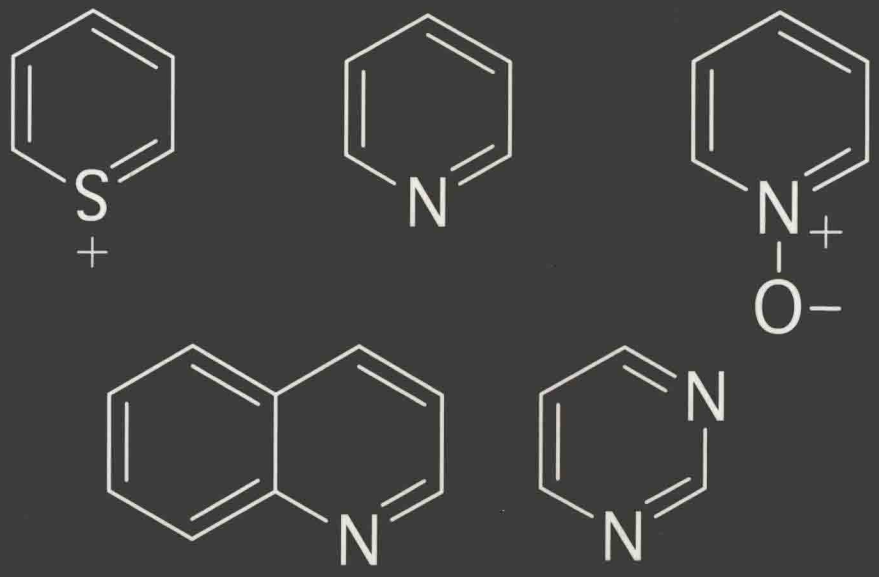
Advances in
HETEROCYCLIC CHEMISTRY



VOLUMES 99, 100, AND 101 ARE ALL PUBLISHED IN 2010 TO MARK THE SERIES REACHING 100 VOLUMES.

Volume 99

Advances in

HETEROCYCLIC CHEMISTRY

VOLUME **99**

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VOLUME **99**

Editor
ALAN R. KATRITZKY, FRS
Kenan Professor of Chemistry
Department of Chemistry
University of Florida
Gainesville, Florida

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CONTRIBUTORS

Numbers in parentheses indicate the pages on which the author's contribution begins.

Edgars Abele (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

Nuzhat Arshad (33)
Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

Alexandru T. Balaban (61)
Texas A&M University at Galveston, 5007 Ave, U. Galveston, TX 77551, USA

Luba Ignatovich (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

C. Oliver Kappe (33)
Institute of Chemistry, Karl-Franzens University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

L.I. Belen'Kii (143)
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia

Edmunds Lukevics (107)
Latvian Institute of Organic Synthesis, 21 Aizkraukles, Riga, LV-1006, Latvia

A. I. Mikhaleva (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

Albert Padwa (1)
Emory University, Department of Chemistry, Atlanta, GA 30322, USA

J. Schantl (185)
Institut für Organische Chemie, Universität Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

E. Yu. Schmidt (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

L. N. Sobenina (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

B.A. Trofimov (209)
A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 Favorsky Str., Irkutsk 664033, Russian Federation

MILESTONE OF 100 VOLUMES OF ADVANCES IN HETEROCYCLIC CHEMISTRY MARKED BY THE PUBLICATION OF VOLUMES 99, 100, AND 101 AS A CELEBRATORY SET

It is hard to believe that it is now 50 years since I conceived the concept of periodical volumes of these "Advances" that would record progress in Heterocyclic Chemistry. In 1960, heterocyclic chemistry was slowly emerging from the dark ages; chemists still depicted purines by the archaic structural designation introduced (was it by Emil Fischer?) 50 years before that. Together with Jeanne Lagowski I had published in 1959 a modern text on heterocyclic chemistry, the first that treated this subject in terms of structure and mechanism and attempted to logically cover significant methods of preparation and reactions of heterocyclic compounds as a whole, all in terms of reactivity.

The first two volumes of Advances contained extensive chapters on the tautomerism of various classes of heterocycles. Despite the great influence the precise structure of heterocyclic compounds has on chemical and biological properties (we only have to remember base pairing of nucleotides to illustrate this), at that time the literature was replete with incorrectly depicted tautomers. The basis for the position of tautomeric equilibria was usually completely misunderstood. Although great progress has been made in the last 50 years, there still exist holdouts even among otherwise reputable chemists who persist in depicting 2-pyridone as "2-hydroxypyridine" which is a very minor component of the tautomeric equilibrium under almost all conditions.

Over the years Advances in Heterocyclic Chemistry has indeed monitored many of the advances in the subject: the series is now boosted by "Comprehensive Heterocyclic Chemistry" of which the first edition was published in 1984 in 8 volumes, followed by the second edition in 1996 in 11 volumes and the third in 2008 in 15 volumes. Heterocyclic chemistry has now taken its place as one of the major branches (by several criteria the most important) of Organic Chemistry.

Chemistry has rapidly become the universal language of molecular interactions; it has essentially taken over biochemistry and is rapidly gaining dominance in zoology, botany, physiology and indeed in many branches of medicine.

Chemical structural formulae are quite basic to this progress and have enabled us to rationalize many natural phenomenon and countless reactions both simple and exotic discovered in the laboratory.

Now we have reached the milestone of 100 volumes of the series. In place of a single volume we are offering the three volume set 99, 100 and 101 which contain a fascinating variety of reviews covering exciting topics in heterocyclic chemistry.

Alan R. Katritzky
Gainesville, Florida

PREFACE TO VOLUME 99

Dr. Albert Padwa (Emory University) starts the volume with a fascinating chapter on the cycloaddition and cyclization chemistry of 2H-azirines, an area in which he has been closely connected with some of the most interesting developments. Dr. Nuzhat Arshad and Dr. Oliver Kappe of the University of Graz (Austria) update our knowledge of heterocyclic BINAP analogues, important ligands for asymmetric synthesis.

Professor Alexandru Balaban (Texas A&M University) has contributed a focused account of monocycle hetarenes possessing a π-electron aromatic sextet; this illustrates the wide variety of possible systems, many of which remain unknown or little explored. Professor Edmund Lukevics, with Drs Abele and Ignatovich, reviews the chemistry of biologically active silacyclanes covering some lesser known aspects of silicon chemistry and the evidently very wide range of possible structures here.

Professor Leonid Belen'kii (Zelinsky Institute, Moscow) has rationalized the orientation of substitution in furan, thiophene, and pyrrole. Professor Joachim Schantl of University of Innsbruck (Austria) surveys the chemistry of cyclic azomethine imines derived from azo compounds, illustrating the diversity of their possible [3+2] cycloaddition reactions.

Finally, Professor Boris Trofimov, together with three colleagues from the Irkutsk Institute of the Russian Academy of Sciences, gives an account recent advances in the chemistry of *N*-vinylpyrroles obtained from ketones and acetylenes.

Alan R. Katritzky
Gainesville, Florida

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CHAPTER 1

Cycloaddition and Cyclization Chemistry of 2*H*-Azirines

Albert Padwa

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1. INTRODUCTION

Azirines can be regarded as one of the most simple of all heterocyclic systems, one which is characterized by the presence of two carbon atoms and one nitrogen atom in a three-membered ring containing a π-bond.

Emory University, Department of Chemistry, Atlanta, GA 30322, USA

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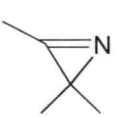
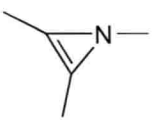
While numerous members of the 2*H*-azirine (**1**) ring systems are known and have been fully characterized, derivatives of the 1*H*-azirine ring system (**2**) are known only as transient intermediates. Interest in these nitrogen-containing small rings is due to the general influence of ring strain upon chemical reactivity, to the degree to which the 1*H*-azirine ring, for example, is destabilized by conjugation of the nitrogen lone pair electrons with the π-bond, and to the potential of derivatives of these compounds to act as precursors to more elaborate heterocyclic molecules. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. With 1*H*-azirines, cyclic delocalization of the lone pair electrons is believed to destabilize the ring to an extent which precludes isolation but not detection of the 4π-electron containing antiaromatic ring system. Polarization toward the more electronegative nitrogen atom of the 2*H*-azirine ring results in a shorter C–N bond and a longer C–C bond, consistent with the dimensions of 2*H*-azirines found by single crystal X-ray data (97CEJ1757). The stability of the 2*H*-azirine ring can be attributed not only to the combined effects of bond shortening and angle compression, but also to the presence of the electron-rich nitrogen atom. The strain energy associated with these heterocycles is principally due to deformation of the normal bond angles between the atoms of the ring. The total ring-strain energy of 2*H*-azirine has been estimated at 48 kcal mol^{-1} (91AG238, 02EJOC1750) although lower values of 44.6 and 46.7 kcal mol^{-1} have been reported using *ab initio* calculations at the MP2/6-31G* and B3LYP/6-31G* levels of theory (98JCC912). The chemistry of 2*H*-azirines is dominated by processes in which the strain of the three-ring system is relieved. They readily participate in cycloaddition reactions as 2π-components and undergo ring cleavage on photochemical excitation to give nitrile ylides. These dipoles then undergo a subsequent 1,3-dipolar cycloaddition reaction with a variety of π-bonds. Thermal ring cleavage produces vinyl nitrenes by cleavage of the N–C_2 bond, which then undergo ring expansion reactions. The theoretical, biological applications, and the synthetic chemistry of 2*H*-azirines have been extensively explored and a number of general reviews have appeared (01EJOC2401, 02OPP219) (Figure 1).



1; 2*H*-Azirine



2; 1*H*-Azirine

Figure 1 Isomeric azirine ring system.

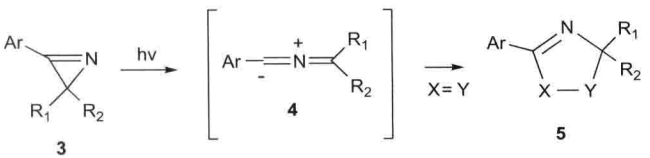
A major and characteristic reaction of the 2*H*-azirine ring is its reactivity toward a wide variety of reagents, an effect undoubtedly resulting from the necessary compression of bond angles in the three-membered ring. Thus, this system is extremely susceptible toward ring cleavage because of the favorable release of strain energy involved. For this reason, 2*H*-azirines have been converted to a wide variety of functionalized compounds. 2*H*-Azirines are capable of acting in reactions as nucleophiles and electrophiles, as 2π-components in thermal cycloadditions, and as 4π-components in photochemical cycloadditions. These reactions can be regarded in general terms as involving the participation of the C=N, C–C and C–N bonds of the 2*H*-azirine ring. The cycloaddition and cyclization reactions of 2*H*-azirines have invoked considerable interest in recent years. In this chapter, some of the more important "*cyclo*" transformations of this unique heterocyclic system are described.

2. PHOTOCYCLOADDITION REACTIONS OF 2*H*-AZIRINES

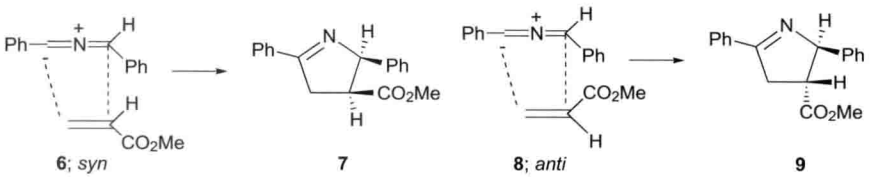
2.1 Bimolecular [1,3]-dipolar cycloadditions

2*H*-Azirines undergo irreversible ring opening on electronic excitation to give nitrile ylides **4** as reactive intermediates (Scheme 1) (76ACR371, 77H143, 73JA1954). Nitrile ylides may be classified as nitrilium betaines, a class of 1,3-dipoles containing a central nitrogen atom and a π-bond orthogonal to the 4π-allyl system. They can be intercepted with a wide variety of dipolarophiles to form five-membered heterocyclic rings (e.g., **5**).

The photocycloaddition of arylazirines with electron deficient alkenes to produce Δ^1-pyrrolines (73JA1954) exhibits all the characteristics of a concerted reaction, including stereospecificity and regioselectivity. 1,3-Dipolar additions proceed *via* a "two-plane" orientation complex where the dipole and dipolarophile approach each other in parallel planes (Scheme 2) (68JOC2291). For the case of diphenylazirine and methyl acrylate, two possible orientation complexes (**6** or **8**) exist. The interaction of substituent groups in the *syn* complex **6** can be of an attractive (π-overlap, dipole–dipole interaction) or a repulsive nature (van der Waals' strain). Both effects are negligible in the *anti* complex **8**. The ratio of the products obtained gives insight into the interplay of steric and



Scheme 1

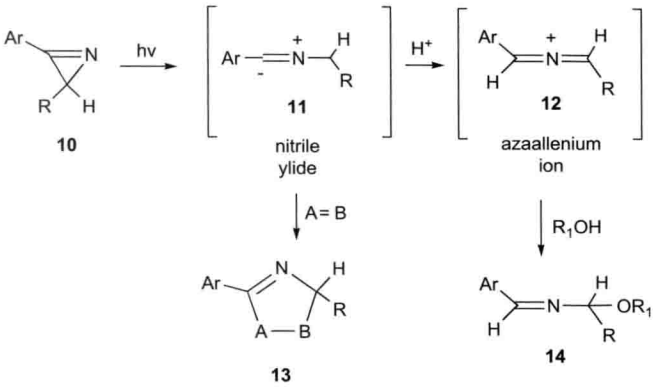


Scheme 2

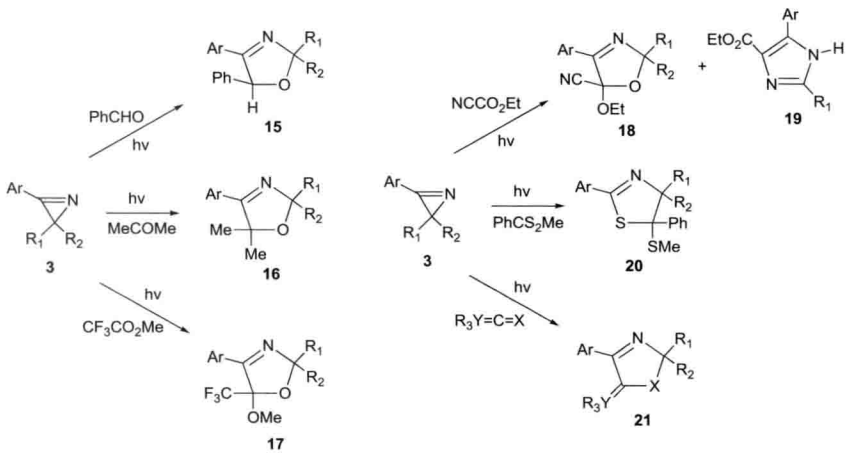
electronic substituent effects in the transition state of 1,3-dipolar addition and emphasizes the important role these effects have in controlling the stereochemical distribution of the products obtained.

Frontier molecular orbital theory correctly rationalizes the regioselectivity of most 1,3-dipolar cycloadditions (73JA7287). When nitrile ylides are used as 1,3-dipoles, the dipole highest occupied (HOMO) and dipolarophile lowest unoccupied (LUMO) orbital interaction importantly stabilizes the transition state. The favored cycloadduct is that formed by union of the atoms with the largest coefficient in the dipole HOMO and dipolarophile LUMO. An electron deficient alkene has the largest coefficient on the unsubstituted carbon in the LUMO. In order to predict regioselectivity in the photocycloaddition of arylazirines, the relative magnitudes of the coefficients in the HOMO of the nitrile ylide must be known. The photoconversion of arylazirines to alkoxyimines **14** indicates that in the HOMO of the nitrile ylide the electron density at the disubstituted carbon is greater than at the trisubstituted carbon atom. With this conclusion, all the regiochemical data found in the photoaddition of arylazirines with dipolarophiles can be explained. In alcohols as solvents, the nitrile ylides are protonated to yield azallenium cations **12** which are then trapped by the alcohol to furnish alkoxyimines **14**. The protonation rate of the ylide in alcohol increases with the acidity of the alcohol. On the basis of a large kinetic isotope effect ($k_H/k_D = 5.5$) for protonation of the ylide, the transition state for the nitrile ylide protonation was concluded to be linear (97JA11605). Cycloaddition of the 2*H*-azirine ring to give pentagonal heterocycles **13** by photochemical activation has become a well known reaction of this heterocyclic system (Scheme 3) (95HCA935).

The photochemistry of 3-methyl-2-(1-naphthyl)-2*H*-azirine has been investigated by the direct observation of reactive intermediates in Ar matrixes and by the characterization of reaction products in solution (05JA2628). Interestingly, the irradiation of this particular 2*H*-azirine with long-wavelength light resulted in selective cleavage of the C–N bond. On the other hand, products derived from C–C bond cleavage were obtained when the irradiation was carried out with short-wavelength light. On the basis of MO calculations using the INDO/S method, it was proposed that C–N bond cleavage occurs from an excited triplet state having an electronic character of a localized π–π^* excitation on the naphthyl moiety.



Scheme 3



Scheme 4

The photochemical addition of 2*H*-azirines to the carbonyl group of aldehydes, ketones and esters is completely regiospecific (77H143). Besides the formation of the isomeric oxazolines **18** from **3** and ethyl cyanoformate, there is also formed the imidazole **19** from addition to the C═N in the expected regioselective manner. Thioesters lead to thiazolines **20**, while isocyanates and ketenes produce heterocycles **21** (Scheme 4). The photocycloaddition of arylazirines with a variety of multiple bonds proceeds in high yield and provides a convenient route for the synthesis of five-membered heterocyclic rings. Some of the dipolarophiles include azodicarboxylates, acid chlorides, vinylphosphonium salts and *p*-quinones.