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1,3-DIPOLAR CYCLOADDITIONS IN AQUEOUS MEDIA

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Dedicated to Professor Gaetano Zecchi on the occasion of his 65th birthday.

Abstract – 1,3-Dipolar cycloadditions in aqueous media represents a useful, non conventional protocol in the synthesis of a variety of five-membered heterocycles. In addition, water as the solvent may significantly enhance cycloaddition rates and/or stereoslectivities. The literature data on this subject are reviewed in a systematic way, with an emphasis to improvements with respect to cycloadditions performed in the usual, non-aqueous conditions.

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I. INTRODUCTION

As a matter of fact, the overwhelming majority of organic reactions are carried out in non-aqueous media, since a large number of classic synthetic methodologies are currently developed in anhydrous solvents and/or under an inert atmosphere. This generally lead to a strict exclusion of water from reaction mixtures contributing to make organic transformations carried out in water or in aqueous mixtures as chemical curiosities, thus neglecting their synthetic utility. However, despite the aggressive nature of water towards many classes of organic functionalities, there has been a rediscovery of water-promoted organic reactions in recent years, as is testifed by a number of authoritative reviews[1-3] and books.[4] Very fashinating topics like stereoselective organic reactions in aqueous media,[5] the development of novel Lewis acid catalysts for such transformations[6] and catalytic asymmetric C-C bond formation in aqueous media[7] have also been

recently reviewed. This trend is a consequence of the fact that water itself displays a number of desirable features: (*i*) the pH of the reaction medium can be easily controlled, (*ii*) reaction rates can be significantly increased, (*iii*) product separation can often be achieved by simple filtration of the crude reaction mixture, and (*iv*) environmentally-friendly procedures can be successfully elaborated. Among the organic transformations which appear to benefit from aqueous media, Diels-Alder reactions[8] and the closely related 1,3-dipolar cycloadditions occupy a prominent place from long time. In focusing on 1,3-dipolar cycloadditions, early contributions by Grundmann described nitrile oxide cycloadditions in biphasic aqueous-organic mixtures,[9] and later further examples of dipolar cycloadditions in water or aqueous media have been expanded to cover nitrile oxide,[10] azomethine ylide[11] and azide[12] cycloaddition chemistry. Despite all these efforts, little space have been deserved for 1,3-dipolar cycloadditions in general reviews concerned to water-promoted organic reactions.[1-3] The aim of this paper is to present the first review devoted to the growing field of 1,3-dipolar cycloadditions carried out in aqueous media in a systematic way according to the type of the 1,3-dipole. Emphasis will be given to improvements with respect to cycloadditions performed in the usual, non-aqueous conditions.

II. NITRILIUM BETAINES

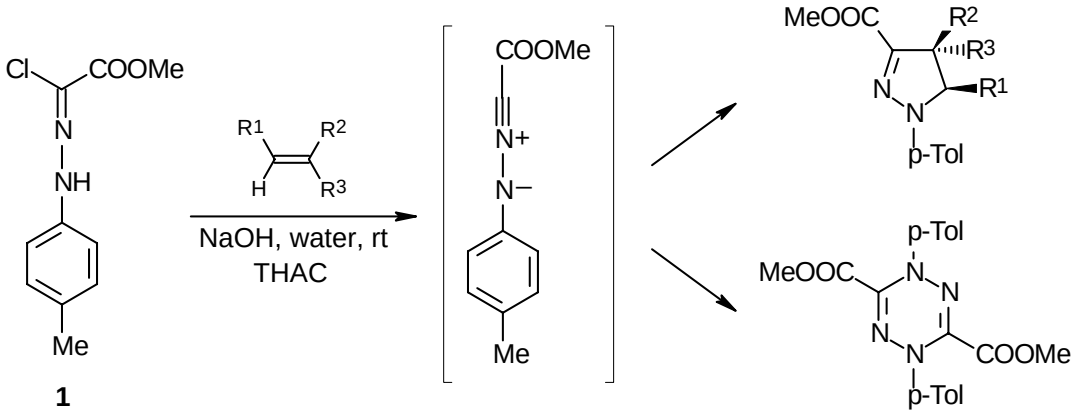
The presentation of cycloadditions performed in aqueous media involving nitrilium betaines is divided into two parts. First, nitrilimine cycloadditions; then reactions in which nitrile oxides acts as the dipolar reagent. No literature data are known on nitrile ylides, the other main representative of nitrilium betaines.

II.1. Nitrilimine cycloadditions in aqueous media

It is well known that the *in situ* generation of nitrilimines from the corresponding hydrazonoyl chlorides occurs in homogeneous phase by base treatment of the latter.[13] However, dipolar cycloadditions between nitrilimine (**1**) and a variety of alkenyl dipolarophiles were successfully performed by mechanical shaking of a heterogeneous mixture of the reactants in aqueous 0.1 M sodium hydroxide as the base and in the presence of tetrahexylammonium chloride (THAC) as the catalyst (Scheme 1).[14] Since sizeable amounts of tetrazine by-product (**2**) were obtained in some cases, further work was concerned with the refinement of the above method. The best results were obtained by mechanical shaking of a heterogeneous mixture of the reactants with aqueous sodium carbonate in the presence of THAC at room temperature (Scheme 2, Table 1).[15] Some of the nitrilimine-alkene cycloadditions carried out in aqueous media were subjected to significant rate acceleration in comparison with similar water-free cycloadditions. It seems that hydrophobic effect[16] causes the close association of organic reactants, and the catalyst acts as a genuine phase transfer catalyst driving the basic agent from the bulk aqueous medium into the organic aggregate. The generation of the labile nitrilimine intermediate would then occur into the organic aggregate, which is characterised by a high local concentration of the dipolarophile.

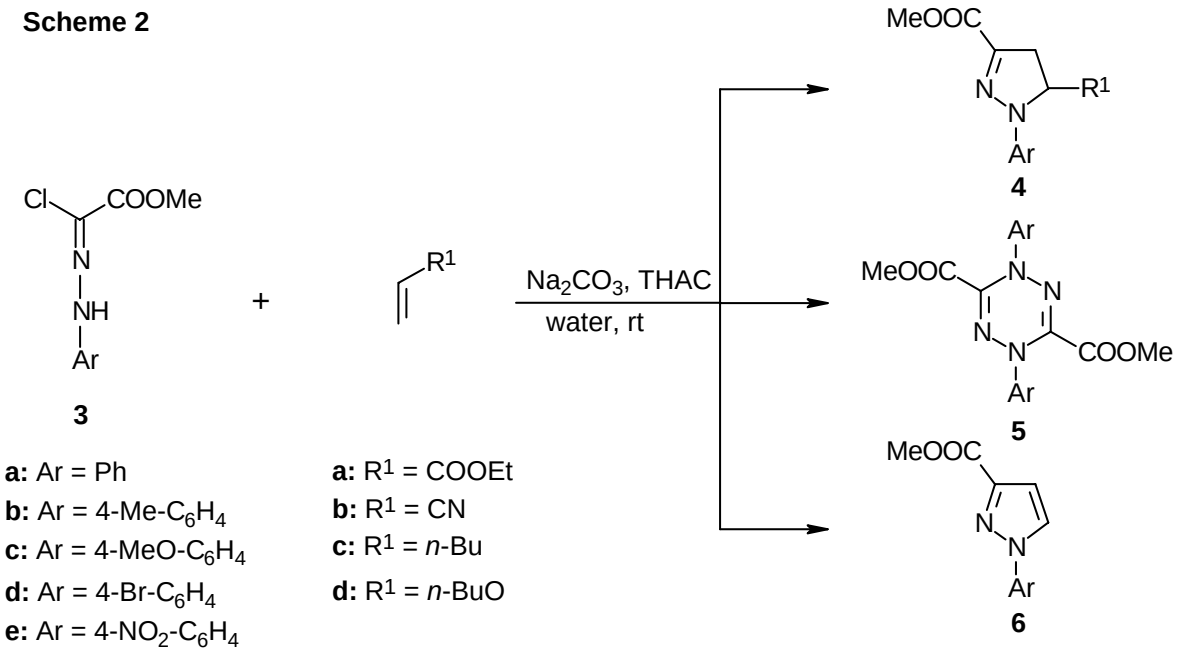
The best results obtained with electron-poor dipolarophiles and electron-rich nitrilimines reflects the usual HOMO-dipole (LUMO-dipolarophile) controlled nature of nitrilimine cycloadditions.[17] To provide an adequate level of theory for the cycloadditions under investigation, a computational effort was undertook at the HF/IPCM and DFT/B3LYP/IPCM level also taking into account explicit water molecules.[18]

Scheme 1



Entry	R^1	R^2	R^3
a	COOEt	H	H
b	-$OCH_2CH_2CH_2$-		H
c	CN	H	H
d	COOMe	H	COOMe
e	COOEt	H	Me
f	CH_2OH	H	H
g	COONa	H	H

Scheme 2



a: Ar = Ph
b: Ar = 4-Me-C_6H_4
c: Ar = 4-MeO-C_6H_4
d: Ar = 4-Br-C_6H_4
e: Ar = 4-NO_2-C_6H_4

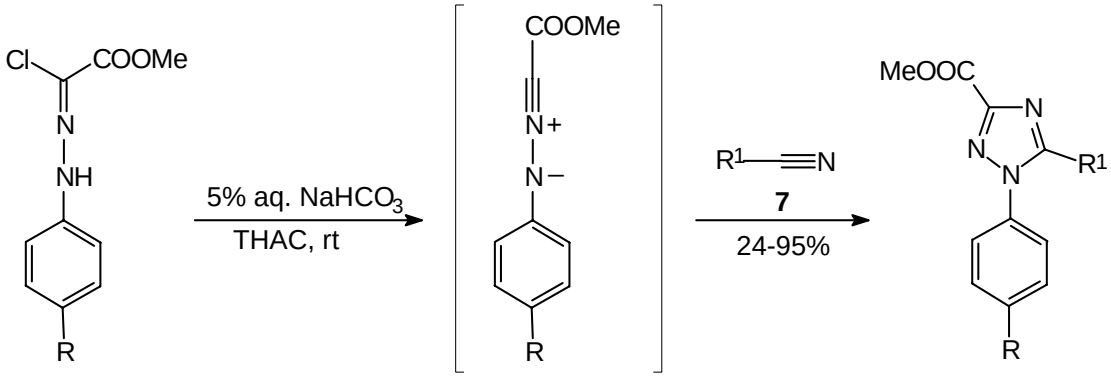
a: R^1 = COOEt
b: R^1 = CN
c: R^1 = *n*-Bu
d: R^1 = *n*-BuO

Table 1. Cycloaddition between hydrazonoyl chlorides (**3**) and alkenes in aqueous media.

Entry	Ar	R^1	Time (min)	Products and yields (%)			
				(**3**)	(**4**)	(**5**)	(**6**)
1	Ph	COOEt	10	—	95	—	—
2	Ph	CN	70	10	56	26	—
3	Ph	*n*-Bu	90	5	17	42	—
4	Ph	*n*-BuO	150	—	—	—	15
5	4-Me-C_6H_4	COOEt	10	—	95	—	—
6	4-Me-C_6H_4	CN	60	—	78	—	—
7	4-Me-C_6H_4	*n*-Bu	90	9	31	25	—
8	4-Me-C_6H_4	*n*-BuO	105	—	24	21	15
9	4-MeO-C_6H_4	COOEt	10	—	93	—	—
10	4-MeO-C_6H_4	CN	45	—	80	—	—
11	4-MeO-C_6H_4	*n*-Bu	120	—	52	33	—
12	4-MeO-C_6H_4	*n*-BuO	180	—	27	15	28
13	4-Br-C_6H_4	COOEt	70	—	68	17	—
14	4-Br-C_6H_4	CN	105	8	30	43	—
15	4-Br-C_6H_4	*n*-Bu	105	—	—	67	—
16	4-Br-C_6H_4	*n*-BuO	90	—	25	27	29
17	4-NO_2-C_6H_4	COOEt	100	—	3	—	—
18	4-NO_2-C_6H_4	CN	180	—	—	—	—
19	4-NO_2-C_6H_4	*n*-Bu	360	12	—	—	—
20	4-NO_2-C_6H_4	*n*-BuO	360	—	10	—	10

Nitrilimine cycloadditions to nitriles constitutes a valuable entry to the 1,2,4-triazole ring.[19] This regioselective reaction occurs in cases where the cyano function is activated by conjugation or by an oxygen atom in the α position.[20] The usual reaction conditions are quite severe, since prolonged times in boiling benzene or in boiling neat nitrile dipolarophile are required. However, cycloadditions between nitrilimines and the cyano group of activated nitriles (**7**) were exploited in aqueous sodium hydrogencarbonate as reaction media in the presence of THAC as surfactant. Short reaction times and mild conditions were experienced affording 1-aryl-5-substituted 1,2,4-triazoles (**8**).[21]

Scheme 3



R = H, Me, F, Cl, NO_2
R^1= COOEt, COOBn, CCl_3

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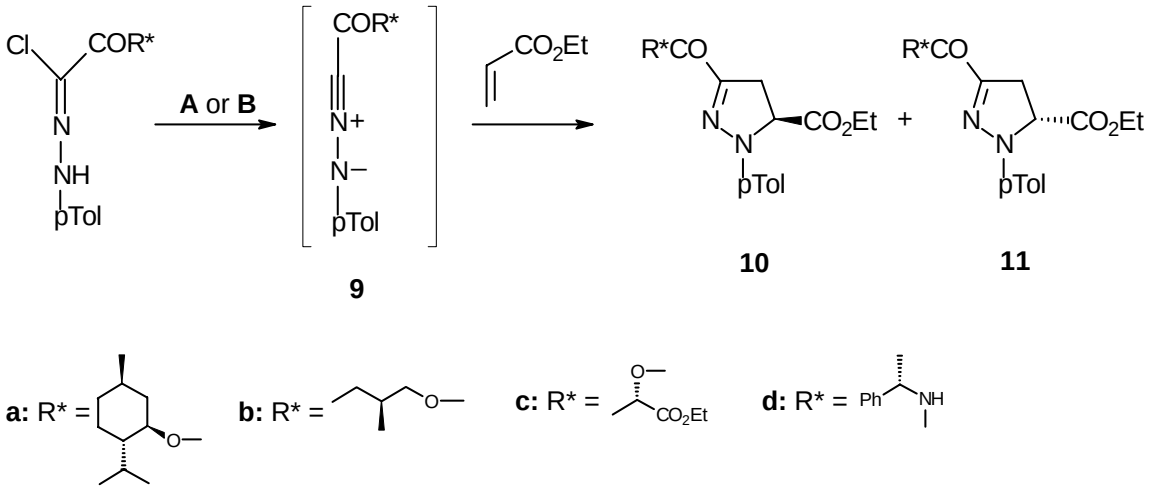
As far as diastereoselective cycloadditions are concerned, enantiopure nitrilimines (**9**) reacted with ethyl acrylate giving 4,5-dihydropyrazoles (**10**) and (**11**) (Scheme 4), which were separated by differential crystallisation. These cycloadditions were carried out through two different reaction conditions and media: (*i*) in dry toluene and in the presence of triethylamine (homogeneous conditions), and (*ii*) in aqueous sodium hydrogen carbonate (heterogeneous conditions).[22] It was noted that rate acceleration and better diastereoselectivity were experienced in aqueous media (Table 2). Furthermore, reaction work-up was greatly simplified.

Scheme 4



Method **A**: Et_3N, toluene, Δ; method **B**: aq. $NaHCO_3$, THAC, rt

Table 2. Cycloadditions of nitrilimines (**9**) to ethyl acrylate.

Nitrilimine	Method	Overall yield (%)	Stereoselective ratio (**10**):(**11**)
9a	**A**	80	60:40
9a	**B**	73	68:32
9b	**A**	81	65:35
9b	**B**	74	68:32
9c	**A**	43	57:43
9c	**B**	70	60:40
9d	**A**	40	65:35
9d	**B**	75	72:28

II.2. Nitrile oxide cycloadditions in aqueous media

Since a number of studies have been pursued within the field of nitrile oxide cycloadditions in aqueous media, this section will be further divided into four parts: *II.2.1*, theory and kinetics; *II.2.2*, intermolecular cycloadditions, *II.2.3*, intramolecular cycloadditions, and *II.2.4* synthetic applications.

II.2.1 Theory and kinetics

Ab initio MO calculations have been used to investigate structures and transition states of cycloadditions between benzonitrile oxide and ethylene, cyclopentene, acrylonitrile and tetracyanoethylene in heptane and water.[23] The difference of binding energies between the computed transition states and the reactants show enhanced hydrogen bonding of water to the transition state in the reaction with cyclopentene. The calculated interaction energies (0.70 kcal/mol) indicates that hydrogen bonding between the oxygen of the 1,3-dipole and an explicit water molecule does occur, thus it is expected the reaction should be accelerated in water. The same theoretical treatment was applied to the reaction between benzonitrile oxide and acrylonitrile and showed a reversed effect in good agreement with previous kinetic data.[24]

The second-order rate constants for the cycloaddition between benzonitrile oxide and a variety of ethylenic dipolarophiles were determined in aqueous media, namely: pure water, water-ethanol mixtures and micellar solutions.[25] Cycloadditions with electron-rich dipolarophiles were accelerated in water, whereas an aqueous medium had no special effects when electron-poor dipolarophiles were involved. These observations find explanation on the basis of the simple FMO theory[26] provided that (*i*) electron-rich dipolarophiles are weak hydrogen-bond acceptors, which means that their FMOs are only slightly affected by hydrogen bond interactions; (*ii*) the preferred complexation of nitrile oxides with Lewis acids[27] indicates that the former are good Lewis bases, hence the FMOs of these 1,3-dipolar species are stabilized in protic solvents; and (*iii*) FMOs of electron-poor dipolarophiles are stabilized by hydrogen bonding in a lesser extent than that of nitrile oxides (Figure 1).

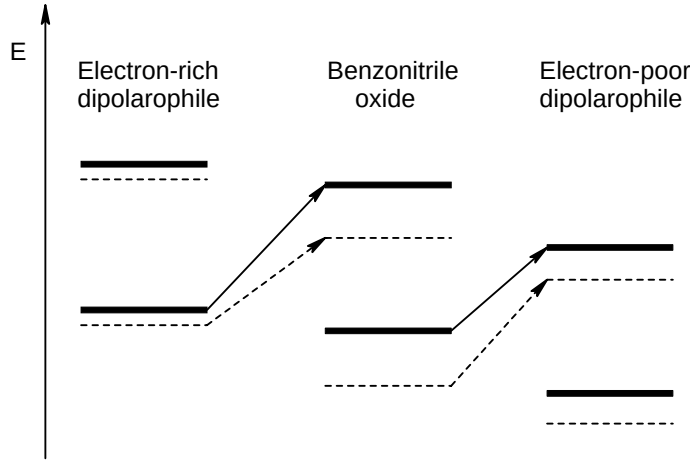


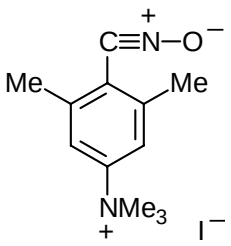
Figure 1. Schematic drawing of the FMO of electron rich dipolarophiles, electron poor dipolarophiles and benzonitrile oxide. The solid lines depict the FMOs in *n*-hexane, the dashed lines depict the FMOs in water.

A systematic study on the reactions of benzonitrile oxide with a series of *N*-alkyl maleimides showed modest solvent effects because hydrogen bonding occurs to both reactants with opposite effects; a pattern which can be rationalized within the frame of FMO theory.[28, 29]

The cycloaddition of 4-substituted benzonitrile oxides towards acrylonitrile in water follows a simple second-order kinetics, while Hammett σ values gave ρ = +0.36.[30] This small positive ρ value is consistent with previous values obtained in organic solvents for similar nitrile oxides.

II.2.2 Intermolecular cycloadditions

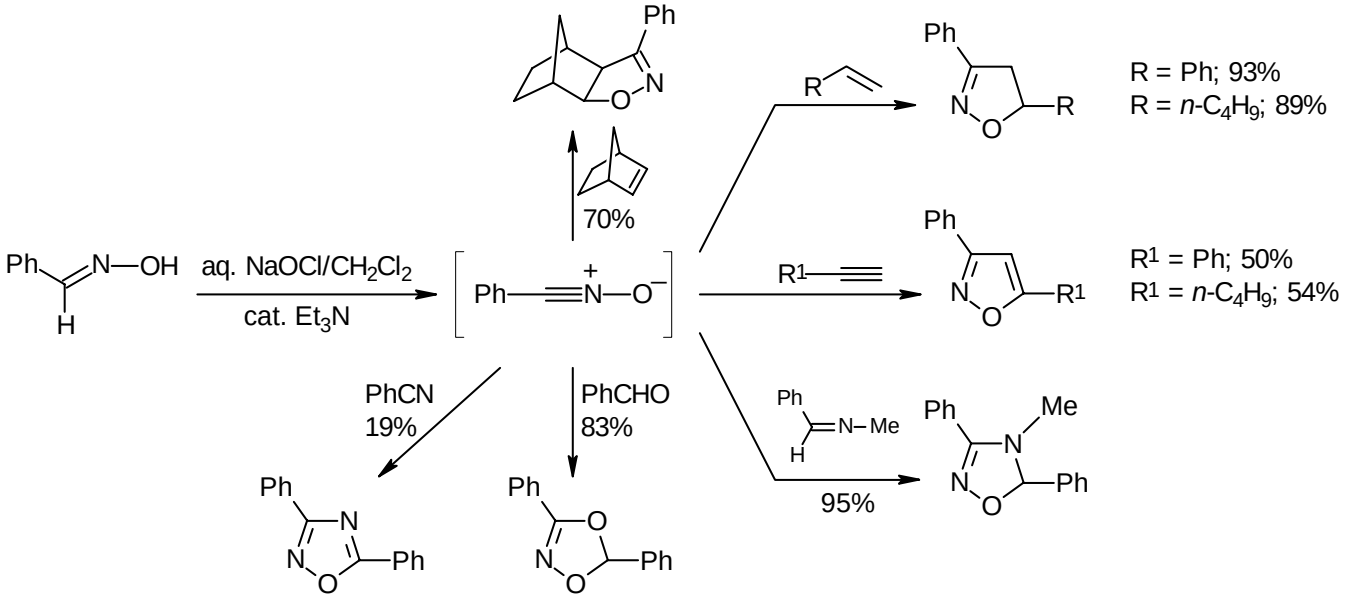
Since the discovery of the first water-soluble nitrile oxide, namely the iodide (**12**),[9] a number of studies dealing with the intermolecular nitrile oxide cycloadditions in aqueous media have been done.



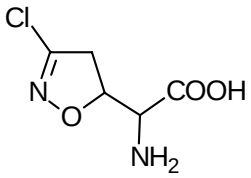
12

A very simple procedure for the generation *in situ* of benzonitrile oxide, which provides a convenient one-pot procedure to a number of heterocycles, rely upon a biphasic system. The corresponding oxime is dissolved in a water immiscible organic solvent containing an equivalent amount of the dipolarophile and a catalytic quantity of triethylamine. Then, aqueous sodium hypochlorite is added to the solution to promote cycloaddition *via* oxidative dehydrogenation of the starting oxime (Scheme 5).[31]

Scheme 5



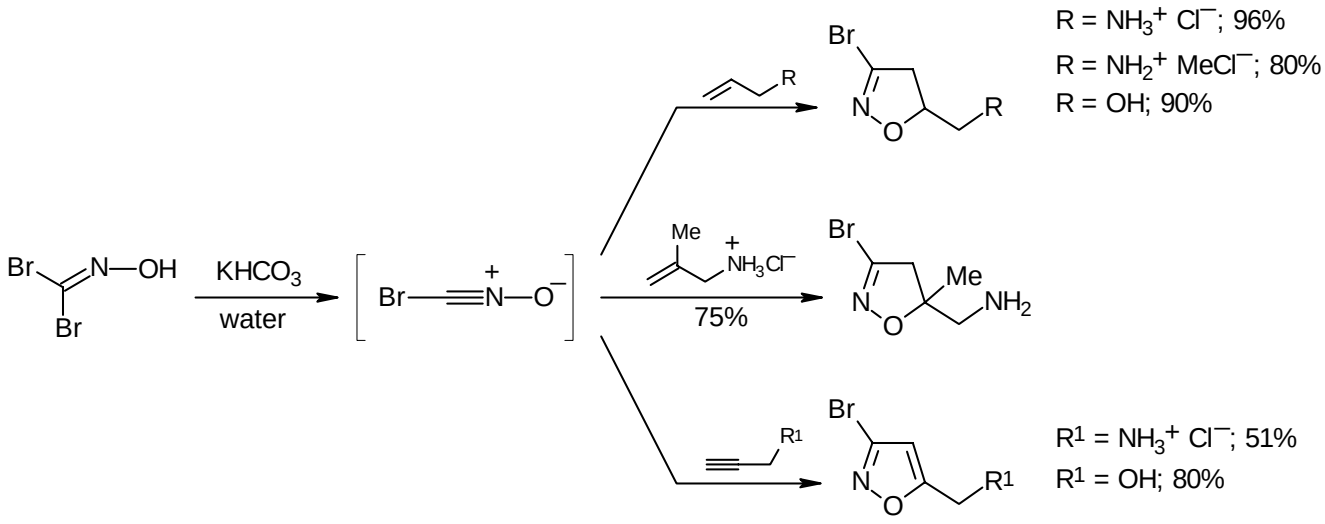
The discovery of the amino-acid antibiotic Acivicin (**13**) has stimulate considerable interest in the synthesis and pharmacology of the 3-chloro-4,5-dihydroisoxazole ring system.[32]



13 (Acivicin)

A general synthetic approach to 5-substituted-3-bromo-4,5-dihydroisoxazoles is based upon the cycloaddition between bromonitrile oxide (BrCNO) and a terminal ethylenic dipolarophile. BrCNO was generated in water under acidic conditions, and the allylic amines were utilized as hydrochlorides without the need for inefficient group protection.[33] A variety of water-soluble ethylenes and acetylenes were reacted with BrCNO in these conditions (Scheme 6) with high yields. Work-up and purification of the cycloadducts was quite easy since any BrCNO polymer formed precipitated out and was removed by filtration.

Scheme 6



The diastereofacial selectivity of 2,6-dichlorobenzonitrile oxide on racemic 2-cyclopentenones (**14**) (Scheme 7) is quite similar to that obtained in toluene.[34] In Table 3 are reported only the data obtained in water/dioxane 35:65 mixtures.

Scheme 7

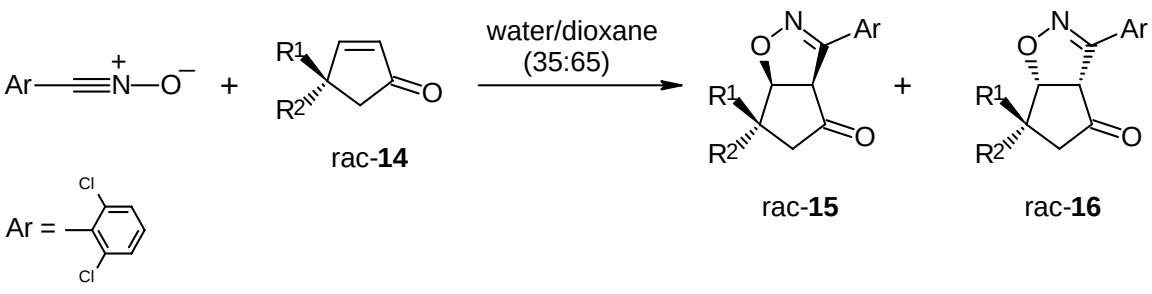


Table 3. Cycloadditions of 2,6-dichlorobenzonitrile oxide with racemic (**14**) in water/dioxane 35:65.

R^1	R^2	Overall yield (%)	Stereoselective ratio (**15**):(**16**)
OH	Me	85	44:56
OH	H	78	25:75
OAc	Me	70	57:43
OAc	H	67	0:100
Me	H	72	33:67

As far as nitrile oxide cycloaddition regioselectivity is concerned, it is known that alkyl cinnamates give mixtures of regioisomers in the usual, non-aqueous conditions.[35] Baker's yeast in a pH 7.2 aqueous buffer enhances the regioselectivity of these cycloadditions leading exclusively to the isomer (**17**) when the dipolarophile contains *t*-butyl group or the nitrile oxide bears an electron-donating group (Scheme 8 and Table 4). A lower level of selectivity is found in the cycloaddition of 2,4,6-trimethylbenzonitrile oxide.[36,37] It must be pointed out, however, that it was later reported that baker's yeast was not required in order to achieve high regio- or stereoselectivities.[38]

Scheme 8

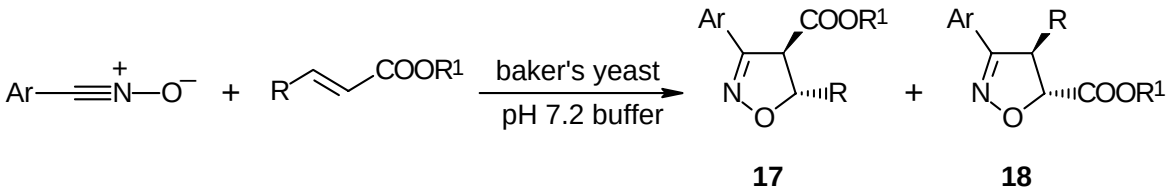


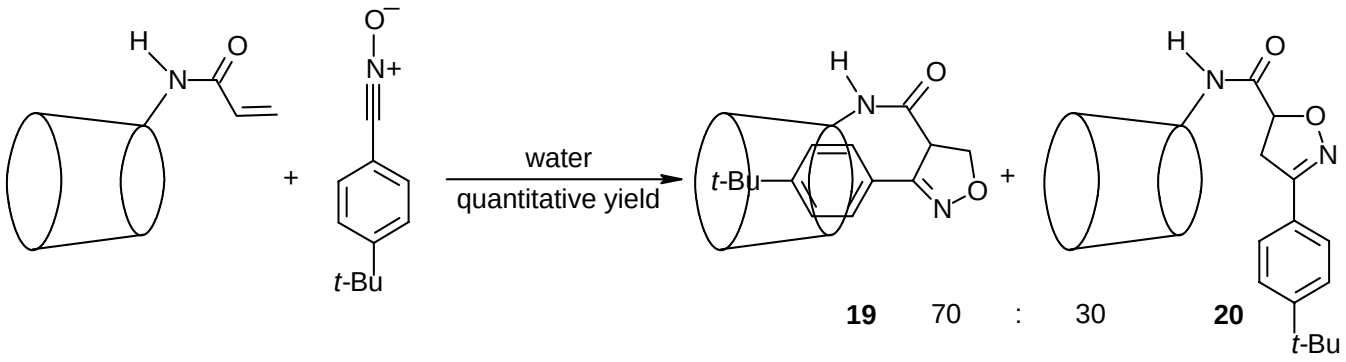
Table 4. Cycloadditions between nitrile oxides and alkyl cinnamates in aqueous pH 7.2 buffer.[a]

Ar	R	R^1	Product ratio (**17**):(**18**)
2,6-dichlorophenyl	Ph	CMe_3	100:0
2,4,6-trimethylphenyl	4-Me-C_6H_4	CMe_3	100:0
2,4,6-trimethoxyphenyl	Ph	CMe_3	100:0
2,4,6-trimethylphenyl	Ph	Et	65:35
2,4,6-trimethylphenyl	4-Me-C_6H_4	Et	65:35
2,6-dichlorophenyl	Ph	Et	100:0
2,6-dichlorophenyl	4-Me-C_6H_4	Et	100:0
2,4,6-trimethoxyphenyl	Ph	Et	100:0
2,4,6-trimethoxyphenyl	4-Me-C_6H_4	Et	100:0

[a]Yields not given by ref. 36.

The normal regioselectivity of some nitrile oxide cycloadditions, which give 5-substituted isoxazolines with monosubstituted ethylenes,[18] can be reversed by tethering the dipolarophile to β-cyclodextrin.[39,40] In particular, dipolar cycloaddition between 4-*t*-butylbenzonitrile oxide with 6^A-acrylamido-6^A-deoxy-β-cyclodextrin in aqueous solutions favours formation of the 4- substituted isoxazoline (**19**) (Scheme 9). 4-*t*-Butylbenzonitrile oxide was selected since alkyl substituted aromatic compounds of this type are known to form thermodynamically stable inclusion complexes with β-cyclodextrin.[41] The inclusion of the hydrophobic moiety of the 4-*t*-butylbenzonitrile oxide within the annulus of the modified cyclodextrin establish the right alignement for the unusual orientation of this cycloaddition.

Scheme 9



Another example of cyclodextrin-modified regioselectivity comes from the cycloaddition between nitrile oxides and adamantylidenefulvene (**21**).[42] The ratio of about 50:50 of cycloadducts (**22**) and (**23**) in THF were enhanced up to 99:1 in water (Scheme 10, Table 5).

Scheme 10

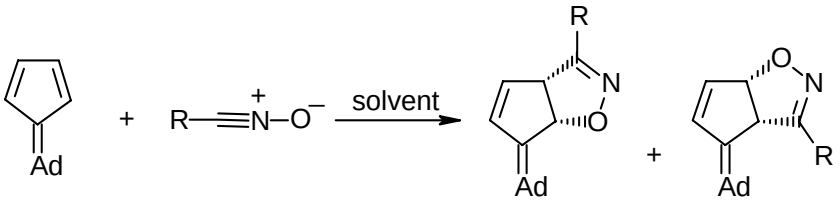


Table 5. Cycloadditions of nitrile oxides to adamantylidenefulvene (**21**).

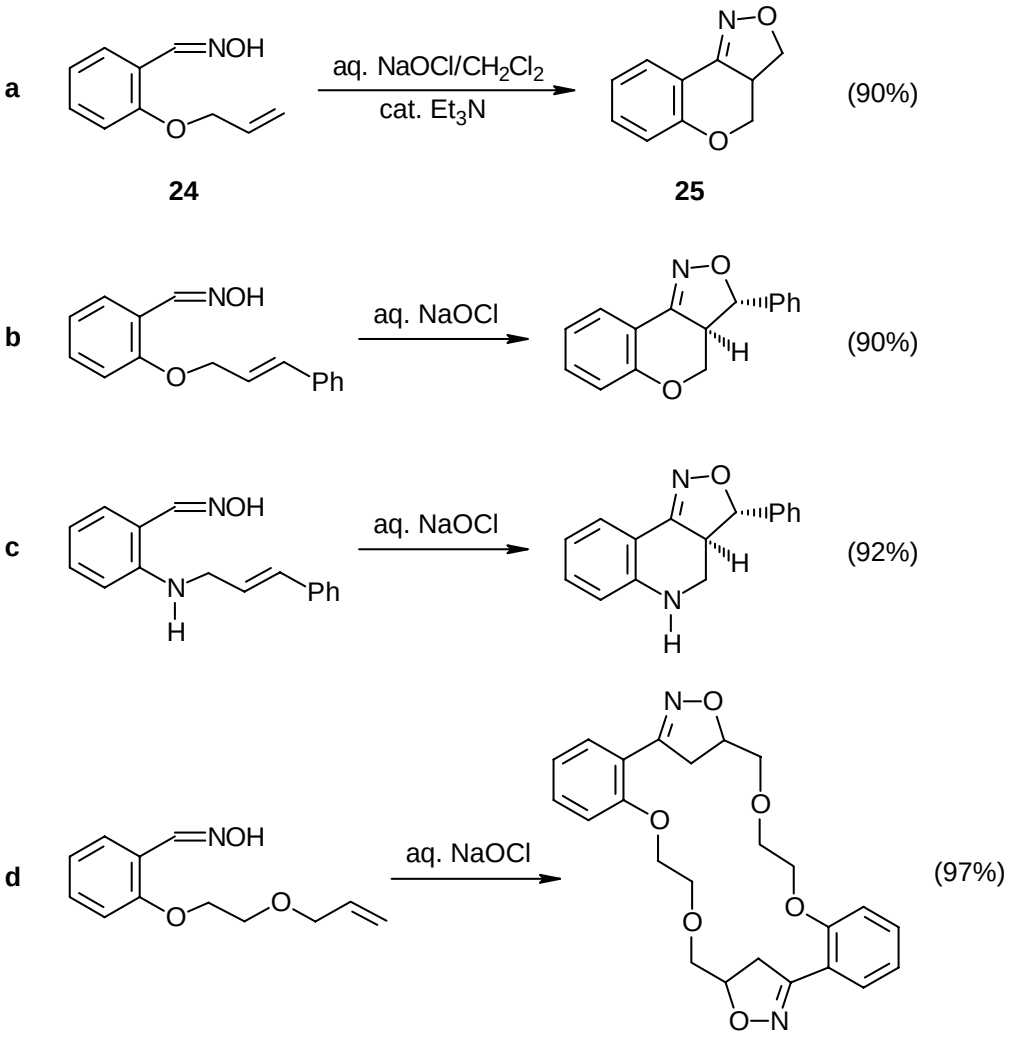
R	Solvent	Additive	Overall yield (%)	Product ratio (**22**):(**23**)
Ph	THF	—	41	60:40
Ph	water	β-cyclodextrin	[a]	71:29
4-*t*-Bu-C_6H_4	THF	—	60	51:49
4-*t*-Bu-C_6H_4	water	β-cyclodextrin	[a]	99:1

[a]Yields between 20 and 30% (ref. 42).

II.2.3 Intramolecular cycloadditions

The first example of nitrile oxide intramolecular cycloaddition in aqueous media was performed onto the oxime of 2-allyloxybenzaldehyde (**24**) in a biphasic system (reaction **a**, Scheme 11).[31] The fused bicyclic isoxazoline (**25**) was isolated in 90% yield with respect to 42% early obtained in non-aqueous conditions.[43] Some other intramolecular cycloaddition are also listed in Scheme 11. The obtainment of a *bis*-3,5-pyrazolophane by a double inter-intramolecular cycloaddition with 97% yield (reaction **d**) is particularly worth of noting.[44]

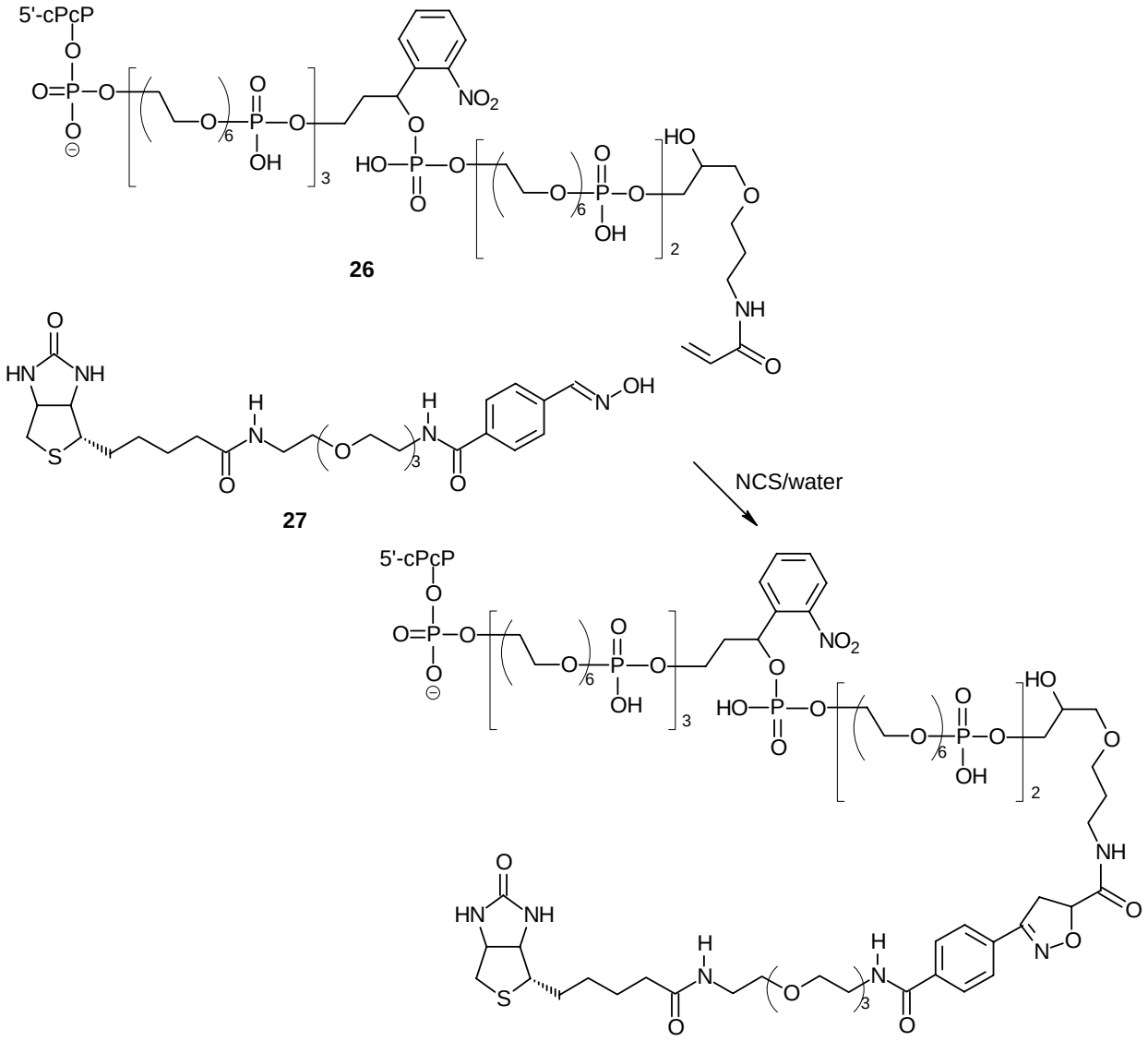
Scheme 11



II.2.4. Synthetic applications

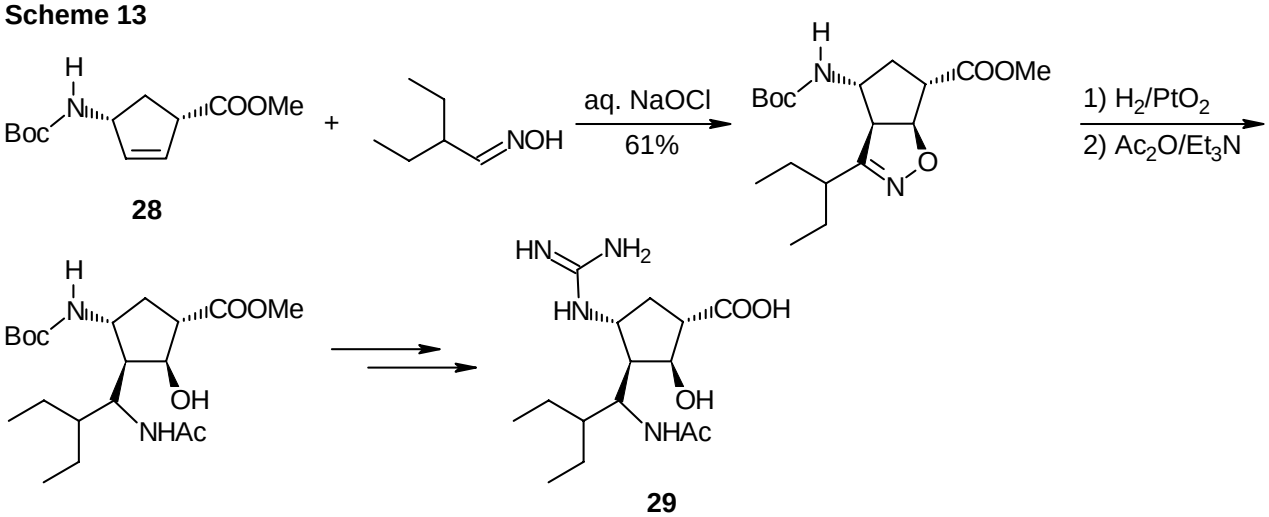
A strategy have been reported in order to isolate RNA molecules catalyzing a 1,3-dipolar cycloaddition between nitrile oxides and an acrylate moiety connected to RNA of **26**. The 1,3-dipolar cycloaddition was performed in water by *N*-chlorosuccinimide treatment of the appropriate oxime (**27**) using a modified dinucleotide tethered to the dipolarophilic substrate (Scheme 12).[45]

Scheme 12



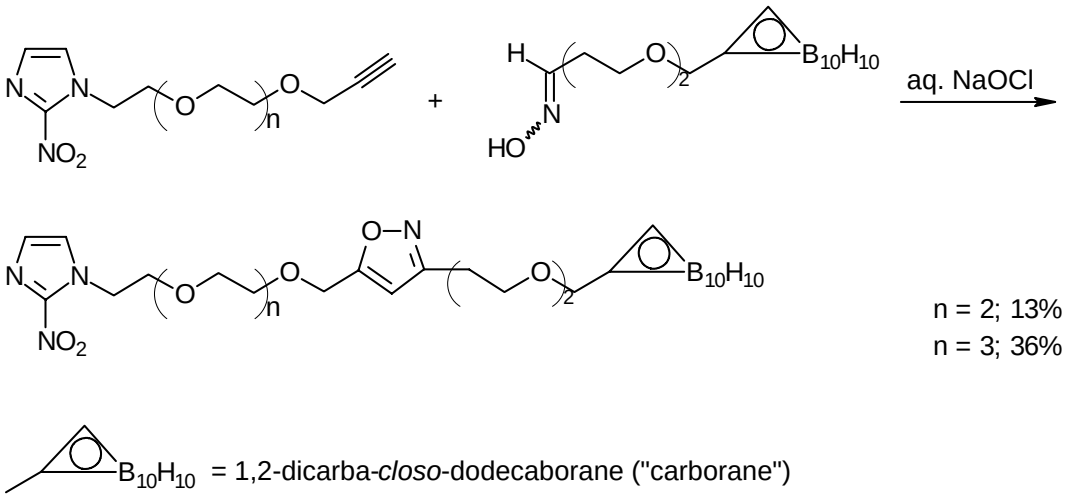
A convergent and versatile racemic total synthesis of the anti-influenza agent BCX-1812 (RWJ-270201) (**29**) was accomplished on the basis of a sequence of stereoselective reactions (Scheme 13). The nitrile oxide cycloaddition occur as the key step in aqueous bleach with 61% yield.[46]

Scheme 13



Carboranes targeted to specific tumor tissues are important for boron capture therapy of cancer. 1-Substituted 2-nitroimidazoles are known to be selectively retained in poorly vascularized tumor tissues by reductive metabolism to electrophiles.[47] Hence, it was proposed that compounds containing 10-12 boron atoms linked to the 2-nitroimidazole ring would form a useful method of concentrating boron in solid tumors. Thus, derivatives of 1,2-dicarba-*closo*-dodecaboranes were synthesised by means of a nitrile oxide cycloaddition in aqueous bleach (Scheme 14).[48]

Scheme 14



III. DIAZONIUM BETAINES

III.1. Diazocompound cycloadditions in aqueous media.

The first cycloaddition of diazocarbonyl compounds with alkynes was developed by using an $InCl_3$ catalyzed cycloaddition in water (Scheme 15 and Table 6).[49] The initial investigation started with the reaction of ethyl diazoacetate and ethyl propiolate. When water was replaced by organic solvents, as usual for diazo chemistry, only a trace amount of the target product was obtained.

Scheme 15

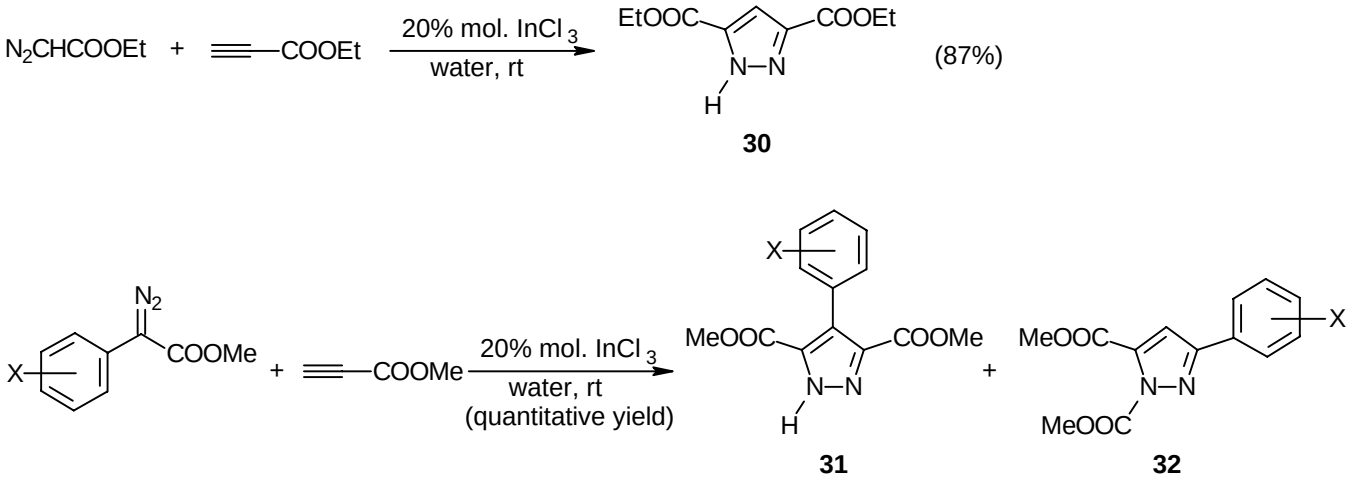
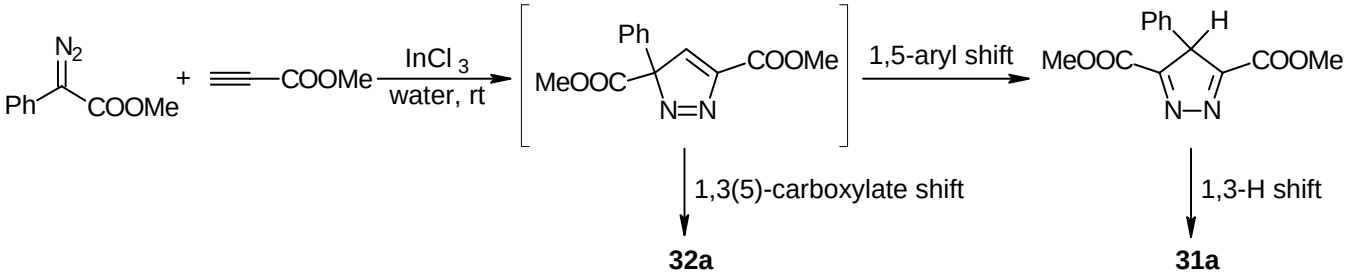


Table 6. Cycloadditions of diazocarbonyl compounds with methyl propiolate in water.

Entry	X	Product ratio (**31**):(**32**)
a	H	91:9
b	3-MeO	92:8
c	4-MeO	94:6
d	4-F	89:11
e	3-Br	88:12
f	3-CF_3	86:14

The reaction mechanism was found to proceed by a domino 1,3-dipolar cycloaddition-hydrogen (alkyl or aryl migration) as described in Scheme 16.

Scheme 16



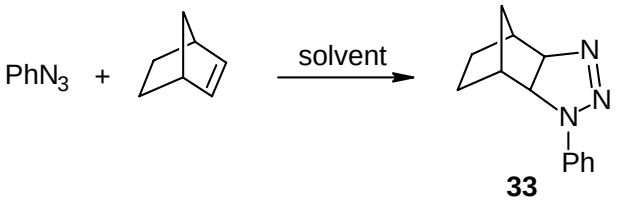
III.2. Azide cycloadditions in aqueous media

Azide cycloadditions have experienced a rebirth from 2001, after the "click" chemistry approach was disclosed.[50] Classical studies on azide cycloadditions[51] pointed out that: (*i*) standard reaction should be performed in refluxing organic solvents; and (*ii*) mixtures of regioisomeric cycloadducts are usually obtained. By contrast, in water or aqueous media reaction times are quite shorter and reaction conditions are usually very mild, while only the 4-substituted regioisomer is obtained in the "click" conditions, say, in the presence of Cu (I) catalyst. Only the most recent applications of the "click" approach will be cited here, since this subject have been recently reviewed.[50b] For the sake of clarity, this section will be further divided into two parts: *III.2.1*, intermolecular cycloadditions, and *III.2.2*, synthetic applications.

III.2.1 Intermolecular cycloadditions

Second-order rate constants for the cycloaddition of phenyl azide to norbornene were determined both in organic solvents and in water-alcohols mixtures (Scheme 17 and Table 7).[52] In organic solvents this reaction shows a very small solvent effect, which is typical for a concerted process. In highly aqueous media however, remarkable accelerations were observed. Although it is unlikely that this dipolar cycloaddition is accelerated by hydrogen-bonding interactions, the limited solubility of the reactants prevented kinetic studies in pure water.

Scheme 17



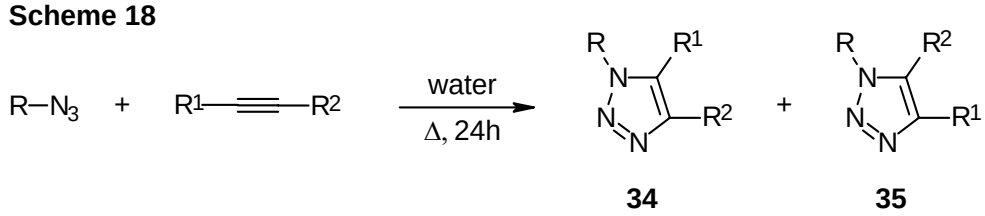
33

Table 7. Second-order rate constants for cycloadditions of phenyl azide with norbornene.

Solvent	$10^5\ k_2$ ($M^{-1}s^{-1}$)
n-Hexane	4.7
H_2O/MeOH (75:25)	35
H_2O/iPrOH (98:2)	83
H_2O/1-cyclohexyl-2-pyrrolidone (99:1)	250

Reaction of an arylacetylene with azide in hot water gave 1,4-disubstituted 1,2,3-triazoles in high yields, while similar reaction between a terminal aliphatic alkyne and an azide, except 3-nitroazidobenzene, afforded a mixture of regioisomers with ratio (**34**):(**35**) between 75:25 to 97:3 (Scheme 18, Table 8).[53]

Scheme 18



34 **35**

Table 8. Azide-alkyne cycloadditions in hot water.

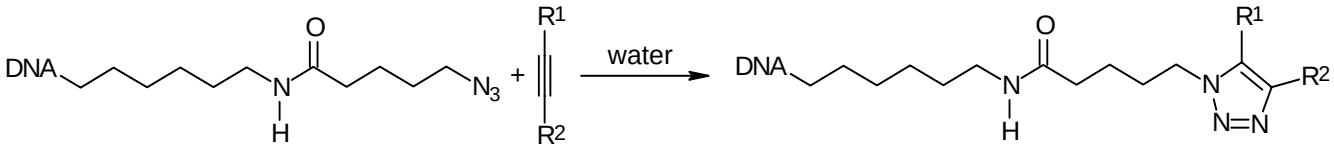
Entry	R	R^1	R^2	T (°C)	Overall yield (%)	Product ratio (**34**):(**35**)
1	Ph	H	Ph	85	81	100:0
2	Ph	H	4-Me-C_6H_4	85	81	100:0
3	4-Me-C_6H_4	H	Ph	120[a]	85	100:0
4	4-MeO-C_6H_4	H	Ph	85	97	100:0
5	4-Cl-C_6H_4	H	Ph	85	71	100:0
6	3-NO_2-C_6H_4	H	Ph	85	96	100:0
7	3-NO_2-C_6H_4	H	4-Me-C_6H_4	85	90	100:0
8	3-NO_2-C_6H_4	H	CH_2OCOMe	85	89	100:0
9	3-NO_2-C_6H_4	H	COOEt	85	95	100:0
10	Ph	H	CH_2OCOMe	120[a]	63	94:6
11	Ph	H	COOEt	120[a]	90	85:15
12	4-Me-C_6H_4	H	COOEt	120[a]	90	83:17
13	4-Cl-C_6H_4	H	CH_2OCOMe	120[a]	91	75:25
14	4-Cl-C_6H_4	H	COOEt	120[a]	87	80:20
15	4-MeO-C_6H_4	H	CH_2OCOMe	120[a]	63	97:3
16	Ph	Ph	Ph	120[a]	72	100:0

[a]Autoclave.

It can be noted that if an electron-withdrawing group attached to the phenyl ring of the azide is present, the reaction proceeds more efficiently (entries 6-9, Table 8). This observation is not consistent with that reported in organic solvents,[54] since it is known that in non-aqueous media electron-deficient dipolarophiles react more easily with azides carrying electron-releasing substituents and *vice versa*. This lack of consistency with the requirements of FMO theory have been explained with more advanced calculations (HSAB principle developed within the framework of DFT) in the reaction between several arylazides and methyl propiolate in aqueous media.[55]

It has been recently reported that several alkynes with at least one neighboring electron-withdrawing group proceeds with azide cycloaddition in water at room temperature.[56] Following this finding, a series of electron-deficient alkynes were coupled with an azido-DNA in order to provide a simple method for introducing functional groups to DNA under biological conditions (Scheme 19, Table 9).[56]

Scheme 19



36 **37**

Table 9. Azido-DNA cycloadditions to electron deficient alkynes.

R^1	R^2	Yield (%)
COOEt	COOEt	45
H	COOEt	67
H	COOEt	60[a]

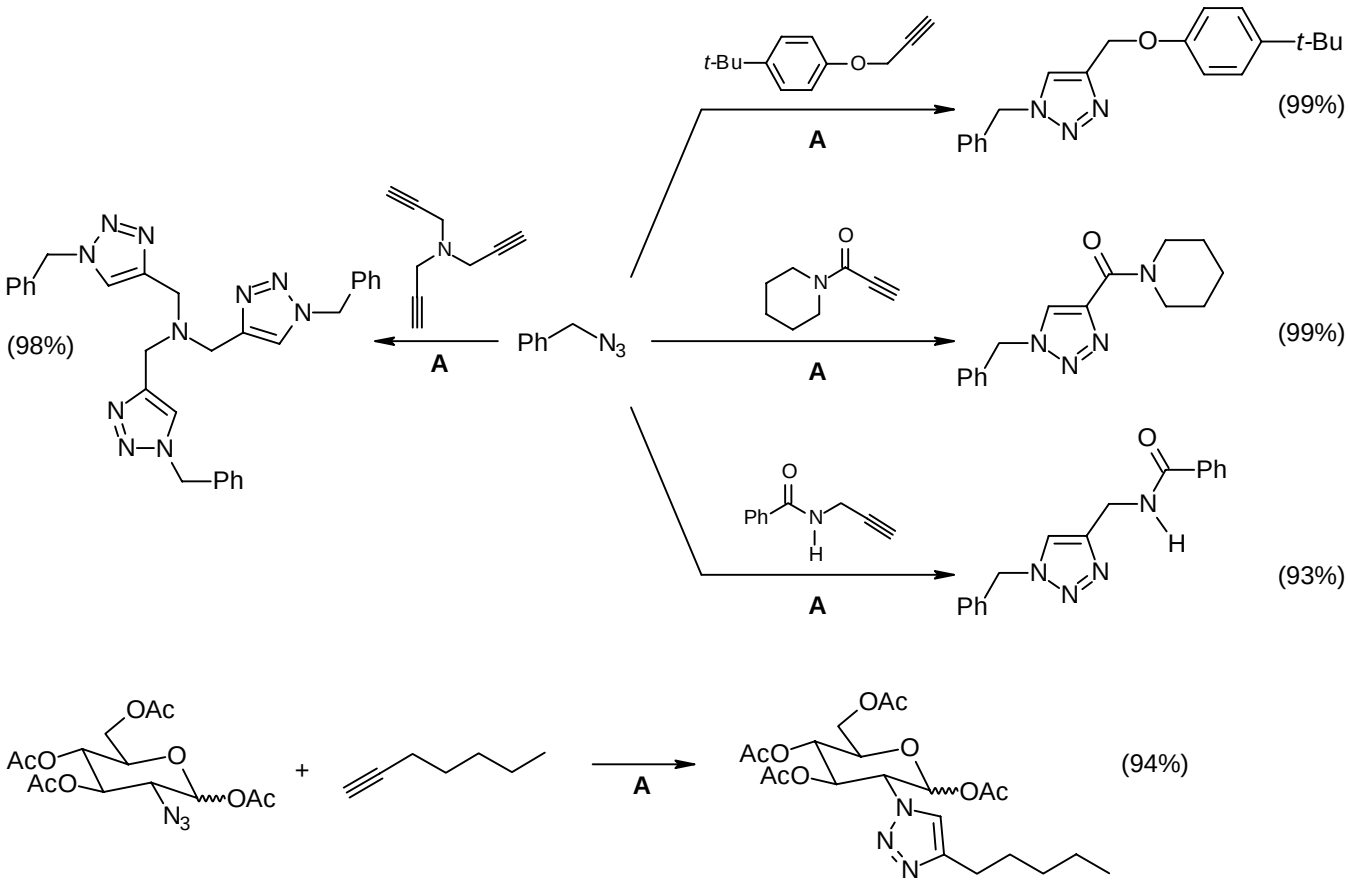
[a]In the presence of CuI and *N*,*N*-diisopropylethylamine.

The use of dichloromethane as a co-solvent with water in the copper (I)-catalized "click" cycloadditions of organic azides and alkynes increased reaction rates and provided the corresponding 1,2,3-triazoles in excellent yields compared to other organic co-solvent systems.[57] This biphasic protocol was applied to the synthesis of multifunctional compounds in excellent yields (Scheme 20). It needs to be added, however, that the reason for the observed increased yields and reduced reaction times was not elucidated exactly. As a possible explanation, it have been suggested that the high solubility of the reacting substrates in dichloromethane may make the reaction faster.

*N*H-1,2,3-Triazoles (**39**) have been prepared *via* the copper (I)-catalised cycloaddition between terminal alkynes and three *N*-protected organic azides, namely azidomethyl pivalate, azidomethyl morpholino-4-carboxylate and azidomethyl *N*,*N*-diethylcarbamate (Scheme 21).[58] These azides underwent cycloaddition

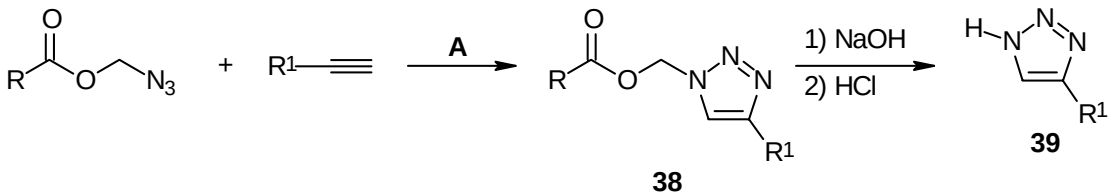
with commercially available alkyl- and aryl-substituted alkynes using the copper (II) sulfate-sodium ascorbate conditions resulting in 1,4-disubstituted 1,2,3-triazoles (**38**) in moderate to excellent yields. Cleavage of the protecting group was achieved very simply with aqueous sodium hydroxide.

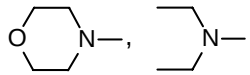
Scheme 20



A = $CuSO_4 \cdot 5H_2O$ (0.05 mol); sodium ascorbate (0.15 mol); dichloromethane/water 1:1

Scheme 21



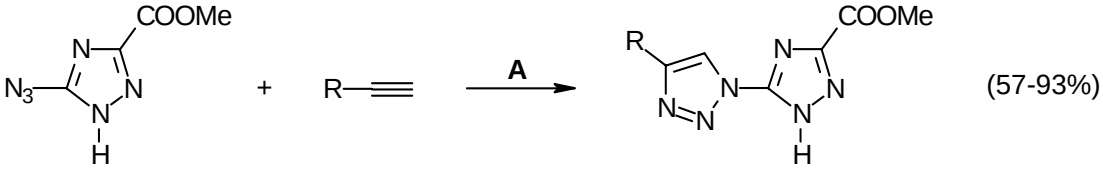
R = Me_3C, 

R^1 = Ph, 4-MeO-C_6H_4, 4-NH_2-C_6H_4, 4-CN-C_6H_4, 2-CF_3-C_6H_4, 2-NO_2-C_6H_4, 2-pyridyl, 3,5-*bis*-CF_3-C_6H_3, $(CH_2)_3COOH$, $CH(OEt)_2$, 1-OH-cyclohexyl

A = $CuSO_4 \cdot 5H_2O$ (0.05 mol); sodium ascorbate (0.3 mol); *t*-BuOH/H_2O 2:1

A further application of the azide-alkyne cycloaddition catalysed by copper (I) in aqueous media is related to the synthesis of bitriazolyl compounds with good yield (Scheme 22).[59]

Scheme 22



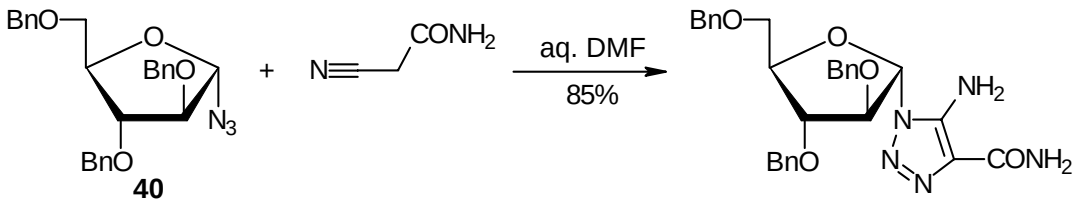
R = MeOOC, EtOOC, 1-OH-cyclohexyl, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 4-Me-$C_6H_3SO_2$

A = $CuSO_4 \cdot 5H_2O$ (0.16 mol); sodium ascorbate; THF/H_2O 1:2

III.2.2 Synthetic applications

The 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl azide (**40**) was reacted with cyanoacetamide in aqueous DMF at room temperature. One cycloaddut was isolated with 85% yield, whose formation have been ascribed by the Authors to a genuine two-step cycloaddition.[60]

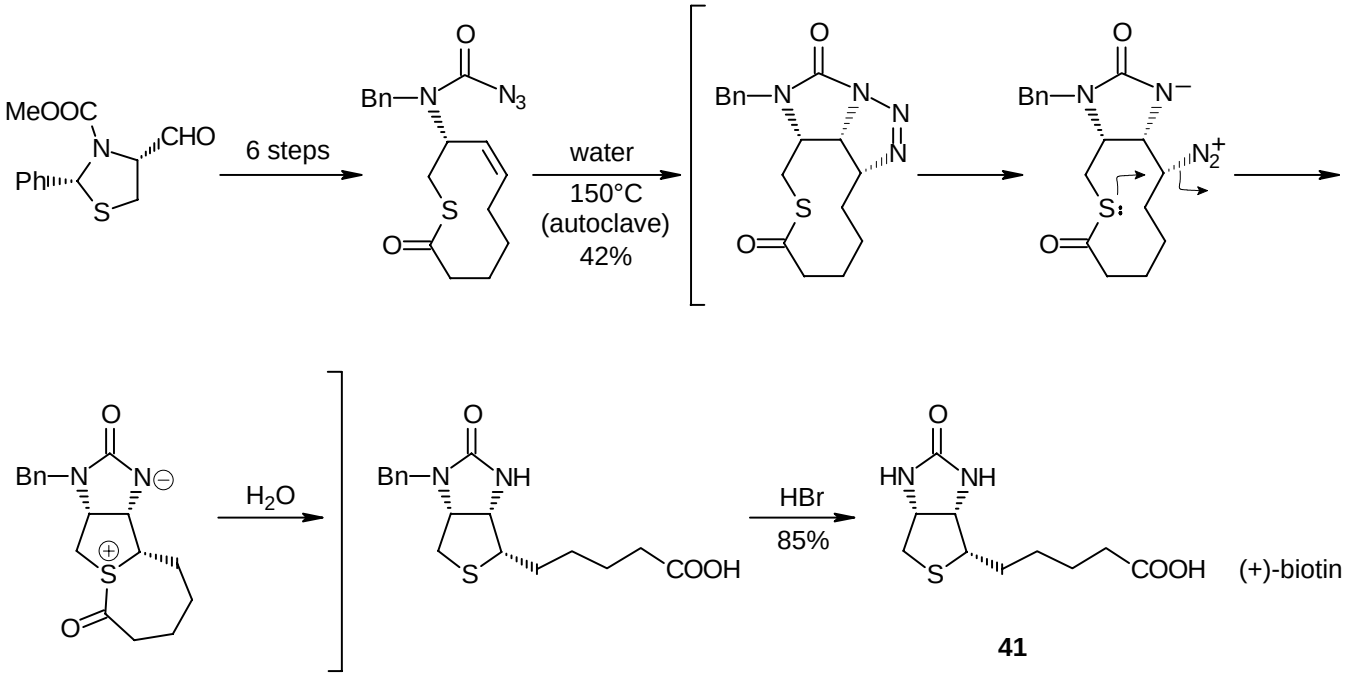
Scheme 23



An attractive 12-step enantioselective synthesis of (+)-biotin (**41**) from *L*-cysteine have been reported based upon an intramolecular 1,3-dipolar cycloaddition sequence involving an acylazide intermediate in water at 150°C (autoclave) (Scheme 24).[61] The high efficiency of this cycloaddition is surprising in the light of the known behaviour of acylazides in undergoing Curtius rearrangement.[62]

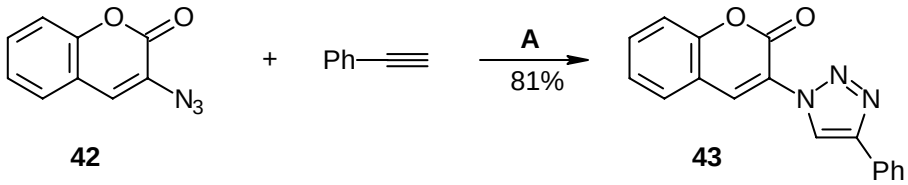
Copper (I) catalyzed cycloadditions between nonfluorescent 3-azidocoumarine (**42**) and terminal alkynes in water/ethanol 1:1 afforded intense fluorescent 1,2,3-triazole products (**43**) (Scheme 25).[63] The mild reaction conditions allowed to construct a large library of pure fluorescent coumarin dyes. Since both azide and alkyne are quite inert to biological systems, this reaction may have potential in bioconjugation and bioimaging applications. Dipolar cycloaddition between alkynyl 6-carboxyfluorescein (**44**) and azido-labeled single-strained DNA (**45**) was carried out under aqueous conditions to produce labeled DNA in quantitative yield.[64] This labeled DNA was succesfully used as a primer to produce DNA sequencing products with single-base resolution.

Scheme 24



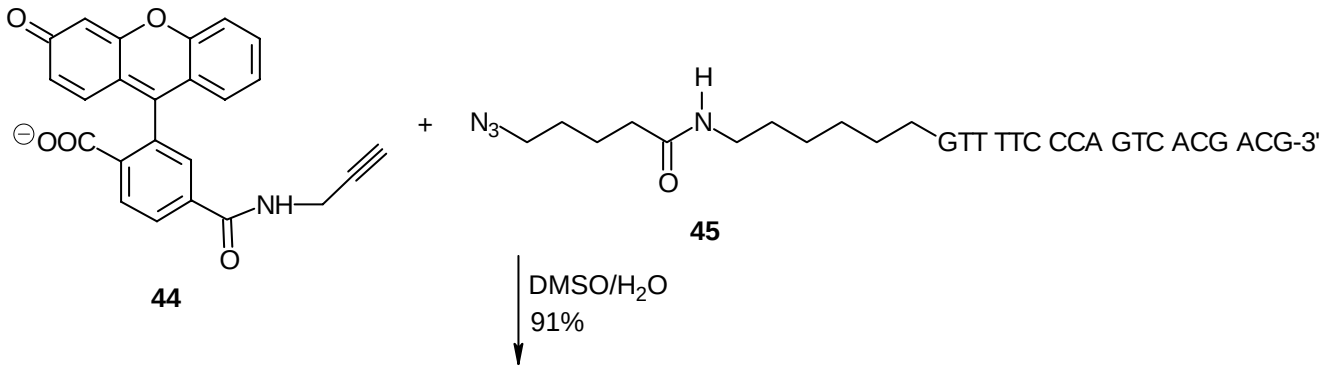
41

Scheme 25



42 **43**

A = $CuSO_4 \cdot 5H_2O$ (0.05 mol); sodium ascorbate (0.10% mol); EtOH/H_2O 1:1



44 **45**

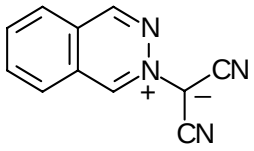
mixture of regioisomeric 1,2,3-triazoles

Some successful synthetic application of the azide-alkyne cycloaddition performed in the aqueous "click" conditions have been expolited very recently. Cationic, anionic and nonionic calix[4]arenes were prepared from a common azidocalixarene intermediate,[65] pH-responsive diblock polypseudorotaxanes[66] and a novel *P*,*N*-type ligand family (ClickPhine)[67] have been obtained.

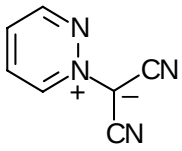
IV. AZOMETHINIUM BETAINES

IV.1. Azomethine ylide cycloadditions in aqueous media

The influence of water on the kinetic of dipolar cycloadditions of phthalazinium-2-dicyanomethanide (**46**) and pyridazinium dicyanomethanide (**47**) with a wide range of dipolarophiles was reported.[68] Water enhanced the rates of all cycloadditions with respect to those measured in acetonitrile. The dipolarophilic species were classified into two groups; water-normal and water-superdipolarophiles. The former displays enhancements of <20 times and the latter gave rate enhancements >45 times on changing the solvent from acetonitrile to water. As an example, a ketone carbonyl conjugated to an ethylenic double bond constitutes a water superdipolarophile (see Table 10). The causes of these water effects were explored both experimentally and theoretically, thus revealing that hydrophobic effects and special hydrogen bonding interactions are the main factors involved.[69,70]



46



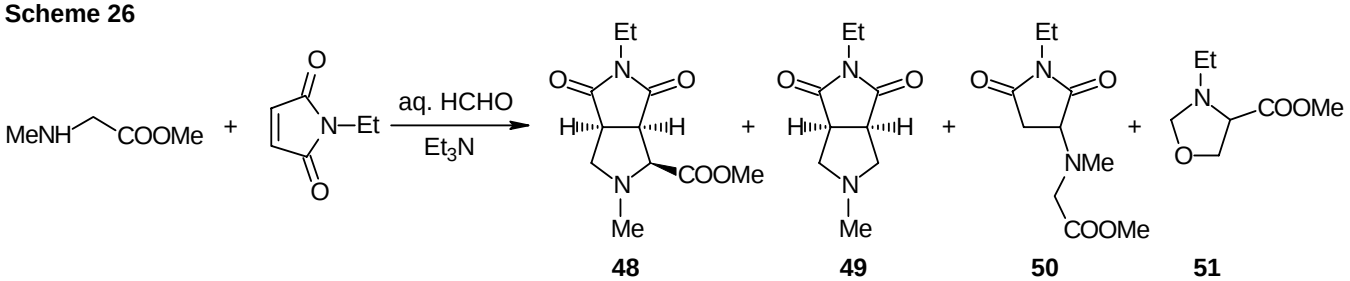
47

Table 10. Selected cycloaddition rates of (**46**).

Dipolarophile	k_2 (MeCN) (M^{-1} s^{-1})	k_2 (MeCN/H_2O 9:1) (M^{-1} s^{-1})
Methylvinylketone	62.0	1079
Methyl acrylate	37.7	187.9
Methyl propiolate	31.8	83.7
Acrylonitrile	6.3	14.4
Styrene	2.45	15.1
N-Methylmaleimide	317.7	1279

The ability of aqueous formaldehyde to generate azomethine ylides has been used onto *N*-methyl glycinate in the presence of dipolarophiles obtaining pyrrolidine cycloadducts (Scheme 26, Table 11).[71] The formation of Michael addition products (**50**) and byproducts (**51**) was also observed. It needs to be added that the competing Michael addition is accelerated in water and could be prevent by adding THF.

Scheme 26



48 **49** **50** **51**

Table 11. Azomethine ylide cycloadditions to *N*-methyl maleimide.

Solvent	T (°C)	Time (h)	Products and yields (%)			
			(**48**)	(**49**)	(**50**)	(**51**)
Toluene	110	2	48	51	—	—
Water	40	2	18	15	32	3
Water/ THF 1:3	40	24	31	53	—	6
Water/MeOH 1:3	40	21	25	32	12	3
Water/DMF 1:3	40	6	34	38	—	—

1,8-Diazafluorenone (**52**) reacts with α-aminoacids *via* imine formation to give decarboxylated azomethine ylides. These compounds undergo cycloaddition to the C=C double bond of *N*-maleimide in water/ethanol mixtures (Scheme 27 and Table 12).[72]

Scheme 27

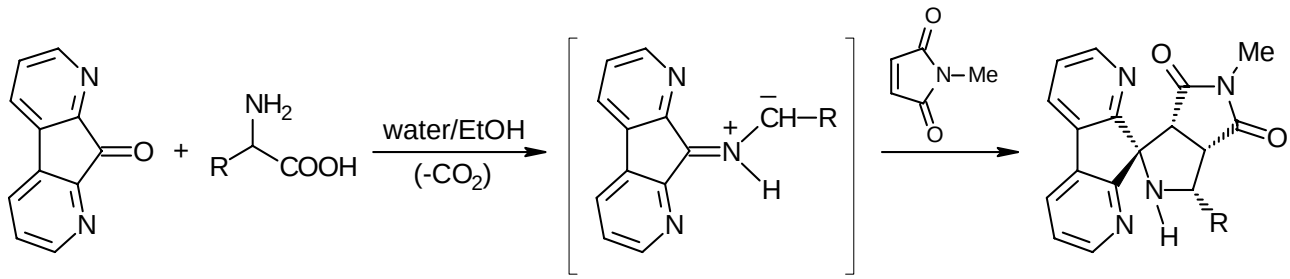


Table 12. Cycloadditions of (**53**) in aqueous media.

R	(**54**) (%)
H	70
Me	77
3-Indolylmethyl	79
$(CH_2)_2SMe$	71

[a]In boiling 20% aq. DMF.

Azomethine ylide cycloadditions in aqueous media have found useful applications in the field of material science. Easy access to water-soluble fullerenes via azomethine ylide cycloaddition to C_{60}[73] and the synthesis of water soluble fulleropyridines bearing biologically active arylpiperazines[74] have been achieved. Furthermore, amino acid functionalisation of water soluble carbon nanotubes[75] have been performed by derivatisation with *N*-protected glycine.

IV.2. Nitrone cycloadditions in aqueous media

Second-order rate constants of the reaction between *C*,*N*-diphenylnitrone and dibutyl fumarate were obtained in various solvents (Scheme 28, Table 13).[76] It was observed that the solvent effect was small

and rate constants decrease with increase of solvent polarity. Kinetic measurements show that the reaction in water is 126 times faster than that in ethanol, hence it can be stated that the polarity of solvent is not an important factor affecting the rate of cycloadditions in aqueous solutions. Rate changes by addition of alkali metal salt or urea can be explained recognizing that: (*i*) alkali metal salts decrease solubility of apolar solutes in water; (*ii*) urea, by contrast, increases the solubility of apolar solutes in water, and hence the hydrophobicity of the reactants decreases.

Scheme 28

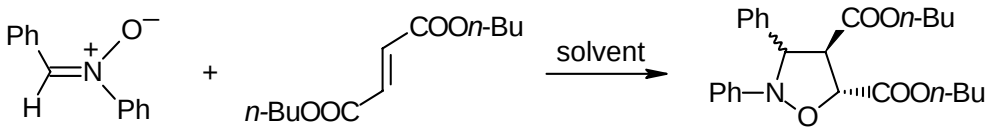
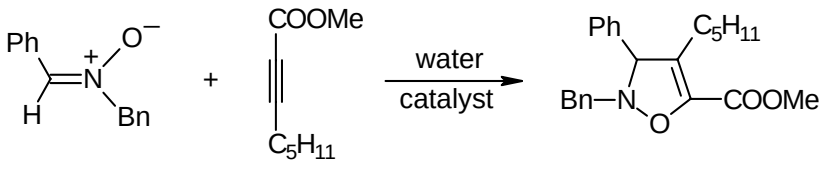


Table 13. Solvent-dependent second-order rate constants for the cycloaddition of *C,N*-diphenyl nitrone.

Solvent	k_2 (M^{-1} s^{-1})
EtOH	1.9 ± 0.1
Toluene	5.8 ± 0.17
Water	237 ± 8
Water + 2M LiCl	985 ± 13
Water + 2M urea	142 ± 5.8

The ability of triphenylphosphine to catalyze the reaction of the scarcely reactive nitrone (**55**) have been exploited onto methyl 2-octinoate as dipolarophile in water (Scheme 29, Table 14).[77] Addition of LiCl, which enhances the hydrophobic effect, increased the reaction yield up to a significant 68%.

Scheme 29



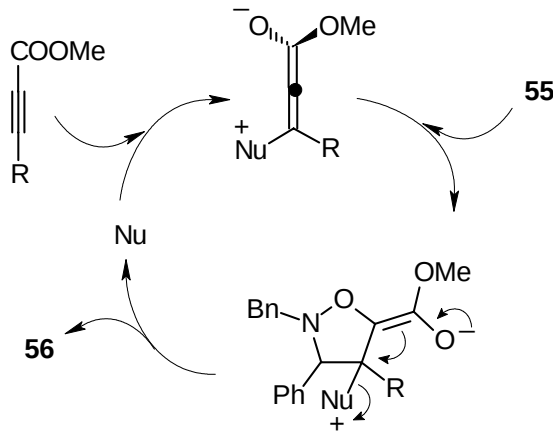
55 **56**

Table 14. Cycloaddition of nitrone (**55**) in water.

Catalyst	Additive	(**56**) (%)
—	—	—
Ph_3P	—	10
Ph_3P	LiCl	68

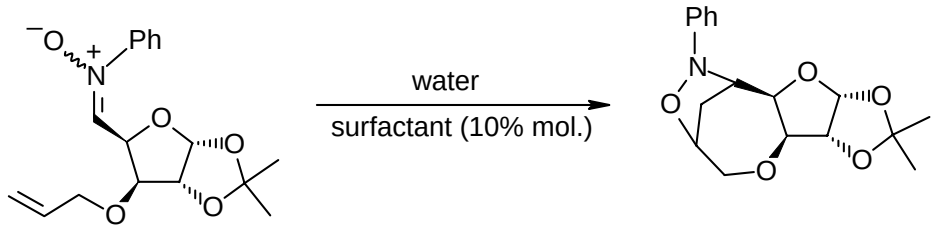
Theoretical calculations support the intervention of a catalytic model in which a zwitterionic allenolate act as the reactive dipolarophile; the proposed catalytic cycle is depicted in the Scheme 30.

Scheme 30



As the only example of intramolecular nitrone cycloadditions carried out in aqueous media, it was investigated the stereoselective behaviour of 3-*O*-allyl carbohydrate nitrone (**57**) in the synthesis of enantiopure tricyclic adducts (**58**) (Scheme 31).[78] Carrying out the intramolecular cycloaddition in water and in the presence of a surfactant, it was found that the type of surfactant used influenced both the yield and the reaction time (Table 15).

Scheme 31



57 **58**

Table 15. Intramolecular cycloaddition of (**57**) in water.

Surfactant	(**58**) (%)	Surfactant	(**58**) (%)
—	—	Triton X-100	80
CTAB	79	Tween-20	80
SDS	75	DBSA	61
SDBS	75	Triton CF 10	79

ACKNOWLEDGEMENTS

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