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Uncommon 1,2-Migration of a Nitro Group Within a β-Nitrostyryl Moiety: Synthetic Scope and Mechanistic Details

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The unusual migration of a nitro group from the β- to the α-position of a β-aryl-α-nitroethenyl moiety, following a nitrocyclopropane to isoxazoline *N*-oxide isomerization, has been studied from a mechanistic and synthetic points of view. As a result, two series of isomeric isoxazoline *N*-oxides could be obtained under controlled conditions. When reacted with diazomethane, a model transposed isoxazoline cleanly furnished a new, interesting pyrazolylisoxazole.

Introduction

Isoxazolines and isoxazoles are ubiquitous heterocycles whose interest among chemists is testified by the continuous appearance of articles, reviews, and/or monographs concerning preparations,[1] synthetic applications[2] and biological/pharmacological relevance.[3]

In the context of a long-standing project on the synthetic exploitation of highly functionalized dinitrobutadienes **2**, easily obtainable by ring-opening of 3,4-dinitrothiophene (**1**) with diethylamine followed by arylation with Grignard reagents (Scheme 1, Steps a and b),[4] we have published a number of new approaches to linear, homo- and heterocyclic compounds[5] over the last twenty years, which maintain the original four-carbon skeleton, thus sharing the common feature of total "carbon-atom economy". Some of the derivatives obtained along the way also possess significant pharmacological activity, thus justifying further developments of the project.[5g–5l]

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Among the synthetic procedures already reported, reaction of dinitrobutadienes **2** with diazomethane represents an interesting route[6] to 1,1′-bis(cyclopropane)s **3** (Scheme 1, Step c) and to corresponding isomeric 3,3′-bis(isoxazoline *N*-oxide)s **4**, through a thermal iodide-assisted process (Scheme 1, Step d).[7] Compounds **4** may in turn be further modified by reduction of the *N*-oxide functionality (Scheme 1, Step e), followed by aromatization with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; Scheme 1, Step f), to give bis-isoxazoles **5**[7] as ultimate products.

On the other hand, the reaction with diazomethane proves of utility in chemically differentiating the two identical conjugated nitrovinylic moieties of dinitrobutadienes **2**: thus, by a careful treatment with one molar equivalent of reactant (Scheme 2, Step a), monocyclopropane derivatives **6** were obtained as the main products together with minor amounts of corresponding **3**.[6]

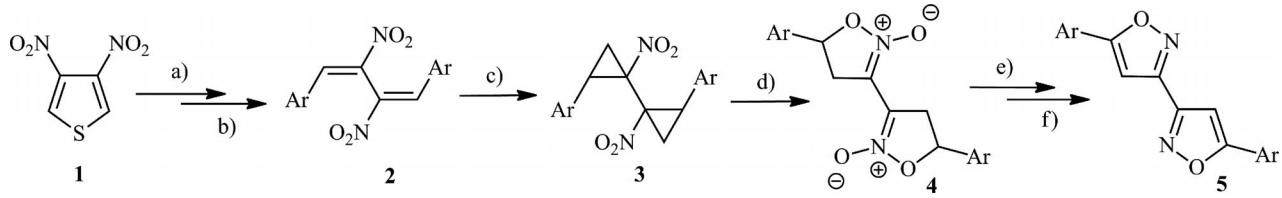
As a logical extension of previously studied **3** to **4** isomerization, we studied the application of relevant methodology to nitrovinylcyclopropanes **6** (Scheme 2), with the aim of obtaining new isoxazoline derivatives. Nevertheless, preliminary results[8] showed unexpected behavior whereby NaI-catalyzed nitrocyclopropane to isoxazoline *N*-oxide rearrangement (Scheme 2, Step b) is followed by an unexpected migration of the residual nitro group of **7** (Scheme 2, Step c) to afford α-nitrostyryl derivatives **8**.

Hereinafter we report full details of this appealing process, together with optimization of the experimental conditions for the effective isolation of primarily formed products **7**.

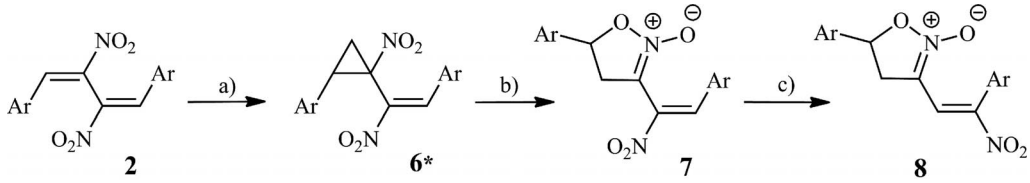
Results and Discussion

Evidence for Sequential 6 to 7 to 8 Isomerizations

Heating monocyclopropanes **6** in the presence of NaI under the experimental conditions previously applied to bi-



Scheme 1. (a) Et_2NH (excess), EtOH, 0 °C, overnight; (b) ArMgBr (2.2 mol equiv.), THF, 0 °C, 15–45 min; then acidic (HCl) quenching; (c) CH_2N_2 (excess), Et_2O, 0 °C to room temp., overnight; (d) NaI (2 mol equiv.), DMSO, 60 °C, 4–22 h; (e) $P(OMe)_3$, (40 mol equiv.), anhydrous dioxane, heated to reflux under argon, 17–24 h; (f) DDQ (4–6 mol equiv.), dry toluene, heated to reflux under argon.



* Minor amounts (9–22%) of the corresponding bicyclopropyl derivatives **3** are obtained throughout

Scheme 2. (a) CH_2N_2 (1.2 mol equiv.), Et_2O, 0 °C to room temp., overnight; (b) and (c) NaI, DMSO, 60 °C.

Table 1. ^1H NMR spectroscopic study on the **6**→**7**→**8** conversion rate in [D_6]DMSO in the presence of NaI.[a]

Entry	Ar in **6**	*t* = 1 h **6/7/8** ratio[b]	*t* = 2 h **6/7/8** ratio[b]	*t* = 5 h **6/7/8** ratio[b]	*t* = 24 h **6/7/8** ratio[b]	Disappearance[c] of **7** after:
1	**6a**: Ph	74:26:0	52:48:0	31:67:2	0:15:85	48 h
2	**6b**: 2-MeC_6H_4	25:75:0	8:92:0	0:94:6	0:45:55	72 h
3	**6c**: 4-MeC_6H_4	72:28:0	48:52:0	10:90:0	0:42:58	72 h
4	**6d**: 4-$MeOC_6H_4$	38:62:0	13:87:0	0:100:0	0:83:17	144 h
5	**6e**: 3-ClC_6H_4	82:18:0	65:28:7	32:30:38	0:0:100	24 h
6	**6f**: 4-ClC_6H_4	84:16:0	71:25:4	39:43:18	0:0:100	24 h
7	**6g**: 1-naphthyl	0:100:0	0:100:0	0:86:14	0:12:88	48 h
8	**6h**: 2-naphthyl	52:48:0	27:73:0	0:83:17	0:3:97	48 h
9	**6i**: 2-thienyl[d][e]	0:100:0	0:100:0	0:100:0	0:100:0	144 h
10	**6j**: 3-thienyl[e]	73:27:0	63:37:0	38:61:0	0:0:0	24 h

[a] At 60 °C; NaI: 1 mol-equiv. [b] Normalized. [c] The disappearance of **7** is due to the formation of **8** and/or to decomposition pathways. [d] The substrate is relevant isoxazoline *N*-oxide **7i**, as **6i** isomerized to **7i** during the chromatographic separation of the final mixture from monocyclopropanation. [e] Increasing decomposition signals were observed until complete disappearance of **7i** and **7j**.

s(cyclopropane)s **3**[7] brings to evidence (TLC, ^1H NMR spectroscopy) the accumulation of transient intermediate **7**, which slowly converts to final product **8**. Such behavior, initially observed for model phenyl derivative **6a** (Ar = Ph), was found to be general over the series of substrates (**6a**–**6j**) as the reaction scope was defined.

Preliminary tests to follow the progress of the reaction by NMR spectroscopy in [D_6] dimethyl sulfoxide (DMSO; cf. Table 1) defined the most convenient time for a work-up finalized to the isolation of **7**: a result which was eventually obtained, at least in the most favorable cases, by chromatography of the crude residue, with no attempt, at this time, to determine absolute yields (on this aspect, see "Solvent effect"). Of course, final product **8** could be most easily isolated from reactions extended until complete disappearance of both substrate **6** and **7** (Table 1).

The structure of both **7** and **8** was assigned by means of single-crystal X-ray analyses carried out on the products isolated from the reaction on phenyl derivative **6a**;[8] the ORTEP drawings are shown in Figure 1. Spectroscopic (^1H and ^{13}C NMR) similarities with **7a** and **8a** allowed all isolated analogous structures **7** and **8**, respectively, to be assigned (see Exp. Section).

Although **7** is the expected result of the iodide-catalyzed nitrocyclopropane to isoxazoline *N*-oxide isomerization of **6** (Scheme 2, Step b), the structure of **8** reveals an intriguing 1,2-migration of a nitro group under relatively mild experimental conditions (Scheme 2, Step c).

Justification of the Nitro Group Transfer

The shift of a vinylic nitro group onto the adjacent C_{sp2} atom is an example[9,10] of a well-known, more general process undergone by unsaturated systems characterized by the presence of a heteroatom directly bonded to a C_{sp2} atom.[11] As far as arylnitroethenyl (nitrostyryl) derivatives are concerned, the literature exclusively reports examples of irreversible base-catalyzed rearrangements towards the isomer that takes full thermodynamic advantage of the through conjugation between the aryl and the nitro group (i.e. Scheme 3, B).[9a]

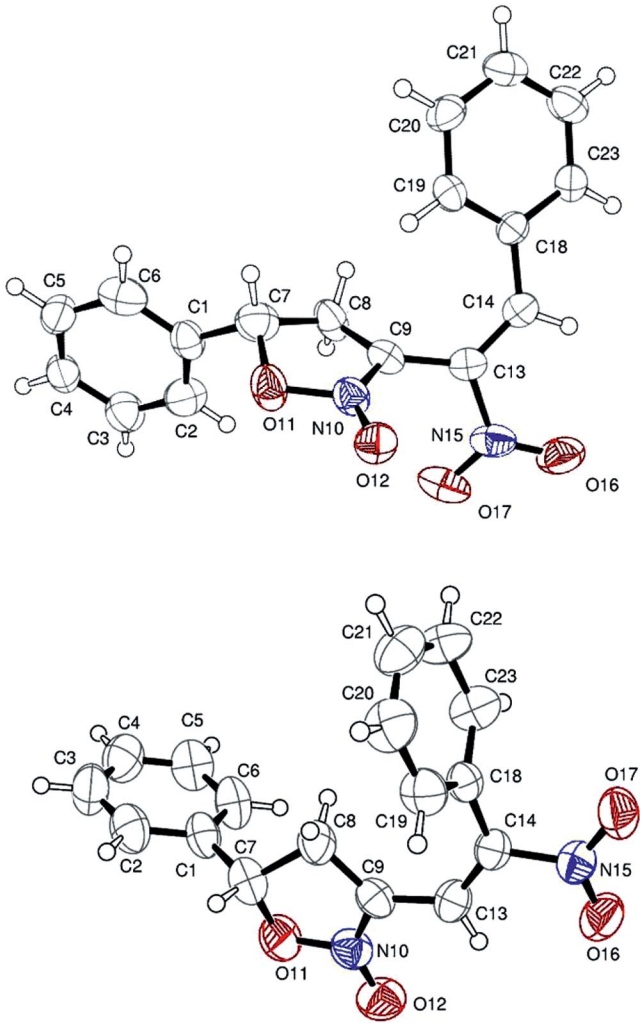
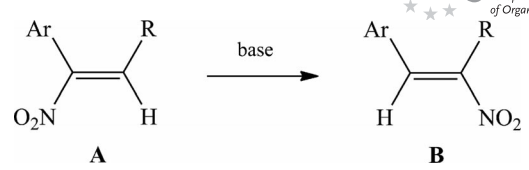


Figure 1. ORTEP drawing of the crystal structure of **7a** (top) and **8a** (bottom). Ellipsoids are shown at 50% probability.



Scheme 3.

In our case the nitro group migration proceeds in the opposite direction to that shown in Scheme 3: thus the outcome requires proper rationalization, for which both electronic and steric factors likely concur. To this end, in the preliminary communication[8] we undertook a computational study at the DFT level[12] both in solution (DMSO) and in the gas phase,[8] whereby the geometries of representative "critical" structures were optimized for a model phenyl derivative (Ar = Ph; see, Figure 2). For isoxazoline **7a**, the relief of repulsive interactions between the cyclic nitronate and the nitro group allows significant through resonance between the nitro group and Ph in the *s-cis* conformation, corresponding to an effective stabilization of about 2 kcal/mol with respect to the *s-trans* conformation. When considering analogous structures for isomerized isoxazoline **8a**, whereas the *s-cis* conformation matches in energy (at least in solution) *s-cis*-**7a**, the *s-trans* conformation seems to minimize any steric and/or stereoelectronic interactions, thus taking full advantage from a new extended through-conjugation between the cyclic nitronate and the shifted nitro group thanks to effective coplanarity.

Thus, we can rationalize the driving force for the nitro group shift basically as a release of unfavorable through-space interactions, whereas the nitro group/phenyl conjugation of **7** (highlighted in blue color in Figure 2) is replaced by a similarly effective nitro group/nitronate one through the ethenyl moiety (highlighted in red in Figure 2) in **8**.

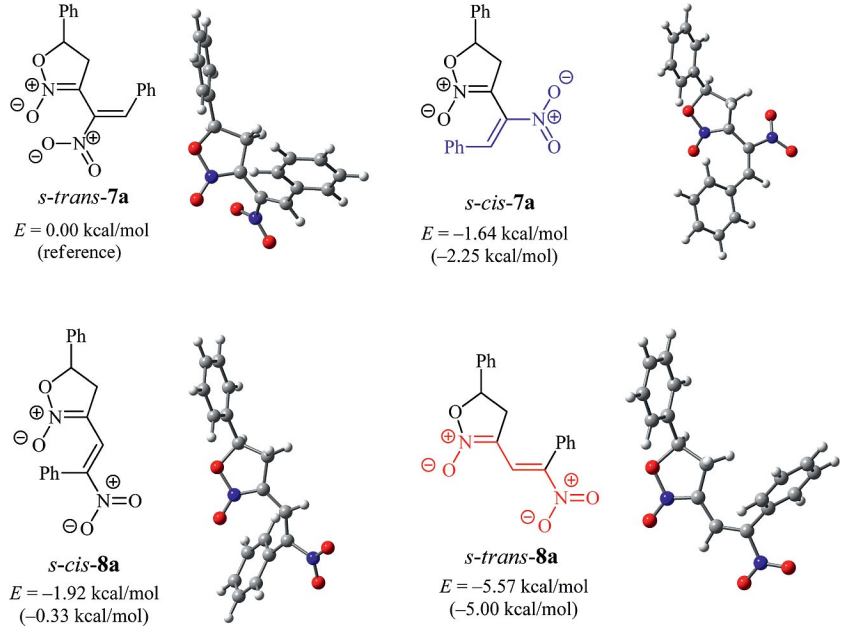
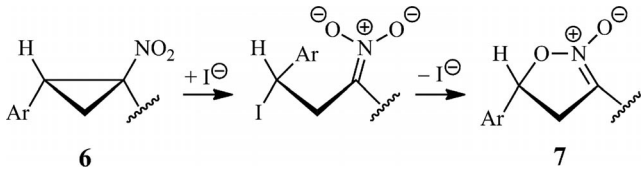


Figure 2. Calculated relative energies in DMSO and in the gas phase (in parentheses) for optimized geometries.

It should be emphasized that, in the crystal structure, **7a** adopts an apparently less stable *s-trans*-like conformation (see Figure 1), whereas the spatial arrangement of **8a** seems to match the optimized *s-trans* geometry in solution.[13]

Mechanistic Details, the Catalytic Role of NaI

The catalytic significance of NaI in the nitrocyclopropane to isoxazoline *N*-oxide ring-enlargement (**6** to **7** isomerization) has already been reported from our lab for the **3** to **4** transformation of Scheme 1, whereby the role of the nucleophilic catalyst was attributed to the iodide anion within a double S_N2 process (Scheme 4) and on the grounds of the observed diastereospecificity.[7]



Scheme 4.

Herein, an analogous mechanism can be suggested, although the fact that the substrate is represented by a racemic mixture prevents the same kind of stereochemical evidence. Interestingly, in some cases, **7** is effectively formed in the absence of NaI (Table 3, Entry 8), with complete **6** to **7** isomerization within 24 h for the 1-naphthyl derivative. Thus, a concurrent, different pathway must be invoked in these cases, represented by a S_N1-like process involving a particularly stable benzylic-like carbocation, as corroborated by the behavior of **6d** and **6g** (Table 3, Entries 6 and 8).

As far as the nitro group transfer is concerned, the literature claims for a base-catalyzed mechanism through a cyclic intermediate (Scheme 5),[9a,9b] grounded on the results of tests of isotopic labeling either of substrate (sizeable kinetic deuterium isotope effect) or of added nitrite (absence of ^{15}N uptake into the product), find herein further support. Thus, in agreement with the mechanistic hypothesis of Scheme 5,[14] cyclopropyl derivative **6c**-d_2 (prepared from dideuterated 3,4-dinitrothiophene **1**-d_2) furnished, by means of comparative semi-quantitative tests with **6c** (Table 2), a significant kinetic isotope effect ($k_H/k_D \approx 3$). Such an outcome, which remains well above any reasonable secondary isotope effect, clearly indicates that a proton transfer is involved in the rate-determining step of the nitro group transfer. Incidentally, the data at $t = 4$ h clearly exclude (as expected) any appreciable isotope effect for the **6** to **7** isomerization of Scheme 4.

Table 2. Deuterium isotope effect in the **6**→**7**→**8** conversion for 4-methyl derivative **6c** in [D_6]DMSO in the presence of NaI.[a]

Entry	Substrate	t = 4 h **6/7/8** ratio[b]	t = 24 h **6/7/8** ratio[b]	t = 48 h **6/7/8** ratio[b]
1[c]	**6c**	16:84:0	0:35:65	0:8:92
2[c]	**6c**-d_2	17:83:0	0:74:26	0:56:44
3[d]	**6c**	17:83:0	0:30:70	0:5:95
	6c-d_2	18:82:0	0:68:32	0:54:46

[a] Reactions followed by ^1H NMR spectroscopy. [b] Normalized. [c] Parallel tests. [d] Competitive test, with both substrates in the same sample tube.

Herein, it should be accepted that the role of the base (Scheme 5, **B**) cannot be played by anything other than the iodide anion. Accordingly, we could verify (cf. Table 3) that (a) **7** to **8** isomerization does not proceed in the absence of NaI (Table 3, Entries 6 and 8), and (b) with respect to the standard conditions (NaI, 1.0 mol equiv.), 2 equiv. of NaI significantly accelerates the **7** to **8** isomerization (Table 3, Entries 3a and 4), whereas 0.5 equiv. slows it down (Table 3, Entries 1b and 2c).

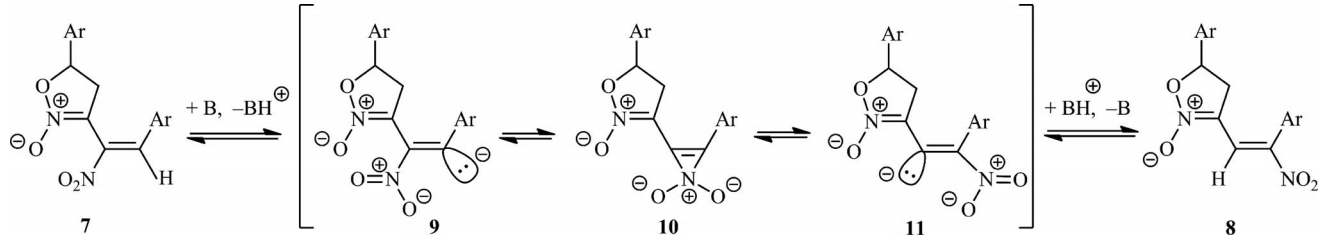
Substituent Effect on the Nitrocyclopropane to Isoxazoline *N*-Oxide (6 to 7) Isomerization

Considering the data in Table 1, with respect to the model substrate (Table 1, Entry 1; Ar = Ph), the **6** to **7** con-

Table 3. Effect of catalyst on the **7**→**8** conversion rate in DMSO.[a]

Entry	Substrate	Ar	Catalyst (mol equiv.)	Reaction time [h] and **6/7/8** molar ratio[b]	
1	**6a**	Ph	NaI (1.0)	a) 3	36/64:0
				b) 24	0:15:85
2	**6a**	Ph	NaI (0.5)	a) 3	58:42:0
				b) 6	39:58:3
				c) 24	9:18:63
3	**6c**	4-MeC_6H_4	NaI (1.0)	a) 24	0:42:58
				b) 48	0:8:92
4	**6c**	4-MeC_6H_4	NaI (2.0)	24	0:0:100
5	**6d**	4-MeOC_6H_4	NaI (1.0)	a) 24	0:83:17
				b) 48	0:59:41
6	**6d**	4-MeOC_6H_4	none	a) 24	43:57:0
				b) 48	11:89:0
7	**6g**	1-naphthyl	NaI (1.0)	a) 24	0:12:88
				b) 48	0:0:100
8	**6g**	1-naphthyl	none	a) 24	2:98:0
				b) 48	0:100:0[c]

[a] At 60 °C. [b] Normalized. [c] No **8** detected after 140 h.



Scheme 5.

version becomes faster (a) when the aryl moiety carries electron-repulsive (Table 1, Entries 2 and 3) or electron-donating substituents (Table 1, Entry 4), (b) in the presence of more extensively conjugated systems (Table 1, Entries 7 and 8), or (c) when steric hindrance occurs (Table 1, Entries 2 and 7). It should also be noted that, for 2-thienyl derivative **6i** (Table 1, Entry 9), the conversion to **7i** is particularly favoured, because it takes place spontaneously at room temperature during the chromatographic purification of the crude, possibly owing to the catalytic effect of silica gel itself. This is in line with the electron-rich nature of the thiophene ring.

However, a disfavouring effect is played by a chloro substituent in the aryl ring, either from the *meta* or from the *para* position with respect to the vinyl moiety (Table 1, Entries 5 and 6, respectively).

Overall, the observed electronic effects upon the **6** to **7** isomerization process are in agreement with the fact that the nitrocyclopropane ring-opening occurs as a heterolitic breakage of the more substituted bond involving the nitrogroup-bearing carbon atom. Such a breakage, whether iodide-assisted or not, generates an incipient positive charge on the benzylic carbon atom which obviously takes advantage of charge delocalization onto the aryl ring.[7] The occurrence of significant uncatalyzed pathways (described in the mechanistic details above) could well find a rationale in the weakening of the bond to be broken owing to the stabilization (e.g. by a *p*-MeO group) of an incipient carbocation. In this regard, it should be recalled that a similar uncatalyzed isomerization has already been observed on substrates bearing a $PhSO_2$ group on the nitrated carbon. In that instance, the "weakening" of the bond to be broken is achieved by the concomitant effect of two strong electron-withdrawing groups stabilizing the negative charge.[15]

Substituent Effect on the Nitro Group Migration (7 to 8)

For the 1,2 nitro group migration, the trend is opposite to that observed for the **6** to **7** isomerization. Only in the cases of the chloro substituted substrates (Table 1, Entries 5 and 6) we observed the completion of the overall process after 24 h. Other systems, particularly the 4-methoxy substituted one (Table 1, Entry 4), lagged well behind. Thus, for this second step, the approximate reactivity order: 3-Cl > 4-Cl > 2-Naph > Ph ≈ 1-Naph > 4-Me ≈ 2-Me > 4-MeO, is in agreement with the increasing conjugative ability of the aryl group towards the β-nitrogroup within the nitrostyrenic moiety, and mirroring the reluctance of the system to renounce a stabilizing effect in final product **8**. It should be underlined that, even if the complete conversion to **8** (last column of Table 1) requires increasing times following the reactivity order above, the process does definitely occur even in the least favourable case (e.g. the methoxy derivative **d**). This fact proves that the release of steric and/or stereoelectronic strain is the most important factor underlying the chemical outcome.

No isomerization to **8i** and **8j** was observed for the two thienyl derivatives **7i** and **7j**, which are consumed through competitive decomposition pathways. To establish whether kinetic or thermodynamic reasons prevent effective nitrotransfer, we evaluated the relative stabilities within the two couples of isomers, **7i** versus **8i**, and **7j** versus **8j**. Quantomechanical calculations suggest that for both the 2- and 3-thienyl derivatives the stabilization achievable for the **7**→**8** isomerization is considerably reduced (both in solution and in the gas phase), relative to the case of the phenyl derivative, and almost negligible in the case of **7i**. This outcome agrees with a rationalization based on a lower gain from steric-hindrance release for a five-membered ring relative to a six-membered one.

Solvent Effect: an Optimized Approach to Intermediate Isoxazoline *N*-Oxides 7

The substituent effect outlined above mirrors a conceivable significant polarity of the transition states for both the **6**→**7** and **7**→**8** isomerizations. Thus, for the overall process, but in particular as far as the second isomerization is concerned (in which proton exchanges are involved), an important role of the solvent (and of its proton affinity) is expected.

In order to better understand such a role, we decided to change the reaction medium, testing two solvents: methanol (a polar protic solvent) and acetonitrile [a polar aprotic solvent (ε = 35.94) "similar" to DMSO (ε = 46.45) but characterized by a marked protophobicity].[10c]

Preliminary tests performed in CD_3OD showed (^{1}H NMR spectroscopy) a rather awkward outcome, characterized by the formation of complex final mixtures for which minor signals attributable to structures different from **7** or **8** were detected. Such a solvent seems to be a too reactive medium and additional, competitive processes take place.

Pleasingly, analogous tests performed in CD_3CN revealed (Table 4) a remarkable opposite effect on the rate of the two consecutive processes. The isoxazoline formation is significantly accelerated throughout, as evidenced by the data at differing reaction times in Table 1. In addition, a significant negative effect on the nitro group migration results in either a decreased isomerization rate (Table 4, Entries 5, 6, and more markedly 1, 3), or in the total prevention of the process (Table 4, Entries 2, 4, 7 and 8). As already observed in DMSO, in CD_3CN, 3-thienyl derivative **7j** does not undergo any nitro transfer. For the 2-thienyl derivative, spontaneous **6**→**7** isomerization coupled with failure of the **7**→**8** shift in DMSO, clearly voids the significance of analogous tests.

Overall, the preliminary results just described are gratifying both from a mechanistic and synthetic point of view. The almost general, unfavourable effect of acetonitrile on the migration process supports the proposed mechanism, that was supposed to require initial deprotonation of **7**. Indeed the protophobicity of such a solvent, with respect to DMSO, is well known and evidenced by the donicity parameters (0.36 and 0.77, respectively).[10c]

Table 4. ^{1}H NMR spectroscopic study on the **6**→**7**→**8** conversion rate in CD_3CN in the presence of NaI.[a]

Entry	Ar in **6**	*t* = 1 h **6/7/8** ratio[b]	*t* = 2 h **6/7/8** ratio[b]	*t* = 5 h **6/7/8** ratio[b]	*t* = 24 h **6/:7/8** ratio[b][c]	Last control after:
1	**6a**: Ph	65:35:0	40:60:0	14:86:0	0:86:14	48 h (0:68:32)
2	**6b**: 2-MeC_6H_4	10:90:0	0:100:0	0:100:0	0:100:0	144 h (0:100:0)
3	**6c**: 4-MeC_6H_4	46:54:0	10:90:0	0:100:0	0:95:5	168 h (0:37:63)
4	**6d**: 4-MeOC_6H_4	9:91:0	0:100:0	0:100:0	0:100:0	144 h (0:100:0)
5	**6e**: 3-ClC_6H_4	45:55:0	28:72:0	0:84:16	0:21:79	48 h (0:0:100)
6	**6f**: 4-ClC_6H_4	50:50:0	32:68:0	6:84:10	0:17:83	48 h (0:0:100)
7	**6g**: 1-naphthyl	0:100:0	0:100:0	0:100:0	0:100:0	96 h (0:100:0)
8	**6h**: 2-naphthyl	0:100:0	0:100:0	0:100:0	0:100:0	96 h (0:100:0)
9	**6j**: 3-thienyl	35:65:0	23:77:0	0:100:0[d]	0:0:0	24 h (0:0:0)

[a] At 60 °C; NaI: 1 mol equiv. [b] Normalized. [c] Decomposition occurs throughout. [d] Significant decomposition.

Acetonitrile offers the possibility of stopping the process after formation of **7**, prior to migration and thus could be the solvent of choice to prepare isoxazoline *N*-oxide **7** in pure form.

Table 5 shows yields of isolated isoxazoline *N*-oxides, reported for preparative reactions carried out in CH_3CN typically at 60 °C, which were more than satisfactory. As far as the 1-naphthyl derivative is concerned, the outcome of Table 5, Entry 7 represents an alternative to effective isolation of **7g**, which can be performed in DMSO in the absence of NaI. The entry relevant to the 2-thienyl derivative, refers to the already mentioned (cf. Table 1) isomerization of **6i** to **7i** during the chromatographic separation of the final mixture from the cyclopropanation reaction.

Table 5. Results of experiments performed on preparative scale, at 60 °C.[a]

Entry	Ar	**6**→**7** (MeCN) Reaction time	**7**: Yield%	**7**→**8** (DMSO) Reaction time	**8**: Yield%
1	Ph	6 h	**7a**: 90%	24 h	**8a**: 80%
2	2-MeC_6H_4	3 h	**7b**: 88%	72 h	**8b**: 68%
3	4-MeC_6H_4	5 h	**7c**: 87%	48 h	**8c**: 65%
4	4-MeOC_6H_4	3 h	**7d**: 98%	72 h	**8d**: 75%
5	3-ClC_6H_4	3 h	**7e**: 68%	24 h	**8e**: 40%
6	4-ClC_6H_4	3 h	**7f**: 73%	24 h	**8f**: 44%
7	1-naphthyl	2 h[b]	**7g**: 82%	48 h	**8g**: 32%
8	2-naphthyl	3 h	**7h**: 78%	24 h	**8h**: 53%
9	2-thienyl	[c]	**7i**: 87%	–	–
10	3-thienyl[d]	24 h	**7j**: 74%	–	–

[a] In the presence of NaI (1 mol equiv.), if not otherwise stated. [b] Isolation of **7g** (89%) can also be performed in DMSO, after 1 h at 70 °C in the absence of NaI. [c] Complete isomerization to **7i** occurs during the chromatographic separation of the final mixture from the cyclopropanation reaction. [d] No catalyst was employed. Isomerization to **7j** occurs on silica (50% after 24 h).

As expected, treatment of isolated **7a**–**7h** at 60 °C with NaI (1 mol equiv.) in DMSO led to nitro group migration, although some yields are less satisfactory: an outcome that can be attributed, in part, to some instability of both substrate and final product. It should be remarked that the substituent effect for the **7** to **8** isomerization in DMSO (as explained above) is qualitatively confirmed by the gross reaction times required for completion, reported in Table 5 in the same solvent, and determined by TLC monitoring of disappearance of substrate.

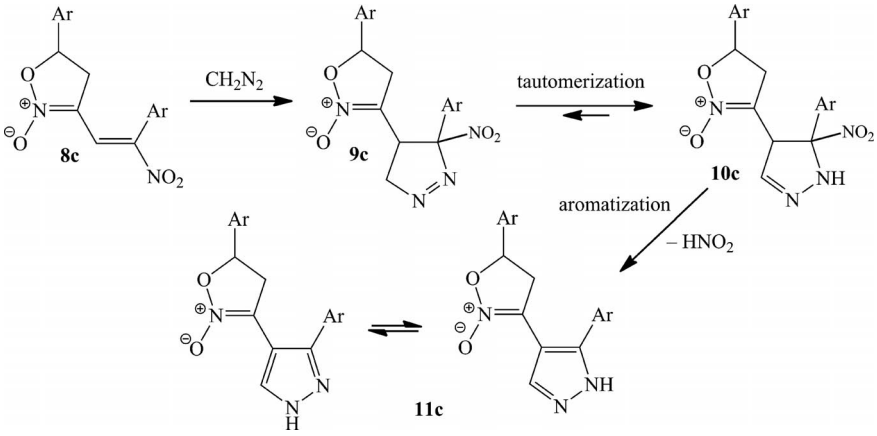
Reaction of Isoxazoline 8c with Diazomethane: A Viable Breakthrough to New, More Complex Bis-Heterocyclic Systems

Attempts to further exploit our system for heterocyclic synthesis, e.g. assembling a new homo- or heterocycle with the existing isoxazoline ring, by means of cyclopropanation of the nitrovinylic moiety of **7c**, met with little success.

A much more rewarding result was obtained when treating with diazomethane in tetrahydrofuran (THF) at 0 °C transposed isoxazoline **8c**, as pyrazolyl derivative **11c** was isolated in almost quantitative yields. Formation of **11c** (structure confirmed by NOE experiments, see Supporting Information) can be explained by means of an initial regioselective [3+2] dipolar cycloaddition between diazomethane and the nitroethenyl moiety, followed by tautomerization of the pyrazoline intermediate and aromatization by nitrous acid elimination (Scheme 6).

Conclusions

These results provide further support to the possibility of the ring opening of 3,4-dinitrothiophene **1** as a window to a vast range of heterocycles. The chemical differentiation of the two nitrovinyl moieties of **2**, obtained in this case through monocyclopropanation to **3**,[6] seems to guarantee the possibility of new synthetic routes. The functionalities of compounds **6**, **7** or **8** could be in turn exploited to gain access to targets for applications in, for example, pharmacology. The easy high-yielding transformation of **8c** into **11c** represents a clear and valuable example of such potential, leading to bis(heterocycle)s characterized by two differing heterorings.[16]



Scheme 6.

Experimental Section

Materials and Methods: ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported relative to TMS as internal reference. IR spectra were recorded with a Perkin–Elmer 881 Infrared Spectrophotometer. MS (ESI) analyses were recorded with a Micromass Z0MD Waters instrument (30 V, 13.2 KV). HRMS were recorded with a FINNIGAN MAT95XP apparatus. Melting points were determined with a Büchi 535 apparatus. Petroleum ether and light petroleum refer to the fractions with b.p. 40–60 and 80–100 °C, respectively. Silica gel 230–400 mesh was used for column chromatography, all solvents being distilled before use. THF was purified by standard methods and distilled from potassium benzophenone ketyl before use. All other commercially available reagents were used as received. 4-Chlorophenyl- and 3-thienylmagnesium iodide were available as commercial THF or Et_2O solutions, which were titrated just before use.

Compounds **2a**,[4b] **b**–**e**, **g**, **i**[17] and **h**[5h] have been already described. Compounds **2f** and **2j** are new compounds, prepared according to a reported procedure.[4b,17]

4,4′-[(1*E*,3*E*)-2,3-Dinitro-1,3-butadiene-1,4-diyl]bis(chlorobenzene) (2f): Yellow solid, m.p. 155–156 °C (toluene). ^{1}H NMR ($CDCl_3$): δ = 6.76 and 7.17 (AA′BB′, J = 8.4 Hz, 4H each), 8.42 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 127.88, 129.05, 129.99, 131.64, 139.19, 140.11 ppm. HRMS: calcd. for $C_{16}H_{10}Cl_2N_2O_4$ 364.0018; found 364.0014.

3,3′-[(1*E*,3*E*)-2,3-Dinitro-1,3-butadiene-1,4-diyl]dithiophene (2j): Yellow solid, m.p. 144–145 °C (toluene/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 7.15 (dd, J = 5.2, 1.4 Hz, 2 H), 7.34 (dd, J = 5.1, 2.9 Hz, 2 H), 7.80 (dd, J = 2.9, 1.2 Hz, 2 H), 8.58 (s, 2 H) ppm; (CD_3SOCD_3): δ = 7.21 (dd, J = 5.1, 1.4 Hz, 2 H), 7.64 (dd, J = 5.1, 2.9 Hz, 2 H), 8.37–8.45 (m, 2 H), 8.82 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 126.66, 128.59, 131.50, 134.84, 135.57, 138.17 ppm. HRMS: calcd. for $C_{12}H_8N_2O_4S_2$ 307.9925; found 307.9920.

Compounds **6a**, **6c**–**e**, **6g**, **6i** have been already described.[6]

Compounds **6b** (80%), **6f** (76%), **6h** (67%) and **6j** (62%) are new and were prepared according to the same procedure.[6]

(*E*)-1-Methyl-2-{2-nitro-2-[1-nitro-2-(2-methylphenyl)cyclopropyl]-vinyl}benzene (6b): Yellow solid, m.p. 148–149 °C (ethanol). ^{1}H NMR ($CDCl_3$): δ = 1.49 (t, J = 8.3 Hz, 1 H), 2.30 (dd, J = 10.7, 7.3 Hz,1 H), 2.43 (s, 3 H), 2.48 (s, 3 H), 4.07 (t, J = 10.0 Hz, 1 H), 6.28 (d, J = 7.6 Hz, 1 H), 6.92–7.52 (m, 7 H), 8.56 (s, 1 H) ppm; (CD_3SOCD_3): δ = 1.62 (dd, J = 10.5, 4.8 Hz, 1 H), 2.39 (s, 3 H), 2.41 (s, 3 H), 2.47 (app. t part overlapped with the previous signal, J = 6.9 Hz, 1 H), 4.04 (app. t, J = 10.0 Hz, 1 H), 6.42 (d, J = 7.4 Hz, 1 H), 7.00–7.12 (m, 1 H), 7.12–7.27 (m, 3 H), 7.33–7.60 (m, 3 H), 8.71 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.00, 20.12, 24.00, 35.96, 68.47, 123.70, 125.54, 126.37, 126.72, 128.13, 128.49, 129.38, 129.53, 131.09, 131.87, 138.14, 140.03, 140.81, 141.54 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1263.

(*E*)-1-Chloro-4-{2-[2-(4-chlorophenyl)-1-nitrocyclopropyl]-2-nitrovinyl}benzene (6f): Yellow solid, m.p. 214–215 °C (ethanol). ^{1}H NMR ($CDCl_3$): major conformer δ = 1.52 (dd, J = 10.0, 7.0 Hz, 1 H, part overlapped with the signal of water), 2.50 (dd, J = 10.4, 7.0 Hz, 1 H), 3.96 (app. t, J = 9.7 Hz, 1 H), 6.86 and 7.22 (AA′BB′, J = 8.2 Hz, part overlapped with the signals of minor conformer, 2 H each), 7.37 and 7.52 (AA′BB′, J = 8.1 Hz, part overlapped with the signals of minor conformer, 2 H each), 8.39 (s, 1 H) ppm; minor conformer δ = 1.98 (app. t, J = 8.2 Hz, 1 H), 2.94 (app. t, J = 9.2 Hz, 1 H), 3.54 (t, J = 10.0 Hz, 1 H), 6.43 and 6.76 (AA′BB′, J = 8.0 Hz, 2 H each), 6.91 and 7.21 (AA′BB′, J = 7.2 Hz, part overlapped with the signals of major conformer, 2 H each), 8.25 (s, 1 H) ppm; (CD_3SOCD_3): major conformer δ = 1.92 (dd, J = 9.3, 7.6 Hz, 1 H), 2.75 (dd, J = 10.4, 7.6 Hz, 1 H), 4.11 (app. t, J = 9.9 Hz, 1 H), 7.09 and 7.32 (AA′BB′, J = 8.5 Hz, part overlapped with the signals of minor conformer, 2 H each), 7.66 (br. s, 4 H), 8.67 (s, 1 H) ppm; minor conformer δ = 2.65 (dd, J = 9.7, 7.5 Hz, 1 H), 2.85 (dd, J = 10.8, 7.5 Hz, 1 H), 3.83 (dd, J = 10.7, 9.7 Hz, 1 H), 6.91 (br. s, 4 H), 7.04 and 7.31 (AA′BB′, J = 8.6 Hz, part overlapped with the signals of major conformer, 2 H each), 8.45 (s, 1 H) ppm. The ratio major/minor conformer is 83:17 in $CDCl_3$ and 77:23 in CD_3SOCD_3. ^{13}C NMR ($CDCl_3$): the sample is a mixture of two conformers and only a few signals are unambiguously assigned: δ = 24.39 (major conformer), 25.87 (minor conformer), 37.76 (minor conformer), 38.34 (major conformer), 67.32 (minor conformer), 67.36 (major conformer), 128.03, 128.19, 128.49, 129.03 (major conformer), 129.23, 129.37 (major conformer), 129.58, 129.92 (major conformer), 130.71, 131.63 (major conformer), 134.81, 138.80, 141.32 (major conformer), 142.37 (minor conformer) ppm. HRMS: calcd. for $C_{17}H_{12}Cl_2N_2O_4$ 378.0174; found 378.0172.

(*E*)-2-{2-[2-(2-Naphthyl)-1-nitrocyclopropyl]-2-nitrovinyl}naphthalene (6h): Yellow oil. ^{1}H NMR ($CDCl_3$) major conformer: δ = 2.41 (dd, J = 8.8, 6.9 Hz, 1 H), 2.84 (dd, J = 10.5, 7.0 Hz, 1 H), 4.06 (app. t, J = 9.6 Hz, 1 H), 6.76–8.15 (m, 14 H), 8.57 (s, 1 H) ppm; minor conformer: δ = 1.75 (app. t, J = 8.0 Hz, 1 H), 2.60

(dd, J = 10.5, 7.2 Hz, 1 H), 4.06 (app. t, J = 9.6 Hz, 1 H), 6.76–8.15 (m, 14 H), 8.39 (s, 1 H); the signals of the 14 aromatic H of the two conformers overlap: 6.92–7.07, 7.08–7.18, 7.29–7.39, 7.40–7.54, 7.55–7.62, 7.62–7.70, 7.70–7.80, 7.80–7.90, 7.90–8.30 (9m, 14 H in all) ppm; (CD_3SOCD_3): δ = 2.10 (app. t, J = 8.4 Hz, 1 H), 2.91 (dd, J = 10.4, 7.7 Hz, 1 H), 4.27 (app. t, J = 9.8 Hz, 1 H), 6.86–7.17, 7.17–7.32, 7.38–7.63, 7.64–7.76, 7.77–7.92 and 7.94–8.25 (6m, 14 H in all), 8.79 (s, 1 H) ppm; the ratio major/minor conformer is 67:33 in $CDCl_3$, whereas in CD_3SOCD_3 only one conformer is present. ^{13}C NMR (CD_3SOCD_3): δ = 14.25, 28.97, 64.81, 115.37, 120.22, 121.44, 121.59, 121.70, 122.01, 122.11, 122.18, 123.22, 123.96, 124.22, 126.07, 126.97, 128.86, 132.55, 144.83 (6 C accidentally isochronous) ppm. HRMS: calcd. for $C_{25}H_{18}N_2O_4$ 410.1267; found 410.1267.

(*E*)-3-{2-Nitro-2-[1-nitro-2-(thiophen-3-yl)cyclopropyl]vinyl}-thiophene (6j): Yellow solid, m.p. 142–143 °C (diethyl ether). ^1H NMR ($CDCl_3$): major conformer δ = 1.74 (dd, J = 8.9, 6.7 Hz, 1 H), 2.70 (dd, J = 10.4, 6.7 Hz, 1 H), 4.00 (dd, J = 10.4, 8.8 Hz, 1 H), 6.78 (dd, J = 5.0, 1.4 Hz, 1 H, part overlapped with the signals of minor conformer), 6.87 (ddd, J = 3.0, 1.4, 0.7 Hz, 1 H), 7.16–7.30 (m, part overlapped with the signals of minor conformer, 2 H), 7.51 (ddd, J = 5.1, 3.0, 0.6 Hz, 1 H), 7.74 (ddd, J = 3.0, 1.4, 0.7 Hz, 1 H), 8.39 (s, 1 H) ppm; minor conformer δ = 1.93 (dd, J = 9.1, 7.4 Hz, 1 H), 2.97 (dd, J = 10.6, 7.3 Hz, 1 H), 3.76 (dd, J = 10.6, 9.1 Hz, 1 H), 6.33 (dd, J = 5.0, 1.4 Hz, 1 H), 6.57 (dd, J = 2.7, 1.4 Hz, 1 H), 6.93 (dd, J = 4.9, 2.9 Hz, 1 H), 8.26 (s, 1 H) ppm (the remaining 3 aromatic H are covered by the signals of major conformer); (CD_3SOCD_3): major conformer δ = 2.12 (dd, J = 9.1, 7.0 Hz, 1 H), 2.94 (dd, J = 10.5, 7.1 Hz, 1 H, part overlapped with the signals of minor conformer), 4.05 (dd, J = 10.6, 9.1 Hz, 1 H, part overlapped with the signals of minor conformer), 6.87 (dd, J = 4.9, 1.5 Hz, 1 H), 7.29 (dd, J = 2.8, 1.3 Hz, 1 H), 7.38–7.44 (m, 2 H), 7.78 (dd, J = 5.0, 2.9 Hz, 1 H), 8.38 (dd, J = 3.0, 1.4 Hz, 1 H, part overlapped with the signals of minor conformer), 8.59 (s, 1 H) ppm; minor conformer δ = 2.46 (dd, J = 9.3, 7.1 Hz, 1 H, part overlapped with the signal of solvent), 2.86 (dd, J = 10.7, 7.3 Hz, 1 H, part overlapped with the signals of major conformer), 4.06 (t, J 10.0 Hz, 1 H, part overlapped with the signals of major conformer), 6.71 (dd, J = 5.0, 1.4 Hz, 1 H), 6.98 (dd, J = 5.0, 1.4 Hz, 1 H), 7.07 (dd, J = 5.0, 3.0 Hz, 1 H), 7.17 (dd, J = 2.7, 1.3 Hz, 1 H), 7.52 (dd, J = 5.1, 2.9 Hz, 1 H), 7.89 (dd, J = 3.0, 1.4 Hz, 1 H), 8.38 (s, 1 H, part overlapped with the signals of major conformer) ppm; the ratio major/minor conformer is 81:19 in $CDCl_3$ and 7:3 in CD_3SOCD_3. ^{13}C NMR ($CDCl_3$): the sample is a mixture of two conformers and only a few signals are unambiguously assigned: δ = 26.44 (major conformer), 27.63 (minor conformer), 29.85 (minor conformer), 34.66 (major conformer), 67.08 (major conformer), 67.85 (minor conformer), 123.30, 123.66 (major conformer), 124.50, 125.03, 125.79, 126.60 (major conformer), 127.28, 127.67 (major conformer), 127.72, 128.04 (major conformer), 128.15 (major conformer), 128.46, 131.31, 132.96, 133.03, 133.59, 133.99, 136.01 (major conformer), 137.62, 140.20 ppm. HRMS: calcd. for $C_{13}H_{10}N_2O_4S_2$ 322.0082; found 322.0081.

Preparative Isomerization of 6 to 7: In a flask equipped with a magnetic stirring-bar, appropriate **6** (0.8 mmol) was dissolved in dry CH_3CN (20 mL) and NaI (120 mg, 0.8 mmol, 1 mol equiv.) was added. The flask was then closed with a rubber septum equipped with a silica-gel trap and kept at 60 °C as long as necessary. At the end, the solvent was removed under vacuum to obtain a crude mixture that was separated by column chromatography on silica gel.

(*E*)-3-(1-Nitro-2-phenylethenyl)-5-phenyl-4,5-dihydroisoxazole 2-Oxide (7a):[8] Yellow solid, m.p. 104–105 °C (petroleum ether/dichloromethane). IR (Nujol): $\tilde{\nu}$ = 3452, 1568, 1304, 1277, 1224, 1149 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.40 (dd, J = 16.4, 7.0 Hz, 1 H), 3.84 (dd, J = 16.3, 9.7 Hz, 1 H), 5.91 (dd, J = 9.3, 6.9 Hz, 1 H), 7.29–7.55 (m, 10 H), 8.32 (s, 1 H); (CD_3SOCD_3): δ = 3.32 (dd, J = 17.0, 6.5 Hz, 1 H, part overlapped with the signal of water), 3.88 (dd, J = 17.0, 9.6 Hz, 1 H), 6.11 (dd, J = 9.5, 6.5 Hz, 1 H), 7.36–7.62 (m, 10 H), 8.48 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.59, 77.84, 106.97, 125.86, 129.21, 129.30, 129.43, 130.70, 132.57, 137.25, 138.14, 140.83, 141.43 ppm; (CD_3SOCD_3): δ = 39.16, 77.37, 107.53, 126.02, 128.01, 128.98, 129.23, 129.40, 130.79, 137.20, 138.65, 140.67, 142.16 ppm. MS (ESI): m/z = 349 $[M + K]^+$, 644 $[2M + Na]^+$, 659 $[2M + K]^+$.

(*E*)-5-(2-Methylphenyl)-3-[2-(2-methylphenyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7b): Yellow oil. ^1H NMR (CD_3SOCD_3): δ = 2.25 (s, 3 H), 2.38 (s, 3 H), 3.04 (dd, J = 17.0, 5.9 Hz, 1 H), 3.81 (dd, J = 17.0, 10.0 Hz, 1 H), 6.16 (dd, J = 9.9, 5.9 Hz, 1 H), 7.07–7.17 (m, 2 H), 7.19–7.44 (m, 6 H), 8.49 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.11, 20.25, 38.80, 75.36, 106.75, 125.01, 126.70, 126.74, 127.96, 128.91, 129.64, 131.11, 131.16, 132.12, 134.49, 136.45, 138.61, 139.22, 139.36 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1265.

(*E*)-5-(4-Methylphenyl)-3-[2-(4-methylphenyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7c): Yellow oil. ^1H NMR ($CDCl_3$): δ = 2.39 (s, 6 H), 3.39 (dd, J = 16.6, 7.4 Hz, 1 H), 3.76 (dd, J = 16.6, 9.4 Hz, 1 H), 5.85 (dd, J = 9.4, 7.5 Hz, 1 H), 7.20 (half AA′BB′, J = 8.1 Hz, 2 H), 7.23–7.31 (m, 4 H), 7.37 (half AA′BB′, J = 8.1 Hz, 2 H), 8.27 (s, 1 H); (CD_3SOCD_3): δ = 2.35 (s, 3 H), 2.37 (s, 3 H), 3.31 (dd, J = 17.2, 7.1 Hz, 1 H, part overlapped with the signal of water), 3.83 (dd, J = 17.0, 9.6 Hz, 1 H), 6.06 (app. t, J = 8.3 Hz, 1 H), 7.22–7.35 (m, 4 H), 7.38–7.48 (m, 4 H), 8.45 (s, 1 H) ppm [the peaks are broad; global spectral deconvolution (GSD) analysis shows the presence of a minor conformer with the same pattern of signals almost completely overlapped with the main one]. ^{13}C NMR ($CDCl_3$): δ = 21.31, 21.87, 39.50, 78.04, 107.46, 126.01, 127.10, 129.78, 130.21, 130.95, 134.95, 136.28, 139.25, 140.81, 143.79 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1262.

(*E*)-5-(4-Methoxyphenyl)-3-[2-(4-methoxyphenyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7d): Yellow solid, m.p. 127–128 °C (petroleum ether/dichloromethane). IR (Nujol): $\tilde{\nu}$ = 1617, 1594, 1303, 1259, 1173, 1024, 919, 837, 722 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.49 (dd, J = 16.6, 7.8 Hz, 1 H), 3.79 (dd, J = 16.6, 9.3 Hz, 1 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 5.88 (dd, J = 9.2, 7.8 Hz, 1 H), 6.94 and 6.99 (AA′BB′, J = 8.8 Hz, 2H each), 7.35 and 7.45 (AA′BB′, J = 8.8 Hz, 2H each), 8.31 (s, 1 H); (CD_3SOCD_3): δ = 3.37 (dd, J = 17.1, 7.3 Hz, 1 H), 3.79 (s, 3 H), 3.80 (dd, J = 16.9, 9.1 Hz, 1 H, part overlapped with the previous signal), 3.85 (s, 3 H), 6.04 (dd, J = 9.4, 7.4 Hz, 1 H), 7.04 and 7.06 (AA′BB′, J = 8.6 Hz, 2H each), 7.49 and 7.53 (AA′BB′, J = 8.6 Hz, 2H each), 8.44 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.35, 55.40, 55.57, 77.99, 107.80, 114.41, 114.97, 122.22, 127.67, 129.51, 133.43, 134.43, 140.41, 160.34, 163.30 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_6$ 370.1165; found 370.1160.

(*E*)-5-(3-Chlorophenyl)-3-[2-(3-chlorophenyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7e): Yellow oil. ^1H NMR ($CDCl_3$): δ = 3.38 (dd, J = 16.6, 6.9 Hz, 1 H), 3.91 (dd, J = 16.4, 9.7 Hz, 1 H), 5.87 (dd, J = 9.6, 6.8 Hz, 1 H), 7.11–7.47 (m, 8 H), 8.24 (s, 1 H); (CD_3SOCD_3): δ = 3.41 (dd, J = 17.3, 6.3 Hz, 1 H, part overlapped with the signal of water), 3.95 (dd, J = 17.3, 9.8 Hz, 1 H), 6.11 (dd, J = 9.7, 6.2 Hz, 1 H), 7.39–7.66 (m, 8 H), 8.48 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.84, 75.60, 118.00, 122.99, 123.02, 123.24, 123.63, 123.76, 124.17, 124.29, 124.54, 129.28, 130.68, 131.19,

137.50, 138.13, 138.90 ppm. HRMS: calcd. for $C_{17}H_{12}Cl_2N_2O_4$ 378.0174; found 378.0171.

(*E*)-5-(4-Chlorophenyl)-3-(2-(4-chlorophenyl)-1-nitrovinyl)-4,5-dihydroisoxazole 2-Oxide (7f): Yellow solid, m.p. 83–84 °C (petroleum ether/dichloromethane). ^{1}H NMR ($CDCl_3$): δ = 3.39 (dd, J = 16.5, 6.9 Hz, 1 H), 3.86 (dd, J = 16.5, 9.4 Hz, 1 H), 5.87 (dd, J = 9.3, 7.0 Hz, 1 H), 7.20–7.31 (m, 2 H), 7.32–7.52 (m, 6 H), 8.26 (s, 1 H) ppm; (CD_3SOCD_3): δ = 3.34 (dd, J = 17.1, 6.7 Hz, 1 H, part overlapped with the signal of water), 3.89 (dd, J = 17.0, 9.6 Hz, 1 H), 6.10 (dd, J = 9.5, 6.7 Hz, 1 H), 7.49–7.60 (m, 8 H), 8.49 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 39.66, 76.23, 106.73, 127.29, 128.36, 129.52, 129.84, 131.80, 135.46, 136.44, 137.38, 139.07, 139.44 ppm. HRMS: calcd. for $C_{17}H_{12}Cl_2N_2O_4$ 378.0174; found 378.0168.

(*E*)-5-(1-Naphthyl)-3-[2-(1-naphthyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7g): Yellow oil. ^{1}H NMR ($CDCl_3$): major conformer δ = 3.16 (dd, J = 16.4, 5.5 Hz, 1 H), 3.92 (dd, J = 16.4, 9.8 Hz, 1 H, part overlapped with the signal of minor conformer), 6.40 (dd, J = 9.8, 5.4 Hz, 1 H, part overlapped with the signal of minor conformer), 7.16–7.34, 7.34–7.72 and 7.73–7.97 (3 m, 14H in all), 8.90 (s, 1 H) ppm; minor conformer δ = 3.46 (dd, J = 16.6, 7.0 Hz, 1 H), 3.99 (dd, J = 16.6, 9.7 Hz, 1 H, part overlapped with the major conformer), 6.47 (dd, J = 9.9, 7.3 Hz, 1 H, part overlapped with the major conformer), 8.67 (s, 1 H) ppm; (CD_3SOCD_3): major conformer δ = 3.11 (dd, J = 16.9, 5.0 Hz, 1 H), 4.03 (dd, J = 16.9, 10.0 Hz, 1 H), 6.70 (dd, J = 9.8, 5.1 Hz, 1 H), 7.15–7.52, 7.55–7.65 and 7.89–8.11 (3 m, 14H in all), 8.95 (s, 1 H) ppm; minor conformer δ = 3.79 (dd, J = 16.6, 7.2 Hz, 1 H), 4.37 (dd, J = 16.1, 9.4 Hz, 1 H), 6.81 (app. t, J = 8.4 Hz, 1 H), 8.84 (s, 1 H) ppm (the signals of the 14 aromatic H of the minor conformer are hidden by those of the major, both in $CDCl_3$ and in CD_3SOCD_3); the ratio major/minor conformer is 73:27 in $CDCl_3$ and 19:1 in CD_3SOCD_3. ^{13}C NMR (CD_3SOCD_3): δ = 34.64, 75.74, 115.52, 116.36, 116.39, 116.69, 117.02, 122.10, 122.24, 122.39, 122.42, 122.47, 122.53, 122.62, 122.87, 122.96, 123.03, 123.15, 123.28, 123.48, 123.56, 129.40, 135.62, 136.93, 138.22 ppm. HRMS: calcd. for $C_{25}H_{18}N_2O_4$ 410.1267; found 410.1269.

(*E*)-5-(2-Naphthyl)-3-[2-(2-naphthyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (7h): Yellow oil. ^{1}H NMR (CD_3CN): δ = 3.47 (dd, J = 17.1, 6.5 Hz, 1 H), 3.96 (dd, J = 17.2, 9.8 Hz, 1 H), 6.18 (dd, J = 9.7, 6.5 Hz, 1 H), 7.35–7.70, 7.71–7.80, 7.80–7.89 and 7.90–8.11 (4m, 14H in all), 8.50 (s, 1 H) ppm; (CD_3SOCD_3): δ = 3.52 (dd, J = 17.1, 6.8 Hz, 1 H), 4.02 (dd, J = 17.6, 9.4 Hz, 1 H), 6.32 (dd, J = 9.7, 6.7 Hz, 1 H), 7.42–7.74, 7.80–7.94 and 7.95–8.16 (3m, 14H in all), 8.64 (s, 1 H) ppm. ^{13}C NMR (CD_3SOCD_3): δ = 35.16, 74.91, 114.92, 116.56, 116.71, 121.59, 122.37, 122.73, 122.96, 123.06, 123.30, 123.92, 124.02, 124.82, 127.64, 136.73, 137.91, 138.22 ppm (7 C are accidentally isochronous). HRMS: calcd. for $C_{25}H_{18}N_2O_4$ 410.1267; found 410.1261.

(*E*)-3-[1-Nitro-2-(2-thienyl)vinyl]-5-(2-thienyl)-4,5-dihydroisoxazole 2-Oxide (7i): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.70 (dd, J = 16.6, 8.5 Hz, 1 H), 3.84 (dd, J = 16.6, 9.2 Hz, 1 H), 6.18 (app. t, J = 8.8 Hz, 1 H), 7.07 (dd, J = 5.0, 3.6 Hz, 1 H), 7.21 (dd, J = 5.1, 3.8 Hz, 1 H), 7.30 (dd, J = 3.5, 1.1 Hz, 1 H), 7.44 (dd, J = 5.1, 1.2 Hz, 1 H), 7.53 (dd, J = 3.8, 1.4 Hz, 1 H), 7.81 (dd, J = 5.0, 1.1 Hz, 1 H), 8.57 (s, 1 H) ppm; (CD_3SOCD_3): δ = 3.58 (dd, J = 17.3, 8.0 Hz, 1 H), 3.91 (dd, J = 17.3, 9.5 Hz, 1 H), 6.40 (app. t, J = 8.6 Hz, 1 H), 7.13 (dd, J = 5.0, 3.6 Hz, 1 H), 7.33 (dd, J = 8.6, 3.6 Hz, 1 H), 7.40 (dd, J = 3.4, 1.3 Hz, 1 H), 7.71 (dd, J = 5.0, 1.4 Hz, 1 H), 7.92 (dd, J = 3.7, 1.4 Hz, 1 H), 8.23 (dd, J = 5.3, 1.2 Hz, 1 H), 8.87 (s, 1 H) ppm (Both in $CDCl_3$ and CD_3SOCD_3 the peaks are broad: GSD analysis shows the presence of a minor conformer with the same pattern of signals almost completely overlapped with the main one). ^{13}C NMR ($CDCl_3$): δ = 29.80, 39.34, 74.54, 127.45, 127.52, 127.70, 128.45, 128.98, 134.10, 135.27, 136.44, 138.34, 139.46 ppm. HRMS: calcd. for $C_{13}H_{10}N_2O_4S_2$ 322.0082; found 322.0079.

(*E*)-3-[1-Nitro-2-(3-thienyl)vinyl]-5-(3-thienyl)-4,5-dihydroisoxazole 2-Oxide (7j): Orange oil. ^{1}H NMR ($CDCl_3$): δ = 3.53 (dd, J = 16.5, 6.6 Hz, 1 H), 3.86 (dd, J = 16.3, 9.2 Hz, 1 H), 5.99 (dd, J = 9.1, 6.6 Hz, 1 H), 7.04 (dd, J = 5.1, 1.3 Hz, 1 H), 7.21 (d, J = 1.6 Hz, 1 H), 7.41 (dd, J = 5.1, 2.8 Hz, 1 H), 7.45 (dd, J = 5.1, 3.0 Hz, 1 H), 7.56 (dd, J = 5.1, 1.3 Hz, 1 H), 7.68 (dd, J = 3.4, 1.6 Hz, 1 H), 8.37 (s, 1 H) ppm; (CD_3CN): δ = 3.46 (dd, J = 16.9, 6.6 Hz, 1 H), 3.83 (dd, J = 17.0, 9.3 Hz, 1 H), 6.06 (dd, J = 9.2, 6.6 Hz, 1 H), 7.11 (dd, J = 5.0, 1.5 Hz, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 7.44 (d, J = 5.5 Hz, 1 H), 7.53 (dd, J = 4.9, 2.1 Hz, 1 H), 7.60 (d, J = 3.0 Hz, 1 H), 7.88 (d, J = 5.6 Hz, 1 H), 8.41 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.37, 77.39, 117.72, 118.53, 119.56, 120.25, 120.89, 120.95, 127.09, 131.31, 131.58, 142.61, 144.07 ppm. HRMS: calcd. for $C_{13}H_{10}N_2O_4S_2$ 322.0082; found 322.0085.

Preparative Isomerization of 7 to 8: The reactions were performed under the same conditions described above, except for the solvent DMSO. After the required time, water was added, the mixture extracted with diethyl ether, washed with water, and dried with Na_2SO_4. The solvent was then removed under vacuum to obtain a crude mixture that was purified by column chromatography on silica gel.

(*E*)-3-(2-Nitro-2-phenylvinyl)-5-phenyl-4,5-dihydroisoxazole 2-Oxide (8a):[8] Yellow solid, m.p. 180–181 °C (petroleum ether/dichloromethane). IR (Nujol): $\tilde{\nu}$ = 2722, 1305, 1156, 970, 891, 722 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.50 (dd, J = 16.6, 8.1 Hz, 1 H), 2.79 (dd, J = 16.6, 9.3 Hz, 1 H), 5.52 (dd, J = 9.3, 8.0 Hz, 1 H), 7.22–7.31 (m, 4 H), 7.35–7.50 (m, 6 H), 8.21 (s, 1 H) ppm; (CD_3SOCD_3): δ = 2.45 (dd, J = 16.3, 8.3 Hz, 1 H, part overlapped with the signal of solvent), 2.80 (dd, J = 16.3, 9.4 Hz, 1 H), 5.70 (app. t, J = 8.8 Hz, 1 H), 7.29–7.41 (m, 5 H), 7.41–7.56 (m, 5 H), 7.96 (s, 1 H) ppm; (CD_3COCD_3): δ = 2.63 (dd, J = 16.5, 8.2 Hz, 1 H), 2.97 (dd, J = 16.4, 9.4 Hz, 1 H), 5.71 (dd, J = 9.3, 8.2 Hz, 1 H), 7.34–7.42 (m, 5 H), 7.45–7.53 (m, 5 H), 8.08 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 37.74, 78.10, 113.59, 122.01, 125.95, 128.61, 129.07, 129.21, 129.51, 130.93, 131.01, 137.03, 150.26 ppm; (CD_3SOCD_3): δ = 36.92, 77.92, 114.93, 121.48, 126.61, 128.11, 128.64, 128.91, 129.24, 130.56, 131.18, 137.26, 149.79 ppm; (CD_3COCD_3): δ = 38.23, 79.05, 115.05, 122.47, 127.23, 129.05, 129.76, 130.00, 130.24, 131.32, 132.14, 138.71, 150.98 ppm. MS (ESI): m/z = 311 [M + H]$^+$, 349 [M + K]$^+$, 644 [2M + Na]$^+$, 659 [2M + K]$^+$.

(*E*)-5-(2-Methylphenyl)-3-[2-(2-methylphenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8b): Yellow solid, m.p. 158–159 °C (light petroleum/toluene). ^{1}H NMR (CD_3SOCD_3): δ = 2.10 (s, 3 H), 2.18 (s, 3 H), 2.70 (dd, J = 16.4, 9.5 Hz, 1 H), 2.90 (dd, J = 16.2, 9.8 Hz, 1 H), 5.92 (dd, J = 16.0, 8.7 Hz, 1 H), 7.15–7.44 (m, 8 H), 8.01 (s, 1 H) ppm. ^{13}C NMR (CD_3SOCD_3): δ = 14.40, 14.58, 34.64, 78.27, 115.22, 120.09, 121.33, 121.36, 121.70, 121.80, 124.77, 125.16, 126.04, 126.35, 130.50, 130.92, 133.75, 140.43, 142.38 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1261.

(*E*)-5-(4-Methylphenyl)-3-[2-(4-methylphenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8c): Yellow solid, m.p. 165–166 °C (light petroleum/toluene). IR (Nujol): $\tilde{\nu}$ = 1569, 1304, 1276, 1225, 1150, 966, 892, 817, 772, 724 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3 H), 2.39 (s, 3 H), 2.55 (dd, J = 16.6, 8.2 Hz, 1 H), 2.78 (dd, J = 16.7, 9.2 Hz, 1 H), 5.48 (app. t, J = 8.8 Hz, 1 H), 7.03–7.28 (m, 8 H), 8.18 (s, 1 H) ppm (The peaks are broad: GSD analysis shows the presence of a minor conformer with the same pattern of signals

almost completely overlap with the major one); (CD_3SOCD_3): δ = 2.27 (s, 3 H), 2.31 (s, 3 H), 2.42 (app. t, J = 12.5 Hz, 1 H, part overlapped with the signal of the solvent), 2.78 (dd, J = 16.3, 9.4 Hz, 1 H), 5.64 (app. t, J = 8.9 Hz, 1 H), 7.07–7.47 (m, 8 H), 7.92 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.34, 21.68, 37.79, 78.35, 113.96, 121.73, 126.09, 126.20, 129.31, 129.83, 130.89, 133.92, 139.65, 141.29, 150.47 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_4$ 338.1267; found 338.1262.

(*E*)-5-(4-Methoxyphenyl)-3-[2-(4-methoxyphenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8d): Yellow solid, m.p. 169–170 °C (light petroleum/toluene). IR (Nujol): $\tilde{\nu}$ = 1572, 1304, 1227, 1178, 1151, 1032, 969, 924, 891, 840, 736, 686 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.57 (dd, J = 16.7, 8.5 Hz, 1 H), 2.79 (dd, J = 16.7, 9.2 Hz, 1 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 5.48 (app. t, J = 8.8 Hz, 1 H), 6.89 and 6.94 (AA′BB′, J = 8.2 Hz, 2H each), 7.19 and 7.25 (AA′BB′, J = 8.5 Hz, 2H each), 8.17 (s, 1 H) ppm; (CD_3SOCD_3): δ = 2.56 (dd, J = 16.4, 8.7 Hz, 1 H), 2.78 (dd, J = 16.4, 9.3 Hz, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 5.65 (app. t, J = 8.9 Hz, 1 H), 6.94 and 6.99 (AA′BB′, J = 8.2 Hz, 2H each), 7.32 and 7.41 (AA′BB′, J = 8.3 Hz, 2H each), 7.91 (s, 1 H) ppm (The peaks are broad: GSD analysis shows the presence of a minor conformer with the same pattern of signals almost completely overlap with the major one). ^{13}C NMR ($CDCl_3$): δ = 37.80, 55.53, 55.55, 78.39, 114.04, 114.55, 114.91, 121.68, 127.67, 127.84, 128.62, 132.57, 150.30, 160.60, 161.42 ppm. HRMS: calcd. for $C_{19}H_{18}N_2O_6$ 370.1165; found 370.1159.

(*E*)-5-(3-Chlorophenyl)-3-[2-(3-chlorophenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8e): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.49 (dd, J = 16.5, 7.6 Hz, 1 H), 2.89 (dd, J = 16.5, 9.5 Hz, 1 H), 5.53 (dd, J = 9.4, 7.5 Hz, 1 H), 7.03–7.56 (m, 8 H), 8.19 (s, 1 H) ppm; (CD_3SOCD_3): δ = 2.53 (dd, J = 15.9, 7.6 Hz, 1 H, part overlapped with the signal of solvent), 2.90 (dd, J = 16.3, 9.5 Hz, 1 H), 5.74 (dd, J = 9.5, 8.0 Hz, 1 H), 7.28–7.70 (m, 8 H), 7.96 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.51, 75.46, 113.03, 116.76, 122.99, 123.02, 123.79, 124.29, 124.54, 124.58, 124.96, 125.19, 129.28, 130.68, 131.70, 139.58, 144.33 ppm. HRMS: calcd. for $C_{17}H_{12}Cl_2N_2O_4$ 378.0174; found 378.0180.

(*E*)-5-(4-Chlorophenyl)-3-[2-(4-chlorophenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8f): Yellow solid, m.p. 178–179 °C (petroleum ether/dichloromethane). ^{1}H NMR ($CDCl_3$): δ = 2.48 (dd, J = 16.5, 7.7 Hz, 1 H), 2.86 (dd, J = 16.5, 9.3 Hz, 1 H), 5.53 (app. t, J = 8.5 Hz, 1 H), 7.19 and 7.24 (AA′BB′, J = 8.2 Hz, 2H each), 7.36 and 7.43 (AA′BB′, J = 8.5 Hz, 2H each), 8.19 (s, 1 H) ppm; (CD_3SOCD_3): δ = 2.52 (dd, J = 16.5, 8.0 Hz, 1 H, part overlapped with the signal of solvent), 2.90 (dd, J = 16.4, 9.5 Hz, 1 H), 5.74 (dd, J = 9.4, 8.0 Hz, 1 H), 7.41 and 7.47 (AA′BB′, J = 8.6 Hz, 2H each), 7.51–7.56 (m, 4 H), 7.96 (s, 1 H) ppm (The peaks are broad; GSD analysis shows the presence of a minor conformer with the same pattern of signals almost completely overlap with the major one). ^{13}C NMR ($CDCl_3$): δ = 38.01, 77.34, 112.98, 122.31, 127.29, 127.36, 129.04, 129.52, 132.34, 135.44, 135.59, 137.38, 148.98 ppm. HRMS: calcd. for $C_{17}H_{12}Cl_2N_2O_4$ 378.0174; found 378.0175.

(*E*)-5-(1-Naphthyl)-3-[2-(1-naphthyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8g): Yellow oil. ^{1}H NMR ($CDCl_3$): first conformer: δ = 2.01 (dd, J = 16.6, 6.1 Hz, 1 H), 2.42 (dd, J = 16.6, 9.5 Hz, 1 H), 6.00 (app. t, J = 8.6 Hz, 1 H), 8.51 (s, 1 H) ppm; second conformer: δ = 2.55 (dd, J = 16.5, 7.7 Hz, 1 H), 2.93 (dd, J = 16.6, 9.7 Hz, 1 H), 6.09 (dd, J = 9.6, 6.1 Hz, 1 H), 8.48 (s, 1 H); the signals of the 14 aromatic H of the two conformers overlap: 7.18–7.38, 7.40–7.52, 7.55–7.71, 7.76–7.86 and 7.89–7.94 (5m, 14 H in all) ppm; (CD_3SOCD_3): first conformer: δ = 1.78 (dd, J = 16.4, 5.9 Hz, 1 H), 2.47 (dd, J = 14.4, 9.6 Hz, 1 H, part overlapped with the signal of solvent), 6.34 (app. t, J = 8.9 Hz, 1 H, part overlapped with the signal of the second conformer), 8.28 (s, 1 H) ppm; second conformer: δ = 2.57 (dd, J = 16.7, 8.5 Hz, 1 H, part overlapped with the signal of solvent), 3.12 (dd, J = 16.5, 9.9 Hz, 1 H), 6.39 (dd, J = 9.7, 5.8 Hz, 1 H, part overlapped with the signal of the first conformer), 8.26 (s, 1 H); the signals of the 14 aromatic H of the two conformers overlap: 7.16 (app. d, J = 7.14 Hz, 1 H), 7.33–7.37, 7.41–7.45, 7.47–7.52, 7.53–7.63, 7.69–7.71, 7.80–7.86, 7.89–7.96, 8.00–8.05 (8m, 13 H in all) ppm (The two conformers have approximately the same abundance, both in $CDCl_3$ and in CD_3SOCD_3). ^{13}C NMR ($CDCl_3$): signals are not attributable to a particular conformer: δ = 36.00, 36.50, 75.36, 75.85, 115.42, 116.64, 119.60, 120.86, 121.90, 122.09, 122.79, 123.18, 123.56, 123.58, 123.84, 124.26, 124.38, 124.61, 124.76, 124.86, 125.16, 125.35, 126.14, 126.29, 126.43, 126.82, 126.96, 127.06, 127.77, 128.13, 128.64, 129.00, 129.25, 129.40, 129.53, 129.78, 129.91, 129.95, 131.59, 132.16, 133.92, 148.90, 149.07 ppm. HRMS: calcd. for $C_{25}H_{18}N_2O_4$ 410.1267; found 410.1272.

(*E*)-5-(2-Naphthyl)-3-[2-(2-naphthyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide (8h): Yellow oil. ^{1}H NMR ($CDCl_3$): δ = 2.50 (dd, J = 15.1, 8.7 Hz, 1 H), 2.84 (dd, J = 15.3, 8.1 Hz, 1 H), 5.61 (app. t, J = 8.7 Hz, 1 H), 7.03–7.39, 7.40–7.64, 7.66–7.82, 7.83–7.99 and 8.00–8.15 (5m, 14H in all), 8.61 (s, 1 H) ppm; (CD_3SOCD_3): δ = 2.56 (dd, J = 16.1, 7.8 Hz, 1 H), 2.90 (dd, J = 16.2, 9.6 Hz, 1 H), 5.83 (dd, J = 9.3, 8.1 Hz, 1 H), 7.36–7.75, 7.77–7.92, 7.93–8.07 and 8.07–8.26 (4m, 14H in all), 8.60 (s, 1 H) ppm. ^{13}C NMR (CD_3SOCD_3): δ = 33.83, 74.83, 111.54, 115.08, 116.55, 116.71, 120.18, 121.59, 122.37, 122.42, 122.81, 122.87, 122.96, 123.59, 123.82, 123.92, 124.03, 124.82, 126.48, 127.64, 138.90, 143.74 (3 C are accidentally isochronous) ppm. HRMS: calcd. for $C_{25}H_{18}N_2O_4$ 410.1267; found 410.1267.

Deuterated Compounds: Deuterated substrates **12**,[4] **2c**-d_2[17] and **6c**-d_2,[6] are new compounds, prepared according to already reported procedures.[18]

(1*E*,3*E*)-1,4-Bis(diethylammino)-2,3-dinitro-1,3-butadiene-d_2 (12): Yellow solid, m.p. 147–148 °C (ethanol). ^{1}H NMR ($CDCl_3$): δ = 1.09 (t, J = 7.2 Hz, 6 H), 1.33 (t, J = 7.2 Hz, 6 H), 3.22 (dq, J = 14.3, 7.2 Hz, 2 H), 3.41 (dq, J = 14.3, 7.3 Hz, 2 H), 3.44 (dq, J = 14.4, 7.4 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.76, 14.92, 42.48, 52.17, 115.27, 149.49 (t, J = 24.7 Hz) ppm.

(1*E*,3*E*)-1,4-Bis(4-methylphenyl)-2,3-dinitro-1,3-butadiene-d_2 (2c-d_2): Yellow solid, m.p. 143–144 °C (toluene/light petroleum). ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 6 H), 7.15 and 7.35 (AA′BB′, J = 8.2 Hz, 4H each) ppm.

1-Methyl-4-{(*E*)-2-[2-(4-methylphenyl)-1-nitrocyclopropyl]-2-nitrovinyl}benzene-d_2 (6c-d_2): Yellow solid, m.p. 150–151 °C (ethanol). ^{1}H NMR (CD_3SOCD_3): major conformer: δ = 1.77 (d, J = 7.2 Hz, 1 H), 2.23 (s, 3 H), 2.41 (s, 3 H), 2.73 (d, J = 7.0 Hz, 1 H), 6.88 and 7.04 (AA′BB′, J = 7.8 Hz, 2 H each), 7.40 and 7.54 (AA′BB′, J = 8.0 Hz, 2 H each) ppm; minor conformer: the only distinguishable signals are: δ = 2.09 (s, 3 H), 2.30 (s, 3 H), 6.64 and 6.71 (AA′BB′, J = 8.3 Hz, 2 H each) ppm.

The study of the deuterium isotope effect in the **6**→**7**→**8** conversion rate was performed by means of both parallel and competitive tests. The parallel tests were performed by dissolving in two NMR sample tubes 10.0 mg (0.03 mmol) of substrate (**6c** and **6c**-d_2, respectively) in [D_6]DMSO (1.0 mL) in the presence of NaI (5.0 mg, 0.03 mmol). The tubes were kept at 60 °C as long as necessary and checked by ^{1}H NMR spectroscopy at scheduled times (see Table 2). The competitive test was performed under the same conditions described above, except for dissolving both substrates in the same tube.

(*E*)-5-(4-Methylphenyl)-3-[2-(4-methylphenyl)-1-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide-d_2 (7c-d_2): Yellow oil. ^{1}H NMR (CD_3SOCD_3): δ = 2.36 (s, 3 H), 2.37 (s, 3 H), 3.31 (d, J = 17.1 Hz, 1 H), 3.82 (d, J = 17.1 Hz, 1 H), 7.29 (app. t, J = 8.5 Hz, 4 H), 7.41 and 7.44 (AA′BB′, J = 8.2 Hz, 2H each) ppm.

(*E*)-5-(4-Methylphenyl)-3-[2-(4-methylphenyl)-2-nitrovinyl]-4,5-dihydroisoxazole 2-Oxide-d_2 (8c-d_2): Yellow solid, m.p. 162–163 °C (light petroleum/toluene); ^{1}H NMR (CD_3SOCD_3): δ = 2.28 (s, 3 H), 2.32 (s, 3 H), 2.49 (d, J = 16.4 Hz, 1 H, part overlapped with the signal of solvent), 2.79 (d, J = 16.4 Hz, 1 H), 7.15–7.28 (m, 4 H), 7.29–7.40 (m, 4 H) ppm.

Preparation of Pyrazolylisoxazole 11c: In a flask equipped with a rubber septum and a magnetic stirring-bar, substrate **8c** (1 mmol) was dissolved in dry THF (40 mL), and the temperature kept at 0 °C. Diazomethane in ether was added in three portions (0.5 mmol, 0.5 mol equiv. each). After the third portion, the reaction mixture was left to gradually reach room temperature overnight. The solution was then concentrated under vacuum at room temperature and the crude mixture taken up with diethyl ether and precipitated by adding petroleum ether.

5-(4-Methylphenyl)-3-[3(5)-(4-methylphenyl)-1*H*-pyrazol-4-yl]-4,5-dihydroisoxazole 2-Oxide (11c): White solid, m.p. 75–76 °C (taken up with diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3 H), 2.39 (s, 3 H), 2.97 (dd, J = 16.7, 8.2 Hz, 1 H), 3.25 (dd, J = 16.8, 9.1 Hz, 1 H), 5.52 (app. t, J = 8.6 Hz, 1 H), 7.13–7.30 (m, 8 H), 8.65 (s, 1 H) ppm (NH proton was not detected within the spectral width –2–12 ppm); (CD_3SOCD_3): δ = 2.29 (s, 3 H), 2.32 (s, 3 H), 2.96 (dd, J = 16.5, 7.9 Hz, 1 H), 3.34 (dd, J = 16.4, 9.1 Hz, 1 H), 5.61 (app. t, J = 8.4 Hz, 1 H), 7.10–7.37 (m, 8 H), 8.26 and 8.51 (2 br. s, 1 H in all) ppm (NH proton was not detected within the spectral width –2–12 ppm). ^{13}C NMR ($CDCl_3$): δ = 21.32, 21.51, 40.14, 107.58, 110.34, 126.12, 128.12, 129.36, 129.47, 129.63, 133.70, 135.26, 138.93, 139.48, 147.34 (one C overlapped with $CHCl_3$) ppm; (CD_3SOCD_3): δ = 20.74, 20.84, 76.08, 106.28, 109.72, 126.22, 128.60, 128.93, 129.18, 129.29, 135.62, 138.09, 138.80, 141.27, 149.62 ppm (one C overlapped with DMSO). HRMS: calcd. for $C_{20}H_{19}N_3O_2$ 333.1477; found 333.1477.

Supporting Information (see footnote on the first page of this article): Spectroscopic data and copies of the ^{1}H and ^{13}C NMR spectra for all compounds. Diagnostic NOE interactions in compound **11c**.

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[1] For the most recent work, see: a) E. Y. Schmidt, I. V. Tatarinova, E. V. Ivanova, N. V. Zorina, I. A. Ushakov, B. A. Trofimov, *Org. Lett.* **2013**, *15*, 104–107; b) L. Wang, X. Yu, X. Feng, M. Bao, *Org. Lett.* **2012**, *14*, 2418–2421; c) Z. She, D. Niu, L. Chen, M. A. Guanawan, X. Shanja, W. H. Hersh, Y. Chen, *J. Org. Chem.* **2012**, *77*, 3627–3633; d) E. Trogu, C. Vinattieri, F. De Sarlo, F. Machetti, *Chem. Eur. J.* **2012**, *18*, 2081–2093; e) M. Ueda, Y. Ikeda, A. Sato, Y. Ito, M. Kakiuchi, H. Shono, T. Miyoshi, T. Naito, O. Miyata, *Tetrahedron* **2011**, *67*, 4612–4615; f) G. D. Vilela, R. R. da Rosa, P. H. Schneider, I. H. Bechtold, J. Eccher, A. A. Merlo, *Tetrahedron Lett.* **2011**, *52*, 6569–6572; g) C. Zhong, L. N. S. Gautam, J. L. Petersen, N. G. Akhmedov, X. Shi, *Chem. Eur. J.* **2010**, *16*, 8605–8609; h) S. Tang, J. He, Y. Sun, L. He, X. She, *J. Org. Chem.* **2010**, *75*, 1961–1966; i) O. Debleds, E. Gayon, E. Ostaszuk, E. Vrancken, J.-M. Campagne, *Chem. Eur. J.* **2010**, *16*, 12207–12213; j) C.-Y. Zhu, X.-L. Sun, X.-M. Deng, J.-C. Zheng, Y. Tang, *Tetrahedron* **2008**, *64*, 5583–5589.

[2] For examples, see: a) T. Tsujihara, T. Shinohara, K. Takenaka, S. Takizawa, K. Onitsuka, M. Hatanaka, H. Sasai, *J. Org. Chem.* **2009**, *74*, 9274–9279; b) A. A. Fuller, B. Chen, A. R. Minter, A. K. Mapp, *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383; c) D. Kim, J. Lee, P. J. Shim, J. I. Lim, H. Jo, S. Kim, *J. Org. Chem.* **2002**, *67*, 764–771; d) J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424.

[3] For examples, see: a) J. B. Sperry, D. L. Wright, *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723–740; b) M. P. Giovannoni, C. Vergelli, C. Ghelardini, N. Galeotti, A. Bartolini, V. Dal Piaz, *J. Med. Chem.* **2003**, *46*, 1055–1059; c) W.-T. Li, D.-R. Hwang, C.-P. Chen, C.-W. Shen, C.-L. Huang, T.-W. Chen, C.-H. Lin, Y.-L. Chang, Y.-Y. Chang, Y.-K. Lo, H.-Y. Tseng, C.-C. Lin, J.-S. Song, H.-C. Chen, S.-J. Chen, S.-H. Wu, C.-T. Chen, *J. Med. Chem.* **2003**, *46*, 1706–1715; d) D. Kovács, Z. Kádár, G. Mótyán, G. Schneider, J. Wölfling, I. Zupkó, E. Frank, *Steroids* **2012**, *77*, 1075–1085.

[4] a) C. Dell'Erba, D. Spinelli, G. Leandri, *J. Chem. Soc. Chem. Commun.* **1969**, 549–549; b) C. Dell'Erba, A. Mele, M. Novi, G. Petrillo, P. Stagnaro, *Tetrahedron Lett.* **1990**, *31*, 4933–4936.

[5] For reviews, see: a) L. Bianchi, M. Maccagno, G. Petrillo, F. Sancassan, D. Spinelli, C. Tavani, *2,3-Dinitro-1,3-butadienes: versatile building-blocks from the ring opening of 3,4-dinitrothiophene*, in: *Targets in Heterocyclic Systems - Chemistry and Properties*, Società Chimica Italiana, Rome; **2006**, vol. 10, p. 1–23; b) L. Bianchi, C. Dell'Erba, M. Maccagno, S. Morganti, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, C. Tavani, *Arkivoc* **2006** (*vii*), 169–185. For recent examples, see: c) L. Bianchi, G. Giorgi, M. Maccagno, G. Petrillo, C. Scapolla, C. Tavani, *Tetrahedron Lett.* **2012**, *53*, 752–757; d) C. Dell'Erba, A. Gabellini, A. Mugnoli, M. Novi, G. Petrillo, C. Tavani, *Tetrahedron* **2001**, *57*, 9025–9031; e) C. Dell'Erba, A. Mugnoli, M. Novi, M. Pani, G. Petrillo, C. Tavani, *Eur. J. Org. Chem.* **2000**, 903–912; f) C. Dell'Erba, A. Mugnoli, M. Novi, M. Pertici, G. Petrillo, C. Tavani, *Eur. J. Org. Chem.* **1999**, 431–435; g) A. Fontana, M. Viale, S. Guernelli, C. Gasbarri, E. Rizzato, M. Maccagno, G. Petrillo, C. Aiello, S. Ferrini, D. Spinelli, *Org. Biomol. Chem.* **2010**, *8*, 5674–5681; h) M. Viale, G. Petrillo, M. Maccagno, P. Castagnola, C. Aiello, C. Cordazzo, M. A. Mariggiò, S. A. Jadhav, L. Bianchi, G. Leto, E. Rizzato, A. Poggi, D. Spinelli, *Eur. J. Pharmacol.* **2008**, *588*, 47–51; i) G. Petrillo, M. A. Mariggiò, C. Fenoglio, C. Aiello, C. Cordazzo, S. Morganti, E. Rizzato, D. Spinelli, M. Maccagno, L. Bianchi, C. Prevosto, C. Tavani, M. Viale, *Bioorg. Med. Chem.* **2008**, *16*, 240–247; j) M. Viale, G. Petrillo, C. Aiello, C. Fenoglio, C. Cordazzo, M. A. Mariggiò, A. Cassano, C. Prevosto, E. Ognio, M. Maccagno, L. Bianchi, R. Vaccarone, E. Rizzato, D. Spinelli, *Pharmacol. Res.* **2007**, *56*, 318–328; k) G. Petrillo, C. Fenoglio, E. Ognio, C. Aiello, D. Spinelli, M. A. Mariggiò, M. Maccagno, S. Morganti, C. Cordazzo, M. Viale, *Investigational New Drugs* **2007**, *25*, 535–544; l) M. Novi, M. Ottone, C. Dell'Erba, F. Barbieri, B. Chiavarina, M. Maccagno, M. Viale, *Oncol. Rep.* **2004**, *12*, 91–96.

[6] T. Armaroli, C. Dell'Erba, A. Gabellini, F. Gasparrini, A. Mugnoli, M. Novi, G. Petrillo, C. Tavani, *Eur. J. Org. Chem.* **2002**, 1284–1291.

[7] L. Bianchi, C. Dell'Erba, F. Gasparrini, M. Novi, G. Petrillo, F. Sancassan, C. Tavani, *Arkivoc* **2002** (*xi*), 142–158.

[8] L. Bianchi, G. Giorgi, M. Maccagno, G. Petrillo, E. Rizzato, D. Spinelli, M. Stenta, C. Tavani, *Lett. Org. Chem.* **2007**, *4*, 268–272.

[9] a) L. Leseticky, V. Fidler, M. Prochazka, *Collect. Czech. Chem. Commun.* **1973**, *38*, 459–464; b) L. Leseticky, M. Prochazka, *Collect. Czech. Chem. Commun.* **1971**, *36*, 307–311; c) V. Kral, L. Leseticky, *Collect. Czech. Chem. Commun.* **1975**, *40*, 2816–2825; d) G. Hesse, V. Jager, *Justus Liebigs Ann. Chem.* **1970**, *740*, 85–90.

[10] a) F. Guerrera, L. Salerno, L. Lamartina, D. Spinelli, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1243–1246; b) D. Spinelli, P. Zanirato, E. di Miceli, L. Lamartina, F. Guerrera, *J. Org. Chem.* **1997**, *62*, 4921–4923; c) B. Cosimelli, L. Lamartina, D. Spinelli, *Tetrahedron* **2001**, *57*, 8903–8911; d) B. Cosimelli, L. Lamartina, C. Z. Lanza, D. Spinelli, R. Spisani, F. Vegna, *Tetrahedron* **2003**, *59*, 7189–7201.

[11] D. L. H. Williams, in: Supplement F2, *The Chemistry of Amino, Nitroso, Nitro and Related Groups* (Ed.: S. Patai), Wiley, New York, **1996**.

[12] See note 8 in ref.[8].

[13] See note 4 in ref.[8].

[14] It should further be emphasized that the mechanistic hypothesis of Scheme 5 is fully consistent with the lack of any significant configurational isomerization around the vinylic double bond.

[15] L. Bianchi, G. Giorgi, M. Maccagno, G. Petrillo, V. Rocca, F. Sancassan, C. Scapolla, E. Severi, C. Tavani, *J. Org. Chem.* **2007**, *72*, 9067–9073.

[16] K. Karthikeyan, T. Veenus Seelan, K. G. Lalitha, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3370–3373.

[17] C. Dell'Erba, A. Mele, M. Novi, G. Petrillo, P. Stagnaro, *Tetrahedron* **1992**, *48*, 4407–4418.

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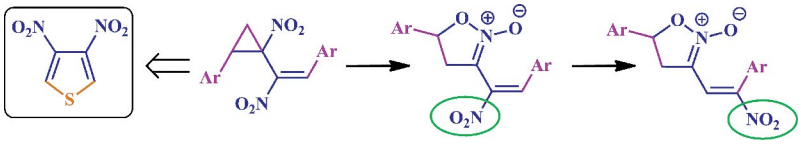

In spite of its infrequency, the migration of a nitro group from the β- to the α-position of a β-nitrostyryl moiety can be rationalized by stereo-electronic factors, as shown here by means of computational and experimental studies. From the synthetic point a view, two series of isomeric isoxazoline *N*-oxides can be obtained under controlled conditions.

Keywords: Synthetic methods / Heterocycles / Nitro group migration / Alkenes

