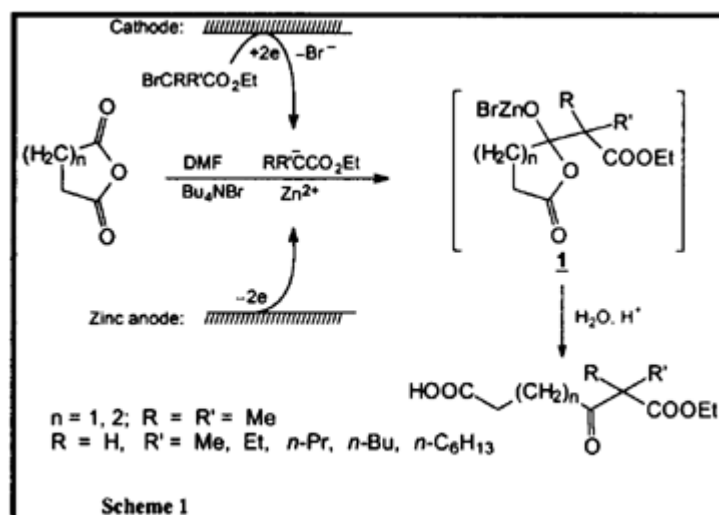# ELECTROCHEMICAL METHODS IN ORGANIC SYNTHESIS OF VALUABLE INTERMEDIATES

by Murat E. Niyazymbetov
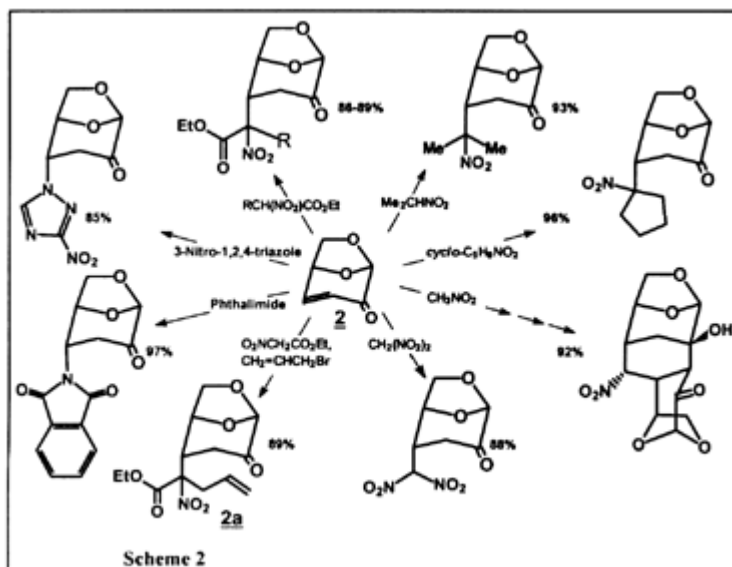
Over the past 25-30 years the use of electrochemistry as a synthetic tool in organic chemistry has increased remarkably.According to [1] Pletcher and Walsh[2a] more than 100 electroorganic synthetic processes have been piloted at levels ranging from a few tons up to 10^5 tons. Such examples include reductive dimerization of acrylonitrile, hydrogenation of heterocycles, pinacolization, reduction of nitro aromatics, the Kolbe reaction, Simons fluorination, methoxylation, epoxidation of olefins, oxidation of aromatic hydrocarbons etc.[2] In this brief report we would like to review the use of electrochemical methods as a tool in lab scale synthesis, solving R&D objectives for a multi-step targeted synthesis, or one-step synthesis of intermediates or starting materials. There are many excellent reviews and monographs and publications we refer readers to some of them.[1,3] These cover a broad spectrum of applications of electrochemical methods in organic synthesis including their use in the pharmaceutical industry.[3h,k] Herein, we review some recent advances in using electrochemical methods in fine organic synthesis. Moreover we will demonstrate that electrochemical methods are a tool that should become widely accepted in this area.

Example 1. Zinc-induced formation of *b*-hydroxyalkonates from *a*-haloesters and aldehydes or ketones (Reformatsky reaction) is an important method and was used for synthesis of a wide variety of compounds including complex natural products.[4a] The problem of this reaction is associated with preparation of highly active metallic zinc. Many precautions are required to achieve good yields; however, Reformatsky reactions are often difficult to control.
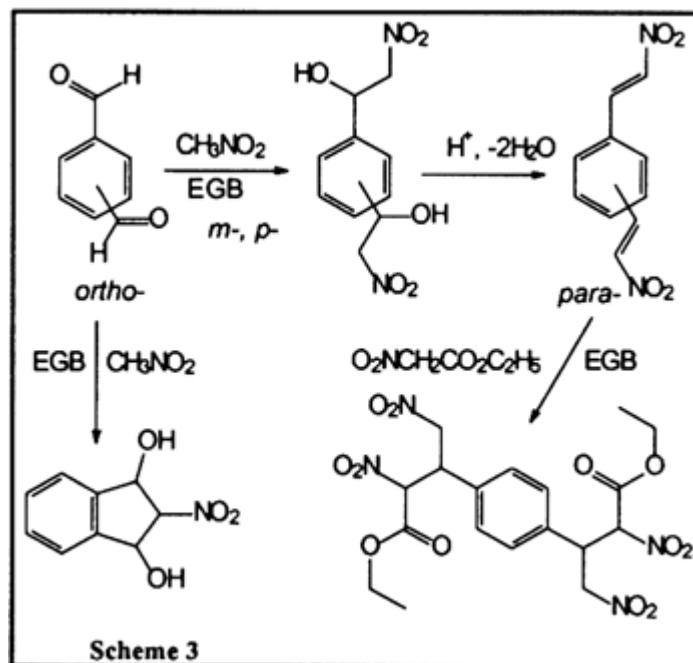

Scheme 1

The electrochemical version of the Reformatsky reaction[4b,c] is based on the use of the sacrificial zinc anode in an undivided cell. The Reformatsky reagent is formed by direct reaction of cathodically generated carbanion from a-bromoacetate and anodically generated zinc cation. The intermediate organozinc reagent further reacts with succinic or glutaric aldehyde with formation of intermediate **1**.[4c] The mild reaction conditions and good yields of the products, along with the fact that activated zinc is not required, make the electrochemical version of the Reformatsky reaction very promising to be widely used in organic synthesis.

Example 2. Base catalyzed Michael addition is one of the most synthetically important reactions. As an example we would like to review some reactions of levoglucosenone[5] (**2**), which is easily obtained by the pyrolysis of cellulose and serves as a useful chiral building block to prepare natural and other compounds due to its highly functionalized structure. The reactions of levoglucosenone under basic conditions are often accompanied by side-reactions and the yield of desired product not always high. In contrast the reactions of **2** in the presence of the electrogenerated base (EGB), superoxide anion, proceeds very smoothly[6] and addition of nitrocompounds and nitrogen-containing heterocycles to **2** results in formation of the products in much higher yield compared with chemical version of that reaction (Scheme 2).

Scheme 2

Cathodically initiated Michael addition of thiols to **2** using small currents produces the previously unknown *threo* addition product. It has been shown that simply by changing the current density it is possible to prepare either erythro- or threo-isomers of thioalkyl and thioaryl derivatives of **2**.[6b]

Example 3. Small nitrated molecules like nitromethane or ethyl nitroacetate are useful building blocks in organic chemistry since they allow the formation of interesting carbon skeleton by stepwise nucleophilic substitution, Michael addition or Knovenagel condensation type of reactions. All of these reactions can be effectively performed under electrochemical conditions. Starting from the meta- or para-benzenedicarboxyaldehydes and nitromethane, it is possible to prepare selectively the single or double addition products by changing the current density and the charge passed[7] (Scheme 3). Since the reaction conditions are very mild, in contrast to the chemical methods, no spontaneous dehydration occurred. However, the (bis)nitroalcohols could be dehydrated almost quantitatively using dilute phosphoric acid.

Scheme 3

The dinitrolefin formed is then used as a Michael acceptor for the electrochemically generated nitrocarbanions and heteroatom-anions. The ortho derivative, phthalaldehyde, reacts in a much different way to give the bicyclic nitro indanediol.
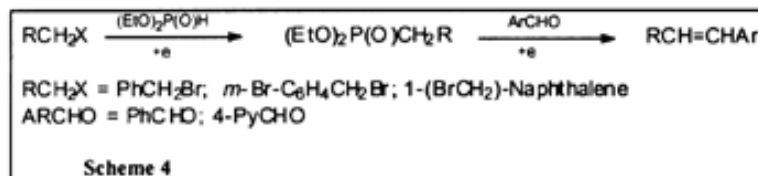
The method of EGB is applicable to many base catalyzed chemical reactions. The key step of the reaction is the cathodic generation of EGB, which deprotonates an organic acid with formation of a carbanion or heteroatom-anion. The use of tetraalkylammonium salts as a supporting electrolyte provides a very high reactivity of this anion,[8] which therefore reacts rapidly with substrate, e.g. Michael acceptor, with the result that the reaction medium remains essentially neutral.

This has the advantage of circumventing unwanted base-catalyzed transformation of starting and final materials. For a recent review on EGB and the utility of organic anions in electrosynthesis see Ref. 3e.

Thus the mild conditions, ease of control of both solvent and counter-ions (upon which the reactivity of nucleophiles strongly depends[8]) high yields and selectivities as well as the use of readily available equipment,[2b] simply designed cells and regular organic glassware make the electrochemical versions of the aforementioned reactions very competitive to the conventional methods in organic synthesis. In most cases isolation of the product is simple: a solution of the crude product is filtered through layer of silica gel, and after evaporation of the solvent, the analytically pure product is obtained.
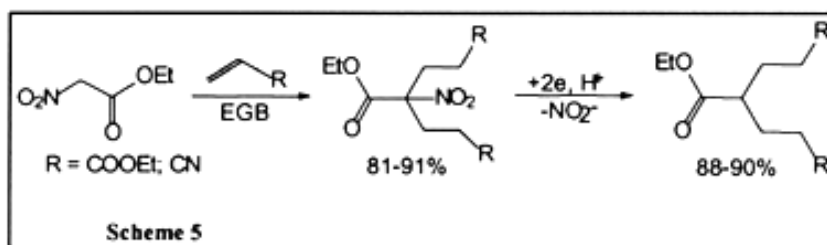
One-Pot Procedure Electrochemical Reactions

One of the advantages of electrochemical methods is that different kinds of transformations can be performed under similar conditions by using the same solvent, supporting electrolytes and electrode materials. Several steps can then be performed in the same solution without isolation of intermediate products. The electrochemical approach allows preparation of olefins in a one-pot reaction from dialkylphosphites, organic halides and carbonyl compounds.[9] This reaction includes two transformations: the first is the alkylation of dialkylphosphites with formation of alkylphosphonates. The second reaction is a base catalyzed reaction of phosphonates with carbonyl compounds

$$RCH_2X \xrightarrow[+e]{(EtO)_2P(O)H} (EtO)_2P(O)CH_2R \xrightarrow[+e]{ArCHO} RCH=CHAr$$

$RCH_2X = PhCH_2Br; \ m\text{-}Br\text{-}C_6H_4CH_2Br; \ 1\text{-}(BrCH_2)\text{-}Naphthalene$
$ARCHO = PhCHO; \ 4\text{-}PyCHO$

Scheme 4

(Wittig-Horner reaction) to form olefins in good overall yield (Scheme 4).
It has been shown that under electrochemical conditions, selective monoalkylation of ethyl nitroacetate and further Michael addition reaction can be carried out in a one-pot procedure.[10] This approach was used for synthesis of the ethyl 2-nitro-4-pentenoate derivative of levoglucosenone **2a**[7a,c] (Scheme 2).
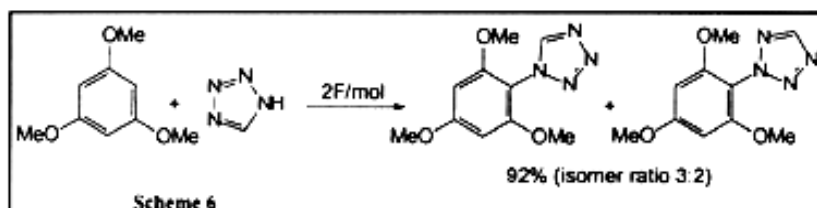
Another example includes Michael addition of ethyl nitroacetate to activated olefins and further electroreductive removal of the nitro group[11] (Scheme 5). In the first step any reaction can be used (e.g., alkylation, aromatic nucleophilic substitution or anodic coupling of anions) for functionalization of ethyl nitroacetate followed by electroreductive denitration.
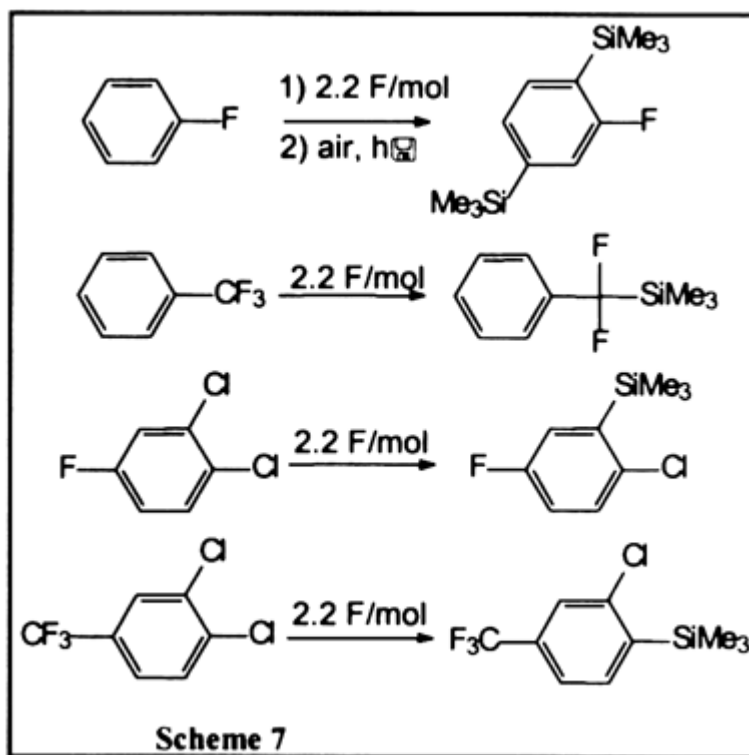
Scheme 5

Anodic reactions are also amenable to one-pot synthesis as well as the combinations of anodic and cathodic processes. We believe that the one-pot approach can be very useful for R&D work and especially for larger lab scale synthesis of valuable compounds being considered for industrial application.

Paired Electrosynthesis

The synchronous utilization of anodic and cathodic reactions in synthesis was recently reviewed.[3e] The reaction of cathodically generated heterocyclic anions with the anodically generated aromatic cation-radicals offers a very simple one-step way of synthesis of *N*-aryl triazoles and tetrazoles[12] (Scheme 6).
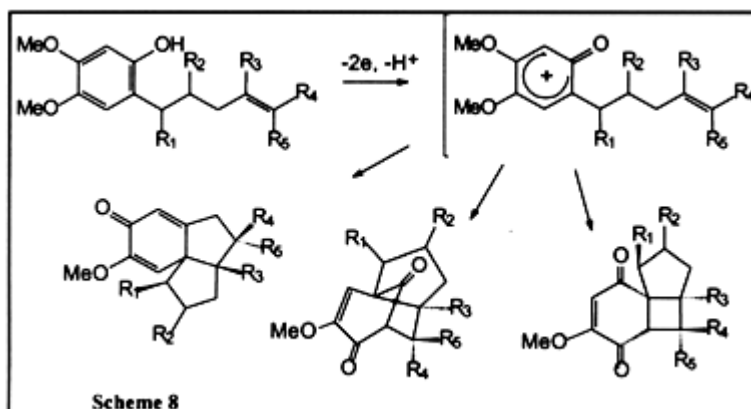

Scheme 6

The use of sacrificial anodes (for reviews see Ref. 13) is an effective way for the preparation of metallo-organic compounds by cathodic generation of organic anions and anodic generation of metal cations. This approach was very successful for synthesis of the organosilicon compounds.[14] The electroreduction of trialkychlorosilanes with Mg anode and cathode gives hexaalkyldisilanes in excellent isolated yield, while reduction of dialkyldichlorosilanes under the same conditions results in formation of the corresponding polysilanes.[14b] A variety of fluorinated organosilicon compounds can be synthesized using a sacrificial Al anode and a stainless steel cathode under very mild conditions and in good yields[14f] (Scheme 7).

Scheme 7

Synthesis of Complex Molecules

Anodic oxidation of phenols (for a review see Ref. 2a, p. 615) is attracting much attention because of the wide variety of transformations that can be done by changing electrolysis conditions and the structure of starting compounds. This reaction was successfully used as a key step in the synthesis of a number of natural compounds, such as isofutoquinol A, asatone, helminthosporal and others.[15a] Oxidation of 3,4-dimethoxyphenols with a double bond in the side chain under various conditions results in the formation of three different types of tricyclic compounds. These can serve as starting materials for synthesis of a series of bioactive terpenoids (Scheme 8).

Scheme 8

Electrooxidation of 3,4-dimethoxyphenols with benzyl thioether groups at the *ortho*-position to the OH-group offers a simple way to construct the euglobal and chroman skeletons.[15b] Reaction proceeds via formation of orthoquinone methides which then react with a terpene present in the solution. Little and coworkers have developed a strategy for synthesis of the natural products, which is based on electroreductive cyclization (ERC).[16] So, the use of ERC as a key step makes the overall synthesis of (-)-C_{10}-desmethyl arteannuin B more simple and efficient compared with the earlier reported procedures.[16b] Moeller is successfully developing a strategy for synthesis of complex natural and unnatural products based on anodic methoxylation and olefin coupling reactions.[17] For more examples of using electrochemical methods in synthesis of natural and pharmaceutical products see Ref. 2a (p. 765) and 4f-i.

Conclusion

Discoveries of new types of electroorganic reactions based on coupling and substitution reactions, cyclisation and elimination reactions, electrochemically promoted rearrangements, recent advances in selective electrochemical fluorination, electrochemical versions of the classical synthetic reactions and successful use of these reactions in multistep targeted synthesis allow the synthetic chemist to consider electrochemical methods as one of the powerful tools of organic synthesis. Traditionally, electrochemical organic reactions were classified according to types of substrates that underwent the electrochemical change (for example reduction of nitrocompounds, oxidation of sulphur compounds, reduction of aldehydes, oxidation of alcohols, etc.). Now classification of electroorganic reactions is being made with emphasis to their synthetic applications.

The consideration of the electrochemical methods as part of the strategy from the very beginning of the multi-step targeted synthesis can offer much shorter ways to success. Therefore if electrochemistry is to be used successfully, it is important that the electrochemist be involved in the developing of the synthetic strategy from the earliest stages.

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The possibilities for organic electrochemistry are very broad. If you would like to discuss further the development of specific electroorganic reactions, please contact us at (716) 684-0513, ex. 111 or e-mail info@electrosynthesis.com .