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Ionic liquid-promoted [3+2]-cycloaddition reactions of nitroformonitrile oxide generated by the cycloreversion of dinitrofuroxan

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ABSTRACT

A new approach to the synthesis of 3-nitroisoxazoles and 3-nitroisoxazolines based on the [3+2]-cycloaddition of nitroformonitrile oxide (NFNO), generated by the cycloreversion of dinitrofuroxan (DNFO), to acetylene and ethylene derivatives, under ionic liquid catalysis is developed. The approach is of a general nature and applicable to cycloaddition reactions with other dipolarophiles.

The 1,3-dipolar cycloaddition of 1,3-dipoles to dipolarophiles is one of the most convenient and general methods for the synthesis of five-membered heterocyclic compounds of various classes,[1] which are widely used as medical and crop protection agents.[2] Nitrile oxides are amongst the most reactive 1,3-dipoles employed to construct five-membered *N,O*-containing heterocycles (isoxazoles, isoxazolines and 1,2,4-oxadiazoles).[3] It is well-known that isoxazoles, and their partially hydrogenated analogues, isoxazolines, constitute classes of heterocycles possessing a wide range of applications as versatile building blocks in organic synthesis.[4] Their biological activity includes antibacterial, antiviral and antifungal behaviour.[5a] Also, they can act as glutamate and GABA receptor ligands and display herbicide activity.[5b,c] Along with the 1,3-dipolar cycloaddition of nitrile oxides to acetylene and ethylene derivatives, the reaction of hydroxylamine with 1,3-diketones or α,β-unsaturated ketones is applied to construct isoxazoles with various substituents.[5a] However, no reports on the synthesis of 3-nitrosubstituted isoxazoles and isoxazolines by either of the methods are available in the literature. Meanwhile these compounds are important as antibacterial agents.[6]

Only a few synthetic approaches for the preparation of 3-nitrosubstituted isoxazoles have been described. These compounds can be obtained by intramolecular cyclization of substituted nitrolic acids generated from propargyl halides[7] or 1,3-dihalopropanes[8] and sodium nitrite. Another method is based on the reaction of chloronitrolic acids with Grignard derivatives of acetylene.[9] An interesting approach to the synthesis of mono- and disilyl-substituted 3-nitroisoxazoles is via the reaction of tetranitroethylene with trimethylsilyl-substituted acetylenes.[10] Recently, a new method for the preparation of 3-nitroisoxazoles based on the heterocyclization of electrophilic alkenes under the action of tetranitromethane activated by Et_3N was published.[11] However, the authors later refuted this information and unambiguously established that the reaction products were 5-nitroisoxazoles.[12]

The best approach for the synthesis of 3-nitroisoxazoles or 3-nitroisoxazolines might be via the [3+2]-cycloaddition of nitroformonitrile oxide (NFNO) to the appropriate dipolarophiles. However, the known methods for NFNO generation (treatment of dinitromethane potassium salt with 30% fuming sulfuric acid at 20 °C, or 95% H_2SO_4 at 100 °C and nitration of 2-methyl-1-nitro-1-propene with a sulfuric-nitric acid mixture)[13a,b] cannot be used for our purpose.

Here we present our research on a new approach for the synthesis of 3-nitrosubstituted isoxazoles **1** and isoxazolines **2** via the [3+2]-cycloaddition reaction of acetylene and ethylene derivatives to NFNO, generated in situ by the cycloreversion of dinitrofuroxan (DNFO) under the catalysis of ionic liquids (ILs).

The nitrile oxides for the heterocycle construction are usually prepared in situ in the presence of the corresponding dipolarophiles. Typical pathways to nitrile oxides are the

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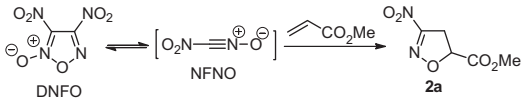
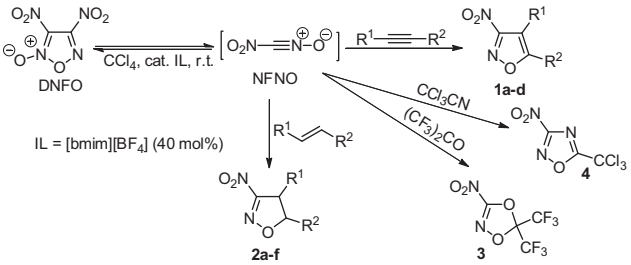
0040-4039/



Scheme 1. Synthesis of isoxazoline **2a**.



Scheme 2. Synthesis of 3-nitroheterocycles by [3+2]-cycloaddition of NFNO to dipolarophiles.

dehydrochlorination of hydroxamic acid chlorides under the action of bases, thermolysis of nitrolic acids and dehydration of nitroalkanes.[3,4] An important approach to nitrile oxides is the cycloreversion of symmetrically substituted 1,2,5-oxadiazol-2-oxides (furoxans) resulting in two molecules of the nitrile oxides, from which the furoxans were originally constructed. As a rule, a cycloreversion proceeds at high temperature,[14,15] though, as we found earlier,[16] the cycloreversion of DNFO in CCl_4 can occur at room temperature to afford an equilibrium mixture of DNFO and its monomeric form–NFNO, where the cyclic form predominates dramatically.

The reactions between DNFO and activated nitriles (trichloroacetonitrile, methoxycarbonyl cyanide) in CCl_4 allowed the synthesis of two representative 3-nitro-1,2,4-oxadiazoles. The reactions were completed in seven days at rt (TLC monitoring) and the final products were obtained in low yields (21% and 23%), whilst remaining DNFO decomposed under the reaction conditions. An increase in the reaction temperature did not promote the cycloaddition, but accelerated DNFO decomposition. Attempts to synthesize 3-nitroisoxazoles or 3-nitroisoxazolines by the reaction of DNFO with appropriate dipolarophiles, in particular phenylacetylene and *trans*-stilbene, failed under the above-mentioned conditions. Evidently, the rate of DNFO decomposition exceeded that of the DNFO cycloaddition to the dipolarophiles.

Ionic liquids (ILs) are widely used as reaction media or catalysts for the promotion of many reactions (especially heterolytic examples). ILs have become beneficial in modern 'green' chemistry owing to their useful physicochemical properties (non-flammability, low vapour pressure, possible recovery, etc.).[17] ILs consisting of non-coordinated ions form an ideal environment for 1,3-dipolar intermediates, which may lead to an unprecedented increase in the rate and selectivity of these processes.[18] Nitrile oxide cycloaddition reactions with olefins in the ILs, $[bmim]BF_4$ and $[bmim]PF_6$, have been exemplified.[19]

To this end, we decided to study these reactions using ILs as the reaction media or catalysts, with a view to develop methods for the preparation of 3-nitroisoxazoles **1** or 3-nitroisoxazolines **2** on the basis of the [3+2]-cycloaddition of NFNO, generated by the cycloreversion of DNFO, to the appropriate dipolarophiles. To optimize the reaction conditions we used methyl acrylate as a dipolarophile, which was added in considerable excess (5 mol per 1 mol DNFO) because of the low NFNO concentration (Scheme 1, Table 1). An attempt to perform the reaction between DNFO and methyl acrylate in 1-butyl-3-methylimidazolium tetrafluoroborate ($[bmim]BF_4$) caused an explosion! Therefore, in subsequent experiments, the ILs were used in catalytic amounts and reactions were carried out in CCl_4 since DNFO had been obtained in this solvent[13] (Scheme 1, Table 1). Different ILs were added to the reaction mixtures in amounts from 20 to 100 mol % (entries 2–5). The completion of the reaction was determined by the disappearance of DNFO in the reaction mixture (TLC monitoring). The optimum amount of IL was found to be 40 mol % (entry 3) and both the reaction time and 3-nitroisoxazoline **2a** yield did not depend on the IL structure (entries 3, 6 and 7). For further investigations we selected $[bmim]BF_4$ as the IL because of its ready availability and low cost. By varying the amount of the dipolarophile, a value of 5 mol of dipolarophile per 1 mol of DNFO was found to be optimum. The yield of the final compound **2a** was lower on both decreasing and increasing the amount of methyl acrylate (entries 8–12).

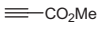
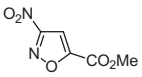
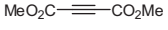
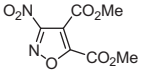
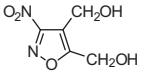
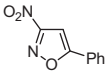
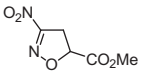
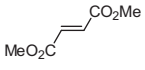
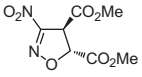
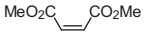
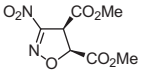
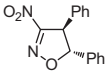
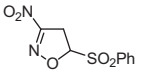
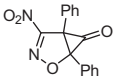
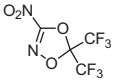
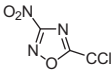
Using the optimized conditions, both terminal and internal acetylene and ethylene derivatives successfully reacted with DNFO (Scheme 2, Table 2, entries 1–10), including those dipolarophiles that had been inactive in our previous research[16] (entries 4 and 8). The corresponding 3-nitroisoxazoles **1** and 3-nitroisoxazolines **2** were obtained in moderate yields in all cases. Moreover, the reaction was found to be general as the carbonyl group participated in the cycloaddition with NFNO (compound **3**, entry 11), whereas the reaction with diphenylcyclopropenone only occurred on the double bond (entry 10). As expected, the rate of the reaction with trichloroacetonitrile (compound **4**) increased under IL catalysis (entry 12). The low yields of the final products could be attributed to partial decomposition of DNFO under the reaction conditions.

Table 1
Optimization of the [3+2]-cycloaddition reaction of NFNO to methyl acrylate under IL catalysis

Entry	Solvent	IL (mol %)	Methyl acrylate/DNFO (mol/mol)	Time (h)	Yield[a] (%) **2a**
1	$[bmim]BF_4$ as solvent		5.0	Explosion!	
2	CCl_4	$[bmim]BF_4$ (20)	5.0	60	30
3	CCl_4	$[bmim]BF_4$ (40)	5.0	36	32
4	CCl_4	$[bmim]BF_4$ (60)	5.0	36	28
5	CCl_4	$[bmim]BF_4$ (100)	5.0	36	25
6	CCl_4	[emim]OTf (40)	5.0	36	31
7	CCl_4	$[emim]HSO_4$ (40)	5.0	36	29
8	CCl_4	$[bmim]BF_4$ (40)	1.0	240	Trace[b]
9	CCl_4	$[bmim]BF_4$ (40)	2.0	240	4[c]
10	CCl_4	$[bmim]BF_4$ (40)	3.0	160	9[c]
11	CCl_4	$[bmim]BF_4$ (40)	4.0	50	14[c]
12	CCl_4	$[bmim]BF_4$ (40)	6.0	36	30

[a] Isolated yield after purification.
[b] Determined by ^1H NMR spectroscopy.
[c] Some DNFO was recovered.

Table 2
Reaction of DNFO with different dipolarophiles under [bmim]BF_4 catalysis

Entry	Dipolarophile	Product[a]	Time	Yield[b] (%)
1			12 h	22 (**1a**)
2			12 h	24 (**1b**)
3			12 h	21 (**1c**)
4			12 h	26 (**1d**)
5			36 h	32 (**2a**)
6			48 h	38 (**2b**)
7			3 d	32 (**2c**)
8			3 d	26 (**2d**)
9			3 d	14 (**2e**)
10			36 h	23 (**2f**)
11			48 h	19 (**3**)
12			48 h	23 (**4**)

[a] All products were characterized from ^1H, ^{13}C and ^{14}N NMR and MS spectral data and by elemental analysis.
[b] Isolated yield after purification.

In conclusion, we have reported a new approach for the synthesis of substituted 3-nitroisoxazoles **1** and 3-nitroisoxazolines **2** from dinitrofuroxan–a unique source of nitroformonitrile oxide–via its [3+2]-cycloaddition with acetylene and ethylene derivatives under ionic liquid catalysis.[20] The developed method is the first general synthetic route to 3-nitroisoxazoles and 3-nitroisoxazolines, which has allowed us to enlarge libraries of these compounds. In addition, the described approach to the preparation of NFNO is general and can be extended to cycloaddition reactions with other dipolarophiles. Such investigations are now in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.112.

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20. *General procedure for the synthesis of **1** and **2**:* [bmim]BF_4 (0.051 g, 0.228 mmol) and the appropriate dipolarophile (2.85 mmol) were added to the DNFO solution (0.57 mmol) in CCl_4 (2 ml) with stirring at room temperature. The mixture was stirred for the time indicated in Table 2. Next, H_2O (5 ml) was added, and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent–CH_2Cl_2/CCl_4). Caution! Dinitrofuroxan must be used only as a solution in CCl_4 due to its propensity to explode.