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Recent advances and applications in 1,2,4,5-tetrazine chemistry

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Contents

Abbreviations: Ac, acetyl; Ar, aryl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; Bz, benzoyl; CBz, benzylcarboxy; DABCO, 1,4-diazabicyclo[2.2.2]-octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMA, *N*,*N*-dimethylacetamide; DMAP, 4-(dimethyl-amino)-pyridine; DMSO, dimethyl sulfoxide; DMPY, 3,5-dimethylpyrazol-1-yl; DOPA, 3,4-dihydroxyphenylalanine; DSC, differential scanning calorimetry; EDG, electron-deficient group; EGA, evolved gas analysis; EWG, electron-withdrawing group; LG, leaving group; LHMDS, lithium hexamethyl-disilazide; LUMO, lowest unoccupied molecular orbital; nAChR, nicotinic acetylcholine receptor; NBS, *N*-bromosuccinimide; NΔH_f, normalised heat of formation; *m*-CPBA, *meta*-chloroperbenzoic acid; MOM, methoxymethyl; Ra-Ni, Raney-nickel; Red-Al, sodium bis(2-methoxyethoxy)aluminium hydride; PIFA, bis[(trifluoroacetoxy)iodo]benzene; *p*-TosOH, *para*-toluenesulfonic acid; SEM, (trimethylsilyl)ethoxymethyl; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TGA, thermogravimetric analysis; TG-FTIR, thermogravimetric analyzer-Fourier-transform infrared spectrometer; TIPS, triisopropysilyl; TMS, trimethylsilyl; TPP, *meso*-tetraphenylporphyrin.

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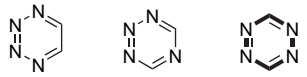
1. Introduction



1 2 3

There are three possible tetrazine isomers. To date, the chemistry of 1,2,3,4-tetrazine (**1**) has been reviewed,[1–4] but there have been no surveys concerning 1,2,3,5-tetrazine (**2**) derivatives, which are the least-known class of tetrazine isomers. Several excellent reviews of the 1,2,4,5-tetrazine (**3**) literature have, however, been published in various journals[5–11] and in the first and latest editions of *Comprehensive Heterocyclic Chemistry*.[2,12] Furthermore, reviews on annelated [1,2,3,4]tetrazines and the coordination chemistry of 1,2,4,5-tetrazines have been published by Shawali and Elsheikh[13] and by Kaim,[14] respectively. The present review focuses on the chemistry of 1,2,4,5-tetrazine and its derivatives in the last 10 years from 1996 up to the first half of 2006, because these compounds are still of synthetic and theoretical interest to organic chemists, due to their high reactivity as dienes in cycloaddition reactions.

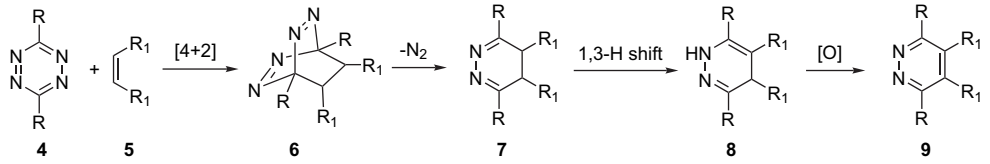
1,2,4,5-Tetrazines are mostly able to take part in $LUMO_{diene}$-controlled [4+2] *inverse*-Diels–Alder cycloaddition processes, which efficiently lead to the construction of substituted dihydropyridazine and pyridazine systems. This process is known as the Carboni–Lindsey reaction.[15] Tetrazines **4** react with dienophiles **5** to give the bicyclic adducts **6**. The pronounced localisation of the N=N bond in the highly strained adduct **6** favours extrusion of molecular nitrogen. The termination step of the reaction oxidises dihydropyridazines **8** to pyridazines **9**, followed by a 1,3-hydrogen shift from **7** (Scheme 1). Pyridazines can be prepared by direct cycloaddition of an alkyne as dienophile with 1,2,4,5-tetrazines.

2. Synthesis of new 1,2,4,5-tetrazine derivatives and their applications

2.1. High-nitrogen materials

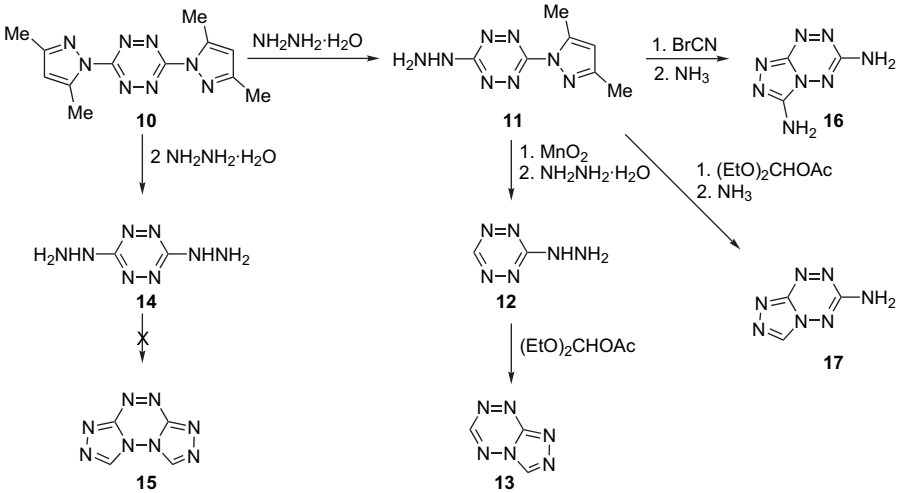
Organic compounds with a high-nitrogen content currently attract significant attention from many researchers, due to their novel energetic properties.[1,16–24] 3-Hydrazino-1,2,4,5-tetrazine (**12**) was synthesised by Chavez and Hiskey.[25] The synthesis of **12** was realised in three steps starting from the readily available 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**10**). The reaction of **12** with diethoxymethyl acetate gave the triazolo[4,3-*b*][1,2,4,5]tetrazine bi-heterocyclic ring system **13**. Furthermore, Chavez and Hiskey reported similar reactions of 3-(3,5-dimethylpyrazol-1-yl)-6-hydrazine-1,2,4,5-tetrazine (**11**) to give 3,6-disubstituted derivatives of the triazolo[4,3-*b*][1,2,4,5]tetrazine ring system (Scheme 2).[25] The synthesis of the tetrazine **14** and the bistriazolo compound **15** was not achieved.

The thermal decomposition of nitrogen-rich tetrazole and tetrazine structures was investigated by Löbbecke and coworkers.[26] The thermal decomposition behaviour of the samples was characterised by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and evolved



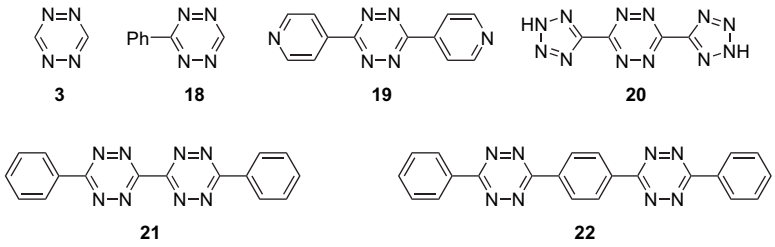
4 5 6 7 8 9

Scheme 1.



10 11 16 14 12 17 15 13

Scheme 2.



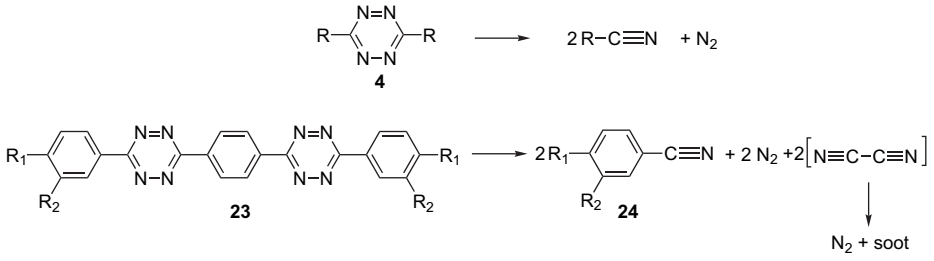
Scheme 3.

gas analysis (EGA). The structures of some of the tetrazines **3**, **19**–**22** used are given in Scheme 3.

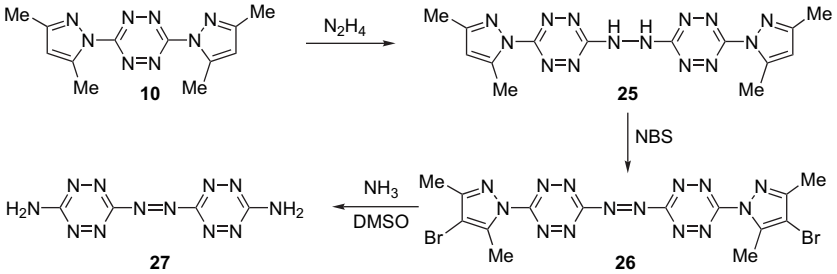
The thermal decomposition of the tetrazine derivatives resulted in opening of the heterocyclic ring to give the nitriles and N_2, and dicyanogen transforms into N_2 and soot, as shown in Scheme 4. The formation of nitriles was identified by gas chromatography and EGA. The most interesting thermal behaviour was exhibited by the tetrazolyl-substituted tetrazine **20**. The molar decomposition enthalpy measured for **20** is remarkably high and resembles that of a high explosive.

3,3-Azobis(6-amino-1,2,4,5-tetrazine) (**27**), a novel high-nitrogen energetic material, was prepared by Hiskey and co-workers (Scheme 5).[27] The hydrazo compound **25** was obtained by treatment of the readily available **10** with 0.5 equiv of hydrazine. Oxidation of **25** to give **26** was achieved with *N*-bromosuccinimide (NBS), which is used as both an oxidant and a brominating agent. When **26** was reacted with ammonia in dimethyl sulfoxide (DMSO), a red-brown precipitate, which is the bis-DMSO solvate of **27**, was isolated. The structure of the bis-DMSO solvate of **27**, confirmed by X-ray crystal structure analysis, provides the first evidence for the synthesis of an azo-1,2,4,5-tetrazine. Treatment of the DMSO solvate with boiling water gives pure **27**, which was found to be thermally stable up to 252 °C, and the heat of formation was determined to be +862 kJ mol^{-1} by combustion calorimetry. The synthesis, characterisation, structural analysis and thermal analysis of **27** were also investigated by Kerth and Löbbecke and by Hiskey and group.[18,28] They showed that the azobis-(amino-tetrazine) **27** is a new high-nitrogen material with remarkable thermal stability and insensitivity against friction and impact and which decomposes at relatively high temperatures (>250 °C), releasing one of the highest heats of decomposition ever measured by DSC. The decomposition pathway and thermal analysis of the products were, however, described. Talawar's group suggested that TG-FTIR studies indicate the presence of NH_2CN/NH_3 and HCN as major decomposition products during the thermal studies of **27**.[29]

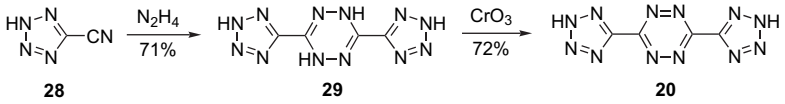
Although 3,6-bis(2*H*-tetrazol-5-yl)-1,2,4,5-tetrazine (**20**) was first synthesised by Curtius et al.,[30a] the reactions of **20** have not yet been reported.[30b] Tetrazolyl-tetrazine **20** was synthesised via the Curtius protocol by Sauer et al., as shown in Scheme 6, and these workers showed that **20** is a versatile bifunctional building block for the synthesis of linear oligoheterocyles with redox-active heterocycles.[30b]



Scheme 4.



Scheme 5.



Scheme 6.

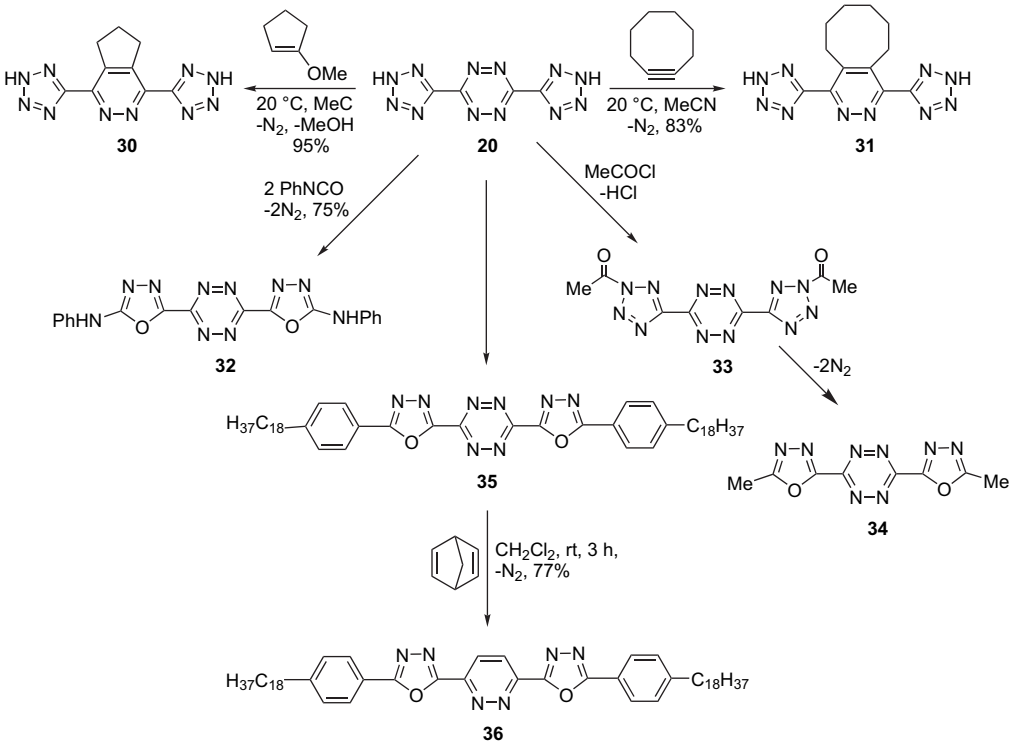
In spite of the high-energy content of **20**, Sauer et al. stated that the tetrazine derivative **20** can be used as a highly reactive diene in *inverse*-Diels–Alder reactions, as long as the necessary safety rules are obeyed. The pyridazine derivatives **30** and **31** were isolated in high yield from the reaction of **20** with 1-methoxycyclopentene and cyclooctyne (Scheme 7). When **20** was reacted with phenyl isocyanate as the acylating agent, the bis(oxadiazine)-tetrazine **32** was isolated in 75% yield. Unfortunately, their attempts to perform the synthesis of the analogues with phenyl isothiocyanate or dicyclohexyl carbodiimide were unsuccessful. The tetrazine **20** was reacted with 2 equiv of an aliphatic, aromatic or heteroaromatic acyl chloride to form the 5-substituted 3,6-bis(1,3,4-oxadiazol-2-yl)-1,2,4,5-tetrazines **32**–**34** (Scheme 7). The cycloaddition reaction of the bis(oxadiazol-2-yl)-1,2,4,5-tetrazine **35** with norborna-2,5-diene as an angle-strained dienophile could also be achieved.

3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**10**) has frequently been used to synthesise novel high-nitrogen materials, as shown in Scheme 8.[31–34] The normalised heat of formation ($N\Delta H_f$) for the 3,6-diazido-1,2,4,5-tetrazine (**40**), experimentally determined using an additive method, was shown to be the highest positive $N\Delta H_f$, compared to other organic molecules. Furthermore, unexpected azido-tetrazole tautomerisations and irreversible tetrazole transformations for **40** are described by Nuynh et al.[35]

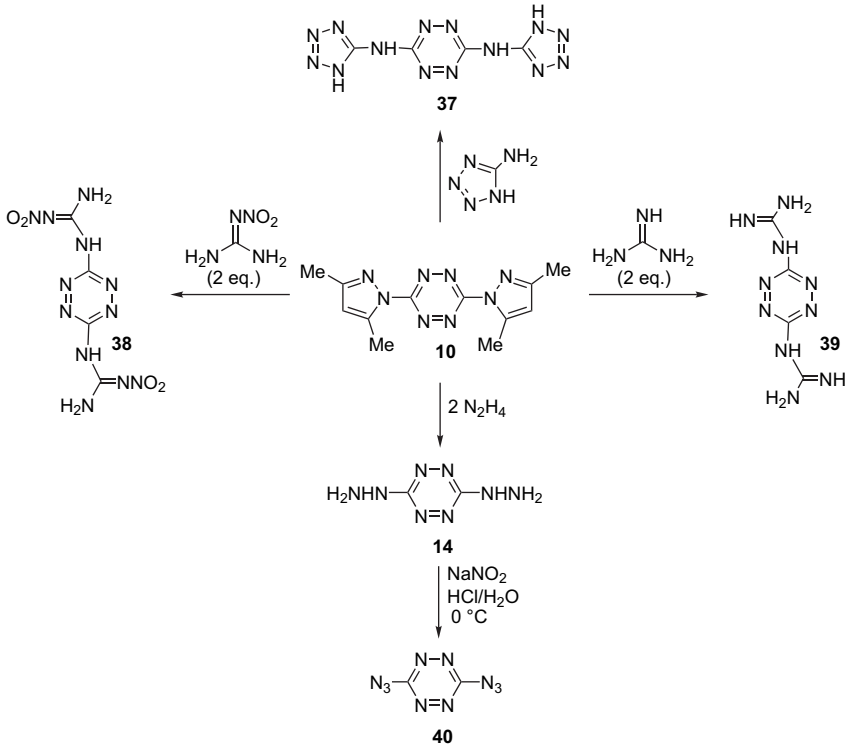
2.2. Unsymmetrical substituted 1,2,4,5-tetrazines

The unsymmetrical disubstituted 1,2,4,5-tetrazines have been studied less extensively, because they are synthetically less accessible. 3,6-Bis(methylthio)-1,2,4,5-tetrazine (**41**) has been the most widely utilised to synthesise unsymmetrical 1,2,3,4-tetrazines.[36–38] The selective preparation of 3-methoxy-6-methylthio-1,2,4,5-tetrazine (**42**) and 3,6-dimethoxy-1,2,4,5-tetrazine (**43**) was reported by Sakya and co-workers (Scheme 9).[39] The preparation of **42** and **43** was accomplished by reacting **41** with a catalytic quantity of sodium methoxide in methanol. The minor amount of the dihydrotetrazine **44** formed was deoxidised to **42** upon treatment with ferric chloride. The unsymmetrical tetrazine **42** underwent a Diels–Alder reaction in a predictable manner with electron-rich (enamines, silyl enol ethers) and neutral dienophiles as well as conjugated and unconjugated alkynes with the resulting regioselective formation of the products **45** and **46** (Table 1).

Five new unsymmetrical 1,2,4,5-tetrazines, namely 6-[(*tert*-butyloxycarbonyl)-amino]-3-(methylthio)-1,2,4,5-tetrazine (**47**), 6-(acetylamino)-3-(methylthio)-1,2,4,5-tetrazine (**48**),

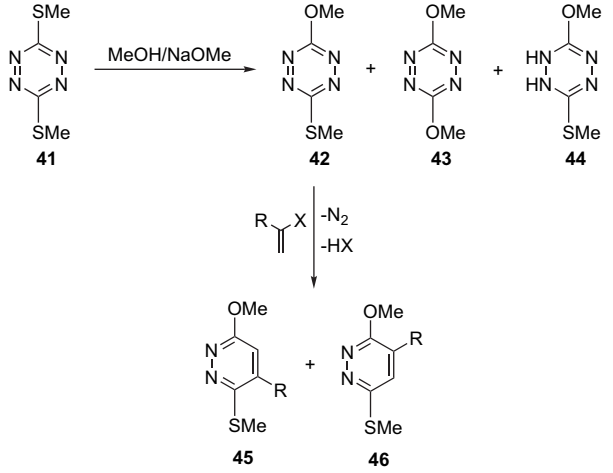


Scheme 7.



Scheme 8.

3-methylsulfinyl-6-(methylthio)-1,2,4,5-tetrazine (**49**), 6-(benzyloxycarbonyl)amino-3-(methylthio)-1,2,4,5-tetrazine (**50**) and 3-(benzyloxycarbonyl)amino-6-methylsulfinyl-1,2,4,5-tetrazine (**51**), were prepared by Boger et al. at different times,[40,41] and the scope of their participation in regioselective *inverse*-demand Diels–Alder reactions was disclosed. The tetrazines **47**, **48** and **50** were obtained by the selective displacement of one methylthio group of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**41**) with the anions of *tert*-butyl carbamate, acetamide and benzyl carbamate in a one-step procedure. The sulfur oxidation of **41** and **50** with the DABCO–Br_2 complex and *m*-CPBA gave the other tetrazines **49** and **51**, respectively (Scheme 10). Some cycloadducts of the five tetrazines are given in Table 2.

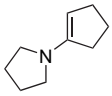
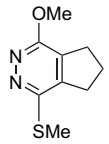
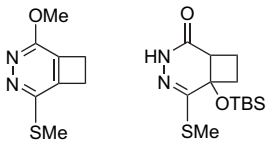
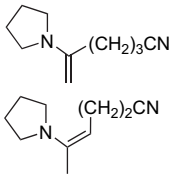
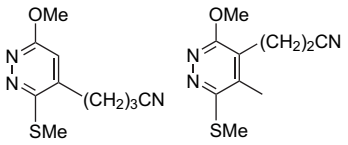
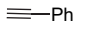
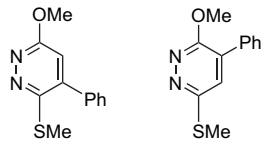
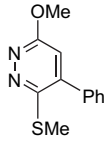
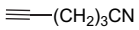
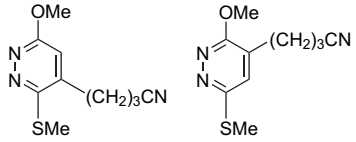
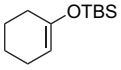
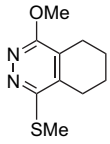
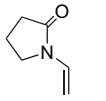
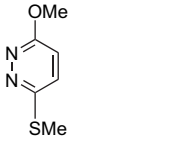


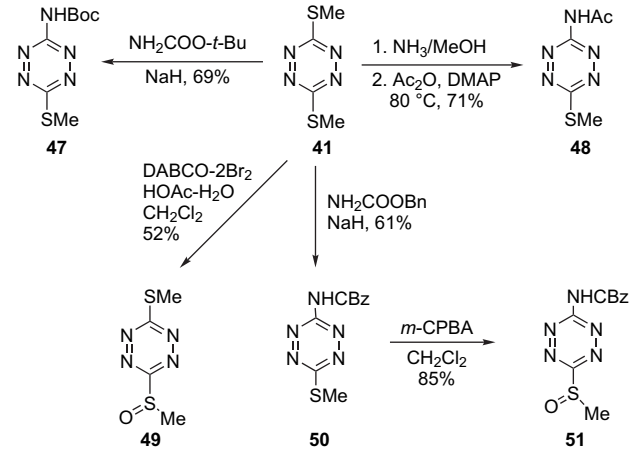
Scheme 9.

Boger and co-workers also reported the relative reactivity of tetrazines **41**–**43**, **47** and **48** towards *N*-vinyl pyrrolidinone.[40] The corresponding experiments indicated that the reactivity of tetrazine **48** is greater than that of the other tetrazines. The experimental findings were consistent with Austin model 1 (AM1) computational studies of a full range of substituted 1,2,4,5-tetrazines, where the LUMO of both **47** and **48** was at a higher energy than that of 3,6-dicarbomethoxy-1,2,4,5-tetrazine, but lower than those of 6-methoxy-3-(methylthio)-**42** or 3,6-dimethoxy-1,2,4,5-tetrazine (**43**) (Fig. 1). The regioselectivity of the cycloadditions for **47**, **48** and **49** is consistent with the expectation that the methylthio group controls by stabilising a partial negative charge at C-3 (Fig. 2).[41] The dienophile follows by the added ability of the acylamino group to stabilise a partial positive charge on C-6 of the electron-deficient tetrazine. The observed regioselectivity is supported by AM1 computational studies. In an analogous manner, the methylsulfinyl group for **51** would control the reaction orientation by stabilising a partial negative charge at C-3. These predictions are supported by AM1 and MNDO computational studies. C-3 of both **49** and **50** bears a significant partial negative charge, while C-6 is more electropositive (Fig. 2).

Heuschmann and Hartmann investigated the steric effects on the regioselectivity in the two-step Diels–Alder reaction of unsymmetrical substituted tetrazines **56b**,**c** with 2-cyclopropylidene-4,5-dihydro-1,3-dimethyl-imidazolidine.[42] The selected 1,2,4,5-tetrazines **56b**,**c** were prepared from diacylhydrazides **52** according to a procedure developed by Stolle.[43] The reaction of the hydrazides **52** with phosphorus pentachloride afforded the hydrazidedioyl dichlorides **53**

Table 1. Diels–Alder reactions of 3-methoxy-6-methylthio-1,2,4,5-tetrazine (**42**)

Dienophile	Product	Dienophile	Product
			
			
			
			



Scheme 10.

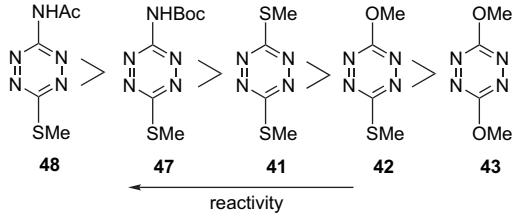
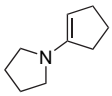
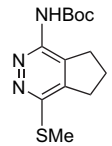
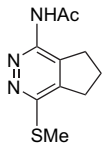
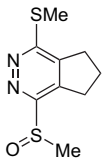
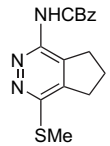
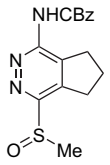
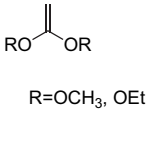
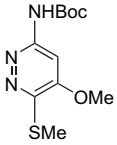
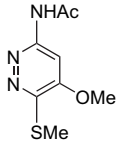
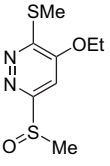
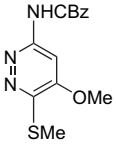
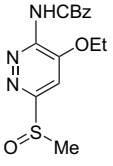
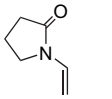
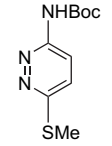
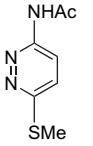
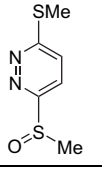
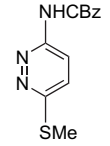
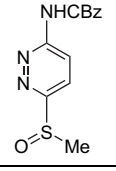


Figure 1.

or the 1,3,4-oxadiazoles **54**, which were reacted with hydrazine hydrate to yield the dihydrotetrazines. The hydrotetrazines **55** were oxidised to the tetrazines **56** by nitrous gases (Scheme 11).

Table 2. Cycloadducts for unsymmetrical-1,2,4,5-tetrazines **47**–**51**

Dienophile	Products of **47**	Products of **48**	Products of **49**	Products of **50**	Products of **51**
					
					
					

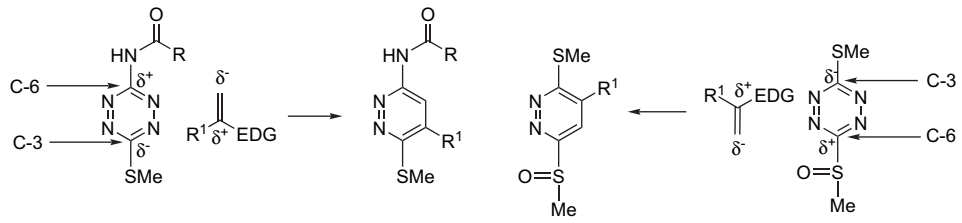
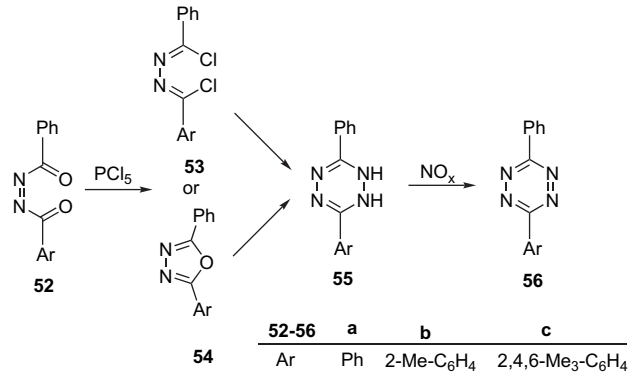


Figure 2.



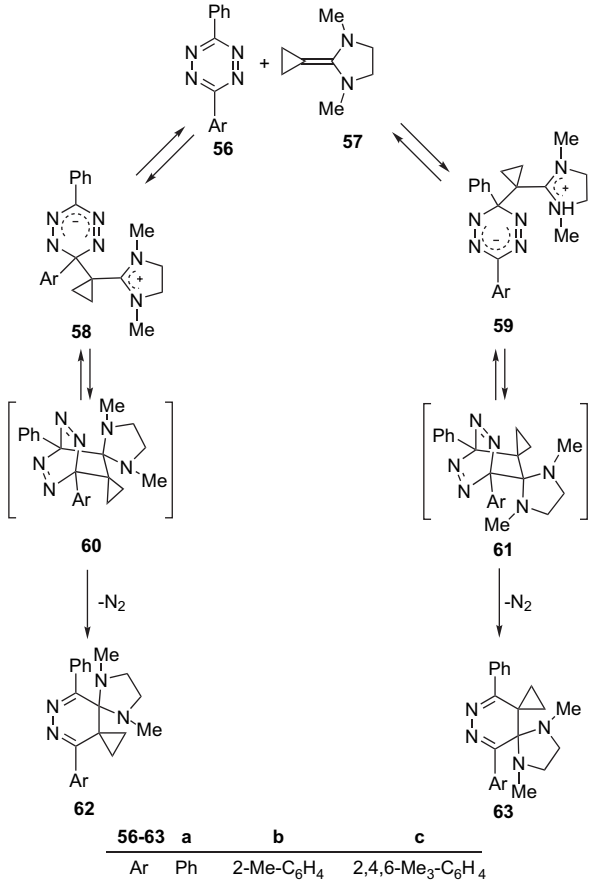
Scheme 11.

3,6-Diphenyl-1,2,4,5-tetrazine **56a** reacted rapidly at room temperature with cyclopropylidene-imidazolidine **57** to give a spiro adduct **62a** via [4+2] cycloaddition in accordance with a general mechanism. Heuschmann and co-workers reported the reaction of the unsymmetrical tetrazine **56b** with **57** at low temperature (−10 °C) (Scheme 12).[42] After this reaction was completed, the reaction mixture was characterised as a mixture of zwitterions **58b** and **59b** (33:67) by NMR spectroscopy at −50 °C. After the solution of zwitterions (33:67) was allowed to warm to room temperature, only the spiro adduct **62b** could be identified, besides 44% of the tetrazine **56b**. The reaction of **56b** with **57** in tetrahydrofuran was completed at room temperature in a few minutes and 84% of isomer **62b** was isolated after recrystallisation. When the dienophile **57** was added to the other tetrazine **56c** at −10 °C, only one regioisomeric zwitterion **59c** was formed. With warming of this zwitterion to room temperature, dispiro adducts **62c** or **63c** could not be identified and the zwitterion decomposed to the starting materials **56b** and **57**. These experimental results showed that the first reversible step of the cycloaddition affording zwitterions **58** and **59** is controlled by steric effects. The overall regioselectivity is, however, determined in the second step of cycloaddition, and a methyl group in the 2- or 6-position of the aryl ring will completely prevent nucleophilic attack at the adjacent side from the same side of the tetrazine ring.

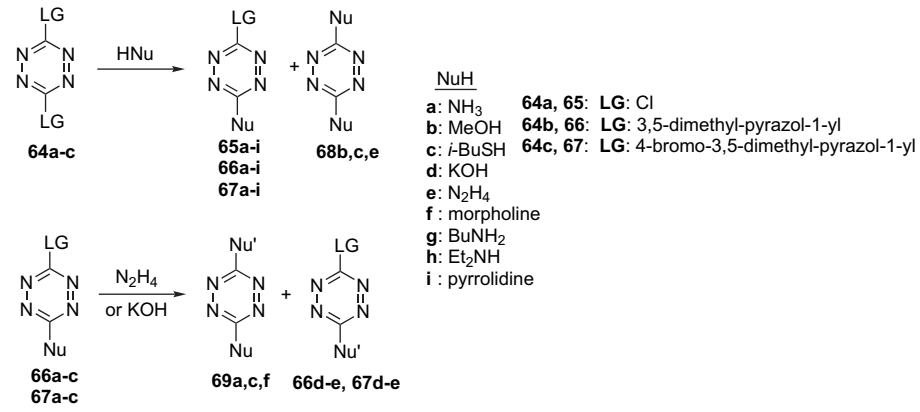
Kotschy et al. investigated the reactions of tetrazines **64a–c** bearing a leaving group with various nucleophiles to give the monosubstitution products **65**, **66** and **67** (Scheme 13).[44] When methanol and isobutyl mercaptan are used as nucleophile, the disubstitution products (**68b**,**c**,**e**) are also formed. The reaction of the chlorotetrazines **65a–c** with hydrazine and potassium hydroxide resulted only in decomposition. When tetrazines **66a–c** and **67a–c** were reacted with the hydrazine, they showed outstanding reactivity, and both **66b** and **67b** gave only *ipso*-substitution products **66e** and **67e**, respectively, which were unexpected. Furthermore, *ipso*-substitution products **66d**,**e** and **67d**,**e** and normal substitution products **69a**,**c**,**f** were obtained from **66a–c** and **67a–c**. The influence of the nucleophiles and substituents used on tetrazines was supported by quantum chemical calculations.

Novak and Kotschy reported the results of the first cross-coupling reactions on tetrazines.[45] They reacted a series of substituted chlorotetrazines **64a**, **70a–h** with different terminal alkynes **71a–d** under Sonogashira and Negishi coupling conditions to yield the alkynyl-tetrazines **72** (Scheme 14).

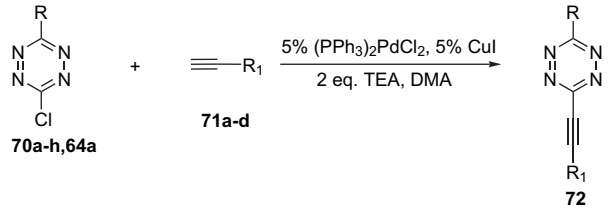
New 1,2,4,5-tetrazines **73** and **74** and the known 1,2,4,5-tetrazines **64a**, **70g** and **43** were synthesised and their electrochemical and fluorescence properties, including the lifetimes of the excited states in solution and in the solid



Scheme 12.

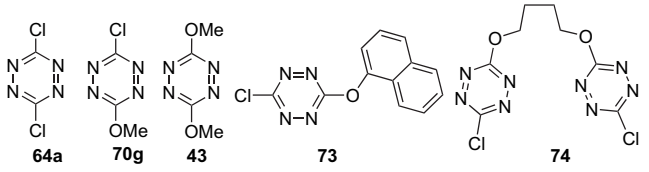


Scheme 13.



70a R = morpholin, **70b** R = pyrrolidinyl, **70c** R=NEt_2, **70d** R = NHBu, **70e** R = NH_2, **70f** R = dimethylpyrazolyl, **70g** R = OMe, **64a** R = Cl, **71a** R_1 = $C(Me)_2OH$, **71b** R_1 = Ph, **71c** R_1 = Bu, **71d** R_1 = TMS

Scheme 14.

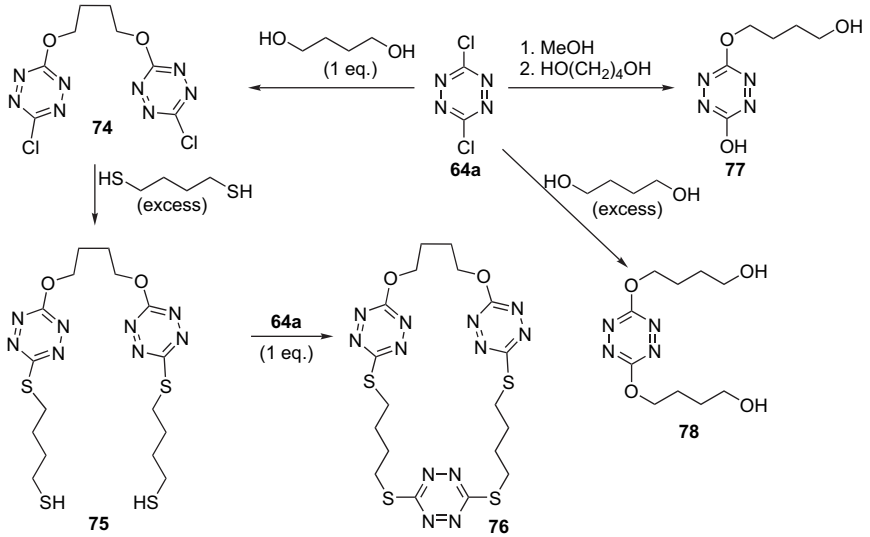


Scheme 15.

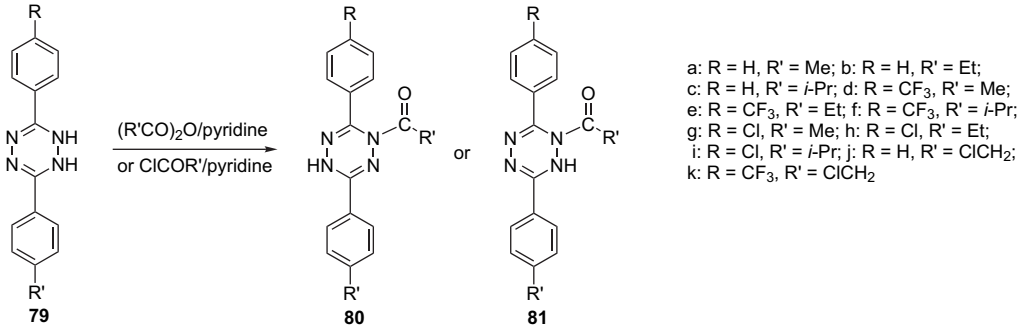
state, were investigated by Audebert et al.,[46] who compared the same features for the already known dichlorotetrazine **64a** (Scheme 15).

Audebert and co-workers described the properties of several new substituted tetrazines, which display fully reversible electrochemical behaviour and an intense fluorescence, both in solution and in the solid state. The results showed that the fluorescence lifetimes are long and the emission can be efficiently quenched by electron donors such as aromatic compounds, which highlights the ability of these new compounds to be used in sensor devices. The new tetrazines **73** and **74** were synthesised from the nucleophilic substitution reaction of 3,5-dichloro-1,2,4,5-tetrazine (**64a**) with 1-naphthol and butane-1,4-diol. Audebert et al. reported the synthesis and electrochemical properties of new tetrazines **75**–**78** using a similar approach (Scheme 16).[47]

Rao and Hu reported the synthesis, X-ray crystallographic analysis and antitumour activity of 1-acyl-3,6-disubstituted phenyl-1,4-dihydro-1,2,4,5-tetrazines **80a**–**k** or **81a**–**k** as shown in Scheme 17.[48] The title compounds were prepared



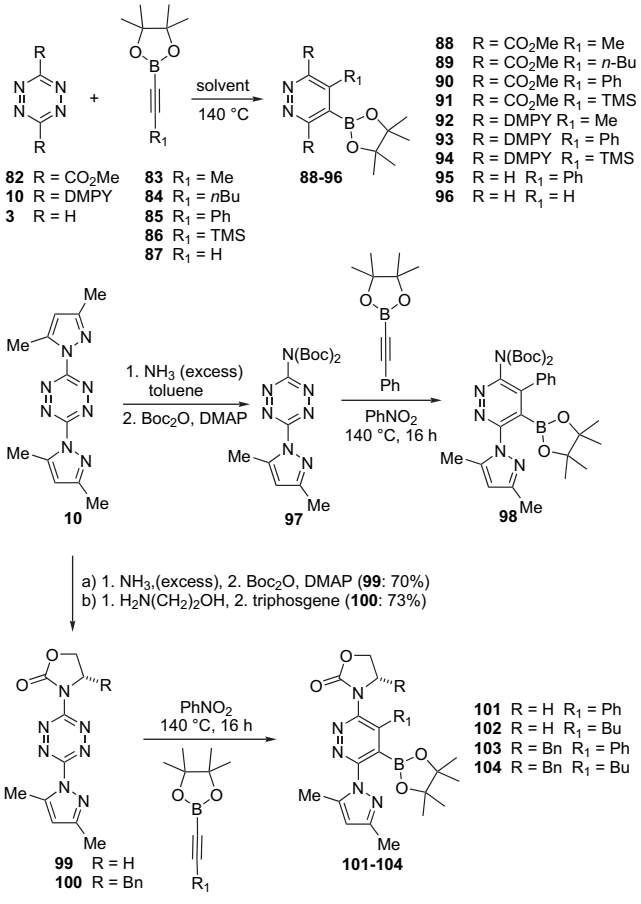
Scheme 16.



79 **80** **81**

Scheme 17.

from the dihydro-1,2,4,5-tetrazines **79a–k**, anhydrides or acyl chlorides. This reaction yields 1,4-dihydro derivatives possessing an obvious boat conformation rather than 1,2-dihydro derivatives. Their antitumour activities were evaluated in vitro by the SRB method for A-549 cells and by the MTT method for P-388 cells. The findings obtained show that these acyl derivatives may have potential antitumour activities, and compound **80j** is especially effective against A-549, with **80c** and **80j** highly effective against P-388. Recently, Rao and Hu have reported further work[49] in this area and prepared 14 compounds of both 3,6-disubstituted-1,4-dihydro-1,2,4,5-tetrazine and 1,2,4,5-tetrazine derivatives, with their antitumour activities being evaluated.



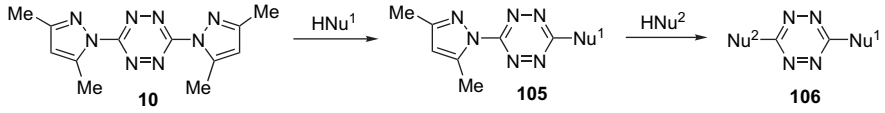
Scheme 18.

Arylboronic acids and esters represent one of the most commonly used classes of synthetic intermediates.[50–53] Harrity et al. reported the synthesis of highly functionalised pyridazine boronic esters **88–104** using the cycloaddition reactions of some substituted alkynylboronic esters **83–87** with symmetrical tetrazines **3**, **10** and **82** and the synthesis and cycloadditions of unsymmetrical tetrazines **97**, **99** and **100** using **10**, which was employed as a common intermediate for the preparation of the unsymmetrical tetrazines (Scheme 18).[54]

The nucleophilic substitution of the dimethylpyrazolyl moiety in 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**10**) with aliphatic, cycloaliphatic, and aromatic amines, and also with NH-heterocycles, was applied by Rusinov and co-workers to synthesise both unsymmetrical tetrazines **105a–f** and **106a–f** (Scheme 19 and Table 3) and symmetrical tetrazines, which are shown in Section 2.3 (see Scheme 22 and Table 5).[55]

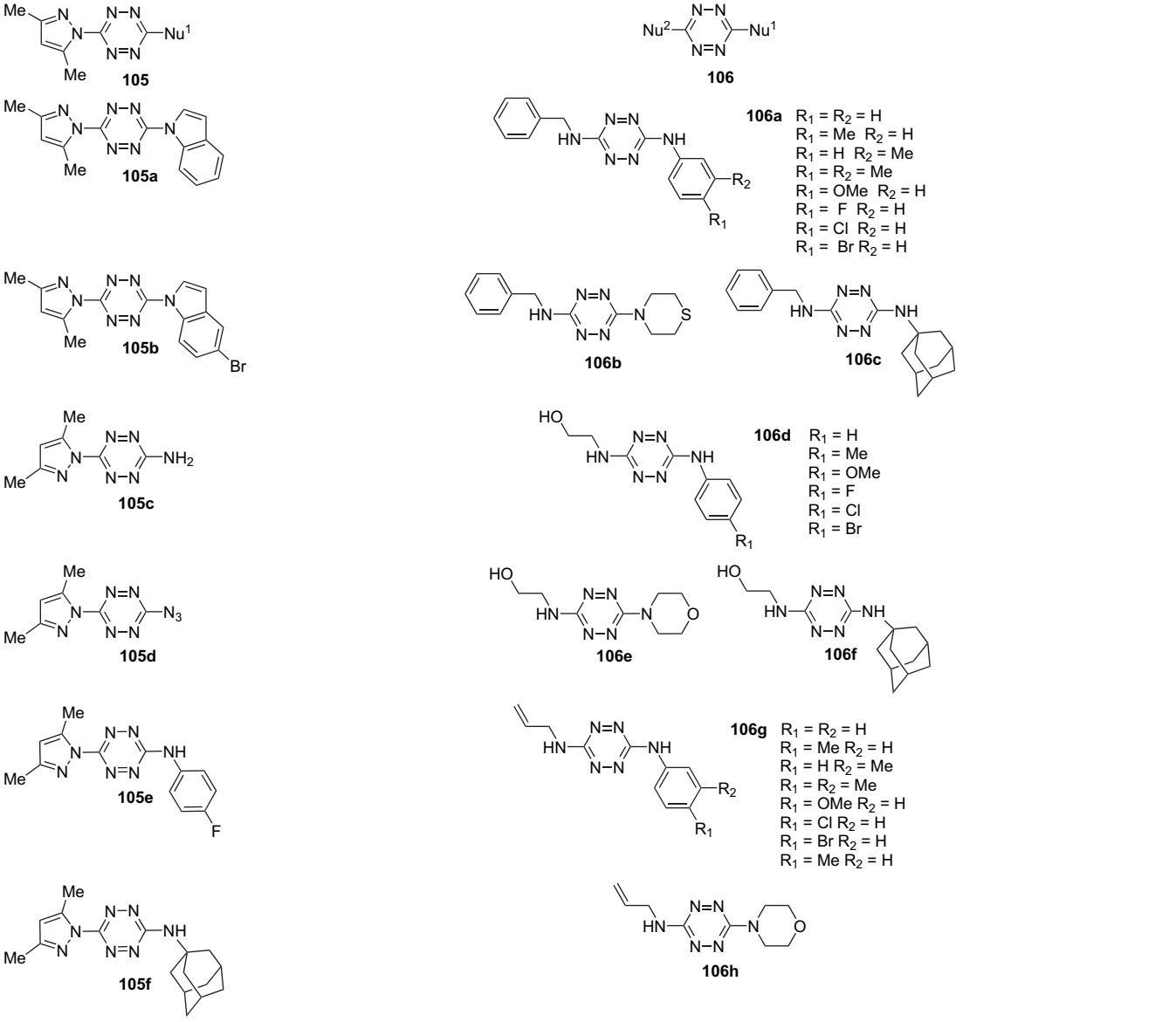
At the same time, Rusinov and co-workers reported heteroaryl displacements in 3,6-disubstituted 1,2,4,5-tetrazines **10**, **107–111** with 1-methyl- and 1,6-dimethylquinaldinium iodides **112a**,**b** in the presence of triethylamine in acetonitrile.[56] These displacements gave the *C*-nucleophilic substitution products **113–118a**,**e** in excellent yield (50–98%) (Scheme 20). When the substitution reaction of **10** with 1,6-dimethylquinaldinium iodide **112b** was carried out in less polar solvents such as toluene, the addition products **119** and **120** were formed instead of the substitution product **113b**, as depicted in Scheme 20.

There are only two previous papers on the synthesis of 3,6-dibenzoyltetrazines, and their reactivity as azadienes was



Scheme 19.

Table 3. Unsymmetrical substituted 1,2,4,5-tetrazines



not investigated.[57,58] Snyder and co-workers reported the direct conversion of heteroaromatic esters into methyl ketones with trimethylaluminum.[59] While tetrazine **82** did not react cleanly with Me_3Al, the 1,4-dihydro-1,2,4,5-tetrazine **121**, which is the synthetic precursor of **82**, reacted with Me_3Al to produce the monoketone **122**. Both the synthesis and cycloadditions of the unsymmetrical tetrazines **123** and **125** were, however, also reported (Scheme 21 and Table 4).

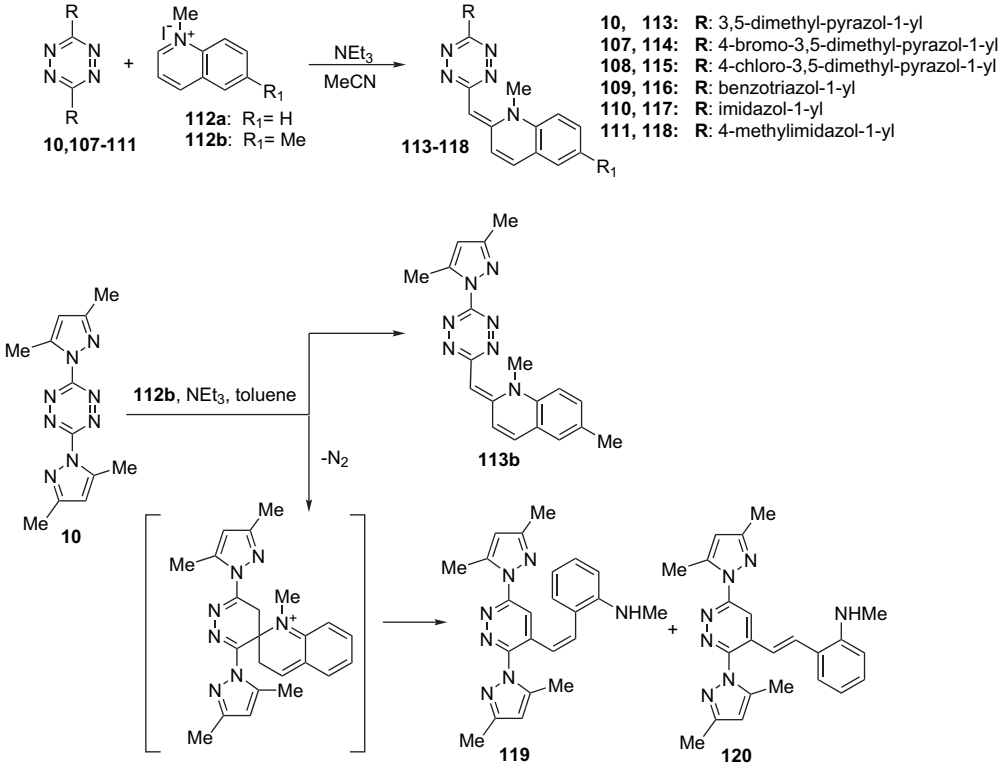
2.3. Symmetrical substituted 1,2,4,5-tetrazines

The synthesis of symmetrical tetrazines **126a–l** via the nucleophilic substitution of the dimethylpyrazolyl moiety in 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**10**) was performed by Rusinov et al. (Scheme 22 and Table 5).[55]

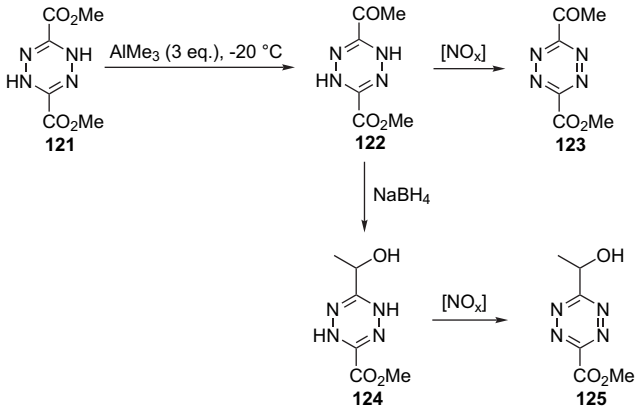
Katritzky et al. prepared the 3,6-bis-(4-halophenyl)-1,2,4,5-tetrazines **130** and **131** by modifying the general Pinner method.[60] Aminobenzonitrile (**127**) was cyclised by heating with anhydrous hydrazine into the previously unreported 3,6-bis-(4-aminophenyl)-1,2-dihydro-1,2,4,5-tetrazine(**128**) in 51% yield. After the isolation and oxidation of dihydrotetrazine **128** to **129**, diamine **129** was converted by a Sandmeyer reaction into the iodophenyl **130** and bromophenyl **131** derivatives (Scheme 23).

The synthesis of 3,6-diacyl-1,2,4,5-tetrazines and their participation in the Diels–Alder reaction are limited. Snyder et al. also achieved the synthesis and cycloadditions (**134** and **135**) of diketone **133** obtained from the reaction of the 1,2-dihydro-1,2,4,5-tetrazine **121** with Me_3Al depending upon the reaction conditions (Scheme 24).[59]

Tetrazine **141** was synthesised by Boger et al. in five steps and in 28% overall yield from the commercially available 3,4-dimethoxybenzaldehyde (**136**), as depicted in Scheme 25.[61] The first systematic study of the [4+2] cycloaddition reactions of 3,6-diacyl-1,2,4,5-tetrazines was reported.



Scheme 20.



Scheme 21.

Diels–Alder cycloadditions of **141** were also observed towards both electron-rich and neutral alkenes and alkynyl dienophiles (Table 6), as demonstrated by the formation of 1,2-diazines. Typically, the alkyne dienophiles were not as reactive as the corresponding alkenes (Fig. 3).

3. Natural product synthesis

3.1. Total synthesis of ningalin A

First isolated in 1997 by Fenical and Kang, the ningalins constitute a family of structurally interesting and biologically active natural marine products.[62] Ningalin A (**145**) and the related ningalins B–D are the newest members of the family of DOPA-derived *o*-catechol metabolites that include the tunichromes. Boger et al. reported the concise and efficient total synthesis of ningalin A (**145**) based on a heterocyclic azadiene Diels–Alder strategy (1,2,4,5-tetrazine → 1,2-diazine → pyrrole).[63] The Diels–Alder reaction of the 1,2,4,5-tetrazine **82** with the acetylene **142** to give the diazine **143** was the first step in the synthesis. Subsequent reductive ring contraction of 1,2-diazine **143** from the treatment with zinc in AcOH afforded the desired pyrrole **144**. After deprotection of the MOM group and the first lactonisation, more forcing conditions (DBU) were required for the formation of the second lactone. Demethylation with BBr_3 completed the first total synthesis of the ningalin A (**145**) (Scheme 26).

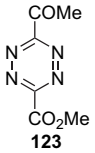
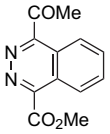
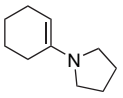
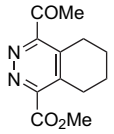
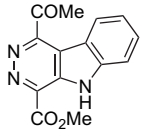
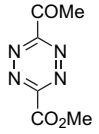
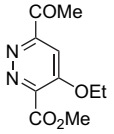
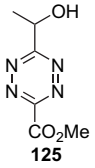
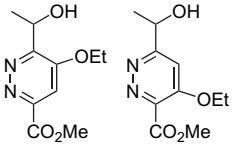
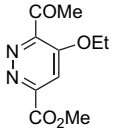
3.2. Total synthesis of lamellarin O and lukianol A

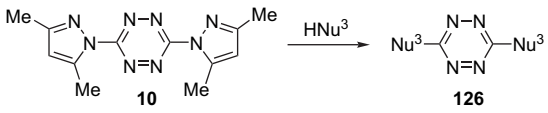
Lamellarin O (**150**) is a prototypical member of a rapidly growing class of natural marine products.[64] Lukianol A (**151**) was shown to exhibit cytotoxic activity against a cell line derived from human epidermatoid carcinoma.[65,66] Boger et al. prepared the 1,2-diazine **147** by intramolecular cycloaddition using acetylene **146** and 1,2,4,5-tetrazine **82**. After Zn-reductive ring contraction followed by N-alkylation of the pyrrole, the symmetric diester **148** was selectively hydrolysed with LiOH to provide the mono acid. Decarboxylation of the resulting acid afforded the trisubstituted pyrrole **149**. This key compound was converted into lamellarin O (**150**) and lukianol A (**151**) (Scheme 27).[63]

3.3. Total synthesis of permethyl storniamide A

Storniamide A is a secondary metabolite.[67] The same synthesis methodology for ningalin A (**145**), lamellarin O (**150**) and

Table 4. Cycloadditions of unsymmetrical tetrazines **123** and **125**

Tetrazine	Dienophile	Product	Tetrazine	Dienophile	Product
 **123**					
			 **123**		
 **125**		 (4:96)			 (1:1)

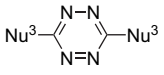


10 **126**

Scheme 22.

lukianol A (**151**) was also applied in the synthesis of permethyl storniamide (**155**).[63] The cycloaddition of **152** with the tetrazine **82** followed by zinc reductive ring contraction provided the pyrrole compound **154**. After N-alkylation and diamidation, thioether oxidation with subsequent thermal sulfoxide elimination gave the separable dienamide **155** (Scheme 28).

Table 5. Symmetrical substituted 1,2,4,5-tetrazines



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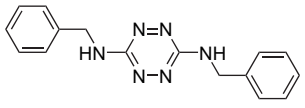

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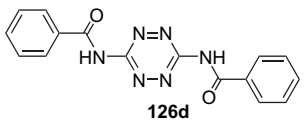
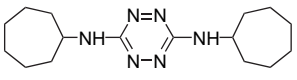
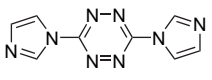


126d



126g



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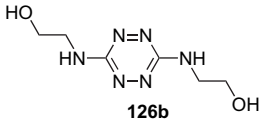
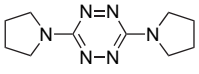


126b



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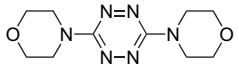

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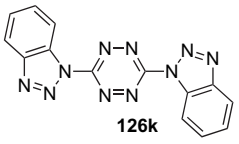

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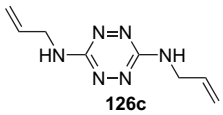
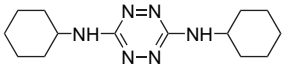
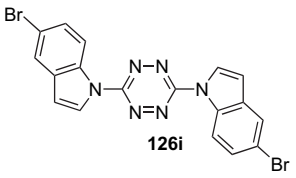


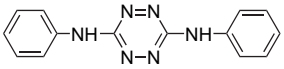
126c



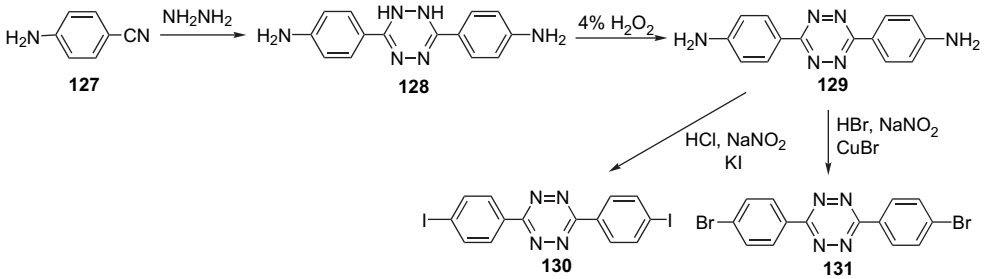
126f



126i

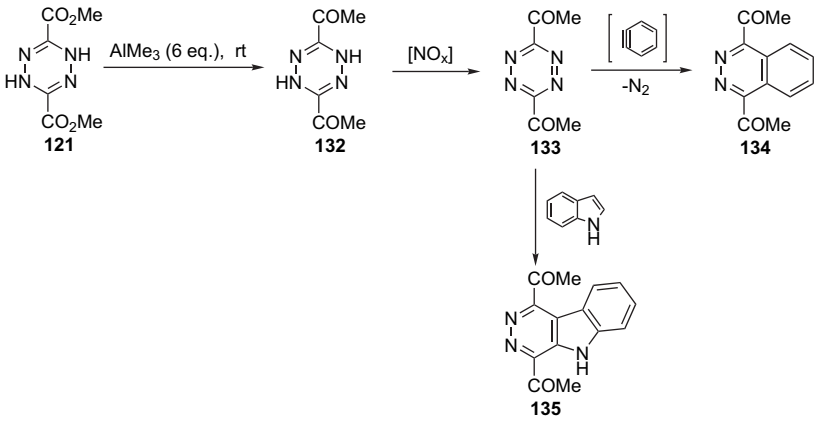


126l

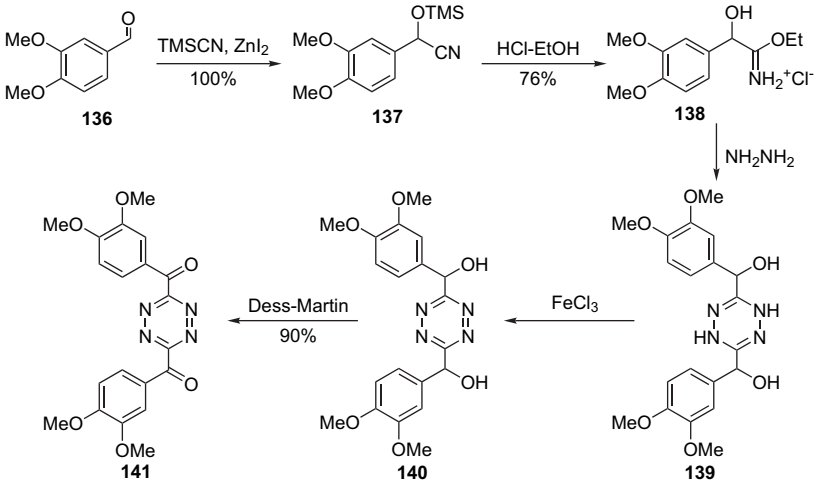


127 **128** **129** **130** **131**

Scheme 23.



Scheme 24.

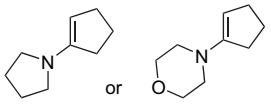
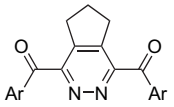
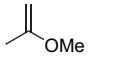
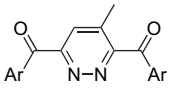
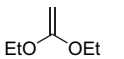
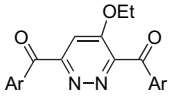
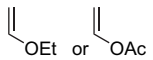
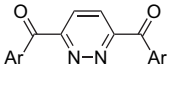
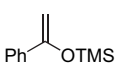
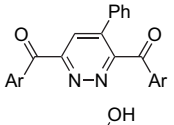
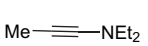
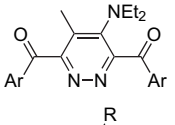
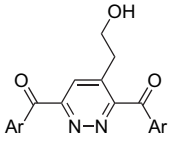
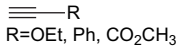
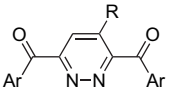


Scheme 25.

3.4. Total synthesis of ningalin B

Ningalin B (**161**) is a natural product possessing a 3,4-diaryl-substituted pyrrole nucleus.[62] Boger et al. described a concise and efficient approach to the total synthesis of ningalin B.[68] The Diels–Alder reaction of the acetylene **156** with the 1,2,4,5-tetrazine **82** afforded the 1,2-diazine **157** in excellent yield. The transformation of the 1,2-diazine **157** to the pyrrole **158** was performed with Zn in AcOH. After N-alkylation, lactonisation and decarboxylation, demethylation

Table 6. Diels–Alder reactions of 3,6-bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine (**141**) with alkenes and alkynes

Dienophile	Product	Dienophile	Product
			
			
			
		 R=OEt, Ph, CO_2CH_3	 R=OEt, Ph, CO_2Me
			No reaction

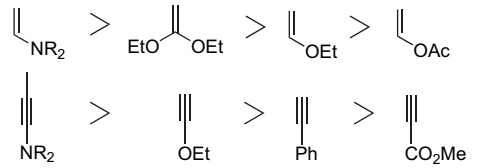
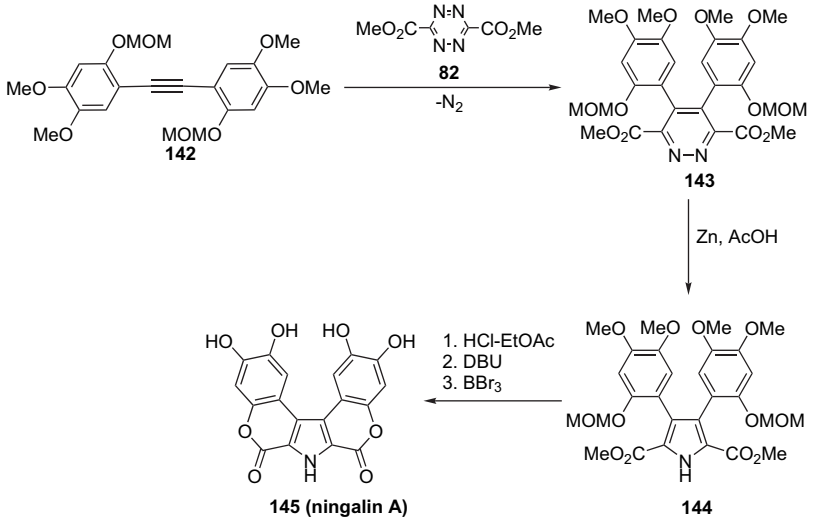


Figure 3. Relative dienophile reactivity towards **141**.

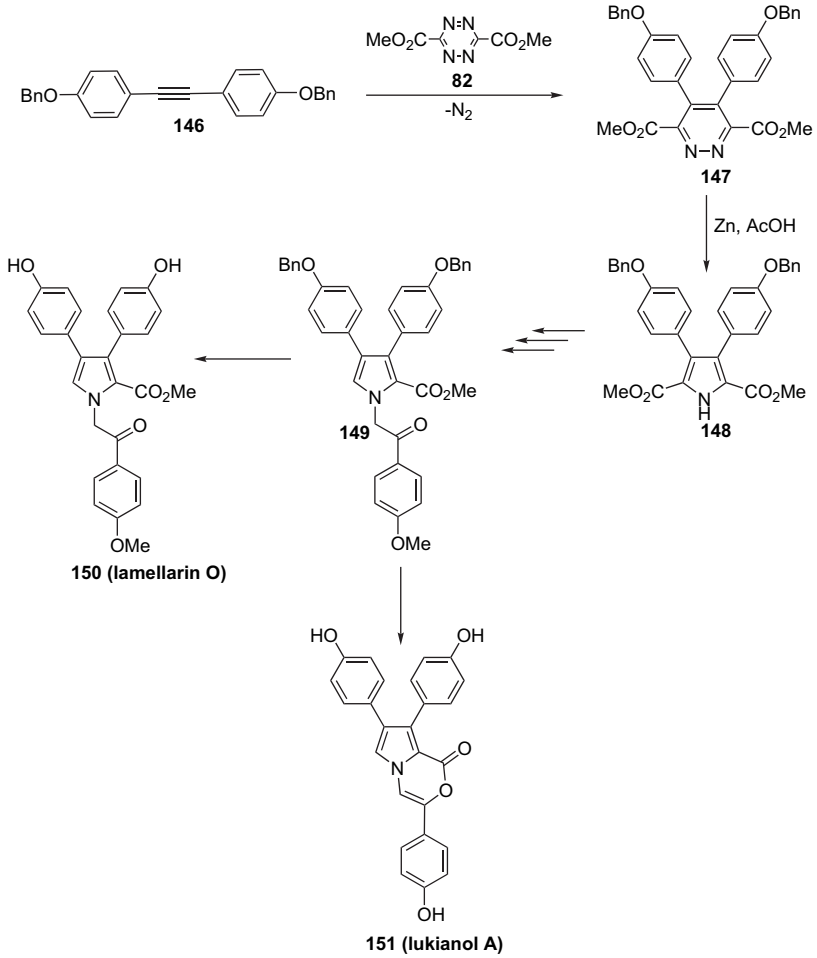
with BBr_3 completed the total synthesis of ningalin B (**161**) (Scheme 29).

3.5. Total synthesis of ningalin D

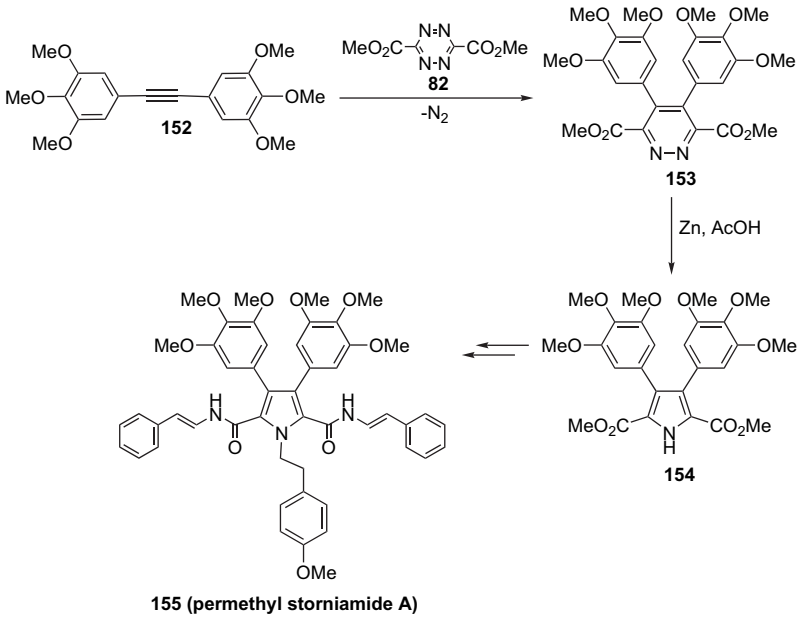
Boger et al. also achieved the total synthesis of ningalin D (**165**) using a nine-step reaction.[69] The first step of the



Scheme 26.



Scheme 27.

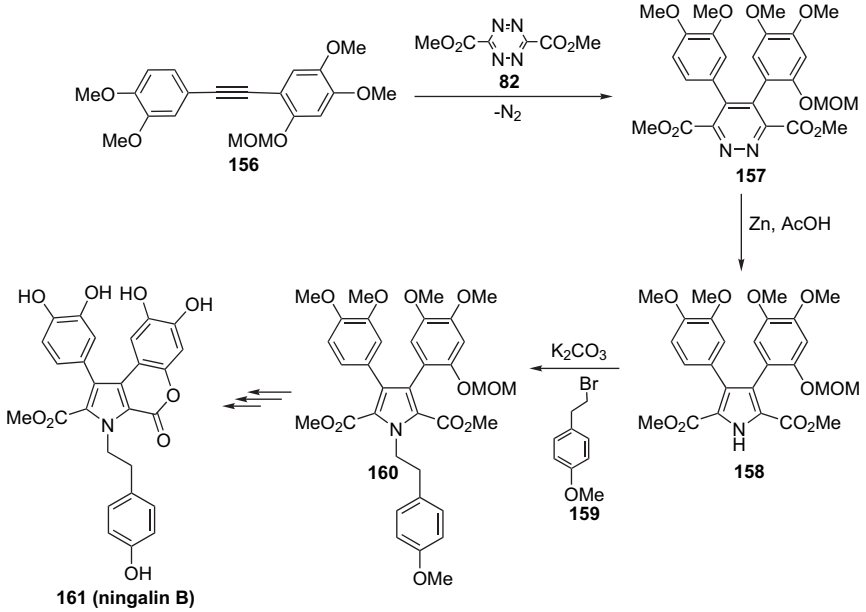


Scheme 28.

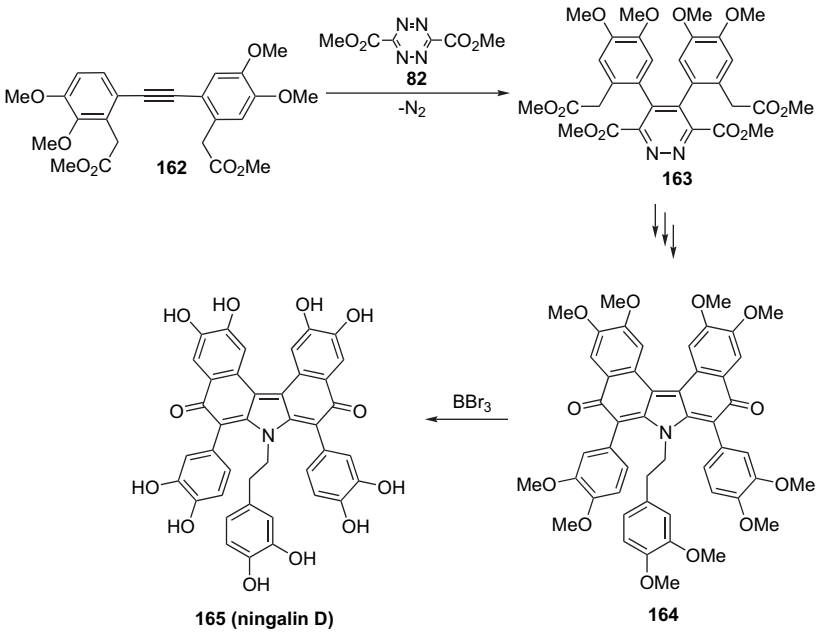
synthesis is the preparation of the diazine **163** from the symmetrical alkyne **162** and tetrazine **82**. The transformation of **163** into the pyrrole is the second step. N-Alkylation, a double Dieckmann condensation and Suzuki coupling afforded the ningalin D skeleton. The final step was deprotection with BBr_3 to give ningalin D (**165**) (Scheme 30).

3.6. Total synthesis of *Amaryllidaceae* alkaloids

Lycorine alkaloids isolated from *Amaryllidaceous* plants have potent biological activity. Hippadine[70] (**173**) inhibits fertility in male mice, while anhydrolycorinium chloride[71] (**174**) exhibits cytotoxic activity against a number of tumour cells. The natural product, anhydrolcorinone[72,73] (**172**), serves as an intermediate for the synthesis of **173** and **174**. Boger and Wolkenberg reported the fascinating synthesis of **172**, **173** and **174** from *Amaryllidaceae* alkaloids.[74] Their strategy is based on the intramolecular *inverse*-Diels–Alder reaction of the unsymmetrical tetrazine **167**, which was prepared by the reaction of 3,6-bis(methylthio)-1,2,4,5-tetrazine (**41**) with 1-amino-3-butyne **166**. The first intramolecular [4+2] cycloaddition was achieved at room temperature during N-acylation of **167** with Boc_2O/DMAP. After the 1,2-diazine **168** was *N*-Boc deprotected, the resulting compound **169** was submitted to the N-acylation reaction to yield **170**. The second intramolecular [4+2] cycloaddition at high temperature and the aromatisation via elimination of methanol provided the anhydrolcorinone precursor **171**.



Scheme 29.



Scheme 30.

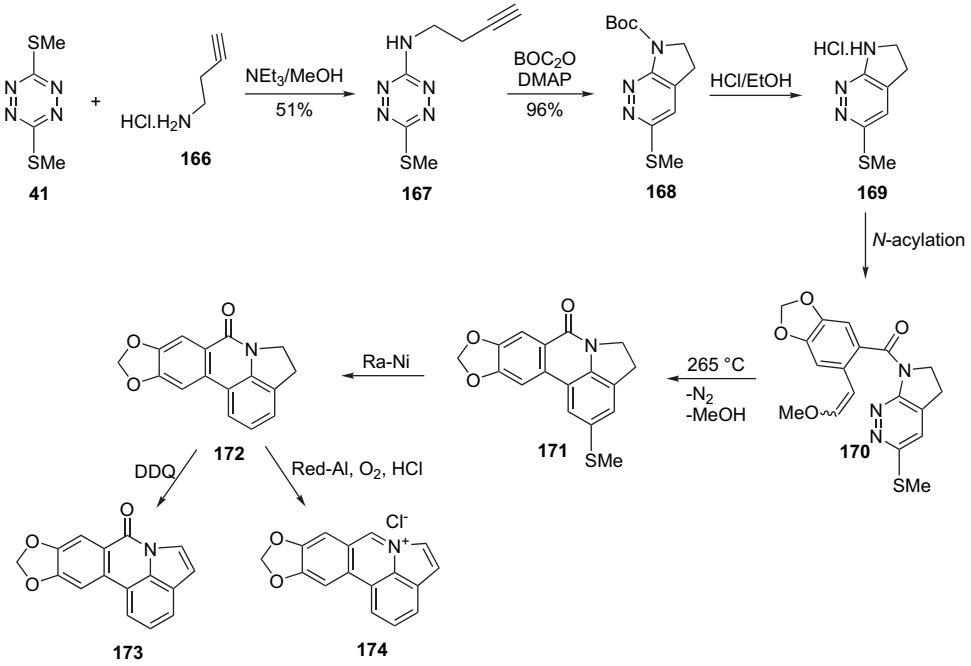
Reductive desulfurisation of **171** with Ra-Ni yielded anhydrolycorinone (**172**), which was transformed into hippadine (**173**) and anhydrolycorinium chloride (**174**) (Scheme 31).

3.7. Asymmetric total synthesis of *ent*-(−)-roseophilin

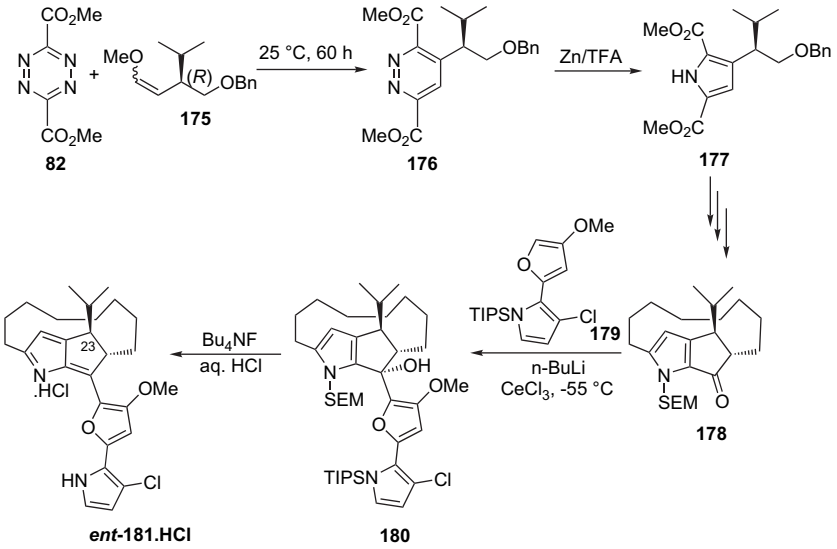
Roseophilin[75] (**181**) is a novel antitumour antibiotic possessing a pentacyclic skeleton. A Diels–Alder reaction of dimethyl-1,2,4,5-tetrazine-3,6-dicarboxylate (**82**) with optically active enol ether **175** bearing the C23 chiral centre provided the optically active 1,2-diazine **176**.[76] Reductive ring contraction of **176** gave the pyrrole **177** in good yield. This sequence provided the tricyclic core **178** in 19 steps (Scheme 32). Condensation of **178** with **179** followed by final deprotection afforded (22*S*,23*S*)-**181**.

3.8. Structural revision and synthesis of cytotoxic marine alkaloid, zarzissine

The cytotoxic natural marine product, zarzissine,[77] deduced to be 2-amino-1*H*-imidazo[4,5-*d*]pyridazine (**182**), was reported to have a broad range of activities, being active against *Staphylococcus aureus*, and the fungi *Candida albicans* and *C. tropicais*, as well as against several tumour cell lines (Fig. 4). Snyder et al. reported that 2-substituted



Scheme 31.



Scheme 32.

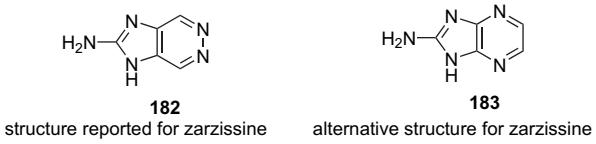


Figure 4. Possible structures for zarzissine.

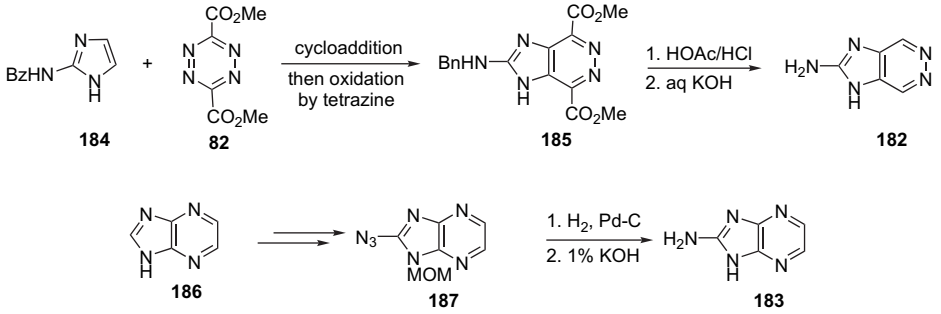
imidazoles have proved to be good dienophiles with 1,2,4,5-tetrazine to produce imidazo[4,5-*d*]pyridazines in excellent yields.[78] This group synthesised the structure reported for the marine cytotoxic agent, zarzissine, 2-amino-1*H*-imidazo[4,5-*d*]pyridazine (**182**), from the cycloaddition of 2-amino-1*H*-imidazole **184** and dimethyl 1,2,4,5-tetrazine-3,5-dicarboxylate **82** and it proved to have spectroscopic data quite different from those reported for zarzissine (Scheme 33). They thought that the most reasonable structure for zarzissine is the 2-amino-1*H*-imidazo[4,5-*b*]-pyridazine (**183**) and this compound was also synthesised, but the true identity of zarzissine remains unconfirmed (Scheme 33).

4. Annulations of pyridazine moiety to natural products, alkaloids or drugs

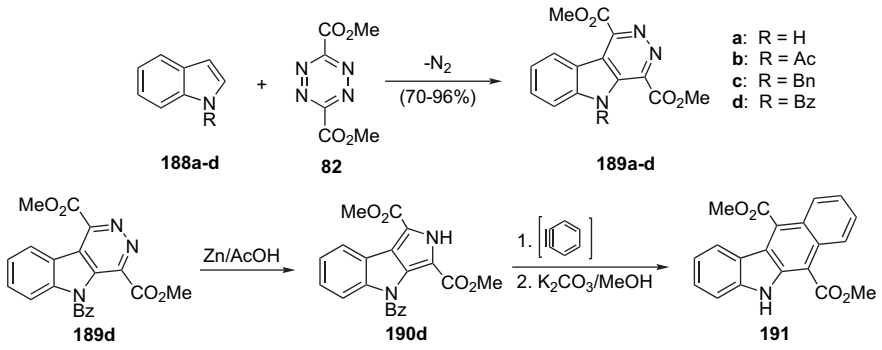
Indole-2,3-quinodimethanes and their related stable equivalents have been exploited for years for the synthesis of carbazole alkaloids.[79,80] Snyder and co-workers reported that reductive ring contraction of dimethyl 5*H*-pyridazino[4,5-*b*]indole-1,4-dicarboxylate **189d** (and **189a–c**) formed from the reaction of indole **188d** (and **188a–c**) and tetrazine **82** produced dimethyl 2,4-dihydropyrrole[3,4-*b*]indole-1,3-dicarboxylate **190d**.[81] Benzo[*b*]carbazole derivative **191** was obtained by the reaction of pyrroleindole **190d** with benzyne (Scheme 34).

Carbapenems are a class of *beta*-lactam antibiotics, and tricyclic carbapenem GG-326 has received considerable attention due to its broad spectrum of antibacterial activity and resistance to hydrolysis by *beta*-lactamases.[82–85] The synthesis of novel tricyclic diazocarbapenem precursor **195** and the protected carbapenems **196** and **197** was described by Sakya et al. (Scheme 35).[86] The tricyclic carbapenem skeleton was accomplished by an intramolecular nucleophilic substitution of diazine sulfone **194**, which was obtained from the *inverse*-Diels–Alder reaction of alkyne **192** with tetrazine **41**.

Psoralens, natural products known as furocoumarins, are commonly used in the photochemotherapy of several skin diseases, including psoriasis, vitiligo, and T-cell lymphoma, and a number of autoimmune disorders.[87] Uriarte et al. reported the results of Diels–Alder reactions between methoxypsoralenes and 1,2,4,5-tetrazines.[88] The reaction of 8-methoxypsoralen (**198c**) and 3,6-bistrifluoromethyl-



Scheme 33.

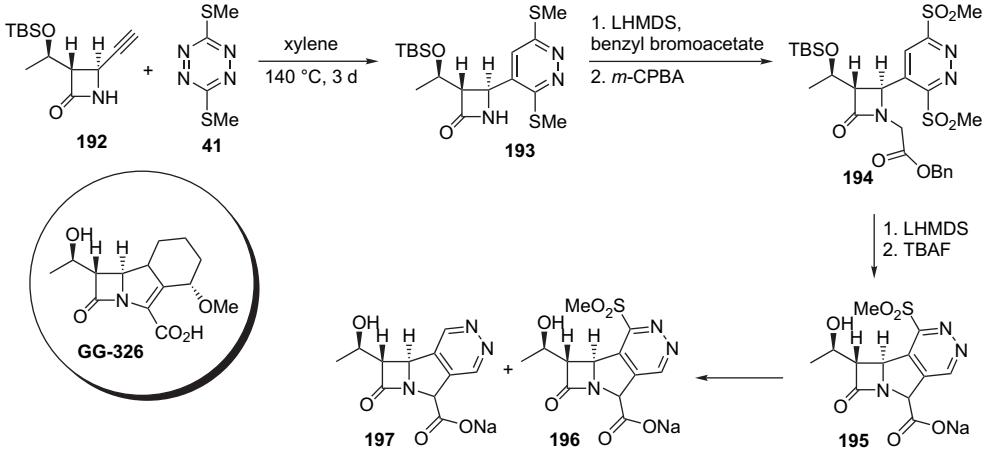


Scheme 34.

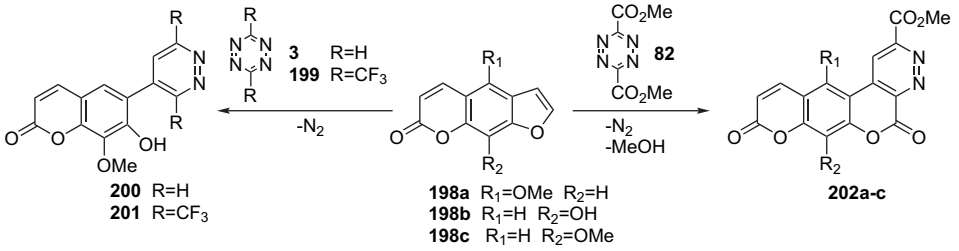
1,2,4,5-tetrazine (**199**) was accomplished by the release of diatomic nitrogen and opening of the furan ring to leave a 6-pyridazinocoumarin **201**. When 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (**82**) was used as diene, cycloaddition occurred by conversion of the furan ring into a pyrone ring **202a–c** (Scheme 36).

In order to prevent the opening of the furan ring in the furocoumarin during the cycloadditions of 3,6-bistrifluoromethyl-1,2,4,5-tetrazine (**199**), Uriarte and co-workers developed a new strategy to synthesise linear and angular pyridazine furocoumarins.[89] This group used didhydrofuro[2,3-*h*]coumarin-9-one, which is accompanied by an enol form, as a dienophile in the cycloadditions for the fusing of the pyridazine ring. From the one-step reaction of **203** and tetrazine with concomitant loss of N_2 and water, angular pyridazine furocoumarin **204** was synthesised in a good yield. Linear pyridazine furocoumarin **207** was obtained by a two-step reaction using **205** (Scheme 37). The same group also synthesised new pyridazinofurocoumarins and their carboxamide derivatives at C4 or C1 and C4 by a similar strategy (Scheme 38).[90,91] Furthermore, this approach was used to prepare the 4-carboxamide derivatives of pyridazino[4,5-*b*]benzo[*b*]furan **225** and pyridazino[4,5-*b*]indole **226** (Scheme 39).[92]

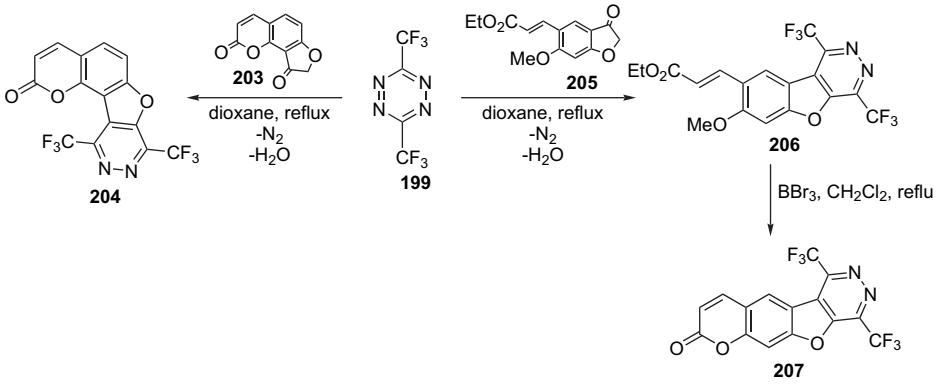
Gonzales–Gomez and Uriarte prepared 2-chloro-pyridazino[4,3-*h*]psoralen **229** from the Diels–Alder reaction of 3,6-dichloro-1,2,4,5-tetrazine (**64a**) and 8-methoxy-psoralen (**198c**) in a one-pot procedure.[93] The transformation of this intermediate **229** into the 2-triflate derivative **230** allowed a Pd-catalysed reduction, methoxycarbonylation and Sonogashira cross-coupling reactions at C2 (Scheme 40).



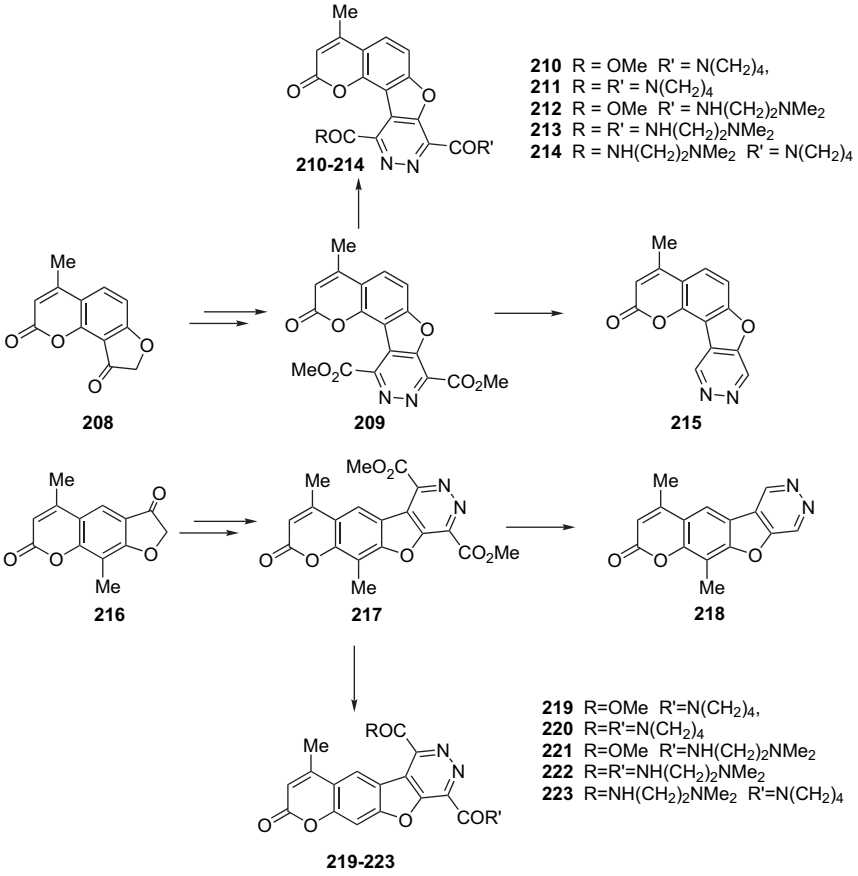
Scheme 35.



Scheme 36.



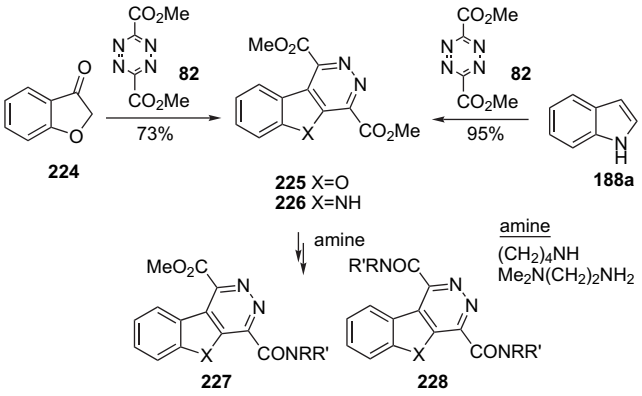
Scheme 37.



Scheme 38.

Gonzales-Gomez and co-workers achieved a convenient preparation of the parent benzodifuran **234** from resorcinol followed by DDQ oxidation.[94] The cycloaddition of the benzodifuran **234** and **235** with the tetrazine **82** afforded novel pyridazino-psoralen derivatives (**236**–**239**) upon the expected furan ring expansion (Scheme 41).

The *Aspidosperma* family, particularly the complex pentacyclic ABCDE framework, represents one of the largest groups of indole alkaloids, with more than 250 compounds isolated from various biological sources.[95–98] Snyder and co-workers reported tryptamine-tethered tetrazines as **241**, which were prepared by the displacement of methylthiolate from both 3,6-bis-(methylthio)-1,2,4,5-tetrazine (**41**) with tryptamine

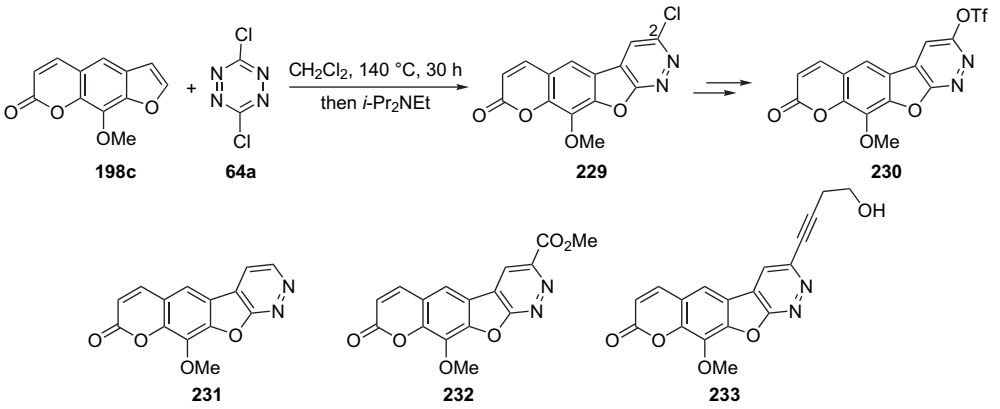


Scheme 39.

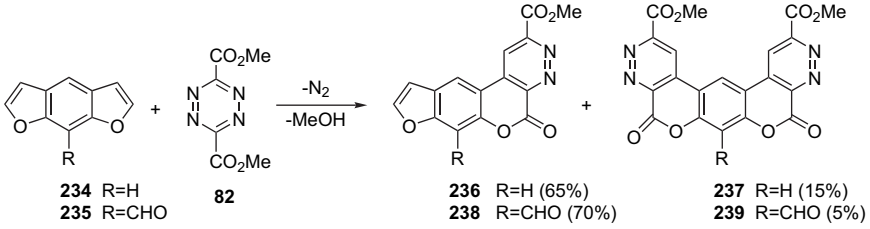
240 via ethylamine.[99] Their attempts to convert the tethered diazine **243** into the pentacyclic core **244** of aspidosperma alkaloids were unsuccessful (Scheme 42).

Epibatidine (**245**), a pyridylazabicyclo[2.2.1]heptane, is an alkaloid isolated from the skin of a South American frog.[100] It is one of the most potent analgesics known, some 10-fold more potent than morphine. Seitz and co-workers presented a new strategy for the synthesis of novel epibatidine analogues, in which the 2-chloropridinyl moiety of epibatidine is replaced by differently substituted pyridazine rings.[101] As outlined in Scheme 43, the commercially available 3-tropanone **246** could be converted in seven steps into the electron-rich dienophilic enol ether **247**. The enol ether **247** reacted with the tetrazines **199**, **248**, **64a** and **3** to yield the respective *N*-protected epibatidine analogues **249a–d** in good yields after inverse cycloaddition, release of nitrogen and elimination of methanol, respectively. Removal of the protecting groups from **249a** and **249b** afforded the pyridazine analogues **250** and **251** of epibatidine. The deprotection of **249c** into **252** furnished complex mixtures, while that of **249d** resulted in the formation of an unexpected cyclohexene derivative **254** in addition to small amounts of the epibatidine analogue **255** (Scheme 43). The pyridazine analogue **253** of (±)-epibatidine and its *N*-methyl derivative **255** was found to be the most active, retaining much of the potency of natural epibatidine.

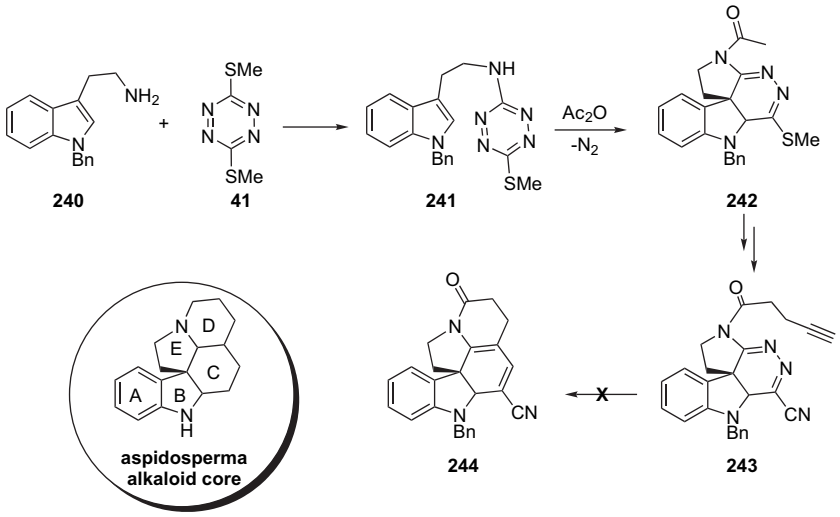
(+)-Anatoxin-a (**256**) is a potent neurotoxic alkaloid isolated from blue-green algae.[102,103] It is one of the most potent



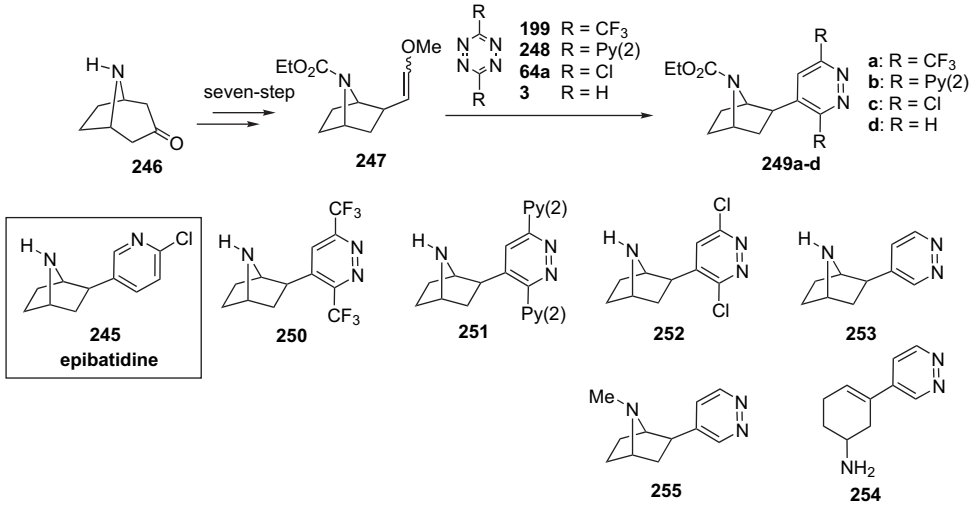
Scheme 40.



Scheme 41.



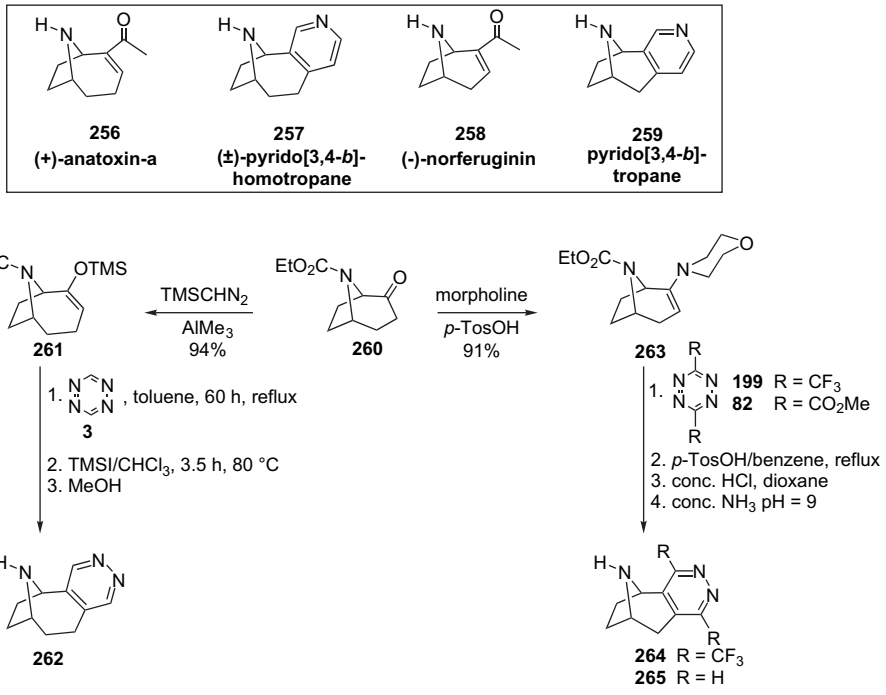
Scheme 42.



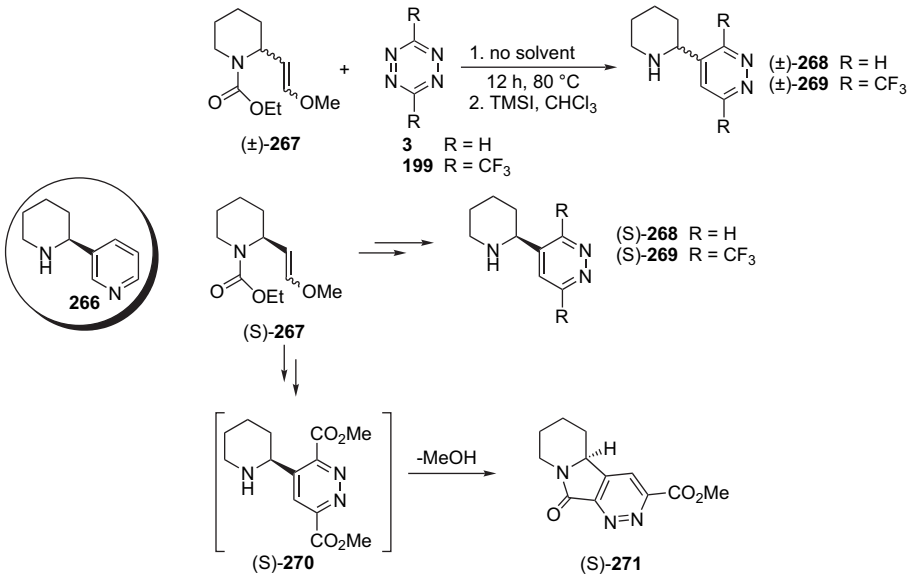
Scheme 43.

agonists at the nicotinic acetylcholine receptor (nAChR) discovered to date.[104,105] Both (+)-anatoxin-a (**256**) and (−)-norferuginin (**258**) are derivatives of tropane alkaloids.[106–108] Racemic (±)-pyrido[3,4-*b*]homotropane[109,110] (**257**) is the first bioisosteric and conformationally constrained variation, while the enantiomerically pure pyrido[3,4-*b*]tropane[111] (**259**) is the conformationally restricted bioisosteric variant of (−)-norferuginin (**258**). Because of their unusual biological properties, these alkaloids provide an attractive lead for the design of novel structural analogues. Seitz et al. developed a strategy for the synthesis of novel pyridazine and pyrimidine analogues of **257** and **259**.[112] The versatile chiral building block, (+)-2-tropinone **260**, is transformed into the ring-expanded silyl enol ether **261** and into the enamine **263**. The *inverse*-Diels–Alder reactions of both compounds with 1,2,4,5-tetrazines provided the enantiopure target compounds **262**, **264** and **265** (Scheme 44).

Seitz and co-workers synthesised anabasine analogues with potential nicotinic acetylcholine receptor agonist activity.[113] (−)-Anabasine (**266**) is one of several minor tobacco alkaloids.[114–118] These workers described a novel multistep synthesis of anabasine analogues containing a pyridazine moiety instead of a pyridine nucleus in the 2-position of the piperidine ring of the alkaloid. The new racemic or enantiopure 2-(2-methoxyethenyl)-piperidines **267** were synthesised as electron-rich dienophiles. The *inverse* cycloaddition process of these dienophiles with 1,2,4,5-tetrazines (**3**, **82** and **199**) gave the racemic and enantiopure 4-(piperidine-2-yl)-pyridazines **268**, **269** and **271** (Scheme 45).



Scheme 44.



Scheme 45.

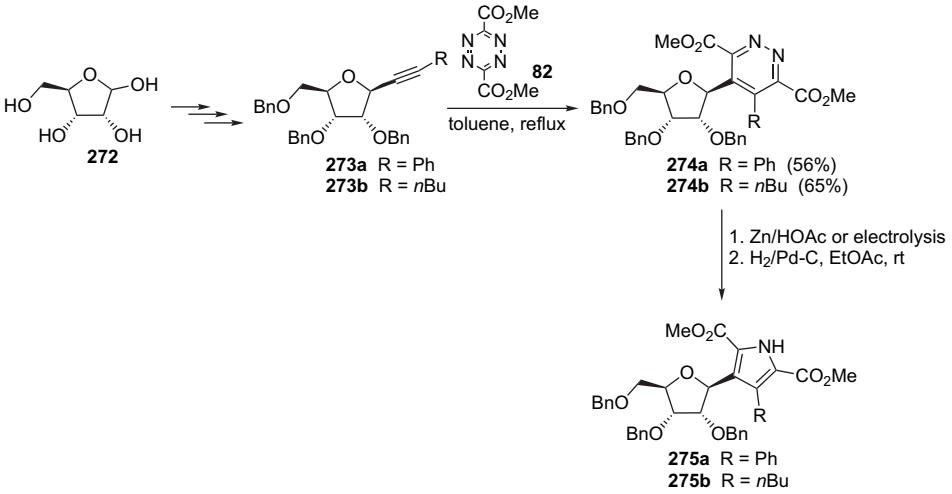
C-Nucleosides bearing five-membered nitrogen heterocycles are known to possess varied biological activities.[119–123] The pyrrole C-nucleosides also exhibit anticancer activity, while simple substituted pyrroles are known to exhibit antineoplastic and antileukemic activities.[124,125] Dubreuil et al. prepared[126a] the pyridazine C-nucleosides **274a**,**b** by using **272** with the procedure described by Seitz and Richter (Scheme 46).[126b] The last step was conversion of these pyridazine C-nucleosides **274a**,**b** on extrusion of a nitrogen atom into the corresponding pyrrole derivatives **275a**,**b** by electrochemical or chemical methods.

5. Other applications

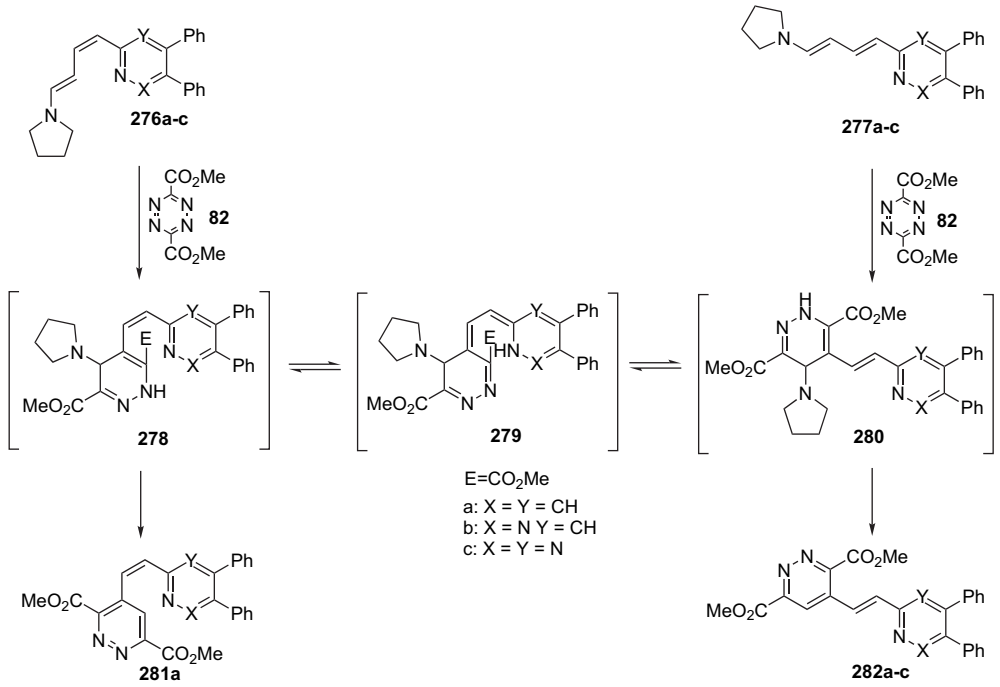
5.1. Pyridazine-based syntheses and transformations

Hajos and co-workers reported that the azinyldienamines **276a–c** and **277a–c** underwent a Diels–Alder reaction with 1,2,4,5-tetrazine **82** to yield azinylvinylpyridazines.[127] They also observed that all the reactions of the three diphenylazinyl-substituted 1-*trans*-3-*trans* dienes **277a–c** with tetrazine gave the expected *trans*-azinylvinylpyridazines **282a–c**, while, interestingly, the three 1-*cis*-3-*trans* azinyldienes **276a–c** furnished different products. The cis product **281a** was obtained from **276a**, whereas the other two cis molecules **276b**,**c** afforded the same trans products **282b**,**c**, which were also produced from the fully trans isomer (Scheme 47). This group suggested that such isomerisation may be due to the tautomeric equilibrium of the intermediate. The semiempirical calculations also supported the importance of the influence of the hetaryl group in such isomerisations.

Smith and co-workers described the synthesis of a new azo-bridged ring system using an intramolecular tandem cyclisation process as the key step.[128] The cycloaddition reaction of dienamine **283** with diester tetrazine **82** afforded the intermediate product, 1,2-dihydropyridazine **284**. Finally,



Scheme 46.

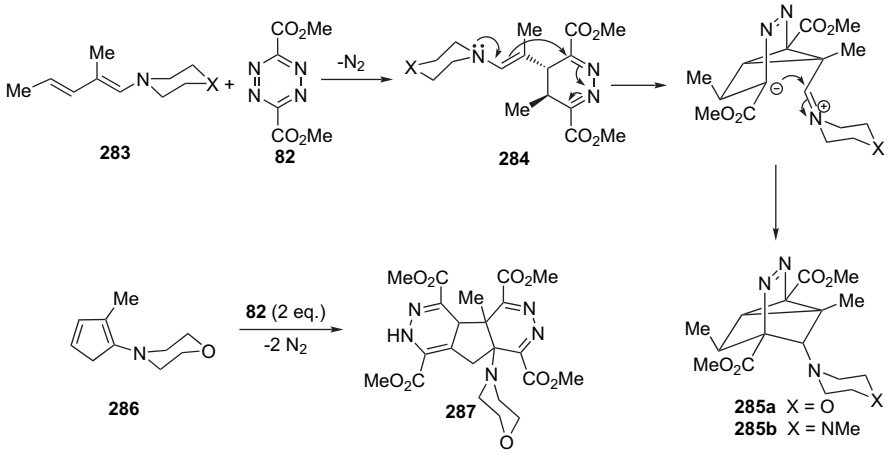


Scheme 47.

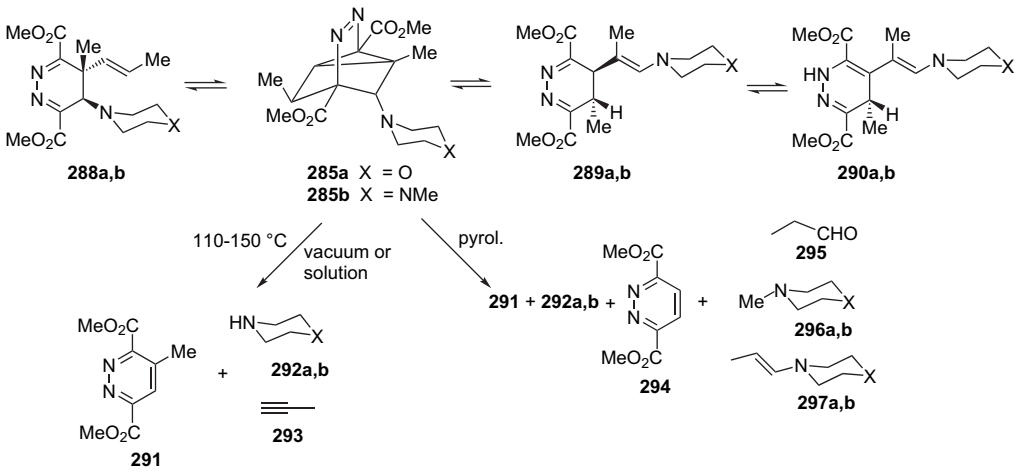
a tandem cyclisation reaction of the intermediate **284** provided the azo-bridged tricyclic ring system **285**. In contrast to 2-methy-1-morpholin-1,3-pentadiene (**283**), **286** reacted with 2 mol of tetrazine to give the dipyridazine structure **287** (Scheme 48). Kotschy et al. also investigated the thermal decomposition at 110–150 °C of the azo-bridged tricyclic ring system **285a**,**b** to give dimethyl 4-methylpyridazine-3,6-dicarboxylate **291** in excellent yield.[129] When samples of **285a**,**b** were heated at 200, 250 and 300 °C, however, the increasing pyrolysis temperature caused an increase in the proportion of side products. They proposed a mechanism for the decomposition and this mechanism was supported by quantum chemical calculations and experimental evidence. According to the proposed mechanism, the initial step of the thermal decomposition of **285a**,**b** is a retro-Diels–Alder reaction that leads either to **288a**,**b** or **289a**,**b**, which is in tautomeric equilibrium with **290a**,**b** (Scheme 49).

Appropriately substituted azolyldienamines **298a–c** underwent double *inverse*-Diels–Alder reactions with tetrazine derivatives to give azolylpyridazines **301** and dihydropyridazines **302**, as depicted in Scheme 50.[130] Smith et al. accomplished the reaction of dienamines with dimethyl ester tetrazine **82** to yield the *m*- and *p*-phenylene-bridged bis-azolylvinyl-pyridazines **306a**,**b** and **307a**,**b** (Scheme 51).[131]

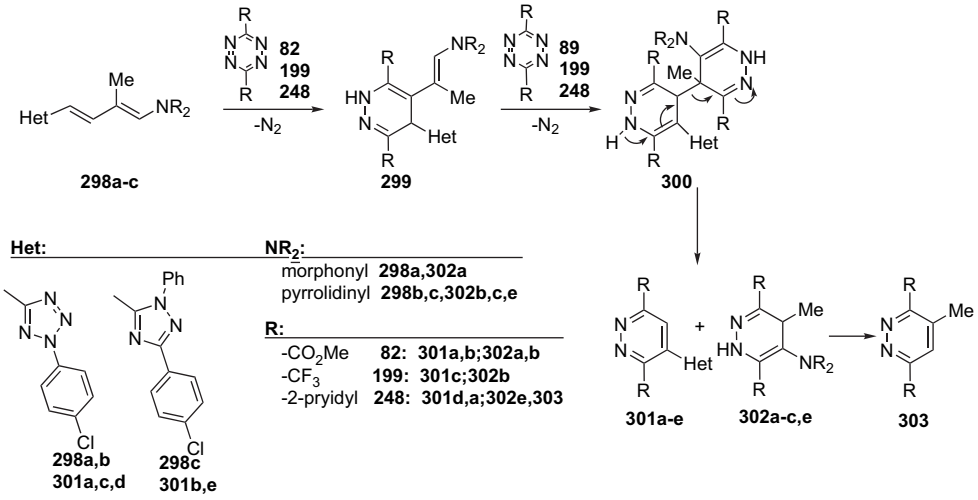
Further intensive studies of the parent compound **3** have been hindered, due to the fact that the preparation of **3** is often accompanied by various synthetic obstacles. This compound has become readily available, however,



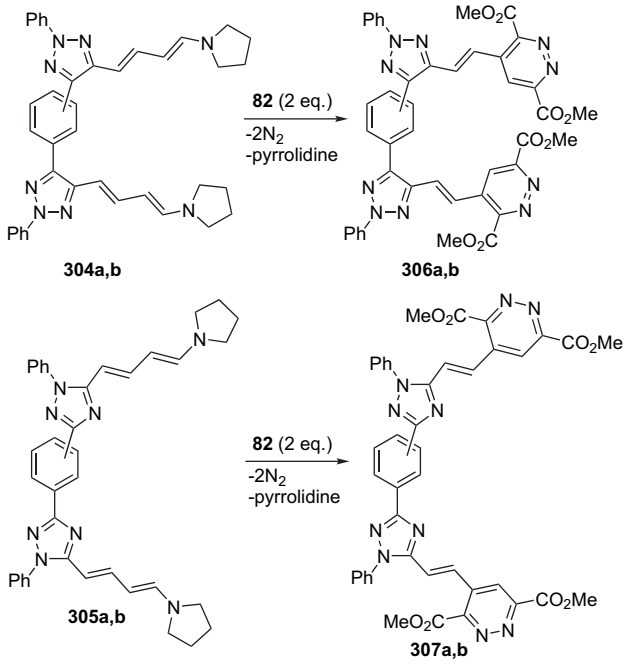
Scheme 48.



Scheme 49.

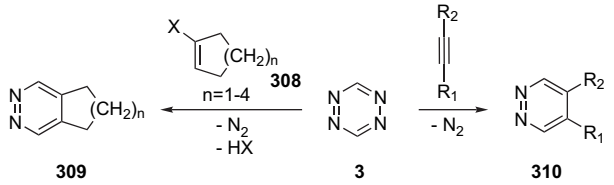


Scheme 50.



Scheme 51.

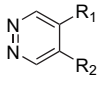
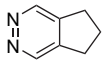
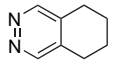
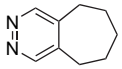
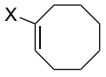
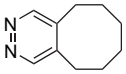
through a method developed by Sichert[132a] and a similar procedure published by van der Plas.[132b] Sauer et al. optimised the synthesis procedure for 1,2,4,5-tetrazine (**3**) and investigated its reaction kinetics and reactivity to yield simple 4- and 4,5-substituted pyridazines **310** using electron-rich alkenes and alkynes as dienophiles (Scheme 52).[133,134] They also synthesised both metalated (metal=Si, Ge and Sn) and unmetalated substituted pyridazines (Table 7).



Scheme 52.

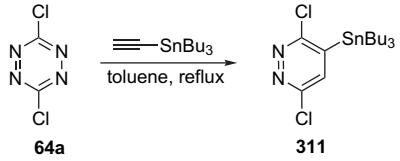
The use of analogues of 3,6-dichloro-1,2,4,5-tetrazine (**64a**) as herbicides has been reported.[135] Sparey and Harrison described the rapid access to a range of highly functionalised pyridazines (Table 8) by using the 3,6-dichlorotetrazine **64a** as an efficient azadiene in *inverse* electron-demand

Table 7. Cycloadducts of 1,2,4,5-tetrazine (**3**)

Product (**310**)		Dienophile (X: NMe_2, OMe, $OSiMe_3$)	Product (**309**)
			
R_1	R_2		
H	H		
H	CMe_3		
H	Ph		
H	C_6H_4-*p*OMe		
H	C_6H_4-*p*ONO_2		
H	NMe_2		
H	OMe		
H	SMe		
H	$SnBu_3$		
H	$GeBu_3$		
H	$SiMe_3$		
MeS	NMe_2		
MeS	SMe		
Me_3C	CMe_3		
Me_3Sn	$SnMe_3$		
Bu_3Sn	$SnBu_3$		
Me_3Ge	$GeMe_3$		
Me_3Si	$SiMe_3$		

cycloadditions with alkenes and alkynes, as depicted in Scheme 53 for the synthesis of **311**.[136]

1,8-Bis(dimethylamino)naphthalene (**312**) is both a 'proton sponge' and unusually highly reactive in electrophilic substitution reactions.[137–139] In spite of the large steric strains in this molecule, the *peri*-dimethylamino groups retain their strong electron-donating effect towards the aromatic π-system. In order to form new possible 'proton sponges', Ozeryanskii and co-workers performed [4+2] cycloadditions of 5,6-bis(dimethylamino)acenaphthalene (**313**), dimethylamino-acenaphthalene **314**, acenaphthalene **315** and 1,8-bis(dimethylamino)-4-vinylnaphthalene (**316**) with tetrazines **56a** and **82** to yield new pyridazine derivatives **318–322** (Scheme 54).[140] They showed that these compounds can change the site of protonation, depending on the solvent, and obtained quantitative data on the reactivities of the 'proton sponge'. The obtained data were also compared with the corresponding data for a series of close analogues.



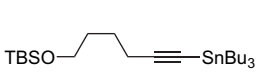
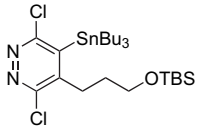
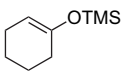
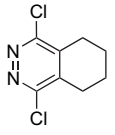
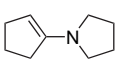
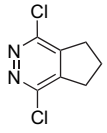
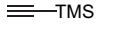
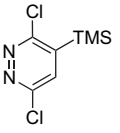
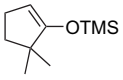
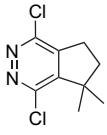
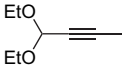
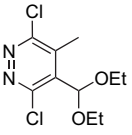
Scheme 53.

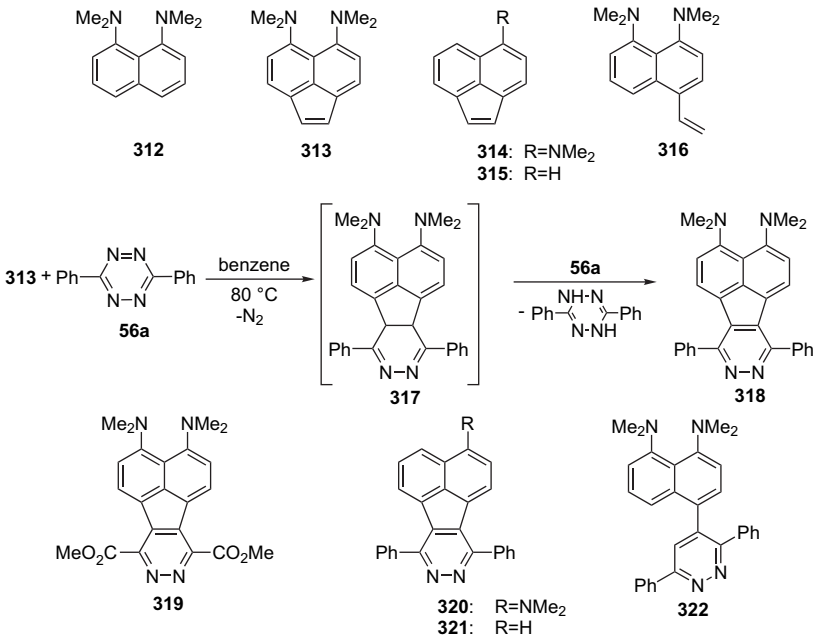
The pyridazine nucleus is of considerable interest because of its synthetic applications and important pharmacological activities. Balci and co-workers reported the first synthesis of unusual bicyclic endoperoxides containing both pyridazine and peroxide units and their chemical transformations. *Inverse*-Diels–Alder cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**82**) with unsaturated bicyclic endoperoxides (**323**, **327**, **332**, **335** and **343**) gave the products **324**, **328**, **333**, **334**, **336**, **337**, **344** and **345** containing bicyclic endoperoxide-pyridazine rings.[141,142] Balci et al. also investigated various transformations of these endoperoxides, yielding new pyridazine derivatives **325–348** (Schemes 55–59).

The aza substitution in the larger polycyclic aromatic hydrocarbons can either enhance or diminish the biological activity.[143] Therefore, Balci et al. also aimed to synthesise the phthalazine-type dihydrodiols and diol epoxides.[144] The reaction of dimethyl ester tetrazine **82** with benzene *cis*-diol **349** as dienophile in CH_2Cl_2 to form the main core **351** gave the dihydrodiol **350** containing the 1,4-dihydropyridazine ring. Attempts to oxidise the dihydropyridazine **350** to the pyridazine **351** resulted in the formation of the 5- and 5,6-dihydroxy-phthalazine derivatives **352** and **353**. We have investigated the Diels–Alder reaction of tetrazine with cyclohexadiene acetonide **354** and epoxy-ketal cyclohexene **356**.[144] These reactions led to the possible carcinogenic phthalazine type of dihydrodiol **355** and diol epoxide **357**, where the hydroxyl groups are protected (Scheme 60).

The unexpected cycloaddition of ketones and aldehydes to dipyridinyl-1,2,4,5-tetrazine **248** under microwave conditions was described by Schubert et al. as an alternative route for the synthesis of substituted pyridazines.[145] The reaction

Table 8. Cycloadducts of 3,6-dichloro-1,2,4,5-tetrazine (**64a**)

Dienophile	Product	Dienophile	Product
			
			
			

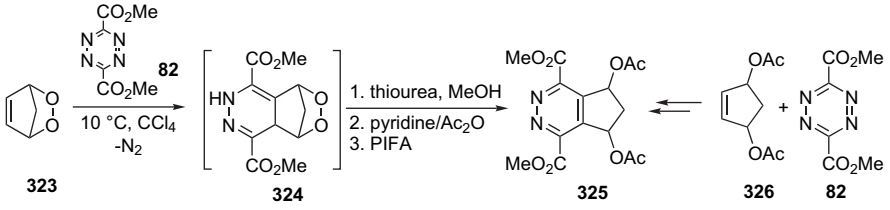


Scheme 54.

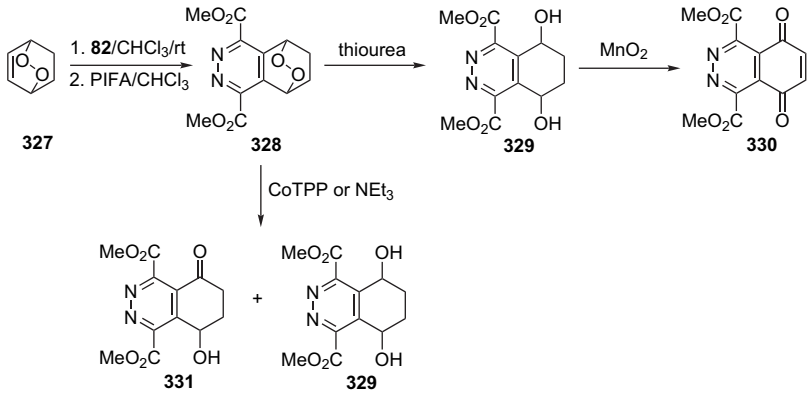
mechanism they suggested included the enol tautomer of the ketone participating in the cycloaddition instead of the keto tautomer and the rapid elimination of water occurring, resulting in the respective pyridazine derivative **359**–**365** (Scheme 61 and Table 9). This result showed a shift in the keto-enol equilibrium to the enol tautomer under microwave conditions. Reaction of 3-methyl-2-butanone possessing two enol tautomers with tetrazine **248** gave the pyridazine derivatives **366** and **367**. Moreover, heating of **248** with water for 20 min to 150 °C under microwave irradiation resulted in the quantitative formation of pyridine-2-carboxylic acid (pyridin-2-ylmethylene)-hydrazide (**368**).

5.2. Synthesis and studies on systems with the exception of pyridazine

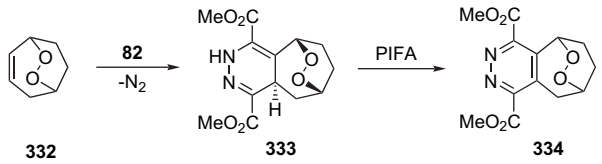
Warrener and co-workers demonstrated the preparation of new building block structures (**371**, **373**–**376**) containing rigidly linked pyrimidines suitable for uracil and cytosine elaboration, as shown in Scheme 62.[146]



Scheme 55.



Scheme 56.

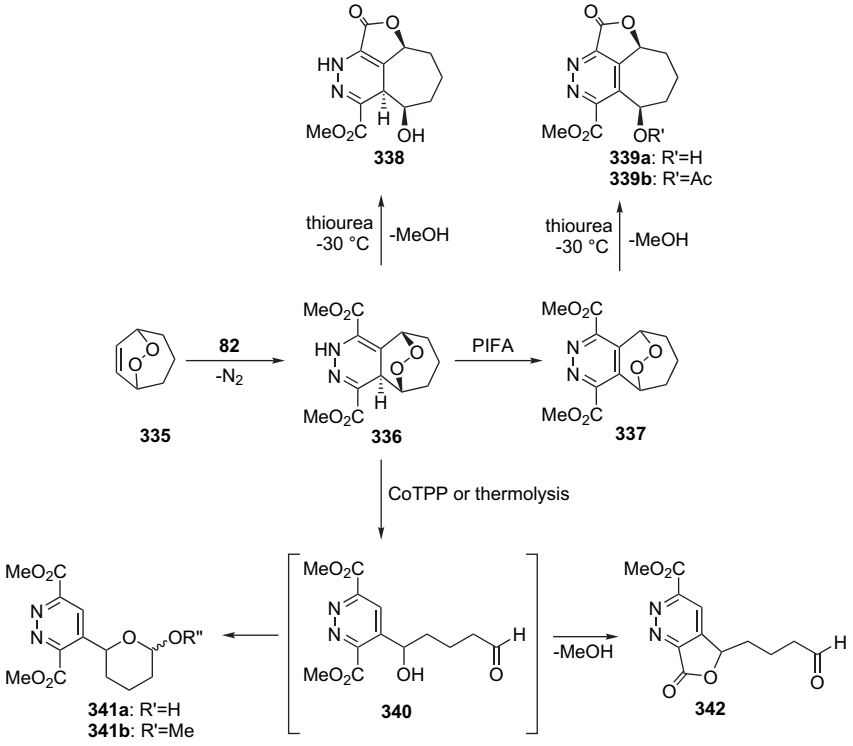


Scheme 57.

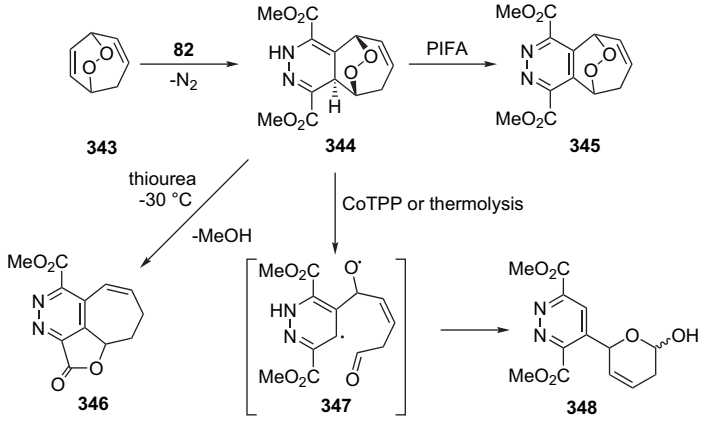
Extensive kinetic studies of sulfur- and selenium-carbon hetero double bonds as dienophiles towards various cyclic and acyclic dienes in [4+2] cycloadditions were reported by Sauer et al.[147] The reactions of substituted thiobenzophenones **377a–e** with tetrazine **199** were performed in toluene at 100 °C to furnish the products **378a–e**, possessing a 6*H*-[1,3,4]thiadiazine skeleton (Scheme 63).

Nyitrai and co-workers investigated the light-reductive ring contractions of some six-membered cyclic iminium ions.[148] A consecutive reaction of 1,2(4)-dihydrotetrazine **379** to give 3,5-diphenyl-1*H*-triazole (**382**) has been known for a long time via a pathway A.[149,150] This group determined that the photoconversion of **379**, on raising the concentration of HCl in 2-propanol, was markedly accelerated and furnished the triazole **382** as a single product in a yield of 50% (pathway B in Scheme 64).

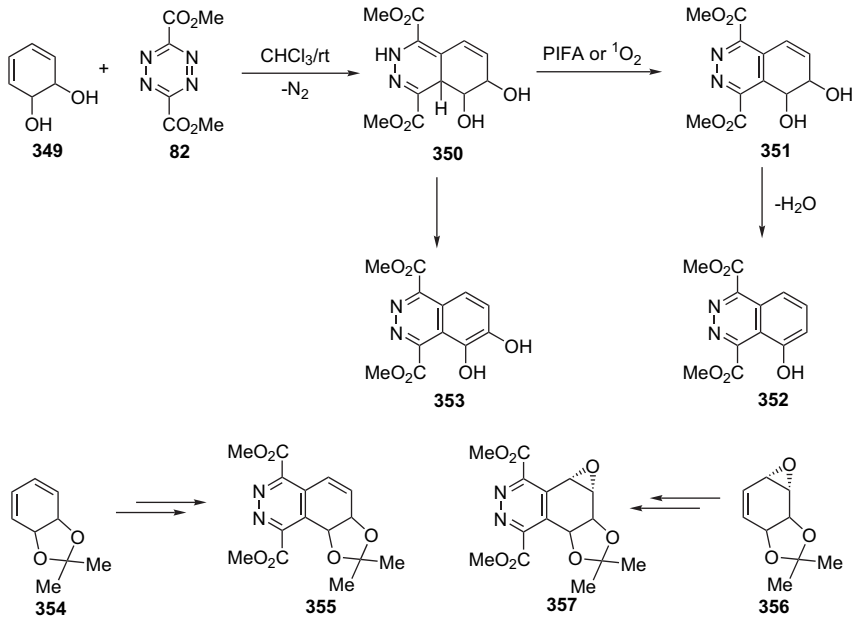
Klug and co-workers determined that, according to quantum mechanical calculations, 1,4-*N*,*N* cycloaddition of alkenes or alkynes to 1,2,4,5-tetrazines is possible as an alternative to 1,4-*C*,*C* cycloaddition (Carboni–Lindsey reaction).[151] The reaction of **56a** with 1,4-dimethylpyridinium iodide in the



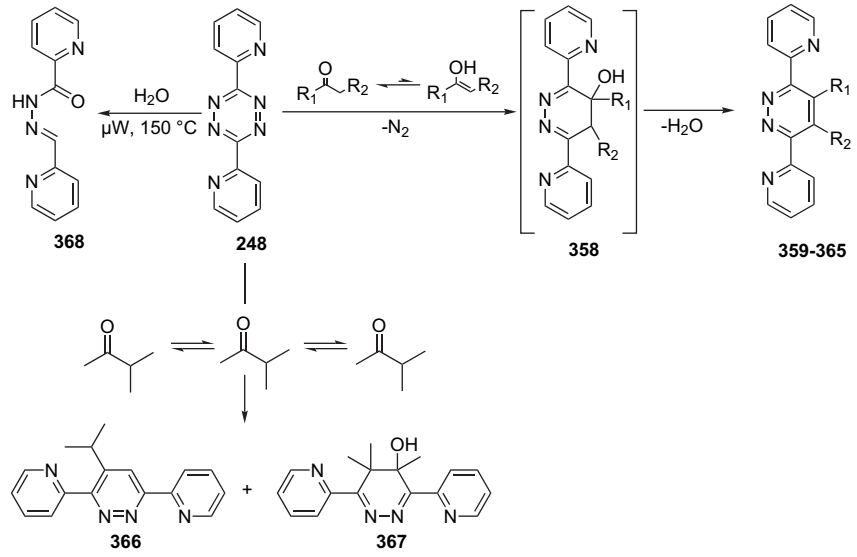
Scheme 58.



Scheme 59.



Scheme 60.



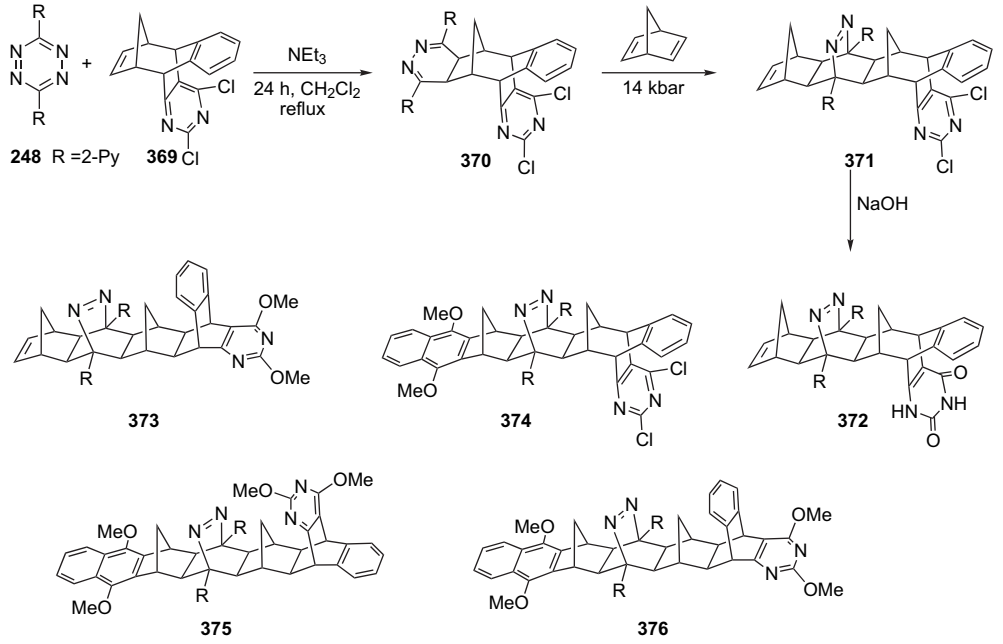
Scheme 61.

Table 9. Cycloadducts of microwave-assisted *inverse*-Diels–Alder reactions between **248** and various ketones and aldehydes

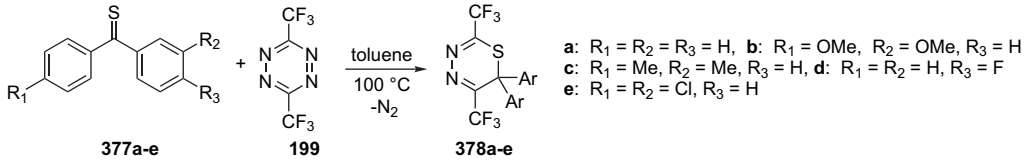
Reagent	Product	R_1	R_2	Reagent	Product	R_1	R_2
Acetone	**359**	Me	H	Butanal	**360**	Et	H
2-Butanone	**360**, **361**	Et, Me	H, Me	Hexanal	**364**	*n*-Butyl	H
3-Pentanone	**362**	Et	Me	Octanal	**365**	*n*-Hexyl	H
Acetaldehyde	**363**	H	H				

presence of triethylamine in DMF for 24 h gave the pyrazole derivative **388**, which formally corresponds to *C*,*C*-[4+2] cycloaddition, N_2 elimination, rearrangement and oxidation steps (pathway A in Scheme 65). Klug et al., however, isolated only **392** as a major product from the refluxing of a mixture of 1,4-dimethylpyridinium iodide and triethylamine in ethanol for 24 h. They explained that the formation of **392** can be rationalised by *N*,*N*-[4+2] cycloaddition, benzonitrile elimination, rearrangement and oxidation steps (pathway B in Scheme 65).

Sauer and co-workers described in detail the synthesis of 3,4-diazanorcaradienes **395**, **396**, **399** and **400** together with the tetracyclic aliphatic azo compounds **397** and **398**, which

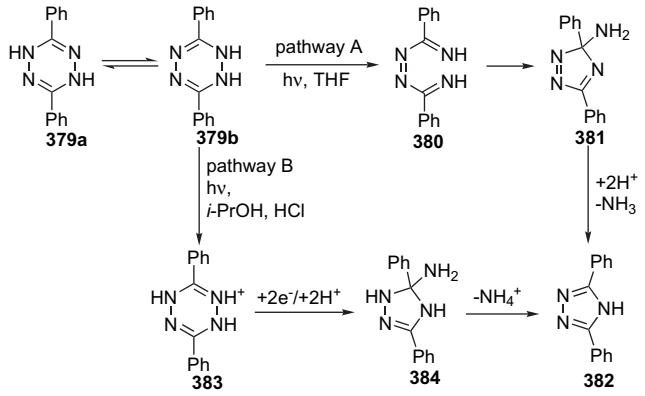


Scheme 62.



Scheme 63.

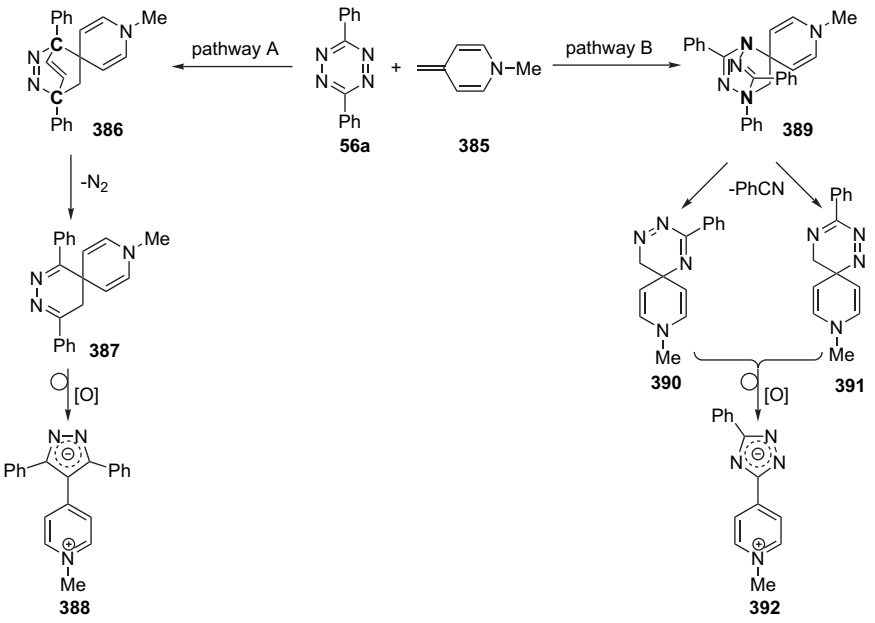
are versatile starting materials in thermolysis and photolysis reactions (Scheme 66).[152] 3,4-Diazanorcaradienes were obtained from the reaction of 1,2,4,5-tetrazines **393** (R_1=CO_2Me, CO_2H, CN, CF_3, phenyl, aryl and heteroaryl) and cyclopropenes **394a**,**b** (a: R_2=H and b: R_2=Me) in two steps including addition and loss of nitrogen. The reaction of diazanorcaradienes **395** and **396** with cyclopropenes gave the bisadducts **397** and **398** (R_1=CO_2Me, CO_2H, CN, CF_3, aryl and heteroaryl; R_2=H and Me). Furthermore, detailed kinetic studies of diazanorcaradienes were undertaken by Sauer et al. The kinetic data showed that norcaradienes **395** and **396** were much less reactive dienes than 1,2,4,5-tetrazines by a factor of 10^3–10^4 for the rate constant. The coupling constants for the ABX_2 spin system and the chemical shift difference between 7-H_{syn} and 7-H_{anti} in **395** are in accordance with the diazanorcaradiene structure. The addition reactions of 3,4-diazanorcardienes **399** (R_1=R_2=SMe; R_1=SMe, R_2=OMe; R_1=R_2=OMe; R_1=Ph, R_2=SMe; R_1=Ph, R_2=OMe) and **400** (R_1=R_2=SMe; R_1=R_2=OMe) to form bisadducts of the type **397** and **398** were unsuccessful. This unreactivity showed that the resonance energy of one or two imino ester units in **399** and **400** has to be sacrificed.



Scheme 64.

Sauer et al. also reported that 1,2,4,5-tetrazines **393** (R=Me, CO_2Me, CO_2H, CN, CF_3, phenyl, aryl and heteroaryl) and 3,3-bicyclopropenyl **401** readily react to afford the semibullvalenes **404** in a one-pot method, as depicted in Scheme 67.[153] The reaction progresses upon the cycloaddition–loss of nitrogen–intramolecular cycloaddition–valence isomerisation steps. The observed kinetic results for the two-model system are in agreement with the proposed reaction mechanism.

Benzo[*c*]furan (isobenzofuran) is a reactive diene that readily undergoes a Diels–Alder reaction with dienophiles to restore their aromaticity.[154–158] Wong et al. attempted to prepare an isolable versatile building block for linear polycyclic aromatic compounds.[159] For the preparation of silylated polycyclic aromatic hydrocarbons (PAH), 5,6-bis(trimethylsilyl)benzo[*c*]furan (**406**) was chosen as their target molecule. The generation of **406** was achieved by treating **405**

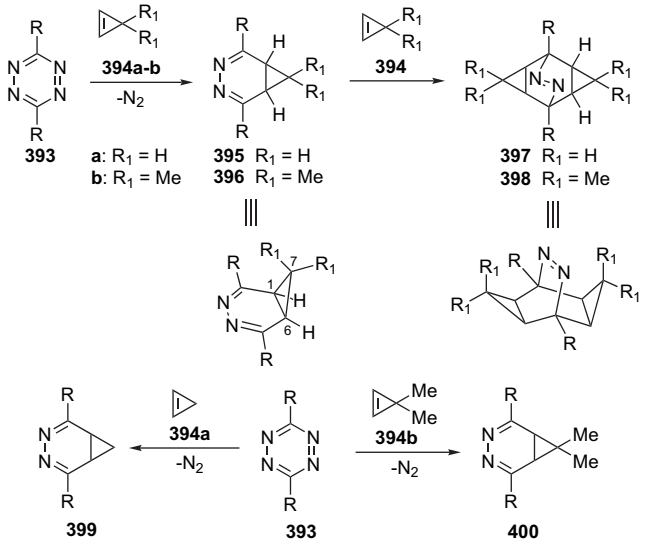


Scheme 65.

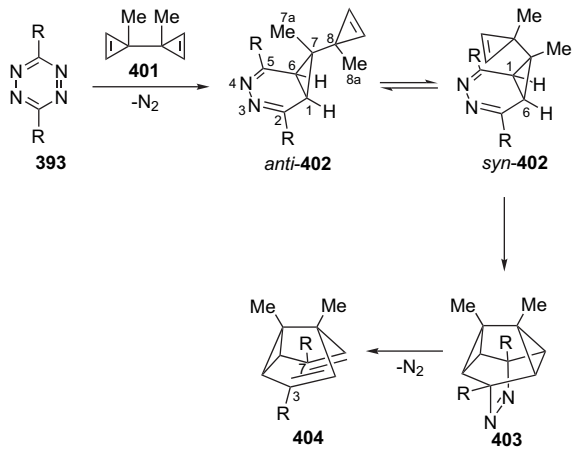
with 3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (**248**) using the Warrener approach[160] as the key step. In the presence of various dienophiles, benzo[*c*]furan **406** provided the desired Diels–Alder trapping adducts **408–411** (Scheme 68).[159,161] Dehydration of **408** to the naphthalenenitrile **412** was accomplished by the reaction of lithium iodide and 1,8-diazabicyclo[5.4.0]undec-1-ene (DBU) in refluxing THF. The dehydrations in refluxing 90% acetic acid of three quinone adducts of benzo[*c*]furan **406** provided the aromatic compounds **413–415**.

In the absence of methyl groups, dihydropyrene **419** is thermally stable, whereas the steric interaction between the heterocycle-methyl hydrogens in **418** destabilises the dihydropyrene more than [2$_2$]metacyclophanedienes with a furan **416** or pyrrole **417** on the bridge.[162] Mitchell and co-workers synthesised[163] [2$_2$]metacyclophanedienes **420**, **421** and **422a**,**b** with furan bridges using the Warrener approach.[160] The key synthetic step to generate the furans (**420–422**) was a Diels–Alder reaction of an aryne-oxonorbornadiene with dipyridyltetrazine **248** as described in Scheme 69. The degradation of the bis adduct **424** gave the desired furan **421**.

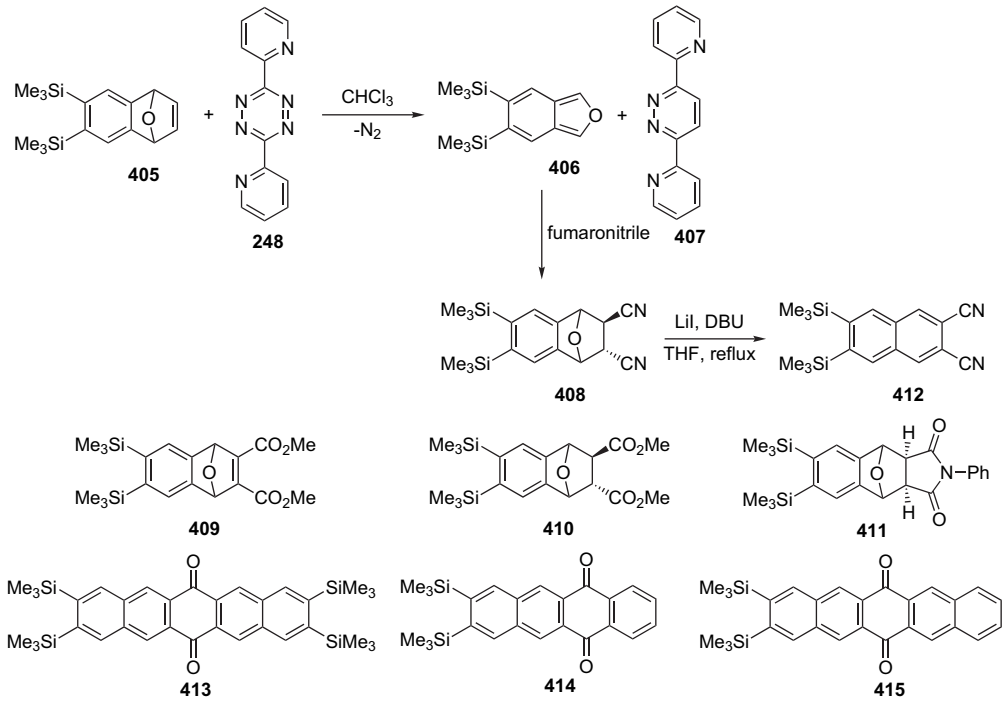
Similar protocols were applied for the synthesis of 1,2-dicyano-4,5,6,7-tetrafluoronaphthalene (**428**), which transformed fluorine-containing metal naphthalocyanines, and their nonlinear transmissions were studied by Hanack et al.[164] The generation of *N*-methyl-4,5,6,7-tetrafluoroisoindole (**426**), which is a moderately stable compound, is the key step. The monomer **429** was obtained by reacting **426** with dicyanoacetylene, followed by *m*-CPBA oxidation to remove the methylamino group in a one-pot reaction. The isoindole **426** was used for the synthesis of soluble π-stacking tetracene derivatives **432a–d**. Swager and co-workers also discussed the crystal packing, electrochemical behaviour and UV–vis absorbance spectroscopy of these materials (Scheme 70).[165]



Scheme 66.

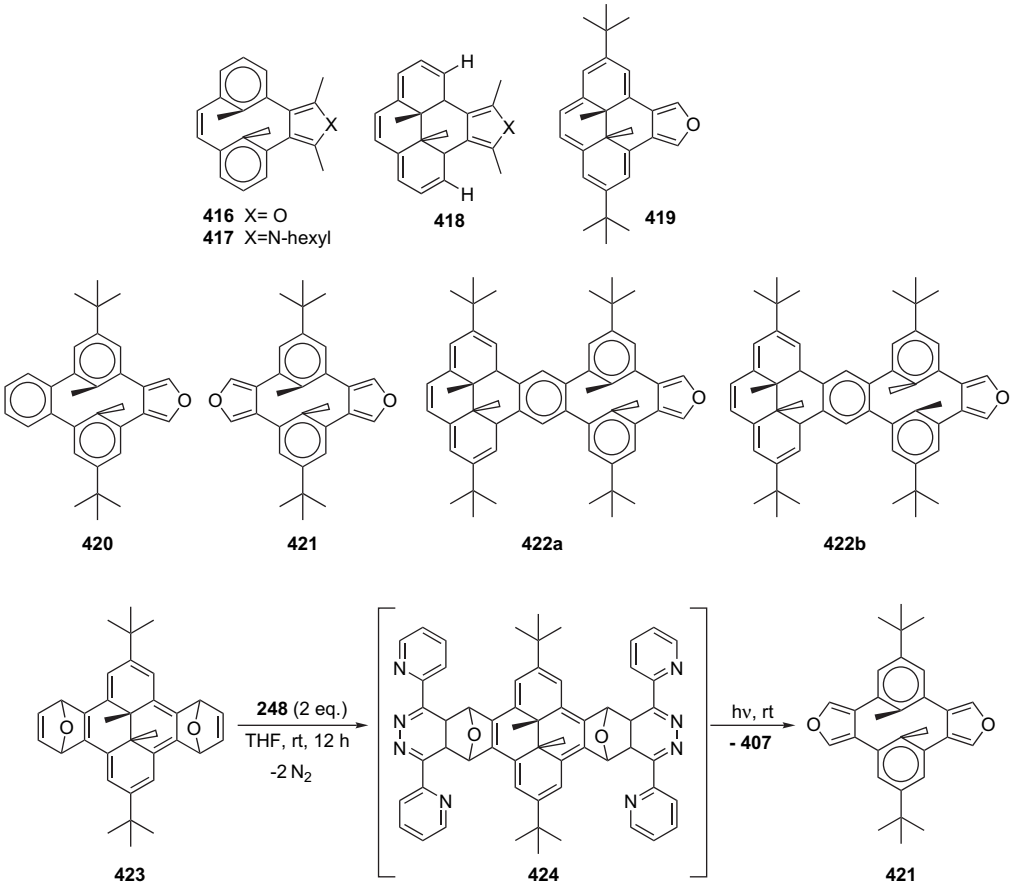


Scheme 67.

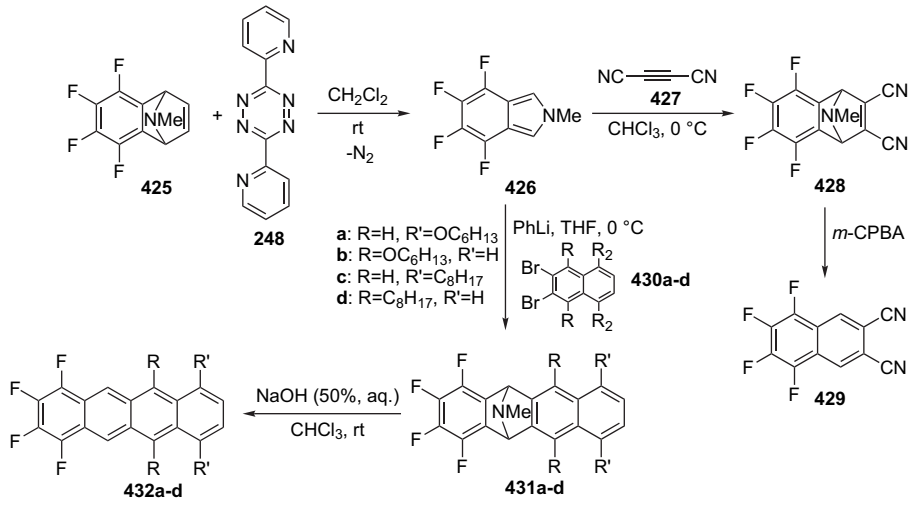


Scheme 68.

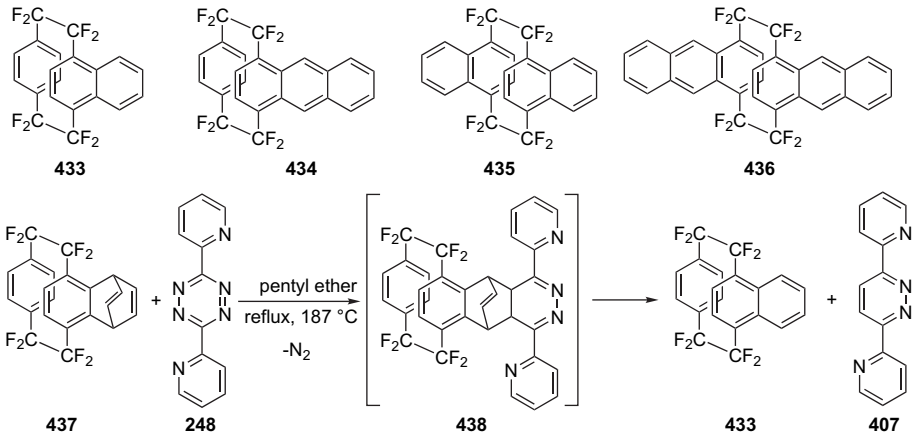
The rigid skeleton and high strain energy of the [2.2]paracyclophane system leads to unique transannular interactions that affect both the chemistry and the spectroscopy of these systems.[166,167] The synthesis of four novel bridge-fluorinated [2.2]paracyclophanes **433–436** containing naphthalene and anthracene condensed polycyclic subunits was



Scheme 69.



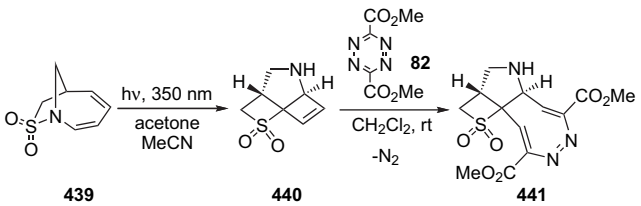
Scheme 70.



Scheme 71.

achieved by Dolbier and co-workers using the Warrener approach,[160] as depicted in Scheme 71,[168] and details of their NMR and UV spectra were provided.

Paquette et al. devised a route to the doubly unsaturated bridgehead sultam **439**.[169] The irradiation of **439** at 350 nm resulted in the formation of the structurally novel spiro heterocycle **440** via a two-photon process. These workers suggested the probable mechanism of the generation of **440**. The strained nature of the double bond in **440** was also established by a Diels–Alder cycloaddition with 1,2,4,5-tetrazine **82**. The reaction gave dihydro-diazocine **441** via the loss of nitrogen, followed by cleavage of the cyclobutane ring (Scheme 72).

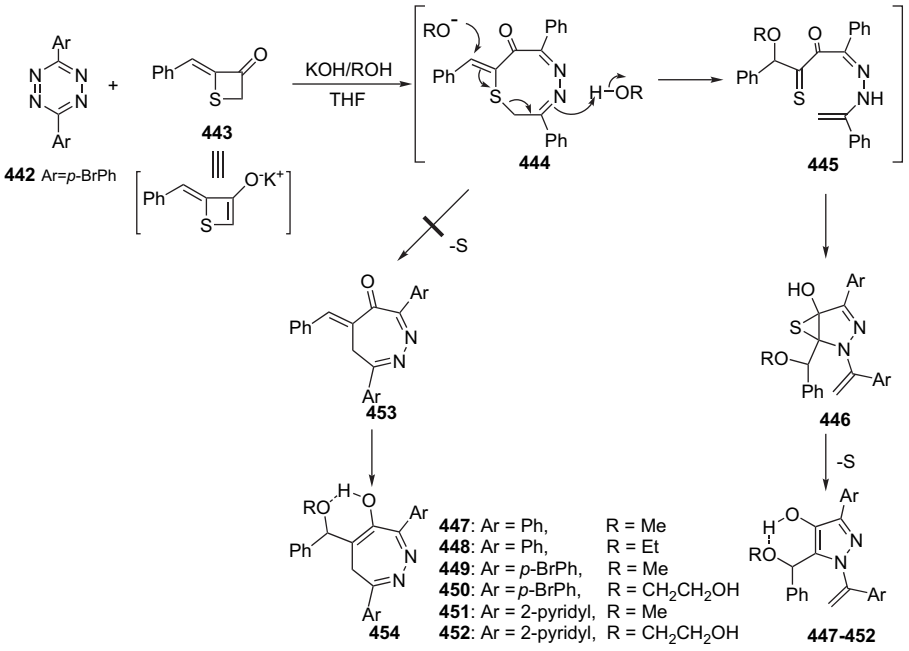


Scheme 72.

A novel one-step, non-obvious route to fully substituted pyrazol-4-ols was reported by Kurth and co-workers.[170] The reaction of thietanone **443** with tetrazine **428** in 5% methanolic KOH resulted in the formation of an unexpected product **447**, instead of **444** or **453–454**, as shown in Scheme 73. They isolated the sulfur-extruded products **447–452** from the reaction of **443** with aryl-substituted tetrazines **56a**, **442** and **248** in methanol, ethanol or ethylene glycol.

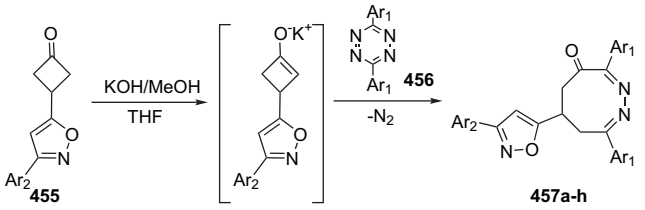
Kurth et al. designed the synthesis of diazocinones and investigated their conformational analysis.[171a] The condensation of aryl-substituted 1,2,4,5-tetrazines **456** with isoxazolylcycobutanones **455** in methanolic KOH provided a general route to novel isoxazole-substituted dihydrodiazocinones **457** (Scheme 74). The conformational methods of these eight-membered diaza heterocycles by spectral, crystallographic, kinetic and computational methods showed that the major contributor was provided by the twist-boat-chair conformation of *cis*,*cis*-1,3-cyclooctadiene, as described by Anet and Yavari.[171b]

In their continuing work on the Diels–Alder reactions of unsaturated bicyclic endoperoxides with tetrazine, Balci and co-workers reported the trapping of highly reactive



Scheme 73.

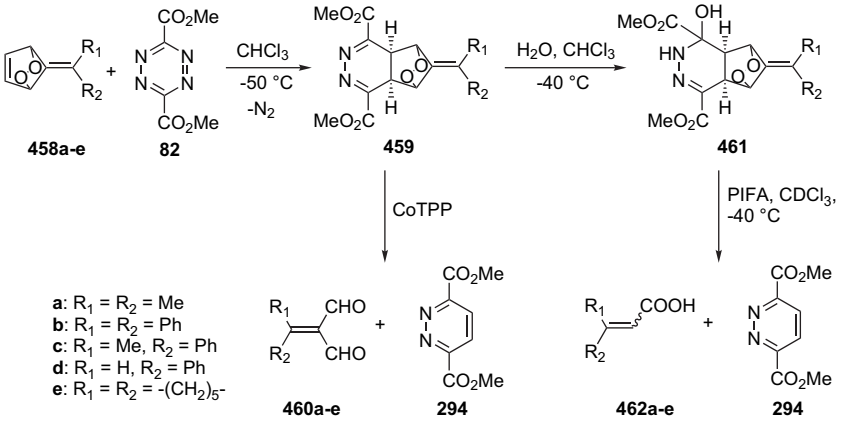
fulvene endoperoxides **458a–e** with dimethyl 1,2,4,5-tetrazine carboxylate **82**. Treatment of the trapping products **459** with cobalt(II) *meso*-tetraphenylporphyrin (CoTPP) gave alkylidene- and arylidenemalonaldehydes **460a–e** via Warrener[160] cleavage.[172] The reaction of the trapping products **459** with water, followed by bis[(trifluoroacetoxy)-iodo]benzene (PIFA) oxidation, provided acrylic acid derivatives **462a–e** and dimethyl pyridazine-3,6-dicarboxylate (**294**) via unusual fragmentation (Scheme 75).[173]



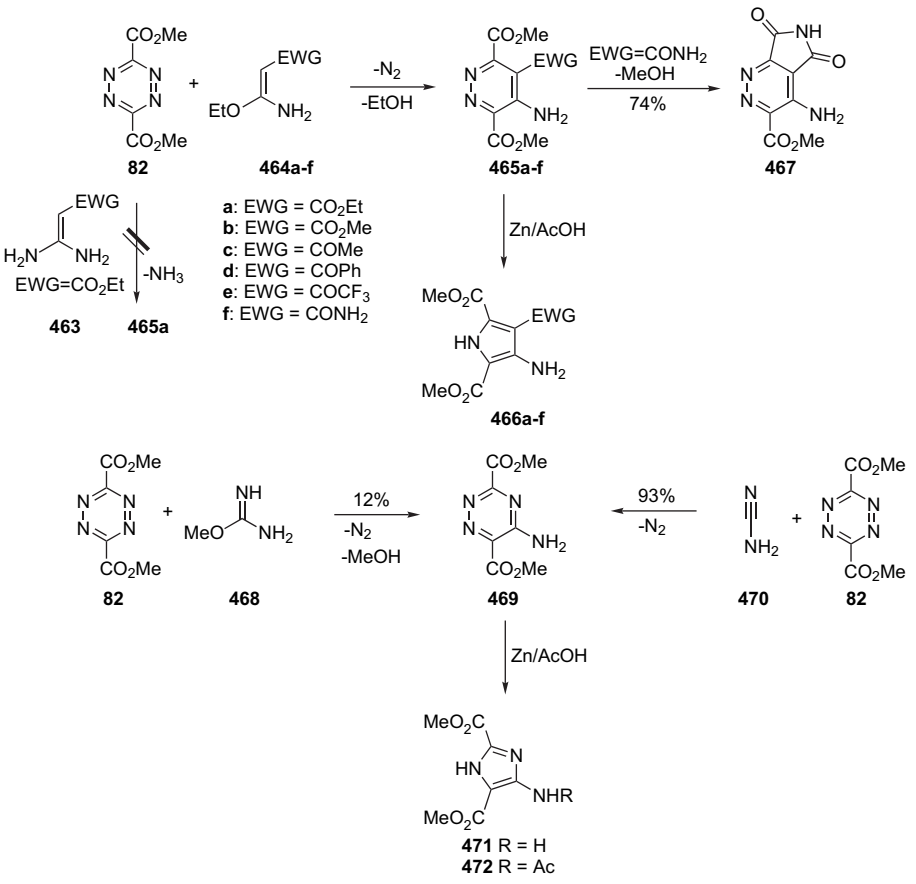
a: Ar_1 =Ph, Ar_2= Ph **b**: Ar_1 = 4-ClC_6H_4, Ar_2 = Ph **c**: Ar_1 = 4-BrC_6H_4, Ar_2 = Ph
d: Ar_1 = 4-MeC_6H_4, Ar_2 = Ph, **e**: Ar_1 = Ph, Ar_2 = 4-$MeOC_6H_4$
f: Ar_1 = 4-ClC_6H_4, Ar_2 = 4-$MeOC_6H_4$ **g**: Ar_1 = 4-BrC_6H_4, Ar_2 = 4-$MeOC_6H_4$
h: Ar_1 = 4-MeC_6H_4, Ar_2 = 4-$MeOC_6H_4$

Scheme 74.

Troschurtz and Müller tested the reactivity of ketene *N*,*N*-acetal (EWG=CO_2Et) **463** with tetrazine **82** at various temperatures in different solvents.[174] This reaction gave no products that could be characterised. Therefore, they turned their attention to the cycloaddition reaction of EWG-substituted ketene *N*,*O*-acetals **464a–f** with tetrazine **82**. A series of *N*,*O*-acetals **464a–f** were reacted with the tetrazine **82** to give the tetrafunctionalised pyridazines **465a–f**. Reductive ring contraction of the pyridazines gave the 4-aminopyrrole derivatives **466a–f**. The cycloaddition of the ketene acetal **464f** and the tetrazine **82** gave the mixture of the pyridazine **465f** and the imide **467**, the formation of which can be explained by an intramolecular imidation. Furthermore, the synthesis of the 5-amino-1,2,4-triazine derivative **469**, which was rearranged to 4-aminoimidazole-2,5-dicarboxylic acid dimethyl ester **471**, was achieved by



Scheme 75.



Scheme 76.

the cycloaddition of the tetrazine **82** with *O*-methylisourea (**468**) or cyanamide (**470**) (Scheme 76).

6. Conclusions

We have described in this review the advances and applications in 1,2,4,5-tetrazine chemistry over the last 10 years. 1,2,4,5-Tetrazine is a highly reactive diene for $LUMO_{diene}$-controlled [4+2] *inverse*-Diels–Alder cycloaddition processes and an excellent precursor to attain the pyridazine ring, which can also be transformed by reductive ring contraction to the respective pyrrole ring. Therefore, there is increased interest among synthetic chemists in both the synthesis and the applications of new asymmetric and symmetric 1,2,4,5-tetrazine motifs. 1,2,4,5-Tetrazines have, however, been very widely utilised for the highly effective synthesis of natural products, bioactive compounds, ligands, highly energetic materials, building blocks, diazocinones, imidazoles, alkylidene-/arylidenemalonaldehydes, acrylic acid derivatives, pyrazoles and polycyclic aromatic compounds. Such applications of 1,2,4,5-tetrazines continue to increase rapidly in number.

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References and notes

1. Benson, F. R. *The High Nitrogen Compounds*; Wiley-Interscience: New York, NY, 1984.
2. Neunhoeffer, H. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, Chapter 2.21, pp 531–572.
3. Hurst, D. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, Chapter 6.22, pp 957–965.
4. Churakov, A. M.; Tartakovsky, V. A. *Chem. Rev.* **2004**, *104*, 2601.
5. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
6. Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
7. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
8. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
9. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, CA, 1987.
10. Boger, D. L. *Bull. Soc. Chim. Belg.* **1990**, *99*, 599.
11. Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149.
12. Sauer, J. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 6, p 901.
13. Shawali, A. S.; Elsheikh, S. M. *J. Heterocycl. Chem.* **2001**, *38*, 541.
14. Kaim, W. *Coord. Chem. Rev.* **2002**, *230*, 127.
15. Kovalev, E. G.; Postovskii, I. Y.; Rusinov, G. L.; Shegal, I. L. *Chem. Heterocycl. Compd.* **1981**, *17*, 1063.
16. Ritter, S. *Chem. Eng. News* **2004**, *82*, 44.

17. Chavez, D. E.; Hiskey, M. A.; Gilardi, R. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1791.
18. Kerth, J.; Lobbecke, S. *Propellants, Explos., Pyrotech.* **2002**, *27*, 111.
19. Huynh, M. H. V.; Hiskey, M. A.; Hartline, E. L.; Montoya, D. P.; Gilardi, R. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4924.
20. Zhou, G.; Zhang, J.-L.; Wong, N.-B.; Tian, A. *J. Mol. Struct. Theochem.* **2004**, *668*, 189.
21. Neutz, J.; Grosshardt, O.; Schaufele, S.; Schuppler, H.; Schweikert, W. *Propellants, Explos., Pyrotech.* **2003**, *28*, 181.
22. Huynh, M. H. V.; Hiskey, M. A.; Pollard, C. J.; Montoya, D. P.; Hartline, E. L.; Gilardi, R. D. *J. Energ. Mater.* **2004**, *22*, 217.
23. Churakov, A. M.; Smirnov, O. Y.; Ioffe, S. L.; Strelenko, Y. A.; Tartakovsky, V. A. *Eur. J. Org. Chem.* **2002**, *14*, 2342.
24. Tartakovsky, V. A. *Mater. Res. Soc. Symp. Proc.* **1996**, *418*, 15.
25. Chavez, D. E.; Hiskey, M. A. *J. Heterocycl. Chem.* **1998**, *35*, 1329.
26. Löbbecke, S.; Pfeil, A.; Krause, H. H.; Sauer, J.; Holland, U. *Propellants, Explos., Pyrotech.* **1999**, *24*, 168.
27. Chavez, D. E.; Hiskey, M. A.; Gilardi, R. D. *Angew. Chem.* **2000**, *112*, 1861.
28. Michael A. H.; David E. C.; Naud, D. U.S. Patent 6,342,589 B1, 2002.
29. Talawar, M. B.; Sivabalan, R.; Senthilkumar, N.; Prabhu, G.; Asthana, S. N. *J. Hazard. Mater.* **2004**, *113*, 11.
30. (a) Curtius, T.; Darapsky, A.; Muller, E. *Chem. Ber.* **1915**, *48*, 1614; (b) Sauer, J.; Pabst, G. R.; Holland, U.; Him, H.-S.; Loebbecke, S. *Eur. J. Org. Chem.* **2001**, *13*, 697.
31. Chavez, D. E.; Hiskey, M. A.; Naud, D. L. *Propellants, Explos., Pyrotech.* **2004**, *29*, 209.
32. Chavez, D. E.; Hiskey, M. A.; Gilardi, R. D. *Org. Lett.* **2004**, *6*, 2889.
33. Nuynh, M. H. V.; Hiskey, M. A.; Archuleta, J. G.; Roemer, E. L.; Gilardi, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 5658.
34. Chavez, D. E.; Tappan, B. C.; Hiskey, M. A.; Son, S. F.; Harry, H.; Montoya, D.; Hagelberg, S. *Propellants, Explos., Pyrotech.* **2005**, *30*, 412.
35. Nuynh, M. H. V.; Hiskey, M. A.; Chavez, D. E.; Naud, D. L.; Gilardi, R. *J. Am. Chem. Soc.* **2005**, *127*, 12537.
36. Boger, D. L.; Sakya, S. M. *J. Org. Chem.* **1988**, *53*, 1415.
37. Boger, D. L.; Zhang, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 4230.
38. Sandstrom, J. *Acta Chem. Scand.* **1961**, *15*, 1575.
39. Sakya, S. M.; Groskopf, K. K.; Boger, D. L. *Tetrahedron Lett.* **1997**, *38*, 3805.
40. Boger, D. L.; Schaum, R. P.; Garbaccio, R. M. *J. Org. Chem.* **1998**, *63*, 6329.
41. Hamasaki, A.; Ducray, T.; Boger, D. L. *J. Org. Chem.* **2006**, *71*, 185.
42. Hartmann, K.-P.; Heuschmann, M. *Tetrahedron* **2000**, *56*, 4213.
43. Stolle, R. *J. Prakt. Chem.* **1906**, *73*, 277.
44. Novak, Z.; Bostai, B.; Csekei, M.; Lorincz, K.; Kotschy, A. *Heterocycles* **2003**, *60*, 2653.
45. Novak, Z.; Kotschy, A. *Org. Lett.* **2003**, *5*, 3495.
46. Audebert, P.; Miomandre, F.; Clavier, G.; Vernieres, M.-C.; Badre, S.; Meallet-Renault, R. *Chem.—Eur. J.* **2005**, *11*, 5667.
47. Gong, Y.-H.; Audebert, P.; Tang, J.; Miomandre, F.; Clavier, G.; Badre, S.; Meallet-Renault, R.; Marrot, J. *J. Electroanal. Chem.* **2006**, *592*, 147.
48. Rao, G.-H.; Hu, W.-X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3174.
49. Rao, G.-H.; Hu, W.-X. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3702.
50. Masahiro, M. *Angew. Chem.* **2004**, *116*, 2251; *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.
51. Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
52. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
53. Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.
54. Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889.
55. Rusinov, G. L.; Latosh, N. I.; Ganebnykh, I. I.; Ishmetova, R. I.; Ignatenko, N. K.; Chupakhin, O. N. *Russ. J. Org. Chem.* **2006**, *42*, 757.
56. Rusinov, G. L.; Ishmetova, R. I.; Ganebnykh, I. N.; Chupakhin, O. N. *Heterocycl. Commun.* **2006**, *12*, 1.
57. Asinger, F.; Neuray, D.; Leuchtenberger, W.; Lames, U. *Liebigs Ann. Chem.* **1973**, 879.
58. Yates, P.; Meresz, O. *Tetrahedron Lett.* **1967**, *8*, 77.
59. Girardot, M.; Nomak, R.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 10063.
60. Katritzky, A. R.; Soloducho, J.; Belyakov, S. *Arkivoc* **2000**, *1*, 37.
61. Soenen, D. R.; Zimpleman, J. M.; Boger, D. L. *J. Org. Chem.* **2003**, *68*, 3593.
62. Kang, H.; Fenical, W. *J. Org. Chem.* **1997**, *62*, 3254.
63. Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
64. Urban, S.; Butler, M. S.; Capon, R. J. *Aust. J. Chem.* **1994**, *47*, 1919.
65. Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuer, P. J. *Helv. Chim. Acta* **1992**, *75*, 1721.
66. Quesada, A. R.; Gravalos, M. D. G.; Puentes, J. L. F. *Br. J. Cancer* **1996**, *74*, 677.
67. Palermo, J. A.; Brasco, M. F. R.; Seldes, A. M. *Tetrahedron* **1996**, *52*, 2727.
68. Boger, D. L.; Soenen, D. R.; Boyce, C. W.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 2479.
69. Hamasaki, A.; Zimpleman, J. M.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 10767.
70. Chattopadhyay, S.; Chattopadhyay, U.; Marthur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983**, *49*, 252.
71. Pettit, G. R.; Gaddamidi, V.; Goswami, A.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 796.
72. Goshal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003.
73. Humber, L. C.; Kondo, H.; Kotera, K.; Takagi, S.; Takeda, K.; Taylor, W. I.; Thomas, B. R.; Tsuda, Y.; Tsukamoto, K.; Uyeo, H.; Yajima, H.; Yanaihara, N. J. *J. Chem. Soc.* **1954**, 4622.
74. Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120.
75. Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701.
76. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.
77. Bouaicha, N.; Amade, P.; Puel, D.; Roussakis, C. *J. Nat. Prod.* **1994**, *57*, 1455.
78. Wan, Z.-K.; Woo, G. H. C.; Snyder, J. K. *Tetrahedron* **2001**, *57*, 5497.
79. Erfanian-Abdoust, H.; Pindur, U. *Chem. Rev.* **1989**, *89*, 1681.
80. Pindur, U. *Adv. Nitrogen Heterocycl.* **1995**, *1*, 121.
81. Daly, K.; Nomak, R.; Snyder, J. K. *Tetrahedron Lett.* **1997**, *38*, 8611.
82. Di Modugno, E.; Erbetti, I.; Galassi, G.; Hammond, S. H.; Xerri, L. *Antimicrob. Agents Chemother.* **1994**, *38*, 2362.

83. Perboni, A.; Tamburini, B.; Rossi, T.; Donati, D.; Tarzia, G.; Gaviraghi, G. *Recent Advances in the Chemistry of Anti-infective Agents*; Bently, P. H., Ponsford, R., Eds.; RSC: Cambridge, 1992; pp 21–35.
84. Padova, A.; Roberts, S. M.; Donati, D.; Perboni, A.; Rossi, T. *J. Chem. Soc., Chem. Commun.* **1994**, 441.
85. Andreotti, D.; Rossi, T.; Marchioro, C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2589.
86. Sakya, S. M.; Strohmeyer, T. W.; Lang, S. A.; Lin, Y.-I. *Tetrahedron Lett.* **1997**, *38*, 5913.
87. Bethea, D.; Fullmer, B.; Syed, S.; Seltzer, G.; Tiano, J.; Rischko, C.; Gillespie, L.; Brown, D.; Gasparro, F. P. *J. Dermatol. Sci.* **1999**, *19*, 78.
88. Gonzales, J. C.; Dedola, T.; Santana, L.; Uriarte, E.; Begala, M.; Copez, D.; Podda, G. *J. Heterocycl. Chem.* **2000**, *37*, 907.
89. Gonzales-Gomez, J. C.; Santana, L.; Uriarte, E. *Synthesis* **2002**, 43.
90. Gonzales-Gomez, J. C.; Santana, L.; Uriarte, E. *Tetrahedron* **2003**, *59*, 8171.
91. Begala, M.; Gonzales-Gomez, J. C.; Podda, G.; Santana, L.; Tocco, G.; Uriarte, E. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 564.
92. Gonzales-Gomez, J. C.; Uriarte, E. *Synlett* **2002**, 2095.
93. Gonzales-Gomez, J. C.; Uriarte, E. *Synlett* **2003**, 2225.
94. Gonzales-Gomez, J. C.; Santana, L.; Uriarte, E. *Tetrahedron* **2005**, *61*, 4805.
95. Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.
96. Saxton, J. E. *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, NY, 1998; Vol. 50.
97. Saxton, J. E. *The Alkaloids*; Cordell, G. A., Ed.; Academic: New York, NY, 1998; Vol. 51, Chapter 1.
98. Toyota, M.; Ihara, M. *Nat. Prod. Rep.* **1998**, 327.
99. Benson, S.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165.
100. Spande, T. F.; Garaffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.
101. Che, D.; Wegge, T.; Stubbs, M.; Seitz, G.; Meier, H.; Methfessel, C. *J. Med. Chem.* **2001**, *44*, 47.
102. Mansell, H. L. *Tetrahedron* **1996**, *52*, 6025.
103. Wegge, Th.; Schwarz, S.; Seitz, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1405.
104. Holladay, M. W.; Lebold, S. A.; Lin, N. H. *Drug Dev. Res.* **1995**, *35*, 191.
105. Abreo, M. A.; Lin, N.-H.; Garvey, D. S.; Gunn, D. E.; Hettinger, A.-M.; Wasicak, J. T.; Pavlik, P. A.; Martin, Y. C.; Donnelly-Roberts, D. L.; Anderson, D. J.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1996**, *39*, 817.
106. Bick, I. R. C.; Gillard, J. W.; Leow, H. M. *Aust. J. Chem.* **1979**, *32*, 2523.
107. Campbell, H. F.; Edwards, O. E.; Kolt, R. *Can. J. Chem.* **1977**, *55*, 1372.
108. Wegge, Th.; Schwarz, S.; Seitz, G. *Pharmazie* **2000**, *55*, 779.
109. Kanne, D. B.; Abood, L. G. *J. Med. Chem.* **1988**, *31*, 506.
110. Kanne, D. B.; Ashworth, D. J.; Cheng, M. T.; Mutter, L. C. *J. Am. Chem. Soc.* **1986**, *108*, 7864.
111. Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861.
112. Gündisch, D.; Kampchen, T.; Schwarz, S.; Seitz, G.; Siegl, J.; Wegge, T. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 1.
113. Stehl, A.; Seitz, G.; Schulz, K. *Tetrahedron* **2002**, *58*, 1343.
114. Spath, E.; Kuffner, F. *Fortschr. Chem. Org. Naturst.* **1939**, *2*, 248.
115. Marion, L. *The Alkaloids*; Manske, R. H. F., Homes, H. L., Eds.; Academic: New York, NY, 1950; Vol. 1, pp 228–253.
116. Eiden, F. *Pharm. Unserer Zeit* **1976**, *5*, 1.
117. Ehrenstein, M. *Arch. Pharm.* **1931**, *269*, 627.
118. Spath, E.; Kesztler, F. *Chem. Ber.* **1937**, *70*, 704.
119. Petrie, C. R.; Revankar, G. R.; Dalley, N. K.; George, R. D.; McKernan, P. A.; Hamill, R. L.; Robins, R. K. *J. Med. Chem.* **1986**, *29*, 268.
120. Hammerschmidt, F.; Peric, B.; Ohler, E. *Monatsh. Chem.* **1997**, *128*, 183.
121. Franchetti, P.; Marchetti, S.; Cappellacci, L.; Yalowitz, J. A.; Jayaram, H. N.; Goldstein, B. M.; Grifantini, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 67.
122. Hungerford, N. L.; Armitt, D. J.; Banwell, M. G. *Synthesis* **2003**, 1837.
123. Fernandez-Bolanos, J.; Mota, J. F.; Ramirez, I. R. *An. Quim., Ser. C: Quim. Org. Bioquim.* **1984**, *80*, 123.
124. Lam, K. S.; Glersaye, S.; Patel, K.; Najmi, S.; Burnham, B. S. *Abstracts of Papers*, 225th ACS National Meeting, New Orleans, LA, March 23–27, 2003.
125. Anderson, W. K.; Heider, A. R. *J. Med. Chem.* **1986**, *29*, 2392.
126. (a) Joshi, U.; Josse, S.; Pipelier, M.; Chevallier, F.; Pradere, J.-P.; Hazard, R.; Legoupy, S.; Huet, F.; Dubreuil, D. *Tetrahedron Lett.* **2004**, *45*, 1031; (b) Richter, M.; Seitz, G. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 365.
127. Kotschy, A.; Hajos, G.; Timari, G.; Messmer, A. *J. Org. Chem.* **1996**, *61*, 4423.
128. Kotschy, A.; Smith, D. M.; Benyei, A. C. *Tetrahedron Lett.* **1998**, *39*, 1045.
129. Novak, Z.; Vincze, Z.; Czegeny, Z.; Magyarfalvi, G.; Smith, D. M.; Kotschy, A. *Eur. J. Org. Chem.* **2006**, 3358.
130. Kotschy, A.; Novak, Z.; Vincze, Z.; Hajos, G. *Tetrahedron Lett.* **1999**, *40*, 6313.
131. Kotschy, A.; Farago, J.; Smith, D. M. *Tetrahedron* **2004**, *60*, 3421.
132. (a) Sichert, H. Ph.D. Dissertation, University of Regensburg, 1980; (b) Marcelis, A. T. M.; van der Plas, H. C. *J. Heterocycl. Chem.* **1987**, *24*, 545.
133. Heldmann, D. K.; Sauer, J. *Tetrahedron Lett.* **1997**, *38*, 5791.
134. Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2885.
135. Schirmer, U.; Wuerzer, B.; Meyer, N.; Neugehauer, F. A.; Fischer, H. Ger. Often. DE 3508214, 1986.
136. Sparey, T. J.; Harrison, T. *Tetrahedron Lett.* **1998**, *39*, 5873.
137. Pozharskii, A. F. *Russ. Chem. Rev.* **1998**, *67*, 1.
138. Kurasov, L. A.; Pozharskii, A. F.; Kuzmenko, V. V.; Klyuev, N. A.; Chernyshev, A. I.; Goryaev, S. S.; Chikina, N. L. *Zh. Org. Khim.* **1983**, *19*, 590.
139. Vistorobskii, N. V.; Pozharskii, A. F. *Zh. Org. Khim.* **1989**, *25*, 2154.
140. Pozharskii, A. F.; Ozeryanskii, V. A.; Vistorobskii, N. V. *Russ. Chem. Bull., Int. Ed.* **2003**, *52*, 218.
141. Balci, M.; Saracoglu, N.; Menzek, A. *Tetrahedron Lett.* **1996**, *37*, 921.
142. Ozer, G.; Saracoglu, N.; Balci, M. *J. Org. Chem.* **2003**, *68*, 7009.
143. Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure–Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC: Boca Raton, FL, 1988; pp 31–58.

144. Ozer, G.; Saracoglu, N.; Menzek, A.; Balci, M. *Tetrahedron* **2005**, *61*, 1545.
145. Hoogenboom, R.; Moore, B. C.; Schubert, U. S. *J. Org. Chem.* **2006**, *71*, 4903.
146. Warrener, R. N.; Golic, M.; Butler, D. N. *Tetrahedron Lett.* **1998**, *39*, 4721.
147. Rohr, U.; Schatz, J.; Sauer, J. *Eur. J. Org. Chem.* **1998**, 2875.
148. Nagy, J.; Madarasz, Z.; Rapp, R.; Szöllösy, A.; Nyitrai, J.; Döpp, D. *J. Prakt. Chem.* **2000**, *342*, 281.
149. Scheiner, P. *J. Org. Chem.* **1969**, *34*, 199.
150. Scheiner, P.; Dinda, J. F., Jr. *Tetrahedron* **1970**, *26*, 2619.
151. Zhou, X.; Kovalev, E. G.; Klug, J. T.; Khodorkovsky, V. *Org. Lett.* **2001**, *3*, 1725.
152. Sauer, J.; Bauerlein, P.; Ebenbeck, W.; Charalampos, G.; Sichert, H.; Troll, T.; Utz, F.; Wallfahrer, U. *Eur. J. Org. Chem.* **2001**, 2629.
153. Sauer, J.; Bauerlein, P.; Ebenbeck, W.; Schuster, J.; Sellner, I.; Sichert, H.; Stimmelmayr, H. *Eur. J. Org. Chem.* **2002**, 791.
154. Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.
155. Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599.
156. Paquette, L. A. *J. Org. Chem.* **1965**, *30*, 629.
157. McCullogh, R.; Rye, A. R.; Wege, D. *Tetrahedron Lett.* **1969**, *10*, 5231.
158. Wilson, W. S.; Warrener, R. N. *Tetrahedron Lett.* **1970**, *11*, 5203.
159. Yick, C.-Y.; Chan, S.-H.; Wong, H. N. C. *Tetrahedron Lett.* **2000**, *41*, 5957.
160. Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346.
161. Chan, S.-H.; Yick, C.-Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413.
162. Mitchell, R. H.; Ward, T. R.; Wang, Y.; Dibble, P. W. *J. Am. Chem. Soc.* **1999**, *121*, 2601.
163. Mitchell, R. H.; Ward, T. R.; Wang, Y. *Heterocycles* **2001**, *54*, 249.
164. Yang, G. Y.; Hanack, M.; Lee, Y. W.; Chen, Y.; Lee, M. K. Y.; Dini, D. *Chem.—Eur. J.* **2003**, *9*, 2758.
165. Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273.
166. Haenel, M. W.; Schweitzer, D. *Advances in Chemistry Series*; Ebert, L. B., Ed.; American Chemical Society: Washington, DC, 1988; Vol. 217, pp 333–355.
167. Ernst, L. *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *37*, 47.
168. Zhai, Y.; Ghiviriga, I.; Battiste, M. A.; Dolbier, W. D., Jr. *Synthesis* **2004**, 2747.
169. Paquette, L. A.; Barton, W. R. S.; Gallucci, J. C. *Org. Lett.* **2004**, *6*, 1313.
170. Suen, Y. F.; Hope, H.; Nantz, M. H.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2005**, *70*, 8468.
171. (a) Robins, L. I.; Carpenter, R. D.; Fettinger, J. C.; Haddadin, M. J.; Tinti, D. S.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2480; (b) Anet, F. A.; Yavari, I. *J. Am. Chem. Soc.* **1978**, *100*, 7814.
172. Ozer, G.; Saracoglu, N.; Balci, M. *Heterocycles* **2000**, *53*, 761.
173. Ozer, G.; Saracoglu, N.; Balci, M. *J. Heterocycl. Chem.* **2003**, *40*, 529.
174. Müller, J.; Troschutz, R. *Synthesis* **2006**, 1513.

Biographical sketch

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