Green protocols in heterocycle syntheses via 1,3-dipolar cycloadditions

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Abstract

The aim of this review is to provide an overview of green protocols for the organic synthesis of heterocycles via 1,3-dipolar cycloaddition. Particular attention has been devoted to the use of green solvents; reactions performed in ionic liquids, fluorinated solvents and water have been included. Also explored are several protocols that make use of catalyst-free reaction conditions, the use of microwave irradiation and activation by light exposure. Improvements over commonly used organic solvents will be underlined in order to highlight environmental protection aspects and enhancements in regio- and stereoselectivity.

Introduction

The development of efficient and environmentally benign synthetic protocols is of primary importance to green pharmaceutical chemistry. The selection of suitable starting materials, methodologies with good atomic balance, a minimum number of steps and green solvents will allow this beneficial goal to be achieved. Heterocyclic chemistry plays a key role in drug production and the application of efficient green synthetic processes has a significant impact on pharmaceutical industries. There are a number of successful example of benign synthetic protocol and includes the use of non conventional technologies such as microwave of ultrasound irradiation (Garella et al., 2013) and, the use of water or green organic solvents (Moulay and Touati, 2010; Butler and Coyne, 2016). In the last decade, in this areas, green chemistry and click chemistry respect a pathway of rigorous principles , by means of which more efficient and environmentally benign processes can be delineated (Anastas and Eghbali, 2010). Copper-catalysed azide−alkyne cycloaddition (CuAAC), since the capital discovery by the teams of Meldal (Tornøe et al., 2002) and Sharpless (Rostovtsev et al., 2002) provides regioselectively under mild conditions substituted triazole. Based on its large applicability, an increasing number of disciplines have taken advantage of the unique benefits and this reaction can be considered the click reaction *par antonomasia*. More in general, 1,3-dipolar cycloadditions are six π-electron, concerted reactions that have a wide range of applications in organic chemistry and, specifically, in the synthesis of five membered heterocyclic rings. Their good atomic balance and their synthetic potential resulted maximized when 5 terms heterocycles are obtained in sustainable solvents with high stereo or enantioselectivity.

Many authors still use the terms "[2+3] or [3+2] cycloaddition", which count the number of involved atoms, but do not follow IUPAC recommendations. We follow IUPAC assignments in this paper, meaning that all reactions are referred to in accordance with the following rules:

1) *A (i + j + ...) cycloaddition is a reaction in which two or more molecules (or parts of the same molecule), provide units of i, j, in which i and j stand for linearly connected atoms. In the final product, these units become joined by new σ-bonds so as to form a cycle containing (i + j + ...) atoms.*

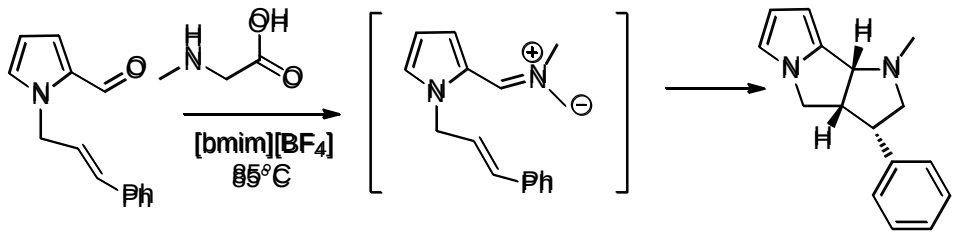
2) *The terminology [i + j + ...] for a cycloaddition identifies the numbers, i and j, of π electrons in the interacting units that participate in the transformation of reactants to products.* (See http://goldbook.iupac.org/html/C/C01496.html)

The aim of this review is to provide an overview of green protocols for the organic synthesis of heterocycles via 1,3-dipolar cycloaddition. The cycloaddition reactions between azides with alkynes, well-known as Huisgen cycloadditions will not be take highly into account because of its large redundancies in literature, both in original publication and in review. In the present review particular attention has been devoted to the use of green solvents; reactions performed in ionic liquids, fluorinated solvents and water have been included. Also explored are several protocols that make use of catalyst-free reaction conditions, the use of microwave irradiation and activation by light exposure. Improvements over commonly used organic solvents will be underlined in order to highlight environmental protection aspects and enhancements in regio- and stereoselectivity.

2.1 1,3-dipolar cycloaddition in ionic liquids

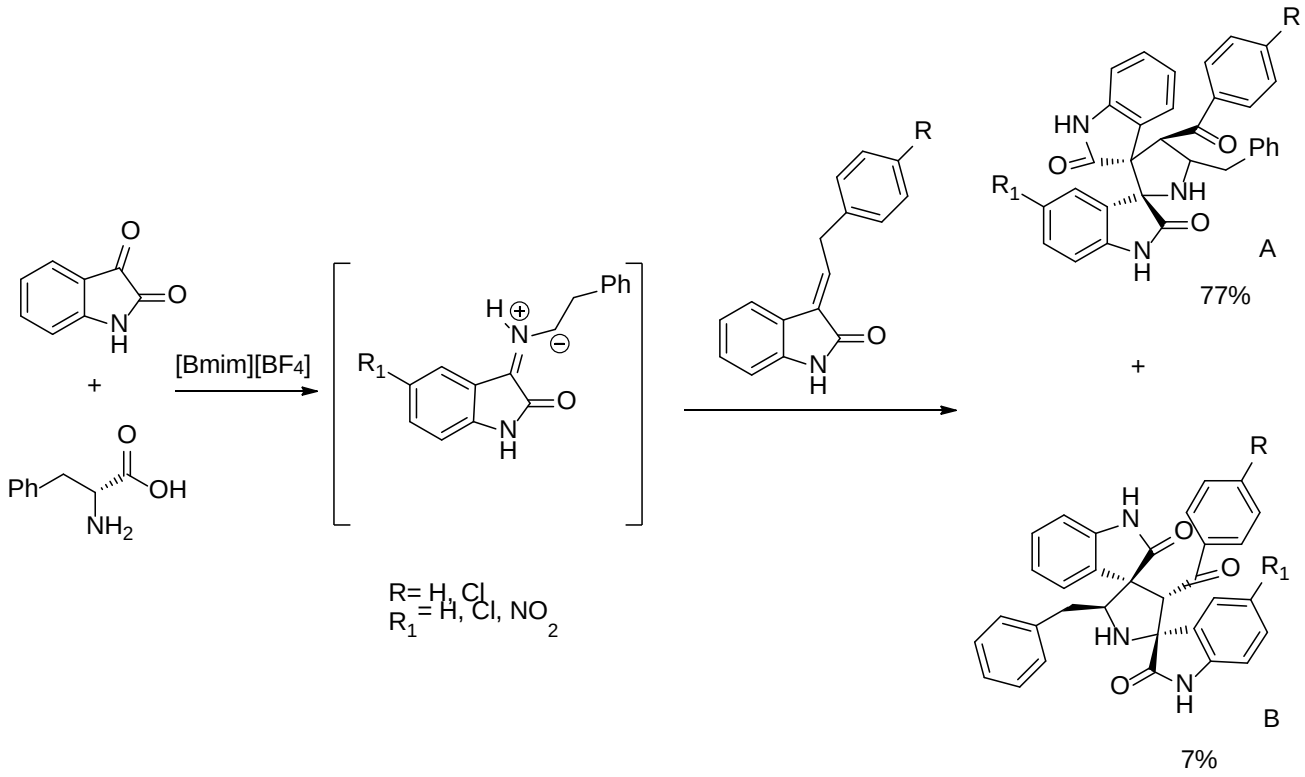
The elimination of the use of volatile organic solvents and their replacement by non-inflammable, non-volatile, non-toxic and inexpensive green solvents is an important aspect of green chemistry. Their unique properties, including high chemical and thermal stability, solvating ability, ability to behave as both acidic and basic catalysts and recyclability, have led to ionic liquids gaining widespread recognition as green solvents that are advantageous to use in organic synthesis. Their use in this context has therefore emerged as an important facet of green chemistry. Interestingly, the solubility, density, refractive index, viscosity, acidic or basic character and associated catalysing ability of ionic liquids can be tuned by judiciously modifying the structure of their anion/cation to suit different applications. Thus, the use of ionic liquids as reaction media for multicomponent reactions and cycloaddition reactions, including 1,3-dipolar cycloadditions, is particularly interesting.

In 2007, 1,3-dipolar azomethine ylide cycloaddition reaction has been studied in ionic liquid and the authors observed that pyrrolizidines can be obtained in high yield at 50 °C in ionic liquid 1-butyl-3-methylimidazolium [bmim][BF_4] in 10-40 min while under conventional condition in boiling acetonitrile it requested 90-300 min (Jadidi et al., 2007). In 2013, Kathiravan and Raghunathan (Kathiravan and Raghunathan, 2013) studied an intramolecular 1,3-dipolar in [bmim][BF_4] as the medium and pyrrolo[2,3-a]pyrrolizidino derivatives were obtained as described in Scheme 1. Starting from pyrrole-2-carbaldehyde and allyl bromide, the authors obtained N-alkenyl pyrrole-2-carbaldehyde that converted in presence of sarcosine in pyrrolo[2,3-a]pyrrolidines, pyrrolizidines, indolizidines and isoquinolines. The reaction was performed at 85 °C and in 3h, and pyrrolopyridines were obtained in good yields (80-92%) from the 1,3-dipolar cycloaddition reactions. To provide a n optimization of the method the authors also carried out the reaction in various organic solvents, including toluene, methanol and acetonitrile. The reaction was slower and afforded lower yields of the desired products when performed in the organic solvents compared to ionic liquid.

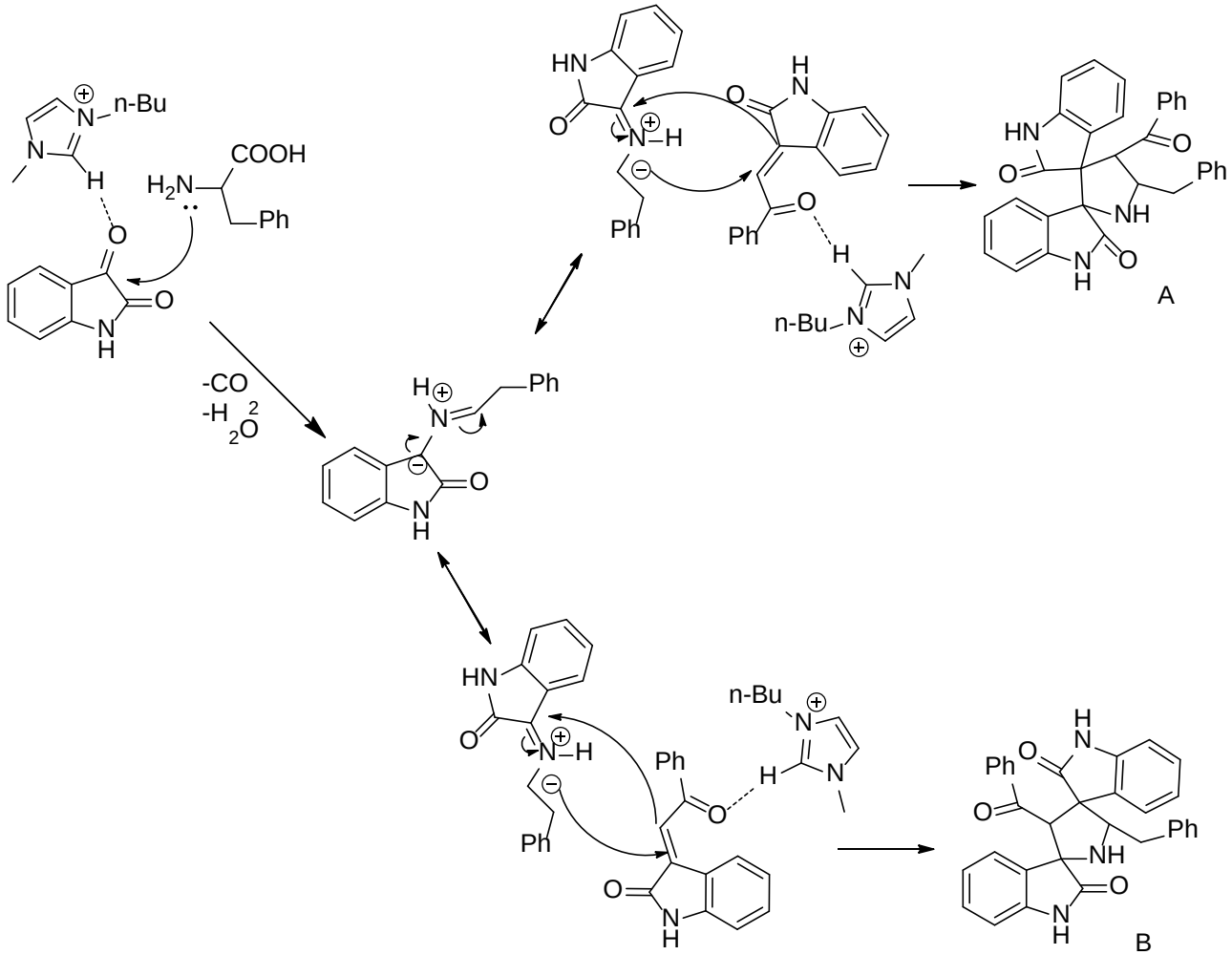


Scheme 1. Synthesis of *N*-methylpyrrol[2,3-a]pyrrolizidine.

A one-pot, three component 1,3-dipolar cycloaddition reaction have been described by Almansour *et al.*, (Almansour et al., 2015) to obtain dispirooxindolopyrrolidines. Azomethine ylides, generated *in situ* from L-phenylalanine and substituted isatins were used in equimolar ratio with a series of unusual (E)-2-oxoindolino-3-ylidene acetophenone in the ionic liquid [bmim][BF_4] to furnish the cycloadducts in 70-77% yield and high regioselectivity (Scheme 2). When compared with organic solvent such as methanol, ethanol, dioxane and a dioxane/methanol (1:1) mixture under heating in an oil-bath, they gave the desired product in lower yield (28-38%) with low selectivity. The same reaction was investigated in ionic liquids using catalyst in 10 mol %, [bmim][BF_4]/CuI, [bmim][BF_4]/$Zn(OTf)_2$. These reactions furnished both regioisomers A and B, but good yield and high selectivity was observed toward the product A. The ionic liquids [bmim]BF_4 and [bmim]Br were found to be the most suitable reaction media and as described by the authors in the proposed mechanism (Scheme 3), ionic liquids play the dual roles of solvent and catalyst and an increase in reaction rate is observed when compared to other organic solvents.

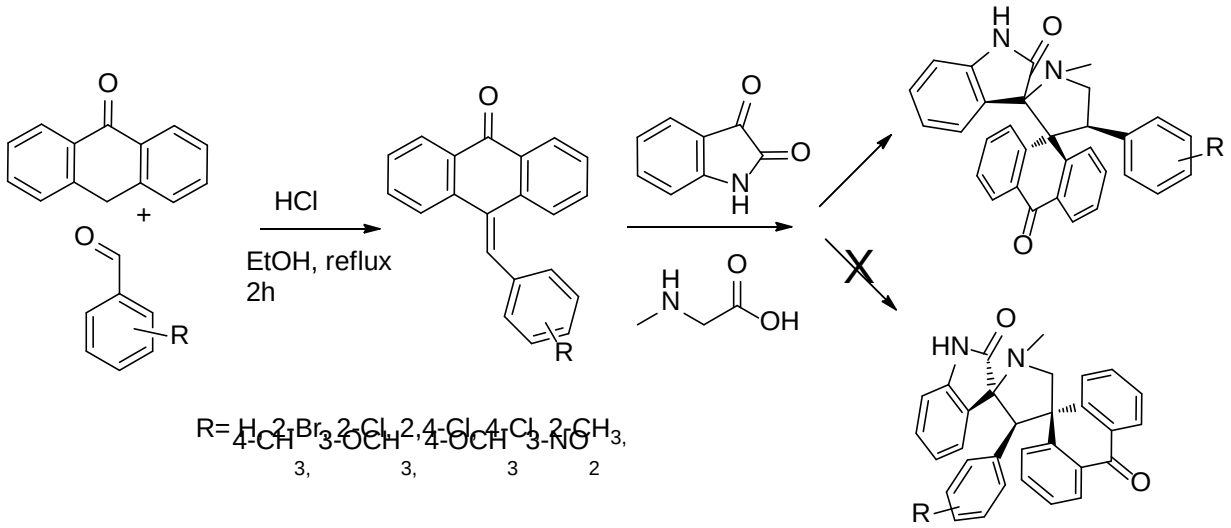


Scheme 2. Synthesis of dispirooxindolopyrrolidines.



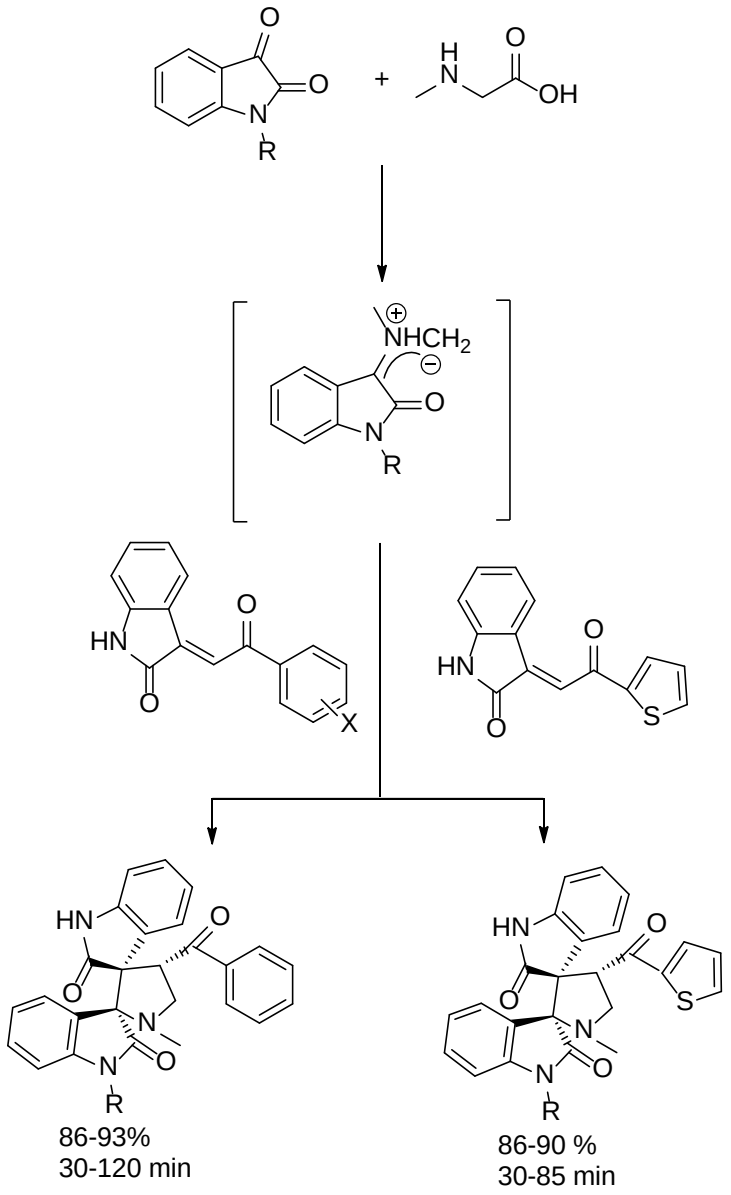
Scheme 3. Possible mechanism of the synthesis of dispirooxindolopyrrolidine regioisomers.

Another example of one pot three components reactions was published in 2015 by the same authors (Arumugam *et al*., 2015) that described a general and efficient approach for the regio- and stereoselective synthesis of dispirooxindole-fused anthrones. The reaction was reaction pathway (Scheme 4) started from acid-catalysed condensation of anthracen-9(10*H*)-one in presence of benzaldehydes to obtain 10-benzylideneanthracen-9(10*H*)-ones that was submitted to 1,3-dipolar cycloaddition with non-stabilised azomethine ylide generated *in situ* from isatin and sarcosine. When performed in ethanol, methanol, dioxane and a dioxane/methanol (1:1 v/v) at reflux, the 1,3-dipolar cycloaddition failed. The desired product was obtained in 65 % yield in 3 h in DMF at reflux. When the reaction was carried out in the presence of [bmim]Br at 100 °C, the product was obtained in 89% yield and the reaction rate increase compared to DMF. Moreover, the ionic liquid was recovered and reused. The reaction was proved as regioselective. The reaction showed high tolerance toward substituted benzaldehyde and electron donating as well as electron-withdrawing substituents at *ortho, meta* and *para* positions gave satisfactory yields. ^{1}H-,^{13}C- and 2D-NMR spectroscopy was exploited to elucidate the stereochemistry of the final product and unambiguously it was confirmed using a single crystal X-Ray diffraction study.



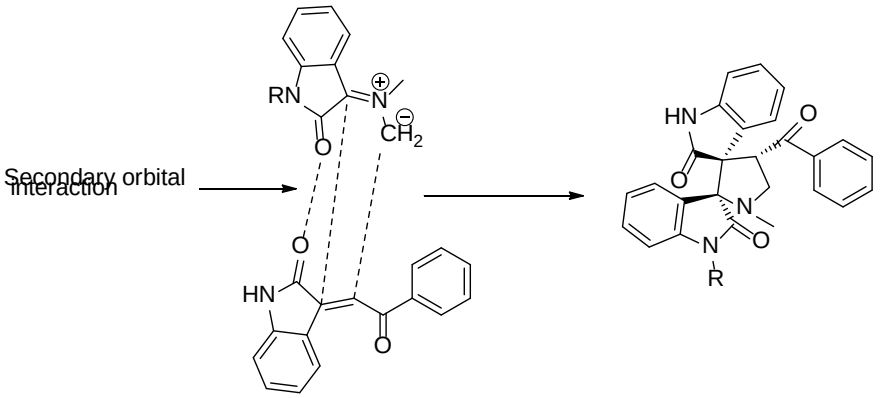
Scheme 4. Synthesis of 9-arylmethylene-10-anthrone and following 1,3-dipolar cycloaddition to bis-spiro compound.

Also Jain *et al.*, (Jain et al., 2012) reported the enhancement in yield and rate due to the use of ionic liquid in 1,3-dipolar cycloaddition reaction *via* the generation of azomethine ylides from isatin and sarcosine (Scheme 5) to synthesise dispiropyrrolidine-bisoxindole. The dipolarophile employed was the olefin obtained by Knoevenagel condensation of isatin and un/substituted acetophenones and 2-acetylthiophene. In presence of [bmim]PF_6, the azomethine ylides approached the dipolarophiles regioselectively and excellent yield in short reaction times were obtained. Furthermore, there was no need for further purification processes, such as column chromatography and the products were characterised by spectroscopic and analytical studies.



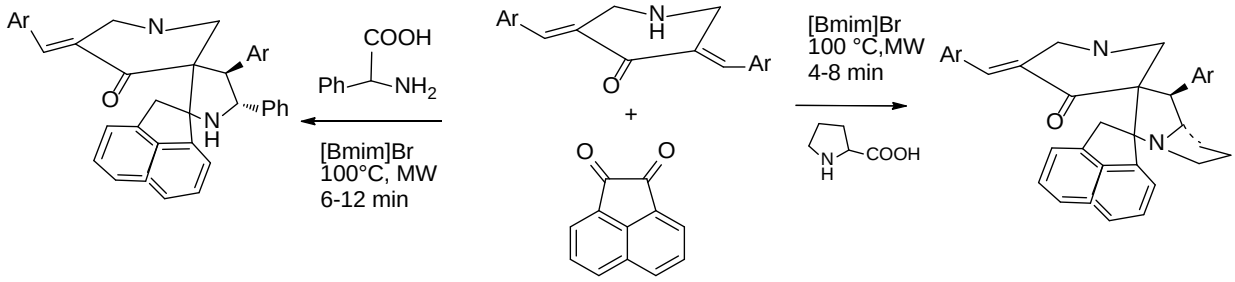
Scheme 5. Synthesis of dispiropyrrolidine derivatives.

The stereoselectivity of the 1,3 dipolar cycloaddition is governed by both the orientation at which the dipole and dipolarophile approached and the conformation of the ylide. In the described study, the authors hypothesize that constraints dictate that only one particular isomer can be involved in the transition state of the cycloaddition reaction. As described in the Scheme 6 the reaction occurs through one of the ylide geometries therefore its addition to dipolarophiles takes place under the control of relative stereochemistry at the spiro centre. The formation of sterically hindered ylide was not observed maybe due to the unfavourable steric repulsion between the carbonyl group of oxindole and the methyl group of sarcosine. Ionic liquid recyclability was proved by the authors.



Scheme 6. Schematic representation of plausible secondary orbital interaction of azomethine ylide.

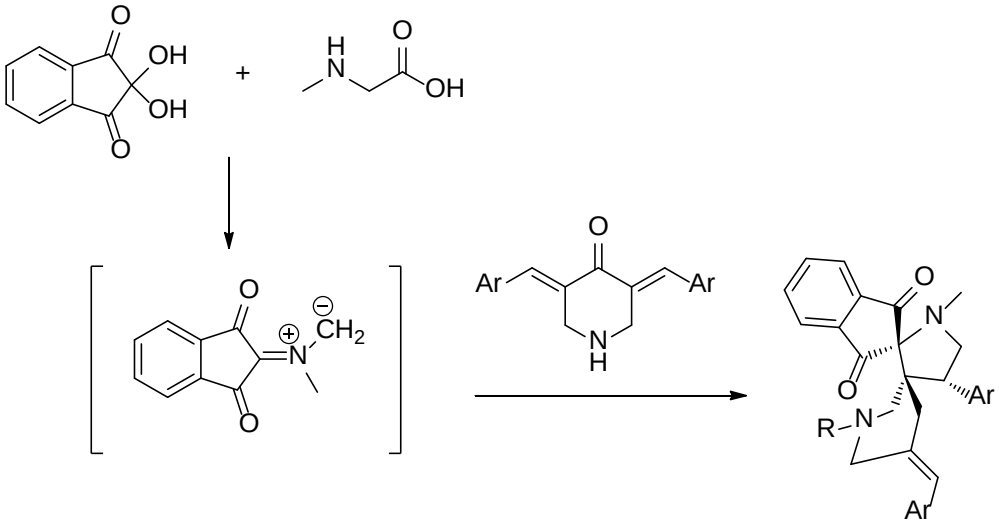
The parallel synthesis of novel molecular frameworks, has been greatly enhanced by the discovery of the synergy between microwave irradiation and ionic liquid. Being heterocycles of immense importance because of its potential biological activity, 1,3 dipolar cycloaddition under MW irradiation in ionic liquid has been explored for facilitating accelerations in drug discovery. Kumar *et al.,* (Kumar et al., 2015) have studied the molecular recognition of cage compounds and attempted the incorporation into their structure or a second cavity that can participate in structure recognition. 1,3- dipolar cycloaddition between *N*-unsubstituted 3,5-*bis*[(E)-arylmethylidene]tetrahydro- 4(1H)-pyridinones and azomethine ylides was exploited to the synthesis of novel diazahexa- and diazaheptacyclic ring. azomethine ylides were generated *in situ* from acenaphthenequinone and α-amino acids (initially, proline and then phenylglycine). Initially the authors performed the reaction under conventional conditions and methanol, ethanol, ethanol–1,4-dioxane mixture (1:1 v/v) and 1,4-dioxane were employed in refluxing to afford the heptacyclic cage structure in 72%, 60%, 70% and 69% yields, respectively. When the reaction was performed in [bmim]Br at 100 °C, the product desired product was recovered in 81% yield in 20 min. The synergic effected of MW irradiation and ionic liquid was proved when an equimolar mixture of the starting materials in [bmim]Br was subjected to MW irradiation at 100 °C for 4 minutes. The cage compound was recovered in 85% yield after purification by extraction and crystallisation. The ionic liquid [bmim]Br was dried under reduced pressure after product extraction and its recyclability was investigated in successive syntheses of the cage compound, revealing that its efficacy was not significantly diminished in the three subsequent runs (Scheme 7).



Scheme 7. Synthetic route of diazapoycyclic cage compounds.

Nowadays also guanidine ionic liquids (GILs) emerged and were efficiently used, as new-generation ionic liquids, in many organic reactions, such as the Henry reaction, aldol reaction and Heck reaction. The preparation of novel dispiropyrrolidine derivatives under green conditions was studied by Dandia e*t al.,* (Dandia et al., 2012) exploiting the task-specific ionic liquid 1,1,3,3-tetramethylguanidine acetate [TMG][Ac] as the recyclable solvent in a 1,3-dipolar cycloaddition. The reaction was

performed in presence of an equimolar mixture of ninhydrin, sarcosine and 1-benzyl/methyl-3,5-bis[(E)-arylidene]-piperidin-4-one and at 80°C in 1,1,3,3- tetramethylguanidine acetate [TMG][Ac] for 3 to 6 h and the desired products were in good yields (86-92%). When different solvents were compared, the authors employed methanol, ethanol, toluene, dioxane and acetonitrile, as well as several ionic liquids, including [bmim] BF_4 and [bmim]Cl. All these solvents were found to give comparatively low product yields and [TMG][Ac] was the best solvent, giving higher yields and shorter reaction times. A single regioisomer was isolated in all cases (Scheme 8).

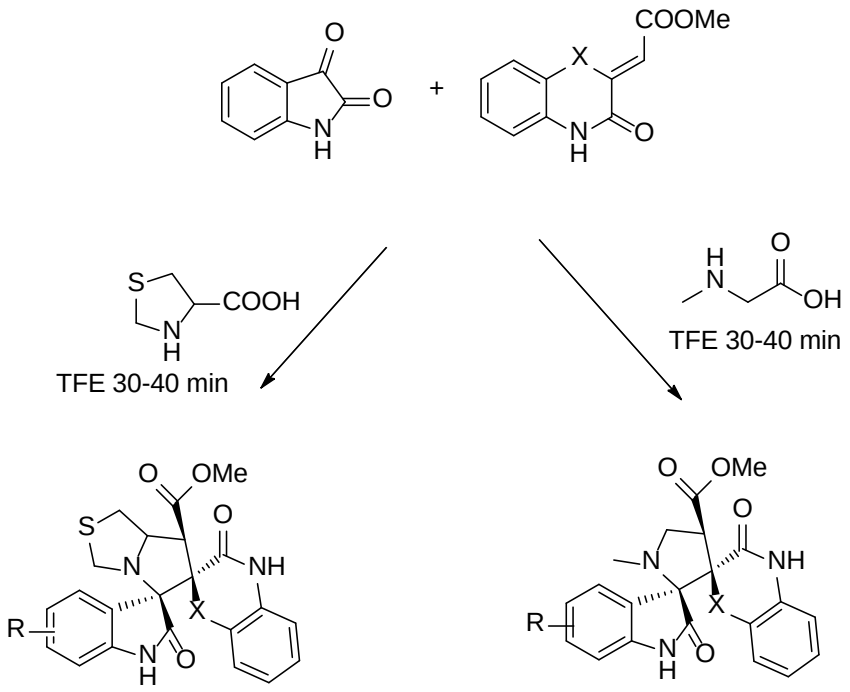


Scheme 8. Synthesis of dispiropyrrolidine derivatives.

2.2 1,3-dipolar cycloaddition in fluorinated solvents

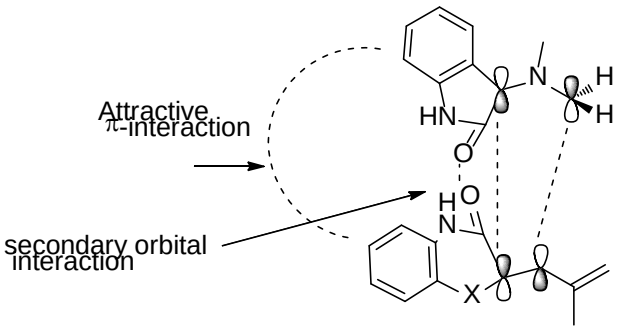
2,2,2-trifluoroethanol is considered an ideal solvent and co-solvent because of its high ionizing power and strong hydrogen bond donating ability, which provide good catalytic potential in a variety of organic transformations.

The use of 2,2,2-trifluoroethanol as a recoverable greener solvent was explored by Dandia, to obtain efficiently regio- and stereoselectely a series of novel dispiropyrrolidinyl/thiapyrrolizidinyl hybrid molecules via the 1,3-dipolar cycloaddition of a benzo[1,4]oxazine-derived dipolarophile, isatin and sarcosine/1,3-thiazolane-4-carboxylic acid (Dandia et al., 2015). The dipolarophile was synthesised under catalyst-free conditions from o-aminophenol and dimethyl acetylene dicarboxylate (DMAD) in good yields. The authors studied the cycloaddition reaction in various solvents: toluene, 1,4-dioxane, acetonitrile, ethanol, methanol, hexafluoro isopropanol and 2,2,2-trifluoroethanol. The best results were obtained using 2,2,2-trifluoroethanol, which gave a single regioisomer in a higher yield and a shorter reaction time than the other solvents. The reaction was complete in 30 min versus 6h requested in presence of different solvents (Scheme 9).



Scheme 9. Synthesis of benzo[1,4]oxazine (X=O) and benzo[1,4]thiazine (X=S) based dispiroheterocycles *via* azomethine ylides.

The 1,3-dipolar cycloaddition reactions proceeded in a concerted manner, meaning that the reaction is stereospecific. In this case, the stereochemistry of alkene benzo[1,4]oxazine would influence the stereochemistry at the 3 and 4 positions. As described by the authors, the formation of only one diastereomer is explained by the plausible transition state (Scheme 10) which is somewhat favoured by an attractive π-interaction between the aromatic rings as well as the secondary orbital interaction (SOI) between the orbitals of the carbonyl group of the dipolarophile and the ylide.



Scheme 10. Plausible transition state.

2.3 1,3-dipolar cycloaddition in water

Organic synthesis in water has attracted the attention of scientists for many years. Despite water's unique properties, it is still not commonly used as most organic compounds do not dissolve in it, meaning that a cosolvent is needed to increase solubility. This choice tends to diminish the advantages of low cost, no-toxicity, ease of workup and product isolation that water has over traditional solvents. Therefore, the currently burgeoning field of organic synthesis in aqueous media includes a large

family of reactions that are performed both in homogeneous and in heterogeneous conditions (Chanda and Fokin, 2009).

As described by Sharpless *et al*. in their study of pericyclic cycloaddition, such reactions often proceed optimally in pure water and particularly so when the organic reactants are insoluble in the aqueous phase. In fact, this substantial rate acceleration can be due to "on water" conditions that are created when insoluble reactants are stirred in an aqueous suspension (Narayan et al., 2005). This concept has been studied and applied to several different reactions. Even when the rate acceleration is negligible, this approach can still be considered successful as it makes product isolation easier and above all, improves safety thanks to water's high heat capacity and unique redox stability.

Studies of the comparative rates of 1,3-dipolar cycloaddition reactions in water and organic solvents have attracted attention. It is worth noting that the introduction of water as a cosolvent in cycloaddition reactions in organic solvents, such as acetonitrile and acetone, gave remarkable exponential rate increases as the solvent mixture approached pure water (Butler *et al.*, 2004). Reactions of methyl vinyl ketone, ethyl vinyl ketone and but-3-yn-2-one with pyridazine dicyanomethanide 1,3-dipole, which is soluble in water, display rate enhancements on changing from MeCN to H_2O (Figure 1). As has already been observed in pericyclic cycloadditions, such as the Diels Alder reaction, the rate enhancement may be due to: a) hydrophobic effects, which aggregate the organic reactants; b) a lowering of the activation energy by special hydrogen bonding in the transition state, and b) the cycloaddition transition state in water has higher polarity than its analogue in organic solvents and, consequently, displays increased solvation stabilisation in water (Butler et al., 2002).

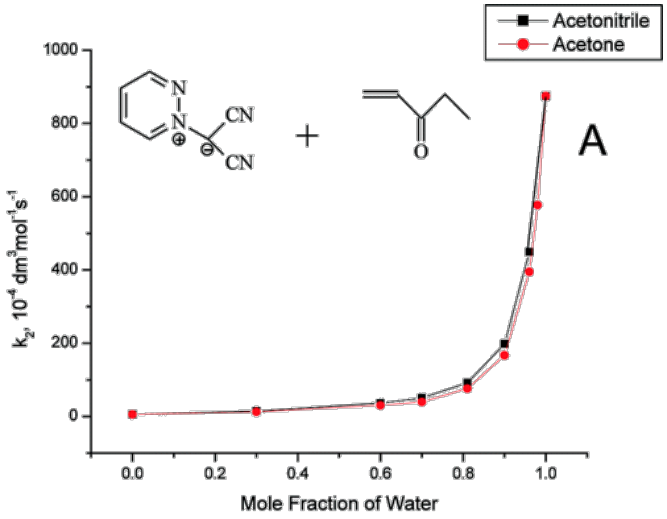


Figure 1. Reprinted with permission from Butler, R.N., Cunningham, W.J., Coyne, A.G., and Burke, L.A. (2004). *J. Am. Chem. Soc.* 126(38)**,** 11923-11929. Copyright (2018) American Chemical Society.

The vast number of publications that employ nitrones in the construction of a variety of compounds of biological interest pays testament to their huge synthetic potential. 1,3 dipolar nitrone-olefin cycloaddition has been used to obtain isoxazolidines, and even more complex bi- or tri-cyclic isoxazolidines, of biological significance and others that are useful synthetic intermediates for target molecules (De March et al., 1999; Fisera, 2007; Molteni, 2016). The fact that the formation of nitrones is due to the dehydration reactions of substituted hydroxylamine and carbonyl compounds drove A. Chatterjee *et al.*, to explore the formation of nitrones in aqueous media using surfactants. As depicted

in Figure 2, the micelles are hydrophobic and protect water-labile molecules from hydrolytic decomposition (Chatterjee et al., 2003).

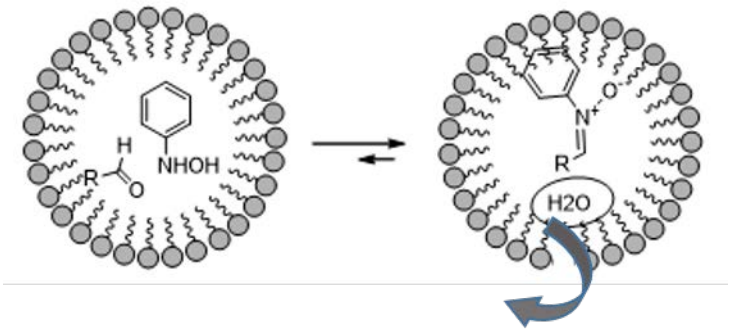
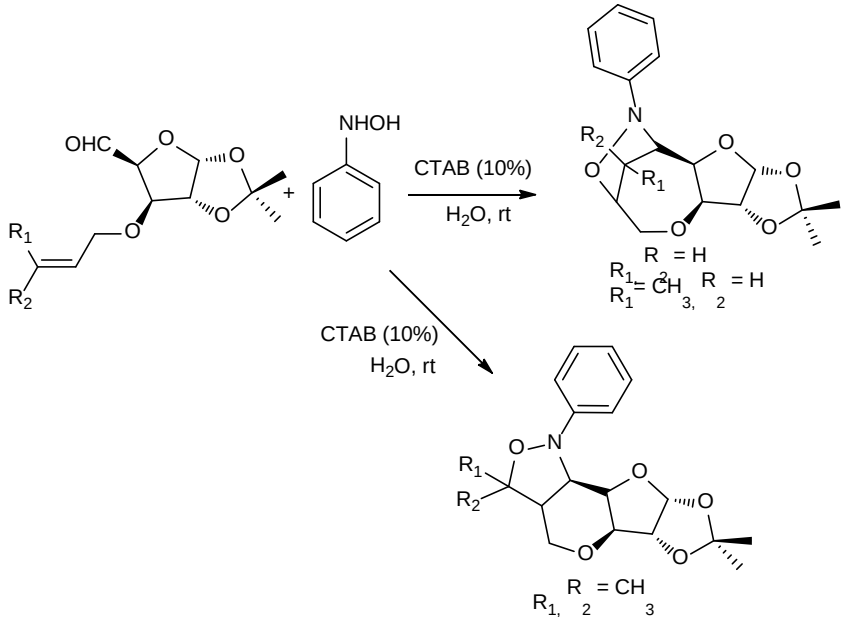


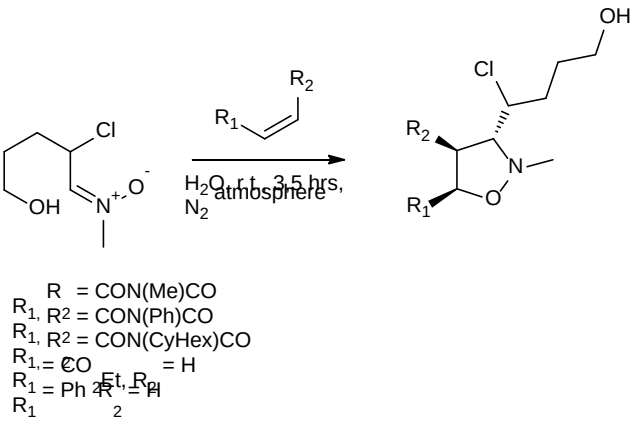
Figure 2. Schematic representation of nitrones synthesis in micelle

The authors started with a model reaction between phenyl hydroxylamine and various aldehydes, in which cetyl trimethylammonium bromide (CTAB) showed better performance than sodium dodecyl sulphate (SDS) in preparing nitrones. This is presumably due to stronger binding with the substrate. Interestingly, no reaction was observed when the reaction was performed in water in the absence of a surfactant or neat. The same procedure was therefore used to obtain a stereoselective intramolecular nitrone cycloaddition (Chatterjee and Bhattacharya, 2006). Furanoside-5-aldehydes derivatives were reacted with phenyl hydroxylamine to form the corresponding nitrones in aqueous media and the reaction was catalysed by a surfactant at room temperature. The nitrone intermediate underwent stereoselective intramolecular cycloaddition as described in Scheme 11. Interestingly, the authors observed the formation of only one of the four possible isomers in these surfactant-mediated intramolecular nitrone cycloadditions. The nitrones of 3-O-allyl glucofuranose produce bridged isoxazolidines-oxepanes, as do the nitrones of crotyl derivatives. By contrast, nitrones of prenyl derivatives produce pyrans. This may be due to methyl-methyl steric repulsion restricting the formation of the oxepane skeleton.



Scheme 11. 1,3-dipolar cycloaddition with furanoside-5-aldehydes derivatives and phenyl hydroxylamine.

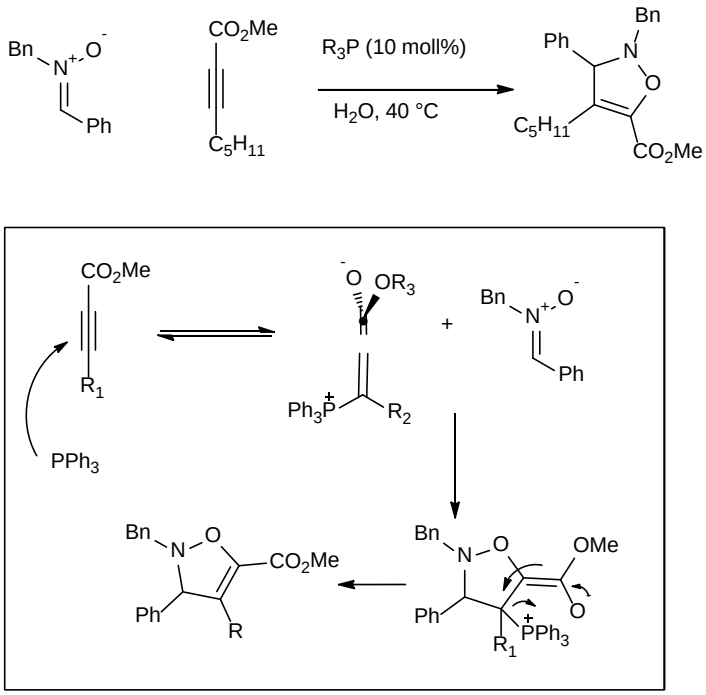
Several other attempts to perform 1,3 dipolar cycloadditions in the presence of previously synthesized nitrones have been performed in water without the addition of a surfactant. *N*-methyl-α-chloro nitrone reacted in a quick reaction with three different maleimides (*N*-methyl/phenyl/cyclohexyl), ethyl acrylate and styrene (Scheme 12). Yields were in the range of 91 to 97% and the ratio *anti/syn* was 7:3 in average (Chakraborty et al., 2010; Chakraborty et al., 2012).



Scheme 12. 1,3 dipolar cycloaddition of *N*-methyl-α-chloro nitrone.

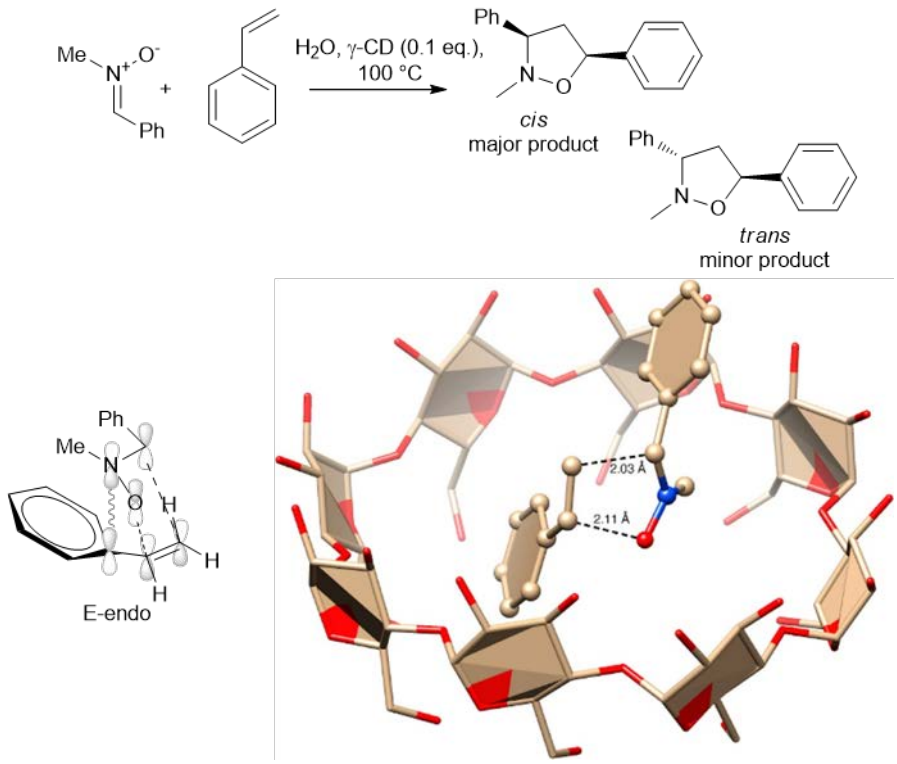
The 1,3-dipolar cycloaddition of nitrones in water has also been used to react two free sugar derivatives to produce pseudo-disaccharides, which bear imino-galactofuranose and galactofuranose units, in a 51% yield (Liautard et al., 2008). The reaction exploited the reactivity of water soluble nitrones with high enantioselectivity.

Triphenylphospine and tertiary amines can be used to activate conjugated carbonyl alkynes towards 1,3-dipolar cycloaddition. In fact, β-phosphonium (or ammonium) allenolates perform as reactive dipolarophiles in aqueous 1,3-dipolar cycloadditions and have been used to give 2,3-dihydroisoxazole (Scheme 13) (Gonzalez-Cruz et al., 2006). The reaction gives higher yields when LiCl is used and interestingly only one regioisomer was isolated, while no reaction was observed in toluene and DCM. By comparison with tertiary amines, PPh_3 showed the best catalytic activity in the presence of aromatic nitrone, while quinuclidine was more active with aliphatic nitrones. As has already been reported, reagents do not need to be water-soluble as they react when suspended in water (‘‘on water’’).



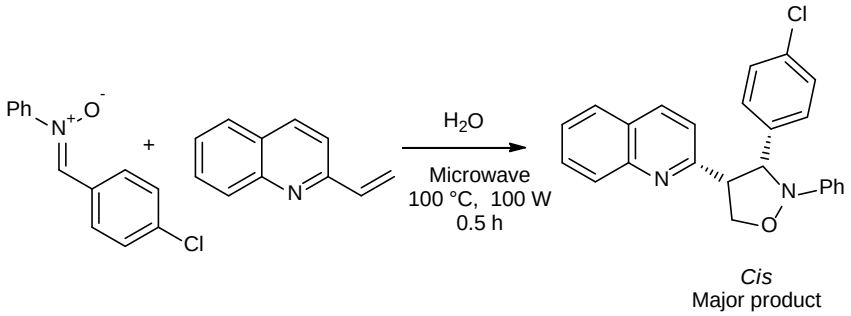
Scheme 13. Dipolar cycloaddition of β-phosphonium (or ammonium) allenolates to obtain isoxazolidine derivatives

A catalytic amount of γ-cyclodextrin (γ-CD) has been used by G. Floresta *et al.*, to produce 3,5-diarylisoxazolidines via the 1,3-dipolar cycloaddition of several *p*-substituted nitrones, styrenes and cinnamate derivatives (Floresta *et al.*, 2017). The cyclodextrin cavity acted as a reactor and heating at 100 °C for 8−12 h gave a set of derivatives in good yields with moderate to excellent diastereoselectivity. Interestingly, β-CD was inactive as a nano-reactor, while γ-CD was found to efficiently form inclusion complexes. The formation of the complex was confirmed by HR FT-ICR MALDI-MS Studies and NMR spectra. The authors rationalised by an *in silico* study the cycloaddition process and an E-*endo* transition state and that the cis major adduct is that derived from the minor, but more reactive, rotamer of the nitrone. The calculation suggests that the transition stage is positioned within the CD reactor, as depicted in Scheme 14.



Scheme 14. Schematic representation of synthesis of 3,5-diarylisoxazolidines via the 1,3-dipolar cycloaddition in presence of γ-CD and plausible transition stage to obtain the major E-*endo* derivative. The image was reprinted adapted with permission from Floresta, G., Talotta, C., Gaeta, C., De Rosa, M., Chiacchio, U., Neri, P., et al. (2017) *J. Org. Chem*. 82(9), 4631-4639. Copyright (2018) American Chemical Society.

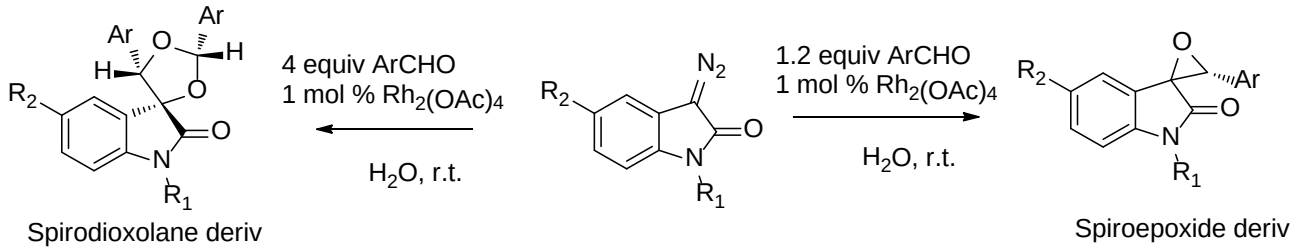
Is in 2008, an interesting publication demonstrated the influence that the solvent can have on the production of isoxazolidine. Alkenylazaarenes were utilised as dipolarophiles for the preparation of 4-substituted and 5-substituted isoxazolidines with nitrones giving high regioselectivity under a range of reaction conditions. Interestingly, only 5-substituted isoxazolidines were produced, in high to excellent yields, under microwave irradiation with water as the solvent in a sealed system, while the 4-substituted analogues were obtained as the major products when a Lewis acid, TMSOTf, was used as the catalyst in DCM at room temperature (Scheme 15) (Tong et al., 2018).



Scheme 15. Synthesis of 5-substituted isoxazolidines with nitrones in water under microwave irradiation.

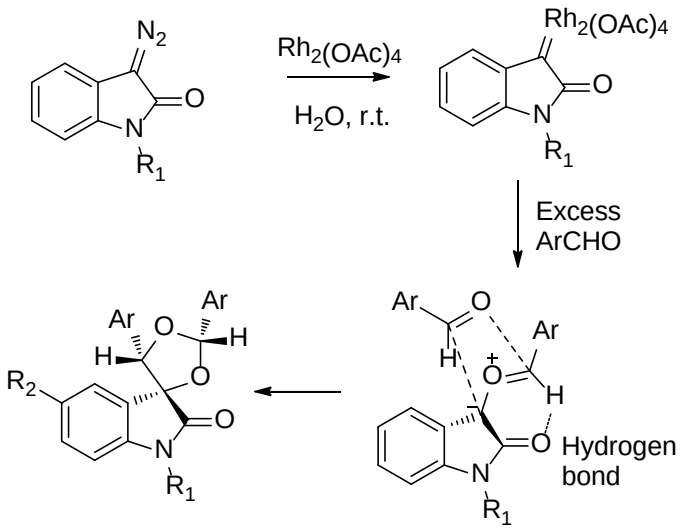
Oxindole derivatives that bear a spirocyclic quaternary stereocentre at the C3 position are interesting heterocyclic motifs that are generally found in a number of natural products and drugs.

Several green approaches for the synthesis of spiro-indole have been described as occurring in the presence of water as a solvent. Despite the common use of halogenated organic solvents, the "on-water" generation of carbonyl ylides using carbenoids was described in 2015 (Muthusamy and Ramkumar, 2015). The proposed synthesis afforded spiro-oxiranes from the reaction of carbonyl ylide dipoles, from diazoamides (3-diazooxindoles), in the presence of a rhodium(II) acetate dimer as the catalyst (Scheme 16). Spiro-dioxolanes were obtained with complete diastereoselectivity when carbonyl ylides were obtained using aromatic aldehydes with electron-withdrawing substituents, while 1,3-dipolar cycloaddition reactions occurred when aromatic aldehydes with electron-donating substituents were used.



Scheme 16. Schematic representation of spiro-indole synthesis from 3-diazooxindole derivatives.

The reaction afforded *cis* products in both the spiro-oxirane and spiro-dioxolane syntheses. In the presence of 1.2 equivalents of aromatic aldehyde, the acyclic carbonyl ylide underwent the intermolecular stereoselective dipolar cyclization in a particular conformation, which involved an intramolecular hydrogen bond, to give epoxides (Scheme 17). When an excess of aldehyde was used (4 equivalents), the reaction happened "on water" as the nucleophilic addition of water was not observed to occur. Nevertheless, the free interfacial-water OH groups may stabilise the possible transition state.

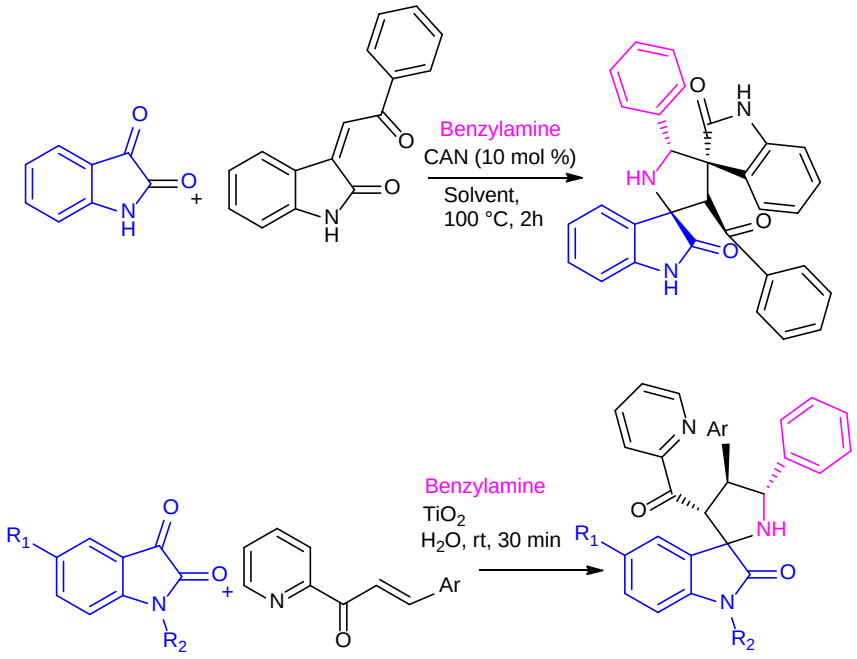


Scheme 17. Proposed mechanism.

A three-component, 1,3-dipolar cycloaddition of azomethine ylides, which were generated *in situ* from isatin derivatives and benzylamine, with benzylideneacetone can be employed to give spiro pyrrolidine-oxindoles (Peng *et al.*, 2014). This reaction can be performed in water to give the desired product in a 23 % yield and a 68:32 regioisomeric ratio.

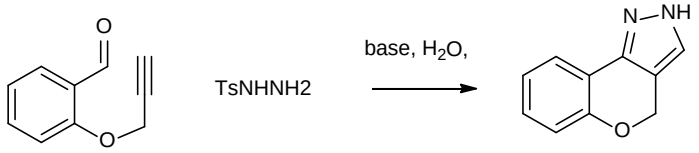
The use of Lewis acids, such as Ceric Ammonium Nitrate (CAN) or TiO_2, in the formation of spirooxindoles in water has been investigated, giving excellent results (Scheme 18) (Ramesh et al.,

2016; Ramesh et al., 2018). The 1,3 dipolar cycloaddition was performed with 1 mol % of CAN in 2 h, while the reaction was complete after 30 min when heterogeneous TiO_2 nanoparticles were used. Both reactions showed excellent regioselectivity and stereoselectivity, and the TiO_2 nanocatalyst was reused 5 times without losing catalytic activity. 20 different spirooxindole-pyrrolidines were obtained, in 65 to 90 % yields, with CAN and the reaction showed increased average yield in the presence of TiO_2.



Scheme 18. Synthesis of spyro indole by 1,3 dipolar cycloaddition with TiO_2 in water and with CAN in solvent.

Diazoalkanes can be generated from the decomposition of tosylhydrazones and are efficient 1,3-dipoles exploitable for the synthesis of several nitrogen containing heterocycles (Munro and Sharp, 1984). An intramolecular 1,3-dipolar cycloaddition strategy for rapid access to pyrazoles or triazoles makes use of the *in situ* generated diazomethanes, in a two-step sequence, in which diazomethanes undergo smooth cycloaddition with alkyne or nitrile moieties (Padwa and Ku, 1980). As described in Scheme 19, this process can be used as a step-economical route to benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazone. This reaction, which is usually performed in DMF, can be performed in water with K_2CO_3, providing excellent yields (more than 80%).

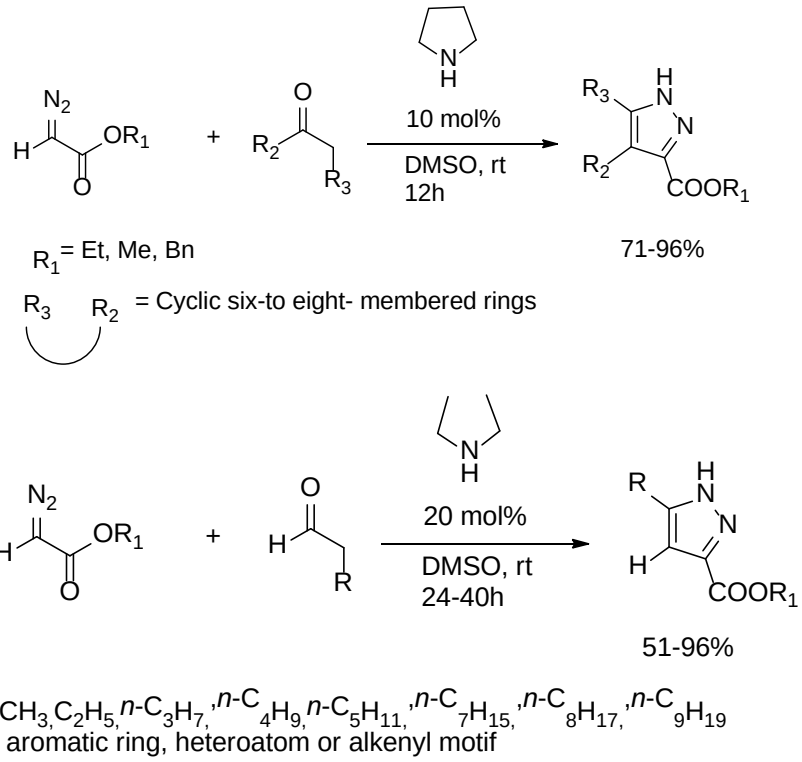


Scheme 19. Synthesis of benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazine.

2.4 Organo-catalysed and Catalyst Free 1,3 dipolar-cycloaddition

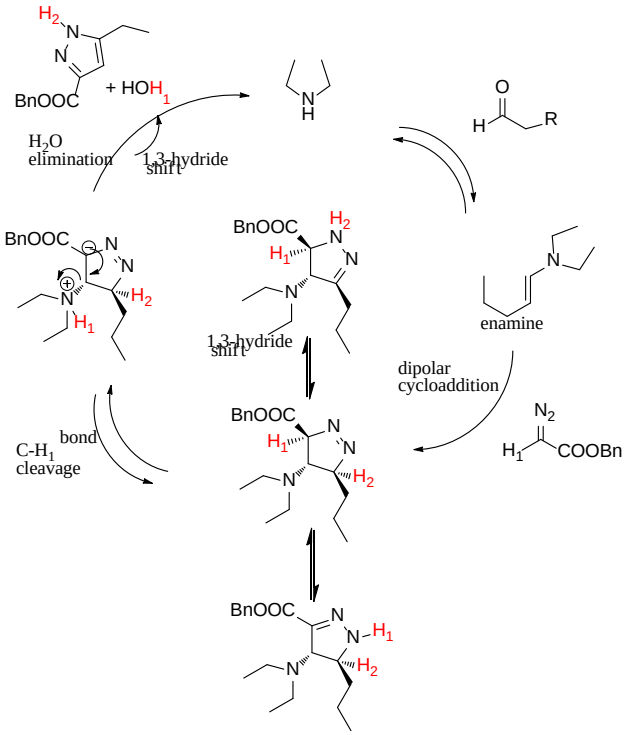
Pyrazoles are known to be potent insecticides and herbicides, and have been also studied for their anti-tumour, anti-inflammatory, anti-microbial and anti-psychotic properties. Diazo compounds may react with alkynes to provide efficient synthesis of pyrazole via 1,3-dipolar cycloaddition. The 1,3-

dipolar cycloaddition of electron-rich diazo compounds to alkynes is well known, whereas the intermolecular 1,3-dipolar cycloaddition of electron-poor diazocarbonyl compounds with alkynes is much less often reported because of the to the high HOMO–LUMO energy gap between diazocarbonyl compounds and alkynes. In presence of Lewis acid or transition metals LUMO of the alkyne dipolarophiles is lowered. Lei Wang *et al.*, in 2013 (Wang et al., 2013) developed an organocatalytic inverse-electron-demand [4+2] cycloaddition reaction between a range of carbonyl compounds and diazoacetates. Secondary amines we employed as "green promoters", to catalyse the cycloaddition reaction and produce the target pyrazole ring (Scheme 20). Pyrrolidine was selected as the most effective catalyst and of DMSO as best solvent for this transformation. The optimized protocol was performed in DMSO at room temperature with 10 mol% of pirrolidine and a 1:2 ratio of diazoacetates and carbonyl compounds.



Scheme 20. Polysubstituted pyrazoles synthetic route from diazoacetates and carbonyl compounds.

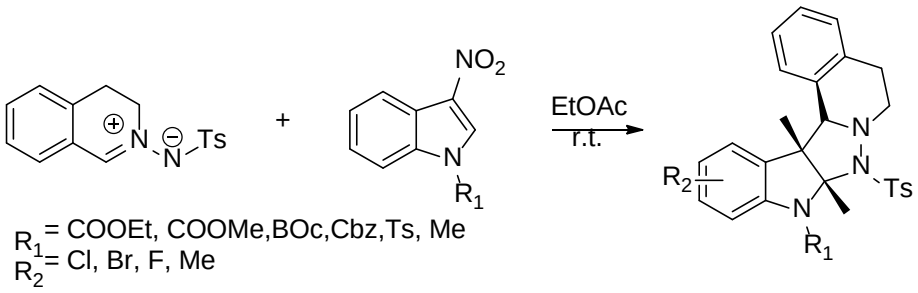
When the reaction was performed with unsymmetrical cyclic ketones high levels of regioselectivity was achieved. Nonetheless the authors discovered that in the reaction between diazoacetates and aldehydes performed better in presence of acyclic secondary diethyl amine catalysis. moderate-to-excellent yields of the corresponding adducts were obtained and a certain level of variation was possible in the side-chain of the carbonyl group.



Scheme 21. Postulated reaction pathway.

The hypothesis of selective C-H_1 bond-breaking was confirmed by a deuterium labelling experiment. The enamine-promoted cycloaddition reaction with α-deuterated benzyl diazoacetate yielded the final compound without any deuterium being incorporated into the pyrazole ring, which supports the proposed, selective breaking of the C-H_1 bond. The authors supposed that the C-H_1 bond is activated by the adjacent electron-withdrawing ester group, which results in its selective cleavage over the C-H_2 bond. Lastly, an elimination step, followed by tautomerisation, leads to the generation of the final product (Scheme 21)

Liu *et al.*, (Liu et al., 2017) have presented the first catalyst-free 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines and 3-nitroindoles to prepare a series of highly functionalised, five-ring-fused tetrahydroisoquinolines, which feature an indoline scaffold with excellent diastereoselectivity. The reaction was performed the use of catalysts or additives and more than 95% yield was obtained in EtOAc (Scheme 22). In the presence of 20 mol% $Cu(OTf)_2$ in $CHCl_3$ the cycloaddition reaction afforded the corresponding product with only 23% conversion after 24 h at room temperature. When $Ni(OAc)_2{\cdot}4H_2O$ was used in $CHCl_3$ the conversion was enhanced to 89 %. N-tosyl and *N*-alkoxycarbonylated protected, 3-nitroindoles performed very well and delivered the corresponding cycloadducts in high to excellent yields. Because of its reduced electrophilicity *N*-Methyl-protected 3-nitroindole failed to undergo the transformation. To prove the generality of this protocol various structurally diverse C,N-cyclic azomethine imines were synthesised.



Scheme 22. Synthesis of polycyclic tetrahydroisoquinoline derivatives.

1,2,3-triazoles have a wide range of applications as potential bioactive compounds and are frequently used for the preparation of new drugs with diverse biological activities. A general and efficient methods for their fabrication came in the early 2000s with the novel concept of "click" chemistry and the Cu-catalysed alkyne–azide cycloaddition reaction provides the regioselective formation of 1,4-disubstituted 1,2,3-triazoles. The metallo-catalysed alkyne–azide cycloaddition reaction for the formation of 1,5-disubsituted 1,2,3-triazoles was published later. However, it should be noted that the reactions mentioned above have made use of heavy metals, which has limited their practical applications.

Alternative synthetic pathways for 1,2,3-triazoles have also been developed and 1,2,3 triazoles have freely been obtained from a combination of azides with a range of reaction partners: e.g. cycloadditions of either β-keto esters or nitriles to azides catalysed by secondary amines (Costa *et al.*, 2017), cycloaddition of a triple domino sequence of reactions between azide, amine and 5-bromo-2-furylcarbinol (Yang *et al.*, 2015), the reaction of enols and enamines with azides (Blastik *et al.*, 2018), nitro methylene-based three-component synthesis (Thomas *et al.*, 2014), and others. However, these methods entail the use of organic azides or sodium azides, which are difficult to handle and toxic, particularly on a large scale. In a 2017 review, Ahmed (Ahmed *et al.*, 2017) presented some less well-known synthetic protocols for 1,2,3-triazoles under azide-free and metal-free environments. (Figure 3)

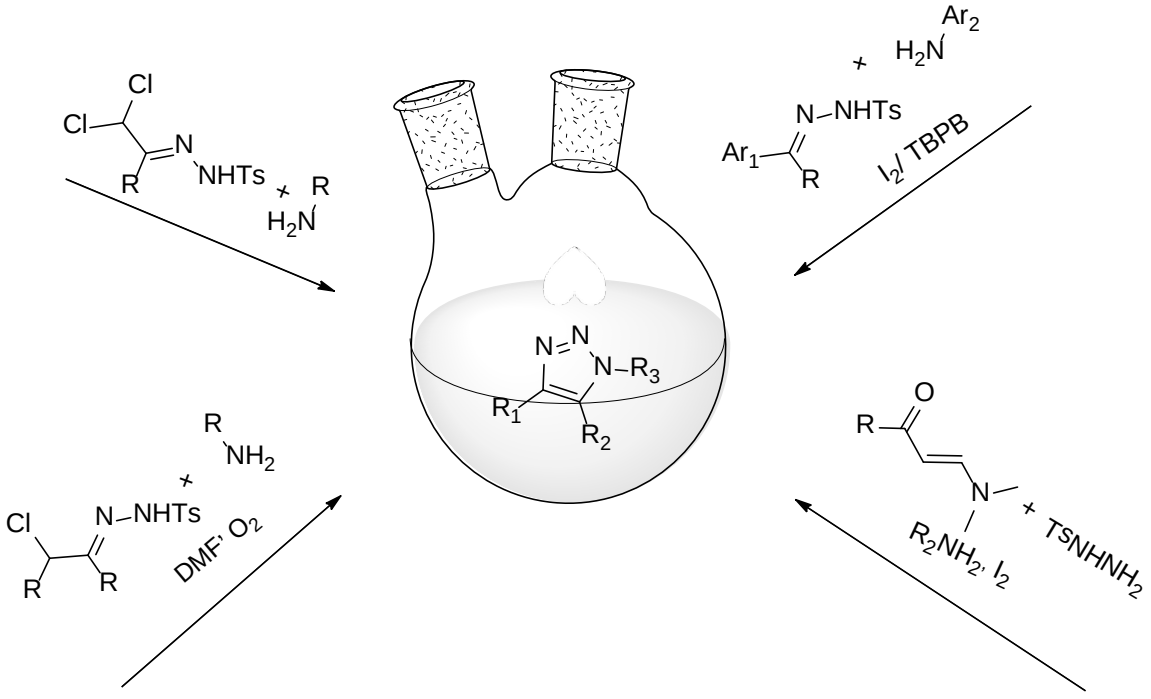
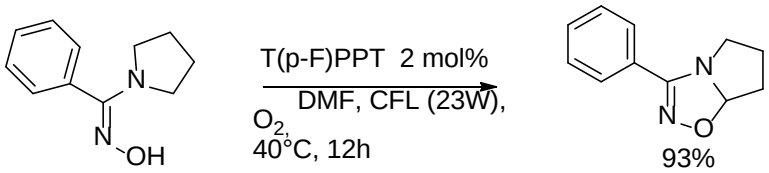


Figure 3. “Metal-free” and “azide-free” syntheses of triazoles.

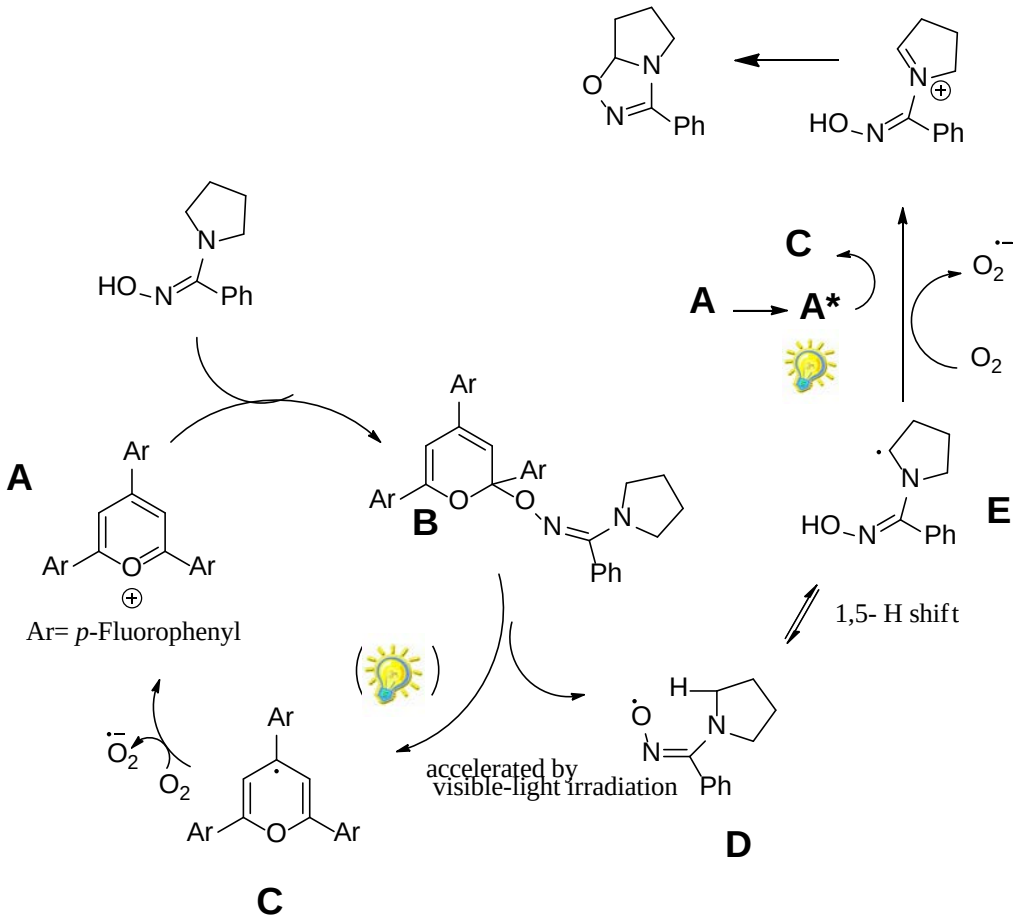
2.6 Light induced

The importance of aza-heterocycles relates to their presence as natural products, drugs and biologically relevant compounds. A variety of methods have been developed for the synthesis of 1,2,4-oxadiazolines, and these are generally carried out via the [4+ 2] cycloaddition of a nitrile oxide (generated *in situ* from the corresponding hydroxamoyl chloride or nitroalkane) with an imine. The development of new methodologies for the synthesis of 1,2,4-oxadiazolines, especially greener methods, is highly desirable because many of these methods suffer from one or more drawbacks. Soni *et al.,* (Soni et al., 2018) have very recently presented a sustainable methodology for the synthesis of 1,2,4-oxadiazolines via an intramolecular oxidative cyclisations of amidoximes in the presence of an organocatalyst and molecular oxygen. The authors optimised the reaction conditions to give 3-phenyl- 5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole from phenyl(pyrrolidin- 1-yl)methanone oxime, which was used as a model substrate. The optimized conditions involved 2 mol% of an organophotocatalyst, 2,4,6- tris(4-fluorophenyl)pyrylium tetrafluoroborate (T(p-F)PPT) at a 0.2 M concentration in DMF under an atmosphere of molecular oxygen. Visible-light irradiation was provided by a compact fluorescent lamp (CFL, 23 W). The use of an organophotocatalyst minimises the drawbacks associated with transition metals, including toxicity and threshold metal levels in pharmaceutical products. (Scheme 23)



Scheme 23. Synthesis of bicyclic 1,2,4-oxadiazolines.

The authors investigated a variety of pyrrolidinyl oxime derivatives. α-(Pyrrolidin- 1-yl)benzaldehyde oxime derivatives, with electron-donating or electron-withdrawing substituents, underwent oxidative cyclization to afford 1,2,4-oxadiazolines in high yields. A plausible mechanism for the oxidative cyclization of amidoximes was proposed (Scheme 24).



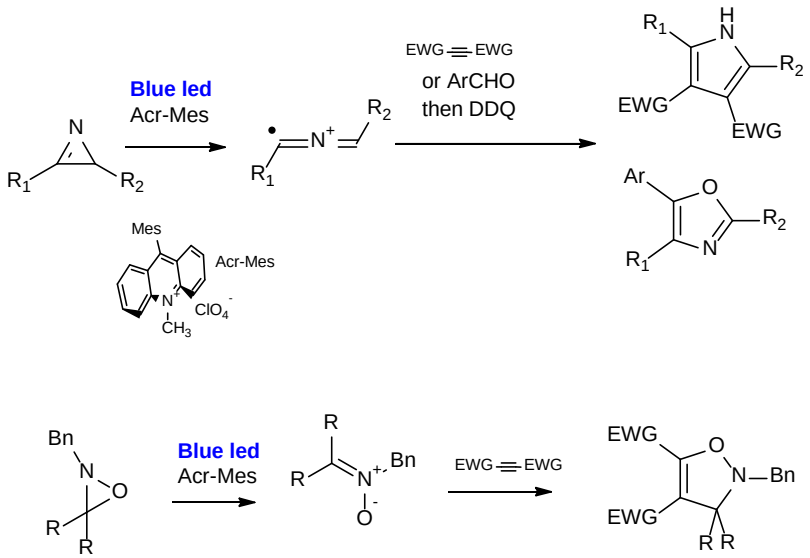
Scheme 24. Plausible mechanism for the synthesis of 1,2,4-oxadiazolines.

The observations that triphenylpyrylium (TPP) derivatives were the only effective photocatalysts of those examined, and that the reaction proceeded even in the absence of light, albeit less efficiently, suggests that T(p-F)PPT functions as both an electrophilic catalyst and a photocatalyst in this transformation. As described in the Scheme 24, the reaction begins with the nucleophilic addition of starting material to the triphenylpyrylium ion (A) to generate intermediate B. The dissociation of the C-O bond in B then produces radicals C and D; this is the step that is slow and inefficient in the absence of light but is promoted by exposure to visible-light. The oxidation of C by molecular oxygen regenerates catalyst A. On the other hand, the iminyloxyl radical D undergoes an intramolecular 1,5-hydrogen atom transfer (HAT) to give the carbon-centred radical E, which is subsequently oxidised to the iminium ion F. The intramolecular cyclization of F finally yields the 1,2,4-oxadiazoline.

Visible-light-driven photoredox catalysis is attracting interest because of its inherent features of green chemistry and sustainability. In addition to a number of radical reactions, several [2+3] cycloaddition applications have been describe in the literature (Narayanam and Stephenson, 2011; Nakajima et al., 2016; Staveness et al., 2016; Savateev and Antonietti, 2018).

2*H*-azirines can react with activated alkynes or aldehydes to produce polysubstituted pyrroles or 2,5-dihydrooxazole, respectively, under very mild reaction conditions (visible-light irradiation, metal-free and room temperature). As described by Xuan J. *et al.*, the optimised procedure is catalysed by 9-mesityl-10-methyl-acridinium perchlorate in dichloroethane under irradiation from a 3 W white

LED light. Excellent results were obtained when a range of substituted 2H-azirines were reacted with dimethyl but-2-yne-dioate (Xuan *et al*., 2014). 2*H*-Azirines reacted with aldehydes in the presence of Li_2CO_3. This was done to avoid the oxidation of aldehydes to carboxylic acids, and 2,3-dichloro5,6-dicyano-1,4-benzoquinone (DDQ) was added to the reaction system in order to perform the one-pot synthesis of oxazole. The applicability of the reactions was demonstrated using a panel of twelve 2,4,5 trisubstituted oxazoles, giving yields in the 40-80% range (Scheme 25) (Zeng *et al*., 2015).



Scheme 25. Visible-light mediated synthesis of pyrroles and isozazoles from of *2H*-azirines and *2H*-oxazirine.

The ring-opening of 2*H*-oxazirine has been reported as occurring via visible-light-mediated photoredox-catalysed single-electron transfer (SET), giving nitrone precursors. The 1,3 dipolar cycloaddition was therefore used for the synthesis of 4-isoxazolines. 9-mesityl-10-methyl-acridinium perchlorate was the strategic choice as catalyst because of its high oxidizing power in the excited state (+2.06 V) and strong absorption band in the visible region. The [3 + 2] cycloaddition reaction of oxaziridine with dimethyl acetylenedicarboxylate gave very good results when performed in CH_3CN in the presence of water, used as an additive, and a large set of 4-isoxazolines was synthesized with a good average yield.

The first attempt to describe the mechanism of pyrrole cyclization focused on a radical cycloaddition of the intermediate 2-azaallenyl radical cation, which was in equilibrium with a 1,3 radical-cationic species. Subsequently, the publication mentioned that the synthesis of the dihydroisoxazole a hypothesis of a polar cycloaddition. In fact, the authors proposed the single-electron reduction of the nitrone radical to a nitrone species.

3 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4 Acknowledgments

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