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Heterocyclization of electrophilic alkenes with tetranitromethane revisited: regiochemistry and the mechanism of nitroisoxazole formation

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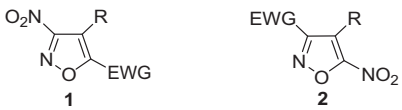
ABSTRACT

Revised regiochemistry for the heterocyclization of electrophilic alkenes with tetranitromethane (TNM) in the presence of triethylamine, providing rapid access to nitroisoxazoles, is reported. The formation of 5-nitroisoxazoles previously incorrectly assigned as 3-nitro regioisomers, has now been established unambiguously by X-ray crystallography. Empirical computations with ACD/CNMR Predictor, based both on hierarchical ordering of spherical environments (HOSE) and an algorithm of artificial neural networks (ANN), and also Density Functional Theory computations of the ^{13}C NMR chemical shifts for the 3- versus 5-nitroisoxazoles are shown to consistently match the spectra of the experimentally observed 5-regioisomers.

We previously described a novel reaction between tetranitromethane (TNM) and electrophilic alkenes in the presence of triethylamine which yielded functionalized nitroisoxazoles.[1] Both ^{1}H and ^{13}C NMR data for the nitroisoxazoles obtained[1] and known 3-nitroisoxazoles,[2] together with mechanistic arguments such as the reactivity of TNM toward olefins[3] led us to assume that 3-nitroisoxazoles **1** (Fig. 1, EWG = electron-withdrawing group) were formed in this reaction. As an example, the C(4)H protons in the ^{1}H NMR spectra of the obtained nitroisoxazoles gave singlets at 7.3–7.6 ppm which was in a good agreement with 3,5-disubstituted isoxazoles bearing two electron-withdrawing groups. According to our own previous results and limited literature data, the resonance peaks of the carbon atoms C(4)H are typically observed in the region of 97–104 ppm and exhibit little dependence on the nature of the substitution on the heterocycle, whether electron-withdrawing groups,[1,2b] alkyl, or aryl substituents.[2a] Relatively narrow, and at the same time, overlapping ranges of ^{13}C chemical shifts in the obtained products were present for carbons C3 and C5 at 162–167 ppm and 154–164 ppm, respectively. To the best of our knowledge, there is no literature information on the ^{13}C NMR spectral data of 3-nitro-5-EWG-substituted isoxazoles available for accurate comparison.

However, reduction of the previously obtained nitroisoxazoles **2a** (EWG = propanoyl) with Zn-AcOH in isopropanol (Scheme 1) yielded 5-aminoisoxazole **3a** as the sole product.[4,5] The location of the amino group at C5 of isoxazole **3a** was established by X-ray analysis.[6] The ^{1}H and ^{13}C NMR spectra were consistent with the formation of 5-aminoisoxazole **3a**. In the ^{1}H NMR spectrum of **3a** the signal due to the C(4)H proton was observed at 5.50 ppm, which corresponds with the known ethyl 5-aminoisoxazole-3-carboxylate.[7a] It is approximately 1 ppm upfield of the same signal in the isomeric ethyl 3-aminoisoxazol-5-carboxylate.[7b] Also, in the ^{13}C NMR spectrum, the position of the C4 signal (78.5 ppm) was in good agreement with literature data for 5-aminoisoxazoles.[7b,8] This result provided initial evidence that the nitroisoxazoles obtained via the triethylamine-catalyzed addition of TNM to electrophilic alkenes were in fact the corresponding 5-nitro substituted regioisomers **2**.



EWG = C(O)R', CHO, CO_2R', C(O)NR'R", S(O)R', P(O)$(OEt)_2$, NO_2
R = H, Alkyl

Figure 1. The structures of the 3- and 5-regioisomers of nitroisoxazoles.

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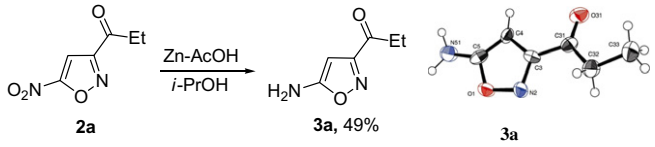


Scheme 1. Reduction of **2a** to 5-aminoisoxazole **3a**.

In view of these findings, we undertook an X-ray study of a number of nitrosubstituted isoxazoles for which we had obtained satisfactory crystals (Fig. 2). All the heterocycles were found to be 5-nitro-substituted isoxazoles, **2a–e**[9] (see the Supplementary data).

To probe whether the theoretical predictions of chemical shifts for 3- and 5-nitroisoxazoles would allow for unambiguous assignment of the regioisomers, we carried out empirical and DFT computations. Empirical calculations were performed for the regioisomeric 3- and 5-nitroisoxazoles **1a–d**,**f**, and **2a–d**,**f**,**g** using the Hierarchical Ordering of Spherical Environments code,[10] and also the algorithm of artificial neural networks, ANN[11] (Table 1). DFT calculations of ^{13}C chemical shifts were carried out for the same set of nitroisoxazoles at the B3LYP or mPW1PW91 levels of theory and several basis sets using the GAUSSIAN 09 package.[12] Table 2 summarizes the ^{13}C chemical shift data for 3- and 5-nitroisoxazoles **1a–d**,**f**, and **2a–d**,**f**,**g** calculated with the selected mPW1PW91/6-311+G(d,p) (**I**) and mPW1PW91/EPR-III (**II**) functionals and basis sets (additional results for the B3LYP functional and other basis sets can be found in the Supplementary data, although the chemical shifts calculated at the B3LYP level were inferior).

To assign the experimental spectra we took the following two observations into the account:[1] (1) the signal of the NO_2-bearing carbon atom is significantly broadened; (2) the signal of the C4 carbon atom is shifted upfield by 50 ppm relative to the two other carbon atoms of the heterocycle. The ^{13}C NMR experimental chemical shift values for the ring carbon atoms of the synthesized nitroisoxazoles are listed in Tables 1 and 2.

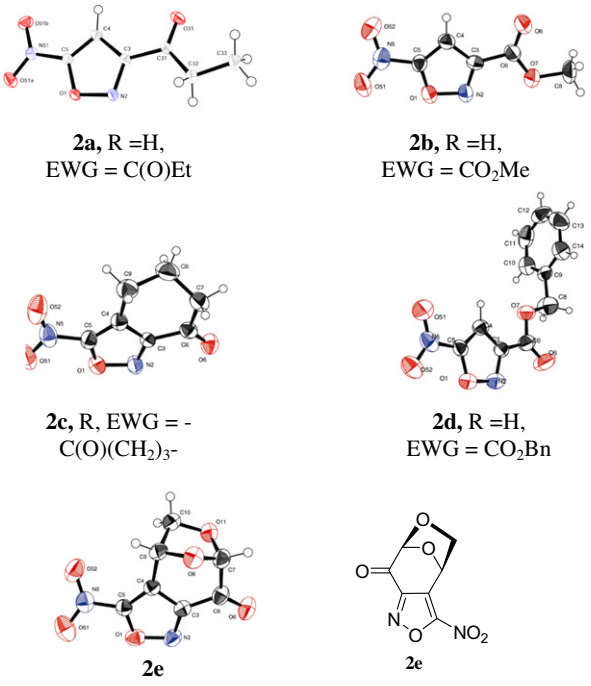


Figure 2. X-ray crystal structures of compounds **2a–e** (ORTEP-3).[6]

The chemical shifts of the carbon atoms calculated by the empirical method were in good agreement with those observed for both regioisomers (Table 1), the correlation coefficients of linear regressions (R) being over 0.99. While the standard errors for 5-nitroisoxazoles are usually less than for the 3-nitro isomers, they are comparable to the difference in shielding of the C(EWG) and $C(NO_2)$ atoms which is 1.4–8.2 ppm in these compounds. The biggest difference between observed and calculated values of δ_C (6.5 ppm) was obtained for compounds **1c** and **2c**, which formally contain three substituents on the cycle whose reciprocal influence is difficult to evaluate using the additive schemes.

As expected, the quantum-chemical method gives more precise and encouraging results with a correlation coefficient R >0.999 for the 5-nitroisoxazoles and R >0.992 for the 3-nitro isomers. The δ_C values calculated for the 5-nitro isomers corresponded better to the experimental spectra. As can be seen from Table 2, the difference in observed and calculated δ_C values for the C (EWG) atoms are 0.5–1.6 ppm in 5-nitroisoxazoles and 1.8–8.0 ppm for 3-nitroisoxazoles. In spite of the small sample of data studied, we note that the standard errors in the calculated chemical shifts for the 5-regioisomers are three times smaller than those for the 3-regioisomers. Average root mean square deviation (rmsd) values for all the methods of calculation are 1.6–2.1 ppm for the 5-nitro isomers and 5.7–6.4 ppm for the 3-nitro isomers.

It is important to question whether the calculations consider the influence of the substituent on the shielding of the carbon atoms of the five-membered ring. Notable changes in δ_C values (ca. 10 ppm) are observed only for C (EWG), and the influence of the EWG on the distant C (NO_2) atom is small. Indeed, for the 5-nitroisoxazoles, experimental values of δ_C C(EWG) correlate well (R = 0.97) with the data calculated using quantum-chemical and empirical (excluding compound **2c**) methods. Such correlation was not observed for 3-nitroisoxazoles. Thus, the results of the chemical shift calculations provide arguments in favor of the 5-nitro isomers.

5-Nitroisoxazoles are a less well known type of heterocycle compared to 3-nitro substituted examples. According to described methods, 5-nitroisoxazoles are obtained by [3+2]-cycloaddition of arylnitrile oxides to nitroethylene followed by oxidation of the intermediate 5-nitroisoxazolines.[13] A few examples of 5-nitroisoxazoles were synthesized by specific reactions which were not extended to general procedures.[14] Using our method, functionalized 5-nitroisoxazoles can be obtained as the sole products in yields of up to 85% after chromatographic purification.

The X-ray data also led us to revise the mechanism for the heterocyclization of electrophilic alkenes using TNM–Et_3N. A proposed mechanism for the formation of 5-nitroisoxazoles is outlined in Scheme 2 using 1,3-unsaturated carbonyl compounds as a model. In fact, the process should involve addition of some type to both the α and β positions of the double bond to form the heterocyclic structure. As mentioned in our previous work,[1] the molecule of TNM is polarized upon reaction with triethylamine to give the ionic complex **A** via a charge-transfer complex (CTC).[3a,b] In other words, the interaction of TNM and triethylamine led to a more polarized species (such as **A**), having pronounced anionic character for the trinitromethyl group [up to pure anionic $^-C(NO_2)_3$ structure]. On the other hand, species of the type $[Et_3N–NO_2]^+$ can be considered as a reagent for electrophilic nitration.[3a,b] Indeed, the nitration by TNM of aromatic hydrocarbons and nucleophilic double bonds of alkenes is well known and reviewed.[3a,b] We have also published on the nitration of electrophilic alkenes with TNM in the presence of Et_3N.[15] It should be emphasized that TNM does not react with electrophilic alkenes in the absence of an amine.

Also, there is some evidence in the literature that polynitromethanes may produce nitrosation agent(s) in the presence of nucleophiles.[14e] The preparative method for the synthesis of

Table 1
Empirical calculations (HOSE and ANN)[a] for the ring carbon atoms of 3- and 5-nitroisoxazoles and experimental ^{13}C NMR (100.6 MHz, $CDCl_3$) chemical shifts (ppm)

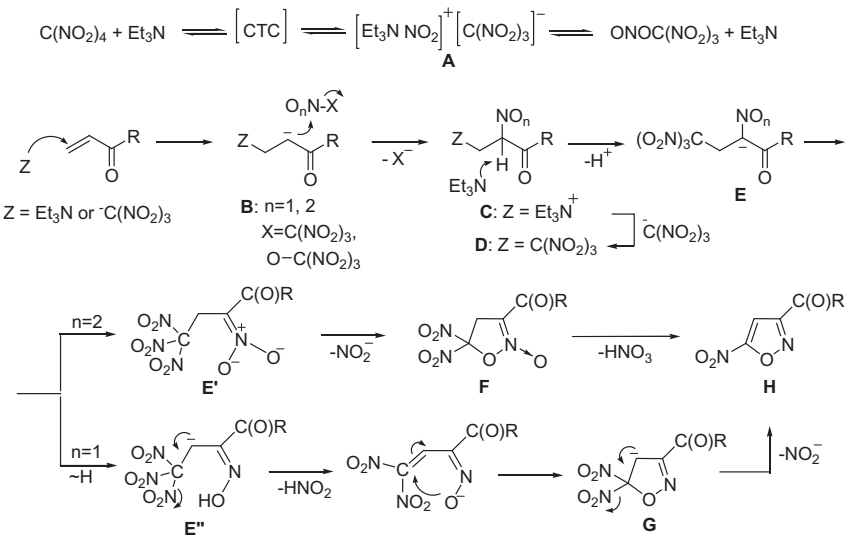
R	Nitroisoxazole		C3		C4		C5		rmsd[b]	
	EWG		HOSE	ANN	HOSE	ANN	HOSE	ANN	HOSE	ANN
H	C(O)Et	**1a**	166.25	166.23	100.60	100.24	164.48	165.23	1.76	3.61
		2a	161.38	160.65	102.74	102.38	164.48	164.65	1.81	2.71
			Experimental: 162.9 C(EWG), 100.4 (C4H), 165.7 C(NO_2)							
H	CO_2Me	**1b**	166.36	166.34	106.01	105.65	160.54	160.90	4.67	4.65
		2b	155.66	154.83	107.66	107.30	165.44	165.62	2.18	2.66
			Experimental: 158.0 C(EWG), 102.4 (C4H), 165.6 C(NO_2)							
$-CH_2CH_2CH_2-C(O)-$		**1c**	167.39	167.37	123.85	118.68	161.15	164.19	4.94	3.83
		2c	165.41	160.60	123.85	121.26	166.21	166.39	2.70	2.65
			Experimental: 158.9 C(EWG), 119.1 (C4), 160.9 C(NO_2)							
H	CO_2Bn	**1d**	166.45	166.43	106.47	106.12	158.87	159.23	4.06	3.25
		2d	156.02	153.57	107.96	107.61	165.53	165.71	2.70	2.52
			Experimental: 157.5 C(EWG), 102.4 (C4H), 165.7 C(NO_2)							
H	$P(O)(OEt)_2$	**1f**	165.27	167.16	104.44	104.09	160.20	164.19	3.61	3.62
		2f	156.27	159.13	111.13	105.12	165.11	165.29	3.44	0.91
			Experimental: 159.5 C(EWG), 104.2 (C4H), 165.5 C(NO_2)							
H	NO_2	**2g**	166.24	166.22	102.33	101.99	162.75	162.92]	2.57	2.38
			Experimental: 167.1 C(NO_2), 99.1 (C4H), 165.7 C(NO_2)							

[a] Hierarchical Ordering of Spherical Environments code (HOSE) and algorithm of artificial neural networks (ANN).
[b] Root mean square deviation (rmsd).

Table 2
DFT (mPW1PW91) calculations for the ring carbon atoms of 3- and 5-nitroisoxazoles and experimental ^{13}C NMR (100.6 MHz, $CDCl_3$) chemical shifts (ppm)

R	Nitroisoxazole		C3		C4		C5		rmsd[a]	
	EWG		6-311+G(d,p)	EPR-III	6-311+G(d,p)	EPR-III	6-311+G(d,p)	EPR-III	6-311+G(d,p)	EPR-III
H	C(O)Et	**1a**	166.1	165.8	100.9	100.5	167.4	167.4	5.2	5.0
		2a	161.7	161.9	101.4	100.8	167.0	166.8	1.7	1.4
			Experimental: 162.9 C(EWG), 100.4 (C4H), 165.7 C(NO_2)							
H	CO_2Me	**1b**	165.7	165.5	105.0	104.8	162.1	162.1	6.2	6.1
		2b	157.3	157.4	104.0	103.8	166.9	166.0	1.7	1.6
			Experimental: 158.0 C(EWG), 102.4 (C4H), 165.6 C(NO_2)							
$-CH_2CH_2CH_2-C(O)-$		**1c**	163.4	162.9	122.2	123.3	161.9	161.7	7.0	7.0
		2c	157.3	157.1	120.0	120.8	162.7	162.1	2.8	2.8
			Experimental: 158.9 C(EWG), 119.1 (C4), 160.9 C(NO_2)							
H	CO_2Bn	**1d**	165.4	165.5	104.8	104.8	162.4	162.5	6.2	6.4
		2d	157.7	157.7	104.1	103.9	166.7	166.9	1.3	1.4
			Experimental: 157.5 C(EWG), 102.4 (C4H), 165.7 C(NO_2)							
H	$P(O)(OEt)_2$	**1f**	165.0	164.9	104.8	104.9	167.2	167.5	3.7	3.8
		2f	160.0	160.6	104.3	104.4	166.5	166.3	1.7	1.8
			Experimental: 159.5 C(EWG), 104.2 (C4H), 165.5 C(NO_2)							
H	NO_2	**2g**	167.0	167.0	98.3	98.3	166.5	166.4	0.7	0.6
			Experimental: 167.1 C(NO_2), 99.1 (C4H), 165.7 C(NO_2)							

[a] Root mean square deviation (rmsd).



Scheme 2. Proposed mechanism for the heterocyclization affording 5-nitroisoxazoles.

N-nitrosoamines based on the reaction of secondary and tertiary amines with TNM has been described.[3a,b] It was assumed that the reaction involves N-nitration of the amine followed by oxidation of one of the *N*-alkyl groups into an aldehyde with concurrent reduction of the nitro to a nitroso group. Alternatively, recent calculation data showed that an increase in the number of NO_2 groups in a polynitromethane provides the driving force for increased nitro-to-nitrite transformation.[16] Hence, it is possible that Et_3N catalyzes the TNM to ONO–$C(NO_2)_3$ rearrangement thereby highlighting the nitrosating properties of TNM.

The first step of the heterocyclization involves either attack of Et_3N on the electrophilic double bond (Baylis–Hillman like mechanism) or direct Michael addition of $^-C(NO_2)_3$ as the nucleophile to give anionic species **B**. The next step may be either nitration or nitrosation of intermediate **B**. Both processes lead either to ketone **C** which transforms into **D** by successive elimination of Et_3N and addition of the $C(NO_2)_3$ nucleophile, or directly into **D**. Subsequent transformation of anion **E** is independent of NO_n-X reagents.[17] The intramolecular cyclization of **E**′ proceeds accompanied by the elimination of a nitrite anion and HNO_3. The resulting 5-nitroisoxazole **H** is probably formed via deoxygenation of isoxazoline oxide **F** under the reaction conditions. The alternative cyclization of oximino derivative **E**″ appears to be more rational, because similar processes are known.[14e]

In conclusion, it has been unambiguously established by X-ray analysis that heterocyclization of electrophilic alkenes under the action of TNM activated by Et_3N proceeds with the formation of 5-nitro-substituted regioisomers of functionalized isoxazoles and not the 3-nitro-substituted regioisomers as previously reported.[1]

Acknowledgements

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Supplementary data

Supplementary data (X-ray data and DFT calculations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.039.

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4. We elaborated the preparative method for the synthesis of 5-aminoisoxazoles by reduction of 5-nitroisoxazoles. This method will be the subject of a further publication.
5. 1-(5-Aminoisoxazol-3-yl)propan-1-one (**3a**): ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H, CH_3), 3.00 (q, J = 7.3 Hz, 2H, CH_2), 4.59 (br s, 2H, NH_2), 5.50 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 7.5 (CH_3), 32.8 (CH_2), 78.5 (CH), 163.0 (C), 169.4 (C), 195.8 (CO); IR (KBr) 2930 (s), 1470 (s), 1385 (s) cm^{-1}; HRMS-ESI: Anal. Calcd for $C_6H_9N_2O_2^+$: 141.0664. Found: 141.0659.
6. The X-ray structures described herein and in the supplementary data have been submitted to the CCDC and have been assigned the following numbers: **2a**, 823614; **2b**, 820551; **2c**, 820548; **2d**, 820552; **2e**, 820550; **3a**, 820549.
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9. 5-Nitroisoxazoles **2a**–**e** were synthesized in accordance with the described procedure.[1] All spectral characteristics (^{1}H and ^{13}C NMR) were identical with those of the compounds previously described as 3-regioisomers.
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12. ^{13}C NMR shift calculations were performed using the mPW1PW91/6-311+G (d,p), mPW1PW91/EPR-III, mPW1PW91/6-31G(d), mPW1PW91/6-311G(d,p), B3LYP/6-31G(d), B3LYP/6-311+G(2d,p) and B3LYP/EPR-III functional and basis sets.
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