

Electrochemical Synthesis of Alkyl Nitroaromatic Compounds

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Abstract: Alkyl nitroaromatic compounds were readily prepared via nucleophilic aromatic substitution for hydrogen or a heteroatom by electrochemical oxidation of the σ -complex. Butyllithium and butylmagnesium chloride were used as nucleophiles, and several nitrocompounds were tested to explore the possibilities of the NASH and NASX reactions promoted electrochemically.

The nitration of alkyl benzenes, in a mixture nitric acid/acetic anhydride at 0 °C, leads to *m*-, *o*-, *p*-alkyl nitrobenzenes.¹ This process constitutes the main industrial synthesis of alkyl nitro benzenes. The ortho-substitution is less important when the size of the alkyl group increases, for instance, when the ratio for toluene is 50/1.3/60 and that for ethyl benzene is 31/2.3/70. Alkyl 2,4- and 2,6-dinitrobenzenes (ratio = 80:20) were obtained by nitration of alkyl nitrobenzenes or alkyl benzenes.

The new methods of alkylation of the aromatic nitro compound are of remarkable interest in view of the fact the few classical synthetic methods of preparing alkyl nitro compounds have serious drawbacks.² Recently, a synthesis of alkyl nitro benzenes via nucleophilic aromatic substitution has been reported,³ using *p*-dinitrobenzene and alkyl boranes as reagents in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol. Its furnishes *p*-alkyl nitrobenzenes in good yields.

Nucleophilic aromatic substitution is one of the most widely used approaches for the functionalization of aromatics and forms the backbone of numerous important syntheses of pharmaceuticals and potential drugs. In this sense, C–C bond formation has been previously investigated.⁴ Nitrocompounds react with organometallic

compounds (RM with M = Li, MgX), at *o*- and *p*-positions, yielding the corresponding σ^H -adducts.

These σ^H -adducts are relatively stable, particularly at low temperatures, due to the effective participation of the nitro group delocalizing the negative charge. Moreover, the formation of a partial O–M covalent bond aids in stabilizing the σ^H -adducts. Those σ^H -adducts decompose easily by addition of mineral acids leading to the corresponding alkyl-substituted nitroso benzenes.⁵ A chemical oxidation, via external oxidation agents (bromine, dichlorodicyano-*p*-benzoquinone (DDQ), or potassium permanganate) is also possible and leads to alkyl-substituted nitrocompounds.⁶

The oxidation step of the σ -complex remains to be solved, since the use of chemical oxidants represents a significant environmental hazard when scaling-up the reactions. Our previous work⁷ has demonstrated that the electrochemical oxidation of σ -complexes leads to substitution products. For cyanation, amination, and reaction with enolate anions, fair to good yields were obtained in what can be considered a “green” process.

This electrochemical approach to the alkylation of nitroarenes is reported herein for the first time. The σ -adducts were prepared, under nitrogen atmosphere, by careful stoichiometric addition to 5 mL of a 40 mM solution of nitroaromatic compound in anhydrous THF at 0 °C to a solution 2.5 M of butyllithium in hexane or 2.0 M butylmagnesium chloride in THF. A 5 mL DMF solution of the supporting electrolyte (0.40 g of TEABF₄) was prepared under a nitrogen atmosphere. This DMF solution was carefully added to the nitroaromatic solution. After exhaustive electrolysis, at 1.30 V vs SCE, the corresponding alkyl-substituted nitrocompounds were obtained.

Products and yields from this nucleophilic aromatic substitution of hydrogen (NASH) by means of electrochemical oxidation are presented in Table 1. The global yield in the reaction nitrobenzene/BuLi was 88%, with 47% yield of disubstitution products. Moreover, a better yield of monosubstituted products, 75%, is possible in the reaction nitrobenzene/BuMgCl (global yield of 85%). In this case, only 10% of disubstitution products was achieved. We obtained the same results with 1,3-dinitrobenzene as a reactant; with BuMgCl, only monosubstituted products (36%) were obtained, but with BuLi, mono- (43%) and disubstitution products (30%) were obtained. Therefore, the reaction can be directed depending on the desired products (mono- or disubstitution products). These yields are rather good considering that, apart from the substitution product, only the nonreacted starting material was recovered.

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TABLE 1. NASH in Nitrobenzenes by Action of Organometallic Compounds via Electrochemical Oxidation at 1.3 V vs SCE

nitroarene	reagent	NASH products	yield ^a [corrected yield] ^b
nitrobenzene	BuLi	1-butyl-4-nitrobenzene	41 [46]
		2,4-dibutyl-1-nitrobenzene	47 [52]
nitrobenzene	BuMgCl	1-butyl-2-nitrobenzene	35 [41]
		1-butyl-4-nitrobenzene	40 [47]
		2,4-dibutyl-1-nitrobenzene	10 [12]
1,3-dinitrobenzene	BuLi	4-butyl-1,3-dinitrobenzene	43 [57]
		4,6-dibutyl-1,3-dinitrobenzene	30 [40]
1,3-dinitrobenzene	BuMgCl	4-butyl-1,3-dinitrobenzene	36 [100]
1,3,5-trinitrobenzene	BuLi	5-butyl-1,3-dinitrobenzene	<5 ^c
1,3,5-trinitrobenzene	BuMgCl	5-butyl-1,3-dinitrobenzene	<5 ^c

^a Yields were calculated by gas chromatography. Final products were identified by gas chromatography, mass spectrometry, and ¹H NMR and by comparison with authentic samples. ^b After correction for unreacted starting material. ^c 1,3,5-Trinitrobenzene was recovered in quantitative yield, after the electrolysis.

TABLE 2. NASX in 1,4-Dinitrobenzene by Action of Organometallic Compounds via Electrochemical Oxidation

nitroarene	reagent	NASX products	yield ^a [corrected yield] ^b
1,4-dinitrobenzene ^b	BuLi	1-butyl-4-nitrobenzene	41 [58]
		2,4-dibutyl-1-nitrobenzene	20 [29]
		4-nitrophenol ^d	7 [10]
1,4-dinitrobenzene ^b	BuMgCl	1-butyl-4-nitrobenzene	12 [30]
		2,4-dibutyl-1-nitrobenzene	28 [70]
1-chloro-2,4-dinitrobenzene	BuLi	2-butyl-1-chloro-4-nitrobenzene	<5 ^c
	BuMgCl	2-hydroxy-1-chloro-4-nitrobenzene	<5 ^c
		2,4-dinitrophenol ^d	<5 ^c
1-chloro-2,4,6-trinitrobenzene	BuMgCl	1-butyl-2-chloro-3,5-dinitrobenzene	<5 ^c
		2-chloro-3,5-dinitrophenol	<5 ^c
		picric acid ^d	<5 ^c

^a Yields were calculated by gas chromatography. Final products were identified by gas chromatography, mass spectrometry, and ¹H NMR and by comparison with authentic samples. ^b After correction for unreacted starting material. ^c Only the reactant, apart from substituted products, was recovered after the electrolysis. ^d From residual water present in the solvent in the presence of BuLi or BuMgCl.

Good results were obtained when the *p*-dinitrobenzene was used as a nitroaromatic compound. A nitro group can be replaced by a butyl group via electrochemical oxidation of the σ^X -complex formed in a NASX process (Nucleophilic Aromatic Substitution of Heteroatom). As in a NASH process, the reaction can be directed toward mono- or disubstitution products by using BuLi or BuMgCl. The unreacted starting material was the only product recovered, apart from the substitution product. No chloro atom displacement by the butyl group was observed when 1-chloro-2,4-dinitrobenzene and 1-chloro-2,4,6-trinitrobenzene were used. The results are shown in Table 2. The SNAr addition–elimination mechanism was excluded because before the electrolysis the cyclic voltammogram of the reaction mixture never presented a reduction wave of alkyl nitrobenzene product ($E^\circ = -1.21$ V vs SCE). Only the reduction waves corresponding to 1,4-dinitrobenzene are obtained ($E_1^\circ = -0.58$ V, $E_2^\circ = -0.83$ V vs SCE).

Use of equivalent amounts of the nitro aromatic and organometallic reagents was found to be essential for the best completion of reaction because an excess of organometallic reagents makes it more difficult to oxidize the mixture and larger yields of dialkylated substituted products are obtained.

The butyllithium produces higher yields than the butylmagnesium chloride in our reactions, although the mixture reaction is cleaner with butylmagnesium chloride. The reaction was also carried out in THF (resistive media). It was not possible to perform the reaction in DMF, since DMF decomposes in the presence of butyllithium.

The yields obtained applying the “clean” electrochemical method are comparable with those reported in the literature using chemical oxidants, and even better in some cases. In addition, this is the first time that alkylation of dinitroderivates has been achieved with reasonable yields.

In the Scheme 1, the established⁷ oxidation mechanism of σ -complexes (Meisenheimer complexes) is described.

The use of electrochemical techniques is very attractive in the field of nucleophilic aromatic substitution reaction. We are currently working to establish the scope and limitation of this methodology. A full account will be published in the foreseeable future elsewhere.

Experimental Section

General Remarks: Electrochemical Measurements. The electrochemical cell and measurement procedures for cyclic voltammetry have been described previously.^{7,8} All potentials are reported vs an aqueous saturated calomel electrode. A glassy carbon was used as a working electrode (0.05 mm diameter) in CV experiments. A graphite rod was used as a working electrode in electrolysis experiments.

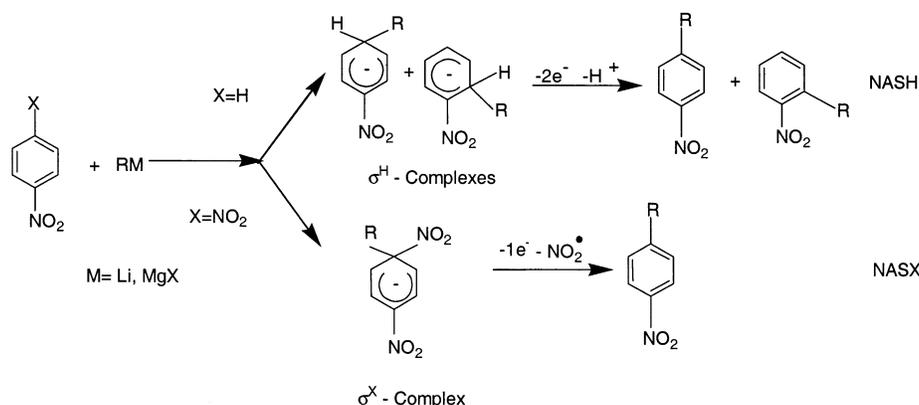
Materials. DMF (SDS pour synthèses peptidiques), anhydrous tetrahydrofuran 99.9%, and nEt₄NBF₄ were used without purification.

1-Nitrobenzene, 1,3-dinitrobenzene, 1,4-dinitrobenzene, 1-chloro-2, 4-dinitrobenzene, and 1,3,5-trinitrobenzene were purchased commercially.

1-Chloro-2,4,6-trinitrobenzene was synthesized in our laboratory. Following the method described in the literature,⁹ 15 mL

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SCHEME 1



of POCl_3 were added to 22 mmol of picric acid. Next, 2.5 mL of pyridine was added carefully. The mixture was heated to 120–125 °C for 1 h. After the mixture was cooled 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%).

Butylmagnesium chloride, 2.0 M solution in THF, and butyllithium, 2.5 M in hexane, were purchased commercially.

General Procedure for NASH or NASX in Nitroarenes. General Experimental details were given in previous papers.⁷ A solution of nitroarene (40 mM) in 5 mL of anhydrous THF at 0 °C was prepared under a nitrogen atmosphere. The corresponding σ^{H} -complex was prepared by careful addition of the nucleophile 1:1 (butyllithium or butylmagnesium chloride solutions in hexane/THF, 2.5 and 2.0 M, respectively) to the solution of the nitroarene under a nitrogen atmosphere. Finally, the addition of 5 mL of DMF, which contains 0.4 g of NEt_4BF_4 (0.1 M) as a supporting electrolyte, was carried out.

The oxidation peak potentials of the σ^{H} -complexes were measured by cyclic voltammetry.

Then, electrolysis was carried out at values of potentials ca. 1.3 V using a carbon graphite rod electrode as a working electrode. The electrolysis was stopped when no σ -complexes were detected in the mixture (cyclic voltammetric analyses were carried out to follow the electrochemical oxidation). Then, the mixture was extracted with water/toluene. The organic layer was dried with Na_2SO_4 and evaporated, affording a residue that was analyzed by gas chromatography. *Gas Chromatography*. GC

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measurements were made with an HP-5 column (cross-linked 5% Ph–Me silicone, 30 m \times 0.32 mm \times 0.25 μm). Five control (experimental) variables were used. The following were the settings: initial temperature, 100 °C; initial time, 1 min; temperature gradient, 12 °C/min; maximum oven temperature, 240 °C; final time, 15 min.

The analysis showed the presence of nitro compounds. The final products were analyzed by gas chromatography/mass spectroscopy, ^1H NMR, and cyclic voltammetry and identified by comparison of their spectroscopic behavior with that reported in the literature for them or related compounds depending on the cases.^{2d,5,10} The product yields were not optimized and were calculated by gas chromatography after verification from the ^1H NMR of the crude that only the substitution products and starting material were present and by cyclic voltammetry.

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Supporting Information Available: Cyclic voltammetry experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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