Tetrahedron 68 (2012) 2383–2390

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Electrochemical coupling of mono and dihalopyridines catalyzed by nickel complex in undivided cell

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ARTICLE INFO

Article history:
Received 21 November 2011
Received in revised form 9 January 2012
Accepted 10 January 2012
Available online 16 January 2012

Keywords:
C–C coupling
Homogeneous catalysis
Nickel complex
Terpyridines
Electrochemical process

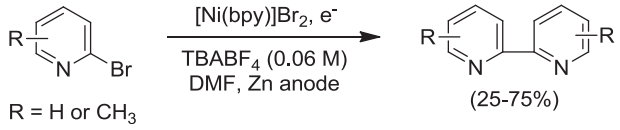
ABSTRACT

One step nickel-catalyzed electroreductive homocoupling among 2-bromopicolines and 2-bromopyridine has been investigated by our group in an undivided cell and using zinc or iron as sacrificial anode. In this work, it was developed mono and dihalopyridines coupling to obtain possible products from hetero-coupling. A series of reactions were carried out in order to develop a synthetic method for the preparation of unsymmetrical 2,2′-bipyridines and 2,2′:6′,2″-terpyridines. Statistical yields (50%) were observed for 2-bromopyridines/2-bromo-6-methylpyridine heterocoupling. In a preliminary study devoted to terpyridines preparation, good results were obtained for 2,6-dihalopyridines homocoupling, affording 2,6-dichloro-2,2′-bipyridine (46%) and 2,6-dibromo-2,2′-bipyridine (56%), at controlled reaction time. At major reaction time, it was observed that the direct electroreduction of the 2,6′-dihalo-2,2′-bipyridines intermediates and 2,6″-dihalo-2,2′:6′,2″-terpyridines products on the cathode surface. A reasonable isolated product yield of 6,6″-dimethyl-2,2′:6′,2″-terpyridine (10%) was only observed in the reaction between 2,6-dichloropyridine and 2-bromo-6-methylpyridine (1:2).

1. Introduction

Because of the high interest and application of 2,2′-bipyridines, notably as chelating precursors[1] for new transition metal complexes,[2,3] several synthetic methods have been described in the literature, including some reviews.[1,4]

The nickel-catalyzed homocoupling of aryl halides has received considerable attention[5] since the coupling proceeds under mild conditions compared to the classical Ullmann reaction,[6] to give the corresponding biaryls in good to high yields. The yield of the coupled products has been found to be dependent on the nature of the low-valent nickel complex and the solvent. In 1981, Semmelhack et al. were one of the first groups to report an efficient homocoupling procedure with alkenyl[7] or aryl[8] halides series. In this paper, they also pointed out the importance of the ligand regarding the reaction efficiency. Later, Iyoda et al.[9] described some aryl halides homocouplings using $[Ni(PPh_3)]Br_2$ complex as catalyst precursor in THF and tetraethylammonium iodide, using zinc as reducing agent. Additionally, the nickel catalyst associated to the ligand 2,2′-bipyridine (**bpy**) has also been employed in the electroreductive homocoupling and cross-coupling of aryl, alkenyl, and alkyl halides.[10] The successful homocoupling method with 2-bromopyridines and 2-bromomethylpyridines using such ligand has been reported.[11–15] Initially, the complex $[Ni(\mathbf{bpy})]Br_2$ was employed in DMF in the presence of 0.06 M of tetrabutylammonium tetrafluoroborate ($TBABF_4$) as the supporting electrolyte (Scheme 1) yielding 75% of 6,6′-dimethyl-2,2′-bipyridine.[11] All reactions summarized in Scheme 1 were carried out in an undivided cell fitted with a zinc rod as the sacrificial anode. When extending this method to the homocoupling reaction of various 2-bromomethylpyridines, we found that yields were quite dependent on the position of the methyl group, rising gradually from 25% to 75% for the shift of the methyl group from carbon 3 to 6.[12]



Scheme 1. Preparation of 2,2′-bipyridines using $[Ni(\mathbf{bpy})]Br_2$ as the catalyst.

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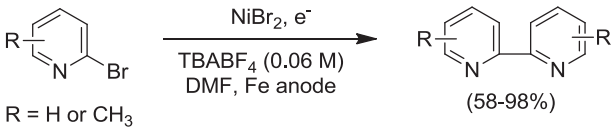
doi:10.1016/j.tet.2012.01.017

In an effort to further improve these homocouplings, several reaction parameters were investigated. We notably found that product yields could be higher for all substrates by using iron instead of zinc anode (Scheme 2). The good results can be attributed to the trapping of the free bipyridine generated by iron ions added to solution due to constant sacrificial anode oxidation, thus avoiding passivation of the nickel catalyst.[12] It should be reminded that the use of the sacrificial anode involves the production of salts in stoichiometric amounts, which may play a key role in the overall process, and even in some cases a synergistic effect along with the catalyst, as already illustrated in previous papers.[9,13,16,17] In addition, since reagents and products are pyridine derivatives that may act as ligands, reactions can be carried out starting from $NiBr_2$ salt (Scheme 2).[13]



Scheme 2. Preparation of 2,2′-bipyridines using $NiBr_2$ as the catalyst.

A transmetallation step affording a stable organozinc intermediate in the presence of the supporting electrolyte $TBABF_4$ was another observed parallel effect occurring during nickel-catalyzed 2-bromopyridines homocoupling reactions, using Zn as the sacrificial anode.[13,18] In this case, the homocoupling performance can be increased by replacing the $TBABF_4$ supporting electrolyte by NaI.[13]

The heterocoupling of aryl halides has already been described by using a nickel catalyst.[14] If the two organic halides possess similar reactivity, in the oxidative addition step, a 2:1:1 statistical distribution of the three possible compounds is expected, respectively, one unsymmetrical and two symmetrical products. If the reactivity of the two compounds is quite different, an acceptable yield can be obtained only if the reagent concentration ratio is adjusted by a slow addition of the most reactive halide throughout the electrolysis. The coupling of two aryl halides, in which the first aryl halide is substituted by an electron-withdrawing group and the second partner by an electron-donating group is also described.[15a,19]

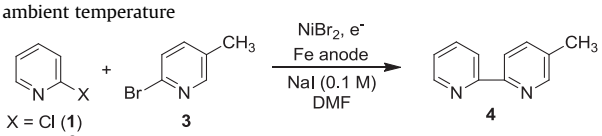
The preparation of unsymmetrical 2,2′-bipyridyl derivatives was reported by Jones et al.[20] to obtain the mono-*N*-oxide-2,2′-bipyridine derivative, which leads to major reactivity and ensuing the functionalization only in the oxidized ring. Since then, other methods were developed to synthesize unsymmetrical 2,2′-bipyridine in several steps with poor overall yield.[4]

In this paper we present a detailed study focusing on the heterocoupling of halopyridines in the aim of developing a synthetic method to access unsymmetrical 2,2′-bipyridines and 2,2′:6′,2″-terpyridines. The couplings are based on indirect electrochemical reactions associated to a nickel catalyst using a zinc or iron sacrificial anode in an undivided cell.

2. Results and discussion

The heterocoupling of monohalopyridines was first studied taking into account parameters previously determined for homocoupling reactions.[12,13] An undivided cell fitted with iron or zinc sacrificial anode was employed in the presence of nickel bromide catalyst. This form of the catalyst has been used since the starting reagent and/or products could act as ligand (L) to generate $[Ni(L)_n]Br_2$ (n=1 or 2) in situ. Table 1 shows the results from the heterocoupling of 2-chloro or 2-bromopyridine (**1** or **2**) versus 2-bromo-5-methylpyridine (**3**) (entries 1 and 4). In the chloro substituted reagent, it can be observed that the use of reagents with different reactivities lead to the heterocoupling product, 5-methyl-2,2′-bipyridine (**4**) in low yields.

Table 1
Heterocoupling of 2-halopyridines with **3**, using 1.25 mmol of each substrate (total 2.5 mmol), DMF (20 mL), 0.1 mol L^{-1} NaI, Fe anode, I=100 mA (total charge=1200 C) and ambient temperature



Entry		$NiBr_2$(%)	**4** (%)	**5**[c] (%)	**bpy** (%)	 (%)	 (%)
1	**1**	7	14	38	34	7	7
2	X=Cl	50	16	44	34	1	5
3[a]		7	18	33	43	1	5
4	**2**	7	37	28	18	7	10
5	X=Br	50	41	26	24	3	6
6[b]		7	30	34	30	3	3
7[a]		7	37	25	23	3	12

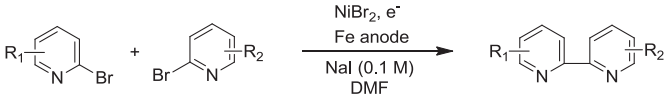
[a] Starting with 0.5 equiv of **3**+1 equiv of X-py, followed by addition of 0.5 equiv of **3** after 30 min.
[b] Starting with 0.5 equiv of **2**+1 equiv of **3**, followed by addition of 0.5 equiv of **2** after 30 min.
[c] 5,5′-Dimethyl-2,2′-bipyridine (**5**).

In increasing the amount of catalyst, no relevant modification of the product yields was observed, and 5,5′-dimethyl-2,2′-bipyridine (**5**) remains the major product (44%) together with 2,2′-bipyridine (**bpy**) (34%) (entry 2). The partial addition (0.5 equiv of **1**) of one of the reagents was investigated in entry 3, giving no significant yield variation of **4**.

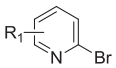
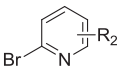
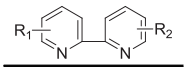
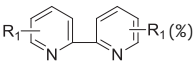
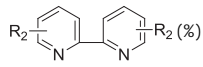
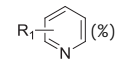
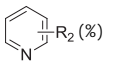
Reactions involving bromo substituted reagents, i.e., compounds with similar reactivity (entries 4 and 5), promoted a major amount of the unsymmetrical 2,2′-bipyridine **4** (37–41%). It was observed that increasing the catalyst amount does not change the results; only in the presence of high catalyst amount (50%) it was observed a slight increase of the desired product yield (entry 5), also diminishing the amount of secondary reduction products (pyridine and picoline). In another attempt to increase the amount of unsymmetrical product, electrolysis (entries 6 and 7) were also carried out with 0.5:1 equiv of each reagent, with posterior addition of 0.5 equiv of the minority reagent, but no significant modification was observed in the unsymmetrical product yield.

Another series of heterocoupling reactions was conducted between 2-bromo-6-methylpyridine (**6**) and **2** (Table 2, entries 1 and 2) giving 6-methyl-2,2′-bipyridine (**7**) as major product in a catalyst concentration of 7% or 50%. An additional pair of substrates was tested: 2-bromo-4-methylpyridine (**8**) and **2** (entries 3 and 4). Similar results from that obtained with the isomer **3** (Table 1, entries 4 and 5) can be observed, with 4-methyl-2,2′-bipyridine (**9**) yields of around 35% (Table 2, entry 3). The heterocoupling of several 2-bromopicolines was carried out with similar results, i.e., the heterocoupling reaction products from **6** (Table 2, entries 5–7): 3,6′-dimethyl-2,2′-bipyridine (**10**), 4,6′-dimethyl-2,2′-bipyridine (**11**), and 5,6′-dimethyl-2,2′-bipyridine (**12**) were obtained with yields around 50%; highlighting that the reagent 2-bromo-3-methylpyridine (**13**) is not very reactive due the methyl group hindrance,[12,13] even so a good yield (45%) of **10** was observed. Finally, entry 8 shows the heterocoupling between the substrates **3** and **8** giving 33% yield of 4,5′-dimethyl-2,2′-bipyridine (**14**).

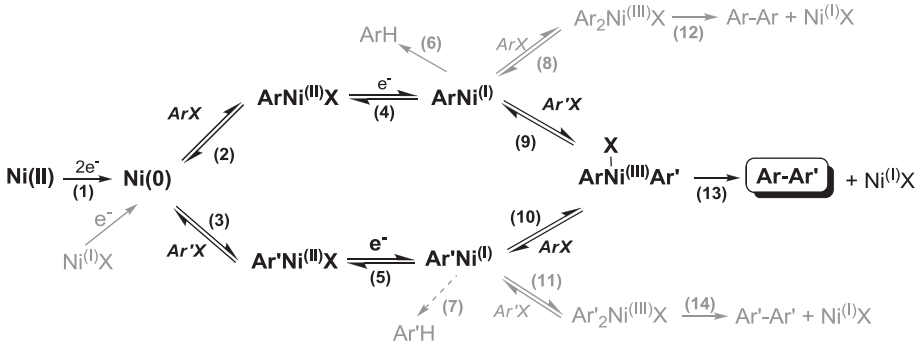
Table 2
Heterocoupling of 2-bromopyridines with 2-bromomethylpyridines, using 1.25 mmol of each substrate (total 2.5 mmol), DMF (20 mL), 0.1 mol L^{-1} NaI, Fe anode, I=100 mA (total charge=1200 C) and ambient temperature



R_1 = H (**2**), 3-CH_3 (**13**), 4-CH_3 (**8**), 5-CH_3 (**3**)
R_2 = 4-CH_3 (**8**), 5-CH_3 (**3**), 6-CH_3 (**6**)

Entry			$NiBr_2$ (% cat.)	 Prod.	(%)	 (%)	 (%)	 (%)	 (%)
1	**2** R_1=H	**6** R_2=6-CH_3	7	**7**	52	21	24	1	2
2	**2** R_1=H	**6** R_2=6-CH_3	50	**7**	56	14	25	2	3
3	**2** R_1=H	**8** R_2=4-CH_3	7	**9**	35	22	26	6	11
4	**2** R_1=H	**8** R_2=4-CH_3	50	**9**	45	20	26	3	6
5	**13** R_1=3-CH_3	**6** R_2=6-CH_3	7	**10**	45	7	30	12	6
6	**8** R_1=4-CH_3	**6** R_2=6-CH_3	7	**11**	54	21	20	4	1
7	**3** R_1=5-CH_3	**6** R_2=6-CH_3	7	**12**	49	22	23	4	2
8	**8** R_1=4-CH_3	**3** R_2=5-CH_3	7	**14**	33	15	22	13	17

The results described herein should be discussed firstly with a statistical consideration. If all halopyridines studied in the heterocoupling reaction catalyzed by nickel complex reacts with the same kinetics, the lowest yield of heterocoupling product should be 50%, in addition to the other two homocoupling products, with 25% each one. However, it can be observed that statistical rule is not followed for all reactions. Only reactions involving reagent **6** showed the expected statistical yield (Table 2, entries 1, 2, 5–7). The observed behavior can be explained by following steps involved in the reaction mechanism of catalysis (Scheme 3).[14,15]



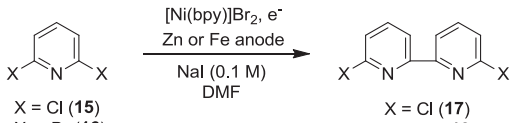
Scheme 3. Halopyridine reaction mechanism catalyzed by Ni complex.

According to the formation of the heterocoupling product, the key step is the reductive elimination (step 13). The corresponding intermediate [$ArNi^{III}Ar'$]X should be obtained by two routes depending from two chemical steps and an electrochemical one. Normally, electrochemical steps involving cathodic electron transfer are very fast, therefore, in major reactions described in the Tables 1 and 2, the slow step of the process corresponds to reductive elimination steps (12–14) of the catalytic process,[2,12] in which the coupling product is expulsed from coordination sphere regenerating the Ni complex catalyst.

However, in the case of the reagent **6** the steric hindrance caused by methyl group at *ortho* position may collaborate for a kinetic increasing effect, changing the slow steps from (12–14) to (8–11), i.e., the second oxidative addition becomes the slow step of the process, making the reaction in agreement with the statistical rules since this step is collision dependent. This could explain the better heterocoupling results observed for all reactions in which **6** is present.

In the second part of our investigation, we turned our attention to the homocoupling of 2,6-dihalopyridines. Table 3 shows the homocoupling reactions of 2,6-dichloropyridine (**15**) and 2,6-dibromopyridine (**16**), giving 6,6′-dichloro-2,2′-bipyridine (**17**) and 6,6′-dibromo-2,2′-bipyridine (**18**) as products, respectively. Firstly, C–C homocoupling reactions in the presence of **15** or **16** were carried out in the presence of $NiBr_2$ for generation of the in situ catalyst,[12,13] but no coupling product was observed, probably due to the presence of halogen atom at *ortho* positions of the pyridine, which deactivates the pyridine as ligand and also due the steric hindrance. Therefore, reactions were performed in the presence of 7% [Ni(**bpy**)]Br_2 as catalyst. Homocoupling of **15** was carried out with Fe and Zn sacrificial anodes giving low yields of **17**

Table 3
Homocoupling of 2,6-dihalopyridines, using 2.5 mmol of each substrate, DMF (20 mL), 0.1 mol L^{-1} NaI, Zn or Fe anode, I=100 mA, 7% [Ni(**bpy**)]Br_2, ambient temperature



X = Cl (**15**)
X = Br (**16**)

X = Cl (**17**)
X = Br (**18**)

Entry	Reagent (2.5 mmol)	Anode	Charge (C)	**17** (%)	**18** (%)	**bpy**[a] (%)
1	**15**	Fe	1200	29	—	25
2	**15**	Zn	1200	25	—	37
3	**16**	Fe	1200	—	0	80
4	**16**	Zn	1200	—	0	68
5	**15**	Fe	360	24	—	11
7	**15**	Zn	360	40	—	16
6	**16**	Fe	360	—	11	23
8	**16**	Zn	360	—	14	7

The electrolysis theoretical charge is about 212 C.
[a] Initial concentration of **bpy**=7% from the catalyst. In all entries, pyridine was identified as by-product. Yields were determined by GC.

(Table 3, entries 1 and 2). With a charge to 1200 C (five times of theoretical charge), 40% of the starting material was recovered in the presence of Fe sacrificial anode giving 29% of **17** and 25% of **bpy** as side reaction product; by other way, in the presence of Zn anode **15** was totally consumed but the yield was the same that observed in entry 1, due to the formation of **bpy** in larger amount.

The homocoupling of **16** gave **bpy** as main product in the presence of both sacrificial anodes (entries 3 and 4), **18** was not observed. The reactions described for **15** were repeated stopping the reaction at 360 C (entries 5 and 6), and the amount of **17** was increased to 40% in the presence of Zn anode and 24% in the presence of Fe anode, observing that the amount of **bpy** diminished to 11% and 16%, respectively. The same procedure was repeated for **16** (entries 7 and 8) and a small amount of **18** (11%) was detected in the presence of Fe anode. Evaluating all results in Table 3, it is surprising that so elevated amounts of **bpy** were detected since only 7% of the catalyst [Ni(**bpy**)]Br_2 was used.

Therefore, the homocoupling reactions were followed up as showed in the Fig. 1, by choosing Zn as sacrificial anode due best results and increasing the catalyst amount to 20% in attempt to increase the reaction kinetics. As mentioned before, the presence of Zn ions in the reaction medium promotes the stable organozinc intermediate formation in a transmetalation reversible process, which is responsible by slowing the homocoupling reaction, buffering the activity of the reagent.[13] For both reagents, **15** and **16**, homocoupling products are produced with a maximum yield of 42% and 26%, respectively, and consumed at same time, giving the **bpy** as final product. The formation of 2-chloropyridine and 2-bromopyridine can also be observed with posterior consumption.

We decided to work with higher scale to prepare **17** and **18** as described in the Experimental section; the homocoupling reaction was performed with 10.0 mmol of **15** or **16**. We followed up the formation of **17** or **18** and stopping these reactions at the maximum concentration of the target product. The isolated yield of **17** was 46% according to Scheme 4. Traces of the 6′,6″-dichloro-2,2′:6,2″-terpyridine (**19**) were detected in this case and isolated in few mg (7%). Surprisingly, the homocoupling of **16** was carried out under the same conditions and **18** was isolated with 56% yield. The 6′,6″-dibromo-2,2′:6,2″-terpyridine (**20**) was also isolated (10%) (Scheme 4).

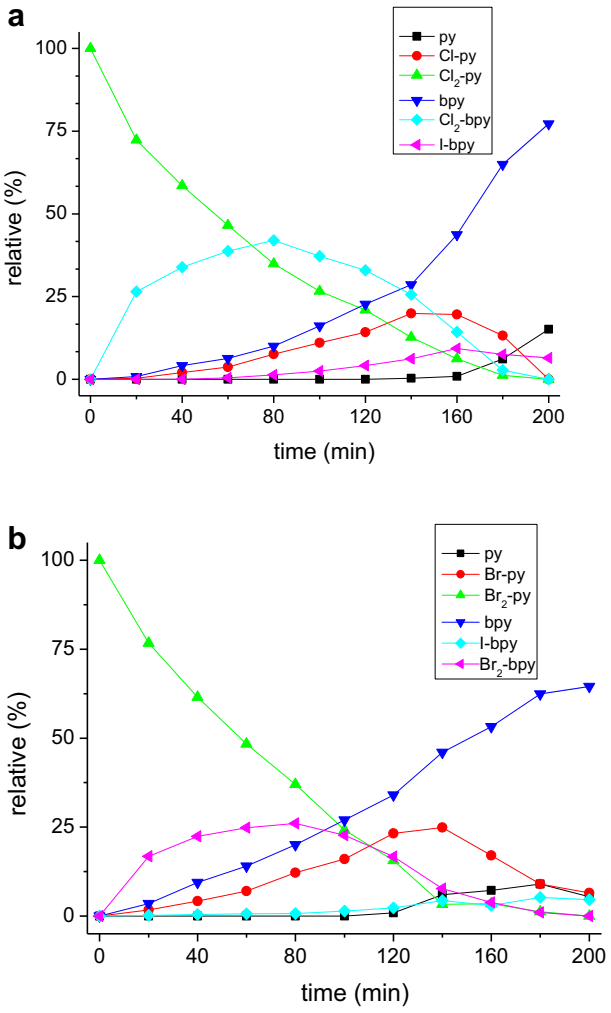
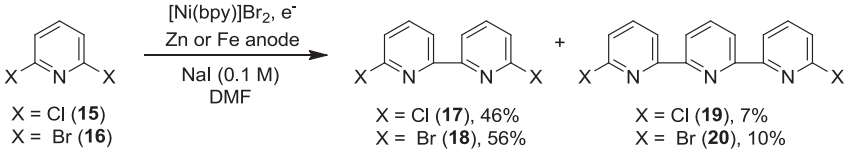


Fig. 1. Homocoupling of (a) **15** (5.0 mmol) and (b) **16** (5.0 mmol), in 20 mL of DMF+0.1 M NaI using 20% [Ni(**bpy**)]Br_2 as catalyst and Zn as sacrificial anode. The concentration of the pyridylzinc intermediate was represented by 2-iodo-2,2′-bipyridine after iodolysis.



Scheme 4. Best conditions for **15** and **16** homocoupling reactions.

Therefore, for a better understanding of the reaction procedure and identification of side reactions occurring at the same time than homocoupling reactions, cyclovoltammetric analysis of **17** were carried out in DMF+$TBABF_4$ as supporting electrolyte, as shown in Fig. 2. Two irreversible systems can be observed at cathodic region, the first peak at E_{cp}=−1.77 V and second one at E_{cp}=−1.96 V versus Ag/AgCl, corresponding to two electrons transfer steps (1 and 3) and C–Cl bond cleavage, followed by protonation steps (2 and 4) from the solvent residual water. A third reversible system (step 5) can be observed at $E_{p1/2}$=−2.11 V versus Ag/AgCl, which corresponds to the **bpy** redox pair.

$$\text{Cl–}\mathbf{bpy}\text{–Cl} + 2e^- \rightarrow \text{Cl–}\mathbf{bpy}^- + Cl^- \quad (1)$$

$$\text{Cl–}\mathbf{bpy}^- + H^+ \rightarrow \text{Cl–}\mathbf{bpy}\text{–H} \quad (2)$$

$$\text{Cl–}\mathbf{bpy}\text{–H} + 2e^- \rightarrow \text{H–}\mathbf{bpy}^- + Cl^- \quad (3)$$

$$\text{H–}\mathbf{bpy}^- + H^+ \rightarrow \mathbf{bpy} \quad (4)$$

$$\mathbf{bpy} + e^- \rightleftharpoons \mathbf{bpy}^{\cdot -} \quad (5)$$

The same procedure was carried out for **15**, **16**, **18**–**20**, and the peak potentials identified (Table 4). As previously reported,[12] the direct reduction potentials of 2-bromopyridines and 2-bromomethylpyridines occurs at around E_{cp}=−2.4 V versus Ag/AgCl, which is very distant from [Ni(**bpy**)]Br_2 catalyst reduction

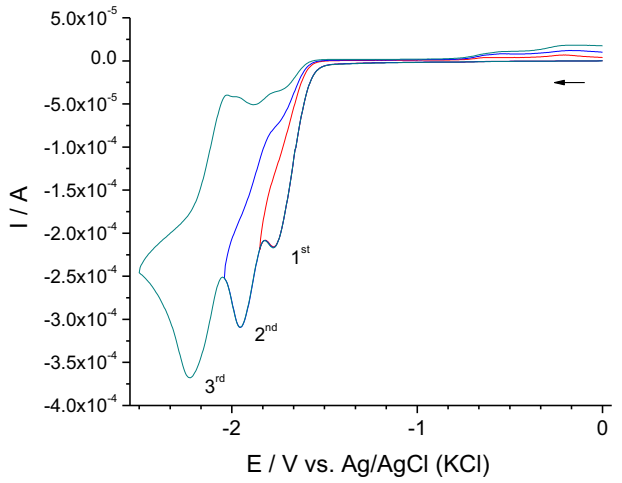
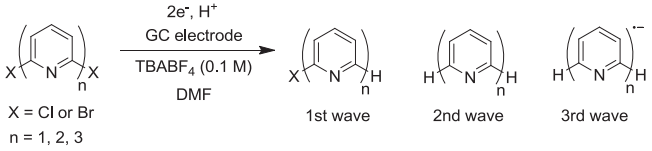


Fig. 2. Cyclic voltammogram of a 1.0×10^{-2} M 6,6′-dichloro-2,2′-bipyridine (**17**) in DMF+0.1 M $TBABF_4$, on vitreous carbon electrode (3.0 mm diameter) at v=100 mV s^{-1} and room temperature.

Table 4
Direct reduction potential (E_{cp} vs ECS) on glassy carbon electrode, determined by cyclic voltammetry in DMF+0.1 mol L^{-1} $TBABF_4$ using 0.1 mol L^{-1} of substrate



Entry	n	Reagent (1.0×10^{-2} mol L^{-1})	E_{cp1} (V)	E_{cp2} (V)	E_{cp3} (V)	E_{ap3} (V)
1	1	**15** (X=Cl)	−2.12	−2.41	−2.82	−2.58
2		**16** (X=Br)	−1.99	−2.31	−2.76	−2.56
3	2	**17** (X=Cl)	−1.77	−1.96	−2.23	−2.02
4		**18** (X=Br)	−1.64	−1.85	−2.21	−2.01
5	3	**19** (X=Cl)	−1.81	−2.04	−2.44	—
6		**20** (X=Br)	−1.62	−1.81	−2.23	−2.01

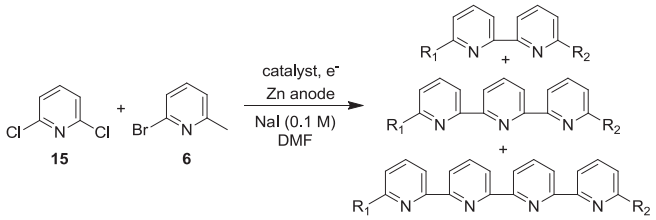
potential (E_{cp}=−1.16 V vs Ag/AgCl), avoiding its direct reduction on electrode surface during electrolysis. Compounds **15** and **16** are reduced at intermediary potentials (−2.12 and −1.99 V vs Ag/AgCl), while **17**–**20** present the first reduction potentials E_{cp} between −1.62 and −1.81 V versus Ag/AgCl (Table 4), which may be considered high enough for direct reduction on the electrode surface at electrolysis conditions. This electrochemical behavior explains elevated yields of **bpy** observed in the homocoupling reactions of **15** and **16**.

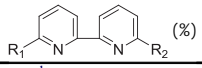
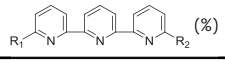
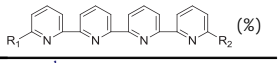
2.1. Dimethyl-2,2′:6,2″-terpyridines

Taking into account the heterocoupling and homocoupling results described above, we tried to prepare 6′,6″-dimethyl-2,2′:6,2″-terpyridine (**21**) starting from **15** and **6** reagents using conditions described in Table 5. $NiBr_2$ or [Ni(**bpy**)]Br_2 were used as catalysts (20%), relative amounts of reagents were varied, in DMF and Zn sacrificial anode. It was observed the formation of three groups of products: bipyridines, terpyridines, and tetrapyridines. In all essays described in Table 5, the main reaction product obtained belongs to the group of bipyridines: 6,6′-dimethyl-2,2′-bipyridine (**22**), 6-methyl-2,2′-bipyridine (**23**), and **bpy**.

Entries 1 and 2 show that the variation of relative amount of reagents during the reaction, in the presence of [Ni(**bpy**)]Br_2 as catalyst, generates the homocoupling product coming from the reagent in excess (**22** or **bpy**, which is formed from reduction of **17**). Interestingly, no significant change was observed in the product yields of the terpyridine and tetrapyridine groups, whatever the proportion of the reagents. In entries 3 and 4, we tested $NiBr_2$, and it was evident that this catalyst promotes the formation of **22** as main product (entry 3, 56%, entry 4, 78%). Regarding the group of tetrapyridines only traces were observed, and in the group of terpyridines it was observed a small yield increase of **21** (entry 3, 19%). Therefore, the similar reactivity of these pyridines does not enable to obtain terpyridines selectively. This process follows statistical rule and it is very difficult to separate the different compounds due to the similar polarities. Even so,

Table 5
Heterocoupling preparative reactions for 2,6-dichloropyridine and heterocoupling for 2,2′:6′,2″-terpyridine, DMF (20 mL), 0.1 mol L^{-1} NaI, Zn anode, I=100 mA, 20% catalyst, and ambient temperature



Entry	Reagents	Catalyst[a]	 (%)	 (%)	 (%)
1	**15** (2.5 mmol)+**6** (5.0 mmol)	Ni(**bpy**)Br_2 20%	**bpy**[b] (16%) H-**bpy**-CH_3 (18%) **22**, H_3C-**bpy**-CH_3 (29%)	tpy[c] (4%) H-tpy-CH_3 (9%) **21**, H_3C-tpy-CH_3 (11%)	tetpy[d] (2%) H-tetpy-CH_3 (4%) H_3C-tetpy-CH_3 (6%)
2	**15** (2.5 mmol)+**6** (4×1.25 mmol)	Ni(**bpy**)Br_2 20%	**bpy** (47%) H-**bpy**-CH_3 (13%) **22**, H_3C-**bpy**-CH_3 (14%)	tpy (1.4%) H-tpy-CH_3 (7%) **21**, H_3C-tpy-CH_3 (10%)	tetpy (1%) H-tetpy-CH_3 (2%) H_3C-tetpy-CH_3 (3%)
3	**15** (1.0 mmol)+**6** (4.0 mmol)	$NiBr_2$ 20%	**bpy** (1.4%) H-**bpy**-CH_3 (10%) **22**, H_3C-**bpy**-CH_3 (56%)	tpy (0%) H-tpy-CH_3 (3%) **21**, H_3C-tpy-CH_3 (19%)	tetpy (0%) H-tetpy-CH_3 (1%) H_3C-tetpy-CH_3 (6%)
4	**15** (1.0 mmol)+**6** (4×1.0 mmol)	$NiBr_2$ 20%	**bpy** (0%) H-**bpy**-CH_3 (4.2%) **22**, H_3C-**bpy**-CH_3 (78%)	tpy (0%) H-tpy-CH_3 (1%) **21**, H_3C-tpy-CH_3 (11%)	tetpy (0%) H-tetpy-CH_3 (0%) H_3C-tetpy-CH_3 (3%)

[a] The catalyst amount was calculated from the total number of moles of reactants.
[b] 2,2′-Bipyridine.
[c] 2,2′:6′,2″-Terpyridine.
[d] 2,2′:6′,6″:2″,2‴-Tetrapyridine.

a preparative electrolysis was carried out as described in the Experimental section; the heterocoupling reaction was performed with 5 mmol of **15** and 10 mmol of **6** until total consumption of the reagents. The mixture of terpyridines was separated from bipyridines by distillation followed by column chromatography purification, furnishing 130 mg (10%) of **21**.

3. Conclusion

In conclusion, the one step nickel electrocatalytic method affords unsymmetrical 2,2′-bipyridines in moderate to good yields. Statistical amounts of homocoupling products were performed in the cases of 2,6-dichloro or 2,6-dibromopyridine. The optimization of reaction conditions allowed to isolate 6,6′-dichloro and 6,6′-dibromo-2,2′-bipyridine in good yields in a one-pot reaction. Measuring the reduction potential of dihalogenated 2,2′-bipyridines and 2,2′:6′,2″-terpyridines showed that the direct reduction on the cathode surface competes with the Ni catalyzed process.

4. Experimental section

4.1. General

The controlled current preparative electrolysis were carried out with a potentiostat/galvanostat equipment. Undivided cells with 20 mL compartment were used. Zn or Fe metallic rod with 8 mm diameter was used as the sacrificial anode. Ni foam (6 cm×3.5 cm) was used as the cathode. It could be re-used after washing with a 6 M HCl solution following by water and acetone, and dried. The same solution was used to clean the anode. A 5 mL DMF solution containing 7% or 20% of $NiBr_2 \cdot xH_2O$ or [Ni(**bpy**)]Br_2[21] and *x* mmol of the corresponding mixture of 2-bromomethylpyridines or 2,6-dihalopyridines (heterocouplings in Tables 1, 2, 4 and 5), or (2.5 mmol) of 2,6-dihalopyridines (homocoupling in Table 3) was stirred or sonicated before the electrolysis, to ensure the solubilization of reagents. A pre-electrolysis was carried out with 15 mL of the electrolytic solution (DMF, 0.1 M NaI and 0.75 mmol of 1,2-dibromoethane), passing a charge of 146 C (*I*=150 mA). Then, the previous prepared solution of bromopicoline or bromopyridine and the catalyst in 5 mL DMF, was added to the electrolytic cell and the constant current electrolysis (*I*=100 mA) applied. It is important to ensure that the cell potential must not exceed 1.8 V in order to avoid the reduction of the substrate on the cathode surface. After the total consumption of the reagent (number of coulombs described in the tables), the reaction was stopped and the solvent removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with several portions of a 6 M NH_4OH solution. After drying over Na_2SO_4, the organic layer was evaporated under reduced pressure.

All products: 2,2′-bipyridine (**bpy**) [366-18-7], 3,3′-dimethyl-2,2′-bipyridine [1762-32-9], 4,4′-dimethyl-2,2′-bipyridine [1134-35-6], 6,6′-dimethyl-2,2′-bipyridine [4471-80-7], 2-chloropyridine (**1**) [109-09-1], 2-bromopyridine (**2**) [109-04-6], 2-bromo-5-methylpyridine (**3**) [3510-66-5], 5-methyl-2,2′-bipyridine (**4**) [56100-20-0], 5,5′-dimethyl-2,2′-bipyridine (**5**) [1762-34-1], 2-bromo-6-methylpyridine (**6**) [5315-25-3], 6-methyl-2,2′-bipyridine (**7**) [56100-22-2], 2-bromo-4-methylpyridine (**8**) [4926-28-7], 4-methyl-2,2′-bipyridine (**9**) [56100-19-7], 3,6′-dimethyl-2,2′-bipyridine (**10**), 4,6′-dimethyl-2,2′-bipyridine (**11**) [74001-75-5], 5,6′-dimethyl-2,2′-bipyridine (**12**) [245678-74-4], 2-bromo-3-methylpyridine (**13**) [3430-17-9], 4,5′-dimethyl-2,2′-bipyridine (**14**) [282541-27-9], 2,6-dichloropyridine (**15**) [2402-78-0], 2,6-dibromopyridine (**16**) [626-05-1], 6,6′-dichloro-2,2′-bipyridine (**17**) [53344-72-2], 6,6′-dibromo-2,2′-bipyridine (**18**) [49669-22-9], 6,6″-dichloro-2,2′:6′,2″-terpyridine (**19**), 6,6″-dibromo-2,2′:6′,2″-terpyridine (**20**) [100366-66-3], 6,6″-dimethyl-2,2′:6′,2″-terpyridine (**21**) [33777-92-3], 6,6′-dimethyl-2,2′-bipyridine (**22**) [4411-80-7], 6-methyl-2,2′-bipyridine (**23**) [56100-22-2], were monitored by gas chromatography and identified by GC/MS, and the yield determined by using 4-methylpyridine or pyridine as internal standard.

For analytical experiments, aliquots of 0.5 mL were taken from reaction mixture in a glass tube containing an iodine crystal. After reaction, the iodine excess was treated with $Na_2S_2O_3$ (10%) solution until it becomes colorless, followed by addition of 3 mL ammonium hydroxide 1 M solution. The reaction products were extracted in the same tube with 2 mL of diethyl ether and the relative percentage determined by gas chromatography.

Gas chromatogram/mass spectra were taken with a 30 m capillary column, using 60–200 °C temperature range (20 °C min^{-1}). Comparisons with authentic sample were performed to identify reaction products and reagents, and confirmed by GC/MS.

4.2. Preparative electrolysis/general

All reactions were carried out under argon atmosphere. All reagents and solvents were purchased from commercial suppliers and used without further purification or distillation. Melting points (mp) were measured on a melting point apparatus and are uncorrected. NMR spectrometer operating at 400 MHz was used for recording the NMR spectra. Chemical shifts for ^1H and ^{13}C spectra were referenced internally according to the residual solvent resonances and reported relative to tetramethylsilane (TMS). Infrared spectra were recorded on FTIR equipment.

4.3. Typical procedure for preparative reactions

To an undivided electrochemical cell, fitted by a zinc rod as the anode and surrounded by a nickel foam as the cathode, were added DMF (50 mL), 0.1 M NaI, and 1,2-dibromoethane (2.5 mmol, 215 μL). The mixture was electrolyzed under argon at a constant current intensity of 0.2 A at room temperature for 15–20 min. Then the current was stopped, and [Ni(**bpy**)]Br_2 complex[21] (1 mmol, 375 mg), 2,6-dichloropyridine (10 mmol, 1.48 g) or 2,6-dibromopyridine (10 mmol, 2.38 g) were sequentially added. The solution was electrolyzed at 0.1 A and room temperature until the starting material was totally consumed (3.3 h).

4.4. Typical workup

The reaction mixture was poured into a round-bottomed flask and solvents were removed under low pressure to dryness. A saturated tetrasodium EDTA solution (40 mL) was added to the crude oil, and the solution was extracted with dichloromethane containing 5% of methanol (3×70 mL) then with dichloromethane (1×70 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum.

4.5. Typical purification for the 2,6-dichloropyridine coupling reaction

The evaporated crude product was purified by flash chromatography on silica (35–70 μm) (previously washed with (1%) triethylamine/pentane), eluted with a gradient mixture of solvents (100% pentane, mixture of pentane/CH_2Cl_2 to 100% CH_2Cl_2). Product **17** (518 mg, 46% yield) and **19** (52 mg, 7% yield, respectively) were obtained.

*4.5.1. 6,6′-Dichloro-2,2′-bipyridine (**17**).* Mp: 221–226 °C (lit.:[22] 218–219 °C); ATR-FTIR (neat, cm^{-1}) 1573, 1541, 1415, 1265, 1153, 1133, 1076, 988, 785, 725, 627. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J*=8.1 Hz, 2H), 7.78 (t, *J*=8.0 Hz, 2H), 7.34 (d, *J*=8.0 Hz, 2H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 155.4, 151.1, 139.8, 125.0, 120.0. MS, *m*/*z* (relative intensity) 226 (47), 224 (M^+, 75), 191 (32), 190 (12), 189 (100), 153 (37), 126 (14).

*4.5.2. 6′,6″-Dichloro-2,2′:6,2″-terpyridine (**19**).* Mp: 251–254 °C. ATR-FTIR (neat, cm^{-1}): 1573, 1553, 1466, 1421, 1367, 1299, 1267, 1157, 1090, 1069, 989, 908, 872, 802, 789, 710, 662, 631. ^1H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J*=7.2 and 7.8 Hz, 4H), 7.96 (t, *J*=7.8 Hz, 1H), 7.82 (t, *J*=7.3 Hz, 2H), 7.37 (d, *J*=7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 153.9, 151.0, 139.5, 138.2, 124.4, 121.9, 119.5. MS, *m*/*z* (relative intensity): 304 (10), 303 (61), 302 (M^+, 21), 301 (100), 268 (36), 267 (18), 266 (94), 230 (16). HRMS *m*/*z* (ER^+) calcd for $C_{15}H_{10}N_3Cl_2$ $(M+H)^+$ 302.0252, found 302.0263.

4.6. Typical purification for the 2,6-dibromopyridine coupling reaction

The evaporated crude product was purified by flash chromatography on silica (35–70 μm) (previously washed with (1%) triethylamine/pentane), eluted with a gradient mixture of solvents (pentane/CH_2Cl_2 50/50–100% CH_2Cl_2). Product **18** (885 mg, 56% yield) and **20** (65 mg, 10% yield) were obtained.

*4.6.1. 6,6′-Dibromo-2,2′-bipyridine (**18**).* Mp: 227–236 °C (lit.:[23] 221–223 °C). ATR-FTIR (neat, cm^{-1}) 1570, 1533, 1407, 1375, 1260, 1152, 1116, 1069, 984, 781, 725, 703, 623. ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J*=8.7 Hz, 2H), 7.67 (t, *J*=8.2 Hz, 2H), 7.50 (d, *J*=7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 142.0, 139.4, 128.9, 120.3. MS, *m*/*z* (relative intensity): 316 (48), 315 (15), 314 (M^+, 100), 312 (52), 253 (21), 251 (20), 235 (46), 233 (52), 154 (37), 153 (40), 126 (19).

*4.6.2. 6′,6″-Dibromo-2,2′:6,2″-terpyridine (**20**).* Mp: 260–262 °C. ATR-FTIR (neat, cm^{-1}): 1580, 1566, 1547, 1463, 1416, 1365, 1297, 1265, 1155, 1121, 1064, 985, 909, 859, 799, 786, 762, 691, 654, 627. ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J*=8.1 Hz, 2H), 7.67 (d, *J*=8.1 Hz, 2H), 7.95 (t, *J*=7.8 Hz, 1H), 7.71 (t, *J*=7.4 Hz, 2H), 7.52 (d, *J*=7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 154.0, 141.8, 139.4, 138.4, 128.3, 122.2, 120.0. MS, *m*/*z* (relative intensity): 393 (31), 392 (13), 391 (M^+, 74), 389 (47), 313 (14), 312 (89), 311 (17), 310 (100), 231 (21), 230 (44), 203 (15), 126 (11).

4.7. Procedure for 2,6-dichloropyridine+2-bromo-6-methylpyridine preparative coupling reaction

To an undivided electrochemical cell, fitted by a zinc rod as the anode and surrounded by a nickel foam as the cathode, were added DMF (50 mL), 0.1 M NaI, and 1,2-dibromoethane (2.5 mmol, 215 μL). The mixture was electrolyzed under argon at a constant current intensity of 0.2 A at room temperature for 20 min. Then the current was stopped, and [Ni(**bpy**)]Br_2 complex[21] (2.6 mmol, 562 mg), 2,6-dichloropyridine (5 mmol, 0.74 g), and 2-bromo-6-methylpyridine (10 mmol, 1.72 g) were sequentially added. The solution was electrolyzed at 0.1 A and room temperature until the starting material was totally consumed (8 h).

4.7.1. Workup. The reaction mixture was poured into a round-bottomed flask and solvents were removed under low pressure to dryness. A saturated tetrasodium EDTA solution (50 mL) and 6.5 mol L^{-1} NH_4OH solution (50 mL) were added to the crude oil, and the mixture was stirred over night with chloroform (100 mL). The organic layer was separated from the mixture and the aqueous solution was washed with chloroform (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum.

4.8. Typical purification for the 2,6-dichloropyridine+2-bromo-6-methylpyridine coupling reaction

The evaporated crude product was distilled in a bulb to bulb distillation apparatus (Kugelrohr) at 7 mmHg. The bipyridine mixture was distilled at 156–190 °C and separated from the terpyridine mixture, distilled at 210–250 °C. The terpyridine mixture was purified by flash chromatography on silica (35–70 μm) (previously washed with (1%) triethylamine in $CHCl_3$/hexane (8:2)), and eluted with a mixture of $CHCl_3$/hexane (8:2). The product **21** was obtained as a white solid, and the same procedure was applied two times to the remaining terpyridine mixture to obtain 130 mg, 10% yield.

*4.8.1. 6′,6″-Dimethyl-2,2′:6,2″-terpyridine (**21**).* Mp: 169–170 °C (lit.:[24] 170–171 °C); FTIR (KBr, cm^{-1}) 1571, 1438, 1077, 778, 635. ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J*=7.6 Hz, 2H), 8.25 (t, *J*=8.0 Hz, 2H), 7.91 (d, *J*=7.6 Hz, 1H), 7.71 (d, *J*=7.6 Hz, 1H), 7.15 (d, *J*=7.2 Hz, 1H), 2.63 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 155.7, 155.6, 137.7, 137.0, 123.3, 120.8, 118.2, 24.6. MS, *m*/*z* (relative intensity): 261 (100), 246 (35), 219 (11), 169 (10), 130 (16), 117 (11), 92 (08).

Acknowledgements

The authors thank CNPq and CAPES/COFECUB (Proc. 532/06) exchange program for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.01.017.

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