Check for updates

Highly conjugated architectures and labile reaction intermediates from coupling between 10π electron-deficient heteroaromatics and *sym*-trihydroxy- or triamino-benzene derivatives†

Gabriele Micheletti, [ID] *[a] Carla Boga,[a] Silvia Cino,[a] Silvia Bordoni[a] and Elena Chugunova[bc]

The C–C coupling reaction between neutral aromatic carbon nucleophiles such as 1,3,5-triamino- and 1,3,5-trihydroxy-benzene derivatives and 7-chloro-4,6-dinitrobenzofuroxan (**Cl-DNBF**) or 7-chloro-4,6-dinitrobenzofurazan (**Cl-DNBZ**) gave in high yield the corresponding conjugated structures, which are of potential interest in the materials field. When chlorine is absent on the electrophile, as in 4,6-dinitrobenzofurazan (**DNBZ**), the reaction with 1,3,5-triaminobenzene derivatives produces Wheland–Meisenheimer (**WM**) zwitterionic intermediates, intercepted and fully characterized *via* NMR at low temperature, whereas stable Meisenheimer complexes (**M**) were isolated in the reaction of phloroglucinol with 1,3,5-trimethoxybenzene. The latter also gave exclusively **M** complexes when reacted with 4,6-dinitrobenzofuroxan (**DNBF**), or 4,6-dinitrotetrazolopyridine (**DNTP**). The detection of **WM** or **M** intermediates can be rationalized by invoking the substituent stabilization ability of the positive charge in **WM** intermediates, on going from neutral carbon nucleophiles 1,3,5-triaminobenzenes to 1,3,5-trihydroxybenzene derivatives. Furthermore, variable-temperature NMR experiments on the **M** intermediates gave insights into the rotational barrier about the newly formed C–C bond.

## Introduction

Benzofurazan and benzofuroxan derivatives are heterocyclic compounds, which possess interesting properties useful for different applications in many applied fields. For example, they exhibit a broad spectrum of biological activities including antibacterial, antifungal, antileukemic, and acaricide activities. Benzofuroxans are also of great interest as NO donors[1–4] and have found applications as dyes, fluorescent biosensors and high energy materials.[5,6]

Due to the 10π-electron ring heteroaromatic structure,[7] they behave also as electrophiles and they have been classified as superelectrophilic heteroaromatic compounds[8,9] when one or more nitro groups are bound to the carbocyclic ring. For this peculiarity, they are of great interest from the mechanistic point of view. For instance, the 4,6-

dinitrobenzofuroxan (**DNBF**) ring is able to stabilize the negative charge in the Meisenheimer complexes.[7,10–12] Furthermore, when **DNBF** was combined with neutral aromatic nucleophilic species, such as triaminobenzene derivatives **1–3**, the detection and characterization of **WM** intermediates (Scheme 1), simultaneously Wheland type on the nucleophilic moiety and Meisenheimer on the electrophilic one, was achieved for the first time.[13]
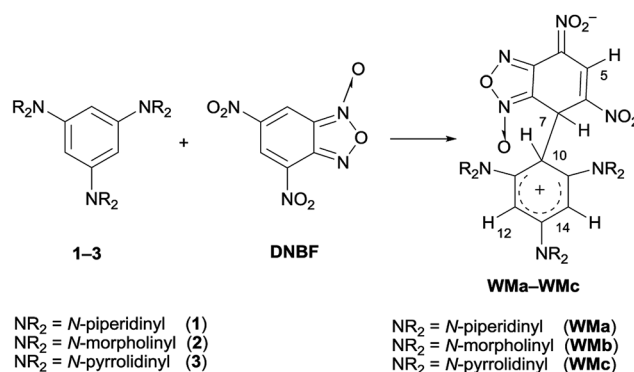
Scheme 1 Formation of Wheland–Meisenheimer complexes (**WMa–WMc**) from the reaction between 1,3,5-tris(*N*,*N*-dialkylamino)benzenes and **DNBF**.

[a]Department of Industrial Chemistry 'Toso Montanari', Alma Mater Studiorum Università di Bologna, Viale Del Risorgimento, 4, 40136 Bologna, Italy. E-mail: gabriele.micheletti3@unibo.it

[b]Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of RAS, Akad. Arbuzovst. 8, Kazan, Tatarstan 420088, Russia

[c]Kazan Federal University, 18 Kremlyovskaya St., Kazan, Tatarstan 420008, Russia

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra09460h

Analogous behaviour was further observed with 4,6-dinitrotetrazolopyridine (**DNTP**),[14] which acts as an electrophile stronger than **DNBF** ($E_{\text{Mayr DNBF}} = -5.06$ (ref. 8) $E_{\text{Mayr DNTP}} = -4.67$ (ref. 16)), according to the Mayr's electrophilicity scale.[15] The species **DNFB** and **DNTP** gave rise to **WM** complexes, not only with triaminobenzene derivatives **1–3** (ref. 13 and 14) but also with 2-aminothiazole derivatives.[17,18] Thus, the zwitterionic intermediates are stable enough to be characterized by NMR spectroscopy, owing to the lack of good leaving groups on the electrophilic moiety, that makes difficult the evolution to the substitution products by hydride departure. In the case of the coupling between 2,4-dipyrrolidinylthiazole and **DNBF** or **DNTP**, the stability of the **WM** intermediates was so evident to permit the first structural determination of **WM** complexes through X-ray diffraction.[18] The access to structures with a scaffold, bearing both electron-donor and electron-acceptor moiety, is of great interest in the applied fields, such as solar energy conversion[19] or optoelectronic devices.[20] An efficient procedure to obtain such conjugated structures can be $S_E Ar/S_N Ar$ reactions between aromatic electrophiles as 7-chloro-4,6-dinitrobenzofuroxan (**Cl-DNBF**) or 7-chloro-4,6-dinitrobenzofurazan (**Cl-DNBZ**) and aromatic nucleophiles. The compounds **Cl-DNBF** and **Cl-DNBZ** have been reported to react with 2,4,6-trinitroaniline[21,22] and 1,3-diaminobenzenes,[23] but never with *sym*-triaminobenzenes **1–3**. As described by the pioneering works of Effenberger, they have been coupled with a variety of electrophiles as proton,[24–32] halogens,[33,34] acyl-,[35–37] alkyl-,[38] and aryl-halides[39] giving Wheland complexes, whose high stability has been ascribed to the great ability of the three amino substituents to stabilize the positive charge on the carbocyclic ring. Recently, the coupling of triaminobenzenes with **DNBF**,[13] **DNTP**,[14] proton,[40] aryldiazonium salts,[41–45] trinitrothiophene[46] and chloro-nitrobenzofurazanes[47] produced novel intermediates of the aromatic substitution reaction, together, sometimes, with unexpected species.

Based on the above findings and by considering the importance to find novel conjugated structures, we planned to investigate the reactivity of 7-chloro-4,6-dinitrobenzofurazan (**Cl-DNBZ**) and 7-chloro-4,6-dinitrobenzofuroxan (**Cl-DNBF**) with 1,3,5-triaminobenzene derivatives and 1,3,5-trihydroxybenzene derivatives (phloroglucinol and 1,3,5-trimethoxybenzene). Thus, we extended our previous studies on $S_N Ar/S_E Ar$ reaction intermediates to the reactions of 1,3,5-triaminobenzenes **1–3** with **DNBZ** and to the less nucleophilic phloroglucinol or 1,3,5-trimethoxybenzene with **DNBZ**, **DNBF** or **DNTP**.

Results and discussion

For the sake of simplicity, this part has been divided in subheadings. The first part focused on the construction of novel aromatic architectures by coupling **Cl-DNBF** and **Cl-DNBZ** with 1,3,5-triaminobenzenes, 1,3,5-trihydroxybenzene, and 1,3,5-trimethoxybenzene. The second section is dealing with the 1,3,5-triaminobenzenes **1–3** coupled with **DNBZ** and 1,3,5-trihydroxybenzene (**12**) and 1,3,5-trimethoxybenzene (**13**) coupled with **DNBZ**, **DNBF**, and **DNTP**.

Reactions of 7-chloro-4,6-dinitrobenzofuroxan (4) and 7-chloro-4,6-dinitrobenzofurazan (5) with neutral carbon aromatic nucleophiles
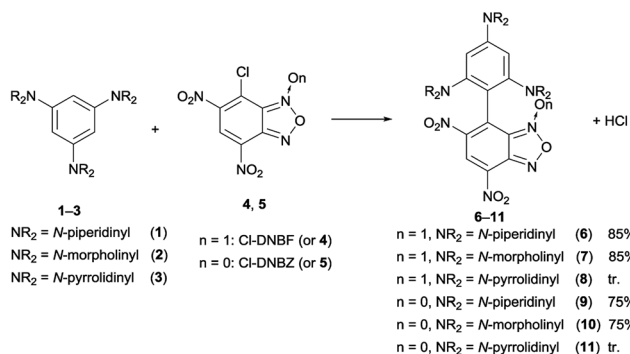
Reactions with 1,3,5-triaminobenzene derivatives 1–3. The reactions between triaminobenzene derivatives **1–3** and 7-chloro-4,6-dinitrobenzofuroxan (**4**) (Scheme 2) were run by mixing equimolar amount of reagents, at room temperature and in the presence of a base to neutralize the hydrochloric acid.

When NaHCO$_3$ was used as a base, the solution promptly turns to deep green and the crude was subjected to work-up after about 1 h; the new substitution products **6** and **7** obtained in 85% yield after purification by chromatography on column chromatography on silica gel were fully characterized. They resulted to be stable as solids, whereas decompose after 24 h in CDCl$_3$ or CD$_3$CN solution, as indicated by the presence of ^{1}H NMR unidentified signals. On the contrary, their salts were stable for several days, as confirmed by adding an equimolar amount of picric acid to a deuterochloroform solutions of **6** and monitoring the ^{1}H NMR signals of picrate (**6H$^+$picrate**) for seven days.

In the ^{1}H NMR spectrum of the crude reaction mixture between 1,3,5-tris(*N*-pyrrolidinyl)benzene (**3**) and **4**, the presence of signals belonging to unidentified species, likely due to the high reactivity of the reactants, was detected, and only traces of **8** were obtained after chromatographic purification.

The reactions of 7-chloro-4,6-dinitrobenzofurazan (**5**, **Cl-DNBZ**) with **1–3** (Scheme 2) were run in acetonitrile by using two-fold molar excess of nucleophile. After 1 h the solvent was removed and the new products **9** and **10** (derived from the coupling of **5** with **1** and **2**, respectively) were isolated in high yield. In the case of the reaction between **3** and **5**, the coupling gave species **11** which was observed exclusively if the reaction was run in the NMR spectroscopy tube.

Therefore, the reaction courses were monitored in the absence of a base: the ^{1}H NMR spectrum of mixtures of equimolar amount of **Cl-DNBF** and **1** (or **2**), in CDCl$_3$ at 25 °C, evidenced signals consistent only with those of the salt **6H$^+$Cl$^-$** (or **7H$^+$Cl$^-$**) (Fig. 1). The reaction between 4-chloro-7-nitrobenzofurazan (**ClNBZ**) and **1** or **2** has previously been[47] reported affording the related substitution product in 60% or

Scheme 2 Reactions between 1,3,5-triaminobenzene derivatives **1–3** and 7-chloro-4,6-dinitrobenzofuroxan (**4**) (in CHCl$_3$) or 7-chloro-4,6-dinitrobenzofurazan (**5**) (in CH$_3$CN).
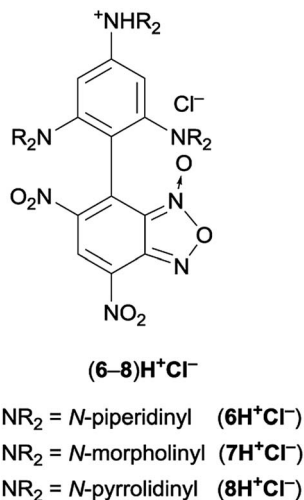
Fig. 1 Salts derived from the reaction between equimolar amount of 1–3 and 4.

18%, respectively, in the case of **1** or **2** after 96 h. The increased electrophilicity of **Cl-DNBF**, due to the presence of the additional EWG nitro group with respect to **ClNBZ**, is likely responsible of the higher conversion and shorter reaction time.

The comparison of the results obtained by 7-chloro-4,6-dinitrobenzofuroxan with those obtained with 4-chloro-7-nitrobenzofurazan instead of 4-chloro-7-nitrobenzofuroxan is permitted taking into account that **Cl-DNBF**[48] and **Cl-DNBZ**[8] have the same Mayr's electrophilicity value ($E_{Mayr} = -6.11$).

Finally, we carried out the reaction between **1–3** and **4** by direct mixing of the reagents in the NMR spectroscopy tube at low temperature to eventually trap reaction intermediates. Previously, the coupling between **1–3** and 4,6-dinitrobenzofuroxan (**DNBF**) allowed the NMR detection at low temperature of the first Wheland–Meisenheimer complexes (**WM1–3** in Scheme 1).[13] Although we were aware that the occurrence of a chlorine atom in the 7-chloro-4,6-dinitrobenzofuroxan, causing good leaving group in S$_N$Ar, makes hard the challenge to intercept the zwitterionic **WM** species (Scheme 3), the ability of amino group in stabilizing the positive charge enables the intent to spectroscopically intercept the **W** intermediate (Scheme 3). It has to be noted that similar stable intermediates have been previously observed in the reaction between **3** and **ClNBZ**.[47]

First, our strategy pursued to select **4** to be reacted with **3**, since it is well known that the latter is able to stabilize the positive charge of Wheland intermediates. In this case, the ^{1}H
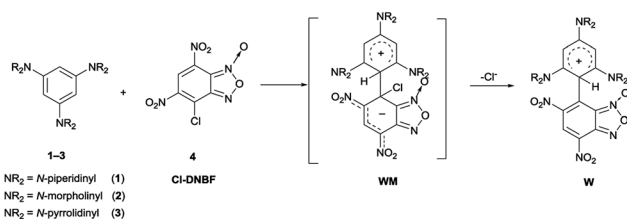
NMR spectrum, recorded in CD$_2$Cl$_2$ at −70 °C, as the reactants were mixed, showed a set of signals compatible with those of the salt **8H$^+$Cl$^-$** (Fig. 1). In particular, a broad singlet at $\delta = 11.35$ ppm was ascribed to the NH signal and the presence of a singlet at $\delta = 8.9$ ppm and of two singlets at $\delta = 6.02$ and 5.96 ppm (integrating 1 : 1 : 1) was attributed to the proton belonging to the benzofuroxanyl moiety and to the aromatic protons of the triaminobenzene moiety, respectively.

The latter resulted not equivalent due to the restricted rotation around the new C–C bond formed, as also confirmed by the splitting of the signals of the methylene hydrogen atoms of the pyrrolidinyl moiety in the aliphatic region. On raising the temperature, the two singlets belonging to the hydrogen atoms on the aminobenzene moiety and those of the pyrrolidinyl groups, gradually broadened until coalescence at about −43 °C; above this value they gradually sharpened. The spectrum exhibited further signals increasing the temperature from +2 °C to +25 °C, indicating a possible evolution to unidentified compounds, explaining the failure of our previous attempts to isolate **8**.

An analogous behavior was observed when the reaction between **2** and **4** was carried out at −88 °C in CD$_2$Cl$_2$: after reaction mixture the ^{1}H NMR spectrum showed disappearance of the reactant signals and appearance of new signals at $\delta = 8.98$, 7.52, and 6.39 ppm in the aromatic region integrating 1 : 1 : 1, respectively, attributable to the salt **7H$^+$Cl$^-$**. The morpholinyl signals, at this temperature, were distinct due to the restricted rotation around the new formed C–C bond. On gradually raising the temperature, as observed in the previous case, the signals belonging to the aminobenzene moiety gradually sharpened, and the coalescence situation was reached around −37 °C. The phenomenon was reversible on gradually lowering the temperature from 25 °C until −88 °C, since the final spectrum was equal to that obtained after mixing the two reagents at the same temperature. When the sample has been extracted from the NMR probe, a solid was observed on the bottom of the NMR tube; after filtration, it was dissolved in CD$_3$CN and analyzed through ^{1}H, ^{13}C NMR and DEPT experiments and its spectral data were consistent with those of structure **7H$^+$** (Fig. 1). This solid was percolated through Al$_2$O$_3$ eluting with acetonitrile and the ^{1}H NMR spectrum of the residue was in agreement with that of the neutral form **7**.

Reactions with 1,3,5-trihydroxybenzene derivatives 12 and 13. The reaction between 1,3,5-trihydroxybenzene (**12**, phloroglucinol) and **Cl-DNBF** (**4**) (Scheme 4), was run, by directly adding the reagents in equimolar amount, dissolved in CD$_3$CN in the NMR spectroscopy tube at room temperature: after 15 min the ^{1}H NMR spectrum of the crude showed a 30 : 70 relative % molar ratio of residue reactants (**4** or **12**) and the coupling product **14**. The hydrogen relative signal integration between compounds **4** and **14**, became approximately 1 : 4, after 5 h and the conversion appeared almost complete after 24 h. Analogous behavior was observed for the reaction between **5** and **12**, yielding **16**.

The reaction between 1,3,5-trimethoxybenzene (**13**) and **4** (Scheme 4) was carried out under the analogous conditions used for phloroglucinol: after 15 min, the spectrum showed

Scheme 3 Possible intermediates (WM and W) from the reactions between 1–3 and 4.
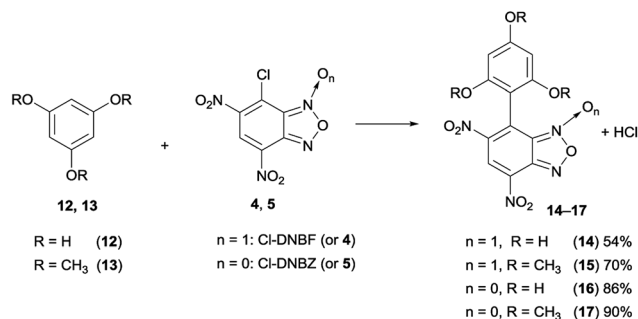
Scheme 4 Reactions between **12** and **13** and 7-chloro-4,6-dinitrobenzofuroxan (**4**) or 7-chloro-4,6-dinitrobenzofurazan (**5**), yields are after purification by FC (more details in Experimental section).

Scheme 5 WM intermediates from the C–C coupling between **1–3** and DNBZ.

a 86 : 14 relative percent molar ratio between the starting materials and the coupling product **15**; then the ratio increased, until the conversion reached 84% after 24 h. The spectral data of compound **15** (**17**), obtained in 70% (90%) yield after purification by silica gel flash chromatography is in agreement with those reported in the literature.[49]

The data obtained by monitoring the reactions by NMR clearly reveal that the reaction of **4** with phloroglucinol is more facile than that with **13**. This observation can be due to higher electron donor effect of hydroxyl, with respect the methoxy group ($\sigma_{OH}^+ = -0.92$, $\sigma_{OMe}^+ = -0.78$)[50] and to the occurrence of tautomeric equilibria involving phloroglucinol, as recently investigated.[51] Further, the reaction carried out between **12** and 4-chloro-7-nitrobenzofurazan (**ClNBZ**) did not occur, even if in refluxing acetonitrile, in contrast with the already reported results between **ClNBZ** and **1–3**; these findings indicate that the lower nucleophilicity of trihydroxybenzene derivatives with respect to triaminobenzenes requires the presence of a further nitro group to permit the aromatic substitution reactions.

Reactions between neutral carbon aromatic nucleophiles and 10π electron-deficient heteroaromatics without good leaving groups

C–C coupling between 4,6-dinitrobenzofurazan (DNBZ) and 1,3,5-triaminobenzene derivatives 1–3. The reactions between equimolar amount of 4,6-dinitrobenzofurazan (**18**, or **DNBZ**) and 1,3,5-triaminobenzene derivatives (**1**, **2**, or **3**) were carried out directly in the NMR spectroscopy tube, at −54 °C in CDCl₃, monitoring the system at variable temperatures. In all cases, the solution changed color immediately after the reagent mixing, and the ¹H NMR spectrum showed a variety of newly born signals, belonging to the intermediates **WM1**, **WM2**, or **WM3** (Scheme 5).

Particularly diagnostic was the presence of a single signal owing to hydrogen atom of the electrophilic moiety (H-5 in Scheme 5, e.g. at 9.09 ppm for **WM1**) together with four signals in the δ 5.8–4.0 interval.

Two of them were ascribed to H-7 and H-10 (two doublets at 5.00 and 4.82 ppm, $J = 2.6$ Hz, for **WM1**, respectively), which were shielded with respect to the corresponding starting signals due to the sp² to sp³ hybridisation change of the relative carbon atom. Analogously, the anisochronous signals of H-12 and H-14
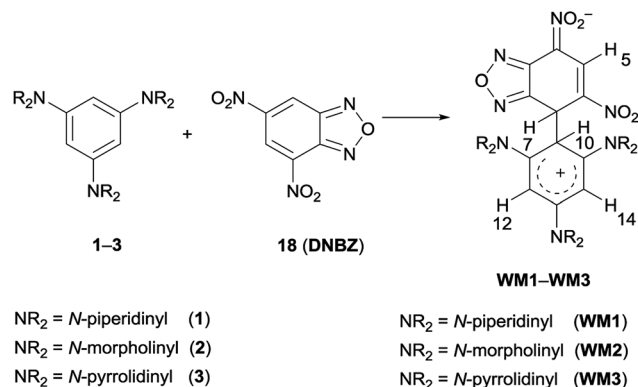
(i.e. 5.54 and 4.93 ppm for ¹H NMR of **WM1**) in both the ¹H and ¹³C NMR spectra are attributable to the restricted rotation about C-2–C-10 bond.[52,53] The same effect was observed for the atoms belonging to the amino rings. The signals, related to H-7, H-10, H-12, H-14 and amino moiety, gradually broadened on increasing the temperature, as a result of an exchange process. The signals coalesce at −5 °C for **WM1** and at −37 °C for **WM2**, then gradually sharpened. In case of **WM1** in CD₂Cl₂ or **WM3** in CDCl₃, the coalescence occurred at +3 °C/+6 °C respectively, and involved H-10, H-12, and H-14 signals, whereas the sharp H-7 signal appeared independent from the temperature, recalling the observed phenomenon, which involved coupling between **1–3** and **DNBF**[13] or **DNTP**[14] Warming the solution from −54 °C to room temperature and cooling again, a spectrum identical to the starting one was obtained indicating the occurrence of a reversible dynamic process.

Furthermore, the coupling between **DNBZ** and 4-(3,5-di(piperidin-1-yl)phenyl)morpholine (**19**) (Scheme 6) was run in the same conditions. The ¹H NMR spectrum of the reaction mixture, recorded at −54 °C, showed a set of signals compatible with those of the two distinct **WM4** and **WM5** zwitterionic intermediates, as shown in Scheme 6, reflecting the same behavior observed for **WM1–WM3**.[13,14]

In principle, also a double attack might occur to give structures **A**- or **C**-like, that might evolve to di-Meisenheimer species **B**- or **D**-like. Significant examples of similar anionic diadducts have been actually reported by coupling between ambient nucleophiles with **DNBF**[54a] or trinitrobenzene.[54b,c] In current case, the signals and their relative integration in the ¹H NMR spectrum, together with the absence of those belonging to unreacted **19**, permit to exclude the presence of the above structures **A–D**.

The structure of the intermediates **WM1–WM5** was confirmed also by ¹³C NMR spectroscopy and/or direct proton to carbon (g-HSQC sequence) correlation experiments (Fig. S26–S35†). In the case of the morpholinyl derivative **WM2**, the ¹H NMR signals belonging to H-7, H-10, H-12, H-14, and to the morpholinyl moiety, appeared broad in the spectrum recorded in CDCl₃ at −54 °C. Thus, the reaction was carried out in CD₂Cl₂ at −80 °C to achieve a better resolution; in this case the coalescence was reached at −33 °C. By comparison, the reaction
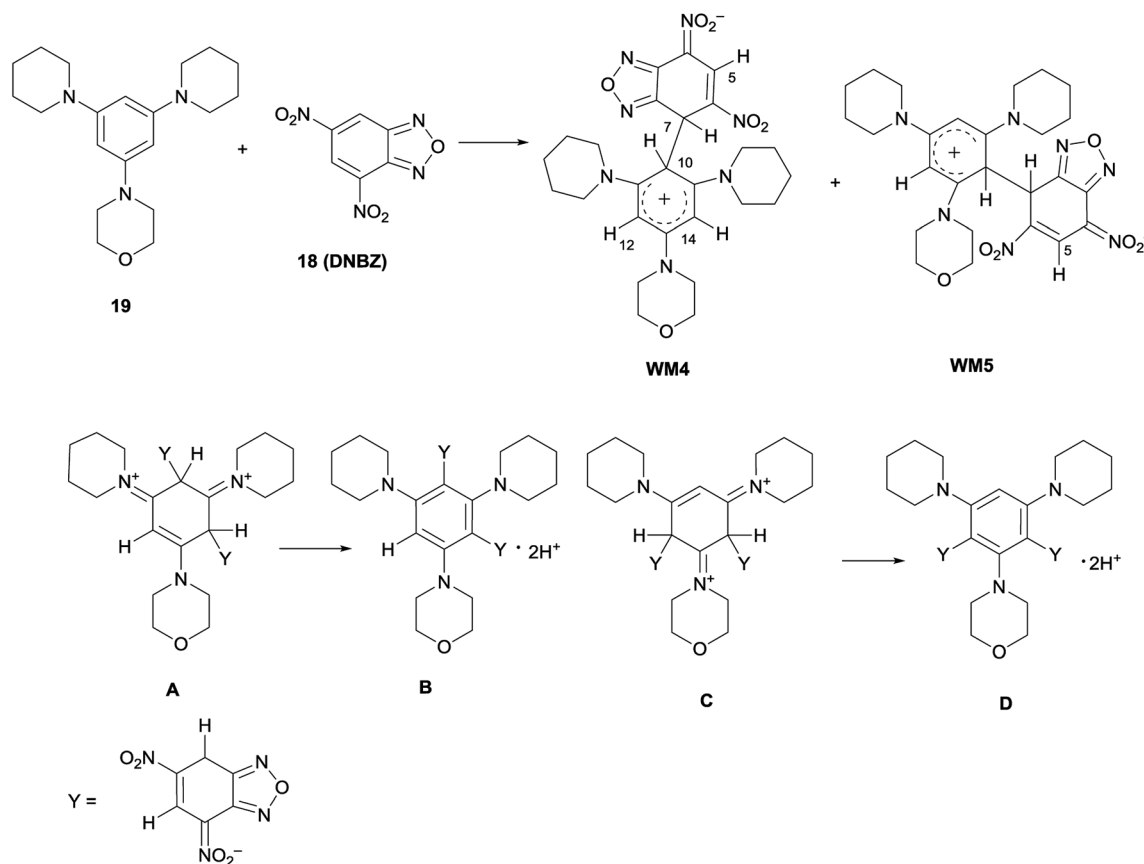
Scheme 6 Zwitterionic reaction intermediates **WM4** and **WM5** formed from **18** and **19** and structure of other possible intermediates.

between **1** and **18** was also carried out in CD$_2$Cl$_2$ at −80 °C. As previously reported for **WMa–c**,[13,14] the signal belonging to H-7 atom remained sharp on varying the temperature. Furthermore, **WM1–WM5** resulted to be unstable when kept in CDCl$_3$ at 25 °C overnight, since the solution presents several ^{1}H NMR signals, belonging to unidentified compounds.

### Reactions of 4,6-dinitrobenzofuroxan (DNBF), 4,6-dinitrotetrazolopyridine (DNTP), and 4,6-dinitrobenzofurazan (DNBZ) with 1,3,5-trihydroxybenzene (12) and 1,3,5-trimethoxybenzene (13)

Based on previous and current findings, which have shown the formation of **WM** intermediates at low temperature between **1–3** and 4,6-dinitrobenzofuroxan (**DNBF**),[13] 4,6-dinitrotetrazolopyridine (**DNTP**),[43] or 4,6-dinitrobenzofurazan (**DNBZ**, see above section), we planned to investigate the behavior of the above electrophiles with **12** and **13**. Each nucleophile/electrophile combination was realized by adding the two reagents directly in the NMR spectroscopy tube at low temperature (−35 °C in CD$_3$CN, or −80 °C in acetone-d$_6$ for the **DNBZ/12** couple) and by ^{1}H NMR monitoring. In all cases, the Meisenheimer **M1–M6** complexes (Scheme 7) were observed and characterized by ^{1}H NMR, ^{13}C NMR, DEPT and/or g-HSQC experiments. In most cases, due to the poor stability in solution at room temperature of these intermediates, the ^{13}C NMR spectrum was recorded at low temperature.

Although the first step of the S$_N$Ar/S$_E$Ar reaction consists in the formation of the **WM** intermediate, the detection of only the **M1–M6** intermediates by NMR measurements at low temperature indicates that **WM6–WM11** species, derived from the coupling with **12** or **13** (Scheme 7), are less stable than **WM1–WM5** (Schemes 5 and 6). The presence of hydroxy- or methoxy-substituents on the carbocyclic ring of **12** and **13** causes very elusive species on the NMR time-scale detection due to the minor stabilization of the Wheland moiety positive charge by hydroxy (or methoxy) substituents with respect to the amino substituents. On the other hand, the **M1–M6** anionic intermediates resulted stable enough, due to the ability to stabilize the negative charge by the moieties derived from **DNBF**, **DNBZ**, and **DNTP**.

Moreover, the ^{1}H NMR spectra recorded at low temperature showed non-equivalence of the hydrogen atoms belonging to the nucleophilic moiety of **M1–M6** and, in case of **M2**, **M4**, and **M6** to methyl groups also. This may be ascribed to rotational constraints at low temperature, about the C–C bond, formed between the nucleophilic and the electrophilic moiety. Coalescence phenomenon was observed on raising temperature, then the signals gradually sharpened. From the proton NMR spectra of **M1–M6**, recorded under dynamic conditions, the free activation energy ($\Delta G^{\#}$) was derived by means of the Eyring equation.[56] The Fig. 2 shows the line shape simulation for **M2** and the $\Delta G^{\#}$ values obtained are reported in Table 1.
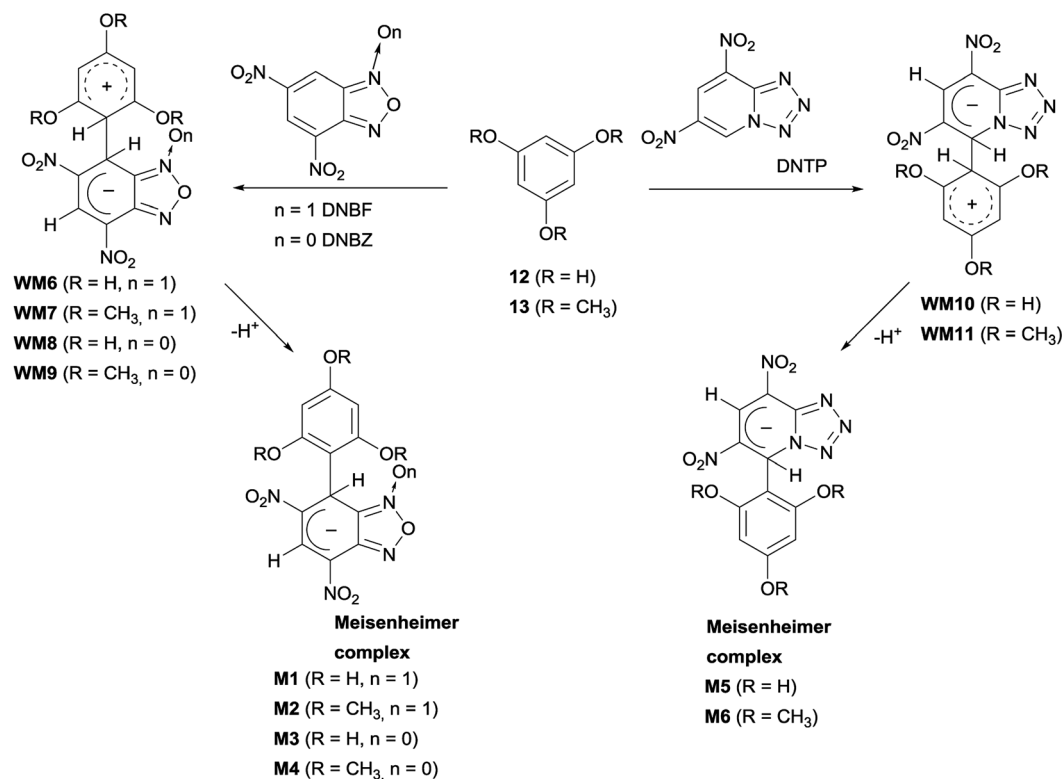
Scheme 7 Reaction intermediates from the reactions of **12** and **13** with DNBF, DNBZ, and DNTP.

The $\Delta G\#$ values obtained are in line with those commonly reported for rotational processes.[57] In particular, slightly different values have been found on changing the electrophile, but appear almost the same by altering the nucleophilic moiety; thus indicating that the rotational constraints are independent from the hydroxy- or methoxy- substituents on the nucleophilic moiety.

Concerning the formation of the σ-adducts, the **M2** and **M4** have previously been obtained by Terrier and coll. in DMSO.[55] In the case of **M2**, the authors observed the spontaneous oxidation to **15** in 50% yield in the same solvent. In the current case, adducts **M2** and **M4** have instead been prepared in CD$_3$CN solution, and **M2** undergo departure of the hydride ion to be completed in about three days. Evolution to **15** was confirmed by spectral data comparison of authentic **15** obtained as shown in Scheme 4. Analogous behavior has been observed for the reaction of **13** with **DNBZ**. These findings agree with those previously reported[55] about the facile oxidation of some **DNBF** and **DNBZ** σ-adducts and provide further examples of formal hydride displacement from an aromatic ring.
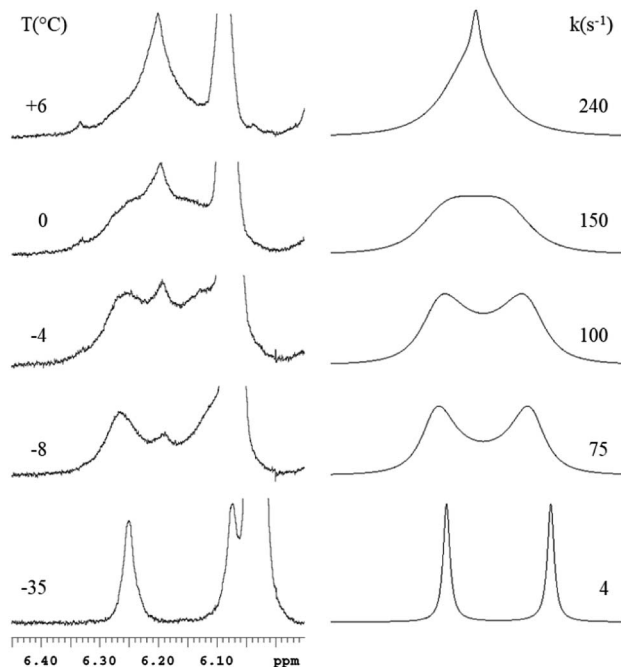

Fig. 2 Left: experimental variable temperature ^{1}H NMR spectra in CDCl$_3$ of **M2**. Right: line-shape simulation obtained with the rate constant indicated. The reported real spectra results partially hidden by the signal of residual starting material.

Table 1 $\Delta G^{\#}$ values for the rotational process around the C–C bond in intermediates **M1–M6**

	$\Delta G^{\#}$ (kcal mol^{-1})	Solvent
M1	13.2 ± 0.2	CD$_3$CN
M2	13.2 ± 0.2	CD$_3$CN
M3	13.9 ± 0.2	CD$_3$COCD$_3$
M4	14.1 ± 0.2	CD$_3$CN
M5	12.4 ± 0.2	CD$_3$CN
M6	12.5 ± 0.2	CD$_3$CN

Conclusions

New compounds, interesting for several potential applications, have been obtained in good yield by aromatic substitution reaction of triamino- and trihydroxybenzene derivatives with 7-chloro-4,6-dinitrobenzofuroxan (**Cl-DNBF**) and 7-chloro-4,6-dinitrobenzofurazan (**Cl-DNBZ**).

Novel **WM** intermediates from the reaction between 1,3,5-triaminobenzenes and 4,6-dinitrobenzofurazan (**DNBZ**) have been detected and characterized by NMR.

Contrarily to what observed by reacting 1,3,5-tri-aminobenzene derivatives and 4,6-dinitrobenzofuroxan, 4,6-dinitrobenzofurazan, or 4,6-dinitrotetrazolopyridine, the reactions between the latter electrophiles and 1,3,5-trihydroxybenzene (or 1,3,5-trimethoxybenzene), carried out directly at low temperature in the NMR tube, did not evidence Wheland–Meisenheimer intermediates, but solely Meisenheimer complexes **M1–M6**. The different behaviour with respect to that of triaminobenzene derivatives may be devoted to the lower ability to stabilize positive charge on the nucleophilic moiety of **WM** intermediates in the hydroxy- or methoxy-substituted benzene species. Further, the low temperature NMR dynamic behaviour of **M1–M6** species showed non-equivalent signals, which, increasing the temperature, gradually broadened to a coalescence situation, until they sharpen again. The observed spectra allowed determine the free activation energy of the restricted rotational process at low temperature.

Experimental section

The ^{1}H and ^{13}C NMR spectra were recorded with a Mercury 400 and Inova 600 (Varian, Palo Alto USA) spectrometers operating at 400, or 600 MHz (for ^{1}H NMR) and 100.56, or 150.80 MHz (for ^{13}C NMR), respectively. J values are given in hertz (Hz). Signal multiplicities were established by DEPT experiments. Chemical shifts were referenced to the solvent [($\delta = 5.31$ and 53.8 ppm for CD$_2$Cl$_2$), ($\delta = 1.96$ and 118.2 ppm for CD$_3$CN), ($\delta = 2.50$ and 39.5 ppm for CD$_3$SOCD$_3$), ($\delta = 2.10$ and 30.2 ppm for CD$_3$COCD$_3$), and ($\delta = 7.26$ and 77.0 ppm for CDCl$_3$) for ^{1}H and ^{13}C NMR, respectively].

The variable-temperature NMR spectra and 2D low temperature spectra were recorded on Mercury 400 or Inova 600 instruments with a direct PFG Probe. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out using a PC version of the DNMR-6 program.[58]

ESI-MS spectra were recorded with a WATERS 2Q 4000 instrument. Chromatographic purifications were carried out on silica gel (0.037–0.063 mm, Merck) columns at medium pressure. Thin layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum foils (Fluka). Melting points were measured on a Stuart SMP3 apparatus and are uncorrected. Solvents were commercial materials (Aldrich or VWR International) if not specified. 1,3,5-Tris(dialkylamino)benzenes **1–3** were prepared as described previously.[13] 7-Chloro-4,6-dinitrobenzofuroxan (**Cl-DNBF**, **4**),[3b] **DNBF**,[12] **DNBZ**,[12] and **DNTP**[14] were synthesized and purified as described in the literature.

Synthesis of 7-chloro-4,6-dinitrobenzofurazan (5)

In a three-necked round bottom flask, equipped with thermometer, dropping funnel, and kept in an ice bath, 0.5 g of 4-chloro-7-nitrobenzofurazan (**ClNBZ**) were introduced and dissolved in conc. H$_2$SO$_4$ 96% (7 mL). The solution was magnetically stirred then a solution of conc. HNO$_3$ 65% (0.75 mL) conc. H$_2$SO$_4$ 96% (2 mL) was slowly drop-wise added. The reaction temperature was maintained at 0 °C during the addition of the sulfonitric mixture. Then the mixture was increased until 40 °C and kept at this temperature for 12 h. The reaction mixture was put into a becker with ice and, once the ice was fused, the solid obtained was isolated by filtration on Buchner funnel, washed with water until the pH of filtrate was neutral, and dried in a desiccator. Chemico-physical data of the solid agreed with literature data.[59]

General procedure for the synthesis of compounds 6–8 and related salts

To a solution of 1,3,5-triaminobenzene derivative (6×10^{-5} mol) in CDCl$_3$ (10 mL), 1.3 eq. of sodium bicarbonate and an equimolar amount of 7-chloro-4,6-dinitrobenzofuroxan (**4**) were added at room temperature. The mixture was magnetically stirred and the reaction progress was monitored through TLC and ^{1}H NMR analysis. After solvent removal, the reaction products were purified by column chromatography on silica gel (FC). Compound **6** was obtained using as eluent first a 6/4 diethyl ether/light petroleum and then diethyl ether; in the case of compound **7**, the eluent was diethyl ether/ethyl acetate (1/1). In the case of the reaction between **3** and **4**, due to the formation of many compounds, only traces of a compound which ^{1}H NMR spectrum, reported below, is compatible with that of **8**, were obtained.

The reaction between equimolar amount of **1** and **4** was carried out also in CDCl$_3$ directly in the NMR spectroscopy tube without base and the corresponding salt **6H$^+$Cl$^-$** was obtained. Picrate salt of **6** (**6H$^+$picrate**) was obtained by adding to **6** equimolar amount of picric acid. The reaction between equimolar amount (7.7×10^{-5} mol) of **1** and **4** dissolved in CH$_2$Cl$_2$ (6 mL) was carried out also at room temperature: immediately the colour of the solution became dark green and after one night a green solid precipitated and was isolated by filtration. Its chemico-physical data agreed with those of compound **6H$^+$Cl$^-$**. A solution of this solid was percolated through Al$_2$O$_3$ (eluent: CH$_3$CN) and the ^{1}H NMR spectrum of the residue was equal to that of the neutral form **6**. Analogous behavior was observed for the reaction between **2** and **4**. Chemico-physical data of the obtained compounds are reported below.

4,6-Dinitro-7-(2,4,6-tripiperidin-1-ylphenyl)-2,1,3-benzoxadiazole 1-oxide (6). Dark green solid, 85% yield, mp > 180 °C (dec.) ^{1}H NMR (CDCl$_3$, 400 MHz, 25 °C), δ (ppm): 8.90 (s, 1H), 6.36 (s, 2H), 3.33 (t, $J = 4.86$ Hz, 4H), 2.75–2.57 (m, 8H), 1.78–1.60 (m, 4H), 1.41–1.18 (m, 14H). ^{13}C NMR (CDCl$_3$, 100.56 MHz, 25 °C), δ (ppm): 155.59, 155.56, 145.1, 141.7, 134.2, 132.5, 128.6, 115.0, 107.9, 102.0, 54.4, 48.9, 26.5, 25.8, 24.4, 24.2. MS (ES$^+$) m/z: 552 [M + H]$^+$, 574 [M + Na]$^+$, 590 [M + K]$^+$; HRMS calc. for C$_{27}$H$_{34}$N$_7$O$_6^+$: 552.2565; found: 552.2562.

4,6-Dinitro-7-(4-(piperidin-1-ium-1-yl)-2,6-di(piperidin-1-yl) phenyl)benzo[c][1,2,5]oxadiazole 1-oxide chloride (6H⁺Cl⁻). ¹H NMR (CDCl₃, 600 MHz, 25 °C), δ (ppm): 8.90 (s, 1H), 7.31 (br.s., 2H), 3.60–3.30 (m, 4H), 2.75–2.66 (m, 4H), 2.66–2.56 (m, 4H), 2.00–1.60 (m, 6H), 1.42–1.32 (m, 4H), 1.32–1.17 (m, 8H). ¹³C NMR (CDCl₃, 150 MHz, 25 °C), δ (ppm): 155.2, 153.6, 144.4, 142.3, 134.3 (br.s.), 132.0 (br.s.), 127.7 (CH), 114.1, 108.3 (br.s.), 90.8 (CH), 53.9 (br.s.), 26.1 (br.s.), 23.6 (br.s.).

1-[3-(3,4-Dihydropyridin-1(2H)-yl)-4-(3-oxido-4,5,6,7-tetrahydro-2,1,3-benzoxadiazol-4-yl)-5-piperidin-1-ylphenyl] piperidinium 2,4,6-trinitrobenzenolate (6H⁺picrate). ¹H NMR (CDCl₃, 600 MHz, 25 °C), δ (ppm): 9.01 (s, 2H), 8.90 (s, 1H), 6.86 (s, 2H), 3.56 (t, J = 5.51 Hz, 4H), 2.69–2.58 (m, 4H), 2.58–2.48 (m, 4H), 2.10–2.00 (m, 4H), 1.80–1.70 (m, 2H), 1.40–1.18 (m, 12H); ¹³C NMR (CDCl₃, 150 MHz, 25 °C), δ (ppm): 158.6, 155.4, 149.2, 144.5, 142.4, 140.3, 134.5, 132.0, 127.8 (CH), 126.5, 126.4 (CH), 116.0, 114.2, 106.7 (CH), 55.2 (CH₂), 54.0 (CH₂), 26.2 (CH₂), 24.1 (CH₂), 23.7 (CH₂), 22.5 (CH₂).

4,6-Dinitro-7-(2,4,6-trimorpholin-4-ylphenyl)-2,1,3-benzoxadiazole 1-oxide (7). Dark green solid, 85% yield, mp > 180 °C (dec.). ¹H NMR (CDCl₃, 400 MHz, 25 °C): δ (ppm): 8.88 (s, 1H), 6.45 (s, 2H), 3.89 (t, J = 4.6 Hz, 4H), 3.48–3.36 (m, 8H), 3.34 (t, J = 4.9 Hz, 4H), 2.80–2.63 (m, 8H); ¹³C NMR (CDCl₃, 100.56 MHz, 25 °C) δ (ppm): 154.3, 153.8, 144.4, 142.5, 133.9, 132.1, 127.7, 127.3, 114.3, 103.0, 66.8, 66.3, 52.9, 48.3. MS (ES⁺) m/z: 558 [M + H]⁺, 580 [M + Na]⁺, 596 [M + K]⁺; HRMS calcd for C₂₄H₂₈N₇O₉⁺: 558.1943; found: 558.1940.

7-(2,6-Dimorpholino-4-(morpholino-4-ium)phenyl)-4,6-dinitrobenzo[c][1,2,5]oxadiazole 1-oxide chloride (7H⁺Cl⁻). Dark green solid, ¹H NMR (CD₂Cl₂, 400 MHz, 25 °C), δ (ppm): 8.91 (s, 1H), 7.19 (s, 2H), 4.16 (t, J = 4.6 Hz, 4H), 3.41–3.34 (m, 4H), 3.42–3.30 (m, 8H), 2.78–2.70 (m, 4H) 2.70–2.62 (m, 4H); ¹H NMR (CD₃CN, 400 MHz, 25 °C), δ (ppm): 8.85 (s, 1H), 7.02 (s, 2H), 4.02 (t, J = 4.7 Hz, 4H), 3.50 (m, t, J = 4.7 Hz, 4H), 3.41–3.30 (m, 8H), 2.77–2.65 (m, 8H); ¹³C NMR (CD₃CN, 100.56 MHz, 25 °C), δ (ppm): 154.6, 151.1 (br.s.), 146.0, 144.1, 136.0, 131.3, 129.7, 129.5, 115.2, 107.0 (br.s.), 67.3, 65.8 (br. s.), 53.3, 52.0 (br.s.).

4,6-Dinitro-7-(2,4,6-tripyrrolidin-1-ylphenyl)-2,1,3-benzoxadiazole 1-oxide (8). ¹H NMR (CDCl₃, 400 MHz, 25 °C), δ (ppm): 8.98 (s, 1H), 5.96 (s, 2H), 3.42–3.35 (m, 4H), 2.95–2.80 (m, 4H), 2.06–1.97 (m, 4H) 1.75–1.55 (m, 8H). The signals in the ¹H NMR spectrum of the mixture obtained by adding in the NMR tube equimolar amount of 3 and 4, and ascribable to 8H⁺Cl⁻ are the following: ¹H NMR (CD₂Cl₂, 400 MHz, 0 °C), δ (ppm): 8.87 (s, 1H), 6.22 (s, 2H), 3.52–2.80 (m, 12H), 2.23–1.70 (m, 12H).

Variable temperature NMR experiments for the reaction between 1–3 and 5. Typical procedure

Cl-DNBF (4, 0.038 mmol) was dissolved in CD₂Cl₂ (1 mL) and introduced in a NMR spectroscopy tube, that was inserted in the NMR probe. When the probe temperature reached −88 °C, an equimolar amount of 1,3,5-tris(morpholinyl)benzene (2) was added to the solution, that became blue then dark green, and the ¹H NMR spectrum of the resulting solution was quickly recorded. The system was monitored with times and the spectra

were recorded at different temperatures until 25 °C was reached. The spectra showed the presence of signals ascribable to the salt 7H⁺Cl⁻. At low temperature the signals in the spectrum showed non-equivalence of the hydrogen atoms belonging to the carbocyclic ring; on raising the temperature the signals broadened until to reach a coalescence situation. After, the peaks became sharp and a re-cooling produced again their broadening until to their splitting as observed after the reagents mixing at low temperature. The systems were monitored until no further change could be detected in the recorded spectra.

General procedure for the synthesis of compounds 9–11

To a solution of 1,3,5-triaminobenzene derivative (0.14 mmol) in CD₃CN (10 mL), 7-chloro-4,6-dinitrobenzofurazan (5, 0.07 mmol) was added at room temperature. The mixture was magnetically stirred and the reaction progress was monitored through TLC and ¹H NMR analysis. After solvent removal, the reaction products were purified by column chromatography on silica gel (FC). Compound 9 was obtained using dichloromethane as eluent; in the case of compound 10, the eluent was dichloromethane/ethyl acetate (from 10/1 until 8/2). In the case of the reaction between 3 and 5, due to its easy decomposition to many unidentifiable compounds, compound 11 was only characterized by ¹H NMR of the crude reaction mixture after solvent removal.

5,7-Dinitro-4-(2,4,6-tri(piperidin-1-yl)phenyl)benzo[c][1,2,5] oxadiazole (9). Dark blue solid, 75% yield, mp > 180 °C (dec.). ¹H NMR (CD₃CN, 599.7 MHz, 25 °C, δ (ppm): 8.94 (s, 1H), 6.55 (s, 2H), 3.38–3.31 (m, 4H), 2.72–2.64 (m, 4H), 2.64–2.56 (m, 4H), 1.74–1.63 (m, 6H), 1.34–1.25 (m, 6H), 1.20–1.10 (m, 6H). ¹³C NMR (CD₃CN, 100.6 MHz, 25 °C, selected data), δ (ppm): 155.5, 135.4, 128.7 CH), 104.1 (CH), 54.2 (NCH₂), 49.7 (NCH₂), 26.7 (NCH₂CH₂), 26.2 (NCH₂CH₂), 24.9 (NCH₂CH₂CH₂), 24.5 (NCH₂CH₂CH₂). MS (ES⁺) m/z: 536 [M + H]⁺,558 [M + Na]⁺; HRMS calc. for C₂₇H₃₄N₇O₅⁺: 536.2616; found: 536.2618.

5,7-Dinitro-4-(2,4,6-trimorpholinophenyl)benzo[c][1,2,5]oxadiazole (10). Dark blue solid, 75% yield, mp > 180 °C (dec.). ¹H NMR (CD₃CN, 599.7 MHz, 25 °C), δ (ppm): 8.95 (s, 1H), 6.73 (s, 2H), 3.92–3.79 (m, 4H), 3.40–3.33 (m, 4H), 3.29–3.18 (m, 8H), 2.77–2.57 (m, 8H). ¹³C NMR (CD₃CN, 100.6 MHz, 25 °C). δ (ppm): 155.5, 154.1, 153.0, 147.2, 144.0, 135.8, 134.1, 128.5 (CH), 105.0, 104.9 (CH), 67.3 (CH₂), 67.1 (CH₂), 53.1(CH₂), 49.0(CH₂). MS (ES⁺) m/z: 542 [M + H]⁺, 564 [M + Na]⁺;HRMS calc. for C₂₄H₂₈N₇O₈⁺: 542.1994; found: 542.1997.

5,7-Dinitro-4-(2,4,6-tri(pyrrolidin-1-yl)phenyl)benzo[c][1,2,5] oxadiazole (11). ¹H NMR (CD₃CN, 300 MHz, 25 °C): δ, ppm: 8.93 (s, 1H), 6.41 (s, 2H), 4.00–3.00 (m, 12H), 2.10–1.80 (m, 12H).

General procedure for the synthesis of compounds 14–17

To a magnetically stirred solution of 12 or 13 (2 × 10⁻⁴ mol) dissolved in CD₃CN (5 mL and 10 mL, respectively), an equimolar amount of 7-chloro-4,6-dinitrobenzofuroxan (4) or 7-chloro-4,6-dinitrobenzofuroxan (5), was added at room temperature. ¹H-NMR analysis and TLC were used to monitor the reaction progress. Compound 14 was purified by precipitation from diethyl ether and light petroleum. Compound 15 was

purified by column chromatography on silica gel (FC), using as eluent diethyl ether/light petroleum (7 : 3). Compound **16** was isolated from the concentrated crude after treatment with a little amount of CH_2Cl_2 and removal of the unreacted phloroglucinol by filtration. Compound **17** was purified by column chromatography on silica gel (FC), using as eluent diethyl ether/light petroleum (2/8) then CH_2Cl_2/ethyl acetate 9/1. Although the reactions carried out in NMR spectroscopy tube showed conversion almost quantitative, the yields in isolated product were lower likely due to the purification methods, but we did not focus our efforts on yields optimization.

All the products were characterized by usual spectroscopic methods. Chemico-physical data are reported below.

2-(5,7-Dinitro-3-oxido-2,1,3-benzoxadiazol-4-yl)benzene-1,3,5-triol (14). Red greasy solid, 54% yield. ^1H NMR (CD_3CN, 300 MHz, 25 °C), δ (ppm): 8.78 (s, 1H), 7.59 (br.s., 3H, OH), 6.02 (s, 1H). ^{13}C NMR (CD_3CN, 100.56 MHz, 25 °C), δ (ppm): 162.7, 157.6, 146.0, 144.3, 135.8, 129.8, 129.1, 116.4, 95.9, 95.7. MS (ES^+) m/z: 373 $[M + Na]^+$, 389 $[M + K]^+$. MS (ES^-) m/z: 349 $[M - H]^-$; HRMS calcd for $C_{12}H_7N_4O_9^+$: 351.0208; found: 351.0205.

4,6-Dinitro-7-(2,4,6-trimethoxyphenyl)-2,1,3-benzoxadiazole 1-oxide (15). Red solid, 70% yield. ^1H NMR (CD_3CN, 300 MHz, 25 °C), δ (ppm): 8.80 (s, 1H), 6.34 (s, 2H), 3.92 (s, 3H), 3.73 (s, 6H, OCH_3). ^{13}C NMR (CD_3CN, 150.80 MHz, 25 °C), δ (ppm): 166.1, 159.9, 146.0, 144.6, 135.9, 129.2, 129.0, 116.3, 97.9, 92.0, 56.8, 56.5. MS (ES^+) m/z: 415 $[M + Na]^+$; HRMS calcd for $C_{15}H_{13}N_4O_9^+$: 393.0677; found: 393.0675.

2-(5,7-Dinitrobenzo[c][1,2,5]oxadiazol-4-yl)benzene-1,3,5-triol (16). Bordeaux red solid, 86% yield; ^1H NMR: (CD_3CN, 599.7 MHz, 25 °C), δ (ppm): 8.92 (s, 1H), 7.60 (br. s., 3H, OH), 6.10 (s, 2H). ^{13}C NMR: (CD_3CN, 150.8 MHz, 25 °C), δ (ppm): 162.2, 157.1, 152.1, 148.0, 143.8, 136.3, 130.9, 128.2 (CH), 99.1, 96.0 (CH). MS (ES^+) m/z: 357 $[M + Na]^+$; HRMS calcd for $C_{12}H_7N_4O_8^+$: 335.0258; found: 335.0260.

5,7-Dinitro-4-(2,4,6-trimethoxyphenyl)benzo[c][1,2,5]oxadiazole (17). Bordeaux red solid, 90% yield. ^1H NMR (CD_3CN, 399.9 MHz, 25 °C), δ (ppm): 8.93 (s, 1H), 6.40 (s, 2H), 3.93 (s, 3H, OCH_3), 3.71 (s, 6H, OCH_3). ^{13}C NMR (CD_3CN, 100.6 MHz, 25 °C), δ (ppm): 165.7, 159.5, 152.1, 148.1, 143.8, 136.4, 130.4, 128.1 (CH), 101.3, 92.5 (CH), 56.7 (OCH_3), 56.4 (OCH_3). MS (ES^+) m/z: 399 $[M + Na]^+$; HRMS calcd for $C_{15}H_{13}N_4O_8^+$: 377.0728; found: 377.0731.

Formation and detection of Wheland–Meisenheimer intermediates WM1–WM5

A solution of 1,3,5-triaminobenzene derivative (0.025 mmol) was dissolved in $CDCl_3$ or CD_2Cl_2 (1 mL) and introduced in a NMR spectroscopy tube that was inserted in the NMR probe. When the probe temperature reached −54 °C (in $CDCl_3$) or −80 °C (CD_2Cl_2), an equimolar amount of **DNBZ** (5.17 mg, 0.025 mmol) was added to the solution, that became dark red-coloured, and the ^1H NMR spectrum was quickly recorded. The system was monitored at various times and at different temperatures until 25 °C. Immediately after the mixing, the spectrum showed the appearance of new signals, ascribed to zwitterionic intermediates **WM**, as confirmed by ^{13}C NMR,

DEPT or g-HSQC experiments. On raising the temperature, signals belonging to **WM** gradually broadened and the return to the previous temperature lead to the re-appearance of sharp signals. Complexes **WM1–WM5** resulted not stable for long time in solution, as noted when they were kept at room temperature for a night to record the ^{13}C NMR spectra: the day after, the spectrum was complicated by the presence of new signals belonging to unidentified compounds. In the case of formation of **WM4** and **WM5** the integration of the signals revealed that the two species were formed in 42 : 58 percent relative molar ratio but we were not able to assign the signals of one or the other of these structures, thus, below, we describe the signals as belonging to the major (Maj) or the minor species (Min). The names of complexes **WM1–WM5** have been created from ChemDraw Professional 17.1 version by drawing the canonical resonance form bearing the negative charge of the Meisenheimer moiety situated on the nitro group in *para* position with respect to the new bond formed and the positive charge of the Wheland moiety situated on the nitrogen atom of the amino substituent in *para* position to the new bond formed.

(6-Nitro-7-(4-(piperidin-1-ium-1-ylidene)-2,6-di(piperidin-1-yl)cyclohexa-2,5-dien-1-yl)benzo[c][1,2,5]oxadiazol-4(7H)-yli-dene)azinate (WM1). ^1H NMR (400 MHz, $CDCl_3$, −54 °C), δ (ppm): 9.09 (s, 1H, H-5), 5.54 (s, 1H, H-10), 5.00 (br.s, 1H, H-12 or H-14), 4.93 (s, 1H, H-7), 4.82 (br.s, 1H, H-12 or H-14), 4.25–4.01 (m, 1H), 3.93–3.75 (m, 2H), 3.70–2.97 (ms, 9H), 1.95–1.32 (m, 18H). ^{13}C NMR ($CDCl_3$, 100.6 MHz, −43 °C), δ (ppm): 161.0, 160.3, 159.4, 156.7, 146.5, 135.9 (CH), 120.2, 113.9, 91.0 (CH), 89.5 (CH), 49.9, 49.7, 49.5, 49.5 (2 sign. overl.), 49.3 (2 sign. overl.), 43.5 (CH, C-7), 40.2, (CH, C-10), 26.4, 26.3, 26.0, 24.4, 24.1, 24,0, 23.7 (2 signals overl.). ^1H NMR (400 MHz, CD_2Cl_2, −80 °C), δ (ppm): 8.91 (s, 1H, H-5), 5.52 (s, 1H, H-10), 4.90 (br.s, 2H, H-12 or H-14 and H-7), 4.75 (s, 1H, H-12 or H-14), 4.12–3.99 (m, 1H), 3.91–3.78 (m, 2H), 3.65–3.32 (ms, 3H), 3.23–2.85 (m, 6H), 1.99–1.30 (m, 6H). ^{13}C NMR (CD_2Cl_2, 100.6 MHz, −80 °C): δ, ppm: 160.2, 159.8, 159.0, 146.3, 146.2, 135.4 (CH), 120.3, 113.2, 90.2 (CH), 89.1 (CH), 49.5 (CH_2), 49.3 (CH_2), 49.2 (CH_2), 49.1 (2 sign. overl., CH_2), 48.4 (CH_2), 43.2 (CH, C-7), 39.4, (CH, C-10), 26.9 (CH_2), 26.3 (CH_2), 25.9 (2 sign. overl., CH_2), 24.9 (CH_2), 24.0 (CH_2), 23.9 (2 sign. overl., CH_2), 23.4 (CH_2).

(7-(2,6-Dimorpholino-4-(morpholino-4-ium)cyclohexa-2,5-dien-1-yl)-6-nitrobenzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (WM2). ^1H NMR (600 MHz, CD_2Cl_2, −80 °C), δ (ppm): 8.97 (s, 1H, H-5), 5.58 (s, 1H), 4.98 (s, 1H), 4.94 (s, 1H), 4.74 (s, 1H), 4.50–4.34 (m, 1H), 4.10–2.81 (m.s, 23H). ^{13}C NMR (CD_2Cl_2, 100.6 MHz, −80 °C): δ, ppm: 161.3, 160.8, 160.6, 146.2, 135.8, 135.5 (CH), 119.3, 113.3, 91.6 (CH), 90.3 (CH), 66.7 (br.s., CH_2), 65.5 (br.s., CH_2), 64.5 (br.s., CH_2, signals overlapped), 49.1 (br.s., CH_2, signals overlapped), 44.2 (CH), 39.2, (CH).

(6-Nitro-7-(4-(pyrrolidin-1-ium-1-ylidene)-2,6-di(pyrrolidin-1-yl)cyclohexa-2,5-dien-1-yl)benzo[c][1,2,5]oxadiazol-4(7H)-yli-dene)azinate (WM3). ^1H NMR (400 MHz, $CDCl_3$, −54 °C), δ (ppm): 8.91 (s, 1H, H-5), 5.03 (d, 1H, J = 2.9 Hz, H-7), 4.82 (s, 1H, H-12 or H-14), 4.43 (s, 1H, H-12 or H-14), 4.38–4.30 (m, 1H, NCH), 4.20 (s, 1H, H-10), 3.79–3.67 (m, 1H, NCH), 3.51–3.38 (m, 3H, NCH), 3.38–3.29 (m, 1H, NCH), 3.29–3.19 (m, 1H, NCH), 3.19–3.03 (m, 2H, NCH_2), 3.03–2.90 (m, 2H, NCH_2), 2.90–2.80

(m, 1H, NCH), 2.20–2.05 (m, 4H, NCH$_2$CH$_2$), 2.05–1.87 (m, 8H, NCH$_2$CH$_2$). ^{13}C NMR (CDCl$_3$, 100.6 MHz, −54 °C), δ (ppm): 158.2, 155.4, 155.2, 150.7, 134.1 (CH), 118.7, 113.8, 109.3, 104.8, 88.8 (CH), 87.6 (CH), 49.4 (CH$_2$), 49.2 (CH$_2$), 48.87 (CH$_2$), 48.86 (CH$_2$), 48.76 (CH$_2$), 48.4 (CH$_2$), 45.1 (CH, C-10), 41.0, (CH, C-7), 26.0 (CH$_2$), 25.7 (CH$_2$), 24.83 (CH$_2$), 24.79 (CH$_2$), 24.7 (CH$_2$), 24.6 (CH$_2$).

(7-(4-(Morpholino-4-ium)-2,6-di(piperidin-1-yl)cyclohexa-2,5-dien-1-yl)-6-nitrobenzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (WM4) and (7-(2-morpholino-4-(piperidin-1-ium-1-ylidene)-6-(piperidin-1-yl)cyclohexa-2,5-dien-1-yl)-6-nitrobenzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (WM5). Signals belonging to the major and minor compound present in the reaction mixture in 58/42 molar ratio are hereafter indicated as Maj and Min, respectively.

^{1}H NMR (400 MHz, CDCl$_3$, −54 °C), δ (ppm): 9.12 (s, 1H Min, H-5), 9.08 (s, 1H Maj, H-5), 5.61 (br.s., 1H Maj, H-12 or H-14), 5.56 (br.s., 1H Min, H-12 or H-14), 5.04 (s., 2H Maj + Min, H-7), 4.98 (br.s., 2H Maj + Min, H-12 or H-14), 4.84 (s, 1H Maj, H-10), 4.76 (s, 1H Min, H-10), 4.23–2.81 (m.s, 16H Maj + Min, OCH$_2$ and NCH$_2$), 2.00–1.31 (m.s, 12H Maj + Min, NCH$_2$CH$_2$, NCH$_2$CH$_2$CH$_2$). g-HSQC (CDCl$_3$, −54 °C): ^{1}H–^{13}C correlations: 136.5–9.12, 136.3–9.08, 93.2–5.61, 91.3–5.56, 44.1–5.04, 91.9–4.98, 89.9–4.98, 40.5–4.84, 39.9–4.76, and 66.5–3.65, 66.4–3.62, 66.2–3.83, 65.3–3.62, 50.1–3.24, 50.0–3.09, 49.97–3.54, 49.87–3.85, 48.3–2.91, 26.8–1.77, 26.6–1.63, 24.3–1.60, 24.2–1.84, 26.5–1.45.

Study on the formation of σ-complexes M1–M6 by NMR spectroscopy

4,6-Dinitrobenzofuroxan (**DNBF**), 4,6-dinitrobenzofurazan (**DNBZ**), or 4,6-dinitrotetrazolopyridine (**DNTP**) (~4.4 × 10^{-5} mol) was dissolved in CD$_3$CN (0.3 mL) and the solution was cooled at −35 °C. This solution was added to an equimolar amount of compound **12** (or **13**) dissolved in CD$_3$CN (0.7 mL) and directly prepared in the NMR spectroscopy tube at −35 °C. The ^{1}H NMR spectra were recorded immediately after the mixing of the reagents and successively at intervals of 5–10 °C, from −35 °C to room temperature. At low temperature the spectrum showed non-equivalence of the hydrogen atoms belonging to the carbocyclic ring; on raising the temperature the signals broadened until to reach a coalescence situation. After, the peaks became sharp and a re-cooling produced again their broadening until to their splitting, as observed after the reagents mixing at low temperature. Complexes **M1** and **M3** were obtained in about 90% yield (calculated from ^{1}H NMR spectrum) while **M2** and **M4** are formed in CD$_3$CN in about 50% yield and, if kept in solution for three days or one night, respectively, evolved to the relevant substitution product **15** or **17**, as ascertained by comparison with authentic samples. ^{13}C NMR spectrum of **M4** has not been reported because, recorded in acetonitrile during one night, it showed presence of signals belonging to the starting nucleophile and the substitution product **17**. The combination **DNBZ/12** was carried out in CD$_3$COCD$_3$ from −80 °C to +25 °C and also in this case the ^{1}H NMR spectrum recorded after having collected ^{13}C NMR spectrum overnight showed presence of new signals belonging to

unidentified compounds; the ^{13}C NMR signals reported below for **M3** have been selected and tentatively ascribed. Reactions of **12** and **13** with **DNBF** were also carried out at 25 °C in DMSO-d$_6$. Herein are reported NMR data obtained for complexes **M1–M6**; see ESI† section for further details.

(6-Nitro-1-oxido-7-(2,4,6-trihydroxyphenyl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (M1). Red/orange solution, ^{1}H NMR (CD$_3$CN, 400 MHz, −35 °C), δ (ppm): 8.23 (d, J = 1.2 Hz, 1H), 7.04 (br.s, 3H), 5.90 (d, J = 1.9 Hz, 1H), 5.78 (d, J = 1.2 Hz, 1H), 5.76 (d, J = 1.9 Hz, 1H). ^{1}H NMR (DMSO-d$_6$, 400 MHz, 25 °C), δ (ppm): 8.57 (s, 1H), 5.68 (s, 1H), 5.65 (s, 2H). ^{13}C NMR (CD$_3$CN, 100.56 MHz, −35 °C) δ (ppm): 158.7, 157.7, 157.2, 147.4, 141.9, 123.7, 114.1, 113.5, 97.1, 94.5, 94.2, 29.3.

(6-Nitro-1-oxido-7-(2,4,6-trimethoxyphenyl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (M2). Red solution, ^{1}H NMR (CD$_3$CN, 400 MHz, −35 °C), δ (ppm): 8.27 (s, 1H), 6.25 (s, 1H), 6.07 (s, 1H), 5.84 (s, 1H), 3.91 (s, 3H), 3.76 (s, 3H), 3.53 (s, 3H). ^{1}H NMR (DMSO-d$_6$, 400 MHz, 25 °C) δ (ppm), δ (ppm): 8.61 (s, 1H), 6.17 (s, 2H), 5.79 (s, 1H), 3.73 (s, 6H), 3.70 (s, 3H). ^{13}C NMR (DMSO-d$_6$, 150.80 MHz, 25 °C), δ (ppm): 161.2, 160.3, 149.7, 131.0, 127.3, 114.1, 110.3, 105.1, 91.4, 55.2, 55.1 (two signals overlapped), 28.8.

(6-Nitro-7-(2,4,6-trihydroxyphenyl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (M3). Red solution, ^{1}H NMR (CD$_3$COCD$_3$, 400 MHz, −10 °C), δ (ppm): 8.40 (d, J = 1.4 Hz, 1H), 6.41 (d, J = 1.4 Hz, 1H), 6.10 (br.s., 1H), 5.86 (br.s., 1H), 4.47 (br.s., OH). ^{13}C NMR (CD$_3$COCD$_3$, 150.8 MHz, 25 °C), δ (ppm): 158.1, 157.2, 152.7, 148.3, 144.1, 137.8, 128.6 (CH), 128.5, 96.4 (CH), 30.7 (CH).

(6-Nitro-7-(2,4,6-trimethoxyphenyl)benzo[c][1,2,5]oxadiazol-4(7H)-ylidene)azinate (M4). Red solution, ^{1}H NMR (CD$_3$CN, 400 MHz, −35 °C), δ (ppm): 8.31 (d, J = 1.4 Hz, 1H, H-7), 6.29 (d, J = 2.3 Hz, 1H, H-12 or 14), 6.17 (d, J = 1.4 Hz, 1H, H-10), 6.06 (d, J = 2.3 Hz, 1H, H-12 or 14), 3.94 (s, 3H, CH$_3$), 3.77 (s, 3H, CH$_3$), 3.46 (s, 3H, CH$_3$).

(6-Nitro-5-(2,4,6-trihydroxyphenyl)tetrazolo[1,5-a]pyridin-8(5H)-ylidene)azinate (M5). Red solution, ^{1}H NMR (CD$_3$CN, 600 MHz, −35 °C), δ (ppm): 8.49 (s, 1H), 7.48 (s, 1H), 5.93 (s, 1H), 5.78 (s, 1H). ^{13}C NMR (CD$_3$CN, 150.80 MHz, −35 °C), δ (ppm): 159.7, 157.3, 153.6, 142.8, 128.0, 127.4, 104.5, 102.3, 94.6, 93.9, 53.7, 30.4.

(6-Nitro-5-(2,4,6-trimethoxyphenyl)tetrazolo[1,5-a]pyridin-8(5H)-ylidene)azinate (M6). Red solution, ^{1}H NMR (CD$_3$CN, 400 MHz, −35 °C), δ (ppm): 8.52 (s, 1H), 7.61 (s, 1H), 6.27 (br.s, 1H), 6.09 (br.s, 1H), 3.95 (br.s, 3H), 3.78 (s, 3H), 3.51 (br.s, 3H). ^{13}C NMR (CD$_3$CN, 150.80 MHz, −35 °C), δ (ppm): 159.7, 157.3, 153.6, 142.8, 128.0, 127.4, 104.5, 102.3, 94.6, 93.9, 53.7.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Notes and references

1 G. N. Nikonov and S. Bobrov, 1,2,5-Oxadiazoles, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K.Taylor, Elsevier, 2008, Vol. 5, p. 315.

2 (a) A. Gasco and A. J. Boulton, *Adv. Heterocycl. Chem.*, 1981, **29**, 251; (b) P. B. Ghosh, B. Terna and M. W. Whitehouse, *Med. Res. Rev.*, 1981, **2**, 158.

3 (a) H. Cerecetto and W. Porcal, *Mini-Rev. Med. Chem.*, 2005, **5**, 57; (b) E. Chugunova, C. Boga, I. Sazykin, S. Cino, G. Micheletti, A. Mazzanti, M. Sazykina, A. Burilov, L. Khmelevtsova and N. Kostina, *Eur. J. Med. Chem.*, 2015, **93**, 349.

4 C. Medana, A. Di Stilo, S. Visentin, R. Fruttero, A. Gasco, D. Ghigo and A. Bosia, *Pharm. Res.*, 1999, **16**, 956.

5 (a) J. F. Callan, A. P. de Silva, J. Ferguson, A. J. M. Huxley and A. M. O'Brien, *Tetrahedron*, 2004, **60**, 11125; (b) F. Davì and D. Rinaldi, *J. Elastoplast.*, 2015, **120**, 197.

6 C. K. Lowe-Ma, R. A. Nissan and W. S. Wilson, *J. Org. Chem.*, 1990, **55**, 3760.

7 (a) F. Terrier, *Nucleophilic Aromatic Displacement*, ed. H. Feuer, VCH, New York, 1991; (b) F. Terrier, *Modern Nucleophilic Aromatic Substitution*, John Wiley & Sons, New York, 2013.

8 F. Terrier, S. Lakhdar, T. Boubaker and R. Goumont, *J. Org. Chem.*, 2005, **70**, 6242.

9 S. Lakhdar, R. Goumont, F. Terrier, T. Boubaker, J. M. Dust and E. Buncel, *Org. Biomol. Chem.*, 2007, **5**, 1744.

10 F. Terrier, *Chem. Rev.*, 1982, **82**, 77.

11 E. Buncel, J. M. Dust and F. Terrier, *Chem. Rev.*, 1995, **95**, 2261.

12 C. Boga and L. Forlani, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1408.

13 C. Boga, E. Del Vecchio, L. Forlani, A. Mazzanti and P. E. Todesco, *Angew. Chem., Int. Ed.*, 2005, **44**, 3285.

14 C. Boga, E. Del Vecchio, L. Forlani, A. Mazzanti, C. Menchen Lario, P. E. Todesco and S. Tozzi, *J. Org. Chem.*, 2009, **74**, 5568.

15 (a) H. Mayr and M. Patz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 938; (b) H. Mayr, B. Kempf and A. R. Ofial, *Acc. Chem. Res.*, 2003, **36**, 66; (c) H. Mayr, M. Patz, M. F. Gotta and A. R. Ofial, *Pure Appl. Chem.*, 1998, **70**, 1993; (d) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remmenikov and N. Schimmel, *J. Am. Chem. Soc.*, 2001, **123**, 9500; (e) H. Mayr and A. R. Ofial, *Acc. Chem. Res.*, 2016, **49**, 952 and ref. therein;(f) H. Mayr, *Tetrahedron*, 2015, **71**, 5095.

16 (a) F. Terrier, S. Lakhdar, R. Goumont, T. Boubaker and E. Buncel, *Chem. Commun.*, 2004, 2586; (b) S. Lakhdar, R. Goumont, F. Terrier, T. Boubaker, J. M. Dust and E. Buncel, *Org. Biomol. Chem.*, 2007, **5**, 1744.

17 C. Boga, E. Del Vecchio, L. Forlani, R. Goumont, F. Terrier and S. Tozzi, *Chem.–Eur. J.*, 2007, **13**, 9600.

18 L. Forlani, C. Boga, A. Mazzanti and N. Zanna, *Eur. J. Org. Chem.*, 2012, **6**, 1123.

19 A. Hagfeldt, G. Boschloo, L. Sun, L. Kloo and H. Pettersson, *Chem. Rev.*, 2010, **110**, 6595.

20 G. S. He, L.-S. Tan, Q. Zheng and P. N. Prasad, *Chem. Rev.*, 2008, **108**, 1245.

21 A. K. S. Mehilal, R. B. Salunk and N. Sikder, *New J. Chem.*, 2001, **25**, 1549.

22 A. K. S. Mehilal, R. B. Salunke and N. Sikder, *J. Energ. Mater.*, 2002, **20**, 39.

23 G. Micheletti, S. Bordoni, E. Chugunova and C. Boga, *Molecules*, 2017, **22**, 684.

24 F. Effenberger and R. Niess, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 1067.

25 F. Effenberger, *Acc. Chem. Res.*, 1989, **22**, 27.

26 F. Effenberger and R. Niess, *Chem. Ber.*, 1968, **101**, 3787.

27 T. Yamaoka, H. Hosoya and S. Nagakura, *Tetrahedron*, 1968, **24**, 6203.

28 T. Yamaoka, H. Hosoya and S. Nagakura, *Tetrahedron*, 1970, **26**, 4125.

29 W. Knoche, W. Sachs and S. Vogel, *Bull. Soc. Chim. Fr.*, 1988, 377.

30 W. Knoche, W. W. Schoeller, R. Schomaecker and S. Vogel, *J. Am. Chem. Soc.*, 1988, **110**, 7484.

31 W. Sachs, W. Knoche and S. Herrmann, *J. Chem. Soc., Perkin Trans. 2*, 1991, **2**, 701.

32 D. T. Glatzhofer, D. Allen and R. W. Taylor, *J. Org. Chem.*, 1990, **55**, 6229.

33 P. Menzel and F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 922.

34 F. Effenberger, P. Menzel and W. Seufert, *Chem. Ber.*, 1979, **112**, 1660.

35 R. Niess, K. Nagel and F. Effenberger, *Tetrahedron Lett.*, 1968, 4265.

36 F. Effenberger, K. E. Mack, K. Nagel and R. Niess, *Chem. Ber.*, 1977, **110**, 165.

37 P. Fkher, K. E. Mack, E. Mhsner and F. Effenberger, *Chem. Ber.*, 1977, **110**, 181.

38 P. Menzel and F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 62.

39 F. Effenberger, W. Agster, P. Fischer, K. H. Jogun, J. J. Stezowski, E. Daltrozzo and G. Kollmannsberger-von Nell, *J. Org. Chem.*, 1983, **48**, 4649.

40 C. Boga, L. Forlani, S. Tozzi, E. Del Vecchio, A. Mazzanti, M. Monari and N. Zanna, *Curr. Org. Chem.*, 2014, **18**, 512.

41 C. Boga, E. Del Vecchio and L. Forlani, *Eur. J. Org. Chem.*, 2004, 1567.

42 C. Boga, E. Del Vecchio, L. Forlani and S. Tozzi, *J. Org. Chem.*, 2007, **72**, 8741.

43 L. Forlani, C. Boga, E. Del Vecchio, A. L. T. D. Ngobo and S. Tozzi, *J. Phys. Org. Chem.*, 2007, **20**, 201.

44 C. Boga, E. Del Vecchio, S. Tozzi, L. Forlani, M. Monari, G. Micheletti and N. Zanna, *ARKIVOC*, 2014, (iv), 51.

45 E. Del Vecchio, C. Boga, L. Forlani, S. Tozzi, G. Micheletti and S. Cino, *J. Org. Chem.*, 2015, **80**, 2216.

46 C. Boga, G. Micheletti, S. Cino, S. Fazzini, L. Forlani, N. Zanna and D. Spinelli, *Org. Biomol. Chem.*, 2016, **14**, 4267.

47 G. Micheletti, C. Boga, M. Pafundi, S. Pollicino and N. Zanna, *Org. Biomol. Chem.*, 2016, **14**, 768.

48 S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial and H. Mayr, *J. Org. Chem.*, 2006, **71**, 9088.

49 Y. P. Semenyuk, P. G. Morozov, O. N. Burov, M. E. Kletskii, A. V. Lisovin, S. V. Kurbatov and F. Terrier, *Tetrahedron*, 2016, **72**, 2254.

50 O. Exner, *Advances in Linear Free Energy Relationship*, ed. N. B. Chapman and J. Shorter, Plenum Press, London, 1972.

51 G. Micheletti, C. Boga, L. Forlani, E. Del Vecchio, N. Zanna, A. Mazzanti and M. Monari, *Eur. J. Org. Chem.*, 2017, 964.

52 W. B. Jennings, *Chem. Rev.*, 1975, **75**, 307.

53 K. Mislow and M. Raban, *Top. Stereochem.*, 1967, **1**, 1.

54 (*a*) J.-C. Hallé, M.-P. Simonnin, M.-J. Pouet and F. Terrier, *Tetrahedron Lett.*, 1983, **24**, 2255; (*b*) J.-C. Hallé,

M.-J. Pouet, M.-P. Simonnin, F. Debleds and F. Terrier, *Can. J. Chem.*, 1982, **60**, 1988; (*c*) M.-P. Simonnin, J.-C. Hallé, F. Terrier and M.-J. Pouet, *Can. J. Chem.*, 1985, **63**, 866.

55 (*a*) F. Terrier, M.-J. Pouet, J.-C. Halle, E. Kizilian and E. Buncel, *J. Phys. Org. Chem.*, 1998, **11**, 707; (*b*) J. C. Halle, M. J. Pouet, M. P. Simonnin and F. Terrier, *Tetrahedron Lett.*, 1985, **26**, 1307.

56 J. Sandstrom, *Dynamic NMR Spectroscopy*, Academic Press, London, 1982, p. 99.

57 *Dynamic Nuclear Magnetic Resonance Spectroscopy*, ed. L. M. Jackman and F. A. Cotton, Academic Press, New York, 1975.

58 *QCPE program no. 633*, Indiana University, Bloomington, IN, USA.

59 A. Tatarov, S. Kurbatov, G. Borodkin, R. Goumont and F. Terrier, *Tetrahedron*, 2010, **66**, 995.