Recent Advances in Ring Transformations of Five-Membered Heterocycles and Their Fused Derivatives

György Hajós,*[a] Zsuzsanna Riedl,[a] and Gert Kollenz[b]

Dedicated to Professor M. Tišler on the occasion of his 75th birthday

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Ring transformations of five-membered heterocycles and their benzologues for the recent 10 years are discussed and reviewed. These transformations are classified into four groups: (a) "classical ring transformations", where the starting and resulting ring system is of the same size, but the heteroatoms and/or their positions have been changed; (b) "degenerate ring transformations", where during the course of the transformation the starting compound and product have the same ring system, but the reaction proceeds by a ring opening and subsequent ring closure process; (c) "ring contractions" and "ring enlargements", where the sizes of the product rings are smaller or larger, respectively, than those of the starting compound; and (d) "pseudo ring transformation" or "ring-chain transfer", where the process is formally a ring transformation, but is realised by a ring closure of a side chain of the starting heterocycle and opening of the original ring. Reaction mechanisms of the most interesting ring transformations are also discussed.

A. Introduction

Rearrangements of heterocyclic rings by temporary opening and subsequent closure to a new molecule are of particular interest both synthetically and theoretically. Such processes may provide fascinating synthetic routes to derivatives that can be obtained only with great difficulties − or not at all − by other procedures.

The term "ring transformation" obviously refers to reactions where a ring in the starting material will be replaced by another ring in the product. This transformation, however, can proceed in very different ways that all are denoted as "ring transformation" in the literature. Four main subclasses should be discussed in this respect:

[a] Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences,
P. O. Box 17, 1525 Budapest, Hungary
Fax: (internat.) + 36-1/325-7863
E-mail: ghajos@chemres.hu
[b] Institute of Chemistry, Karl-Franzens University,
Heinrichstrabe 28, 8010 Graz, Austria
Fax: (internat.) + 43-316/380-9840
E-mail: kollenz@balu.kfunigraz.ac.at

György Hajós (left), after his chemistry diploma at Eötvös University in Budapest, Hungary, received his PhD degree with András Messmer at the same university in 1974. Since that time he has been working for the Chemical Research Center, Institute of Chemistry, Hungarian Academy of Sciences where he has held the post of Head of Department of Heterocyclic Chemistry since 1992. As a postdoctoral student he spent two years (in 1975 as a DFG and in 1985 as a Humboldt fellow) in Germany at University of Bochum with Günther Snatzke. He acquired a D. Sc. degree from the Hungarian Academy of Sciences in 1993. Currently, besides supervising his research department, he is also the research deputy director of the Institute since 1996 and an appointed Professor at Eötvös University.

Zsuzsanna Riedl (center) studied at the same university and received her Ph. D. degree, also with András Messmer, in 1980. She received her Candidate of Science degree from the Hungarian Academy of Sciences in 1992. Presently, she is working as a senior investigator in György Hajós's group and, simultaneously, she is the Head of the Instrumental Organic Analytical Chemistry Laboratory of the Institute.

Their research interests are heterocyclic ring closures and ring openings, reactivity of heteroaromatic systems, especially theoretical and experimental studies of electrophilic reactions of heteroaromatics, rearrangement reactions of heterocycles, and synthesis of biologically active (multi drug resistance inhibitory and intercalating) fused systems.

Gert Kollenz (right) received his Ph. D. degree from Karl-Franzens University of Graz, Austria, with Prof. Erich Ziegler in 1967. After postdoctoral studies at the Isotope Center in Harwell, U.K. (1970) and at CIBA-Geigy AG, Basel, Switzerland (1971), his Habilitation was completed in 1972. Since 1982 he has been Professor and Head of the Isotope Laboratory at the Institute of Chemistry, Organic and Bioorganic Division, Karl-Franzens University of Graz. He has held Visiting Professorships at the Ain Shams University in Cairo, Egypt (1990) and at the University of Queensland, Brisbane, Australia (1993). His research interests are mainly devoted to heterocyclic chemistry, synthesis and application of isotopically labelled compounds and, more recently, macrocyclic ring systems with regard to host-guest chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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(a) A "classical ring transformation" in the most rigorous sense means that a ring of a certain size (e.g. five- or six-membered) is transformed to a ring of the same size in the product. This means, that formally one or more ring atoms are exchanged for other ones to form the new ring.

(b) A "degenerate ring transformation" is a particular case of the above class where a ring within the starting material is converted into the identical one by an intermediate opening and closure process.

(c) "Ring contractions" and "ring expansions" denote those ring transformations where the sizes of the rings in the starting compounds and in the products are different.

(d) Apart from (a), (b), and (c), where most of the atoms (at least half of them) of the starting ring are maintained in the ring of the product, additional transformations exist where the ring of the starting material is opened up to form a chain and, simultaneously, a side chain of the starting material forms a ring. This is called "ring-chain transfer", or "pseudo ring transformation". This latter term indicates that a simultaneous ring closure and ring opening rather than ring transformation takes place as the exchange of the previous ring to the new one is only a formal phenomenon, even if one or two atoms (always less than half of the atoms of the previous ring, i.e. maximum one or two) is (are) located in the ring of the final product.

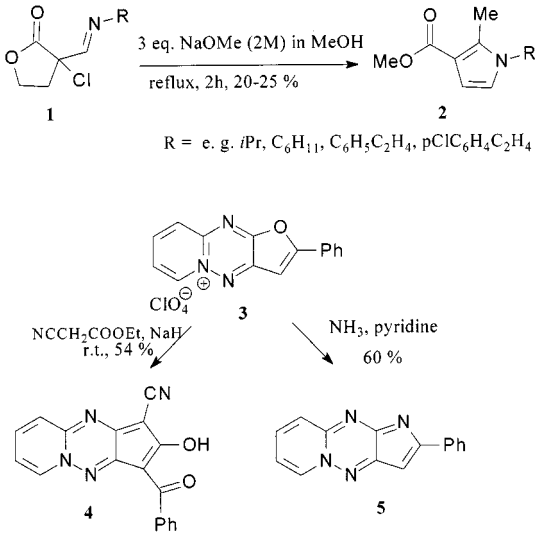
Although the phenomenon of ring transformation has been known for a very long time, and excellent reviews (for instance ref.[1]) appeared on this subject, some recent results in this field indicate that this kind of reactivity of heterocycles is still strongly in highlight of interest. The aim of this review is to discuss some important novelties in the area of ring transformations of five-membered rings and their fused analogues that have appeared in the past 10 years according to the above classifications. A comprehensive review on a similar subject was presented in 1993.[1] Because of the limits of this paper, transformations where the number of the fused rings is different in the starting material and product (e.g. a monocyclic compound is transformed to a bicyclic one) will not be discussed.

B. Classical Ring Transformations

B.1. Ring Transformation of Monocyclic and Fused Furans

Lactones are excellent targets for nucleophiles and are therefore appropriate starting compounds for ring opening reactions. De Kimpe et al.[2] have reported recently a very straightforward procedure for the synthesis of a series of new pyrrole derivatives **2** of biological interest. They found that 2-acetimidoyl-2-chlorobutyrolactones **1**, easily obtainable from the commercially available 2-acetylbutyrolactone, could be transformed into the target compounds by treatment with sodium methoxide under reflux conditions, although the yields were low (Scheme 1).

Another facile ring transformation of furans fused to a positively charged ring system was experienced by the present team of authors.[3] The tricyclic furo-fused azinium salt **3** when treated with cyanoacetic ester underwent intermediate ring opening to afford the cyclopenta-fused ring transformation product **4** in good yield.[4] A similar kind of ring transformation was performed by reaction of **3** with ammonia to result in an exchange of the oxygen to a nitrogen atom to give the tricyclic pyrrole **5**.[3]



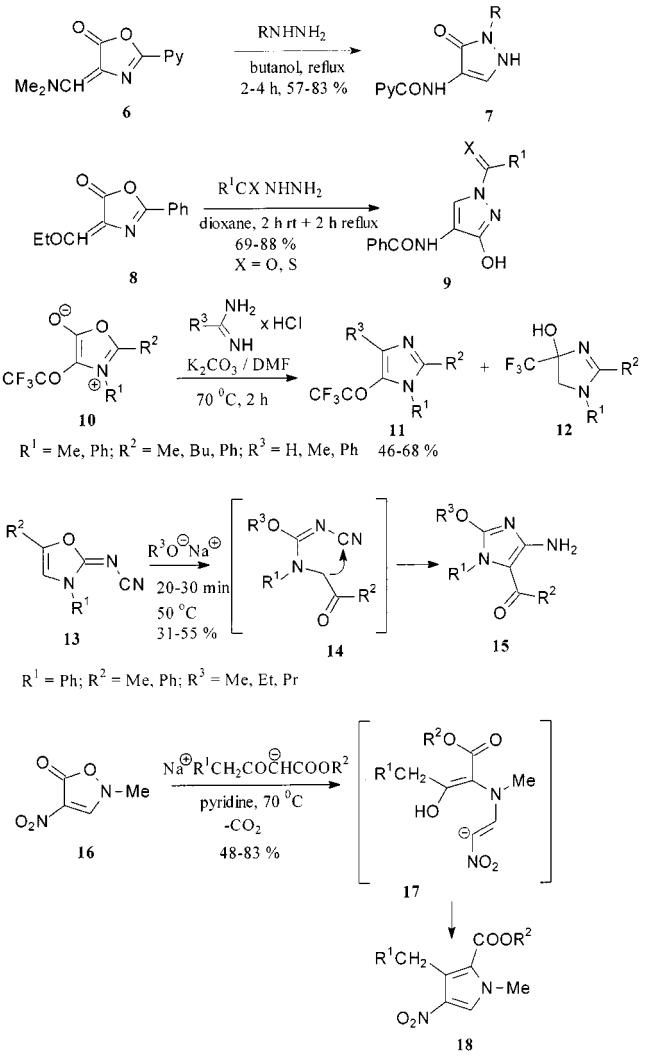
Scheme 1

B.2. Ring Transformation of Oxazoles, Isoxazoles, Thiazoles, and Isothiazoles

Kocevar et al.[5] reported that the oxazolone derivative **6** bearing a (dimethylamino)metheno side chain, when treated with hydrazines in boiling butanol, affords the pyrazole derivative **7** in good yield (57−83%). The same team found also that the related oxazolones **8** underwent ring transformation in reaction with acyl- or thioacylhydrazines to give pyrazololes **9**[6] also in high yields.

Another ring transformation of oxazole derivatives was reported by a Japanese group.[7,8] These authors found that the betaine **10** when treated with formamidine hydrochloride in the presence of solid potassium carbonate in dimethyl formamide gave rise to the imidazole derivative **11** as the main product and, simultaneously, a partially saturated imidazole derivative **12** was also formed, in most of the cases in small amounts (Scheme 2).

Gewald et al.[9] reported that some oxazolylidenecyanamides **13** (R^2 and R^1 = Ph or Me) easily react with sodium alkoxides (methoxide, ethoxide, or propoxide) at 50 °C and within 20 to 30 min to afford imidazoles **15**. The reaction proceeds by a nucleophilic ring opening at the C−O bond to form the supposed intermediate **14**, which undergoes ring closure to the final product. Ring transformations of isoxazoles leading to pyrroles have been reported by Ariga et al.[10] 4-Nitroisoxazolin-5-one **16** was treated with sodium 3-oxobutanoate in pyridine at 70 °C to yield pyrrolecarboxylate derivative **18** in good yield. According to a suggestion of the authors, the N−O bond of the isoxazole ring was cleaved first upon the attack of the nucleophile to yield



Scheme 2

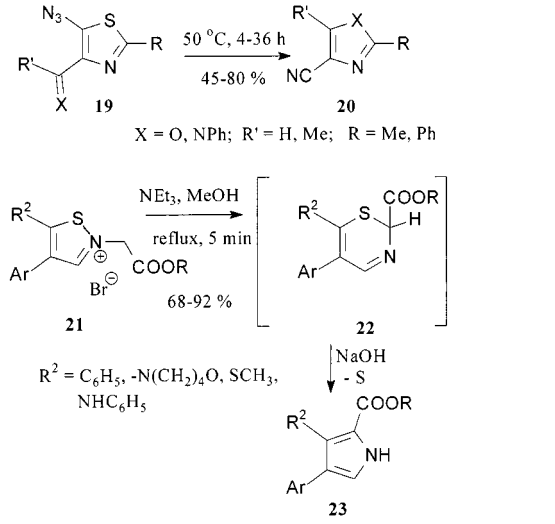
a supposed intermediate **17**, the ring closure of which resulted in formation of the pyrrole ring of the product.

Some azidothiazoles **19** were found to undergo ring transformation to oxazoles and imidazoles **20** (X = O or NPh) upon heating (Scheme 3).[11] The thermolysis was carried out in chloroform at 50 °C for 4−36 h to afford the products in fair to good yields.

Liebscher et al.[12,13] investigated the reactivity of some isothiazolium salts **21** in the presence of a base, and concluded that these compounds undergo ring opening and a subsequent ring closure to a thiazine intermediate **22**, which by ring contraction in aqueous base forms a pyrrole derivative **23**. This ring transformation was found to be applicable to a series of derivatives and proceeded in good to excellent yields (68−92%).

B.3. Ring Transformation of Imidazoles and Pyrazoles

Suwinski et al.[14−16] investigated the ring transformation properties of a nitro-substituted imidazole derivative **24**. They found that this compound reacted with 4-amino[1,2,4]-triazole to give the oxazole derivative **25** in 74% yield,



Scheme 3

whereas the reaction with hydroxylamine yielded the [1,2,3]triazole *N*-oxide compound **26**, also in good (66%) yield. Although the proposed mechanism of this rearrangement involves some unusual reaction steps (Figure 1), the mild reaction conditions used and the acceptable yields (50−60% in most cases) reveal the preparative usefulness of this transformation.

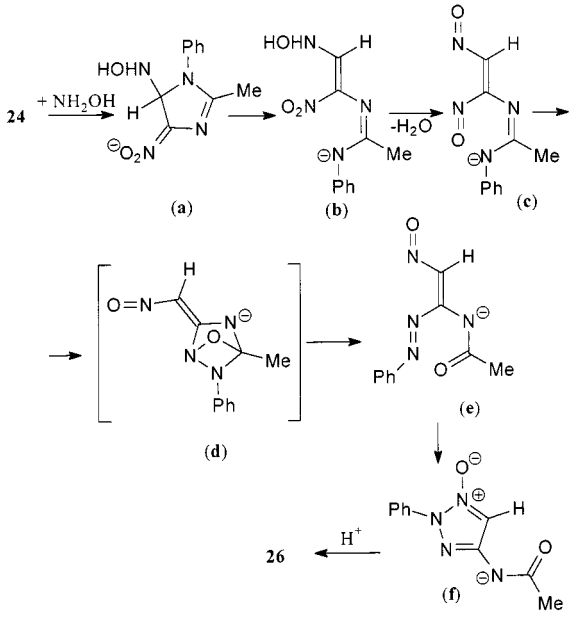
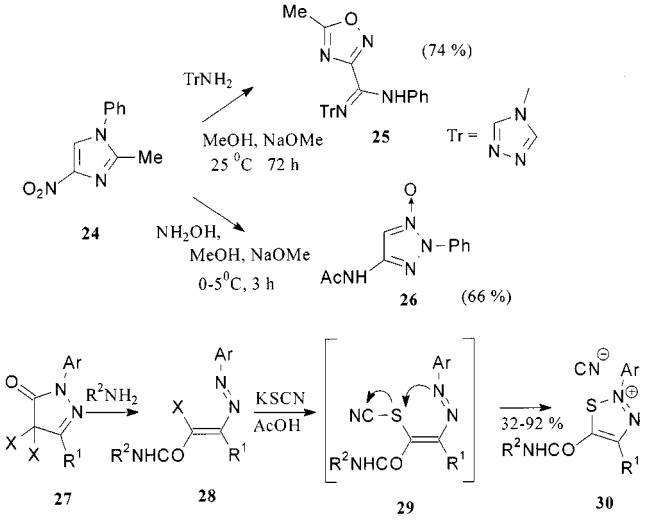


Figure 1. Supposed reaction mechanism for the formation of [1,2,3]triazole *N*-oxides **26** from nitroimidazoles **24**: addition of hydroxylamide anion to the C=C double bond of the imidazole **24** yields intermediate **a** that undergoes ring opening to **b**; elimination of water may yield **c**, then a subsequent double cyclisation, initiated by the negatively charged nitrogen atom, can lead to the strained bicyclic intermediate **d**; ring opening of this species to **e**, a 1,5-cyclisation to **f** and a final protonation affords the end product **26**

A German group reported[17] that some geminal substituted pyrazolin-5-ones **27** (X = halogen or CXX structural unit part of an oxirane ring) could easily be converted into the [1,2,3]thiadiazolium salts **30** in moderate to excellent

yields: The starting pyrazolone **27** was first treated with an amine, then the reaction of the open-chain product **28** with potassium rhodanide – via the intermediate **29** – resulted in the final ring closure to the product (Scheme 4).



Scheme 4

B.4. Ring Transformation of Five-Membered Rings with Three Heteroatoms

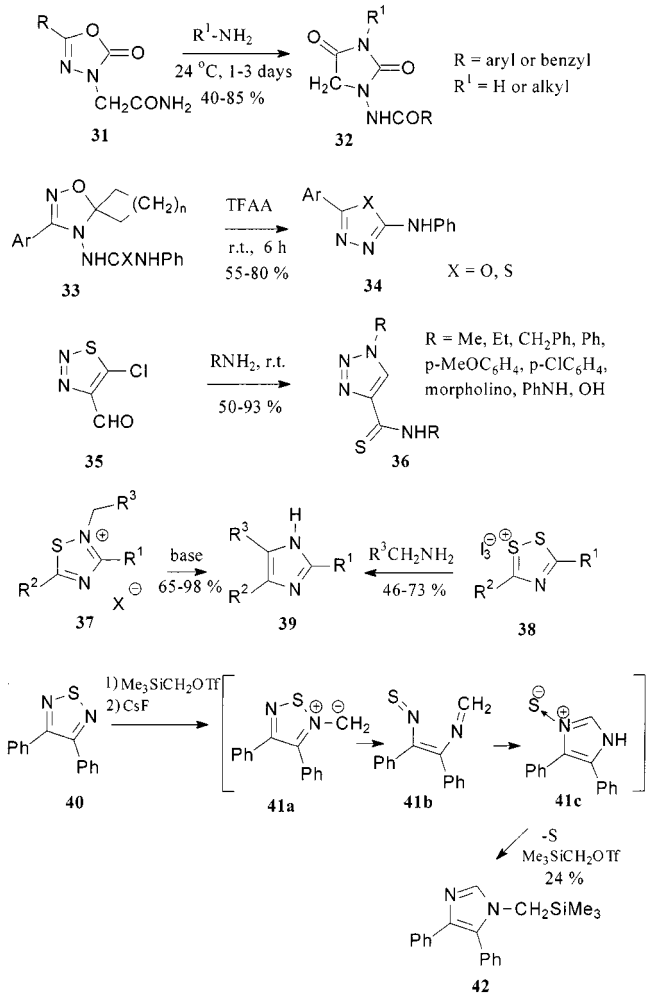
Milcent et al.[18] reported a very efficient approach to some imidazolidinediones (hydantoins). These authors found that the oxadiazolone derivative **31**, when treated with ammonia or primary amine, gave rise to the hydantoin derivative **32**. This transformation was found to be applicable for as many as 21 related compounds.

A German–Jordanian group[19] investigated the reactivity of some specific oxadiazoles **33** having a spirocyclic cycloalkyl moiety. These compounds when treated with trifluoroacetic anhydride at room temperature gave [1,3,4]oxadiazoles and [1,3,4]thiadiazoles **34** (X = O, S) (Scheme 5).

L'Abbé and his co-workers[20–22] investigated the ring transformation abilities of [1,2,3]thiadiazoles in detail. They described a general route to [1,2,3]triazole derivatives **36** by a simple treatment of chlorothiadiazoles **35** with amines, hydrazines or hydroxylamine.

Liebscher et al.[23] found in the course of their thorough studies on [1,2,4]thiadiazolium salts **37** and [1,2,4]dithiazolium salts **38** that these compounds provide easily accessible starting materials for a versatile novel synthesis of imidazoles. Thus, both **37** and **38**, when treated with iodine in the presence of triethylamine, gave rise to the imidazole derivatives **39** in excellent yields. For this ring transformation a similar mechanism, as proposed for the transformation of the related isothiazolium salts discussed above (i.e. formation of **23** from **21**), was anticipated.

Butler et al. recently reported[24] that [1,2,5]thiadiazole **40**, when treated first with trimethylsilylmethyl triflate and then with caesium fluoride, underwent a ring transformation to imidazole derivative **42**. The transformation proceeds via the ylide **41a**, which can undergo ring opening to

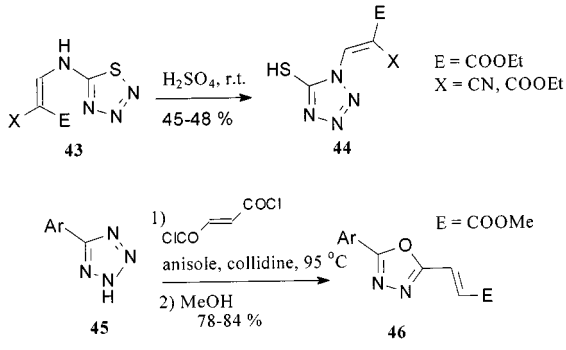


Scheme 5

41b and, finally, attachment of the CH_2 group to the nitrogen atom followed by extrusion of the sulfur atom and alkylation of the nitrogen atom, resulting in the formation of the imidazole ring.

B.5. Ring Transformation of Five-Membered Rings with Four Heteroatoms

Graubaum et al.[25] focused their research on the investigation of a compound which has been known for more than



Scheme 6

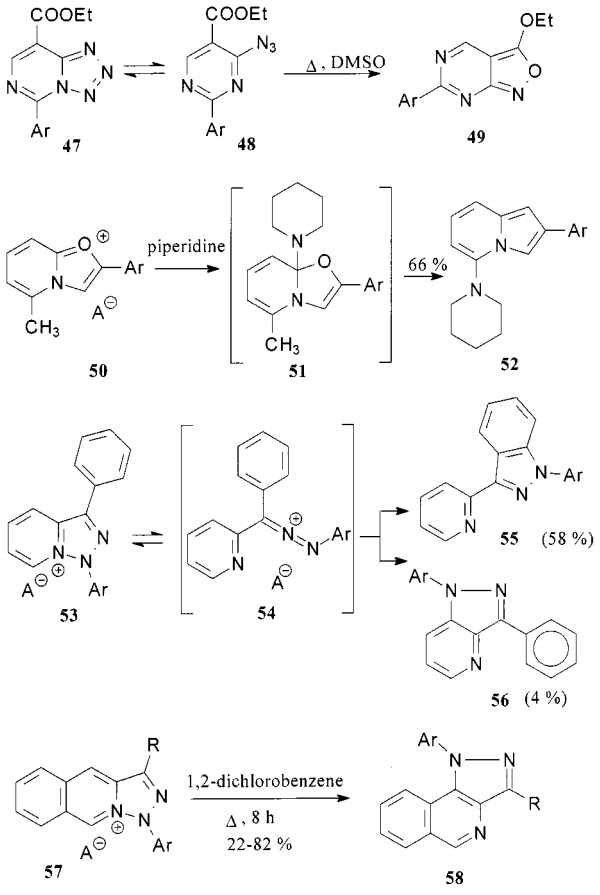
100 years and can be prepared very easily.[26] Derivative **43** can be obtained from 5-amino[1,2,3,4]thiatriazole by one simple reaction step, and treatment of **43** with sulfuric acid results in a ring transformation to an *N*-substituted mercaptotetrazole **44**.

An extensive and excellent review on the ring transformation of tetrazoles appeared in 1998[27] also discussing the synthetic potential leading to and starting from tetrazoles. Since the appearance of that paper, a new ring transformation has been published: Detert et al.[28] reported that some aryltetrazoles **45** reacting with fumaryl chloride eliminate nitrogen, and with participation of one C=O bond of the reagent a [1,3,4]oxazole **46** is formed (Scheme 6).

B.6. Ring Transformation of Polycyclic Ring Systems with Bridgehead Nitrogen Atom

Discussion of ring transformations of fused systems with bridgehead nitrogen atom requires a special category. Although in these cases a five-membered heterocycle also undergoes a basic structural change, this reaction also includes the transformation of the second fused (five- or six-membered) ring attached to the bridgehead nitrogen atom. Three exciting examples are discussed below.

A Russian group reported[29,30] that ethyl 5-aryltetrazolo[1,5-*c*]pyrimidine-8-carboxylate **47**, which is in equilibrium with its azido isomer **48**, undergoes nitrogen elimination upon heating to yield an isooxazolo[3,4-*d*]pyrimidine derivative **49** (Scheme 7). This transformation obviously proceeds by a nitrene attacking the carbonyl oxygen atom of the ester functionality.



Scheme 7

Babaev et al.[31] found in the course of their studies on fused oxazolium salts that the methyl-substituted salt **50**, when treated with piperidine, led to an unexpected reaction: In spite of analogous cases, where the pyridine ring underwent ring opening in such reactions, this compound **50** gave an indolizine derivative **52**. According to the rationalisation of the authors, the nucleophilic amine attacks the bridgehead carbon atom to form a supposed intermediate **51** that rearranges (ring opening and subsequent ring closure) with participation of the methyl substituent.

Recent investigations by the present authors revealed[32,33] that fused [1,2,3]triazolium salts with bridgehead nitrogen atoms generally formed an equilibrium with open-chained diazaallenium species. Thus, the triazolopyridinium salt **53** could, in principle, isomerize to the ring-opened cation **54** that undergoes subsequent ring closure at elevated temperatures (boiling dichlorobenzene) to afford the indazolylpyridine compound **55** as the major product and, as a by-product in very small amounts, the pyrazolopyridine compound **56**. In contrast to **53**, from the linearly fused triazoloisoquinolinium salt **57** the pyrazoloisoquinoline ring-transformed compound **58** was obtained as the main product.

C. Degenerate Ring Transformations of Five-Membered Heterocycles

According to the definition given in the introductory part A, the starting compounds and final products in the following examples exhibit identical ring systems. In some of these examples, only one or two substituents will be changed during the transformation leaving the ring system apparently

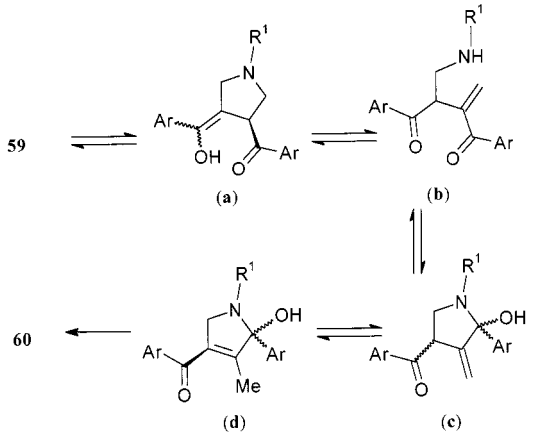


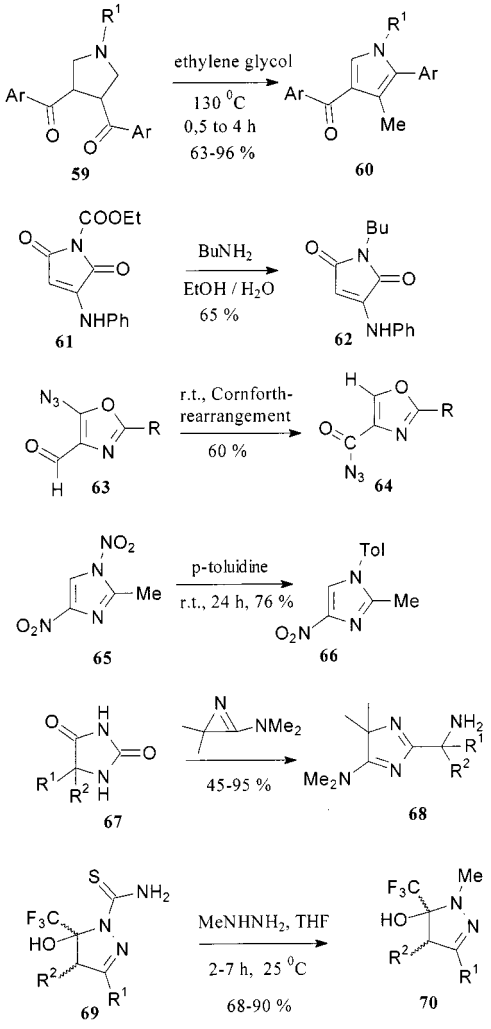
Figure 2. Mechanism of the dehydrative ring transformation of 1-alkyl-3,4-diaroylpyrrolidines **59** into 1-alkyl-4-aroyl-2-aryl-3-methylpyrroles **60**: formation of the tautomer **a**; tautomeric ring opening of the pyrrolidine moiety to **b**; ring-chain tautomerism to **c**; further tautomeric equilibrium to **d**; dehydration to the final product **60**

intact, while in some other cases other substantial changes (e.g. unsaturation, migration) also occur. Some excellent reviews also appeared recently on this particular kind of ring transformation reaction.[34,35] Six selected examples showing degenerate ring transformations of five-membered heterocycles are discussed below.

Mataka et al.[36] found that the pyrrolidines **59** − obtainable by easy procedures[37] − when heated in ethylene glycol for some hours afford 1-alkyl-2-aryl-3-methylpyrroles **60** in high yields. The key step of this ring transformation is the ring opening of the pyrrolidine moiety followed by attack of the nitrogen atom at one of the carbonyl groups as shown in Figure 2.

A Hungarian group also reported on degenerate ring transformations of pyrrole derivatives.[38] They published that the substituted maleimide **61** could be transformed to another maleimide derivative **62** by treatment with primary amines.

Dehaen et al. reported[11,39] a reaction of 5-azidooxazole-4-carboxaldehyde **63** to 4-oxazolylcarboxylic azide **64**. The reaction is supposed to proceed by a Cornforth rearrangement (Scheme 8).



Scheme 8

Ring transformations of some nitro-substituted imidazoles to oxadiazoles and [1,2,3]triazoles studied by Suwinski et al. have already been discussed above. The same research group also found a degenerate transformation of this ring system:[14] The imidazole derivative **65**, when treated with *p*-toluidine, underwent a ring opening and subsequent ring closure so that the $N-NO_2$ unit was exchanged for an *N*-tolyl moiety **66**.

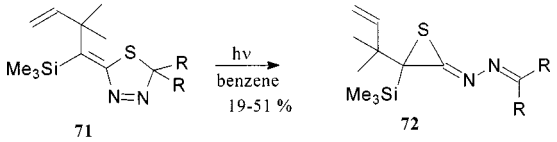
Heimgartner et al.[41] reported an interesting degenerate ring transformation of some hydantoins **67** upon treatment with azirines to yield the substituted 4*H*-imidazole derivative **68**. Since all three atoms of the reagent azirine are found in the five-membered product, the reaction may also be regarded as a ring expansion reaction of the azirine ring to imidazole.

A Brazilian group[42] has recently found that the pyrazolines **69** can undergo ring conversion into differently substituted pyrazolines **70**. The conversion is accomplished by methylhydrazine at room temperature in very good yield.

D. Ring Contractions and Ring Expansions

D.1. Ring Contractions

Many examples are given in the literature for ring contraction reactions of six- or seven-membered heterocycles to five-membered ones, while ring contractions of five-membered rings to a more strained smaller ring can occur only in special cases. The following transformation is representative of such a case. Ando et al. carried out a series of investigations[43−45] on 2-alkylidene-1,3,4-thiadiazolines **71** and found that these compounds, when irradiated with a medium-pressure mercury lamp for 10 min, gave rise to the thiiranimine derivative **72**. The reaction is supposed to proceed by a homolytic cleavage of the S−C bond and subsequent recombination of the intermediate diradical (Scheme 9).



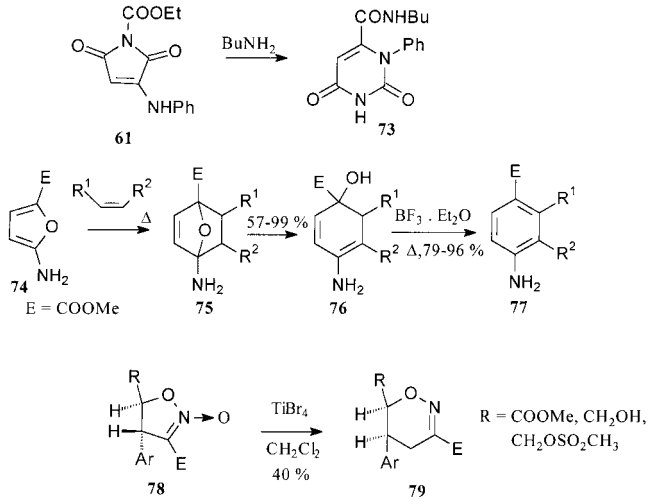
Scheme 9

D.2. Ring Expansions

In one of the previous chapters we have discussed the degenerate ring transformation of the pyrrole compound **61** described by Seres et al.[38] These authors in the same publication also report that treatment of **61** with *n*-butylamine results in a ring expansion to a pyrimidine derivative **73**. The reaction proceeds by a nucleophilic cleavage of the substituted lactam moiety, and a novel ring closure of an open-chain intermediate finally gives the orotic acid derivative **73**.

Five-membered heteroaromatic systems readily undergo Diels−Alder reactions which are well documented in the literature.[46] A very recent paper demonstrates that there is

still high interest − from both preparative and theoretical points of view − in such transformations: Padwa et al.[47,48] report that methyl 5-aminofuran-2-carboxylate **74** readily reacts with several monoactivated olefins by simply heating in benzene at 80 °C to yield a cycloadduct **75** that, after ring opening to **76** and treatment with boron trifluoride−diethyl ether, gave the substituted aniline derivative **77** (Scheme 10).



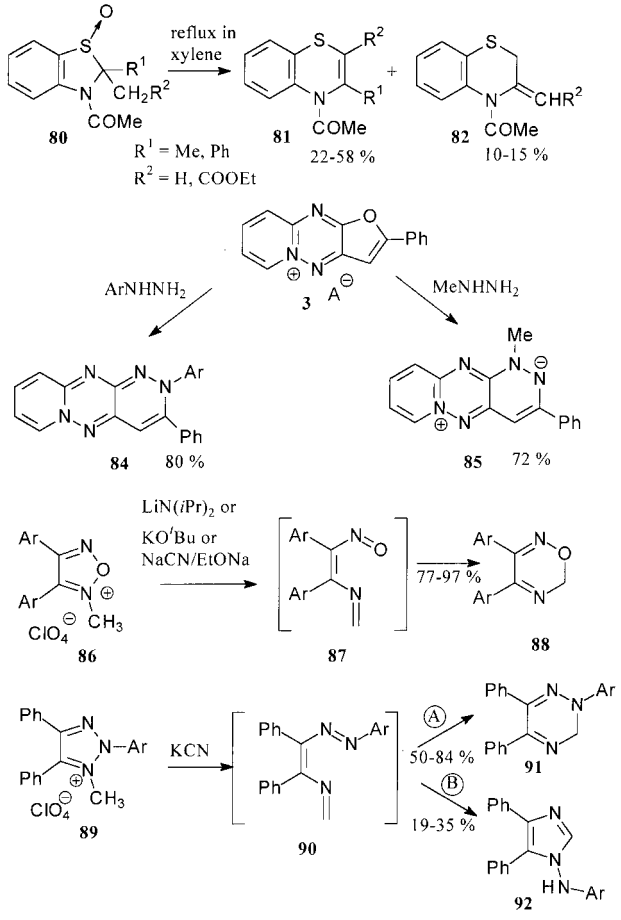
Scheme 10

Harada et al. showed[49] that some isoxazoline *N*-oxides in the presence of Lewis acids can undergo ring expansion to oxazines. Thus, compound **78**, when treated with titanium tetrabromide at ambient temperatures, gave the dihydro-4*H*-[1,2]oxazine compound **79**. An interesting feature of this reaction is its stereoselectivity by transforming the *trans* position of the two hydrogen atoms in the starting compound to *cis* hydrogen atoms in the oxazine product.

While the above examples show ring expansions of monocyclic heterocycles, the next two cases indicate that such ring enlargements can also take place with fused systems. Thus, a recent report[40] on the chemistry of benzothiazoline 1-oxides revealed that the cyclic sulfoxide **80** when heated under reflux in xylene for 4.5 h gave, simultaneously, two ring-expanded products: the benzothiazine derivatives **81** and **82** in low yields.

In chapter B.1. we discussed the ring transformation reaction of the tricyclic furan salt **3** to fused pyrroles and cyclopentanes. The same authors[50] have also reported that treatment of **3** with substituted hydrazines can result in ring expansion to fused pyridazines. Thus, reaction of **3** with arylhydrazines afforded the tricyclic pyridazine **84** as blue crystals, whereas treatment of the same starting compound with methylhydrazine yielded the green zwitterionic **85** having identical ring systems. The interesting difference between these two transformations is due to the different nucleophilicity of the nitrogen atoms in the substituted hydrazines: In the arylhydrazine it is the terminal nitrogen atom that attacks the furan ring at the bridgehead carbon atom, whereas in the case of methylhydrazine the nitrogen atom bearing the methyl group attacks the same position of the starting compound **3**.

Butler et al.[51−53] found that [1,2,5]oxadiazolium salts **86** undergo ring expansion to [1,2,5]oxadiazines **88** upon treatment with a base. The transformation can be carried out in excellent yield and was interpreted to proceed by formation of the open-chain intermediate **87**. Reaction of [1,2,5]triazolium salt **89** takes place in a similar manner to yield the six-membered dihydro-triazine **91**, but in this case the intermediate (**90**, analogous to **87**) has an ambident reactivity: Besides route A (yielding **91**) a route B also occurs and, thus, *N*-arylaminoimidazole **92** is formed simultaneously (Scheme 11).

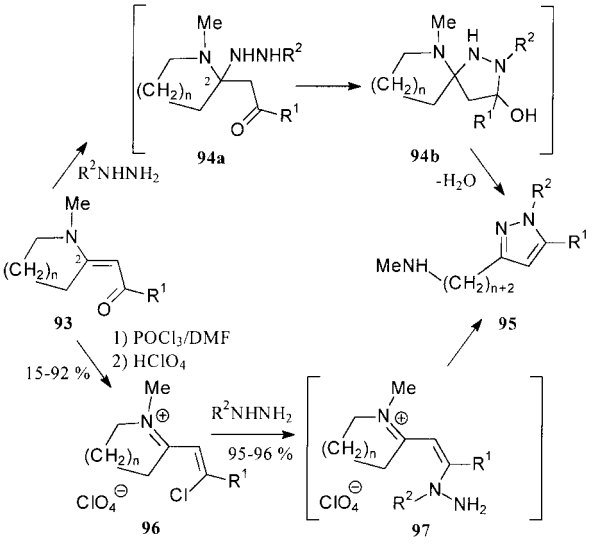


Scheme 11

E. Pseudo Ring Transformations (Ring Chain Transformations)

Liebscher et al. carried out fairly extensive research on ring transformation abilities of *N*-alkylpyrrolidines having an *exo* double bond in position 2 attached to some functional groups appropriate for ring closure reactions. One of the typical transformations is discussed, first involving conversion of the starting pyrrolidines to the heteroaromatic pyrazoles.[54] Some earlier observation indicated[69][70] that the monocyclic enaminone **93**, when treated with hydrazines, is transformed to the pyrazole **95**. The reaction

obviously proceeds by a nucleophilic attack of the reagent at the activated position 2 to form an intermediate **94a**. This compound may undergo an internal ring closure to the spirocyclic **94b** that can be stabilised by opening of the strained saturated ring and elimination of water to give the end product **95**. Liebschers group found[54] that the same reaction could be carried out in better yield by a modified synthetic route: Treatment of **93** with phosphorous oxychloride/DMF and then perchloric acid gave the crystalline perchlorate salt **96** in good yield, which when treated with hydrazine − by substitution of the chlorine atom and formation of intermediate **97** − again afforded the pyrazole derivative **95** (Scheme 12).

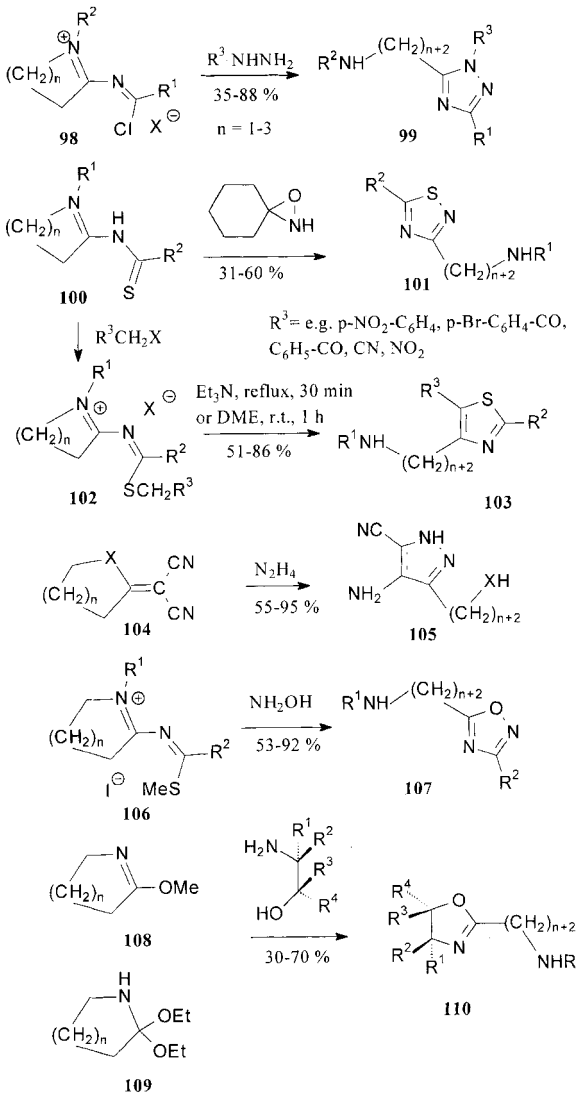


Scheme 12

This synthetic strategy proved to be very convenient for the synthesis of numerous five-membered heteroaromatics, as convincingly demonstrated by a review article.[55] In Scheme 13, the most important examples for transformations of that kind are discussed. All these reactions follow basically the same reaction pathway: Position 2 in the starting pyrrolidine is activated by an *endo* or *exo* double bond and is attacked by a nucleophile to form an appropriate side chain. In the course of the reaction this side chain is closed to a new ring and, simultaneously, the pyrrolidine is opened to form an aliphatic chain.

The cyclic quaternary salt **98**, having an imidoyl chloride side chain was rearranged into [1,2,4]triazoles **99** by hydrazine or arylhydrazines in good yields.[56] The semicyclic thioacylamidine **100** proved to be a suitable starting component for ring closure to [1,2,4]thiadiazoles: An amination reaction at the sulfur atom followed by ring closure yielded the aminoalkyl-substituted thiadiazoles **101**.[57] When **100** was treated with various alkylating agents like substituted benzyl bromides or chlorides, or phenacyl halogenides, the *S*-alkyl derivatives **102** were obtained, which underwent ring closure to thiazoles **103**.[58]

Contrary to the examples described above, the semicyclic aminoacrylonitrile **104** contains an *exo* double bond activating position 2. Its reaction with hydrazine follows the general route, and results in formation of the pyrazole compound **105**.[59]The cyclic iminium salt **106** containing a methylthio group proved to be suitable − by reaction with hydroxylamine − for the synthesis of a series of new [1,2,4]oxadiazoles **107** in good to excellent yields.[60] A similar synthetic strategy has also been applied for the synthesis of some isoxazoles by Dannhardt et al.[61]



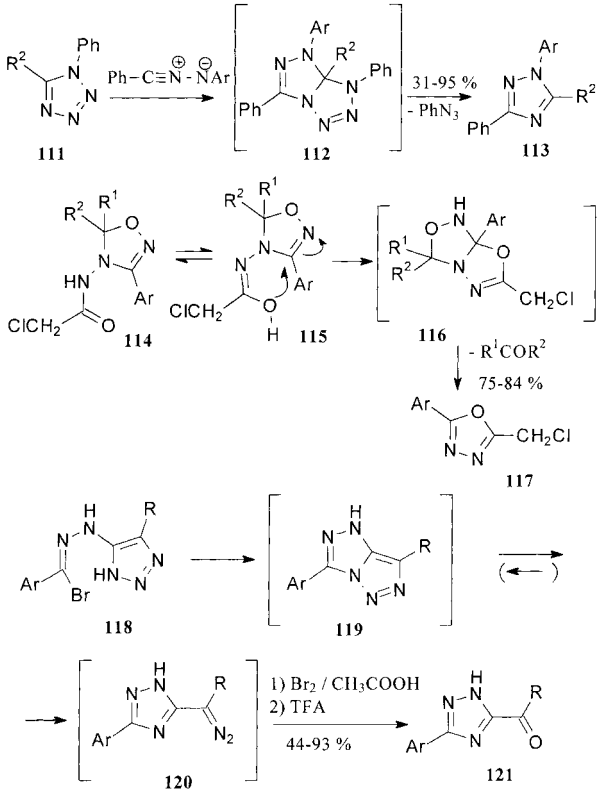
Scheme 13

In a more recent paper of Liebscher et al.[62] ring transformation to chiral oxazolines has been reported. Both the butyrolactim ether **108** and the cyclic acetal **109** could be transformed using a chiral amino alcohol to give the oxazoline **110** as pure enantiomers. The transformation has been applied for 20 various derivatives: All reactions proceeded with complete retention of the configuration of the amino alcohol applied.

In the following three examples formation of the new ring occurred via a fused bicyclic intermediate that underwent ring opening of the originally existing ring to yield the product. Butler et al.[63] found that disubstituted tetrazoles

111 underwent 1,3-dipolar cycloadditions with nitrilimines, and the primary cycloadduct **112** eliminates phenyl azide to afford the 1,2,4-substituted triazole **113**.

Transformation of some [1,2,4]oxadiazoles to [1,3,4]oxadiazoles as reported by Rademacher et al.[64] were found to proceed via a bicyclic fused intermediate: The oxadiazoline compound **114**, which can also be represented by its tautomeric form **115**, was heated under reflux in chloroacetic anhydride to yield the partially saturated oxadiazolooxadiazole **116** as an intermediate. Upon ring opening this intermediate afforded the final product **117**. The authors found experimental evidence for the extrusion of the ketone R^1-CO-R^2 by isolation of its dinitrophenylhydrazone in the reaction mixture, but no rationalisation was given as to how the N atom of the oxadiazoline ring in **116** was removed (Scheme 14).

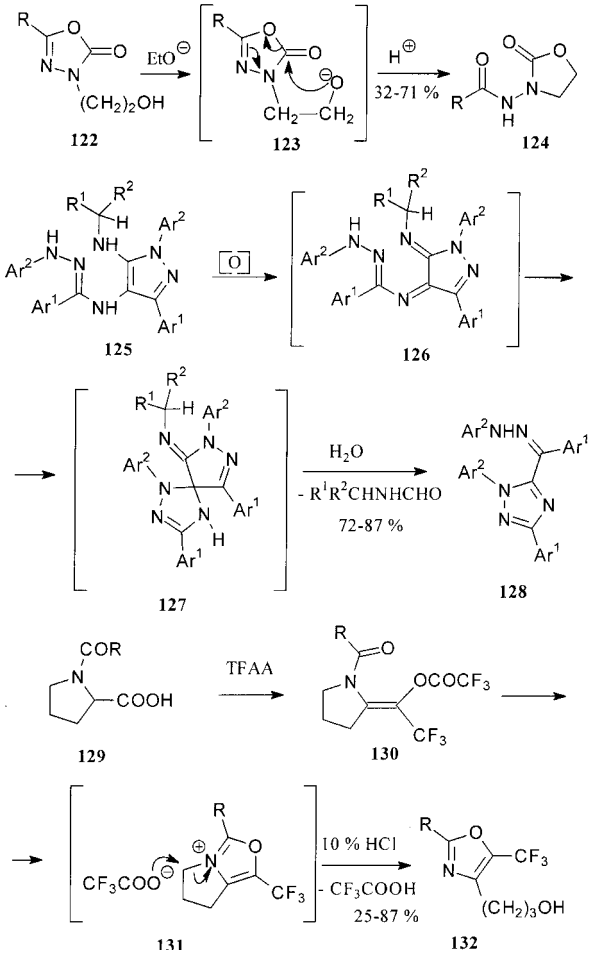


Scheme 14

Moderhack et al.[65] reported a transformation of [1,2,3]triazoles to new functionalised [1,2,4]triazoles. The starting [1,2,3]triazole compound having a hydrazono side chain (**118**) could undergo an internal nucleophilic substitution to the bicyclic intermediate **119** first. This compound then led by valence bond isomerisation to the open-chain diazo compound **120** which by treatment with bromine and then with trifluoroacetic acid gave rise to the [1,2,4]triazolyl ketones **121**.

Milcent et al.[66] described a new general route for the synthesis of 3-acylamino-2-oxazolidinones starting from some [1,3,4]oxadiazolones. The starting compound **122** having a hydroxyethyl substituent at position 3 was treated with sodium ethoxide. The "olate" oxygen atom of the resulting anion **123** attacks the lactone carbon atom, which leads to the breakage of the ring C−O bond and a new oxazolidinone **124** is then formed.

In an interesting and unexpected transformation of some pyrazoles to [1,2,4]triazoles published by Moderhack et al.[67] a spirocyclic intermediate was anticipated. The colourless starting compound **125** containing an arylhydrazone side chain was simply allowed to stand in an ethanolic solution at room temperature, a basic structural change took place within 1−2 weeks and a new compound, a [1,2,4]triazolyl ketone arylhydrazone separated as yellow needles. The transformation was rationalised by anticipating an aereal oxidation first to **126** followed by a ring closure to the spiro compound **127**. Finally, elimination of the formamide $R^1R^2CHNHCHO$ gives rise to the end product **128** (Scheme 15).



Scheme 15

As the final example of pseudo ring transformations a new general method for the preparation of trifluoromethylated oxazoles from α-amino acids published by Kawase et al.[68] should be demonstrated. These authors found that *N*-pivaloylproline **129** when treated with trifluoroacetic anhydride could lead to the oxazole derivative **132**. The transformation is rationalised by formation of the acylated product **130** followed by a ring closure to an intermediate fused oxazolium salt **131** which undergoes acidic cleavage to yield **132**.

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