

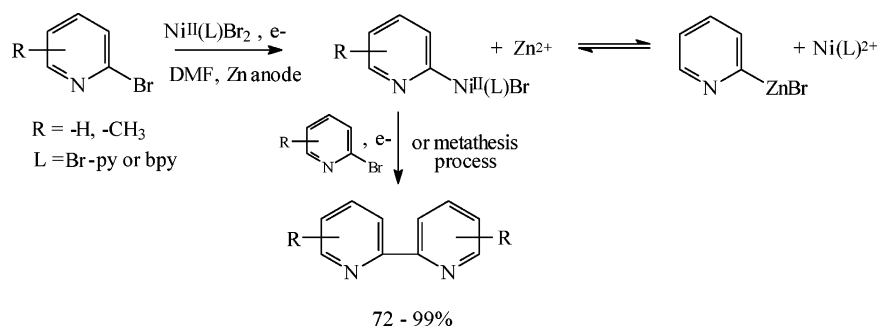
Mixed Effect of the Supporting Electrolyte and the Zinc Anode in the Electrochemical Homocoupling of 2-Bromopyridines Catalyzed by Nickel Complexes in an Undivided Cell

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Received August 18, 2005



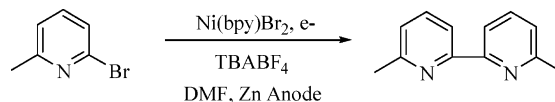
Nickel-catalyzed electroreductive homocoupling of 2-bromomethylpyridines and 2-bromopyridine has been investigated in an undivided cell in the presence of a zinc sacrificial anode. A series of reactions were performed with various types and concentrations of supporting electrolyte. It was observed that a key step in this process is the formation of an arylzinc through a nickel–zinc transmetalation. This intermediate can be transformed back to the reactive arylnickel species to afford the homocoupling as the final product. The back process from the arylzinc intermediate is, however, suppressed in the presence of high concentration (0.2 M) of tetraalkylammonium salts. On the contrary, with NaI, the formation of the dimer is not prevented, whatever the NaI concentration.

Introduction

We recently reported the successful electrochemical dimerization of 2-bromo-6-methylpyridine, yielding 75% of isolated 6,6'-dimethyl-2,2'-bipyridine.¹ [Ni^{II}(bpy)]Br₂ was used as catalyst precursor, DMF as the solvent, and Zn as the sacrificial anode (Scheme 1).

Because of the high interest in their roles,^{2,3} notably as chelate precursors² en route to new transition metal complexes,^{4,5} the electrochemical synthesis of substituted 2,2'-bipyridines is worth a deeper investigation to explore its scope and limitations. The reaction in Scheme 1 was

SCHEME 1



conducted in an undivided cell fitted with a zinc rod as the sacrificial anode. When we extended this method to the dimerization of various 2-bromopyridines, we found that the 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. This effect of the methyl group was partly explained by steric hindrance. It should be mentioned, however, that the faradaic yield for the consumption of the starting bro-

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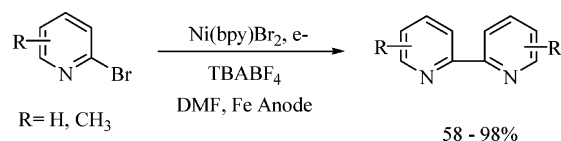
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SCHEME 2



mopicoline was always high. To improve these homocouplings, we investigated several reaction parameters and notably found that yields could be higher for all models with iron instead of zinc as the anode⁶ (Scheme 2).

It should be mentioned that the use of a sacrificial anode involves the production of salts in stoichiometric amounts, and these salts may play a key role in the overall process and in some cases even a synergistic effect along with the catalyst, as already illustrated in previous articles.⁷ There is also a parameter that is often concealed (i.e., the nature of the supporting electrolyte).

In this article we present a reinvestigation of the process to understand why the reaction cannot be efficient with a zinc anode and, notably, if there is an effect of the nature of the supporting electrolyte. Nickel and zinc are indeed classically found in couplings of aromatics. Kumada⁸ and Iyoda⁹ have thus reported an efficient homocoupling process of aryl halides, including pyridyl halides,⁹ using $[\text{Ni}^{\text{II}}(\text{PPh}_3)_2]\text{X}_2$ ($\text{X} = \text{Cl}$,⁸ Br ⁹), along with Zn as reducing agent, DMF⁸ or THF⁹ as solvent, and in the presence of iodide ions (KI ⁸ or Et_4NI ⁹). They reported the yield increase of substituted biaryles in the presence of iodide ion as compared to its absence and explained the role of iodide as a bridging ligand between nickel complexes and zinc ions.

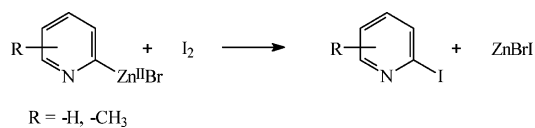
Results and Discussion

The dimerization of 2-bromopyridine was studied as the model reaction. A typical course of the reaction is shown in Figure 1a, TBAI being used as the supporting electrolyte.

There are clearly three stages in this process. During the first 20 min, the reaction goes slowly for both the consumption of the starting halopyridine and the formation of bipyridine. Next, the consumption of the starting reagent follows the coulometry, while the formation of bipyridine remains slow. Actually, another product, iodopyridine, can be detected by GC as the major component if the crude reaction mixture is reacted with iodine and which likely forms by metal–iodine exchange (Scheme 3). Finally, even after holding the current over a long time, the yield in bipyridine remains at around 40%, thus indicating the stability of the reaction intermediate, very likely pyridylzinc halide.

The formation of arylzinc intermediates has already been observed in related reaction conditions involving the use of Zn sacrificial anode. More interestingly, this transformation has been optimized into a method for

SCHEME 3



preparing arylzincs as a good alternative to routes involving Mg–Zn or Li–Zn metal exchange.¹⁰ The nickel–zinc exchange is not favored, however, on the basis of thermodynamics, contrary to the reverse process. Figure 1a, however, shows that this Ni–Zn exchange is efficient in these reaction conditions. We have been able previously to show that, indeed, the Ni–Zn exchange does not occur unless there is an excess (3 to 4 equiv) of the ligand bipyridine versus nickel.¹¹ The reaction investigated here produces bipyridine, which therefore increasingly favors the formation of the arylzinc intermediate as the reaction proceeds. The excess bipyridine may bridge zinc and nickel in a bimetallic intermediate, thus allowing the random distribution of each metal in the vicinity of the aryl group to give one of the two pyridylmetals.

Table 1 shows some other results obtained for the electrochemical homocoupling of the 2-bromo-5-methylpyridine in the presence of a Zn sacrificial anode and of different types and concentrations of supporting electrolytes, while the current intensity and the charge are similar.

We clearly see (Table 1, entries 1 and 2) that a high concentration of an ammonium salt prevents the dimerization and allows for an efficient formation of the arylzinc intermediate based on the GC measurement of the iodo derivative. Also, this is true whatever the nature of the anion (Table 1, entries 3 and 4). On the contrary, with NaI (Table 1, entry 5), even at high 0.2 M concentration, the major product is the expected dimer, while in this case the reduction product, 5-picoline, is also formed in significant amount.

It thus comes out that NaI is more suitable as the electrolyte to conduct the homocoupling of bipyridine when a zinc anode is used. Indeed, with NaI, the shape of the reaction profile looks different (Figure 1b) from the one with TBAI (Figure 1a). Actually, the two first stages look roughly similar and notably regarding the formation of the arylzinc intermediate. This species is not, however, so stable in the presence of NaI, and it can be converted into the dimer if the current is still applied.

The consumption of the organozinc intermediate by transmetalation (Scheme 4) is now thermodynamically favored to regenerate the organonickel intermediate.

The experiments described in Figure 2 show another interesting feature of this process. Theoretically, the electric current is only required for the full consumption of the starting halopyridine, and it appears that it is indeed consumed in about 60 min, which is not far from the theory (40 min at $I = 0.1$ A). If we then set off the current, the consumption of the organozinc continues because of the reversibility of the transmetalation process,^{12,13} and the formation of the homocoupling product (2,2'-bipyridine) occurs. However, the process is very slow, and the arylzinc is only fully consumed after nearly

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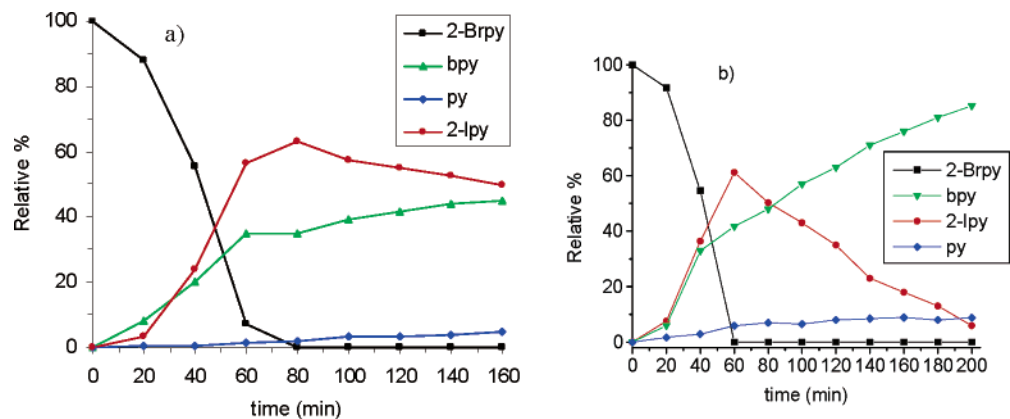
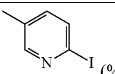

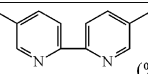


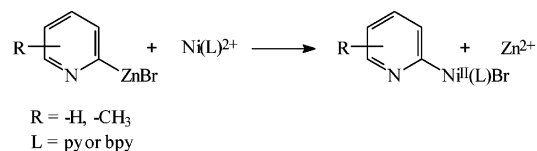
FIGURE 1. Electrochemical homocoupling of 2-bromopyridine using 7% NiBr₂ as catalyst and Zn anode. (a) (0.1 M) TBAI. (b) (0.1 M) NaI. 2-Iodopyridine; figures show the pyridylzinc intermediate concentration (see text).

TABLE 1. Nickel-Catalyzed Electrochemical Homocoupling of (2.5 mmol) 2-Bromo-5-methylpyridine Using NiBr₂ (7%), a Zinc Anode, I = 100 mA, Charge = 1500 C

Entry	Electrolyte (M)	 (%) ^a	 (%) ^a	 (%) ^a
1	TBABF ₄ (0.06)	29	6	65
2	TBABF ₄ (0.2)	73	4	23
3	TBAI (0.2)	78	4	18
4	TEABr (0.2)	72	5	23
5	NaI (0.2)	25	21	50

^a Yields obtained from GC analysis after treating the crude mixture with iodine.

SCHEME 4



17 h. Thus, keeping the current on after the first hour as for the case reported in Figure 1b is quite favorable to run the overall reaction efficiently.

The homocoupling reaction mechanism of haloaromatics^{14,15} and halopyridines⁶ using Ni complexes can be described as follows:

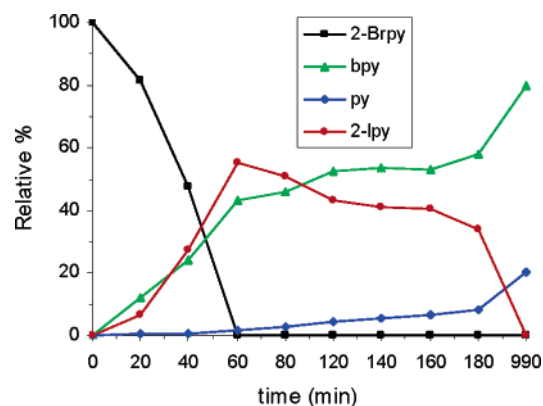
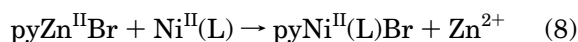
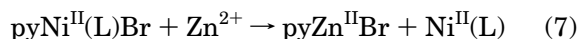
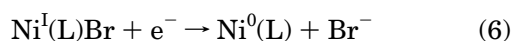
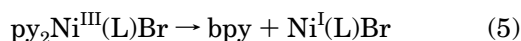
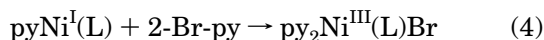
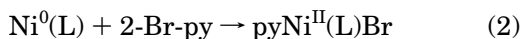
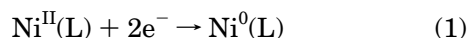


FIGURE 2. Electrochemical homocoupling of 2-bromopyridine using 7% NiBr₂ as catalyst, Zn anode, with current being stopped after 60 min; (0.2 M) NaI. 2-Iodopyridine; Figures show the pyridylzinc intermediate concentration (see text).

Results show (see Figures 1b and 2) that about half of the starting halopyridine is transformed and stored in the form of the arylzinc intermediate during the first hour. It comes out that, in the presence of ammonium salts, either this intermediate is stabilized or the reverse transmetalation (step 8) is prevented. On the contrary, in the presence of NaI, the regeneration of pyNi^{II}(L)Br occurs, and this allows for the further formation of the dimer. When the halopyridine is fully consumed, the process leading to the product can proceed by metathesis (step 9) and is followed by reductive elimination (step 10).^{14,15} These two steps do not require any further electrons. Thus the positive effect of keeping the current supply after the disappearance of the starting compound remains difficult to explain.

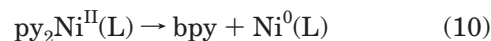
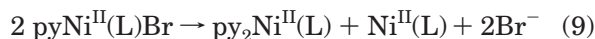


Table 2 shows some interesting results of dimerization of 2-bromopyridine and of isomeric 2-bromopicolines, in

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TABLE 2. Electrocatalytic Homocoupling of (2.5 mmol) 2-Bromomethylpyridines and 2-Bromopyridine, Using (0.1 M) NaI or (0.06 M) TBABF₄ as Supporting Electrolyte, (20 mL) DMF, Current Density of 100 mA, Room Temperature and Zinc Anode

entry	reagent	supporting electrolyte	NiBr ₂ (%)	2,2'-bpy (%)
1	2-bromo-3-methylpyridine	NaI	7	37
2		TBABF ₄	7	25
3	2-bromo-4-methylpyridine	NaI	30	72
4		TBABF ₄	30	42
5	2-bromo-5-methylpyridine	NaI	7	63
6		TBABF ₄	7	47
7	2-bromo-6-methylpyridine	NaI	30	98
8		TBABF ₄	30	93
9	2-bromopyridine	NaI	7	47
10		TBABF ₄	7	49
11	2-bromopyridine	NaI	30	91
12		TBABF ₄	30	95
13	2-bromopyridine	NaI	7	97
14		TBABF ₄	7	65
15	2-bromopyridine	NaI	15	99
16		TBABF ₄	15	68
17	2-bromopyridine	NaI	7	78
18		TBABF ₄	7	48
19	2-bromopyridine	NaI	30	85
20		TBABF ₄	30	71

which the NiBr₂ concentration was set at either 7 or 30% versus the organic reagent, while the anode is still made of zinc. These results now obtained with NaI as the supporting electrolyte are compared to those previously obtained in the presence of TBABF₄.⁶ Results show that the dimerization of 2-bromopyridine and of 2-bromopyridines with the methyl at position 3, 4, or 5 may be favored when NaI is used as the supporting electrolyte. However, 30% of catalyst is necessary to obtain satisfactory yields. On the contrary, this is not more than that necessary for the dimerization of 2-bromo-6-methylpyridine, and a 97% yield is obtained with 7% of catalyst and NaI, instead of 65% with TBABF₄ (Table 2, entries 13 and 14).

Conclusion

An interesting effect in the nickel-catalyzed homocoupling reactions of substituted 2-bromopyridines in the presence of Zn sacrificial anode was detected. A transmetalation step generates an organozinc intermediate that is not reactive in the presence of ammonium salts, notably at concentration higher than 0.1 M. Consequently, the dimerization is inefficient. On the contrary, the use of NaI as the supporting electrolyte does not prevent the dimerization reaction, though the organozinc is also formed, and yields in the dimers are good to high.

Experimental Section

The controlled current preparative electrolyses were carried out with a potentiostat/galvanostat. Undivided cells with 20-mL compartments were used. The sacrificial anode used was a Zn metallic bar with 8-mm diameter. A reference electrode Ag/AgCl, KCl 3 M, placed in parallel and separated from solution, monitored the potential of the working electrode. Ni foam (6 cm × 3.5 cm) was used as the working electrode. The Ni electrode may be reused about 20 times, but should be cleaned with HCl 6 M solution prior to use. The same solution was used to clean the anode. A 5-mL DMF solution containing (7, 15, or 30%) NiBr₂·xH₂O and (2.5 mmol) 2-bromo-methylpyridine (Br-pic) or (2.5 mmol) 2-bromopyridine (Br-py) was stirred or sonicated before the electrocatalytic experiment to ensure Ni(Br-pic)₂Br₂ or Ni(Br-py)₂Br₂ complex formation. A pre-electrolysis was carried out with 15 mL of electrolytic solution (solvent + 0.06, 0.1, or 0.2 M) supporting electrolyte and (0.75 mmol) 1,2-dibromoethane, passing a charge of 146 C (*I* = 150 mA). After this, 5 mL of previously prepared solution of 5 mL of DMF + Br-pic or Br-py + NiBr₂·xH₂O was added to the electrolytic cell, and the constant current electrolysis (*I* = 100 mA) was initiated, taking care to avoid a cell potential of 2.5 V, what could promote the reduction of the substrate on cathode surface. After the total consumption of reagent (1500 C), the reaction was stopped and the solvent was removed at reduced pressure. The residue was dissolved in CH₂Cl₂ and washed with several portions of a diluted ammonium solution until the organic layer became yellow. After being dried with Na₂SO₄, the solvents were removed under reduced pressure.

The products 2,2'-bipyridine [366-18-7], 3,3'-dimethyl-2,2'-bipyridine [1762-32-9], 4,4'-dimethyl-2,2'-bipyridine [1134-35-6], 5,5'-dimethyl-2,2'-bipyridine [1762-34-1], and 6,6'-dimethyl-2,2'-bipyridine [4471-80-7] were analyzed by gas chromatography, identified by time retention, and compared with authentic sample, and the yield was determined by using methylpyridine or pyridine as internal standard. These products may be isolated, purified, and analyzed as described previously.⁶

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 Na₂S₂O₃ (10%) solution until colorless, followed by addition of 3 mL of ammonium hydroxide 1 M solution. The reaction products were extracted in the same tube with 2 mL of diethyl ether, and the relative percentage was determined by gas chromatography.

Gas chromatogram/mass spectra were taken with a 30-m capillary column, using a 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.

Acknowledgment. We thank CNPq and CAPES/COFECUB exchange program for financial support.

JO0517491