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Cultivating the Passion to Build Heterocycles from 1,2-Diaza-1,3-dienes: the Force of Imagination

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The present microreview summarizes our progresses over the last years in the chemistry of 1,2-diaza-1,3-dienes. Beyond the findings reported here, the main target of this microreview is to outline some of the reactive peculiarities that make this class of compounds powerful tools in heterocyclic chemistry.

1. Introduction

Heterocyclic chemistry represents a vast and important research area of interest for academic, as well as for industrial, pharmaceutical and phytopharmaceutical chemists. The remarkable activity in this field is demonstrated not only by the great number of contributions devoted to their fundamental properties, but also by the numerous papers dealing with applications of molecules containing heterocycles in medicinal chemistry and materials science. Furthermore, the majority of the work done in the pharmaceutical and agrochemical industries are about heterocyclic chemistry. Therefore, the development of new strategies to prepare heterocyclic systems is of considerable ongoing interest. With this aim, our group investigated for over thirty years

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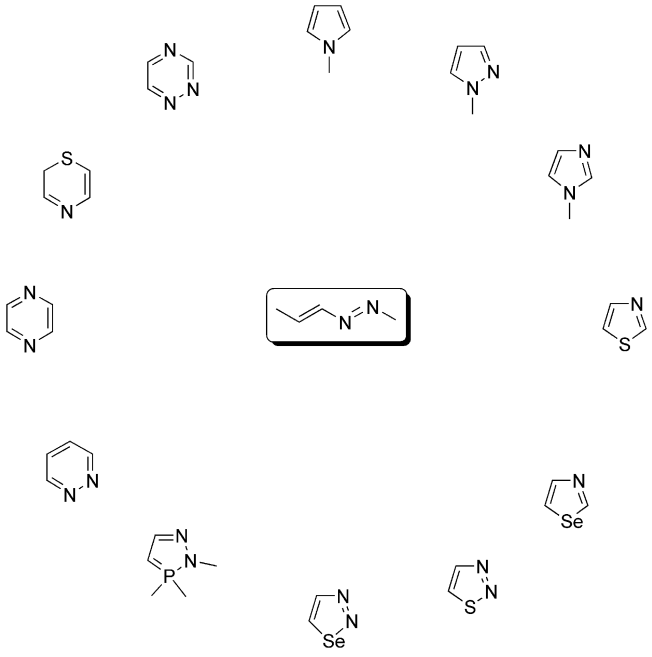
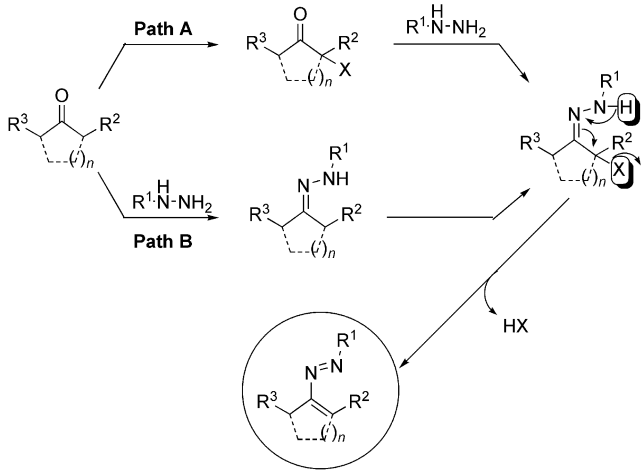
Orazio Antonio Attanasi (centre) studied at Bologna University, where he obtained a doctorate degree in Industrial Chemistry. During 1969–70, he worked as an Organic Chemistry Assistant at Bologna University, and during 1971–75 as a Researcher at the National Council of Research (CNR). In 1976, he was named Organic Chemistry Assistant at Urbino University, in 1982 he became Associate Professor, and in 1986 Professor of Organic Chemistry at Urbino University. Between 1974 and 1975 he attended the Technisch-Chemisches Laboratorium of the Eidgenössische Technische Hochschule Zürich as Visiting Researcher. In 1998 and 2001 he attended as Visiting Professor the Universidade Federal do Rio Grande do Norte and the Universidade Federal do Ceará (Brazil). In 1982 he founded the Center of Natural Organic Products at Urbino University, becoming head of the Center. In 1987 he founded the Organic Chemistry Institute at Urbino University, becoming head of the Institute.
Lucia De Crescentini (third from left) was born in Urbino (Italy) in 1966. In 1990, she received her degree in Biological Sciences at the University of Urbino. From 1990 to 2002 she was a technician at the Institute of Organic Chemistry of the University of Urbino, and from 1st October 2002 she is a Researcher at the same Institute.
Gianfranco Favi (left) was born in Montemarciano (Italy) in 1973. In 1999 he graduated in Chemistry at the University of Bologna. In 2005 he received his Ph.D. degree in Chemistry and Pharmaceutical Sciences at the University of Urbino. From March 2005 to date he has a post-doctorate position at the University of Urbino.
Paolino Filippone (right) is Associate Professor of Organic Chemistry at Urbino University. He earned his degree at Palermo University in 1977. After two years at Bedford College of the University of London and at the School of Chemistry of the University of Leeds (UK), he started working at the Institute of Organic Chemistry of Urbino University in 1980.
Fabio Mantellini (second from left) was born in Castrocaro (Italy) in 1970. In 1996, he received his degree in Industrial Chemistry at the University of Bologna. Since 1996 he has been working at the Institute of Organic Chemistry of the University of Urbino as a Researcher.
Francesca-Romana Perrulli (second from right) was born in Pesaro (Italy) in 1957. She graduated in Pharmacy at the University of Urbino in 1982 and then she collaborated in research at the Institute of Organic Chemistry at the same university. She received a research fellowship, then, in 2003, she became a research assistant in that institute.
Stefania Santeusanio (third from right) was born in Vigevano (Italy) in 1958. She graduated in Biology at the University of Urbino in 1982. Since 1982 she contributes to research programmes of the Institute of Organic Chemistry (Faculty of Sciences and Technologies). From 1989 to 1997 she has worked as a Technician and from 1997 to date she is a Researcher of Organic Chemistry.

the usefulness of 1,2-diaza-1,3-dienes (DD) in the construction of several five- and six-membered heteroring systems. In fact, the search for new and efficient starting materials able to permit smooth access to heteroring compounds is a topical and exciting target. This microreview describes our progresses over the last years in the chemistry of DD, showing their synthetic usefulness as versatile building blocks in the construction of pyrroles, pyrazoles, imidazoles, thiazoles, selenazoles, 1,2,3-thiadiazoles, 1,2,3-selenadiazoles, 1,2,3-diazaphospholes, pyridazines, pyrazines, 1,4-thiazines, 1,2,4-triazines and mixed heterocyclic systems (Scheme 1).[1]



Scheme 1. Heterocycles obtained from DD.



Scheme 2. General procedure for the synthesis of DD.

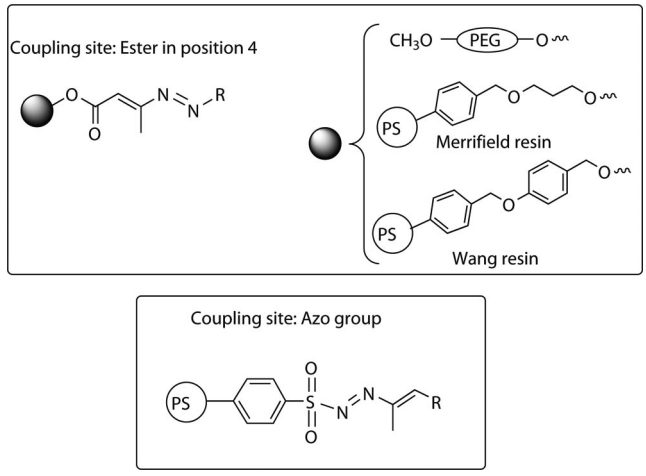


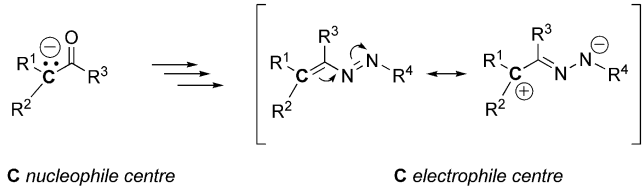
Figure 1. Polymer-bound DD.

2. Synthesis, General Reactivity and Properties of 1,2-Diaza-1,3-dienes

DD can be properly considered hydrazine derivatives of carbonyl compounds.[2] In fact, they are usually prepared by means of 1,4-elimination of a good leaving group X (frequently chloride or bromide) in the α-position with respect to a hydrazone function. The leaving group can be present in the starting carbonyl derivatives (Scheme 2, Path A) or introduced in the hydrazone compounds (Scheme 2, Path B). Both cyclic[3,4] and acyclic[1] ketones can be used in the preparation of DD (Scheme 2).

Polymer-bound DD can also be prepared by using both soluble poly(ethylene glycol) (PEG)[5] or insoluble polystyrene (PS)[6–8] supports. The coupling sites can be both the ester group in the 4-position[5–7] and the azo group[8] of the azo-ene systems (Figure 1).

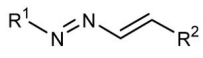
The chemical properties of DD are mainly related to the electron-withdrawing effect of the azo group in the heterodiene system that makes these compounds good Michael acceptors. DD feature an umpolung of the classical carbonyl reactivity,[9] since these neutral compounds enable nucleophilic additions at the terminal carbon atom of the azo-ene system. This atom is originally located in the α-position to the ketone function from which DD are prepared. It is well known that such a carbon atom is a nucleophilic rather than an electrophilic site. Therefore, the reactivity of DD proceeds contrary to the natural polarity of the parent carbonyl derivatives and their employment represents a valid approach to reverse the normal polarity of carbon atom in the α-position to the carbonyl group (Scheme 3).



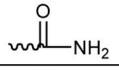
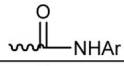
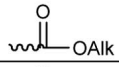
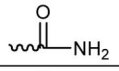
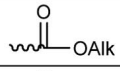
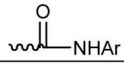
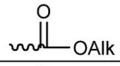
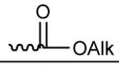
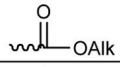
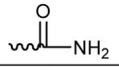
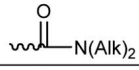
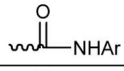
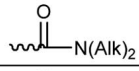
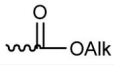
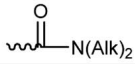
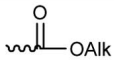
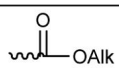
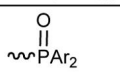
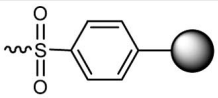
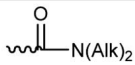
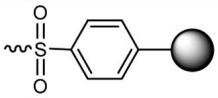
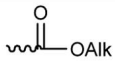
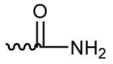
Scheme 3. DD: synthons of hydrazone cations. A useful reversed polarity equivalent.

Substituents influence the physical and chemical properties of DD (Table 1). Electron-withdrawing groups (e.g. esters or amides) on the terminal carbon and/or nitrogen atom favour the stability and enhance the electrophilic character of the heterodiene system.

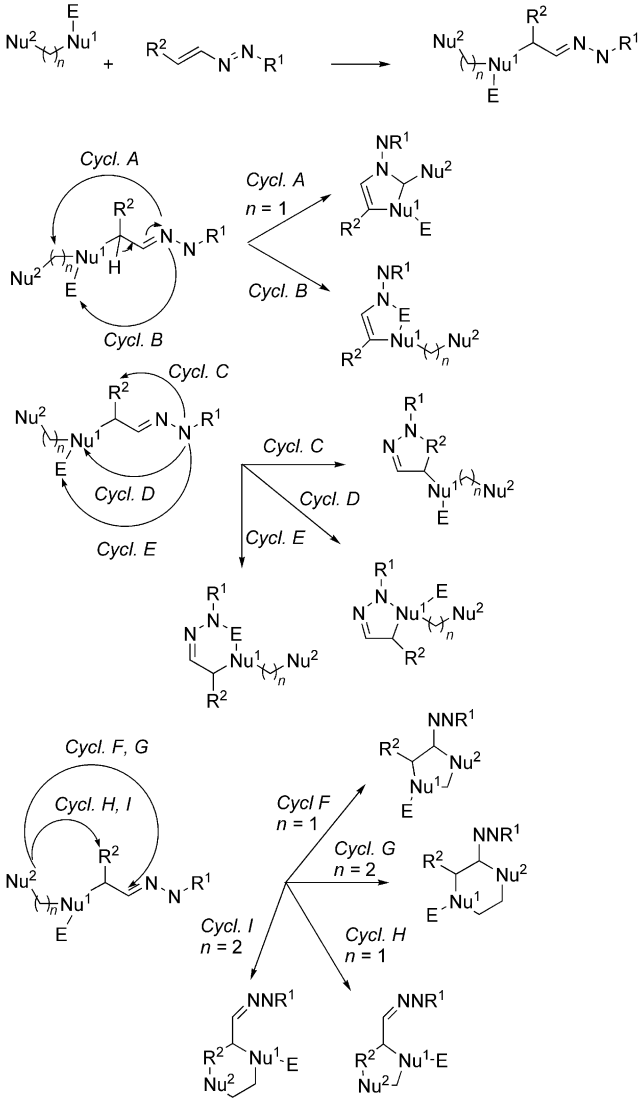
Table 1. Different types of DD **1**.



1

1	R^1	R^2
1a		Cl
1b		Cl
1c		Cl
1d		
1e		
1f		
1g		
1h		
1i		
1j		
1k		
1l		
1m		
1n		

So, the typical reaction of DD is regioselective nucleophilic attack at the terminal carbon atom in the 4-position of the heterodiene system by a variety of carbon and hetero nucleophiles such as oxygen, nitrogen, sulfur, selenium and phosphorus (Nu^1, Scheme 4). These 1,4-additions (Michael-type) produce highly functionalized hydrazones (Scheme 4). In this key step, together with the attacking nucleophiles, we can introduce various other nucleophile (Nu^2, Scheme 4) or electrophile (E, Scheme 4) functions. This occurrence merits special emphasis, since functionalized hydrazones are, in turn, potential starting materials for further interesting structural modifications through controlled regioselective reactions leading to complex heterocyclic systems. In fact, different intramolecular ring closures are possible (Scheme 4). Thus, nucleophilic sites can be either the nitrogen atom from the azo group (Cycl. A, B, C, D, E), or the new group (Nu^2) inserted in the Michael additions (Cycl. F, G, H, I). On the other hand, the electrophiles involved can be the hydrazone C=N bond (Cycl. F, G), the electron-withdrawing group (R^2) in the 4-position of the azo-ene systems (Cycl. C, H, I) or a new group (E) inserted in the Michael additions (Cycl. B, E).



Scheme 4. Michael addition of nucleophiles to DD and possible pathways of annulation from the obtained Michael adduct.

On the other hand, the presence of electron-withdrawing groups on the terminal atoms of the azo-ene system makes DD **1** very good starting materials in the "inverse-electron-demand" Diels–Alder reactions.[2,10] It is noteworthy that all these preparative procedures afford, frequently in one-pot and in good yield, highly substituted heterocycles, many of which are of great importance in organic, biological, pharmaceutical and phytopharmaceutical chemistry.[11] Furthermore, these synthetic methodologies make possible

to widely plan ab initio the substituents of the rings by means of the preliminary preparation of simple and more accessible starting materials. In general, these reactions do not require anhydrous solvents or inert atmospheres, occur under mild conditions and need simple work-up procedures. The yellow, orange, red or amaranth colour of DD, due to their conjugation, is a convenient and useful "internal litmus" to check the progress of the reaction. In fact, the transformation of these compounds is accompanied with the change of the initial colour of the reaction mixture to the final colourless or pale yellow state. As mentioned above, since the construction of heterocycles from DD starts with a preliminary nucleophilic 1,4-addition of different atoms to the heterodiene systems, the discussion is subdivided according to the nature of the nucleophiles.

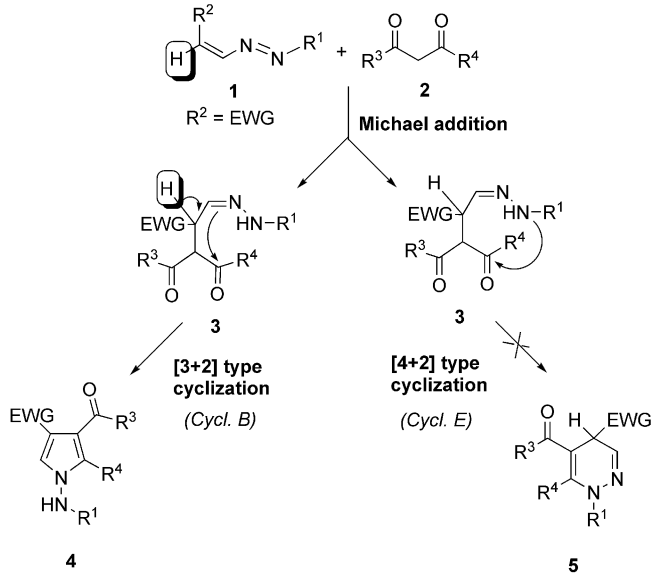
3. Carbon Nucleophiles

Various carbon nucleophiles can easily react with DD to form a new carbon–carbon bond. The Michael-type 1,4 adducts thus obtained can easily give rise to functionalized pyrroles, pyrazoles, 1,2,3-thiadiazoles, 1,2,3-selenadiazoles, pyridazines and cynnolines.

3.1. Base-Activated Carbon Nucleophiles

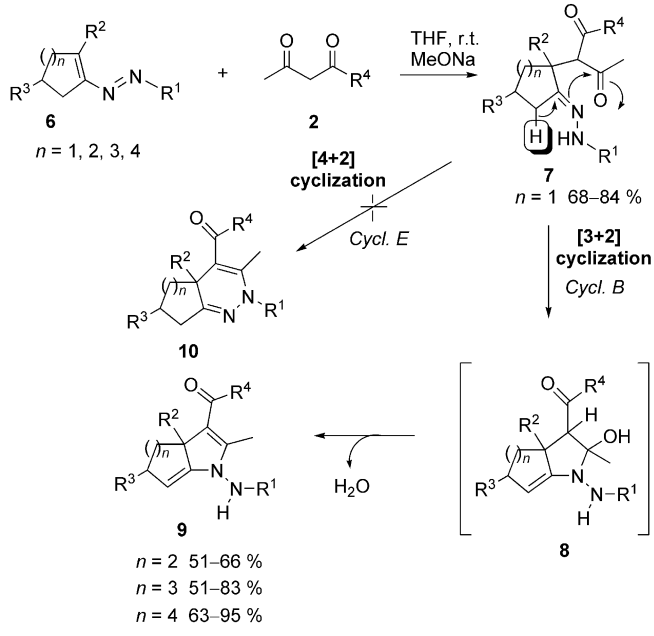
Among the manifold of carbon–carbon bond forming reactions, the Michael addition is considered one of the most versatile methods in organic synthesis.[12] In the course of our activity, we have tested a large variety of carbon nucleophiles[1] and we have found that the reaction between DD **1** and β-dicarbonyl compounds containing activated methylene groups **2** always generate pyrroles **4** rather than dihydropyridazine rings **5**, as erroneously reported previously.[13] This behaviour is a consequence of the preliminary Michael-type 1,4-addition that leads to α-substituted hydrazone intermediates **3** and subsequent internal ring closure by the hydrazone sp^2 nitrogen atom. Thus, when the nucleophilic reagent bears a ketone function in the α-position with respect to the attacking carbon atom, the annulation occurs with a [3+2] (Cycl. B) instead of a [4+2] (Cycl. E) cyclization process. This ring closure is promoted by the presence of an acidic hydrogen atom on the intermediates **3** originally placed in the 4-position of the azo-ene system **1** and activated by two electron-withdrawing groups (EWG): the EWG and hydrazone moieties (Scheme 5).[14]

We then investigated the reactions of cyclic DD **6**, lacking the above-mentioned hydrogen atom, with the same β-dicarbonyl derivatives **2**. Even in this case, we observed the regioselective synthesis of functionalized cycloalkenylidene-pyrroles of different sizes **9** by alternative [3+2] cyclization.[3,15] In fact, after the formation of hydrazone intermediates **7**, the regioselective conjugate nucleophilic attack of the hydrazone sp^2 nitrogen atom at the ketone function is promoted again by the extrusion of the proton in the α-position to the hydrazone moiety. This occurrence produces intermediates **8**, which spontaneously furnish the final



Scheme 5. Regioselective annulation process in the reaction between DD **1** and β-dicarbonyl compounds **2**.

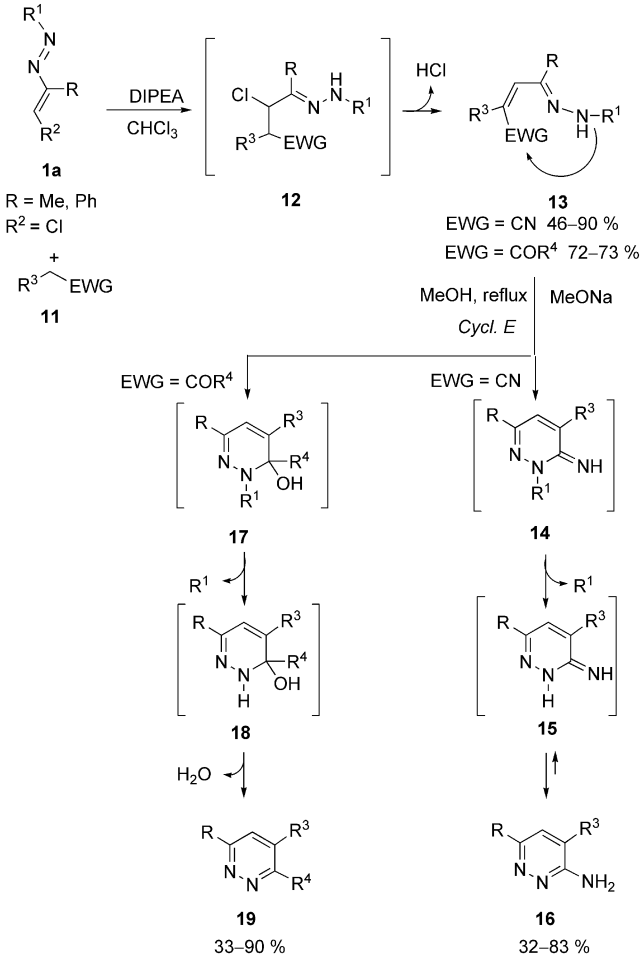
fused cycloalkenylidene-pyrroles of different sizes **9**, by elimination of a water molecule (Cycl. B). It is noteworthy that, even though the final products **9** are unable to acquire aromatic stabilization, no [4+2] ring closure (Cycl. E) occurred, and pyridazine derivatives **10** were not formed (Scheme 6).



Scheme 6. Synthesis of fused cycloalkenylidene-pyrroles **9** by reaction of cyclic DD **6** and β-dicarbonyl derivatives **2**.

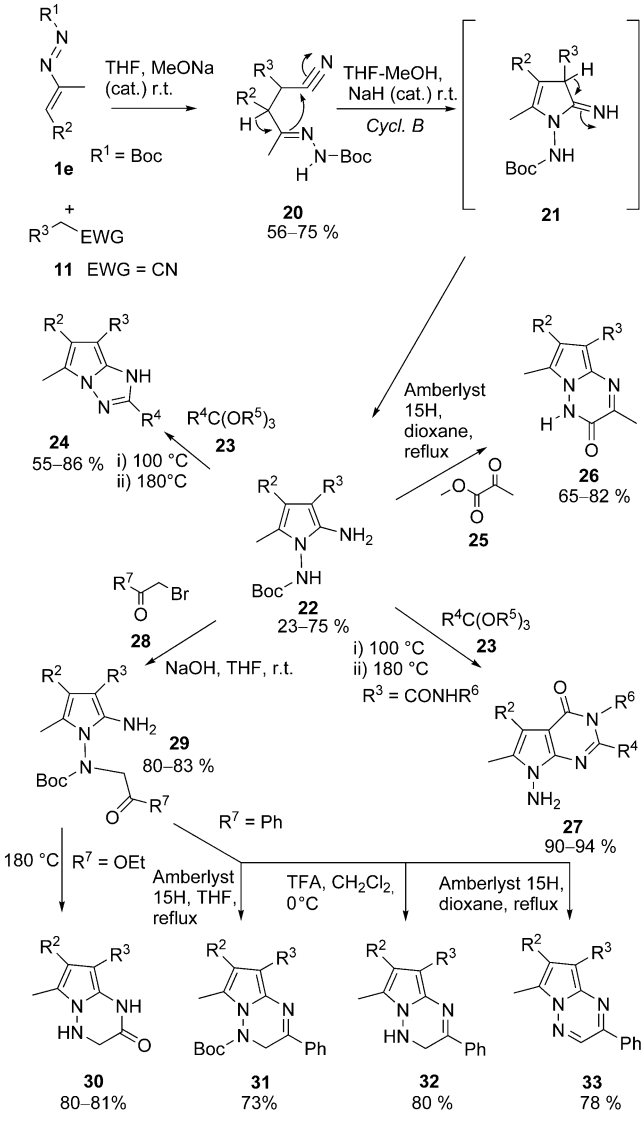
The reaction of 4-chloro-DD **1a** (R^2 = Cl) with a variety of different active methylene compounds **11** furnished α,β-unsaturated hydrazones **13**, that, in turn, gave rise to intramolecular ring closure (Cycl. E), affording diversely functionalized pyridazines **16** and **19**. The transformation starts from the base-promoted attack of the active carbon atom

of **11** at the terminal carbon atom of the azo-ene system to generate the adduct intermediate **12** followed by dehydrohalogenation to give **13**. Subsequently, intramolecular base-promoted [4+2] cyclization by nucleophilic attack of the hydrazone sp^3 nitrogen atom at the nitrile or carbonyl function (Cycl. E) results in the formation of dihydropyridazine rings **14** or **17**, respectively. The spontaneous loss of carbamic residue R^1 produces **15** or **18**, respectively. The tautomerism NH/NH_2 of **15** and the elimination of a water molecule from **18** leads to pyridazines **16** or **19**, respectively. It is important to note that the success of this [4+2] cyclization depends on the presence of a leaving group on the terminal carbon atom of the azo-ene system. In fact, the elimination of this group with the formation of the carbon–carbon double bond prevents the possible [3+2] ring closure to give the pyrrole derivatives (Scheme 7).[16]



Scheme 7. Synthesis of pyridazines **16** and **19** starting from 4-chloro-DD **1a** and active methylene compounds **11**.

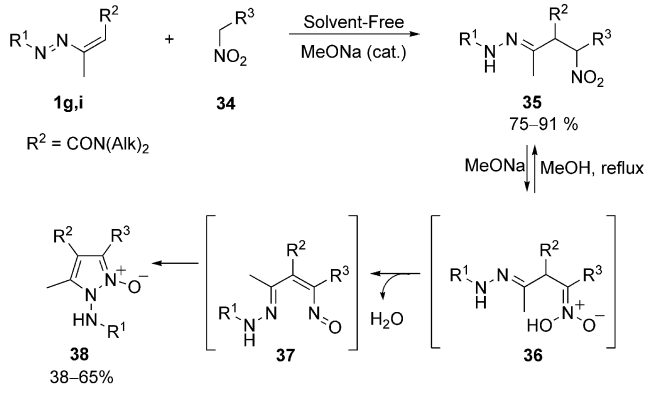
The reaction of the activated methylene group of nitrile derivatives **11** with 1-*tert*-butoxycarbonyl-DD **1e** (R^2 = Boc) provided hydrazone 1,4 adducts **20**, and then the 1-Boc-protected 1,2-diaminopyrroles **22** were achieved by [3+2] intramolecular ring closure of the hydrazone sp^2 nitrogen atom on the nitrile function (Cycl. B) through NH/NH_2 tautomerism of the related imino intermediate **21**. Pyrroles **22** were in turn useful substrates for some condensation-deprotection or deprotection-condensation sequences with ortho esters **23** to give pyrrolo[1,2-*b*][1,2,4]triazoles **24** and pyrrolo[2,3-*d*]pyrimidin-4-ones **27**, or with different carbonyl compounds **25** and **28** for the synthesis of pyrrolo[1,2-*b*][1,2,4]triazin-3-ones **26**, pyrrolo[1,2-*b*][1,2,4]triazin-2-ones **30** and pyrrolo[1,2-*b*][1,2,4]triazines **31**–**33** (Scheme 8).[17]



Scheme 8. Synthesis of various fused heterocycles by reaction of 1-*tert*-butoxycarbonyl-DD **1e** with nitrile derivatives **11**.

1-Amido-DD **1g,i** [R^2 = $CON(Alk)_2$] easily reacted in solvent-free conditions at room temperature with nitroalkanes **34** in the presence of a catalytic amount of sodium methoxide to give β-nitrohydrazones **35**. Also in this case, the reaction proceeds by nucleophilic attack of nitronate anion produced from nitroalkanes **34** at the azo-ene system of **1**, affording the relevant 1,4 adducts **35**. Subsequent treatment with one equivalent of sodium methoxide in methanol under reflux led to the formation of widely functionalized pyrazole *N*-oxides **38** in good yields.[18] The reac-

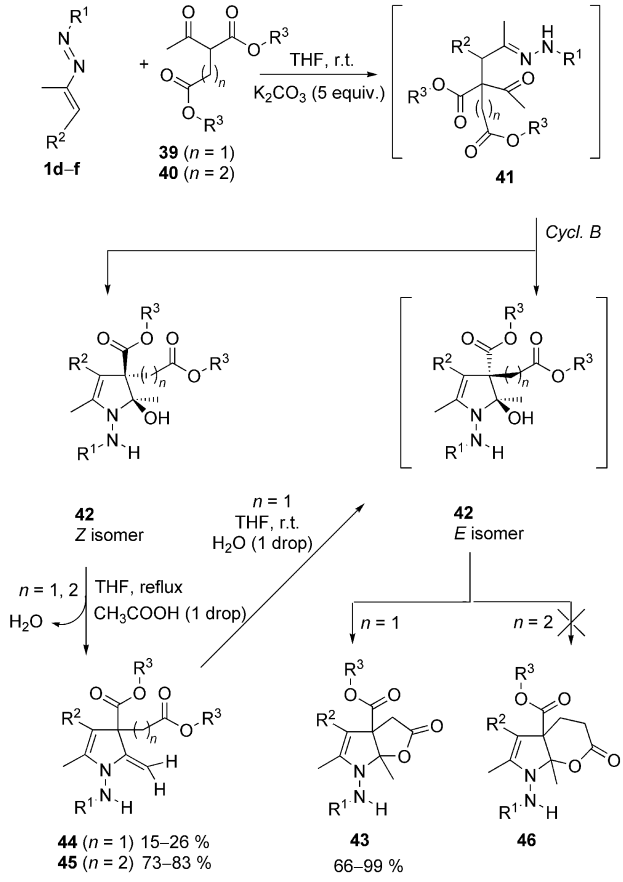
tion probably occurs with the formation of tautomers **36**, which afford the conjugated nitroso compounds **37** by loss of a water molecule. The formation of the final pyrazole *N*-oxides **38** is then a consequence of a thermal electrocyclic reaction that involves the nitroso conjugated 6π-electron-5-atom system of compounds **37** (Scheme 9).[19]



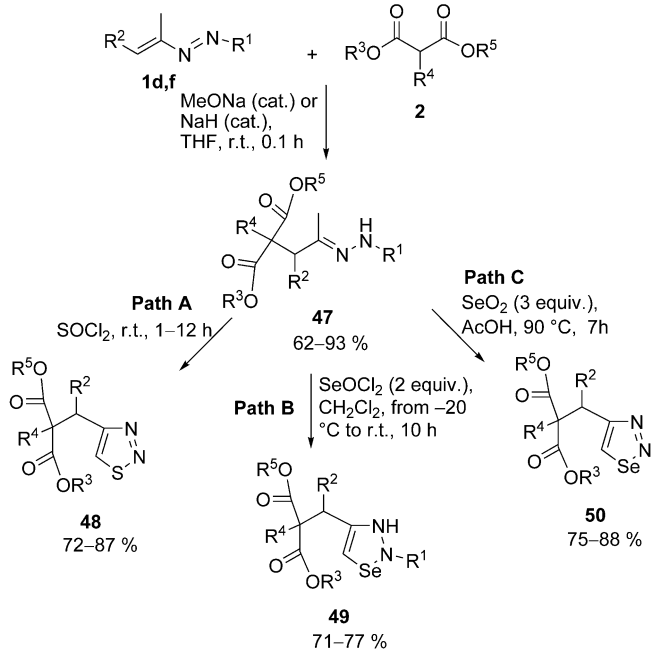
Scheme 9. Synthesis of pyrazole *N*-oxides **38** by reaction of DD **1g**,**i** with nitroalkanes **34**.

New and interesting 2-oxo-furo[2,3-*b*]pyrroles **43** and unknown 2-methylenepyrroles **44** have been obtained in good yields by the base-catalyzed one-pot reaction of DD **1d**–**f** with diethyl or dimethyl acetylsuccinates **39** (n = 1). A plausible mechanism involves the preliminary base-promoted 1,4-addition of the activated methine carbon atom of compounds **39** to the heterodiene system of **1** to give hydrazone intermediates **41**, followed by the intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the ketone function with the consequent first ring closure (Cycl. B). Only in a few cases, it was possible to isolate these 2-hydroxy-1-aminopyrroline intermediates **42** in the *Z* isomeric form. Probably, the conversion under basic conditions (potassium carbonate) of the *E* isomer into 2-oxo-furo[2,3-*b*]pyrroles **43** is favoured, and the second annulation occurs by means of an internal nucleophilic attack of the hydroxy group at the ester function. Likely, this step is difficult for the *Z* isomers of **42**, so the elimination of a water molecule becomes predominant, leading to the formation of the exocyclic double bond of compounds **44**. The addition of a drop of water to a solution of **44** in tetrahydrofuran led to the corresponding 2-oxo-furo[2,3-*b*]pyrroles **43** via 2-hydroxy-1-aminopyrroline **42** in its *E* isomeric form. When the nucleophile is diethyl 2-acetylglutarate **40** (n = 2), its reaction with DD **1** afforded directly 2-methylenepyrroles **45**. In this case, no formation of 2-oxapyra[2,3-*b*]pyrroles **46** was detected, probably because of thermodynamic factors (Scheme 10).[20]

The 1,4-addition of β-diesters **2** to DD **1d**,**f** can be directed to the exclusive formation of the corresponding α-functionalized hydrazones **47**. In fact, by using a catalytic amount of base in tetrahydrofuran, the subsequent cyclization processes are usually avoided. The so obtained α-substituted hydrazones **47** can be utilized as starting materials in Hurd–Mori type reactions,[21] leading to a variety of sulfur- and selenium-containing heterocycles. In particular, in-



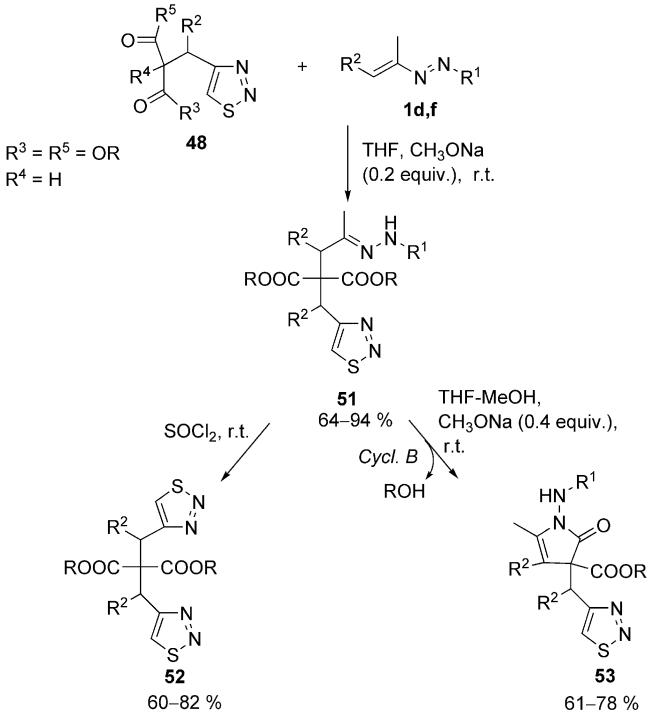
Scheme 10. Synthesis of 2-oxo-furo[2,3-*b*]pyrroles **43** and 2-methylenepyrroles **44** or **45** by reaction of DD **1d**–**f** with dialkyl acetylsuccinates **39** or diethyl 2-acetylglutarate **40**, respectively.



Scheme 11. Synthesis of α-functionalized hydrazones **47** and formation of 4-substituted 1,2,3-thiadiazoles **48**, 4-substituted 2,3-dihydro-1,2,3-selenadiazoles **49** and 4-substituted 1,2,3-selenadiazoles **50** by Hurd–Mori type reactions.

termediates **47** were transformed into 1,2,3-thiadiazoles **48** with thionyl chloride as solvent-reagent (Scheme 11, Path A), into 4-substituted 2,3-dihydro-1,2,3-selenadiazoles **49** with selenium oxychloride (Scheme 11, Path B), and into 4-substituted 1,2,3-selenadiazoles **50** with selenium dioxide (Scheme 11, Path C).[22]

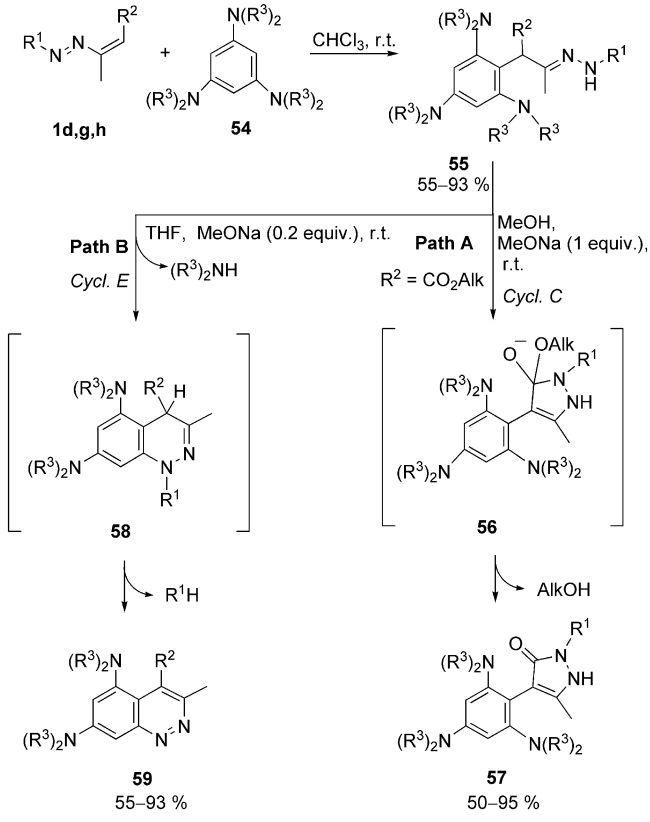
The presence of activated methine groups in the side chain of **48** enables these compounds to behave as nucleophiles. So, they can add to a second molecule of DD **1d**,**f** to give hydrazones **51** stereoselectively in a racemic mixture of *RR*/*SS* enantiomers. By treatment with thionyl chloride, compounds **51** gave 1,3-di-1,2,3-thiadiazolylpropane derivatives **52**, while with sodium methoxide they afforded 1,2,3-thiadiazolyl-2-oxo-2,3-dihydro-1*H*-pyrrole systems **53** (Cycl. B) (Scheme 12).[22]



Scheme 12. Michael addition of 1,2,3-thiadiazoles **48** containing activated methine groups to a second molecule of DD **1d**,**f** with formation of 4-hydrazone-1-(1,2,3-thiadiazolyl)pentanes **51** and synthesis of 1,3-di-1,2,3-thiadiazolylpropanes **52** or 1,2,3-thiadiazolyl-2-oxo-2,3-dihydro-1*H*-pyrroles **53**.

3.2. Neutral Carbon Nucleophiles

The 1,3,5-tris(dialkylamino)benzene derivatives **54**, known to be strongly activated neutral carbon nucleophiles,[23] are able to add themselves to DD **1d**,**g**,**h** to give the corresponding hydrazones **55**. In the presence of sodium methoxide, compounds **55** underwent cyclization to produce pyrazolones **57** (Cycl. C) and cynnolines **59** (Cycl. E) in different relative ratios, depending on the solvent used and on the nature of R^2 group. The formation of pyrazolones **57** as major products occurred in methanol, by means of nucleophilic attack of the hydrazone sp^3 nitrogen atom at the ester function located in the 4-position of the azoene system with loss of an alcohol molecule from intermediates **56** (Scheme 13, Path A). If the ester function was replaced by an amide moiety, this ring closure did not occur. The formation of cynnolines **59** prevailed mainly in tetrahydrofuran through an intramolecular nucleophilic aromatic substitution involving the displacement of a secondary amino group with loss of the R^1 moiety from intermediates **58** (Scheme 13, Path B).[24]

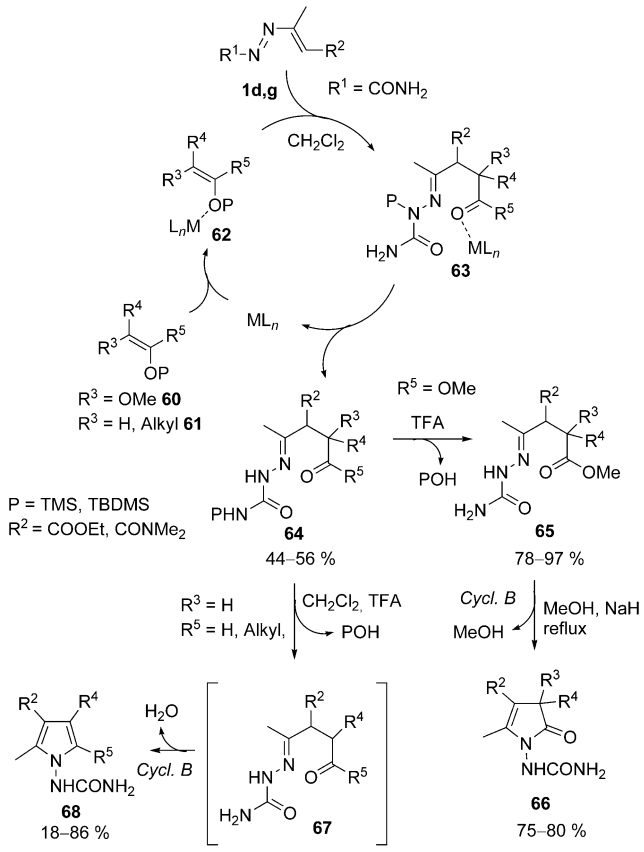


Scheme 13. Synthesis of pyrazolones **57** and cynnolines **59** by reaction of DD **1d**,**g**,**h** with 1,3,5-tris(dialkylamino)benzene derivatives **54**.

3.3. Silyl Derivatives

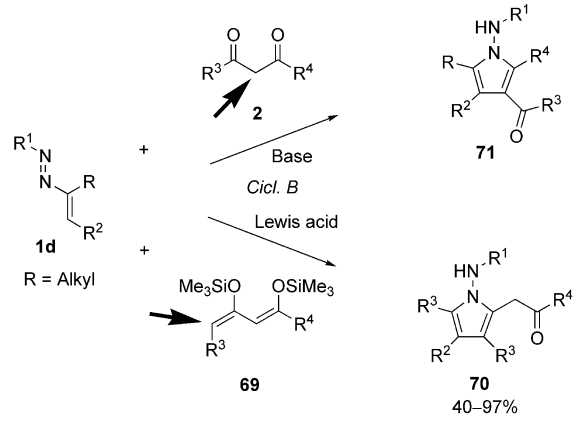
The Lewis acid catalyzed addition of silyl derivatives to α,β-unsaturated carbonyl compounds, introduced by Mukaiyama and co-workers,[25] is a valid alternative to the base-mediated variants. These transformations, usually named Mukaiyama–Michael additions, proceed under mild conditions and rely on the use of silyl enol ethers as nucleophiles.[26] DD **1d**,**g** reacted with various silyl ketene acetals **60** or silyl enol ethers **61** at room temperature in the presence of catalytic amounts of Lewis acid to afford 1-aminopyrrol-2-ones **66** or 1-aminopyrroles **68**, respectively. The mechanism generally accepted for the Lewis acid catalyzed Mukaiyama–Michael addition of enol-silyl derivatives on Michael acceptors involves the coordination of the latter with the Lewis acid followed by the 1,4-addition of the silyl enol compounds.[27] On the contrary, the mechanistic investigations of the reaction between DD **1d**,**g** and silyl enol **60** and **61** demonstrate that this Mukaiyama–Michael-like

reaction proceeds by coordination of the Lewis acid on silyl enol derivatives to form **62** and their conjugate 1,4-addition to the azo-ene system of DD to give hydrazone intermediates **63**. The thermodynamically driven migration of the silyl group from the hydrazine to the amide nitrogen atom proceeds by an intermolecular transfer producing intermediates **64**. The acidic cleavage of the silyl group from **64** afforded hydrazones **65** (from silyl ketene acetals) and **67** (from silyl enol ethers). The subsequent intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom of **65** at the ester group led to 1-amino-pyrrol-2-ones **66** by loss of an alcohol molecule (Cycl. B) (Scheme 14).[28] The attack of the same nitrogen atom of **67** at the carbonyl group provided 1-amino pyrroles **68** by loss of a water molecule (Cycl. B) (Scheme 14).[28]



Scheme 14. Mukaiyama–Michael-type addition/heterocyclization reaction of silyl ketene acetals **60** or silyl enol ethers **61** with DD **1d**,**g** leading to 1-amino-pyrrol-2-ones **66** or 1-aminopyrroles **68**.

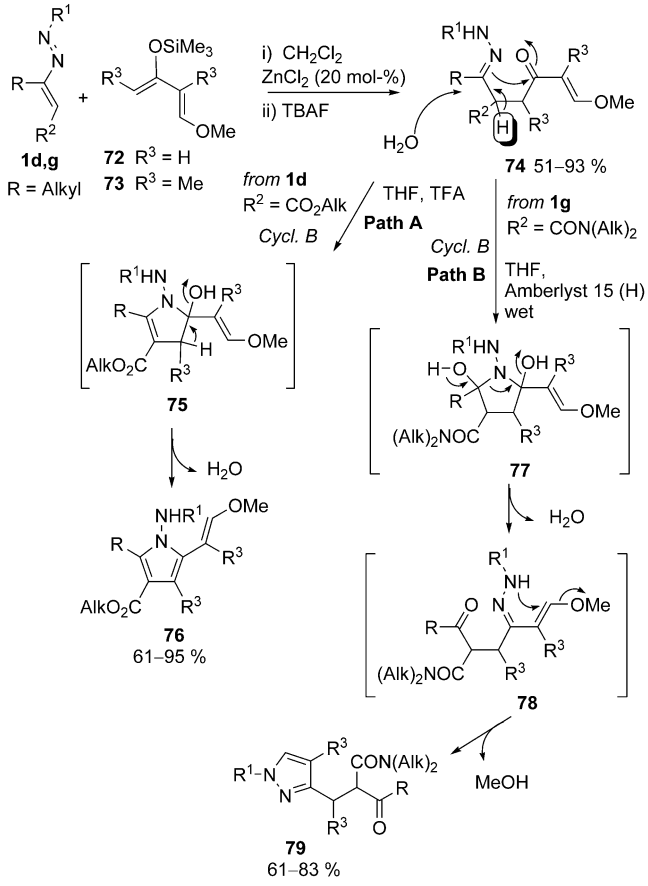
1,3-Bis(silyl enol ethers) **69** represent electroneutral equivalents of 1,3-dicarbonyl dianions,[29] and they generally react with electrophiles by means of their terminal carbon atom. Thus, their reaction with DD **1d** permitted the synthesis of 1-aminopyrroles **70** (Cycl. B), which are different from those obtained with β-dicarbonyl compounds **2**. In fact, the reactions between DD **1** and β-dicarbonyl compounds **2** proceeded by base-catalyzed nucleophilic attack of the activated methylene group at the heterodiene systems, leading to regioisomeric 1-aminopyrroles **71** (Cycl. B) (Scheme 15).[30]



Scheme 15. Regioselective reactions of DD **1d** with β-dicarbonyl compounds **2** or related 1,3-bis(silyl enol ethers) **69** for the construction of functionalized 1-aminopyrroles **70** or **71**, respectively.

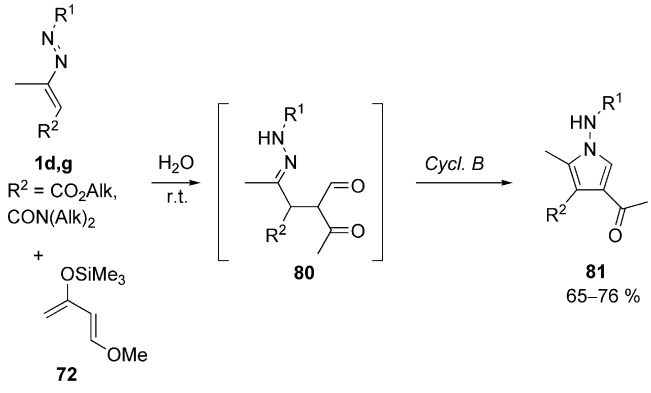
The Mukaiyama–Michael-type 1,4-addition/heterocyclization sequence has provided further proof of its synthetic utility and versatility in the extension of this approach to the reactions of Danishefsky's dienes **72** or **73** with DD **1d**,**g**.[31] The 1,4-addition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene **72** or 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-pentadiene **73** to DD **1** easily occurred in dichloromethane in the presence of zinc(II) chloride, affording the 1,4 adducts **74**. Interestingly, hydrazones **74**, bearing an ester group ($R^2 = CO_2Alk$) in the α-position to the C=N moiety, furnished the relevant 1-amino-2-(2-methoxyvinyl) pyrroles **76** by treatment with TFA (Cycl. B) (Scheme 16, Path A). In contrast, compounds **74**, containing the amido group [$R^2 = CON(Alk)_2$] instead of the ester ($R^2 = CO_2Alk$), did not give products **76**, but rather unexpected pyrazoles **79** by treatment with Amberlyst 15(H) wet in THF (Scheme 16, Path B). It is noteworthy that compounds **79** derive from a rearrangement of the DD skeleton. The formation of **79** can be ascribed to the nucleophilic attack of a water molecule at the hydrazone function of **74** followed by intramolecular cyclization of the hydrazone sp^2 nitrogen atom on the carbonyl group to give a cyclic aminohemiacetal intermediate **77**. By ring opening, **77** collapses into α,β-unsaturated hydrazones **78**, featuring an internal transfer of the hydrazone moiety. In turn, hydrazones **78** aromatize into pyrazoles **79** through an intramolecular Michael addition with loss of a methanol molecule (Cycl. B) (Scheme 16, Path B). However, the same adducts **74** furnish 1-amino-2-(2-methoxyvinyl)-pyrroles **76** by intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom (by phototropism CH/NH) at the carbonyl group, producing intermediates **75**, followed by loss of a water molecule (Scheme 16, Path A). The alternative mechanism of the heterocyclizations depends on a balance of the acidity of the proton in the α-position relative to that of the amide/ester moiety of hydrazone 1,4 adduct **74**.

When Danishefsky's diene **72** reacted with DD **1d**,**g** in water in the absence of Lewis acids, the hydrolysis of **72** produced 3-oxobutanal. Its subsequent 1,4-addition to the



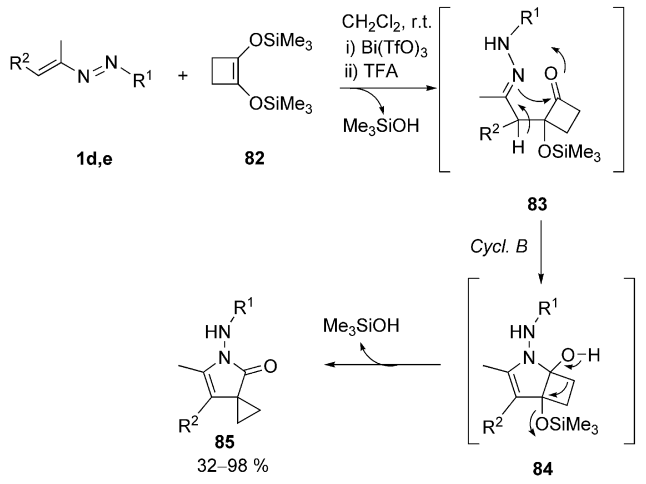
Scheme 16. Zinc(II) chloride catalyzed Mukaiyama–Michael-type addition/heterocyclization sequence of Danishefsky's dienes **72** or **73** with DD **1d**,**g** with formation of 1-amino-2-(2-methoxyvinyl)-pyrroles **76** or pyrazoles **79**, respectively.

azo-ene system of DD **1** furnished intermediates **80**. The following intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the aldehydic carbonyl group afforded new 1-aminopyrroles **81** (Cycl. B) (Scheme 17).[31]



Scheme 17. Water-mediated 1,4-addition/heterocyclization sequence of Danishefsky's diene **72** to DD **1d**,**g** with formation of 1-aminopyrroles **81**.

A further interesting extension of this approach is the reaction of DD **1d**,**e** with 1,2-bis[(trimethylsilyl)oxy]cyclobut-1-ene **82** that provided spiro-cyclopropanated 1-aminopyrrol-2-ones **85**. A plausible mechanism involves the Lewis acid-mediated 1,4-addition of compound **82** at DD **1** to give hydrazone intermediates **83**. Subsequently, intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the carbonyl group affords 5-trimethylsilyloxybicyclo[3.2.0]hept-3-en-1-ol intermediates **84** (Cycl. B). TFA cleavage of the silyl group and cyclobutane ring contraction (pinacol-like rearrangement) provides the final spiro-cyclopropanated 1-aminopyrrol-2-ones **85** (Scheme 18).[32]

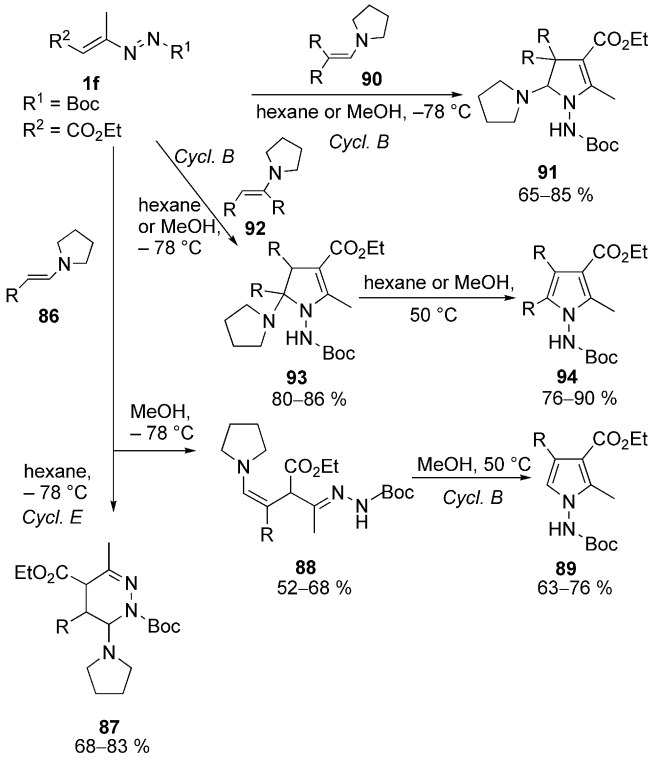


Scheme 18. Regioselective synthesis of functionalized spiro-cyclopropanated 1-aminopyrrol-2-ones **85** by a one-pot reaction of DD **1d**,**e** with 1,2-bis[(trimethylsilyl)oxy]cyclobut-1-ene **82**.

3.4. Enamines

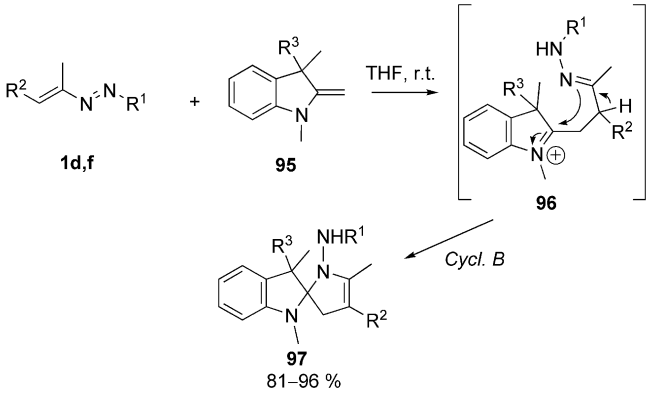
The reaction of DD with various enamines has been extensively studied by several authors.[33] Sommer et al. described the [3+2] and [4+2] cycloadditions of DD with cyclopentanone-derived enamines or 9-vinylcarbazole giving rise to octahydrocyclopenta[*b*]indole and 9-pyridazin-3-yl-9*H*-carbazole in low to moderate yields.[33a,33b] South et al. reported the synthesis and reactions of halo-DD with enol ethers and enamines as a new and general method for accessing substituted pyridazines.[33c–33e] Recently, we have extended these investigations to the solvent dependent divergent synthesis of various functionalized pyrroles or pyridazines starting from 1-*tert*-butyloxycarbonyl-3-methyl-4-ethoxycarbonyl-DD **1f** (R^1 = Boc, R^2 = CO_2Et) and β-substituted enamines **86**. In particular, the reactions between **1f** and **86** proceeded in hexane or in methanol through two different pathways, giving rise to 1,4,5,6-tetrahydropyridazines **87** (Cycl. E) or hydrazones **88**. By warming up the reaction in methanol to 50 °C, hydrazones **88** were converted into the corresponding pyrroles **89** (Cycl. B). On the contrary, the reactions of DD **1f** with β,β-**90**, or α,β-substituted enamines **92** are independent of the solvent polarity, affording dihydropyrroles **91** and **93** or pyrroles **94** (Cycl. B) both in apolar or polar solvents (Scheme 19).[34]

Also Fischer's bases **95** [3-alkyl- or 3-aryl-(1,3-dimethyl-2-methyleneindolines)][35] easily reacted with DD **1d**,**f** to produce the unknown indoline-spiropyrrolines **97** in high



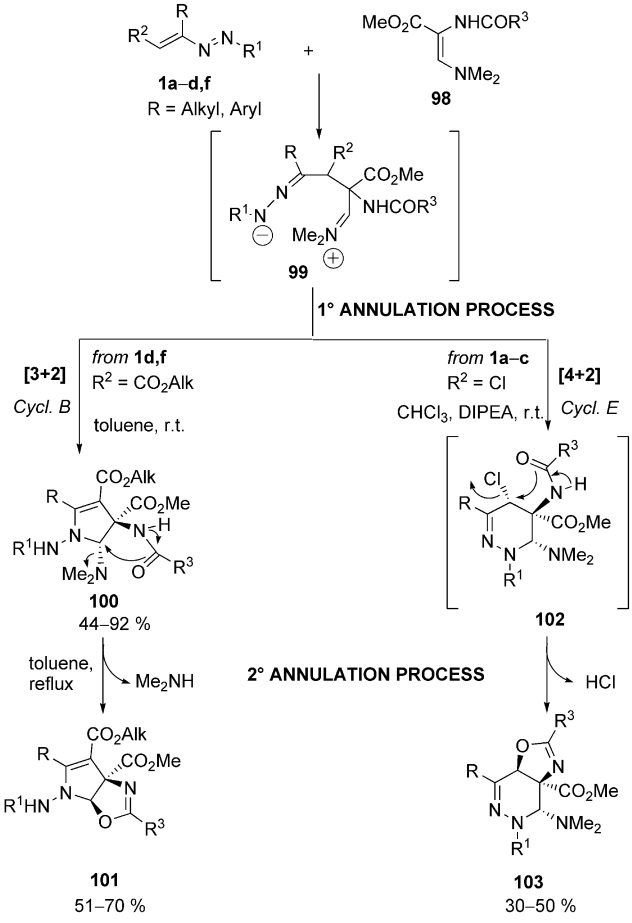
Scheme 19. Chemoselective formation of 1,4,5,6-tetrahydropyridazines **87**, pyrroles **89** and **94** and dihydropyrroles **91** and **93** by reaction of DD **1f** with enamines **86**, **90**, **92** with different solvents and at different temperatures.

yields. The mechanism passes through a preliminary nucleophilic attack of **95** to the azo-ene system of DD **1**, leading to intermediates **96** that undergo to subsequent formal [3+2] cycloaddition by intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the imino carbon atom (Cycl. B) (Scheme 20).[36]



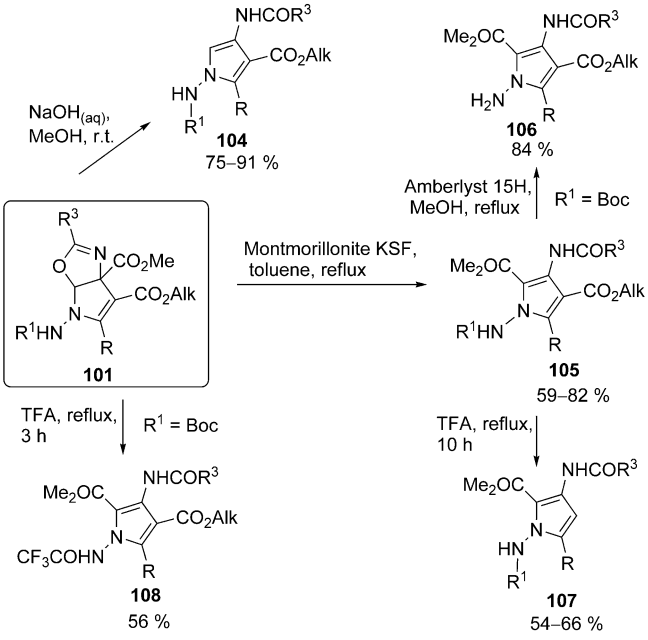
Scheme 20. Synthesis of unknown indoline-spiropyrrolines **97** by reaction of Fischer's bases **95** with DD **1d**,**f**.

3-Dimethylaminopropenoates **98** are interesting starting materials that show both electrophilic and nucleophilic aptitudes.[37] They acted as nucleophiles in the reaction with DD **1**, yielding unknown fused oxazolino-pyrroles **101** or new fused oxazolino-pyridazines **103** through a double cycloaddition sequence. The chemoselectivity of the first annulation process is driven by the substituent in the 4-position of the azo-ene system that influences the delicate balance of the acidity of the proton in the α-position to the hydrazone moiety of intermediates **99**. The synthesis of **101** required 4-alkoxycarbonyl-DD **1d**,**f** ($R^2 = CO_2Alk$) as starting materials. The construction of the pyrroline rings happened by means of a formal [3+2] cycloaddition (Cycl. B) with formation of intermediates **100** in which three atoms (C=C–N) of the initial azo-ene system were involved.[38] By using 4-chloro-DD **1a**–**c** (R^2 = Cl), the first annulation process took place with formal [4+2] cycloaddition (Cycl. E) in which all fours atoms (C–C=N–N) of the former azo-ene system of starting DD **1** were incorporated into the cycloaddition intermediates **102**.[39] The second annulation process, which led to the fused oxazolino rings of **101** and **103**, is common to both sequences and occurred by an intramolecular nucleophilic substitution of the dimethylamino group or chloride atom, respectively, promoted by the oxygen atom of the amido moiety (Scheme 21).[38,39]

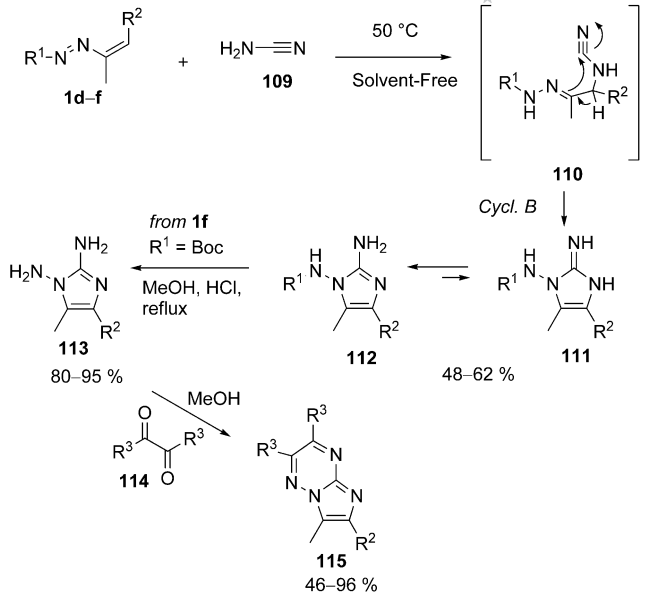


Scheme 21. Reactions of 4-alkoxycarbonyl-DD **1d**,**f** or 4-chloro-DD **1a**–**c** with 3-dimethylaminopropenoates **98** for the construction of different fused oxazolino heterocycles **101** or **103**.

The ring opening of fused oxazolino-pyrroles **101** in acidic or basic media provided highly substituted 1-amino-pyrroles **104**–**108** (Scheme 22).[38]



Scheme 22. Base- and acid-promoted ring opening process of fused oxazolino-pyrroles **101** providing functionalized 1-aminopyrroles **104**–**108**.



Scheme 23. Synthesis of imidazoles **112** and **113** by reaction of DD **1d**–**f** with cyanamide **109**. Synthesis of imidazo[1,2-*b*][1,2,4]triazines **115** by reaction of imidazoles **113** with α-dicarbonyl compounds **114**.

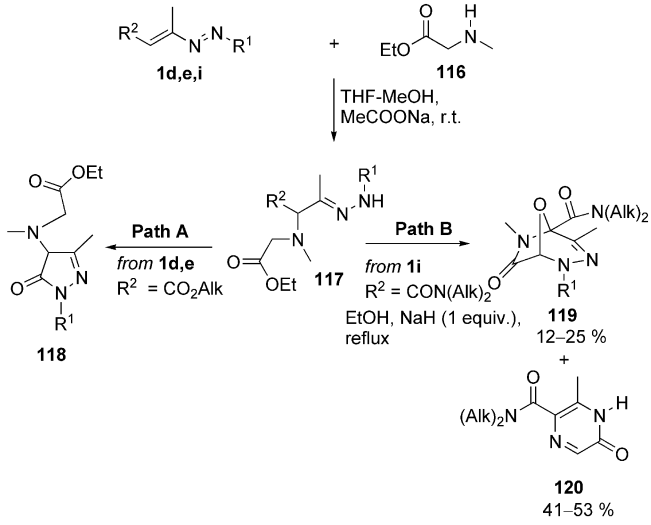
4. Nitrogen Nucleophiles

Various nitrogen-containing nucleophiles can easily add to the azo-ene system of DD to afford the respective α-aminohydrazones. These intermediates, sometimes isolable, are in turn useful starting materials for different types of five-, six-, or seven-membered rings containing more than one nitrogen atom.

4.1. Nucleophiles Containing One Nitrogen Atom

Cyanamide **109** instantaneously reacted with DD **1d**–**f** under solvent-free conditions at 50 °C to afford the preliminary α-aminohydrazone intermediates **110** and then 1-amino-2-imino-2,3-dihydro-1*H*-imidazoles **111** that tautomerize into the corresponding 1,2-diaminoimidazoles **112**. In this case, the formal [3+2] cycloaddition (Cycl. B) occurs by means of the intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the cyano function, giving the five-membered imino-imidazoline/imidazolo derivatives **111** and **112**. The hydrolytic cleavage of the Boc-substituted derivatives **112** produced the 1,2-diaminoimidazoles **113**, which gave rise to substituted imidazo[1,2-*b*][1,2,4]triazines **115** by reaction with α-dicarbonyl compounds **114** (Scheme 23).[40]

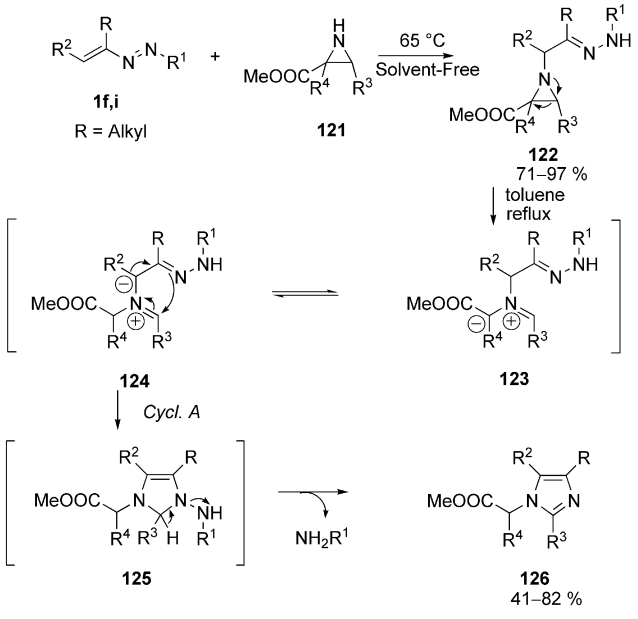
In previous works, we described the synthesis of pyrazol-5-ones **118** from 4-alkoxycarbonyl-DD **1d**,**e** ($R^2 = CO_2Alk$) and sarcosine ethyl ester **116** (Scheme 24, Path A).[41] After the formation of hydrazone intermediates **117**, the cyclization process took place by means of intramolecular nucleophilic attack of the hydrazone sp^3 nitrogen atom at the ester carbonyl group in the 4-position of the azo-ene system, with loss of an alcohol molecule (Cycl. C). More recently, we have also employed 4-amido-DD **1i** [$R^2 = CON(Alk)_2$] as starting materials in the reaction with the same sarcosine ethyl ester **116**. In this case, we isolated two different main products: novel 2,3,6-triazabicyclo[3.2.1]oct-3-enes **119** and 5-oxo-4,5-dihydro-2-pyrazines **120** (Scheme 24, Path B).[42]



Scheme 24. Synthesis of 2,3,6-triazabicyclo[3.2.1]oct-3-enes **119** and 5-oxo-4,5-dihydro-2-pyrazines **120** by reaction of 4-amido-DD **1i** and sarcosine ethyl ester **116**.

Recently, we have devoted our attention to aziridines, which represent a versatile class of building blocks for a wide range of synthetic applications.[43] Their chemistry is characterized by the high ring strain that results in the easy cleavage of the carbon–nitrogen bond by nucleophiles.

However, aziridines are also known to react by thermal or photochemical electrocyclic ring opening at the carbon–carbon bond to give azomethine ylides and represent useful precursors of such highly reactive species.[44] Methoxycarbonylaziridines **121** reacted with DD **1f**,**i** under solvent-free conditions at 65 °C, producing the corresponding α-aziridinohydrazones **122** in excellent yields. The treatment of adducts **122** in toluene under reflux resulted in the formation of imidazoles **126** in good yields. The construction of the imidazole ring can be rationalized by considering the thermolytic cleavage of the aziridine C–C bond of **122** that leads to azomethine ylides **123**, whose formation is favoured by the stabilizing effect of the adjacent electron-withdrawing methoxycarbonyl group. Ylides **123** tautomerize to azavinyl azomethine ylides **124**, which are also stabilized by the adjacent ester group. Subsequently, 1,5-electrocyclic ring closure (Cycl. A) results in the formation of 2,3-dihydroimidazoles **125**, which afford the final imidazoles **126**, by loss of amine. Usually, thermolytic C–C bond cleavage of aziridine to azomethine ylides has been utilized for the preparation of five-membered nitrogen-containing rings by either inter- or intramolecular [3+2] cycloadditions of 1,3-dipoles with dipolarophiles. In such reactions, all three atoms of the parent aziridine ring are incorporated in the final cycloaddition product. On the contrary, in the construction of imidazole ring **126**, the aziridine-derived azomethine ylides originating from **1** participate only with two atoms (C–N), while DD **1** provide the remaining three atoms (C–C–N). To the best of our knowledge, such a reactivity of aziridine-derived azomethine ylides is unprecedented and represents the first example of 1,5-electrocyclization of azavinyl azomethine ylides in which direct C–N bond formation occurs instead of the observed C–C bond formation (Scheme 25).[45]



Scheme 25. Postulated mechanism for the formation of imidazoles **126** by 1,5-electrocyclization of azavinyl azomethine ylides **124** obtained from DD **1f**,**i** and carboxyaziridines **121**.

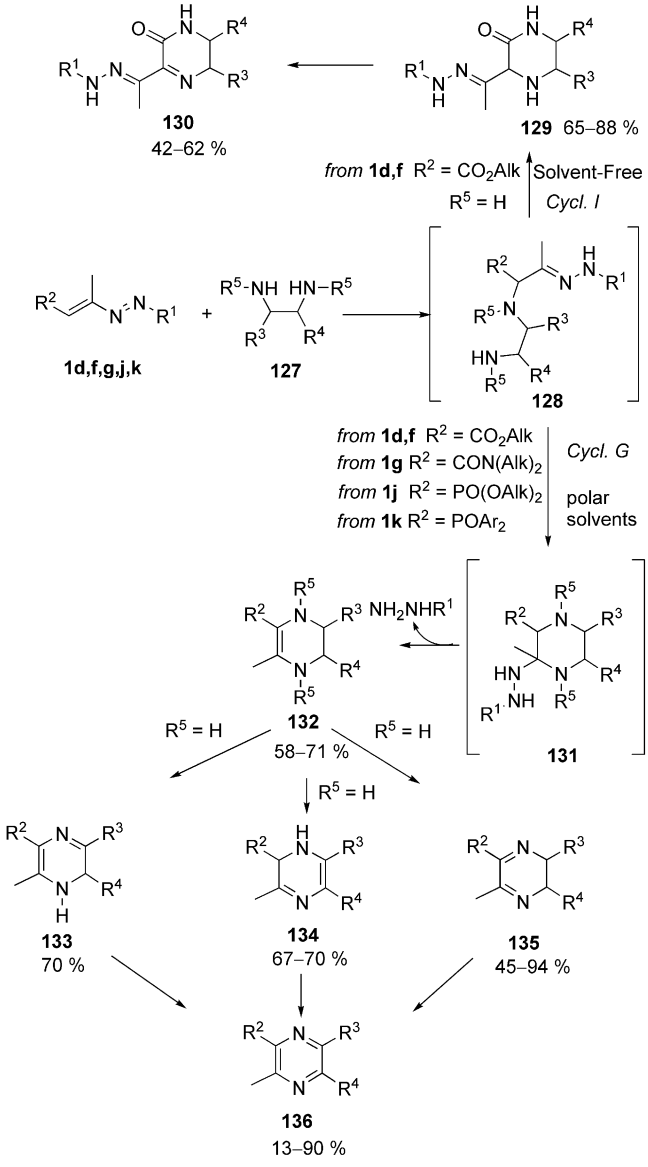
4.2. Nucleophiles Containing Two Nitrogen Atoms

Aliphatic and aromatic 1,2-diamines **127** and **137**, respectively, easily reacted with DD **1** both in the liquid and in the solid phase (Schemes 26, 27 and 28).[8,46] In particular, the reaction between DD **1** and the aliphatic 1,2-diamines **127** had different results in polar solvents or under solvent-free conditions. In fact, new substituted piperazinones **129** and **130** were obtained in satisfactory yields when the reaction was carried out under solvent-free conditions, while in polar solvents the same reagents gave rise to interesting tetrahydropyrazines **132**, dihydropyrazines **133**–**135** or pyrazines **136**. A plausible mechanism for both syntheses starts with nucleophilic attack by one amino group of **127**, leading to hydrazone intermediates **128**. Under solvent-free conditions, the ring closure proceeds by means of a regioselective intramolecular nucleophilic attack of the second amino group of the starting **127** at the ester function with loss of an alcohol molecule (Cycl. I) to afford piperazinones **129** and **130**. In polar solvents, the second amino group of the starting **127** attacks the hydrazone moiety (Cycl. G), producing intermediates **131** that gave rise to tetrahydropyrazines **132** by elimination of the hydrazine group. It is noteworthy that a careful choice of the reaction conditions, as well as of the starting 1,2-diamine derivatives, allows to selectively obtain tetrahydropyrazines **132**, dihydropyrazines **133**–**135**, or pyrazines **136** (Scheme 26).[8,46]

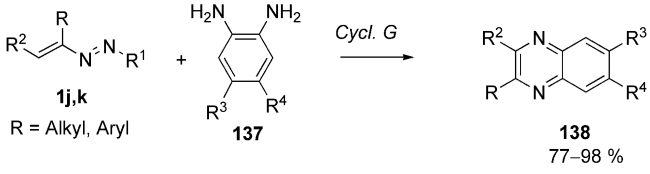
By using aromatic 1,2-diamines **137** as starting nucleophiles, the corresponding quinoxaline derivatives **138** were accessed by reaction with DD **1j**,**k**. Also in this case, the ring closure involves a regioselective attack of the amino group at the hydrazone function (Cycl. G) (Scheme 27) followed by hydrazine elimination.[46]

The mild and simple conditions required from these reactions in the liquid phase allowed the transfer of these methodologies also to the solid phase. The overall yields for the multistep process of the solid-phase reactions are comparable with the ones in solution (Scheme 28).[8,46b]

Arylamidines **139** act as 1,3-dinucleophile reagents. They easily reacted with two molecules of 4-alkoxycarbonyl-DD **1f** (R^2 = CO_2Alk), directly affording unknown spiro-pyrroloimidazole derivatives **143** through a domino reaction. The first nucleophilic attack of arylamidines **139** on DD **1f** gave hydrazone intermediates **140** that were transformed into 2-arylimidazolinone intermediates **141** by means of a further nucleophilic attack of the second nitrogen atom of **139** at the ester function in the 4-position of the azo-ene system with loss of an alcohol molecule (Cycl. H). The base-promoted carbanion formation led to nucleophilic 1,4-addition to another DD **1f** molecule, producing bis-adduct intermediates **142**. Under basic conditions, the two hydrazone side chains of **142** co-operate in the pyrrole ring closure, forming spiro-pyrroloimidazoles **143** (Scheme 29, Path A). Since the ester group in the 4-position of DD **1f** played a key role in the formation of **143**, its replacement with an amide residue (DD **1i**) determined a different regioselectivity, yielding new 2-arylimidazoles **145**. A plausible mechanism implicates the initial formation of hydrazone interme-

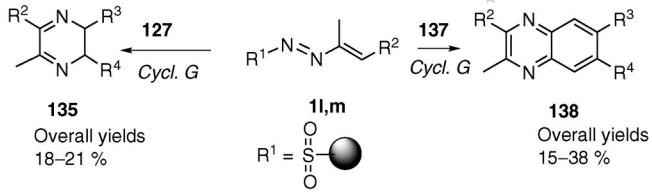


Scheme 26. Regioselective synthesis of piperazinones **129** and **130** or tetrahydropyrazines **132**, dihydropyrazines **133**–**135** and pyrazines **136** by reactions of DD **1d**,**f**,**g**,**j**,**k** with aliphatic 1,2-diamines **127**.

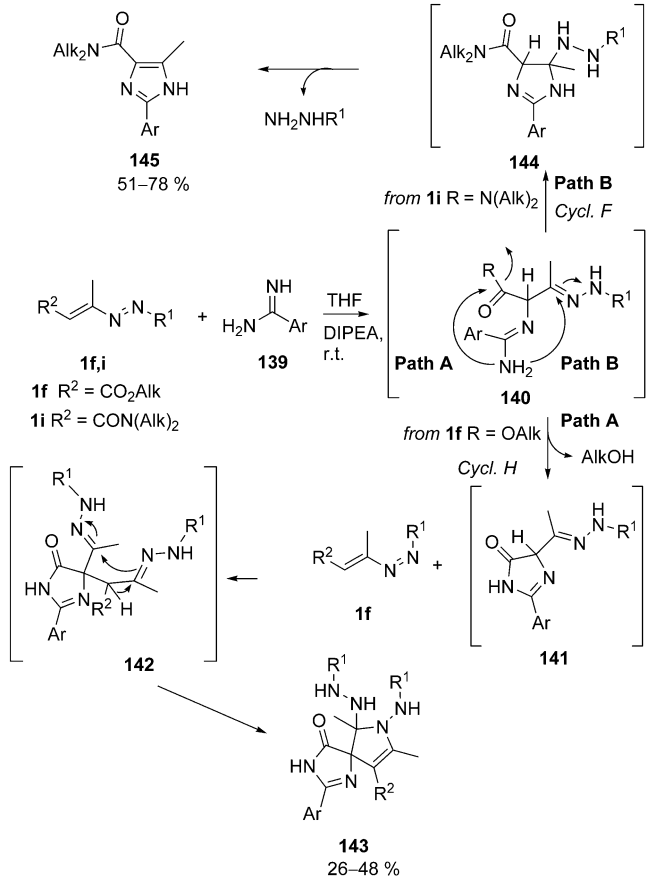


Scheme 27. Synthesis of functionalized quinoxalines **138** by reaction of DD **1j**,**k** with aromatic diamines **137**.

diates **140** that were converted into the final products **145** by means of intramolecular ring closure of the amino moiety at the hydrazone function, producing hydrazine-imidazole intermediates **144** (Cycl. F), followed by loss of the hydrazine residue (Scheme 29, Path B).[47]



Scheme 28. Solid-phase synthesis of dihydropyrazines **135** and functionalized quinoxalines **138**.

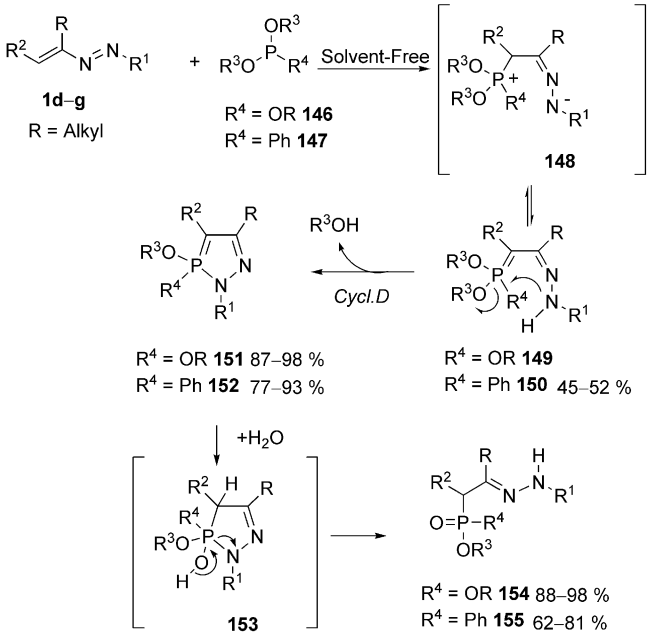


Scheme 29. Synthesis of spiro-pyrroloimidazole derivatives **143** or 2-arylimidazoles **145** from DD **1f** or DD **1i**, respectively, and arylamidines **139**.

5. Phosphorus Nucleophiles

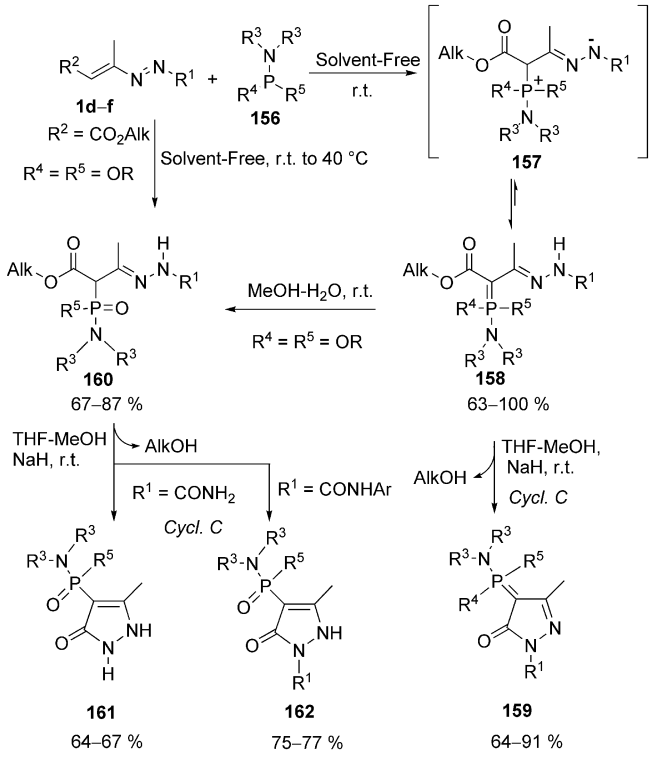
The phospha-Michael (P-Michael) addition, i.e. the addition of a phosphorus nucleophile to an appropriate acceptor, is probably one of the most versatile tools for the formation of the P–C bond.[48] This reaction is important, because it offers an entry to many diversely phosphorylated derivatives, some of which exhibit important biological activity.[49] In the past years, our group examined the reaction between DD and triphenyl-[50a] or trialkylphosphanes[50b] to obtain pyrazoles or 4-phosporanyliden-4,5-dihydropyrazol-5-ones. Recently, we have examined the behaviour of other trivalent phosphorus nucleophiles towards DD with particular attention to the electron-donating effects of different substituents bound to the phosphorus atom. Trialkyl phosphites **146** easily reacted with DD **1d**–**g** at room tempera-

ture under solvent-free conditions, producing the alkyl 3,3-dialkoxy-2*H*-1,2,3λ^5-diazaphospholes **151** in nearly quantitative yields.[51] To avoid their hydrolysis into the corresponding hydrazone-phosphonates **154**, the reactions were performed under a nitrogen atmosphere. The presence of a phenyl group bound to the phosphorus atom in the starting *P*-nucleophiles confers a particular stability to 3-phenyl-2*H*-1,2,3λ^5-diazaphospholes **152** obtained from dialkyl phenylphosphonites **147**, and their synthesis did not require any inert gases.[52] Frequently, 1,4-addition ylide products **150** directly precipitated from the reaction medium, permitting the elucidation of the mechanistic aspects. The initial P-Michael addition produces zwitterionic intermediates **148** that are in equilibrium with their ylide forms **149** or **150**, derived from the 1,4-shift of a proton. Only compounds **150** were isolated, probably because the phenyl group enhances their stability. 1,2,3-Diazaphospholes **151** and **152** were obtained by means of intramolecular nucleophilic attack of the hydrazone sp^3 nitrogen atom at the phosphorus atom (Cycl. D), with loss of an alcohol molecule. 1,2,3-Diazaphospholes easily reacted with water to give hydrazone-phosphonates **154** or **155** by ring opening of intermediates **153**. In the case of **151**, the hydrolysis occurred in the presence of atmospheric moisture, while **152** required a drop of water and tetrahydrofuran (Scheme 30).[51,52]



Scheme 30. Synthesis of the substituted 1,2,3-diazaphospholes **151** or **152** and hydrazone-phosphonates **154** or **155** by reaction of DD **1d**–**g** and trialkyl phosphites **146** or dialkyl phenylphosphonites **147**.

When at least one nitrogen atom was bound to phosphorus nucleophiles **156**, the spontaneous ring closure producing the 1,2,3-diazaphospholes did not occur, and zwitterionic 1,4 adduct intermediates **157** in tautomeric equilibrium with ylide derivatives **158** or (*E*)-hydrazone-phosphonates **160** were formed. These compounds can be easily converted into the corresponding 4-phosphoranyliden-4,5-dihydropyrazol-5-ones **159** or (3-oxo-2,3-dihydropyrazol-4-yl)phosphonamidates **161** and **162**, respectively, simply by treatment with sodium hydride in a mixture of tetrahydrofuran/methanol at room temperature. The ring closure to the pyrazolone is ascribable to an intramolecular nucleophilic attack of the base-activated hydrazone sp^3 nitrogen atom at the ester group with loss of an alcohol molecule (Cycl. C) (Scheme 31).[53]

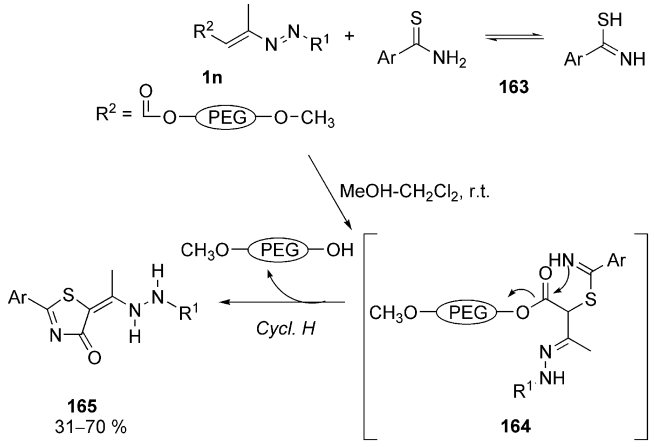


Scheme 31. Synthesis of 4-phosphoranyliden-4,5-dihydropyrazol-5-ones **159** or (3-oxo-2,3-dihydropyrazol-4-yl)phosphonamidates **161** and **162** by reaction between DD **1d**–**f** and aminophosphorus nucleophiles **156**.

6. Sulfur Nucleophiles

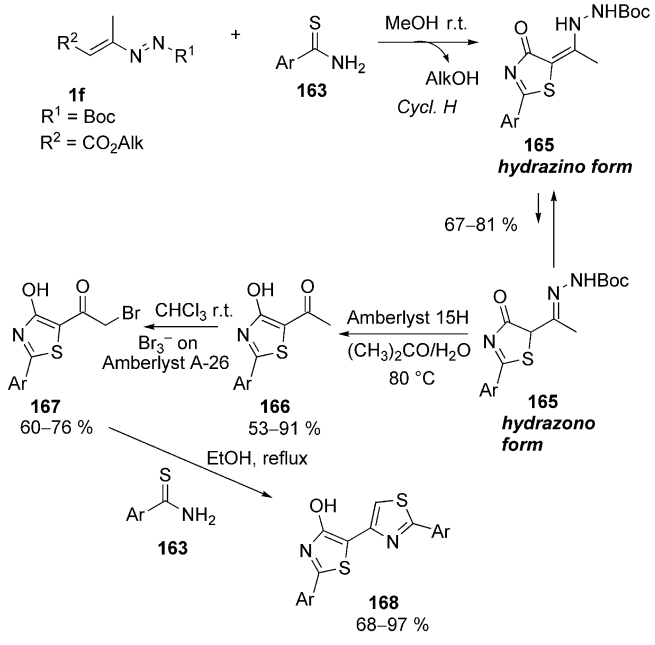
Some years ago, we published the synthesis of the 2-thiazolin-4-ones **165** in the liquid phase by reaction of DD **1d**–**f** with aryl thioamides **163**.[54] The same reaction was studied in a polymer-supported liquid-phase synthesis starting from poly(ethylene glycol)-DD **1n** (PEG-DD). The mechanism implicates the first *S*-nucleophilic attack of the thiolimino form of compounds **163** on the carbon atom in the 4-position of the azo-ene system of PEG-DD **1n**. The subsequent intramolecular *N*-nucleophilic attack at the ester group of hydrazone intermediates **164** with loss of PEG-OH led to thiazolinone ring closure (Cycl. H). The final 2-thiazolin-4-ones **165** were released into the reaction medium, from which they directly precipitated as pure products (Scheme 32).[5]

The reaction between 1-*tert*-butoxycarbonyl-DD **1f** (R^1 = Boc) and aryl thioamides **163** afforded Boc-hydrazone protected 2-thiazolin-4-ones **165** in hydrazine–hydrazone



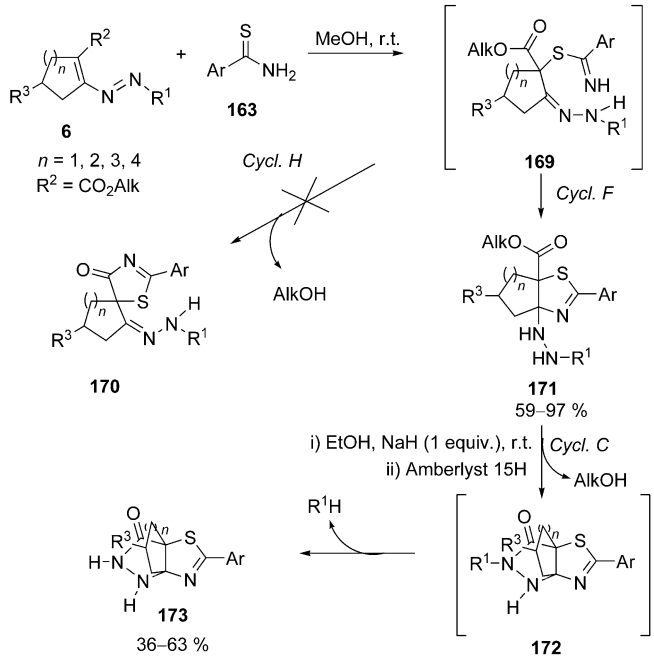
Scheme 32. Polymer-bound liquid-phase synthesis of 2-thiazolin-4-ones **165** by reaction of PEG-DD **1n** with aryl thioamides **163**.

tautomeric equilibrium. The subsequent hydrolytic cleavage of the Boc-hydrazone protecting group with Amberlyst 15H provided the relevant 5-acetyl-4-hydroxythiazoles **166**. The conversion of compounds **166** into α-bromo ketone derivatives **167** was achieved by treatment with polymer-supported tribromide. This route is particularly attractive in view of the large number of unknown 4,5′-bithiazol-4′-ol derivatives **168**, which can be obtained according to the Hantzsch protocol (Scheme 33).[55]



Scheme 33. Synthetic strategy for the preparation of unknown 4,5′-bithiazol-4′-ol derivatives **168** from 1-*tert*-butoxycarbonyl-DD **1f** and aryl thioamides **163**.

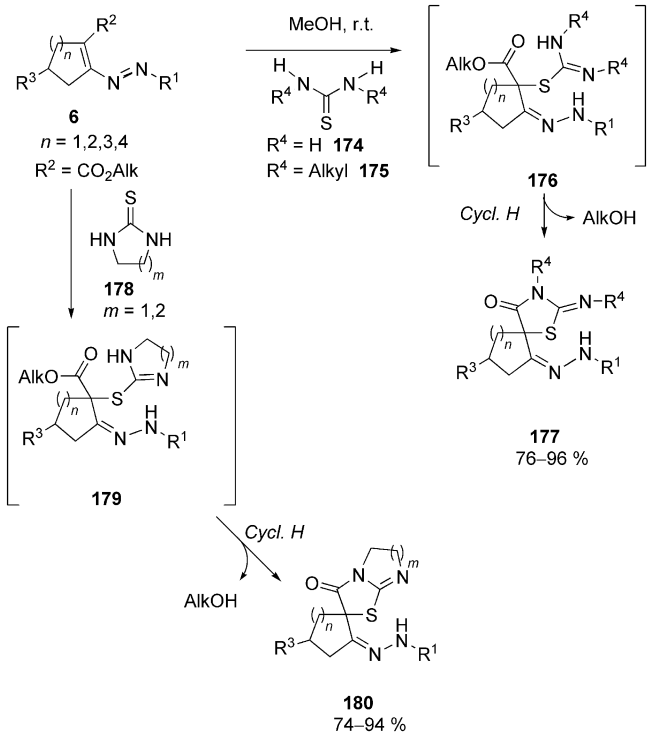
The reaction of the same aryl thioamide derivatives **163** with cyclic DD **6** furnished hydrazone intermediates **169** that, under the same experimental conditions described for the preparation of **165**, did not form spirocycloalkyl-thiazolinones **170** by means of internal *N*-nucleophilic attack at the ester group (Cycl. H). In fact, nucleophilic attack of the imino nitrogen atom occurred exclusively at the hydrazone function, yielding cycloalkyl[*d*][1,3]thiazoline derivatives **171** (Cycl. F). The presence in **171** of both ester and semicarbazide groups makes them able to furnish fused cycloalkyl-thiazoline-pyrazoles **173** by means of base-promoted intramolecular nucleophilic attack of the hydrazine nitrogen atom at the ester function with loss of the hydrazine substituent R^1 of intermediates **172** (Cycl. C) (Scheme 34).[4,56]



Scheme 34. Synthesis of the cycloalkyl[*d*][1,3]thiazolines **171** and fused cycloalkyl-thiazoline-pyrazoles **173** by reaction between cyclic DD **6** and aryl thioamide derivatives **163**.

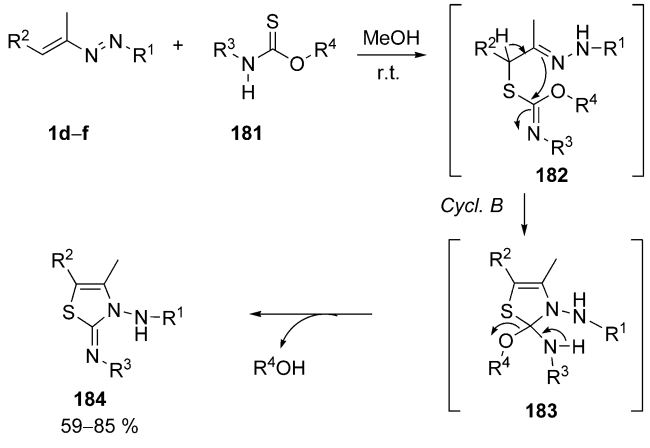
The reaction of the thiourea **174** or *N*,*N*′-dialkylthioureas **175** and imidazolidine-2-thione (m = 1) or tetrahydropyrimidine-2-thione (m = 2) **178** with the same cyclic DD **6** furnished the corresponding spirocycloalkyl-2-iminothiazolidin-4-ones **177** and **180**, respectively. It is noteworthy that compounds **180** represent the spiro-tricyclic counterpart of the relevant spiro-bicyclic **177**. After the preliminary *S*-nucleophilic attack at the carbon atom in the 4-position of the azo-ene system to give the 1,4 adduct intermediates **176** and **179**, the regioselective formation of the thiazolinone core involves an intramolecular nucleophilic attack of the nitrogen atom of the thioureas at the ester function with consequent loss of an alcohol molecule (Cycl. H). In this case, no difference was observed in the regioselectivity of the reactions of thiourea or *N*,*N*′-dialkyl thioureas with cyclic DD **6** or with DD **1** (Scheme 35).[4]

The reaction between DD **1d**–**f** and *O*-alkyl thiocarbamates **181** furnished 2-alkyliminothiazolines **184**. *S*-nucleophilic 1,4-addition of **181** to DD **1** provides intermediates **182**, and subsequent intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the iminoether function affords thiazolines **183** (Cycl. B) that, in turn, were converted into the final 2-alkyliminothiazolines **184** by loss of



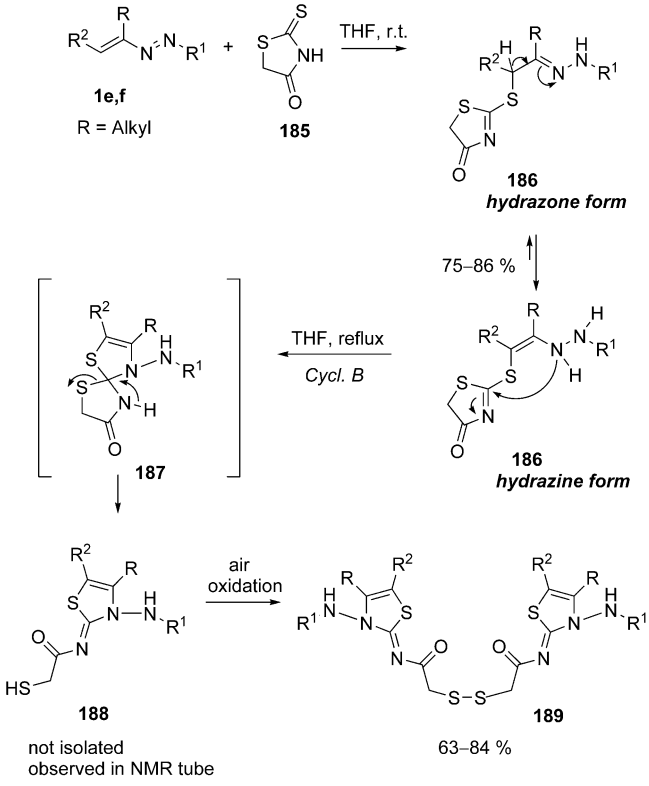
Scheme 35. Synthesis of spirocycloalkyl-2-iminothiazolidin-4-ones **177** and **180** by reaction of cyclic DD **6** with thiourea **174**, *N*,*N*′-dialkylthioureas **175**, imidazolidine-2-thione (m = 1) or tetrahydropyrimidine-2-thione (m = 2) **178**.

an alcohol molecule.[57] In this reaction, DD **1** contribute to the construction of the thiazole skeleton with three atoms (C–C–N), while *O*-alkyl thiocarbamates **181** participate with the remaining two atoms (C–S) (Scheme 36). In the previous syntheses, on the contrary, nucleophiles **163**, **174**, **175** and **178** furnished three atoms (S–C–N) and DD **1** the remaining two C–C atoms (Scheme 32, Scheme 33, Scheme 34, and Scheme 35).



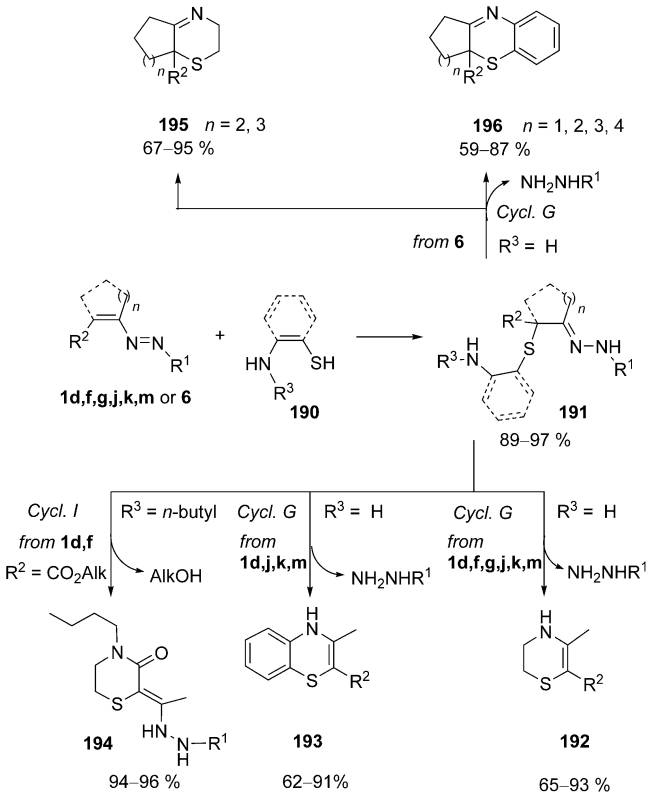
Scheme 36. Synthesis of 2-alkyliminothiazolines **184** by reaction of DD **1d**–**f** with *O*-alkyl thiocarbamates **181**.

The reaction between DD **1e**,**f** and rhodanine **185** gave rise to 2-iminothiazoline disulfide derivatives **189**. A probable sequence of steps starts with the *S*-nucleophilic attack of **185** at the azo-ene system of DD **1**, forming compounds **186** in hydrazine–hydrazone tautomeric equilibrium. Intramolecular nucleophilic attack of the nitrogen atom at the thioimido moiety leads to spirocyclic intermediates **187** (Cycl. B), which undergo ring-opening by imino function formation and C–S bond cleavage to afford 2-iminothiazolines **188** that are oxidized in air to the final products **189** (Scheme 37).[58]



Scheme 37. 1,4-Addition/annulation/ring-opening/air-oxidation sequence for the synthesis of 2-iminothiazoline disulfide derivatives **189** starting from DD **1e**,**f** and rhodanine **185**.

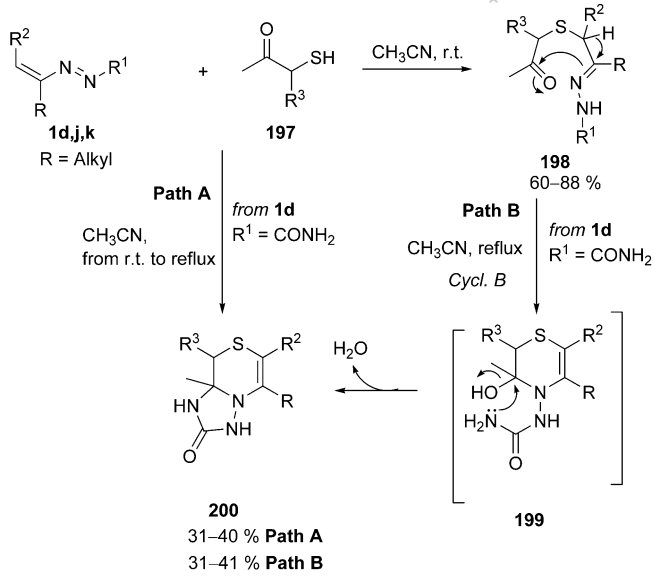
Aliphatic and aromatic 1-mercapto-2-amines **190** easily reacted with DD **1d**,**f**,**g**,**j**,**k**,**m** and cyclic DD **6**, both in the liquid and the solid phase, yielding 1,4-thiazines **192** or **195**, 1,4-benzothiazines **193** or **196** and 1,4-thiazin-3-ones **194**. The formation of these six-membered heterocycles results from a formal [4+2] cycloaddition where four atoms of the nucleophile (S–C–C–N) and two atoms of the DD (C–C) are involved. The first step is the *S*-nucleophilic 1,4-addition of **190** to the azo-ene system of DD **1** or **6**, producing intermediates **191**, followed by intramolecular *N*-nucleophilic attack that produces the 1,4-thiazine ring. We have observed that primary amines (aliphatic or aromatic) attack the hydrazone moiety of 1,4 adduct intermediates **191** to produce thiazines **192**, **193**, **195**, **196** by loss of the hydrazine residue (Cycl. G). The more hindered amine (R^3 = *n*-butyl) attacks the ester function of the 1,4 adduct intermediates **191**, affording 1,4-thiazin-3-ones **194** by loss of an alcohol molecule (Cycl. I) (Scheme 38).[59]



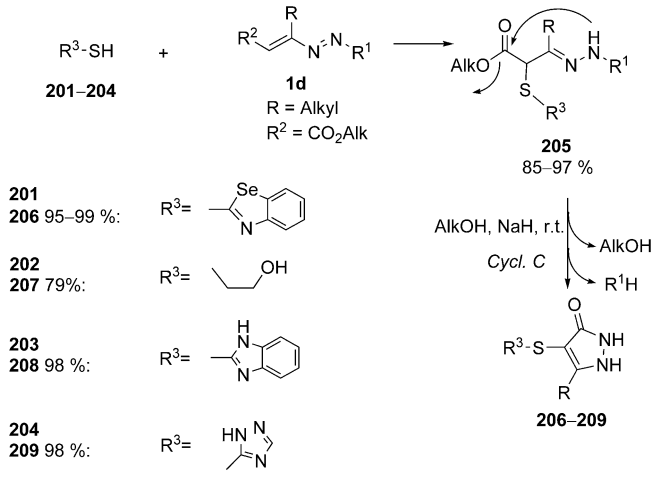
Scheme 38. Reaction of DD **1d**,**f**,**g**,**j**,**k**,**m** or cyclic DD **6** with mercapto 2-amino derivatives **190** to yield 1,4-thiazines **192** or **195**, 1,4-benzothiazines **193** or **196** and 1,4-thiazin-3-ones **194**.

The domino reaction of DD **1d**,**j**,**k** with α-mercaptoketones **197** furnished α-sulfur 1,4 adducts **198** that, in turn, can be converted into the corresponding new 2-oxo-[1,2,4]triazolo[5,1-*c*][1,4]thiazines **200**. The first cyclization occurs by intramolecular nucleophilic attack of the hydrazone sp^2 nitrogen atom at the ketone moiety of **198** (Cycl. B) through the formation of non-isolable 4-[(aminocarbonyl)amino]-3-hydroxy-3,4-dihydro-2*H*-1,4-thiazine-6-carboxylate intermediates **199**. It is noteworthy that the nitrogen atom involved in the formation of the thiazine ring is derived from DD **1**, while in our previous communication[59] and many classical syntheses the nitrogen atom is furnished by the aminothiol derivative.[60] The subsequent intramolecular nucleophilic substitution of the hydroxy group by the ureido nitrogen atom produces compounds **200** through a further ring closure (Scheme 39).[61]

2-Mercaptobenzselenazole **201**, *SH*-containing 1,3-dinucleophiles such as 2-mercaptoethanol **202**, *SH*-containing 1,2-dinucleophiles like 2-mercaptobenzimidazole **203** or 1*H*-1,2,3-triazole-3-thiol **204** reacted with 4-alkoxycarbonyl-DD **1d** (R^2 = CO_2Alk) to furnish the related 1,4 adducts **205**. Compounds **205** can be converted into the corresponding 4-substituted pyrazol-3-ones **206**–**209** by means of base-promoted intramolecular nucleophilic attack of the hydrazone sp^3 nitrogen atom at the ester function by loss of an alcohol molecule (Cycl. C) (Scheme 40).[59,62]



Scheme 39. Domino reaction of DD **1d**,**j**,**k** with α-mercaptoketones **197** to provide the new 2-oxo-[1,2,4]triazolo[5,1-*c*][1,4]thiazines **200**.

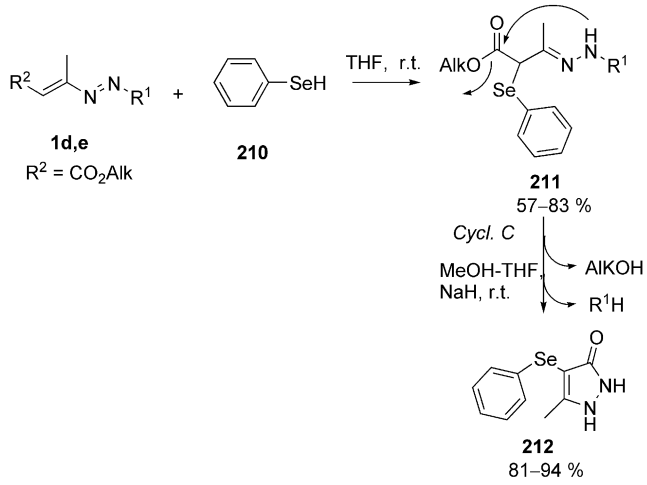


Scheme 40. Synthesis of 4-substituted pyrazol-3-ones **206**–**209** by reactions between DD **1d** and 2-mercaptobenzselenazole **201**, 2-mercaptoethanol **202**, 2-mercaptobenzimidazole **203** or 1*H*-1,2,3-triazole-3-thiol **204**.

7. Selenium Nucleophiles

Considering the growing interest in the biochemical and pharmacological properties of organoselenium compounds and their potential use as therapeutic and chemopreventive agents,[63] we have designed a procedure to prepare Se-substituted pyrazol-3-ones.

The reaction between 4-alkoxycarbonyl-DD **1d**,**e** (R^2 = CO_2Alk) and phenylselenol **210** in tetrahydrofuran at room temperature furnished α-(phenylseleno)hydrazones **211** that, in turn, can be converted into the corresponding 4-(phenylseleno)pyrazol-3-ones **212** (Cycl. C) by addition to the mixture of a stoichiometric amount of sodium hydride (Scheme 41).[62]



Scheme 41. Reaction of DD **1d**,**e** with phenylselenol **210** to obtain α-(phenylseleno)hydrazones **211** that can be converted into the corresponding 4-(phenylseleno)pyrazol-3-ones **212**.

8. Conclusions

The results reported in this microreview demonstrate once again the versatility of DD as powerful Michael acceptors and highlight the utility of these compounds as building blocks in heterocyclic chemistry. DD allow various functionalizations of the carbon atom adjacent to the masked carbonyl moiety that permit the construction of many types of five-, six- and seven-membered heterocycles. Although most of the described reactions formally proceed through a number of chemical steps, in practice they can frequently be executed in one pot, requiring very simple work-up procedures and frequently affording the product in good yields.

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