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Electrochemical cross-coupling between functionalized aryl halides and 2-chloropyrimidine or 2-chloropyrazine catalyzed by nickel 2,2′-bipyridine complex

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Abstract

2-Arylpyrimidines and 2-arylpyrazines have been obtained in good to high yields from 2-chloropyrimidine and 2-chloropyrazine and various functionalized aryl halides by electroreduction using an iron rod as the anode and a catalytic amount of nickel–bipyridine complex in a mixture of DMF and pyridine as solvent.

In relation to a research project devoted to the synthesis of agrochemicals, a recent paper[1] reported the preparation of 2-alkyl- and 2-arylpyrimidines by coupling between 1,1,3,3-tetramethoxypropane and amidine hydrochlorides in a sealed tube at 175°C. Yields of 2-substituted pyrimidines were in the range of 60 to 80%. However, no highlight on the functional group tolerance could be obtained from that work. Another recently published route to 2-phenyl- or 2-(chlorophenyl)pyrimidine is based on the pyrolysis at 550°C of mixtures of 1-substituted pyrazoles and chloroform.[2] Such a route gives poor yields and is far from being general either. These two methods involve the formation of the heterocyclic ring and require rather high reaction temperatures. So far, no direct and simple method of access to 2-arylpyrimidines or -pyrazines from 2-halopyrimidine or 2-halopyrazine and variously substituted aryl halides has been reported.

We have recently described the arylation of 2-halopyridine and 2-halopyrimidine by electrochemical processes based on the combined use of a sacrificial anode and a transition metal catalysis.[3] They involve either the electrochemical preparation of an aryl zinc compound followed by its nickel-catalyzed coupling with 2-chloropyridine or 2-chloropyrimidine, or the direct electroreduction of a mixture of an aryl halide and 2-halopyridine in DMF in the presence of a catalytic amount of $NiBr_2Bpy$ (Eq. (1)).

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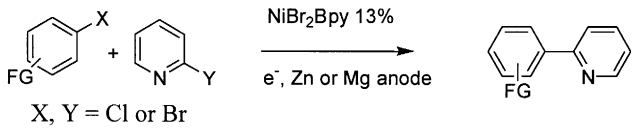
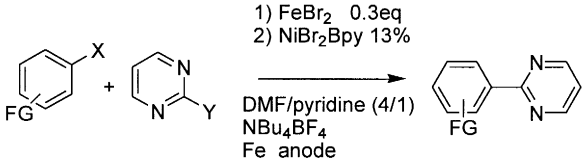


(1)

This latter process was found unsuitable for the synthesis of 2-arylpyrimidine or 2-arylpyrazine, probably because 2-chloropyrimidine or 2-chloropyrazine are so strongly liganded to the nickel catalyst that it becomes inefficient, and only reduction products from the reagents were obtained.

We have now disclosed that the presence of iron salts at the beginning of the electrolysis could circumvent this problem. They are formed by oxidation of an iron anode along with the reduction of 1,2-dibromoethane prior to the introduction of the reagents. Then the usual electrolysis in the presence of the iron anode allows the desired coupling reaction to occur efficiently, as shown in Table 1 for the arylation of 2-chloropyrimidine according to Eq. (2).

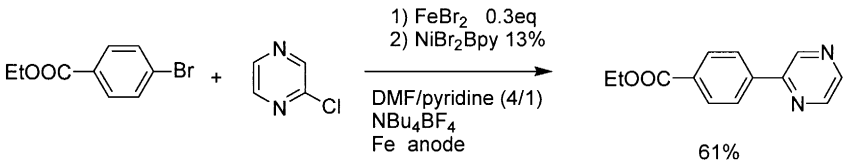


(2)

The coupling procedure is thus as follows: In an undivided cell flushed with argon, equipped with an iron rod as the anode and a nickel foam as the cathode, were introduced DMF (40 ml) and pyridine (10 ml), 1,2-dibromoethane (2 mmol) and NBu_4BF_4 (1 mmol) as the supporting electrolyte. A constant current intensity of 0.2 A was applied at room temperature until a charge of 2 F per mol of the halides had passed. Then the solution was heated at 60°C and we introduced $NiBr_2Bpy$ (1 mmol) as the catalyst precursor, the aryl halide (3.75 mmol) and 2-chloropyrimidine (or 2-chloropyrazine) (3.75 mmol). A current intensity of 0.2 A was applied until a charge of 2 F per mol of halide had passed. We then again introduced aryl halide (3.75 mmol) and 2-chloropyrimidine (or 2-chloropyrazine) (3.75 mmol) and the electrolysis was carried out with the same current intensity until complete consumption of the starting reagents.

According to our previous studies,[3] we assume that FG-C_6H_4NiX is the first formed intermediate, being further reduced to FG-C_6H_4Ni to react preferably with 2-chloropyrimidine or 2-chloropyrazine. We also know that 2-chloropyrimidine and 2-chloropyrazine are more reactive than 2-chloropyridine.[4] This implies that, for the coupling reaction to be efficient, we should have the right halogen on the aryl halide according to the nature of the substituent, i.e. bromine with an electron withdrawing group, and iodine with an electron-donating group.

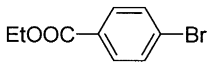
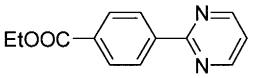
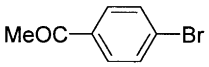
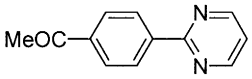
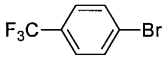
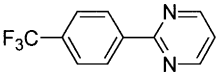
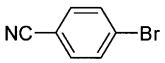
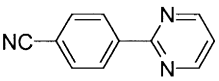
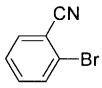
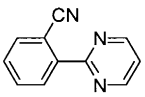
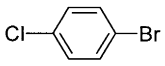
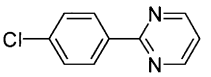
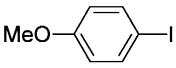
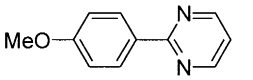
Under the same reaction conditions, 2-chloropyrazine is directly coupled in good yield with aryl bromide substituted by an electron-withdrawing group (Eq. (3)).



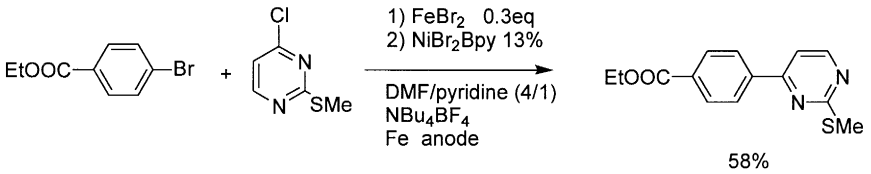
(3)

This process has been successfully applied with the halide on pyrimidine at another position; the coupling of 4-chloropyrimidine also bearing an electron-donating group is also possible (Eq. (4)).

Table 1
Electrochemical cross-coupling between 2-chloropyrimidine and substituted aryl halides

FG-ph-X	product	Yield %(a)
		77
		61
		61
		50
		31
		79
		65

a : isolated yield; all products gave satisfactory ^{1}H NMR, ^{13}C NMR and MS data.



(4)

In conclusion, we have shown that it is possible to prepare various 2-arylpyrimidine, 2-arylpyrazine and 4-arylpyrimidine using a very simple electrochemical process.

References

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