RECENT ADVANCES IN RING TRANSFORMATION
OF FIVE-MEMBERED HETEROCYCLES

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Ring transformations of heterocyclic rings by temporary opening and subsequent closure to a new molecule are of particular interest both synthetically and theoretically. Only rearrangement of five-membered heterocycles 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 expansions" where the sizes of the product rings are smaller or larger, respectively, than those of the starting compound, and (d) "pseudo ring transformations" or "ring-chain transfer", where the process is formally a ring transformation, but is realised by a ring closure of a side chain of

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the starting heterocycle and opening of the original ring. Reaction mechanism of the most interesting ring transformations are also discussed.

Introduction

Rearrangement 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:

Hajós [1] divides ring transformation reactions [1] in this way:

A *"classical ring transformation"* in the most rigorous sense means that a ring of a certain size is transformed to a ring of the same size in the product (Scheme 1 [2]). This means that formally one or more ring atoms are exchanged for other ones to form the new ring.
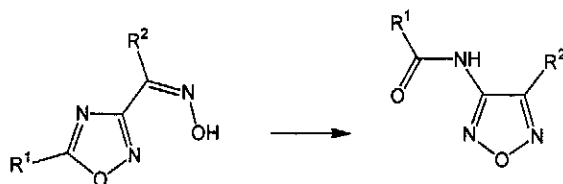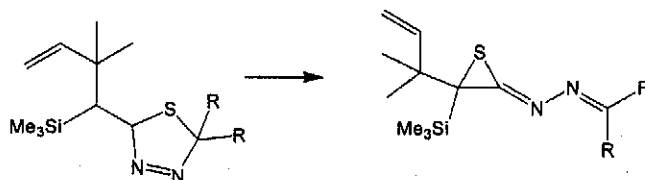

Scheme 1

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 (Scheme 2 [3]).
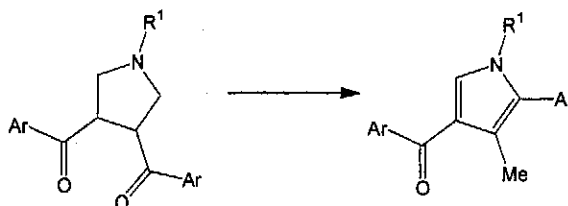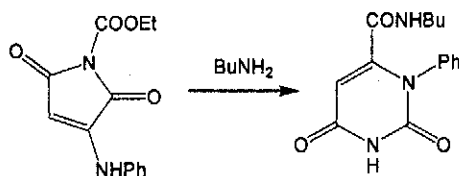

Scheme 2

"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 (Scheme 3 [4–6], Scheme 4 [5]).
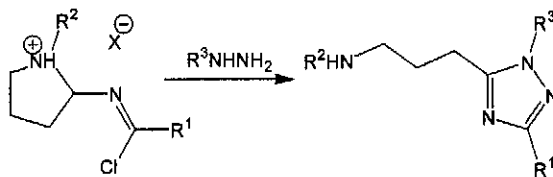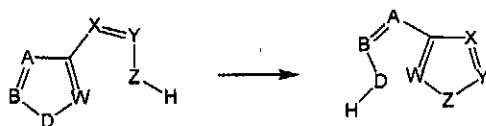

Scheme 3

Scheme 4

Apart from the above, 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"* (Scheme 5 [8]). The 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. one or two at the most) is (are) located in the ring of the final product.

Scheme 5

Nicoló Vivona *et al.* [9] dealt with rearrangement of five membered heterocycles represented by this generalized pattern (Scheme 6)

Scheme 6

where the W pivotal center is a nitrogen (W = N), sulphur (W = S) or carbon atom (W = C) and the side-chain contains three or four participating atoms. Here, one encounters a large variety of ring transformation of five-membered heterocycles into five- or six-membered ones.

The ring transformation proceeds by the nucleophilic attack of the Z atom on the pivotal center W, with a concerted (or subsequent) breaking of the D-W bond in an S_Ni-type reaction. On the other hand, when the side-chain is a ring conjugated allyl moiety containing 4π-electrons, the ring transformation can be viewed as a 6π-assisted heteroelectrocyclic reaction [10–12] into a bicyclic species (as an intermediate or transition state), with subsequent or concerted cleavage of the D-W bond; this latter step, in its turn, could be also considered as a retro-electrocyclic reaction. Moreover, when W = S, thiapentalene-type intermediates or reversible bond-switches at the hypervalent sulphur have been also pictured. Furthermore, a thermally or photo induced ring-opening (or fragmentation) of the starting heterocycle could precede the new ring closure, which therefore implies a heterocyclization of an open-chain species engaging the side group. In this general pattern one could also include ring-opening by the action of an external nucleophilic species.

Discussion

Classical Ring Transformations

Ring Transformation of Five-Membered Rings with One Heteroatom

A typical ring transformation can be recognized in the Wolf-Kishner reduction of 2,5-diphenyl-3-benzoylfuran [13]. In addition to the expected reduction product, the reaction gives the pyrazole (Scheme 7), the formation of which is explained through the hydrazone, although hydrazinolysis of the furan ring is not excluded [14].
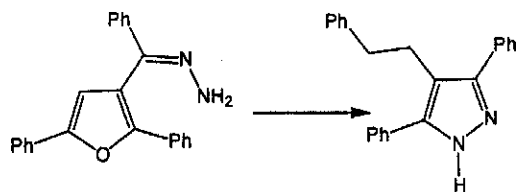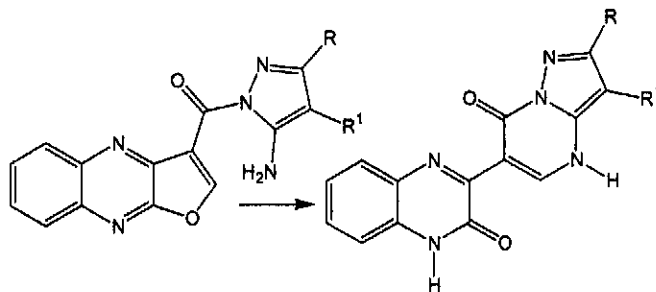
Scheme 7

Lactones are excellent targets for nucleophiles and are, therefore, appropriate starting compounds for ring opening reactions. Recently De Kimpe *et al.* [15] have reported a very straightforward procedure for the synthesis of a series of new pyrrole derivatives of biological interest. They have found that 2-acetimidoyl-2-chlorobutyrolactones, 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 8).
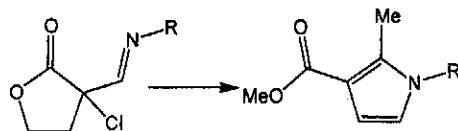
R = e. g. iPr, C_6H_{11}, $C_6H_5C_2H_4$, $pClC_6H_5C_2H_4$
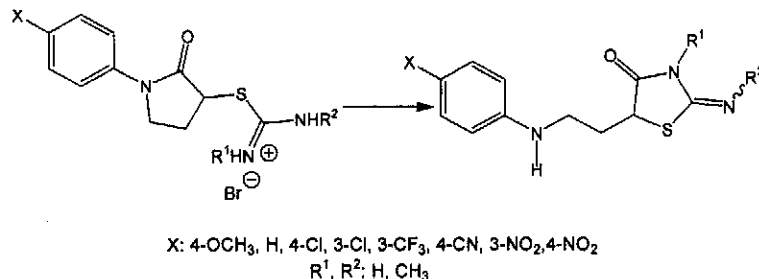
Scheme 8

A real ring transformation involving a four-atom side-chain in a fused furan series is suggested to occur in Scheme 9. Here parent structures represent unisolated intermediates in the reactions of 3-(N,N-dimethylcarbamoyl)furo[2,3-b]quinoxaline hydrochloride with some 5-amino-1H-pyrazoles [16].

Scheme 9

We reported [17] the new ring transformation of substituted S-[1-phenylpyrrolidin-2-on-3-yl]isothiouronium salts to corresponding substituted thiazolidin-4-ones.

Our later papers [18,19] dealt with the study of kinetics and mechanism of this transformation in aqueous solutions of amine buffers and sodium hydroxide solutions (Scheme 10).

X: 4-OCH$_3$, H, 4-Cl, 3-Cl, 3-CF$_3$, 4-CN, 3-NO$_2$,4-NO$_2$
R^1, R^2: H, CH$_3$

Scheme 10

The kinetics observed shows that the transformation reaction is subject to general base, general acid, and hydroxide-ion catalyses. The rate-limiting step of transformation is the splitting-off of a proton from the tetrahedral intermediate. The values of pK_a for the intermediates of base-catalysed transformation have been found [18,19] from the Brønsted dependence (for R^1 = R^2 = H: pK_a ≈ 9.8; R^1 = H, R^2 = CH$_3$: pK_a ≈ 10; R^1 = R^2 = CH$_3$: pK_a > 11.5). The electron-acceptor substituents (4-NO$_2$, 4-CN) on benzene ring do not obey the *Hammett* correlation [19].

Ring Transformation of Five-Membered Rings with Two Heteroatoms

Ring transformation of oxazoles in Scheme 11, which involves nucleophilic attack of the side-chain at the C(5) position and subsequent fission of the ring O–C(5) bond, were considered [20]. Nevertheless, the phenylhydrazide in Scheme 11 does not rearrange into the expected substituted 1,2-dihydro-3*H*-pyrazol-3-one and remains unchanged under various conditions. In this context, unsuccessful attempts are reported for some structurally related 4-substituted oxazoles, whereas specific examples concerning methyl oxazolium salt in Scheme 11 are not mentioned [20].
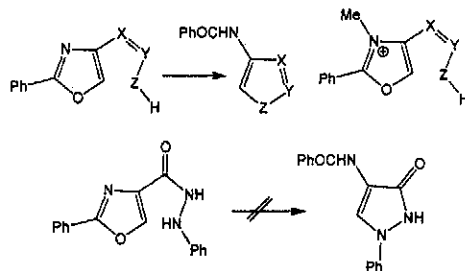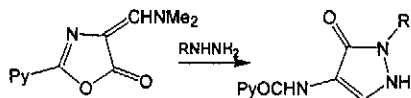

Scheme 11

Examples belonging to this pattern come from the reaction of oxazoleketoester with hydrazine or methylhydrazine. Here the reaction directly produces benzoylaminopyrazoles through unisolated hydrazones (Scheme 12) [21]. As a possible generalization of this ring transformation, 4-ketooxazoles can be considered as precursors of 4-aminopyrazoles (exploiting the reaction with hydrazines), and of other amino heterocycles (exploiting the reaction with various bidentate nucleophiles). Thus, oxazoleketoesters react with guanidine or *N,N*-dimethylguanidine to give transformed pyrimidines via unisolated oxazole in Scheme 12.
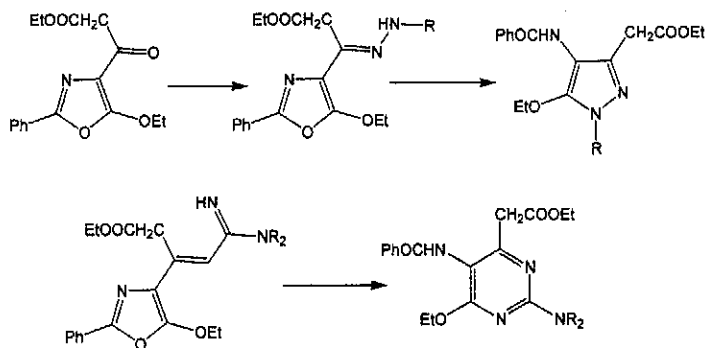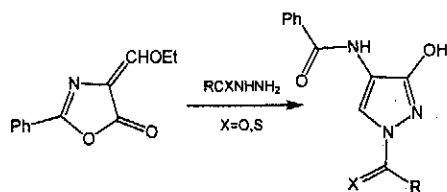

Scheme 12

Kocevar *et al.* reported [22] that the oxazolone derivative bearing a dimethyl-aminomethylidene side chain, when treated with hydrazines in boiling butanol, affords the pyrazole derivative in good yield (57 – 83 %) (Scheme 13).
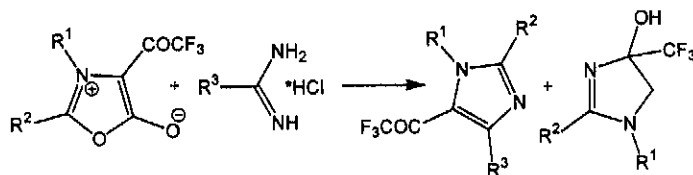

Scheme 13

The same team [22] also found that the related oxazolones underwent ring transformation in reaction with acyl- or thioacylhydrazines to give pyrazololes also in high yields (Scheme 14).
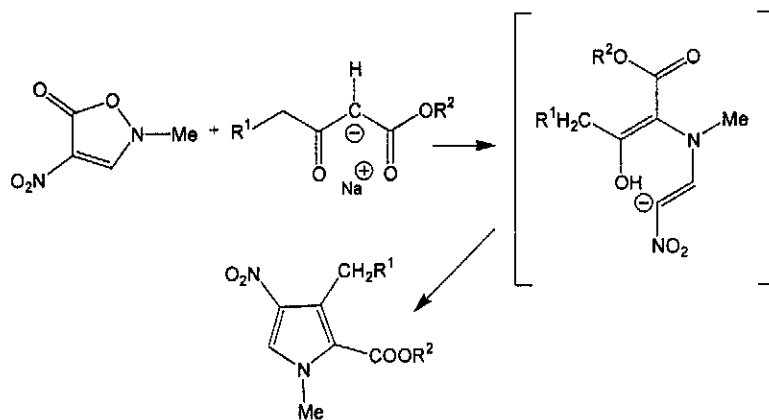

Scheme 14

Another ring transformation of oxazole derivatives was reported by a Japanese group [23,24]. These authors found that the betaine, when treated with formamidine hydrochloride, gave rise to the imidazole derivative as the main product and, simultaneously, a partially saturated imidazole derivative was also formed, in most of the cases in small amounts (Scheme 15).
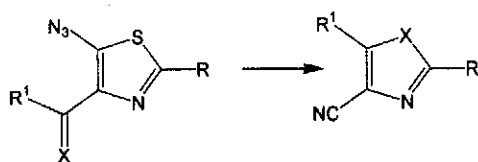

Scheme 15

Ring transformation of isoxazoles leading to pyrroles have been reported by Ariga *et al.* [25]. 4-Nitroisoxazolin-5-one was treated with sodium 3-oxobutanoate in pyridine at 70 °C to give pyrrolecarboxylate derivative 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 nucleohile to yield a supposed intermediate, the ring closure of which resulted in formation of the pyrrole ring of the product (Scheme 16).
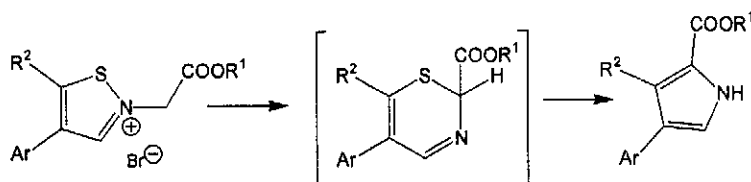

Scheme 16

Some azidothiazoles were found to undergo ring transformation to oxazoles and imidazoles (X = O or NPh) upon heating [26] (Scheme 17). The thermolysis was carried out in chloroform at 50 °C for 4 – 36 h to afford the products in fair to good yields.
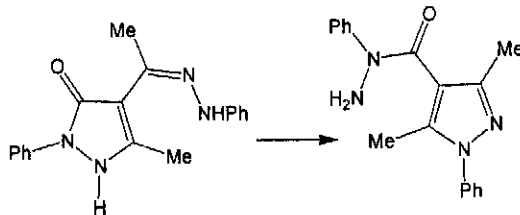
Scheme 17

Liebscher *et al.*[27,28] investigated the reactivity of some isothiazolium salts in the presence of a base and concluded that these compounds undergo ring opening and a subsequent ring closure to a thiazine intermediate, which by ring contraction in aqueous base forms a pyrrole derivative (Scheme18). This ring transformation was found to be applicable to a series of derivatives and proceeded in good to excellent yields (68 − 92 %).
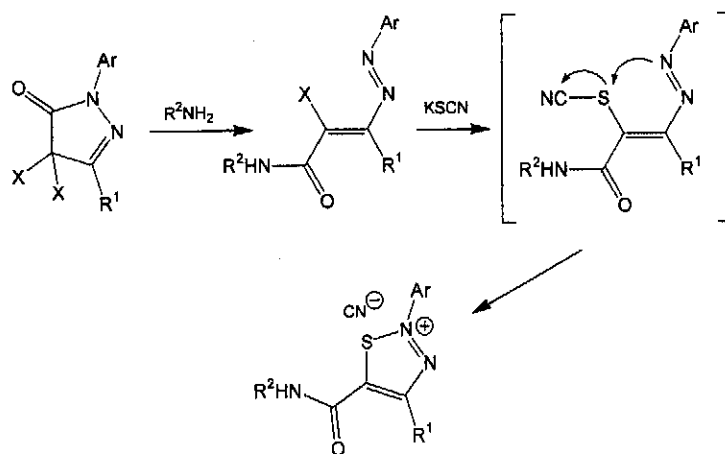

Scheme 18

The acid-induced ring transformation of the phenylhydrazone yields the phenylhydrazidopyrazole [29] and this result allows the correction of the formerly reported structure of 1,6-diphenyl-3,4-dimethylpyrazolo[3.4-c]pyrazole [30] (Scheme 19). The ring transformation proceeds by nucleophilic attack of the phenylhydrazone nitrogen on C(3) of the pyrazole nucleus, with breaking of the N(2)–C(3) bond of the ring. The acid catalysis increases the electrophilicity of the pivotal carbon and favours N–C bond fission [29].
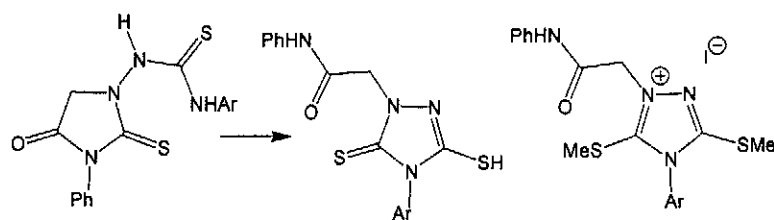

Scheme 19

A German group [31] reported that some geminal substituted pyrazolin-5-ones (X = halogen or CXX structural unit part of an oxirane ring) could be easily converted into the 1,2,3-thiadiazolium salts in moderate to excellent yields: The starting pyrazolone was first treated with an amine, then the reaction of the open-chain

product with potassium rhodanide resulted in the final ring closure to the product (Scheme 20).

Scheme 20

Arylthioureas react with amines in refluxing ethanol to rearrange into 3-sulfhydryltriazoles, which may be isolated after acidification with hydrochloric acid [32] (Scheme 21). A similar pathway that will give directly the triazolium iodides takes place on reacting with an excess of methyl iodide in ethanol, a preliminary S-methylation at the cyclic thione group favours nucleophilic attack by the thiourea side-chain. Ring opening and a subsequent or concomitant second S-methylation explain the final product [32]. Ring transformations involving an *ipso*-attack result from the reaction of some 2-phenacyl-Δ^2-imidazolines with hydroxylamine hydrochloride. In this instance, spiro intermediates arising from the unisolated oximes decompose to 5-(2-aminoethylamino)isoxazoles [33].
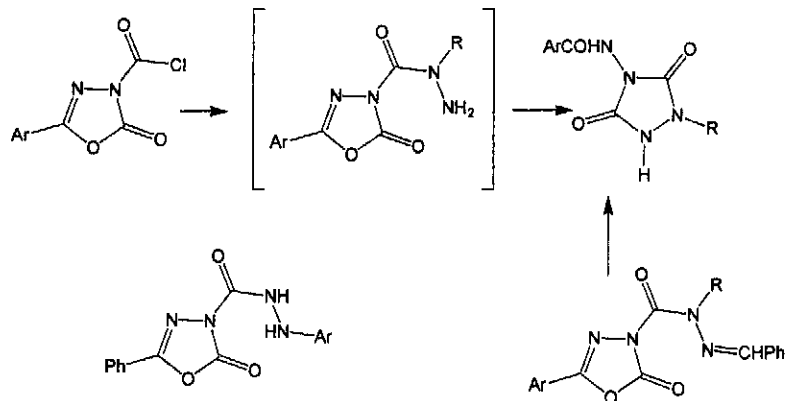

Scheme 21

Ring Transformation of Five-Membered Rings with Three Heteroatoms

Substituted oxadiazoles react with methylhydrazine to give substituted triazoles via the unisolated hydrazide (Scheme 22). By contrast, arylhydrazides do not

transform at the same conditions. Acid hydrolysis of the benzylidenehydra-zides gives directly triazoles. Here, acid catalysis favours the ring transformation of unisolated intermediates [34].
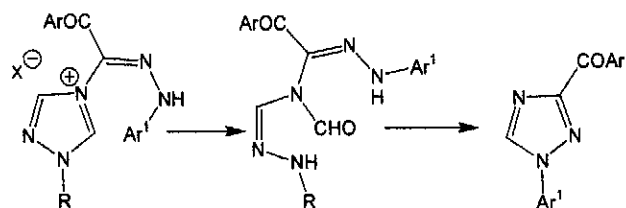

Scheme 22

After two years these authors [35] reported a very efficient approach to some hydantoins. They found that the oxadiazolone derivative, when treated with ammonia or primary amine, gave rise to the hydantoin derivative (Scheme 23). This transformation was found to be applicable for as many as 21 related compounds.
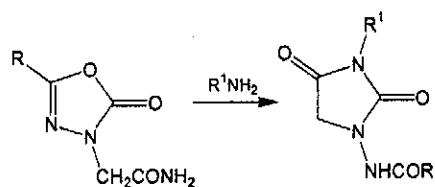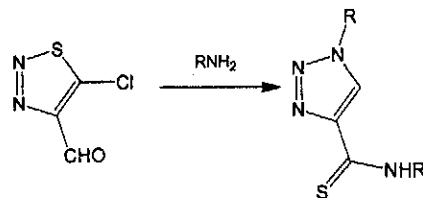

Scheme 23

The base-induced transformation of aroylarylazotriazoles into aroyltriazoles could be framed in the usual context (Scheme 24). However, the reaction may involve hydrolytic ring opening followed by a fragmentative heterocyclization of the former side-chain of the rearranging triazole [36].
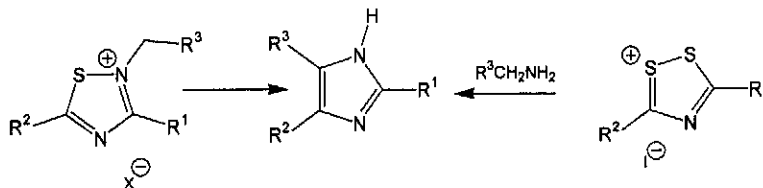

Scheme 24

L'Abbé and his co-workers [37–39] investigated the ring transformation abilities of 1,2,3-thiadiazoles in detail. They described a general route to 1,2,3-triazole derivatives by a simple treatment of chlorothiadiazoles with amines, hydrazines or hydroxylamine (Scheme 25).

Scheme 25

Liebscher *et al.* [40] found in the course of their thorough studies on 1,2,4-thiadiazolium salts and 1,2,4-dithiazolium salts that these compounds provide easily accessible starting materials for a versatile novel synthesis of imidazoles (Scheme 26). Thus, both salts, when treated with iodine in the presence of triethylamine, gave rise to the imidazole derivatives in excellent yields. For this ring transformation a similar mechanism, as proposed for the transformation of the related isothiazolium salts discussed above (Scheme 18), was suggested.
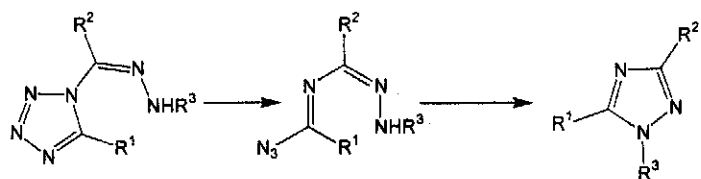

Scheme 26

Ring Transformation of Five-Membered Rings with Four Heteroatoms

Ring transformation of 1-hydrazonoyltetrazoles, which originate together with the 2-hydrazonoyl isomers in the reaction of tetrazoles and nitrilimines, are considered in Scheme 27 [41–43]. Thermolysis of the tetrazole in a suitable solvent assumes the intermediate formation of the azido species. Subsequent fragmentative heterocyclization involves the side-chain and the azido-substituted carbon atom with displacement of hydrazoic acid to give triazole [42,43].

Graubaum *et al.*[44] focused their research on the investigation of a compound which had been known for more than 100 years and can be prepared very easily[45]. The substituted 1,2,3,4-thiatriazole in Scheme 28 can be obtained from 5-amino-1,2,3,4-thiatriazole by one simple reaction step, and treatment of

Scheme 27

this substituted derivative with sulphuric acid results in a ring transformation to an *N*-substituted mercaptotetrazole.


X=CN, COOEt
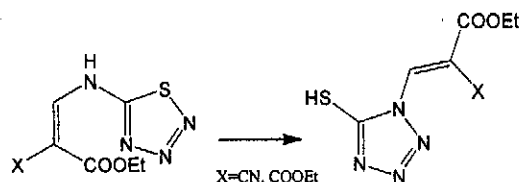
Scheme 28

An extensive and excellent review [46] on the ring transformation of tetrazoles appeared in 1998. This review also discuses the potential synthetic route leading to and starting from tetrazoles. Detert *et al.* [47] reported that some aryltetrazoles reacting with fumaryl chloride by eliminating nitrogen, and with participation of one C=O bond of the reagent a 1,3,4-oxadiazole is formed (Scheme 29).
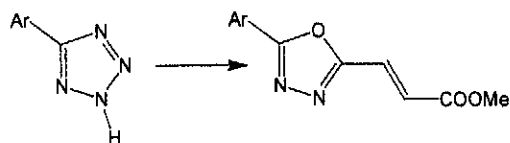
Scheme 29

Thermolysis of tetrazole oximes in suitable hydrocarbon solvent, or a pyrolysis without it, produces 3,5-disubstituted 1,2,4-oxadiazoles (Scheme 30) [42,48,49]. In the case of 5-unsubstituted tetrazoles, the reaction proceeds by two simultaneous pathways, which imply elimination of hydrazoic acid or nitrogen, respectively, to yield both 5-unsubstituted oxadiazoles and 5-aminooxadiazoles. As observed for 1-hydrazonoyltetrazoles, a plausible mechanism assumes ring opening of the tetrazole into the azido species, from which both pathways could take place.

A similar mechanism involving extrusion of nitrogen from an azido species can be envisaged in the formation of 2-aminobenzimidazole from the reduction of
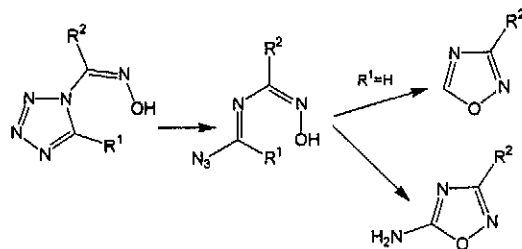
Scheme 30

the 1-(2-nitrophenyl)tetrazole with sodium sulphide in aqueous ethanol [50] (Scheme 31).
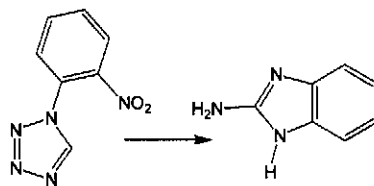
Scheme 31

Ring Transformation of Polycyclic Ring Systems with Bridgehead Nitrogen Atom

Discussion of ring transformation 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. Four exciting examples are discussed below.

Pyrolysis of the 3-azidooxadiazole results in the formation of molecular nitrogen and benzoylcyanide. The reaction assumes an initial azidotetrazole equilibrium, followed by O–N bond breaking and subsequent fragmentation and isomerization (Scheme 32) [51].
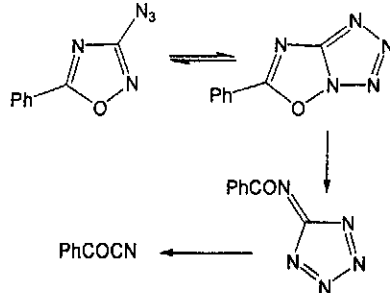
Scheme 32

A Russian group reported [52,53] that ethyl 5-aryltetrazolo[1.5-c]pyrimidine-8-carboxylate, which is in equilibrium with its azido isomer, undergoes nitrogen elimination upon heating to yield an isooxazolo[3.4-d]pyrimidine derivative (Scheme 33). This transformation obviously proceeds by a nitrene attacking the carbonyl oxygen atom of the ester group.
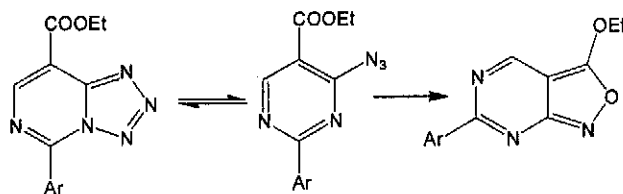
Scheme 33

Babaev et al. [54] found in the course of their studies on fused oxazolium salts that the methyl-substituted salt, 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 gave an indolizine derivative (Scheme 34). According to the rationalisation of the authors, the nucleophilic amine attack the bridgehead carbon atom to form a supposed intermediate that rearranges (ring opening and subsequent ring closure) with participation of the methyl substituent.
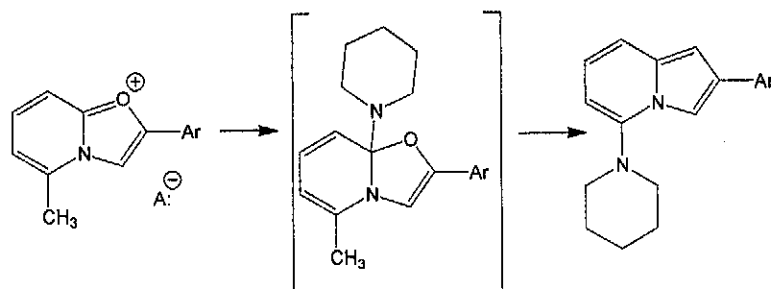
Scheme 34

Recent investigations by the present authors revealed [55,56] that fused 1,2,3-triazolium salts with bridgehead nitrogen atoms generally formed an equilibrium with open-chained diazaallenium species. Thus, the triazolopyridinium salt could, in principle, isomerize to the ring-opened cation that undergoes subsequent ring closure at elevated temperatures (boiling dichlorobenzene) to afford the indazolylpyridine as the major product and, as a by-product in very small amounts, the pyrazolopyridine (Scheme 35).

In contrast to the triazolopyridinium salt, from the linearly fused triazoloisoquinolinium salt the pyrazoisoquinoline ring-transformed compound

was obtained as the main product [56] (Scheme 36).
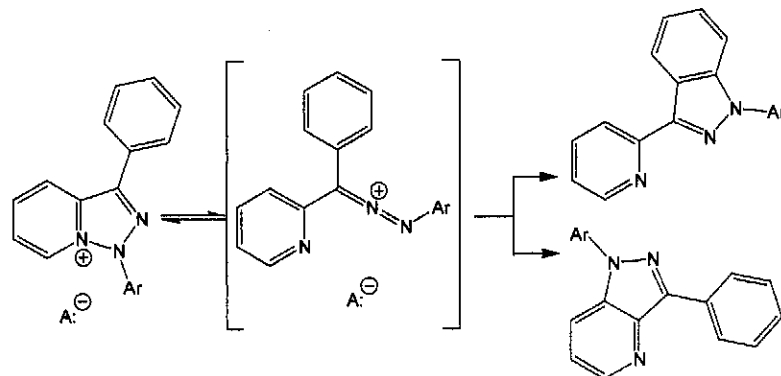
Scheme 35
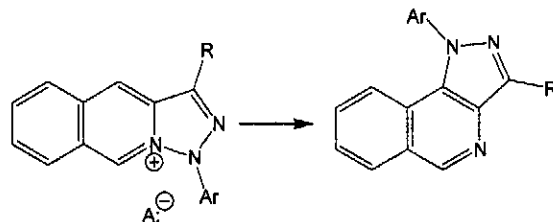
Scheme 36

Degenerate Ring Transformations

According to the definition given in Introduction, the starting compounds and final products in the following examples exhibit identical ring systems. In some those examples, only one or two substituents will be changed during the transformation leaving the ring system apparently intact, while in some other cases other substantial changes (e.g. unsaturation, migration) also occur. Some excellent reviews have also appeared recently on this particular kind of ring transformation reaction [57,58].

A side-chain XYZ = CNO in a 1,2,5-oxadiazole system suggests the occurrence of an isoheterocyclic degenerate ring transformation, which could be also the fully degenerate type. An isoheterocyclic process is reported for amidoximes. Thus, (E)-N,N-disubstituted 1,2,5-oxadiazole (Scheme 37) undergoes the expected acid-induced isomerization into geometrical isomers, which, in turn, can be transformed into furazans under severe conditions such as treatment with bases at 120 – 140 °C.
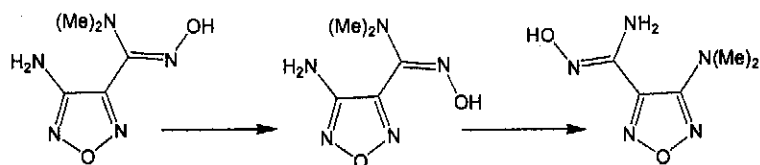
Scheme 37

On the other hand, (E)-N-monosubstituted amidoximes can even be isomerized and then transformed into the corresponding furazans on treatment with bases. Moreover, although in principle reversible, the reverse reaction has not yet been observed (Scheme 38) [59,60].
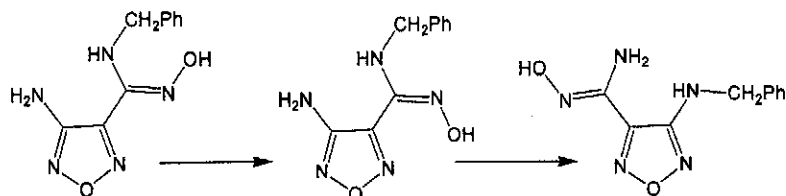
Scheme 38

By using mass spectroscopy, the fully degenerate transformation can be shown for the labelled amidoxime [61]. After heating this compound at 130 – 140 °C in the presence of potassium hydroxide, the mass spectrum of the resulting mixture shows the presence of equimolar amounts of ^{15}N isomers (Scheme 39), thus suggesting the occurrence of the degenerate transformation (preceded and followed by configurational isomerization), likely through the anionic species.
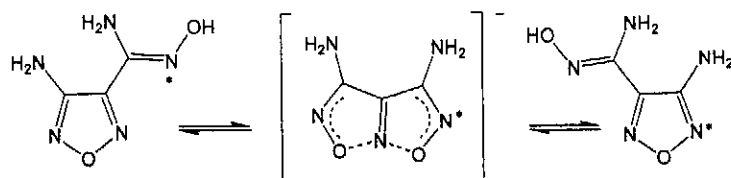
Scheme 39

Mataka *et al.* [3] found that the pyrrolidines — obtainable by easy procedures [62] — when heated in ethylene glycol for some hours afford 1-alkyl-2-methylpyrroles 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 Scheme 2.

A Hungarian group also reported on degenerate ring transformations of

pyrrole derivatives [7]. They published that the substituted maleinimide could be transformed to another maleinimide derivative by treatment with primary amines (Scheme 40).
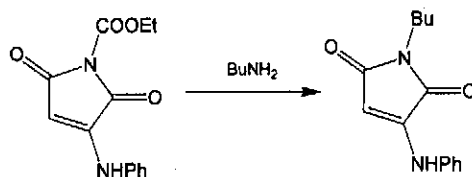
Scheme 40

Heimgartner *et al.* [63] reported an interesting degenerate ring transformation of some hydantoins upon treatment with aziridine to yield the substituted 4*H*-imidazole derivative (Scheme 41). Since all three atoms of the reagent aziridine are found in the five-membered product, the reaction may also be regarded as a ring expansion reaction of the aziridine ring to imidazole.
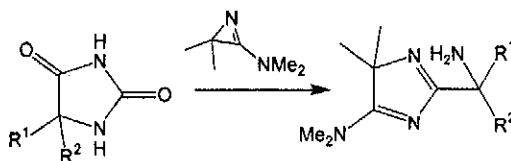
Scheme 41

Dehaen *et al.* reported [26,64] a reaction of 5-azidooxazole-4-carboxaldehyde to 4-oxazolylcarboxylic azide. The reaction is supposed to proceed by a Cornforth rearrangement (Scheme 42).
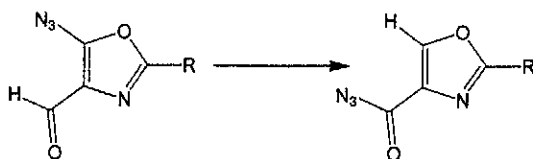
Scheme 42

Degenerate ring transformations are also known in triazoles [65]. A ring opening of the 5-diazomethyltriazoles, followed by heterocyclization involving the three-atoms side group $CH=N_2$ leads to the degenerate ring transformation into triazoles (Scheme 43). The occurrence of this ring transformation is highly dependent on the nature of the substituents. In fact, the 1,4-diphenyl-5-diazomethyltriazole does not transform; moreover, the reaction proceeds only when

strongly electron-withdrawing groups (e.g. nitrophenyl or dinitrophenyl) are bound at the N(1) of the triazole [65], and the driving force lies in the carboxymethyl-stabilized diazo group in the rearranged product. Different ring transformation proceeding via diazoimine intermediates regard heterocyclizations involving side-chains linked at C(4) of the triazole ring [66–68].
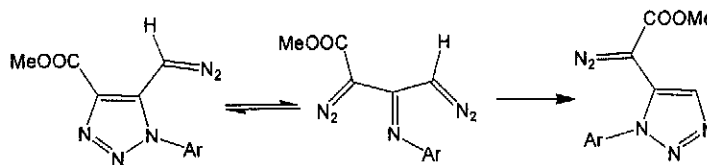
Scheme 43

Ring Contractions and Ring Expansions

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 cases. Ando et al. carried out a series of investigations [4–6] on 2-alkylidene-1,3,4-thiadiazolines and found that these compounds, when irradiated with a medium-pressure mercury lamp for 10 min, gave rise to the thiiranimine derivative (Scheme 3). The reaction is supposed to proceed by a homolytic cleavage of the S–C bond and subsequent recombination of the intermediate diradical.

In one of the previous parts, we have discussed the degenerate ring transformation of the substituted pyrrole compound described by Seres et al. [7] (Scheme 40). These authors in the same publication also report that treatment of this pyrrole with n-butylamine results in a ring expansion to a pyrimidine derivative (Scheme 4). 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. Five-membered heteroaromatic systems readily undergo Diels–Alder reactions which are well documented in literature [69]. A recent paper demonstrates that there is still high interest — from both preparative and theoretical points of view — in such transformations: Padwa et al. [70,71] report that methyl 5-aminofuran-2-carboxylate readily reacts with several monoactivated olefins by simply heating in benzene at 80 °C to yield a cycloadduct that, after ring opening and treatment with boron trifluoride-diethylether, gave the substituted aniline derivative (Scheme 44).

Harada et al. shoved[72] that some isoxazoline N-oxides in the presence of Lewis acids can undergo ring expansion to oxazines. Thus, N-oxide in Scheme 45, when treated with titanium tetrabromide at ambient temperature, gave the dihydro-

4*H*-1,2-oxazine compound. 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.
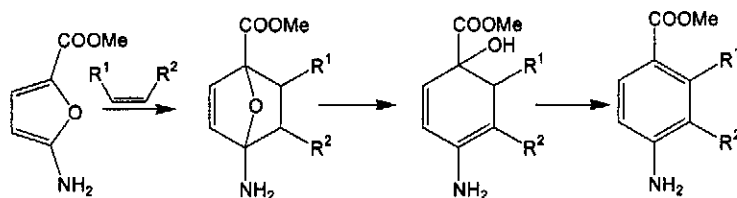
Scheme 44
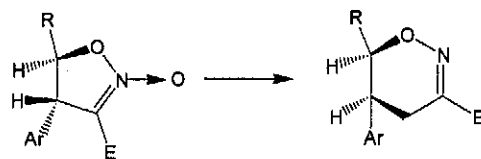
Scheme 45

While the above examples show ring expansion of monocyclic heterocycles, the next two cases indicate that such ring enlargements can also take place with fused systems. Thus, a recent report [73] on the chemistry of benzothiazoline 1-oxides revealed that the cyclic sulfoxide when heated under reflux in xylene for 4.5 h gave, simultaneously, two ring-expanded products: the benzothiazine derivatives in low yields (Scheme 46).
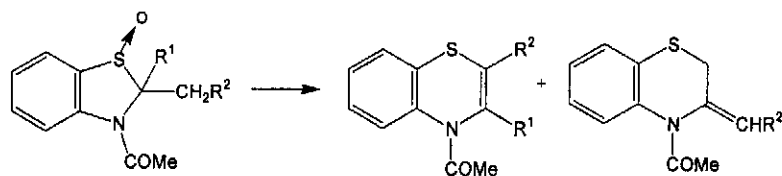
Scheme 46

Butler *et al.* [74–76] found that 1,2,5-oxadiazolium salt undergo ring expansion to 1,2,5-oxadiazines upon treatment with a base. The transformation could be carried out in excellent yield and was interpreted as proceeding by formation of the open-chain intermediate (Scheme 47).

Reaction of 1,2,5-triazolium salt takes place in a similar manner to yield the six-membered dihydro-trazine, but in this case the intermediate, analogous to Scheme 46, has an ambident reactivity: Beside route A a route B also occurs and,

thus, *N*-arylaminoimidazole is formed simultaneously (Scheme 48).
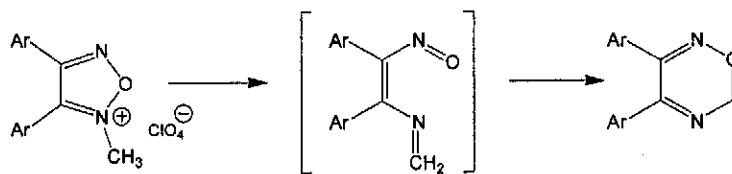
Scheme 47
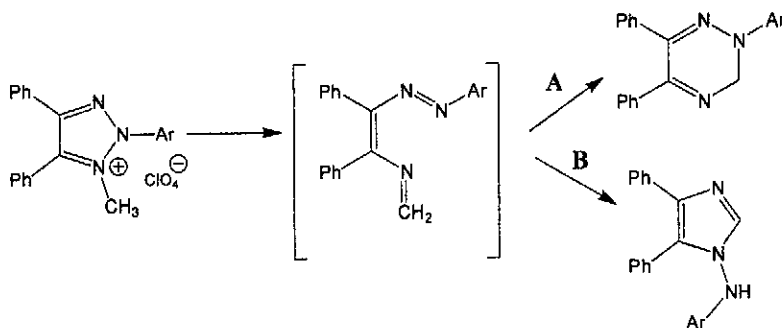
Scheme 48

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 transformation is discussed, first involving conversion of the starting pyrrolidines to the heteroaromatic pyrazoles [77]. Some earlier observation indicated [78,79] that the monocyclic enaminone, when treated with hydrazines, is transformed to the pyrazole (Scheme 49). The reaction obviously proceeds by a nucleophilic attack of the reagent at the activated position 2 to form an intermediate I. This compound may undergo an internal ring closure to the spirocyclic intermediate II that can be stabilised by opening of the strained saturated ring and elimination of water to give the final product — pyrazole. Liebscher's group found [77] that the same reaction could be carried out in better yield by a modified synthetic route: Treatment of monocyclic enaminone with phosphorous oxychloride/DMF and then with perchloric acid gave the crystalline perchlorate salt in good yield, which when treated with hydrazine — by substitution of the chlorine atom and formation of intermediate III — again afforded the pyrazole derivative (Scheme 49).

This synthetic strategy proved to be very convenient for synthesis of numerous five-membered heteroaromatics, as convincingly demonstrated by a review article [80]. In Scheme 48, 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.
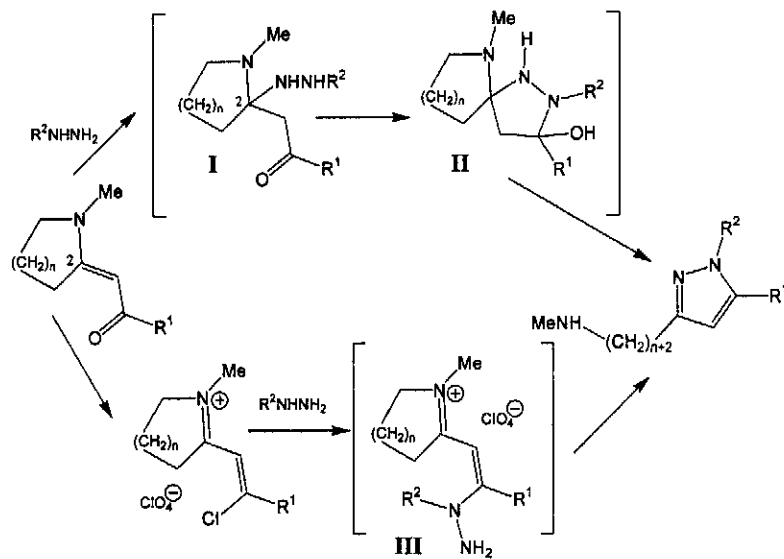
Scheme 49

The cyclic quarternary salt, having an imidoyl chloride side chain was rearranged into 1,2,4-triazoles by hydrazine or arylhydrazines in good yield [8] (Scheme 5).

The semicyclic thioacylamidine proved to be a suitable starting component for ring closure to 1,2,4-thiadiazoles: An amination reaction at the sulphur atom
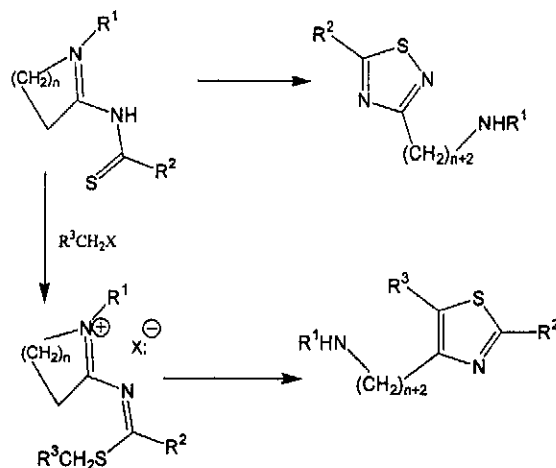
Scheme 50

followed by ring closure yielded the aminoalkyl-substituted thiadiazoles [81] (Scheme 50). When substituted thioacylamidine was treated with various alkylating agents like substituted benzyl bromides or chlorides, or phenacyl halogenides, the S-alkyl derivatives were obtained, which underwent ring closure to thiazoles [82] (Scheme 50).

Contrary to the experiment described above, the semicyclic aminoacrylonitrile contains an *exo* double bond activating position 2. Its reaction with hydrazine follows the general route, and results in formation of the pyrazole compound [83] (Scheme 51).
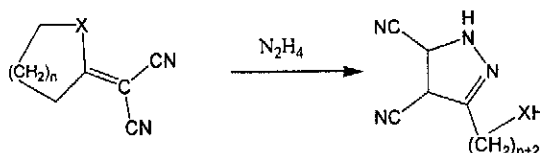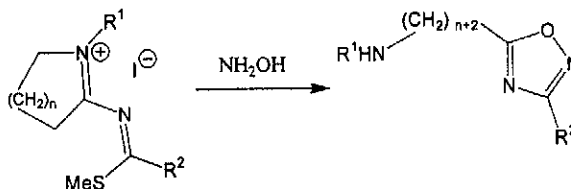

Scheme 51

The cyclic iminium salt containing a methylthio group proved to be suitable — by reaction with hydroxylamine — for the synthesis of a series of new 1,2,4-oxadiazoles in good to excellent yields [84] (Scheme 52). A similar synthetic strategy has also been applied for the synthesis of some isoxazoles by Dannhardt *et al.* [85].

Scheme 52

In a more recent paper of Liebscher *et al.* [86] ring transformation to chiral oxazolines has been reported. Both the butyrolactim ether and the cyclic acetal could be transformed using a chiral amino alcohol to give the oxazoline as pure enantiomers (Scheme 53). The transformation has been applied to 20 various derivatives: All the reactions proceeded with complete retention of the configuration of the amino alcohol applied.

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.* [87] should be demonstrated. These authors found that *N*-pivaloylproline, when treated with trifluoroacetic anhydride, could lead to the oxazole derivative (Scheme 54). The transformation is rationalized by formation

of the acylated product followed by a ring closure to an intermediate fused oxazolium salt which undergoes acidic cleavage to yield of oxazole derivative.
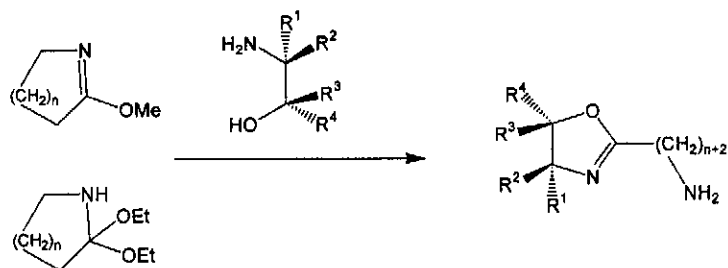
Scheme 53
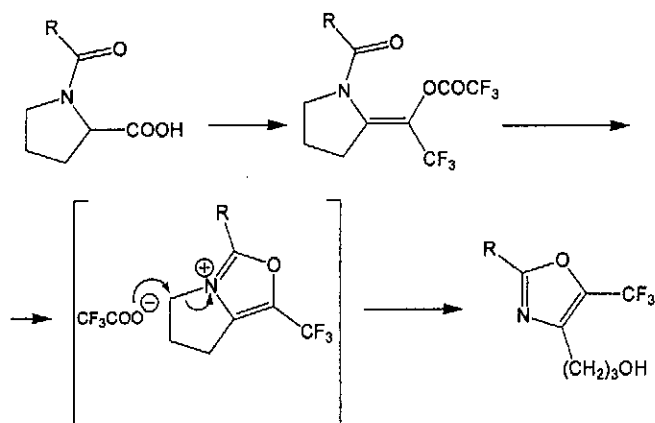
Scheme 54

Conclusion

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.

Rearrangements of heterocyclic rings in which a original ring is decomposed and subsequently another ring is formed are particularly interesting both synthetically and theoretically. Such processes may provide fascinating routes to derivatives that can be obtained only with great difficulties — or not at all — by other procedures.

Acknowledgements

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