REVIEW

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Recent developments in the synthesis, chemistry and applications of the fully unsaturated 1,2,4-oxadiazoles

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Recent major developments in the synthesis (including solid phase methodologies), chemistry and applications of the fully unsaturated 1,2,4-oxadiazole nucleus are reviewed. The review covers the years 1995–2000.

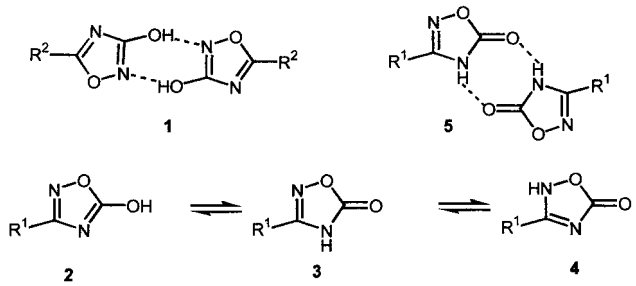
Keywords: 1,2,4-Oxadiazole, amidoxime, *O*-acylamidoxime, synthesis, solid phase synthesis.

1. Introduction and Scope of Review

This topic has been reviewed on several occasions[1–6] and was last reviewed thoroughly in 1996.[7] This review will therefore detail new or major developments reported in the literature from 1995 until the end of 2000, inclusive, although some reference to earlier work will be made for clarity, where appropriate. A significant proportion of the information which has been published in this time deals with the biological applications of 1,2,4-oxadiazoles, and this aspect is dealt with separately in Section 10, below. The review will deal only with the fully unsaturated (*i.e.* fully oxidised, or aromatic) heterocycle. The synthesis of 2- and 4- substituted systems, including the *N*-oxides and the oxadiazoliums, the synthesis of the oxadiazolines (dihydro 1,2,4-oxadiazoles) and the oxadiazolidines (the fully saturated heterocycle), and therefore any fused systems, are beyond the scope of this review. However, systems which are tautomeric with fully unsaturated 1,2,4-oxadiazoles, such as the 3- or 5- oxo systems, will be covered.

2. Physical Properties and Theoretical Studies

Previous reviews[1–7] report comprehensive listings of melting points, X-ray analyses, NMR data, mass spectral data and other physical properties. Recent X-ray crystal structures[8–11] confirm earlier reports[7] that the 1,2,4-oxadiazole ring is planar, with bond lengths being consistent with the ring possessing some aromatic character. An investigation into the effect of solvents on the nitrogen chemical shifts in ^{14}N NMR spectroscopy has appeared,[12] whilst other aspects of the NMR spectra of 1,2,4-oxadiazoles are dealt with elsewhere.[7] The electron impact mass spectrometry of 1,2,4-oxadiazoles is dominated[7] by a (stepwise) 1,3-dipolar cycloreversion process, which proceeds *via* cleavage of the 1,5 (C–O) and 3,4 (C–N) bonds, and a recent report deals with this, and with other fragmentations, in a series of acyl hydrazone substituted 1,2,4-oxadiazoles.[13] Theoretical calculations concerning the directionality and strength of hydrogen bonds formed by methanol and the 1,2,4-oxadiazole system have been performed,[14] and have revealed that hydrogen bonds to the nitrogen atom are more abundant than those to the oxygen atom. The tautomeric behaviour of 3- and 5- amino and 3- hydroxy substituted 1,2,4-oxadiazoles is such that they exist largely as the amino and hydroxy tautomers, the latter being stabilised by the formation of the dimers **1** (Scheme 1). With 5-hydroxy-1,2,4-oxadiazoles **2**, the oxo forms **3** and **4** often dominate as shown in Scheme 1, and the dimerisation of form **3** into the dimers **5** provides a stabilising feature.[15]

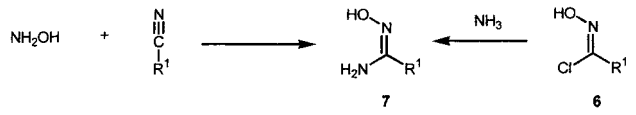


Scheme 1

3. Synthesis of 1,2,4-Oxadiazoles via Cyclisation

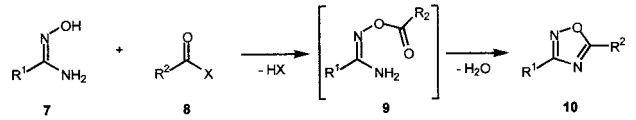
3.1 The Cyclisation of *O*-Acylamidoximes Formed *Via* the *O*-Acylation of Amidoximes

The reaction of an amidoxime with a carboxylic acid derivative, a carbonic acid derivative, or a related species remains[4,5,7] the most popular and most facile entry into the 1,2,4-oxadiazole nucleus. The requisite amidoximes **7** are readily available, usually from the reaction of nitriles with hydroxylamine, or *via* the reaction of imidoyl halides **6** with ammonia, as shown in Scheme 2.



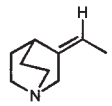
Scheme 2

The carboxylic fragment **8** which reacts with the amidoxime **7**, as shown in Scheme 3, can be a carboxylic acid activated *in situ* by a coupling reagent,[10,16,17,18] an isolated activated carboxylic acid,[17] a symmetrical acid anhydride derived from an amino acid,[18] an acid anhydride,[16c,19,20] succinic anhydride,[21] an acid chloride,[8,19d,20,22] an acid fluoride,[23] or an ester.[9,19d,24] The reaction proceeds *via* an intermediate *O*-acylamidoxime **9** which can undergo spontaneous cyclisation, can be cyclised *in situ*, or can be isolated and then cyclised, to give the 1,2,4-oxadiazole **10**. Some typical examples and yields are shown in Table 1.

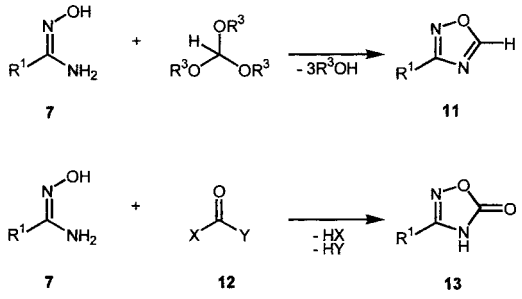


Scheme 3

Table 1 Typical 1,2,4-Oxadiazoles Available From the *O*-Acylation of Amidoximes (see Scheme 3)

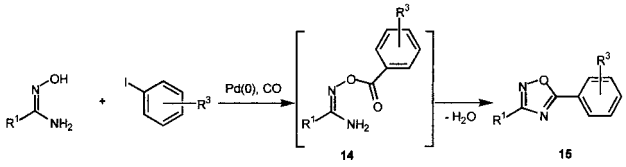
7, R^1 =	**8**, R^2 =	**8**, X =	% Yield of **10**	Notes and Conditions	Ref.
Ph	Me	Cl or OCOMe	90	Tetrabutylammonium fluoride was used as a catalyst	20b
Ph	CF_3	$OCOCF_3$	80	No catalyst required	20b
4-MeC_6H_4	Pr	OH	60	1-(3-Dimethylaminopropyl)-3-ethylcarbodi-imide was used as a coupling agent	16a
4-$CF_3C_6H_4$	4-ClC_6H_4	OH	80	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium salt used as coupling agent	16g
CO_2Et	Boc-Phe-O	Boc-Phe-O	72	The symmetrical anhydride was formed from Boc-Phe and dicyclohexylcarbodi-imide	19c
Xylose	Ph	Cl	85	Heat with pyridine as base	20a
Me	$Me_2NCH_2CH_2$	OMe	39	NaH in THF used as base	24c
Me		OEt	93	NaOEt in EtOH was used as the base at 80°C	24i
Propyl	CF_2Br	OEt	41	Heat only required	24e

The reaction of an amidoxime with an orthoformate[19d,22b] (Scheme 4) allows access to 5-unsubstituted 1,2,4-oxadiazoles **11**, whilst the use of chloroformates,[25] phosgene, thiophosgene or their synthetic equivalent **12**,[25b,26] gives the 5-oxo substituted systems **13** as the final products, also shown in Scheme 4.



Scheme 4

Amidoximes can also be *O*-acylated using a palladium mediated coupling with an aryl iodide in the presence of carbon monoxide, as shown in Scheme 5. Cyclisation of the resultant *O*-acylamidoxime **14** then yields the 3-alkyl-5-aryl-1,2,4-oxadiazoles **15**, which were obtained in yields of up to 71%.[27]

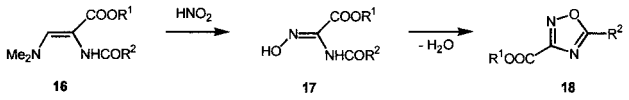


Scheme 5

The use of oximes as starting materials in the synthesis of a wide range of heterocycles, including some reference to the synthesis of 1,2,4-oxadiazoles, has been reviewed.[28]

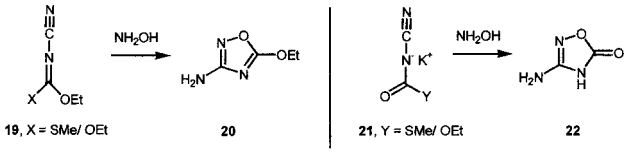
3.2 The Synthesis of 1,2,4-Oxadiazoles *Via* Other Cyclisation Methodologies

The nitrosation of acylamino dialkylaminopropenoates **16** provides a route to the *N*-acylated amidoxime derivatives **17** (Scheme 6), which undergo cyclisation to yield the corresponding 5-substituted 1,2,4-oxadiazole-3-carboxylates **18**, in yields of 63–78%.[29]



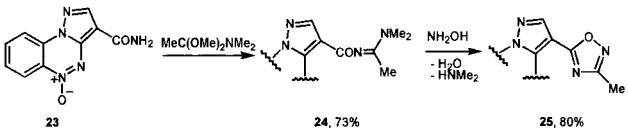
Scheme 6

The treatment of *N*-cyanocarbonimidate derivatives **19**, Scheme 7, with hydroxylamine allows access to 3-amino-5-ethoxy-1,2,4-oxadiazoles **20** in 78–90% yield.[30] Similarly, the use of the potassium salt of the *N*-cyanocarbamate **21** allowed access to the 3-amino-5-oxo derivative **22** in 43% yield.



Scheme 7

The reaction of the amide **23** with dimethylacetamide-dimethyl acetal furnished the acylamidine **24**, which underwent a smooth cyclisation to give the 1,2,4-oxadiazole **25** upon treatment with hydroxylamine, as shown in Scheme 8.[31]



Scheme 8

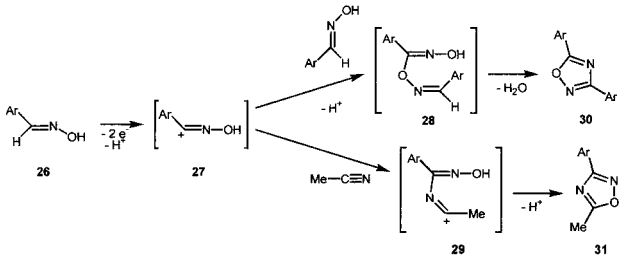
The controlled anodic oxidation of aldoximes **26** (Scheme 9) in acetonitrile led to the proposed intermediate cations **27**, which underwent addition either to the parent aldoxime, or to the acetonitrile solvent, to furnish the 1,2,4-oxadiazoles **30** and **31**, respectively, in combined yields of up to 47%.[32] The reaction was proposed to proceed *via* the intermediate cyclisation precursors **28** and **29**.

4. Synthesis From the 1,3-Dipolar Cycloaddition of Nitrile Oxides to Nitriles and Related Reactions

Historically,[1-7,33] this is a well established route to 1,2,4-oxadiazoles, and remains second in popularity to those routes, outlined in Section 3.1, which rely upon the acylation of

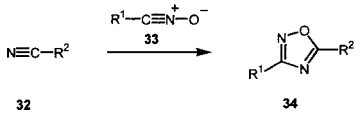
Table 2 Typical 1,2,4-Oxadiazoles From the Cycloaddition of Nitrile Oxides to Nitriles (Scheme 10)

Nitrile Oxide Substituent, R^1	Nitrile Substituent, R^2	% Yield of **34**	Ref.
Ph	S-1-naphthyl	79	33c
Me	4-$NO_2C_6H_4S$	48	33c
Br	*i*Pr	64	33d
Br	CO_2Et	79	33d
PhCO	CH_2CONH_2	90	33e
4-FC_6H_4CO	CH_2CN	32	33e
CF_3	Ph	94	33f
Ph	2-(5-nitrofuryl)	70	33g
Ph	CCl_3	65	33g



Scheme 9

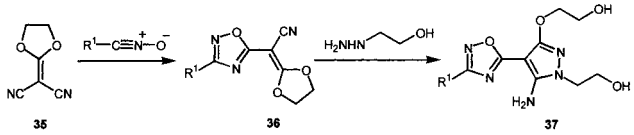
amidoximes. The 1,3-dipolar cycloaddition between a nitrile **32** and a nitrile oxide **33** gives direct access to the 1,2,4-oxadiazole nucleus **34**, as shown in Scheme 10. Table 2 shows a representative range of the 1,2,4-oxadiazoles available *via* this route.



Scheme 10

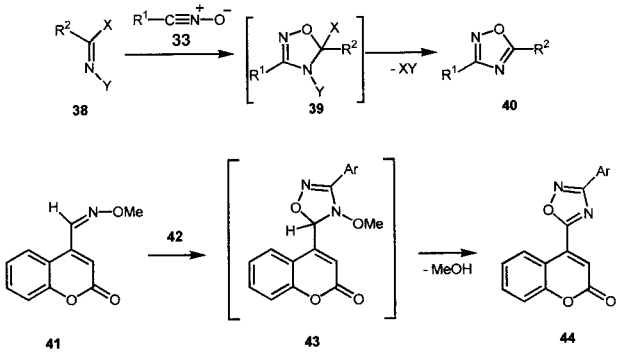
The nitrile oxides **33** are usually generated *via* the dehydrodehalogenation of an imidoyl halide, but can also be generated from the reaction of a nitroalkane with phenylisocyanate (the Mukaiyama-Hoshino method), or by a variety of other, less common methods.[1-7,33a,b] In a recent report, the 1,3-dipolar cycloaddition of some stable nitrile oxides to nitriles under microwave irradiation in solvent-free conditions was investigated,[34] and was shown to give consistently higher yields of 1,2,4-oxadiazoles than the classical methods. 3,5-Dichloro-2,4,6-trimethylbenzonitrile oxide, a stable nitrile oxide, has been shown to undergo a dimerisation reaction accompanied by deoxygenation, to furnish 3,5-*bis*-(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,4-oxadiazole in over 50% yield.[35] The treatment of aldoximes with ceric ammonium nitrate produces nitrile oxides which undergo cycloaddition to aryl and alkyl nitriles to produce 1,2,4-oxadiazoles in 24–73% yield.[36] The irradiation of a series of cobaloxime complexes ($ArCH_2Co$[dimethylglyoximato]$_2$pyridine) in the presence of an alkyl nitrite has been proposed to involve a nitrile oxide intermediate which then undergoes cycloaddition reactions to give 3,5-diaryl-1,2,4-oxadiazoles in yields of 50–70%.[37]

Alkyl and aryl groups, as well as halogen, trifluoromethyl, aroyl, and a variety of other substituents have been used on the nitrile oxide, and the range of products available has been well reviewed.[4,5,7] Since the appearance of these earlier reviews, the generation of cyanogen *N*-oxide (**33**, R^1 = CN) and its use in the synthesis of 1,2,4-oxadiazoles has been reported.[11] Aryl substituted nitriles are most commonly employed as the dipolarophile, but the relatively unreactive aliphatic nitriles will react, particularly in the presence of Lewis acids.[4,5,7] Heterocyclic β-enaminonitriles, cyanates and related species, and a series of *N*-cyano compounds can also function as dipolarophiles, whilst the use of 1,3,5-triazine as a synthetic equivalent of hydrogen cyanide allows access to 5-unsubstituted 1,2,4-oxadiazoles.[4,5,7] More recently published work[38] details the use of dicyanoketene acetal **35** as the nitrile, as shown in Scheme 11. Thus, the addition of a range of aryl nitrile oxides to one of the cyano groups of compound **35** leads to the 1,2,4-oxadiazole dioxalanes **36**, which can be further elaborated to allow access to pyrazole,[38a,b,c] isoxazole,[38b,c] pyrrole[38c] and pyrimidine[38b,c] substituted 1,2,4-oxadiazoles, such as the pyrazole **37**, in good overall yield.



Scheme 11

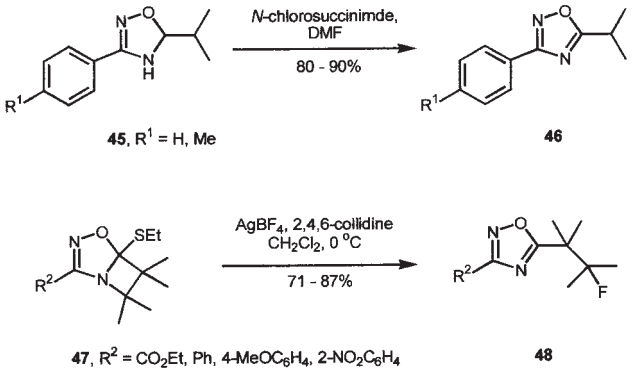
The cycloaddition of nitrile oxides **33** to imines **38**, shown in Scheme 12, followed by *in situ* oxidation of the resultant 1,2,4-oxadiazolines (dihydro 1,2,4-oxadiazoles) **39** can lead to 1,2,4-oxadiazoles.[7] Thus, the addition of 4-methoxybenzonitrile oxide (**42**) to the 4-iminobenzopyran-2-one **41** gave the intermediate **43**, which underwent spontaneous loss of methanol to give the 1,2,4-oxadiazole **44**,[39] also shown in Scheme 12. The cycloaddition of a nitrile oxide to an imine often leads to 1,2,4-oxadiazolines (dihydro 1,2,4-oxadiazoles) **39** which can be isolated. The cycloaddition of a nitrone to a nitrile can similarly lead to stable 1,2,4-oxadiazolines.[34] The subsequent oxidation of such heterocycles offers another route to the fully unsaturated 1,2,4-oxadiazole nucleus, and this approach is detailed in Section 5. Interestingly, the cycloaddition of nitrile oxides to amidoximes leads to 1,2,4-oxadiazole-4-oxides, which can then be deoxygenated (see Section 7).[40]



Scheme 12

5. Synthesis From the Oxidation of Dihydro 1,2,4-Oxadiazoles (Oxadiazolines)

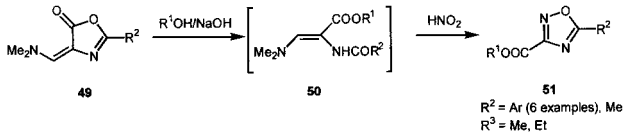
The methods for the synthesis of 1,2,4-oxadiazoles *via* the oxidation of oxadiazolines (dihydro 1,2,4-oxadiazoles) which appeared prior to 1996 have been reviewed.[41] Oxadiazolines are readily available, either from the cycloaddition routes discussed in Section 4, above, or from the condensation of aldehydes with amidoximes,[41] and this makes their oxidation a popular entry into the fully unsaturated 1,2,4-oxadiazole nucleus. The oxidation has been achieved with potassium permanganate, with chlorine in carbon tetrachloride, with sodium hypochlorite, by the oxygen in air, and by a variety of other oxidants.[41] In a recent example,[42a] *N*-chlorosuccinimide was used to bring about the high yielding conversion of the 4,5-dihydro-1,2,4-oxadiazoles **45** into the corresponding fully aromatic system **46**, as shown in Scheme 13. The reaction of a series of arylamidoximes with isobutyraldehyde and the oxidation of the resultant 4,5-dihydro-1,2,4-oxadiazoles with MnO_2, or with nitric acid, was also reported recently.[42b] The treatment of the bicyclic 4,5-dihydro-1,2,4-oxadiazoles **47** with silver tetrafluoroborate and 2,4,6-collidine, also shown in Scheme 13, resulted in the formation of the fluoroalkyl substituted 1,2,4-oxadiazoles **48** in 71–87% yield.[43]



Scheme 13

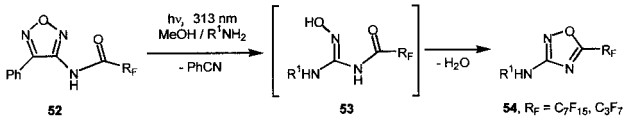
6. The Synthesis of 1,2,4-Oxadiazoles from Other Heterocycles

The treatment of the oxazolones **49** with alcohols, and the reaction of the resultant aminopropenoate **50** with nitrous acid affords 1,2,4-oxadiazole-3-carboxylates **51**, Scheme 14, in 60–78% yield.[29a,b] The oxazolones are readily available from the reaction of *N*-acylglycines with $POCl_3$ in DMF.[29]



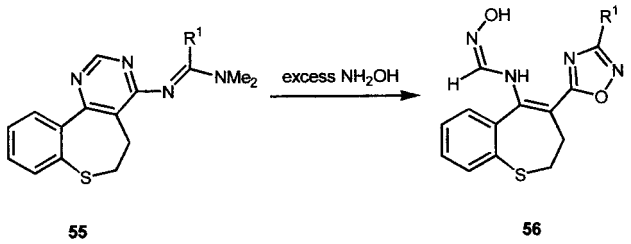
Scheme 14

The molecular rearrangement of one 1,2,4-oxadiazole into a another 1,2,4-oxadiazole, where an appropriate three-atom side-chain is present (the Boulton-Katritzky rearrangement), is well documented.[5,7,8] A recent study[44] in the area looks at substituent effects on the equilibration between 3-aroylamino-5-methyl-1,2,4-oxadiazoles and 3-acetylamino-5-aryl-1,2,4-oxadiazoles, and review articles on the general subject of degenerate ring transformations in heterocyclic systems, including 1,2,4-oxadiazoles, have appeared.[45] The UV irradiation of the 3-perfluoroalkanoylamino-4-phenyl-1,2,5-oxadiazoles **52** in the presence of ammonia or a primary amine, as shown in Scheme 15, resulted in a loss of benzonitrile to give an intermediate *N*-acylamino-amidoximes **53**. Cyclisation then gave the 3-amino-5-perfluoroalkyl-1,2,4-oxadiazoles **54** in yields of 30–50%, although 30–40% of the starting material was recovered.[46]



Scheme 15

The treatment of the (benzothiepino[5,4-*d*]pyrimidin-4-yl)amidines **55** with a large excess of hydroxylamine gave the (benzothiepinyl)(oxadiazolyl)amidoximes **56** (Scheme 16), in good yields (e.g. R^1 = 4-FC_6H_4, 73%).[47]



Scheme 16

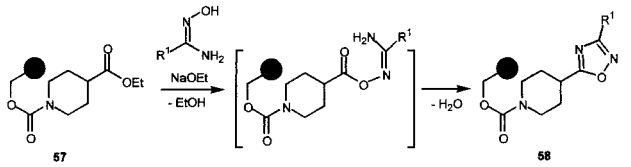
7. Synthesis *via* Deoxygenation of 1,2,4-Oxadiazole-4-Oxides

The 1,3-dipolar cycloaddition of a nitrile oxide to an amidoxime results in the formation of 1,2,4-oxadiazole-4-oxides, which can be deoxygenated with trimethylphosphite (quantitatively),[40] with nitrile oxides (in 50–60% yield),[40] and by UV irradiation in the presence of triethylamine as an electron donor partner (quantitatively).[48]

8. Polymer Supported and Combinatorial Syntheses of 1,2,4-Oxadiazoles

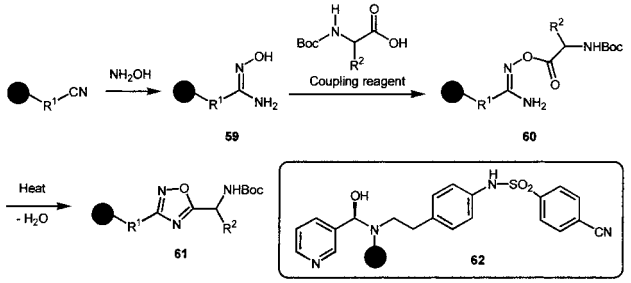
Given the huge amount of interest in the biological properties of the diverse range of molecules that contain the 1,2,4-oxadiazole moiety (see Section 10), it is not surprising that several of the approaches discussed above have been adapted to allow solution phase combinatorial and polymer supported syntheses of this heterocycle. Liang and co-workers[24g] have demonstrated that the use of a TentaGel resin, activated by 4-nitrophenyl chloroformate, and then captured by ethyl isonipecotate gives the resin bound ethyl ester **57**, shown in Scheme 17. Room temperature reaction of this with sodium ethoxide and an amidoxime then furnishes the resin bound isonipecotyl 1,2,4-oxadiazole **58**, which can be cleaved from the resin with trifluoroacetic acid. The process was found to be suited to parallel synthesis using a semi-automated synthesiser. The same workers also demonstrated that the reaction of resin bound carboxylic acids with an amidoxime and a peptide coupling reagent gave 1,2,4-oxadiazoles, although the reaction did require heating and specialised equipment for rocking the tubes at elevated temperature.[24g]

In an alternative approach, shown in Scheme 18, the treatment of a series of resin bound nitriles with hydroxylamine furnished the resin bound amidoximes **59**.[16c] Acylation with a Boc or Fmoc protected amino acid under peptide coupling conditions gave the polymer supported *O*-acylamidoximes **60**,



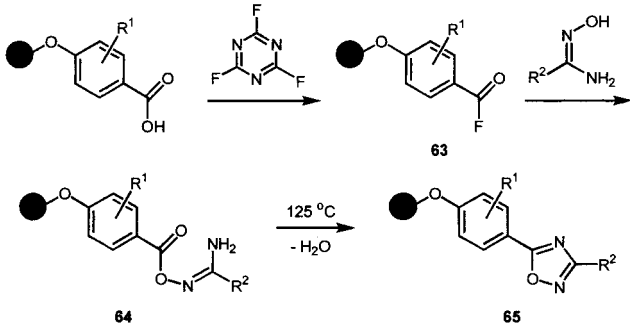
Scheme 17

which, upon heating, underwent cyclisation to produce the resin bound 1,2,4-oxadiazoles **61**. Extremely hindered amino acids, and glutamine and asparagine derivatives gave poor yields of oxadiazoles. Alkyl carboxylic acids, succinic and glycolic anhydrides were successful; however aromatic carboxylic acids gave poor yields.[16c] In a similar approach,[16f] the use of a resin bound nitrile **62** allowed access to the corresponding resin bound amidoximes, which could be converted into 1,2,4-oxadiazoles *via* acylation with either an appropriate acid halide/anhydride in the presence of a base or an acid in the presence of a coupling reagent. Cyclisation of the intermediate *O*-acylamidoxime was achieved by heating in pyridine or diglyme, a step which could be accelerated by the use of a microwave oven.



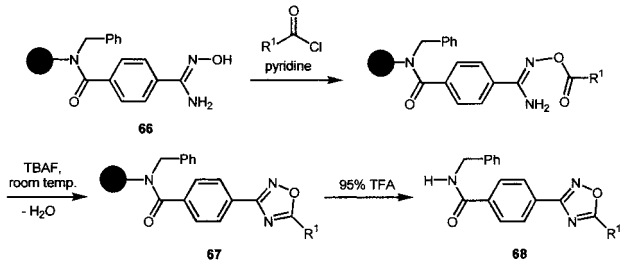
Scheme 18

In another approach (Scheme 19),[23] a series of benzoic acids were bound to the Wang linker and then activated with cyanuric fluoride to give the resin bound acyl fluoride **63**. The reaction of the acid fluoride with an amidoxime gave the resin bound *O*-acylamidoxime **64**, which yielded the resin bound 1,2,4-oxadiazoles **65** upon heating. Cleavage from the resin was facile with a mixture of dichloromethane and trifluoroacetic acid. The procedure tolerated aliphatic, aromatic, polar and non-polar amidoximes, gave an average yield of 82%, and was suitable for automation.



Scheme 19

In a very recent procedure, Rice and Nuss[22d] report that the Argopore MB-CHO polymer supported amidoximes **66** (readily available from the nitrile) can be acylated with acid chlorides in the presence of excess pyridine, as shown in Scheme 20. Cyclisation was carried out with tetra-*N*-butylammonium fluoride (TBAF), in THF as solvent at ambient temperature, to give the polymer supported 1,2,4-oxadiazoles **67**, a process which was found to be broad in scope with only a few limited exceptions. Release of the 1,2,4-oxadiazoles **68** from the polymer support was achieved by treatment of **67** with 95% trifluoroacetic acid.



Scheme 20

The use of polymer supported reagents in combinatorial chemistry has received much attention in recent years, and a polymer supported acylating reagent (supported on a ring opening metathesis polymer backbone) has been used for the synthesis of 1,2,4-oxadiazoles in solution, starting from aromatic amidoximes.[49]

The combinatorial and parallel synthesis of libraries of 1,2,4-oxadiazoles in the solution phase has also received much recent attention,[50,16d,16g] with work concentrated in the area of carboxylic acid activation and the subsequent coupling of the acid to an amidoxime. Coupling reagents that have been used in the construction of these libraries include 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide (EDC) in the presence of hydroxybenzotriazole (HOBT),[50a] 1,1′-carbonyldiimidazole (CDI),[16d] and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU).[16g]

9. Reactions of 1,2,4-Oxadiazoles

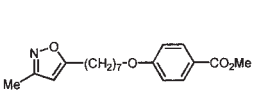
The 1,2,4-oxadiazole nucleus is almost inert to electrophilic attack. Nucleophilic displacement of suitable leaving groups at the 5-position is common, but the substitution of groups at the 3-position is less common. Thermal, photochemical, hydrolytic and reductive reactions of the ring are well known.[4,5,7] The general patterns of reactivity and those reactions peculiar to 1,2,4-oxadiazoles have been reviewed up to 1995.[1–7] Thus, only important reactions specific to 1,2,4-oxadiazoles which have appeared since this time will be detailed here. Standard functional group manipulations will not be included.

5-Vinyl-1,2,4-oxadiazoles have been shown to be excellent Michael acceptors, useful in the synthesis of Nuc-CH_2CH_2-1,2,4-oxadiazoles, where Nuc can be any appropriate nucleophile.[24c] The conversion, by cyclic voltammetry, of a series of 3-substituted 5-(bromodifluoromethyl)-1,2,4-oxadiazoles into the corresponding difluoromethyl anion allows access to a range of difluoromethyl substituted 1,2,4-oxadiazoles.[24e,51] The displacement of the 5-trichloromethyl group is well established in 1,2,4-oxadiazole chemistry,[7] and the group has been displaced with oxygen and nitrogen nucleophiles.[22b] Similarly, a 5-chloro group can be displaced with a variety of nucleophiles,[7] for example, a sulfur nucleophile.[22b] The base induced rearrangement of a series of *o*-substituted *Z*-phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles into 1,2,3-triazoles has been studied.[52] A theoretical study concerning the Boulton-Katritzky rearrangement of 3-formylamino-1,2,4-oxadiazole has appeared.[53] The photoinduced

molecular rearrangement of a series of 1,2,4-oxadiazoles into 1,3,4-oxadiazoles is known.[48,54a] The photoinduced molecular rearrangement of certain 1,2,4-oxadiazoles in the presence of nitrogen nucleophiles leads to 1,2,4-triazoles,[54b] and in the presence of sulfur nucleophiles leads to 1,2,4-thiadiazoles.[54c] The irradiation of a range of 5-aryl-1,2,4-oxadiazoles results in cleavage of the N–O bond, followed by a cyclisation to furnish quinazolin-4-ones.[54d] Hydrogenation of 3-aryl-5-methyl-1,2,4-oxadiazoles over Raney nickel has been used as a route to amidines,[19a,19b,55] ureas and guanidines[30], whereas the use of $LiAlH_4$ allows a ring opening which gives access to *N*-substituted amidoximes.[24g] The hydrolysis of 1,2,4-oxadiazoles follows predictable patterns,[4,5,7] and it has recently been shown that the base promoted fragmentation of 1,2,4-oxadiazole can lead to nitriles;[22d] amides have also been isolated as partial hydrolysis products.[55] The 1,2,4-oxadiazole ring is known to function as a monodentate ligand through the 4-N atom,[7] and a recent report deals with the synthesis of copper(II) complexes containing a 1,2,4-oxadiazolyl moiety which behaves as a bidentate ligand.[56]

10. Biological Applications of 1,2,4-Oxadiazoles

The use of compounds containing the 1,2,4-oxadiazole moiety as antitussives, anti-inflammatory agents, analgesics, coronary dilators, agonists at muscarinic receptors, 5-HT receptor antagonists, benzodiazepine receptor agonists, anthelminthics, plant protection agents, and for a variety of other uses was reviewed in 1996,[57] and interest has continued unabated. Much of the recent interest still stems from the use of the 1,2,4-oxadiazole as an ester bioisostere.[16g,22b,22d,58] Thus, 1,2,4-oxadiazoles have been used as ester bioisosteric replacements in a series of compounds related to the disoxaril precursor **69**, shown below, and their activities against rhinoviruses determined.[22b] The replacement of the ester moiety present in cocaine with a 3-phenyl-1,2,4-oxadiazolyl substituent led to a compound with 50 times the affinity for the dopamine transporter than cocaine itself.[59] Studies regarding the use of 1,2,4-oxadiazoles as peptidomimetic and dipeptidomimetic amino acid-Gly replacements in biologically active peptides have appeared.[18,19c]



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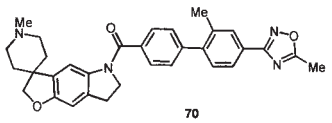

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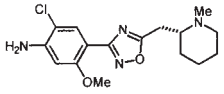

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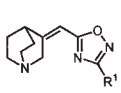

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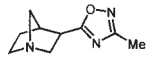
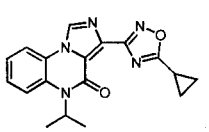


73

Several oxadiazoles, for example compound **70**,[60] shown above, show activity as potent antagonists of the (serotonin) 5-$HT_{1B/D}$ receptors,[24c,24h,55,60] which are vasoconstriction mediating receptors used as putative targets for antimigraine drugs. The 5-(2-piperidylmethyl)-1,2,4-oxadiazole **71** is a selective 5-HT_4 receptor agonist, which may be useful in the search for the treatment of gastrointestinal dysfunctions.[24d] The affinities of a range of (oxadiazolyl)methylene azabicycles **72** for the central nicotinic cholinergic receptors have been investigated, but were found to be lower than those of other heterocyclic systems.[24i] Several reports concerning the use of 1,2,4-oxadiazoles as muscarinic antagonist/agonists, for example the muscarinic receptor "super agonist" **73**, have appeared.[24a,24c,24f,24j]

Further studies regarding the antitussive properties of 1,2,4-oxadiazoles have appeared,[61] including a review in the general area of antitussives.[61c] A number of 1,2,4-oxadiazoles continue to attract interest as benzodiazepine receptor ligands,[62,63] an example being the imidazoquinoxalinone derivative **74**.[63] (1,2,4-Oxadiazolyl methyl)phthalimides,[10,16b] and a series of *N*-acylhydrazone substituted 1,2,4-oxadiazoles[22a] have been shown to have potent analgesic properties. The 5-*n*-pentyl-1,2,4-oxadiazole **75** is a potent and selective β_3 adrenergic receptor agonist,[16e] whilst the corresponding benzyl and phenoxymethylene analogues represent useful tools in the synthesis of β_3 adrenergic receptor agonist antiobesity agents.[16f]



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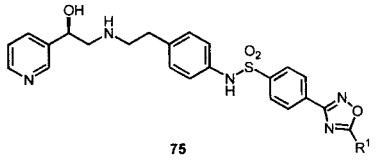
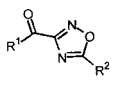


75

A series of α-keto-oxadiazole compounds **76** have been shown to be potent and selective inhibitors of human neutrophil elastase.[64] 3-(Coumarin-4-yl)-1,2,4-oxadiazoles show potent anti-inflammatory activity.[19d] A series of benzimidazole-7-carboxylic acids bearing the 5-oxo-1,2,4-oxadiazole ring have been shown to be potent angiotensin II receptor antagonists.[25a,b] 1,2,4-Oxadiazolyl compounds have been reported that show antitumour activity.[65] A library of 4-[2-(1,2,4-oxadiazolyl)]piperidines has been designed, synthesised and then tested as dopamine D_4 ligands.[50b] The replacement of the isothiourea grouping of known histamine H_3 antagonists (such as clobenpropit) with the 1,2,4-oxadiazole ring resulted in the formation of compound **77**, and a series of analogues, some of which were potent and selective H_3 antagonists.[24b] The protein tyrosine kinase ZAP-70 is a target for immune suppression, and a series of 1,2,4-oxadiazoles, such as compounds **78**, have been shown to be potent and selective SH2 (Src homology-2) inhibitors of the tyrosine kinase ZAP-70, with activities up to 200–400 fold more potent than the native tetrapeptide.[17,66]



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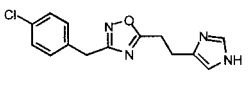

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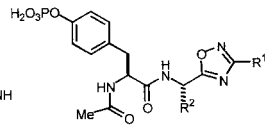

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