SOME RECENT ADVANCES IN THE SYNTHESIS OF THREE-MEMBERED RING HETEROCYCLES

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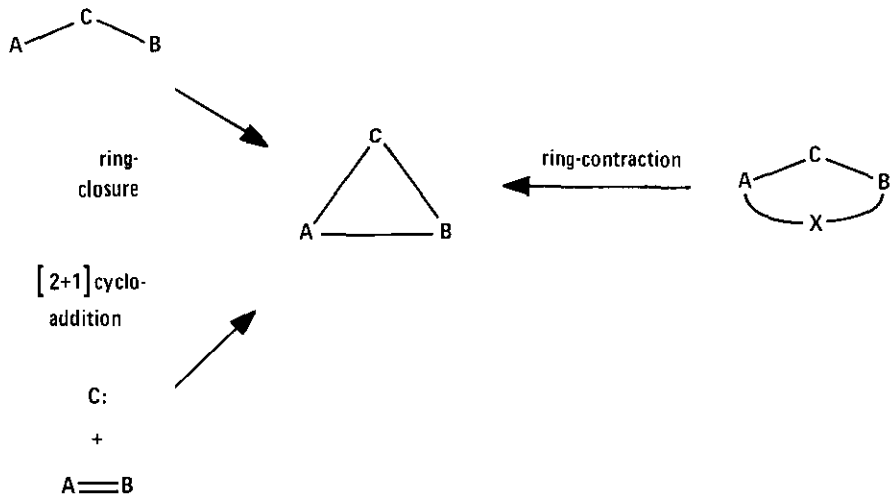
Abstract: The syntheses of some three-membered rings containing phosphorus(V) or sulfur(VI) and of nitrogen analogs of methylene-cyclopropane, **viz.** methylenaziranes, iminoaziranes, and imino-diaziranes, are reviewed. Furthermore, an account is given of the photo-extrusion of nitrogen from 1-pyrazolines and tetrazolines both having exocyclic double bonds, which in most cases leads to the formation of methylenecyclopropane analogs.

The chemistry of small rings, now in the venerable age of 100 years[1], is still expanding at a breath-taking rate. Its rate of growth during the last decade may be inferred from the number of reviews dealing with all facets of small-ring chemistry. For example, a recent compilation of the heterocyclic literature by Katritzky and Jones[2] covering the period between 1966 and 1979 lists some 100 reviews on three-membered ring heterocycles and some 60 reviews on four-membered ring heterocycles. Clearly, this is a clear indication of the importance of the field of small-ring chemistry. On the other hand, it demonstrates the necessity of confining the present report on the synthesis of small heterocycles to certain selected topics. One topic will be concerned with the metamorphosis of highly unstable, elusive species, often only invoked for mechanistic reasons, into stable, well-characterized molecules. From another point of view we will see that a few of the classical synthetic principles may still lead to attractive new systems. For convenience, I will pick most examples from our work on three-membered rings with nitrogen, sulfur, and/or phosphorus as hetero-elements. As this is a colloquium on *hetero*cyclic chemistry, I apologize for the occasional incursion of a *homo*cycle, *viz.* the cyclopropane ring.

As an introduction it may be useful to cast a glance at the principles that underlie the syntheses of three-membered rings which certainly are among the smallest synthetic targets in chemistry. It is, therefore, not surprising, that only a limited number of the ring-forming reactions may be applied to the smallest of all rings. These reactions may be classified in a pragmatic way: i) Closing the ring by making one bond between the termini of a three-membered chain. ii) Making two bonds simultaneously, which corresponds to a [2+1] cycloaddition. iii) Contraction of a larger ring by isomerization or by extrusion of a fragment.

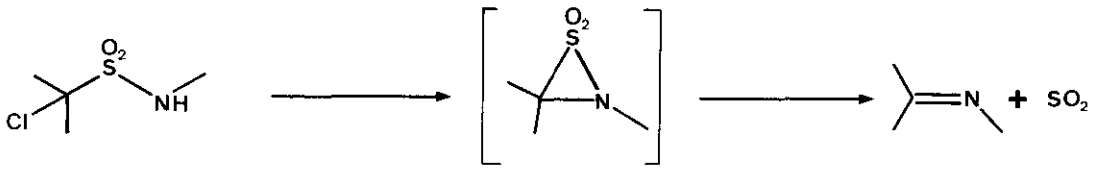


The sketch of the synthetic routes leading to three-membered rings could be depicted in detail by listing the plethora of methods in the interest of converting each synthetic principle into reality, but of course, this would go far beyond the scope of the present report. In our search for new three-membered rings, the base-induced, 1,3-eliminations of hydrogen halides and

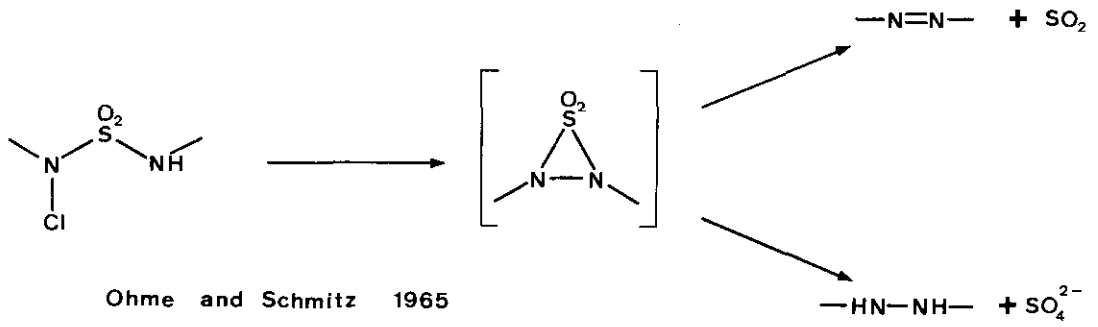
the photochemical extrusion of nitrogen from five-membered rings have predominated, mainly because the synthesis of labile systems seemed to call for such mild reaction conditions. As will be outlined on the following pages, this strategy gratifyingly has turned out quite successful. Thus, novel three-membered ring heterocycles containing sulfur(VI) or phosphorus(V) have been isolated and syntheses of highly reactive hetero-analogs of methylenecyclopropane have been accomplished.

Three-membered Rings of Phosphorus(V) and Sulfur(VI)

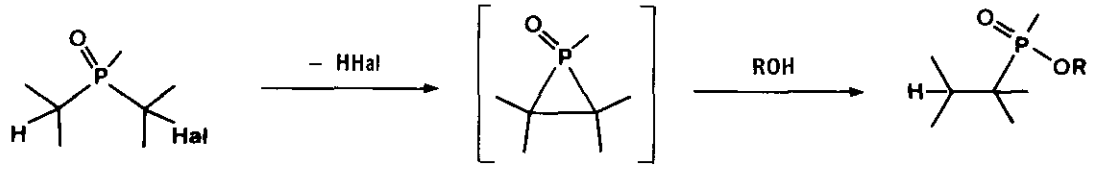
After a slow, steady development in the first half of this century, the three-membered ring chemistry containing elements of higher periods came into bloom during the seventies. Major achievements include the discovery of siliranes[3] and of many three-membered rings containing phosphorus(III)[4, 5]. Our interest in this area was roused by the recognition that a number of



Johnson and Douglass 1941



Ohme and Schmitz 1965



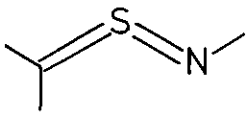
Haake et. al. 1972

Petrov et. al. 1976

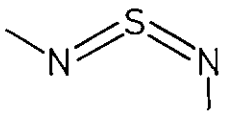
reactions most probably occurr via intermediates involving three-membered rings that contain phosphorus(V) or sulfur(VI), respectively. These reactions, which resemble closely the Favorskii rearrangement[6] and the Ramberg-Bäcklund reaction[7], are the base-induced rearrangements of α-halosulfonamides[8], *N*-chlorosulfamides[9], α-halophosphinates[10] and of α-halophosphane-oxides[10, 11]. Such rearrangements challenged us to design and synthesize stable species of the presumed intermediates. In their design, we were guided by the well-established principle of stabilizing small rings by bulky alkyl groups. Before beginning a search for novel three-membered rings, consideration a few general principles may be in order. For example, one has to take into account the coexistence of acylic 1,3-reactive species (diradicals or 1,3-dipoles) on the potential energy hypersurface. Since usually the energy barriers involved are not very high, it is the relative depth of the energy wells which determines the final result of a synthesis. Therefore, bond energy considerations[12] supported by prior experience may be useful. For example, if we put together the sulfur species which contain carbon and/or nitrogen as members of the eventual ring, it becomes obvious: i) that only for the CSC-system, the three-membered ring forms the most stable arrangement regardless of the oxidation state of the sulfur atom and ii) that only $-SO_2-$ can be expected to yield three-membered rings independent of the nature of the other ring-members[13]. Of course, similar reflections apply to other sulfur-containing systems as well as to the formation of all kinds of phosphorus-containing three-membered rings[14].

Most Stable Arrangements of CSC-, CSN-, and NSN-Systems

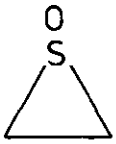
Thiirane



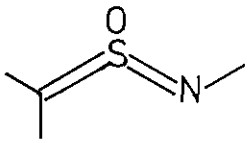
Thione-S-imide



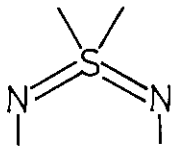
Sulfurdiimide



Thiirane Oxide

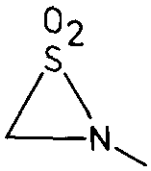


Iminosulfene

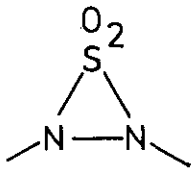


Sulfodiimide

Thiirane Dioxide

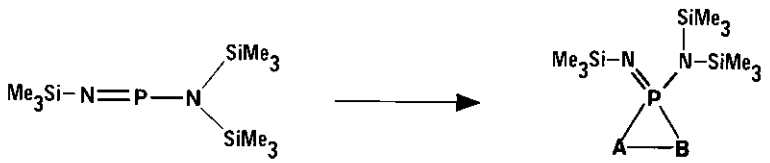


Thiazirane Dioxide

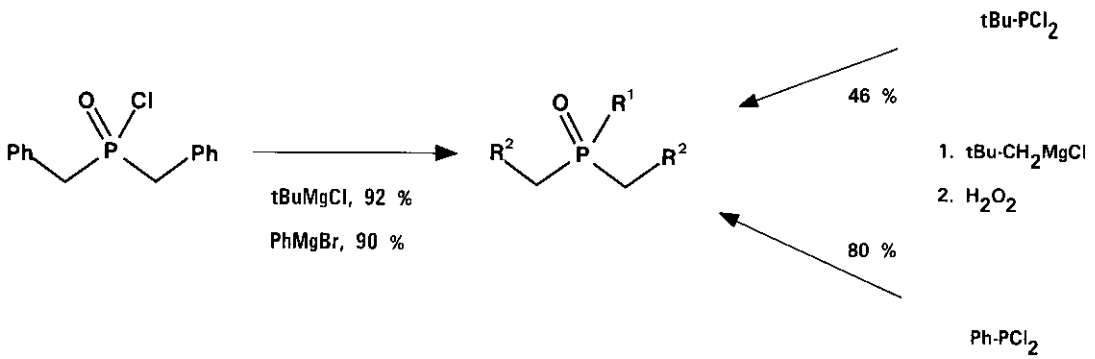


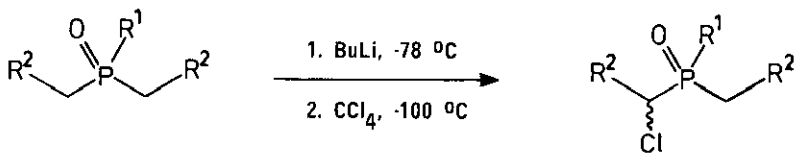
Thiadiazirane Dioxide

When we embarked on the synthesis of novel three-membered rings containing elements of higher periods several years ago, only σ^3,λ^3-phosphiranes[15] and all kinds of thiiranes were known. Subsequently, σ^4,λ^5-phosphiranes[16], a σ^4,λ^5-azaphosphirane[16], and a σ^4,λ^5-oxaphosphirane[17] were isolated. Our approach to phosphirane oxides followed the pattern of the Favorskii rearrangement and the Ramberg-Bäcklund reaction, the first step being the α-halogenation of phosphane oxides[18, 19]. Quite surprisingly, this turned out to be rather difficult. As starting materials we choose phosphane oxides, which exhibit various degrees of steric hindrance. The possibility of a competing 1,2-elimination of hydrogen halide had, of course, to be avoided. The synthesis of such phosphane oxides was accomplished by the Grignard reaction of dibenzylphosphinylchloride or dichlorophosphanes, respectively, followed by hydrogen peroxide oxidation in the latter case. As expected, the reaction con-



	A	B
NIECKE and FLICK, 1975	CH_2	CH_2
	CH_2	N-$SiMe_3$
SCHMUTZLER et al., 1978	$C(CF_3)_2$	O

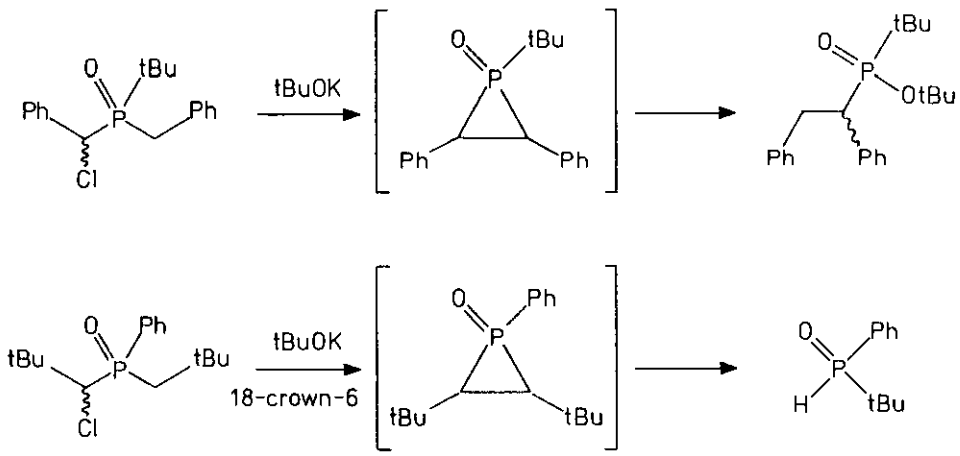


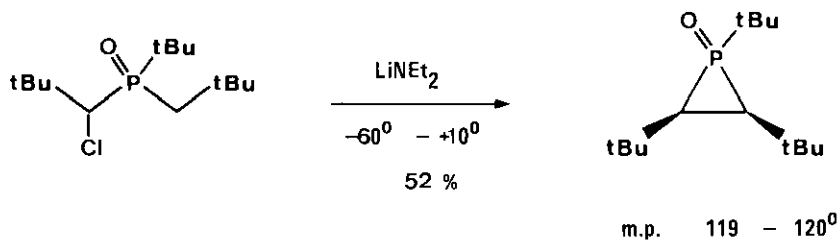


R^1	R^2	%
tBu	tBu	91
tBu	Ph	58
Ph	tBu	86

ditions of the Grignard reactions had to be adjusted to the degree of steric hindrance. After exploring numerous, less successful halogenation experiments, Savignac's method of α-halogenating phosphonates by the action of carbon tetrachloride upon the α-lithiophosphonates[20] was adapted to phosphane oxides. Thus, lithiation of phosphane oxides by butyllithium at low temperature, followed by one equivalent of carbon tetrachloride at very low temperature, produced the desired α-chlorophosphane oxides as separable mixtures of diastereomers.

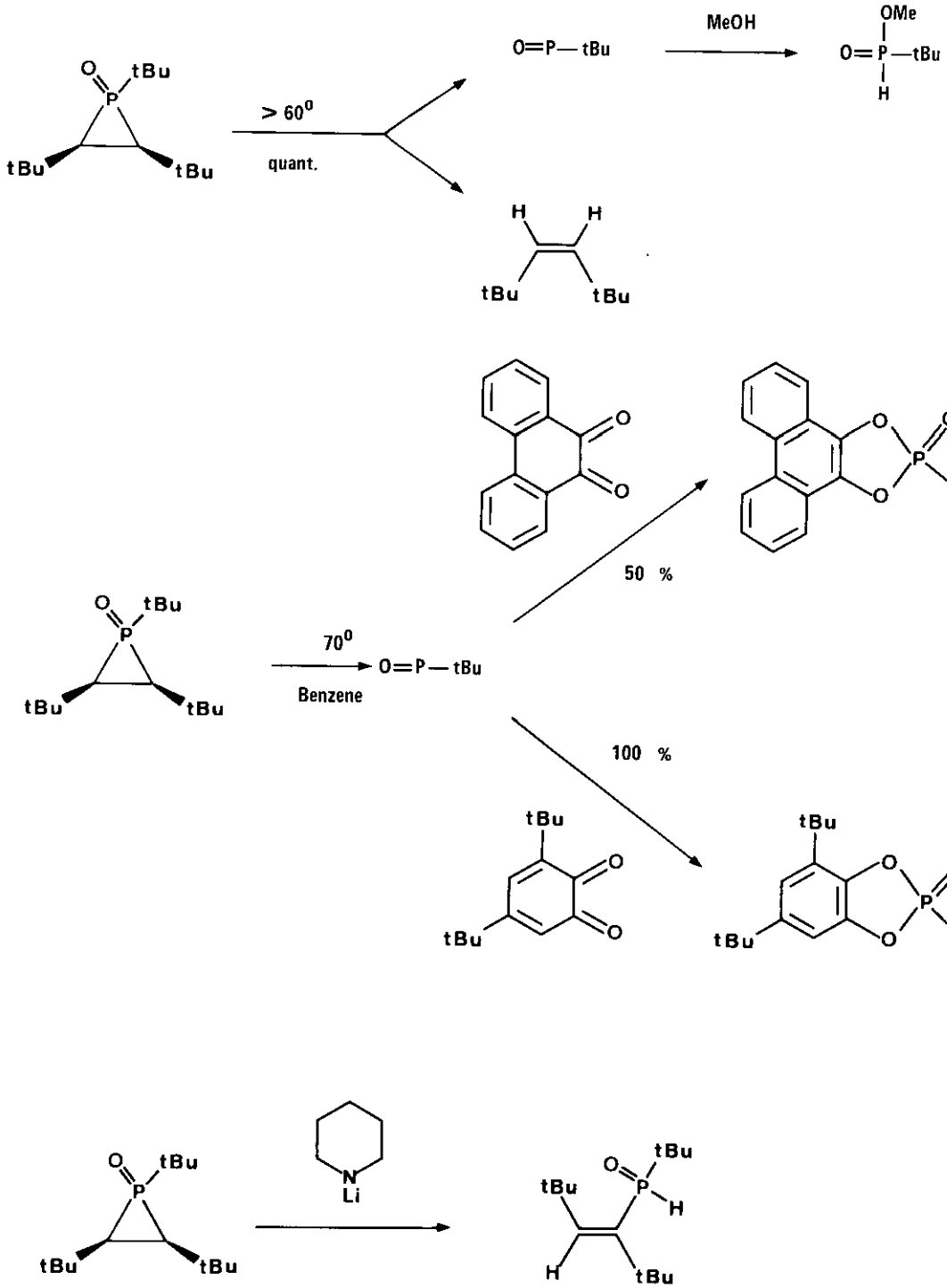
Unfortunately, all attempts to obtain phosphirane oxides by base-induced hydrogen chloride elimination from sterically less hindered precursors met with failure. For example, potassium *tert*-butoxide reacted with such α-chlorophosphane oxides to afford products which indicated the ease of ring-opening of the hypothetical phosphirane oxides under the reaction conditions. The use of more strongly hindered alkoxides than *tert*-butoxide[21] did not improve the results. Obviously, the situation resembled the Favorskii rearrangement of αhaloketones[6], in which only cyclopropanones which are strongly shielded by bulky alkyl groups can survive[22].

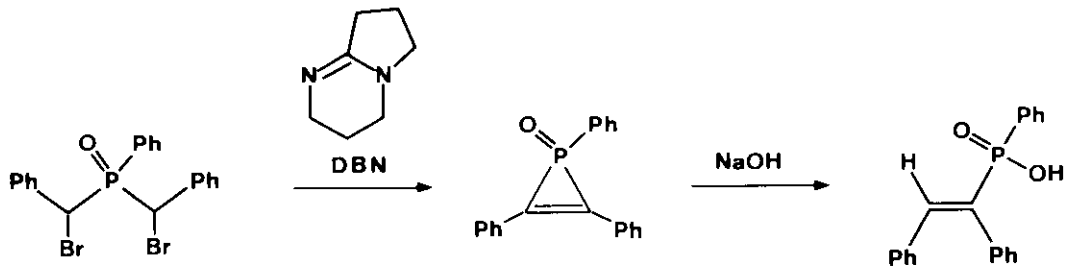




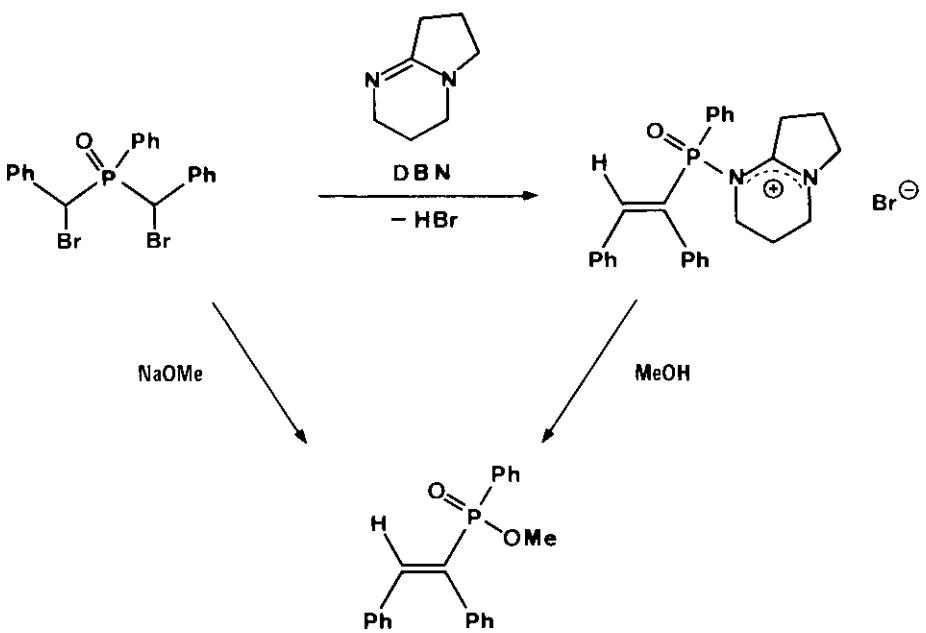
Consequently, we turned to the synthesis of tri-*tert*-butylphosphirane oxide, a compound designed to maximize steric hindrance to attack by external nucleophiles. Nevertheless, the extent to which the introduction of the third *tert*-butyl group was actually effective in this respect came as quite a surprise.

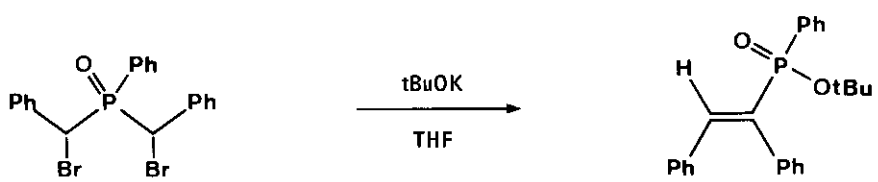
Treatment of the corresponding α-chlorophosphane oxide with an excess of lithium diethylamide in ether at low temperature afforded a 90 % yield of a mixture consisting of the desired phosphirane oxide, its ring-opening product (vide infra), and the chlorine-free phosphane oxide in a ratio of 76 : 6 : 18, respectively. After thin layer chromatography on silica gel, 52 % of pure phosphirane oxide could be isolated. It turned out to be unaffected by strong alkali as well as by strong mineral acids.


tBu
tBu
tBu
> 60°
quant.
O=P—tBu
MeOH
OMe
O=P—tBu
H
H
H
tBu
tBu
O
O
O
O
P
tBu
50 %
70°
Benzene
O=P—tBu
100 %
N
Li
H



STILLE et al., 1972

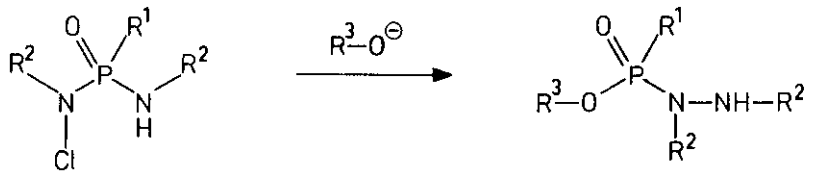




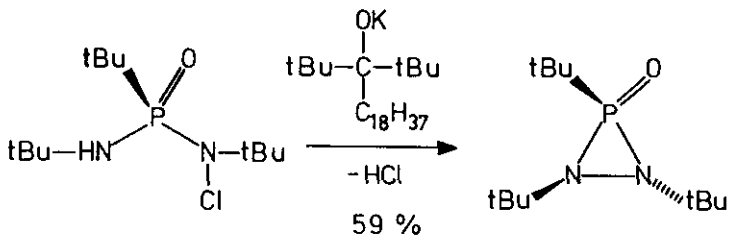
The cis-configuration of the C-*tert*-butyl groups was deduced from the ^1H and ^{13}C nmr spectra and from the quantitative stereospecific formation of (Z)-di-*tert*-butylethylene on thermolysis above 60 °C. As the second fragment in thermolysis, the elusive *tert*-butylphosphinidene oxide could be trapped by methanol or by 1,2-quinones via a [4+1]cycloaddition. Attempts at epimerization at a ring carbon atom by treatment with lithium dialkylamides failed to yield the trans-diastereomer. Instead the ring was opened to a vinylphosphane oxide in which the *tert*-butyl groups are trans to each other. Most probably, an electrocyclic ring-opening via the sterically most favorable path had followed the deprotonation by the strong base[18].

In view of our interest in three-membered ring phosphorus compounds, we were fascinated by the triphenylphosphiren oxide, described already in 1972 and highlighted as "one member of a new class of potentially aromatic phosphacyclopropanes"[23]. Somewhat surprisingly, however, the alleged triphenylphosphiren oxide was reported as an oil, unseparable from the supposed 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) hydrobromide; DBN had been used for the hydrogen bromide elimination. We were able to confirm the formation of an oil in this reaction; but unfortunately we could not confirm its claimed structure as a triphenylphosphiren oxide[24]. Instead, ^1H and ^{13}C nmr offered conclusive evidence for an acyclic structure, having the DBN attached to the phosphorus of the (E)-1,2-diphenylvinyl(phenyl)phosphinyl group. Sodium methoxide or potassium *tert*-butoxide reacted with the α,α'-dibromophosphane oxide to yield the corresponding phosphinates. These were formed also in the solvolysis of the oily DBN product. In these reactions, most probably a phosphirane oxide, perhaps even a genuine phosphiren oxide may be involved, but its existence has yet to be proven.

The extremely useful synthesis of azoalkanes and *N,N'*-dialkylhydrazines from *N,N'*-dialkylsulfamides by Ohme and Schmitz[9] most probably proceeds via thiadiazirane dioxides as intermediates. This prompted us to attempts to isolate such intermediates



R^1	R^2	R^3	%
Me	tBu	Me	60
Me	1-Ad	Me	86
tBu	tBu	Me	82
Ph	tBu	Me	84
Me	tBu	tBu	78
Me	1-Ad	tBu	79
tBu	tBu	tBu	91
Ph	tBu	tBu	82
tBu	tBu	CMe_2Et	59
Ph	tBu	CMe_2Et	42
tBu	tBu	CEt_3	78

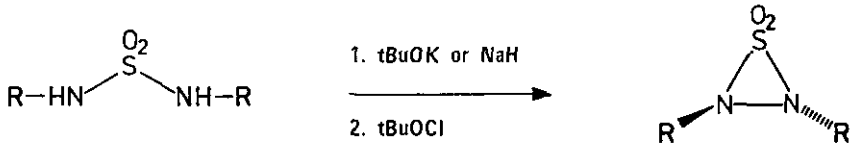


(vide infra) and to a search for their phosphorus counterparts. As a first step towards this goal, a base-induced rearrangement of *N*-chlorophosphonamides patterned after the base-reaction of *N*-chlorosulfamides was investigated. The second step contemplated isolation of the eventual three-membered ring intermediates, i.e. diazaphosphirane oxides.

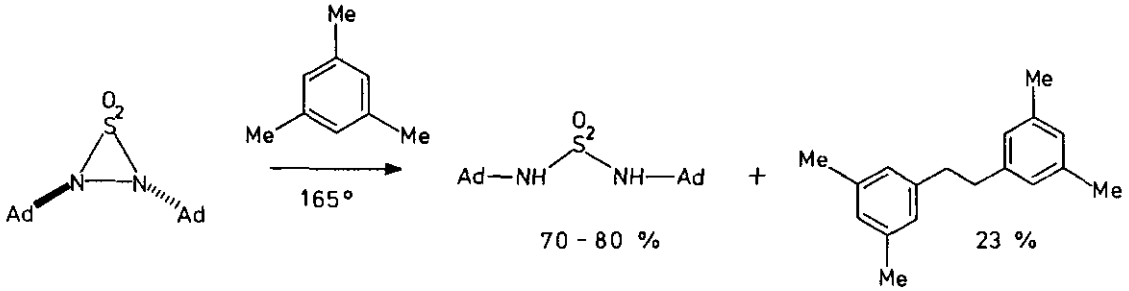
A broad range of phosphonyldiamides, the required starting materials, was readily available from phosphonyldichlorides and primary amines. *N*-Chlorination by *tert*-butylhypochlorite yielded the moderately stable *N*-chlorophosphonyldiamides almost quantitatively. As expected, alkoxides induced a rearrangement in which an N-N-bond was formed, affording hydrazinophosphonates in high yields.[25] Despite the simplicity and the mild conditions of the reaction, the search for the assumed intermediate proved a delicate task. Such difficulties are not uncommon but, in view of the surprising stability of the tri-*tert*-butylphosphirane oxide[18], they were somewhat unexpected in the present case. The problem turned out to be the enormous reactivity of the diazaphosphirane oxide intermediate towards nucleophiles despite the fact that we had chosen the sterically shielded tri-*tert*-butyldiazaphosphirane oxide as the target in our experiments. Even the rather encumbered 1.1-diethylpropoxide failed to prevent the rearrangement at the three-membered ring stage. However, success was granted when an extremely hindered, *tailor made alkoxide derived from a nonvolatile alcohol*[21] *was employed and the sought-for* tri-*tert*-butyldiazaphosphirane oxide could be isolated by high-vacuum sublimation[14, 25].

In an inert environment, the diazaphosphirane oxide resisted decomposition up to 120 °C, however, undefined decomposition products were obtained above 140 °C. The ^{1}H nmr spectrum of the diazaphosphirane oxide proved the trans relationship of the *N*-*tert*-butyl groups. From the temperature dependence of the ^{1}H nmr spectrum a relatively low barrier ΔG_c (−38 °C) = 49 kJ/mole] to nitrogen inversion was calculated , indicating some destabilization of the ground state by steric interaction between the *P*-*tert*-butyl group and one the the *N*-*tert*-butyl groups.

The elegant azoalkane and *N,N'*-dialkydrazine synthesis from sulfamides devised by Ohme and Schmitz[9] stimulated three research groups to attempt the isolation of the proposed thiadiazirane dioxide intermediates. In 1973, this goal was reached in-

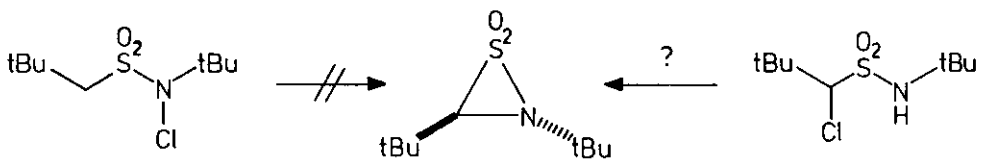


	R
TIMBERLAKE and HODGES 1973	CMe_2CH_2-tBU
CHANG and WEINSTEIN 1973	tBu
QUAST and KEES 1973	1-adamantyl



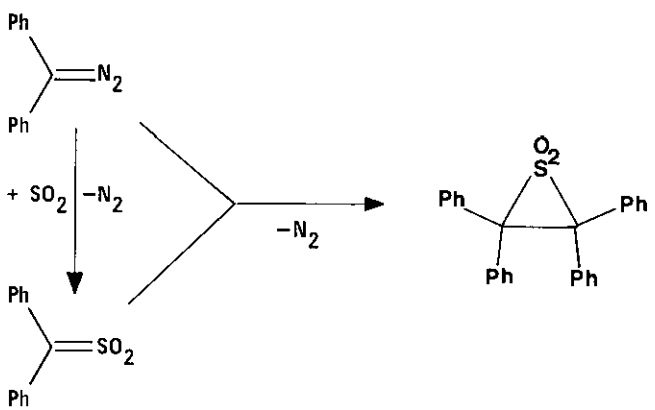
dependently by us [13] and others[26, 27]. The most intriguing property of thiadiazirane dioxides was the surprising thermal stability in the absence of traces of moisture and nucleophiles.[13] Just as unexpected was the course of the thermal decomposition under forcing conditions. In the thermal decomposition of the bisadamantylthiadiazirane dioxide at 160–170 °C loss of sulfur dioxide represented only a minor path (10–15 %). Actually, cleavage of the N-N-bond to a diradical predominated (70–80 %). The diradical abstracted hydrogen from the solvent thereby being reduced to the sulfamide. The presence of solvent derived radicals was confirmed by observing solvent "dimers", e.g. from 2, 4, 6-trimethylbenzene. In contrast, the thermolysis in wet benzene or in ethanol already occured at 80 °C producing mainly the azoalkane. Thus, water or ethanol reacted with the thiadiazirane dioxide and thereby simulated a thermal [2+1] cycloreversion into sulfur dioxide and azoalkane.[13]

A logical consequence of the foregoing experiments was to try our fortune with the thiazirane dioxides that apparently had intervened in 1,3-eliminations of α-halosulfonamides studied some 40 years ago[8].

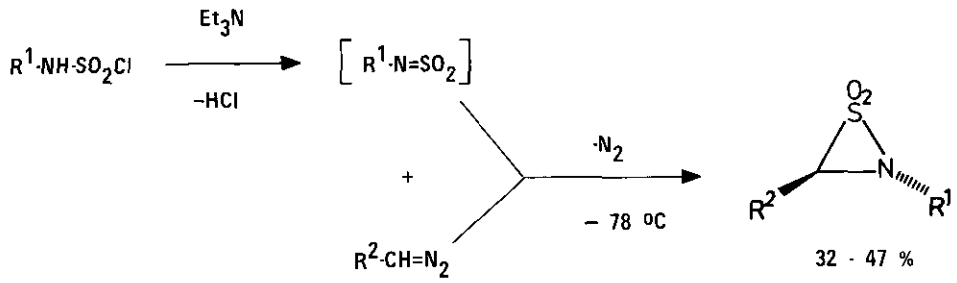


However, our efforts[28] as well as those of Sheehan and coworkers[29] were frustrated by both the thermal lability of the proposed thiazirane dioxide intermediates and the inaccessibility of suitable precursors to hopefully more stable examples. We again chose as the most promising candidate the three-membered ring substituted by two *tert*-butyl groups, but we failed to effect ring-closure of the readily available *N*-chlorosulfonamide as precursor. On the other hand, the presumably more suitable precursor, *viz.* the α-chlorosulfonamide, defied all our attemps at synthesis. This dilemma demanded a fundamentally different approach. A potential alternative route was suggested by Staudinger's discovery of a thiirane dioxide in the reaction between diphenyldiazomethane and sulfur dioxide[30]. This reaction was later shown to involve a sulfene as intermediate[31]. We just had to replace the sulfene by an *N*-sulfonylamine generated by hydrogen chloride elimination from a sulfamoylchloride[32]. It was gratifying to establish the close analogy between sulfenes and *N*-sulfonylamines in their reaction with diazoalkanes.

If the work-up temperature was kept below −30 °C in the reaction of *tert*-alkyldiazomethanes with *N-tert*-alkyl-*N*-sulfonylamindes, the isolation of thermally labile thiazirane dioxides was accomplished in moderate yields[28]. The only reaction so far observed has been the quantitative first-order decomposition at 25 °C into sulfur dioxide and the corresponding aldimine. This thermal lability made the chemistry of thiazirane dioxides somewhat uninteresting. A kinetic study[33] revealed an almost linear increase of the logarithm of the first-order rate constant with the Dimroth-Reichardt solvent parameter E_T[34] [$k_1 = 0.90 \cdot 10^{-4}\,sec^{-1}$ in hexane; $27.7 \cdot 10^{-4}\,sec^{-1}$ in methanol at 25 °C].



STAUDINGER and PFENNINGER 1916

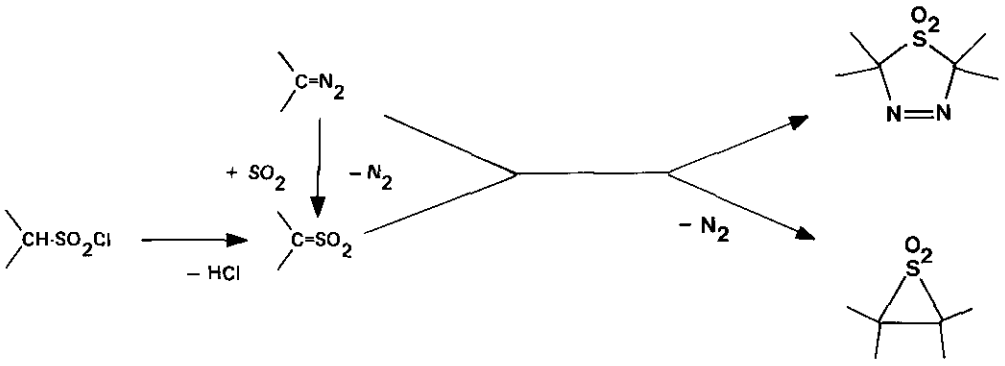


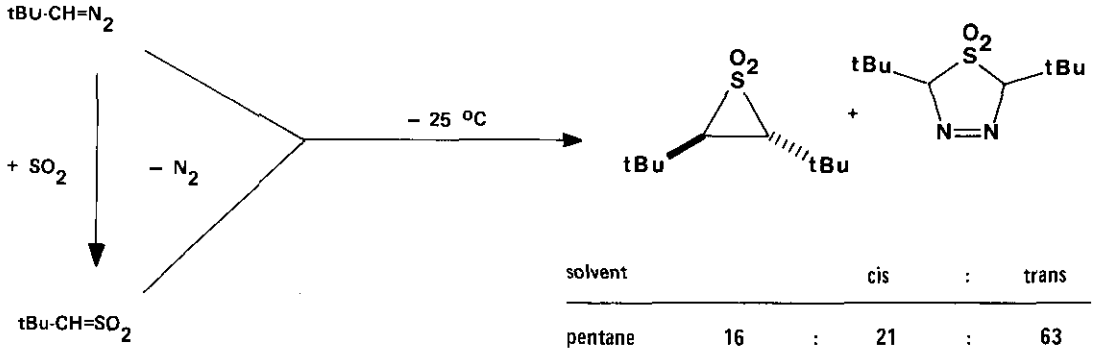
R^1, R^2 = tert-butyl, 1-adamantyl

For a comparison of the relative reactivity of the three-membered rings having sulfur dioxide as a ring member, the di-*tert*-butylthiirane dioxide was required. The Staudinger-Pfenninger reaction between *tert*-butyl-diazomethane and sulfur dioxide offered a good opportunity to prepare the missing link; only a single starting material was required[30]. Therefore, we explored the seemingly well known reaction between diazoalkanes and sulfur dioxide[35]. In virtually all previous investigations of the Staudinger-Pfenninger reaction, as well as the reaction of diazoalkanes with sulfenes generated from sulfonylchlorides[31], a remarkable dichotomy was observed. Aryl-substituted and *mono*alkyl-substituted diazomethanes inevitably yielded thiirane dioxides and/or alkenes as products which were formed via stereospecific decomposition of the intermediary thiirane dioxides. Also small amounts of azines were formed. On the other hand, *di*alkyldiazoalkanes afforded only 2,5-dihydro-1,3, 4-thiadiazol dioxides in a [3+2]cycloaddition.

Tert-butyldiazomethane, however, surprisingly gave both types of products. This prompted a mechanistic study[35]. We found, that the ratio of three-membered to five-membered ring was not influenced by the reaction temperature but depended on solvent polarity. The increase in the latter parameter favored formation of the three-membered ring over the [3+2]cycloaddition product. In contrast, the cis/trans ratio of the thiadiazol dioxides remained virtually unaffected. Most probably, both types of products do not arise from a common (dipolar) intermediate. Since sulfenes possess two low lying empty MO's of different *symmetry but similar energy*[36], it is tempting to attribute the dichotomy of the sulfene-diazoalkane reaction to the existence of these vacant sulfene orbitals. Whatever the mechanistic truth, the possibility of guiding the course of the Staudinger-Pfenninger reaction by means of the solvent polarity should prove useful in synthesis.

The reactions employed for the synthesis of the new three-membered rings of this paragraph have by no means been fully explored. Mutatis mutandis, future experiments can be anticipated to disclose yet unknown systems. Most probably, a considerable part of the synthetic potential of the few simple, *versatile reactions has still to be uncovered for the enrichment* of the three-membered ring chemistry containing the elements of the higher periods.



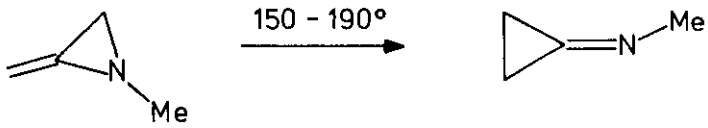


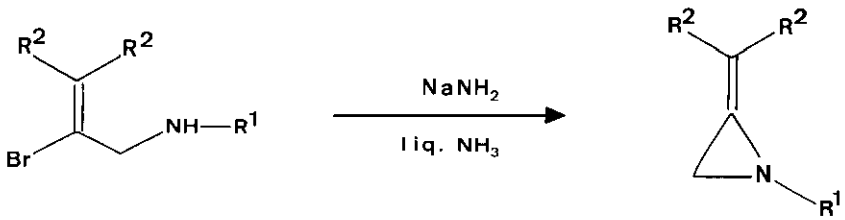
solvent			cis		trans
pentane	16	:	21	:	63
acetonitril	73	:	6	:	21

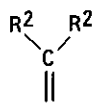
Nitrogen Analogs of Methylenecyclopropane

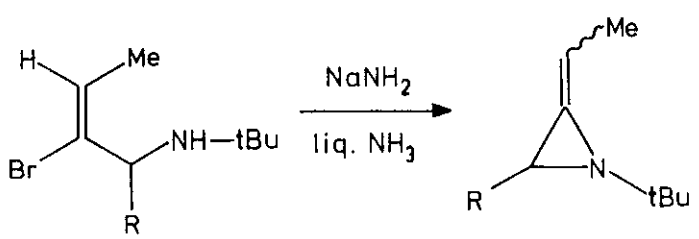
After the foregoing excursion into areas of small-ring chemistry which undoubtedly have an "inorganic" flavor I would like to return to "pure organic" three-membered rings. For several years we have been and still are engaged in a study of nitrogen analogs of methylenecyclopropane which offered many opportunities to solve synthetic problems.

Already in 1951, the first heteroanalog of methylenecyclopropane was found fortuitously by Pollard and Parcell[37], who treated 2-bromoallylamines with sodium amide in liquid ammonia. The correct methylenazirane structure was only assigned some years later by Ettlinger and Kennedy[38] and by Bottini and Roberts[39]. We had realized that on heating methylenaziranes rearranged to the thermodynamically more stable cyclopropanimines[40]. Thus, methylenaziranes could serve as precursors to those of their carbocyclic isomers which are otherwise only accessible with difficulty. In addition, we were intrigued by the stereochemistry and the mechanism of the thermal methylenazirane to cyclopropanimine rearrangement[41]. As a consequence, we explored the scope and limitations of the Pollard-Parcell methylenazirane synthesis[40-42]. A few eexamples may serve to show that so far the synthesis is only limited by the accessibility of the starting material. If (E)/(Z)-isomerism occurred in the starting material then the stereochemistry was critical. Thus, only the (E)-bromoallylamines afforded methylenaziranes, whereas in the case of the (Z)-bromoallylamines, trans-1,2-elimination of hydrogen bromide to yield alkynes was the faster process.[41].



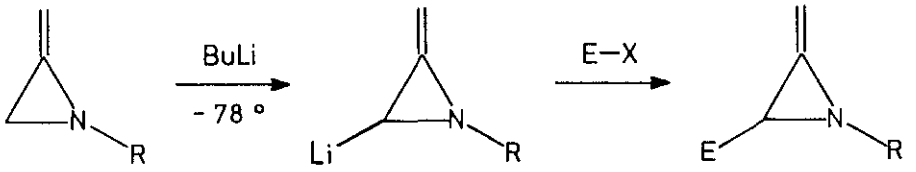


R^1	R^2
CH_2-tBu	H
1-adamantyl	H
Me	Me
tBu	Me
Me	 = 2-adamantylidene

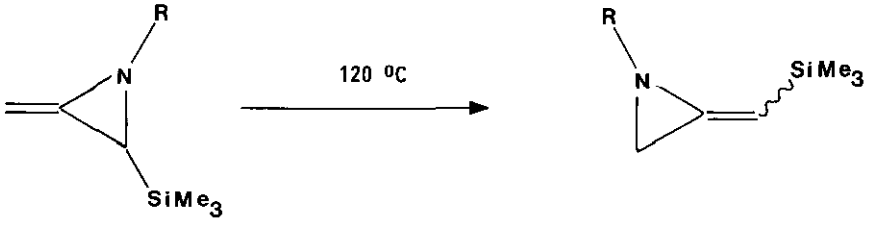


R = H, Me

The range of methylenaziranes could be considerably expanded by substitution at the three-membered ring of readily y available methylenaziranes via lithiation and consecutive quenching with electrophiles[42, 43]. Using Seebach's chiral auxiliary reagent (S,S)–(+)–1,4–Bis(dimethylamino)–2,3–dimethoxybutan [(+)–DDB][44], it was possible via this sequence to introduce a chiral center at the ring and this revealed the inversion of configuration at the migrating carbon in the thermal rearrangement to the isomeric cyclopropanimine[41]. Finally, the readily available methylenaziranes substituted at the ring carbon may be rearranged thermally to the more stable isomers substituted at the exocyclic double bond[40-42]. In summary, the interesting chemistry of the highly reactive methylenaziranes can now be explored with a much broader range of easily synthesized examples.

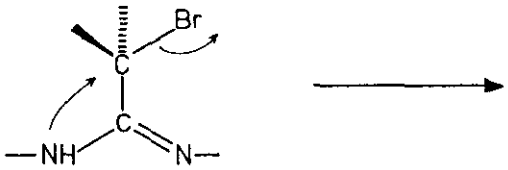


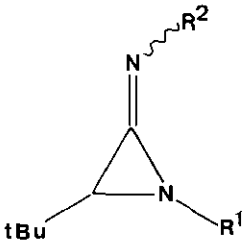
R	E–X	%
Me	Me_3Si–Cl	30
CH_2–tBu	Me_3Si–Cl	57
tBu	Me_3Si–Cl	83
tBu	D–OMe	> 90
tBu	Me–I	60
tBu	Bu–I	80
tBu	Ph–CH_2–Br	77
tBu	H_2C=CH–CH_2–Br	70
tBu		69



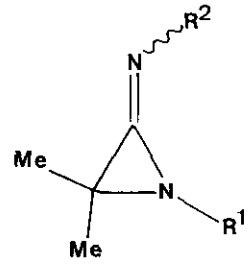
R	(E)	:	(Z)
Me	86	:	14
CH_2-tBu	90	:	10

If one focusses on the functional group attached to the azirane ring, aziranimines may be regarded as intermediate between methylenaziranes and the well-known aziranones (α–lactams)[45]. On the other hand, if the azasubstitution of methylenecyclopropane receives priority, then aziranimines fall structurally between methylenaziranes and diaziranimines as reference (vide infra). We were mainly intrigued[46] by the latter resemblance since it suggested the possibility of an interesting, similar thermal reorganisation[47]. The synthesis of aziranimines was easily accomplished by a base-induced 1,3–elimination of hydrogen bromide, which already had proven the method of choice in the preparation of aziranones[45]. However, unlike aziranones, the aziranimines offered stereo- and regioselectivity problems. At low temperature, the kinetically controlled product of the ring-closure of α–bromoamidines was the aziranimine in the (Z)-configuration (> 90% stereoselectivity)[46]. If the nitrogen atoms carried different substituents, regioselectivity of the 1,3–elimination came into play. For reasons not really understood (probably steric in nature), at this point in some cases a moderate, temperature dependent regioselecitvity was observed[46], while other α–bromoamidines showed a 100% regioselective ring-closure[47]. Thus, a wide range of aziranimines with the same or different substituents at the nitrogen atoms could readily be synthesized. Aziranimines differ considerably with respect to thermal stability which mainly depends on the substituents. At one end of the stability scale we found that the extremely labile 1–(2,4,6–trimethylphenyl)aziranimine decomposes at just above 0 °C via a [2+1]cycloelimination into *tert*-butylisocyanide and 2,2–dimethylpropylidene–2,4,6–trimethylaniline. At the other end of the scale the rather stable adamantane [spiro]aziranimine allowed a kinetic study of its thermal reorganization between 140 and 170 °C. The structure of the adamantane [spiro]aziranimine was confirmed by X-ray crystallography[47].

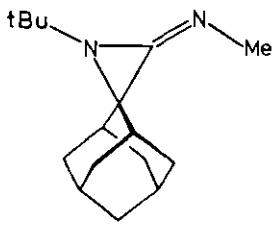




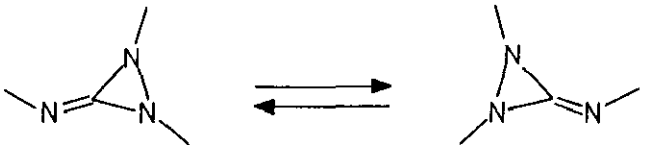
R^1	R^2
Me	Me
iPr	iPr
$CH(iPr)_2$	$CH(iPr)_2$
tBu	tBu
Me	tBu
tBu	Me
CH_2-tBu	tBu
tBu	CH_2-tBu
$Me_3C_6H_2$	tBu



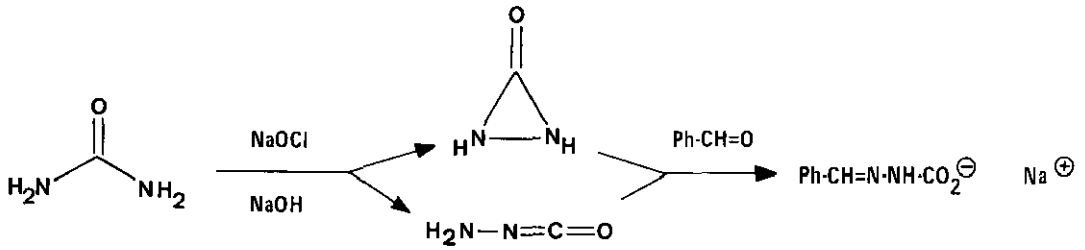
R^1	R^2
Me	Me
CH_2-tBu	CH_2-tBu
CH_2-Ph	CH_2-Ph
iPr	iPr
Me	tBu
tBu	Me
CH_2-tBu	tBu
tBu	CH_2-tBu



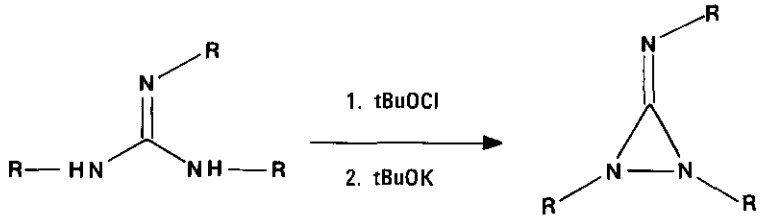
One threefold azasubstitution of the methylenecyclopropane the symmetry of the molecular skeleton is restored. Thus, one arrives at the diaziranimines which reveal themselves to be the most interesting nitrogen analogs of methylenecyclopropane. In view of both the methylenecyclopropane rearrangement and the weakness of the N-N-bond, we originally had hoped to find fluxional structures even in this class of compounds. While we could establish degenerate as well as non-degenerate isomerizations of diaziranimines[48, 49], the energy barriers were found still too high for the observation of dynamic nmr phenomena.



In the synthesis of diaziranimines we followed a well-worn path which had its origin at the turn of the century. At that time, Schestakow treated urea with sodium hypochlorite and sodium hydroxide to isolate hydrazine derivatives[50]. It was not until 1970 that Ohme and Preuschhof[51] proved that Schestakow had probably discovered the archetype of diazirane syntheses[52]. Actually, two mechanisms seem to operate in Schestakow's hydrazine synthesis. Almost as much time elapsed before the first diaziranone was isolated by Greene and Stowell in 1964[53]. While we were engaged in the synthesis of stable diaziranimines[48], the intervention of diaziranimines in the base-induced rearrangement of guanidines with good leaving-groups to semicarbazides was confirmed by ^{15}N-labelling experiments[55]. In fact, the Schestakow reaction could be easily adapted to the synthesis of diaziranimines[48, 49]. Thus, treatment of trialkylguanidines with *tert*-butylhypochlorite, followed by potassium *tert*-butoxide, afforded trialkyldiaziranimines in good yields. In contrast to diaziranones, the stability of which under the conditions of formation critically depended on the presence of *tert*-alkyl groups[53], diaziranimines may even carry three primary alkyl groups. Contrary to an earlier report[56], *N*-chlorination of guanidines substituted by a keto or ester group, followed by treatment with base, did not yield diaziranimines; instead five-memberd heterocycles were formed[56]. In contrast, this sequence could be applied to the synthesis of an *N*-(4-methylphenylsulfonyl)iminodiazirane[57].

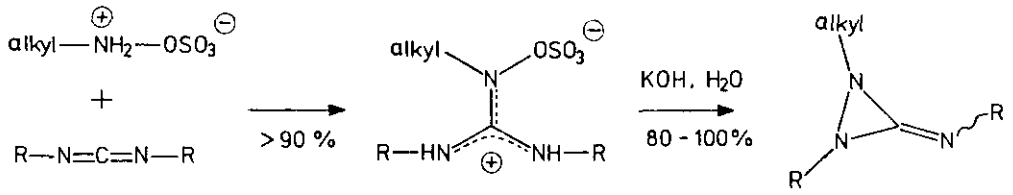


SCHESTAKOW 1903

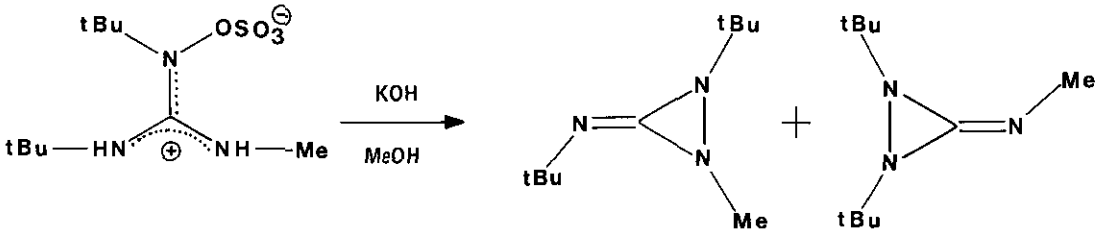


R	%
CH_2·tBu	81
iPr	73
cHex	63
tBu	79

When the guanidine precursor is not symmetrically substituted, then a regioselectivity problem is anticipated and mixtures of isomers are expected as has actually been demonstrated[48]. The inconvenience of isomer separation could be avoided, however, by attaching the leaving group to the differently substituted nitrogen atom of the guanidine. By using hydroxyguanidine *O*-sulfonic acids obtained from symmetrically substituted carbodiimides we realized high yields of isomer-free diaziranimines under extremely simple reaction conditions. Even the somewhat unstable trimethyldiaziranimine was available by this method, albeit only in low yield. Using hydroxyguanidine *O*-sulfonic acids obtained from unsymmetrically substituted carbodiimides, the direction of ring-closure was found to vary depending mainly on the concentration of base, to a minor extent on the solvent (methanol or water), but not on the temperature or the nature of the alkali metal cation[49].

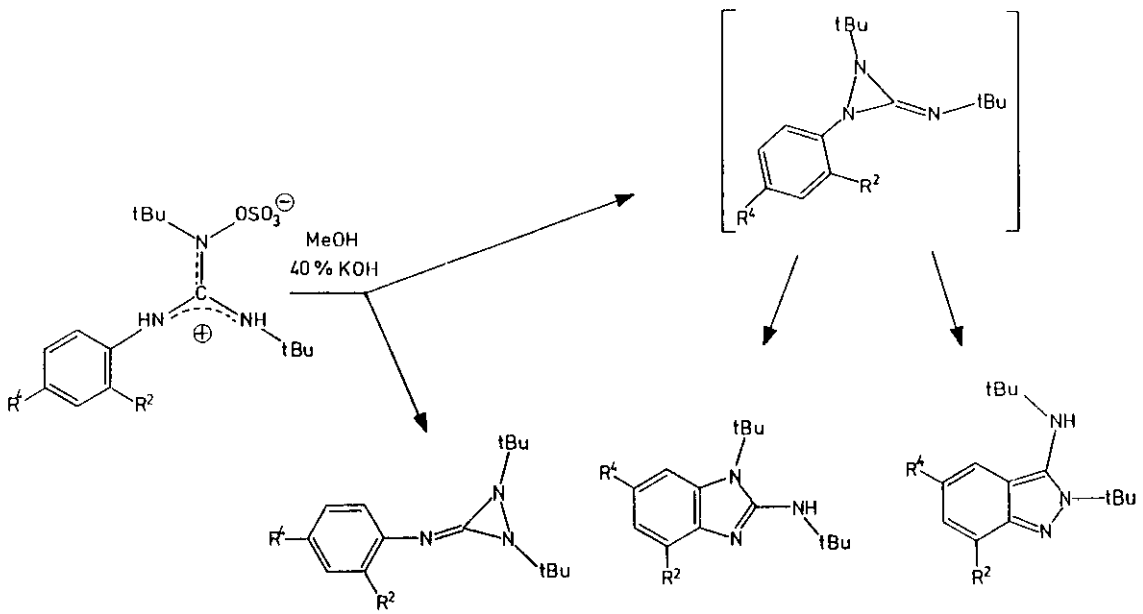


alkyl	R	%
Me	Me	25
Me	tBu	95
iPr	tBu	80
tBu	Me	83

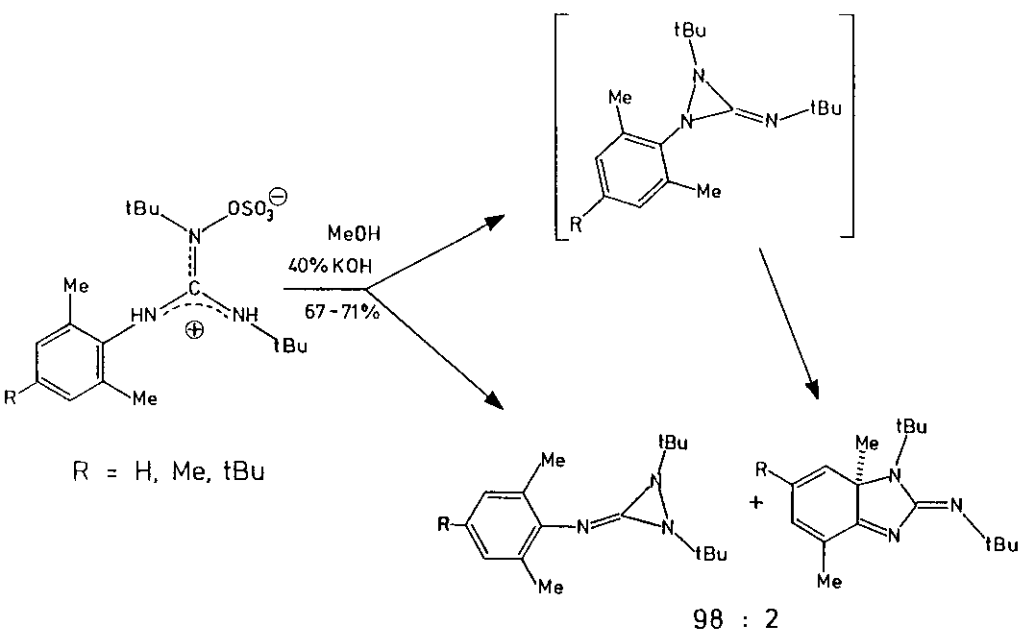


R	base	yield (%)	product ratio
Me	30 % KOH in methanol	74	1 : 99
Me	2 *N* Na_2CO_3 in water	82	22 : 78
tBu	40 % KOH in methanol	81	15 : 85
tBu	1,5 % KOH in methanol	88	73 : 27

Quite unexpected rearrangements were observed, when the synthesis of aryl-substituted diaziranimines was attempted[49]. Starting from *N*-aryl-*N'*-hydroxyguanidine *O*-sulfonic acids, only low yields of diazirane-*N*-arylimines were obtained. The major products were 2-aminobenzimidazoles and 3-aminoindazoles. The isomeric 1-aryldiaziranimines defied all attempts at detection. The ratio of the five-membered benzo-heterocycles depended considerably on the degree of substitution of the benzene ring. In the absence of substituents, formation of the 3-aminoindazole predominated. 2,4-Alkyl substitution directed the course of the reaction towards 2-aminobenzimidazoles. In both cases, the diazirane-N-arylimines remained as minor product, however.



R^2	R^4	%	product ratio
H	H	89	11 : 2 : 85
H	tBu	90	4 : 25 : 71
Me	tBu	98	6 : 85 : 9



R = H, Me, tBu

98 : 2

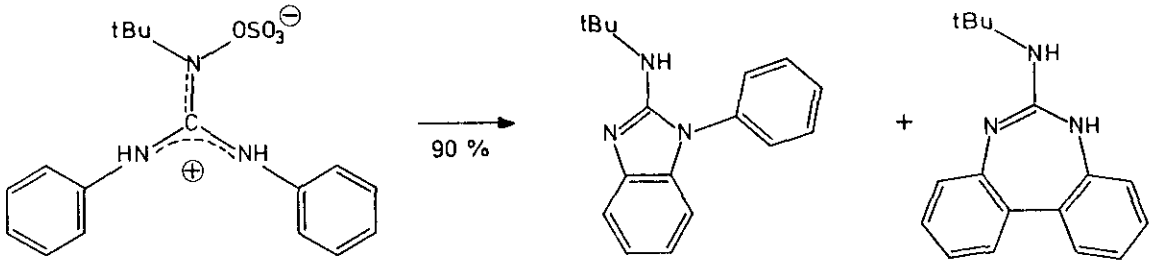
Deuterium-labelling of one of the *tert*-butyl groups of the hydroxyguanidine *O*-sulfonic acids revealed that complete scrambling had occurred during formation of all products. The isolated diazirane-*N*-arylimines were stable under the reaction conditions. Thus, they isomerized only above 50 °C to the five-membered rings which were produced in a similar ratio to that found in the *base reaction of the hydroxyguanidine O-sulfonic acids*. Therefore, the 2-aminobenzimidazoles as well as the 3-aminoindazoles seem to be formed by isomerization of the apparently very labile, elusive 1-aryldiaziranimines.

Blocking both ortho positions of the benzene ring by methyl groups dramatically changed the picture. Now only small amounts of a benzimidazol derivative with sacrified aromaticity resulted from the base-reaction of hydroxyguanidine *O*-sulfonic acids. By far the major products were fairly stable diazirane-*N*-arylimines. Again, deuterium-labelling demonstrated complete scrambling of the *tert*-butyl groups during product formation[49].

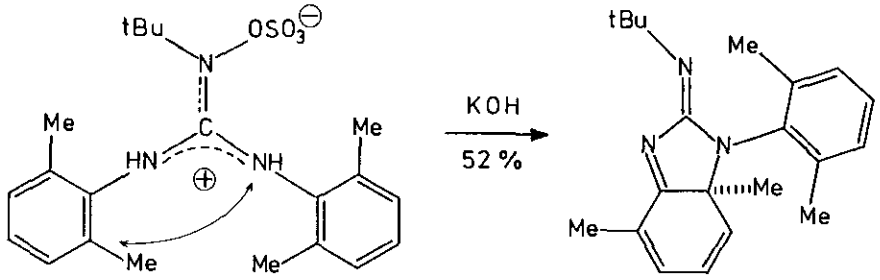
In the base-reaction of an *N,N'*-diphenyl-*N''*-hydroxyguanidine *O*-sulfonic acid, no conditions could be found which led to the *detection of diaziranimines. In fact, the ring-closures involved one of the nitrogen atoms not* bearing the leaving group with an ortho position of a phenyl ring or even an ortho carbon atom of each phenyl ring, giving rise to the formation of an aminodibenzo-1,3-diazepine. Again, the concentration of base influenced the product ratio in an unpredictable way. If the ortho positions of the phenyl rings were substituted by methyl groups, attack of a nitrogen atom at an aryl ring was not prevented; only the bond formation between the aryl rings was suppressed, thus excluding the formation of an *aminodibenzo-1,3-diazepine* derivative. Apparently, the driving force for the reaction can override the aromaticity of only one benzene ring[49].

In summary we note that aryl rings complicate the thermal reorganization of diaziranimines considerably. The system acquires *easy, alternative opportunities of rearranging* to larger rings through a labyrinth of most probably diradical-type sigmatropic paths.

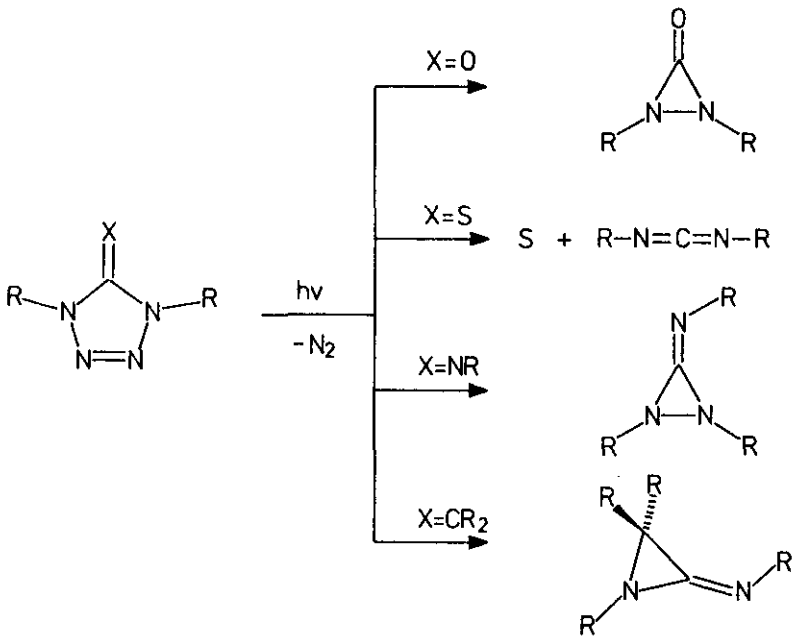
As a result of our synthetic efforts in the field of the nitrogen analogs of methylenecyclopropanes, cyclopropanimines, aziranimines, and diaziranimines have been uncovered. Furthermore, the range of available methylenaziranes has broadened considerably. Future experiments may lead to a more thorough understanding of the chemistry of these highly reactive systems as well as to synthetic and other applications.



base	product ratio
40 % KOH in MeOH	85 : 15
2 N NaOH in H_2O	30 : 70



So far, I have dwelt upon the application of old synthetic principles, e. g. the 1,3-elimination, for the preparation of new

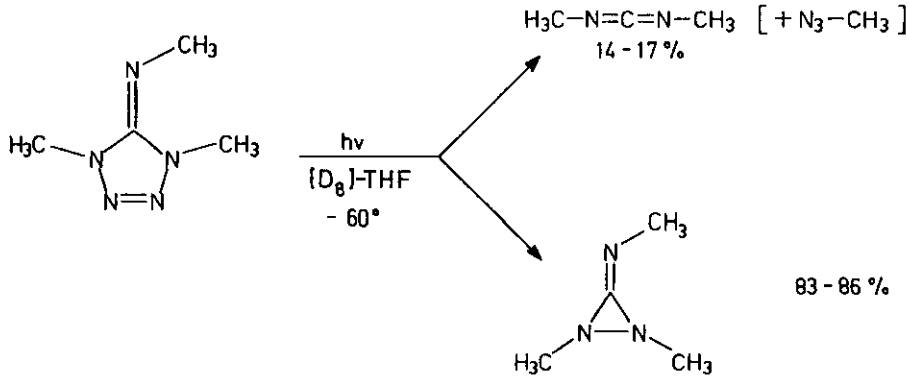


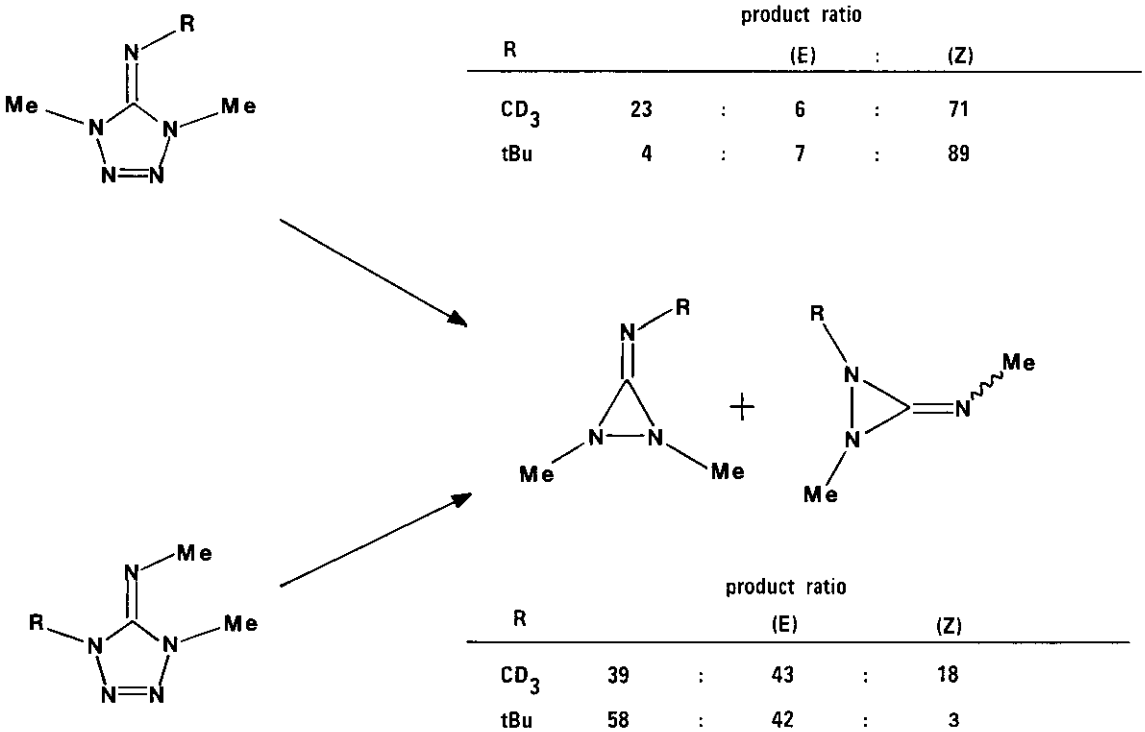
systems. The obvious limitation of the traditional synthetic methods, *viz.* the inaccessibility of many interesting molecules lacking extensive shielding by bulky groups, prompted a search of an alternative method. This alternative synthetic method had to be distinguished by i) a very clean and selective reagent, ii) very mild reaction conditions such as low temperatures and inert media, and finally iii) the formation of inert by-products. Presumably a photo-extrusion reaction promised to meet these stringent requirements. Moreover, we hoped to employ the powerful matrix-isolation technique to provide evidence for the hetero-counterparts of the fascinating trimethylenemethane diradicals[58].

As anticipated, tetrazolines with an exocyclic double bond rapidly lost nitrogen on photolysis, producing heteroanalogs of methylenecyclopropane, except when X = sulfur which afforded carbodiimide and sulfur[59]. This reaction allowed for the first time the synthesis of diaziranones, substituted by groups other than tertiary alkyl groups. From methylenetetrazolines, iminoaziranes were formed preferentially in the thermodynamically more stable (E)-configuration. This is in striking contrast

to the results of the 1,3-elimination of hydrogen bromide from α-bromoamidines which afforded stereoselectively (Z)-aziranimines[46].

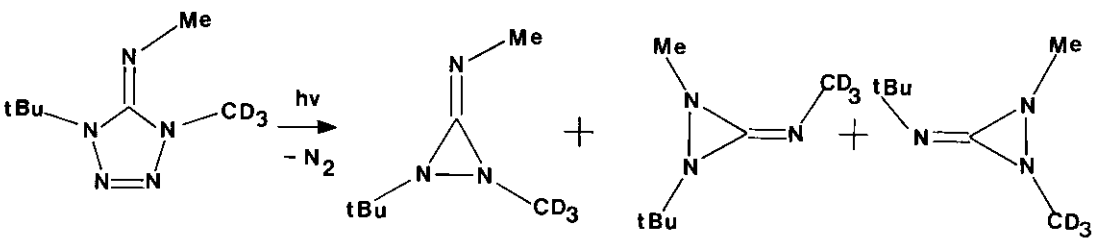
Iminotetrazolines underwent an undesired photochemical [3+2]cycloelimination into carbodiimide and alkyl azide as minor products besides loss of nitrogen with ring-closure to the diaziranimine as major product. In the photolysis of iminotetrazolines, an intriguing question concerns which of the three non-equivalent nitrogen atoms of the iminotetrazoline formed the N-N-bond of the product[60]. As conceivable contrasting pathways of product formation we consider the least motion path and the completely randomizing ring-closure via diradicals. The latter alternative was suggested by the detection of triplet state tris(imino)methane diradicals during the matrix photolysis of iminotetrazolines at liquid nitrogen temperature[61].





We approached this mechanistic problem by photolyzing labelled iminotetrazolines at −60 °C and determining the product ratios by ^{1}H nmr spectroscopy at the same temperature, thus avoiding planar nitrogen inversion as well as rearrangements via 1,3-nitrogen-shifts[60]. The substituents of the iminotetrazolines lie in the plane of the molecule. Therefore, during N-N-bond formation, leading most probably to the more stable *trans*-1,2-substituted iminodiaziranes, the substituents at the participating nitrogen atoms must rotate by 90° out of the molecular plane. In principle, only three different iminodiaziranes can be anticipated to arise from an iminotetrazoline labelled at only one nitrogen atom, *viz.* constitutional isomers, one of which may exist as (E,Z)-diastereomers. Already a cursory inspection of the product ratios obtained from both mono-labelled iminotetrazolines revealed immediately that no randomization of the label had occurred during photolysis. Thus, statistically equilibrating diradical intermediates cannot be involved. Photolysis of the *symmetrically* substituted, labelled iminotetrazoline displayed a pronounced preference for N-N-bond formation involving the exocyclic nitrogen atom of the precursor. Furthermore, the least motion path led only to a minor fraction of the product mixture (the symmetrically substituted iminodiazirane). In the photolysis of the *unsymmetrical*, mono-labelled iminotetrazoline the (E)-iminodiazirane can result in two ways. These are the least motion path and the ring-closure between the exocyclic nitrogen atom and the ring nitrogen atom standing trans to the imino substituent. Therefore, distinction of the two latter modes is impossible in the photolysis of the unsymmetrical, mono-labelled iminotetrazoline. However, the large fraction of the symmetrically substituted iminodiazirane points to the preference of bond formation involving the nitrogen atoms with sterically interacting substituents.

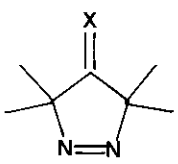
In order to be able to draw more definite conclusions concerning the site of ring-closure, we photolyzed a triply labelled iminotetrazoline which was locked in the (E)-configuration, as evidenced by the ^{1}H nmr spectrum which showed the presence of only one diastereomer. In principle, all three possible modes of N-N-bond formation might be mechanistically distinguishable. In this photolysis, formation of three (E,Z)-diastereomeric pairs of constitutional isomers, hence six different iminodiaziranes, might be anticipated. Actually only three, e. g. the (E)-diastereomers, arose in a ratio close to 1 : 1 : 2, indicating indeed a preference of bond formation between the nitrogen atoms with sterically interacting substituents[60].



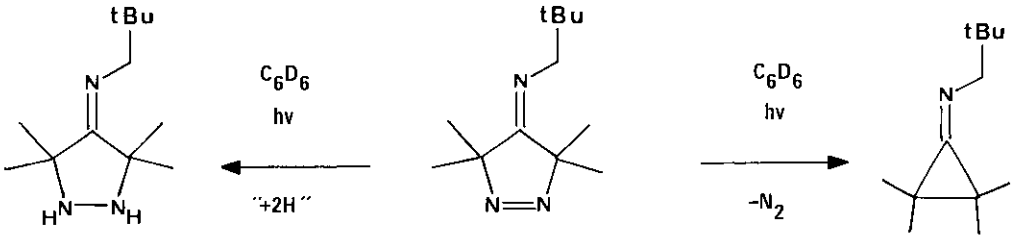
26 : 21 : 53

Stimulated by the photochemical results obtained with the tetrazolines with an exocyclic double bond, we turned our attention to analogous pyrazolines[62, 63]. Although the photolysis of 4-methylenepyrazolines had been studied in considerable detail[64], almost nothing was known about the photolysis of the corresponding pyrazoline-4-ones, pyrazoline-4-thiones, and 4-iminopyrazolines. As we expected thermally labile products in the photolysis of 4-iminopyrazolines, we initially photolyzed at subambient temperatures, using intense light sources above 340 nm[62]. However, under these conditions the 4-iminopyrazolines turned out to be very reluctant to undergo photolysis. After five hours of irradiation at 5 °C, only 6 % of a cyclopropanimine, besides small amounts of the rather unexpected reduction product of the 4-iminopyrazoline, had formed. In striking contrast, at 90 °C, photolysis was rather efficient, producing 87 % of the cyclopropanimine ring within only two hours. We tentatively interpret these results in terms of an activation barrier to nitrogen loss from the excited singlet state. Formation of the reduction product might involve the triplet state.

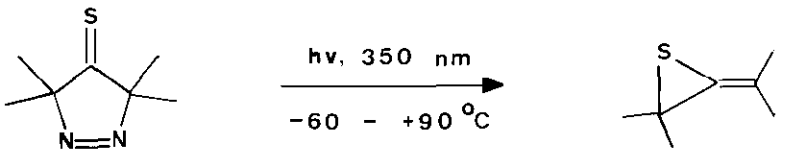
From the photolysis of the pyrazoline-4-thione we had hoped to learn something about the elusive cyclopropanethione[63]. However, at liquid nitrogen temperature the pyrazoline-4-thione proved perfectly stable towards irradiation with intense 350 nm light. At higher temperatures, photolysis afforded the known tetramethylmethylenethiirane[65].



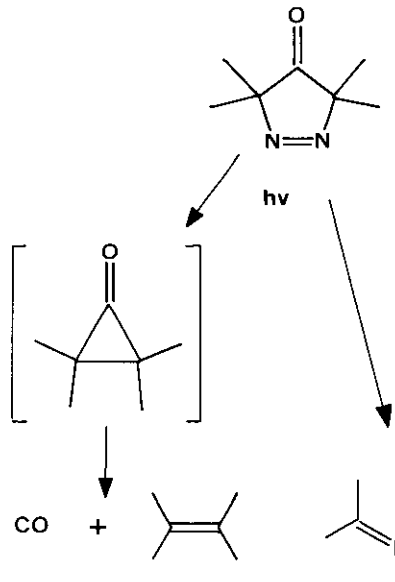
X
CR_2
NR
O
S



2h, 90°C	8	:	3	:	87
5h, 5°C	3	:	91	:	6

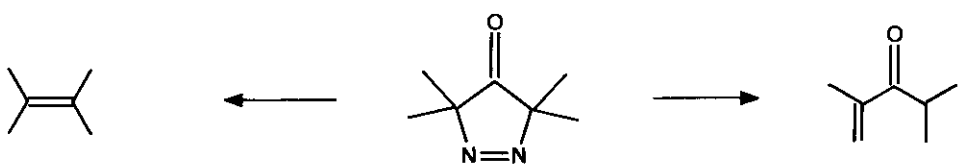


Finally, I would like to turn to a long-standing enigma. Already 15 years ago, the tetramethylpyrazolin-4-one had been designed by Mock as a precursor to tetramethylcyclopropanone[66]. However, it turned out to be surprisingly stable towards both thermolysis and photolysis, the quantum yield of its decomposition by 313 nm light being only 0.012[64]. Now we found that two photochemical cycloreversions compete[63]. A [4+1]cycloreversion into carbon monoxide and acetone azine and a [3+2]cycloreversion producing nitrogen and most probably tetramethylcyclopropanone, which is cleaved further into carbon monoxide and 2,3-dimethyl-2-butene. In fact, the tetramethylcyclopropanone could be trapped as hemiketal during photolysis in methanol as solvent[67]. Apparently, low temperature and solvents of higher polarity favor cyclopropanone formation.



solvent	temp. °C	product ratio
$[D_{12}]$cyclohexane	10	63 : 37
	90	57 : 43
$[D_3]$acetonitrile	10	83 : 17
	90	68 : 32

In striking contrast to the results of photolysis employing conventional light sources, 185 nm photolysis of the tetramethylpyrazolin-4-one produced the same α,ß-unsaturated ketone[68] which is formed on pyrolysis of tetramethylcyclopropanone on a GC column[22]. Flash thermolysis of the tetramethylpyrazolin-4-one afforded both 2,3-dimethyl-2-butene and the ketone in ratios ranging from 3 : 7 at 400 °C to 6 : 4 at 1000 °C[68].



The foregoing results leave no doubt that the photo-extrusion of nitrogen from five-membered rings with an exocyclic double bond opens an entry to several energy surfaces, which embrace ensembles of highly reactive, elusive species as well as stable molecules. They exist in a field which looks equally attractive for synthetic, mechanistic and theoretical studies.

Of course, during the study of the systems mentioned in this summary many new reactions were discovered which could not be covered in the present report because of space limitation. Also, a number of loose ends need yet to be tied together, e. g. logical extensions, old but unanswered questions, and emerging new problems, all of which merit further attention. In complying with one of the general topics of this colloquium, I have tried to emphasize some synthetic aspects of three-membered ring chemistry. Unlike the complicated targets of organic syntheses that deserve most elegant and elaborate, highly sophisticated strategies, the synthesis of small rings apparently still proceeds rather well with a few old-fashioned, straightforward synthetic principles, provided the appropriate experimental methods are employed.

Finally, it is my pleasant duty to acknowledge the important contributions of my coworkers, whose names are mentioned in the references. It was their dedicated and skilled experimental work which resulted in the discovery and exploration of the areas of three-membered ring chemistry covered in this report. Last not least, generous financial support by the *Deutsche Forschungsgemeinschaft* and the *Fonds der chemischen Industrie* is gratefully acknowledged.

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