JOC Article
pubs.acs.org/joc

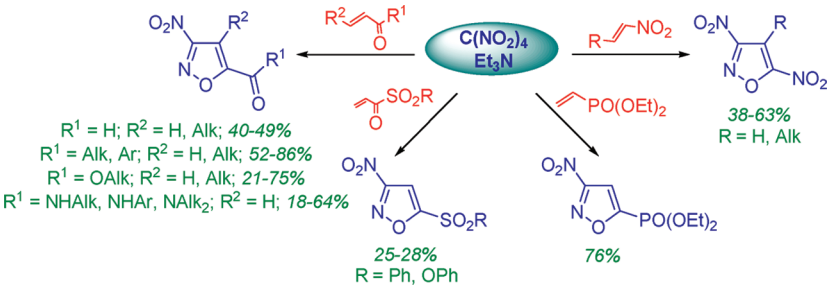
Unexpected Heterocyclization of Electrophilic Alkenes by Tetranitromethane in the Presence of Triethylamine. Synthesis of 3-Nitroisoxazoles

Yulia A. Volkova,[†] Elena B. Averina,*[,†] Yuri K. Grishin,[†] Per Bruheim,[‡] Tamara S. Kuznetsova,[†] and Nikolai S. Zefirov[†]

[†]*Lomonosov Moscow State University, Department of Chemistry, Leninskie Gory, 1-3, Moscow 119992, Russia, and* [‡]*Department of Biotechnology, Norwegian University of Science and Technology, Sem Selands vei 6/8, N-7431 Trondheim, Norway*

elaver@org.chem.msu.ru

Received February 20, 2010



Novel reaction of tetranitromethane (TNM) with electrophilic alkenes in the presence of triethylamine yielding substituted 3-nitroisoxazoles was found and studied. Triethylamine increases the reactivity of TNM toward electrophilic alkenes promoting their heterocyclization, and the reactions proceed in an unusual way. A variety of α,β-unsaturated aldehydes, ketones, esters, amides, phosphonates, and nitro and sulfur compounds was involved in the heterocyclization reaction, and a wide range of functionalized 3-nitroisoxazoles was obtained in good to high yields. The scope and limitations of the reaction and the mechanistic aspects are discussed.

Introduction

Nitronates generated from polynitromethanes have found wide use in organic synthesis as versatile 1,3-dipoles for the cycloaddition reaction with alkenes to yield five-membered *N*,*O*-heterocyclic compounds.[1] This reaction was discovered in the 1960s by the groups headed by Tartakovski[2] and Perekalin.[3] These workers explored heterocyclizations of alkenes using polynitromethanes and showed their potential in the synthesis of mainly dinitroisoxazolidines. Only nucleophilic alkenes were used in these reactions.[1] Moreover, it was mentioned that[4] "electron-withdrawing groups at double bond dramatically reduce the nucleophilicity of alkene and exclude its reaction...with tetranitromethane".

Recently studying the reactions of polynitromethanes with alkenes containing a small ring, we have developed one-pot three component heterocyclization reaction with a variety of alkenes and proposed a preparative approach to highly functionalized nitro-substituted heterocycles, such as isoxazolidines, as well as piperidones, aziridines, and isoxazolines.[5]

(1) (a) Altukhov, K. V.; Perekalin, V. V. *Usp. Khim.* **1976**, *45*, 2050; *Chem. Abstr.* **1977**, *86*, 71774s. (b) Fridman, A. L.; Surkov, V. D.; Novikov, S. S. *Usp. Khim.* **1980**, *49*, 2159; *Chem. Abstr.* **1981**, *94*, 156194t. (c) Shvekhgeymer, G. A.; Zvolinskii, V. I.; Kobrakov, K. I. *Khim. Heterotsikl. Soed.* **1986**, 435; *Chem. Abstr.* **1987**, *106*, 50078j. (d) Nielsen, A. T. In *Nitronic Acids and Esters*; Feuer, H., Ed.; Wiley-VCH: New York, 1981; p 349. (e) Torssell, K. B. G. In *Nitrile oxides, nitrones and nitronates in organic synthesis*; Feuer, H., Ed.; Wiley-VCH:: New York, 1988; p 95. (f) Nielsen, A. T. In *Nitrocarbons*; Feuer, H., Ed.; Wiley-VCH: New York, 1995; p 1. (g) Padwa, A.; Pearson, W. H. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Feuer, H., Ed.; Wiley-VCH: New York, 2002; p 83. (h) Ioffe, S. L. In *Nitrile Oxide, Nitrones and Nitronates on Organic Synthesis*; Feuer, H., Ed.; Wiley-VCH: New York, 2008; p 435. (i) Averina, E. B.; Ivanova, O. A.; Budynina, E. M.; Volkova, Y. A.; Kuznetsova, T. S.; Zefirov, N. S. *Moscow Univ. Chem. Bull.* **2008**, *63*, 131.

(2) Tartakovskii, V. A.; Chlenov, I. E.; Smagin, S. S.; Novikov, S. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 583; *Chem. Abstr.* **1964**, *61*, 4335e.

(3) Altukhov, K. V.; Perekalin, V. V. *Zh. Org. Khim.* **1966**, *2*, 1902; *Chem. Abstr.* **1967**, *66*, 46354j.

(4) Ratsino, E. V.; Altukhov, K. V. *J. Org. Chem. USSR* **1972**, *8*, 2327.

(5) For an account, see: Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Synlett* **2009**, 1543.

DOI: 10.1021/jo100319p Published on Web 04/12/2010

What is more, we have found that combination of tetranitromethane (TNM) with triethylamine may be regarded as a specific reagent, which was used for the ring-opening reaction of oxiranes and *N*-tosylaziridines yielding β-hydroxy nitrate[6] and β-tosylamino nitrates,[7] respectively. It should be noted that TNM itself does not cleave the epoxides and the aziridines directly without activation with basic reagents (Et_3N).

In this paper, we report a novel reaction of TNM in the presence of triethylamine (Et_3N) with conjugated functionalized alkenes containing electron-withdrawing group at the double bond, which, in turn, may be considered as a general method for the synthesis of substituted 3-nitroisoxazoles.

It is well-known that isoxazoles constitute a class of heterocyclic compounds possessing a remarkable variety of applications as versatile building blocks in organic synthesis.[8] Their wide range of biological activity includes antibacterial, antiviral, and antifungal activities; they can act as various glutamate and GABA receptors ligands and also display herbicide activity.[8d,9] The construction of the isoxazole ring can be achieved by two major synthetic approaches, including 1,3-dipolar cycloaddition of unsaturated compounds and the reaction of hydroxylamine with 1,3-diketones or α,β-unsaturated ketones.[8] However, both of these methods are not suitable for the synthesis of 3-nitro-substituted isoxazoles.

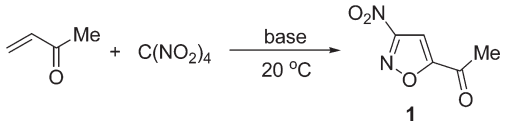
Only a few synthetic routes have been developed for 3-nitrosubstituted isoxazoles having antibacterial activity.[10] 3-Nitroisoxazoles cannot be obtained by the direct nitration of isoxazoles or by the usual [3 + 2]-cycloaddition reactions. According to described methods, nitro group is introduced in the 3-position of isoxazole at the step of intramolecular cyclization of substituted nitrolic acids generated from propargyl halides[11] or 1,3-dihalogenopropanes[12] and sodium nitrite. Another method is based on the reaction of chloronitrolic acid with Grignard derivatives of acetylenes.[13] An interesting example of 3-nitroisoxazole synthesis is the reaction of tetranitroethylene and trimethylsilyl-substituted acetylenes giving mono- and disilylsubstituted 3-nitroisoxazoles.[14]

Here, we present the results of our study of heterocyclization of electrophilic alkenes under the action of TNM in the presence of Et_3N as well as the scope and limitations of this protocol. In fact, eight classes of electrophilic alkenes were studied in this reaction.

Results and Discussion

We have started our studies by examination the reaction of TNM−base complex with α,β-unsaturated compounds containing a carbonyl group. Methyl vinyl ketone was chosen as a model substrate for the optimization of the reaction conditions. Full data concerning the optimization of the type of base and solvent used and the amounts of the reagents are presented in the Supporting Information. We tried several tertiary amines (Et_3N, Bu_3N, Py, TMEDA, DBU, DABCO) and triphenylphosphine as bases, which were used in catalytic or equimolar amounts. In all cases, the principle result was the following: we have observed the formation of 3-nitroizoxazole **1** in accordance with Scheme 1:

SCHEME 1. Heterocyclization of Methyl Vinyl Ketone under the Action of TNM in the Presence of Base



1

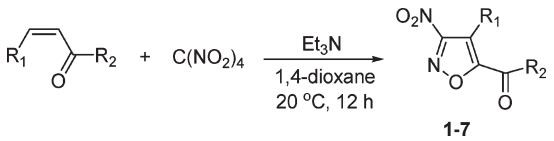
However, in some cases, side product 5,5,5-trinitropentan-2-one was isolated in 6−10% yields. The best result was obtained with Et_3N (80%). The use of other bases such as Bu_3N, Py, TMEDA, and DBU resulted in moderate yields of isoxazole **1** (30−40%), and low yields were obtained when DABCO and Ph_3P were used (20 and 6%, respectively). Variation of the molar ratio of the reagents in the case of triethylamine showed that the optimal yield of isoxazole **1** was achieved using alkene, TNM, and triethylamine in a 1:2.5:2 ratio. After screening the solvents, we found that the heterocyclization proceeded smoothly in dioxane at room temperature and complete conversion of starting olefins was achieved in 12 h with a good yields of isoxazole **1**. It should be noted that if the reaction was carried out in methanol the trinitropentanone was isolated exclusively. The reaction protocol includes a slow addition of alkene at 5 °C to previously prepared complex of TNM with Et_3N. The reaction was scaled up using 10 mmol of methyl vinyl ketone, 25 mmol of TNM, and 20 mmol of Et_3N under standard conditions to produce 80% yield of isoxazole **1**.

Having this general optimization of reaction conditions in hand, we investigated a series of α,β-unsaturated ketones and aldehydes under these conditions; the results are presented in Table 1.

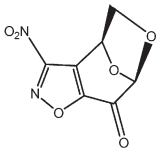
Ketones smoothly reacted with TNM−Et_3N complex at room temperature forming 5-acyl-3-nitroisoxazoles **1**−**7** in high yields. We also succeeded in heterocyclization with

(6) Volkova, Y. A.; Ivanova, O. A.; Budynina, E. M.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett*. **2008**, *49*, 3935.
(7) Volkova, Y. A.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett*. **2010**, *51*, 2254–2257.
(8) For reviews, see: (a) Lang, S. A.; Lin, Y.-I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, p 1. (b) Grünanger, P.; Vita-Finzi, P. *Isoxazoles, Part I, The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Weissberger, A., Eds.; Wiley: New York, 1991; Vol. 49, p 1. (c) Teresa, M. V. D.; Pinho e, Melo *Curr. Org. Chem*. **2005**, *9*, 925. (d) Giomi, D.; Cordero, F. M.; Machetti, F. Isoxazoles. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 4, p 365.
(9) For selected examples on bioactivity: (a) Stein, P. D.; Floyd, D. M.; Bisaha, S.; Dickey, J.; Girotra, R. N.; Gougoutas, J. Z.; Kozlowski, M. L.; Lee, V. G.; Liu, E.C.-K.; Malley, M. F.; McMullen, D.; Mitchell, C.; Moreland, S.; Murugesan, N.; Serafino, R.; Webb, M. L.; Zhang, R.; Hunt, J. T. *J. Med. Chem*. **1995**, *38*, 1344. (b) Madsen, U.; Bang-Andersen, B.; Brehm, L.; Christensen, I. T.; Ebert, B.; Kristoffersen, I. T. S.; Lang, Y.; Krogsgaard-Larsen, P. *J. Med. Chem*. **1996**, *39*, 1682. (c) Solankee, A.; Solankee, S.; Patel, G. *Rasayan J. Chem*. **2008**, *1*, 581. (d) Srinivas, A.; Nagaraj, A.; Reddy, S. *J. Heterocycl. Chem*. **2009**, *46*, 497. (e) Kuz'min, V. E.; Artemenko, A. G.; Muratov, E. N.; Volineckaya, I. L.; Makarov, V. A.; Riabova, O. B.; Wutzler, P.; Schmidtke, M. *J. Med. Chem*. **2007**, *50*, 4205. (f) Pieroni, M.; Lilienkampf, A.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem*. **2009**, *52*, 6287. (g) Dayan, F. E.; Duke, S. O.; Reddy, K. N.; Hamper, B. C.; Leschinsky, K. L. *J. Agric. Food Chem*. **1997**, *45*, 967. (h) Zimecki, M.; Maczynski, M.; Ryng, S. *Acta Polon. Pharm. Drug Res*. **2008**, *65*, 793. (i) Simoni, D.; Rondanin, R.; Baruchello, R.; Rizzi, M.; Grisolia, G.; Eleopra, M.; Grimaudo, S.; Di Cristina, A.; Pipitone, M. R.; Bongiorno, M. R.; Arico, M.; Invidiata, F. P.; Tolomeo, M. *J. Med. Chem*. **2008**, *51*, 4796.
(10) Uhr, H.; Kretschik, O.; Kugler, M.; Wachtler, K. US Patent 2003/0166698, 2003.
(11) (a) Rossi, S.; Duranti, E. *Tetrahedron Lett*. **1973**, *14*, 485. (b) Mechkov, Ts. D.; Sulimov, I. G.; Usik, N. V.; Mladenov, I.; Perekalin, V. V. *Zh. Org. Khim*. **1980**, *16*, 1328; *J. Org. Chem. USSR* **1980**, *16*, 1148.
(12) Diamantini, G.; Duranti, E.; Tontini, A. *Synthesis* **1993**, 1104.
(13) Bravo, P.; Gaudiano, G. *Gazz. Chim. Ital*. **1966**, *96*, 454.
(14) Baum, K.; Tzeng, D. *J. Org. Chem*. **1985**, *50*, 2736.

TABLE 1. Reaction of α,β-Unsaturated Ketones and Aldehydes with TNM−Et_3N Complex



1-7

entry	3-nitro-isoxazoles	R^1 or isoxazole	R^2	yield,[a] %
1	**1**	H	Me	80
2	**2**	H	Et	86
3	**3**	H	Ph	85
4	**4**	-$(CH_2)_3$-		77
5	**5**			52
6	**6**	H	H	40
7	**7**	Me	H	49

[a]Isolated yield.

TNM−Et_3N levoglucosenone, a highly functionalized chiral synthon, which is an excellent starting material and building block for the synthesis of natural compounds.[15] A new chiral 3-nitroisoxazole **5** was obtained in a good yield (Table 1, entry 5). It was found that acrolein and crotone aldehyde also reacted with TNM under the same conditions, producing 5-carbaldehyde-3-nitroisoxazoles **6** and **7** in 40 and 49% yields, respectively. Lower yields of compounds **6** and **7** related to partial polymerization of starting aldehydes under reaction conditions.

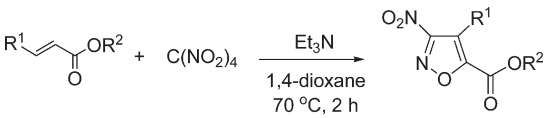
Next, we tried to involve α,β-unsaturated esters in the heterocyclization reaction with TNM−Et_3N complex. We have found that the simplest vinyl ester−methyl acrylate reluctantly reacted with TNM−Et_3N at room temperature for 12 h leading to the corresponding 3-nitroisoxazole **8** in poor yield (10%).[16] However, further investigation revealed that this reaction proceeded smoothly when heated at 70 °C for 2 h, and the yield of **8** increased to 62%. These conditions were found to be optimal for α,β-unsaturated esters, and a series of 3-nitroisoxazole-5-carboxylates **8**−**16** was thus obtained (Table 2).

It is worth noting that increasing the size either substituent R^1 or R^2 led to a moderate decrease of isoxazole yields. For instance, if R^1 in the starting ester was changed from H (Table 2, entry 2) to Et (Table 2, entry 7) and then to $PhCH_2$ (Table 2, entry 9), the yields of the corresponding isoxazoles **9**, **14**, and **16** decreased from 75 to 40 and 20%, respectively.

(15) (a) Miftakhov, M. S.; Valeev, F. A.; Gaisina, I. N. *Russ. Chem. Rev.* **1994**, *63*, 869. (b) Witczak, Z. J. In *Chemicals and Materials from Renewable Resources*; Bozell, J. J., Ed.; American Chemical Society: Washington DC, 2001; No. 784, Chapter 7, p 81.

(16) If the mixture of 1,4-dioxane−CH_3CN was used as a solvent only methyl 4,4,4-trinitrobutanoate in 36% yield was evolved as a reaction product.

TABLE 2. Synthesis of 3-Nitroisoxazole-5-carboxylates

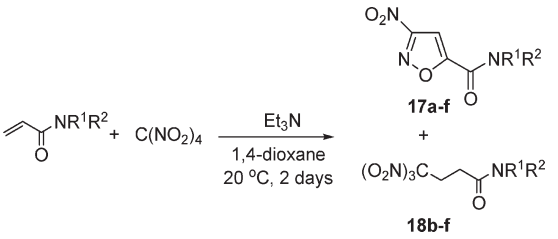


8-16

entry	3-nitroisoxazole	R^1	R^2	yield,[a] %
1	**8**	H	Me	62
2	**9**	H	Et	75
3	**10**	H	Bu	60
4	**11**	H	*t*-Bu	46
5	**12**	H	CH_2Ph	60
6	**13**	Me	Et	50
7	**14**	Et	Et	40
8	**15**	$(CH_2)_3Cl$	Et	46
9	**16**	CH_2Ph	Et	21

[a]Isolated yield.

TABLE 3. Reaction of Acrylamides with TNM−Et_3N Complex



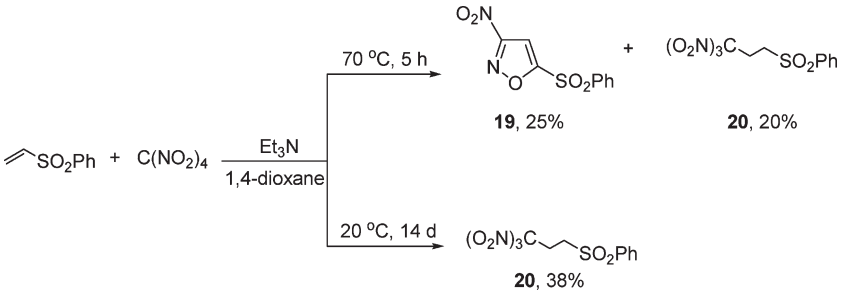
compds **17** and **18**	R^1	R^2	yield of **17**,[a] %	yield of **18**,[a] %
a	H	H	64	-
b	H	Bu	29	21
c	H	CH_2Ph	20	23
d	H	cy-hexyl	41	38
e	H	Ph	24	19
f	C_3H_7	C_3H_7	23	25
g	−$(CH_2)_5$−		18	25

[a]Isolated yield.

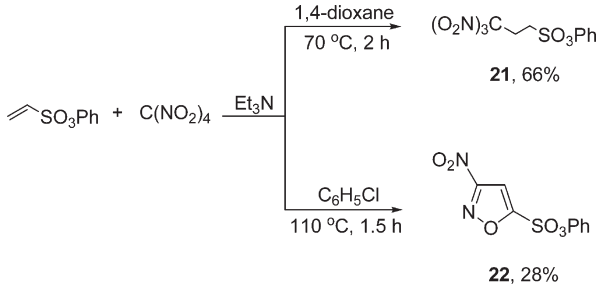
Moreover, it was found that hindered cumarin and (*E*)-ethyl 4-methylpent-2-enoate do not react with complex TNM−Et_3N under the stated conditions. With R^2 = Bu (Table 2, entry 3), the corresponding isoxazole **10** was obtained in 60% yield, while with R^2 = *t*-Bu (Table 2, entry 4) the reaction proceeded affording the product **11** in 46% yield.

We have further extended the heterocyclization to acryl amides. The results of the heterocyclization of N-substituted acryl amides upon the action of TNM−Et_3N are summarized in Table 3. We have found that the complex TNM−Et_3N at 20 °C clearly converted acryl amide into a single product, 3-nitroisoxazole-5-carboxamide **17a**, in 64% yield in 48 h. However, the heterocyclization of N-substituted acryl amides led to the mixtures of the desired nitroisoxazoles **17b**−**f** and the products of formal trinitromethane Michael addition to the starting amides: N-substituted 4,4,4-trinitrobutanamides **18b**−**f**. Optimization of the reaction conditions for selective preparation of 3-nitroisoxazole carbamides was not successful. Mixtures of compounds **17c** and **18c** in nearly equal ratio were obtained in the reaction of *N*-benzyl acryl amide with TNM−Et_3N complex at room temperature in

SCHEME 2. Reaction of Vinylsulfonylbenzene with TNM−Et_3N Complex



SCHEME 3. Reaction of Vinyl Benzenesulfonate with TNM−Et_3N Complex

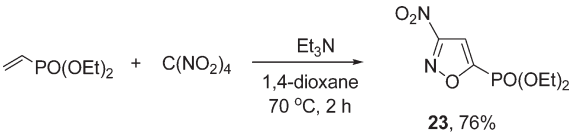


48 h or upon heating at 70 °C in dioxane in 2 h. The use of methylene chloride as a solvent in the reaction of *N*-benzyl acryl amide with TNM−Et_3N complex at room temperature led to trinitroamide **18c** as the sole product in 54% yield in 72 h. The products **17** and **18** were isolated by column chromatography.

A similar result was observed in the reaction of α,β-unsaturated organic sulfur compounds in the reaction with TNM−Et_3N complex. It was found that vinylsulfonyl benzene reacted with TNM in the presence of Et_3N, and the desired 3-nitro-5-(phenylsulfonyl)isoxazole **19** was obtained along with the side product trinitroethylsulfonylbenzene **20** (Scheme 2). The reaction proceeded at 70 °C in dioxane for 5 h. When the reaction was conducted at 20 °C in dioxane for 14 days, only compound **20** was obtained in 38% yield. Increasing the reaction temperature to 100 °C using chlorobenzene as a solvent afforded **19** and **20** in tiny 2% and 3% yields, respectively, and a number of unidentified byproducts.

(17) The isoxazole fragments of the compounds present characteristic spectral patterns with small variations of the ^1H and ^{13}C chemical shift values. The C(4)H protons of heterocycles give singlets at 7.3−7.6 ppm. The signals of the corresponding carbon atoms (C4) are observed in the typical region at 100−104 ppm that reveal weak dependence on substituent at C5. Introduction of the substituent at C4 causes an expected downfield shift (14−20 ppm). Relatively narrow ranges of ^{13}C chemical shifts in a series of compounds are found for carbon atoms C3 (at 162 to 167 ppm) and C5 (at 154 to 164 ppm). It is interesting to note the peculiarity of the signals of quaternary carbon atoms C3 bonded to nitro group due to scalar relaxation mechanism (Becker, E. D. *High Resolution NMR. Theory and Chemical Applications*, 2nd ed.; Academic Press: London, **1980**; p 192). Relaxation of ^{14}N nuclei causes appreciable resonance line broadening for these carbon atoms. In contrast, in the case of 3,5-dinitroisoxazole **24** resolved $^{13}C-^{14}N$ splitting was observed for both CNO_2 groups with J_{CN} equal to 18 and 16 Hz. Nitro groups of this compound give rather narrow resonance signals in ^{14}N NMR spectrum at −33.7 and −38.4 ppm with respect to CH_3NO_2. The ^{13}C resonance of $C(NO_2)_3$ group (at ca. 130 ppm) in trinitrosubstituted adducts **18** and **21** is upfield shifted compared to the CNO_2 group of 3-nitroisoxazoles. The weak ^{13}C signal of this group was not found for compounds **18c−e** and **20**.

SCHEME 4. Synthesis of 3-Nitro-5-phosphonate Isoxazole



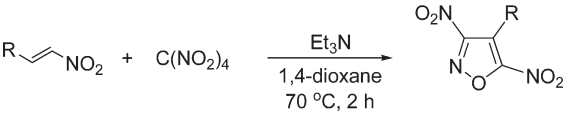
In the case of vinyl benzenesulfonate, when the reaction with TNM−Et_3N was carried out in hot dioxane, trinitromethyl derivative **21** was obtained in good yield (Scheme 3), whereas when the reaction was run at 110 °C in chlorobenzene, only isoxazole **22** was isolated from the reaction mixture.

On the other hand, vinyl sulfinyl benzene in the reaction with TNM−Et_3N did not afford the expected isoxazole, and only benzenesulfonic acid was formed obviously as a result of the oxidation of starting vinylsulfinyl compound by TNM. This result was the same at room temperature and upon heating at 70 °C in dioxane.

We were encouraged to find that vinyl phosphonate ester smoothly reacted with TNM− Et_3N complex in dioxane upon heating at 70 °C to form the desired 3-nitroisoxazole-5-phosphonate **23** in high yield (Scheme 4).

Finally, α,β-unsaturated nitroalkenes were investigated in the reaction with TNM−Et_3N complex. A series of nitroethylenes were found to be active in this reaction at 70 °C in dioxane, and 3,5-dinitroisoxazoles **24−28** were isolated in good yields (Table 4). The yield of **24**

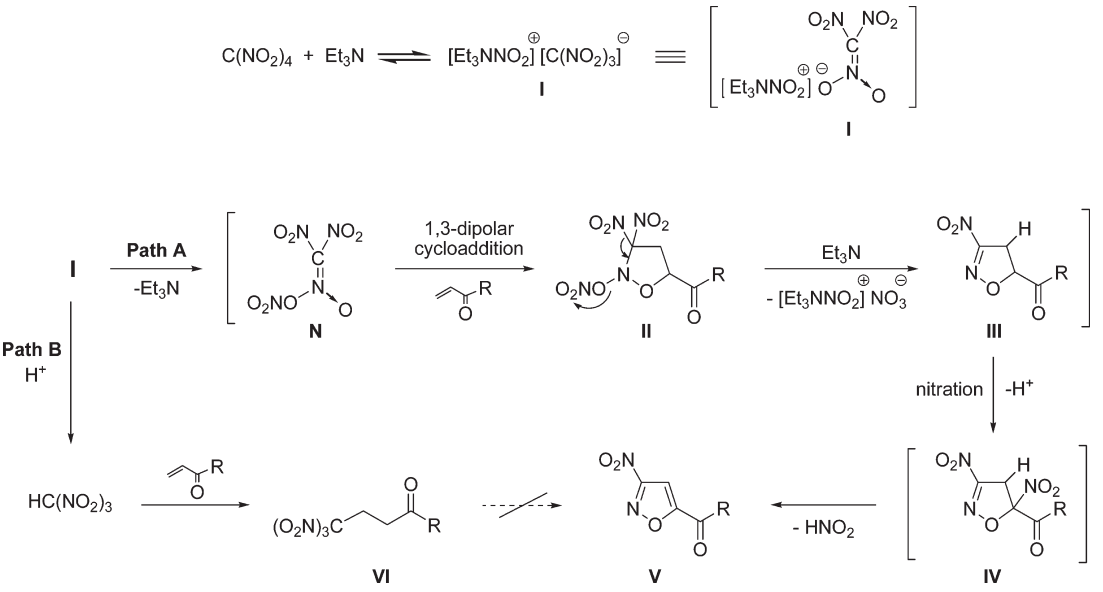
TABLE 4. Synthesis of 3,5-Dinitroisoxazoles



3,5-dinitroisoxazole	R	yield,[a] %
24	H	38
25	Me	63
26	Et	53
27	$(CH_2)_3Cl$	51
28		50

[a]Isolated yield.

SCHEME 5. Proposed Mechanism for the Reaction of α,β-Unsaturated Carbonyl Compounds with TNM−Et_3N Complex



was substantially less due to a partial polymerization of starting nitroethylene under the reaction conditions. The bulky substituents at the double bond have an obvious dilatory effect on the reactivity of starting olefins; e.g., the yield of cyclopropylmethyl substitued isoxazole **28** did not exceed 50%, while isopropylnitroethylene was totally inert in the reaction with TNM under optimized conditions.

Structures of the obtained products were unambiguously confirmed by NMR spectroscopy.[17]

Consider now the mechanistic aspects of the reaction of electrophilic alkenes with TNM−Et_3N complex. A proposed mechanism for this reaction is outlined in Scheme 5 using α,β-unsaturated carbonyl compounds as a model. In the first step, the molecule of TNM is polarized upon the reaction with triethylamine to give complex **I**, which can act in the reaction as nitronic ester *N* (path A). It should be specially emphasized that TNM does not react with electrophilic alkenes in the absence of amine. The stoichiometry of this reaction shows that the elimination of either $2NO_2 + H_2O$ or $HNO_3 + HNO_2$ occurs. In other words, to get the aromatic structure we need several elimination reactions of nitro groups! Thus, triethylamine is needed not only to initiate the reaction but also to bind the forming acids. Nitronic ester **N** reacts further with electrophilic alkene; likewise, the 1,3-dipole generates unstable 3,3-dinitroisoxazolidine **II**. Subsequent elimination of NO_3^- and NO_2^+ produced nitroisoxazoline **III**. Obviously, looking at the structure(s) of the product(s), the next step must be some kind of dehydrogenization reaction leading to an aromatic isoxazole structure. While the reaction mixture contains some potential oxidants, this stage is not thoroughly clear. We suppose that the aromatization process is due to subsequent nitration−elimination of nitrous acid of intermediate **III**. We supposed that NO_2^+ may be participating in this process to yield product **IV**. The final stage is the formation of 3-nitroisoxazole **V** due to elimination of HNO_2. The indirect proof of elimination of molecules HNO_3 and HNO_2 is the successful isolation of the salt $Et_3N \cdot HNO_3$ and *N*-nitrosodiethylamine from the reaction mixture.

Trinitrosubstituted adducts of type **VI** could be formed via path B, which is in fact the Michael addition of trinitromethane to starting electrophilic alkenes. In turn, trinitromethane can be generated in the reaction mixture from trinitromethyl anion (its source is complex **I**) and free proton (its source is the solvent or substrate). This is in a good agreement with the fact that 5,5,5-trinitropentan-2-one was the only product in the reaction of methyl vinyl ketone with TNM−Et_3N in methanol. Acrylic acid reacted with TNM−Et_3N complex at room temperature in 1,4-dioxane to afford the sole product 4,4,4-trinitrobutyric acid in 49% yield. Although the cyclization of 1,1,1,3-tetranitropropane and 1,1,1,3-tetranitro-2-methylpropane described in the literature[18] led to the formation of the corresponding 3,5-dinitroisoxazoles by treatment with dilute mineral acids, our attempts to cyclize the products of the Michael addition of trinitromethane to electrophilic alkenes under variety of conditions were all unsuccessful.

Conclusion

In conclusion, it is has been demonstrated that TNM activated by Et_3N possesses unusual properties and may be used as an efficient and readily available reagent for numerous synthetic purposes. The present investigation describes the employment of TNM−Et_3N complex for heterocyclization of electrophilic alkenes under mild conditions affording hardly accessible 3-nitroisoxazoles in good isolated yields. The reaction tolerates a variety of substituents in alkenes. We have developed a simple, general, and in many cases preparative method for the synthesis of functionalized 3-nitroisoxazoles, which are perspective pharmacologically active compounds. Hopefully, this new reaction will find application in the synthesis of heterocyclic compounds.

(18) Golod, E. L.; Novatskiy, G. N., Bagal, L. I. *Zh. Org. Khim.* **1973**, *9*, 1111; *J. Org. Chem. USSR* **1973**, *9*, 1139.

Experimental Section

Analytical thin-layer chromatography (TLC) was carried out with "Silufol" silica gel plates (supported on aluminum); the revelation was done by UV lamp (254 and 365 nm) and chemical staining (iodine vapor and potassium permanganate solution in water). Column chromatography was performed on silica gel 60 (230−400 mesh). Preparation of starting compounds is referred to the Supporting Information. NMR spectra were recorded at 400.1, 162.0, 100.6, and 28.9 MHz for ^{1}H, ^{31}P, ^{13}C, and ^{14}N, respectively, at room temperature; the chemical shifts δ were measured in ppm with respect to the solvent (^{1}H: $CDCl_3$, δ = 7.26 ppm, DMSO-d_6, δ = 2.49 ppm, CD_3OD, δ = 3.31 ppm; ^{13}C: $CDCl_3$, δ = 77.1 ppm, DMSO-d_6, δ = 39.5 ppm, CD_3OD, δ = 49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constants in hertz (Hz), and integration.

Typical Procedure for the Synthesis of 3-Nitroisoxazoles. Triethylamine (0.28 mL, 2 mmol) was added dropwise to a solution of tetranitromethane (0.3 mL, 2.5 mmol) in 1,4-dioxane (2 mL) at 0 °C (ice bath). The reaction mixture was stirred for 5 min, and alkene (1 mmol) was added in one portion. Then the cooling was removed, and the mixture was stirred either at room temperature for 12 h (for isoxazoles **1**−**7**) or at 70 °C for 2 h (for isoxazoles **8**−**16** and **23**−**28**). The solvent was removed under reduced pressure, and the product was isolated by column chromatography (petroleum ether−EtOAc, 10:1 for **2**, **9**, **15**, **25**, and **27**; petroleum ether−EtOAc, 2:1 for **5** and **7**; $CHCl_3$−MeOH for **23**).

Caution: *Although we did not experience any problem in handling tetranitromethane, full safety precautions should be taken due to its toxicity and explosive nature.*

1-(3-Nitroisoxazol-5-yl)propan-1-one (2): yield 150 mg (86%); pale yellow solid; mp 53−54 °C; R_f 0.67 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H, CH_3), 3.08 (q, J = 7.3 Hz, 2H, CH_2), 7.34 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 7.0 (CH_3), 33.1 (CH_2), 100.4 (CH), 162.9 (C), 165.7 (br s, CNO_2), 192.7 (CO); IR (KBr) 1710 (s), 1546 (s), 1359 (s) cm^{-1}. Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.45; H, 3.54; N, 16.32.

(4*S*,7*R*)-3-Nitro-4,5-dihydro-4,7-epoxyoxepino[4,5-*d*]isoxazol-8-one (5): yield 110 mg (53%); colorless solid; mp 110−112 °C; R_f 0.25 (petroleum ether−EtOAc, 2:1); ^{1}H NMR ($CDCl_3$) δ 4.09 (d, J = 7.8 Hz, 1H, CH_2), 4.20 (dd, J = 4.3, 7.8 Hz, 1H, CH_2), 5.65 (s, 1H, CH), 6.02 (d, J = 4.3 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 68.6 (J_{CH} = 156 Hz, CH_2), 69.9 (J_{CH} = 165 Hz, CH), 99.9 (J_{CH} = 185 Hz, CH), 117.1 (C), 156.4 (CON), 158.4 (br s, CNO_2), 179.0 (CO); IR (Nujol) 1730 (s), 1535 (s), 1340 (s) cm^{-1}. Anal. Calcd for $C_7H_4N_2O_6$: C, 39.64; H, 1.90; N, 13.21. Found: C, 39.81; H, 2.07; N, 13.29.

4-Methyl-3-nitroisoxazole-5-carbaldehyde (7): yield 70 mg (49%); pale yellow liquid; R_f 0.76 (petroleum ether−EtOAc, 2:1); ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H, CH_3), 10.14 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 8.0 (CH_3), 114.1 (C), 161.2 (C), 162.3 (br s, CNO_2), 184.4 (CO); IR (KBr) 1718 (s), 1542 (s), 1359 (s) cm^{-1}. Anal. Calcd for $C_5H_4N_2O_4$: C, 38.47; H, 2.58; N, 17.95. Found: C, 38.31; H, 2.60; N, 17.86.

Ethyl 3-nitroisoxazole-5-carboxylate (9): yield 140 mg (75%); pale yellow liquid; R_f 0.49 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H, CH_3), 4.52 (q, J = 7.2 Hz, 2H, CH_2), 7.41 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 63.4 (CH_2), 102.3 (CH), 157.6 (C), 158.3 (C), 165.6 (br s, CNO_2); IR (KBr) 1740 (s), 1552 (s), 1357 (s) cm^{-1}. Anal. Calcd for $C_6H_6N_2O_5$: C, 38.72; H, 3.25; N, 15.05. Found: C, 38.65; H, 3.24; N, 15.25.

Ethyl 4-(3-chloropropyl)-3-nitroisoxazole-5-carboxylate (15): yield 120 mg (46%); pale yellow liquid; R_f 0.36 (petroleum ether−EtOAc, 5:1); ^{1}H NMR ($CDCl_3$) δ 1.45 (t, J = 7.1 Hz, 3H, CH_3), 2.08−2.15 (m, 2H, CH_2), 3.18−3.24 (m, 2H, CH_2), 3.63 (app t, J = 6.3 Hz, 2H, CH_2), 4.51 (q, J = 7.1 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 20.6, 31.5, 44.0, 63.2 (CH_2), 118.5, 157.1, 158.4 (C), 162.1 (br s, CNO_2); IR (film) 1730 (s), 1540 (s), 1335 (s) cm^{-1}. Anal. Calcd for $C_9H_{11}ClN_2O_5$: C, 41.16; H, 4.22; N, 10.67. Found: C, 41.21; H, 4.13; N, 10.75.

Diethyl 3-nitroisoxazol-5-ylphosphonate (23): colorless liquid; R_f 0.67 ($CHCl_3$−MeOH, 20:1); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 6H, 2 × CH_3), 4.29−4.34 (m, 4H, 2 × CH_2), 7.27 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 16.2 (d, J = 6 Hz, 2 × CH_3), 64.6 (d, J = 6 Hz, 2 × CH_2), 104.2 (d, J = 19 Hz, CH), 159.5 (d, J = 211 Hz, C), 165.5 (br s, CNO_2); ^{31}P NMR ($CDCl_3$) δ −0.12; IR (KBr) 2987 (s), 1554 (s), 1355 (s), 1220 (s) cm^{-1}. Anal. Calcd for $C_7H_{11}N_2O_6P$: C, 33.61; H, 4.43; N, 11.20. Found: C, 33.35; H, 4.30; N, 11.15.

4-Methyl-3,5-dinitroisoxazole (25): yield 110 mg (63%); pale yellow solid; mp 24−28 °C; R_f 0.81 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.71 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 8.5 (CH_3), 110.7 (C), 165.3 (br s, CNO_2), 166.4 (br s, CNO_2); IR (nujol) 1560 (s), 1315 (s) cm^{-1}. Anal. Calcd for $C_4H_3N_3O_5$: C, 27.76; H, 1.75; N, 24.28. Found: C, 27.90; H, 1.67; N, 24.10.

4-(3-Chloropropyl)-3,5-dinitroisoxazole (27): yield 120 mg (51%); pale yellow liquid; R_f 0.42 (petroleum ether−EtOAc, 10:1); ^{1}H NMR ($CDCl_3$) δ 2.16−2.23 (m, 2H, CH_2), 3.27−3.31 (m, 2H, CH_2), 3.69 (app t, J = 6.1 Hz, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_2), 31.0 (CH_2), 43.8 (CH_2), 113.5 (C), 162.3 (br s, CNO_2), 166.2 (br s, CNO_2); IR (film) 1540 (s), 1345 (s) cm^{-1}. Anal. Calcd for $C_6H_6ClN_3O_5$: C, 30.59; H, 2.57; N, 17.84. Found: C, 30.77; H, 2.56; N, 17.69.

Acknowledgment. We thank the Division of Chemistry and Materials Science RAS (Program N 4), the President's grant "Support of Leading Scientific School" N 5538.2008.3, and the Russian Foundation for Basic Research (projects 07-03-00685-a and 10-03-00820-a) for financial support of this work. We are indebted to Dr. L. D. Konyushkin for a sample of levoglucosenone.

Supporting Information Available: General experimental procedures and complete characterization data, copies of NMR spectra for all reaction products, and tables with the information on the optimization of reaction conditions. This material is available free of charge via the Internet at http://pubs.acs.org.