FULL PAPER

Nucleophilic Aromatic Substitution For Heteroatom. An Oxidative Electrochemical Approach

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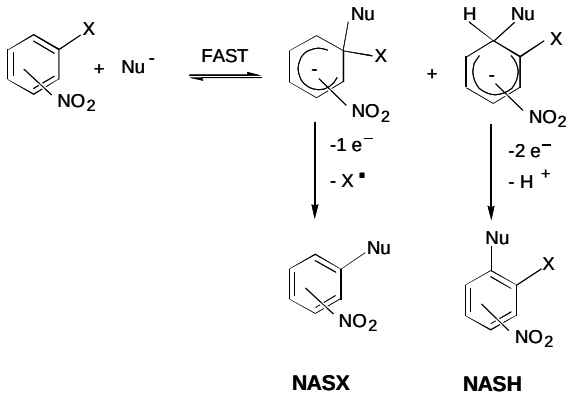

NASX **NASH**

J. Org. Chem., **2001**, submitted

Nucleophilic Aromatic Substitution For Heteroatom. An Oxidative Electrochemical Approach

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Abstract: The nucleophilic aromatic substitution for heteroatom through electrochemical oxidation of the intermediate σ-complexes (Meisenheimer complexes) in simple nitroaromatic compounds is reported for the first time. The studies have been carried out with hydride, cyanide, fluoride, methoxi and ethanethiolate anions and *n*-butylamine as a nucleophiles, at the cyclic voltammetry (CV) and preparative electrolysis level. The cyclic voltammetry experiments allow to detection and characterization of the σ-complexes and they have lead us to a proposal for the mechanism of the oxidation step. Furthermore, the power of the CV technique in the analysis of the reaction mixture throughout the whole chemical and electrochemical process is described.

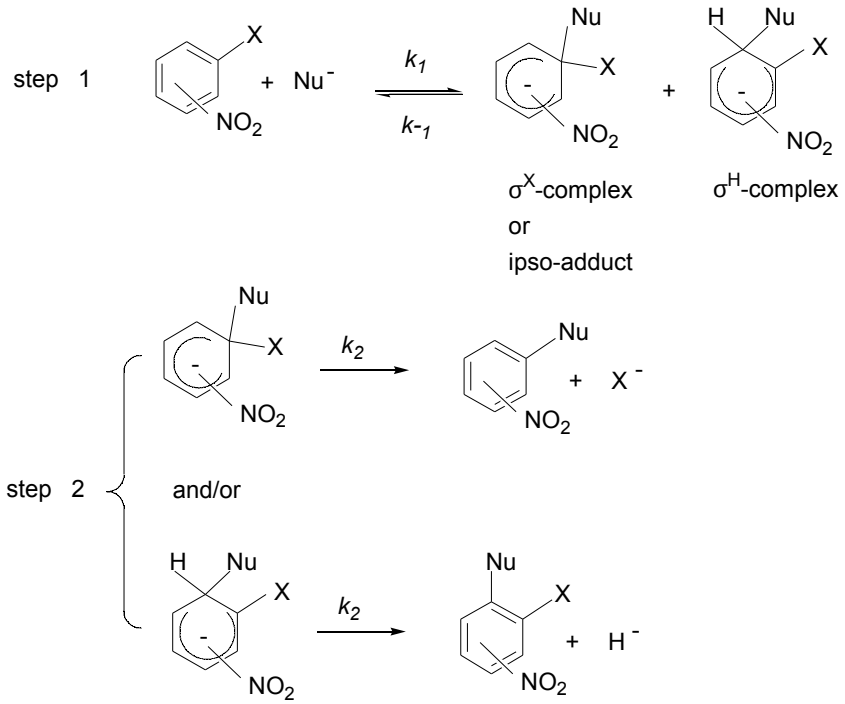
Introduction

There are several mechanisms for aromatic nucleophilic substitution[1]. When activating groups are present on the ring, the S_NAr mechanism is generally found. The S_NAr mechanism, consists of two steps. In the first step, the intermediates, also known as σ-complexes, are formed. These σ-complexes may be σ^H-complexes and σ^X-complexes or *ipso*-adducts. The Ar-X bond (in the σ-complexes) is broken in the second step. Either, the formation or the decomposition of the anionic intermediate, σ-complexes, may be rate limiting (Scheme 1).

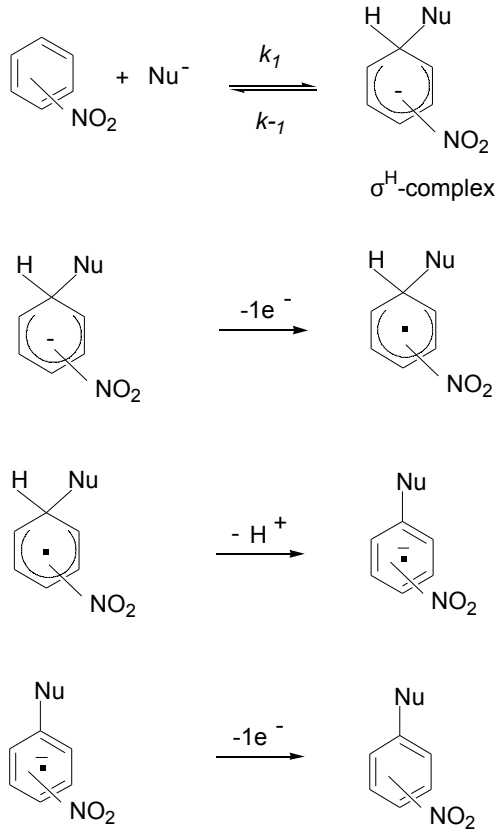
These σ^H-complexes may be converted into products of hydrogen-atom replacement in three ways, vicarious nucleophilic substitution [3-8], chemical oxidation [9-11] and electrochemical oxidation [2,12] . Recent papers [2] have been established the mechanism of electrochemical oxidation of σ^H-complexes. The oxidation occurs in a three-steps mechanism: a initial electron-transfer on the electrode, one chemical reaction and a second electron-transfer probably in solution (Scheme 2).

Furthermore, the electrochemical oxidation [2] of σ^H-complexes formed by addition by CN^- to nitroarenes occur, with good yield, giving rise to rearomatized compound in what formally constitutes a loss of H^-. It is particularly interesting to note that in the cases where a low yield of NASH product (nucleophilic aromatic substitution for hydrogen) is observed , the product NASX (nucleophilic aromatic substitution for heteroatom) is obtained .

The conversion of σ^X-complexes into products of X-atom replacement [1] is strongly dependent on : the nature of the leaving group, the nature of the nucleophilic reagent and the medium effects, being the solvent an important parameter determining the energetics of S_NAr substitutions. S_NAr reactions are normally carried out in protic solvents in order to promote the decomposition of the σ-complex intermediate into the final substitution product in a process acid catalyzed. [1 b] The use of dipolar aprotic solvents (mainly HMPA) has been limited to NO_2 displacements and the mechanism of decomposition of the σ-complex (2^{nd} step) has not been studied. [13,14]



Scheme 1



Nu= H, CN, RNH_2, RCOR'

Scheme 2

The electrochemical methods are a powerful tool [2] for studying the σ^H-complexes formed "in situ", and to force the substitution reaction to occur. Here, our work will show that a similar approach can be used to study the σ^X-complexes and thus to generalise the possibilities of electrochemistry in S_NAr reactions. In this paper we focus our attention in the following points:

a) knowing the efficiency of the nucleophilic aromatic substitution (determining the type of σ-complexes present in the solution - σ^H-orσ^X-complexes- and their relative proportions)
b) establishing the mechanism of the electrochemical oxidation of the σ^X-complexes, and
c) obtaining ,by electrochemical oxidation of the σ^X-complexes in DMF at 10ºC , the rearomatized (substitution) product in preparative useful yields.
d) The electrochemical methods result to be very general, and open new possibilities for the preparation of compounds not easy to obtain by standard chemical methods.

In order to establish the mechanistic details and the synthetic scope of the electrochemical method, this study has been carried out for a wide series of 1,3,5-trinitroderivatives, 1,3-dinitroderivatives and nitroderivatives **1** to **9** (Chart of structures): 2,4,6-trinitroanisole **1**, 1-chloro-2,4,6-trinitrobenzene **2**, 1,3,5-trinitrobenzene **3**, 1,3-dinitrobenzene **4**, 2,4-dinitroanisole **5**, 1-fluoro-2,4-dinitrobenzene **6**, 1-chloro-2,4dinitrobenzene **7**, 3-nitrobenzonitrile **8** and α,α,α-trifluoro-3-nitrotoluene **9** with five anionic nucleophiles H^- ,CN^-,F^-, CH_3O^-, $C_2H_5S^-$and one neutral nucleophile *n*$BuNH_2$, in DMF as a solvent. We have previously verified that spontaneous S_NAr does not occur in the reaction time (even up 24 h) in our conditions (dry DMF, base 13º)

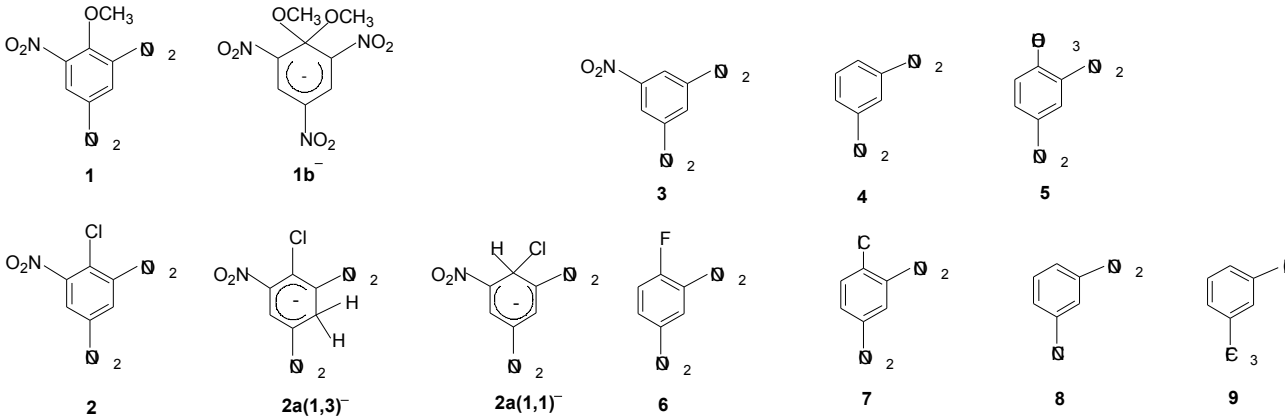


Chart of structures

Results and Discussions

Mechanism of the electrochemical oxidation of σ^X-complexes or *ipso*-adducts

In this part, the σ-complexes **1 b** , **2 a (1,1)** and **2 a (1,3)** (Chart of structures) are studied. Theirs synthesis, purification, characterisation and kinetics has been previously described [15,16] .

Electrochemical Behaviour of **1 b**$^-$ [17]. A typical voltammogram in DMF, at low scan rates, is shown in Figure 1 a. No reduction waves are observed in the first cathodic scan, whereas an irreversible one-electron oxidation wave appears in the oxidation scan (c.a. 1.12 V). On the second cathodic scan a reversible one-electron reduction wave (c.a. –0.73V) is observed [18]. This reduction wave corresponds to the product formed in the first anodic process.

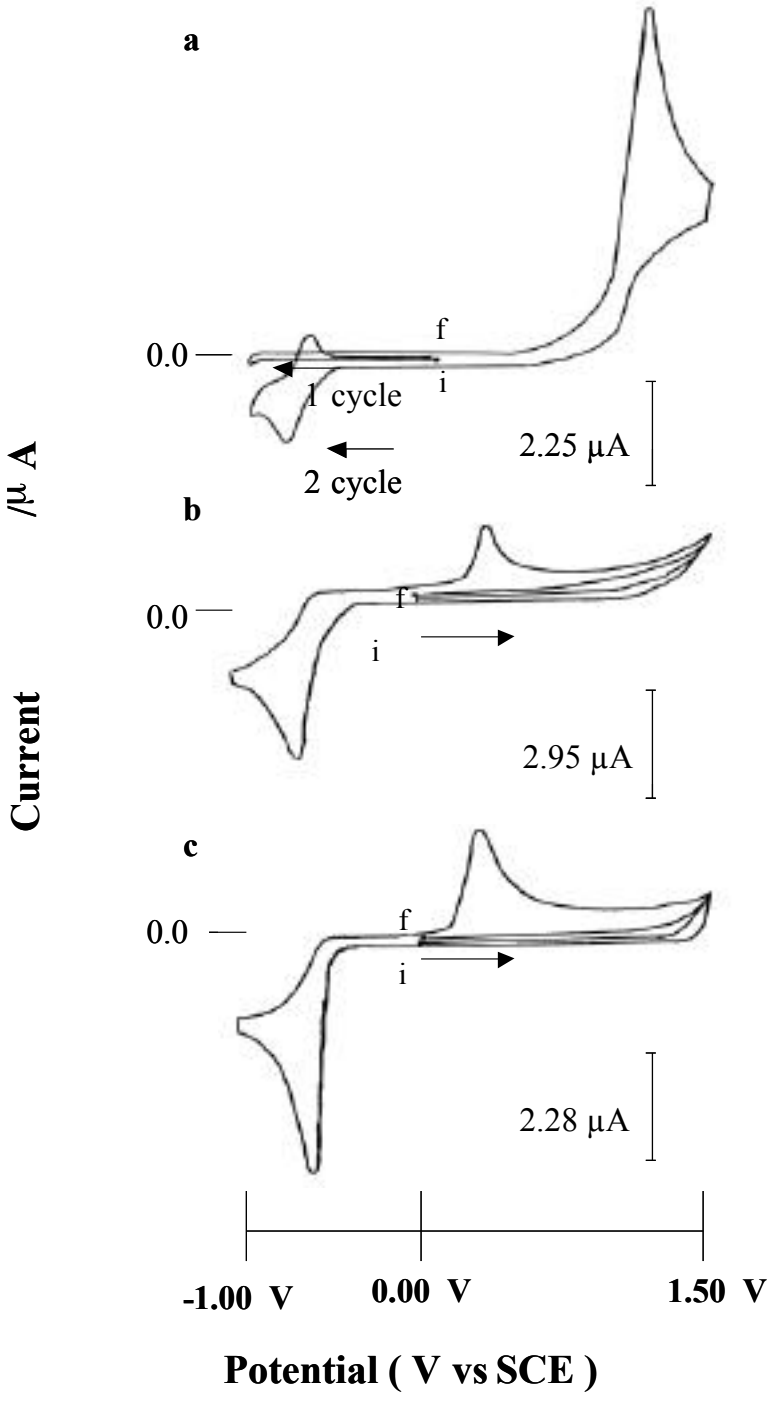


Figure 1. **a)** Cyclic voltammetry of **1b**$^-$ (10.0 mM) in DMF + 0.1M nBu$_4$NBF$_4$ at 10ºC. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/-1.00/1.50/0.00 V (2cycles) **b)** Cyclic voltammetry, after exhaustive electrolysis (1F/mol) of a solution 6mM of **1b**$^-$ at 1.30 in DMF + 0.1M nBu$_4$NBF$_4$ at 10ºC. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/1.50/-1.00/0.00 V (2 cycles) **c)** Cyclic voltammetry of **1** (6.0 mM) in DMF + 0.1M nBu$_4$NBF$_4$ at 10ºC. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/1.50/-1.00/0.00 V (2 cycles)

Figure 1d

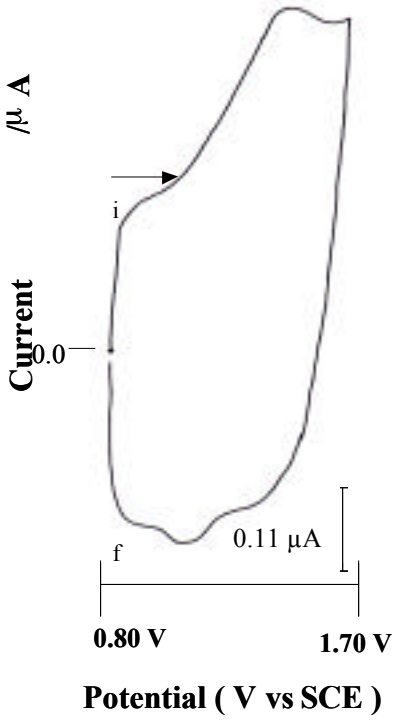


Figure 1d. Cyclic voltammetry of **1b**$^-$ (6.0 mM) in DMF + 0.1M *n*Bu_4NBF_4 at 10ºC. Scan rate 16.129V/s, platinium disk ultamicroelectrode (9.6 μm diameter). The scan is in the potential range: 0.80/1.70/0.80 V.

The peak intensity for the oxidation wave (analysed by comparison with the oxidation of tris-(4-bromophenyl)amine) corresponds to an one-electron process. The shape of the voltammograms (peak width) indicates that the electron transfer is fast with kinetic control by chemical reaction [19] . The peak potential is not concentration depending (in the range 2-20 mM) and the variation of the peak potential with the scan rate is 35 mV by unit log v (scan rate) at low scan rates. The voltammogram of **1 b** presents a single reversible oxidation one-electron wave, with E^o = 1.29 V, at v ≥ 16.125V.s^{-1} (Figure 1 d). We can thus conclude that the initially produced radical reacts by a first order reaction pathway in a stepwise EC mechanism.

After exhaustive (1 F) controlled-potential electrolysis (1.3V) of a solution of **1 b ,** cyclic voltammetric analysis of this solution (Figure 1 b) indicated that **1** (Figure 1 c [20]) was the only final product formed, and that it was produced in quantitative yield. On the first anodic scan, the oxidation wave, at 1.12 V, does not exist; only after the reduction of the product formed in the first cathodic scan, a new oxidation wave appears (c.a. 0.2V). The same behaviour is shown by an authentical sample of **1** (Figure 1 c) . Furthermore the final product **1** was identified by GC+MS, ^{1}H NMR and ^{13}C NMR analyses. (see Experimental Section).

In summary, our experimental results show that after exhaustive oxidation (1 F) of the σ^X-complex or *ipso*-adduct **1 b** , the rearomatized (formally substituted) compound **1**, is obtained. The voltammograms show that the oxidation of σ^X-complex or *ipso*-adduct **1 b** occurs through a two-step mechanism (stepwise mechanism EC): a fast electron-transfer on the electrode ,and a chemical reaction that is the rate determining step (Scheme 3)

$$\mathbf{1b}^- \; - \; 1e^- \longrightarrow \mathbf{1b}^{\bullet} \qquad E^o = 1.29 \text{ V} \qquad \textbf{eqn 2.1}$$

$$\mathbf{1b}^{\bullet} \xrightarrow{k} \mathbf{1} + {}^{\bullet}OCH_3 \qquad k \approx 10^5 \text{ s}^{-1} \qquad \textbf{eqn 2.2}$$

$$\mathbf{1b}^- \; - \; 1e^- \longrightarrow \mathbf{1} + {}^{\bullet}\mathbf{OCH_3} \qquad \textbf{eqn 2.3}$$

Scheme 3

The first step involves loss of one electron by the σ^X-complex or *ipso*-adduct **1 b** with formation of the corresponding radical **1 b** $^{\bullet}$. This radical undergoes first order C-O bond cleavage to give the final rearomatized product **1** [21]. We would like to remark that **1** is obtained after loss of just **one electron** by mol of **1 b** .

Electrochemical Behaviour of **2 a** [22] **(2 a (1,1)** and **2 a (1,3))**. A fresh sample of **2 a** (see the experimental section) was used in electrochemical studies. The voltammograms show the electrochemical behaviour of **2 a** , in all the cases, starting with a cathodic scan no reduction waves appear in the first scan, so neither **2** nor **3**

are initially present in the mixture of reactants. Figure 2 a shows that upon starting with an anodic scan, two waves with E_p = 0.68 V and E_p = 1.24 V are observed. When this anodic scan is followed by a cathodic scan, two waves with E_p = -0.53 V and E_p = -0.56 V appear.

These reduction waves [18 b] correspond, respectively, to 1-chloro-2,4,6-trinitrobenzene **2**, and 1,3,5-trinitrobenzene **3** formed in the oxidation scan.

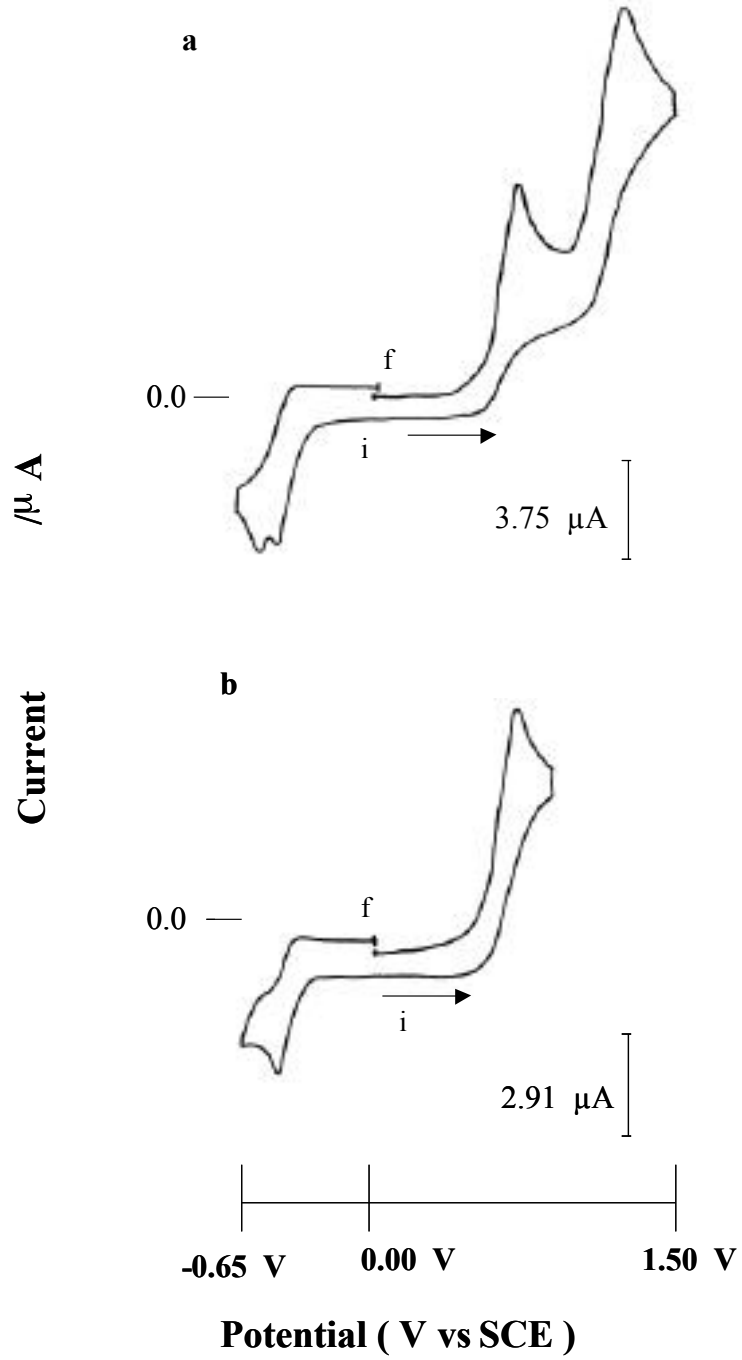


Figure 2. a) Cyclic voltammetry of **2a$^-$ (mixture 2a(1,1)$^-$ and 2a(1,3)$^-$)** (6.0 mM) in DMF + 0.1M nBu$_4$NBF$_4$ at 10ºC. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/1.50/-1.00/0.00 V

b) Cyclic voltammetry of **2a$^-$** (**2a(1,3)$^-$**) (6.0 mM) in DMF + 0.1M nBu$_4$NBF$_4$ at 10ºC. Scan rate 1.0 V/s, glassy carbon disk electrode (0.05 mm diameter). The scan is in the potential range: 0.00/1.00/-1.00/0.00 V

When the anodic scan is reversed after the first oxidation wave (E_p = 0.68 V) (Figure 2 b) ,only one reduction wave is obtained (E_p = -0.53 V). Thus, the oxidation wave at E_p = 1.24 V appears to be connected with the reduction wave at E_p = -0.56 V. That is to say, **2** is obtained after oxidation of **2 a (1,3)** (the σ^H-complex) and **3** is obtained after oxidation of **2 a (1,1)** (the σ^X-complex or *ipso*-adduct). Scheme 4 summarises these results.

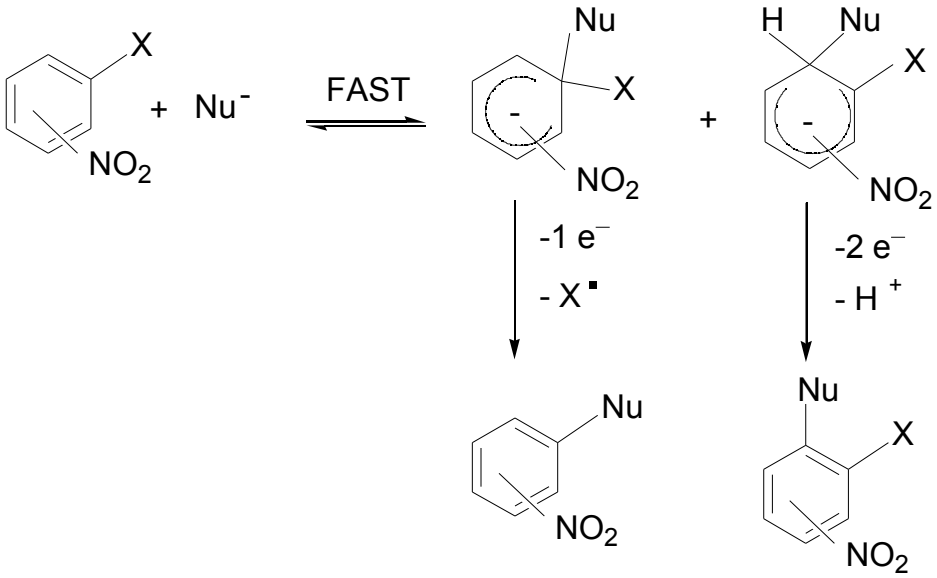
Since the electrochemical oxidation mechanism of σ^H-complexes involves two–electrons (NASH process)[1] and we have just shown that the corresponding oxidation of σ^X-complex involves one-electron (NASX process), it is possible to determine, by direct measure of the relative intensity of the peak potentials, their relative concentrations. From the voltammogram of Fig. 2, σ^H-complex:σ^X-complex = 30:70 in good concordance with what it is reported in the literature [16].

In order to identify and assign the oxidation waves it is worth to notice that the peak potential value in the σ^X-complexes appears close to the oxidation potential of the leaving group (the oxidation of the Cl occurs at 1.12V).

On the other hand, the potential values of some significant σ^H-complexes can be found in the literature [1].

In summary, the cyclic voltammmetry allows for:

a) Determining the type and number of σ -complexes present in the solution (number of waves, peak potential wave) and their relative amounts (intensity of peak wave).
b) Establishing the clean evolution of the σ -complexes to the rearomatized nitroaromatic compounds when oxidated, by observing the reduction wave of the late after one anodic scan of the solution.
c) It should be possible, in principle, to achieve the final substitution products by performing exhaustive electrolysis of solutions of σ -complexes at precise applied potentials. Therefore to obtain substituted products, by means of electrochemical oxidation methods, in the S_NAr reactions with different nucleophiles is the evident extension of this work.



Scheme 4

Synthetic Scope

The σ -complexes were prepared by careful stoichiometric addition of different Nu **(**CN^- ,F^-, CH_3O^-, $C_2H_5S^-$and *n*$BuNH_2$) to solutions 25mM of the nitroarenes, **2** to **9,** in dry DMF+ 0.1M *n*$BuNBF_4$ under inert atmosphere at 10ºC.Their characterisation was carried out by Cyclic Voltammetry (oxidation peak potential and intensity of the remaining nitroarene reduction wave) (columns 6, 10 and 4, Table 1 and 2). The yield of formation of σ -complexes is superior to 40% in all the cases and its formation is fast.

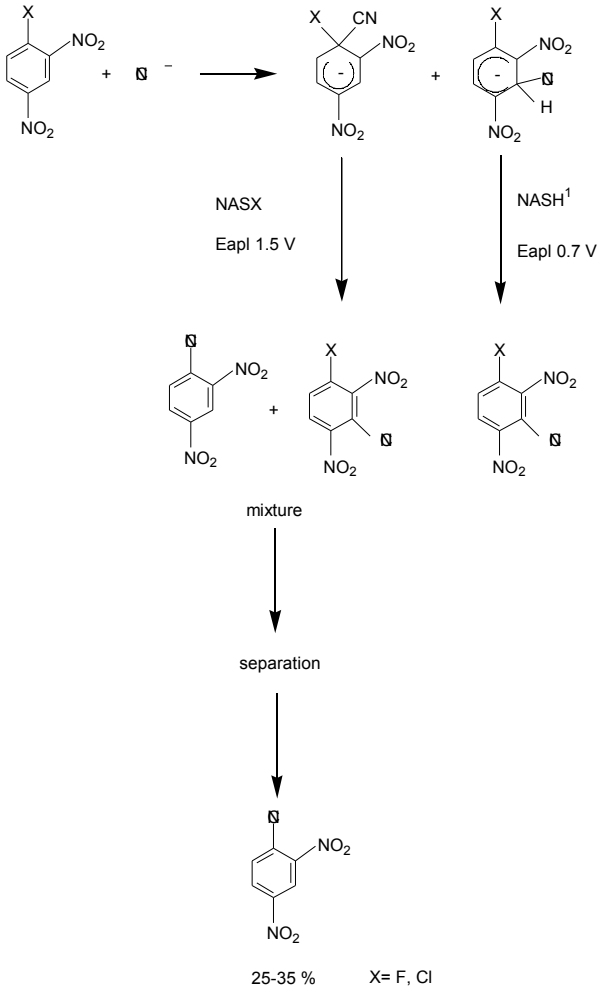
Cyclic voltammetry analysis clearly indicate that in our conditions no spontaneous evolution of the intermediates σ-complexes happens. Blank reactions (entries 1 and 6, Table 1, without oxidation of the mixture) led to less than 10% yields of substitution products, and these products are probably produced in the work up.

Table 1

Table 2

After exhaustive controlled potential electrolysis, at oxidation peak potential (column 8, Table 1 and 2) plus c.a. 100 mV, the rearomatized substituted compound (NASX product: ArNu, column 7, Table 1 and 2) is obtained. Electrochemical efficiency goes from 0.50 to 2.00 (column 11, Table 1 and 2). The values higher than 1.0 can be explained considering that the electrochemical oxidation of σ^X –complexes produces the displacement of the fast equilibrium (Scheme 4) to the right, that is to say, more reactant σ -complexes [23] are produced during the electrochemical reaction. The reaction is clean, only recovering starting material (column 2, Table 1 and 2) apart from the substitution product . When CN^-(Table 1, Entries:3,4,7 and 8. Table2, Entries:1,2,5,6 and 7) (Scheme 5) [1] and n$BuNH_2$ (Table 1, Entry 6) are used, a NASH product was obtained in a yield lower than 15%.

Very interesting is the reaction between CH_3O^- and 1,3-dinitrobenzene (1:1) (Table 2, Entry 3). 100% of σ -complexes is produced and only 5% substituted product , 3-nitroanisole, is obtained (NASX process). The formation of 1-hydride-1-methoxi-2,4-



Scheme 5

dinitrocyclohexadienyl anion (95%) leads, after one-electron oxidation, to starting material (95%). In an excess of $CH_3O^-$and when the electrolysis of the mixture was performed 24 hours later (Table 2, Entry 4) it is possible to obtain the 3-nitroanisole in good yield (90%), what indicates that the initially formed σ^H-complexes evolves to the σ^X-complexes even when X is placed in a non activated position (at least for X = NO_2)

It is important to underline that the oxidation peak potential of σ^X-complexes is very depending on the nature of leaving group, X^-. For the Cl^- or $F^-$is ~ 1.35-1.40V , for the $CH_3O^-$is ~ 0.9V and for the NO_2^- is ~ 0.60-0.80 V. For the σ^H-complexes the oxidation peak potential is only depending on the number of nitro groups present in the aromatic ring [1] : oxidation peak potential for two nitro groups complexes < oxidation peak potential for three nitro groups complexes.

The results described in Table 1 and 2 demonstrate that the electrochemical methodology is a powerful tool for the synthesis of fluorine, thiolate, alcoxi compounds and for the amination and the cyanation of aromatic compounds.

Halogen as leaving group (Table 1)

Synthesis of fluoro compounds **6** (Entry 1): Using, for instance, chloronitrocompounds we obtain fluoronitrocompounds by replacement of a Cl for a F. By mixing 1-Cl-2,4-DNB (**7**) with tetramethylammonium fluoride under nitrogen atmosphere in DMF and followed by electrochemical oxidation at 1.4 V passing 1F we obtain the Sanger's Reactant in good yield (60%) . The products can be easily separated by column chromatography. Furthermore the reactant is fully recovered (40%), being therefore the electrochemical reaction totally selective. Electrochemical oxidation of intermediate σ-complexes allows the substitution of other halogens (chloride) by fluoride in very mild conditions and it is therefore complementary to the well know fluorodenitration [24] as an election method to introduce fluorine in aromatic compounds . Our results open a new avenue for obtaining fluoro compounds, which are specially important due to their chemical and biological applications.

Synthesis of thio compounds,**12** and alcoxy compounds **5**: (Entries 5 and 2).Upon oxidation of the intermediate σ-complex, the chlorine atom in chloronitrocompounds can be easily replaced by a SH-R group. Thus, by mixing 1-Cl-2,4-DNB (**7**) with sodium ethanethiolate under nitrogen atmosphere in DMF followed by electrochemical oxidation at 1.4 V passing 1F we obtain a mixture of the ethyl 2,4-dinitrophenyl thioether (73% yield) and 2,4-dinitrothiophenol (10% yield) (Entry 5). The products were easily separated by column chromatography. Furthermore, the starting material that hasn't reacted was also recovered. Following the same procedure, good results were also obtained when potassium methoxide was used instead of sodium ethanethiolate (Entry 2)

Amination (compounds **13** and **14**) and Cyanation processes (compound **10**): (Entries 6,9 and 3,4,7,8 respectively). Good results were obtained for both processes, especially in the case of amines where substitution percentages are between 80-95% (Entries 6 and 9).

The case of cyanation, even though the yields are not very high, demonstrate the possibilities of the electrochemical technique, since it is well know that no heteroatom substitution is produced in standard S_NAr conditions when cyanide is used as a nucleophile [2] .The results reported in Table 1 (entries 3,4,7 and 8) indicate that upon oxidation of the σ^X-complex, moderate yields of cyanide displacement of halogen are obtained (as far as we know this constitutes the first report of such a substitution). Notice that cyanide has a strong tendency to attack non-substituted positions in the aromatic rings, and we have recently reported that by applying a lower potential (corresponding to the oxidation of the σ^H-complexes) to related reaction mixtures, selective oxidative hydrogen substitution is produced [1]

Leaving groups other than halogen (Table 2)

In Table 2, the oxidative substitution of leaving groups others than halogens is described. Thus, a very poor leaving group such as methoxide can be replaced by a very inactive nucleophile (from the point of view of the S_NAr of heteroatom, as commented in a previous paragraph) such as cyanide, in moderate yields (entries 1 and 2). On the other hand, a *meta* NO_2 group is poorly activating as compared with an *ortho* or *para* NO_2 group, and therefore, very few synthetically useful S_NAr reactions involving displacement of NO_2 group in *m*-dinitrobenzene have been reported [13] . In Table 2 (entries 3,4,5,6 and 7) different examples of oxidative nitro group substitution in *m*-dinitrobenzene by different nucleophiles (CH_3O^-, CN^-) are described with preparative yields that go from modest to good. Again, cyanide shows to be a fair nucleophile in our conditions, even able to displace a non activated nitro group.

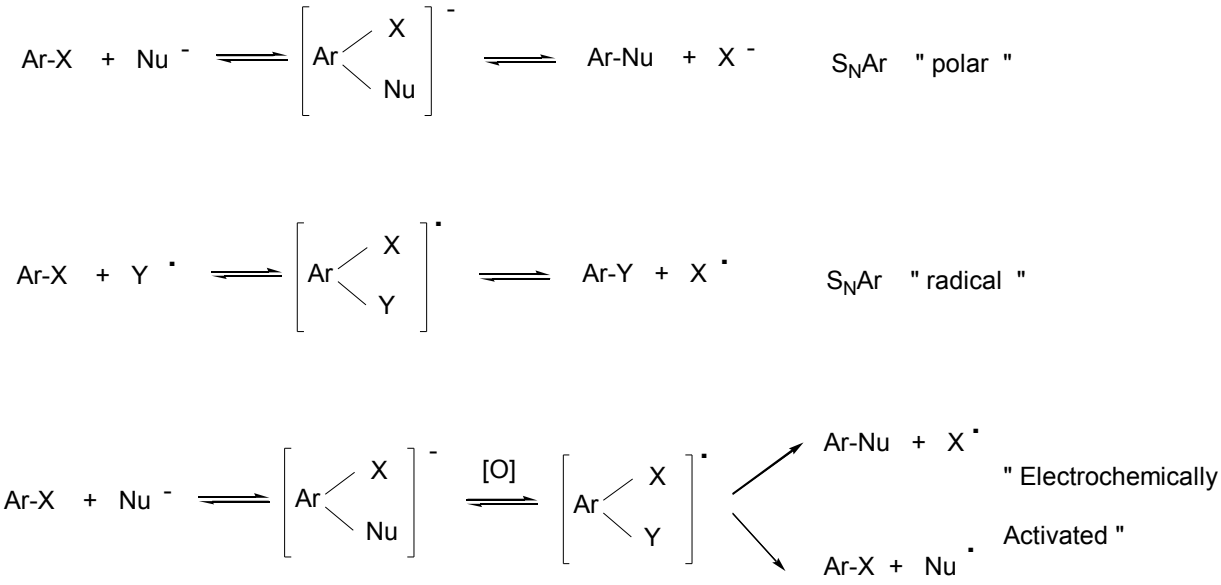
Finally, in entry 8, fluoride displacement of a nitro group in 1,3,5-trinitrobenzene is described.

Summary

The electrochemical oxidation of *ipso*-Meisenheimer complexes has been studied by means of cyclic voltammetry and a mechanism linking intermediates and products has been proposed (Scheme 3). Interestingly enough, electrochemical oxidation of these σ^X-complexes allow to "jump" from the "polar"[2] S_NAr mechanism (1st reaction) to the "radical" [25] *ipso*-substitution in aromatic compounds (2nd reaction), taking the best part of each: easy manipulation of reagents ("polar"), and activation of the intermediate towards decomposition into products ("radical"). In the Scheme 6 a comparison of the three mechanism is depicted.

The use of cyclic voltammetry as a tool in this field ,open multiple applications. For example, the kind and the number of Meisenheimer complexes present in a mixture can be characterised and quantified. It is also possible to know whether the final product obtained as a result of the Meisenheimer complex oxidation will be the substitution product or the initial compound. Considering that in must cases the classical nucleophilic aromatic substitution is not synthetically useful due to poor yields and slowness. Our electrochemical approach opens an avenue in the field of the synthesis of aromatic derivates since electrochemical activation makes possible to overcome the chemical drawbacks broadening the synthetic applications of S_NAr reactions.

As we have described here, it is possible to know the electrochemical features of the Meisenheimer complexes, their oxidation mechanisms. By applying the oxidation potential of the Meisenheimer adduct, precursor of the substituted product in a controlled potential electrolysis, to obtain the substitution product in most case in a selective way.



Scheme 6

Experimental Section

General Considerations. DMF ("SDS pour syntheses peptidiques") and NBu_4BF_4 (Fluka puriss.) were used without further purification.

1,3,5-Trinitrobenzene (**3**) was from Supelco. 1,3-Dinitrobenzene (**4**), 1-fluoro-2,4-dinitrobenzene (**6**), 1-chloro-2,4-dinitrobenzene (**7**), 3-nitrobenzonitrile (**8**), α,α,α-trifluoro3-nitro-toluene (**9**) were from Aldrich. 1-Methoxy-2,4-dinitrobenzene (**5**) was from Across.
All the reactants available commercially were of the highest purity available and were used without further purification.

Synthesis of Starting Materials. 1-Methoxy-2,4,6-trinitrobenzene **1** was synthesised in our laboratory. Following the method described in the literature [26] 20 ml of concentrated H_2SO_4 was added slowly to a mixture of 40 ml of fuming HNO_3 . The mixture was cooled in an ice bath. Immediately after 20ml of H_2SO_4 were added. Next, 4-methoxibenzoic acid (33 mmol) was added carefully to the acidic mixture. The ice bath was removed and the mixture was heated at 70-75º C during 3 hours. After cooling, it was poured into ice-water. The solid was collected and dried. The product obtained was identified as 1-methoxy-2-4-6-Trinitrobenzene **1** (6,8 g , 85 %).

1,1-Dimethoxy-2,4,6,trinitrocyclohexadienyl anion **1 b** potassium salt. It was synthesised following a method described in the literature[15]: A solution of CH_3OK/CH_3OH was prepared adding metallic potassium to anhydrous methanol. 1-methoxy-2,4,6-trinitobenzene (0.4 mmol) was dissolved in 5ml of anhydrous dioxane, under nitrogen atmosphere. The CH_3OK/CH_3OH solution was added to the 1-methoxy-2,4,6-trinitobenzene **1** solution under nitrogen atmosphere. The solution became red and a solid began to precipitate. The solid was collected and dried. It was identified as **1 b .**

1-Chloro-2,4,6-trinitobenzene **2** was synthesised in our laboratory. Following the method described in the literature [27]: 15ml of $POCl_3$ were added to 22mmol of picric acid. Next, 2,5 ml of pyridine were added carefully. The mixture was heated to 120-125ºC during one hour. After cooling the mixture to room temperature, it was poured into ice-water. The solid was collected and dried. It was identified as 1-chloro-2,4,6-trinitrobenzene **2** (3,9 g, 72 %)

Synthesis of a **2 a** in a solid form .Following the method described in the literature [16] :A solution of dry powered tetramethylamonium borohydride (2.0 mmol in 5 ml of tetrahydrofurane) was added to a solution of 1-Chloro-2,4,6-trinitobenzene **2** (2.0mmol in 5ml of tetrahydrofurane) The suspension was stirred, and kept under nitrogen atmosphere during 2 hours. The product formed was precipitated by addition of 50 ml of dry ether, collected by suction under nitrogen atmosphere, washed with dry ether, and dried by passing dry nitrogen there through. Yield 70%. **2 a** is a mixture 30:70 of 1,1-dihydride-3-chloro-2,4,6-trinitrocyclohexadienyl anion **2a(1,3)**$^-$ tetramethylamonium salt and 1-chloro-1-hydride- 2,4,6-trinitrocyclohexadienyl anion **2a(1,1)**$^-$ tetramethylamonium salt.
All products were identified by comparison of their spectroscopy behaviour with the reported in the literature for each case.

General procedure for NASX in nitroarenes. A solution of nitroarene (2-9) 25 mM in 5 ml of DMF, which contains 0.1646 g of NBu_4BF_4 (0.1M) as supporting electrolyte, was prepared under nitrogen atmosphere. The corresponding σ^X-complex was prepared by careful addition of the nucleophile (tetraethylammonium cyanide, tetramethylammonium fluoride, sodium ethanethiolate, N-butylamines or potassium methoxide) to a solution of the nitroarene under nitrogen atmosphere.

The oxidation peaks of σ-complexes were measured by cyclic voltammetry. An electrolysis were carried out at values of potential c.a. 100 mV more positive than the value measured for each σ^X-complex. A carbon graphite electrode was used as a working electrode.

After an exhaustive controlled potential electrolysis, the electrolysis was stopped. The mixture was extracted between toluene/water. The organic layer was dried with Na_2SO_4 and evaporated affording a residue that was analysed by gas chromatography. The final products were analysed by gas chromatography/mass

spectroscopy, ^{1}H RMN and cyclic voltammetry. The analyse showed the presence of nitoaromatic compounds.

Compounds **3-11**, **15-19** were identified by comparison of their spectroscopic behaviour with commercial samples. Compounds **12-14** were identified by comparison of their spectroscopic behaviour with the reported in the literature in each case [28-30].

Instrumentation and Procedures. The instrumentation and procedures were the same as previously described[1,21b,31] .

Acknowledgements. Financial support from the DGES and DGI through projects PB96-1145 and BQU2000-0336 and from "Generalitat de Catalunya" through the project 1999SGR00090 is gratefully acknowledged.

References and Notes

(1) a) Miller, J. *Aromatic Nucleophilic Substitution*. Elsevier. Amsterdam **1968**; b) Terrier, F. *Nucleophilic Aromatic Displacement*. VCH. Weiheim. **1991**; c) O.N. Chupakhin, O.N.; Charushin, V.N.; Van der Plas, H.C. *Nucleophilic Aromatic Substitution of Hydrogen*. Academic Press, **1994**.

(2) a) Gallardo, I.; Guirado, G. ; Marquet, J. *Chem.Eur.J*. **2001,** *7*, 1759 b) Gallardo, I.; Guirado, G. ; Marquet, J.; *Eur.J. Org.Chem*., **2001,** in press c) Gallardo, I.; Guirado, G. ; Marquet, J. *Eur.J. Org.Chem*., **2001,** in press
b) Gallardo, I.;, Guirado, G. ; Marquet, J. ES2000/489

(3) a) Makosza, M., in "*Current Trends in Organic Synthesis*", Pergamon Press, New York, **1983**; b) Makoska, M. ; Winiarski, J. *Acc. Chem. Res*. **1987**, *20*, 282.

(4) a) Makosza, M.; Wojciechowski, K. *Liebigs Ann. Chem*. **1997**, 1805; b) Makosza, M.; Ziobrowski, T.; Serebriakov, M.; Kwast, A. *Tetrahedron*, **1997**,*53*,4739; c) Makosza, M. *Ibidem*, **1998**, *54*,6811 and references therein; d) Makosza, M.; Lemek, T.; Kwast, A. *Tetrahedron Lett*. **1999**,*40*,7541.

(5) Lawrence, N.J.; Liddle, J.; Jackson D.A. *Synlett* **1996**, 55.

(6) Haglund, O.; Nilsson, M. *Synthesis* **1994**,242.
(7) Terrier, F; Goumont, R.; Pouet, M.J.; Hallé, J.C. *J.Chem.Soc.Perkin Trans. 2*,**1995**,1629.

(8) a) Halama, A.; Kaválek, J.; Machacek, V.; Weidlich T. *J.Chem.Soc., Perkin Trans. 1*, **1999**, 1839; b) Halama, A.; Machacek, V. *J.Chem.Soc*., *Perkin Trans. 1*, **1999**, 2495.

(9) Makosza, M.; Bialecki, M. *J.Org.Chem*. **1998**. *63*,4878.

(10) a) Katrizky, A.R.; Laurenzo, K.S. *J.Org.Chem*. **1986**,*51*,5039; b) Katrizky, A.R.; Laurenzo, K.S. *J.Org.Chem*. **1988**, *53*,3978.

(11) a) Huertas, I.; Gallardo, I.; Marquet, J. *Tetrahedron Lett*. **2000**,*41*, 279; b) Cervera, M.; Marquet, J. *Tetrahedron Lett*. **1996**,*37,* 759.

(12) Moutiers, G., Pinson, J. ; Terrier, F. ; Goumont, R. *Chem.Eur.J*. **2001,** *7*, 1712

(13) Kornblum, N. ; Cheng, L. ; Kerber, R.C. ; Kestner, M.M. ; Newton, B.N. ; Pinnick, H.W. ; Smith, R.G. ; Wade, P.A. *J.Org.Chem*.**1974**,*41*,1560

(14) Beck, J.R. *Tetrahedron*,**1978**,*34*,2057.

(15) Byrne, W.E.; Fendler, E.J.; Fendler, J.H.; Griffin, C.E. *J. Org. Chem*. **1967**, 89, 6917

(16) Machacek, V.; Lycka, A.; Nadvornik, M. *Coll.Czech.Chem.Commun*, **1985**, *50*, 2598

(17) Compound **1 b** can be isolated as pure crystalline potassium salt [15] (See Experimental Section)

(18) a) E^{o} = -0.73 V vs SCE. This potential is identical to the one found for the reduction of **1** [18 b] ; b) Guirado, G. Unpublished Results.

(19) a) Andrieux, C.P.; Savéant, J.M. "*Electrochemical Reactions*" in "*Investigation of rates and Mechanism of Reactions*", Techniques of Chemistry, *Vol. 6*, Chapter 2.1(Ed. C.F. Bernasconi),

Wiley, New York, **1986;** b) Andrieux. C.P. "*Organic Electrochemical Mechanisms*" in *"Encyclopedia of Analytical Chemistry",* Wiley, Chichester, **2000**, 9983.

(20) The reduction wave of **1** is reversible at high scan rate ($v > 75\ V.s^{-1}$) and 2 to 20 mM concentration or at scan rate of $1\ V.s^{-1}$ and a low concentration ($c < 1$ mM)[18 b]. 0.1M KBF_4 is needed to observe the reduction wave of **1** reversible if c< 2mM.

(21) a) In cases where $CH_3O^{\cdot}$ must be produced, dismutation to metanol and formaldehide is postulated [21 b]. b) Melloni, G. *J.Org.Chem*., **1992**,*57*,1444, c) Similar reactions have been proposed in the literature [21d] .d) Gallardo, I.; Guirado, G. ; Marquet, J. *J.Electroanal.Chem*., **2000**,*488*,64

(22) Compound **2 a** was obtained in a solid form crystalline tetramethylammonium salt [16] (see Experimental Section).The ^{1}HNMR studies indicates that **2 a** is a mixture (70:30) of adducts: **(1,1)** σ^X-complex and **(1,3)** σ^H-complex, respectively.

(23) For the NASH, the H^+, loss after the first one-electron oxidation, inactivates the nucleophile and the reaction stops.

(24) a) Clark, J.H.; Smith. D.K. *Tetrahedron Lett*. **1985**,*26*,2233; b) Clark, J.H. ;Boechat, J. *J.C.S.Chem.Commun.***1993**,921

(25) a) Tiecco*,* M. *Acc.Chem.Res*.**1980**, *13*, 51; b) Minisci, F. *Top.Curr.Chem*. **1976,** *62*, 1

(26) Reese, C.B.; Pei-Zhuo*,* Z. *J. Chem. Soc. Perkin Trans. I,* **1993***, 2291*

(27) Lam*,* K-B.; Miller, J.; Samenho*,* P.J. *J. Chem. Soc. Perkin Trans. II, **1977**, 457*

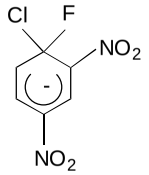
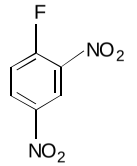
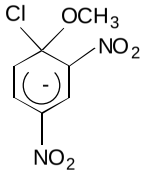
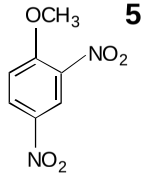
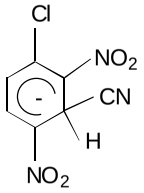
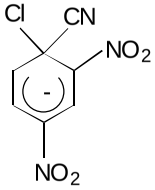
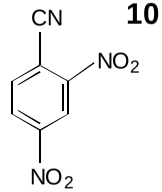
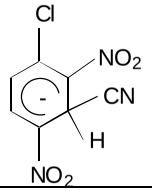
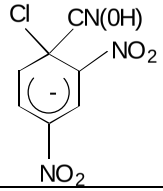
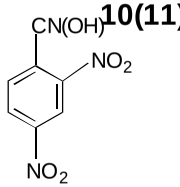
(28) Evans, T.L. ; Kinnard, R.D. *J. Org. Chem*., **1983,** *48*, 2496

(29) Tammilenko, S.; Luthava. S.; Saarnivaara, K.; Toviola, K. *Farm. Aikak*, **1976**, *85*, 69

(30) Zemmanova, E.; Zeman, S. *J. Chromatog*., **1978**, 154, 33

(31) Andrieux, C.P.; Larrumbre, D.; Gallardo, I. *J. Electroanal. Chem*., **1991**, 304, 241

Table 1

Entries	Ar-X	Nu^- Ar-X:Nu^-	[a]TOTAL σ– Complexes (%)	[b]Others σ^H– Complexes	Epa (V) of Others σ– Complexes	$\sigma-^X$ Complex	Epa (V) $\sigma-^X$ Complex	NASX Product (Ar-Nu)	[c]Yield (%) NASX	r (r= |Ar-Nu| / |TOTAL σ-Complexes|)
X=Halogen										
1[h]	**7**	F^- 1:1	40	-	-		1.39	 **6**	60[d]	1.50
2	**7**	$^-OCH_3$ 1:1	40	-	-		1.24	 **5**	80[d]	2.00
3	**7**	CN^- 1:1	58		0.59[e]		1.38	 **10**	25[f]	0.63
4	**7**	CN^- + H_2O 1:1:1	58		0.59[e]		1.38(1.24)	 **10(11)**	10(20)[f]	0.25(0.50)

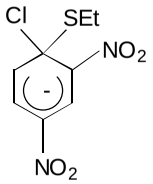
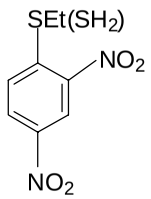
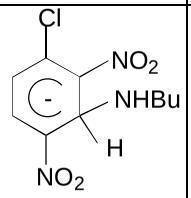
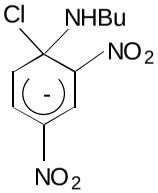
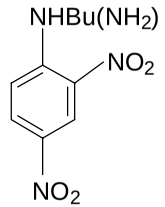
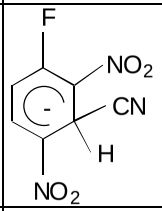
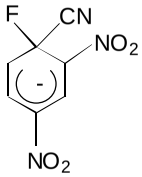
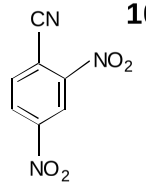
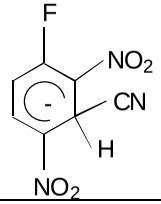
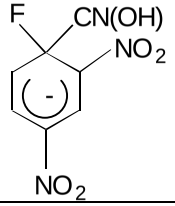
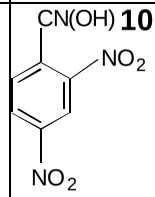
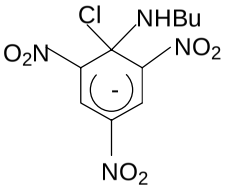
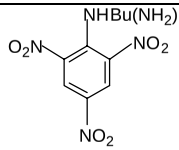
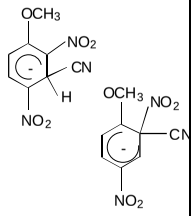
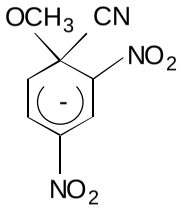
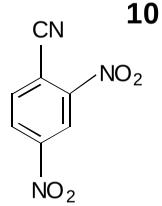
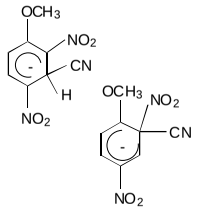
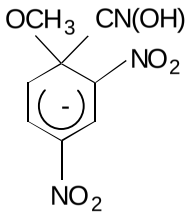
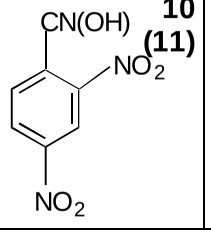
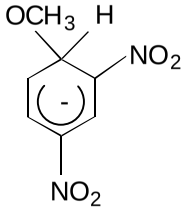
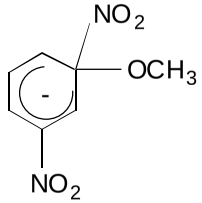
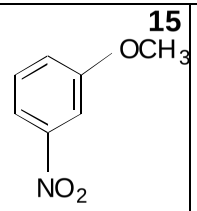
5	**7**	$^{-}$SEt 1:1	58	-	-		1.38	**12** 	73[d](10)	1.26(0.17)
6 [h]	**7**	$BuNH_2$ 1:2	43		1.12[g]		1.35	**13** 	80[d](5)	1.86(0.12)
7	**6**	CN^{-} 1:1	47		0.56[e]		1.38	**10** 	34[f]	0.85
8	**6**	CN^{-} + H_2O 1:1:1	47		0.56[e]		1.34(1.28)	 **10(11)**	18(16)[f]	0.45(0.40)
9	**2**	$BuNH_2$ 1:2	70	-	-		1.35	 **14**	95[d](5)	1.36(0.07)

Table 1. Exhaustive Electrolysis of σ^X- complexes (column 5). Halogen as leaving group.

[a] The σ- complexes were carefully prepared by addition of the nucleophile to solutions of nitroarenes 25 mM in DMF/0.1M *n*-Bu_4NBF_4 under inert atmosphere at 13 ºC [b] Other Meisenheimer complexes present in the mixture [c] The oxidation products were analysed by cyclic voltammetry [1a, 21b], gas chromatography/mass spectroscopy and ^{1}H-RMN [d] Shift of the equilibrium to the right [e] The electrochemical oxidation of the σ^H-adduct leads to a NASH product described in[1] [f] Excess of cyanide can be eliminate by eletrochemical oxidation at 1.33 V [g] The electrochemical oxidation of the σ^H-adduct leads to a NASH product (15%) which will be described in a foreseen future [h] Blank reactions (without oxidation of the mixture) led to less than 10% yields of substitution products.

Entries	Ar-X	Nu^- Ar-X:Nu^-	[a]TOTAL σ– Complexes (%)	[b]Others σ– Complexes	Epa (V) of Others σ– Complexes	$\sigma-^X$ Complex	Epa (V) $\sigma-^X$ Complex	NASX Product (Ar-Nu)	[c]Yield (%) NASX	r (r= |Ar-Nu| / |TOTAL σ-Complexes|)
X=Methoxi group										
1	**5**	CN^- 1:1	40		0.61[e](0.60)		0.83	**10** 	26[d]	0.65
2	**5**	CN^- + H_2O 1:1:1	40		0.61[e](0.60)		1.18(0.83)	**10 (11)** 	13[d](11)	0.33(0.28)
X=Nitro group										
3	**4**	$^-OCH_3$ 1:1	100		0.72[f]		0.77	**15** 	5	0.05

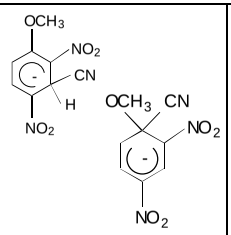
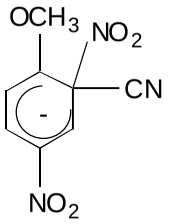
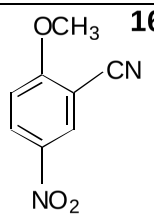
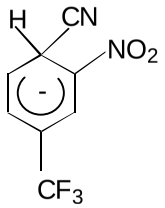
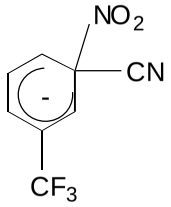
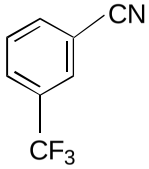
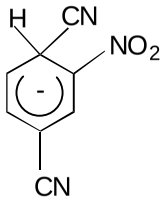
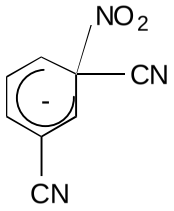
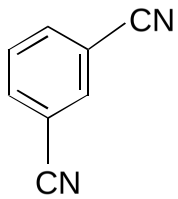
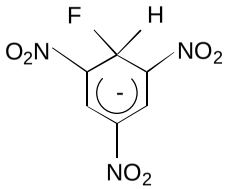
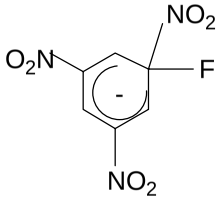
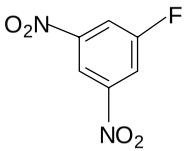
4	**5**	CN^- 1:1	40		g 0.61[e](0.83)		0.60	**16** 	26[d]	0.52
5	**9**	CN^- 1:2	50		0.58[e]		0.86	**17** 	27	0.54
6	**8**	CN^- 1:2	70		0.65[e]		0.94	**18** 	50	0.50
7	**3**	F^- 1:2	100		1.09[f]		0.78	 **19**	10	0.10

Table 2. Exhaustive Electrolysis of σ^X- complexes (column 5). Leaving group other than halogen.

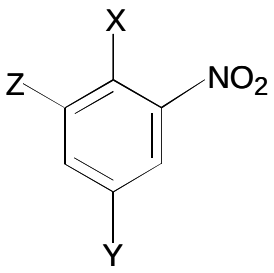
[a] The σ- complexes were carefully prepared by addition of the nucleophile to solutions of nitroarenes 25 mM in DMF/0.1M *n*-Bu_4NBF_4 under inert atmosphere at 13 ºC [b] Other Meisenheimer complexes present in the mixture [c] The oxidation products were analysed by cyclic voltammetry [1a, 21b], gas chromatography/mass spectroscopy and ^{1}H-RMN [d] Shift of the equilibrium to the right [e] The electrochemical oxidation of the σ^H-adduct leads to a NASH product described in[1] [f] The electrochemical oxidation of this σ-adduct leads to the reactant [g] The same experiment was described in Entry 1.

PATENTE DE INVENCIÓN

Preparación Electroquímica Nitro-, Dinitro- y Trinitroderivados Substituidos.

Solicitante: Universitat Autònoma de Barcelona

Inventores: Iluminada Gallardo*, Gonzalo Guirado, Jordi Marquet



Y= NO_2, CN o CF_3

Z= H, NO_2 o CN

X= F, Cl, Br, NH_2, OR', R''

NºSolicitud 200000489

OFICINA ESPAÑOLA DE PATENTES Y MARCAS

INSTANCIA DE SOLICITUD DE:

NUMERO DE SOLICITUD: P200400411

FECHA Y HORA DE PRESENTACION EN LA O.E.P.M.: 00 MAR -1 16:46

(X) PATENTE DE INVENCION ( ) MODELO DE UTILIDAD

(1)
( ) SOLICITUD DE ADICION
( ) SOLICITUD DIVISIONAL
( ) CAMBIO DE MODALIDAD
( ) TRANSFORMACION SOLICITUD EUROPEA

(2) EXPED. PRINCIPAL O DE ORIGEN
MODALIDAD
NUMERO SOLICITUD
FECHA SOLICITUD
MODALIDAD
NUMERO SOLICITUD
FECHA SOLICITUD

FECHA Y HORA PRESENTACION SALIDA OFICINA O.E.P.M.:

(3) LUGAR DE PRESENTACION: MADRID — CODIGO: 28

(4) SOLICITANTE	APELLIDOS O DENOMINACION SOCIAL	NOMBRE	DNI
UNIVERSITAT AUTONOMA DE BARCELONA			

(5) DATOS DEL PRIMER SOLICITANTE
DOMICILIO
LOCALIDAD BELLATERRA — TELEFONO
PROVINCIA BARCELONA — COD POSTAL 08193
PAIS RESIDENCIA ESPAÑA — COD PAIS ES
NACIONALIDAD ESPAÑOLA — COD NACION ES

(6) INVENTORES — (7) ( ) EL SOLICITANTE ES EL INVENTOR (X) EL SOLICITANTE NO ES EL INVENTOR O NO ES EL UNICO INVENTOR

(8) MODO DE OBTENCION DEL DERECHO: (X) LABORAL ( ) CONTRATO ( ) SUCESION

APELLIDOS	NOMBRE	NACIONALIDAD	PAIS RESID.
GALLARDO GARCIA	YOLANDA	ESPAÑOLA	ES
POZUELO LOPEZ	MONTSERRAT	ESPAÑOLA	ES
MARQUET CORTES	JORDI	ESPAÑOLA	ES

(9) TITULO DE LA INVENCION
PREPARACION ELECTROQUIMICA DE ARIL-, HETERIL- Y COMPUESTOS HETEROARILSUSTITUIDOS.

(10) INVENCION REFERENTE A PROCEDIMIENTO MICROBIOLOGICO SEGUN ART. 25.2 L.P. ( ) SI ( ) NO

(11) EXPOSICIONES OFICIALES
LUGAR — FECHA

(12) DECLARACIONES DE PRIORIDAD

PAIS DE ORIGEN	COD PAIS	NUMERO	FECHA

(13) EL SOLICITANTE SE ACOGE A LA EXENCION DE PAGO DE TASAS PREVISTA EN EL ART. 162 L.P. ( ) SI ( ) NO

(14) REPRESENTANTE: APELLIDOS Ponti Salos — NOMBRE Antonio — CODIGO 388/3
DOMICILIO: C. Consell de Cent, 322 — LOCALIDAD Barcelona — PROVINCIA Barcelona — COD POSTAL 08007

(15) RELACION DE DOCUMENTOS QUE SE ACOMPAÑAN

(X) DESCRIPCION Nº DE PAGINAS 21	(X) DOCUMENTO DE REPRESENTACION
(X) REIVINDICACIONES Nº DE PAGINAS 2	( ) PRUEBAS
( ) DIBUJOS Nº DE PAGINAS	(X) JUSTIFICANTE DEL PAGO DE TASAS
(X) RESUMEN	( ) HOJA DE INFORMACIONES COMPLEMENTARIAS
( ) DOCUMENTO DE PRIORIDAD	(X) OTROS SOP. MAGN. Y DECL. JURAD.
( ) TRADUCCION DEL DOCUMENTO DE PRIORIDAD	

FIRMA DEL FUNCIONARIO

FIRMA DEL SOLICITANTE O REPRESENTANTE

(16) NOTIFICACION DE PAGO DE LA TASA DE CONCESION

Se le notifica que esta solicitud se considerará retirada si no procede al pago de la tasa de concesión para el pago de esta tasa dispone de tres meses a contar desde la publicación del anuncio de la concesión en el BOPI, más los diez días que establece el art. 81 del R.D. 10-10-86.

Modelo oficial de la O.E.P.M.

ILMO. SR. DIRECTOR DE LA OFICINA ESPAÑOLA DE PATENTES Y MARCAS

UNE A-4 MOD. 2101

NÚMERO DE SOLICITUD
P200903439

FECHA DE PRESENTACIÓN

PATENTE

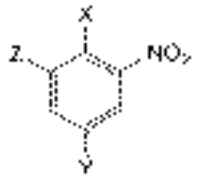
RESUMEN Y GRAFICO

RESUMEN (Máx. 150 palabras)

PREPARACIÓN SELECTIVA DE NITRO-, NITRITO- Y TRIFLUOROMETILADOS ORGÁNICOS

Procedimiento para la funcionalización de derivados dicloroaromáticos de fórmula I con nucleófilos a través de la formación de los correspondientes complejos de Meisenheimer y en posterior oxidación electrogenética.

GRAFICO



X: NO2, CN o CF3;
Z: H, NO2 o CN
Y: H, Cl, Br, NO2, NO, CN, F...

Fórmula I

OFICINA ESPAÑOLA DE PATENTES Y MARCAS

(51) Clasificación Internacional de Patentes

(21) Número (22) Fecha de presentación (23) Fecha de prioridad

A1 (11) PATENTE DE INVENCIÓN

ES 2 000 0489

(43) Fecha de publicación de la solicitud

1 MAR. 2000

(71) Solicitante(s)

UNIVERSITAT AUTONOMA DE BARCELONA

Nacionalidad

ESPAÑOLA

Dirección

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(72) Inventor/es

Licenciado GRILLADO GARCIA, Gonzalo QUIRANO LOPEZ y Jorge MARQUET CORTES

(74) Agente/s

(30) Datos de prioridad

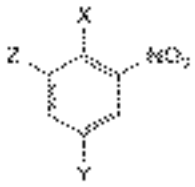
(45) Fecha de la concesión

(45) Fecha de publicación de la concesión

(54) Título

PREPARACION ELECTROQUIMICA DE NITRO-, DINITRO- Y TRINITRODERIVADOS SUSTITUIDOS.

(57) Resumen



Y= NO2, CN o CF3
X= H, NO2 o CN
Z= F, Cl, Br, NO2, SO2, CF3, ...

Fórmula I

(57) Resumen

PREPARACIÓN ELECTROQUÍMICA DE NITRO-, DINITRO- Y TRINITRODERIVADOS SUSTITUIDOS

Procedimiento para la funcionalización de derivados nitroaromáticos de fórmula I con nucleófilos a través de la formación de los correspondientes complejos de Meisenheimer y su posterior oxidación electroquímica.

2

PREPARACION ELECTROQUIMICA DE NITRO-, DINITRO- Y TRINITRODERIVADOS SUBSTITUIDOS

CAMPO TÉCNICO DE LA INVENCIÓN

La presente invención se refiere a un nuevo procedimiento para la funcionalización de derivados nitroaromáticos que comprende la formación de un intermedio aniónico entre un derivado nitroaromático substituido y un nucleófilo y la posterior oxidación de dicho intermedio mediante procedimientos electroquímicos. Mediante un procedimiento según la presente invención, se consigue la Substitución Nucleófila Aromática de compuestos nitroaromáticos substituidos con buenos rendimientos y en condiciones suaves, de manera selectiva y no contaminante. Dicho procedimiento permite la obtención de productos que presentan importantes y diferentes aplicaciones, por ejemplo explosivos, polímeros y productos utilizados dentro de la industria farmacéutica o textil.

ESTADO DE LA TÉCNICA ANTERIOR A LA INVENCIÓN

En el estado de la técnica, es bien conocida la funcionalización de compuestos aromáticos mediante reacciones de substitución nucleófila, encaminadas a la formación del esqueleto fundamental de productos de interés farmacéutico o de importancia industrial (March, J. (1992) *Advanced Organic Chemistry*, John Wiley & Sons, New York, p.641):

$$ArX + Nu^{-} \rightarrow ArNu + X^{-}$$

3

La viabilidad de este tipo de reacciones depende de la estructura del substrato (ArX) y, fundamentalmente, de la naturaleza del grupo saliente (X^-) y del nucleófilo (Nu^-). Así, este tipo de reacciones son satisfactorias únicamente en ciertos casos: a) reacciones activadas por grupos electroatrayentes en posiciones o- y p- respecto del grupo saliente (X), b) reacciones catalizadas por bases fuertes, c) reacciones iniciadas por donadores de electrones y d) reacciones de substitución del nitrógeno de sales de diazonio por un nucleófilo.

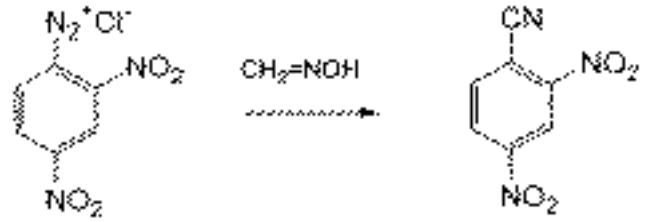
Generalmente, en las reacciones de Substitución Nucleófila Aromática, el reactivo de partida (ArX) es un haloaromático substituido [Zimmermann, W.Z. (1995) *Physiol.Chem.* 233, 257]. La preparación de dichos haloaromáticos substituidos presenta varios inconvenientes: la etapa de introducción de un halógeno a un compuesto aromático para eliminarlo en un paso posterior encarece el proceso y no es conveniente desde el punto de vista del medio ambiente. Por otro lado, las condiciones de reacción que se requieren no son suaves y los rendimientos obtenidos son bajos.

Un método sintético alternativo para la funcionalización de compuestos aromáticos utilizando nucleófilos son las reacciones electroquímicas de substitución anódica [Nawzonek, S. (1971) *Synthesis* 6, 285]. En las reacciones electroquímicas, los electrones, considerados como reactivos, se utilizan para iniciar la reacción. Para que la reacción tenga lugar, el reactivo de partida, ArX, debe ser oxidable en el rango de potenciales accesible en el medio de reacción utilizado, mientras que el nucleófilo, Nu^-, no debe ser oxidable en ese mismo rango de potenciales. Un ejemplo de un proceso de substitución anódica es [Baker, V.B. and Burgett, E.E. (1965) *Tetrahedron Lett.*, 4065]:

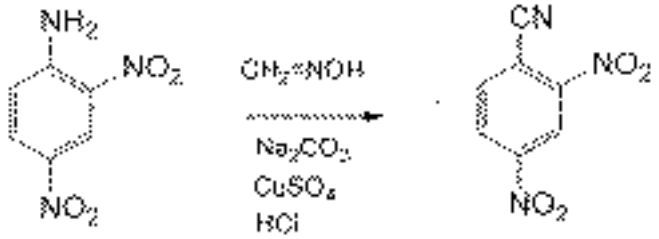
$$ArH + CN^{-} \rightarrow ArCN + H^{+} + 2e^{-}$$

Una importante limitación de este tipo de reacciones es la necesidad de utilizar substratos capaces de ser oxidados a potenciales en los que el nucleófilo sea estable. En particular, estos métodos no son adecuados cuando se utilizan compuestos nitroaromáticos como substratos de partida.

En particular, el 2,4-dinitrobenzonitrilo [4110-33-2] utilizado como precursor del 2,4-diaminobenzonitrilo [Wright, J.B. and Sinkula, A.A. *Ger.Offen.*, 34pp DE2529256] y en la fabricación de polímeros [Frost, L.N. *Fr.Demande*, 20 pp FR2235151] se ha sintetizado mediante métodos químicos alternativos, que se resumen a continuación:

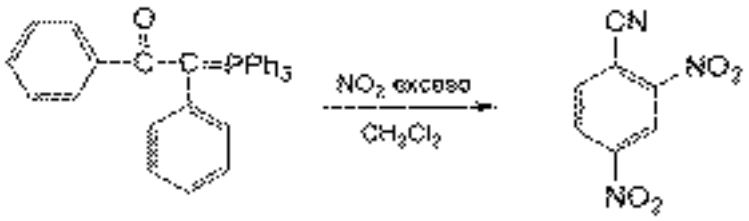


Kopeikin, V.V.; Sosnina, V.A.; Ustinov, G.S.; Mironov. *Deposit Doc.*, 1980, SPSTL, 43 Khb-080, 4pp. Avail SPSTL.

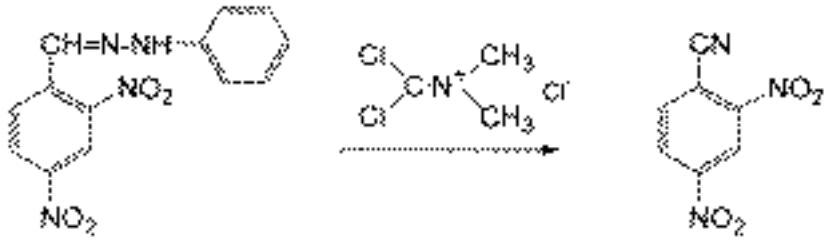


J.X. Wang; *Hua Xuexh Huesh Pao*, 1980, 38, 395

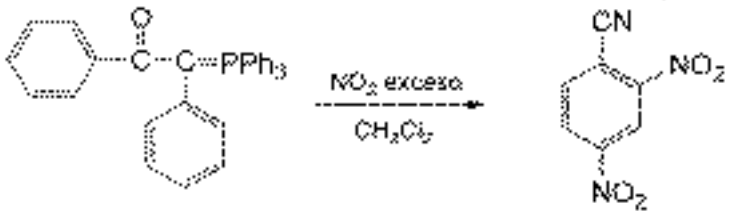
5



C.N. Wang. *K'o Neuek T'ung Pao*, **1981**, 26, 703.



B. Kokel; G. Menichi; M. Hubert-Habart. *Synthesis*, **1985**, 2, 201.



R.A. Aitken; N. Karodina. *Sur. J. Org. Chem.*, **1999**, 1, 251.

Todas las reacciones que acabamos de presentar para la síntesis del 2,4-dinitrobenzonitrilo son en

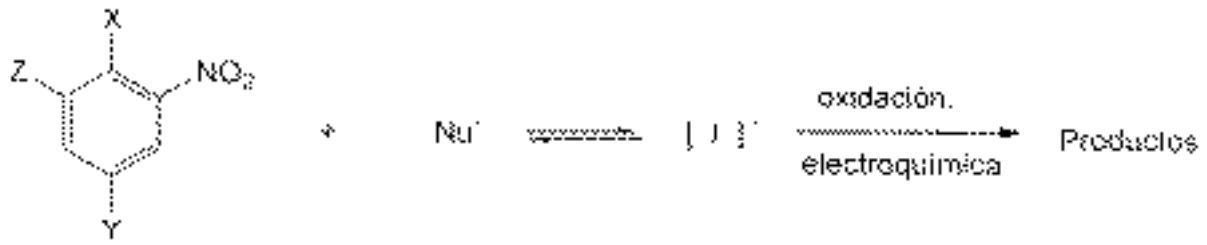
general poco selectivas, obteniéndose rendimientos globales comprendidos entre el 50 y el 90 %. En todo caso, los procedimientos que conducen a los mejores rendimientos parten de reactivos de alto coste, poco apropiados para reacciones a gran escala.

La presente invención proporciona un nuevo procedimiento para la preparación de compuestos nitroderivados substituidos que supera las deficiencias de los procedimientos existentes en el estado de la técnica. Ventajosamente, el procedimiento de la presente invención utiliza condiciones suaves de trabajo y no contaminantes, y es altamente selectivo.

DESCRIPCIÓN DE LA INVENCIÓN

La presente invención se refiere a un procedimiento para la substitución nucleófila aromática de compuestos nitroaromáticos caracterizado por el hecho de ser un procedimiento electroquímico.

Dicho procedimiento comprende la formación de un complejo de adición entre el nucleófilo y el derivado nitroaromático (complejo σ o complejo de Meisenheimer) y la posterior oxidación electroquímica de dicho intermedio.



Más concretamente, el procedimiento según la presente invención comprende dos etapas:

7

a) La primera etapa consiste en la reacción entre el compuesto nitroaromático y el nucleófilo, obteniéndose "in situ" el complejo σ o complejo de Meisenheimer, $[I]^-$:

$$ArH + CN^- \rightarrow [I]^-$$

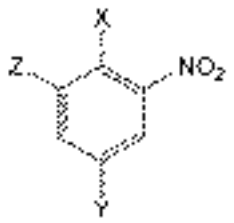
b) Posteriormente se lleva a cabo la oxidación selectiva de los complejos σ mediante métodos electroquímicos, utilizando un potencial siempre inferior al potencial de oxidación del Nu^-:

$$[I]^- \rightarrow ArNu + H^+ + 2e^-$$

En el procedimiento de la presente invención se utilizan disolventes polares apróticos y temperatura ambiente. Según el procedimiento de la presente invención pueden utilizarse relaciones estequiométricas entre el derivado nitroaromático y el nucleófilo comprendidas entre 1:1 y 1:10.

En un procedimiento de síntesis de compuestos nitroaromáticos sustituidos según la presente invención, pueden utilizarse como productos de partida substratos aromáticos que contengan al menos: a) dos grupos nitro en posición 1,3-, b) un grupo ciano y un grupo nitro en posición 1,3- y c) un grupo nitro y un grupo CF_3 en posición 1,3-. Más concretamente, los compuestos nitroaromáticos de partida que pueden utilizarse en un procedimiento según la presente invención responden a la fórmula:

B



- siendo Y: NO_2, CN o CF_3
- siendo Z: H, NO_2 o CN
- siendo X: F, Cl, Br, NH_2, CN, NO_2, OR' o R'', donde R' y R'' representan indistintamente un grupo alquilo, arilo o H.

Según el procedimiento de la presente invención pueden utilizarse diferentes nucleófilos, cargados o neutros. Nucleófilos cargados adecuados para un procedimiento según la presente invención incluyen: H^-, CN^-, NO_2^-, OH^-, ^-OR, ^-SR, ^-OR, F^- y carbaniones. Nucleófilos neutros adecuados para un procedimiento según la presente invención son por ejemplo aminas, entre ellas aminas primarias del tipo RNH_2.

La obtención de derivados nitroaromáticos mediante un procedimiento de electrosíntesis según la presente invención presenta importantes ventajas frente a los procedimientos existentes en el estado de la técnica, entre las cuales destacan:

*las condiciones suaves y no contaminantes de la reacción

*la disponibilidad y bajo coste de los reactivos

*la elevada selectividad y economía de átomos

*la escasez de productos secundarios obtenidos (siendo además productos que poseen su propio mercado, de manera que pueden aprovecharse económicamente).

En consecuencia, el procedimiento de la presente invención es muy susceptible de aplicación industrial. Así, mediante un procedimiento según la presente invención, pueden obtenerse productos de gran importancia industrial. La aplicación industrial concreta de los compuestos nitroaromáticos substituidos obtenidos mediante el procedimiento de la presente invención depende del reactivo de partida y del nucleófilo utilizados.

Por ejemplo, partiendo de 1,3-dinitrobenceno como reactivo pueden obtenerse diferentes productos de importancia industrial en función del nucleófilo utilizado:

→CN^-: 2,4-dinitrobenzonitrilo es un producto ampliamente utilizado en la fabricación de polímeros

→$R-NH_2$: aminoderivados muy utilizados para la preparación de azomoléculas, intermedios de colorantes en tintes de imprenta y como inhibidores de la corrosión

→F^-: reactivo de Sanger, (análisis de proteínas), industria farmacéutica

→$^-OCH_3$: insecticida activo

Por ejemplo, partiendo de 1,3,5-trinitrobenceno y 1,3,5-trinitrobencenos substituidos como reactivos, pueden obtenerse:

→Productos explosivos: 2,4,6-trinitrobenzonitrilo, trinitroanisol, derivados trinitrofluorados

→Fotoconductores: 1,2,4-trinitrobenceno, 1,2,3,5-tetranitrobenceno, 2,3,4-trinitrotolueno

→Herbicidas : tipo trifamlin

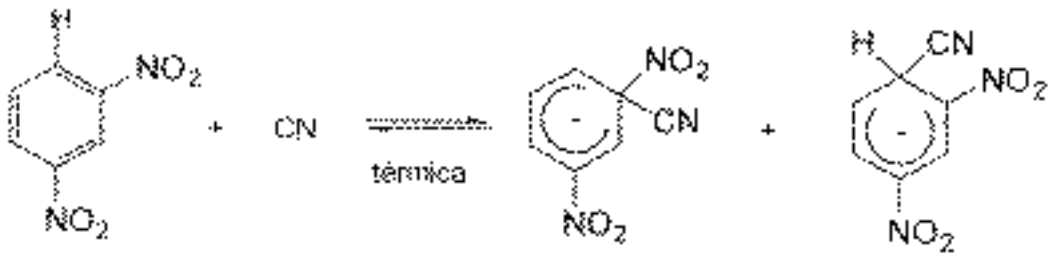
EJEMPLOS

A continuación se incluye un ejemplo a modo ilustrativo no limitativo de la invención, para una mejor

comprensión de lo descrito hasta este punto. A menos que se indique lo contrario, los reactivos se obtuvieron a partir de proveedores comerciales.

Ejemplo 1: Obtención del 2,4-dinitrobenzonitrilo a partir del 1,3-dinitrobenceno y el cianuro de tetraetilamonio (relación 1:1)

a) Se pesan por separado 0.0126 g de 1,3-dinitrobenceno (1,3-DNB) y 0.0117 g de cianuro de tetraetilamonio (CNTEA) y se mantienen separados bajo atmósfera inerte de nitrógeno. Por otro lado, se preparan 5 ml de disolución 0.1M de tetrafluoroborato de tetrabutilamonio (TBA BF_4) en dimetilformamida (DMF) también bajo atmósfera de nitrógeno y en presencia de tamices moleculares. A continuación se disuelve todo el CNTEA en la disolución de DMF y se añade esta nueva disolución sobre el recipiente que contiene el 1,3-DNB, todo bajo atmósfera inerte. Como consecuencia, se observa una coloración marrón-rojiza en la disolución indicativo de la formación de diferentes Complejos de Meisenheimer (Buncel, E.& Zabel, A.W. (1981)Can.J.Chem., 59, 2168) que aparecen al reaccionar el ión cianuro con el 1,3-DNB.



b) La mezcla de reacción química del apartado anterior (5 ml) se introducen en el interior de una celda electroquímica y se lleva a cabo la oxidación electroquímica de los complejos de Meisenheimer formados.

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El Sistema Electroquímico utilizado es de uso habitual en el Laboratorio [Andrieux, C.P. et al. (1994) *Tetrahedron*, 23, 6913] y consta de una celda electroquímica y un Potenciostato-Galvanostato EG&G modelo 273 A.

Se utiliza un sistema a 3 electrodos: un electrodo de trabajo, que es una barra de grafito (ϕ = 450 mm y L = 650 mm), un contralectrodo, que es un hilo de platino (ϕ = 1 mm) y un electrodo de calomelanos saturado (SCE Tacussel XR-110) como electrodo de referencia. Estos dos últimos electrodos están en contacto con la disolución por medio de un puente que contiene en cada uno de los casos unos 2 ml de disolución 0.1M de TBA BF_4 en DMF. La celda se mantiene bajo un burbujeo constante de nitrógeno o argón.

La oxidación electroquímica se lleva a cabo aplicando un potencial de oxidación hasta el consumo total de los Complejos de Meisenheimer formados (7.2375 C).

Una vez finalizada la reacción electroquímica, se procede a separar los productos de reacción del electrolito de fondo (TBA BF_4) mediante extracciones sucesivas utilizando mezclas tolueno/agua (1:1).

Se obtiene un 46% de 2,4-dinitrobenzonitrilo, un 4% de 1,3-nitrobenzonitrilo, un 1% de 2,4-dinitroisoftalonitrilo y se recupera un 49% de 1,3-dinitrobenceno (producto de partida).

Los productos se analizaron por CG-EM, ^{1}H-RMN, Espectroscopia UV-Visible y Voltametría Cíclica.

Se observa que al variar la relación estequiométrica entre los reactivos, aumentando la cantidad de nucleófilo, no varía el tipo de productos obtenidos pero sí su cantidad relativa. En estos casos se recupera una menor cantidad del producto de partida.

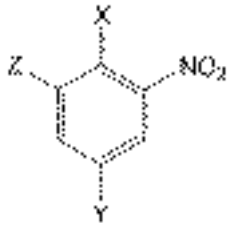
REIVINDICACIONES

1. Procedimiento para la substitución nucleófila aromática de derivados nitroaromáticos caracterizado por ser un procedimiento electroquímico.

2. Procedimiento según la reivindicación 1, que comprende la formación del complejo de Meissenheimer entre dicho derivado nitroaromático y un nucleófilo seguido de la oxidación electroquímica de dicho complejo de Meissenheimer.

3. Procedimiento según cualquiera de las reivindicaciones anteriores, donde el potencial utilizado es inferior al potencial de oxidación del nucleófilo.

4. Procedimiento según cualquiera de las reivindicaciones anteriores, donde la estructura de dicho derivado nitroaromático es:



siendo Y: NO_2, CN o CF_3

siendo Z: H, NO_2 o CN

siendo X: F, Cl, Br, NH_2, CN, NO_2, OR' o R'', donde R' y R'' representan indistintamente un grupo alquilo, un grupo arilo o H.

5. Procedimiento según cualquiera de las reivindicaciones anteriores, donde el nucleófilo es un nucleófilo cargado.

6. Procedimiento según la reivindicación 5, donde dicho

nucleófilo cargado se selecciona entre el grupo formado por H^-, CN^-, NO_2^-, OH^-, ^-SR, ^-OR, F^- y carbaniones.

7. Procedimiento según cualquiera de las reivindicaciones 1 a 4, donde el nucleófilo es neutro.

8. Procedimiento según la reivindicación 7, donde dicho nucleófilo neutro es una amina.

9. Procedimiento según cualquiera de las reivindicaciones anteriores, donde se utilizan disolventes polares apróticos.

10. Procedimiento según cualquiera de las reivindicaciones anteriores, que se lleva a cabo a temperatura ambiente.

11. Procedimiento según cualquiera de las reivindicaciones anteriores, donde la relación estequiométrica entre el derivado nitroaromático y el nucleófilo va desde 1:1 hasta 1:10.

3.5. Conclusiones

3.5. Conclusiones Generales (parte I)

1. Se ha determinado el mecanismo de oxidación electroquímico para todo tipo de compuestos de Meisenheimer (σ^H-aductos y σ^X-aductos) tanto en medios no nucleófilos como en presencia de nucleófilos/bases.

2. Se ha introducido, perfeccionado y consolidado la utilización de la voltametría cíclica, técnica electroquímica, para la obtención de información tanto de tipo cualitativo como cuantitativo, en lo que se refiere al número y la concentración de los complejos presentes en la mezcla de reacción, pudiendo ser utilizada incluso para obtener información estructural (caracterización) de los complejos presentes en la disolución, como ha quedado demostrado en numerosos ejemplos.

En resumen: La introducción de la Voltametría Cíclica como técnica para la realización de determinaciones analíticas, mecanístas e incluso en ocasiones estructurales de σ-complejos, aporta información nueva o adicional muy importante.

3. A partir de estudios voltamétricos previos se puede conocer la extensión de la reacción nucleófila de substitución ya sea de hidrógeno o de heterátomo (procesos NASH o NASX).

4. Se han demostrado las grandes posibilidades sintéticas de los procesos NASH y NASX electroquímicos.

5. Se han esayado con éxito diferentes alternativas para sintetizar el mismo producto, lo que nos da idea de la versatilidad de la técnica y de la adaptabilidad de la misma a nuestras necesidades sintéticas.

6. Se ha ampliado en rango de potenciales de oxidación accesibles por oxidantes químicos, ampliándose así el número de compuestos Meisenheimer oxidables, en lo que es un proceso más limpio, selectivo y en la mayoría de los casos más eficaz.

En resumen: La utilización de oxidaciones electroquímicas de σ-complejos, formados por adición de nucleófilos a nitroarenos, conduce a buenos rendimientos de productos rearomatizados en lo que es un método de síntesis directo, accesible, rápido, limpio y de alta economía de átomos.