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Article

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Synthesis of Triazoles by Electro-Assisted Click Reaction Using a Copper Foil Electrode

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This paper presents an innovative pathway for the synthesis of triazoles using the well-known "click chemistry" assisted by the electrochemical oxidation of metallic Cu^0. The click reaction is used to couple a wide range of biological interest compounds. In this case, faster and less polluting methods for a biological environment was achived by *in situ* Cu^0 electrooxidation, providing the suitable quantity of catalyst required by click reaction. The electrochemical cell was composed of a copper foil as the working electrode, a platinum wire serving as a counter electrode, and an Ag/AgCl wire as the reference electrode. Linear anodic sweep voltammetry in a *tert*-butanol-water medium (1:1), an electrolyte of tetrabutylammonium tetrafluoroborate (TBATFB), showed the onset potential of Cu^0 electrooxidation. Using the same electrode configuration three different triazoles were prepared under constant electrode potential, in a short time (60 min), and splendid yields (78-90%). These results indicate that the *in situ* Cu^I formation occurs on the surface of the copper foil. A pulse potential program has also been implemented in which a yield of 92% was achieved, reducing electrode passivation and consequently increasing the process efficiency. The electro-assisted click reactions are highly efficient to produce triazoles by an innovative electrochemical reaction. The products were characterized by infrared (IR), nuclear magnetic resonance (^1H and ^{13}C NMR), and mass spectrometry (MS).

Keywords: click reaction, azide, triazole, Cu electrooxidation, organic electrosynthesis

Introduction

The click chemistry is a green, selective, qualitative, pH-sensitive, and economical affordable,[1] suitable for the synthesis of a variety of bioconjugates including peptides,[2] proteins,[3] and polysaccharides,[4] among others.

The purpose of the click chemistry is to selectively bind two molecular building blocks, under mild reaction conditions, obtaining high yields and harmless byproducts. Another characteristic is the easy way to separate main products by non-chromatographic methods.[5] Some examples of reactions that fall into the category of click reactions are the synthesis of thiolene,[6] oximes,[7] Diels-Alder reactions,[8] Michael addition,[9] etc., however, the most known is the Cu^I-catalyzed azide-alkyne click cycloaddition (CuAAC).[10] The CuAAC has become one of the most used models due to its wide field of application, its easy scale-up, and its high reaction yield. Another important point is that it is not affected by the presence of functional groups and can proceed with various sources of Cu^I.[10-12]

Thus, the click chemistry has increased the extent of its applications over organic chemistry,[13] pharmaceutical chemistry,[14] diagnoses,[15] materials,[16] and polymer science.[17,18]

Concerning triazoles, Huisgen[19] was the first to perform the 1,3-dipolar cycloaddition of azides with terminal alkynes to form disubstituted 1,2,3-triazoles. Huisgen cycloaddition produces the mixture between the 1,4 and 1,5-disubstituted products. This reaction is carried out by heating (60-120 °C) and can take hours or days. In 2002, Sharpless and co-workers[20] reported the 1,3-dipolar CuAAC reaction, which is completely regioselective for the formation of 1,4-disubstituted triazoles. In this case the reaction is carried out at room temperature and has high conversions at shorter times, compared to the uncatalyzed cycloaddition reported by Huisgen.[19] For this reason the complex CuAAC became the most known click reaction.[20]

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Other strategies have been reported[21-24] to perform the cycloaddition of alkynes and azides without the use of a copper catalyst; however, for these reactions, the kinetics is slow and does not present regioselectivity. Due to these facts, for cycloaddition reactions, copper salts seem to be the better option.

It is important to note that organic electrosynthesis is an excellent alternative since it has a history of more than 200 years of development and has produced a very extensive literature. Electrolysis remains a very little used procedure for the synthesis of organic compounds in both academic and industrial processes.[25] We have previously reported assisted synthesis by electrolysis to improve the synthesis of mono and disubstituted benzimidazoles,[26] hydantoins,[27] and recent chalcones. Analyzing the mechanism of click reactions and looking for an innovative faster procedure to synthesize triazoles, this paper proposes to assist a conventional click reaction by electrochemical methods. Since a metallic species as Cu^0 may be relatively easy to oxidize by electrolysis, the main objective is to generate ionic species of Cu^0 as Cu^I serving to catalyze the triazole click reaction. For this purpose, a suitable electrolytic media, as well as a proper electrochemical cell configuration, were used, first to establish the electrolysis electrode potential and then to test the reaction improvement by the *in situ* electrooxidation of Cu^0, considering the electrons as redox reactants instead of polluting reducing/oxidizing reagents.[28] It is also important to consider that electric current is equivalent to the velocity of the formation of Cu^I.

Experimental

General procedures

All common reagents were obtained from Aldrich (Saint Louis, Missouri, USA) and used without further purification. The synthesized compounds were detected by thin-layer chromatography (TLC) performed on silica gel F_{254} plates (Merck) using UV light. Infrared spectra (IR) were recorded on a PerkinElmer FT-IR 1600 spectrophotometer. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra at 200 and 50 MHz, respectively, were recorded on a Varian Mercury 200 MHz Spectrometer at 300 K using 5 mm sample tubes in $CDCl_3$ and/or dimethyl sulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as the internal standard. Mass spectra (MS) were obtained on an Agilent Technologies 5975C MS Spectrometer at 70 eV by direct insertion. The morphology and the surface elemental composition were determined by field emission scanning electronic microscopy (FESEM) in a JEOL 7800F Prime. The energy dispersive spectroscopy (EDS) was determined in a Bruker QUANTAX 200.

Conventional method for click reaction

In a vial, it was placed benzyl bromide (144 mg, 0.84 mmol), sodium azide (60 mg, 0.92 mmol), the catalyst, $CuSO_4$ (10.5 mg, 0.042 mmol), sodium ascorbate (25 mg, 0.126 mmol) and phenylacetylene (86 mg, 0.84 mmol) in *tert*-butyl alcohol/water (1:1) (4 mL). The vial was capped and placed into hard stirring for 60 min. The reaction was followed by TLC and finally filtered with ethyl acetate (40 mL) in silica and a thin layer of celite.[29] The excess of solvent was eliminated at reduced pressure and the solid obtained was characterized by NMR, MS and IR.

Electrochemical method for click reaction

Tetrabutylammonium tetrafluoroborate (TBATFB) salt (equivalent 0.0001 mol) was placed in a 200.0 mL beaker with 40 mL of *tert*-butyl alcohol/water (1:1) to dissolve, the mixture was kept under stirring for 2 min with a magnetic stirrer to dissolve the solid, after that, it was placed in a volumetric flask (50 mL) to complete the volume with *tert*-butyl alcohol/water (1:1). This salt was an analytical reagent from Merck (Mexico city, Mexico). It is important to mention that TBATFB was selected as a supporting electrolyte because it is soluble in the reaction medium: *tert*-butyl alcohol/water (1:1). Moreover, *tert*-butyl alcohol and tetrabutylammonium have similar structures, making them compatible and miscible, accomplishing the requirements of a supporting electrolyte.

Electrochemical oxidation of metallic Cu foil

The supporting electrolyte (4 mL) was placed in a 20.0 mL undivided electrochemical cell. A typical three-electrode system was used, high purity Cu^0 foil (0.25 cm^2 area) was used as a working electrode (WE), Pt coil was used as a counter electrode (CE), and Ag/AgCl rod immersed in saturated KCl/*tert*-butyl alcohol/water (1:1) solution as a reference electrode. Anodic linear sweep voltammetry was performed to the bare copper foil serving as a working electrode in the supporting electrolyte to select its suitable electrooxidation potential. This electrode potential will be used during the forthcoming triazoles electrochemical synthesis. The experiment was made with a potentiostat-galvanostat from BASI using Epsilon software. Cu^0 oxidation onset was identified at 0.30 V *vs.* $Ag/AgCl/Cl^-_{(\textit{tert}\text{-butyl alcohol/water})}$.[30]

Electrochemical synthesis of triazoles

In the electrochemical cell of 20.0 mL the supporting electrolyte was placed (4.0 mL) as well as electrodes (Cu^0 (working electrode), $Ag/AgCl/Cl^-_{\text{sat KCl (\textit{tert}-butyl alcohol/water)}}$ (reference electrode) and Pt (counter electrode)), then the reaction reagents were added; benzyl bromide (144 mg, 0.84 mmol), sodium azide (60 mg, 0.92 mmol) and phenylacetylene (86 mg, 0.84 mmol). For a first experimental series, a constant voltage of 0.3 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl (\textit{tert}-butyl alcohol/water)}}$ was applied to the working electrode, in the second series a pulse voltage was selected to ensure Cu^0 electrooxidation following a rest time without polarization to allow a relaxation of the interface. Both cases were done using the Autolab potentiostat-galvanostat and stirring constantly for 60 min. Figure 1 shows the pulsed potential program, composed by 40 cycles between oxidation at 0.3 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl (\textit{tert}-butyl alcohol/water)}}$ for 60 s and rest potential at −1 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl (\textit{tert}-butyl alcohol/water)}}$ for 30 s. The reaction was monitored by TLC.

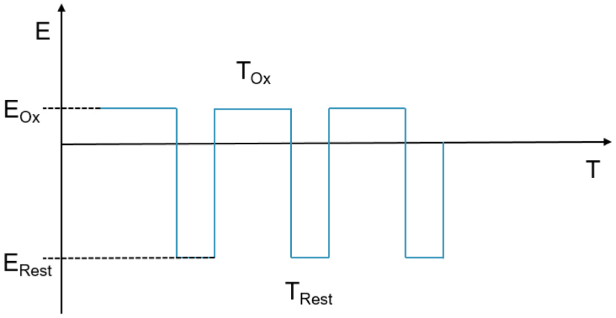


Figure 1. Pulsed potential program for the electrochemical process.

Results and Discussion

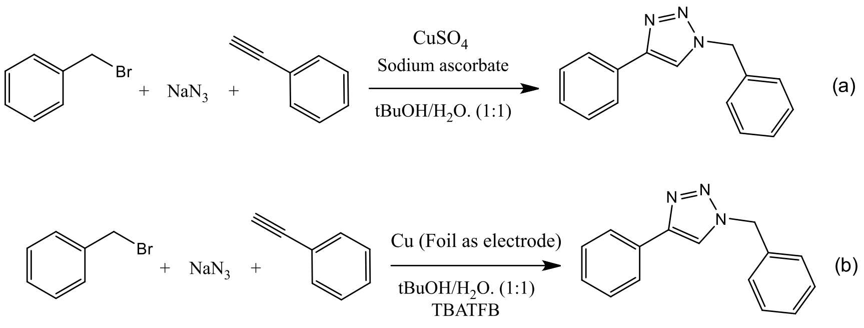
In this paper, three types of experiments are reported: first, a modified click chemistry protocol (Scheme 1a); second, the continuous oxidation of the copper foil electrode; and third, the pulsed oxidation of copper foil electrode, the last two to generate the Cu^I ion that is responsible for the catalysis in the click chemistry (Scheme 1b).

The click chemistry reaction was carried out with benzyl bromide, sodium azide, and phenylacetylene as a starting material, using the base reaction shown in Scheme 1a, consisting of the addition of benzyl bromide and sodium azide to produce benzyl azide (this reaction is carried out in 5 min). Later on, copper sulfate and sodium ascorbate were added followed by phenylacetylene.[21-24] This reaction was carried out using 5 mol% $CuSO_4$ and 15 mol% sodium ascorbate as the source of the Cu^I catalyst required for the formation of the triazole.

Electrochemical Cu^0 oxidation

Cu^0 electrooxidation may form Cu^I and/or Cu^{II} species in an aqueous medium as mentioned in several reports;[31-34] then the expectation was that pure Cu^0 foil in TBATFB/*tert*-butyl alcohol/water would form Cu^I, considering that electrode potential and solution conditions allow this process as Hernandez *et al.*[35] proposed the formation of Cu^I species controlling electrode potential and solution chemistry. This fact was demonstrated by the formation of triazoles using Cu^0 electrooxidation as the source of catalyst used in click reaction.[10]

To offset the influence of the electrolytic medium on the voltammetric response, the copper foil was submerged in the supporting electrolyte to determine its electrooxidation onset potential in 2 mM TBATFB dissolved in *tert*-butyl alcohol/water (1:1), serving as a supporting electrolyte without reagents. Cyclic voltammetry showed in Figure 2 allowed to determine that 0.3 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl}}$ is the onset potential for Cu^0 electro-dissolution in the triazole reaction medium, which is more positive compared with the thermodynamic value of Cu^0 to Cu^{II} electrooxidation in aqueous media (0.12 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl}}$) and the same as that of Cu^0 to Cu^I,[36] confirming the Cu^I formation on the electrode surface. For the organic-electro-assisted-synthesis (OEAS) of triazoles a constant potential of 0.3 V *vs.* $Ag/AgCl/Cl^-_{\text{sat KCl}}$ is going to be used, assuming



Scheme 1. Synthesis of triazole by the reaction of click: (a) conventional and (b) electrochemical methods.

that Cu^0 electrooxidation will also be very slow at this electrode potential.[37]

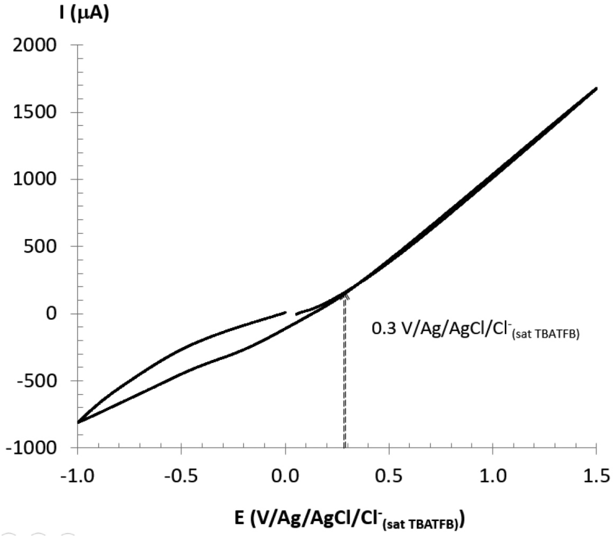


Figure 2. Cyclic voltammetry of the Cu^0 foil in TBATFB dissolved in *tert*-butyl alcohol/water (1:1) as supporting electrolyte.

In Figure 3, the triazole electrochemical assisted synthesis was registered in a current-time plot, representing the bulk electrolysis in the undivided three-electrode cell, using a working electrode Cu^0 of high purity to produce a solid-state catalyst for triazole synthesis, in *tert*-butyl alcohol/water (1:1) at room temperature. For the three triazoles (see Table 1), the plot shows a similar fall of the current in the cell, suggesting surface passivation after the first seconds of reaction. However, when reviewing the graph in Figure 3 in detail, it is noted that triazole **3** has a greater drop in current than those of **2** and **1**, which is a determining factor and the current is inversely proportional to the yield. Surface passivation is mainly an effect produced by triazole.[38] These compounds are well known for their action as metallic corrosion inhibitors.[38]

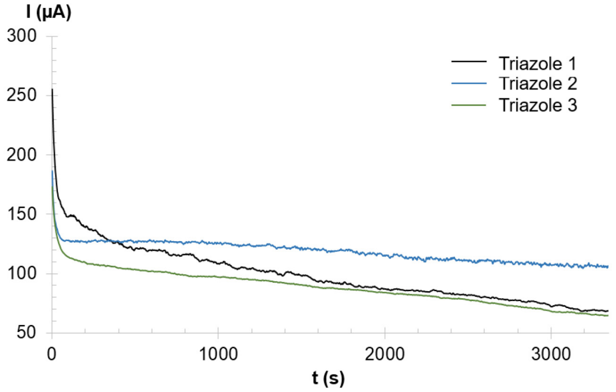
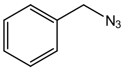
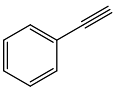
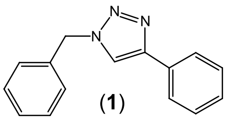
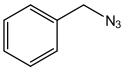
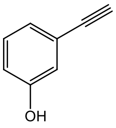
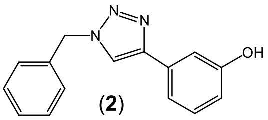
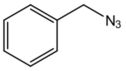
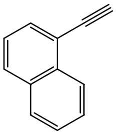
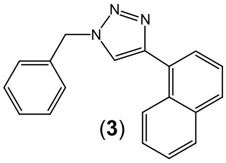


Figure 3. Bulk electrolysis to synthesize the triazole showed in Table 1 assisted by Cu electro-oxidation at a constant voltage 0.3 V *vs.* Ag/AgCl/$Cl^-_{\text{sat KCl}(\textit{tert}\text{-butyl alcohol/water})}$.

Conventional *vs.* electrochemical method

Table 1 presents the reaction yields and reagent types for the two methods. It is important to notice that in both procedures, the reaction yields followed the same trend, i.e., the yields are better by the electrochemical method as shown in the three reactions (**1**, **2** and **3**). These results indicate that the formation of Cu^I on the surface of the Cu foil was very efficient. This result suggests that the formation of Cu^I is greater on the surface of the Cu^0 foil

Table 1. Comparison between the conventional method and the electrochemical method

Azide[a]	Alkyne	Product	Yield / %		Electrolytic molar equiv. Cu^I / µM
			Conventional method	Electrochemical method	
		 (**1**)	56	78	1.36
		 (**2**)	66	86	1.94
		 (**3**)	61	90	1.18

[a]Benzyl azide was prepared *in situ*.

and the reaction speed increases. It was also notable that no additional purification step is required to obtain the final product in the electrochemical method.

For triazole the plot suggests surface passivation after 8 min approximately; however, the reaction yield (Table 1) indicates 78-90%. Surface passivation is mainly an effect produced by triazole. These compounds are well known for their action as metallic corrosion inhibitors. Even though, the yield was remarkably enhanced with *in situ* Cu^0 electrooxidation compared with that using $CuSO_4$-sodium ascorbate as a catalyst. It was demonstrated that the electrochemical process is more efficient and faster.

During the study, the copper foil appeared to dissolve slowly in the reaction solution and turned blue which intensified as the reaction developed. This was a clear indication of the formation of Cu^I.[39] After the study, small holes can be seen on the surface of the working electrode.

For triazole **1**, the general method of synthesis shows 56% of yield at 60 min; for the same time, the electrochemical method shows 78% of yield, which represents a 22% increase in the synthetic performance. For triazole **2**, the electrochemical methods gave us a yield of 86%, an increase of 20% compared with the yield obtained with the general method (66%). For triazole **3**, the general method shows a modest yield of 61%, which was highly improved by the electrochemical method by almost 30%, showing a 90% of the reaction yield in one hour. As can be seen for the three different triazoles, the electrochemical method shows increases of more than 20% in the reaction yield at the same time and under the same conditions of stirring and temperature as the general method.

Surface study and elemental analysis by FESEM

The morphology study of the copper foil, before and after the OEAS, was done by FESEM and EDS elemental analysis. Both samples were analyzed without any previous preparation. Figure 4 shows FESEM images and allows us to describe the effect of electrochemical Cu^0 oxidation on the metallic foil. Figure 4c shows the mapping of the image by the EDS detector and shows the elemental distribution on the copper foil and, in Figure 4d, after the electrosynthesis (constant imposed potential of 0.3 V *vs.* $Ag/AgCl/Cl^-_{(tBuOH:H_2O)}$), it is shown that a new species has been formed on the copper foil.

Table 2 shows copper foil EDS analysis before and after the induced electrolytic process. This result indicates that a new copper phase has been formed and through the postulate of the mechanism is proposed to be the Cu_2O. This fact can be supported by a recent publication[40] reporting that Cu_2O is a suitable crystalline solid formed by the electrochemical deposition of metallic Cu^0.

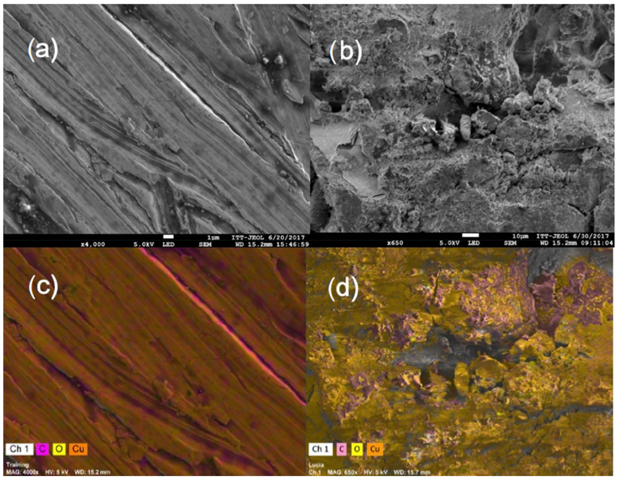


Figure 4. FESEM image of Cu^0 foil: (a) before electrolysis; (b) after electrolysis; (c) EDS elemental analysis map, before electrolysis; (d) EDS elemental analysis map, after electrolysis.

Table 2. Elemental analysis from EDS of Cu^0 electrode, before and after the electrochemical assisted synthetic process

Element	Before electrochemical oxidation / at.%	After electrochemical oxidation / at.%
Cu	95.04	63.32
C	3.02	16.23
O	1.36	10.08
Other	0.58	10.37

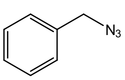
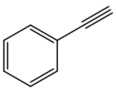
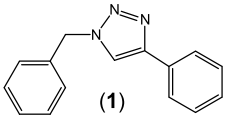
After visualizing the effect of Cu^0 electrooxidation and the decay of current density after 8 min, the hypothesis of passivation was proved. To compensate for this passive film formation, we suggested an OEAS with pulsed potential signals applied to the Cu^0 foil expecting to recover its catalytic activity (constant anodic current density) by a periodic oxidation potential.

Electrochemical pulsed technique

Table 3 compares the yields obtained in the conventional method against those obtained in the pulse method. The pulsed program improves by 36% the performance of the conventional click reaction for triazole **1**, under the same conditions of time, agitation, and temperature, giving a yield of 92% in one hour of reaction.

Figures 3 and 5 show the tendency of the current *versus* time. In the constant potential program (Figure 3), the catalyst is formed throughout the reaction time, but progressively in smaller quantity, since the current decreases noticeably due to the passivation of the surface. On the contrary, in the pulsed potential program

Table 3. Comparison between the conventional method and the electrochemical pulsed method

Azide	Alkyne	Product	Yield / %		Electrolytic molar equiv. Cu^I / μM
			Conventional method	Electrochemical pulsed method	
		 (**1**)	56	92	0.77

(Figure 5), during the first 25 min of the reaction, the current remains constant at 100 μA. Using Faraday's law, it can be calculated that 65% of the total catalyst has been generated in 25 min at a constant potential. For the pulsed potential method at the same time, it is formed only 56% of the catalyst; however, a higher yield is obtained. The pulsed method gives us a more efficient way to synthesize triazoles, with higher yields in 60 min and with a lower amount of copper (μg). Therefore, the good selection of an electrochemical method is very important in the synthesis of triazoles because the reaction proceeds in small amounts of Cu^I ion. This is essential since the Cu^I ion residues will be eliminated and allow synthesized triazoles to be used in a wide variety of biological applications with more security.

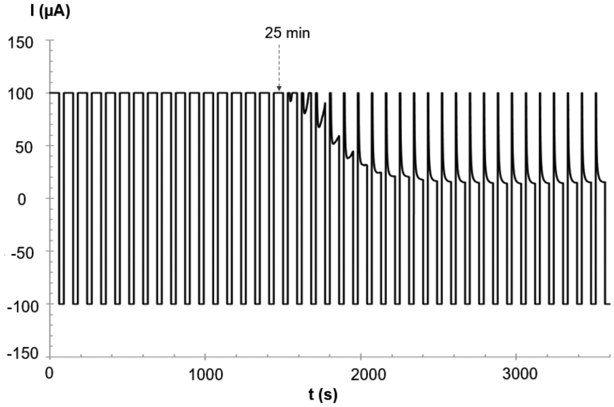


Figure 5. Pulse Cu^0 electrooxidation.

Integrating the current-time plots and using Faraday's law, it was possible to calculate the number of Cu^I moles produced as a catalyst. An estimation of the amount of copper generated to catalyze the reaction in the continuous potential program was ca. 1.5 μmol (average of the three triazoles) in one hour (Table 1), and for the pulsed potential program was 0.77 μmol (triazole **1**, Table 3), that is 10 and ca. 19.5 times less than the amount used in the classical click method, respectively. The efficiency of the method is due to the controlled production of Cu^I by soft electrochemical oxidation conditions.

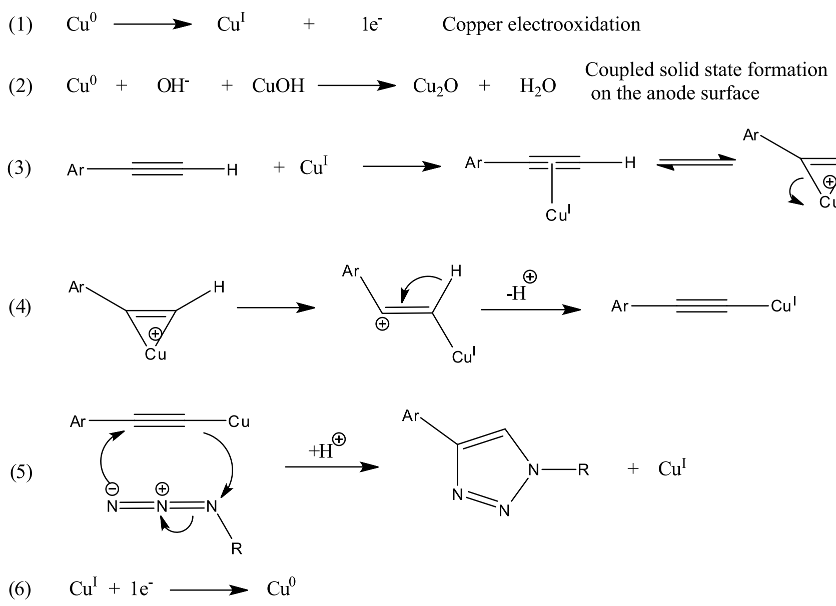
Mechanism for click reaction[41-43]

Encouraging results have been obtained from the click reaction assisted by the electrochemical method. This result requires the postulation of the processes that are carried out during the electro-synthesis reaction (Scheme 2). It begins with the oxidation process on the copper foil which is the working electrode (step 1). The formation of Cu^I cation, in basic condition, can form Cu_2O (step 2). The formation of the Cu^I cation acts as Lewis acid and reacts with the alkyne reagent to get an addition and asymmetrical pyramidal complex (step 3). The pyramidal complex undergoes a rearrangement to form the salt of the copper alkyne (step 4). This salt reacts with the azide to get the triazole product (step 5). Finally, Cu^I can be reduced to Cu^0 (step 6). The Cu^I acts as a catalytic Lewis acid cation because a small amount is sufficient to produce the reaction, and this is reused in a cyclic process until the Cu^I stabilizes as Cu_2O.

Therefore, if the reaction of the cyclic process is very efficient, a very small amount of Cu^I is required and therefore Cu_2O formation will be minimal, as demonstrated by the FESEM analysis.

Conclusions

Two electrochemical methods were developed for the reaction of the click chemistry, obtaining three different triazoles. The use of a copper foil as the working electrode was determinant for the reaction. The organic salt of TBATFB was used as an electrolyte to induce smooth oxidation of copper. The oxidation of copper foil produces Cu^I which is responsible for the activation of the acetylene, forming the salt of the (phenylethynyl)copper which in turn is the reagent that condenses with the azide forming the triazole. The synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole, 3-(1-benzyl-1*H*-1,2,3-triazol-4-yl)phenol and 1-benzyl-4-(naphthalen-1-yl)-1*H*-1,2,3-triazole derivatives via the *in situ* preparation of Cu^I by an electrochemical process was very efficient, safe, and inexpensive since catalyst was obtained under soft conditions reaction



Scheme 2. Proposed mechanism for click reaction.

generating extremely small amounts of electrooxidized Cu (ca. 1.5 µmol in one hour). The analysis of the copper foil by FESEM shows images describing the formation of copper species corresponding to Cu_2O formed after the electrochemical oxidation process. It was possible to implement a program of potential in pulses in which it avoided the passivation of the surface of the metallic copper foil. The amount of copper that is required to activate the click reaction is in the ppm range, therefore it is a very controlled process that will not produce excessive pollution, it is a remarkable faster reaction and the Cu_2O formed is feasible in the same process to achieve the reduction of copper, recovering it as Cu^0. Conventional and electrochemical methods were compared, the last one yielded 78-90% in one hour and the conventional method produced only 35% at the same time. The electro-click is faster and more efficient by the assisted electrochemical method and pulse potential. This procedure can be adapted to the coupling of biological species.

Supplementary Information

Supplementary data (FTIR and NMR spectra) are available free of charge at http://jbcs.sbq.org.br as a PDF file.

Acknowledgments

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