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Electrosynthesis of functionalized 2-arylpyridines from functionalized aryl and pyridine halides catalyzed by nickel bromide 2,2′-bipyridine complex

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Abstract

2-Arylpyridines substituted on aryl and/or on pyridine nuclei can be obtained in good to high yields in one step by electroreduction of mixtures of the corresponding aryl and pyridyl halides using the sacrificial iron anode process and a nickel 2,2′-bipyridine complex catalyst in DMF as solvent.

Arylpyridine sub-units form the basic structure of a large variety of biologically active compounds, notably agrochemicals. Further reactions from these biaryls to the final product require the presence, on one or the two rings, of functional groups such as ester, nitrile, nitro, or acyl groups. Modern chemical methods of metal-catalyzed cross-coupling offer various routes to prepare these biaryls from readily available aryl- and pyridylhalides.[1] However, they all require the preliminary formation of an organometallic intermediate, and this is hardly compatible with the presence of electrophilic functional groups. Even soft organometallics of zinc, tin, or boron are usually obtained by transmetallation from organo-magnesium or -lithium reagents. Therefore, in many cases, one has to introduce functional groups after the cross-coupling.[2]

There is still a need for more simple and more versatile cross-coupling methods. In relation to this, we have already reported in a previous paper[3] the electrochemical synthesis of 2-arylpyridines bearing substituent on the aryl ring. The first one involves the electrochemical preparation of an aryl zinc species followed by its reaction with 2-chloropyridine, these two steps being catalyzed by the same nickel-2,2′-bipyridine (bpy) complex. An alternative more simple method was also used. It consists of the electroreduction of a 1:1 mixture of the two organic halides in the presence of a

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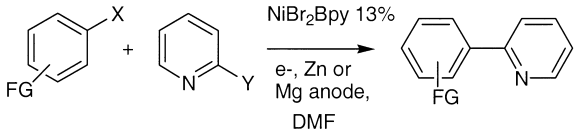
catalytic amount of $NiBr_2bpy$ in DMF as solvent (Eq. (1)). The efficiency of this route makes it the most convenient method to prepare 2-arylpyridine compounds.



(1)

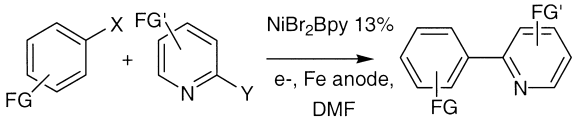
Results and discussion: In this former study we found that the use of a zinc anode was preferable when the substituent on the aryl halide is an electron-withdrawing group (EWG). More recently, however, we found that the use of an iron anode instead of zinc was also quite convenient in the coupling of aryl halides with 2-chloropyrimidine.[4] Therefore, we revisited our previous results for Eq. (1). Results for some model reactions are shown in Table 1. We can see that the yields of the coupling product are increased by about 15% when iron is used instead of zinc as the anode.

Table 1
Comparison of the use of iron or zinc anode in the nickel–bpy catalyzed electrochemical arylation of 2-halopyridine by EWG-substituted aryl halides

FG	X	Y	Yield %(a) with Fe	Yield %(a) with Zn anode
p-COMe	Br	Br	77	60
p-COOMe	Br	Br	81	61
p-SO_2Me	Cl	Cl	69	55
p-Cl	Br	Br	77	65

a. isolated yield, all compounds were characterized by ^1H, ^{13}C NMR, IR and GC/MS analysis.

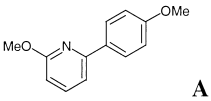
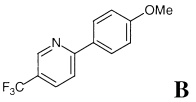
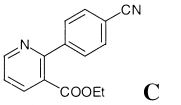
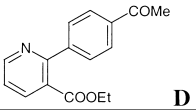
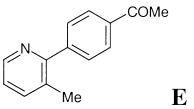
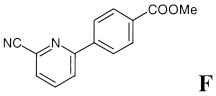
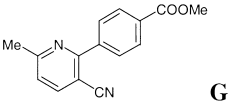
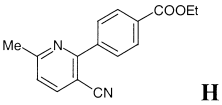
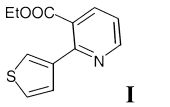
On the basis of these improvements we investigated the electrochemical coupling between substituted 2-halopyridine and substituted aryl halides using an iron anode and $NiBr_2bpy$ as catalyst according to Eq. (2). Results are reported in Table 2.



(2)

The presence of an electron-donating substituent on 2-chloro- or 2-bromo-pyridine does not significantly change their reactivity. So, in this case, and whether the functional group on the aryl bromide is electron-donating or electron-withdrawing, chloro- or bromo-pyridine can be used, and the cross-coupling product is obtained in good yield. We have already observed that 2-chloro-pyridines substituted by an electron-withdrawing group are more reactive toward electro-generated zero-valent nickel than 2-chloropyridine.[5] Therefore, the coupling of EGW-substituted

Table 2
Ni-catalyzed electrochemical cross-coupling between substituted 2-halopyridine and substituted aryl halides

FG	X	FG'	Y	Coupling product	Yield %(a)
p-OMe	Br	6-OMe	Cl	 **A**	76
p-OMe	I	5-CF_3	Cl	 **B**	72
p-CN	Br	3-COOEt	Cl	 **C**	46
p-COMe	Br	3-COOEt	Cl	 **D**	73
p-COMe	Br	3-Me	Br	 **E**	65
p-COOMe	Br	6-CN	Cl	 **F**	59
p-COOMe	Br	3-CN, 6-Me	Cl	 **G**	40
p-COOEt	Br	3-CN, 6-Me	Cl	 **H**	58
		3-COOEt	Cl	 **I**	71

a. isolated yield, all compounds were characterized by ^{1}H, ^{13}C NMR, IR and GC/MS analysis

2-chloropyridines with aryl bromides occurs only when the aryl ring is substituted by electron-withdrawing group. In the case of an electron-donating group on the aromatic ring, the use of the corresponding iodo compound is required. This is in keeping with the postulated mechanism, where the aryl halide should react faster than the pyridyl halide with the Ni(0) to lead selectively to the cross-coupling product.[3] A reverse order of reactivity leads mostly to the formation of the bipyridine. In similar reaction conditions, the cross-coupling occurred in good yield between 3-bromothiophene and ethyl 2-chloronicotinate. All these reactions were conducted with an iron rod as the consumable anode. We could confirm in several cases the advantage of using this metal. For example, the yield of **D** was 73 and 55% with, respectively, iron and zinc as the anode material.

The coupling procedure is as follows: The reactions were performed under an inert atmosphere of argon at 60°C, in commercial DMF without purification. The ionic conductivity is ensured by NBu_4BF_4 (0.01 M), as the supporting electrolyte. In a typical experiment, 50 ml of DMF, 7.5 mmol ArX (0.15 M), 1 mmol $NiBr_2Bpy$ (0.02M) and 7.5 mmol halo pyridine (0.15 M) were introduced in the cell. The electrolysis was conducted at constant current intensity of 0.2 A in an undivided cell (0.01 A/cm^2) using an iron sacrificial anode and a nickel foam cathode. The reaction was stopped after consumption of 2.2 F per mol ArX corresponding to complete consumption of the starting reagents. The cathodic potential during the electrolysis was constant between –1.2 V and –1.3 V/SCE.

In conclusion, we have shown that the use of a consumable iron anode combined with chemical catalysis by $NiBr_2bpy$ is very efficient to perform, in one step, the cross-coupling between substituted 2-halopyridine and substituted aryl halides.

References

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