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Hydrazine-Derived Heterocycles by Conversion of Azo-alkenes

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Dedicated to the late Professor Gerrit L'Abbé

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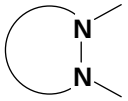
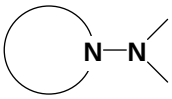
Abstract

This lecture presents and, in part, reviews our work in the area of heterocyclic compounds **I** or **II** incorporating a hydrazine moiety.



I



II

Keywords: Azo-alkene; diazene aminal; diazenium ion; tetrahydropyridazine; 1-amino-2,3-dihydro-1*H*-imidazole-2-thione; 2,3,5,6,7,7a-hexahydro-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione; 2-phenylazo-1-phthalimidoaziridine; 2-phenyl[1,2,3]triazole; 2-phenylhydrazonoalkylideneiminophthalimide; azimine; review.

Introduction

The structural unit of hydrazine can be part of a heterocyclic ring system either with both nitrogen atoms as ring members **I**, or with one nitrogen atom as ring member and the second nitrogen atom attached to it as exocyclic substituent **II**.

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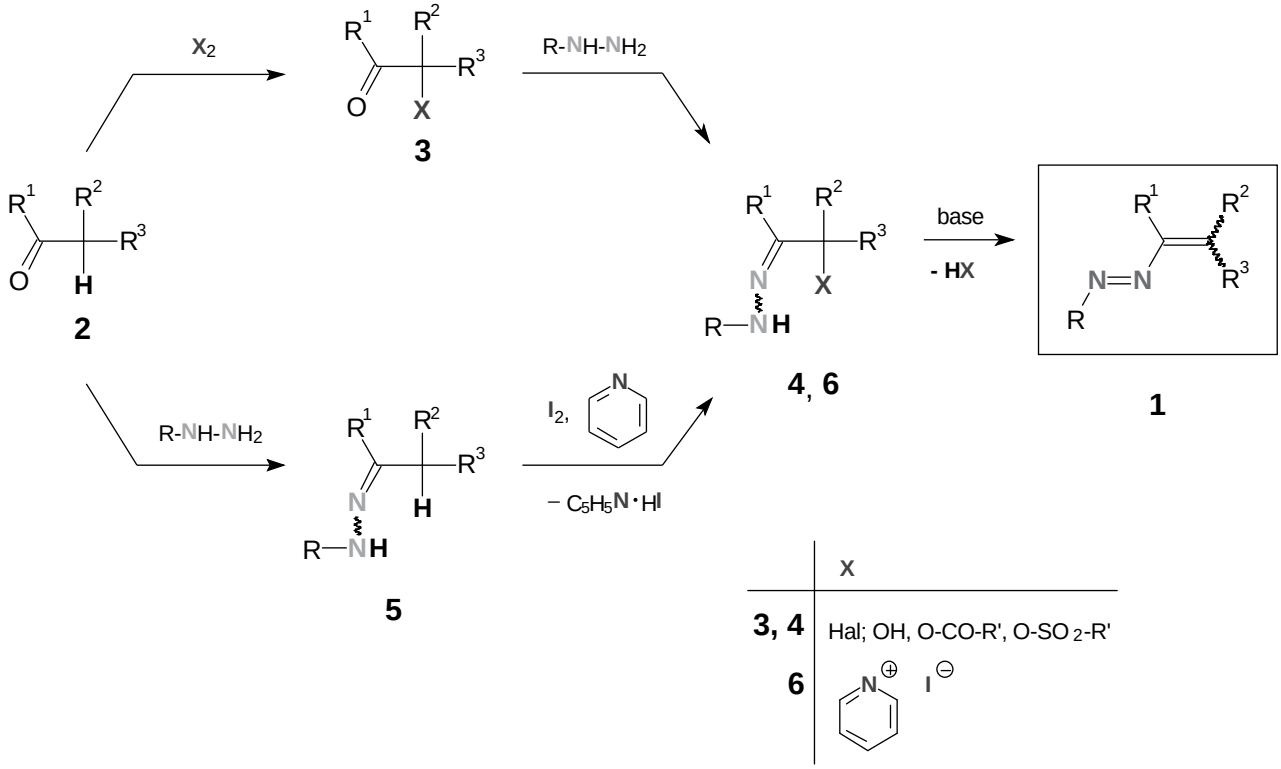
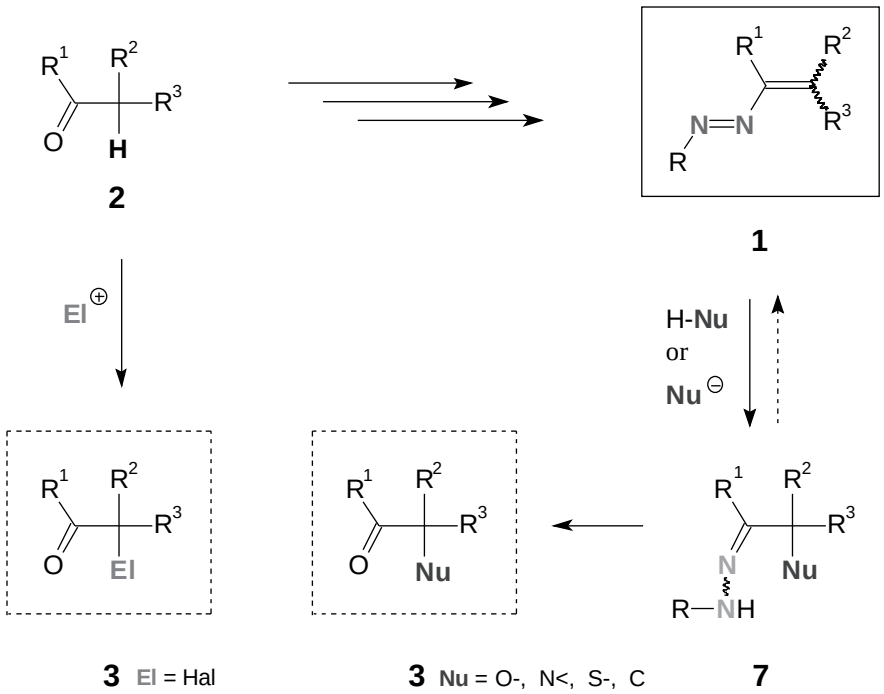
Discusssion

For the synthesis of heterocyclic compounds of both types **I** and **II** azo-alkenes **1** (Scheme 1) turned out to be useful starting materials. Azo-alkenes **1** resemble a class of azo compounds with different ligands attached to the nitrogen atoms of the diazene (azo) group. [1]

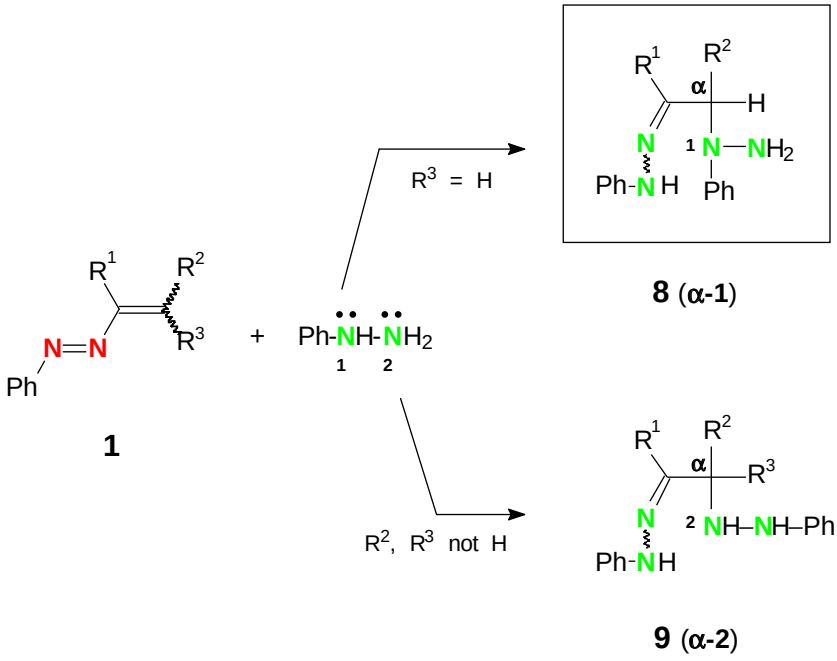
Two typical synthetic approaches to azo-alkenes **1** starting from carbonyl compounds **2** are illustrated in Scheme 1. After transformation into the α–halo derivative **3** (or an



Scheme 1.



Scheme 2.

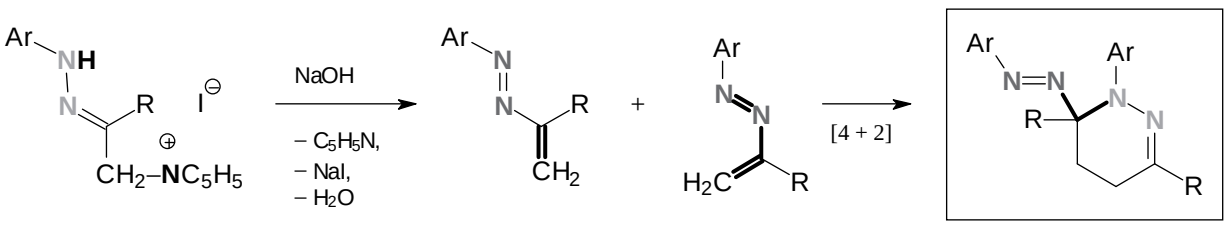


Scheme 3.

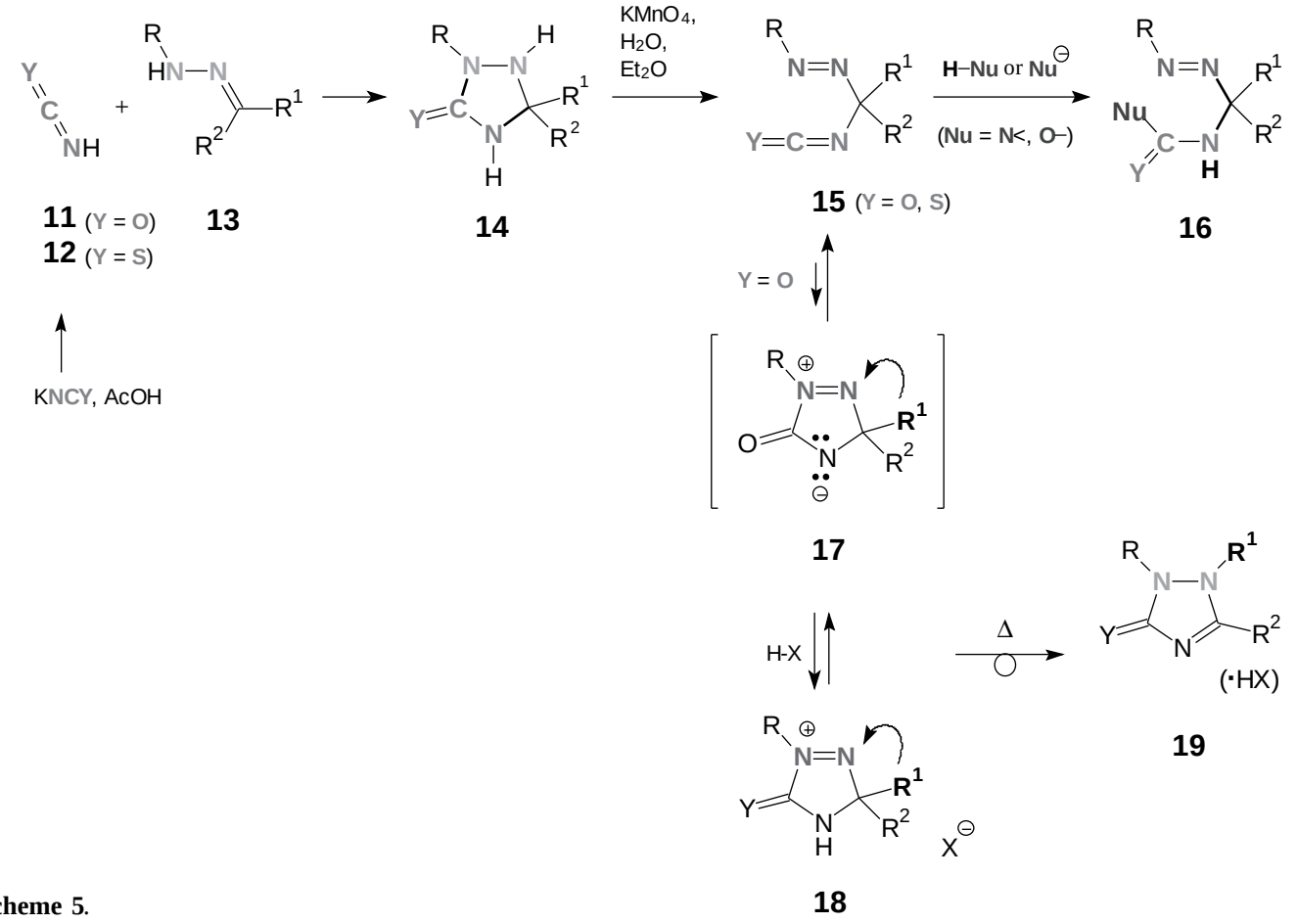
oxygen equivalent) the reaction with a monosubstituted hydrazine affords hydrazone **4**. Since the hydrazine employed may act also as a base and induce the elimination of HX, this reaction condition usually gives rise to the formation of the azo-alkene **1** [1] (or a product derived from subsequent reactions of the azo-alkene **1** [2] *vide infra*). Alternatively, the carbonyl compound **2** is first converted into the hydrazone **5**, and in a second step the reaction with iodine and pyridine forms the corresponding α–pyridinium hydrazone iodide **6** [3]. In many cases the salt **6** is a storable precursor for the preparation of the azo-alkene **1** requiring a base to induce the elimination of pyridine and hydrogen iodide [4].

Azo-alkenes **1** exhibit a marked reactivity of both the olefinic and the diazene function [1]. In many respects the reactivity of azo-alkenes **1** reflects that of α,β–unsaturated carbonyl compounds. Nucleophilic reactants tend to react with azo-alkenes **1** in the manner of a conjugate (1,4-) addition yielding α–substituted hydrazones **7 [**1, 5] (Scheme 2). Typically, carbonyl compounds **2** undergo electrophilic substitution at the α–position and are thus converted into functionalized derivatives **3**, the α–substituent being derived from the electrophilic reagent. By contrast, the α–subtituent of the carbonyl compound **3** obtained from hydrazone **7** is introduced by a nucleophilic reagent into the carbonyl compound **2** in the course of an Umpolung reaction *via* the azo-alkene **1**.

The nucleophilic 1,4-addition of phenylhydrazine to phenylazo-alkenes **1** is a remarkable example [6]. Phenylhydrazine features two nucleophilic sites, and two addition products can be anticipated, the α–1 phenylhydrazinohydrazone **8** and the α–2 isomer **9**. Typically, the α–1 addition product **8** is formed, the substituted nitrogen atom of phenylhydrazine acting as the nucleophile is added to the phenylazo-alkene **1** (R^3 = H). Exceptions are encountered when a phenylazo-alkene **1** with a fully substituted (R^2, $R^3 \neq$ H) terminal carbon atom is subjected to this reaction; presumably, for steric reasons the addition of the unsubstituted nitrogen atom results in the formation of addition product **8** in the latter case (Scheme 3).



Scheme 4.

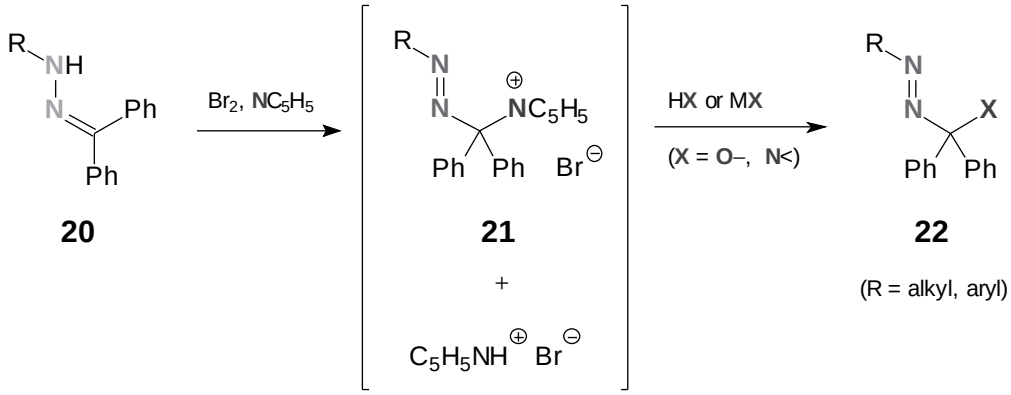


Scheme 5.

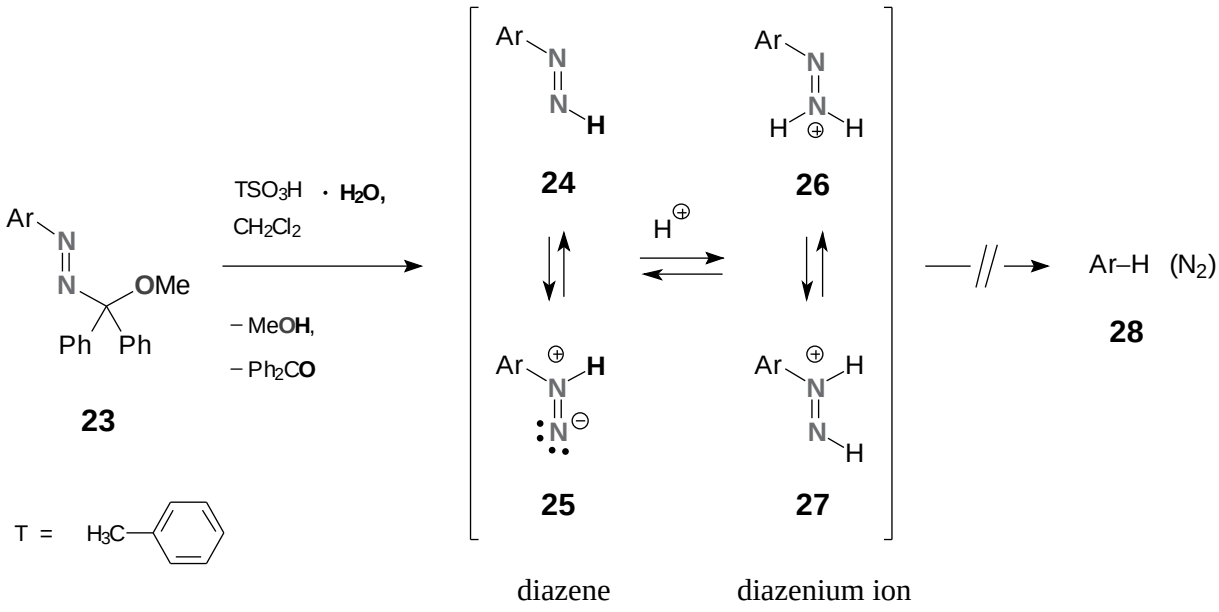
Azo-alkenes **1** without substituents at the terminal carbon position (R^2, R^3 = H) can be generated in solution but cannot be isolated [4a,7]. Like isoelectronic α,β–unsaturated carbonyl compounds (e.g. acrolein) β–unsubstituted arylazo-alkenes **1** undergo cyclodimerization in the course of a hetero Diels-Alder reaction resulting in the formation of 1-aryl-6-arylazo-1,4,5,6-tetrahydropyridazines **10** (Scheme 4).

The cyclodimers **10** feature a special aminal function, comprising the diazene group as a nitrogen ligand of the aminal (aminal-type azo compound, diazene aminal).

Diazene aminals are accessible also by other routes. Keto hydrazone **13** adds isocyanic acid **11** (generated *in situ* from potassium cyanate and acetic acid) in a [3+2] cycloaddition reaction [8] (analogous hetero cumulenes like thiocyanic acid **12** [9] react in the same manner [8,



Scheme 6.

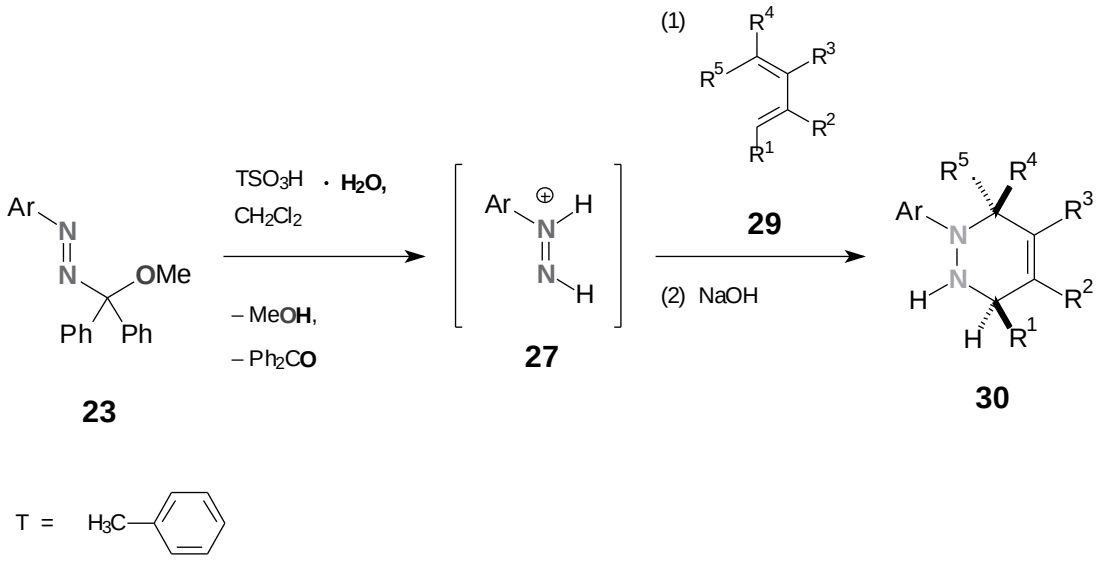


Scheme 7.

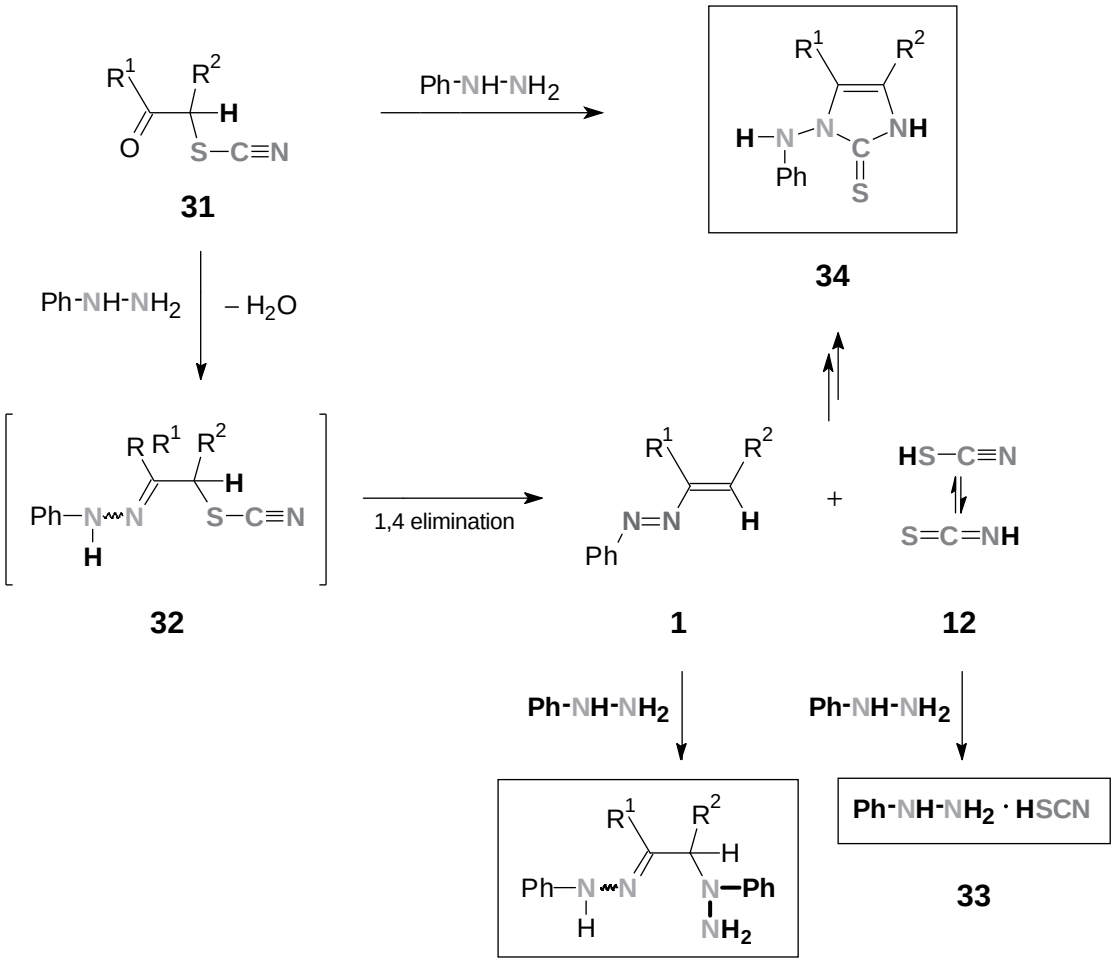
10]). The resultant triazolidine derivative **14**, in turn, undergoes facile oxidation (e.g. with potassium permanganate), and under concomitant ring-opening the *gem* azoalkylisocyanate **15**, [11] (or the respective isothiocyanate [10, 11]) is formed. Various *O*- and *N*-nucleophiles convert the isocyanate function of **15** into carbamic acid derivatives **16**; the latter compounds resembling diazene aminals [8, 10–12] (Scheme 5).

On the other hand, the reactivity of the azoalkylisocyanate **15** is better characterized by the cyclotautomer **17**; the equilibrium between **15** and **17** can be shifted with acids to the protonated cyclic form **18** [13]. Owing to the diazenium ion character the cyclic forms **17** and **18** undergo a 1,2-shift of one of the (carbon) substituent from the tetragonal ring atom to the neighbouring electron deficient (diazenium) nitrogen atom affording the heteroaromatic triazolinone 19 [13] (Scheme 5).

A very efficient procedure for the preparation of diazene aminals involves the conversion of *N*-monosubstituted benzophenone hydrazones **20** with bromine and pyridine into a mixture of pyridinium salts. Nucleophilic displacement of the pyridinium moiety of the azodiphenylmethylpyridinium bromides **21** provides diazene aminals 22 [14] (Scheme 6).



Scheme 8.



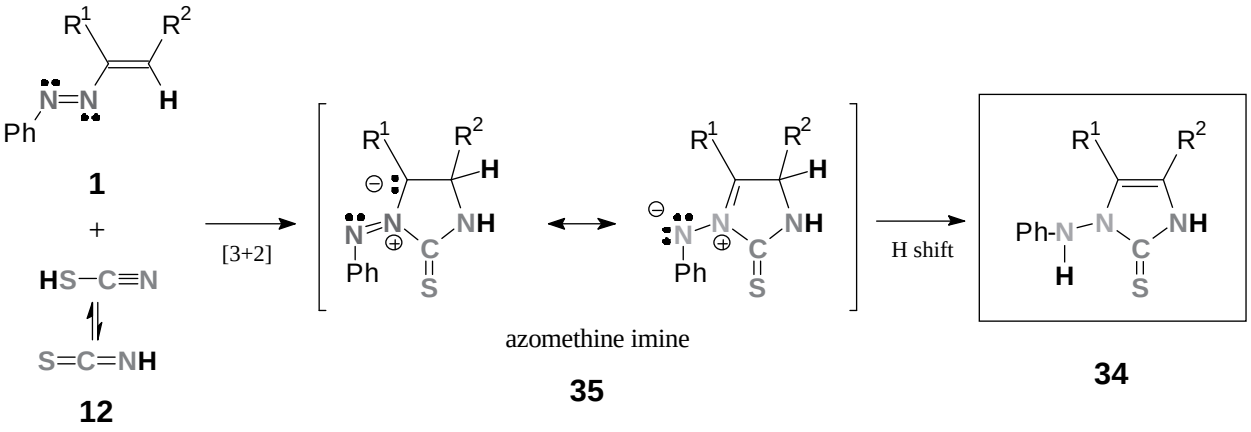
Scheme 9.

Like aminals (and acetals) in general, diazene aminals are readily hydrolyzed with acids [15] Arylazomethoxydiphenylmethanes **23** serve as typical workhorses for the reaction with 4-toluenesulfonic acid monohydrate. Among the hydrolysis products of **23** are the parent carbonyl compound, benzophenone; the methoxy group yields methanol; the arylazo group of **23** is expected to be converted into the monosubstituted diazene **24** or its zwitterionic isomer, the isodiazene **25**; since the reaction is carried out in the presence of an acid, also the formation of conjugate acids, the diazenium ions **26** and **27** has to be considered. Contrary to the typical decomposition of monosubstituted aryldiazenes into the parent aromatic hydrocarbon **28** and molecular nitrogen, monosubstituted diazenium ions **26** and/or **27** [16] are stable enough to be intercepted by suitable reactants (Scheme 7).

Generating monosubstituted diazenium ions **27** in the presence of dienes **29** gives rise to the formation of 1-aryl-1,2,3,6-tetrahydropyridazines **30** which were isolated in mostly very good yields after work-up with base [17, 18]. The reaction is considered to be a hetero Diels-Alder reaction, a number of experimental facts indicate a concerted [4+2] cycloaddition mechanism (Scheme 8).

Phenylazo-alkenes **1** react with thiocyanic acid **12** to yield 1-anilino-2,3-dihydro-1*H*-imidazole-2-thiones **34** [19–21]. The same heterocyclic products **34** emerge from the the reaction of α–thiocyanato carbonyl compounds **31** with phenylhydrazine [22, 23]. Azo-alkenes **1** and thiocyanic acid **12** were found to be intermediates in the latter reaction; they are presumed to be formed after the preceding conversion of the carbonyl compound **31** into the corresponding phenylhydrazone **32** followed by a 1,4-elimination reaction. Evidence for the generation of both intermediates, phenylazo-alkene **1** and thiocyanic acid **12**, is provided by the isolation of two side products. The phenylhydrazinophenylhydrazone **8** is the typical 1,4-addition product of phenylhydrazine to the azo-alkene **1** (*vide supra*), phenylhydrazinium thiocyanate **33** proofs the postulated liberation of thiocyanic acid **12** in the course of this reaction [22, 23] (Scheme 9).

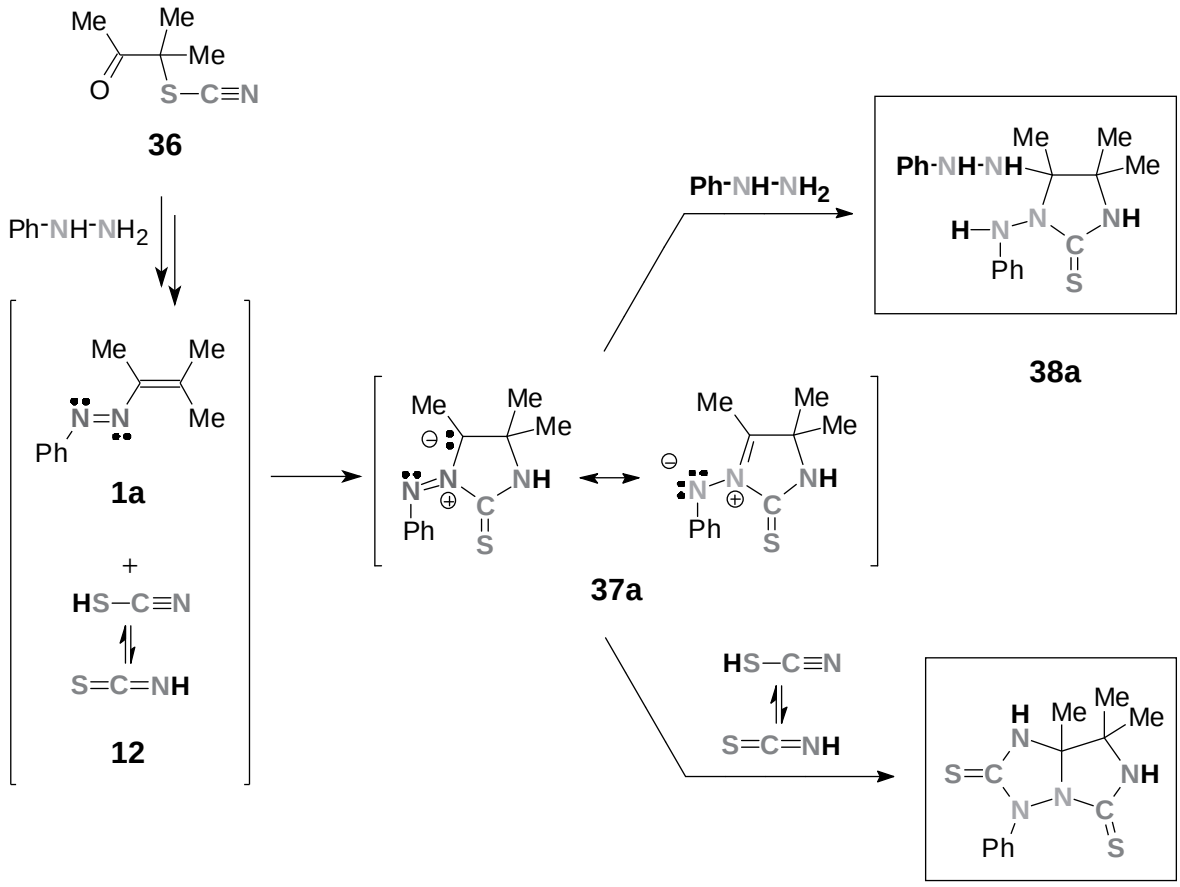
The most likely reaction path leading to the heterocyclic product **34** considers the formation of the heterocyclic ring by way of the [3+2] cycloaddition reaction of the azo-



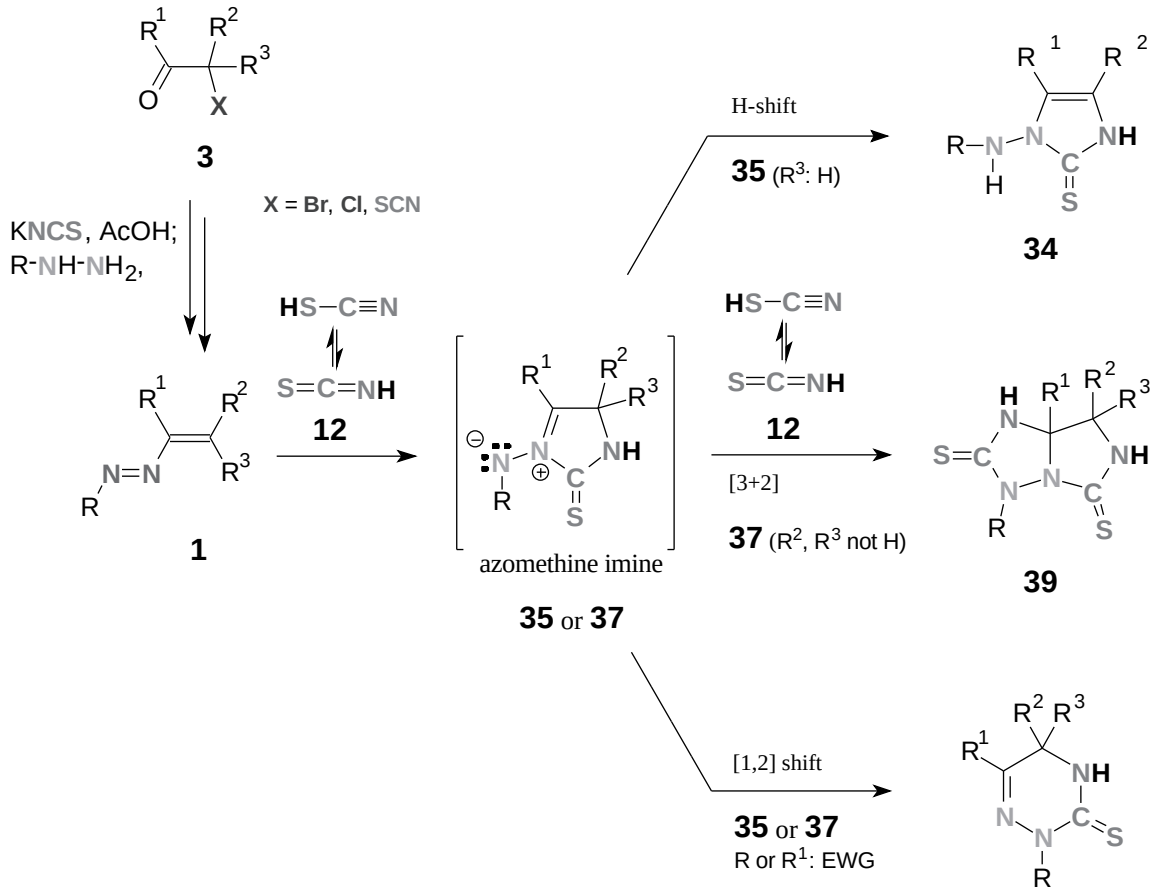
Scheme 10.

alkene **1** and thiocyanic acid **12**. The azo-alkene **1** reacting as a hetero allyl anion equivalent with the olefinic double bond and the lone electron pair at the adjacent nitrogen atom adds to the C,N-multiple bond of thiocyanic acid **12**. The resultant cycloadduct **35**, a heterocyclic azomethine imine derivative upon *H*-shifts ultimately yields the heteroaromatic product **34** (Scheme 10).

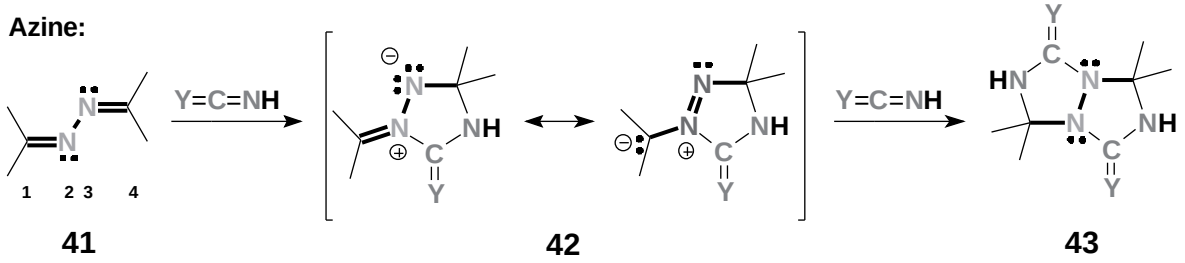
If the α–thiocyanato carbonyl compound **31** does not provide an α–hydrogen atom as in 3-methyl-3-thiocyanato-2-butanone **36** the reaction takes a different course in the final step [22, 23]. The corresponding heterocyclic azomethine imine **37a** is considered as the key intermediate; however, **37a** is prevented to undergo hydrogen shift due to the lack of 4-H. Two products were isolated. Obviously, 1-anilino-4,4,5-trimethyl-5-phenylhydrazino-1*H*-imidazole-2-thione **38a** results from the addition of phenylhydrazine across the polar C-N bond of the azomethine



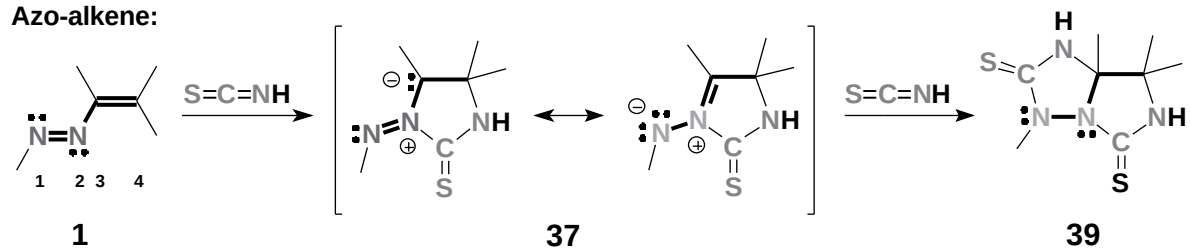
Scheme 11.



Scheme 12.

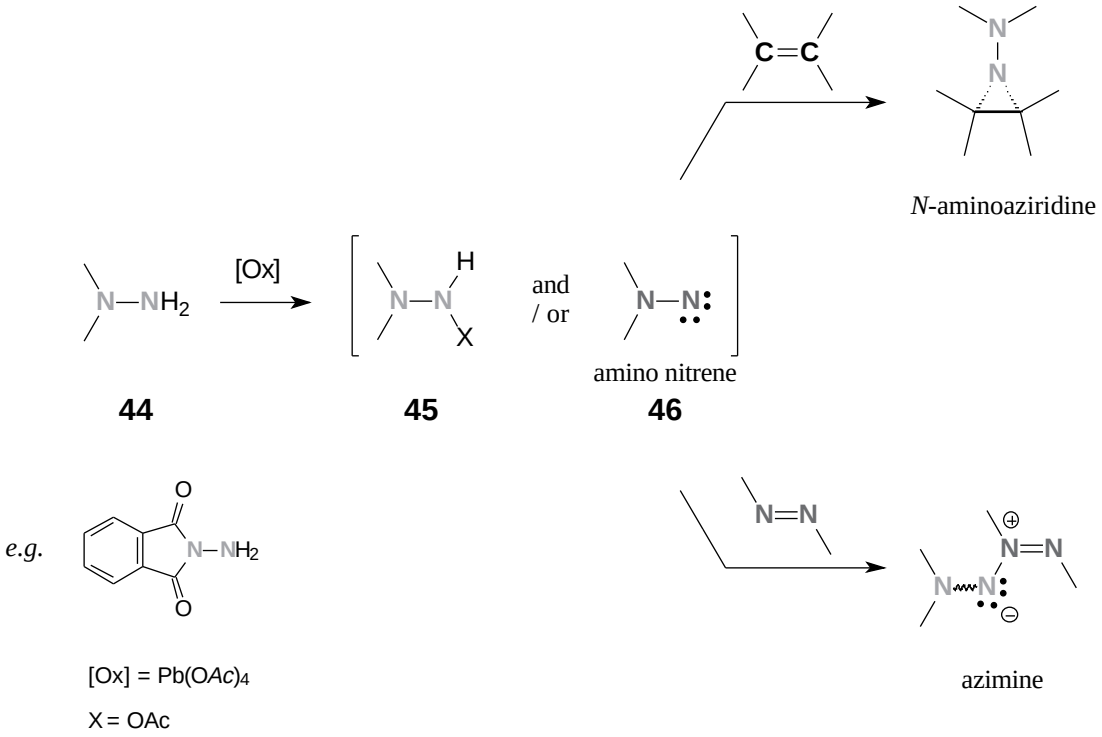


Classical ***"Criss-cross"*** addition: ***Antiparallel*** **tandem cycloaddition** of dipolarophile to **azine.**



Parallel **tandem cycloaddition** of dipolarophile to **azo-alkene** (***Parallel "Criss-cross"*** addition) (second [3+2] cycloaddition with *inverse* regiochemistry)

Scheme 13.



Scheme 14.

imine function of the intermediate **37a**. The bicyclic product, 2,3,5,6,7,7α–hexahydro-7,7,7α–trimethyl-3-phenyl-1*H*-imidazo[1,5-*b*][1,2,4]triazole-2,5-dithione **39a** emerges from the [3+2] cycloaddition reaction of another molecule of thiocyanic acid **12** to the 1,3-dipolar azomethine imine function of the intermediate 37a [22, 23] (Scheme 11).

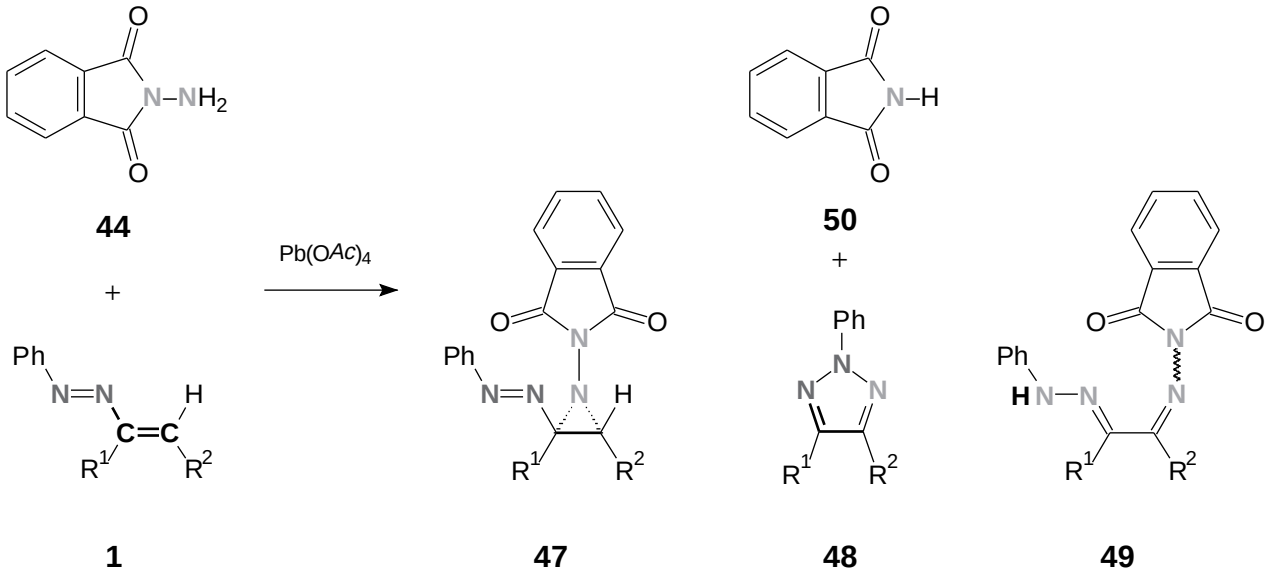
The reaction involving heterocyclic azomethine imines **37** as the presumed key intermediate have been extended to very efficient one-pot procedures starting from readily available α–halo carbonyl compounds **3**, potassium thiocyanate and hydrazines [20, 21, 24, 25]. The final product obtained depends on the structure of the carbonyl compound employed thus determining the reactivity of the corresponding azomethine imine intermediate **35** or **37**. *N*-Substituted 1-amino-2,3-dihydro-1*H*-imidazole-2-thiones **34** result from starting compounds **3** that allow for the *H*-shift of the intermediate [24, 25]. If *H*-shift is prevented due to substitution at ring position 4 of the intermediate **37** (R^2, $R^3 \neq H$) bicyclic products **39** are formed in an overall tandem cycloaddition reaction [20, 21]. Electron withdrawing substituents (R and/or R^1 = EWG) may cause the formation of 2,3,4,5-tetrahydro[1, 2, 4]triazine-3-thiones **40** presumably resulting from a 1,2 shift of the thione group of the intermediates **35** or **37** [20, 21, 26–28] (Scheme 12).

The formation of the bicyclic products **39** is reminiscent of a long known reaction, the classical "Criss-Cross" cycloaddition reaction [29, 30], a tandem [3+2] cycloaddition mostly of heterocumulenes to azines **41** involving the azomethine imine intermediate **42** and yielding the bicyclic products **43** (Scheme 13).

Formal interchange of atoms 1-C and 3-N of the azine skeleton **41** gives rise to the isomeric azo-alkene structure **1**. The tandem reactions of both diaza-1,3-dienes, azine **41** and azo-alkene **1**, pass through an azomethine imine intermediate **42** and **37**, respectively; the different positions of the nitrogen atoms of the isomeric starting compounds entails a different regiochemistry of the second cycloaddition step. In the bicyclic product **43** of the classical "Criss-Cross" cycloaddition reaction the dipolarophiles added to the azine **41** point in opposite directions, whereas in the novel tandem reaction of azo-alkenes **1** the thiocyanic acid moieties of the bicyclic adduct **39** point in the same direction. Thus these tandem reactions have been coined "antiparallel" (for the classical) and "parallel" (for the novel) tandem cycloaddition reaction [21, 22].

Furthermore, azo-alkenes **1** undergo also other cycloaddition reactions. A suitably 1,1-disubstituted hy-drazine like *N*-aminophthalimide **44** upon oxidation with lead tetraacetate gives the transient species of 1,1-disubstituted aminonitrene **46** (isodiazenes) or its precursor **45** [31]. The intermediate **46** has been found to react with π-systems; olefins give rise to *N*-aminoaziridines [31, 32], azo compounds form azimines [32, 33] (Scheme 14).

Both types of π-systems are contained in azo-alkenes **1**. Depending on the substituents R^1 and R^2 of the azo-alkene **1** subjected to the reaction with *N*-aminophthalimide **44** and lead tetraacetate different products have been obtained [34, 35]: 2-Phenylazo-1-phthalimidoaziridines **47** (a novel type of diazene aminals), 2-phenyl-[1,2,3]triazoles **48**, 2-phenylhydrazonoalkylideneimino-



Scheme 15.

phthalimide **49**, and in all cases phthalimide **50**. (Scheme 15). Phthalimide **50** is a complementing product in the formation of 2-phenyl[1,2,3]triazoles **48**. Otherwise, the formation of phthalimide **50** is believed to result from the competing reaction of aminonitrene **46** with *N*-aminophthalimide **44**.

The reaction of 3,3,5-trimethyl-3*H*-pyrazole **51**, a cyclic azo-alkene, with *N*-amino-phthalimide **44** and lead tetraacetate furnishes a mixture of azimines **52** and **53**, and in addition some phthalimide **50** (Scheme 16). Obviously, azimines like **52** and **53** with the azo-alkene moiety being part of a ring are sterically prevented from any reaction with the olefinic double bond (as it is possible with an open-chain compound like **1**, *vide supra*). The mixture of azimines could be only partly separated: One regioisomer **53** has been isolated, an X-ray structure analysis has confirmed structure **53**. The remaining unseparable mixture appears to consist of interconverting *cis* and *trans* stereoisomers of the alternative regioisomer **52** [34, 35].

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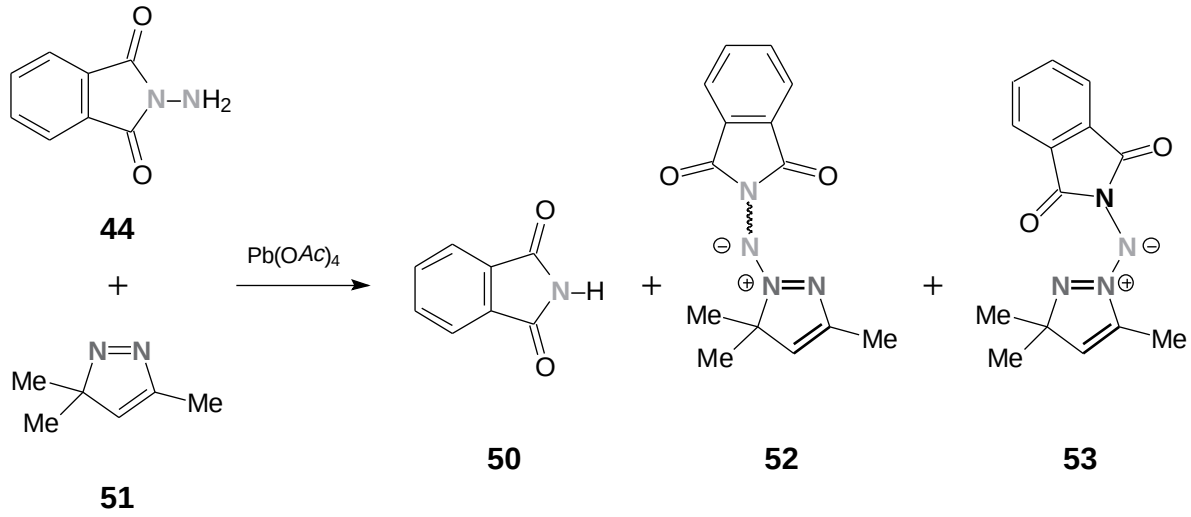

Scheme 16.

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