CYCLOADDITIONS WITH MESOIONIC DIPOLES: STRATEGY AND CONTROL

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Abstract. *The synthesis of and with mesoionic heterocycles is arguably an old field that enjoys renaissances from time to time, given their great value as synthons toward other heterocycles and fine chemicals as well as natural products, drugs and their analogs. Creativity in this domain is largely based on cycloaddition reactions, often in combination with catalytic methods, which enable facile fragment couplings, late stage functionalizations, and asymmetric versions so long as chiral derivatives are employed. This perspective will attempt to show some recent developments in synthetic construction harnessing the versatility of mesoionic heterocycles, mainly focused on their dipolar cycloadditions. A series of well-known mesoionic compounds will illustrate well the electronic and steric control that can be enacted through a cyclic array of multiple heteroatoms, often leading to high chemo-, regio- and stereoselection.*

Contents

1. Introduction and scope

The concept of mesoionic heterocycle and, especially its reactivity as masked dipole, grew up from an academic curiosity to a well-consolidated subfield of heterocyclic chemistry, which has gained progressive interest as synthetic toolkit and *en route* to push-pull structures suitable for molecular optoelectronics. Historically the term mesoionic was coined by Baker and Ollis as early as the 1940s as a nickname combining "mesomeric" and "ionic".[1,2] In this context and in a strict sense, a mesoionic compound is a five-membered heterocycle that cannot be satisfactorily represented by any one Lewis structure not involving charge separation, and possessing a sextet of electrons in association with the atoms comprising the ring. That delocalization gives rise to enough stability to allow isolation in numerous cases, even though the issue of aromaticity in mesoionic rings is debatable.[3] Several resonance structures can then be drawn for a given mesoionic compound, without consensus about a preferred canonical form, each showing its dipolar character. Mesoionics can also be viewed as heterocycles of intermediate ionicity, thus echoing the universal

definition of *meso* (from Greek μεσος (misos) = middle). The above definition indicates that mesoionics belong to the large family of *heterocyclic mesomeric betaines*,[4,5] but excludes explicitly six-membered rings. Yet, papers associating six-membered betaines, and even worse zwitterions, ylides or open-chain dipoles, with the term mesoionic are not unusual, which may indeed be misleading. One might be inclined to neglect another discussion on nomenclature as unimportant. As we and others have emphasized, it is key to get this definition right (rarely things are good when different scientists use the same term to denote different compounds). Accordingly, every effort to make it clear is far from being a truism.

It is customary to group mesoionic rings into two major types, denoted **A** and **B** (Figure 1), covering diazolium olate/thiolate systems to a large extent, although other systems have been introduced in recent years (*e.g.* tetrazolium derivatives),[6] including rings containing main-group heteroatoms other than O, N and S as we shall see later. At first glance, both types show close resemblance, being no more than positional isomers, as labels **a**, **b**, **c**, and **d** indicate atoms with one-electron contribution to the π-system, while two-electron contributions are represented by atoms **x** and **y**. This delusive appreciation can be disclosed through connectivity-matrix analysis,[5] also supported by DFT calculations,[7] which recognize further classes and subclasses of types **A** and **B** mesoionics. In short, the wide variety of mesomeric betaines should now be classified in terms of conjugated, semi-conjugated, and cross-conjugated systems. Thus, while type **A** rings are actually conjugated betaines, the calculated properties of type **B** are consistent with their classification as semi-conjugated heterocyclic betaines and show characteristics similar to those of six-membered semi-conjugated betaines. Most synthetic achievements have been conducted with the first type, whereas the **B** series waits for further developments and explorations, as some predicted subclasses remain unknown, which may account for inherent instability, or such structures exist as the corresponding valence isomers, not yet experimentally detected.

type **A** type **B**

Figure 1. Type **A** and type **B** mesoionic rings (see text for explanation).

From a structural point of view, one cannot forget the similarity of mesoionic betaines with *N*-heterocyclic carbenes (NHCs), which have experienced increasing interest in the last years, especially concerning their role as organocatalysts. Classifications of mesoionic-like structures based on the concepts of abnormal or remote carbenes have also been introduced.[8-10] Since NHCs are usually stabilized by metal ligation, a closer resemblance with metal complexes of mesoionics is likewise evident. The metalation of mesoionic heterocyclic exploits the inherent acidity of some protons at the ring, affording metalated synthons with umpolung reactivity. Lopchuk has recently reviewed this important application covering direct metalation with Li or Mg, transmetalation to some first-row transition metals, as well as metal-mediated couplings.[11] Said that, even if only subtle structural differences are displayed, there are marked dissonances in reactivity between NHCs, either normal or abnormal, with mesoionic *C*-donor complexes generated by metal bonding.[12]

It is unnecessary to underline that heterocyclic frameworks have a significant impact on the manifold properties of natural products and drugs. The development of medicinal chemistry hinges clearly on so-called privileged heterocyclic scaffolds and efficient routes in the synthesis and functionalization of heterocycles. As shown here, mesoionic rings play well this game, and notably some compounds of mesoionic nature exhibit biological activity, against human pathologies as well as herbicides and pesticides, the field being however underestimated so far. A couple of sydnones were developed in Russia in the 1970s, although neither of them received approval by the Food & Drug Administration (FDA) or European Agencies. On the other hand, the use of other mesoionic derivatives as NO-releasing agents represents a promising application.[13]

Although these remarks are invariably pertinent in any introduction on mesoionic chemistry, particularly to newcomers, neither of them will be treated further and the readership is referred to the above-mentioned references for broad and in-depth coverage. Instead we will focus on synthetic achievements that

largely use dipolar cycloadditions as the key strategy, covering only the recent literature spanning from *ca*. 2009 to mid-2017. As noted, the dipolar structure enables further reaction in cycloaddition reactions (mesoionics are actually willing dipoles), a fact recognized and extensively exploited by Rolf Huisgen and his team since the late 1960s. Huisgen's *alma mater* (München Universität / University of Munich) gave name to a well-known mesoionic subclass, i.e. 1,3-oxazolium-5-olates (münchnones).

Among the huge number of potentially available mesoionic structures, a few heterocycles have found enough merit in synthetic pursuits; in particular: 1,2,3-oxadiazolium-5-olates (sydnones, again a chemical toponymy after Sydney, in Australia), 1,3-oxazolium-5-olates (münchnones), 1,3-oxazolium-4-olates (isomünchnones), and 1,3-thiazolium-4-olates (thioisomünchnones), all depicted in a common canonical form in Figure 2. Their chemistry has been detailed comprehensively and the reader is referred to some past reviews for preliminary reading.[14-17]

1,2,3-oxadiazolium-5-olates ***(sydnones)*** **1,3-oxazolium-5-olates** ***(münchnones)*** **1,3-oxazolium-4-olates** ***(isomünchnones)*** **1,3-thiazolium-4-olates** ***(thioisomünchnones)***

Figure 2. Representative mesoionic compounds used in cycloaddition reactions.

The present perspective documents both synthesis and mainly dipolar cycloadditions of such mesoionics, although extensions to other less-known derivatives will also be discussed. We feel that this way the utility and particular reactivity of a given mesoionic ring can be best illustrated. In fact our own research endeavors have been concentrated on these substances during the last decade. Of the approximately 550 peer-reviewed publications spotted in the 2009-2017 period, in a SciFinder® search, about 400 are about synthetic applications, and subsequent scrutinization by mesoionic type reveals that most (*ca*. 390) correspond to sydnones followed by münchnones (*ca*. 45) and isomünchnones and thioisomünchnones (6 each) (Figure 3).

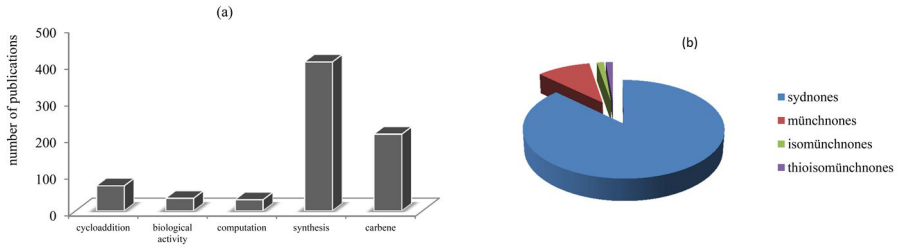
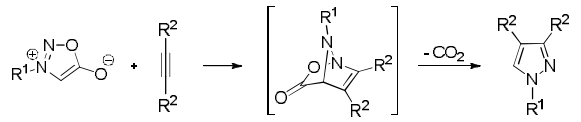


Figure 3. (a) Temporal evolution of publications found for "mesoionic" in a SciFinder® search (subcategories include "cycloaddition" (68), "biological activity" (34), "computation" (30), "synthesis" (406) and "carbene" (209). (b) Distribution of all publications found for type of mesoionic ring in a SciFinder® search (Date: July 2017).

2. Sydnones

As mentioned, this type of oxadiazolium olate system has received considerable attention,[18-20] which reflects their stability and easy isolation in most cases. A common application of sydnones involves their 1,3-dipolar cycloaddition with acetylenic dipolarophiles affording pyrazole rings. This transformation takes place through a non-isolable cycloadduct that losses CO_2 spontaneously giving rise to the corresponding diazole derivative as depicted in Scheme 1. The conventional thermal activation can be significantly improved by means of click-type methods such as the Copper-mediated Sydnone Alkyne Cycloaddition (CuSAC) and Strain-Promoted Alkyne Azide Cycloaddition (SPAAC), which enable the preparation of pyrazoles under milder conditions. As documented in recent reviews, these orthogonal routes have also been

applied to the preparation and modification of novel polymeric materials. The cycloaddition of sydnones with olefins represents another typical synthetic strategy, although it has been employed to a lesser extent.



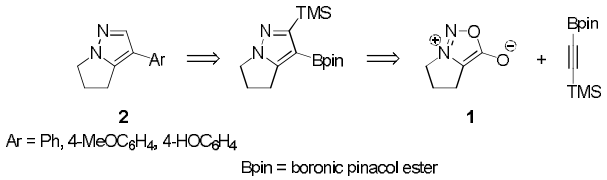
Scheme 1. General cycloaddition reaction between sydnones and symmetrical alkynes.

2.1. Cycloaddition of sydnones with alkynes

As shown in Scheme 1, the reaction of sydnones with both symmetrical and unsymmetrically-substituted alkynes represents an elegant and expeditious protocol to yield functionalized pyrazoles. That cycloaddition exhibits a high level of atom economy releasing carbon dioxide as byproduct. Although the latter is a greenhouse gas, it could be easily trapped and reused. In line with the above-mentioned statements, we shall refer to conventional reactions, generally requiring thermal activation for the cycloaddition to occur, and activated reactions involving either catalysis or structural factors which improve the classical protocol.

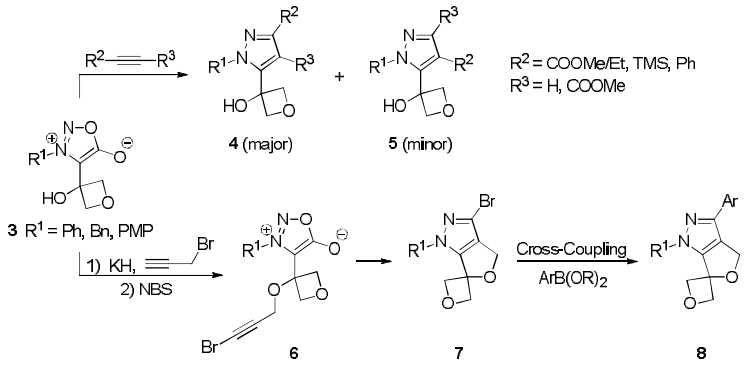
2.1.1. Conventional cycloadditions

Since refluxing conditions are generally compulsory for completion, the use of xylenes or 1,2-dichlorobenzene (DCB) as solvents allow for high reaction temperatures. Some bicyclic sydnones like **1** have been used as synthons for the preparation of pyrazole-containing natural products, as illustrated in Scheme 2 with the withasomnine family (**2**).[21] The regioselective cycloadditions with alkynylboronate acetylenes at reflux, followed by Suzuki cross-coupling yielded the desired withasomnine alkaloids in moderate to good yields.



Scheme 2. Retrosynthetic pathway for the synthesis of withasomnine derivatives (**2**).

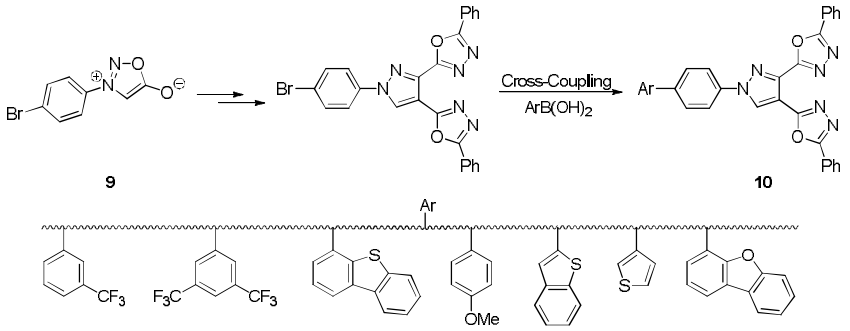
Novel functionalized oxetanyl sydnones (**3**) have been used for inter and intramolecular cycloadditions with alkynes (Scheme 3).[22]



Scheme 3. Synthesis of functionalized oxetanyl pyrazoles (**4** and **5**) and spiro-heterocyclic pyrazoles (**8**) through inter- and intramolecular cycloadditions, respectively.

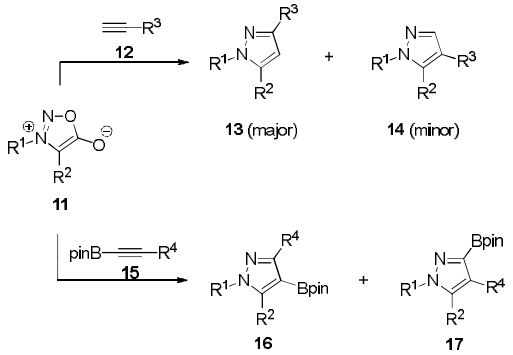
Intermolecular reactions proceeded in moderate yields and regioselective fashion affording a mixture of pyrazoles **4** and **5**, but intramolecular cycloadditions were more efficient and enabled the preparation of spiro-heterocyclic derivatives. Thus, oxetanyl sydnones (**3**) were converted into their bromo derivatives **6**, which underwent intramolecular cycloaddition and then cross-coupling reaction with boronate esters giving rise to compounds **8**. Thermal reactions were conducted in xylene (140 ºC) or 1,2-dichlorobenzene (180 ºC); the use of microwave irradiation led to completion in short reaction times (15-30 minutes).

In following a related methodology, *N*-bromoaryl sydnones (**9**) could be transformed into 1,3,4-oxadiazoles bearing aromatic rings (**10**) (Scheme 4).[23]



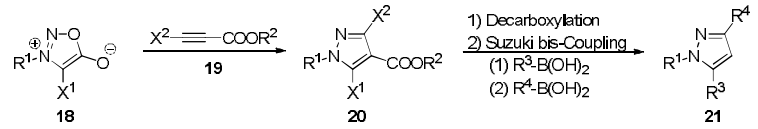
Scheme 4. Synthesis of aromatic 1,3,4-oxadiazole derivatives by sydnone cycloadditions.

A complete regioselectivity in conventional cycloadditions of sydnones with asymmetrical akynes has not yet been reported. However, some 4-trifluoromethyl-substituted sydnones (**11**, $R^2 = CF_3$) gave the corresponding pyrazoles (**13** and **14** with high regioselection by reaction with diverse monosubstituted alkynes (**12**) in DCB at high temperatures. In stark contrast, the cycloadditions of sydnones **11** with asymmetrical dipolarophiles based on boronic esters (**15**) were not regioselective at all (Scheme 5).[24,25] Slightly better results could be obtained by reaction of sydnones **11** ($R^2 = H$) with three terminal alkynes (**12**, R^3 = Ph, 2-Py, 2,6-Py). Nevertheless, the overall picture is indeed complex. Thus, sydnones **11** ($R^2 = H$) reacted with alkynyl boronates **15** (R^4 = Ph) with high regioselectivity, and similar conclusions were obtained for the cycloadditions of sydnones **11** (R^2 = Me, Ph, ^{i}Pr) with other boronates (**15**, R^4 = Ph, TMS) under the same reaction conditions (Scheme 5).[26] A full computational study was performed to shed light into the selectivities observed experimentally. This analysis showed that the presence of substituents at C4 of the dipoles results in unfavorable interactions and bulky boronic ester groups of the dipolarophile cause steric hindrance as well. Notably, when the substituent of the alkynyl boronate (**15**) is a phenyl group and sydnones lack substituents at C4, the dipole approaches perpendicular to the aromatic plane leading to favorable interactions and hence to higher regioselection.[26]



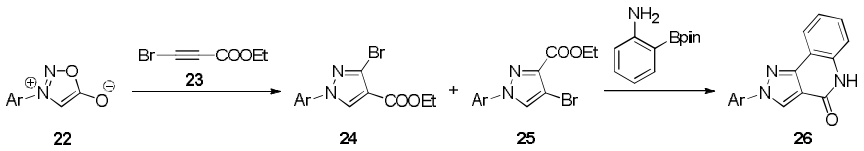
Scheme 5. Cycloaddition reactions of sydnones with terminal alkynes and alkynyl boronates.

Delaunay *et al.* have applied a sequential strategy to obtain substituted pyrazoles from halosydnones or halogenated alkynes followed by cross-coupling Suzuki reactions.[27,28] Thus, *N*-protected halosydnones **18** reacted with halogenated alkynes **19** in refluxing xylene or toluene, affording a mixture of pyrazoles with poor regioselectivity (for clarity, only the major regioisomer is shown). The iodo-derivatives (both dipole and dipolarophile) were by far the most reactive partners. The major regioisomers (**20**) could be separated from the reaction mixture and employed in further derivatization, which involved their decarboxylation in aqueous H_2SO_4 at reflux followed by one pot bis-coupling with two series of heterocyclic boronic acids yielding the corresponding 1,3,5-trisubstituted pyrazoles **21** (Scheme 6).[27,28]



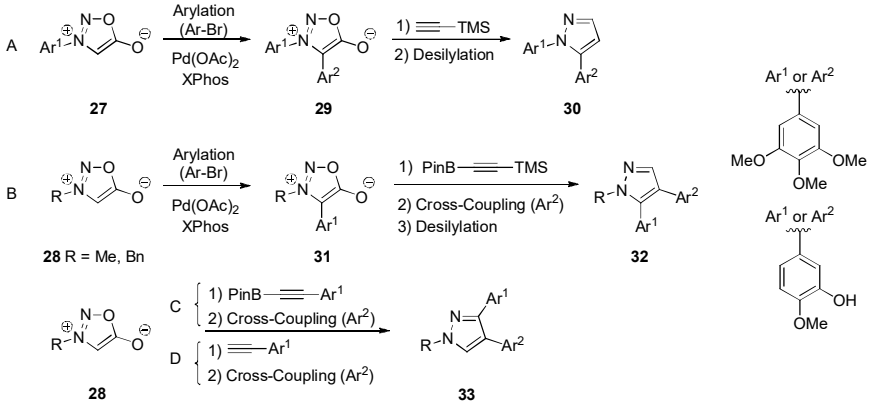
Scheme 6. Cycloaddition reactions of halosydnones and halogenated alkynes, followed by post-functionalization *via* decarboxylation and bis-Suzuki couplings with heterocyclic boronic acids.

In a related protocol, other authors have documented the synthesis of 2-arylpyrazoloquinolinones (**26**, major isomer shown) from aryl sydnones (**22**, Ar = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$). Their cycloaddition with alkyne **23** gave rise to a mixture of regioisomeric and separable pyrazoles (**24** and **25**), which were subjected to cross coupling with an aryl boronate to yield the above-mentioned tricyclic system (Scheme 7).[29]



Scheme 7. Synthesis of 2-arylpyrazoloquinolinones by dipolar cycloaddition of sydnones **22** with alkyne **23** and subsequent Suzuki-type cross coupling.

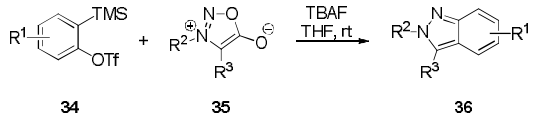
Harrity and co-workers have also developed similar strategies for obtaining highly functionalized pyrazole rings, which involve an initial arylation of halosydnones followed by post-cycloaddition reactions.[30] This group was able to improve the protocol further by performing direct arylation of sydnones by C-H activation (Scheme 8).[31]



Scheme 8. Synthesis of combretastatins A4 analogs, using sydnone-alkyne cycloadditions, leading to 1,5-, 1,4,5-, and 1,3,4-substituted pyrazoles.

The latter was applied to the preparation of some combretastatins A4 analogs, an important class of tubulin-binding agents.[32] Direct arylation of *N*-aryl (**27**) or *N*-alkyl (**28**) sydnones followed by cycloaddition with TMS-substituted alkynes and subsequent desilylation afforded diaryl pyrazoles **30** and **32**, respectively. The corresponding 3,4-disubstituted diaryl pyrazoles (**33**) could also be obtained from sydnones **28** by cycloaddition with alkynyl boronates followed by arylation. Alternatively, cycloaddition with terminal alkynes and arylation gave the same pyrazole derivatives (Scheme 8).

Dipolar cycloadditions involving sydnones and benzyne have been reported as well.[33,34] A wide variety of indazoles (**36**) were obtained in good yields from sydnones (**35**) and arynes (**34**). The *in-situ* generation of the benzyne moiety was accomplished in the presence of tetrabutylammonium fluoride (TBAF) and cycloadditions could be carried out in THF at room temperature (Scheme 9).[33] In this context, indazole derivatives were also generated by reaction of sydnones and benzyne leading to masked diazoimine dipoles, which were subsequently trapped with olefinic reagents (see Section 5.1.).[34]

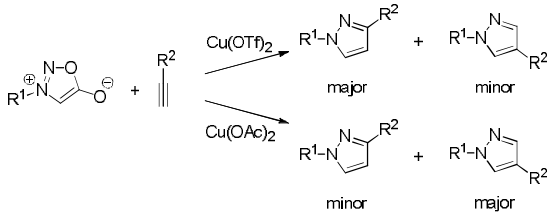


Scheme 9. General synthesis of indazoles (**36**) by dipolar cycloaddition of sydnones and arynes.

2.1.2. Activated cycloadditions

As emphasized previously, sydnone cycloadditions do require harsh conditions that may lead to unwanted side products and/or decomposition. Milder conditions can be attained through activation methods, such as the use of solid-supported reagents. Thus, supported amino acids were converted into sydnones and then subjected to cycloadditions with acetylenes. Although these processes could be accomplished at room temperature for 2-3 h, yields ranged from poor to moderate and no regioselectivity could be observed by using asymmetric dipolarophiles.[35]

Variations using copper salts (CuSAC version) promote the cycloaddition reaction of sydnones with monosubstituted alkynes, thereby reducing the reaction times. Both $Cu(OTf)_2$ and $Cu(OAc)_2$ salts have been employed in the formation of 1,3- and 1,4-disubstituted pyrazoles with high regioselectivity starting from *N*-substituted sydnones and terminal alkynes.[36] Surprisingly changes in the Cu salt switched the regiochemical outcome (Scheme 10).



Scheme 10. Influence of Cu salts in the regiochemical outcome of sydnone cycloadditions with alkynes.

A computational study of the reaction between phenylsydnone and phenylacetylene with both Cu salts suggest two distinctive interpretations. While $Cu(OTf)_2$ acts as Lewis acid activating the sydnone and preserving the regiochemistry of the uncatalyzed cycloaddition (**TS1** in Figure 4), $Cu(OAc)_2$ promotes the formation of a Cu(I) acetylide that approaches the non-substituted nitrogen of the sydnone to the unsubstituted fragment of the alkyne (**TS2**), thus leading to the opposite regioisomer.[36]

A three-step one-pot process, introduced by Taran and associates, has been employed in a CuSAC reaction yielding 1,4-disubstituted pyrazoles with complete regioselectivity.[37] The authors used a disulfonate salt derived from a phenanthroline ligand (**L1**) for copper complexation and inexpensive $CuSO_4$ as Cu source. The formation of sydnones from numerous *N*-aryl amino acids was achieved with *t*-butylnitrite at 60

ºC followed by acid treatment, and the subsequent click reaction with terminal alkynes in presence of the Cu complex required the use of triethylamine (TEA) and sodium ascorbate as reductant (Scheme 11).

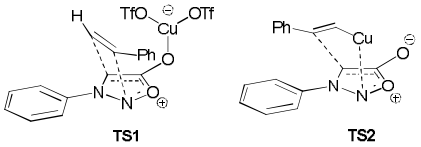
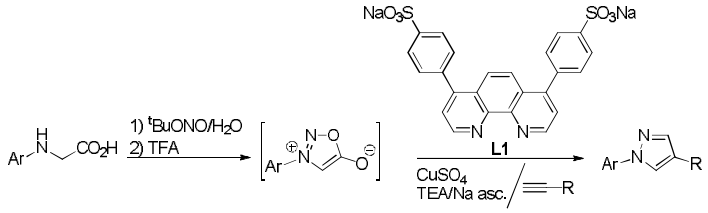
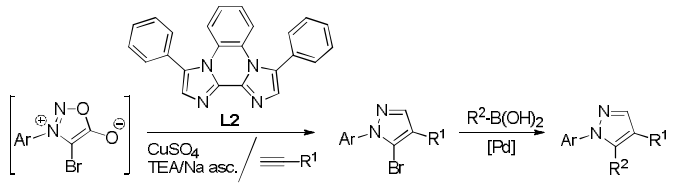


Figure 4. Transition structures proposed for sydnone-alkyne cycloadditions catalyzed by $Cu(OTf)_2$ (**TS1**) and $Cu(OAc)_2$ (**TS2**), calculated at the M06/6-311++G**(SDD)(CPCM) level of theory.



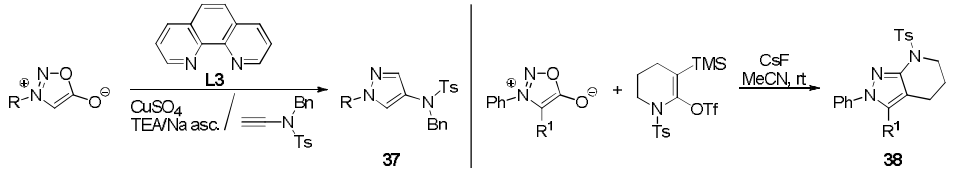
Scheme 11. Three-step one-pot CuSAC reaction yielding 1,4-disubstituted pyrazoles.

The same team generated a series of *N*-aryl-4-bromosydnones which were subjected to CuSAC reactions with terminal alkynes. A different ligand, namely 3,10-diphenyldiimidazo[1,2-*a*:2',1'-c]quinoxaline (**L2**), was employed for Cu complexation under the same conditions as above. The resulting 5-bromopyrazoles were coupled with boronic acids to obtain 1,4,5-trisubstituted pyrazole derivatives in good overall yields (Scheme 12).[38]



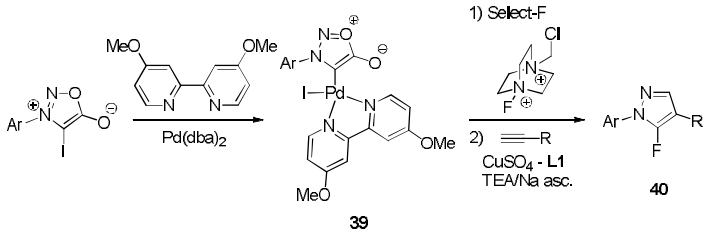
Scheme 12. Cu-catalyzed cycloaddition of *N*-aryl-4-bromosydnones followed by Suzuki coupling to give 1,4,5-trisubstituted pyrazoles.

Aminopyrazoles, as exemplified by compounds **37** and **38**, which are suitable synthons for further heterocyclic elaborations, have been obtained from sydnones through click methodologies (Scheme 13). Thus, compounds **37** were obtained by dipolar cycloaddition with ynamides as dipolarophiles in a CuSAC variation that uses 1,10-phenathroline as ligand (**L3**).[39] The *in-situ* generation of a strained alkyne enabled a copper-free strain-promoted alkyne-azide cycloaddition (SPAAC) that led to novel 4,5,6,7-tetrahydro-2*H*-pyrazolo[x,y-*b*]pyridines (**38**) at room temperature in MeCN. However, such products were a regioisomeric mixture with poor selectivity.[39]



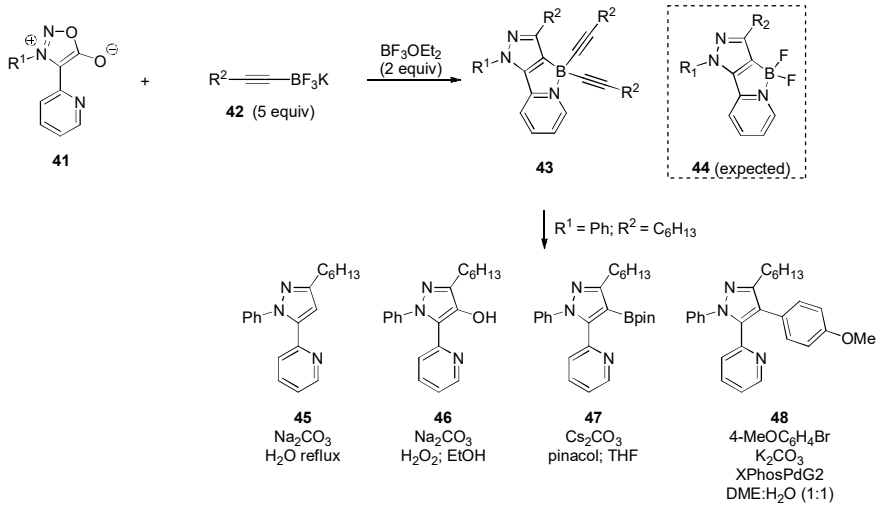
Scheme 13. Synthesis of aminopyrazoles (**37**) from ynamides through CuSAC reaction and regioisomeric 4,5,6,7-tetrahydro-2*H*-pyrazolo-pyridines (**38**) by SPAAC.

Up to date, the fastest reaction of sydnones with alkynes has been developed by Taran and co-workers.[40] These good results were obtained by direct fluorination/CuSAC reaction of a Pd(II)-sydnone complex giving rise to twenty fluoropyrazoles in less than 15 min (Scheme 14). The formation of complexes **39** was carried out from iodosydnones in a Pd-catalyzed reaction at room temperature followed by heating at 60 ºC in THF. All the complexes could be isolated and fully characterized. The subsequent two-step, fluorination/CuSAC reaction in *t*-ButOH/H_2O at 60 ºC led to trisubstituted pyrazoles (**40**) with high regioselectivity.



Scheme 14. Three-step formation of 5-fluoro-1,4-pyrazoles (**40**) from iodosydnones.

The search for novel metal-free cycloadditions, yet conducted under mild conditions and leading potentially to high regioselection, has resulted in some noticeable improvements. With this goal in mind, Harrity and co-workers have recently developed sydnone cycloadditions with alkynyl trifluoroborates, wherein activation takes place by interaction between the boron atom as acceptor and a donor atom of the mesoionic fragment. This concept is illustrated in Scheme 15 by reaction of alkynes **42** with sydnones **41** bearing a 2-pyridyl substituent, whose nitrogen atom exerts the donating interaction.[41] This cycloaddition that can be performed in 1,2-dichloroethane at room temperature, did not afford the expected difluoroborane derivatives (**44**), but rather compounds **43**, which constitute a novel family of pyrazoleboranes. These substances could further be functionalized by removing the dialkynylborane moiety, under different reaction conditions (indicated in Scheme 15) leading to compounds **45**-**48** in good yields and regioselectivity.



Scheme 15. Synthesis of dialkynyl pyrazoleboranes and further conversion into 1,3,4,5-substituted pyrazole rings.

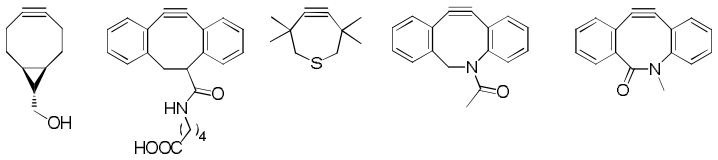
It should finally be mentioned that the CuSAC reaction has been successfully carried out under flow conditions.[42] This scalable protocol, suitable for the pharmaceutical industry, used dilute concentrations of,

for instance, phenylsydnone (**11**, R^1 = Ph, R^2 = H, 0.025 M) and phenylacetylene (0.050 M) through a $Cu(OAc)_2$/silica gel bed.

2.1.3. Application in bioorthogonal chemistry

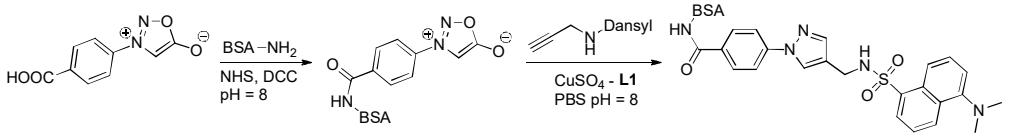
The concept of orthogonal chemistry, or more precisely *bioorthogonal* chemistry, has caused a huge impact in the way chemists and biologists look at numerous *in vivo* processes. In short, the main objective is to track biomolecules by using probes that neither react nor interact with the *in vivo* environment, yet being chemically selective at structural units linked to the biomolecule in question. Some cycloadditive processes, with the Cu-catalyzed alkyne-azide dipolar cycloaddition as paradigmatic example, have largely been employed in bioorthogonal chemistry. Moreover, computation-aided design and assessment of orthogonal reactions provide a rationale in the search for enhanced regioselection and reactivity.[43]

In 2013 Taran and co-workers employed the CuSAC methodology with *N*-phenylsydnone (**11**, R^1 = Ph, R^2 = H) and terminal alkynes in various media, achieving quantitative reactions even in pure human blood plasma.[44] The team also used strained cyclooctynes **49**-**53**, as dipolarophiles, and fluorosydnones getting ultrafast cycloadditions reactions.[40]



49 **50** **51** **52** **53**

The CuSAC variation was also applied to track the BSA (Bovine Serum Albumin) protein through the transformation outlined in Scheme 16, in which BSA is appended to an *N*-aryl sydnone that undergoes selective cycloaddition with a dansylated alkyne.[44]



NHS = *N*-hydroxysuccinimide; DCC = dicyclohexylcarbodiimide; PBS = phosphate-buffered saline

Scheme 16. Dansylation of BSA through sydnone cycloaddition.

Since bioorthogonal reactions must be compatible with *in vivo* environments, the removal of metals and metal ions, even at the trace level, is a crucial issue. Under this premise, metal-free cycloadditions using strained alkynes represents one of the most valuable variations. Thus, *N*-phenylsydnone was reacted with bicyclononyne **49** in aqueous buffer at room temperature without catalyst. Then it was applied to a specific labelling of a genetically encoded bicyclononyne and a sydnone fluorophore, thereby demonstrating the utility of this approach for bioorthogonal protein tracking.[45]

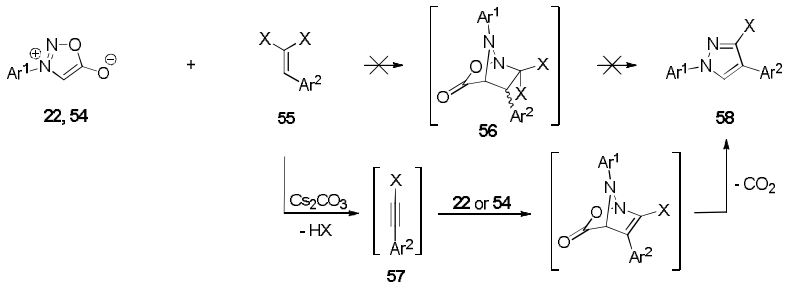
Computational screening of bioorthogonal cycloadditions have been developed by Houk,[43,46] Murphy,[46] and associates. These studies have unveiled the origin of the fast cycloaddition of sydnones with cyclooctynes, which follow the order **52** > **53** > **51**. This computational analysis has been extended to a modified protein, namely BSA-**52**, which reacted with a fluorescent sydnone yielding the corresponding fluorescent labeled protein.[46]

Although not strictly related to bioorthogonality, some oligonucleotides-containing pyrazole rings have been prepared from sydnones to increase the stability of the DNA:RNA complex through stacking effects, getting better results than for oligonucleotides containing triazole or furan units.[47]

2.2. Cycloaddition of sydnones with alkenes

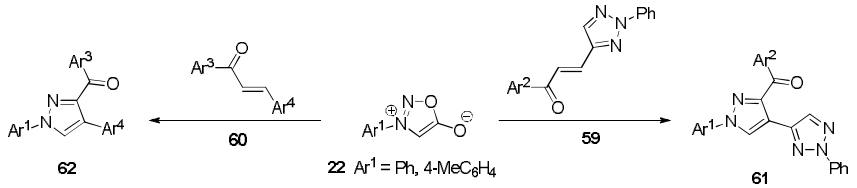
Together with alkynes, the most privileged dipolarophiles in sydnone cycloadditions are olefin derivatives, although as mentioned above, fewer results have been reported. The dipolar cycloaddition with alkenes also lead to pyrazoles and, like alkynes, thermal activation is needed for reaction completion.

Thus, arylsydnones **22** (Ar^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4) and **54** (4-chlorophenylsydnone) reacted with 1,1-dibromo/dichloro-substituted alkenes (**55**) in the presence of Cs_2CO_3 to give the corresponding halogenated pyrazoles **58** (Scheme 17).[48] From a mechanistic viewpoint, however, sydnones did not afford the cycloadducts **56** as intermediates, but alkynes (**57**, not isolated), generated *in situ* by extrusion of HX from alkenes with Cs_2CO_3, which were then trapped by sydnones to give a strained unsaturated cycloadduct that releases CO_2 and produces the pyrazole derivative. Again, high-boiling aromatic solvents (xylenes or DCB) were employed and notably, only the regioisomers shown in Scheme 17 (**58**) were obtained in moderate to good yields.



Scheme 17. Synthesis of halogenated pyrazoles (**58**) by dipolar cycloaddition of aryl sydnones and 1,1-dihaloalkenes.

α,β-Unsaturated monoaryl ketones containing the 1,2,3-triazole moiety (**59**) and α,β-unsaturated diaryl ketones (**60**) underwent dipolar cycloaddition with aryl sydnones in refluxing xylene to give 1,3,4-trisubstituted pyrazole derivatives **61** and **62**, respectively (Scheme 18), with complete regioselectivity and good yields.[49,50]

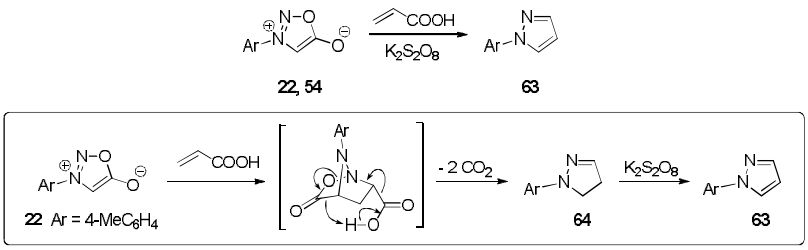


Scheme 18. Synthesis of 1,3,4-trisubstituted pyrazole by sydnone cycloadditions with unsaturated aryl ketones.

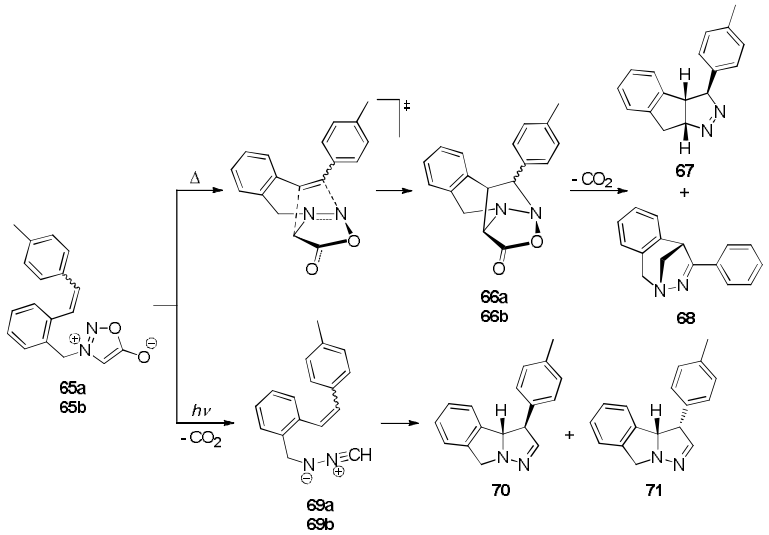
A metal-free synthesis of monosubstituted *N*-arylpyrazoles (**63**) has been reported from common *N*-aryl sydnones and acrylic acid in the presence of $K_2S_2O_8$ (Scheme 19).[51] In order to gain insight into the reaction mechanism, the cyloaddition with sydnone **22** (Ar = 4-MeC_6H_4) was stopped after 16 hours giving a mixture of compounds **63** and **64** (Ar = 4-MeC_6H_4) in a 5 : 95 ratio. When the latter was further oxidized with $K_2S_2O_8$, the pyrazole derivative **63** could be obtained. In line with the mechanistic proposal described in Scheme 17, the dipolar cycloaddition produces a transient cycloadduct that extrudes two molecules of CO_2 affording a dihydropyrazole, which undergoes subsequent oxidation with $K_2S_2O_8$.

New *o*-stilbene-based sydnones (**65a**/**65b**, *cis*- and *trans*-isomers) have been synthesized and subjected to thermal and photochemical conditions to induce intermolecular cycloadditions.[52] The thermal process was conducted in toluene leading to a dihydropyrazole derivative (**67**) and diazatricycle **68** in 50% and 22% yield, respectively. Alternatively, when a mixture of *cis*/*trans*-sydnones **65a**/**65b** in benzene solution was

irradiated at 300 nm, isomeric compounds **70** (*cis*) and **71** (*trans*) could be isolated in low yields (13% and 5%, respectively) (Scheme 20). The authors suggested that the thermal process takes place by ring opening of intermediates **66a**/**66b** leading to the above-mentioned compounds **67** and **68** after CO_2 elimination. On the other hand, photolytic ring opening releases CO_2 as well, producing nitrile imine intermediates (**69a**/**69b**), which would undergo intramolecular cycloaddition to isomeric isoindoles **70** and **71**.



Scheme 19. Synthesis of *N*-arylpyrazoles by sydnone cycloaddition with acrylic acid under oxidizing conditions.

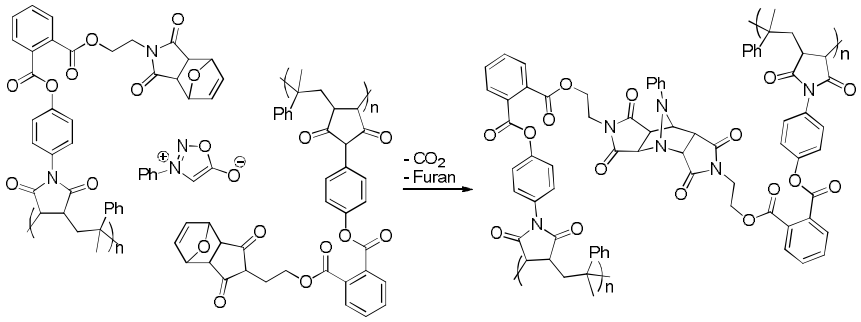


Scheme 20. Thermal and photochemical rearrangements of stilbene-based sydnones (**65a**/**65b**) yielding a series of diazo-polycyclic systems.

2.3. Preparation of polymeric materials

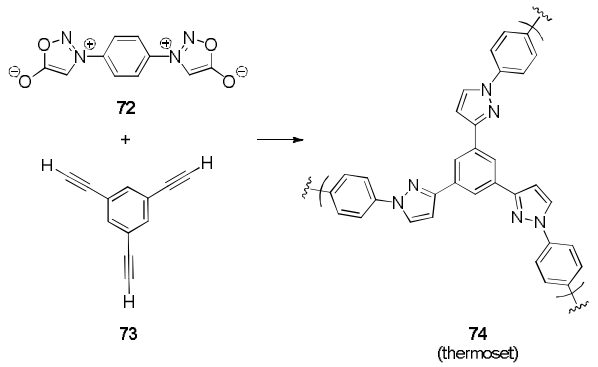
The cycloaddition of sydnones, generally employed in small-molecule modifications, has also been extended to polymeric compounds. Specifically, such cycloadditions can be harnessed in cross-linking transformations leading to polymeric structures endowed with greater thermal stability and other potential electro-optical properties.

In this context, Jen *et al*. have applied a cycloaddition/cycloreversion transformation of sydnones to poly(α-methylstyrene-co-*N*-(4-hydroxyphenyl)maleimide) yielding a cross-linked polymer with high thermal stability (>300 ºC) and producing free-volume thin films, thus decreasing the dielectric constant of the new material (Scheme 21).[53] This procedure was used for obtaining other amorphous polymer-containing furan-masked maleimide, in the solid state. The latter was prepared from a bis or tris-maleimide decorated with a azabicyclic bis(phenylimide) linkage, giving rise to a material that exhibited large both electro-optical coefficients and excellent long-term alignment stability.[54]



Scheme 21. Cross-linked polymer obtained from phenylsydnone plus an oligomeric furan-masked maleimide.

More recently, the cycloaddition reaction of a bis-sydnone (**72**) and an aromatic tris-alkyne (**73**) (1.5 : 1 molar ratio) has been reported to afford a highly cross-linked polypyrazole-based thermoset (**74**) (Scheme 22). These materials possess high thermal stability with negligible weight loss (< 0.1% per day at 225 °C). The key to this performance is the high stability of the functional groups that allowed the thermal activation to give fully aromatic and cross-linked polypyrazole-based thermosets.[55]



Scheme 22. Synthetic strategy for the formation of new pyrazole-based thermosets *via* cycloaddition reactions of bis-sydnone and tris-alkynes.

3. Münchnones

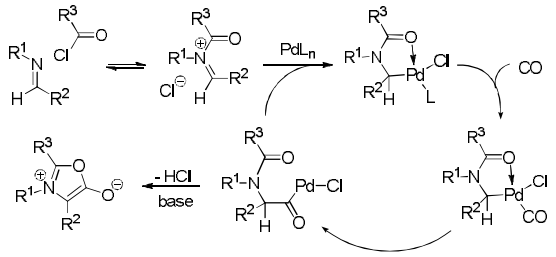
3.1. Synthesis and cycloadditions with alkynes

1,3-Oxazolium-5-olates (münchnones) are known since 1958,[56] after the pioneering studies by Huisgen and co-workers, who explored their 1,3-dipolar reactivity against alkynes[57] as documented in retrospect by Reissig.[58] Since then, a large number of publications have described the most relevant aspects of their synthesis and chemical behavior, both from theoretical and experimental viewpoints. Recently, to overcome the limitations of thermal syntheses, a palladium-catalyzed route to generate münchnones from imines, acid chlorides and carbon monoxide (CO) has been reported (Scheme 23).[59,60] This reaction proceeds in high efficiency and is equally important with substrates that are all easily suitable and inexpensive for polymerization, namely imines, acid chlorides and CO.

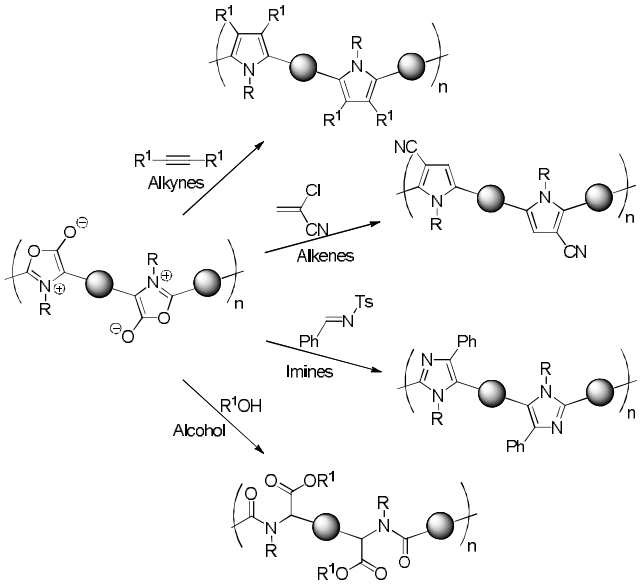
This approach has been used to synthesize conjugated materials *via* a metal catalyzed multicomponent polymerization. This reaction assembles multiple monomer units into a new polymer containing reactive 1,3-dipoles, which can be further modified using cycloaddition reactions (Scheme 24).[61]

The mechanistic studies have provide a clear picture of the impact of catalyst's structure, ligands, and palladium nanoparticles on facilitating the carbonylation of *in-situ* generated iminium salts.[62] A palladium-catalyzed multicomponent synthetic route to polysubstituted pyrroles from aryl iodides, imines, carbon

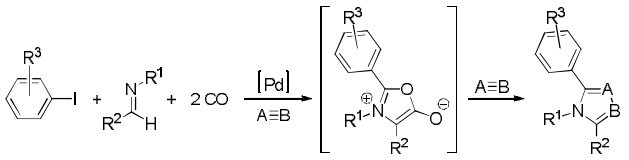
monoxide, and alkynes has been described. Mechanistic studies using $[Pd(allyl)Cl]_2/P^tBu_3$ as catalyst indicates that this reaction proceeds in a concurrent tandem catalytic fashion, and involves the *in-situ* formation of acid chlorides, *N*-acyl iminium salts, and ultimately münchnones, which in the presence of electron-deficient alkynes or alkenes generate diverse families of highly substituted pyrroles in good yield (Scheme 25).[63] This methodology has also been applied to the synthesis of fused-ring pyrroles.[64]



Scheme 23. Mechanistic proposal for the formation of münchnones *via* Pd-catalysis and carbonylation.



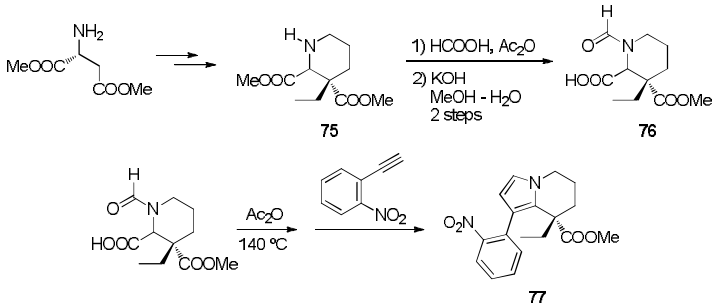
Scheme 24. Transformation of poly-münchnones into families of conjugated polymers.



Scheme 25. Palladium-catalyzed carbonylation and heterocycle synthesis.

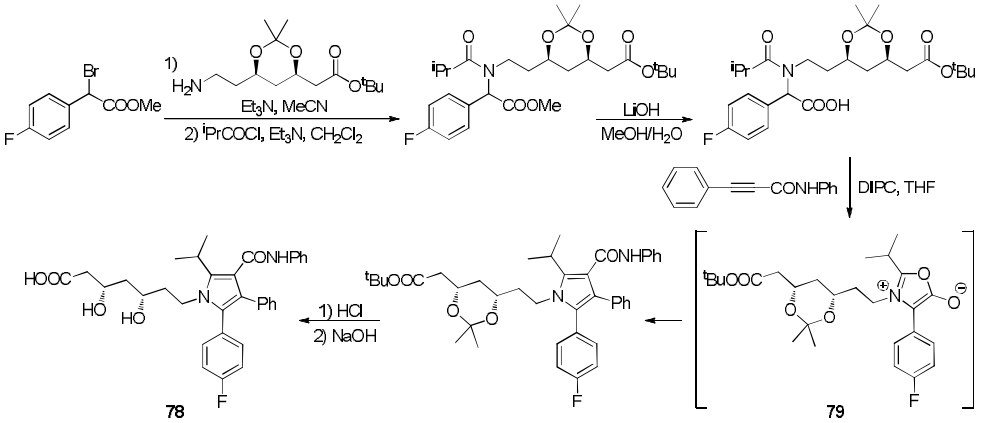
A total synthesis of the alkaloid (–)-rhazinilam has been achieved by two strategies, a regioselective 1,3-dipolar cycloaddition of an optically active münchnone intermediate prepared from D-aspartic acid dimethyl ester, and the construction of the indolizinone core by a gold-catalyzed double cyclization cascade. Based on Rapoport´s procedure,[65] methyl pipecolate (**75**) was synthesized from D-aspartic acid dimethyl ester using a five step sequence. Next, methyl pipecolate was converted to the *N*-formyl pipecolinic acid **76**

by *N*-formylation followed by chemoselective hydrolysis of the diester. The crucial [3+2] cycloaddition proceeded when the functionalized pipecolinic acid and (2-nitrophenyl)acetylene were heated at reflux in acetic anhydride to furnish the 1-aryl tetrahydroindolizine derivative (**77**) as the sole product in good yield (Scheme 26).[66,67]



Scheme 26. [3+2] Cycloaddition of a münchnone as key step in the synthesis of (–)-rhazinilam.

Atorvastatin (**78**), belonging to a recent subfamily of statins, blockbuster drugs employed against atherosclerosis, has been prepared in seven steps from methyl 4-fluorophenylbromoacetate, as outlined in detail in Scheme 27. The key 1,3-dipolar cycloaddition could be carried out regioselectively using a chiral and rather structurally complex münchnone derivative (**79**), which was prepared in four steps.[68]



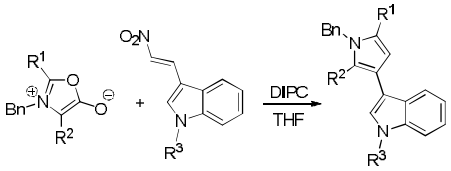
Scheme 27. Synthesis of atorvastatin.

3.2. Cycloadditions with alkenes

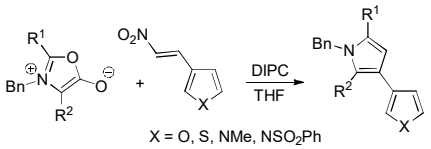
A series of 2- and 3-indolylpyrroles have been generated *via* 1,3-dipolar cycloadditions between (2-nitrovinyl)indoles and symmetrical and unsymmetrical münchnones (Scheme 28).[69]

Likewise, series of furanyl-, thiophenyl-, and pyrrolo-substituted pyrroles were prepared by 1,3-dipolar cycloaddition of unsymmetrical münchnones and nitrovinylheterocycles. The regiochemical outcome of the furan and thiophene cycloadditions are better than previously reported cycloadditions with β-nitrostyrene, while the nitrovinylpyrrole cycloadditions mirror the results observed with nitrovinylindole (Scheme 29).[70]

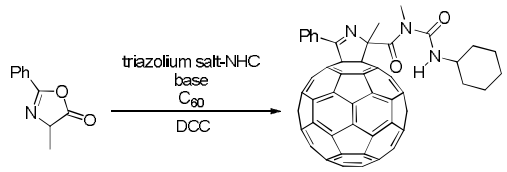
Novel chiral catalytic systems based on both organic compounds and metal salts have been developed for the enantioselective [3+2] cycloaddition of münchnones onto fullerenes and olefins. These two different approaches proved to be efficient and complementary in the synthesis of optically active pyrrolino[3,4:1,2][60]fullerenes with high levels of enantiomeric excess and moderate to good conversions (Scheme 30).[71]



Scheme 28. Reaction of heterocyclic nitroalkenes with münchnones to produce indolylpyrroles.

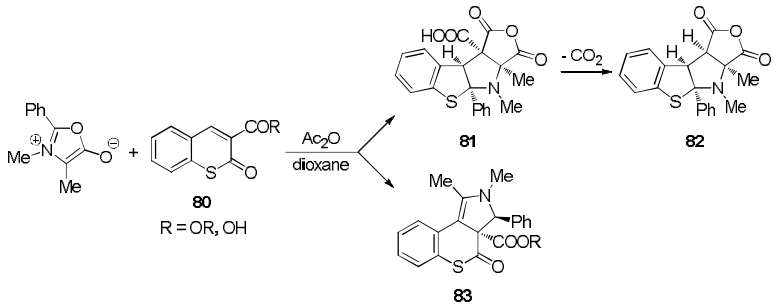


Scheme 29. Synthesis of heteroarylpyrroles by 1,3-dipolar cycloaddition of münchnones with nitrovinylheterocycles.



Scheme 30. Cycloaddition of an azlactone with [60]fullerene.

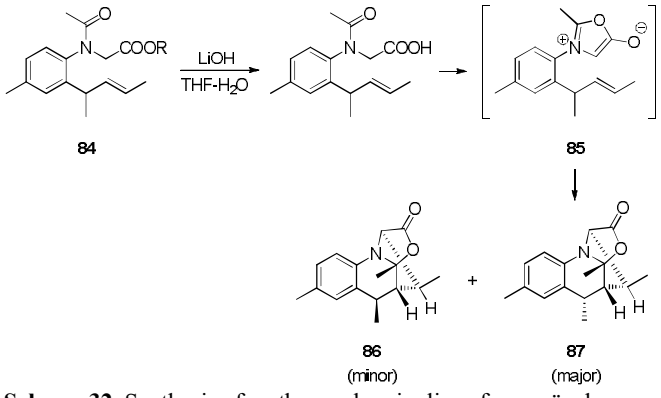
Münchnones react with thiocoumarins (**80**) having an electron-withdrawing group at the 3-position to afford stereodefined fused polycyclic thienopyrroles, such as compounds **81**-**83**. The reaction sequence seems to be triggered by a regiospecific dipolar cycloaddition followed by ring opening of the initial 1:1 cycloadduct and intramolecular rearrangement with an unusual ring contraction (Scheme 31).[72]



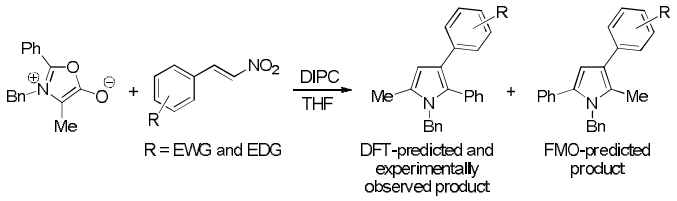
Scheme 31. Synthesis of polycyclic thienopyrroles from münchnones.

The hydrolysis of esters derived from *N*-acetyl-*N*-[2-(pent-3-en-2-yl)phenyl]glycine (**84**) followed by the conversion of the resulting acids into münchnone intermediates (**85**), and their subsequent [3+2]-cycloaddition provided a mixture of functionalized methoxazoloquinoline (**86** and **87**) (Scheme 32).[73]

It is worth pointing out that a computational study, by means of DFT/BDA/ETS-NOCV analyses, of the transition structures involved in the reactions of münchnones and β-nitrostyrenes or phenylacetylene showed that these processes are dominated by steric and reactant reorganization factors, rather than the orbital overlap considerations predicted by Frontier Molecular Orbital (FMO) Theory (Scheme 33).[74]



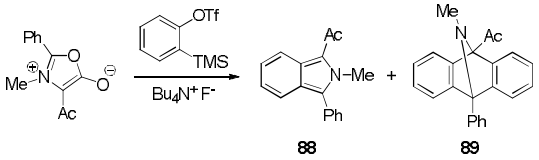
Scheme 32. Synthesis of methoxazoloquinolines from münchnones.



Scheme 33. Regiochemistry in the 1,3-dipolar cycloaddition of a münchnone with nitrostyrenes.

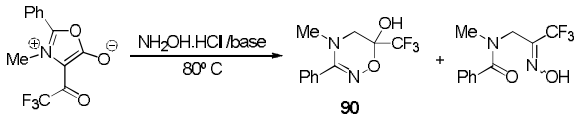
3.3. Other reactions of münchnones

Arynes are able to react with stable münchnones in a [3+2] cycloaddition/[4+2] cycloreversion sequence under mild conditions. The reaction initially affords isoindoles (**88**), but in the presence of excess arynes, such isoindole intermediates readily undergo a further aryne [4+2] cycloaddition to afford 9,10-dihydro-9,10-epiminoanthracenes (**89**) in good to excellent yields (Scheme 34).[75]



Scheme 34. Synthesis of isoindoles and 9,10-dihydro-9,10-epiminoanthracenes from münchnones.

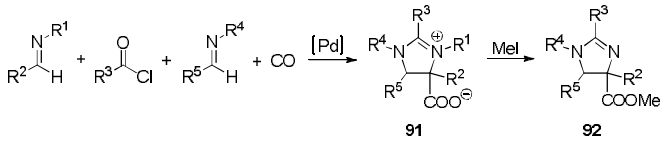
4-Trifluoroacetyl-1,3-oxazolium-5-olates undergo tandem addition of hydroxylamine to afford 6-trifluoromethyl-1,2,4-oxadiazin-6-ols (**90**) in high yields (Scheme 35).[76]



Scheme 35. Condensation of 4-trifluoroacetylmünchnones with hydroxylamine.

A palladium-catalyzed multicomponent synthesis of imidazolinium carboxylates (**91**) and imidazolines (**92**) has been described (Scheme 36). The palladium catalyst, either $[Pd(CH(R^1)N(R^2)COR^3)Cl]_2$ or $[Pd(allyl)Cl]_2$, together with $P(^tBu)_2$(2-biphenyl), can mediate the simultaneous coupling of two imines, acid chloride, and carbon monoxide into substituted imidazolinium carboxylates within hours under mild

conditions. The reaction proceeds in good yield with aryl-, heteroaryl-, and alkyl-substituted acid chlorides, as well as variously functionalized imines.[77]



91 **92**

Scheme 36. Palladium-catalyzed synthesis of imidazolinium carboxylates and imidazolines.

The transformation of münchnones into 1,3-thiazolium-5-thiolates (**93**) by reaction with CS_2 has been investigated in detail by means of both experimental and theoretical methods (Scheme 37). The synthetic strategy can be tuned to incorporate donor and acceptor groups in appropriate positions. Theoretical calculations showed that these sulfur-containing heterocycles exhibit nonlinear optical (NLO) responses, thereby pointing to potential applications of mesoionic structures in the promising field of NLO materials.[78]

93

Scheme 37. Synthesis of 1,3-thiazolium-5-thiolates from münchnones.

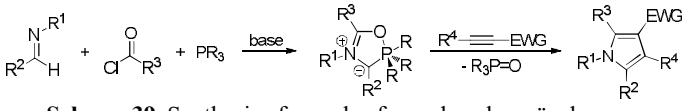
An improved preparation of 1,3-diazolium-4-thiolates (**94**) by [3+2] cycloadditions of münchnones with aryl isothiocyanates has also been reported (Scheme 38). The process took place with high or complete regioselectivity, and fast and clean transformations were observed under microwave heating in DMF. DFT calculations support that this cycloaddition proceeds preferably through a stepwise mechanism. Depending on the substitution pattern around the mesoionic ring, which results in a push-pull system, theoretical estimations predict large hyperpolarizabilities in a few cases, characteristic of molecules exhibiting nonlinear optical responses.[79]

94

Scheme 38. Synthesis of 1,3-diazolium-4-thiolates from münchnones.

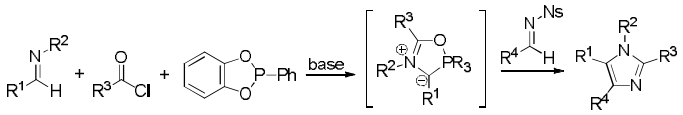
3.4. Phospha-münchnones

The reaction of imines, acid chlorides, PR_3, and base generates phospha-münchnones. These heterocycles undergo cycloadditions with alkynes followed by loss of phosphine oxides to form pyrroles (Scheme 39). The reactivity in cycloadditions is dependent upon the PR_3 employed. Electron-poor phosphonites and phosphites favor a cyclic 1,3-dipolar structure, while electron-rich phosphines instead favor the valence tautomers, acyclic ylides. The reactions of these dipoles with monosubstituted alkynes bearing an electron-withdrawing group occur through stepwise mechanisms. The presence of the phosphorus unit creates a large electronic bias across the 1,3-dipole, allowing for regioselective cycloadditions with substituted alkynes.[80]



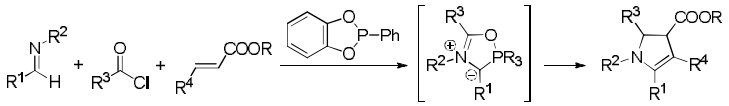
Scheme 39. Synthesis of pyrroles from phospha-münchnones.

A new, one pot synthesis of imidazoles from imines, acid chlorides and *N*-nosyl imines or tethered nitriles has been reported. The reaction is mediated by the phosphonite PPh(catechyl), and proceeds *via* regioselective cycloaddition with an *in-situ* generated phospha-münchnone. This provides an efficient route to construct both highly-substituted and polycyclic imidazoles directly from available substrates, without metal catalysts (Scheme 40).[81]



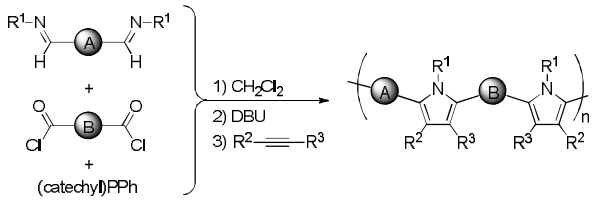
Scheme 40. Synthesis of imidazoles from phospha-münchnones.

The cycloaddition of phospha-münchnones with alkenes has been studied as well. This cycloaddition enables a one-pot route to synthesize 2-pyrrolines in moderate yield from imines, acid chlorides and alkenes (Scheme 41).[82]



Scheme 41. Synthesis of 2-pyrrolines from phospha-münchnones.

A metal-free multicomponent approach to conjugated polymers should be finally noted. This reaction exploits the coupling of imines, acid chlorides, and (catechyl)PPh to generate phospha-münchnone containing polymers, which can be converted to poly(pyrroles) *via* cycloaddition. The platform allows for the efficient synthesis of families of high-molecular weight polymers in one step from readily available monomers (Scheme 42).[83]



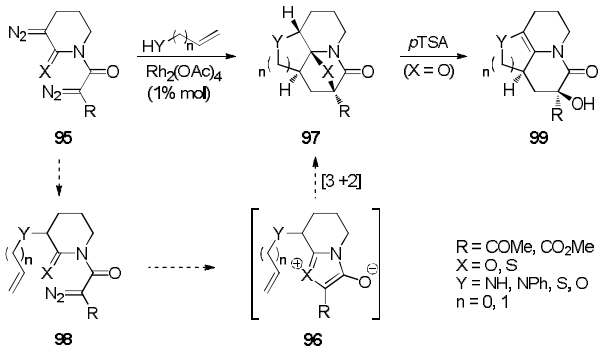
Scheme 42. Synthesis of conjugated polymers from polymeric phospha-münchnones.

4. Isomünchnones and thioisomünchnones

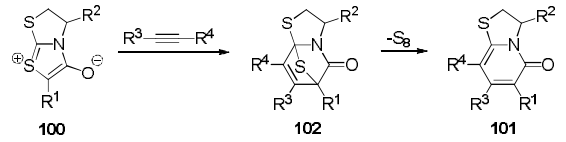
Positional isomers such as isomünchnones and their thio-counterparts, thioisomünchnones, have been exploited successfully in dipolar cycloadditions, although applications are limited relative to other mesoionic rings. Bis-diazocompounds **95** can be employed to generate isomünchnones (and thioisomünchnones) such as **96**, which have been found to be intermediates for the synthesis of fused quinolizinones **97**.[84] The formation of these substances can be rationalized by an initial chemoselective insertion of the Y–H bond of an amine, thiol or alcohol to give **98** (Scheme 43). Then, in the presence of Rh(II) species as catalyst, the remaining diazo group participates in the formation of the mesoionic heterocycles (**96**), which undergo an intramolecular 1,3-dipolar cycloaddition with the attached dipolarophile giving rise to quinolizinones **97** in a diastereoselective manner. Additionally, the acid-catalyzed ring opening of these systems furnished heterocyclic alcohols **99** with complete regioselectivity.

Cycloaddition reactions involving thioisomünchnones have been widely studied with a range of dipolarophiles such as alkynes,[84-86] azodicarboxylates,[87] azodicarboxamides,[88] and isothiocyanates.[89,90] As shown above, the formation of bridged quinolizinones (**97**, Scheme 43) took place by intramolecular cycloaddition of the pendant alkene on thioisomünchnones **96**.[84] Another approach, consisting of

cycloaddition reactions of bicyclic thioisomünchnones **100** with asymmetrically-substituted alkynes, was found to be an efficient method for the synthesis of thiazolo[3,2-a]pyridines **101** (Scheme 44). These transformations proceeded with complete regioselectivity, as suggested by DFT calculations, and involved formation of non-isolated cycloadducts (**102**) followed by a two-step extrusion of sulfur, giving rise to pyridine derivatives **101**.[85,86]

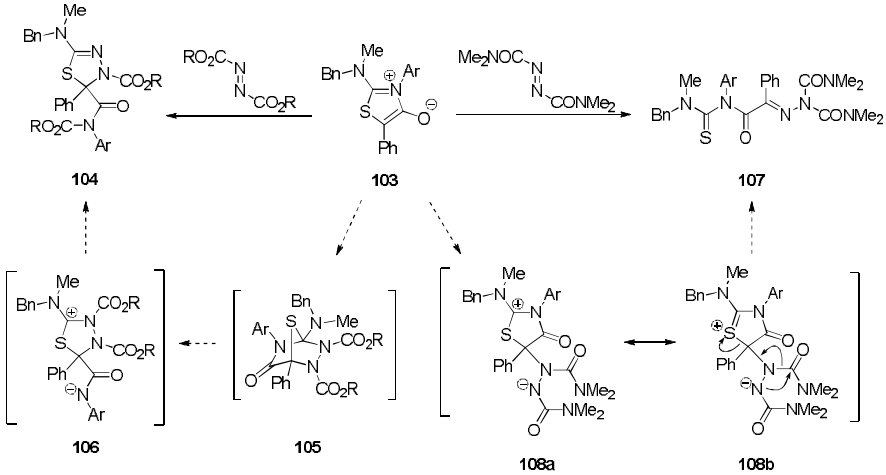


Scheme 43. Regioselective synthesis of fused quinolizinones **97** *via* intramolecular cyclization of isomünchnones/thioisomünchnones (**96**).



Scheme 44. Cycloadditions of thioisomünchnones **100** with asymmetrically-substituted alkynes.

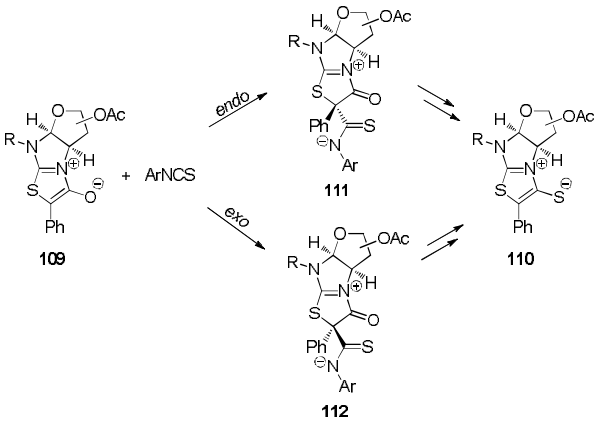
Thioisomünchnones **103** have shown a distinct behavior on reactions with azodipolarophiles (Scheme 45). The use of azodicarboxylates led to 1,3,4-thiadiazoles **104**, and the proposed mechanism of such a transformation involves a one-pot cycloaddition reaction to **105**, further fragmentation to **106** and final intramolecular nucleophilic substitution to afford **104**.[87]



Scheme 45. Reactivity of thioisomünchnones **103** with azodipolarophiles.

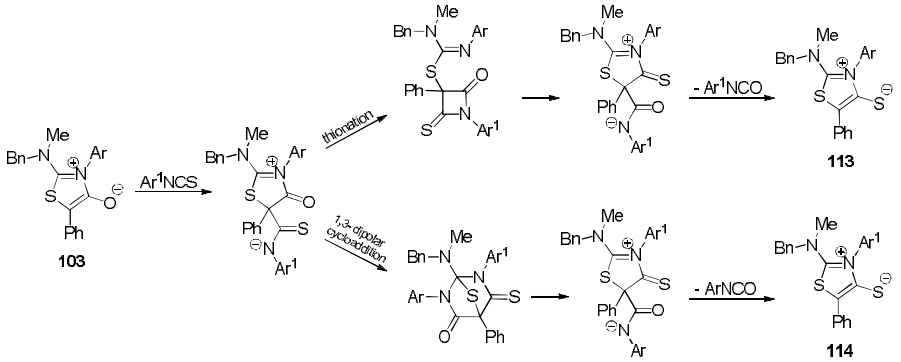
However, when azodicarboxamides were employed, the reaction with the same mesoionic heterocycles yielded thioureido compounds (**107**). Experimental data, supported by computational calculations at the DFT level, suggest an initial nucleophilic addition to give **108**, which subsequently undergoes a rearrangement as plausible mechanism, although a formal cycloaddition-fragmentation process cannot be ruled out either.[88]

The reaction of bicyclic thioisomünchnones **109** with aryl isothiocyanates gave rise to the corresponding thiolates **110** (Scheme 46).[89] The mechanism of this transformation was corroborated by isotopic exchange experiments and by ONIOM-based computational calculations. The formation of 1,3-thiazolium-4-thiolates **110** was explained by a multi-step domino process (see below for a complete thionation mechanism) throughout intermediates **111** (*endo* approach) and **112** (*exo* approach).



Scheme 46. Multi-step domino thionation of thioisomünchnones **109** with aryl isothiocyanates.

However, the reaction of monocyclic thioisomünchnones **103** with aryl isothiocyanates led to mixtures of the thiolates **113** and **114**.[90] These transformations, significantly improved at high temperatures either using microwave irradiation or conventional heating, can take place through two competitive stepwise pathways: thionation (as shown above) or 1,3-dipolar cycloaddition, which were found to be largely dependent on the substitution of the aromatic rings (Scheme 47). Again, ONIOM-based computational calculations were consistent with the experimental findings.

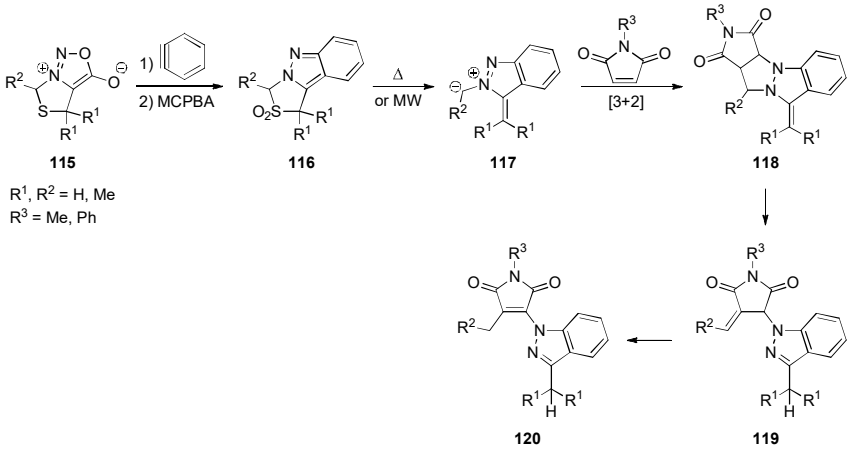


Scheme 47. Thionation *versus* cycloaddition reactions of thioisomünchnones **103** with aryl isothiocyanates.

5. Other mesoionic dipoles

5.1. 1,2-Diazoimines

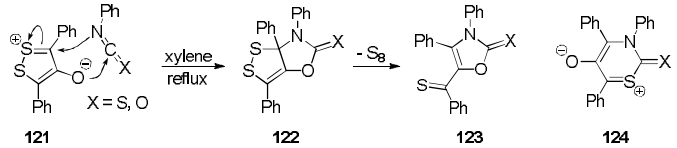
The first example of 1,3-dipolar cycloadditions of thiazolidine-based sydnones (**115**) with dipolarophiles such as benzyne is shown in Scheme 48. Sulfones **116** were formed by oxidation with *m*-chloroperoxybenzoic acid (MCPBA) and underwent SO_2 extrusion either with conventional heating or under microwave irradiation giving rise to benzo-2,3-diazafulvenium methides (**117**). These intermediates were then trapped with *N*-methyl and *N*-phenylmaleimide through an initial [3+2] cycloaddition, followed by pyrazolidine ring-opening and a sigmatropic H-shift affording 1*H*-indoles (**120**). The experimental findings were supported by DFT calculations, thus providing a mechanistic rationale.[34]



Scheme 48. Synthesis of new 1*H*-indazoles (**120**) from 1,3-dipolar cycloadditions of sydnone derivatives (**115**) and benzodiazafulvenium methides (**117**).

5.2. 1,2-Dithiol-4-ones

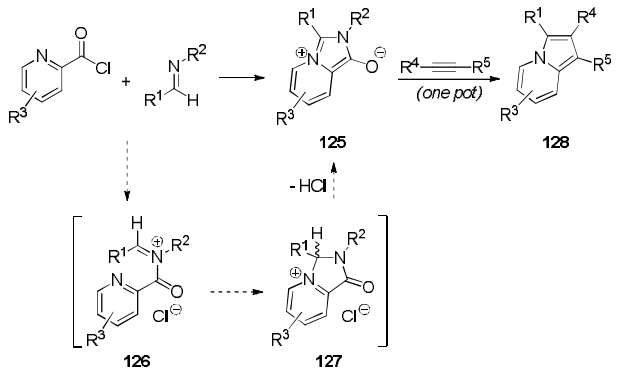
The type B mesoionic **121** undergoes cycloaddition reactions with phenyl isocyanate and phenyl isothiocyanate to give rise to thioketones **123**, rather than mesomeric betaines such as **124** (Scheme 49).[91] The proposed mechanism would explain the formation of **123** *via* [3+2] cycloaddition to **122** and subsequent dithiolene ring opening and sulfur elimination. The structure of thioketone, originally proposed by Rowson,[92] was unequivocally confirmed by single crystal X-ray diffraction analysis.



Scheme 49. Cycloadditions of **121** with phenyl isocyanate and phenyl isothiocyanate.

5.3. 1,3-Diazol-4-ones

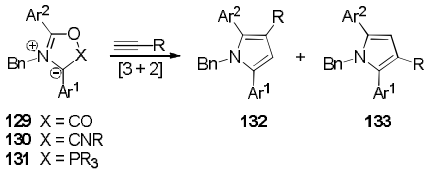
The synthesis of a new type of bicyclic mesoionic heterocycles (**125**) has been recently reported by the reaction of imines and pyridine-derived acid chlorides (Scheme 50).[93] The structure of 1,3-dipole was confirmed by X-ray diffraction analysis. These derivatives reacted rapidly with alkynes, thereby unveiling a simple one-pot procedure to prepare a large variety of indolizines (**128**) from readily available building blocks. As shown below, the formation of dipoles **125** from the starting materials should likely involve the intermediacy of species **126** and its evolution to **127** prior to HCl elimination.



Scheme 50. One-pot synthesis of indolizines **128**.

5.4. 1,3-Oxazol-5-imines

The reactivity and selectivity of the 1,3-dipolar cycloaddition of mesoionic heterocycles such as münchnones **129**, imino-münchnones **130**, and phospha-münchnones **131** with alkynes to generate pyrroles (**132** and/or **133**) have been investigated in detail (Scheme 51).[94] The ionization potential of the dipolarophile, estimated by DFT calculations, seems to be the factor accounting for the reactivity and regioselectivity observed. Thus, münchnones (**129**) and phospha-münchnones (**131**) were more reactive against electron-deficient alkynes (in correlation with the computed ionization potential). On the contrary, regioselectivities were found to correlate with the ionization potential in an inverse manner. Moreover, cycloaddition reactions involving phospha-münchnones (**131**) with electron-poor alkynes were highly regioselective towards the formation of **132**, while münchnones (**129**) exhibited a marked regioselectivity towards **133** by reaction with electron-rich alkynes. Imino-münchnones **130** showed better selectivities than münchnones against electron-poor alkynes, although not as good as those found for phospha-münchnones.



Scheme 51. Cycloadditions of münchnones (**129**), imino-münchnones (**130**) and phospha-münchnones (**131**) with alkynes.

6. Conclusions

We have shown the versatility and wide scope of mesoionic heterocycles in cycloaddition reactions, still a must in synthetic methods. By concentration on a few well-known mesoionic dipoles, this account gives a glimpse on key aspects like molecular diversification, functional-group compatibility, chain elongation, or ring opening/contraction, illustrated by numerous examples during the last decade. More critical issues of regio- and stereoselection will require further attention to achieve complete control, although in some cases excellent results have been reported in high-yielding synthesis. Theoretical calculations not only provide mechanistic insights accounting for experimental results, but they also open the door to new synthetic explorations. Even if mesoionic rings are underestimated synthons, these heterocycles, easily generated and stable enough, should now be regarded as a valuable choice in so varied fields like synthesis of natural products and analogs, including pharmaceuticals, preparation of heteroatom-containing novel materials, or bioorthogonal labeling *via* click-type cycloadditions. The fact that mesoionics can also be transformed into numerous heterocycles, even into other mesoionic dipoles and betaines, make them important ingredients of the organic toolbox for years to come.

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References

1. Baker, W.; Ollis, W. D. *Quart. Rev. (London)* **1957**, *11*, 15-29.
2. Ollis,W. D.; Ramsden, C. A. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, J. A., Eds.; Academic Press: London, 1976; Vol. 19, pp. 1-122.
3. Champagne, P. A.; Houk, K. N. *J. Org. Chem*. **2017**, *82*, 10980-10988 and references cited therein.
4. Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239-2329.
5. Ramsden, C. A. *Tetrahedron* **2013**, *69*, 4146-4159.
6. Moderhack, D. *Heterocycles* **2016**, *92*, 185-233.
7. Oziminski,W. P.; Ramsden, C. A. *Tetrahedron* **2015**, *71*, 7191-7198.
8. Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445-3478.
9. Crabtree, R. H. *Coord. Chem. Rev.* **2013**, *257*, 755-766.
10. Schmidt, A.; Wiechmann, S.; Freese, T. *Arkivoc* **2013**, (*i*), 424-469.
11. Lopchuk, J. M. *Top. Heterocycl. Chem.* **2012**, *29*, 381-414.
12. Albrecht, M. In *Advances in Organometallic Chemistry*; Pérez, P. J., Ed.; Academic Press: London, 2014; Vol. 62, pp. 111-158.
13. Kawase, M.; Sakagami, H.; Motohashi, N. *Top. Heterocycl. Chem.* **2009**, *16*, 135-152.
14. Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; Vol. 2, pp. 1-82.
15. Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123-141.
16. Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp. 681-753.
17. Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Acc. Chem. Res.* **2005**, *38*, 460-468.
18. Browne, D. L.; Harrity, J. P. A. *Tetrahedron* **2010**, *66*, 553-568.
19. Bhosale, S. K.; Deshpande, S. R.; Wagh, R. D. *J. Chem. Pharm. Res.* **2012**, *4*, 1185-1199.
20. Chandrasekhar, R.; Nanjan, M. J. *Mini-Rev. Med. Chem.* **2012**, *12*, 1359-1365.
21. Foster, R. S.; Huang, J.; Vivat, J. F.; Browne, D. L.; Harrity, J. P. A. *Org. Biomol. Chem.* **2009**, *7*, 4052-4056.
22. Nassoy, A-C.; Raubo, P.; Harrity, J. P. A. *Tetrahedron Lett*. **2013**, *54*, 3094-3096.
23. Wang, L-I.; Chang, E.-C.; Yeh, M.-Y.; Chung, Y. H.; Huang, J.-J.; Wong, F. F. *Heteroatom Chem*. **2014**, *25*, 171-177.
24. Foster, R. S.; Adams, H.; Jakobi, H.; Harrity, J. P. A. *J. Org. Chem*. **2013**, *78*, 4049-4064.
25. Foster, R. S; Jakobi, H.; Harrity, J. P. A. *Tetrahedron Lett.* **2011**, *52*, 1506-1508.
26. Browne, D. L.; Vivat, J. F.; Plant, A.; Gomez-Bengoa, E.; Harrity, J. P. A. *J. Am. Chem. Soc*. **2009**, *131*, 7762-7769.
27. Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J-P.; Monteiro, N.; Balme, G. *Org. Lett*. **2010**, *12*, 3328-3331.
28. Delaunay, T.; Es-Sayed, M.; Vors, J.-P.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem*. **2011**, 3837-3848.
29. Chang, E.-C.; Wen, Y.-L.; Chang, C.-H.; Shen, Y.-H.; Wen, S.-B.; Yeh, M.-Y.; Wong, F. F. *Tetrahedron* **2012**, *68*, 5920-5924.
30. Browne D. L.; Taylor, J. B.; Plant, A.; Harrity, J. P. A. *J. Org. Chem*. **2009**, *74*, 396-400.
31. Brown, A. W.; Harrity, J. P. A. *J. Org. Chem*. **2015**, *80*, 2467-2472.
32. Brown, A. W.; Fisher, M.; Tozer, G. M.; Kanthou, C.; Harrity, J. P. A. *J. Med. Chem*. **2016**, *59*, 9473-9488.
33. Fang, I.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem*. **2011**, *76*, 8840-8851.

34. Soares, M. I. L.; Nunes, C. M.; Gomes, C. S. B.; Pinho e Melo, T. M. V. D. *J. Org. Chem*. **2013**, *78*, 628-637.
35. Harju, K.; Vesterinen, J.; Yli-Kauhaluoma, J. *Org. Lett*. **2009**, *11*, 2219-2221.
36. Comas-Barceló, J.; Foster, R. S.; Fiser, B.; Gómez-Bengoa, E.; Harrity, J. P. A. *Chem. Eur. J*. **2015**, *21*, 3257-3263.
37. Specklin, S.; Decuypere, E.; Plougastel, L.; Aliani, S.; Taran, F. *J. Org. Chem*. **2014**, *79*, 7772-7777.
38. Decuypere, E.; Specklin, S.; Gabillet, S.; Audisio, D.; Liu, H.; Plougastel, L.; Kolodych, S.; Taran F. *Org. Lett*. **2015**, *17*, 362-365.
39. Wezeman, T.; Comas-Barceló, J.; Nieger, M.; Harrity, J. P. A.; Bräse, S. *Org. Biomol. Chem*. **2017**, *15*, 1575-1579.
40. Liu, H.; Audisio, D.; Plougastel, L.; Decuypere, E.; David-Alexandre, B.; Koniev, O.; Kolodych, S.; Wagner, A.; Elhabiri, M.; Krzyczmonik, A.; Forsback, S.; Solin, O.; Gouverneur, V.; Taran, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 12073-12077.
41. Brown, A. W.; Comas-Barceló, J.; Harrity, J. P. A. *Chem. Eur. J*. **2017**, *23*, 5228-5231.
42. Comas-Barceló, J.; Blanco-Ania, D.; vand den Broek, S. A. M. W.; Nieuwland, P. J.; Harrity, J. P. A.; Rutjes, P. J. T. F. *Catal. Sci. Technol*. **2016**, *6*, 4718-4723.
43. Liu, F.; Liang, Y.; Houk, K, N. *Acc. Chem. Res*. **2017**, *50*, 2297-2308.
44. Kolodych, S.; Rasolofonjatovo, E.; Chaumontet, M.; Nevers, M.-C.; Créminon, C.; Taran, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 12056-12060.
45. Wallace, S.; Chin, J. W. *Chem. Sci*. **2014**, *5*, 1742-1744.
46. Narayanam, M. K.; Liang, Y.; Houk, K. N.; Murphy, J. M. *Chem. Sci*. **2016**, *7*, 1257-1261.
47. Hornum, M.; Kumar, P.; Podsiadly, P.; Nielsen, P. *J. Org. Chem*. **2015**, *80*, 9592-9602.
48. Yang, Y.; Kuang, C.; Jin, H.; Yang, Q.; Zhang, Z. *Beilstein J. Org. Chem*. **2011**, *7*, 1565-1662.
49. Cheng, F.; Liu, F.-M.; Shi, H.; Cheng, S.-L. *Monatsh. Chem*. **2013**, *144*, 879-884.
50. Zeng, Y.; Liu, F. *J. Heterocyl. Chem*. **2013**, *50*, 696-702.
51. Yang. Y.; Kuang. C. *Synthesis* **2015**, *47*, 2281-2284.
52. Butkovic, K.; Marinic, Z.; Molcanov, K.; Kojic-Prodic, B.; Sindler-Kulyc, M. *Beilstein J. Org. Chem.* **2011**, *7*, 1663-1670.
53. Intemann, J. J.; Huang, W.; Jin, Z.; Shi, Z.; Yang, X.; Yang, J.; Luo, J.; Jen, A. K.-Y. *ACS Macro Lett.* **2013**, *2*, 256-259.
54. Huang, W.; Jin, Z.; Shi, Z.; Intemann, J. J.; Li, M.; Luo, J.; Jen, A. K.-Y. *Polym. Chem*. **2013**, *4*, 5760-5767.
55. Handa, N. V.; Li, S.; Gerbec; J. A.; Sumitani, N.; Hauker, C. J.; Klinger, D. *J. Am. Chem. Soc*. **2016**, *138*, 6400-6403.
56. Lawson, A.; Miles, D. H. *Chem. Ind. (London)* **1958**, 461-462.
57. Huisgen, R.; Gotthardt, H.; Bayer, H. O. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 136-137.
58. Reissig, H.-U.; Zimmer, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 9708-9710.
59. Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474-1475.
60. Lu, Y.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 5430-5433.
61. Leitch, D. C.; Kayser, L. V.; Han, Z.-Y.; Siamaki, A. R.; Keyzer, E. N.; Gefen, A.; Arndtsen, B. A. *Nat. Commun.* **2015**, *6*, 7411-7418.
62. Tjutrins, J.; Dhawan, R.; Lu, Y.; Arndtsen, B. A. *Chem. Eur. J.* **2016**, *22*, 15945-15954.
63. Torres, G. M.; Quesnel, J. S.; Bijou, D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2016**, *138*, 7315-7324.
64. Firoozi, N.; Torres, G. M.; Arndtsen, B. A. *J. Org. Chem.* **2016**, *81*, 11145-11152.
65. Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882-3890.
66. Tokuyama, H. *J. Synth. Org. Chem. Jpn.* **2015**, *73*, 1120-1129.
67. Sugimoto, K.; Miyakawa, Y.; Tokuyama, H. *Tetrahedron*, **2015**, *71*, 3619-3624.
68. Lopchuk, J. M.; Gribble, G. W. *Tetrahedron Lett.* **2015**, *56*, 3208-3211.
69. Lopchuk, J. M.; Gribble, G. W. *Heterocycles* **2011**, *82*, 1617-1631.
70. Lopchuk, J. M.; Song, M.; Butler, B.; Gribble, G. W. *Synthesis* **2015**, *47*, 2776-2780.
71. Marco-Martínez, J.; Reboredo, S.; Izquierdo, M.; Marcos, V.; López, J. L.; Filippone, S.; Martín N. *J. Am. Chem. Soc.* **2014**, *136*, 2897-2904.

72. Cordaro, M.; Grassi, G.; Rescifina, A.; Chiacchio, U.; Risitano, F.; Scala, A. *Tetrahedron* **2011**, *67*, 608-611.
73. Mazgarova, G. G.; Fatykhov, A. A.; Gataullin, R. R. *Russ. J. Org. Chem.* **2014**, *50*, 1155-1160.
74. Lopchuk, J. M.; Hughes, R. P.; Gribble, G. W. *Org. Lett.* **2013**, *15*, 5218-5221.
75. Fang, Y.; Larock, R. C.; Shi, F. *Asian J. Org. Chem.* **2014**, *3*, 55-57.
76. Saijo, R.; Kurihara, K.; Akira, K.; Kawase, M. *Heterocycles* **2013**, *87*, 115-123.
77. Worrall, K.; Xu, B.; Bontemps, S.; Arndtsen, B. A. *J. Org. Chem.* **2011**, *76*, 170-180.
78. Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C.; Rodríguez, V. *Org. Biomol. Chem.* **2010**, *8*, 5367-5374.
79. Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C.; Porro, R. *J. Org. Chem.* **2014**, *79*, 4201-4205.
80. St-Cyr, D. J.; Morin, M. S. T.; Bélanger-Gariépy, F.; Arndtsen, B. A.; Krenske, E. H.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 4261-4273.
81. Aly, S.; Romashko, M.; Arndtsen, B. A. *J. Org. Chem.* **2015**, *80*, 2709-2714.
82. Jackiewicz, V.; Arndtsen, B. A. *Synlett* **2017**, *28*, 433-438.
83. Kayser, L. V.; Vollmer, M.; Welnhofer, M.; Krikcziokat, H.; Meerholz, K.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2016**, *138*, 10516-10521.
84. Muthusamy, S.; Gangadurai, C. *Synthesis* **2016**, *48*, 2213-2225.
85. García de la Concepción, J.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron* **2016**, *72*, 4665-4670.
86. García de la Concepción, J.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron* **2017**, *73*, 1551-1560.
87. Sánchez, B.; Bravo, J. L.; Arévalo, M. J.; López, Ignacio; Light, Mark E.; Silvero, G. *Aust. J. Chem.* **2009**, *62*, 356-359.
88. Sánchez, B.; López, Ignacio; Light, Mark E.; Silvero, G.; Bravo, J. L. *Eur. J. Org. Chem.* **2010**, 1648-1652.
89. Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *J. Org. Chem.* **2009**, *74*, 3698-3705.
90. Cantillo, D.; Ávalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *J. Org. Chem.* **2009**, *74*, 7644-7650.
91. Probert, M. R.; Ramsden, C. A.; Stanforth, S. P. *Tetrahedron Lett.* **2017**, *58*, 1425-1427.
92. Rowson, G. P. *Ph.D. thesis*, University of Sheffield, **1976**.
93. Erguven, H.; Leitch, D. C.; Keyzer, E. N.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 6078-6082.
94. Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A.; Krenske, E. H.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 17349-17358.