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Microwave-Assisted 1,3-Dipolar Cycloaddition: an Eco-Friendly Approach to Five-Membered Heterocycles

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The review describes the use of microwave technology to carry out 1,3-dipolar cycloaddition reactions, an important tool for the construction of five-membered heterocycles. Microwave methodology can be applied to generate 1,3-dipoles (nitrones, nitrile oxides, azomethine ylides, azomethine imines, nitrile imines, azides, carbonyl ylides) and to promote the subsequent cycloaddition and usually avoids harsh reaction conditions. This nonconventional energy source is able to reduce chemical reaction times and to increase yields and in some cases can lead to different outcomes from those obtained with conventional heating. The review highlights the more recent developments in the area with particular emphasis on aspects related to efficiency and to regio- and stereoselectivity.

1. Introduction

The synthetic utility of microwave irradiation in organic synthesis has increased considerably in recent years.[1–5] This nonconventional energy source is able to reduce chemical reaction times and to increase yields, and in some cases can lead to outcomes different from those obtained with conventional heating. Under these singular reaction conditions, dielectric properties, energy transfer, and penetration depth are completely different from those in conventional heating, so enhancement of the chemo-, regio-, and stereoselectivity can be observed. Microwave-assisted reactions are quite often cleaner, faster, and higher-yielding than conventional ones. This methodology can be regarded as environmentally friendly, mainly because solvent-free reactions using solid supports are especially suited to microwave conditions.[6,7]

Microwave technology has been successfully used to perform difficult cycloadditions and to obtain temperature-sensitive compounds. Particularly interesting is 1,3-dipolar cycloaddition, which represents one of the most versatile tools for the construction of five-membered heterocycles. In fact, 1,3-dipolar cycloaddition was one of the first microwave-assisted organic reactions to be explored. The effectiveness of microwave methodology in generating 1,3-dipoles in situ and in promoting the subsequent cycloadditions has been demonstrated, and coverage of this subject can be found in review articles.[8–14]

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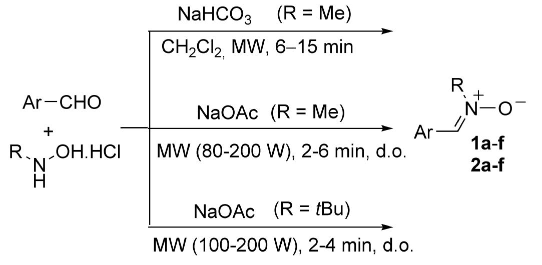
This review focuses on the more recent developments in microwave-assisted 1,3-dipolar cycloadditions, with particular emphasis on aspects relating to efficiency and to regio- and stereoselectivity. Microwave-assisted reactions using domestic ovens (d.o.) are included, because in many cases these are efficient processes. However, reactions under these conditions suffer from poor reproducibility and these data should therefore be treated with caution.

2. Cycloadditions

2.1. Cycloadditions of Nitrones

Nitrones were recognized in the late 1960s as spin trapping agents. On the other hand, though, one of the most intensely studied of these compounds is α-phenyl-*N*-*tert*-butylnitrone, due to its recognized neuroprotective properties.[15–17] Nitrones can be synthesized directly from the corresponding nitro compounds by in situ reduction with Zn/NH_4Cl in the presence of an aldehyde, followed by acidification. Alternatively, the synthesis of nitrones can involve a two-step procedure in which the hydroxylamine obtained by reduction of a nitro compound is isolated and later treated with an aldehyde.[18,19]

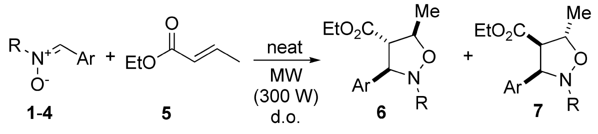
The *N*-methyl-*C*-arylnitrones **1a**–**d** (Scheme 1) were synthesized under microwave irradiation conditions in very high yields and in times of a few minutes from *N*-methylhydroxylamine hydrochloride and the corresponding aryl aldehydes in the presence of sodium hydrogen carbonate, with use of a chlorinated solvent together with an excess of hydroxylamine.[20] Barros et al.[21] developed an improved microwave-assisted synthesis of the *N*-alkyl-*C*-arylnitrones **1a**–**f** and **2a**–**f** (Scheme 1) with yields up to 97%. This methodology avoids the use of excesses of expensive hydroxylamines or organic solvents and the long reaction times required under conventional thermal conditions.



	R	Ar	Base	Yield
1a-d	Me	Ph, pMeOC$_6$H$_4$, pClC$_6$H$_4$, pNO$_2$C$_6$H$_4$	$NaHCO_3$	51–94%
1a-f	Me	Ph, pMeOC$_6$H$_4$, pClC$_6$H$_4$, pNO$_2$C$_6$H$_4$, Furyl, Pyridyl	NaOAc	72–92%
2a-f	*t*Bu	Ph, pMeOC$_6$H$_4$, pClC$_6$H$_4$, pNO$_2$C$_6$H$_4$, Furyl, Pyridyl	NaOAc	85–97%

Scheme 1.

N-Alkyl-*C*-arylnitrones and *C*,*N*-diarylnitrones were used as dipoles in microwave-assisted 1,3-dipolar cycloadditions with ethyl *trans*-crotonate (**5**) in the absence of solvents and/or catalyst.[21] The library of isoxazolidines obtained, the isolated yields for both isomers **6** and **7**, and the diastereoisomeric ratios are presented in Scheme 2. *C*,*N*-Diaryl nitrones exist mainly as their *Z* isomers, due to the presence of the bulky aromatic groups leading predominately to the isoxazolidines resulting from the *endo* approach of the nitrones (**6** and their enantiomers), whereas with *N*-methyl nitrones the diastereoselectivities are low because nitrone *E*/*Z* isomerization is possible. With the more bulky *N*-*tert*-butylnitrones the approach of the dipolarophile is more difficult, requiring longer reaction times. However, the reactions are stereoselective and only products showing 3,4-*trans* and 4,5-*trans* configurations, corresponding to the *endo* approach, were obtained.

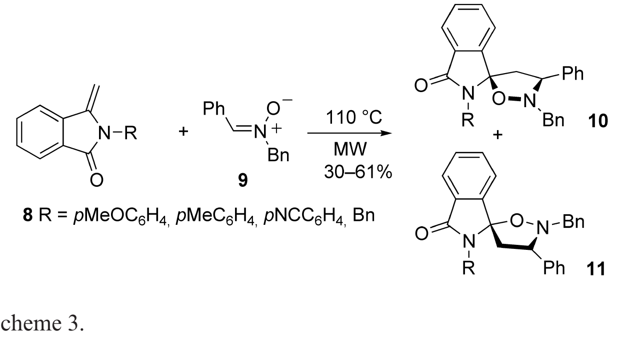


a-f Ar = Ph, pMeOC$_6$H$_4$, pClC$_6$H$_4$, pNO$_2$C$_6$H$_4$, Furyl, Pyridyl

Nitrone	R	reaction time	yield	*endo*/*exo*
1a-f	Me	10 min	75–97%	(55:45) to (76:34)
2a-f	*t*Bu	60 min	78–97%	(100:0)
3a-f	Ph	10 min	79–98%	(78:22) to (94:6)
4a-f	Tol	10 min	71–89%	(76:24) to (94:6)

Scheme 2.

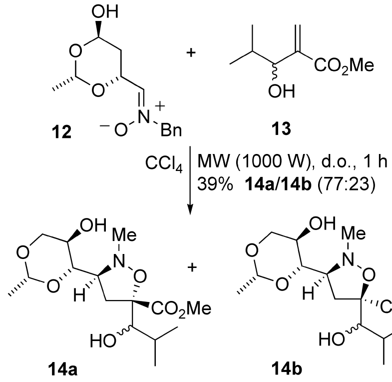
The regiospecific microwave-assisted 1,3-dipolar cycloadditions of the 3-methylene-*N*-substituted isoindolones **8** and the nitrone **9** (Scheme 3) yield the spiro[1*H*-isoindol-1,5′(4′*H*)-isoxazol]-7(6*H*)-ones **10** and **11**. The yields are increased twofold relative to those obtained with conventional heating (from 12–27% to 30–61%). In the case of *C*,*N*-diphenylnitrone and *C*-benzyl-*N*-phenylnitrone there was no advantage in the use of microwave irradiation.[22]



8 R = pMeOC$_6$H$_4$, pMeC$_6$H$_4$, pNCC$_6$H$_4$, Bn

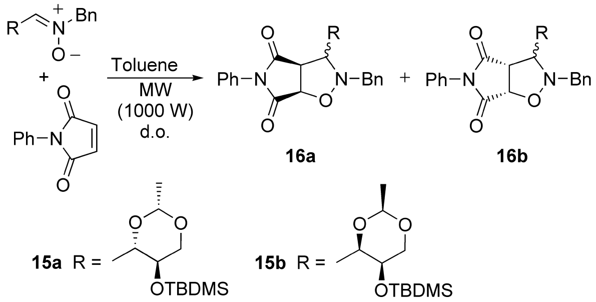
Scheme 3.

1,3-Dipolar cycloadditions of nitrones to the Baylis–Hillman adduct **13** (Scheme 4) proceed under microwave irradiation conditions with complete regioselectivity, giving only the corresponding 5-substituted isoxazolidines (e.g., **14**) in good yield. Attack of the dipole from the less sterically hindered sides of the dipolarophiles affords C-3/C-5 *cis* isoxazolidines as the major products. Addition of Grignard reagents or Lewis acids accelerates the reactions but has only a small effect on the diastereoisomeric product ratios, slightly increasing the portion of C-3/C-5 *trans* isoxazolidines.[23,24]



Scheme 4.

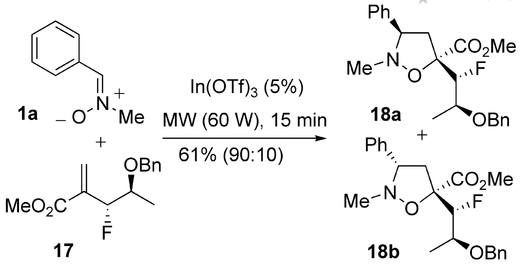
Microwave-assisted 1,3-dipolar cycloadditions of diastereomerically pure *Z* nitrones derived from the cyclic acetals of D-erythrose and D-threose (**15a** and **15b**, respectively; Scheme 5) with *N*-phenylmaleimide afforded diastereomeric isoxazolidines in good overall yields. With the starting nitrone **15a** it was observed that the microwave-assisted reaction was accelerated and gave a reversed ratio of *erythro-trans*/*erythro-cis* adducts.[25]



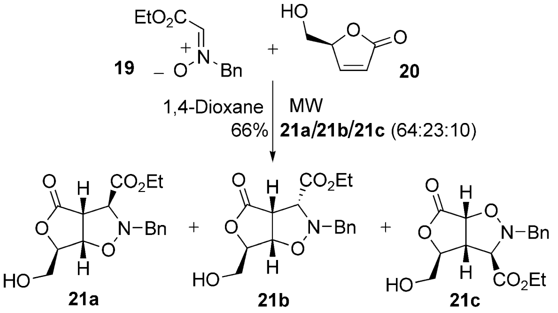
Scheme 5.

The interest in fluorine-containing compounds has greatly increased over the last few decades.[26] Introduction of fluorine into biologically active compounds often induces strong modifications of their chemical, physical, and biological properties, increasing their potential as drug candidates.[27] In this context, Comes-Franchini et al. reported the microwave-assisted 1,3-dipolar cycloaddition, under solvent-free conditions, between the enantiopure allylic fluoride **17** and (*Z*)-α-phenyl-*N*-methylnitrone (**1a**) in the presence of $In(OTf)_3$ as catalyst (Scheme 6). The enantiopure isomeric fluorinated isoxazolidines **18** were obtained in 61% overall yield in a 90:10 ratio.[28]

Cycloaddition between the nitrone **19** and the lactone **20** (Scheme 7) was accelerated under microwave irradiation conditions, with the reaction time decreasing from hours under conventional heating conditions to less than 10 min. However, only small changes in the regio- and stereoselectivity were observed.[29]

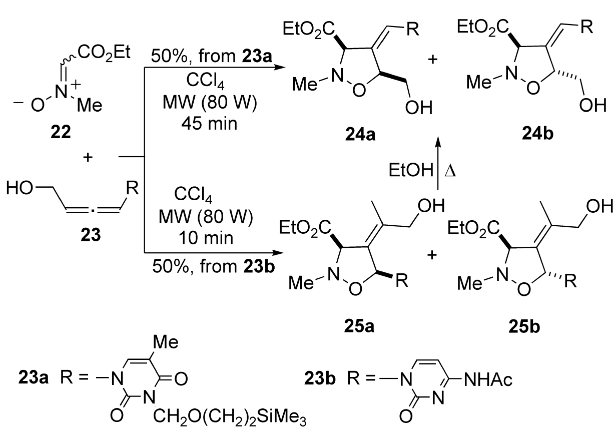


Scheme 6.



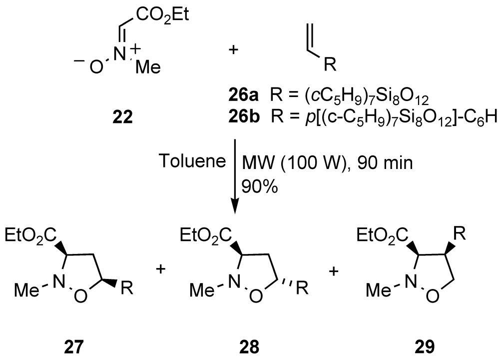
Scheme 7.

The synthesis of methyleneisoxazolidine nucleoside analogues by microwave-assisted nitrone cycloaddition was developed by Chiacchio et al. in 2007.[30] The authors studied the cycloaddition between *C*-ethoxycarbonyl-*N*-methylnitrone (**22**, Scheme 8) and the protected thiamallene **23a** under microwave irradiation conditions over 45 min in CCl_4 as solvent. A 1:1 diastereomeric mixture of compounds **24** was obtained in 50% yield. Conventional heating required 480 min and gave only a 20% yield of the same diastereomeric mixture. When the reaction was performed with the *N*-acetylcytallene **23b** the cycloaddition showed a different site selectivity, with the addition of the nitrone to the internal C–C double bond of the allene. A 1:1 mixture of the compounds **25** was isolated in 50% yield after 10 min. However, these compounds were converted into a mixture of derivatives **24** after prolonged heating in ethanol by a process involving isoxazoline ring opening and closing (Scheme 8).



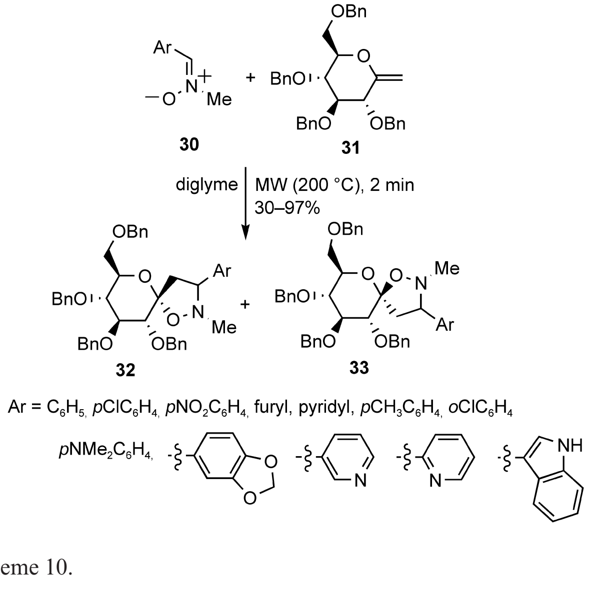
Scheme 8.

Polyhedral oligomeric silsequioxanes (POSSs) – $(RSiO_{1.5})_n$ with n = 6, 8, 10 – contain inner inorganic frameworks covered by organic substituents. The different natures of the organic residues can make these nanostructures compatible with polymers or biological systems. Furthermore, they can be used in biomedical applications as scaffolds for drug delivery, as imaging reagents, and for combinatorial drug development.[31–33] Chiacchio et al.[34] demonstrated that functionalization of the vinyl-POSS **26a** (Scheme 9) or the styryl-POSS **26b** through microwave-assisted 1,3-dipolar cycloadditions with *C*-ethoxycarbonyl-*N*-methylnitrone (**22**) leads to a faster and more efficient process than conventional heating. The pericyclic reactions showed good regio- and stereoselectivities, with the *trans* isomer **28** being the major product when starting with **26a**, whereas complete inversion of the diastereoselectivity was obtained with **26b** as dipolarophile, with the major product now being **27**.



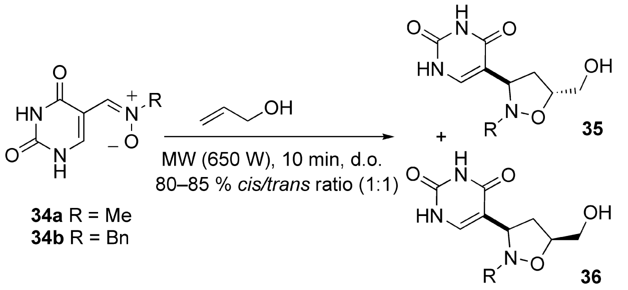
Scheme 9.

The microwave-assisted 1,3-dipolar cycloadditions between *C*-aryl-*N*-methyl nitrones **30** and the *exo*-glucal **31** to give the isoxazolidines **32** and **33** (Scheme 10) were reported by Li and co-workers. With microwave irradiation, the reactions afforded better yields in shorter reaction times (5 min) than in toluene at reflux (60–120 h). However, no significant improvement in the stereoselectivity outcomes was observed.[35]



Scheme 10.

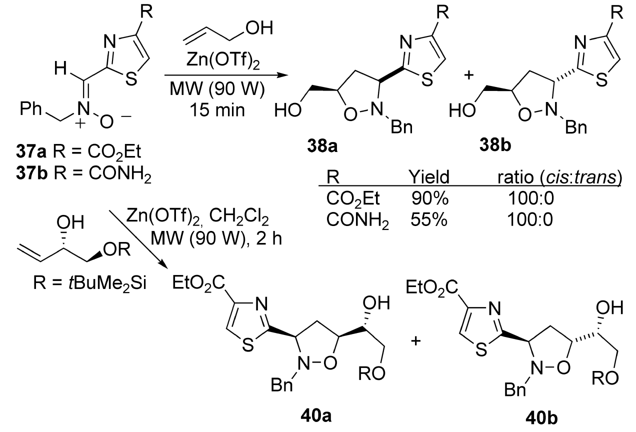
Heterocyclic nucleosides have attracted considerable attention over recent years.[36–38] One of the strategies followed in drug design to improve the biological properties of naturally occurring and synthetic *C*-nucleosides is the substitution of the natural ribose unit with a different heterocyclic moiety, such as an isoxazolidine analogue.[39–41] One interesting approach to compounds of this type is nitrone cycloaddition, which can be carried out under microwave irradiation conditions as illustrated in Scheme 11. In fact, the *N*-benzyl- and (*Z*)-*N*-methyl-*C*-(5-uracil)nitrones **34**[42] participate as 1,3-dipoles in cycloadditions with allylic alcohol to give the *trans* and *cis* isoxazolidinyl pseudouridines **35** and **36**. Under microwave irradiation conditions for 10 min, in the absence of solvent or additives, the products were obtained in 80–85% yields. This represent a significant improvement from sealed-tube thermolysis, which requires heating at 140 °C for 12 hours with Nafion as additive.[43]



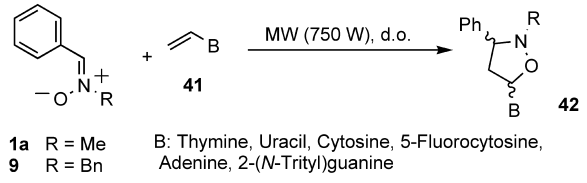
Scheme 11.

Analogues of Tiazofurin,[44] a *C*-nucleoside with potent antitumor activity against several human cancers, have also been synthesized through 1,3-dipolar cycloadditions between nitrones **37** and allylic alcohol (Scheme 12). Under microwave irradiation and solvent-free conditions, the nitrones **37** react with allylic alcohol (10 equiv.) to give the isoxazolidines **38** in 60–80% yields. The reaction times of 15–20 days under conventional heating conditions are dramatically decreased to 1–3 h under microwave irradiation conditions. The addition of a Lewis acid – $Zn(OTf)_2$ – increases the selectivity, allowing the synthesis of the *cis* isoxazolidine derivative **38a** as a single product in just 15 min. The nitrone **37a** reacts with chiral dipolarophiles with complete *cis* selectivity in the presence of $Zn(OTf)_2$ as catalyst and in dichloromethane as solvent. These reactions afforded 4:1 mixtures of *cis* adducts **40** (Scheme 12).

Solvent-free 1,3-dipolar cycloadditions, under microwave irradiation conditions, between the unprotected vinyl nucleobases **41** (Scheme 13) and *N*-methyl-*C*-phenylnitrone (**1a**) or *N*-benzyl-*C*-phenylnitrone (**9**) afford the 4′-aza-2′,3′-dideoxynucleosides **42** in good yields and short reaction times. The two reaction partners were ground together in a mortar and mixed in a vortex before the reaction. The reactions are regioselective for the formation of the 1′-substituted isoxazolidines, with diastereochemical outcomes in the range of 70:30 *endo*/*exo* ratios.[45]



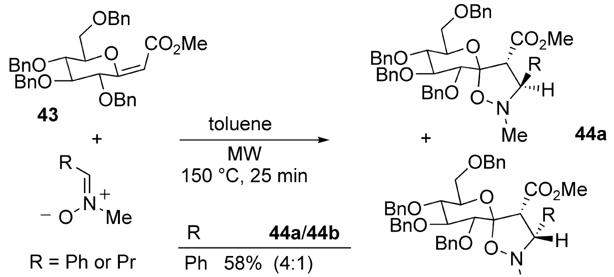
Scheme 12.



B	**42** (R = Me)	**42** (R = Bn)
Thymine	80% (80:20)	80% (80:20)
Uracil	80% (78:22)	80% (70:30)
Cytosine	50% (75:25)	60%(65:35)
5-Fluorocytosine	90% (84:16)	90% (71:29)
Adenine	70% (70:30)	72% (72:28)
2-(*N*-Trityl)guanine	20% (75:25)	

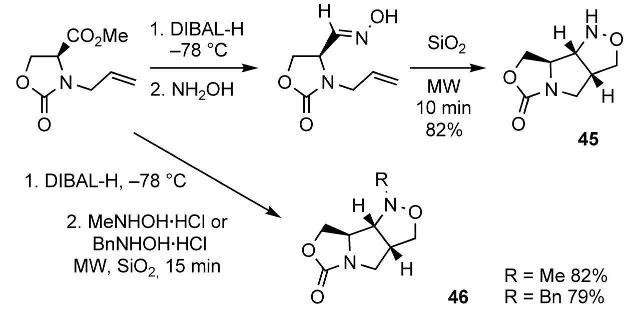
Scheme 13.

Spiro-isoxazolidines (e.g., **44**) were obtained in a regioselective and stereoselective fashion from microwave-assisted 1,3-dipolar cycloadditions between *exo*-glycals and *N*-methylnitrones (Scheme 14). The high yields obtained after 25 min under microwave irradiation conditions contrast with the absence of reaction products under conventional thermal conditions.[46]



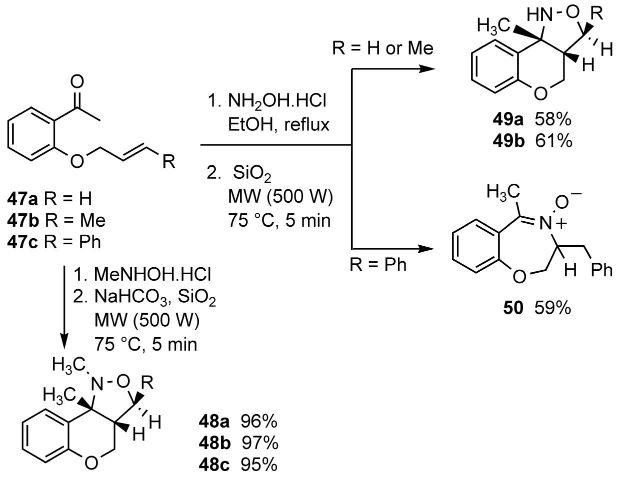
Scheme 14.

Intramolecular cycloaddition reactions of oximes and nitrones derived from L-serine methyl ester, on the surface of silica gel, without solvent and under microwave irradiation conditions, result in the preparation of chiral tricyclic isoxazolidines **45** and **46** in yields of ca. 80% (Scheme 15). The synthesis of **46** under thermal conditions requires heating at 170 °C in toluene in a sealed tube for 16 h and leads to the formation of a by-product.[47]



Scheme 15.

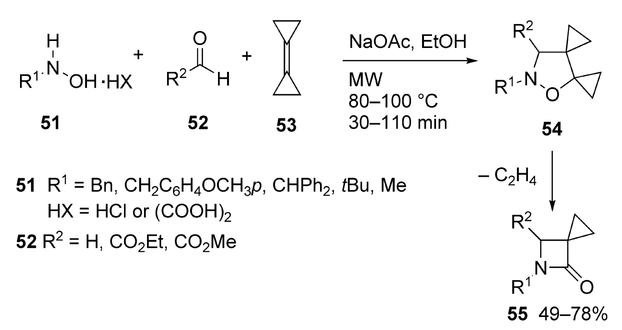
N-Unsubstituted nitrones and *N*-methylnitrones generated from oximes derived from compounds **47** (Scheme 16) underwent intramolecular 1,3-dipolar cycloaddition reactions under microwave irradiation and solvent-free conditions. The *N*-methylnitrone derivatives led to fused isoxazolidines **48** in yields of up to 97%. The reactions of the *N*-unsubstituted nitrone derivative afforded the expected isoxazolidines **49** when starting from **47a** and **47b**, but **47c** led to the bicyclic nitrone **50** as the only product (Scheme 16).[48]



Scheme 16.

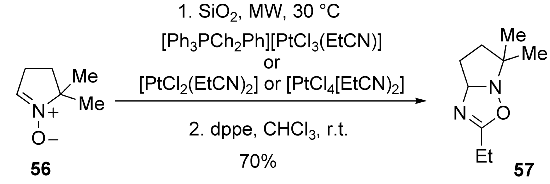
Microwave-induced cycloadditions of methylenecyclopropane (**53**, Scheme 17) and nitrones generated in situ from oximes **51** and aldehydes **52** afford β-lactams **55**. The spirocyclopropanated isoxazolidines **54** are generated as intermediates and undergo rearrangement, giving the β-lactams in isolated yields of up to 78% after reaction times from 30 to 120 min.[49]

1,3-Dipolar cycloadditions of nitrones to nitriles afford 2,3-dihydro-1,2,4-oxadiazoles. Unlike alkenes, though, nitriles are poorly reactive in cycloadditions and as a consequence the synthesis of 2,3-dihydro-1,2,4-oxadiazoles is less developed. However, coordination of a nitrile to a metal center, usually Pd^{II} or Pt^{II}, has been used to improve the 1,3-dipolar cycloaddition.[50] One example of a set of reactions between nitrones and uncoordinated nitriles under mi-



Scheme 17.

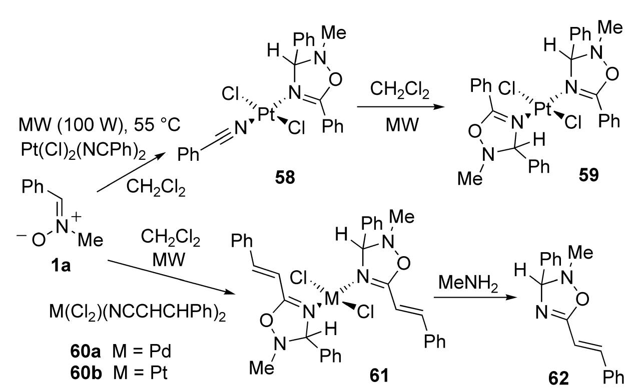
crowave irradiation conditions is known.[50,51] *C*,*N*-Diphenylnitrone reacts with $NCCO_2Et$ under microwave irradiation conditions to afford the corresponding oxadiazole in 39% yield. Under conventional thermal conditions the same compound could only be obtained in 4% yield. Coordinated nitriles such as ethanonitrile platinum compounds react with the cyclic nonaromatic nitrone **56** (Scheme 18) under microwave irradiation conditions, leading to decreases in the reaction times from days to hours or minutes.[52]



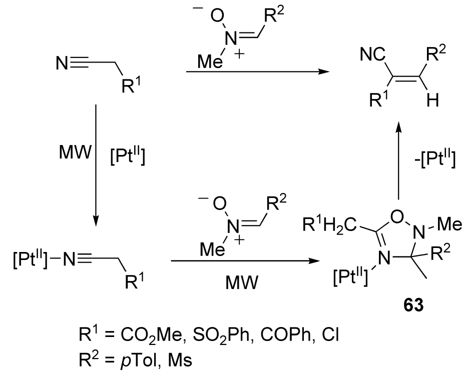
Scheme 18.

Rate enhancement was also observed in the 1,3-dipolar cycloaddition between nitrone **1a** (Scheme 19) and benzonitrile coordinated to Pt^{II}. The monocycloaddition leading to **58** achieved a 50% conversion after 3 min, 25 times faster than in the conventional thermal reaction. The bis(adduct) **59** can be obtained in 50% yield after microwave irradiation for 65 min.[53] A similar effect is achieved in the cycloaddition between *N*-methyl-*C*-tolylnitrone and acetonitrile coordinated to the analogous Pd^{II} complex.[54] Cycloadditions between *N*-methyl-*C*-phenylnitrone (**1a**) and the cinnamonitrile complexes **60** (Scheme 19) are very slow under thermal conditions and require 2 days at 60 °C to yield the bis(oxadiazoline) complex **61**. Under microwave irradiation conditions the reactions are complete within 2 hours.[55]

Organonitriles bearing acidic α-methylenic groups react with acyclic nitrones to form polysubstituted *E* alkenes. When the organonitriles are coordinated to Pt^{II} they undergo [3+2] cycloadditions with the acyclic nitrones to afford the oxadiazoline complexes **63** (Scheme 20). Upon liberation and retrocycloaddition, the oxadiazoline complexes generate cyano-alkenes and MeHNOH. The reactions were accelerated by microwave irradiation, especially when performed on solid phase (SiO_2), displaying yields of up to 80%.[56]



Scheme 19.

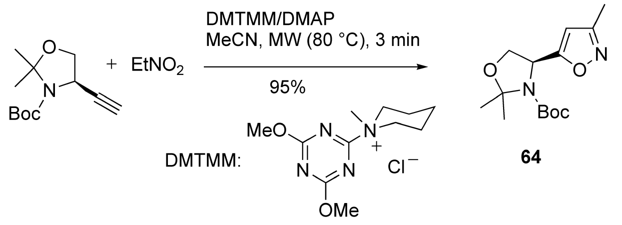


Scheme 20.

2.2. Cycloadditions of Nitrile Oxides

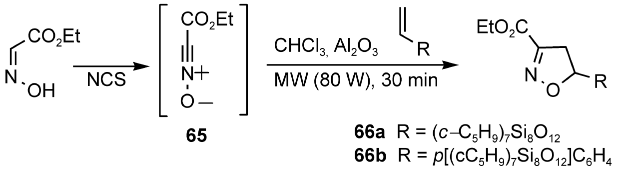
The study by Quilico et al. on the formation of isoxazoles from nitrile oxides and unsaturated compounds is a milestone in the chemistry of isoxazoles.[57] Since then, 1,3-dipolar cycloadditions of nitrile oxides have became an important approach to isoxazoles. Nitrile oxides can undergo dimerization to give furoxans, the rate of this process being strongly dependent on the nature of the nitrile oxide substituent.[58] In order to avoid the dimerization, nitrile oxides are usually generated in situ by dehydrochlorination of hydroximoyl chlorides (or bromides) with triethylamine, dehydration of primary nitro compounds, or oxidation of aldoximes.

An efficient method for the in situ generation and cycloaddition of nitrile oxides from nitroalkanes under mild conditions through microwave irradiation, using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium (DMTMM) chlorides and 4-(dimethylamino)pyridine (DMAP) as catalyst, has been reported. When these reactions are carried out in the presence of the appropriate alkenes or alkynes, isazolines and isoxazoles are obtained in high yields. By this methodology the chiral isoxazole **64** (Scheme 21) was obtained in 95% yield without loss of optical purity. This approach to isoxazoles can also be applied to solid-phase synthesis. Efficient synthesis of isoxazolines was also achieved when the nitrile oxides were generated in the presence of alkenes.[59]



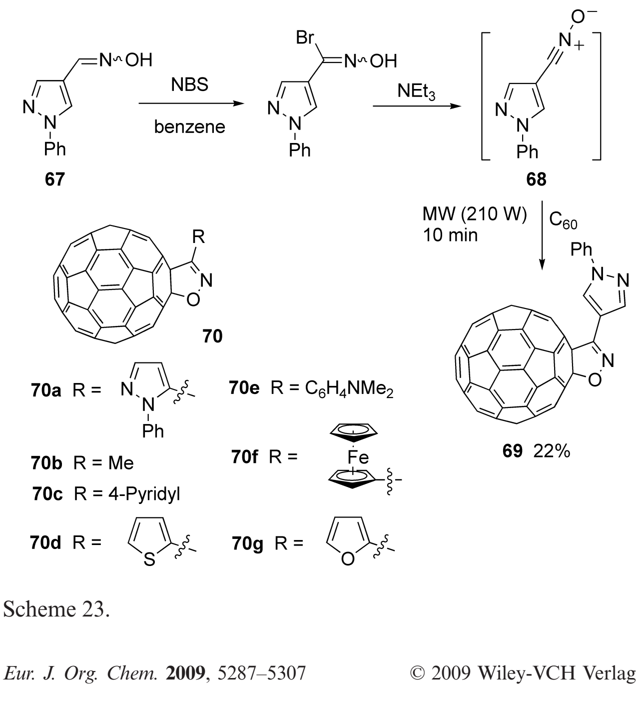
Scheme 21.

Isoxazolines **66** (Scheme 22) were obtained by microwave-assisted 1,3-dipolar cycloadditions of nitrile oxide **65** with vinyl-POSSs (1.0 equiv.) as dipolarophiles in the presence of Al_2O_3. The reaction times were reduced from 20 h to 30 min and the reaction yields were increased from ca. 50% to ca. 70% under microwave irradiation conditions.[34]



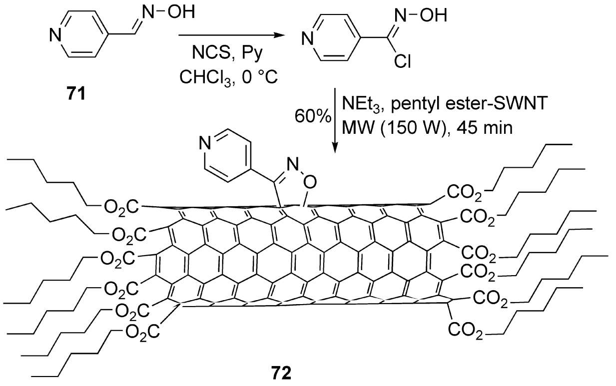
Scheme 22.

The 3′-(*N*-phenylpyrazol-4-yl)isoxazolo[60]fullerene dyad **69** (Scheme 23) has been prepared in 22% yield through a microwave induced 1,3-dipolar cycloaddition between the pyrazole nitrile oxide **68** and C_{60}.[60] The oxime **67** was treated with NBS, followed by the addition of Et_3N, to generate the dipole, which reacted in situ with C_{60} under microwave irradiation conditions. A significant accelerating effect (10 min vs. 24 h) under the microwave conditions was observed. The scope of the reaction has been demonstrated by the one-pot preparation of a series of isoxazolino[60]-fullerenes **70** in yields ranging from 16% to 36%.[61]



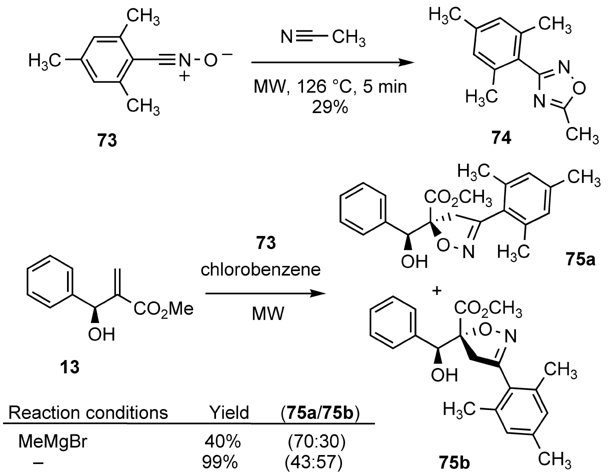
Scheme 23.

The isoxazolino-SWNT (single-wall carbon nanotube) derivative **72** (Scheme 24) was synthesized in 65% yield through the microwave-assisted 1,3-dipolar cycloaddition between the nitrile oxide generated in situ from pyridine-4-carbaldehyde oxime (**71**) and the pentyl ester-SWNT.[62]



Scheme 24.

Microwave-induced cycloadditions between nitrile oxides and nitriles under solvent-free conditions have been reported. Under classical heating conditions the reaction between the nitrile oxide **73** (Scheme 25) and acetonitrile leads only to traces of the cycloadduct, whereas under microwave irradiation conditions the 1,2,4-oxadiazole **74** is obtained in 29% yield.[63] With the Baylis–Hillman adduct **13** (Scheme 25), on the other hand, dipole **73** regioselectively affords the 5-substituted isoxazolines **75**. The addition of a Grignard reagent (MeMgBr) acting as a Lewis base leads to the reversal of the diastereoselectivity, as the result of an imposition of the chelated transition state, with a different geometry from the non-chelated transition state.[64] In this case, the microwave irradiation allows the formation of the desired products in shorter reaction times, but the reaction yields are lower than those obtained by conventional thermolysis.

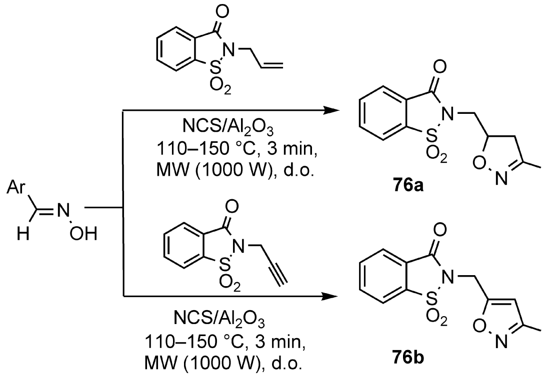


Reaction conditions	Yield	(**75a**/**75b**)
MeMgBr	40%	(70:30)
–	99%	(43:57)

Scheme 25.

The novel *N*-isoxazoline- and *N*-isoxazole-substituted saccharin derivatives **76** (Scheme 26) were obtained through one-pot 1,3-dipolar cycloaddition reactions between *N*-

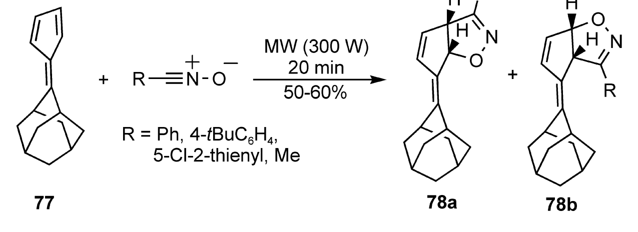
allyl- or *N*-propargylsaccharin and arylnitrile oxides. These 1,3-dipoles were generated in situ from aromatic oximes under microwave conditions in solvent-free systems with use of NCS/Al_2O_3 as catalyst. The use of microwave irradiation disfavored the dimerization of nitrile oxides into furoxans, improving the reaction yields (81–95%) and considerably decreasing the reaction times. The nonthermal microwave effects, demonstrated by the absence of reaction products when the reactions were carried out under conventional heating conditions, were explained by considering the development of polarities between ground state and transition state estimated from PM3 calculations of the dipole moments of reagents, products, and transition states.[65]



Ar = Ph, pMeC$_6$H$_4$, pMeOC$_6$H$_4$, pClC$_6$H$_4$, pNO$_2$C$_6$H$_4$, oClC$_6$H$_4$, 3,4-(NO$_2$)C$_6$H$_4$

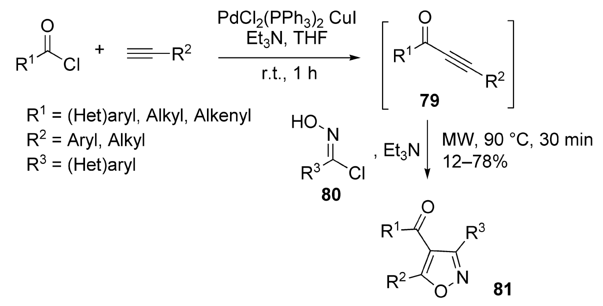
Scheme 26.

1,3-Dipolar cycloadditions between adamantylidenefulvene (**77**, Scheme 27) and nitrile oxides was achieved under microwave irradiation conditions in 20 min, with higher reaction yields and better stereoselectivity than were obtained with use of conventional heating in THF at reflux for 24 h.[66]



Scheme 27.

Müller et al. developed the synthesis of 3,4,5-substituted isoxazoles by a one-pot, three-component reaction pathway.[67] Alkynones **79** (Scheme 28), obtained by coupling of acid chlorides with terminal alkynes at room temperature, react with hydroximinoyl chlorides **80** to form the corresponding isoxazoles **81** through 1,3-dipolar cycloadditions with aromatic nitrile oxides generated in situ. Through the employment of microwave heating for the cycloaddition step reaction times could be reduced from three days to 30 min, whereas increased yields of the final products and less by-product formation (dimerization of nitrile oxides to furoxan oxides) were observed.

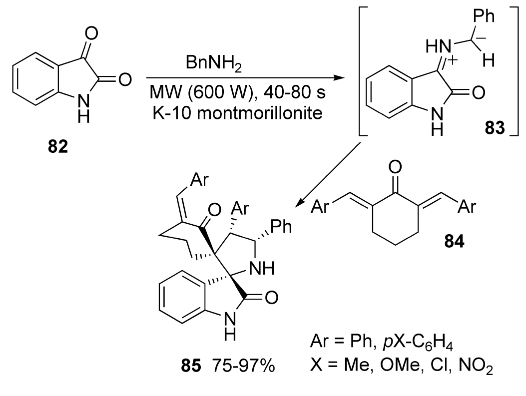


Scheme 28.

2.3. Cycloadditions of Azomethine Ylides

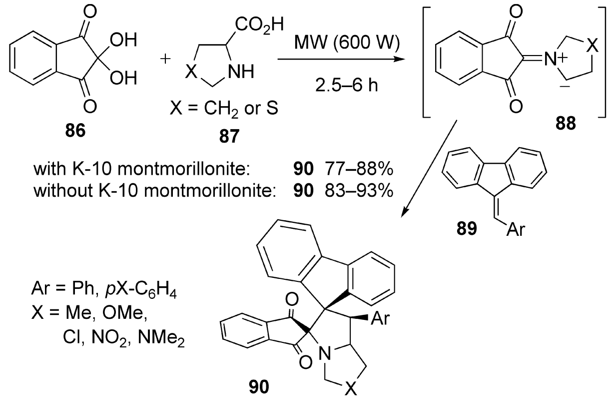
Azomethine ylides can be generated in situ from a wide variety of easily accessible starting materials, variously by thermolysis or photolysis of aziridines, by decarboxylation of imminium ions derived from α-amino acids, or by prototropy of imines of α-amino esters. These dipoles undergo 1,3-dipolar cycloadditions to afford pyrrolidine derivatives.

1,3-Dipolar cycloadditions between the azomethine ylide **83** (Scheme 29), generated from isatin and benzylamine through a 1,5-prototropic shift, and the 2,6-bis(arylmethylidene)cyclohexanones **84** regioselectively give the dispiroheterocycles **85**. When these reactions were carried out in methanol or acetonitrile at reflux, long reaction times were required (14–26 h) and low yields were obtained (27–38%). Under solvent-free conditions, by grinding the reactants together with K-10 Montmorillonite, and microwave irradiation, however, compounds **85** were obtained in good yields (75–97%) in short times.[68]



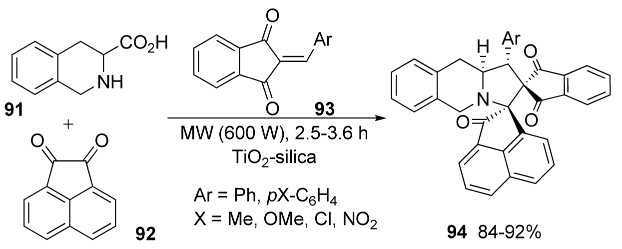
Scheme 29.

A similar approach has been used for the synthesis of other dispiro heterocycles.[69,70] The multicomponent microwave-assisted solvent-free synthesis of the dispiro heterocyclic compounds **90** (Scheme 30), for example, was achieved through reactions between 9-arylidene-9*H*-fluorenes **89** and the azomethine ylides **88**, generated in situ through decarboxylative condensations of ninhydrin and proline or thiazolidine-4-carboxylic acids.



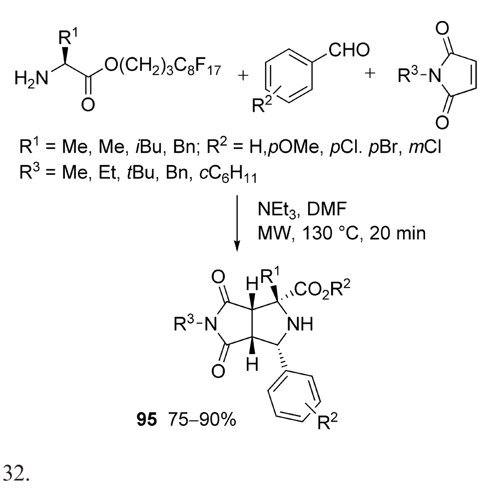
Scheme 30.

TiO_2-impregnated silica gel was used as a solid-supported catalyst for the synthesis of dispiropyrrolo-isoquinoline ring systems in one-pot, three-component reactions as illustrated in Scheme 31.[71] Microwave-induced reactions between tetrahydroisoquinoline-3-carboxylic acid (**91**) and acenaphthenequinone (**92**) in the presence of 2-arylidene-1,3-indanediones **93** lead to single cycloadducts in high yields.



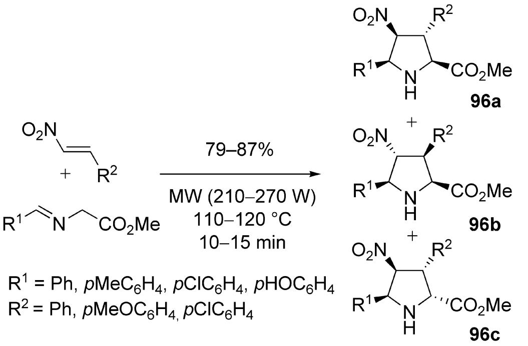
Scheme 31.

Solution-phase syntheses of proline-fused heterocyclic systems by the microwave-assisted intermolecular 1,3-dipolar cycloaddition approach have been reported.[72–74] The one-pot three-component reactions of maleimide derivatives with the in situ generated azomethine ylides afford bicyclic prolines (e.g. **95**) in good yields (Scheme 32).



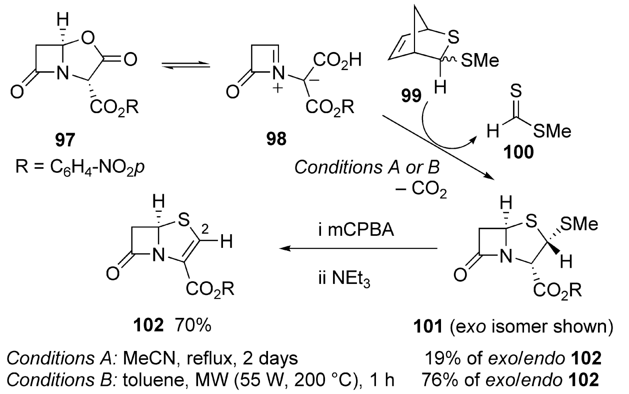
Scheme 32.

Solvent-free microwave-assisted [3+2] cycloadditions of stabilized azomethine ylides and nitrostyrenes lead to the stereoisomeric 4-nitropyrrolidines **96** within 10–15 min and in 79–87% yields (Scheme 33).[75]



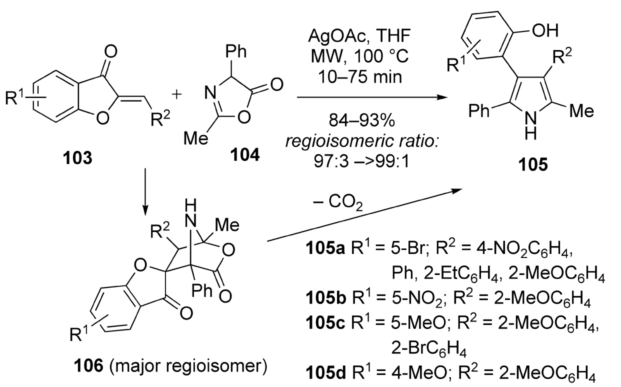
Scheme 33.

Syntheses of *C*(2)-unsubstituted penems from β-lactam-based azomethine ylides and *S*-alkyl dithioformates have been described. Carrying out the thermolysis in MeCN at reflux required 2 days and the product could only be obtained in 19% yield. The reaction between **97** and **100** (Scheme 34) in toluene under microwave irradiation conditions led to the same product in 76% yield, with the reaction requiring only 1 h to go to completion. Compound **101** was then converted into the target *C*(2)-unsubstituted penem **102** by mild oxidation with *m*CPBA and subsequent base treatment.[76,77]



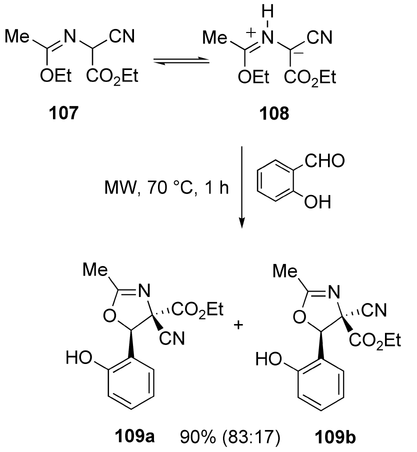
Scheme 34.

Regioselective synthesis of tetrasubstituted pyrroles can be achieved through 1,3-dipolar cycloadditions between the α,β-unsaturated benzofuran-3(2*H*)-ones **103** (Scheme 35) and the masked azomethine ylide generated from azalactone **104**. The microwave-induced regioselective [3+2] cycloadditions lead to the cycloadducts **106**, which are converted into the pyrrole derivatives **105** in high yields through spontaneous decarboxylation and subsequent ring opening of the benzofuran-3(2*H*)-ones.[78] The authors demonstrated that other azalactones can also be used successfully.

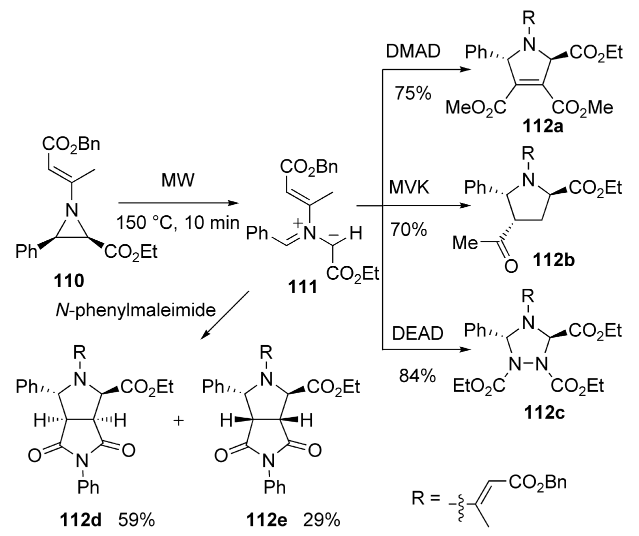


Scheme 35.

1,3-Dipolar cycloadditions of the azomethine ylide **108** (Scheme 36) without solvent under focused microwave irradiation conditions have been used for the synthesis of highly functionalized oxazolines.[79] The imidate **107** is the precursor of a 1,3-dipole that reacts with aromatic aldehyde dipolarophiles (e.g., salicyl aldehyde) at 70 °C without solvent under microwave irradiation conditions to afford mixture of diastereoisomers (e.g., **109**) in high yields. However, an alternative pathway involving cycloaddition of the nitrile ylide, generated from **107** by EtOH elimination, could not be ruled out because the primary cycloadduct could not be isolated. *N*-Benzylidene methylamine can also act as the dipolarophile in reactions of this type.



Scheme 36.



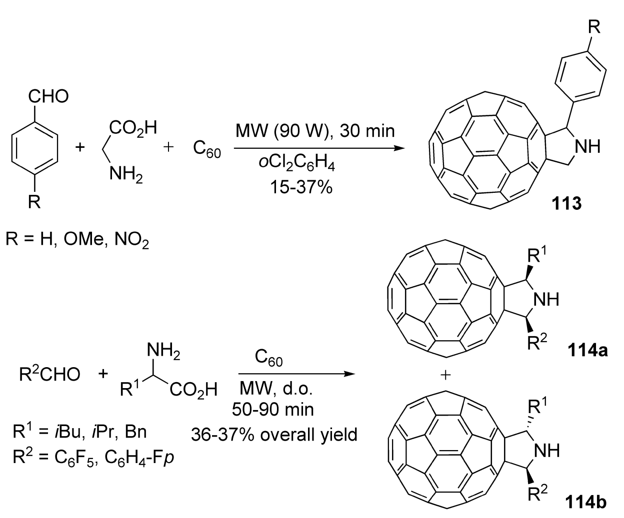
Scheme 37.

1,3-Dipolar cycloadditions of azomethine ylide **111** (Scheme 37), generated by ring opening of the *N*-vinyl aziridine **110**, gave a range of nitrogen-containing *N*-vinyl heterocycles **112**. The stereoselective synthesis of the 1,3-cycloadducts **112** was achieved by use of microwave methodology for the conrotatory ring-opening of the corresponding aziridine in the presence of dipolarophiles. Under conventional heating conditions the synthesis proved less efficient.[80]

Rate acceleration has been observed in microwave syntheses of oxazolines in room-temperature ionic liquids through the 1,3-dipolar cycloaddition reaction between 2-ethoxybenzaldehyde and an azomethine ylide generated from diethyl (*Z*)-2-(1-ethoxyethylideneamino)propanedioate.[81]

Fullerenes are particularly useful compounds for optoelectronic organic devices. They show low reactivity, however, and under conventional thermolysis conditions long reaction times are required for reactions to occur. Microwave technology is therefore very useful in the chemistry of fullerenes.

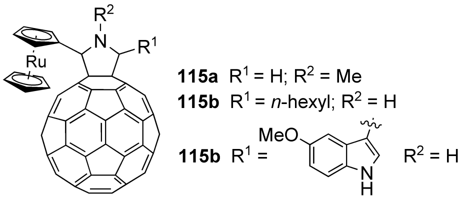
A general method for the functionalization of [60]fullerene is the 1,3-dipolar cycloaddition of azomethine ylides. This strategy was first described by Prato and leads to fulleropyrrolidines.[82] Langa et al. showed that microwave-assisted 1,3-dipolar cycloadditions between C_{60} and azomethine ylides generated from decarboxylation of imminium ions derived from the condensation of glycine with benzaldehydes, giving the fulleropyrrolidines **113** (Scheme 38), compete favorably with conventional reaction conditions.[83]

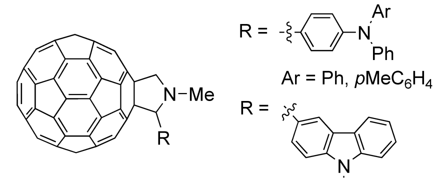


Scheme 38.

2,5-Disubstituted C_{60}-pyrrolidine derivatives were also prepared under microwave irradiation conditions. In a modified domestic microwave oven at 80 W, reactions between C_{60}, α-amino acids, and fluorinated benzaldehydes (Scheme 38) allowed the synthesis of the corresponding fluorinated C_{60} diastereoisomers **114**.[84] The results are comparable to those obtained by classical heating, including the ratios of *cis* and *trans* isomers. However, a significant reduction in the reaction time was achieved (conventional heating: reflux in toluene, 10 h).

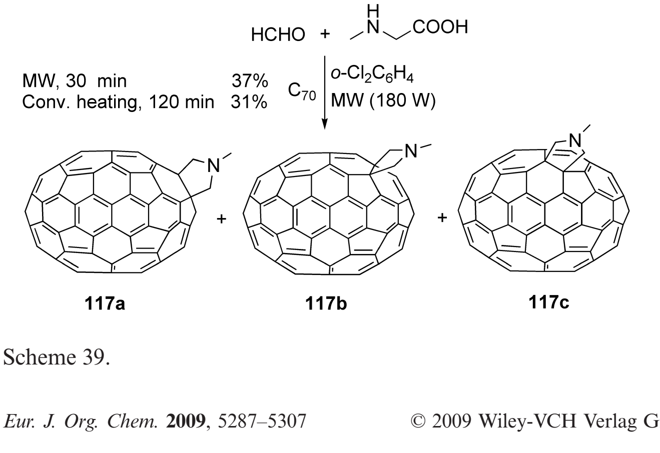
The synthesis of [60]fullerene-donor dyads capable of undergoing photoinduced electron transfer can be achieved by 1,3-dipolar cycloadditions of azomethine ylides. The fullerenes **115**, with ruthenocene as a covalently linked electron donor fragment, were obtained in 24–31 % yields from microwave-assisted cycloadditions of ruthenocenecarbaldehyde, glycine or *N*-methylglycine, and C_{60} in toluene (irradiation at 210 W for 45 min in a focused microwave oven).[85] A similar synthetic methodology can be used for the synthesis of other covalently linked donor-fullerene systems: namely, derivatives based on pyrrolidino[60]fullerenes **116**.[86]





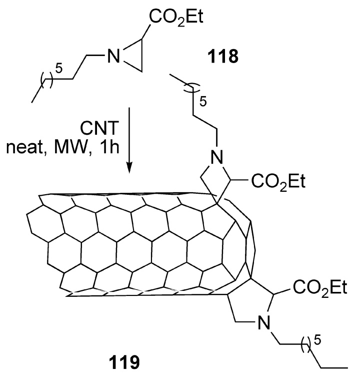
116

The dipolar cycloaddition of an *N*-methylazomethine ylide to C_{70} under microwave irradiation conditions has also been reported. Unlike under conventional heating, in which the isomer **117a** predominates, under microwave irradiation conditions the isomer **117b** is the major product and isomer **117c** is not even formed (Scheme 39).[87]



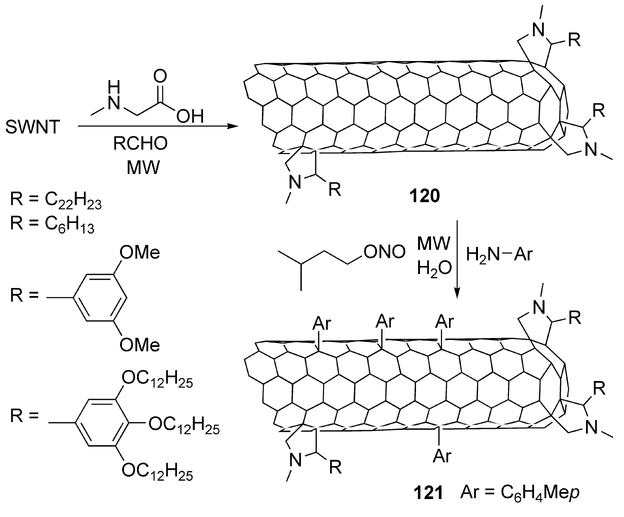
Scheme 39.

Microwaves were used to functionalize nanotubes (CNTs) though 1,3-dipolar cycloadditions of an azomethine ylide generated from ethyl 1-octylaziridine-2-carboxylate (**118**, Scheme 40). Single-wall carbon nanotubes were suspended in a dichloromethane solution of the aziridine, the mixture was sonicated for 5 min, and the solvent was then evaporated off. Irradiation for 1 h under solvent-free conditions then afforded the desired nanotubes (e.g., **119**).[88]



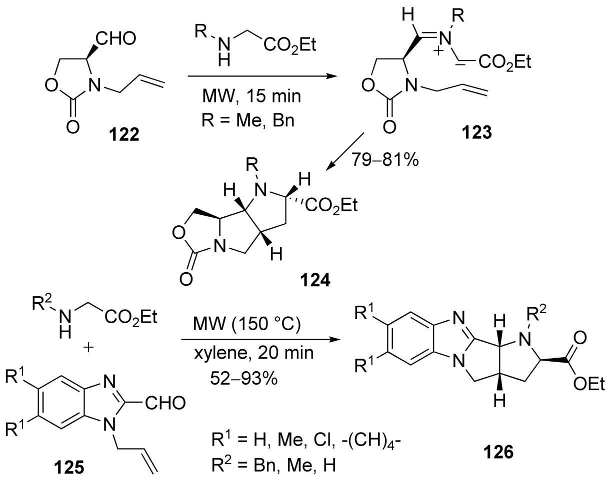
Scheme 40.

Multifunctionalization of single-walled carbon nanotubes by a combination of two microwave-induced reactions – 1,3-dipolar cycloadditions of azomethine ylides and additions of diazonium salts – has been reported (Scheme 41). The authors observed that radical arene addition saturated more reactive sites than the cycloaddition, so that starting with cycloaddition with subsequent arene addition is the best approach by which to attach two different functional groups to the carbon nanotubes (e.g., synthesis of **121**). The 1,3-dipolar cycloadditions were carried out with different aldehydes and sarcosine in solvent-free systems under microwave irradiation conditions for 1 h.[89]



Scheme 41.

Highly stereoselective intramolecular 1,3-dipolar cycloadditions involving chiral azomethine ylides were reported by Cheng et al.[47] The azomethine ylides **123** (Scheme 42) were generated in situ, after which intramolecular cycloadditions were induced by microwave irradiation on the surface of silica gel without solvent, giving the chiral cycloadducts **124** in good yields.

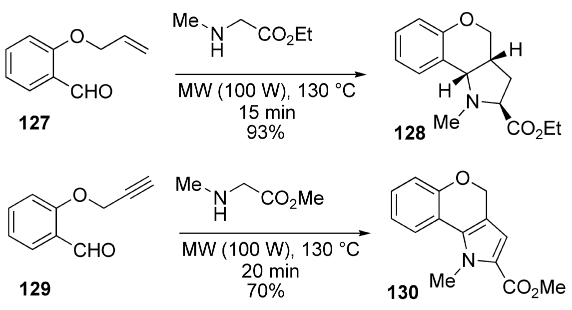


Scheme 42.

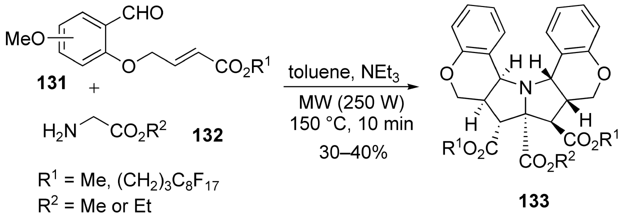
Microwave-assisted intramolecular cycloadditions of azomethine ylides derived from the 1-allyl-1*H*-benzo[*d*]imidazole-2-carbaldehydes **125** (Scheme 42) and *N*-alkyl-α-amino esters were applied for the construction of polycyclic pyrrolidine ring systems. The reactions were carried out in xylene and delivered the pyrrolidino[2′,3′:3,4]pyrrolidino[1,2-*a*]benzimidazoles **126** in good yields.[90]

Microwave irradiation has also been used to promote the intramolecular cycloadditions of azomethine ylides resulting from condensations of *O*-allylic and *O*-propargylic salicylaldehydes with *N*-alkyl glycine esters.[91,92] Two selected examples leading to the syntheses of the tricyclic compounds **128** and **130** are shown in Scheme 43.[90] Parallel comparative reactions were carried out under conventional reaction conditions, leading to the conclusion that the microwave procedure favors the reaction times and the purities of the crude products, which are obtained in comparable yields. With *N*-benzyl glycine ethyl ester as the azomethine ylide precursor, slightly more forcing conditions (300 W, 200 °C for 15 min) were required.[92] On the other hand, bulkier *N*-substituents (e.g., *N*-isopropyl) were found to slow the rate of cycloaddition or to prevent it altogether (e.g. *N*-*tert*-butyl, *N*-adamantyl). Cycloaddition with *N*-phenyl glycine ethyl ester was also unsuccessful. The replacement of the ethoxy carbonyl substituent in the generated dipole by a cyano group or by an isopropoxy- or *tert*-butoxycarbonyl groups leads to a decrease in the yield of formation of the corresponding hexahydrochromeno[4,3-*b*]pyrrole derivative.[93]

One-pot double intramolecular [3+2] cycloaddition reactions of azomethine ylides leading to the hexacyclic ring system **133** (Scheme 44) have been reported. The reactions between the *O*-allyl salicylaldehydes **131** and amino esters **132** were conducted under microwave irradiation conditions. The major diastereoisomers **133** were isolated in yields ranging from 30 to 40%, but small amounts (10–15%) of minor diastereoisomers were detected by LC-MS. These reactions represent an interesting approach to highly condensed ring skeletons because they generate four rings and seven stereocenters in one-pot fashion.[94]

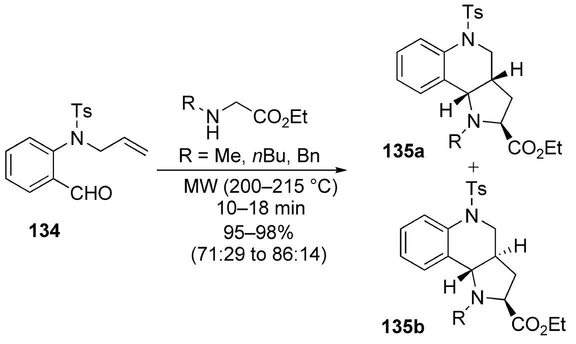


Scheme 43.



Scheme 44.

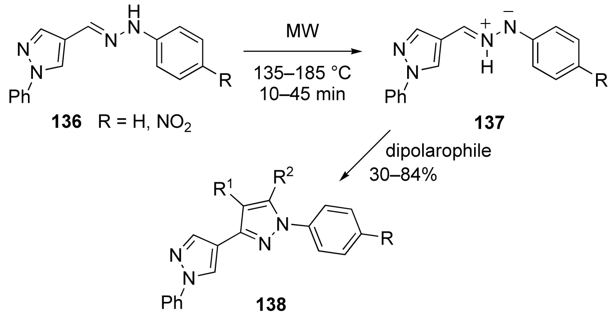
The hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2-carboxylates **135** were prepared by microwave-assisted intramolecular 1,3-dipolar cycloadditions under solvent-free conditions. The aldehyde **134** was condensed with *N*-alkyl glycine ethyl esters to give the tricyclic heterocycles **135** as diastereoisomeric mixtures in high yields (Scheme 45).[95]



Scheme 45.

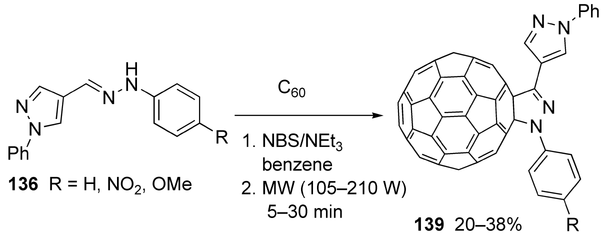
2.4. Cycloadditions of Azomethine Imines and Nitrile Imines

Bipyrazolyl derivatives can be prepared by 1,3-dipolar cycloadditions in solvent-free systems under microwave irradiation conditions (Scheme 46).[96–99] Thermal isomerization of the pyrazolyl hydrazones **136** to the corresponding azomethine imines **137** followed by cycloaddition with electron-deficient dipolarophiles leads to the bipyrazolyl adducts **138** in 30–84% yields. High regioselectivities were observed in the reactions between dipoles **137** and unsymmetrical dipolarophiles.[96]



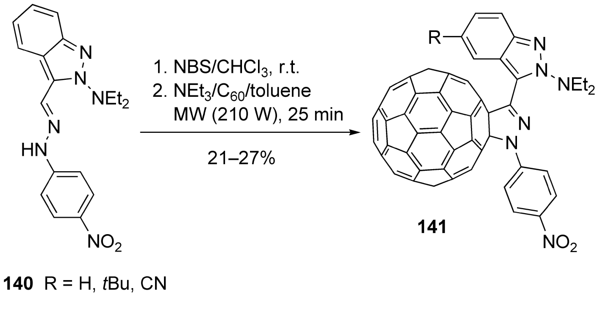
Scheme 46.

The same authors reported microwave-assisted syntheses of the 1-aryl-3-(1-phenylpyrazol-4-yl)pyrazolo[60]fullerene adducts **139** (Scheme 47) in moderate yields from nitrile imines, generated in situ from the corresponding hydrazones and NBS in the presence of Et_3N, and C_{60}.[97] The microwave-induced cycloadditions of nitrile imines to C_{60} were extended to the syntheses of other pyrazolylpyrazolino[60]-fullerenes.[99]



Scheme 47.

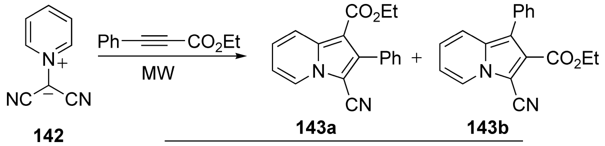
The isoindazolylpyrazolino[60]fullerene dyads **141** (Scheme 48) were isolated in 21–27% yields from 1,3-dipolar cycloadditions between isoindazolyl nitrile imines, generated in situ from the corresponding isoindazole hydrazones **140**, and C_{60}. Treatment of compounds **140** with NBS in $CHCl_3$ at room temperature and subsequent addition of C_{60} and Et_3N in toluene and irradiation at 210 W for 25 min afforded the final products.[100] Langa et al. applied this methodology to obtain fullero-dendrimers (31–34%), fullerenepyrazolines substituted with an oligophenylenevinylene moiety (43–57%), and pyrazolino[60]fullerene derivatives containing electron-withdrawing substituents on both sides of the pyrazoline ring (25–42%).[101–103] A study on the thermal stabilities of pyrazolino[60]fullerenes has recently been reported.[104]



Scheme 48.

2.5. Cycloadditions of Pyridinium Methylides

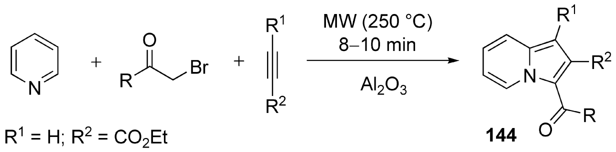
The 1,3-dipolar cycloaddition between pyridinium dicyanomethylide (**142**) and ethyl phenylpropiolate under microwave irradiation conditions leads to the indolizine derivatives **143**. It was observed that the selectivity changes from 88:12 to 98:2 when the solid support is changed from silica gel to neutral Bentonite (Scheme 49).[105]



	143a	143b
Silica gel	88%	12%
Bentonite	98%	2%

Scheme 49.

Microwave-mediated three-component reactions of acyl bromides, pyridine, and acetylenes, catalyzed by basic alumina, allow one-pot syntheses of indolizines. Basic alumina acts as catalyst for the generation of dipoles in situ from the *N*-acylpyridinium salts, which is followed by 1,3-dipolar cycloadditions with the acetylenes to give 2-acylindolizines **144** in high yields. The reactions can be carried out on solid phase or in solution, although higher yields are obtained under the solid-phase reaction conditions (Scheme 50).[106]



R^1 = H; R^2 = CO_2Et
R^1 = R^2 = CO_2Me
R = Ph, *p*Tol, styryl

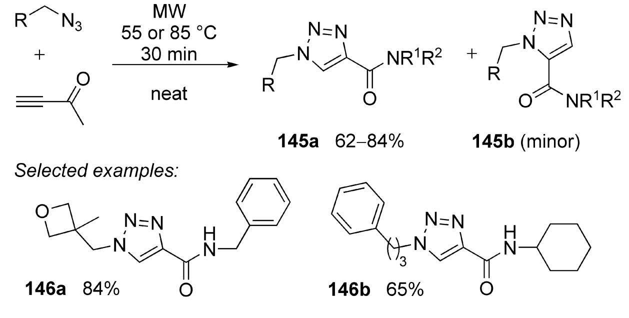
Solid-phase reaction:	87–94%
Reaction carried out in toluene:	60–71%

Scheme 50.

2.6. Cycloadditions of Azides

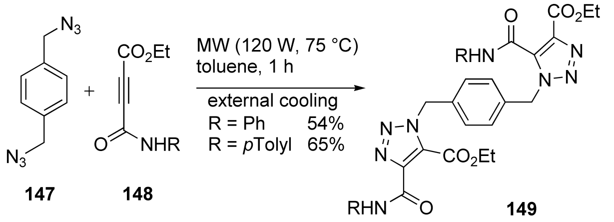
1,2,3-Triazoles are generally prepared by 1,3-dipolar cycloadditions between alkynes and azides at high temperatures. Palacios et al. demonstrated that when the reactions between phosphonate azides and acetylenic esters are carried out under microwave irradiation conditions in solvent-free systems, the corresponding 1,2,3-triazoles **145** (Scheme 51) are obtained with decreases in reaction times from 30–40 h under conventional thermolysis conditions to 5–30 min.[107] On the other hand, direct preparation of *C*-

carbamoyl-1,2,3-triazoles (e.g., **146**) in good yields can be achieved by cycloadditions between acetylenic amides and organic azides under microwave irradiation conditions in solvent-free systems.[108]



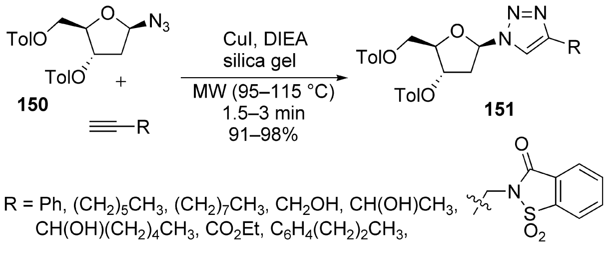
Scheme 51.

Katritzky et al. described the syntheses of bis(triazoles) through 1,3-dipolar cycloadditions between 1,4-bis(azidomethyl)benzene (**147**, Scheme 52) and monoacetylenes in a microwave synthesizer featuring simultaneous irradiation and external air-cooling. The major isomers **149** were isolated in 54–65% yields.[109]



Scheme 52.

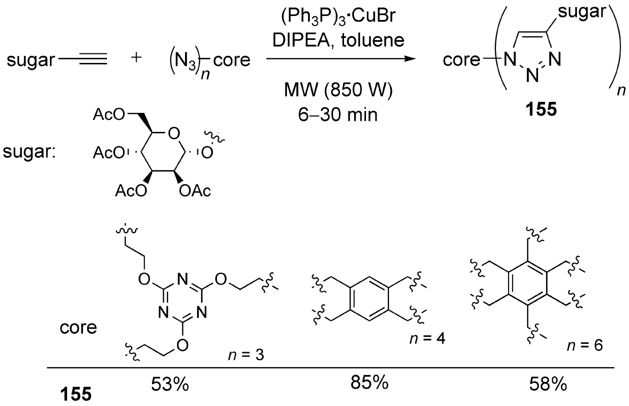
The syntheses of the α- and β-2′-deoxy-1,2,3-triazolyl-nucleosides **151** can be achieved through microwave- and Cu^I-assisted "click-chemistry". Under solvent-free conditions and with silica gel as a solid support, α- or β-azido-2-deoxyribose, an alkyne, CuI, and diisopropylethylamine (DIEA) react under microwave irradiation for 1.5–3 min to give the target compounds in high yields. Selected examples of this synthetic methodology starting with the β-azido-2-deoxyribose **150** are presented in Scheme 53.[110]



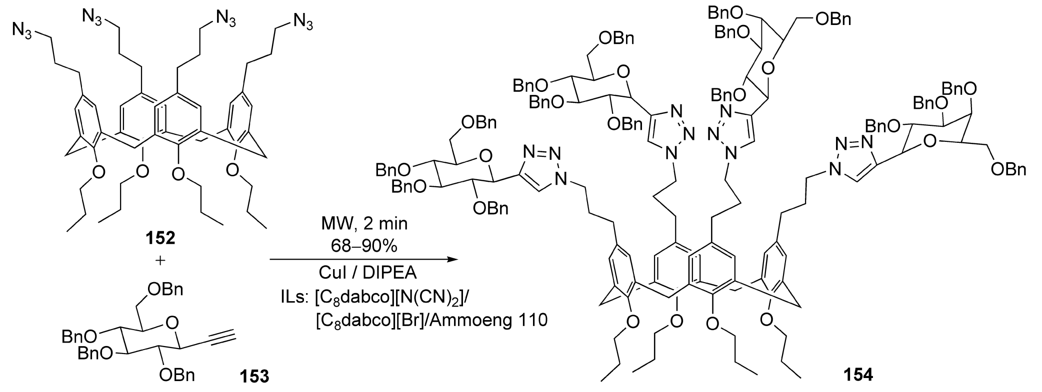
Scheme 53.

The glycocluster **154** (Scheme 54) was prepared by the reaction between the tetraazidocalix[4]arene derivative **152** and ethynyl tetra-*O*-benzyl-*C*-galactoside (**153**) in ionic liquids (ILs). The reaction can be performed under microwave irradiation for 2 min, giving the target molecule in good yield. The work was extended to reactions between other sugar alkynes and the tetraazide **152**.[111]

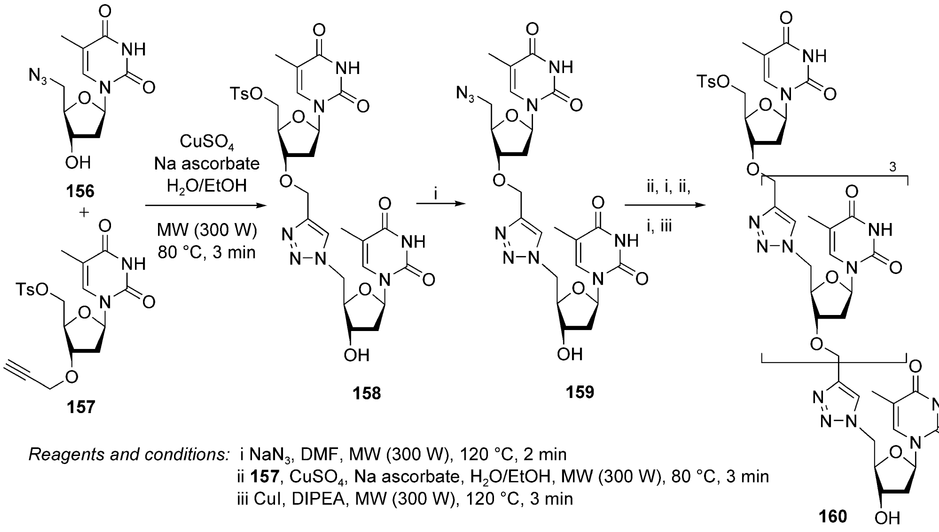
The glycoconjugates **155** are efficiently prepared by catalytic cycloadditions between alkynes and azides in the presence of organic-soluble complexes such as $(Ph_3P)_3$·CuBr or $(EtO)_3P$·CuI. The reactions can be carried out at room temperature, but the combination with microwave irradiation shortens the reaction times considerably. Some representative examples are shown in Scheme 55.[112]



Scheme 55.



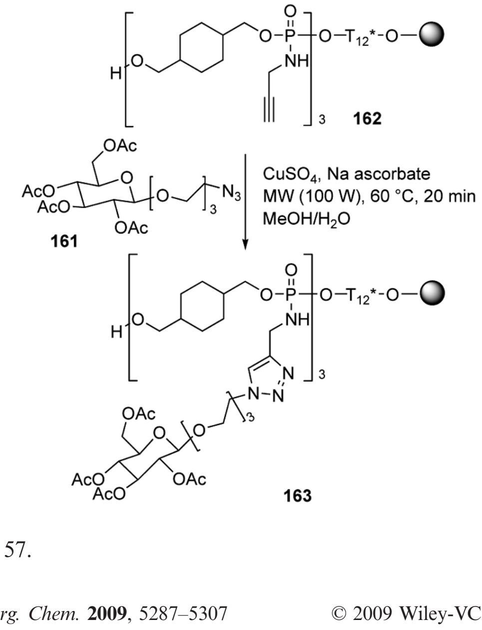
Scheme 54.



Scheme 56.

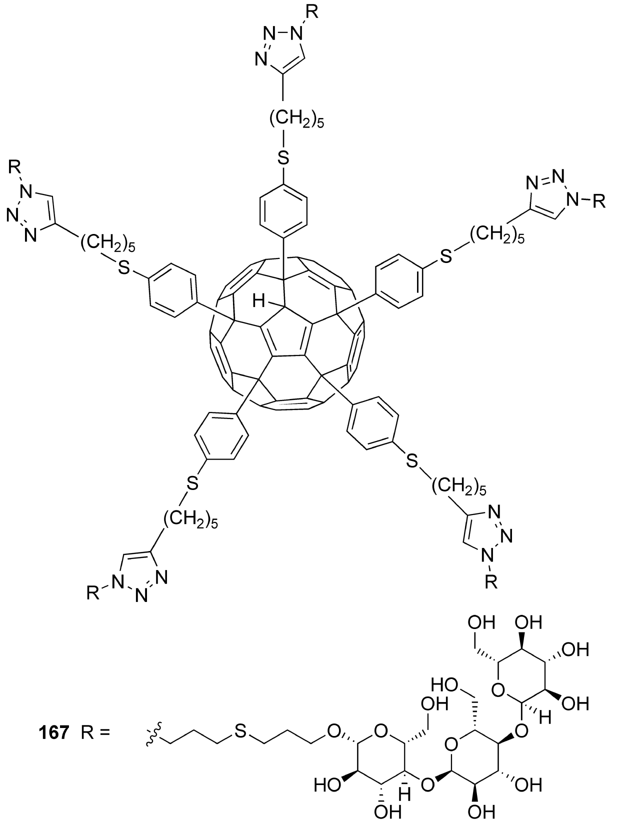
The 3′,5′-pentathymidine **160** (Scheme 56) was prepared in high yield by a synthetic procedure involving alternating azidation and microwave-induced Cu-catalyzed 1,3-dipolar cycloaddition reactions.[113] The azide **156** and the alkyne **157** were coupled, giving the 1,4-dithymidine-substituted-1,2,3-triazole **158** in 92% yield. The reaction mixture was directly used in the following step. The tosyldithymidine **158** was converted into the azide **159**, which reacted with further **157** to give the corresponding cycloadduct in 94% yield. Sequential azidation and 1,3-dipolar cycloaddition reactions allowed the synthesis of the target molecule **160**. The whole process, including workup, was completed in just 18 min.

"Click-chemistry" is one approach for anchoring carbohydrate derivatives to solid-supported oligonucleotides. The coupling of the alkyne-bearing oligonucleotide **162** with the azide-functionalized galactoside **161** under microwave irradiation conditions at 60 °C for 20 min thus quantitatively affords the solid-supported carbohydrate oligonucleotide **163** (Scheme 57).[114]

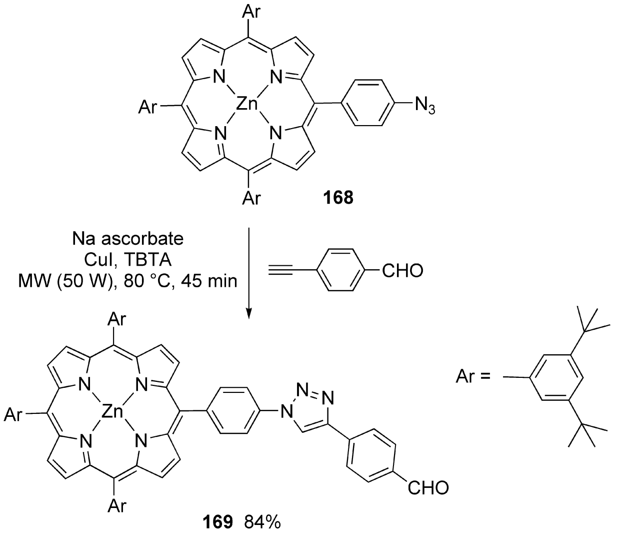


Scheme 57.

The fullerene-carbohydrate conjugate **167** is obtained in high yield (93%) through a copper-catalyzed microwave-induced [3+2] cycloaddition between a pentaalkynyl[60]fullerene and an azide-functionalized sugar.[115]

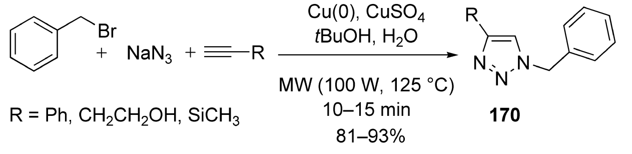


The azidoporphyrins **168** (Scheme 58) react in microwave-assisted reactions with 4-ethynylbenzaldehyde in the presence of copper iodide, sodium ascorbate, and tris(benzyltriazolylmethyl)amine (TBTA) to afford the porphyrin triazoles **169** in 84% yield; these were used to prepare triazole-linked porphyrin-fullerenes. On the other hand, porphyrin triazoles were obtained by combining alkynyl prophyrins with 4-azido- and 3-azidobenzaldehyde by "click chemistry" under microwave irradiation conditions.[116]



Scheme 58.

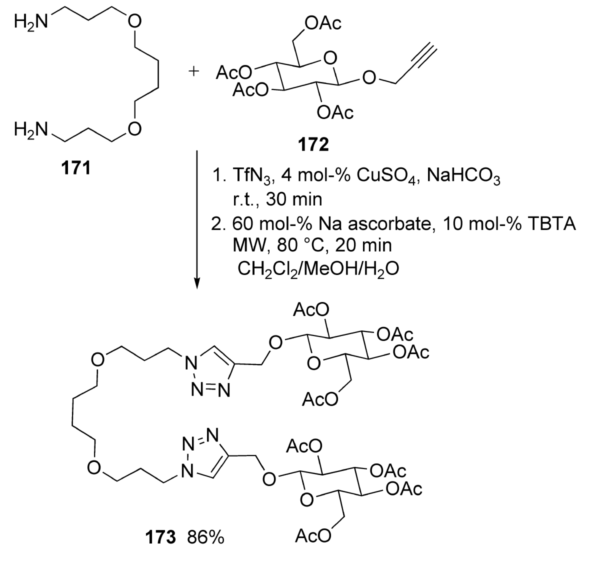
The synthesis of 1,4-disubstituted 1,2,3-triazoles through microwave-assisted copper(I)-catalyzed three-component reactions is known.[117] The azides are generated in situ from alkyl halides and captured by copper(I) acetylides, affording the corresponding 1,2,3-triazoles **170**, obtained in good yields with the exclusive formation of the 1,4-regioisomers (Scheme 59).



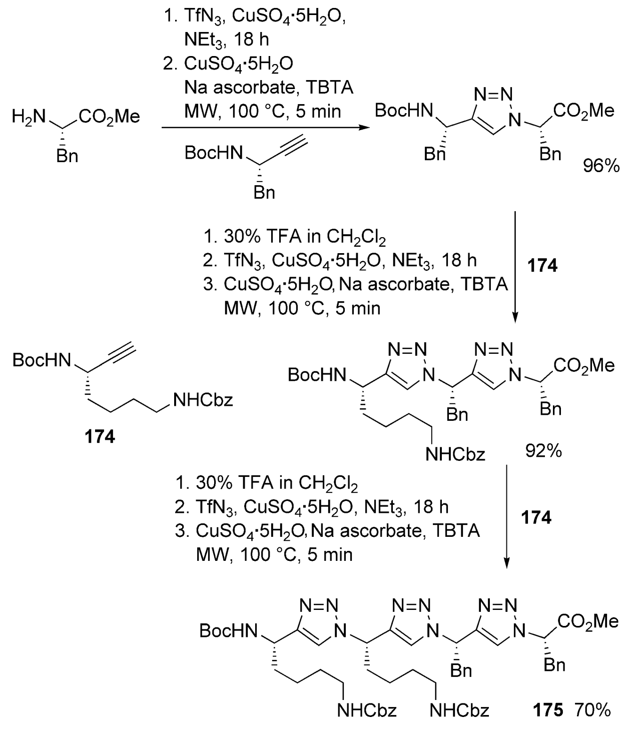
Scheme 59.

1,4-Disubstituted 1,2,3-triazoles can also be obtained efficiently from amines by a one-pot procedure involving sequential diazo transfer and azide–alkyne cycloaddition reactions. Organic azides are generated in situ by Cu^{II}-catalyzed diazo transfer to amines with the use of trifluoromethanesulfonyl azide. Subsequent cycloadditions with acetylenes are carried out in the presence of sodium ascorbate and TBTA under microwave irradiation conditions. This methodology can be illustrated with the synthesis of the divalent glucoconjugate **173**, prepared in 86% yield from the diamine **171** and the propargyl glucoside **172** (Scheme 60).[118]

Amino-acid-derived amines can be converted into 1,2,3-triazoles by a one-pot, two-step sequence of diazo-transfer and azido–alkyne cycloaddition reactions.[119] This microwave-induced methodology was applied to the synthesis of the triazole trimer **175** (Scheme 61).



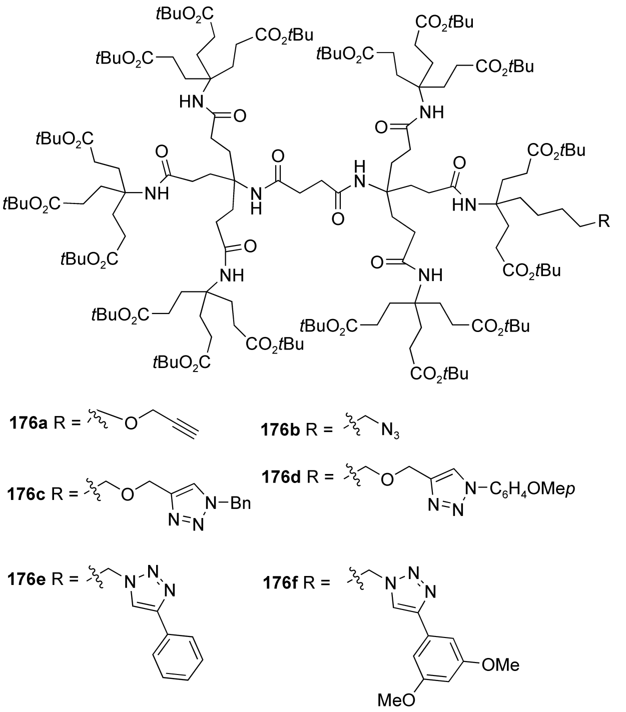
Scheme 60.



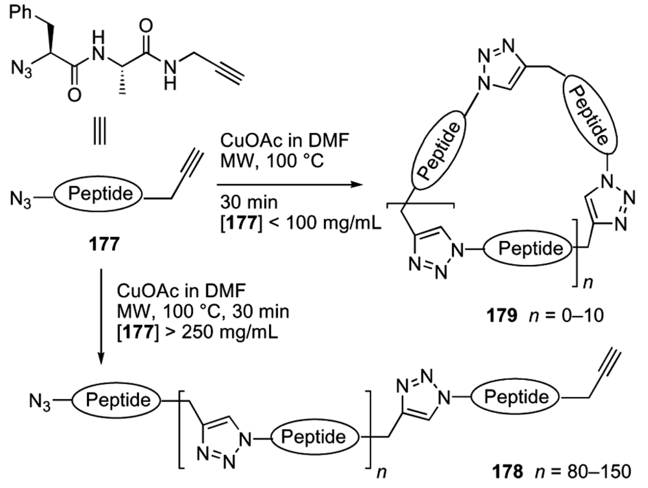
Scheme 61.

Monofunctionalized polyamide-based dendrimers containing either terminal azide or alkyne moieties (**176a** and **176b**) can also be obtained by microwave-assisted azide–alkyne 1,3-dipolar cycloadditions. The reactions were carried out with sodium ascorbate and $CuSO_4{\cdot}5H_2O$ in 1:1 mixtures of *t*BuOH and H_2O at 100 W irradiation power with the temperature set to 100 °C and were complete after 10 min, giving the monofunctionalized dendrimers **176c**–**176f** in high yields (95–98%).[120]

The monomer azido-phenylalanyl-alanylpropargyl amide (**177**) was converted into amino-acid-based polymers by microwave-assisted "click reactions". Depending on the reaction conditions, either the high-molecular-weight linear



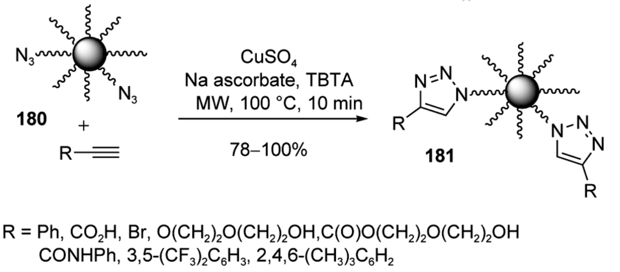
polymers **178** (Scheme 62) or the medium-sized cyclic polymers **179** were obtained. The microwave heating was found to be superior to conventional heating.[121]



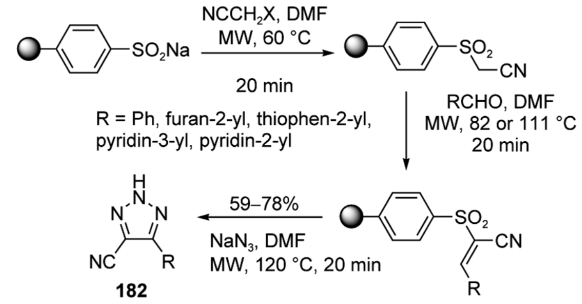
Scheme 62.

Functionalization of thiol-coated gold nanoparticles can be performed with the aid of microwave-induced copper-catalyzed "click-chemistry". Cycloadditions between the azide-functionalized nanoparticles **180** (Scheme 63) and a range of alkynes afforded the target nanoparticles **181** in high yields.[122]

Regioselective syntheses of 1,2,3-triazoles through 1,3-dipolar cycloadditions between polymer-bound vinyl sulfones (polystyrene/1% divinylbenzene sodium sulfinate resin) and sodium azide have been reported. The authors observed that microwave irradiation provides significant rate enhancements in all steps of the three-step protocol, leading to 4,5-disubstituted-1,2,3-triazoles such as **182** (Scheme 64). The preparation of 2,4,5-trisubstituted 1,2,3-triazoles and monosubstituted 1,2,3-triazoles is also described.[123]

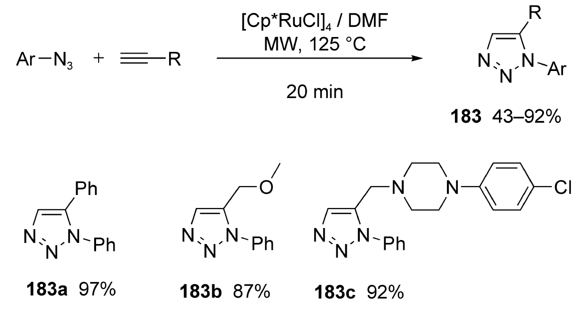


Scheme 63.



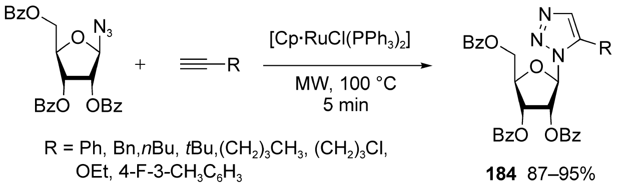
Scheme 64.

Azide–alkyne cycloadditions using (pentamethylcyclopentadienyl)ruthenium(II) chloride tetramer – [Cp*RuCl]$_4$ – provide regioselective access to 1,5-disubstituted 1,2,3-triazoles such as **183a**–**183c** (Scheme 65). It was demonstrated that under microwave irradiation conditions the reactions provide higher yields and shorter reaction times.[124]



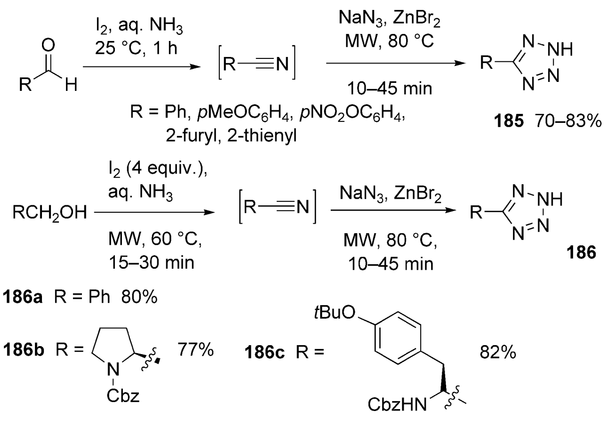
Scheme 65.

The synthesis of the 1,5-disubstituted 1,2,3-triazolonucleosides **184** (Scheme 66) through Ru^{II}-catalyzed azide–alkyne cycloadditions is known. Compounds **184** can be obtained by conventional thermolysis (THF, 50 °C, 6 h) in yields ranging from 54 to 83%. However, the cooperative effect of the Ru^{II} catalyst and the microwave activation affords the target compounds in only a few minutes in high yields.[125]



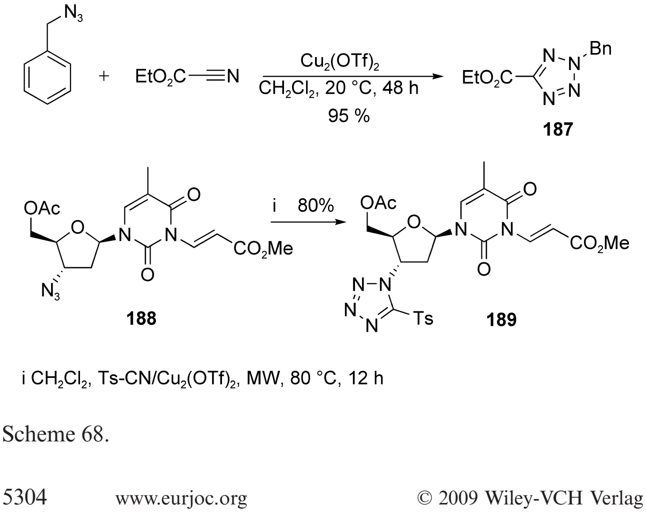
Scheme 66.

Microwave-assisted one-pot tandem reactions of aldehydes or primary alcohols in aqueous media leading to tetrazole derivatives have been reported (Scheme 67).[126] Oxidation of the aldehydes with I_2 in aq. ammonia gave the intermediate nitriles, which underwent 1,3-dipolar cycloadditions with sodium azide to afford the 5-aryl-tetrazoles **185** in 70–83% overall yields. In a similar way, benzyl alcohol, *N*-Cbz-prolinol, and a tyrosine-derived primary alcohol were converted into 1,2,3,4-tetrazoles **186** in good yields.



Scheme 67.

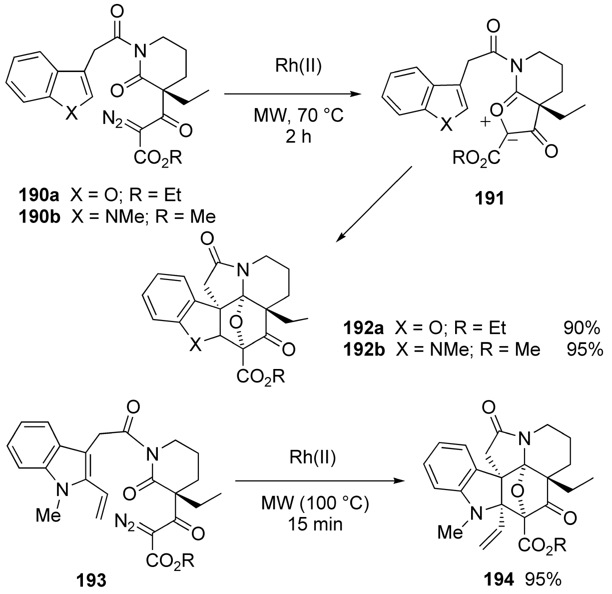
Vilarrasa et al. have reported copper-catalyzed syntheses of tetrazoles (e.g., **187**, Scheme 68) from nitriles bearing electron-withdrawing groups and organic azides; they can be carried out at room temperature, making this procedure one of the safest methods for the formation of tetrazoles. For the reluctant secondary azide **188**, an AZT derivative, however, it was found that heating at 80 °C under microwave irradiation conditions for a few hours was able to force the reaction to proceed.[127]



Scheme 68.

2.7. Cycloadditions of Carbonyl Ylides

Treatment of the substituted diazo imides **190** (Scheme 69) with rhodium(II) pivalate at 100 °C in benzene and under microwave irradiation conditions affords the corresponding rhodium carbenoid species, which undergo cyclization with the neighboring imide carbonyl groups to form the carbonyl ylide dipoles **191**. These dipoles participate in 1,3-dipolar cycloadditions across the heteroaromatic π-bonds to give the corresponding cycloadducts **192** in high yields and in a stereocontrolled fashion. The pentacyclic compounds **194** were also obtained by push-pull dipole generation from the Rh^{II}-catalyzed reactions of diazoimides **193**, followed by [3+2] cycloaddition.[128]

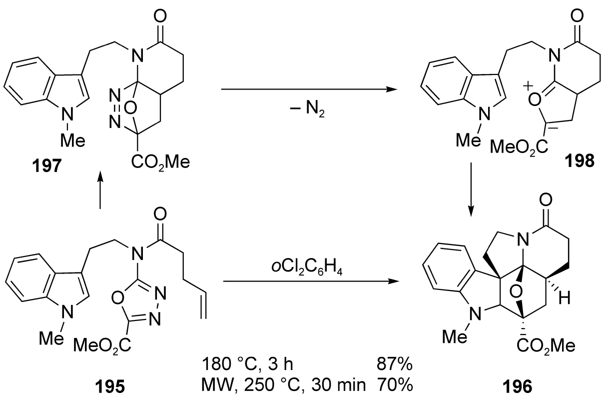


Scheme 69.

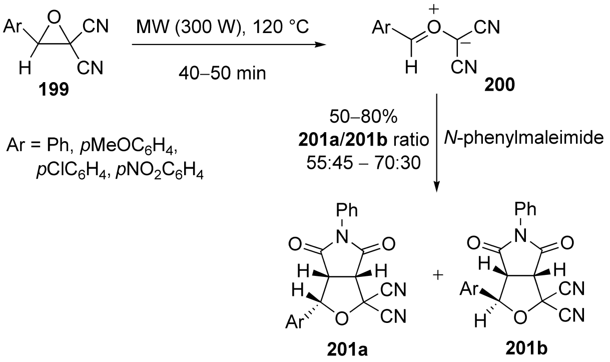
A tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition reaction of the 1,3,4-oxadiazole **195** (Scheme 70) was used to prepare the pentacyclic derivative **196**. The initial inverse-electron-demand Diels–Alder reaction provides the cycloadduct **197**, which loses N_2 to generate the carbonyl ylide **198**, which further reacts with the internal dipolarophile to give the 1,3-dipolar cycloadduct **196** in good yield. In this case the thermal cycloaddition cascades are so clean and efficient that microwave irradiation does not provide significant improvement.[129]

1,3-Dipolar cycloadditions between carbonyl ylides **200**, generated from the *gem*-dicyano epoxides **199**, and alkenes gives the corresponding tetrahydrofurans in good overall yields.[1] An illustrative example is shown in Scheme 71. With *N*-phenylmaleimide as dipolarophile and under microwave irradiation conditions for 40–50 min, the 1*H*-furo-[3,4-*c*]pyrrole derivatives **201** were obtained as diastereoisomeric mixtures.[130]

Diastereoselective syntheses of oxazolidines are achieved through reactions between *gem*-dicyano epoxides and imines (e.g. synthesis of **202**, Scheme 72).[131] A similar synthetic strategy was applied to the synthesis of 1,3-dioxol-

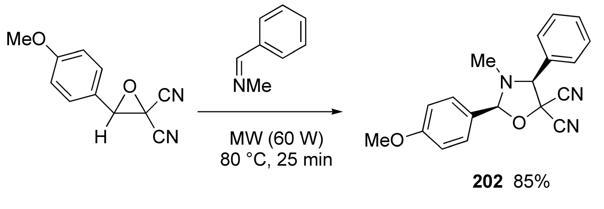


Scheme 70.



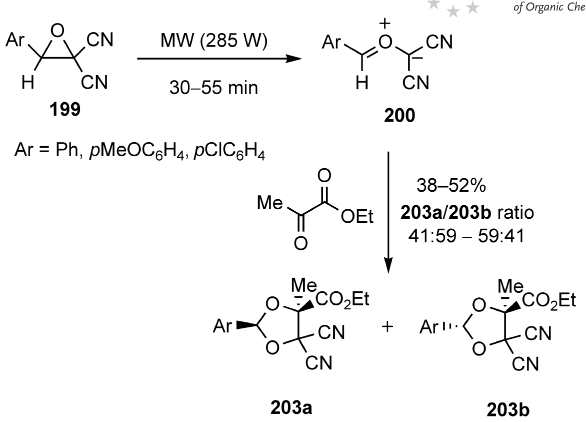
Scheme 71.

anes with aldehydes acting as dipolarophiles.[132] The mechanisms of 1,3-dipolar cycloadditions between carbonyl ylides and aldehydes or imines have been theoretically investigated by DFT methods.[131]



Scheme 72.

The carbonyl ylides **200** also participate in cycloaddition reactions with ketones (Scheme 73).[133] The reactions between 2,2-dicyano-3-(4-substituted)phenyloxiranes and ethyl pyruvate afford the corresponding 5,5-dicyano-4-methyl-2-phenyl-1,3-dioxolane-4-carboxylates **203**. Carrying out the reaction under microwave irradiation conditions in solvent-free systems gives significant reductions in reaction times in relation to reactions in toluene at reflux (30–55 min against 14–27 h).



Scheme 73.

Conclusions

The use of microwave reactors for organic synthesis in recent years has allowed for the improvement of reaction reproducibility and for safer conditions than are obtained with domestic ovens. The synthetic utility of microwave irradiation in organic synthesis has therefore increased considerably.

In this review we have shown that microwave irradiation is an efficient methodology to promote 1,3-dipolar cycloaddition reactions, leading to the enhancement of yields and shorter reaction times. Both solution and solvent-free microwave-assisted reactions of a range of 1,3-dipoles have been explored. Among them, nitrones, azomethine ylides, and azides are the most widely studied 1,3-dipoles.

The low reactivities of fullerenes and nanotubes under conventional thermolysis conditions make microwave technology very useful for the functionalization of structures of this type. Also particularly interesting is the microwave-assisted "click reaction", especially for the syntheses of calyx[4]arene derivatives, glycoconjugates, dendrimers, and polymers.

The significant impact that microwave-assisted chemistry has already achieved in organic synthesis is an indication that this is a fruitful area for future study.

Acknowledgments

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