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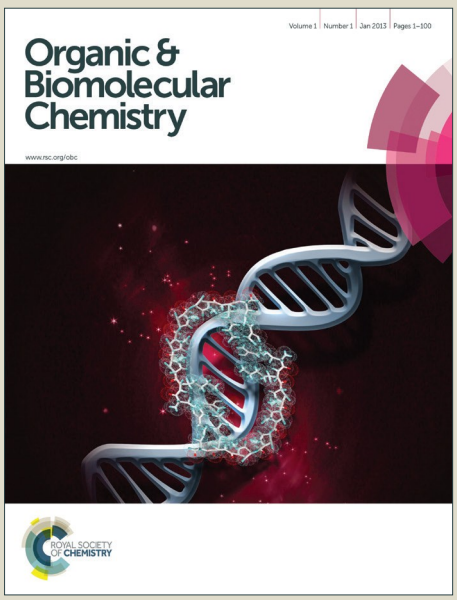

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ARTICLE

C–C Coupling between trinitrothiophenes and triaminobenzenes: zwitterionic intermediates and new all-conjugated structures

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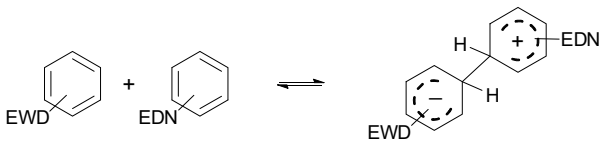
The reactions of 1,3,5-triaminobenzene derivatives with 2,3,4-trinitrothiophene and 2-bromo-3,4,5-trinitrothiophene gave new all-conjugated compounds bearing both an electron-withdrawing and an electron-donor moiety on the same unit. The reactions with 2,3,4-trinitrothiophene offered evidence, by NMR spectroscopy at low temperature, of formation of new labile Wheland-Meisenheimer intermediates whereas at room temperature stable unexpected products derived from the attack of the nucleophile at C-4 with replacement of the nitro group were isolated. Their formation caused, in turn, the obtainment of the salt between 1-nitroso-2,4,6-triaminobenzenes and 2,4-dinitrothiophen-3-ol. The reactions with 2-bromo-3,4,5-trinitrothiophene produced in good yields the S_NAr substitution product with displacement of the bromide. All the new coupling products obtained are of applicative interest, considering the increasing concern for highly conjugated π-systems in solar energy conversion or optoelectronic devices.

Introduction

Heteroaromatics with electron-donor and -acceptor architectures are receiving growing interest in diverse applicative fields such as solar energy conversion[1] and optoelectronic devices,[2] with particular attention to thiophene-based structures. An easy synthetic route to such a kind of compounds might be the C–C coupling between aromatic electron-poor and electron-rich partners through S_EAr/S_NAr reactions,[3] that are long since among our main research interests.[4] It must be remarked that the so-called nucleophilic and electrophilic aromatic substitutions represent taxonomic definitions useful for didactic uses, in fact when there is a nucleophilic reagent, there shall be an electrophilic reagent as partner (often called 'substrate'). So, the conventional classification is poorly significant; for example, in nucleophilic aromatic substitution (S_NAr) the electron-poor partner is considered the substrate, probably because the nucleophilic reagent is often used in excess and the same considerations are valid for the S_EAr reaction.

In principle, the mechanism of both aromatic substitution reactions is in the same coordinate/energy path. Consequently, the parameters affecting S_NAr reactions are the same influencing S_EAr reactions, by inverting the sign (or the electron density) of the charge on the involved reaction centers.

This situation appears evident in the case of the reactions between two partners with opposite electronic requirements and very activated, used in the same amount to yield an intermediate which is at the same time a σ-cationic complex (Wheland intermediate, on the electron rich reagent) and a σ-anionic one (Meisenheimer intermediate, on the electron poor reagent). We called these intermediates Wheland/Meisenheimer (**WM**) complexes[5] (Scheme 1).



EWD = electron-withdrawing groups
EDN = electron-donor groups

Wheland-Meisenheimer complex (**WM**)

Scheme 1. Aromatic substitution between neutral aromatic reagents.

When heterocycles bearing electron-withdrawing groups (mainly nitro groups) are mixed with strongly nucleophilic reagents such as *sym*-triaminobenzene derivatives, the C–C coupling can occur under mild conditions and almost quantitatively as in the case recently reported about their reaction with a series of chloro-nitrobenzofurazans.[7] When 1,3,5-(*N*-piperidinyl)-, 1,3,5-(*N*-morpholinyl)-, and 1,3,5-(*N*-pyrrolidinyl)-benzene were mixed with super-electrophiles[8] such as 4,6-dinitrobenzofuroxan (**DNBF**) and 4,6-dinitrotetrazolopyridine (**DNTP**) the first evidence for Wheland/Meisenheimer (**WM**) complex formation was obtained.[5,6]

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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: Copies of the ^1H, ^{13}C NMR and mass spectra of new compounds, g-COSY and g-HSQC of WMa and WMc. See DOI: 10.1039/x0xx00000x

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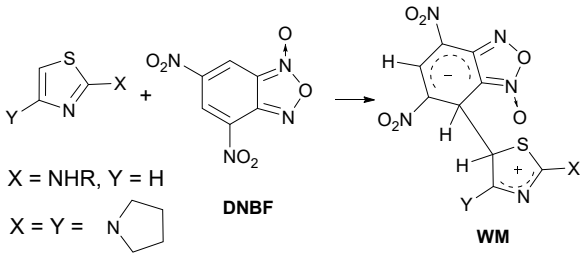
Later, the first examples of **WM** intermediates derived from aromatic pentatomic heterocycles as nucleophiles were obtained by the coupling between 2-amino-1,3-thiazole derivatives and **DNBF**;[9a] moreover, the reaction of 2,4-dipyrrolidinyl-1,3-thiazole with **DNBF** or **DNTP** offered the first X-ray diffraction analyses of **WM** complexes (Scheme 2).[9b]



Scheme 2. WM intermediates from **DNBF** and 2-aminothiazole derivatives

Pentatomic heterocycles such as thiophene, furan, and pyrroles are known as π-excessive (electron-rich) substrates able to react with electron-poor reagents (electrophiles). This point of view was so diffuse that in 1968 J. Miller[10] stated that these heteroaromatics are not prone to give S_NAr reactions even if at that time some authors[11] had given strong evidence about the ability of nitrothiophenes to react with electron-rich reagents.

Actually, the introduction of one or more strong electron-withdrawing groups in thiophenes makes these compounds more and more prone to interact with electron-rich reagents; this fact represents a general characteristic of pentatomic heterocyclic compounds (thiophene, selenophene, and furane). We think that the ability of nitrothiophenes to fast react with nucleophiles depends from two factors:[4b] a) 'the low resonance stabilization energy of thiophene with respect to benzene, which causes a lower loss of stabilization energy on going from starting products to transition states'[11d] b) the geometry of the thiophene ring with 'the internal angles along the ring carbon atoms (ca. 111–112°) very similar to the figure corresponding to sp^3-hybridazed carbon atoms' 'implies a lower energy, with respect to benzene, for the formation of the transition state'.

The above hypothesis is confirmed by comparing the results observed in piperidinodebromination of 4-nitro-bromobenzene, 2-bromo-5-nitrothiophene, 2-bromo-5-nitroselenophene, and 2-bromo-5-nitrofuran. As matter of fact their reactivities largely increase as their aromaticities decrease (a relationship between their logarithmic reactivity and Bird aromaticity indexes has been observed).[12]

Going on with this investigation, now we are looking for gaining information on S_NAr/S_EAr reactions between thiophene derivatives activated by nitro groups, as 2-bromo-3,4,5-trinitrothiophene (**1**) and 2,3,4-trinitrothiophene (**2**), and *sym*-triaminobenzenes, 'strongly' activated nucleophilic reagents at the neutral carbon atom. In nitrothiophene series, several examples of formation of π neutral (with naphthalene) and σ anionic complexes (with anionic nucleophiles) have been reported.[4b]

Obviously, when the electrophile bears a powerful leaving group X (*e.g.* the bromide in **1**), the isolation of a σ-complex is a very hard goal: the σ-anionic complexes formation, in such kind of substrates, is 'only' an hypothesis, but when X = H, it is expected to isolate moderately stable σ-complexes, because of the low ability of the hydride to act as a leaving group: actually, in this case there is a lot of evidences of the presence in the reaction mixtures of σ-complexes as well as of their isolation.

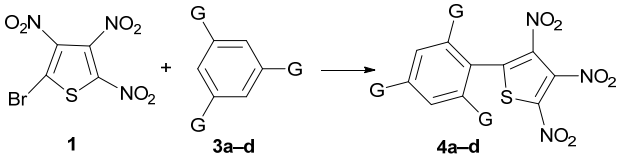
It has been reported[14a] that 3-bromo-3,4,5-trinitrothiophene (**1**) reacts with aromatic amines giving, depending on the experimental conditions, either displacement of the nitro group in position 4 or of both this group and the bromine atom. Also thiophenols replace simultaneously these groups whereas benzenesulfinic acid displaces the bromine and the nitro group in position 5. Only a few papers have appeared so far on the reactivity of **1**[4b,14,11b] and no reactions with carbon nucleophiles, thus, the behavior of **1** with triaminobenzene derivatives is far from predictable.

Rarer still are the reports on 2,3,4-trinitrothiophene (**2**): its chemical properties have been scarcely[11b,15b] investigated and no reaction were reported, except the formation of a π-complex with naphthalene.[15a]

Moreover, in planning the present study, we considered that the possible new coupling products that will be obtained bear simultaneously an electron-rich and an electron-poor moiety; contrarily to the most known thiophene-based structures, those expected to be obtained from the trinitrothiophenes **1** and **2** possess the thiophene moiety as electron-withdrawing part, giving structures that might be of interest in several applied fields.[1,2,16]

Results and discussion

The reactions between 2-bromo-3,4,5-trinitrothiophene (**1**) and tris(*N*,*N*-dialkylamino)benzene derivatives **3a** and **3b**, carried out in acetonitrile with the reactants in equimolar ratio, gave compounds **4a** and **4b**, derived from the substitution reaction at the carbon bearing the bromine atom, in 61 and 55% yield (Scheme 3).



G = *N*-piperidinyl (**a**)
G = *N*-morpholinyl (**b**)
G = *N*-pyrrolidinyl (**c**)
G = methoxy (**d**)

Scheme 3. Reactions between 2-bromo-3,4,5-trinitrothiophene (**1**) and nucleophiles **3a**–**d**.

Under the above conditions, the formed hydrobromic acid reacts with **3** giving the relevant salt: the finding that

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compounds **4a** and **4b** have been obtained in yield higher than 50% can be considered an indication of an only partial salification of the bases present in the mixture.

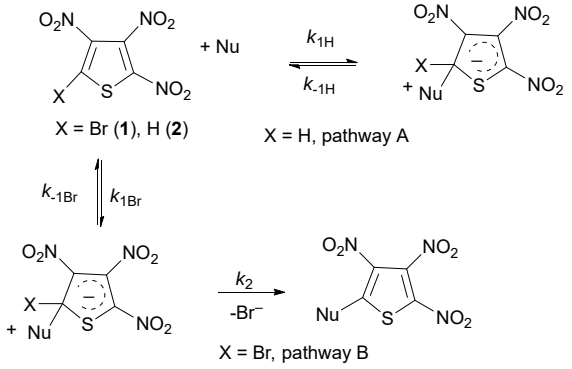
When the reactions of Scheme 3 were carried out in equimolar ratio of reagents and in the presence of basic alumina to avoid the formation of salts between HBr and the starting nucleophiles (or reaction products), **4a** and **4b** were obtained in 82% and 65% yield, respectively. In contrast, the reaction between **1** and **3c** afforded a complex reaction mixture.

To extend this behaviour to other nucleophilic benzenes, we carried out the reaction between 1,3,5-trimethoxybenzene (**3d**) and **1**: the reaction appears slower that those with **3a-c** and the compound **4d** was obtained in 47% yield.

Blatt and coworkers[11b] and, later, some of us[4b,14] reported that the reactions of **1** with anionic or neutral nucleophiles yielded both bromo and nitro substitution. In the present case, also carrying out the reactions with two or more equivalents of tris(amino)benzene only the product **4** of monosubstitution was isolated: the replacement of the bromine atom is surely the main process even if in the reaction mixtures there are, in some cases, low amount of starting materials and traces of unidentified compounds.

It is known[3,17] that the attack of a nucleophile on a non-substituted carbon is a process faster than the attack on a carbon bearing a leaving group (exerting steric/electronic repulsions towards the electron-rich entering reagent).

Therefore, one can expect that σ covalent complexes may be more easily observed in the absence of leaving groups, also because the departure of H^- is a difficult process and the formed σ complex can only return-back to starting materials, as depicted in Scheme 4 (pathway A).



Scheme 4. Reaction pathways for the trinitrothiophene derivatives/nucleophile interactions

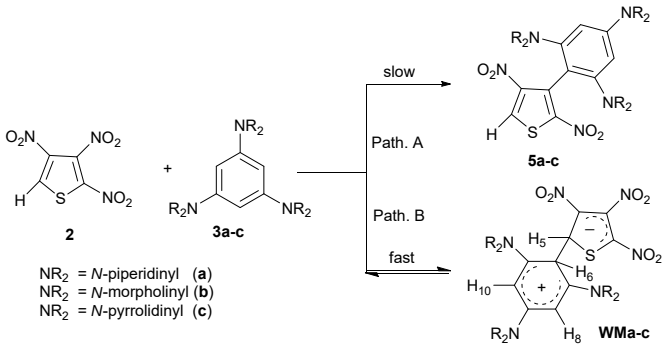
In Scheme 4 $k_{1H}>k_{1Br}$, while k_2, concerning the departure of the leaving group, represents (in our experimental conditions) a fast step.

Turning attention to 2,3,4-trinitrothiophene (**2**), the inspection by variable temperature ^{1}H NMR spectroscopy (from –70°C to +25°C) of the reaction mixtures obtained by mixing at –70 °C equimolar amounts of **2** and **3a** (or **3c**) in CD_2Cl_2 showed that this reaction is complicated by the presence of several products. Among them, **WMa** and **WMc** complexes (Scheme 5) were identified owing the presence, in the ^{1}H NMR spectrum, of signals in the region typical of the diagnostic signals of **WM** complexes.[5,6,9]

In particular, immediately after the mixing of **2** and **3a**, four broad singlets with the same integration value appeared at δ = 5.48, 5.36, 4.98, and 4.95 ppm. Direct proton to carbon correlation (Figure SI-51) obtained at –70 °C showed that the two signals at δ = 4.95 and 4.98 ppm are connected directly to carbon atoms resonating at δ = 55.3 and 39.3 ppm, respectively, a clear evidence for the sp^3 hybridization of these carbon atoms (C-5 and C-6, spectra S52 and S53). The two hydrogen atoms which resonate at δ = 5.48 and 5.36 ppm are connected to two carbon atoms at δ = 91.8 and 87.4 ppm, chemical shift values typical for the sp^2-hybridized CH carbon atoms of 1,3,5-triaminobenzene derivatives.[5,6] The two distinct hydrogen (and carbon) signals are due to the presence of an asymmetric carbon center on the thiophene moiety and a "C-2 center" (sp^3 carbon) of the triaminobenzene moiety that makes diastereotopic the two carbon atoms C-8 and C-10 (and also the hydrogen atoms H-8 and H-10, Scheme 5) and thus anisochronous signals in both the ^{1}H and ^{13}C NMR spectra appear.

We like to remember that this observation represents the first evidence of formation of a chiral center on a sp^3-hybridized CH carbon in a nucleophilic reaction involving a thiophene derivative.

The reaction between **2** and **3c** also evidenced the presence of the zwitterionic intermediate (**WMc**) in the NMR spectrum at –70 °C, whose structure was ascertained by both direct proton to carbon and carbon to carbon correlation experiments (Fig.s SI-55–SI-57). When the temperature was slowly increased the signals related to **WMa** and **WMc** gradually broadened until to disappear at about –30 °C (a subsequent lowering of the temperature did not give return-back to the **WM** signals).



Scheme 5. Formation of intermediates **WMa-c** and products **5a–c.**

It is noteworthy that among other compounds formed during the mixing of the reagents at –70 °C, whose signals remained almost unchanged until +25 °C, we were able to isolate and identify compounds **5a** and **5c**.

No evidence of **WMb** was obtained from the reaction carried out in CD_2Cl_2 at –70 °C between **2** and **3b**; only peaks of starting reagents and traces of **5b** were present in the spectrum until about 0 °C whereas at 25 °C the spectrum

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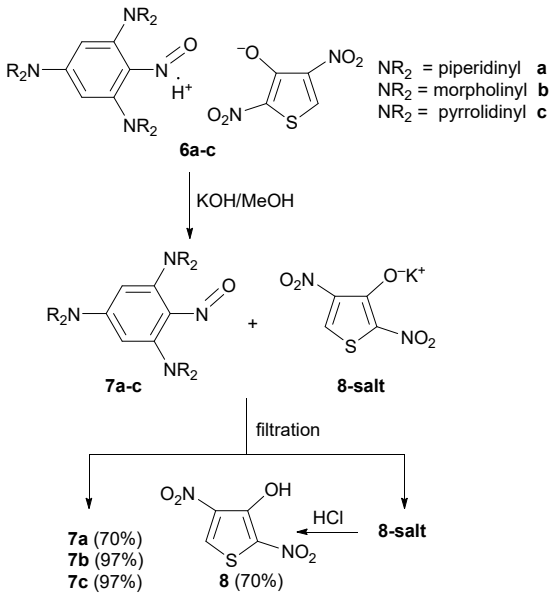
became more complex and the signals of **5b** gradually increased as those of the starting reagents disappeared.

Compounds **5a**–**c** arise from a de-nitro-substitution reaction in position 3 of the thiophene ring. They have been obtained in yield no higher than 45% and their structure was attributed by means of NMR data (NOESY-1D) and comparison with ^{13}C NMR signals of the starting reagent **2**; attempts to obtain structure by single crystal X ray diffraction of compound **5a** gave no satisfactory refinement of data but confirmed the position of the triaminobenzene moiety between the two nitro groups.

It is noteworthy that after each experiment carried out in the NMR spectroscopy tube between **2** and **3a–c** we noted the presence of a precipitate. This solid was separated and its ^1H NMR signals matched with those of minor signals observed in the spectra of the reaction mixture recorded at different temperatures; likely, due to its scarce solubility in CD_2Cl_2, this compound seemed to be a minor constituent in the reaction mixture.

After isolation by filtration, the unexpected structure **6** was first supposed for this solid on the basis of ESI^+ and ESI^- mass spectra, and later it was confirmed by NMR spectral data and by isolation and characterization of its neutral constituents **7** and **8** (Scheme 6). NMR data of the free bases, *i.e.* 1-nitroso-2,4,6-(*N*,*N*-dialkylamino)benzene derivatives **7a–c**, obtained by treatment of **6a**–**c** with methanolic solution of KOH, agree with literature data[18] whereas 2,4-dinitrothiophen-3-ol (**8**) obtained by treatment of **8-salt** with HCl solution, has never been reported so far.

Moreover, the mixing of equimolar amounts of compound **7b** and **8** directly into the NMR spectroscopy tube produced ^1H NMR signals of the triaminobenzene moiety matching with those of **6b**.



Scheme 6. Isolation of compounds **7a–c** and **8**.

On the base of our previous paper[19] on the interaction between triaminobenzenes and proton, there are three main possibilities (**A**-**C** in Figure 1) about the position of the proton on the cationic part of the salt **6**.

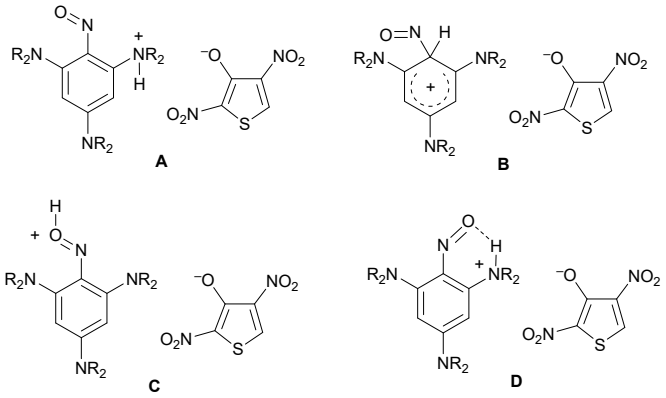
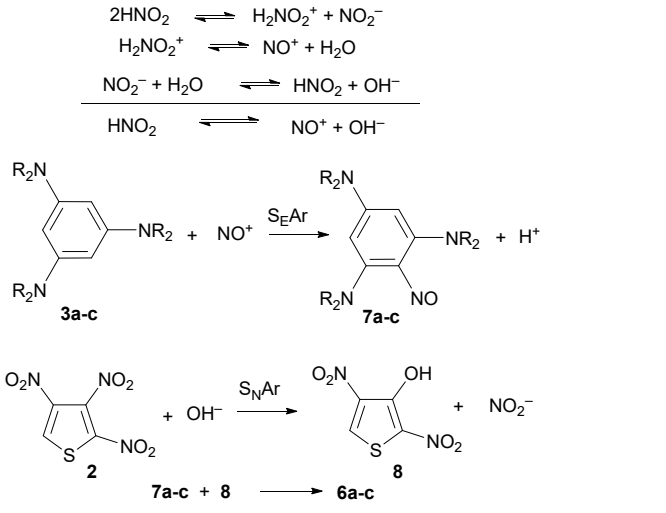


Figure 1. Possible structures of salts 6a–c.

Structure **A** shows the proton on a nitrogen atom of the piperidine moiety. **B** is a Wheland complex which may be in equilibrium with **A**.[19] **C** presents the protonated nitroso group, similarly to what indicated by Effenberger[18] in a paper in which compounds **6a**–**c** were prepared from **3a**–**c** and N_2O_4. In the ^1H NMR spectra of salts **6a**–**c**, two signals related to protons bound to aromatic ring are recorded, indicating structure **A** as the probable one, owing the symmetry of the two protons of the aromatic ring in **B** and **C**. In our opinion, more probable of structure **A** is that depicted as **D**, in which the proton bound to the nitrogen atom is involved in a hydrogen bond between the piperidinyl nitrogen and the oxygen atom of the nitroso group.

It has to be noted that compounds **6a**–**c** have been obtained in yields much higher than those of the corresponding **5a**–**c**; the unexpected formation of salts **6a**–**c** might be tentatively explained by the pathways depicted in Scheme 7.



Scheme 7. Proposed reaction pathway to explain the formation of compounds **6a**–**c**.

Nitrous acid, derived from the reaction between **2** and **3a–c** to give **5a–c**, can decompose, in the absence of water (reactions

were carried out in dichloromethane or in acetonitrile) into nitrosonium and hydroxide ions through the self-protonation process depicted in Scheme 7 (top). The two naked ions thus formed can attack triaminobenzene and trinitrobenzene by S_EAr and S_NAr, respectively.

The reaction produces, besides **7a–c** and **8**, a further amount of nitrous acid that, in turn, can decompose promoting the formation of a further amount of **7a–c** and **8**, like in an autocatalytic cycle.

Compounds **7a–c** and **8** can form the salts **6a–c**, as experimentally confirmed by adding **7a** to a CD_3CN solution of **8**. On the basis of the all above findings, we hypothesized that the more plausible structure for **8** might be that reported in Schemes 6 and 7, even if, since we were not able to obtain crystals suitable for X-Ray diffraction analysis, other isomeric structures cannot be completely ruled out.

In the whole, the occurrence of these reactions might be the possible reason of both, the low yields found for compound **5a**–**c** and the high yields of the recovered salts **6a**–**c**.

Conclusions

In conclusion, the present study reports the first examples of reactions between trinitrothiophene derivatives and sym-triaminobenzene derivatives **3a–c**, strongly activated aromatic neutral carbon nucleophiles. The structure of the coupling product obtained using 2-bromo-3,4,5-trinitrothiophene (**1**) as electrophile revealed that only the de-bromination substitution reaction occurs and no evidence of de-nitrosubstitution reactions was obtained.

A very peculiar reactivity was observed when 2,3,4-trinitrothiophene (**2**) was reacted with **3a**–**c**: the latter showed the ability to attack, in a fast step, the unsubstituted carbon atom (C-5) of the thiophene ring and offered the first evidence of **WM** complexes in thiophene series and also the first example with an electrophilic partner belonging to the class of aromatic monocyclic pentatomic heterocycles. The attack at the C-5 carbon atom of the electrophile competes with the attack on the carbon bearing the nitro group in position 3 of the thiophene ring that produces new compounds with the triaminobenzene moiety bound at the C-3 carbon atom; the consequent nitro group departure eliminates the possibility to return-back to the starting materials while the only possibility for **WM** is the return to the starting reagents.

The reaction is complicated by other processes, one of them is the formation of a salt that, after neutralization, provided 1-nitroso-2,4,6-triaminobenzene derivatives and the hitherto unknown 2,4-dinitrothiophen-3-ol. Therefore, present findings can be considered a new method to synthesize 1-nitroso-2,4,6-triaminobenzenes and, even more interestingly, the C–C coupling products **4a,b,d** and **5a–c** herein reported gives access to new highly conjugated structures, bearing both electron-poor and electron-rich moieties, of possible interest in applied chemistry.

Experimental

Experimental Details.

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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 measured in δ (ppm) with reference to the solvent [for ^1H and ^{13}C NMR, respectively: δ = 5.30 ppm and 54.2 ppm for CD_2Cl_2; δ= 7.26 ppm and 77.0 ppm for $CDCl_3$; δ = 2.50 ppm and 39.50 ppm for $(CD_3)_2SO$; δ = 3,31 ppm and 49.2 ppm for CD_3OD; δ = 1.96 ppm and 118.1 ppm for CD_3CN]. The variable–temperature NMR spectra and 2D low-temperature spectra (*g*-COSY and *g*-HSQC) were recorded on a 400 MHz spectrometer. ESI-MS and HR-ESI-MS spectra were recorded using Waters 2Q 4000 and Xevo instrument, respectively. Chromatographic purifications were carried out on columns of silica gel (0.037-0.063 mm) or aluminium oxide, activated, basic, Brockmann I, standard grade ca. 150 mesh at medium pressure. In the Supporting Information are provided copies of the ^1H NMR, ^{13}C NMR and mass spectra of all new compounds and for the known compounds whose NMR and mass data were never or only partially reported; crude salts **6a**–**c** have been treated without purification to obtain neutral components **7a–c** and **8**. 1,3,5-Trimethoxybenzene (**3d**) is commercially available, 1,3,5-tris(*N*,*N*-dialkylamino)benzenes **3a**–**c** were prepared as described previously,[5] as well as bromotrinitrothiophene (**1**) and trinitrothiophene (**2**).[11b] Given that NMR spectra of **1** and **2** have been never reported so far, we report them below (we notice that ^{13}C NMR spectra show some signals as triplet, likely due to carbon-nitrogen coupling).[20] **2-Bromo-3,4,5-trinitrothiophene (1**): ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ = 140.1 (br.s, C), 136.8 (br.s, C), 136.2 (t, $J_{C\text{-}N}$ = 15.0 Hz, C), 121.5 ppm (C). **2,3,4-Trinitrothiophene (2)**. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.57 ppm; ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ = 142.3 (t, $J_{C\text{-}N}$ = 13.2 Hz, C), 137.8 (br.s, C), 135.8 (t, $J_{C\text{-}N}$ = 14.8 Hz, C), 129.9 ppm (CH).

Compounds **7a-c** were described previously[18] and their data agree with those reported;[18] their ^1H NMR data have been reported only partially and below their ^1H NMR, ^{13}C NMR and mass data are reported.

Preparation of compounds 4a,b,d. General procedure. 2-Bromo-3,4,5-trinitrothiophene (**1**) (0.030 g, 0.1 mmol) was added to an equimolar amount of 1,3,5-tris(*N*,*N*-dialkylamino)benzene **3a**, **3b**, or **3c** (or of trimethoxybenzene **3d**) dissolved in CH_3CN (5 mL). Immediately after mixing, the colour of the reaction mixture turned to red or blue. The progress of the reaction, magnetically stirred, was monitored by TLC and ^1H NMR analysis. The product was purified by flash chromatography on silica gel (petroleum light/Et_2O 8/2 v/v for **4a**, n-hexane/ethyl acetate 4/6 for **4b** and **4d**). The reactions were carried out also in the presence of basic alumina; that was filtered off after disappearance of starting material on TLC, products were then quickly purified as above described. The yields reported below are referred to the first procedure with equimolar amount of reagents.

1,1',1''-[2-(3,4,5-Trinitro-2-thienyl)benzene-1,3,5-triyl]tripiperidine (4a): blue-violet solid, 33 mg (61%) mp > 300

°C (dec.); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 6.36 (s, 2 H, aromatics), 3.32 (t, *J* = 4.78 Hz, 4 H, NCH_2), 2.80–2.66 (m, 8 H, NCH_2), 1.74–1.62 (m, 6 H), 1.62–1.53 (m, 8 H), 1.53–1.43 ppm (m, 4 H). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ = 154.9 (C), 154.8 (C), 144.6 (C), 137.0 (C), 136.0 (C), 134.4 (C), 107.6 (C), 102.0 (CH), 54.0 (NCH_2), 48.6 (NCH_2), 25.7(NCH_2CH_2), 25.6 (NCH_2CH_2), 24.2 ($NCH_2CH_2CH_2$), 24.1 ppm ($NCH_2CH_2CH_2$). ESI MS (ES^+) m/z: 545 (M^+ + 1), 567 (M^+ + Na), 583 (M^+ + K); elemental analysis calcd (%) for $C_{25}H_{32}N_6O_6S$: C 55.13, H 5.92, N 15.43. Found: C 55.21, H 5.94, N 15.45.

4,4',4''-[2-(3,4,5-Trinitro-2-thienyl)benzene-1,3,5-triyl]trimorpholine (4b): purple solid, 30.3 mg (55%), mp 200 °C (dec.); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 6.43 (s, 2 H, aromatics), 3.87 (t, *J* = 4.9 Hz, 4 H, OCH_2), 3.70 (t, *J* = 4.9 Hz, 8 H, OCH_2), 3.31 (t, *J* = 4.9 Hz, 4 H, NCH_2), 2.85-2.79 ppm (m, 8 H, NCH_2). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ = 154.9 (C), 153.5 (C), 143.1 (C), 137.0 (C), 136.6 (C), 134.8 (C), 108.7 (C), 102.4 (CH), 66.51 (OCH_2), 66.45 (OCH_2), 52.6 (NCH_2), 47.5 ppm (NCH_2). ESI MS (ES^+) m/z: 573 (M^+ + Na), 589 (M^+ + K); elemental analysis calcd (%) for $C_{22}H_{26}N_6O_9S$: C 48.00, H 4.76, N 15.27. Found: C 48.12, H 4.78, N 15.30.

2,3,4-Trinitro-5-(2,4,6-trimethoxyphenyl)thiophene (4d): orange solid, 18.1 mg (47%). ^{1}H NMR (600 MHz, CD_3CN, 25 °C): δ = 6.35 (s, 2 H, aromatics), 3.92 (s, 3H, OCH_3), 3.84 ppm (s, 6 H, OCH_3). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 6.18 (s, 2 H, aromatics), 3.89 (s, 3H, OCH_3), 3.81 ppm (s, 6 H, OCH_3). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ (selected) = 165.0 (C), 158.8 (C), 152.1 (C), 150.3 (C), 140.5 (C), 97.7 (C), 91.0 (CH), 55.9 (OCH_3), 55.7 ppm (OCH_3). ESI-MS (ES^+) m/z: 386 (M^+ + 1), 408 (M^+ + Na); elemental analysis calcd (%) for $C_{13}H_{11}N_3O_9S$: C 40.52, H 2.88, N 10.91. Found: C 40.41, H 2.89, N 10.88.

Preparation of compounds 5a–c and 6a–c. General procedure.

Compounds **5a**–**c** and **6a**–**c** were first isolated by chromatography on silica gel column of the final reaction mixture between **2** and **3** (or **3b**, **3c**) derived from experiments carried out in the NMR spectroscopy tube. Compounds **6a–c** were isolated by filtration from the above reaction mixture. Compounds **5a**–**c** were also obtained carrying out the reaction in a larger scale: to a magnetically stirred solution of 1,3,5-tris(dialkylamino)benzene (0.15 mmol) in CH_2Cl_2 or CH_3CN (10 mL), an equimolar amount of 2,3,4-trinitrothiophene (**2**) was added. Immediately after mixing, the reaction mixture became dark red or violet. The solution was stirred for 1 hour (using **3a** or **3c**) and 12 hours (for **3b**) and the progress of the reaction was monitored by TLC and ^{1}H NMR analysis. During the reaction time a solid was formed and then separated from the reaction mixture by filtration. Compounds **5a–c** (very dark solids) were purified by flash chromatography on silica gel (eluent:dichloromethane/n-hexane, in different ratio depending on the polarity of the different products) of the concentrated mother liquor. The solid precipitated were compounds **6a**–**c**; in some cases precipitation was favored by addition of diethyl ether to the reaction mixture. Crude compounds **6a**–**c** were subjected to treatment for obtaining neutral components without purification (see below).

1,1',1''-[2-(2,4-Dinitro-3-thienyl)benzene-1,3,5-triyl]tripiperidine (5a): dark blue solid, 18.7 mg (25%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.22 (s, 1 H, CH thioph), 6.41 (s, 2 H, CH arom.), 3.24 (t, *J* = 5.7 Hz, 4 H, NCH_2), 2.70–2.56 (m, 8 H, NCH_2), 1.78–1.66 (m, 4 H, NCH_2CH_2), 1.66–1.57 (m, 2 H, NCH_2CH_2), 1.42–1.29 ppm (m, 12 H, NCH_2CH_2 and $NCH_2CH_2CH_2$). ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 154.2 (C), 154.0 (C), 146.6 (C), 145.6 (C), 133.5 (C), 127.3 (CH), 111.7 (C), 103.0 (CH), 53.6 (NCH_2), 49.5 (NCH_2), 26.4 (2 sign. overlapped, NCH_2CH_2), 25.9 (CH_2), 24.3 ppm ($NCH_2CH_2CH_2$). ESI MS (ES^+) m/z: 500 (M^+ + 1), 522 (M^+ + Na), 538 (M^+ + K); elemental analysis calcd (%) for $C_{25}H_{33}N_5O_4S$: C 60.10, H 6.66, N 14.02. Found: C 60.19, H 6.68, N 14.05. X-ray diffraction analysis of a single crystal of **5a** showed that the triaminobenzene moiety is bound at the C-3 of the thiophene ring but, unfortunately, due to the symmetry of the cell, the resolution of the structure was not satisfactory for the requirements for the deposit in CCDC.

4,4',4''-[2-(2,4-Dinitro-3-thienyl)benzene-1,3,5-triyl]trimorpholine (5b): dark purple solid, 21.2 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.27 (s, 1 H, CH thioph), 6.46 (s, 2 H, arom), 3.88 (t, *J* = 4.9 Hz, 4 H, OCH_2), 3.53–3.47 (m, 8 H, OCH_2), 3.27 (t, *J* = 4.9 Hz, 4 H, NCH_2), 2.72–2.65 ppm (m, 8 H, NCH_2). ^{13}C NMR (150.8 MHz, $CDCl_3$, 25 °C): δ = 153.5 (C), 152.6 (C), 146.5 (C), 146.1 (C), 132.1 (C), 127.5 (CH), 113.0 (C), 103.1 (CH), 67.0 (OCH_2), 66.7 (OCH_2), 52.4 (NCH_2), 48.4 ppm (NCH_2). ESI MS (ES^+): 506 (M^+ + H), 528 (M^+ + Na); elemental analysis calcd (%) for $C_{22}H_{27}N_5O_7S$: C 52.27, H 5.38, N 13.85. Found: C 52.33, H 5.39, N 13.81.

1,1',1''-[2-(2,4-Dinitro-3-thienyl)benzene-1,3,5-triyl]tripyrrolidine (5c): dark brown solid, 30.2 mg (44%). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 8.10 (s, 1 H, CH thioph), 5.94 (s, 2 H, arom), 3.34 (t, *J* = 6.6 Hz, 4 H, NCH_2), 2.83–2.78 (m, 4 H, NCH_2), 2.78–2.72 (m, 4 H, NCH_2), 2.01–1.97 (m, 4 H, NCH_2CH_2), 1.77–1.65 ppm (m, 8 H, NCH_2CH_2); ^{1}H NMR (400 MHz, CD_2Cl_2, –70 °C): δ = 8.13 (s, 1 H), 5.76 (s, 2 H), 3.25 (br.t, *J* = 6.11 Hz, 4 H), 2.73–2.55 (m, 8 H), 1.90 (br.t, *J* = 6.11 Hz, 4 H), 1.70–1.53 ppm (m, 8 H); ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 8.35 (s, 1 H), 5.96 (s, 2 H), 3.33 (t, *J* = 6.7 Hz, 4 H), 2.82–2.75 (m, 4 H), 2.75-2.67 (m, 4 H), 2.05–2.00 (m, 4 H), 1.75–1.63 ppm (m, 8 H). ^{13}C NMR: (150.8 MHz, CD_2Cl_2, 25 °C): δ = 151.6 (C), 150.5 (C), 148.2 (C), 145.9 (C), 136.8 (C), 128.0 (CH), 104.1 (C), 95.6 (CH), 52.1 (NCH_2), 48.3 (NCH_2), 26.3 (NCH_2CH_2), 25.7 ppm (NCH_2CH_2). ESI MS (ES^+) m/z: 458 (M^+ + 1), 480 (M^+ + Na), 496 (M^+ + K); elemental analysis calcd (%) for $C_{22}H_{27}N_5O_4S$: C 57.75, H 5.95, N 15.31. Found: C 57.72, H 5.96, N 15.28.

1-(2-Nitroso-3,5-dipiperidin-1-ylphenyl)piperidin-1-ium 2,4-dinitrothiophen-3-olate (**6a**): dark red solid, 49.1 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.31 (s, 1 H, thioph), 5.36 (d, *J* = 1.9 Hz, 1 H, arom), 5.24 (d, *J* = 1.9 Hz, 1 H, arom), 3.62–3.56 (m, 4 H, NCH_2), 3.53–3.47 (m, 4 H, NCH_2), 3.37–3.19 (m, 4 H, NCH_2), 1.88–1.56 ppm (m, 18 H, NCH_2CH_2 and $NCH_2CH_2CH_2$). ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 162.0 (C), 160.8 (C), 157.2 (C), 151.0 (C), 141.0 (C), 140.6 (C), 134.6 (CH), 124.5 (C), 87.4 (CH), 86.5 (CH), 51.2 (NCH_2), 50.8 (NCH_2), 49.5 (NCH_2), 26.18 (NCH_2CH_2), 25.8 (NCH_2CH_2), 25.5 (NCH_2CH_2), 24.1 ($NCH_2CH_2CH_2$), 24.0 ($NCH_2CH_2CH_2$), 23.8 ppm ($NCH_2CH_2CH_2$).

HRMS (ES^+) m/z: (M^+) calcd for $C_{21}H_{33}N_4O$ 357.2649 found 357.2650; ESI MS (ES^+) m/z: 357 (M^+); ESI MS (ES^-) m/z: 189 (M^-).

4-(3,5-Dimorpholin-4-yl-2-nitrosophenyl)morpholin-4-ium 2,4-dinitrothiophen-3-olate (**6b**): dark red solid, 53.8 mg (65%). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): δ = 8.71 (s, 1 H, thioph), 5.77 (br.s, 1 H, arom), 5.66 (br.s., 1 H, arom), 3.85–3.67 (m, 4 H, OCH_2), 3.74–3.64 (m, 12 H, OCH_2 and NCH_2), 3.62–3.49 (m, 4 H, NCH_2), 3.44–3.30 ppm (m, 4 H, OCH_2). ^{13}C-NMR (100.56 MHz, DMSO-d_6 , 25 °C): δ = 161.6 (C), 160.7 (C), 156.4 (C), 150.8 (C), 141.9 (C), 140.8 (C), 137.1 (CH), 121.1 (C), 89.0 (CH), 87.4 (CH), 66.0 (OCH_2), 65.8 (OCH_2), 49.6 (NCH_2), 48.2 ppm (NCH_2). HRMS (ES^+) m/z: (M^+) calcd for $C_{18}H_{27}N_4O_4$ 363.2027 found 363.2030; ESI MS (ES^+) m/z: 363 (M^+); ESI MS (ES^-) m/z: 189 (M^-).

1-(2-Nitroso-3,5-di(pyrrolidin-1-yl)phenyl)pyrrolidin-1-ium 2,4-dinitrothiophen-3-olate (**6c**): dark red solid, 31.0 mg (41%); ^{1}H NMR (400 MHz, CD_3CN, 25 °C): δ = 8.39 (s, 1 H, thioph), 5.00 (d, *J* = 2.3 Hz, 1 H, arom), 4.89 (d, *J* = 2.3 Hz, 1 H, arom), 3.83–3.20 (m, 12 H, NCH_2), 2.10–1.95 ppm (m, 12 H, NCH_2CH_2). ^{13}C NMR (100.56 MHz, CD_3CN , 25 °C): δ = 163.7 (C), 162.8 (C), 159.2 (C), 154.3 (C), 151.6 (C), 149.8 (C), 144.9 (C), 136.2 (CH), 87.2 (CH), 85.9 (CH), 51.8 (NCH_2), 50.2 (NCH_2), 50.1 (NCH_2), 25.8 (NCH_2CH_2), 25.4 (NCH_2CH_2), 25.3 ppm (NCH_2CH_2). HRMS (ES^+) m/z: (M^+) calcd for $C_{18}H_{27}N_4O$ 315.2179 found 315.2180; ESI MS (ES^+) m/z: 315 (M^+); ESI MS (ES^-) m/z: 189 (M^-).

Isolation of compounds 7a–c and 8. General procedure

A $3.9x10^{-2}$ M methanolic/KOH solution was added to an equimolar amount (0.05 mmol) of the salt **6** dissolved in methanol. After about 30 min a red solid precipitated; this solid was collected by filtration and dried. NMR analysis indicated presence of a single product. The solid was treated with an equimolar amount of 0.15 M aqueous hydrochloric acid. After dilution with water and extraction with ethyl acetate, the organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. and chemico-physical data of the residue agreed with structure **8**. The mother liquor remained after treatment of **6** with KOH/CH_3OH was concentrated and the ^{1}H NMR of the residue revealed the presence of a main product that was isolated by chromatography on basic alumina (eluent: dichloromethane/methanol, 9.5/0.5) and was identified as the neutral compound **7**. Mixing equimolar amount of **7b** and **8** in CD_3CN gave signals of **6a**. Moreover, the treatment of compound **7a** (or **7b**) with one equivalent of picric acid produced ^{1}H NMR signals of the triaminobenzene moiety similar to those of **6a** (or **6b**) (see spectra in Fig. SI-38 and SI-42). Chemico-physical data of compounds **7a**–**c** were according to those reported in the literature[18] but since they were partial, below we report complete NMR and mass data.

1,1',1''-(2-Nitrosobenzene-1,3,5-triyl)tripiperidine (7a):[18] red solid, 12.5 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.50 (s, 2 H, arom), 3.48–3.42 (m, 4 H, NCH_2), 3.36–3.24 (m, 8 H, NCH_2), 1.81–1.61 ppm (m, 18 H, NCH_2CH_2 and $NCH_2CH_2CH_2$). ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 158.0 (C), 147.7 (C), 103.0 (C), 88.6 (CH), 52.5 (NCH_2), 48.5 (NCH_2), 25.8 (NCH_2CH_2), 25.6 (NCH_2CH_2), 24.5 ($NCH_2CH_2CH_2$), 24.4 ppm ($NCH_2CH_2CH_2$). HRMS (ES^+) m/z: (M^+) calcd for $C_{21}H_{33}N_4O$ 357.2649 found 357.2651; ESI MS (ES^+) m/z: 357 (M^+ + 1), 379 (M^+ + Na).

4,4',4''-(2-Nitrosobenzene-1,3,5-triyl)trimorpholine (7b):[18] green solid, 17.5 mg (97%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.60 (s, 2 H, arom), 3.94 (t, *J* = 4.4 Hz, 8 H, OCH_2), 3.82 (t, *J* = 4.4 Hz, 4 H, OCH_2), 3.43 (t, *J* = 4.4 Hz, 4 H, NCH_2), 3.25 (t, *J* = 4.4 Hz, 8 H, NCH_2). ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ (selected) = 157.5 (C), 149.0 (C), 89.5 (CH), 66.7 (OCH_2), 66.4 (OCH_2), 52.1 (NCH_2), 47.0 ppm (NCH_2). HRMS (ES^+) m/z: (M^+) calcd for $C_{18}H_{27}N_4O_4$ 363.2027 found 363.2031; ESI MS (ES^+) m/z: 363 (M^+ + 1), 385 (M^+ + Na), 401 (M^+ + K).

1,1',1''-(2-Nitrosobenzene-1,3,5-triyl)tripyrrolidine (7c):[18] dark red solid 15.2 mg (97%). (400 MHz, $CDCl_3$, 25 °C): δ = 5.02 (d, *J* = 2.1 Hz, 1 H, arom), 4.80 (d, *J*= 2.3 Hz, 1 H, arom), 3.75–3.61 (m, 4 H, NCH_2), 3.44 (t, *J* = 6.6 Hz, 4 H, NCH_2), 3.39–3.20 (m, 4 H, NCH_2), 2.03–1.88 ppm (m, 12 H, NCH_2CH_2); ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ (selected) = 156.1 (C), 155.8 (C), 145.0 (C), 85.0 (CH), 83.6 (CH), 51.7 (br.s., NCH_2), 51.02 (br.s., NCH_2), 48.3 (NCH_2), 25.8 (NCH_2CH_2), 25.6 (NCH_2CH_2), 25.4 ppm (NCH_2CH_2). HRMS (ES^+) m/z: (M^+) calcd for $C_{18}H_{27}N_4O$ 315.2179 found 315.2182; ESI MS (ES^+) m/z: 315 (M^+ + H), 337 (M^+ + Na).

2,4-Dinitrothiophene-3-ol (8): mustard-color solid, 6.7 mg (70%) mp > 120 °C (dec.); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 8.77 ppm (s, 1 H). ^{13}C NMR (100.56 MHz, CD_3OD, 25 °C): δ = 151.4 (C), 138.1 (C), 133.8 (CH), 130.0 ppm (C). HRMS (ES^-) m/z: $[M-H]^-$ calcd for $C_4HN_2O_5S$ 188.9612 found 188.9614.

Formation and detection of Wheland-Meisenheimer intermediates WMa and WMc.

A solution of 1,3,5-triaminobenzene derivative (**3a** or **3c**, 0.04 mmol) was dissolved in CD_2Cl_2 (1 mL) and introduced in a NMR spectroscopy tube that was inserted in the NMR probe. When the probe temperature reached –70°C, an equimolar amount of 2,3,4-trinitrothiophene (9.5 mg, 0.04 mmol) was added to the solution, that became blue-coloured, and the ^{1}H NMR spectrum of the resulting solution was quickly recorded. The system was monitored after various times and at different temperatures until 25 °C. Immediately after the mixing, the spectrum at –70 °C showed the appearance of new signals, some of them ascribed to compound WM, also with the aid of g-COSY and g-HSQC experiments (see Supporting information). On raising the temperature, signals belonging to WM gradually broadened then disappeared at about –35 °C for **WMa** and –30 °C for **WMc**; a return-back from previous temperature did not produced re-appearance of signals of WM. In case of reaction of **2** with **3a**, the ^{1}H NMR spectrum recorded at –70 °C immediately after the mixing of the reagents at –70 °C showed presence of compound **5a** in a relative molar ratio 57/43 with **WMa**.

In case of reaction of **2** with **3c**, the ^{1}H NMR spectrum recorded at –70 °C immediately after the mixing of the reagents showed presence of other signals, some of them ascribed to compound **5c** and **6c**. These latter fall in the same region of **WMc** but were distinguishable because the signals of **WMc** broadened and disappeared on raising the temperature

while those of **6c** increased on raising the temperature probe and remained stable.

3,4,5-Trinitro-2-(2,4,6-tri(piperidin-1-yl)cyclohexa-2,4-dien-1-ylium-1-yl)-2,3-dihydrothiophen-3-ide (**WMa**): ^{1}H NMR: (400 MHz, CD_2Cl_2, −70 °C): d = 5.48 (br.s, 1 H), 5.36 (br.s, 1 H), 4.98 (br.s, 1 H), 4.95 (br.s, 1 H), 4.05−3.51 (m, 4 H), 3.5−3.23 (m, 8 H), 1.85−0.90 ppm (m, 18 H, overl. with those of **5a**). g-HSQC (CD_2Cl_2, −70 °C): ^{1}H-^{13}C correlations (solvent signal set at δ = 54.47 ppm): 5.48-91.8, 5.36-87.4, 4.95-55.3, 4.98-39.3.

3,4,5-Trinitro-2-(2,4,6-tri(pyrrolidin-1-yl)cyclohexa-2,4-dien-1-ylium-1-yl)-2,3-dihydrothiophen-3-ide (**WMc**): ^{1}H NMR: (400 MHz, CD_2Cl_2, −70 °C): δ = 5.03 (d, *J* = 2.36, 1 H), 4.87 (br.s, 1 H), 4.78 (br.s, 1 H), 4.73 (br.s, 1 H), 3.82−3.40 and 2.20−1.50 ppm (signals overl. with those of other compounds); *g*-COSY (CD_2Cl_2, −70 °C): ^{1}H-^{1}H correlation: 5.03−4.73; *g*-HSQC (CD_2Cl_2, −70 °C): ^{1}H-^{13}C correlations: 5.03-54.9, 4.87-89.4, 4.78-85.8, 4.73-44.6.

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