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HETEROCYCLES IN FOCUS

Recent progress in the synthesis of nitroisoxazoles and their hydrogenated analogs *via* [3+2] cycloaddition reactions (microreview)

Radomir Jasiński[1]*

[1] *Department of Organic Chemistry and Technology, Cracow University of Technology, 24 Warszawska St., Cracow 31-155, Poland; e-mail: radomir.jasinski@pk.edu.pl*

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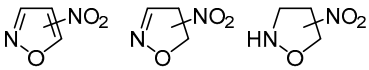


In this microreview, the application of [3+2] cycloaddition reactions for the selective preparation of nitroisoxazoles and their hydrogenated analogs was analyzed on the basis of recent publications. It was found that most discussed processes are realized at room temperature with high or full selectivity.

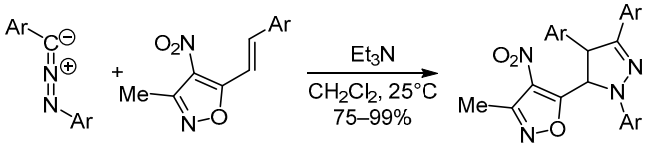
Introduction

Isoxazoles and their hydrogenated analogs (dihydroisoxazoles and tetrahydroisoxazoles) play an important role as key molecular fragments of many important compounds characterized by high biological activity.[1–3] The presence of the nitro group at the heterocyclic ring additionally stimulates bioactive functions[4] and, subsequently, creates a wide range of potential possibilities of the further functionalization.[5] The synthesis of these structures can be realized by different pathways.[6–10]

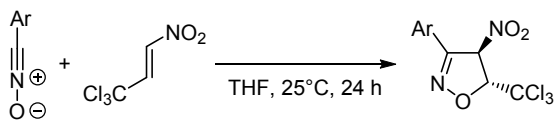
The most general approach is however evidently the [3+2] cycloaddition (32CA) reactions[11] with the participation of unsaturated nitro compounds (they can be easily prepared using commercially available and cheap starting materials[12]). It should be emphasized, that the 32CA processes are realized with the 100% atomic economy and under relatively mild conditions as well as with good selectivity.[6–8] In light of aforementioned, the strategy for the preparation of the title compounds is actually very interesting for scientists.

Synthesis of nitroisoxazoles and 4,5-dihydronitroisoxazoles

Direct synthesis of the parent nitroisoxazoles *via* 32CA reactions is problematic because of unstable nature of nitroacetylenes theoretically regarded as partners for cycloaddition to the nitrile oxides.[13] The 32CA approach can be however applied for the functionalization of molecules including nitroisoxazole moiety. For example, 5-(2-arylethenyl)-3-methyl-4-nitroisoxazole reacts with generated *in situ* diarylnitrile imines.[14]



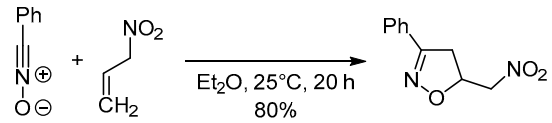
Dihydroisoxazoles functionalized by NO_2 group can be directly prepared in reaction between nitrile *N*-oxides and nitroalkenes. For example, the 32CA reactions of benzonitrile *N*-oxides and (*E*)-3,3,3-trichloro-1-nitroprop-1-ene are realized with the full regioselectivity and lead to the respective 3-aryl-4-nitro-5-trichloromethyl-4,5-dihydroisoxazoles.[15] The regioselectivity observed can be easily explained within Molecular Electron Density Theory.[16]



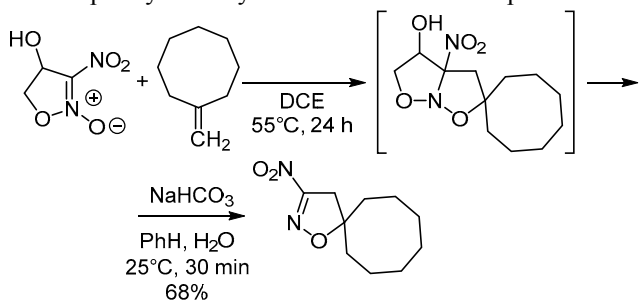
Radomir Jasiński was born in 1975 in Radom, Radomskie voivodship, Poland. He received PhD in Chemistry in 2004 (Cracow University of Technology), and the habilitation in 2014 (Silesian University of Technology). At present, he works as the head of the Organic Chemistry Research Group at the Faculty of Chemical Technology and Engineering, Cracow University of Technology. In addition, he holds the function of the Vice-Dean of this Faculty. His research interests include kinetic aspects and selectivity of cycloaddition reactions, chemistry of conjugated nitroalkenes, and applications of DFT methods for the exploration of organic reaction mechanisms.

Synthesis of nitroisoxazoles and 4,5-dihydronitroisoxazoles (continued)

Opposite regioselectivity is observed within similar reaction with the participation of allylic type nitroalkenes. For example, benzonitrile *N*-oxide reacts with the 3-nitroprop-1-ene yielding 5-nitromethyl-3-phenyl-4,5-dihydroisoxazole.[17]

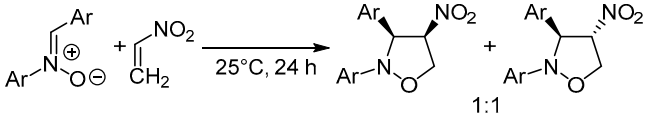


Preparation of the 3-nitro-substituted 4,5-dihydroisoxazole molecular system is possible *via* 32CA of 3-nitro-4-hydroxyisoxazoline *N*-oxide to methylidenecyclooctane. Under the reaction conditions, the primary product is converted into 3-nitro spirocyclic dihydroisoxazole molecular platform.[18]

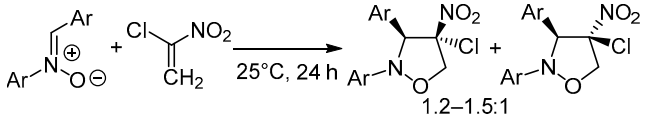


Synthesis of 2,3,4,5-tetrahydronitroisoxazoles

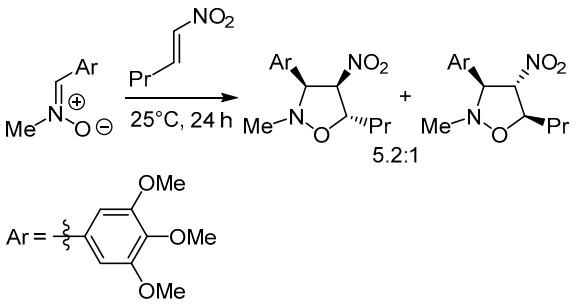
Nitroethene reacts with diarylnitrones at room temperature. These reactions lead to equimolar mixtures of respective 3,4-*cis*- and 3,4-*trans*-2,3-diaryl-4-nitrotetrahydroisoxazoles.[19,20]



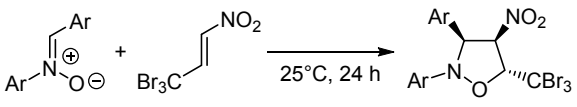
For the comparison, similar reactions with the participation of more electrophilic 1-chloro-1-nitroethene are realized with a preference for 4-nitro adducts with the 3,4-*cis* configuration.[21]



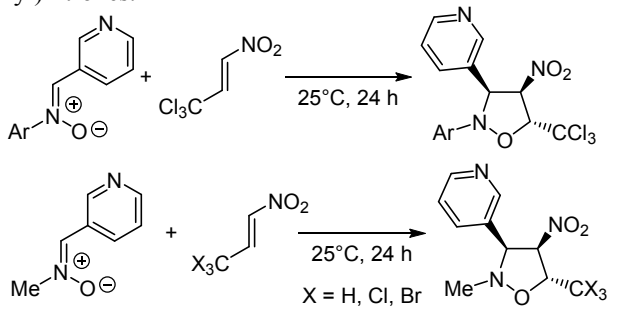
Next, in the case of 32CA between (*Z*)-*N*-methyl(3,4,5-trimethoxyphenyl)nitrone and (*E*)-1-nitropent-1-ene, 3,4-*cis*-2,3-arylmethyl-4-nitro-5-propyltetrahydroisoxazole evidently dominates in the postreaction mixture.[22]



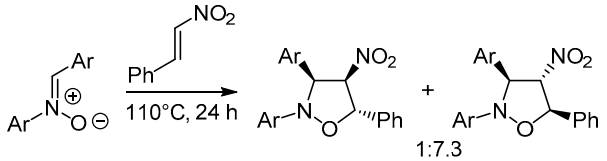
Full regio- and stereocontrol is possible in the case of analogous 32CAs between diarylnitrones and little known (*E*)-3,3,3-tribromo-1-nitroprop-1-ene. Within these reactions, 3,4-*cis*-2,3-diaryl-4-nitro-5-tribromomethyltetrahydroisoxazoles are formed as single cycloaddition products.[23]



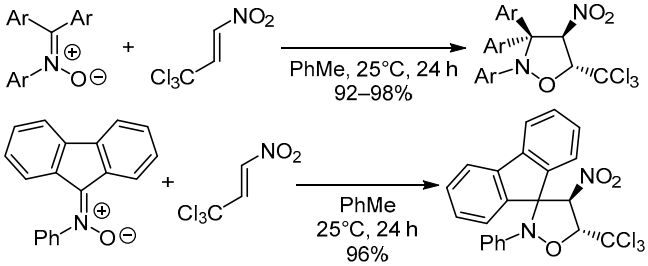
Similar regioselectivity is also observed in the case of the synthesis of nitro-functionalized nicotinoids on the basis of (*Z*)-*N*-aryl(pyridin-3-yl)nitrones[24] and (*Z*)-*N*-methyl(pyridin-3-yl)nitrones.[25]



In contrast, 32CA of (*Z*)-*C*,*N*-diarylnitrones to (*E*)-2-phenylnitroethene yielded the mixture of respective 3,4-*cis*- and 3,4-*trans*-2,3,5-triaryl-4-nitrotetrahydroisoxazoles with the clear preference for the *trans* diastereoisomeric form. This reaction requires relatively high temperature of about 110°C.[26]

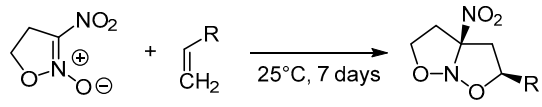


In the case of electrophilically activated nitroethenes, preparation of nitrotetrahydroisoxazoles is possible even *via* 32CA reactions with the participation of sterically crowded nitrones. For example, *C*,*C*,*N*-trisubstituted nitrones react at room temperature with the (*E*)-3,3,3-trichloro-1-nitroprop-1-ene with the formation of respective 4,5-*trans*-2,3,3-triaryl-4-nitro-5-trichloromethyltetrahydroisoxazoles.[27,28]



Synthesis of 2,3,4,5-tetrahydronitroisoxazoles (continued)

It is interesting that in any mentioned case of nitrone–nitroalkene 32CA reactions, 5-nitro-substituted tetrahydroisoxazoles are not formed. This phenomenon can be easily explained by the nature of the local nucleophile–electrophile interactions.[29] The unique example of the synthesis of 5-nitro-2,3-diphenyl-4-R-tetrahydroisoxazoles was described very recently regarding to the 32CA reactions with the participation of nitroacrylic acid derivatives.[30] Preparation of tetrahydroisoxazole skeleton functionalized by NO_2 group at position 3 is possible *via* 32CA reactions with the participation of the 3-nitroisoxazoline 2-oxide.[31]



Finally, it should be underlined that all the presented 32CA processes are realized with the retention of the primary configuration of the reagents. This is a consequence of one-step mechanism, which in the light of the Domingo terminology should be classified as polar, one-step/two-stage.[32]

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