

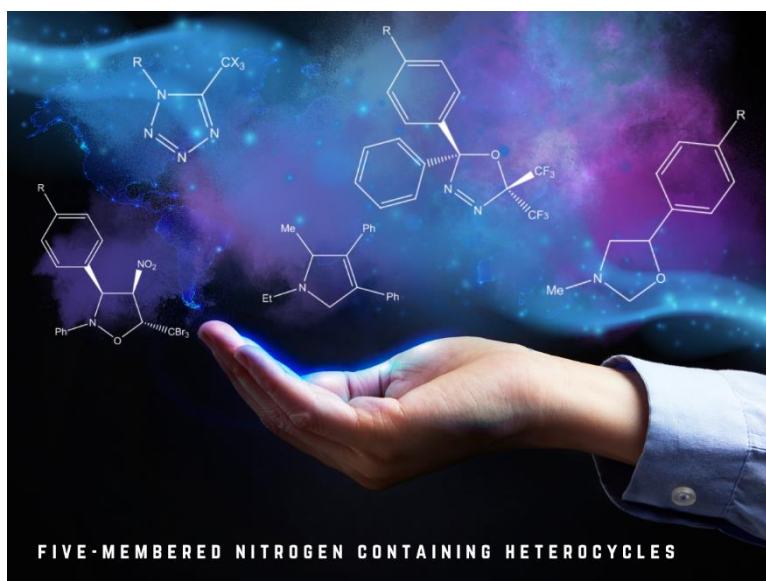
# SciRad SCIENTIAE RADICES

## Thermal [3+2] cycloaddition reactions as most universal way for the effective preparation of five-membered nitrogen containing heterocycles

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**Abstract:** The possibility of the construction of five-membered heterocycles, including single heteroatom or systems with two, three and four heteroatoms were critically reviewed based on the recent reports regarding to the [3+2] cycloaddition reactions. Almost all of analysed reaction are realized with high regio- and stereoselectivity.

**Keywords:** [3+2] cycloaddition, five-membered heterocycles, regioselectivity, stereoselectivity

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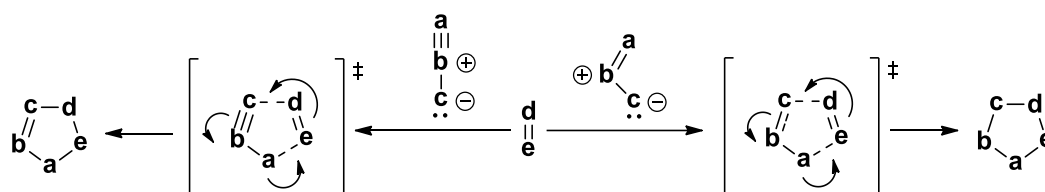
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## Introduction

[3+2] cycloaddition (32CA) is a reaction, within it two unsaturated molecules react with the formation of a new five-membered ring. The first historical [3+2] cycloaddition was described in 1890 year [1,2]. The first approach for the general definition of the 32CA and classification of its components was performed by Huisgen in the half of XX century [3,4]. Huisgen proposed "concerted" mechanism with the ideal pericyclic redistribution of six  $\pi$ -electrons within aromatic transition state independently of nature of addents, and 1,3-dipolar nature for  $4\pi$ -electron components of reaction.



Scheme 1. „Concerted“ mechanism of [3+2] cycloaddition proposed by Huisgen in the half of XX century.

Some Huisgen rules are actual for today, such as: (a) no sigma bonds can brake within the course of cycloaddition, (b) new sigma bonds are formed with  $\pi$  or n-electrons, (c) the mass of the product molecule is a sum of masses of the addents. The theory of "concerted" redistribution of electron density in transition state was however is fully undermined. Firstly, some examples of the 32CAs with the zwitterionic intermediates were detected [5–9]. Next, the ELF exploration of the nature of electron density distribution showed that this process always is a sequence of different-typed changes, without formation of hypothetical "aromatic" system and without pericyclic electron flux [10]. Next, it was found, that many "1,3-dipoles" exhibit not dipolar but biradical, pseudoradical or carbenoid nature. So, these components should be abbreviated as Three Atom Components (TACs) [11,12].

Table 1. Examples of different-type, nitrogen containing TACs according to Domingo classification [11].

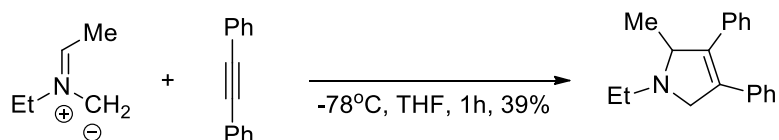
Azomethine imines	Nitrones	Nitrile ylides
Pseudoradical	Zwitterionic	Carbenoid
Pmr-type	Zw-type	Cb-type

Today many different types of unsaturated molecular systems are known as components of 32CA. With its help, it is possible to construction different types of saturated and unsaturated five-membered heterocyclic rings. This review offers a quick view on the preparative range of this class of organic reactions. We prepared our study regarding to the nitrogen containing heterocyclic rings, which are a component of several bioactive compounds.

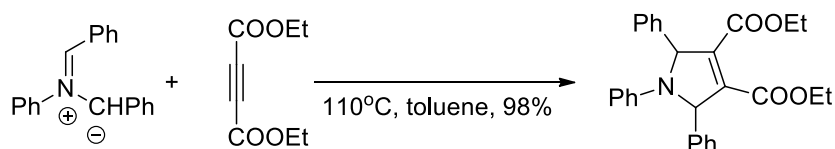
## The application of [3+2] cycloaddition reactions for the construction of five heterocyclic skeletons

### Pyrroles

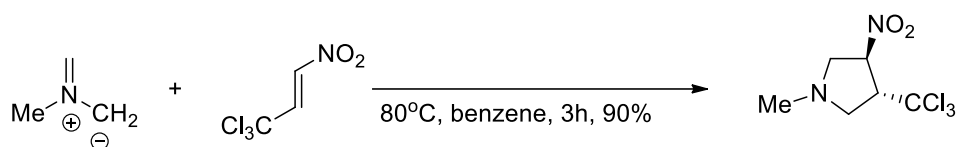
The direct preparation of pyrrole skeleton via [3+2] cycloaddition is rather difficult. Dihydro- and tetrahydro analogues of the pyrrole (pyrrolines and pyrrolidines respectively) can however be prepared on this way. So, simple azomethine ylides react rapidly with acetylenes giving respective dihydropyrroles ( $\Delta^3$ -pyrrolines). As an example of this type of process one can considered 32CA between 1-methyl-2-ethylazomethine ylide with the diphenylacetylene [13].



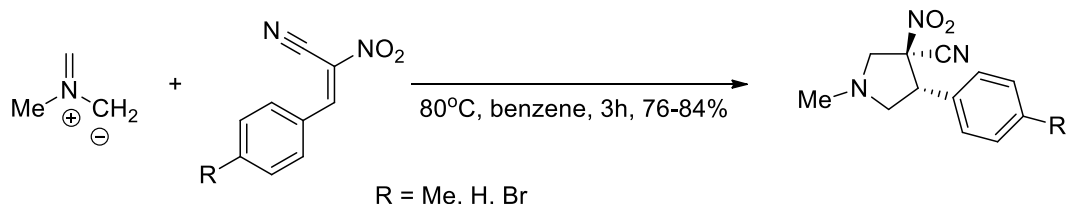
Next example of this group of transformations is 32CA between 1,2,3-triphenylazomethine ylide and diethyl acetylenedicarboxylate, which lead with almost qualitative yield to expected 1,2,3-triphenyl-4,5-dikarboethoxy- $\Delta^3$ -pyrroline [14].



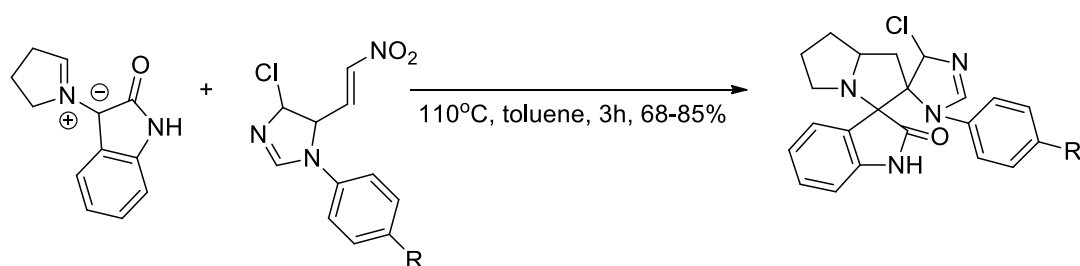
32CA of azomethine ylides with alkenes are generally better known. The simplest TAC from this group known as the component of 32CAs is N-methyl azomethine ylide. It reacts very easily with electrophilically activated nitroalkenes. For example, the 32CA between this TAC and E-3,3,3-trichloro-1-nitroprop-1-ene is realised within 3h and yields 1-methyl-3-nitro-4-trichloromethylpyrrolidine [15].



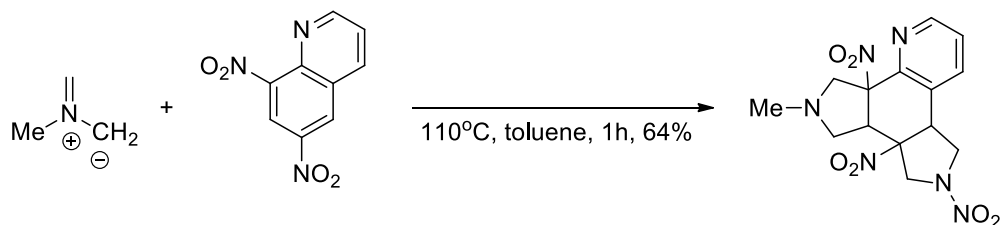
Strongly screened E-2-arylo-1-cyano-1-nitroethenes react very similarly with the same ylide due to their high global electrophilicity [16].



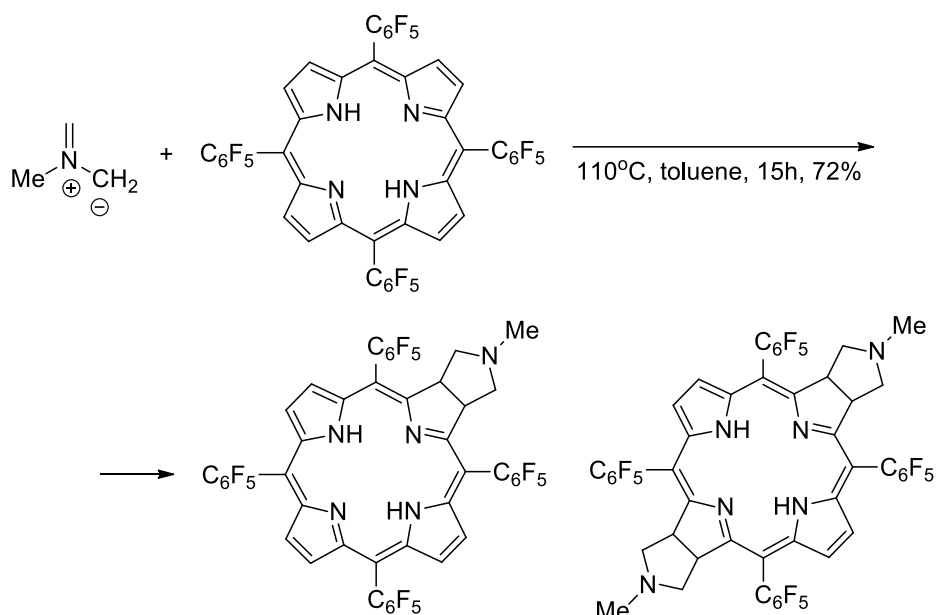
Independently of acyclic azomethine ylides, its cyclic analogues can also react with alkenes yielding respective pyrrolidine molecular systems. As examples, 32CAs with the participation of 1-aryl-4-chloro-5-(2-nitrovinyl)-1H-imidazoles can be considered. These-type processes lead to expected cycloadducts with 68-85% yields [17].



It is generally established, that arenes cannot be treated as analogues of alkenes. Some arenes however, react with azomethine ylides via analogous manner as ethylene and its substituted analogues. As the example the 32CA between N-azomethine ylide and dinitrobenzopyridine can be considered [18].

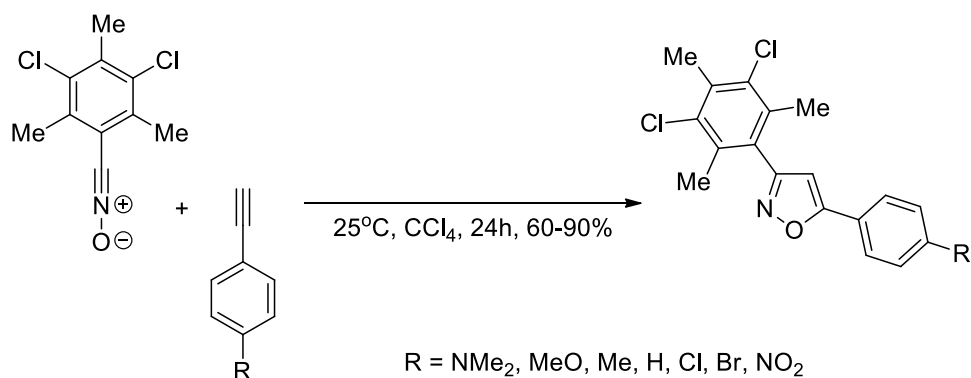


The construction of advanced molecular systems including pyrrolidine segments is also possible on the considered way. For example, the same ylide reacts with the porphyrin analogues yielding mixture of mono- and bis-adducts with overall yield better than 70% [19].

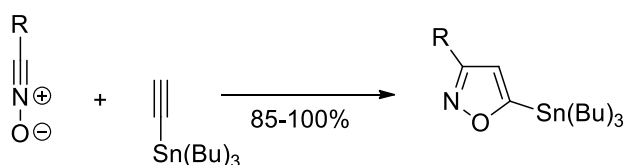


### Isoxazoles

Preparation of isoxazole skeleton is realized via 32CA with the participation of nitrile N-oxides and alkynes. Unfortunately, the parent nitrile N-oxide (formonitrile N-oxide) is not known as an individual compound [20]. On the other hand, some cycloadditions involving simple, functionalized N-oxides are described. For example, 2,4,6-trimethyl-3,5-dichlorobenzonitrile N-oxide reacts with arylacetylenes with full regioselectivity yielding respective 2,5-diarylisoxazoles [21,22].



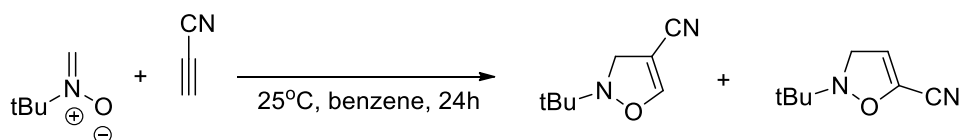
The 32CA with participation of ethynyltributylstannane opens a possibility of the preparation of tributylstannyl functionalised isoxazoles, which exhibit wide range of possibilities for further functionalisation. As TAC in this type transformations different nitrile N-oxides were tested. It was found that these transformations are realised with full regioselectivity and lead, with high yield, to respective 3-R-5-(tributylstannyl)-isoxazoles [23]. Unfortunately, authors of the mentioned communication have not specified the reaction conditions.



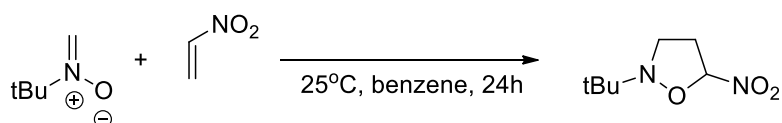
R = Me, Ph, COOMe

Nitrile N-oxides can also react with alkenes. Transformations of this type exhibit the possibility of the preparation of dihydro analogues of isoxazoles ( $\Delta^2$ -isoxazolines) [24,25].

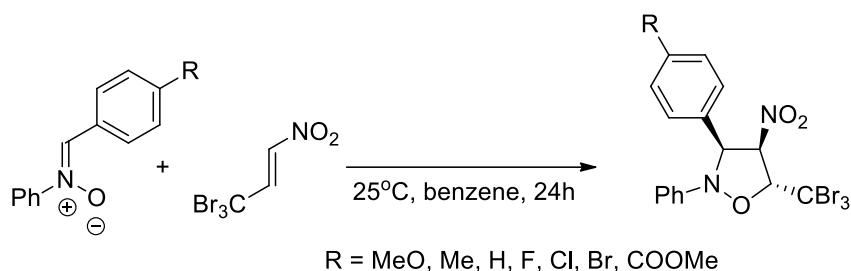
4,5-dihydro analogues of isoxazole ( $\Delta^4$ -isoxazolines) can be also prepared using 32CAs. For this purpose, imine N-oxides (nitrones) should be used as TACs. The parent nitron (formylimine N-oxide) is not known and was a subject only of theoretical works [26–28]. On the other hand, mono-substituted nitrones, are prepared and described as unstable intermediates characterized by great reactivity to different types of alkynes. One of simplest processes from this group is the 32CA between N-t-butyl nitron and cyanoacetylene. This reaction is realized at room temperature in benzene solution and leads to equimolar mixture of regioisomeric cyano-substituted adducts [29].



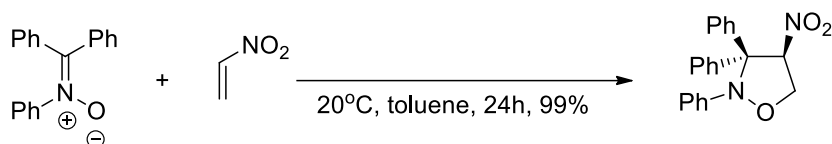
Better known are 32CAs of nitrones with alkenes. These type of reaction open a very good known way for the preparation of tetrahydro analogues of isoxazole (isoxazolidines). So, the mentioned N-t-butyl nitron reacts with the nitroethene with full regioselectivity giving 2-t-butyl-5-nitroisoxazolidine with practically quantitative yield [29].



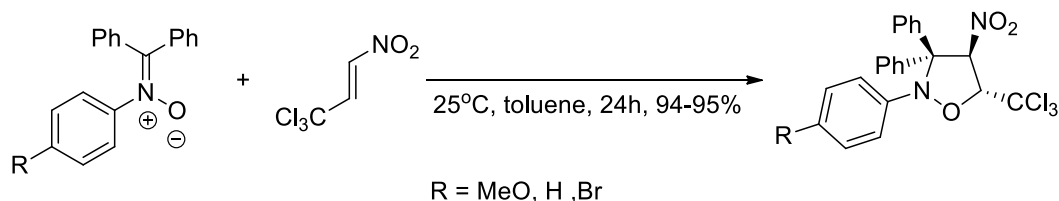
It should be noted, that 32CA reaction offer the possibility to introduce a rare in heterocyclic systems -CBr<sub>3</sub> group within the one, simple step. An example of these type of transformations are reactions of Z-C-aryl-N-phenylnitrones with E-3,3,3-tribromo-1-nitroprop-1-ene [30]. 32CAs with the participation of mentioned addents are realised with full regio- and stereoselectivity and lead to respective 3,4-cis-4-nitroisoxazolidines.



C,C,N-trisubstituted nitrones are less reactive due to strong effect of the screening of  $>C=N(O)^-$  moiety. Despite of this, C,C,N-triphenylnitronium reacts relatively easily with the electrophilic agents such as nitroethene, which leads to the 2,3,3-triphenyl-4-nitroisoxazolidine [31]. For the contrast, under similar conditions, analogous reaction with the participation of 1-bromo-1-nitroethene does not proceed [32].



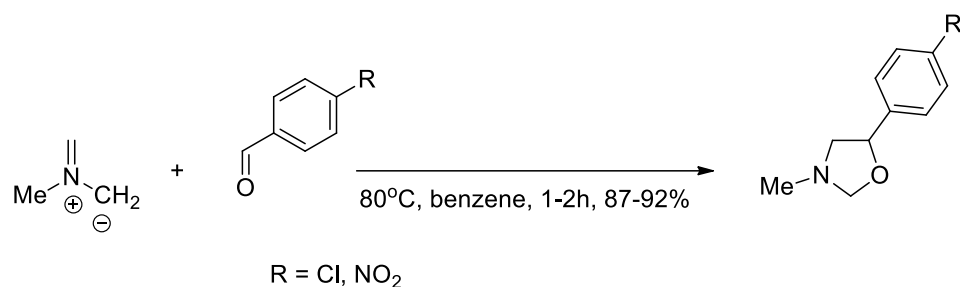
Parallely, more electrophilically activated nitroethenes, with the second substituent at 2 position instead of 1, can react with C,C,N-trisubstituted nitrones. As an example 32CA involving E-3,3,3-trichloro-1-nitroprop-1-ene can be considered [32].



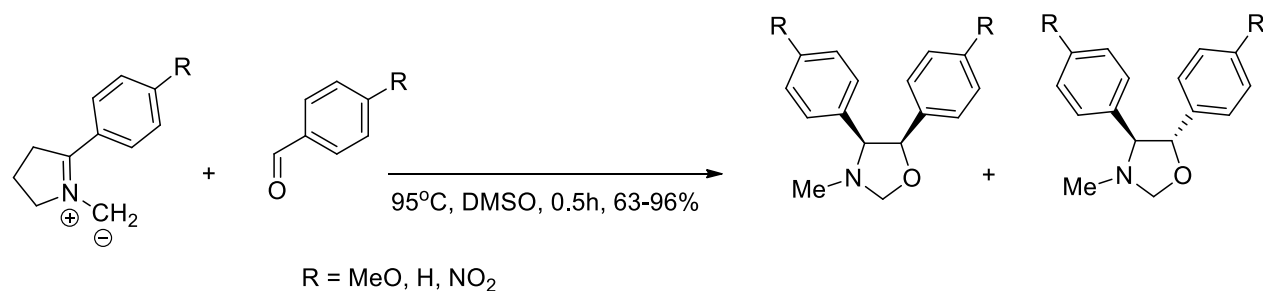
Siadati et al. [33] study a very interesting cycloaddition reaction C18NB fullerene with 4-pyridine nitrile oxide.

### Oxazoles

In the case of isoxazoles, both heteroatoms are derived from the TAC compound. For oxazole analogues, the strategy of the construction of heterocyclic ring must be slightly different. In particular, the nitrogen atom is introduced from the azomethine ylide, whereas the oxygen atom from carbonyl compound. As the base for these-type transformations different aldehydes can be considered. For example, 32CAs between simple N-methyl azomethine ylide and aromatic aldehydes give respective 5-aryl-3-methyloxazolines with great yields [34].

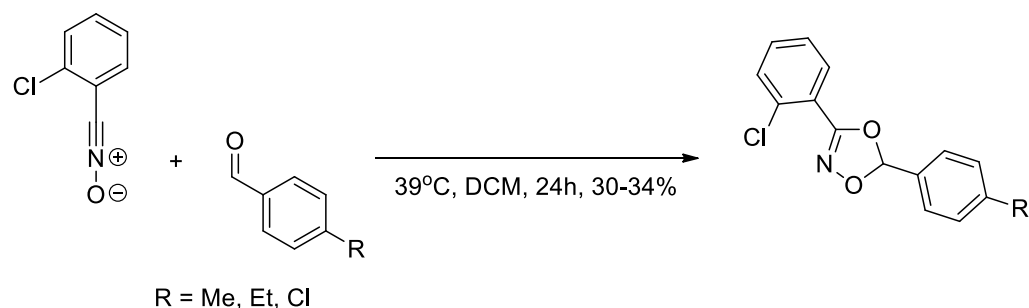


In similar transformations, cyclic ylides can also participate [35].



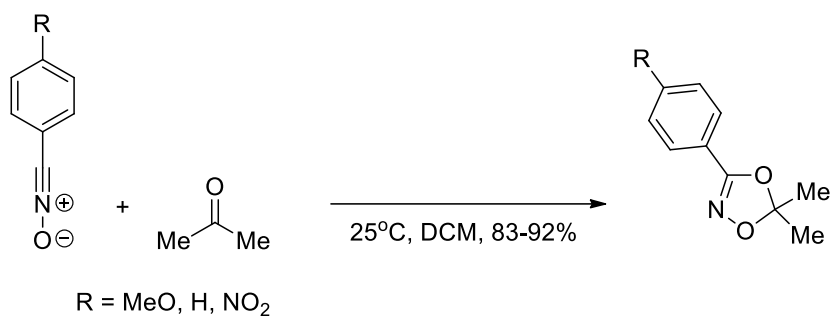
### Dioxazoles

The preparation of  $\Delta^4$ -1,3-diox-4-azoline molecular skeleton is possible via 32CA between nitrile N-oxides and carbonyl compounds. For this purpose, different type  $2\pi$ -components can be used. For example, aromatic aldehydes react with 2-chlorobenzonitrile N-oxide in boiling DCM giving 3,5-diarylisoxazolines as single cycloaddition product [36].

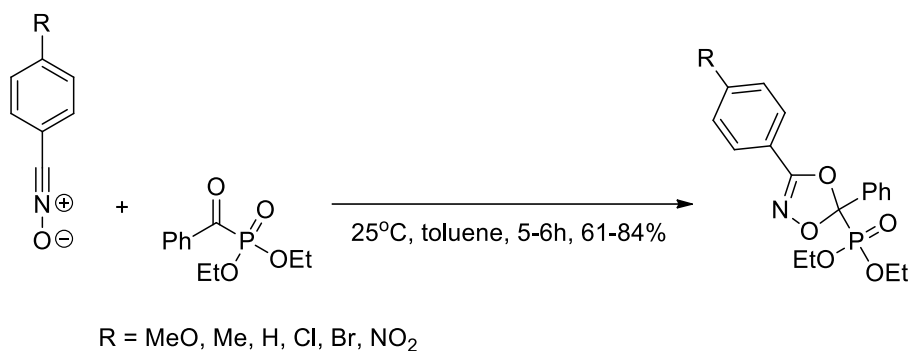


Ketones are also known as a component of similar type transformations. For example, aromatic nitrile N-oxides, independently of electronic nature of the TAC, react easily with the parent ketone (acetone) yielding 3-(4-methoxyphenyl)-5,5-dimethyl- $\Delta^4$ -1,3-diox-4-azoline as single cycloadducts [37].

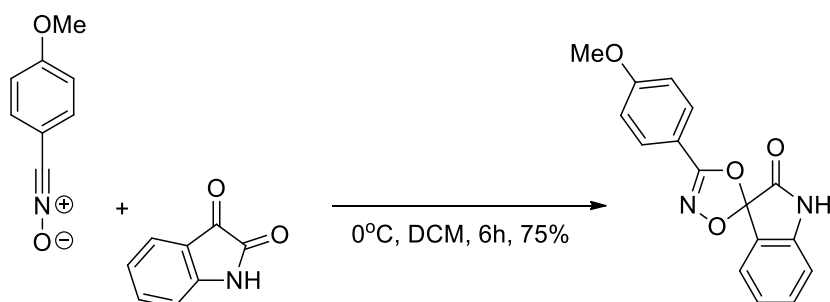




Ketones functionalized by heteroatomic segments participate in the same type of transformations. So, acyl phosphonates react with aromatic nitrile N-oxides at room temperature in full regioselective manner yielding expected cycloadducts with yields up to 84% [38].



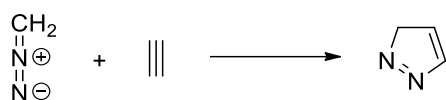
In analogous manner, some spirocyclic molecular systems can be prepared. So, 32CA between 4-methoxybenzonitrile N-oxide and isatin is realised with full chemo- and regioselectivity and leads to the cycloadduct with 76% yield [39].



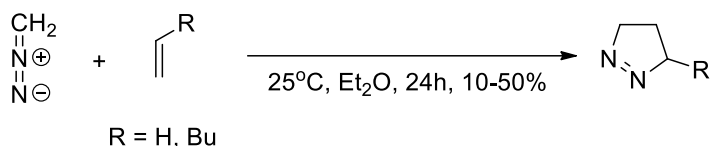
Finally, it should be noted, that examples of the synthesis of 1,2-diox-3-azoline skeletons via 32CA reactions are not known.

### Diazoles

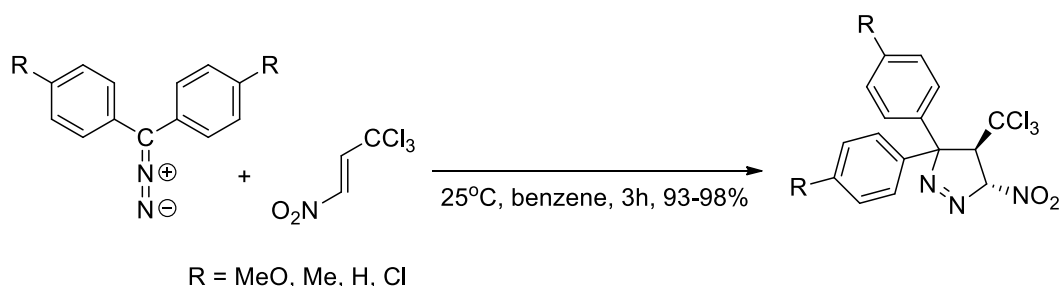
The simplest example of synthesis of parent pyrazole ring was described in the last years of XIX century [40] regarding the 32CA between diazomethane and acetylene. Unfortunately, the reaction conditions were not described completely.



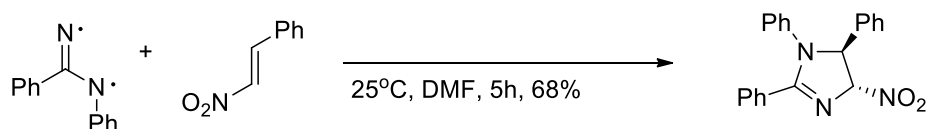
More information is available for the analogous reaction with the participation of ethane and 1-pentene [41]. These reactions realized at room temperature and yielded expected adducts with the yields 10% and 50% respectively.



Synthesis of sterically crowded pyrazolines is possible in the reaction involving electrophilically activated alkenes [42,43]. As the example of these-type transformation 32CA between diaryldiazomethanes and E-3,3,3-trichloro-1-nitroprop-1-ene can be considered [44].

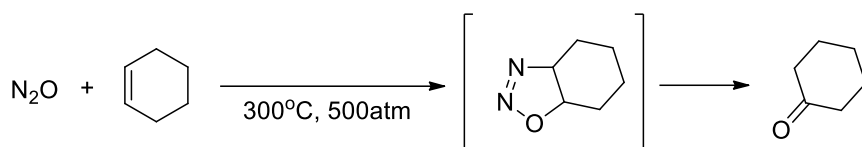


The preparation of imidazole molecular segment using 32CA process is very difficult, but not impossible. One of unique examples of these-type transformations is the reaction leading to the 1,2,4-tetraphenyl-5-nitroimidazoline [45].



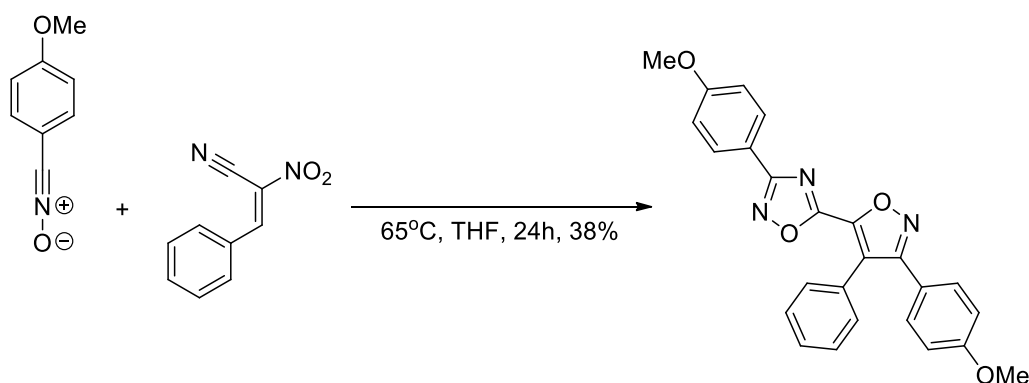
### Oxadiazoles and tiadiazoles

The construction of oxa-2,3-diazole molecular system is theoretically possible via 32CA with the participation of nitrous oxide as the TAC and alkenes [46]. However, these-type transformations require dramatic conditions and lead to unstable cycloadducts. For example, nitrous oxide reacts with cyclohexene under high pressure (500atm) and at 300°C. Under these conditions, the primary cycloadduct decomposes rapidly to more stable cyclohexanone [47].

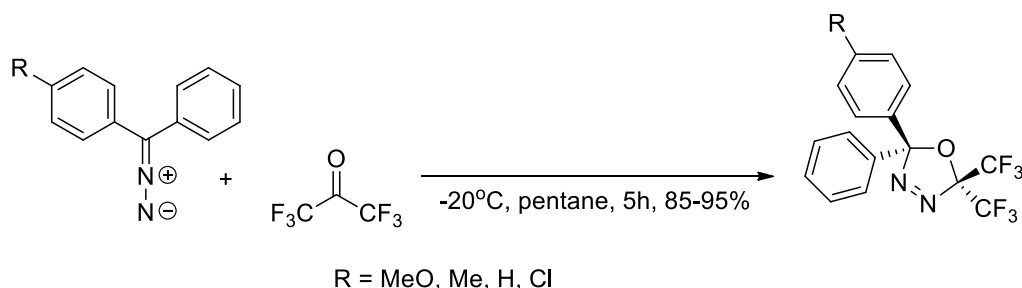


Similar problems were detected during approach to the synthesis of oxa-2,3-diazoles via 32CA with the participation of acetylene and its analogues [48].

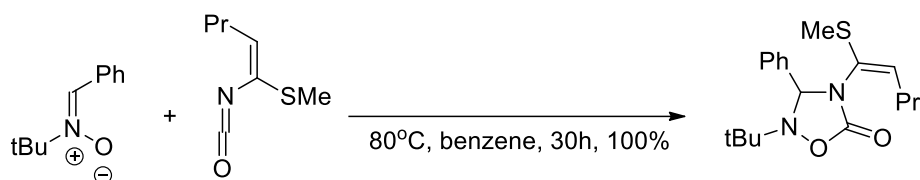
The direct preparation of oxa-2,4-diazole ring via 32CA is difficult, but not impossible. As an example of these-type transformations the reaction with the participation of 4-methoxybenzonitrile N-oxide and E-2-phenyl-1-cyano-1-nitroethene can be considered [49].



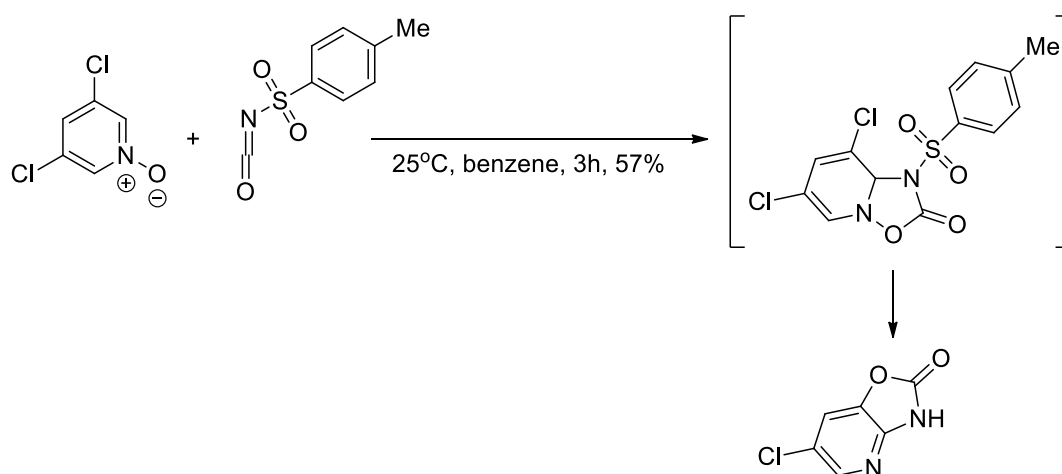
Generally, this process is evidently rare example of the formation of oxa-2,4-diazole ring via 32CA with the participation of nitrile N-oxide, because, the CN group is only slightly active. Most known cases of addition reaction to this group require the presence of transition metal catalysts [50,51]. Similarly, universally low nature exhibit 32CAs of diazocompounds to carbonyl group. This group of 32CAs opens the way for the preparation of dihydro-1-oxa-3,4-diazoles. For example, 32CAs between diaryldiazomethanes and perfluoroacetone are realised under mild conditions and lead with high yields and full regioselectivity to expected cycloadduct [52].



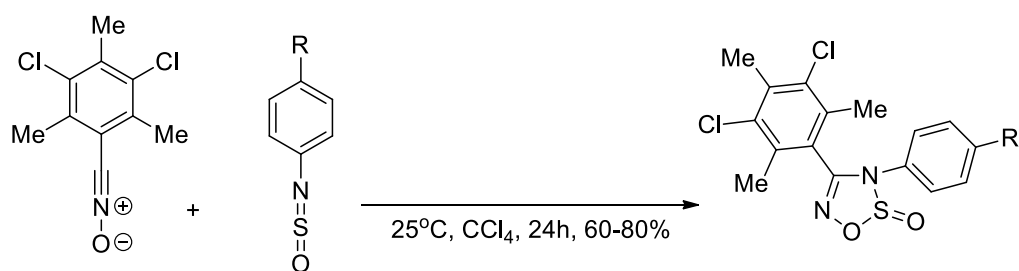
The most universal protocol for the synthesis of tetrahydro oxa-2,4-diazole molecular skeleton are [3+2] reactions between nitrones and isocyanates. For example, 32CA between (Z)-C-phenyl-N-methylnitron and 3-methyl-1-(methylthio)-1-butenyl isocyanate [53] is realised with full regioselectivity in boiling benzene within 30h.



Oxides of aromatic amines formally are not classified as nitrones. In the practice however, some compounds from this group react as TACs via 32CA scheme. For example, within the 32CA of 3,5-dichloropyridine N-oxide and tosyl isocyanate the unstable oxa-2,4-diazole system is formed [54]. This adduct, under the reaction conditions, converts spontaneously in to respective benzazo-1,3-oxazole molecular system.



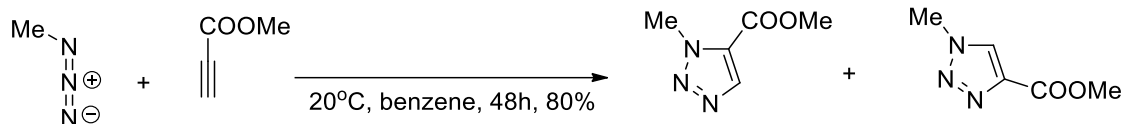
Other approach for the preparation of heterocycles including two nitrogen atoms and one sulphur atom is based on the 32CA between nitrile N-oxides and sulfinylanilines. These-type transformations are realized under mild conditions and with the full regioselectivity [55].



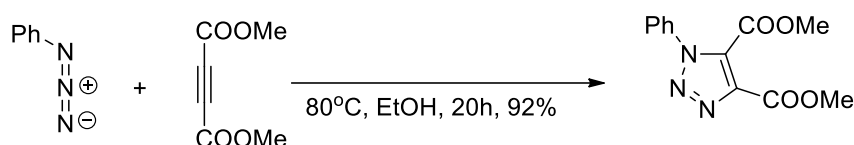
R = EtO, MeO, Me, H, Cl, Br

### Triazoles

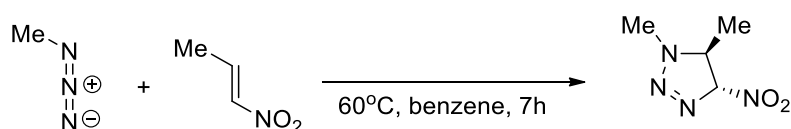
Preparation of aromatic 1,2,3-triazole molecular segment is possible via 32CA with the participation of azides and alkynes. For example, the methyl azide reacts with the methyl propiolate yielding mixture of 4- and 5-carbomethoxy substituted cycloadducts [56].



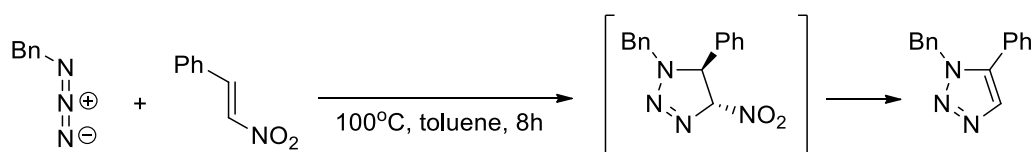
A similar reaction with the participation of the phenyl azide and dimethyl ester of acetylene dicarboxylate requires higher temperature and leads to 4,5-dicarbomethoxytriazole [57].



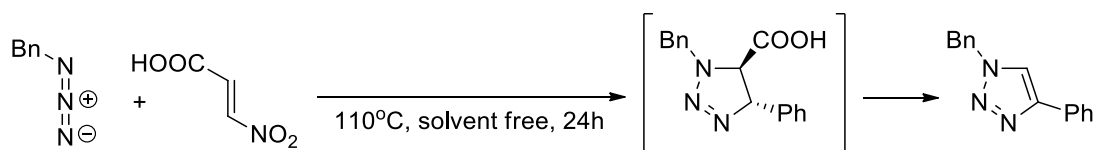
Analogous processes with the participation of alkenes exhibit generally higher regioselectivity. So, the methyl azide reacts rapidly with the E-1-nitroprop-1-ene in fully regioselective manner yielding 3,4-dimethyl-5-nitrotriazoline. The obtained product exhibits relatively low stability and convert easily to aromatic triazole system via dehydronitration / rearrangement sequence [58].



A similar transformation based on the benzyl azide and nitrostyrene require higher temperature. Under the reaction conditions, the nitrous acid extrusion is realized from primary formed triazoline molecular system [59].

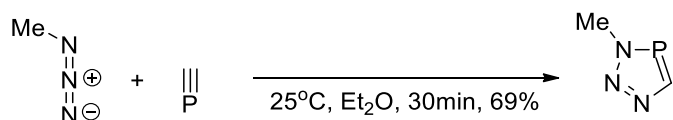


The completely different regioselectivity is observed in the case of similar reaction with the participation of cinnamic acid [60].

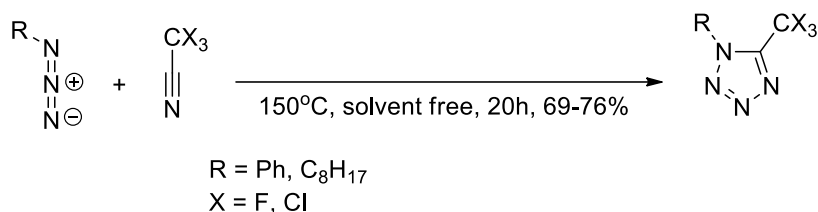


### Other heterocyclic systems

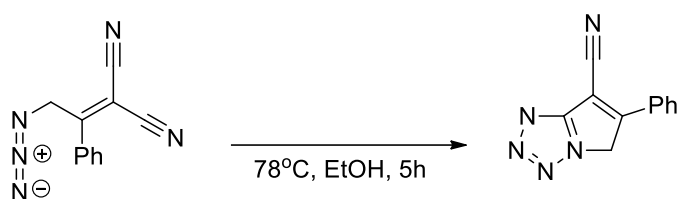
32CAs with the participation of organic azides are attractive protocol for the synthesis of heterocyclic skeletons including three nitrogen atoms and additionally next one heteroatom. For example, methyl azide reacts rapidly with the phosphonylene giving 5-phosfonelyn-1,2,3-triazole as single cycloaddition product [61].



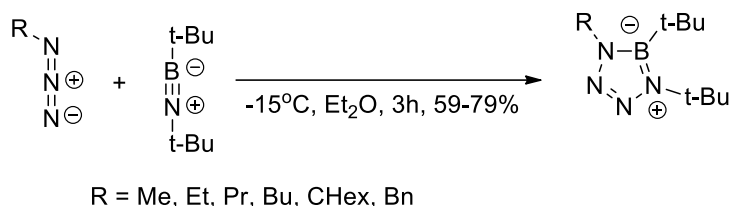
The construction of heterocyclic systems including four nitrogen atoms is more difficult. The reaction conditions are generally more dramatic. Additionally, some adducts from this group are unstable under reaction conditions. This type of transformation is possible via 32CA with the participation of organic azides and nitriles. For example, octyl azide react with the nitriles of trihaloacetic acids yielded single cycloaddition product [62].



In some cases, similar formation of tetrazole ring can also realise via intramolecular reaction protocol [63].



Analogous transformations are possible also in the case of the regioselective preparation of analogous heterocycles including boron atom [64]. Its interesting, that the replacement of -N≡B- moiety exhibit dramatically higher reactivity than the -C≡N. In the consequence, the mentioned cycloadditions are proceeding rapidly at low temperature within only 3h.



## Conclusions

[3+2] cycloaddition reactions with the participation of three atom components and alkene/alkyne molecular systems offer wide range of possibilities of the synthesis of different type five-membered heterocycles with a single heteroatom as well as two, three or four heteroatoms. Many of these processes are realized under mild conditions and with high regio and stereoselectivity. It should be underlined at this point, that recent discoveries shed interesting light on the mechanistic aspects of [3+2] cycloaddition reactions. This area was recently a subject of a separate review [65].

## References

- [1] Buchner, E.; Einwirkung von diazoessigäther auf die aether ungesättigter säuren. *Ber. Dtsch. Chem. Ges.* **1890**, 23 (1), 701–707. DOI: [10.1002/cber.189002301113](https://doi.org/10.1002/cber.189002301113)
- [2] Siadati, S.A.; Rezazadeh, S.; The extraordinary gravity of three atom 4π-components and 1,3-dienes to C<sub>20-n</sub>X<sub>n</sub> fullerenes: A new gate to the future of nano technology. *Sci. Rad.* **2022**, 1 (1), 46–68. DOI: [10.58332/v22i1a04](https://doi.org/10.58332/v22i1a04)
- [3] Huisgen, R.; Cycloadditions— Definition, Classification, and Characterization. *Angew. Chem. Int. Ed. Engl.* **1968**, 7 (5), 321–328. DOI: [10.1002/anie.196803211](https://doi.org/10.1002/anie.196803211)
- [4] Huisgen, R.; Kinetics and mechanism of 1,3-dipolar cycloadditions. *Angew. Chem. Int. Ed. Engl.* **1963**, 2 (11), 633–645. DOI: [10.1002/anie.196306331](https://doi.org/10.1002/anie.196306331)
- [5] Huisgen, R.; Mlostoń, G.; Langhals, E.; The first two-step 1,3-dipolar cycloadditions: Non-stereospecificity. *J. Am. Chem. Soc.* **1986**, 108 (20), 6401–6402. DOI: [10.1021/ja00280a053](https://doi.org/10.1021/ja00280a053)
- [6] Huisgen, R.; Mlostoń, G.; Langhals, E.; The first two-step 1,3-dipolar cycloadditions: Interception of intermediate. *J. Org. Chem.* **1986**, 51 (21), 4085–4087. DOI: [10.1021/jo00371a039](https://doi.org/10.1021/jo00371a039)
- [7] Jasiński, R.; A stepwise, zwitterionic mechanism for the 1,3-dipolar cycloaddition between (Z)-C-4-methoxyphenyl-N-phenylnitrene and gem-chloronitroethene catalysed by 1-

- butyl-3-methylimidazolium ionic liquid cations. *Tetrahedron Lett.* **2015**, 56 (3), 532–535. DOI: [10.1016/j.tetlet.2014.12.007](https://doi.org/10.1016/j.tetlet.2014.12.007)
- [8] Jasiński, R.; Competition between one-step and two-step mechanism in polar [3+2] cycloadditions of (Z)-C-(3,4,5-trimethoxyphenyl)-n-methyl-nitrone with (Z)-2-EWG-1-bromo-1-nitroethenes. *Comput. Theor. Chem.* **2018**, 1125, 77–85. DOI: [10.1016/j.comptc.2018.01.009](https://doi.org/10.1016/j.comptc.2018.01.009)
- [9] Jasiński, R.; In the searching for zwitterionic intermediates on reaction paths of [3+2] cycloaddition reactions between 2,2,4,4-tetramethyl-3-thiocyclobutanone S-methylide and polymerizable olefins. *RSC Adv.* **2015**, 5 (122), 101045–101048. DOI: [10.1039/C5RA20747A](https://doi.org/10.1039/C5RA20747A)
- [10] Domingo, L.R.; Ríos-Gutiérrez, M.; Silvi, B.; Pérez, P.; The mysticism of pericyclic reactions: A contemporary rationalisation of organic reactivity based on Electron Density Analysis. *Eur. J. Org. Chem.* **2018**, 9, 1107–1120. DOI: [10.1002/ejoc.201701350](https://doi.org/10.1002/ejoc.201701350)
- [11] Ríos-Gutiérrez, M.; Domingo, L.R.; Unravelling the mysteries of the [3+2] cycloaddition reactions. *Eur. J. Org. Chem.* **2019**, 2, 267–282. DOI: [10.1002/ejoc.201800916](https://doi.org/10.1002/ejoc.201800916)
- [12] Domingo, L.R.; Kula, K.; Rios-Gutierrez, M.; Jasinski, R.; Understanding the participation of fluorinated azomethine ylides in carbenoid-type [3+2] cycloaddition reactions with ynal systems: A molecular electron density theory study. *J. Org. Chem.* **2021**, 86 (18), 12644–12653. DOI: [10.1021/acs.joc.1c01126](https://doi.org/10.1021/acs.joc.1c01126)
- [13] Chastanet, J.; Roussi, G.; Study of the Regiochemistry and stereochemistry of the [3+2] cycloaddition between nonstabilized azomethine ylides generated from tertiary amine N-oxides and various dipolarophiles. *J. Org. Chem.* **1988**, 53 (16), 3808–3812. DOI: [10.1021/jo00251a026](https://doi.org/10.1021/jo00251a026)
- [14] Heine, H.W.; Peavy, R.; Aziridines XI. Reaction of 1,2,3-Triphenylaziridine with diethylacetylene dicarboxylate and maleic anhydride. *Tetrahedron Lett.* **1965**, 6 (35), 3123–3126. DOI: [10.1016/S0040-4039\(01\)89232-7](https://doi.org/10.1016/S0040-4039(01)89232-7)
- [15] Żmigrodzka, M.; Sadowski, M.; Kras, J.; Desler, E.; Demchuk, O.M.; Kula, K.; Polar [3+2] cycloaddition between N-methyl azomethine ylide and trans-3,3,3-trichloro-1-nitroprop-1-ene. *Sci. Rad.* **2022**, 1 (1), 26–35. DOI: [10.58332/v22i1a02](https://doi.org/10.58332/v22i1a02)
- [16] Żmigrodzka, M.; Dresler, E.; Hordyjewicz-Baran, Z.; Kulesza, R.; Jasiński, R.; A unique example of noncatalyzed [3+2] cycloaddition involving (2E)-3-aryl-2-nitroprop-2-enenitriles. *Chem. Heterocycl. Comp.* **2017**, 53 (10), 1161–1162. DOI: [10.1007/s10593-017-2186-6](https://doi.org/10.1007/s10593-017-2186-6)
- [17] Chornous, V.A.; Mel'nik, O.Ya.; Mel'nik, D.A.; Rusanov, E.B.; Vovk, M.V.; Polyfunctional imidazoles: XI. Reaction of 1-aryl-4-chloro-5-(2-nitroviny)-1H-imidazoles with



- nonstabilized azomethine ylides. synthesis of (1-aryl-4-chloro-1H-imidazol-5-yl)-substituted nitropyrrolidines and nitropyrrrolizines. *Russ. J. Org. Chem.* **2015**, 51 (10), 1423–1429. DOI: [10.1134/S1070428015100115](https://doi.org/10.1134/S1070428015100115)
- [18] Starosotnikov, A.M.; Bastrakov, M.A.; Pechenkin, S.Yu.; Leontieva, M.A.; Kachala, V.V.; Shevelev, S.A.; 1,3-dipolar cycloaddition of unstabilized N-methyl azomethine ylide to nitrobenzene annelated with azoles. *J. Heterocycl. Chem.* **2011**, 48 (4), 824–828. DOI: [10.1002/jhet.599](https://doi.org/10.1002/jhet.599)
- [19] Silva, A.M.G.; Tomé, A.C.; Neves, M.G.P.M.S.; Silva, A.M.S.; Cavaleiro, J.A.S.; 1,3-dipolar cycloaddition reactions of porphyrins with azomethine ylides. *J. Org. Chem.* **2005**, 70 (6), 2306–2314. DOI: [10.1021/jo048349i](https://doi.org/10.1021/jo048349i)
- [20] Kurzer, F.; Fulminic acid in the history of organic chemistry. *J. Chem. Educ.* **2000**, 77 (7), e851. DOI: [10.1021/ed077p851](https://doi.org/10.1021/ed077p851)
- [21] Beltrame, P.; Sartirana, P.; Vintani, C.; Relative rates of the concurrent reactions in the addition of a substituted benzonitrile oxide to arylacetylenes. *J. Chem. Soc.*, **1971**, 814–817. DOI: [10.1039/j29710000814](https://doi.org/10.1039/j29710000814)
- [22] Beltrame, P.; Veglio, C.; Simonetta, M.; Kinetics and mechanism of 1,3-cycloaddition of a substituted benzonitrile oxide to a series of arylacetylenes. *J. Chem. Soc.* **1967**, 867–873. DOI: [10.1039/j29670000867](https://doi.org/10.1039/j29670000867)
- [23] Kondo, Y.; Uchiyama, D.; Sakamoto, T.; Yamanaka, H.; Synthesis and reactions of 5-(tributylstannyl)isoxazoles. *Tetrahedron Lett.* **1989**, 30 (32), 4249–4250. DOI: [10.1016/S0040-4039\(01\)80702-4](https://doi.org/10.1016/S0040-4039(01)80702-4)
- [24] Zawadzińska, K.; Ríos-Gutiérrez, M.; Kula, K.; Woliński, P.; Mirosław, B.; Krawczyk, T.; Jasiński, R.; The participation of 3,3,3-trichloro-1-nitroprop-1-ene in the [3+2] cycloaddition reaction with selected nitrile N-oxides in the light of the experimental and MEDT quantum chemical study. *Molecules* **2021**, 26 (22), e6774. DOI: [10.3390/molecules26226774](https://doi.org/10.3390/molecules26226774)
- [25] Zawadzińska, K.; Kula, K.; Application of  $\beta$ -phosphorylated nitroethenes in [3+2] cycloaddition reactions involving benzonitrile N-oxide in the light of a DFT computational study. *Organics* **2021**, 2 (1), 26–37. DOI: [10.3390/org2010003](https://doi.org/10.3390/org2010003)
- [26] Tanaka, J.; Kanemasa, S.; Ab initio study of lewis acid catalyzed nitronc cycloaddition to electron deficient alkenes. Does a lewis acid catalyst change the reaction mechanism? *Tetrahedron* **2001**, 57 (5), 899–905. DOI: [10.1016/S0040-4020\(00\)01045-0](https://doi.org/10.1016/S0040-4020(00)01045-0)
- [27] Komaromi, I.; Tronchet, J.M.J.; Geometry and electronic structure of model small nitrones and their tautomers. *J. Mol. Struct.* **1996**, 366 (3), 147–160. DOI: [10.1016/0166-1280\(96\)04584-8](https://doi.org/10.1016/0166-1280(96)04584-8)

- [28] Sustmann, R.; Sicking, W.; Huisgen, R.; The high reactivity of the CS double bond in 1,3-dipolar cycloadditions of nitrones: A molecular orbital theoretical analysis. *J. Am. Chem. Soc.* **1995**, 117 (38), 9679–9685. DOI: [10.1021/ja00143a009](https://doi.org/10.1021/ja00143a009)
- [29] Sims, J.; Houk, K.N.; Reversal of nitron cycloaddition regioselectivity with electron-deficient dipolarophiles. *J. Am. Chem. Soc.* **1973**, 95 (17), 5798–5800. DOI: [10.1021/ja00798a079](https://doi.org/10.1021/ja00798a079)
- [30] Zawadzińska, K.; Gadocha, Z.; Pabian, K.; Wróblewska, A.; Wielgus, E.; Jasiński, R.; The first examples of [3+2] cycloadditions with the participation of (E)-3,3,3-tribromo-1-nitroprop-1-ene. *Materials* **2022**, 15 (21), e7584. DOI: [10.3390/ma15217584](https://doi.org/10.3390/ma15217584)
- [31] Jasiński, R.; The question of the regiodirection of the [2+3] cycloaddition reaction of triphenylnitron to nitroethene. *Chem. Heterocycl. Comp.* **2009**, 45 (6), 748–749. DOI: [10.1007/s10593-009-0318-3](https://doi.org/10.1007/s10593-009-0318-3)
- [32] Jasiński, R.; Mróz, K.; Kačka, A.; Experimental and theoretical DFT study on synthesis of sterically crowded 2,3,3,(4)5-tetrasubstituted-4-nitroisoxazolidines via 1,3-dipolar cycloaddition reactions between ketonitrones and conjugated nitroalkenes. *J. Heterocycl. Chem.* **2015**, 53 (5), 1424–1429. DOI: [10.1002/jhet.2442](https://doi.org/10.1002/jhet.2442)
- [33] Siadati, S.A.; Alinezhad, M.; (2015). A theoretical study on the functionalisation process of C<sub>18</sub>NB fullerene through its open [5,5] cycloaddition with 4-pyridine nitrile oxide. *Prog. React. Kinet. Mech.* **2015**, 40 (2), 169–176. DOI: [10.3184/146867815X14262612008408](https://doi.org/10.3184/146867815X14262612008408)
- [34] Nyerges, M.F.I.; Virányi, A.; Groundwater, P.W.; Töke, L.; A new and convenient synthesis of 1-aryl-2-dimethylaminoethanols. *Synthesis* **2004**, 2001 (10), 1479–1482. DOI: [10.1055/s-2001-16077](https://doi.org/10.1055/s-2001-16077)
- [35] Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P.; 1,3 dipolar cycloadditions of azomethine ylides with aromatic aldehydes. Syntheses of 1-oxapyrrolizidines and 1,3-oxazolidines. *Tetrahedron* **1988**, 44 (2), 519–541. DOI: [10.1016/S0040-4020\(01\)85842-7](https://doi.org/10.1016/S0040-4020(01)85842-7)
- [36] Bhat, A.R.; Athar, F.; Azam, A.; New derivatives of 3,5-substituted-1,4,2-dioxazoles: Synthesis and activity against entamoeba histolytica. *Eur. J. Med. Chem.* **2009**, 44 (2), 926–936. DOI: [10.1016/j.ejmech.2008.02.001](https://doi.org/10.1016/j.ejmech.2008.02.001)
- [37] Couturier, M.; Tucker, J.; Proulx, C.; Boucher, G.; Dubé, P.; Andresen, B.M.; Ghosh, A.; 5,5-dimethyl-1,4,2-dioxazoles as versatile aprotic hydroxamic acid protecting groups. *J. Org. Chem.* **2002**, 67 (14), 4833–4838. DOI: [10.1021/jo0256890](https://doi.org/10.1021/jo0256890)

- [38] Polat-Cakir, S.; 1,3-dipolar cycloaddition reactions of acyl phosphonates with nitrile oxides: synthesis of phosphonate-containing dioxazole derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2021**, 196 (5), 461–467. DOI: [10.1080/10426507.2020.1854259](https://doi.org/10.1080/10426507.2020.1854259)
- [39] Bouhfid, R.; Joly, N.; Essassi, E.M.; Lequart, V.; Massoui, M.; Martin, P.; Synthesis of new spiro[1,4,2-dioxazole-5,3'-indolin]-2'-one by 1,3-dipolar cycloaddition. *Synth. Commun.* **2011**, 41 (14), 2096–2102. DOI: [10.1080/00397911.2010.497595](https://doi.org/10.1080/00397911.2010.497595)
- [40] Pechmann, H.V.; Pyrazol aus acetylen und diazomethan. *Ber. Dtsch. Chem. Ges.* **1898**, 31 (3), 2950–2951. DOI: [10.1002/cber.18980310363](https://doi.org/10.1002/cber.18980310363)
- [41] Huisgen, R.; Koszinowski, J.; Ohta, A.; Schiffer, R.; Cycloadditions of diazoalkanes to 1-alkenes. *Angew. Chem. Int. Ed. Engl.* **1980**, 19 (3), 202–203. DOI: [10.1002/anie.198002021](https://doi.org/10.1002/anie.198002021)
- [42] Kula, K.; Łapczuk, A.; Sadowski, M.; Kras, J.; Zawadzińska, K.; Demchuk, O.M.; Gaurav, G.K.; Wróblewska, A.; Jasiński, R.; (2022). On the question of the formation of nitro-functionalized 2,4-pyrazole analogs on the basis of nitylimine molecular systems and 3,3,3-trichloro-1-nitroprop-1-ene. *Molecules* **2022**, 27 (23), e8409. DOI: [10.3390/molecules27238409](https://doi.org/10.3390/molecules27238409)
- [43] Sadowski, M.; Utnicka, J.; Wójtowicz, A.; Kula, K. The global and local reactivity of C,N-diarylnitrile imines in [3+2] cycloaddition processes with trans- $\beta$ -nitrostyrene according to Molecular Electron Density Theory: A computational study. *Curr. Chem. Lett.* **2023**, 12 (2), 421–430. DOI: [10.5267/j.ccl.2022.11.004](https://doi.org/10.5267/j.ccl.2022.11.004)
- [44] Kula, K.; Dobosz, J.; Jasiński, R.; Kačka-Zych, A.; Łapczuk-Krygier, A.; Mirosław, B.; Demchuk, O.M.; [3+2] cycloaddition of diaryldiazomethanes with (e)-3,3,3-trichloro-1-nitroprop-1-ene: An experimental, theoretical and structural study. *J. Mol. Struct.* **2020**, 1203 e127473. DOI: [10.1016/j.molstruc.2019.127473](https://doi.org/10.1016/j.molstruc.2019.127473)
- [45] Tang, D.; Wu, P.; Liu, X.; Chen, Y.-X.; Guo, S.-B.; Chen, W.-L.; Li, J.-G.; Chen, B.-H.; Synthesis of multisubstituted imidazoles via copper-catalyzed [3+2] cycloadditions. *J. Org. Chem.* **2013**, 78 (6), 2746–2750. DOI: [10.1021/jo302555z](https://doi.org/10.1021/jo302555z)
- [46] Dresler, E.; Wróblewska, A.; Jasiński, R.; Understanding the regioselectivity and the molecular mechanism of [3+2] cycloaddition reactions between nitrous oxide and conjugated nitroalkenes: A DFT computational study. *Molecules* **2022**, 27 (23), e8441. DOI: [10.3390/molecules27238441](https://doi.org/10.3390/molecules27238441)
- [47] Bridson-Jones, F.S.; Buckley, G.D.; Cross, L.H.; Driver, A.P.; 666. Oxidation of organic compounds by nitrous oxide. Part I. *J. Chem. Soc.* **1951**, 2999–3008. DOI: [10.1039/jr9510002999](https://doi.org/10.1039/jr9510002999)

- [48] Banert, K.; Plefka, O.; Synthesis with perfect atom economy: Generation of diazo ketones by 1,3-dipolar cycloaddition of nitrous oxide at cyclic alkynes under mild conditions. *Angew. Chem. Int. Ed.* **2011**, 50 (27), 6171–6174.  
DOI: [10.1002/anie.201101326](https://doi.org/10.1002/anie.201101326)
- [49] Woliński, P.; Kačka-Zych, A.; Demchuk, O.M.; Łapczuk-Krygier, A.; Mirosław, B.; Jasiński, R.; Clean and molecularly programmable protocol for preparation of bis-heterobiaryllic systems via a domino pseudocyclic reaction as a valuable alternative for TM-catalyzed cross-couplings. *J. Clean. Prod.* **2020**, 275, e122086.  
DOI: [10.1016/j.jclepro.2020.122086](https://doi.org/10.1016/j.jclepro.2020.122086)
- [50] Wagner, G.; Pombeiro, A.J.L.; Kukushkin, V.Yu.; Platinum(IV)-assisted [2+3] cycloaddition of nitrones to coordinated organonitriles. synthesis of  $\Delta^4$ -1,2,4-oxadiazolines. *J. Am. Chem. Soc.* **2000**, 122 (13), 3106–3111. DOI: [10.1021/ja993564f](https://doi.org/10.1021/ja993564f)
- [51] Wagner, G.; Haukka, M.; Fraústo Da Silva, J.J.R.; Pombeiro, A.J.L.; Kukushkin, V.Yu.; [2+3] cycloaddition of nitrones to platinum-bound organonitriles: Effect of metal oxidation state and of nitrile substituent. *Inorg. Chem.* **2001**, 40 (2), 264–271.  
DOI: [10.1021/ic000477b](https://doi.org/10.1021/ic000477b)
- [52] Shimizu, N.; Bartlett, P.D.; Cycloaddition of diazoalkanes to penta- and hexafluoroacetones. Isolation of  $\Delta^3$ -1,3,4-oxadiazolines and their decomposition via carbonyl ylides. *J. Am. Chem. Soc.* **1978**, 100 (13), 4260–4267.  
DOI: [10.1021/ja00481a042](https://doi.org/10.1021/ja00481a042)
- [53] Ohshiro, Y.; Komatsu, M.; Okamura, A.; Agawa, T.; Cycloaddition of vinyl isocyanate to 1,3-dipoles. *Bull. Chem. Soc. Jpn.* **1984**, 57 (3), 901–902. DOI: [10.1246/bcsj.57.901](https://doi.org/10.1246/bcsj.57.901)
- [54] Hisano, T.; Harano, K.; Fukuoka, R.; Matsuoka, T.; Muraoka, K.; Shinohara, I.; Reaction of aromatic N-oxides with dipolarophiles. XI 1,3-dipolar cycloaddition reaction of pyridine n-oxides with tosyl isocyanate and one-pot synthesis of 2-oxooxazolo(4,5-b)-pyridine derivatives. *Chem. Pharm. Bull.* **1986**, 34 (4), 1485–1492.  
DOI: [10.1248/cpb.34.1485](https://doi.org/10.1248/cpb.34.1485)
- [55] Beltrame, P.; Vintani, C.; Kinetics and mechanism of 1,3-cycloaddition of a substituted benzonitrile oxide to N-sulphonylanilines. *J. Chem. Soc.* **1970**, 873–876.  
DOI: [10.1039/j29700000873](https://doi.org/10.1039/j29700000873)
- [56] Pokhodylo, N.T.; Tupyshak, M.A.; Shyyka, O.Ya.; Obushak, M.D.; Some aspects of the azide-alkyne 1,3-dipolar cycloaddition reaction. *Russ. J. Org. Chem.* **2019**, 55 (9), 1310–1321. DOI: [10.1134/S1070428019090082](https://doi.org/10.1134/S1070428019090082)

- [57] Abu-Orabi, S.T.; Atfah, M.A.; Jibril, I.; Mari'i, F.M.; Ali, A.A.-S.; Dipolar cycloaddition reactions of organic azides with some acetylenic compounds. *J. Heterocycl. Chem.* **1989**, 26 (5), 1461–1468. DOI: [10.1002/jhet.5570260541](https://doi.org/10.1002/jhet.5570260541)
- [58] Cailleux, P.; Piet, J.C.; Benhaoua, H.; Carrié, R.; Cycloaddition des méthylazide et phénylazide au  $\beta$ -nitrostyrène et au nitropropène homologue. *Bull. Soc. Chim. Belg.* **2010**, 105 (1), 45–51. DOI: [10.1002/bscb.19961050108](https://doi.org/10.1002/bscb.19961050108)
- [59] Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E.; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P.; Ce(OTf)<sub>3</sub> - catalyzed [3+2] cycloaddition of azides with nitroolefins: regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles. *J. Org. Chem.* **2014**, 79 (10), 4463–4469. DOI: [10.1021/jo5004339](https://doi.org/10.1021/jo5004339)
- [60] Rengasamy, R.; Vijayalakshmi, K.; Punitha, N.; Raj, J.P.; Karthikeyan, K.; Elangovan, J.; A novel route to 1,4-disubstituted-1,2,3-triazoles through metal-free decarboxylative azide-alkene cycloaddition. *Tetrahedron Lett.* **2021**, 84, 153440. DOI: [10.1016/j.tetlet.2021.153440](https://doi.org/10.1016/j.tetlet.2021.153440)
- [61] Fuchs, E.P.O.; Hermesdorf, M.; Schnurr, W.; Rösch, W.; Heydt, H.; Regitz, M.; Binger, P.; Ungewöhnlich koordinierte Phosphorverbindungen. *J. Organomet. Chem.* **1988**, 338 (3), 329–340. DOI: [10.1016/0022-328X\(88\)80006-8](https://doi.org/10.1016/0022-328X(88)80006-8)
- [62] Carpenter, W.R.; The formation of tetrazoles by the condensation of organic azides with nitriles. *J. Org. Chem.* **1962**, 27 (6), 2085–2088. DOI: [10.1021/jo01053a043](https://doi.org/10.1021/jo01053a043)
- [63] Sarvary, A.; Khosravi, F.; Ghanbari, M.; Synthesis of fused 1,5-disubstituted tetrazoles via a one-pot knoevenagel condensation/nucleophilic substitution/intramolecular /intermolecular [3+2] cycloaddition reaction. *Monatsh. Chem.* **2018**, 149 (1), 39–45. DOI: [10.1007/s00706-017-2062-1](https://doi.org/10.1007/s00706-017-2062-1)
- [64] Kröckert, B.; Van Bonn, K.-H.; Paetzold, P.; The Iminoborane tBuB≡NtBu as a dipolarophile in (2+3) cycloadditions. *Z. anorg. allg. Chem.* **2005**, 631 (5), 866–868. DOI: [10.1002/zaac.200500010](https://doi.org/10.1002/zaac.200500010)
- [65] Jasiński, R.; Dresler, E.; On the question of zwitterionic intermediates in the [3+2] cycloaddition reactions: A critical review. *Organics* **2020**, 1 (1), 49–69. DOI: [10.3390/org1010005](https://doi.org/10.3390/org1010005)

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