. The usual product of the *intermolecular* variant is an oxazine, arising from a Diels–Alder type reaction in which the N-acyliminium ion acts as the diene.[2d] As far as we know, the obtention of this kind of product from an *intramolecular* process has not been published. This is primarily due to the fact that intramolecular reactions have been mostly conducted with N-acyliminium ions in which the diene part is locked in a *s-trans* conformation, thus unable to give a Diels–Alder product. The usual products of the intramolecular olefin reaction thus are of type **40.3**, i.e. the result of electrophilic addition. This process is mechanistically closely related to the well-known cationic olefin cyclization, recently rediscussed by Dewar and Reynolds.[239] Figure 1 shows the mechanistic rationale for a cyclization reaction, in which the double bond is connected with the nitrogen of the N-acyliminium ion via an ethylene bridge.

The N-acyliminium ion **A** is in equilibrium with π-complex **B** or **C**. The ring formed has a chair-like conformation in **B** and a boat-like conformation in **C**. Consequently, **B** is much more favourable. (In the N-acyliminium literature **B** has also been depicted as bridged carbenium ion **B'**.) Note, that in these π-complexes the geometry of the double bond is retained. **B** can then react with a nucleophile to give either **D** or **E** or a mixture of these products depending on the ring size of the lactam and the nature of R^1, R^2 and R^3. Alternatively, if R^1, R^2 or R^3 are (strongly) cation-stabilizing groups, **B** may transform into discrete carbenium ions **F** or **G**. These ions lead to thermodynamic mixtures of products on reaction with a nucleophile. Virtually all of the olefin cyclization reactions discussed in the sequel can be adequately explained on the basis of the mechanistic scheme of Fig. 1.

E.a. *Monosubstituted and Vicinally Disubstituted Olefins*

With respect to the site of attachment of the chain containing the π-nucleophile three types of cyclization, i.e. **40.A**, **40.B** and **40.C** can be distinguished. Ring closures of type **40.A**, exemplified by the conversions **40.4a** to **40.5a**, **40.4b** to **40.5b** and **40.4c** to **40.5c** ($X = CH_2$ or CH_2CH_2, $Y = H$), lead to high



41.1 41.2 41.3 41.4

a X = $(CH_2)_2$; R = H
b X = S ; R = H
c X = S ; R = Me
d X = CH_2 ; R = Me

a Y = OCHO ; Z = H
b Z = H ; Y = OCHO

41.5 41.6 41.7 41.8

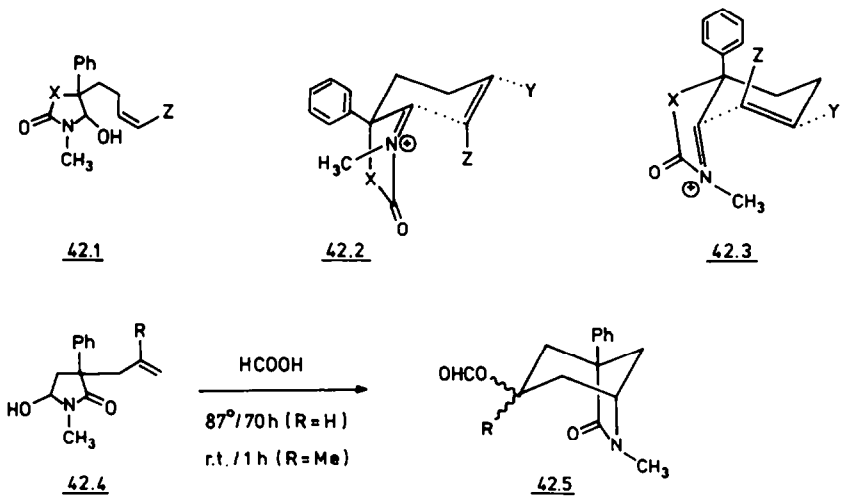
Scheme 41.

yields of single isomers.[240] The relative size of substituents R^3 and R^4 determine on which side of the lactam the new C—C bond is preferentially formed. Thus, **40.4d** (X = CHOMe, Y = H) gives **40.5d**[241] and **40.4e** (X = S, Y = H) **40.5e**[104] as the exclusive products. The high stereoselectivity of this latter conversion is really surprising. A similar result has been obtained in the total synthesis of (+)-heliotridine, where an acetoxy group directs the ring closure (R_3 = H, R_4 = OAc).[95] All cyclizations **40.4** to **40.5** proceed completely stereospecifically, i.e. the olefin geometry is retained in the product.

Whereas for the tertiary hydroxy lactam **40.4a** (X = CH_2, Y = CH_3) ring closure to **40.5a** is observed, the lactam **40.5b** (X = CH_2, Y = CH_3) fails to cyclize,[114] presumably indicating a major steric effect of the tertiary carbenium ion on the attainment of the necessary conformation for cyclization. Such effects have also been noted for bifunctional π-nucleophiles (Section E.e). In addition, different tertiary hydroxy lactams may be used as initiators. Thus **40.4a** (X = CH_2, Y = CH_2Ph) and (—$\overline{CHS(CH_2)_3S}$) both give the formates **40.5a** in yields of 60–65% upon treatment with formic acid.[114] From extensive work on ring annelated lactams **40.6** of type **40.A** which cyclize to **40.7** no deviations from the stereochemical pattern were detected.[242]

Although the methodology outlined above is best suited for the construction of six-membered rings, larger rings can also be synthesized in acceptable yields. Thus compounds **41.1** are obtained as 3 : 1 mixtures of formate epimers in about 70% yield.[104] In view of the slower rate of cyclization (r.t./119 h/HCOOH) only gem-disubstituted (e.g. **41.1**, R = Me) products can be obtained since otherwise enamide formation and subsequent isomerization or dimerization are becoming competitive. The cyclohexenyl precursor **41.2a** undergoes cyclization to a 54 : 46 mixture of formates, the expected **41.3a** and the rearranged **41.3b** upon reaction in formic acid. The composition of the mixture turned out to be dependent on the acidity and nucleophilicity of the medium used.[240] The structure of lactam and the presence of additional substituents also influences the results as is illustrated by the cyclization of **41.2b–d** resulting in the formation of type **41.3** compounds in addition to the elimination product **41.4**.[104] The N-acyliminium–olefin technique has been used in syntheses of a number of natural products. Illustrating this respect are the preparation of the elaeokanine B precursor **41.6** by cyclization of **41.5**[243] and the ring closure of amide **41.7** to lactam **41.8** in prostaglandin work.[244]

In the second type of ring closure **40.B** mixtures of diastereomers are expected, the composition of which will depend on the type of substituent R. Thus, in the synthesis of alkaloids containing the



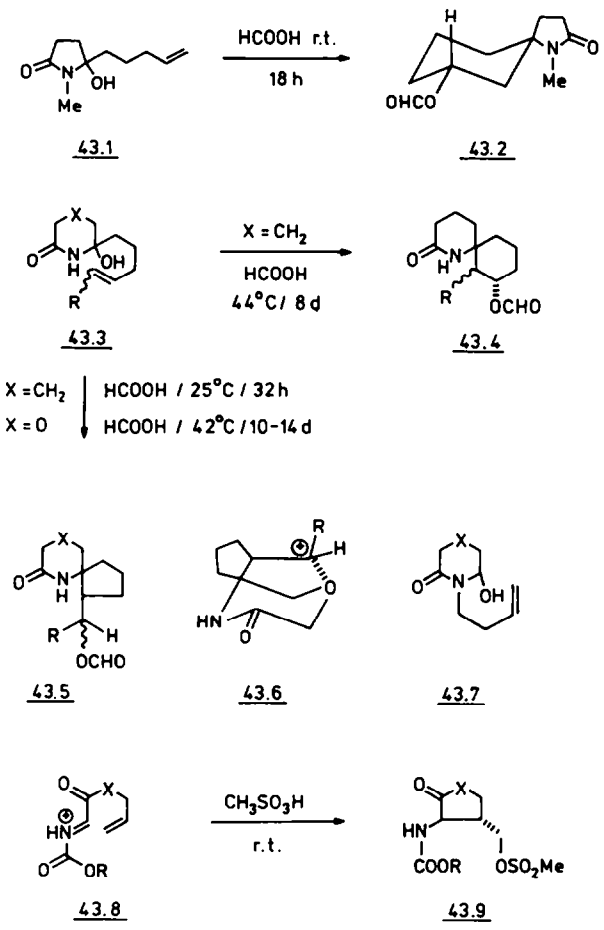
Scheme 42.

arylpyrrolidine fragment the cyclization of **42.1a** (X = CH_2, Z = H) preferably gives the isomer resulting from transition state **42.2a** in which the phenyl group occupies the equatorial position.[245] The Et-substituted thiazolidone **42.1b** (X = S, Z = Et) also exclusively cyclizes according to **42.2b**. The unsubstituted alkene **42.1c** (X = S, Z = H), however, surprisingly only gives the cyclic product formed via **42.3c** in which the sulfur atom is equatorial and the phenyl group axial. In all cases *cis* fused bicyclics are obtained.[214] A related process is the ring closure of lactams **42.4**. Whereas treatment of **42.4a** (R = H) with HCOOH at r.t. gives no ring closure, the corresponding reaction at 87° for 70 h leads to the 6-azabicyclo[3.2.1]octanes **42.5a** as a 3:2 mixture of formate epimers in 70% yield. The Me-substituted olefin **42.4b** (R = Me) smoothly cyclizes in HCOOH at r.t. to **42.5b** as a single epimer.[246] From these data it may be inferred that minor variations in ring structure may have a profound influence on the stereochemical outcome of an N-acyliminium ring closure.

Cyclizations of type **40.C** lead to spirocyclic compounds. Thus, azaspirane **43.2** has been prepared in good yield by ring closure of the lactam **43.1**.[247] The conversion of **43.3** (X = CH_2) to **43.4** constitutes the key step in the total synthesis of perhydrohistrionicotoxin[248] and is interesting for several reasons. Firstly, the reactive centre involved is a tertiary N-acyliminium ion while the C—C bond formation is of the spiro-type. Secondly, the regioselectivity of the process is remarkable, since in pure HCOOH only a 6-endo-trig process is observed leading to **43.4** in 30% yield, whereas in a parallel study in addition to **43.4** (33%) a substantial amount of epimers **43.5** is obtained.[249] While the origin of this conflicting solvent effect is unclear—neither the possibility of a Wagner–Meerwein rearrangement of **43.5** → **43.4** nor the question of kinetic vs thermodynamic control has been investigated—the closely related (*Z*)-alkene carbinolamide **43.3** (X = O) exclusively affords a single stereoisomer of **43.5** while the corresponding reaction of the (*E*)-alkene isomer of **43.3** (X = O) gives the alternative epimer of **43.5**.[248] The latter result may be explained by assuming a directive influence of the oxygen atom as indicated in **43.6** and a synchronous bond formation process occurring. In related systems such as morpholine and thiazine precursors **43.7** only 6-endo products are obtained.[250] Five-membered ring formation has also been noted in amidoalkylations of linear precursors **43.8** affording 5-exo-trig products **43.9** (X = O, NH)[251] possibly because of the greater stability of the heterocyclic ring.

E.b. *Allylic Substituents*

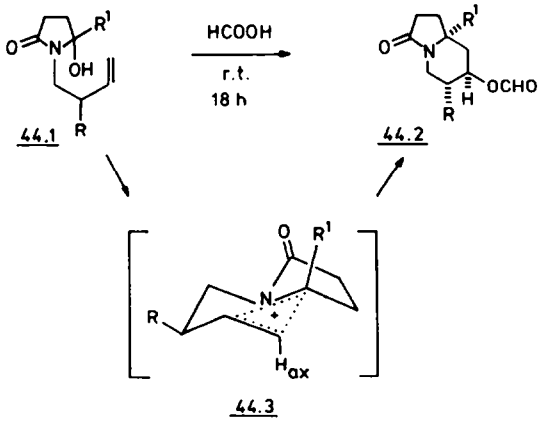
Reactions of **44.1** (R = CH_3, CH_2OBz, CH_2Ar; R^1 = H, CH_3)[217,252,253] in formic acid at r.t. proceed in high yield to afford the bicyclic lactams **44.2**. The exclusive formation of products with the indicated stereochemistry can be explained by assuming a preference for a chair-like transition state with an equatorially oriented R group (**44.3**) so that an eventual 1,3-diaxial interaction between R and H_{ax} is avoided. In addition, attack of the formate anion on **44.3** would be difficult for steric reasons, if the group R were axially disposed. In the case of **44.1** (R = Ph, R^1 = H) an aza-Cope rearrangement precedes N-acyliminium ion cyclization, leading to a product with a five-membered ring (cf. Section G).



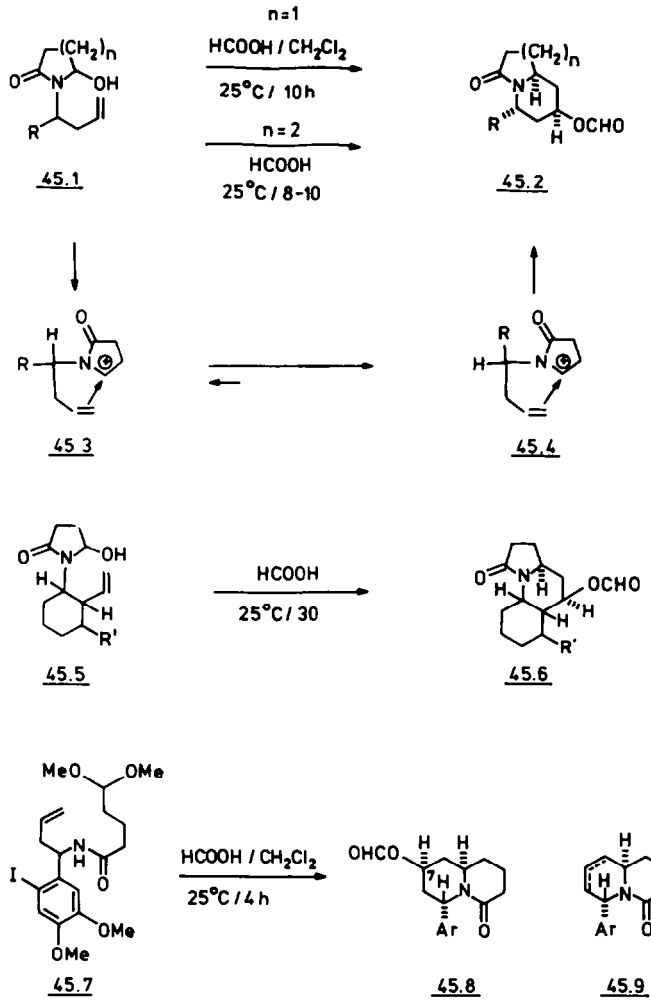
Scheme 43.

E.c. *Homoallylic Substituents*

A distinct stereocontrol was observed for ring closures **45.1** ($n = 1$, R = *n*-Pr);[254] ($n = 2$, R = Ph)[255] preferentially leading to **45.2** in which R and both methine hydrogens are *cis* related. This result has been explained on the basis of an unfavourable $A^{(1,3)}$-strain in the transition state **45.3** favouring the alternate structure **45.4**. A closely related example is represented by the reaction of **45.5** leading to **45.6**.[256] The compound **45.1** ($n = 2$, R = Ar) is an intermediate in the HCOOH cyclization of



Scheme 44.

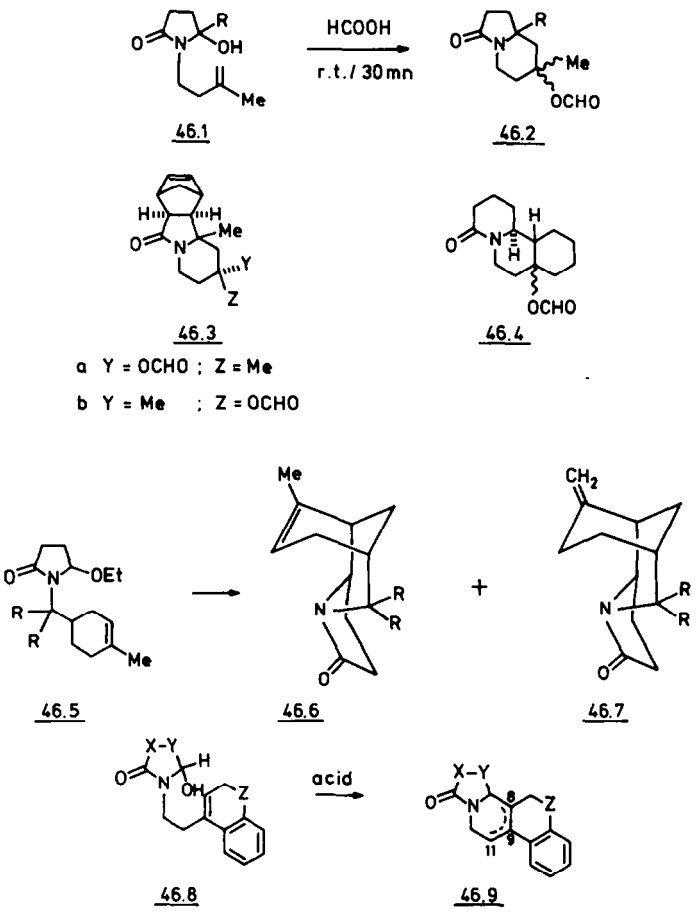


Scheme 45.

45.7 to **45.8** and **45.9** which leads to the Lythraceae alkaloid vertaline. This is also one of the examples where an open amido-acetal is applied as a precursor for a cyclic N-acyliminium ion.[257] Compounds **45.3** (R = CH=CH_2) have been used in the synthesis of depentylperhydrogephyrotoxin[256] and gephrotoxin.[258–260] For a discussion of the tendency of the N-acyliminium ion derived from **45.1** to undergo an aza-Cope rearrangement[254] see Section G.

E.d. 2-*Alkylsubstituted Olefins*

In contrast with the results discussed so far, cyclization of **46.1** (R = H, Me) affords a thermodynamic mixture of epimers **46.2** the composition of which can be only slightly influenced by the type of acid used.[240] Ring closure is rapid and most likely proceeds via a discrete carbenium ion intermediate. That the formation of a kinetically controlled isomer is also possible is demonstrated by the results in the norbornyl derivative **46.3** in which after initial formation of **46.3a** a slow isomerization to **46.3b** occurs.[244] Such a process is also noted in the formation of lactam **46.4** consisting of a mixture of *cis* and *trans* isomers the composition of which depends on the type of acid used and the reaction conditions. The olefin mixture **46.6** + **46.7** (9:1) was exclusively formed upon ring closure of **46.5** (R = H),[240] for R = CH_3 **46.5** cyclized to a 3:1 mixture of **46.6** and **46.7**.[261] Lastly, lactams **46.8** (X—Y = CH_2CH_2; Z = CH_2 or S)[262] or (X—Y = O—$C(CH_3)_2$, S—CH_2 and NH—$C(CH_3)_2$; Z = CH_2)[263] have been cyclized to the corresponding tetracyclic products **46.9** which were obtained as Δ9,11 isomers in HCOOH at r.t. or as Δ8,9/Δ9,11 mixtures depending on the conditions.

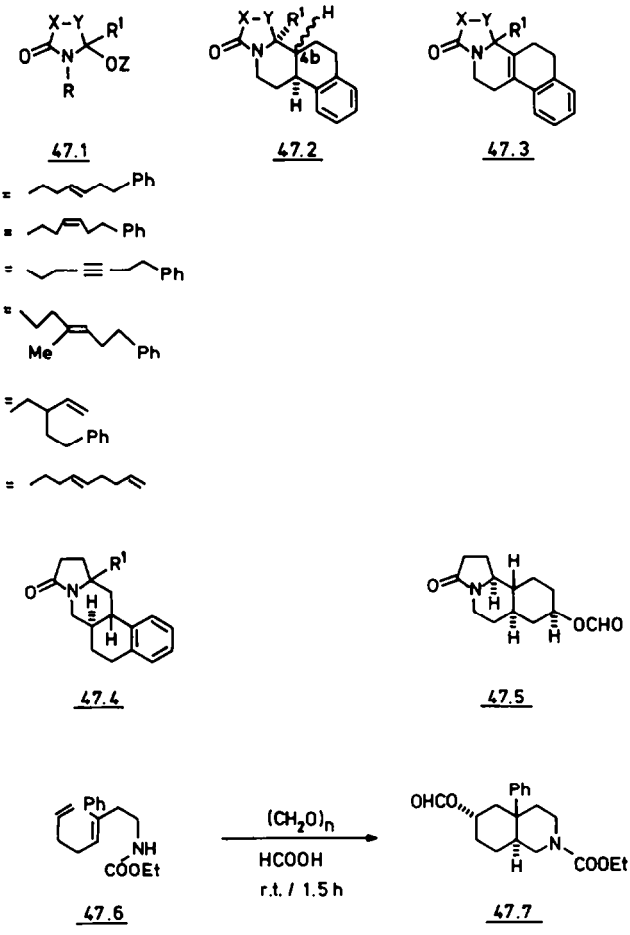


Scheme 46.

E.e. *Diolefins: Formation of Two Carbon–Carbon Bonds*

The impressive results obtained in the stereoselective polyolefin conversions to condensed carbocyclics by Johnson promoted a search for similar reactions in related fields.[264] Thus, as a highly versatile intermediate in cationic alkene cyclization the N-acyliminium ion was probed in reactions of bifunctional π-nucleophiles. As initiating species the hydroxy lactams **47.1** were employed in which X—Y has been chosen as CH_2CH_2, **47.1a–47.1d, 47.1f**;[265] CH_2CH_2 **47.1e**;[252] S—$C(CH_3)_2$ **47.1b**;[104] CHOMe—CHOMe **47.1a, 47.1b**.[266]

In general the reactions are highly stereoselective, giving *trans* products **47.2** (β-H_{4b}) from (*E*)-olefin **47.1a** (R^1 = H or CH_3) and *cis* products **47.2** (α-H_{4b}) from (Z)-olefin **47.1b** (R^1 = H or CH_3). The latter process is a cyclization leading to an all-*cis* stereochemistry. Somewhat remarkable are the cyclizations of **47.1b** (R^1 = CH_3) and **47.1d** (R^1 = CH_3) since the first represents a (*Z*)-olefin ring closure mediated by a tertiary N-acyliminium species (cf. Section E.a) while the second is another example of full stereocontrol of a 2-alkyl-substituted olefin (cf. Section E.d). Apparently, in the transition state the phenyl ring will induce and/or influence the necessary conformation for ring closure, while it may also be a better nucleophile to trap the first formed π-complex. Acetylenes may function equally well in this type of double cyclization as is indicated in the conversion **47.1c** → **47.3**. A different type of aryl olefin is represented by **47.1e** (R^1 = H, CH_3). The product formed in this case almost quantitatively is tetracycle **47.4** its stereochemistry again explained on the basis of a chair-like transition state, the phenylethyl residue occupying an equatorial position.[252] As the terminal π-nucleophile also an olefin may be chosen. Thus **47.1f** cyclizes in HCOOH/r.t. to a mixture of products from which **47.5** is obtained in 70% yield.[264] Similarly, the 1,5-diene **47.6** upon treatment with paraformaldehyde in HCOOH gives the isoquinoline derivative **47.7**.[267]



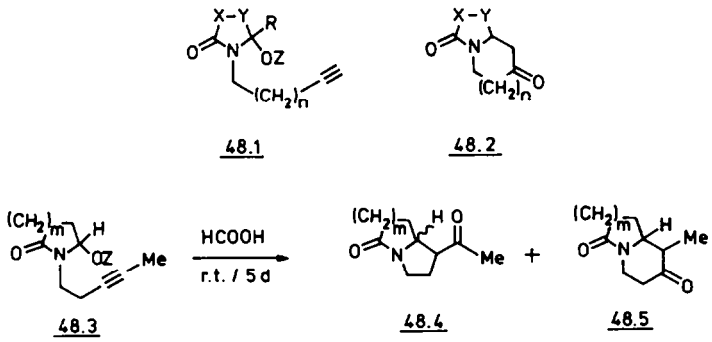
Scheme 47.

E.f. *Alkynes*

Participation of the alkyne function in cationic carbon–carbon bond forming processes has been applied in a number of syntheses.[242] The hydroxy lactams **48.1** (X—Y = $(CH_2)_2$, $(CH_2)_3$; $n = 2,4$; R = H);[17] (X—Y = $(CH_2)_2$; $n = 2$; R = CH_3);[114] (X—Y = CHOMe—CHOMe; $n = 2$, 4; R = H);[241] (X—Y = S—$C(CH_3)_2$; $n = 2$, 4; R = H)[104] also undergo smooth cyclization to the corresponding ketones **48.2** in high yields. In view of the energy difference between the two possible intermediate vinyl cations only *endo*-dig type ring closure occurs even in case of macrocyclic synthesis **48.1** → **48.2** (R = H, $n = 10$).[268] Only in electronically unbiased acetylenes, e.g. **48.3** where ring strain effects interfere with the order of stability of linear and bent vinyl cations different results are obtained. Thus cyclization of **48.3** ($m = 1$) gives a 10 : 90 mixture of **48.4** and **48.5**. On the other hand **48.3** ($m = 2$) affords a 85 : 15 mixture of **48.4** and **48.5**.[17] Finally, from a preparative point of view it is to be remarked that alkynes are efficient terminators in N-acyliminium cyclizations, giving rise to ketones which cannot be prepared easily by condensations of active methylene compounds (cf. Section F).

E.g. *Other Types of π-Nucleophiles*

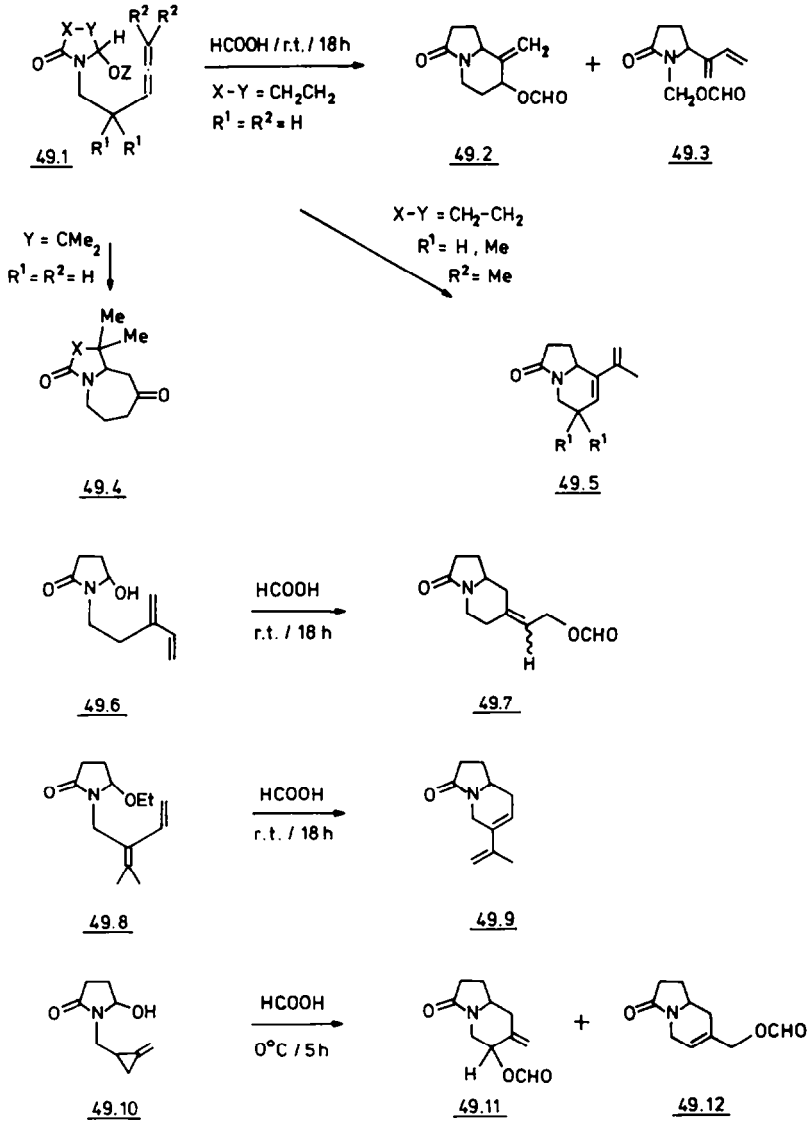
Allenes **49.1** (X—Y = CH_2—CH_2; $R^1 = R^2$ = H) exhibit two types of C—C bond formation upon treatment with acid.[269] The major product is the epimer mixture **49.2**; in addition, the aza-Cope type compound **49.3** is obtained in yields up to 50% depending on the type of acid used. Introduction of Me groups for R^1 and/or R^2 changes the course of the reaction. An exclusive aza-Cope type process occurs for **49.1** (X—Y = CH_2CH_2; R^1 = Me, R^2 = H) (cf. Section G). In case R^2 = Me sole formation of **49.5** takes place. The presence of substituents at the carbon atom adjacent to the reacting centre greatly affects the pathway described above. Thus both **49.1** (X—Y = CH_2—$C(CH_3)_2$ and S—$C(CH_3)_2$;



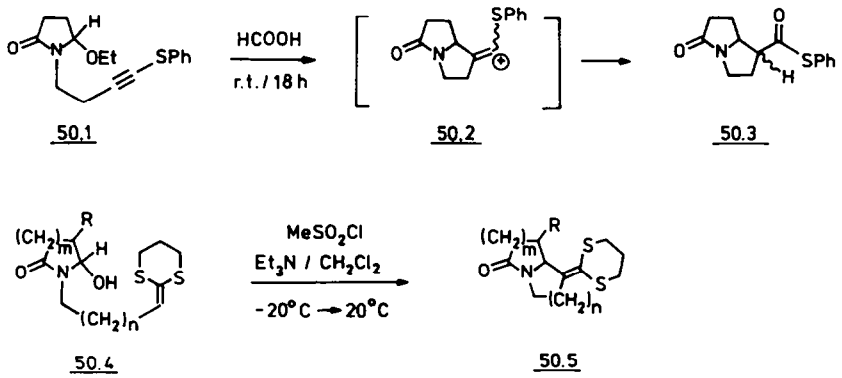
Scheme 48.

$R^1 = R^2 = H$) cyclize to the seven-membered ring **49.4** by the unusual reaction mode of the terminal allenic carbon[214] since for steric reasons the reaction at the central carbon is blocked.

The ring closures of dienes **49.6** and **49.8** afford formates **49.7** (1 : 1 mixture of isomers) and diene **49.9** in nearly quantitative yield.[217] The cyclopropyl derivative **49.10** gives a mixture of formate **49.11** (1 : 2



Scheme 49.



Scheme 50.

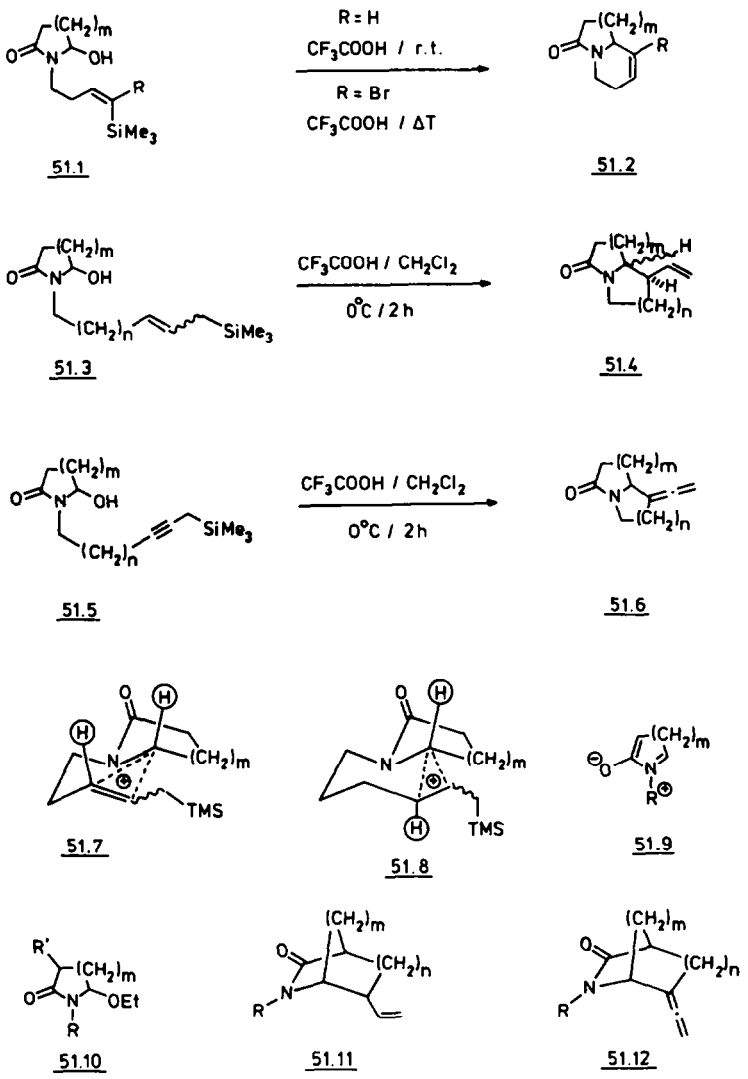
mixture of epimers) and **49.12** in a ratio of 3 : 4. The origin of the latter products is visualized to arise from the allylic cation resulting from a disrotatory electrocyclic ring opening of the cyclopropane cationic intermediate.[217]

E.h. *Sulfur and Silicon Directive π-Nucleophile Substituents*

The reactivity patterns discussed so far can be entirely changed by auxiliary elements connected with the π-nucleophile thereby allowing the synthesis of otherwise difficultly accessible ring systems. Thus, formation of **50.3** as a 4 : 1 epimer mixture by ring closure of **50.1** is explained by a preferred 5-*exo*-dig process leading to **50.2** and subsequent capture of the nucleophile.[270] The ketene dithioacetal function also proved highly effective as a directive substituent. For $m = 1, 2$ and $n = 1, 2, 3$ (R = H) cyclization of **50.4** to **50.5** could be easily effected.[69,271] In view of the acid lability of the ketene dithioacetal group a modification of the usual methodology has been applied which consists of the enhancement of the leaving group ability of the OH moiety. Thus upon conversion of the OH in **50.4** into the OSO_2Me function at −20° and warming to 20° spontaneous cyclization into **50.5** occurs (cf. Section C.e.1). By applying a similar technique to the lactam obtained from (*S*)-malic acid the acetoxy derivative **50.5** (R = OAc, $n = m = 1$) is obtained as a single enantiomer which has been ultimately converted into (+)-heliotridine.[96]

An increasingly important role is reserved for silicon derivatives. As versatile terminators for olefin cyclizations vinyl, propargyl, and allyl silanes have been used, all categories showing excellent reaction behaviour towards the N-acyliminium ion. Thus, upon CF_3COOH treatment of lactams **51.1** ($m = 1, 2$, R = H) nearly quantitative yields of bicyclic systems **51.2** are obtained. Even the bromo derivative **51.1** ($m = 1$, R = Br) cyclizes in refluxing CF_3COOH yielding the alkene **51.2** ($m = 1$, R = Br) in which the unsaturated moiety is regioselectively functionalized.[272] Allyl silanes **51.3** ($m = n = 1$, both (*E*) and (*Z*); $m = n = 2$, (*Z*)) also effectively cyclize to bicyclic lactams **51.4** upon acid treatment.[273] For both $n = 1$ and 2 complete stereocontrol is exerted : for $n = 1$ the vicinal hydrogens in **51.4** are *cis*-oriented, while for $n = 2$ a *trans*-relationship is found. This behaviour is adequately accounted for by assuming reaction via transition states **51.7** and **51.8**. In case $n = 3$, a 2 : 1 mixture of stereoisomers **51.4** is obtained. By the same method allenes **51.6** are formed upon CF_3COOH/CH_2Cl_2 treatment of propargyl silanes **51.5**.[273]

A useful modification of this technique consists of the ring closure of lactams **51.10** leading to bicyclic systems of types **51.11** and **51.12**. The starting ethoxy lactams **51.10** (R^1 = H) may be considered as masked 1,3-dipoles **51.9** and C—C bond formation through both the anionic and cationic part is feasible. The cyclization often shows high stereocontrol ; e.g. for **51.10a** (R = CH_2Ph, $R^1 = CH_2CH_2\,CH\overset{(Z)}{=}CHCH_2TMS$, $m = 1$) the yield of vinyl compound **51.11** ($m = 1$; $n = 2$) is 82% upon reaction in HCOOH.[274] It is important to note that the ring closure of an ordinary alkene, e.g. **51.10b** (R = CH_2Ph, $R^1 = CH_2CH_2\,CH\overset{(Z)}{=}CHCH_2CH_3$, $m = 1$) only affords in addition to about 50% of elimination a complex mixture of compounds possibly arising from cyclization. Thus the excellent function of the silicon substituent in promoting carbon–carbon bond formation is clearly underlined.



51.1 51.2 51.3 51.4 51.5 51.6 51.7 51.8 51.9 51.10 51.11 51.12

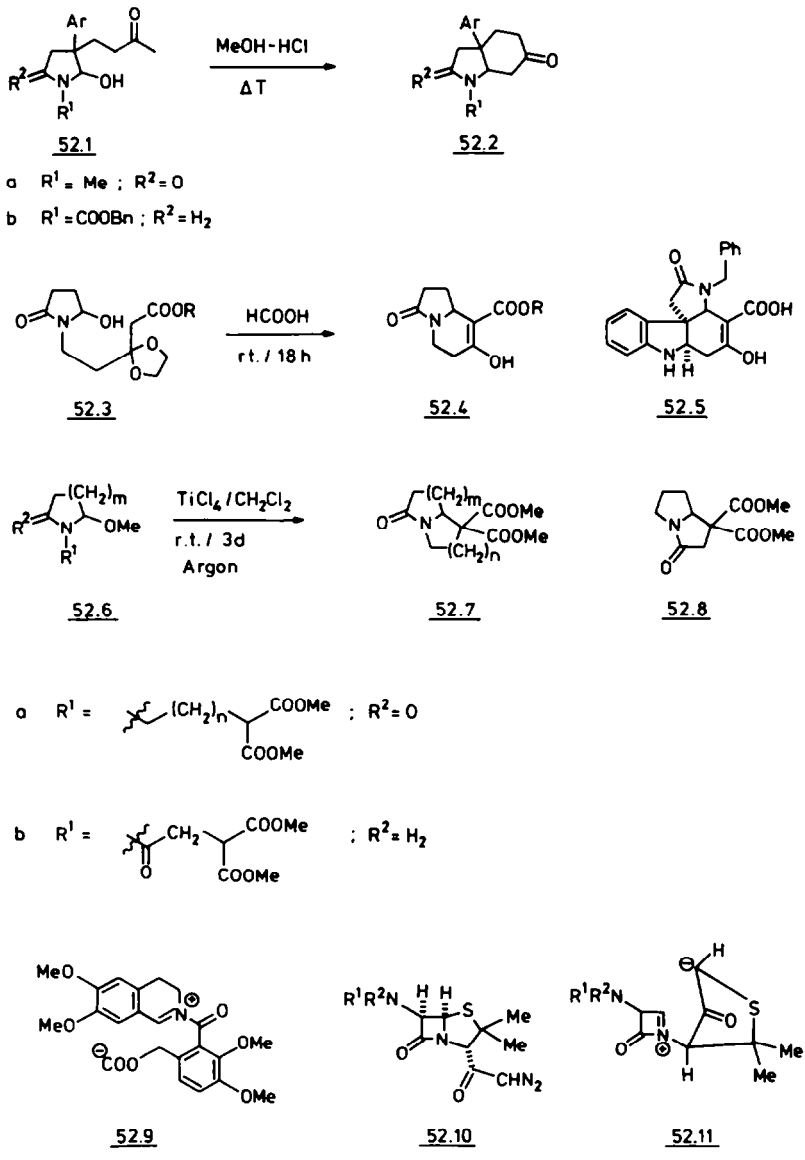
Scheme 51.

Finally, the compounds can be converted into novel types of amino acid derivatives by opening of the lactam ring.

F. ACTIVE METHYLENE COMPOUNDS

While the intermolecular amidoalkylation of enolates, enols and enol ethers constitutes a substantial number of transformations, the intramolecular counterpart is not extensively applied. A possible factor explaining such omission is the fact that products of similar type can be obtained also via ring closure of a suitable π-nucleophile. Acid catalyzed ring closure of the ketal of **52.1a** leads to cyclic ketone **52.2a** which is an intermediate in the synthesis of mesembrine.[242] Similarly acid treatment of hydroxy lactam **52.1b** affords **52.2b**.[275] In both cyclizations fairly drastic acid conditions are required to effect a satisfactory enol concentration in the N-acyliminium intermediate. Activation by a β-ester substituent provides the ketoester, possessing a higher enol content, as the nucleophile which reacts under milder conditions. Thus ring closure of **52.3** in formic acid provides **52.4** in quantitative yield.[276] This reaction was applied in the total synthesis of vindorosine via the tetracyclic lactam **52.5**.[277]

In contrast to the facile proton catalyzed condensation of Mannich-type intermediates with dialkyl malonates the corresponding reaction with alkoxy lactams completely fails. Due to side reactions only polymeric products derived from the intermediate enamide can be isolated. By using a Lewis type



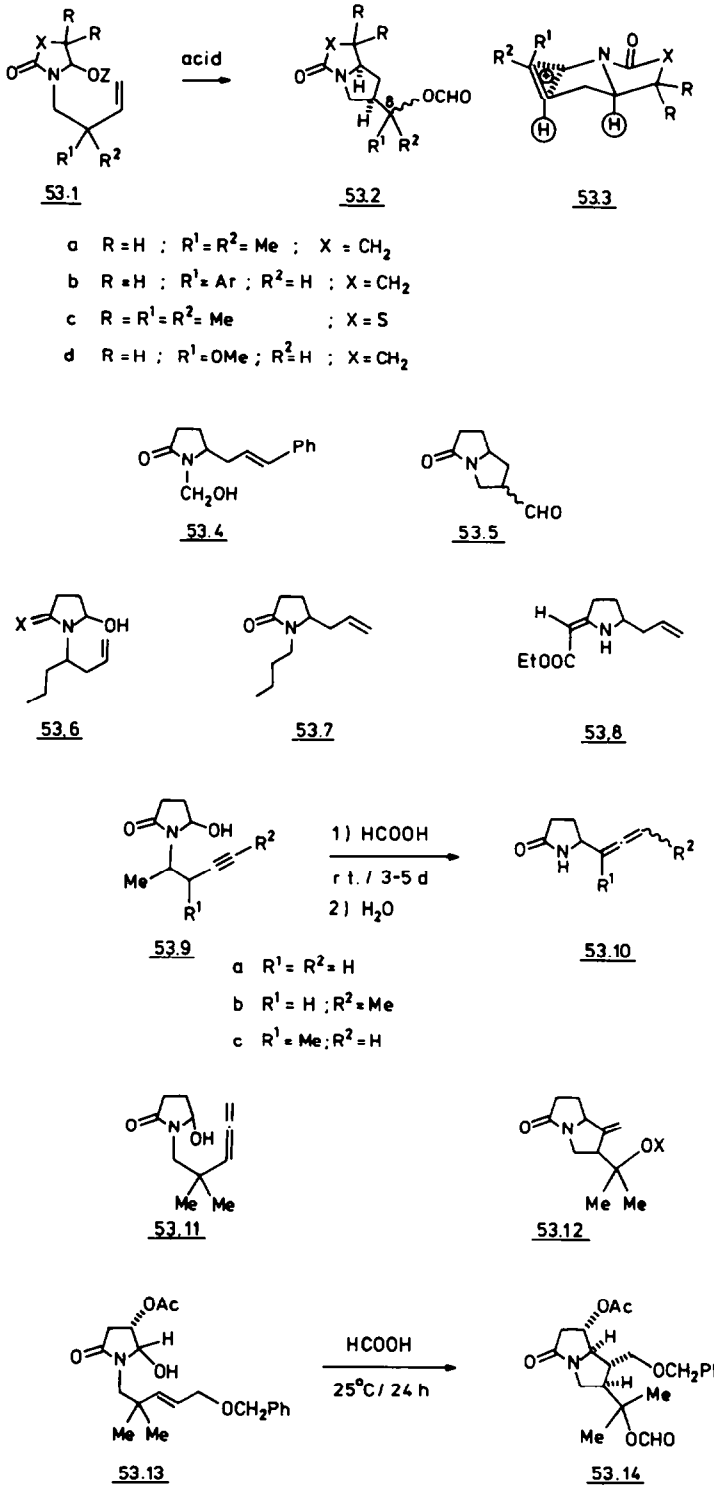
Scheme 52.

catalyst, however, good yields of condensation products can be obtained.[278] Thus a number of alkaloids has been synthesized via the diester **52.7** obtained by $TiCl_4$ mediated ring closure of the alkoxy lactam **52.6a** ($m = 2, 3, n = 1, 2$).[279] Similarly, pyrrolizidine **52.8** has been prepared from **52.6b** ($m = n = 1$) by a $AlCl_3$ catalyzed bond formation.[280]

It may be recalled (cf. Section C.a.3) that isoquinoline imines react with homophthalic anhydrides by way of intermediate **52.9**, the process is also a condensation at an activated methylene carbon.[281] Finally in the β-lactam field the metal-catalyzed decomposition of diazoketones **52.10** leads to intermediates of type **52.11** which subsequently cyclize to a *trans* β-lactam in the usual manner.[282] Similar reactions have been reported by other workers.[283,284]

G. PERICYCLIC REACTIONS

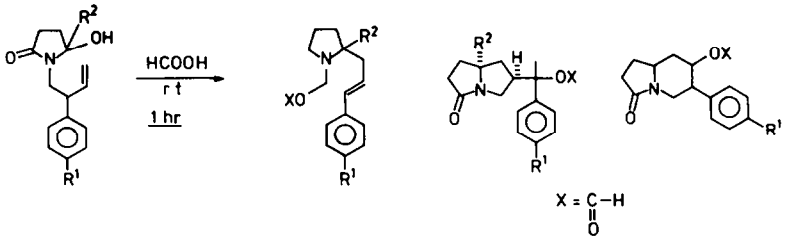
A remarkable deviation of the generally observed reaction pattern of intramolecular N-acyliminium cyclizations is exhibited by compounds of type **53.1a**. Whereas for $R^1 = H$, $R^2 = Me$ a diastereomerically controlled synthesis of indolizidines is observed (Section E.b) the introduction of a second alkyl substituent changes the outcome dramatically.[285,286] Instead of the indolizidine now the pyrrolizidine **53.2a** is obtained in high yield. Its formation is rationalized by a [3,3] sigmatropic



Scheme 53.

equilibrium between the secondary N-acyliminium ion **54.A** and its primary form **54.B** (Scheme 54). Although it seems probable that **54.A** is less unstable than **54.B** product formation may still occur via **54.B** if the ensuing cyclization is a fast reaction. This is very likely for the reaction of a primary N-acyliminium ion with a more nucleophilic π-bond as in **54.B**. Such behaviour was investigated in the reaction of **53.1b** by varying the aromatic substitution pattern.[287] From the results collected in Table 3 a dependence of the 5,5-product formation in relation to the type of aromatic substituent is easily

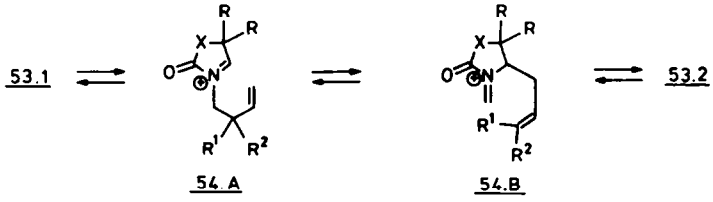
Table 3. Time dependent aza-Cope N-acyliminium cyclizations



a $R^1 = H$; $R^2 = H$				
	32	56	12	<1
b. $R^1 = OCH_3$; $R^2 = H$				
	16	11	73	<1
c. $R^1 = Cl$, $R^2 = H$				
	48	47	3	2
d $R^1 = H$; $R^2 = CH_3$				
	24	50	26	<1
Time	4 hr			
a	4	65	26	5
b	<1	<1	99	<1
c.	5	74	12	9
d.	1	12	82-84	3-5

verified. The stereochemical outcome is understood by assuming a favourable chair-like transition state of bridged intermediate **53.3** leading to the product **53.2b** with *cis* C_{4a}—H, C_6—H stereochemistry as a 1 : 1 mixture of two C_8 stereoisomers. In case of **53.1b** (Ar = phenyl) the intermediate primary N-acyliminium ion can be trapped as the hydroxy lactam **53.4** by carrying out the cyclization in CF_3COOH/CH_2Cl_2 followed by SiO_2 chromatography. Other types of hydroxy lactams, e.g. **53.1c** and **53.1d** also show an aza-Cope rearrangement leading to products **53.2c** and **53.5**, respectively.

Whereas the N-acyliminium ion **54.B** is intramolecularly captured, which promotes the aza-Cope type reaction, the equilibrium **54.A** ⇄ **54.B** can also be influenced by the introduction of substituents at the methylene carbon of the iminium moiety of **54.B**. Thus, upon treatment of **53.6** (X = O) with acid in the presence of triethylsilane the lactam **53.7** was found in a yield up to 45% among the products formed.[254] This result again confirms the existence of two types of N-acyliminium ions in rapid equilibrium with each other. A similar observation was made in the treatment of **53.6** (X = CHCOOEt) with acid and subsequent hydrolysis leading to **53.8**.[256] Upon reaction of the propargyl derivatives **53.9a–c** a series of allenic derivatives **53.10a–c** have been prepared by the aza-Cope rearrangement followed by hydrolysis of the intermediate N-acyliminium ion.[288] As may be expected from previous results with acetylenic π-nucleophile[5] (Section E.f) the rearrangement takes place only with N—C_α substituted acetylenes **53.9**. A final category of π-nucleophiles easily undergoing the aza-



Scheme 54.

Cope rearrangement is exemplified by the allene **53.11**. The exclusive material formed, is the pyrrolizidine **53.12**[269] which is obtained in 94% yield as a 4:1 mixture of formate (X = CHO) and alcohol (X = H). A synthetic application of the rearrangement is constituted by the total synthesis of (−)-hastanecine[289] in which the conversion of **53.13** to **53.14** is the key step.

CONCLUSION

In this review we have attempted to cover the past and present of one of the finest intermediates for the synthesis of heterocyclic molecules. Because of space limitations some aspects have not been included such as the intramolecular formation of carbon–heteroatom bonds and the role of the intermediate in bio-organic chemistry. Other topics form part of a much broader field (e.g. β-lactams and natural product synthesis) and have only been marginally discussed.

As can be evaluated from the examples cited here and in recent other reviews[2] the interest in the practical application of the amidoalkylation is still considerable. Moreover, the added dimension of regio- and stereoselectivity coupled with the use of new terminators and an upsurge in the methods for generating the intermediate opened up new possibilities for its use. We are therefore confident about the future of the N-acyliminium ion and hope that the synthetic community will join this expectation.

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