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PAPER

Electrochemically promoted nucleophilic aromatic substitution in room temperature ionic liquids—an environmentally benign way to functionalize nitroaromatic compounds

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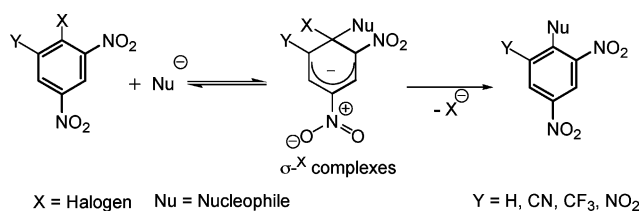
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The current manuscript shows the electrochemical studies performed to rationalize the mechanism and develop new green synthetic routes for the synthesis of substituted nitroaromatics based on the advantages of the electrochemical approach to the nucleophilic aromatic substitution reaction (such as (a) low cost and ready availability of reagents, (b) atom economy, (c) high yields, approaching 100%) and the use of Room Temperature Ionic Liquids (RTILs) as green alternative solvents to organic aprotic solvents. Four of the most popular RTILs (1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF₄]), 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF₆]), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide ([BMIM][TFSI]) and 1-butyl-3-methylimidazolium acetate ([BMIM][AcO]) have been chosen since they have different properties in terms of solvation effects that can increase the regioselectivity of the reaction. The nucleophiles used to study the feasibility and viability of the reaction were the classical hydride, methoxide, ketones, cyanides and amines, whereas the nitroarenes selected were 4-nitrotoluene, 1,3-dinitrobenzene, 2,4-dinitroaniline, 1,3,5-trinitrobenzene, 1,3-dinitronaphthalene, 1-chloro-2,4,6-trinitrobenzene and 2,4,6-trinitroanisole. The electrocatalysis and regioselectivity effects of using RTILs are also investigated. The article concludes by analyzing the economic cost of performing this electrosynthesis in RTILs and organic solvent electrolyte systems, which contain 0.1 M of supporting electrolyte.

1. Introduction

Nucleophilic aromatic substitution of halogen or other nucleofugal groups in nitroarenes, according to the S_NAr addition-elimination mechanism (Scheme 1),¹ is a classical reaction of major practical value. Studies of the mechanisms of aromatic substitution of electron-deficient aromatic and heteroaromatic compounds, establishing the factors that affect the choice of mechanistic path and the regioselectivity within a given mechanism, can have a major impact on such important areas as drug synthesis, polymer research, and environmental chemistry.^{2,3} So, a thorough understanding of these mechanisms will be of high value in the practical choice of conditions, solvents, and nucleophiles for the preparation of those compounds and in the choice of procedures used in environmental amelioration.



Scheme 1 General overview of a S_NAr reaction.

The conversion of intermediate σ^X -complexes into products through the promoted nucleophilic aromatic substitution of a heteroatom *via* spontaneous departure of the leaving group, the NASX process, is strongly dependent on the nature of the leaving group, the nature of the nucleophilic reagent and the effects of the medium, as has been previously described.⁴ The solvent is one of the most important parameters in S_NAr reactions since it determines its thermodynamics. Changes in the polarity of the solvent from protic to aprotic solvents affect the nature of the substitution product as well as the required time to complete the reaction.⁴ Nucleophilic aromatic substitution of hydrogen (NASH) reactions formally require the replacement of a hydride

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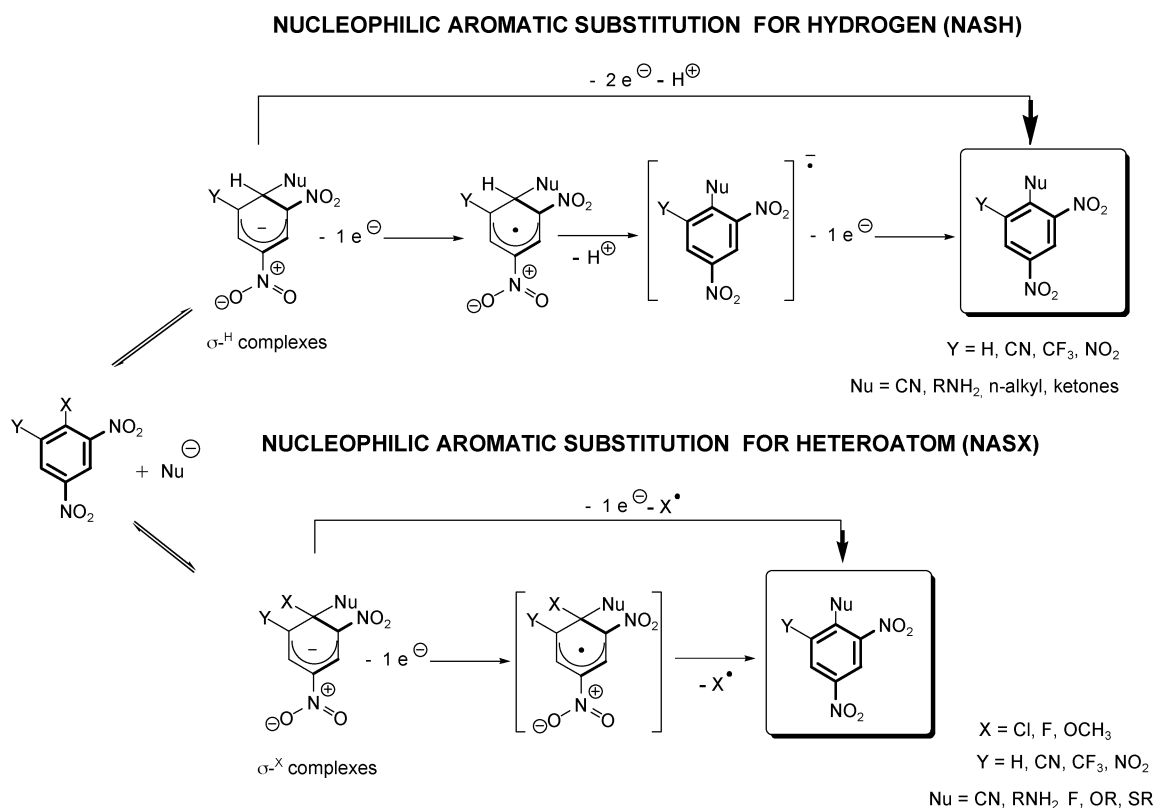
ion, and they either proceed “spontaneously” with consumption of part of the starting material in the oxidation step, or are promoted by the addition of external oxidants. In both cases, low yields (with few exceptions)^{5,6} and a lack of generality are the main drawbacks of these synthetic procedures. Moreover, some of the chemical substances used as chemical oxidants are inherently hazardous.

We were one of the first groups to focus our attention on performing the NASH and NASX reactions by electrochemical methods without the need to use halogenated starting materials or intermediates (Scheme 2).^{7,8} The mechanism for the electrochemical oxidation of the σ^H -complex involves the loss of two electrons and a proton, which corresponds to the formal elimination of a hydride anion. The NASX electrochemical mechanism also involves the elimination of a leaving group, although its departure is as a radical rather than an anion, as the rearomatization of the σ^X or *ipso* complex involves the loss of an electron.

The electrochemical approach to the NASH reaction overcomes most of the previously mentioned drawbacks and introduces numerous advantages in comparison with the chemical route, such as low cost, ready availability of reagents, atom economy and high yields (approaching 100% based on unrecovered starting material). This environmentally friendly electrochemical approach to this reaction has been successfully applied^{7–13} to the cyanation,⁷ amination⁹ and alkylation^{12,13} of nitroarenes. Moreover, it has been reported by some of us that the use of electrochemical techniques also makes it possible to perform and accelerate the nucleophilic aromatic substitution of

a heteroatom (NASX process)^{14,15} when a substituted position is attacked by the nucleophile.

The main advantage of the electrochemical approaches to the synthesis of functionalized nitroaromatic compounds is that electrons flowing as current are regarded as one of the reagents, thus the route is environmentally friendly. Moreover, reactions take place in low-temperature conditions, reducing the local consumption of energy and the risk of corrosion, material failure, and accidental release. Finally, it is important to highlight that electrodes can be regarded as heterogeneous catalysts that are easily separated from the products. The low volatility or non-volatility of reaction media are other factors to be taken into account. In this sense, the main drawbacks are the use of organic polar solvents and supporting electrolytes. An interesting alternative would be to replace those solvents with safer ones. Hence, the use of Room Temperature Ionic Liquids (RTILs) would be very attractive not only due to their chemical features (they are non-flammable, non-volatile and thermally stable over a wide range of temperatures) but also to their electrochemical ones.^{16–19} These solvents are a liquid consisting of only ions, so from moderate to high conductivities are guaranteed and there is no need to use a supporting electrolyte. Moreover, their electrochemical stability (from 0 to 1.7 V *vs.* SCE for oxidation processes) makes them an environmentally benign replacement for classic electrolyte solutions.²⁰ With the exception of a single study, this approach has been almost completely neglected in the literature.²¹ In our continuous effort to rationalize the mechanism and develop new synthetic routes, this manuscript is devoted to developing a “greener”

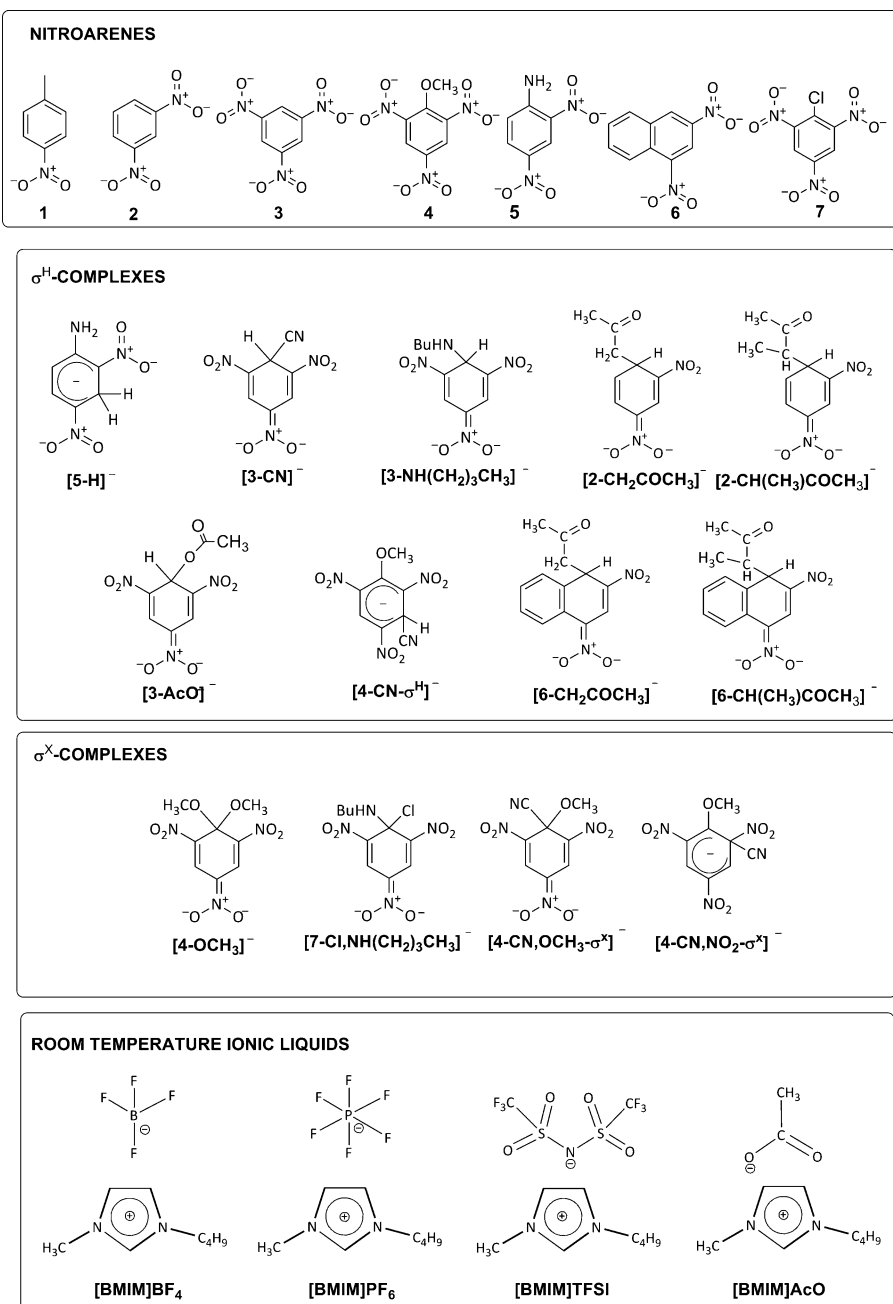


route for the synthesis of nitroarene derivatives based on the advantages of an electrochemical approach to the nucleophilic aromatic substitution reaction and the current trends in Green Chemistry of using environmentally friendly solvents, such as RTILs. In the current manuscript, the electrochemical NASH and NASX reactions were performed on four of the most popular RTILs, such as 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF₄), 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM]PF₆), 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide ([BMIM]TFSI) and 1-butyl-3-methylimidazolium acetate ([BMIM]AcO) using several nitroarenes (**1–7**) and nucleophiles (BH₄⁻, ⁻OCH₃, CN⁻, ketones and amines). Those starting materials, as well as the σ -complexes, are depicted in Scheme 3.

2. Experimental

2.1. Chemicals

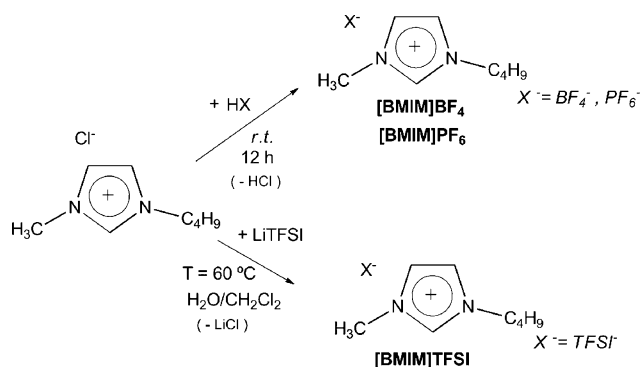
N,N-dimethylformamide (DMF) was stored in an inert atmosphere and molecular sieves were purchased from Across. *n*Bu₄NBF₄ (Fluka, puriss.) was used without further purification. 4-Nitrotoluene (**1**), 1,3-dinitrobenzene (**2**), 2,4-dinitroaniline (**5**), 1,3-dinitronaphthalene (**6**) was purchased from Aldrich. Whereas, 1,3,5-trinitrobenzene (**3**) was provided by Supelco and 2,4,6-trinitroanisole (**4**) and 1-chloro-2,4,6-trinitrobenzene (**7**) were synthesized according to methods previously described in the literature.^{22,23} All the commercially available reactants are of the



Scheme 3 The structures of the nitroarenes, σ -complexes and RTILs.

highest purity available and are used without further purification.

RTILs ([BMIM]BF₄, [BMIM]PF₆ and [BMIM]AcO) were first purchased from Solvionic, who guarantees that the amount of water present is always less than 500 ppm. Later both the RTILs [BMIM]BF₄, [BMIM]PF₆ and [BMIM]TFSI were prepared from BMIMCl (Fluka) aqueous solutions according to previously published procedures (Scheme 4).^{24–26} The solvents are purified by repeated washing with water and purified by column chromatography over silica under continuous nitrogen-flow. The ionic liquid was conveniently dried until the theoretically expected electrochemical response was obtained for water sensitive redox probes, such as 2,4-dinitroaniline, when either the commercial or the prepared RTILs were used.



Scheme 4 The synthesis of the RTILs ([BMIM]BF₄, [BMIM]PF₆ and [BMIM]TFSI).

2.2. Cyclic voltammetry experiments

An electrochemical conical cell equipped with a methanol jacket, which makes it possible to fix the temperature by means of a thermostat, is used for the set-up of the three-electrode system. For cyclic voltammetry experiments, the working electrode is, in all cases, a glassy carbon disk of a diameter of 0.5 mm. It is polished using a 1 µm diamond paste. The counter electrode is a Pt disk of a diameter of 1 mm. All of the potentials are reported *versus* an aqueous saturated calomel electrode (SCE) isolated from the working electrode compartment by a salt bridge. The salt solution of the reference calomel electrode is separated from the electrochemical solution by a salt-bridge ended with a frit, which is made of a ceramic material, allowing ionic conduction between the two solutions and avoiding appreciable contamination. Ideally, the electrolyte solution present in the bridge (pure RTIL in the ionic liquid experiments) is the same as that used for the electrochemical solution so as to minimize junction potentials. So, the above-described electrochemical set-up makes it possible to accurately determine the redox potential at which the electrosynthetic processes should be performed.

Due to the low conductivity and larger viscosity of RTILs and in order to facilitate direct comparison between the cyclic voltammograms of redox probes in the different media, the current values obtained are first normalized with respect to the concentration and the scan rate ($I_p/c.v^{1/2}$). The relationship between the four solvents can be expressed by a total normalization coefficient. This coefficient can be expressed as a ratio between DMF/[BMIM]BF₄, DMF/[BMIM]PF₆, DMF/[BMIM]TFSI

and DMF/[BMIM]AcO, the ratio being 8.1, 12.1, 4.1 and 12.7, respectively. Note that the organic solvent electrolyte system, which is labeled DMF, is a solution of DMF + 0.1 M of TBABF₄.

2.3. General procedure for NASH and NASX in nitroarenes

The corresponding anions ([5-H][−], [3-CN][−], [3-NH-(CH₂)₃CH₃][−], [2-CH₂COCH₃][−], [2-CH(CH₃)COCH₃][−], [3-AcO][−], [4-CN-σ^H][−], [6-CH₂COCH₃][−], [6-CH(CH₃)COCH₃][−], [4-OCH₃][−], [7-Cl,NH-(CH₂)₃CH₃][−], [4-CN,OCH₃-σ^X][−], [4-CN,NO₂-σ^X][−]) are either prepared “*in situ*” or transferred into the RTILs and oxidized electrochemically (exhaustive controlled potential electrolysis) using a carbon graphite as a working electrode. When the reaction is complete, the mixture is extracted in water/dichloromethane mixtures. The organic layer is dried with Na₂SO₄ and evaporated affording a residue that is analyzed by gas chromatography–mass spectrometry. The analysis shows the presence of substituted nitrocompounds (2,4-dinitroaniline, 2,4,6-trinitroanisole, 1-(2,4-dinitrophenyl)acetone, 3-(2,4-dinitrophenyl)-2-butanone, 1-(2,4-dinitro-1-naphthyl)acetone, 3-(2,4-dinitro-1-naphthyl)-2-butanone, *N*-butyl-2,4,6-trinitroaniline, 2,4,6-trinitrobenzonitrile, 2-methoxy-3,5-dinitrobenzonitrile, 2,4,6-trinitrobenzonitrile and 3-methoxy-2,4,6-trinitrobenzonitrile, respectively). Later, either the NASH or NASX products are analyzed by ¹H NMR and cyclic voltammetry and identified by comparison of their spectroscopic behaviour with that of pure samples available in our laboratory in each case. At the end of the process the RTILs are suitably recovered and recycled by water/dichloromethane washings and are used again in a new set of experiments.

2.4. Instrumentation

The cyclic voltammetry at low scan rates and controlled potential electrolysis are performed using a PAR 273A potentiostat controlled by a computer. Powersuite software is used for data acquisition and data treatment.

3. Results and discussion

The aim of this work is to establish the synthetic scope and versatility of the electrochemical approach to the S_NAr reaction in RTILs. Thus, it should be mandatory to first establish the electrochemical behaviour and the chemical stability of the nitroaromatic compounds (main reactants in the S_NAr reactions) in RTILs. The next step will be to analyze the electrochemical mechanism of the electrochemical oxidation of the σ^H-complexes and σ^X-complexes in RTILs. Finally, we will discuss whether the electrochemical oxidation of the σ-complexes leads to the substitution product, and to what extent, by formally replacing a hydride (H[−]) or halide (X[−]) following a NASH or NASX mechanism in RTILs.

3.1. Reactivity of neutral, anion radical and dianion of nitroderivatives using RTILs

We have previously established²⁷ the electrochemical behaviour of a large family of nitroaromatic compounds, such as 4-nitrotoluene (**1**), 1,3-dinitrobenzene (**2**), 1,3,5-trinitrobenzene (**3**) and 2,4,6-trinitroanisole (**4**) in second generation RTILs

Table 1 Cathodic and anodic peak potential, standard potential, and ΔE_p for **1**, **2**, **3** and **4** in different solvents at 20 °C (Scan rate 1.0 V s⁻¹)

COMPOUND	SOLVENT	E_{pc} (V) ^a	E_{pa} (V) ^a	E^0 (V) ^a	ΔE_p (mV) ^b
1	DMF ^c	-1.267	-1.176	-1.222	91
	[BMIM]BF ₄	-1.142	-1.064	-1.103	78
	[BMIM]PF ₆	-1.367	-1.239	-1.303	128
	[BMIM]TFSI	-1.220	-1.137	-1.179	83
	[BMIM]AcO	-1.036	-0.923	-0.978	113
2	DMF ^c	-0.954	-0.866	-0.910	78
	[BMIM]BF ₄	-0.845	-0.785	-0.815	60
	[BMIM]PF ₆	-1.009	-0.928	-0.969	81
	[BMIM]TFSI	-0.950	-0.866	-0.907	84
	[BMIM]AcO	-0.763	-0.654	-0.708	109
3^d	DMF ^c	-0.581	—	—	51
	[BMIM]BF ₄	-0.720	—	—	57
	[BMIM]PF ₆	-0.763	—	—	58
	[BMIM]TFSI	-0.725	—	—	58
	[BMIM]AcO ^e	-1.100 ^e	—	—	110
4^d	DMF ^b	-0.649	—	—	59
	[BMIM]BF ₄	-0.674	—	—	50
	[BMIM]PF ₆	-0.887	—	—	58
	[BMIM]TFSI	-0.716	—	—	62
	[BMIM]AcO ^e	-1.075 ^e	—	—	89

^a Potential values given vs. SCE ^b $\Delta E_p = E_{pa} - E_{pc}$; ^c Solution of DMF + 0.1 M TBABF₄; ^d Trinitrobenzene derivatives show an irreversible reduction wave; ^e This value corresponds to the first reduction wave detected in [BMIM]AcO.

[BMIM]BF₄ and [BMIM]PF₆. This study is now extended to one of the most popular second generation RTILs ([BMIM]TFSI) and a third generation RTIL ([BMIM]AcO). The main difference between the second and the third generation of RTILs is related to their reactivity in the presence of water and to the nature of the counter anion. In the case of the second generation RTILs the main feature is the hydrophobic character of the counter anion (BF₄⁻, PF₆⁻ and TFSI⁻), whereas in the case of the third generation, the RTILs contain a task specific counter anion (AcO⁻).

Due to the low conductivity and high viscosity of RTILs and in order to facilitate direct comparison between the cyclic voltammograms, the current values obtained have been normalised with respect to the concentration of the nitroaromatic compound and the scan rate ($I_p/cv^{1/2}$). Fig. 1 shows the electrochemical behaviour of **1** in several solvents. A well-defined one-electron reversible wave is obtained in DMF + 0.1 M TBABF₄ and in RTILs, so neither the nature of the reactant nor the reactivity of the electrogenerated anion radical is affected in those media. However, the cyclic voltammetry experiments

reveal differences in the E^0 values (Table 1), which are strongly related to ion-pairing effects.^{27,28} This effect on the shift of the E^0 values is also observed when compound **2** is studied in those solvents (Table 1). Compound **2** shows the same electrochemical behaviour as **1** in terms of the E^0 value shift, so it can be used as a model compound for dinitroderivatives, 2,4-dinitroaniline (**5**) and 1,3-dinitronaphthalene (**6**). In the case of trinitrobenzene derivatives (compounds **3** and **4**) the peak potential value (E_{pc}) is also strongly dependent on the solvent, being more easily reduced in DMF + 0.1 M TBABF₄ than in RTILs.

When [BMIM]AcO is used, a new effect that is mainly negligibly for compound **1** and it is related to the stability of the reactant, is observed. For compound **2**, Fig. 2a shows that the height of the two successive one-electron reversible reduction peaks corresponding to the formation of the anion radical and dianion, respectively, decreases over time. After 15 min, the peak current value of the first peak decreases by 25% and, after 30 min, it has decreased by 60% and the solution becomes purple.²⁹ These facts can be explained by the nucleophilic attack of the acetate anion on the nitroaromatic compounds. This effect becomes very important in the case of trinitrobenzene derivatives (**3** and **4**), for which the reduction wave associated to **3** or **4** is not observed after a few seconds (Fig. 2b). Note that the reduction wave at ca. -1.1 V detected for compounds **3** and **4** corresponds, in both cases, to the reduction of the σ^H -complex, [3-AcO]⁻, formed in solution (Table 1).

3.2. Electrochemical behaviour of σ^H -complexes and σ^X -complexes in RTILs

In order to analyse the stability of the σ^H -complexes and σ^X -complexes, the key intermediates, to establish the synthetic scope of the methodology, and disclose the electrochemical behaviour and chemical stability of those intermediates in RTILs; two stable σ^H -complexes and an σ^X -complex were synthesised and isolated in their solid form according to previously reported

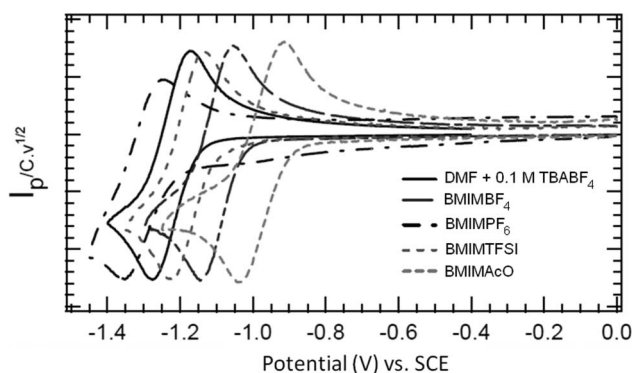


Fig. 1 Cyclic voltammograms of **1** showing the reduction of a 5 mM solution in DMF + 0.1 M TBABF₄ and RTILs on a glassy carbon disk (0.5 mm diameter), scan rate 1.0 V s⁻¹.

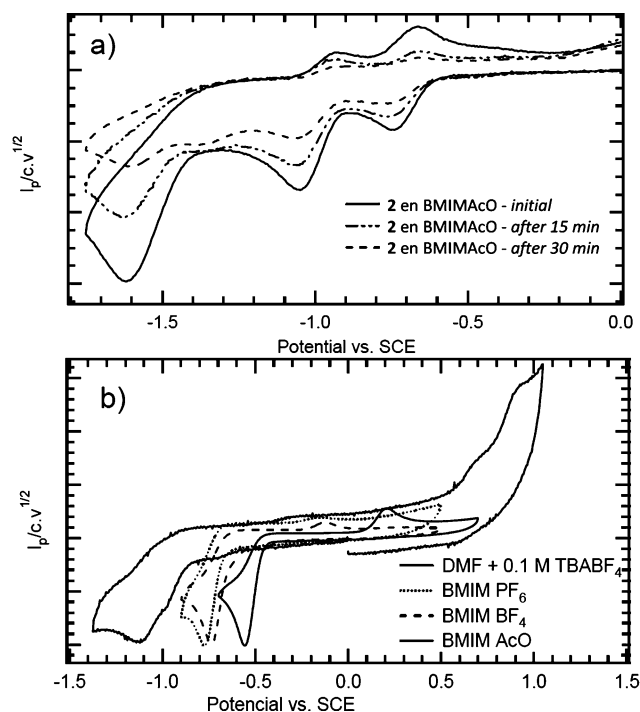


Fig. 2 Cyclic voltammograms showing the reduction of a 5 mM solution in BMIMAcO on a glassy carbon disk (0.5 mm diameter), scan rate 1.0 V s^{-1} of a) **2** with time b) **4** initial.

procedures.^{30,31} The use of hydride (tetramethylammonium tetra-borohydride) as a nucleophile and 2,4-dinitroaniline (**5**) as a nitroaromatic reactant yields the tetramethylammonium salt of the σ^{H} -complex $[\mathbf{5}\text{-H}]^-$, whereas the use of potassium methoxide and 2,4,6-trinitroanisole (**4**) leads to the σ^{X} -complex $[\mathbf{4}\text{-OCH}_3]^-$.

From a qualitative point of view, the electrochemical behaviour of the σ^{H} -complex $[\mathbf{5}\text{-H}]^-$ in RTILs is very similar to the one reported in organic solvent electrolyte systems (DMF + 0.1 M TBABF₄) (Fig. 3).⁴ In all the RTILs investigated, an irreversible two electron oxidation wave is observed in the anodic

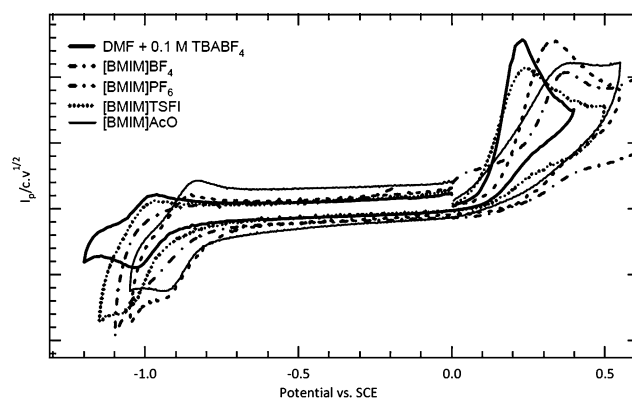


Fig. 3 Cyclic voltammograms of $[\mathbf{5}\text{-H}]^-$, 5 mM in DMF + 0.1 M TBABF₄ and RTILs on a glassy carbon disk (0.5 mm diameter), scan rate 1.0 V s^{-1} (Scan Range 0.0/0.5/-1.2/0.0 V).

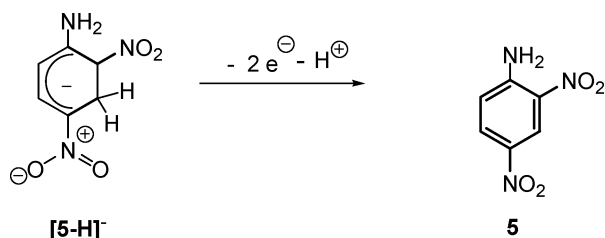
forward scan, whereas a one electron reversible reduction wave is shown in the cathodic back scan. It is important to remark that when the CV is scanned first is in cathodic direction, the reversible reduction wave does not exist while the two electron irreversible wave appears unchanged on the reverse scan; on the second cycle, the reduction wave is present in the cathodic scan. This means that the reduction wave corresponds to the electrochemical behavior of the product formed after the oxidation of the σ^{H} -complex $[\mathbf{5}\text{-H}]^-$. In order to characterize the oxidation product a controlled potential electrolysis was performed at a potential *ca.* 100 mV more positive than the peak potential value determined for the σ^{H} -complex. After the passage of 2F and the chemical treatment of the sample, the compound recovered is 2,4-dinitroaniline (**5**) in a 100% yield.

This experimental result shows that the electrochemically promoted NASH process leads to the re-aromatized compound **5** after the passage of 2 electrons and the loss of one proton, which corresponds to the “formal” loss of a hydride in RTILs (Scheme 5). It is important to highlight that the oxidation peak is shifted depending on the RTIL used, which can be explained in terms of solvation (Table 2). A stronger solvation

Table 2 The anodic peak potential for σ -complexes $[\mathbf{5}\text{-H}]^-$ and $[\mathbf{4}\text{-OCH}_3]^-$, standard potential and cathodic peak potential of the NASH and NASX products obtained after the electrochemical oxidation of the sample in different solvents at 20 °C

σ^{H} -complexes	SOLVENT	E_{pa} (V vs. SCE)	NASH Product	$E^\circ(\mathbf{5})$ (V vs. SCE) ^b
$[\mathbf{5}\text{-H}]^-$	DMF ^a	0.210	5	-1.012
	[BMIM]BF ₄	0.326	5	-0.903
	[BMIM]PF ₆	0.365	5	-1.016
	[BMIM]TFSI	0.208	5	-1.009
	[BMIM]AcO ^c	0.369	5	-0.879
σ^{X} -complexes	SOLVENT	E_{pa} (V vs. SCE)	NASX Product	$E_{\text{pc}}(\mathbf{6})$ (V vs. SCE) ^b
$[\mathbf{4}\text{-OCH}_3]^-$	DMF ^a	1.217	4	-0.649
	[BMIM]BF ₄	1.170	4	-0.674
	[BMIM]PF ₆	0.968	4	-0.887
	[BMIM]TFSI	1.045	4	-0.716
	[BMIM]AcO ^c	0.947	4	-0.746

^a Solution of DMF + 0.1 M TBABF₄; ^b Standard Potential (E°) or Cathodic Peak Potential (E_{pc}) Values obtained after measuring a solution by cyclic voltammetry, which has previously been oxidized by exhaustive controlled potential electrolysis at 1.0 V s^{-1} ; ^c After exhaustive controlled potential electrolysis in [BMIM]AcO the acetate anion has been probably protonated and the produced acetic acid is a much weaker nucleophile. Moreover, it could also have been oxidised so its concentration would be considerably decreased.



Scheme 5 The electrochemically promoted NASH process in RTILs.

(a stronger ion pairing) of the σ^H -complex by the cation of the RTIL or of the supporting electrolyte would render its oxidation more difficult (more positive potential). Thus the σ^H -complex would be more strongly solvated by the BMIM cation than by tetrabutylammonium cation (in DMF). The σ^H -complex would be more strongly solvated in [BMIM]BF₄ and [BMIM]AcO than in [BMIM]TFSI because the σ^H -complex would displace the BF₄⁻ and AcO⁻ anions more easily than the larger TFSI⁻ anion. At this point, it is possible to establish an electrocatalytic effect when [BMIM]TFSI is used, since the electrochemical reaction can be performed at a lower oxidation potential than in the other RTILs, as well as in organic aprotic solvents. However, since the [BMIM]TFSI is more expensive than the other two RTILs, we decided to perform the electrochemical NASH approach, which will be explained in the next sections, in [BMIM]BF₄ or [BMIM]PF₆ in order to make scaling-up processes more feasible in the future.

Analogous electrochemical studies have been performed for the σ^X -complex [**4-OCH₃**]⁺ so as to study the electrochemically promoted NASX process in RTILs. The typical voltammogram in DMF + 0.1 M TBABF₄, at low scan rates, is shown in Fig. 4a. No reduction waves are observed in a first reduction scan, while an irreversible one electron wave appears in the oxidation scan at 1.12 V vs. SCE. On the second cathodic scan a reduction wave at -0.73 V is observed. This reduction wave corresponds to the product formed in the first anodic scan (Fig. 4a). The same general electrochemical behaviour described in DMF + 0.1 M TBABF₄ is observed when the experiments are performed in all the RTILs (Fig. 4b–d). However, a closer look at the cyclic voltammograms registered in RTILs reveals some important differences. For instance, when the cyclic voltammetry experiments are performed in [BMIM]PF₆, the peak intensity for the oxidation wave corresponding to the σ^X -complex [**4-OCH₃**]⁺ corresponds to 0.55 electrons (Fig. 4b) instead of 1 electron.³² Moreover, the reduction wave corresponding to the reduction of **4** at ca. -0.90 V is observed in the first cathodic scan (Fig. 4c).³³ It is therefore possible to conclude that methoxy is a good leaving group in [BMIM]PF₆, the extension of the S_NAr reaction following the classic addition–elimination mechanism corresponds to a 45% yield (Scheme 6). The stability of the intermediate can be increased using [BMIM]BF₄, [BMIM]TFSI or [BMIM]AcO, which means that the “chemical” route for the S_NAr reaction can be reduced to 20%, 18% or 15% (Fig. 4d), respectively; in other words, the number of electrons associated to the first oxidation wave is 0.80, 0.82 and 0.85, respectively. In all cases, the S_NAr can be electrochemically completed by exhaustive controlled potential electrolysis at ca. 1.30 V (a potential about 180 mV more positive than

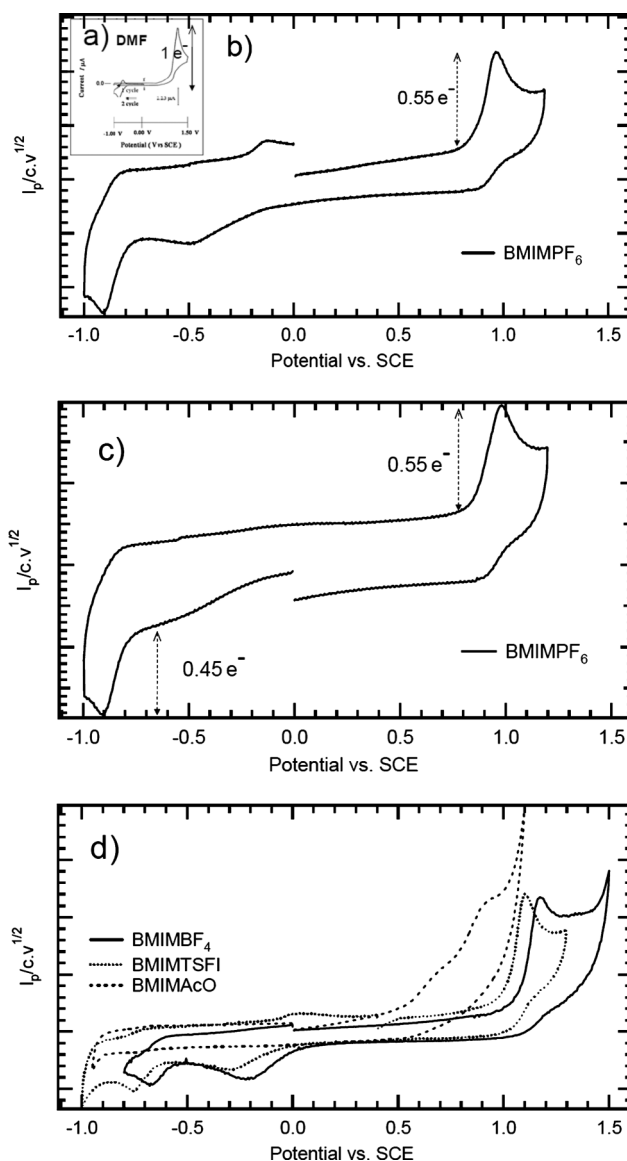


Fig. 4 Cyclic voltammograms of [**4-OCH₃**]⁺ 5 mM on a glassy carbon disk (0.5 mm diameter), scan rate 1.0 V s⁻¹ a) in DMF+0.1 M TBABF₄ (Scan Range 0.0/1.5/-1.0/0.0 V, 2 cycles) b) [BMIM]PF₆ (Scan Range ca. 0.0/1.5/-1.0/0.0 V) c) [BMIM]PF₆ (Scan Range ca. 0.0/-1.0/1.5/0.0 V) d) in [BMIM]BF₄, [BMIM]TFSI and [BMIM]AcO.

the oxidation potential). The re-aromatized product obtained after the electrochemical oxidation is 2,4,6-trinitroaniline (**4**) in a quantitative yield. So, the electrochemical oxidation of the σ^X -complex [**4-OCH₃**]⁺ leads to **4** after the loss of a methoxy radical. Finally, it is also remarkable that a very efficient electrocatalytic effect is found for the S_NAr of heteroatom in [BMIM]PF₆ or [BMIM]AcO since the oxidation potential is considerably lower than in the other RTIL or aprotic solvents studied (Table 2).

After disclosing that the electrochemical oxidation of the σ -complexes yields the substitution product by formally replacing a hydride (H⁻) or halide (X⁻) following a NASH or NASX mechanism in RTILs, it is time to establish the synthetic scope and versatility of the synthetic methodology.

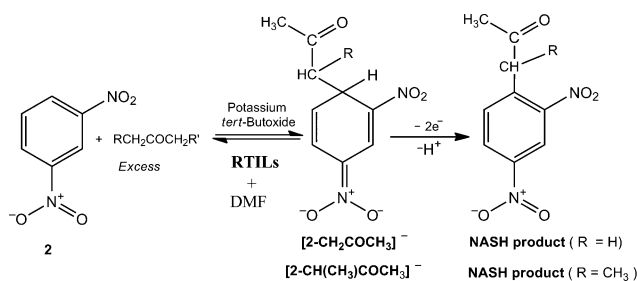
		Yield
	DMF + 0.1 M TBABF ₄	0 %
	[BMIM]PF ₆	45 %
	[BMIM]BF ₄	20 %
	[BMIM]TFSI	18 %
	[BMIM]AcO	15 %
	DMF + 0.1 M TBABF ₄	100 %
	[BMIM]PF ₆	55 %
	[BMIM]BF ₄	80 %
	[BMIM]TFSI	82 %
	[BMIM]AcO	85 %

Scheme 6 Comparison between the percentages of substitution product obtained either “chemically” or electrochemically promoted through Nucleophilic Aromatic Substitution of Heteroatom Reaction (NASX process).

3.3. Electrochemically Promoted NASH Process

This section is devoted to reporting for the first time in terms of cyclic voltammetry and preparative electrolysis on the scope and limitations of electrochemical NASH in RTILs. These results can be compared with those previously obtained by our group using DMF + 0.1 M TBABF₄ where the NASH product was obtained when ketone enolates, cyanides and amines were used as nucleophiles in the above-described conditions.^{7,9–10}

3.3.1. Electrochemical synthesis of nitroaromatic ketones and nitriles. Formation of a C–C bond. The electrosynthesis of nitroaromatic ketones in RTILs has been performed with compounds **2** and **6** using acetone and 2-butanone as nucleophiles. The base used to deprotonate the ketones to promote the nucleophilic attack is potassium *tert*-butoxide in all cases. The order of addition of the reactants is important in order to favour the stoichiometric formation of the most stable carboanion present in the reaction mixture and a fast quantitative nucleophilic attack on it. The nitroaromatic compound is dissolved in a large excess of ketone under nitrogen atmosphere. After that, the potassium *tert*-butoxide is slowly and uniformly added. Then a mixture of solvents DMF (without supporting electrolyte) and RTILs (at a 1 : 1 ratio) is added. Finally, the sample is analyzed and fully oxidized in terms of electrochemical techniques. The addition of DMF makes the electrochemical oxidation process faster to help with the conductivity of the media. The same results are obtained when the reaction is performed in the absence of DMF (Scheme 7).



Scheme 7 Electrochemically promoted NASH process to obtain substitution aromatic using ketones as a nucleophile in basic media.

Fig. 5a and 5b show the cyclic voltammetry of a reaction mixture of **2** (5 mM) and ketone (acetone or butanone, respectively) in the presence of potassium *tert*-butoxide in a DMF-RTIL mixture ([BMIM]BF₄ and [BMIM]PF₆, respectively) prior to the electrochemical oxidation of the solutions. In both cases, the nitroaromatic compound almost completely reacted with the nucleophile since, in the first scan in the cathodic direction, the intensity of the reduction wave corresponding to 1,3-dinitrobenzene (**2**) is very low. Moreover, the quantitative formation of σ^H -complexes, [2-CH₂COCH₃][–] and

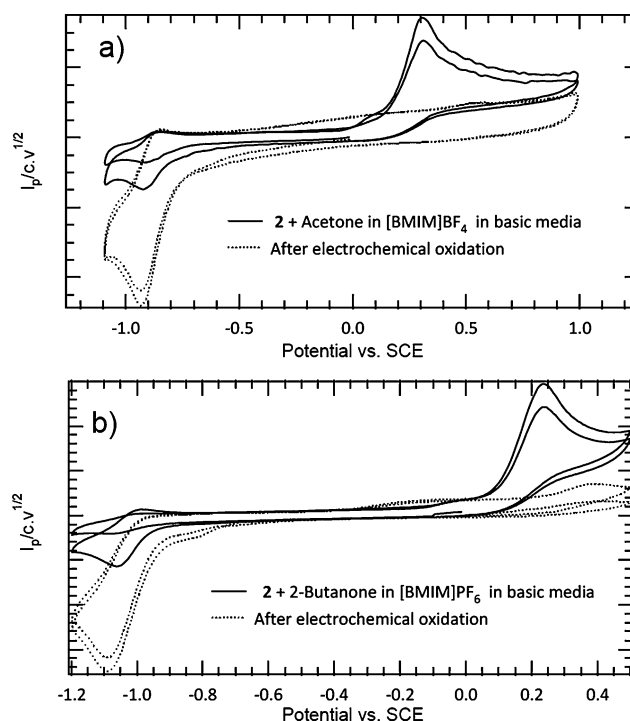


Fig. 5 Cyclic voltammograms of a) 5.0 mM of “*in situ*” generated [2-CH₂COCH₃][–] and b) [2-CH(CH₃)COCH₃][–] before (solid line) and after (dotted line) exhaustive controlled potential electrolysis of the sample in [BMIM]BF₄ and [BMIM]PF₆ RTILs, respectively, on a glassy carbon disk (0.5 mm diameter), scan rate 1.0 V s^{–1} (Scan Range 0.0/0.5/–1.2/0.0 V, 2 cycles).

Table 3 Exhaustive electrolysis of σ^H -complex, NASH processes

Compound	Solvent	Nucleophile (number of eq.)	σ^H -complex (%)	E_{pa} σ^H -complex (V vs. SCE)	NASH Product (%)
2	DMF + 0.1 M TBABF ₄	tBuOK/CH ₂ COCH ₃ (1 : 160 eq)	[2-CH ₂ COCH ₃] ⁻ (100) ^a	0.47	90
2	BMIMBF ₄	^t BuOK/CH ₂ COCH ₃ (1 : 160 eq)	[2-CH ₂ COCH ₃] ⁻ (93) ^a	0.314	82
2	BMIMBF ₄	^t BuOK/CH ₃ COCH ₂ CH ₃ (1 : 18 eq)	[2-CH(CH ₃)COCH ₃] ⁻ (100) ^a	0.449	100
6	BMIMPF ₆	^t BuOK/CH ₂ COCH ₃ (1 : 160 eq)	[6-CH ₂ COCH ₃] ⁻ (95) ^a	0.233	80
6	BMIMPF ₆	^t BuOK/CH ₃ COCH ₂ CH ₃ (1 : 12 eq)	[6-CH(CH ₃)COCH ₃] ⁻ (80) ^a	0.294	91
3	DMF + 0.1 M TMAPF ₆	KCN (1 : 2.35 eq)	[3-CN] ⁻ (82) ^a	1.040	80
3	BMIMBF ₄	TEACN (1 : 1.5 eq)	[3-CN] ⁻ (100) ^a	0.650	100
3	DMF + 0.1 M TBABF ₄	<i>n</i> -BuNH ₂ (1 : 3 eq)	[3-NH-(CH ₂) ₃ CH ₃] ⁻ (30) ^b	1.12	30
3	BMIMBF ₄	<i>n</i> -BuNH ₂ (1 : 12 eq)	[3-NH-(CH ₂) ₃ CH ₃] ⁻ (100) ^b	0.755	25
3	BMIMAcO	<i>n</i> -BuNH ₂ (1 : 63 eq)	[3-NH-(CH ₂) ₃ CH ₃] ⁻ (94) ^b	0.710	94

^a Percentage σ^H -complex calculated by cyclic voltammetry (oxidation peak potential and intensity of the remaining nitroarene reduction wave) ^b Since the excess of amine can modify the intensity of the oxidation wave; the percentage σ^H -complex was only calculated from the intensity of the remaining nitroarene reduction in the cyclic voltammogram.

[2-CH(CH₃)COCH₃]⁻, can be deduced from the peak current value of the oxidation wave associated to each intermediate (0.45 and 0.35 V, respectively). In a second cathodic scan, the reduction wave presumably corresponding to the substitution product is observed at *ca.* -1.00 V vs. SCE. Finally, controlled-potential electrolysis are performed at *ca.* 0.6 V, after the σ^H -complex oxidation wave. The cyclic voltammograms of the oxidation mixture show, in both cases, the oxidation of the σ^H -complex (no oxidation wave is detected) and the consequent formation of the substitution product (reduction wave). Analysis of the oxidised reaction mixture, after the chemical treatment of the sample (*see Experimental Section*), makes it possible to obtain the substitution product in high yields (80–100%).

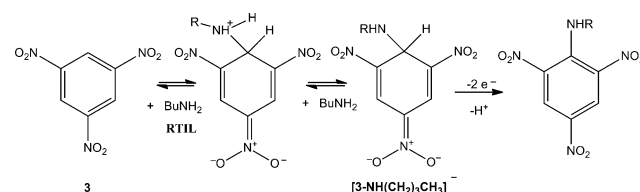
It is important to remark that the reaction is totally selective, only one C-arylation product is obtained when compounds **2** and **6** react either with acetone or with 2-butanone. In the case of using 2-butanone, the retroanalysis of the product obtained, 3-(2,4-dinitrophenyl)-2-butanone or 3-(2,4-dinitro-1-naphthyl)-2-butanone, when **2** and **6** react with 2-butanone, indicates not only that the reaction takes place with the most stable enolate but also on the most stable σ^H -complex. This indicates that the reaction is operating under thermodynamic conditions. The results of the electrochemically promoted NASH process are summarized in Table 3, excellent yields of the substitution product are obtained in all cases. At this point, it is worth concluding that in spite of the good results obtained in DMF + 0.1 M of TBABF₄, it is possible to obtain similar results using RTILs and avoid the use of large quantities of supporting electrolyte and even reduce the quantity of nucleophile, either in the presence or the absence of DMF.

The NASH process in RTILs is also applied to the cyanation of nitroarenes. Salts of either tetraethylammonium or potassium cyanide are used as a nucleophile and 1,3,5-trinitrobenzene (**3**) as a nitroarene. The best results are obtained for an electrolyzed mixture of **3** in the presence of 1.5 equivalents of tetraethylammonium cyanide using [BMIM]BF₄ as a solvent. It is important to highlight that the best yield obtained in RTILs is 20% higher than the yield obtained in DMF + 0.1 M

tetramethylammonium hexafluorophosphate (TMAPF₆) even when reducing the number of nucleophile equivalents (Table 3).

3.3.2. Electrochemical synthesis of nitroaromatic amines.

Formation of a C–N bond. For the study of the electrochemical synthesis of nitroanilines by means of a NASH the selected nitroaromatic compound is **3** and the RTILs are [BMIM]BF₄ and [BMIM]AcO. Previous studies performed in DMF + 0.1 M TBABF₄ demonstrated that the use of an excess of amine leads to the substituted nitroaromatic products in moderate yields (30–40%).⁶ The first RTIL studied is [BMIM]BF₄. A controlled excess of *n*-butylamine (12 equivalents) is added to a solution of **3** in 200 μ l of DMF (Table 3). When the reaction is complete, which means that there is no unreacted nitroaromatic material, 5 mL of [BMIM]BF₄ is added.³⁴ A controlled potential electrolysis of the mixture leads to 25% of *N*-butyl-2,4,6-trinitroaniline, the NASH substitution product. In order to improve the reaction yield, a larger excess of amine is added. However, this did not improve the yield. The fact that yields are not ameliorated when a huge excess of amine is added, and also that there is no presence of unreacted starting material, seems to indicate that most of the nitroaromatic compound is mainly in a zwitterionic form (Scheme 8).³⁵ Therefore, to increase the reaction yield it would be mandatory to shift the equilibrium from the zwitterionic complex to the σ^H -complex. At this point the use of [BMIM]AcO as solvent seems to be the most appropriate RTIL due to the basicity of the acetate group. Analysis of the reaction mixture after exhaustive controlled potential electrolysis at 1.00 V replacing the [BMIM]BF₄ for with



Scheme 8 A NASH electrochemically promoted process for obtaining substituted aromatic compounds using amines as nucleophiles in RTILs.

[BMIM]AcO yields 94% of the expected substitution product.³⁶ Moreover, when RTILs are used an important electrocatalytic effect is observed, since the peak potential of the σ^H -complex is shifted to less positive potentials compared to those measured in DMF (see Table 3).

3.4. Electrochemically promoted NASX process

The electrochemical NASX reaction is less attractive than the NASH reaction in terms of designing an environmentally friendly route, since the leaving group is different from hydrogen. However, it can be a nice alternative to overcome the low yields obtained when the electrochemical NASH approach is used. This situation can be illustrated by, for instance, synthesizing *N*-butyl-2,4,6-trinitroaniline in [BMIM]BF₄. As described in the previous section, the reaction of **3** with *N*-butylamine affords 25% substitution product through an electrochemically promoted NASH process. However, it is possible to obtain 88% of the *N*-butyl-2,4,6-trinitroaniline in [BMIM]BF₄ using an excess (21 equivalents) of *N*-butylamine (nucleophile) and 1-chloro-2,4,6-trinitrobenzene (**7**), as nitroaromatic starting materials after controlled potential electrolysis of the σ^X -complex formed in the reaction mixture ([7-Cl,NH-(CH₂)₃CH₃]⁺). Better results are obtained when [BMIM]PF₆ is used as a solvent, where it is possible to reach almost 100% yield by changing the electrochemical solvent and increasing the number of amine equivalents five times (Table 4). As in the previously described case of intermediate [4-OCH₃]⁺, it is possible that part of the departure of chloride in the intermediate [7-Cl,NH-(CH₂)₃CH₃]⁺ can take place spontaneously, this route being more important in [BMIM]PF₆ than in [BMIM]BF₄. Note that the oxidation potential of the σ^X -complex is considerably lower than in DMF or [BMIM]BF₄, which makes this solvent extremely attractive for performing NASX reactions due to its electrocatalytic effects.

The electrochemical synthesis of 2,4,6-trinitrobenzonitrile can also be designed using a NASX process. It could be expected that the reaction of 2,4,6-trinitroanisole (**4**) with cyanide would lead to the 2,4,6-trinitrobenzonitrile. However, this reaction is strongly dependent on the solvent. The use of different solvents or mixtures of solvents modify the regioselectivity of the products (Scheme 9, Table 4). This study demonstrates the power of electrochemistry and RTILs in terms of selectivity, good yields and environmentally friendly routes. It is important to remark that as far as we are aware there is no spontaneous

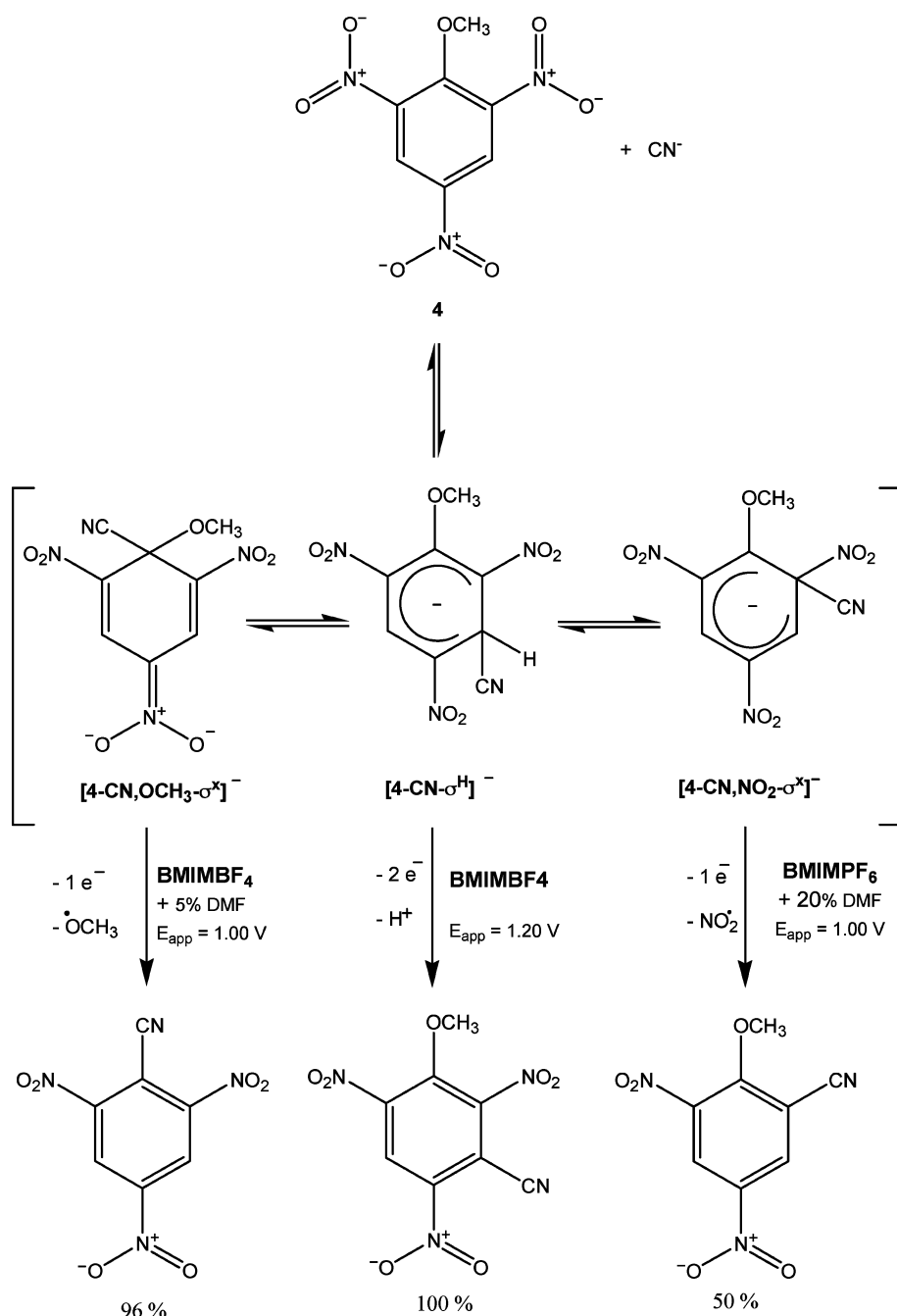
S_NAr substitution of a heteroatom when cyanide is used as a nucleophile.^{14,37}

Scheme 9 shows that the cyanide can attack three different positions of the aromatic ring, one non-substituted ([4-CN- σ^H]⁺) and two substituted ([4-CN,OCH₃- σ^X]⁺ or [4-CN,NO₂- σ^X]⁺). Notice that the cyanide mainly attacks a non-substituted position when [BMIM]BF₄ is used as a pure solvent, and the oxidation of the corresponding [4-CN- σ^H]⁺ leads to the NASH product. When 5% of DMF is added to the [BMIM]BF₄, the cyanide exclusively attacks position 1 of the nitroaromatic ring leading to [4-CN,OCH₃- σ^X]⁺, so a controlled potential electrolysis of the solution affords 2,4,6-trinitrobenzonitrile quantitatively. On the other hand, if the [BMIM]BF₄ is replaced with [BMIM]PF₆ and the percentage of DMF presented in solvent mixture is increased to 20%, the main intermediate formed is [4-CN,NO₂- σ^X]⁺, so the final product obtained after oxidation of the sample mixture is 50% 2-methoxy-3,5-dinitrobenzonitrile. Finally, it is important to highlight that, as previously demonstrated for the anion radical and dianion of nitroaromatic compounds, the solvation effects of the RTILs can modify the relative thermodynamic stability of the σ -complexes introducing an amazing regioselective effect. The electrochemical oxidation can take advantage of this effect by promoting the quick departure of the leaving group. So, the environmental advantages of using RTILs as green solvents and the electrochemical methods to promote nucleophilic aromatic substitution as a green technology, open an excellent route to overcoming the main drawbacks associated with the S_NAr reaction.

Finally, in the analysis of the feasibility and viability of replacing organic aprotic solvents that contain 0.1 M tetraalkylammonium salts (supporting electrolyte) by RTILs, it is important to take into account the following points: cost of each experiment DMF + 0.1 M of TBABF₄ and cost of the RTILs either commercially available or synthesized in the laboratory. So, the expense of one single experiment in a commercially available RTIL, such as [BMIM]BF₄, is almost twice that of performing it in DMF + 0.1 M of TBABF₄. However, if the RTILs are synthesized in the laboratory, in all cases ([BMIM]BF₄, [BMIM]PF₆, [BMIM]TFSI and [BMIM]AcO), the cost of the experiment is almost the same as in DMF + 0.1 M of TBABF₄. However, since the RTILs are recyclable, which means that at the end of the experiment 60–70% can be recovered and reused again, the cost of the following experiments are reduced by more than 60% in comparison with the initial charges in DMF + 0.1 M TBABF₄.

Table 4 Exhaustive electrolysis of σ^X -complex, NASX processes

Compound	Solvent	Nucleophile (number of eq.)	σ^X -complex (%)	E_{pa} σ^H -complex (V vs. SCE)	NASX Product (%)
7	DMF + 0.1 M TBABF ₄	<i>n</i> -BuNH ₂ (2 eq)	[7-Cl,NH-(CH ₂) ₃ CH ₃] ⁺ (70)	1.350	95
7	BMIMBF ₄	<i>n</i> -BuNH ₂ (21 eq)	[7-Cl,NH-(CH ₂) ₃ CH ₃] ⁺ (40)	1.267	88
7	BMIMPF ₆	<i>n</i> -BuNH ₂ (103 eq)	[7-Cl,NH-(CH ₂) ₃ CH ₃] ⁺ (100)	0.686	91
4	BMIMBF ₄	TEACN (2.35 eq)	[4-CN- σ^H] ⁺ (50)	0.600	96(NASH product)
4	BMIMBF ₄ + 5% DMF	TEACN (3.5eq)	[4-CN,OCH ₃ - σ^X] ⁺ (100)	0.75	100
4	BMIMPF ₆ + 20% DMF	TEACN (6.0eq)	[4-CN,NO ₂ - σ^X] ⁺ [4-CN,OCH ₃ - σ^X] ⁺ [4-CN- σ^H] ⁺	0.45 0.75 0.60	50 16 34



Scheme 9 NASH and NASX in different RTILs when cyanide is used as a nucleophile.

4. Conclusions

The use of RTILs as a solvent for performing electrochemically promoted nucleophilic aromatic substitution reactions of hydrogen (NASH) or of a heteroatom (NASX) opens an attractive “green route” for synthesizing substituted nitroaromatic compounds. Cyclic voltammetry makes it possible to evaluate not only the nature and stability of the σ -complex but also the extension of the reaction in RTILs. Moreover, it has been demonstrated that the stability and nature of the σ -complexes can be modulated depending on the RTIL

used. The use of controlled potential electrolysis makes it possible to fast and selectively complete the desired oxidation product. The results obtained are similar or even higher than those obtained in organic solvent electrolyte systems (DMF + 0.1 M TBABF₄), the experimental conditions used being less polluting. In summary, the described methodology is a friendly environmental route, which is economically feasible and accomplishes most of the important principles of green chemistry, such as safer solvents (non-flammable, non-volatile and thermally stable over a wide range of temperatures), low cost of the reactant, ready availability of the reagents, atom

economy, high yields (approaching 100% based on unrecovered starting material). We are currently working on the extension of this methodology to new RTILs and substrates.

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- 29 The color of the solution is characteristic of the formation in solution of σ^H -complexes. For more information about the UV-Vis features of σ^H -complexes see references 1–4.
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- 32 The value of the number of electrons involved in each electron transfer in the different media used are calculated by comparison with the oxidation of redox probes, *i.e.* tris(4-bromophenyl)-amine, for more information see reference 27.
- 33 The presence of a reduction pre-peak between -0.5 and 0.0 V, depending on the RTILs, is related with reduction **4** in the presence of potassium. See reference 14.
- 34 The absence of the reduction wave associated with the 1,3,5-trinitrobenzene in the cyclic voltammogram indicates that there is no "free" nitroaromatic compound in solution.
- 35 The fact that it is not possible to shift the equilibrium from reactants to products even when using an excess of amine, indicates that most of the intermediate is in zwitterionic complex form rather than σ^H -complex. The oxidation of the zwitterionic complex leads to the reactant, whereas the oxidation of the σ^H -complex yields the NASH products. It is also possible that some important part of the amine in excess could be protonated in RTILs and it would not contribute to shifting the equilibrium and increasing the reaction yield.
- 36 Exhaustive controlled potential electrolysis is performed until there is no presence of an oxidation wave. Since the reaction takes place in [BMIM]AcO, it is possible that the anion attacks the NASH product. This is not a problem in terms of NASH product yield. Although the time of electrolysis is longer, the electrochemical oxidation of the σ^H -complex (NASH product-acetate) provokes the departure of the acetate.
- 37 The absence of the reduction wave associated to the 2,4,6-trinitroanisole after 1 h of preparation of the reaction mixture indicates that there is no "free" nitroaromatic compound in solution.