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Intriguing enigma of nitrobenzofuroxan's 'Sphinx': Boulton–Katritzky rearrangement or unusual evidence of the *N*-1/*N*-3-oxide rearrangement?†

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The S_EAr/S_NAr reaction between 7-chloro-4,6-dinitrobenzofuroxan (CIDNBF) and 2-morpholinyl-, 2-piperidinyl-, or 2-pyrrolidinylthiazole afforded unexpectedly two isomeric products, bearing the benzofuroxanyl moiety bound to the C-5 carbon atom of the thiazole ring. The relative ratio for the two isomers was dependent on temperature and solvent, suggesting the occurrence of an equilibrium between the two novel species. In order to investigate their structure and to design a plausible mechanistic pathway, a series of synthetic and spectroscopic experiments was planned. The isomer's structure was unambiguously assigned when the reduction of furoxanyl to the furazanyl ring of the products gave exclusively a single species whose NMR data were coincident with those obtained by reacting the starting 2-aminothiazole derivatives with the 7-chloro-4,6-dinitrobenzofurazan (CIDNBZ). Possible mechanistic pathways might involve *N*-1/*N*-3 oxide tautomerism or Boulton–Katritzky rearrangement and the current study is the first attempt to compare these two reactions. The data collected agree with the first one and DFT calculations permitted also a significant correlation with ^{13}C NMR experimental data and the assignment of the structure of each isomer. Finally, only one Meisenheimer intermediate for each electrophile/nucleophile combination was isolated by coupling the 2-aminothiazole derivatives with 4,6-dinitrobenzofuroxan (DNBF).

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Introduction

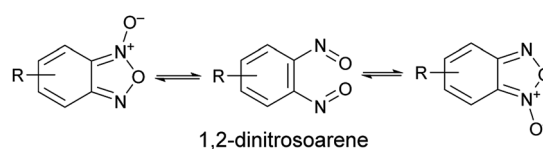
Benzofuroxan and its derivatives belong to a class of heterocycles of wide and growing interest both in mechanistic and applied fields.^{1–4} They can be exploited for many applications, ranging from energetic materials^{5,6} to biologically active compounds, depending on the type of substituents. As bioactive compounds, they can behave as anti-parasitic, anti-microbial, anti-fungal, immunosuppressive and anticancer agents, and have anti-aggregating and vasorelaxant activity owing to their ability to release NO under physiological conditions.^{7,8}

Since its discovery,⁹ the benzofuroxanyl ring has been a considerable challenge to structure attribution.^{10,11} First,

benzofuroxans were proposed to exhibit a dioxime peroxide or *o*-dinitroso skeleton configuration, until 1912 when the current benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide formulation was suggested,¹² which was unequivocally confirmed only 50 years later through NMR and X-ray crystal structure determinations.^{13,14}

Benzofuroxan derivatives are still an interesting source of peculiar structural features. The first one is the possibility to undergo isomerisation between the *N*-1-oxide and *N*-3-oxide form, a transformation that is believed to occur *via* 1,2-dinitrosoarene as transient intermediate (Scheme 1).

Since the *N*-1-oxide/*N*-3-oxide tautomerism is a fast equilibrating system at room temperature, the 1,2-dinitrosoarene constitutes a fugitive species. The existence of this elusive species has been supported by both kinetic studies^{15,16} and theoretical calculations.^{17,18} Spectroscopic indications (IR and



Scheme 1 *N*-1-Oxide/*N*-3-oxide tautomerism in benzofuroxan (and its derivatives).

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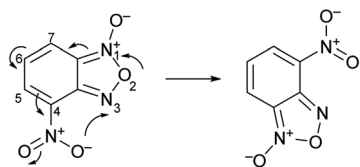
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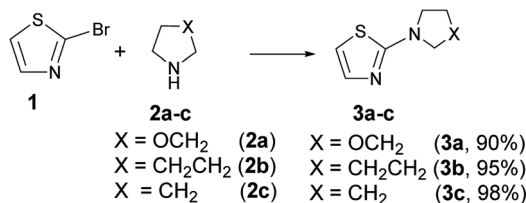


Scheme 2 BKR rearrangement of 4-nitrobenzofuroxan.

UV/Vis spectra) of its presence were obtained by photolysis of benzofuroxan in argon matrices at 14 K.¹⁹ Further, the reaction products recovered when benzofuroxan was reacted with acetonitrile, methyl sulfide,²⁰ *p*-anisyl azide and diphenyldiazomethane²¹ were explained invoking the intermediacy of 1,2-dinitrosoarene species. A similar dinitroso derivative was also substantiated in the work of Terrier *et al.*, that reported the recovery and characterization of a diadduct from a Diels–Alder cycloaddition as result of the reaction with a *o*-dinitroso species.²² Recently, a ruthenium complex of the 1,2-dinitrosoarene intermediate derived from the opening of the pentatomic ring of benzofuroxan has been reported.²³

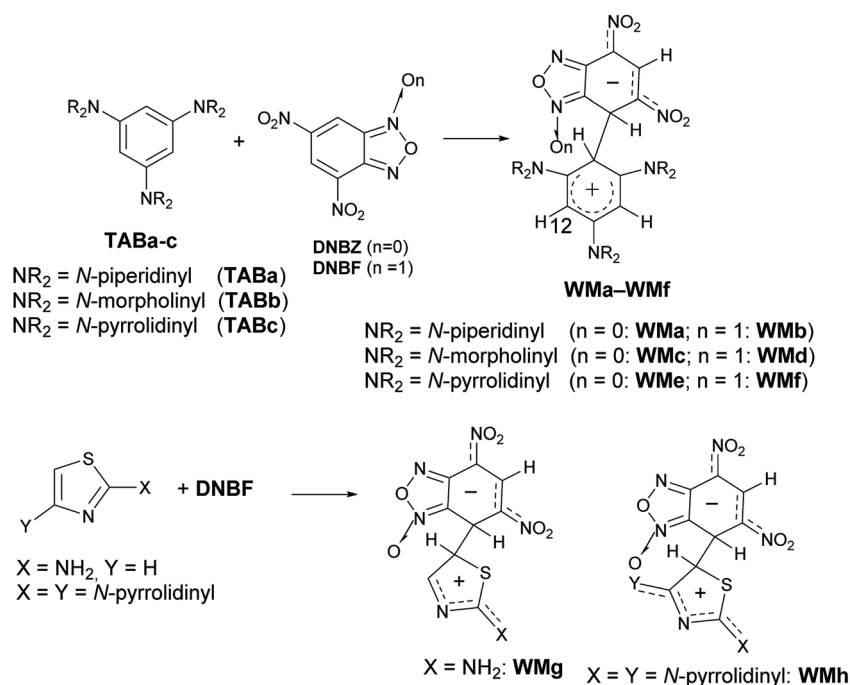
The second characteristic feature of substituted benzofuroxans is their susceptibility to undergo Boulton–Katritzky rearrangement (BKR)^{24,25} (Scheme 2). The BKR of 4-nitrobenzofuroxan can be considered as a prototype reaction for a class of molecular rearrangements and can compete with the *N*-1-oxide/*N*-3-oxide tautomerization; the direction of this rearrangement depends on the substituent in 5 or 7 position.^{26,27}

A third peculiar aspect of benzofuroxans resides into their 10 π -electron structure which is able to confer electrophilic properties.

Scheme 4 Synthesis of 2-aminothiazole derivatives **3a–c** from 2-bromothiazole (**1**) and amines **2a–c**.

In particular, when two nitro substituents are bound to the carbocyclic ring of the benzofuroxan (or benzofurazan) or their derivatives, these compounds are so much electrophilic to be defined (labeled) as superelectrophiles.^{28,29} Actually, it is well-known^{4,30–35} that the reaction of 4,6-dinitrobenzofuroxan (**DNBF**) produces stable Meisenheimer intermediates, as well as 4,6-dinitrobenzofurazan (**DNBZ**), with a series of charged or neutral nucleophiles. Recently, the coupling of 1,3,5-triaminobenzene derivatives (**TABa–c**) or 2-aminothiazoles with a series of electrophiles,^{35–38} including **DNBF** or **DNBZ**, gave evidence of the zwitterionic intermediate – contemporaneously Wheland and Meisenheimer – formed in these S_EAr/S_NAr aromatic substitution reactions (*e.g.* **WMa–h** in Scheme 3). In Scheme 3 we represented the *N*–O position of **WM** intermediates on the basis of X-ray diffraction analysis on **WMh**.

In the thiazole series in particular, the coupling between 2,4-dipyrrolidinylthiazole and **DNBF** produced the intermediate **WMh** (Scheme 3, bottom), which was stable enough to provide the first X-ray crystal structure along the class of zwitterionic intermediates, likely due to the high stabilization of the positive charge conferred to the Wheland moiety by both the

Scheme 3 Examples of **WM** intermediates detected and characterized using **DNBF** or **DNBZ** as electrophiles.

pyrrolidinyl groups.³⁸ On the other hand, 2,4-dipyrrolidinyl thiazole is such an activated nucleophile that gives a very complicated mixture of products when reacted with electrophiles such as aryldiazonium salts.³⁹

On the contrary, when 2-pyrrolidinylthiazole reacted with aryldiazonium salts, the corresponding azo derivatives bound in position 5 (ref. 39) of the thiazole ring were formed in good yields.

A literature survey revealed that both the 2-pyrrolidinylthiazole and the analogous 2-piperidinyl- and 2-morpholinyl-derivatives (**3a–c** in Scheme 4) have been poorly studied so far.

Since it is well known that chloronitro- or chlorodinitro-benzofuroxans and -benzofurazans easily give C–C coupling with many nucleophiles^{30,31,36,40–42} producing a plethora of compounds of interest in applied fields (e.g. pharmaceutical, energetic, optoelectronic), we designed to carry out the reaction of the 2-aminothiazole derivatives with 7-chloro-4,6-dinitrobenzofuroxan (**CIDNBF**) or 7-chloro-4,6-dinitrobenzofurazan (**CIDNBZ**) to obtain novel hybrids bearing two moieties, the thiazolyl- and the benzofuroxanyl (or benzofurazanyl) one.⁴³

Inspired by these considerations, we focused our investigations on the above reactions to obtain novel highly conjugated systems and to exploit new insights on their mechanistic behavior.

Results and discussion

2-Morpholinylthiazole (**3a**), 2-piperidinylthiazole (**3b**) and 2-pyrrolidinylthiazole (**3c**) have been synthesized at room temperature and under solvent-free conditions by reacting 2-bromothiazole (**1**) with morpholine (**2a**), piperidine (**2b**), or pyrrolidine (**2c**), respectively (Scheme 4).

Compounds **3a–c** have been synthesized within 24, 4 and 2 h reaction time affording 90, 95 and 98% yield respectively; the different reaction time required to reach the above indicated yields is likely due to the different nucleophilicity of the starting amines whose values, according to the nucleophilicity scale developed by Mayr,^{44–47} are, in acetonitrile at 20 °C, $N_{\text{Mayr}} = 15.65$, 17.35, and 18.64 for morpholine, piperidine, and pyrrolidine, respectively.⁴⁸

It is known that 2-aminothiazoles can behave as nucleophiles at three distinct positions, namely, exocyclic nitrogen

atom, endocyclic nitrogen atom, and C-5. However, the selected substrates **3a–c** bear a secondary amino group in position 2 that prevents the tautomeric equilibrium occurring when a $-\text{NH}_2$ or $-\text{NHR}$ group is present in that position. Thus, only the products **5a–c** derived from the nucleophilic attack at C-5 were expected to be formed (Scheme 5), as previously found for aryldiazonium salts.³⁹

As soon as the reaction between **3a–c** and 7-chloro-4,6-dinitrobenzofuroxan (**4**, or **CIDNBF**), run at room temperature in acetonitrile with 2 : 1 molar ratio, started, the color of the mixture turned from pale yellow to deep blue.

The reaction was monitored by TLC, showing the spot relative to novel blue species at R_f higher than those related to the starting reactants. After 24 h (for the combination **3a/4**), 12 h (for **3b/4**), or 4 h (for **3c/4**), the crude product obtained was subjected to column chromatography on silica gel (FC) leading to isolation of the novel species.

The ESI-MS spectrum of the blue solid isolated by FC was in agreement with that of a product derived from the aromatic substitution between **3a–c** and **4**, but the ^1H - and ^{13}C -NMR spectrum showed a number of signals higher with respect to those expected for species **5a–c**. In particular, the ^1H NMR spectrum in CD_3CN of the solid derived from the reaction between **3c** and **4** exhibited four singlets in the aromatic region (Fig. S30, in ESI†). The signal multiplicity and the relative integration suggested the presence of two isomers in 62/38 relative molar ratio bearing the benzofuroxanyl moiety bound to the C-5 of the thiazole moiety, labeled as **5c** and **5'c** in Scheme 5. After many attempts, the separation of two blue spots was achieved on preparative TLC plate by eluting with a mixture of diethyl ether: light petroleum (7 : 3 v/v). Then, each spot was scraped and worked-up (see Experimental), and the organic residues were dissolved in CD_3CN and analyzed by NMR spectroscopy. Surprisingly, each spectrum showed presence of two compounds, as previously observed after FC, thus suggesting the occurrence of a re-equilibration phenomenon.

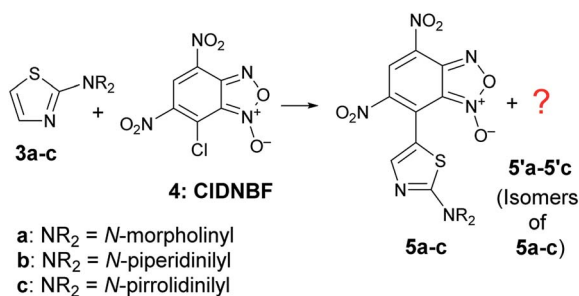
This prompted us to plan further experiments to shed some light on this behavior and, for the sake of clarity, below we report in sub-headings the results obtained.

Is the isomeric ratio affected by solvent nature or temperature?

First, we investigated whether the relative ratio between the two isomers **5** and **5'** could be influenced by the reaction conditions such as the solvent or the temperature. For this purpose, we planned to investigate the behavior of the isomeric mixture **5c** + **5'c** derived from the combination of **3c** and **4**, since in case **c** the reaction occurs in a considerably shorter time.

A first series of experiments has been run by recording the ^1H NMR spectrum of the isomeric mixture, after its isolation by FC, in different solvents at 25 °C. We attributed the two set of signals to the isomers labelled as **A** and **A'** without direct relation to the structure **5c** or **5'c** of Scheme 5. The results are reported in Table 1.

From the relative integration of the signals of the two species, and by supposing the same trend of related chemical



Scheme 5 C–C coupling reaction between **3a–c** and **4** with formation of the expected products **5a–c** together with unexpected isomers.



Table 1 Relative ratio of the isomers^a derived from the reaction between **3c** and **4** in different solvents

Entry	Solvent polarity ^b	Solvent	Isomer ^c A (%)	Isomer A' (%)
1	Benzene 0.111	Benzene-d ₆	53	47
2	THF 0.207	Tetrahydrofuran-d ₈	50	50
3	CHCl ₃ 0.259	Chloroform-d ₁	55	45
4	Acetone 0.355	Acetone-d ₆	57	43
5	CH ₃ CN 0.460	Acetonitrile-d ₃	60	40
6	DMSO 0.444	DMSO-d ₆	67	33
7	CH ₃ OH 0.762	Methanol-d ₄	59	41

^a After isolation by FC. ^b Data from ref. 49. ^c Calculated from the ¹H NMR spectrum recorded at 25 °C.

shift along the solvents, it can be evinced that their relative ratio is always in favor of the same isomer (except in THF-d₈, entry 2 of Table 1). The most relevant difference was observed in DMSO-d₆ (entry 6 of Table 1). On going from THF to acetonitrile (entries 2–5 of Table 1) it emerge that the relative ratio is slightly dependent from the solvent even if, from the data obtained, a clear correlation with the solvent polarity cannot be advanced.

In a second series of experiments we analyzed the ¹H NMR spectrum of the mixture **A** + **A'**, isolated by FC, at variable temperature and in different solvents; the results are reported in Table 2.

In DMSO-d₆ the spectrum of the mixture was recorded from 25 °C to 80 °C (Table 2, entries 1–5): on raising the temperature, a gradual increase (until 15%) of the minor isomer was observed. On the contrary, no significant variation of the isomeric ratio was observed both in acetonitrile (from 25 °C to 40 °C, Table 2, entries 6–10) and in acetone (from +25 °C to –90 °C, Table 2, entries 11–15).

In a third series of experiments, the reaction was carried out by mixing the reagents directly in the NMR spectroscopy tube and monitoring it with time. When reagents **3c** and **4** (in 2 : 1 molar ratio) were mixed at 25 °C in CDCl₃, CD₃CN, or DMSO-d₆,

the ¹H NMR spectra recorded in the first two solvents showed that the **A/A'** ratio was the same to what reported in entries 3 and 5 of Table 1, respectively. Surprisingly, no product was formed when the reagents were mixed in DMSO-d₆.

In Table 3 are reported the results obtained by ¹H NMR spectroscopy, from the reaction between **3c** and **4** carried out at

Table 3 Variable temperature^a experiments by monitoring^a the reaction between **3c** and **4** in different solvents^b

Solvent	Temp (°C)	Conversion	A/A' ^c
CDCl ₃	–48	32	43/57
	–37	40	36/64
	–26	50	34/66
	–15	58	31/69
	–4	71	41/59
	+30	90	55/45
	+40	93	56/44
CD ₃ CN	–43	36	75/25
	–32	42	80/20
	–21	45	85/15
	–9	66	78/22
	+6	74	73/27
	+13	84	72/28
	+24	91	62/38
	+24 after 1 day	99	62/38
CD ₃ COCD ₃	–93 ^d	7	95/5
	–82 ^d	7	93/7
	–71 ^d	8	92/8
	–59 ^d	8	95/5
	–48 ^d	11	96/4
	–37 ^d	22	96/4
	–26 ^d	35	96/4
	–15	51	93/7
	–15 after 10 min.	61	87/13
	–4	71	72/28
	–4 after 10 min.	78	63/37
	+8 ^d	86	59/41
	+25 ^d	94	58/42

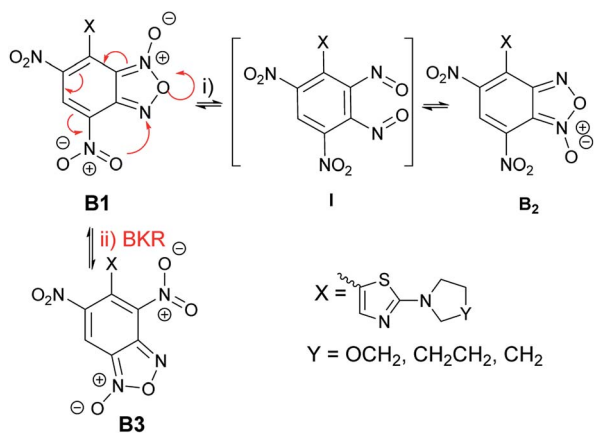
^a Reaction carried out directly in the NMR spectroscopy tube by mixing, at the lowest temperature indicated in the Table 3, **3c** and **4** in 2 : 1 molar ratio. ^b Monitoring of the reaction conversion and isomeric ratio of the products through ¹H NMR spectroscopy at variable temperature. ^c The % molar ratio was calculated from the NMR spectrum of the crude reaction mixture. ^d The conversion and relative ratio values remained unchanged within 10 min after varying the temperature.

Table 2 Isomeric ratio of the products^a derived from **3c** and **4** in different solvents at different temperatures

Entry	Solvent	Temperature (°C)	Isomer A ^b (%)	Isomer A' ^b (%)
1	DMSO-d ₆	25	67	33
2		35	65	35
3		50	64	36
4		70	60	40
5		80	57	43
6	CD ₃ CN	25	62	38
7		35	61	39
8		45	59	41
9		55	58	42
10		65	58	42
11	CD ₃ COCD ₃	25	57	43
12		0	60	40
13		–20	60	40
14		–50	60	40
15		–90	60	40

^a After isolation by FC. ^b Calculated from the ¹H NMR spectrum.





Scheme 6 Possible rearrangements of the product derived from the reaction between CIDNBF and 3a–c. *via* (i): *N*-1/*N*-3-oxide equilibrium forming two structural isomers **B1** and **B2**; *via* (ii): BKR from **B1** to **B3**.

low temperature directly in the NMR tube inserted in a cryo-probe. The reaction was monitored with time and at different temperatures.

The reaction was carried out in acetone- d_6 at -93°C , in CDCl_3 at -48°C , and in CD_3CN at -43°C . In all cases, the conversion was low and the ^1H NMR spectrum showed prevalence of signals for one isomer. On raising the temperature, the conversion gradually increased. At $+25^\circ\text{C}$ the conversion was complete and the relative isomeric ratio was in all cases about 6/4, in agreement with results obtained from reaction carried out at room temperature (Table 1). It has to be noted that, in CDCl_3 , once the reaction was complete, the major isomer was the opposite with respect to that formed at low temperature.

In acetone- d_6 the conversion and the isomeric ratio ($\sim 95/5$) remained almost unchanged from -93°C to -60°C , then they gradually changed. At 25°C , the reaction goes to completion and the isomeric ratio gradually was 58/42.

The behavior in acetone may suggest that isomer **A** could be kinetic product (**A** is almost the exclusive species at lower

temperatures), but limited conversion at lower temperatures and trend of the isomer ratio and conversion on raising the temperature (see data of Table 3) do not permit to infer if the formation of **A** and **A'** is ruled by kinetics or thermodynamic control (or by both).

Moreover, it is worth note that, in the ^1H NMR spectra recorded when the conversion was not complete, the signals belonging to the unreacted starting aminothiazole result coincident to the salified one. This observation indicates that the two species (*i.e.* protonated and not-protonated 2-aminothiazole) are in equilibrium, as we already reported in analogous protonation reactions.^{39,50}

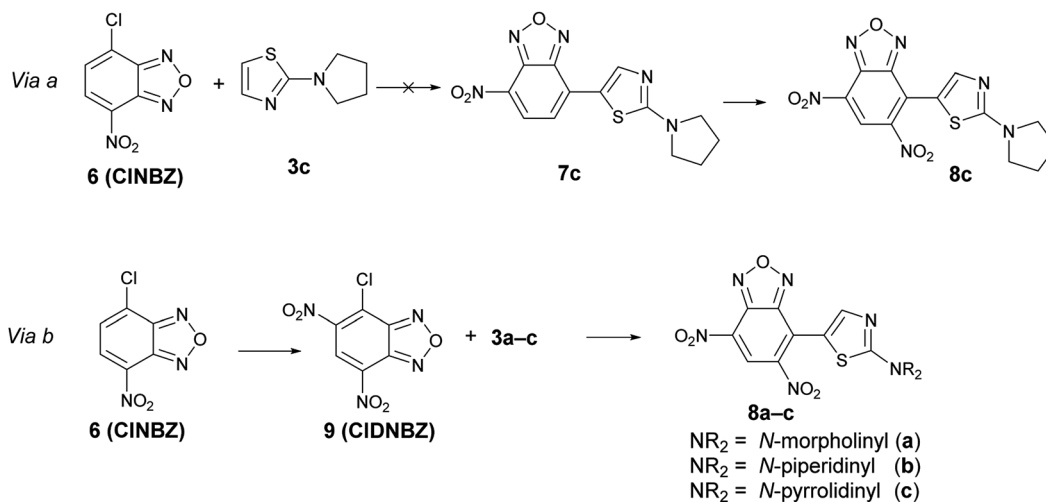
Finally, we want to point out the peculiarity of the behavior showed by the herein reported coupling between **4** and 2-aminothiazole derivatives **3a–c**; actually, in our previous studies on the C–C coupling between CIDNBF and diamino-, triamino- or trihydroxybenzene derivatives, solely one product was always isolated.^{35,42}

^1H NMR experiments of CIDNBF from $+25$ to -93°C in acetone- d_6 were also carried out to test the opportunity to detect the presence of two species or to trap the suggested dinitroso intermediate, but no variation was detected.

What about the structure of the two isomers?

The unexpected finding for the reaction between CIDNBF and aminothiazoles **3a–c** related to the formation of two isomers (**5a–c** and **5'a–c**) give rise to questions on their structure and mechanism of formation.

From the mechanistic point of view, it has to be considered that, in principle, the products from the reaction between **3a–c** and CIDNBF might undergo structural rearrangement through two main pathways: (i) *N*-1-oxide/*N*-3-oxide tautomerism (*via* (i) in Scheme 6) or Boulton-Katritzky rearrangement (BKR, *via* (ii), red arrows in Scheme 6). The first equilibrium is a ring open-closure *via* the 1,2-dinitroso intermediate which, in the current case, might produce species **B1** and **B2** (Scheme 6), with a formal shift of oxygen atom from *N*-1 to *N*-3.



Scheme 7 Synthetic routes designed to obtain **8c**.



The second reaction pathway, *i.e.* BKR, occurs when the benzofuroxan moiety bears a nitro group bound to the carbon atom belonging to the carbocyclic ring and adjacent to the fusion carbon, as occurs in current case. In Scheme 6 we indicated the occurrence of BKR on the reaction product **B1**, since it has been reported that **4** does not undergo BKR rearrangement.⁵¹

Although both the mechanisms might simultaneously occur, the presence in the ¹H NMR spectrum of the crude reaction mixture of signals ascribable to two novel species prevents this hypothesis. Actually, in case of occurrence of both the rearrangements, the signals of three products, namely **B1**, **B2**, and **B3** must be expected in the spectrum. Therefore, we planned further experiments to discriminate between the two pathways. Focusing attention to the possible *N*-1/*N*-3 oxide interconversion, we realized that the reduction of **B1** and **B2** from furoxan derivatives to furazans would produce the same product. Thus, the isomeric mixture **5c**/**5'c** (also indicated as **A** and **A'** in Tables 1–3, without correspondence of the structure of **A** or **A'** with **5c** in Scheme 5) derived from the reaction between **3c** and **4** was subjected to reduction with triphenylphosphine in xylene. Since only one compound has been recovered, the occurrence of the 1-oxide/3-oxide tautomerism sketched in Scheme 6 is therefore strongly supported.

However, it is not possible to exclude, '*a priori*', the occurrence of the preferential reduction of one of the two species involved in the BKR rearrangement; in this case, due to the equilibrium, only one isomer might be recovered after reduction. To shed light on this aspect, it has been necessary to

ascertain the structure of the product derived from the reduction of the mixture **A** + **A'**. For this purpose, we planned to prepare an authentic sample of the product that might derive from the reduction of **B1** and **B2**, namely **8c**, in order to compare the spectroscopic data with those of the product obtained by reduction of the mixture **5c** + **5'c**. As our first approach, we designed to obtain **8c** by nitration of **7c**, in turn obtained from 4-chloro-7-nitrobenzofurazan (**6**, **CINBZ**) and **3c** (*via a* in Scheme 7) but the S_NAr with **CINBZ** did not occur, likely due to the poor electrophilicity of **6** with respect to **4**.

Therefore we used *via b* as alternative procedure (Scheme 7). 4-Chloro-5,7-dinitrobenzofurazan (**9**) was prepared by nitration of **CINBZ** and reacted with **3c** to give **8c**, whose chemico-physical data were in agreement with the unique compound obtained by reduction of the two isomers **5c** and **5'c**. Moreover, by adding a little amount of **8c** to the product obtained by reduction of the mixture **A** + **A'**, increasing of the related ¹H NMR signals was significantly observed. Through an analogous procedure we synthesized also **8a** and **8b**. Compounds **8a–c** are novel and might be of interest in applied field, since they bear contemporarily an electron-donor and an electron-withdrawing moiety.

Summarizing, the above findings bring to exclude structure **B3** in favor of 1/3-oxide rearrangement, by considering that upon reduction of the furoxan ring of **A** + **A'** to furazan one, only product **8c** was formed. One plausible explanation for the not formation of **B3** might be ascribed to the steric hindrance of the two nitro substituents in *ortho* position with respect to the thiazole moiety in the BKR product.

Table 4 Calculated energies for **A** and **A'** tautomers. Experimental and calculated ¹³C chemical shifts^a

Energy (kcal mol ⁻¹)	0.0		0.23	
¹³ C chem. shifts	Calc.	Exp. ^a (A , major isomer)	Calc.	Exp. ^a (A' , minor isomer)
C _{3a}	106.12	105.95	144.84	144.89
C ₄	127.03	124.97	126.21	125.38
C ₅	125.03	127.87	128.71	128.53
C ₆	138.13	137.95	137.51	138.93
C ₇	127.38	128.04	129.73	130.72
C _{7a}	151.20	151.26	114.73	113.43
C ₈	115.67	113.83	110.92	109.06
C ₉	157.53	156.57	156.59	153.85
C ₁₀	171.60	172.54	173.37	172.38
C ₁₁	50.64	50.76	50.97	50.76
C ₁₂	27.23	25.61	27.21	25.55

^a Data from spectra recorded at *T* = 25 °C in CDCl₃.



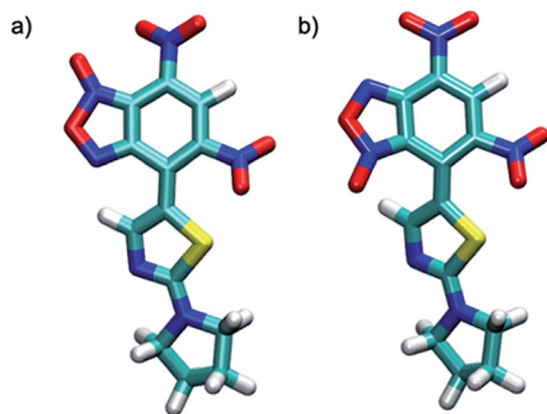


Fig. 1 Molecular structure of (a) *N*-3-oxide, (b) *N*-1-oxide tautomers.

These findings are in agreement with those previously reported by Chistyakov *et al.* on the reaction between **4** and *N*-methylpyrrole that gave two 1,3-*N*-oxide tautomers.⁵²

DFT calculations

The relative ¹³C NMR signals of **A** and **A'**, owing to their different relative ratio were attributed by *g*-HSQC NMR experiments (Table 4). However, the tautomeric structure of **A** and **A'** (due to the 1/3-oxide rearrangement) in solution cannot be unambiguously assigned by NMR experiments solely.

One of the main difficulties in studying these compounds spectrometrically resides mainly in the lack of spin markers (protons). The *g*-HSQC experiments allowed to assign with confidence only correlations with the H5 and H9 signals while other correlations are usually too weak to be used in structural elucidation. Quantum mechanical calculations of ¹³C NMR chemical shifts are widely used to make easier signal assignment. Thus, a joint analysis of experimental and calculated NMR ¹³C

chemical shifts was used for the assignment of the ¹³C chemical shifts of the two tautomers. The ¹³C theoretical chemical shifts (Table 4) correlate very well with the experimental data, with correlation coefficients of least-squares linear fits (*R*²) close to unity (0.9995 and 0.9992 respectively for **A** and **A'**).

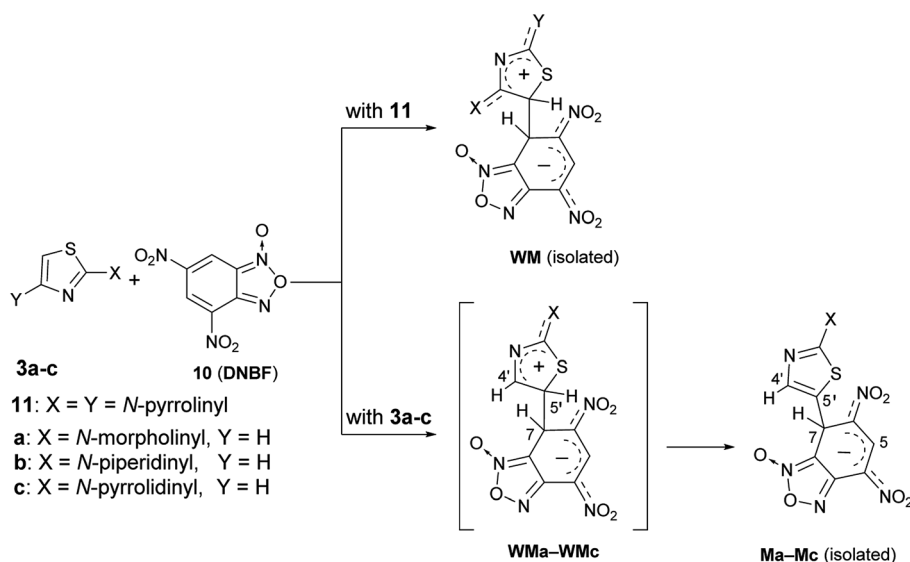
Theoretical calculations allowed also the determination of the energy of the tautomers **A** and **A'**. In agreement with the assignment of the ¹³C chemical shifts of the two tautomers, the most abundant tautomer **A** (*N*-3-oxide) is also energetically more stable than **A'** (*N*-1-oxide). The energetic difference between the two tautomers is very small (0.23 kcal mol⁻¹), explaining their presence in a isomeric mixture (Table 1).

The two tautomers show a similar structure (Fig. 1), the main factor that control their relative stability is (i) the presence of an non-standard intramolecular hydrogen bond between C9–H9 and N-1 in tautomer **A** and *N*-1-oxide in tautomer **A'**, (ii) the steric/electrostatic repulsions between the *N*-oxide moieties with the nitro-group in tautomer **A** or C9–H9 bond in tautomer **A'**.

Further mechanistic insights: reaction of 3a–c with 4,6-dinitrobenzofuroxan

The above finding of two isomeric species derived from the aromatic substitution reaction involving **CIDNBF** has never reported before.

By using nucleophilic species such as diamino- or triamino-benzenes, only one substituted product has been recovered from the reaction with **CIDNBF**. Further, no evidence of isomeric intermediates such as Meisenheimer (**M**) or Wheland-Meisenheimer (**WM**) species was so far reported from C–C coupling reactions of 4,6-dinitrobenzofuroxan (**10**, **DNBF**) either with amino- (or hydroxy)-benzenes or 2,4-dipyrrolidinylthiazole (**11** in Scheme 8). In the latter case, the isomeric structure of the isolated intermediate (**WM** in Scheme 8) was ascertained by X-ray diffraction analysis. The particular behavior found by coupling 2-aminothiazoles **3a–c** with **CIDNBF** suggested us to



Scheme 8 Formation of stable intermediates of reactions between DNBF and 2,4-dipyrrolidinylthiazole (**11**) or 2-aminothiazoles **3a–c**.



investigate the reaction with **DNBF**. Equimolar amount of **DNBF** and **3a** (or **3b**, **3c**) were mixed in acetone- d_6 at $-93\text{ }^\circ\text{C}$ in a NMR spectroscopy tube and the mixture was analyzed by NMR at $-93\text{ }^\circ\text{C}$. Immediately after mixing, new born ^1H NMR signals appeared in the spectrum, compatible with those of the σ -anionic intermediate **Ma** (or **Mb**, **Mc**) (Scheme 8). In particular, diagnostic was the signal at high field (5–6 ppm) and ascribable to the sp^3 hybridized carbon atom bound to H-7, which is involved in the newly formed C–C bond. Moreover, two singlets belonging to H-5 and H-4' were present in the 5–10 ppm region (see Spectra in ESI†).

On gradually raising the temperature, the intensity of signals of **Ma–Mc** increased, whereas those of reactants gradually disappear (at $25\text{ }^\circ\text{C}$ and $0\text{ }^\circ\text{C}$ completely for cases **b** and **c**, respectively; whereas, in case of **a** traces of reagents were present at $25\text{ }^\circ\text{C}$).

Once the conversion has been complete, a red solid appeared at the bottom of the tube extracted from the NMR probe. The solid was collected, then dissolved in DMSO- d_6 for ^1H NMR, ^{13}C NMR and g -HSQC experiments that confirmed the Meisenheimer structure. The solid was stable enough to be analyzed also through ESI mass spectrometry (negative ion mode).

In principle, in the reactions between **3a–c** and **10** the species **WMa–WMc** (Scheme 8) are the first covalent intermediates but only **M** species were spectroscopically detected.

Conversely, the presence of two amino groups on the thiazole moiety (as in compound **11**), stabilizes so strongly the corresponding zwitterionic **WM** intermediate to allow its isolation and the first example of X-ray structural determination in such elusive species³⁸ (**WM** in Scheme 8). This indicates that the lack of the second amino group give rise to zwitterionic fugitive species **WMa–WMc** undetectable on the NMR time scale. Further, as a matter of facts, only one **M** species has been detected and isolated for each electrophile/nucleophile combination by coupling **3a–c** with **10**. In Scheme 8 (as well as in Scheme 3) we have represented the structure of **WMa–WMc** and **Ma–Mc** intermediates as *N*-1 oxides by analogy with the structure of **WM**, and also in agreement with literature data from which it emerges that the *N*-oxide in **CIDNBF** and **DNBF** is situated on the nitrogen farthest from the nitro group in *peri* position (and adjacent to the junction carbon). Moreover, in current case, as well as in those represented in Scheme 3, in which **DNBF** is used (and chlorine is absent), the experimental finding of only one intermediate might be explained taking into consideration that the formation of the two isomers (*N*-1-oxide and *N*-3-oxide) through the passage to dinitrosobenzene is disadvantaged or impeded as the tautomeric process involves rearomatization of the carbocyclic ring which is unlikely when a negative charge still exists on the latter as in **M** or **WM** and the departure of the hydride ion is generally difficult. On the contrary, in the case in which the starting electrophile is **CIDNBF**, as in current case, likely the isomerization occurs immediately after the departure of the chloride, which would make stable, even if for a very short life time, the dinitrosobenzene, thus making possible the formation of the two isomers **A** and **A'**.

Experimental

General

The ^1H and ^{13}C NMR spectra were recorded at 300, 400, or 600 MHz (^1H NMR) and 75.46, 100.56, or 150.80 MHz (^{13}C NMR), respectively. *J* values are given in Hz. Signal multiplicities were established by DEPT-135 experiments. Chemical shifts were referenced to the solvent [$\delta = 7.27$ and 77.0 ppm for CDCl_3], ($\delta = 1.96$ and 118.26 ppm for CD_3CN), ($\delta = 2.05$ and 30.2 ppm for CD_3COCD_3), ($\delta = 2.50$ and 39.5 ppm for DMSO- d_6) for ^1H and ^{13}C NMR, respectively]. ESI-MS spectra were recorded using a Waters 2Q 4000 instrument. Chromatographic purifications (FC) were carried out on silica gel columns at medium pressure. TLC was carried out on aluminum coated silica gel with 254 nm fluorescence indicator (Fluka, DC-Alufolien-Kieselgel).

CINBZ was commercially available, whereas 2-pyrrolidinylthiazole (**3c**),³⁹ 7-Chloro-4,6-dinitrobenzofurazan (**CIDNBZ**, **9**),³⁵ 7-Chloro-4,6-dinitrobenzofuroxan (**CIDNBF**, **4**),⁴³ and 4,6-dinitrobenzofuroxan (**DNBF**, **10**),³⁴ were synthesized and purified as previously described. All novel solid compounds decomposed when heated in melting point apparatus. Although the reactions carried out in NMR spectroscopy tube showed conversion almost quantitative, the yields in isolated products were lower, likely due to purification methods, but we did not focus our efforts on yield optimization. Computational and variable temperature NMR experimental details are reported in ESI.†

Synthesis of compounds **3a–c**

General procedure. 2-Bromothiazole (0.56 mL, 6.22 mmol) was added to 5 mL of amine (morpholine, piperidine, pyrrolidine) and the mixture was kept at reflux under magnetic stirring. The conversion of 2-bromothiazole was monitored through TLC (eluent: diethyl ether/petroleum light 8/2; $R_F = 0.45$) and GC-MS. After 24 h, 4 h and 2 h in case of use of morpholine, piperidine or pyrrolidine, respectively, the excess of amine was removed under vacuum in a rotavapor then the product was purified through column chromatography on silica gel (eluent: diethyl ether/petroleum light 8/2; $R_F = 0.45$). The product obtained after FC sometimes appeared as viscous liquid; in this case, the residual solvent was removed by adding little amount of chloroform or dichloromethane then filtering off the liquid. Compounds **3a–c** were obtained in yield of 90 (**3a**), 95 (**3b**), and 98% (**3c**), respectively, and their data agreed with those reported in the literature (ref. 53, 54 and 39 for **3a**, **3b**, and **3c**, respectively). They were stored in freezer and in the dark.

Reaction between **3a–c** and **CIDNBF**

General procedure. To a solution of **CIDNBF** (0.023 g, 0.088 mmol) in acetonitrile (7 mL), 0.030 g of **3a**, **3b** or 0.028 g for **3c** (0.177, 0.179, or 0.181 mmol, respectively) were added at room temperature. Immediately, the solution turned blue and was monitored by TLC (eluent: CH_2Cl_2 /ethyl acetate 9/1) under magnetic stirring. After 24, 12 and 4 h, respectively, the solvent was removed *in vacuo* and the residue subjected to FC eluting



with CH_2Cl_2 until the first blue eluate was obtained, then with the CH_2Cl_2 : ethyl acetate 9 : 1. The collected fractions were concentrated *in vacuo* and analyzed through ^1H NMR and ^{13}C NMR, and mass spectrometry. The NMR analysis indicated presence of two species. Many attempts to obtain crystals suitable for X-ray diffraction analysis failed. The mixture was subjected to preparative TLC and the two separated spot were scraped but, once each was dissolved in CD_3CN to be analyzed, the ^1H NMR revealed presence of a mixture of two compounds in relative ratio equal to that found prior to separation. Thus, below we report the physico-chemical data of the mixture of isomers and, due to the presence of two isomers, we considered sufficient to record ESI-MS data. In particular, when, from the ^1H NMR spectrum, it was evident that the two species were present in different amount, we indicated as Maj or Min the signals of the isomer present in major or minor amount, respectively. On the basis of the analysis derived from experimental data/DFT calculations, below we report the names of the isomers attributing structure A' to **5c** and A to **5'c**, and assuming analogous behaviour also for cases **a** and **b**.

7-(2-Morpholinothiazol-5-yl)-4,6-dinitrobenzo[c][1,2,5]oxadiazole 1-oxide (5a) and 4-(2-morpholinothiazol-5-yl)-5,7-dinitrobenzo[c][1,2,5]oxadiazole 1-oxide (5'a). Dark blue solid, 0.008 g, 24% yield; ^1H NMR (300 MHz, CD_3CN , 25 °C, isomeric Maj (5'a)/Min (5a) ratio = 67 : 33) δ (ppm): 8.73 (s, 1H, Maj), 8.47 (s, 1H, Min), 8.32 (s, 1H, Min), 7.71 (s, 1H, Maj), 3.85–3.75 (m, 8H, Maj + Min), 3.67–3.59 (m, 8H, Maj + Min); ^1H NMR (399.9 MHz, CDCl_3 , 25 °C, isomeric Maj/Min ratio = 50 : 50) δ (ppm): 8.69 (s, 1H), 8.65 (s, 1H), 8.24 (s, 1H), 7.79 (s, 1H), 3.89–3.84 (m, 8H), 3.78–3.74 (m, 4H), 3.71–3.67 (m, 4H); ^{13}C NMR: (150.8 MHz, CDCl_3 , 25 °C) δ (ppm, selected data): 176.0, 175.9, 154.9 (CH), 152.1 (CH), 151.1, 144.6, 139.5, 132.4, 127.9 (CH), 125.0, 124.6, 124.2 (CH), 113.5, 113.3, 108.6, 105.8, 66.0 (OCH_2), 65.9 (OCH_2), 48.9 (NCH_2), 48.8 (NCH_2); ESI-MS (m/z): 393 ($\text{M} - \text{H}$) $^-$; HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_6\text{O}_7\text{S}^+$: 395.0404; found: 393.0412.

4,6-Dinitro-7-(2-(piperidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazole 1-oxide (5b) and 5,7-dinitro-4-(2-(piperidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazole 1-oxide (5'b). Night blue solid, 0.010 g, 29% yield. ^1H NMR: (599.7 MHz, CDCl_3 , 25 °C, isomeric Maj (5'b)/Min (5b) ratio = 56 : 44) δ (ppm): 8.79 (s, 1H, Maj), 8.71 (s, 1H, Min), 8.29 (s, 1H, Maj), 7.94 (s, 1H, Min), 3.80–3.73 (m, 4H, Min), 3.73–3.68 (m, 4H, Maj), 1.83–1.73 (m, 12H, Maj + Min); ^{13}C NMR: (150.8 MHz, CDCl_3 , 25 °C) δ (ppm): 176.1, 175.8, 157.1 (CH), 155.1 (CH), 151.3, 145.0, 138.6, 138.0, 130.4, 128.7 (CH), 127.9, 125.4, 125.0, 124.9 (CH), 113.8, 113.3, 109.4, 105.9, 50.5 (NCH_2 , 2 signals overlapped), 25.4 (NCH_2CH_2), 23.8 ($\text{NCH}_2\text{CH}_2\text{CH}_2$), 23.7 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{13}\text{N}_6\text{O}_6\text{S}^+$: 393.0612; found: 393.0632.

4,6-Dinitro-7-(2-(pyrrolidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazole 1-oxide (5c) and 4-(2-morpholinothiazol-5-yl)-5,7-dinitrobenzo[c][1,2,5]oxadiazole 1-oxide (5'c). Brilliant dark green shiny, 0.019 g, 57% yield. ^1H NMR: (400 MHz, CDCl_3 , 25 °C, isomeric Maj (5'c, or A)/Min (5c, or A') ratio = 59 : 41) δ (ppm): 8.81 (s, 1H, Maj), 8.71 (s, 1H, Min), 8.28 (s, 1H, Maj), 7.96 (s, 1H, Min), 4.00–3.35 (m, 8H, Maj + Min), 2.27–2.03 (m, 8H, Maj + Min); ^1H NMR: (300 MHz, CD_3CN , 25 °C, isomeric

Maj/Min ratio = 56 : 44) δ (ppm): 8.73 (s, 1H, Maj), 8.66 (s, 1H, Min), 8.35 (s, 1H, Min), 7.90 (s, 1H, Maj), 3.72–3.33 (m, 8H, Maj + Min), 2.14–1.94 (m, 8H, Maj + Min); ^{13}C NMR: (150.8 MHz, CDCl_3 , 25 °C) δ (ppm): 172.8, 172.7, 156.8 (CH), 154.9 (CH), 151.3, 145.0, 138.6, 137.9, 130.3, 128.6 (CH), 127.9, 125.6, 125.0, 124.9 (CH), 113.9, 113.3, 109.2, 106.0, 50.6 (NCH_2 , 2 broad signals overlapped), 29.7 (NCH_2CH_2), 25.6 (NCH_2CH_2); HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_6\text{O}_6\text{S}^+$: 379.0455; found: 379.0466.

Synthesis of 7-(2-dialkylaminothiazol)-4,6-dinitrobenzo[c][1,2,5]oxadiazoles

General procedure. To a solution of **CIDNBZ** (0.018 g, 0.074 mmol) in acetonitrile (9 mL) 0.028 g of **3a** (or **3b**, or **3c**) (0.165, 0.167, 0.182 mmol, respectively) were added. Immediately after the reagents mixture, the colour of the solution turned blue. The reaction was carried out at room temperature and under magnetic stirring, and the conversion was monitored through TLC analysis (eluent: CH_2Cl_2). After 4 h, 3 h and 2 h, for the reaction with **3a**, **3b**, or **3c**, respectively, the solvent was removed *in vacuo* and the crude residue was chromatographed on silica gel column eluting with CH_2Cl_2 giving pure substitution compounds **8a–c**. Compound **8c** was obtained also from reduction of the isomeric mixture **5c/5'c** with P(Ph)_3 in xylene using the procedure already reported of reduction of benzo-furoxans to benzofurazans.⁵⁵

4-(2-Morpholinothiazol-5-yl)-5,7-dinitrobenzo[c][1,2,5]oxadiazole (8a). Dark blue solid, 0.007 g, 25% yield. ^1H NMR: (599.7 MHz, CD_3CN , 25 °C) δ (ppm): 8.80 (s, 1H), 8.78 (s, 1H), 3.83–3.80 (m, 4H), 3.77–3.73 (m, 4H); ^{13}C NMR: (150.8 MHz, CD_3CN , 25 °C) δ (ppm): 177.4, 157.1 (CH), 151.4, 144.3, 130.1, 130.0, 127.7 (CH), 126.1, 116.3, 66.5 (OCH_2), 49.8 (NCH_2); HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_6\text{O}_6\text{S}^+$: 379.0455; found: 379.0466.

5,7-Dinitro-4-(2-(piperidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazole (8b). Green-blue solid, 0.006 g, 22% yield. ^1H NMR (300.0 MHz, CD_3CN , 25 °C) δ , ppm: 8.90 (s, 1H), 8.79 (s, 1H), 3.83–3.73 (m, 4H), 1.80–1.70 (m, 6H); ^1H NMR (599.7 MHz, CDCl_3 , 25 °C) δ , ppm: 9.06 (s, 1H), 8.79 (s, 1H), 3.79 (br. s, 4H), 1.79 (br. s, 6H); ^{13}C NMR: (150.8 MHz, CDCl_3 , 25 °C) δ , ppm: 176.1, 159.3 (CH), 149.9, 142.9, 136.7, 129.1 (CH), 128.3, 125.4, 116.3, 50.7 (br. s. NCH_2), 25.5 (NCH_2CH_2), 23.8 ($\text{NCH}_2\text{CH}_2\text{CH}_2$); HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{13}\text{N}_6\text{O}_5\text{S}^+$: 377.0663; found: 377.0680.

5,7-Dinitro-4-(2-(pyrrolidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazole (8c). Dark blue solid, 0.004 g, 15% yield. ^1H NMR: (599.7 MHz, CD_3CN , 25 °C) δ (ppm): 8.94 (s, 1H), 8.80 (s, 1H), 4.00–3.33 (br. m, 4H), 2.15–2.10 (br. m, 4H); ^{13}C NMR: (150.8 MHz, CD_3CN , 25 °C) δ (ppm): 174.0, 159.4 (CH), 151.4, 144.4, 138.1, 130.5 (CH), 129.4, 126.4, 116.8, 51.8 (br. s. NCH_2), 26.1 (br. s. NCH_2CH_2); HRMS (ESI^+) m/z : [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_6\text{O}_5\text{S}^+$: 363.0506; found: 363.0513.

Reactions between 1–3 and DNBf (10). Formation of **Ma–Mc** (experimental details on variable temperature NMR reactions are reported in ESI^+).

(7-(2-Morpholinothiazol-5-yl)-6-nitro-1-oxidobenzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (Ma). ^1H NMR: (399.9 MHz,



acetone-d₆, −48 °C, conversion: 53%) δ (ppm): 8.73 (s, 1H, H-5), 7.29 (s, 1H, H-4'), 5.63 (d, J = 0.53 Hz, 1H, H-7), 3.77 (br. t, J = 5.3 Hz, 4H, OCH₂), 3.48 (br. t, J = 5.5 Hz, 4H, NCH₂). After heating until +25 °C **Ma** was recovered as red solid, 0.018 g, 94%, ¹H NMR: (599.7 MHz, DMSO-d₆, 25 °C) δ (ppm): 8.64 (s, 1H, H-5), 7.34 (s, 1H, H-4'), 5.64 (s, 1H, H-7), 3.69 (br. t, J = 4.8 Hz, 4H, OCH₂), 3.44 (br. t, J = 4.8 Hz, 4H, NCH₂); ¹³C NMR: (150.8 MHz, DMSO-d₆, 25 °C) δ (ppm): 169.3, 147.9, 131.1 (br. s, CH, C-4'), 130.9 (CH), 124.5, 120.8, 112.1, 109.7, 64.9, (OCH₂), 48.6 (NCH₂), 32.1 (C-7); ESI-MS: 395 (M – H)[−].

(6-Nitro-1-oxido-7-(2-(piperidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (Mb). ¹H NMR: (399.9 MHz, acetone-d₆, −93 °C, conversion: 67%) δ (ppm): 8.71 (s, 1H, H-5), 7.38 (s, 1H, H-4'), 5.64 (s, 1H, H-7), 3.58–3.46 (m, 4H, NCH₂), 1.72–1.55 (m, 6H, NCH₂CH₂ + NCH₂CH₂CH₂). After heating until +25 °C **Mb** was recovered as red solid, 0.018 g, 94%; ¹H NMR: (300.0 MHz, DMSO-d₆, 25 °C) δ (ppm): 8.65 (s, 1H, H-5), 7.40 (s, 1H, H-4'), 5.64 (s, 1H, H-7), 3.55–3.45 (m, 4H, NCH₂), 1.69–1.51 (m, 6H, NCH₂CH₂ + NCH₂CH₂CH₂); ¹³C NMR: (75.4 MHz, DMSO-d₆, 25 °C) δ (ppm): 168.2, 148.2, 131.5 (CH), 127.0 (br. s, CH, C-4'), 124.2, 120.1, 112.3, 110.3, 50.7, (NCH₂), 32.5 (C-7), 24.7 (NCH₂CH₂), 22.9 (NCH₂CH₂CH₂); ESI-MS: 393 (M – H)[−].

(6-Nitro-1-oxido-7-(2-(pyrrolidin-1-yl)thiazol-5-yl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (Mc). ¹H NMR: (399.9 MHz, acetone-d₆, −93 °C, conversion: 81%) δ (ppm): 8.71 (s, 1H, H-5), 7.52 (s, 1H, H-4'), 5.65 (s, 1H, H-7), 3.77–3.32 (m, 4H, NCH₂), 2.20–1.98 (m, 4H, NCH₂CH₂). After heating until +25 °C **Mc** was recovered as red solid, 0.016 g, 87%; ¹H NMR: (399.9 MHz, DMSO-d₆, 25 °C) δ (ppm): 8.66 (s, 1H, H-5), 7.51 (br. s., 1H, H-4'), 5.67 (d, J = 0.6 Hz, 1H, H-7), 3.47 (t, J = 7.4 Hz, 4H, NCH₂), 2.03–1.98 (m, 4H, NCH₂CH₂); ¹³C NMR: (100.6 MHz, DMSO-d₆, 25 °C) δ , ppm: 164.3, 147.8, 131.2 (CH), 127.1 (br. s, CH, C-4'), 123.6, 119.7, 111.8, 109.9, 51.3, (NCH₂), 32.1 (C-7), 25.3 (NCH₂CH₂), ESI-MS: 379 (M – H)[−].

Conclusions

The S_EAr/S_NAr reaction by combination of **Cl-DNBF** and 2-aminothiazole derivatives **3a–c** gave two isomeric products, bearing the benzofuroxanyl moiety bound to the C-5 carbon atom of the thiazole ring. Experiments carried out by changing the reaction conditions showed that the two isomers were formed in relative ratio depending on the reaction temperature and the solvent nature. The behavior observed suggests the occurrence of an equilibrium between the two novel species. Further experiments have been performed in order to shed some light on the reaction mechanism and to elucidate the structure of the two isomers. The reduction of the furoxanyl ring to furazanyl one of the isomeric mixture (**5c** + **5'c**) gave the same product derived from the reaction between **3c** and 7-chloro-4,6-dinitrobenzofurazan (**Cl-DNBZ**). This permitted to solve the dilemma of a unambiguous assignment of the isomeric forms structure supporting their origination from *N*-1/*N*-3-oxide isomerization. DFT calculations confirm the correlation between the NMR signals and the isomeric structures. Current study is, to the best of our knowledge, the first attempt to

compare *N*-1/*N*-3-oxide and BKR isomerizations. Finally, a unique Meisenheimer intermediate **Ma**, **Mb**, or **Mc**, were isolated by coupling the 2-aminothiazole derivative **3a**, **3b**, or **3c** with 4,6-dinitrobenzofuroxan (**DNBF**).

Conflicts of interest

There are no conflicts to declare.

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