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Pure acetonitrile as solvent for the efficient electrochemical conversion of aryl bromides in organozinc species and their coupling reaction with acetyl chloride

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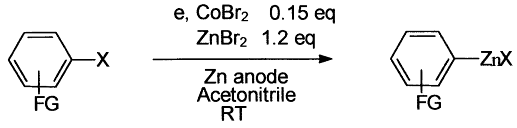
Abstract—Conversion of functionalized aryl bromides in an electrochemical cell fitted with a sacrificial anode and in the presence of cobalt bromide without ligand in acetonitrile as solvent affords the corresponding organozinc species in good yields. Their coupling with acetyl chloride is efficient using a palladium catalyst.

The reaction of organozinc reagents with various electrophiles has been extensively studied during the last few years. Twenty years ago, Negishi et al. developed the use of palladium catalysts to achieve the cross-coupling of organozinc species with different organic halides[1] including acyl chlorides.[2] More recently, Knochel et al. promoted the coupling reaction between these organometallic reagents and electrophiles using a CuCN, 2 LiCl mixture.[3] Generally, organozinc compounds are useful organometallic intermediates due to their broad group tolerance which allows the preparation of highly functional derivatives. The preparation of organozinc species from aromatic halides was formerly possible through transmetallation of organolithium or Grignard reagents using zinc halides; but, such procedures could not be applied to compounds bearing reactive electrophilic functional groups (CO, CN, COOR...) because very low reaction temperatures were required.[4] This drawback was circumvented by synthesizing the organozinc species from aryl bromides using an activated zinc[5] called Rieke's zinc, but the difficulty of handling this reagent makes this procedure very sensitive.

In our laboratory, arylzinc compounds have been successfully synthesized using two different electrochemical procedures. The former one was based upon the catalytic activity of a nickel complex in dimethylformamide as solvent.[6] Recently, we have developed a simpler catalytic system involving cobalt halides in DMF–pyridine or acetonitrile–pyridine mixtures.[7] The use of cobalt salts allowed us to realize our electrochemical syntheses of organozinc reagents using the dissolving anode process with a wider variety of solvents and was additionally recommended for environmental reasons. Unfortunately, if organozinc reagent yields were high, our reaction conditions did not allow us to realize the coupling between these species and acyl chlorides. Indeed, the presence of pyridine in the reaction medium gave rise to the formation of a pyridinium salt when the acyl chloride was added in the electrochemical cell. This reactivity was utilized in a previous work dealing with additions of electrogenerated organozinc species at the 4-position of pyridinium salts which were simply obtained by adding acetyl chloride to the reaction mixture.[8]

Therefore, aiming to establish a versatile organozinc electrochemical synthesis we have tried to replace or simply remove pyridine from the reaction mixture. We wish to describe herein a new, simple electrochemical process which allows us to form arylzinc compounds from aryl bromides in acetonitrile without using pyridine as cosolvent. Several attempts toward cross-cou-



Scheme 1. Formation of functionalized aryl zinc species via a cobalt catalysis in pure acetonitrile.

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pling reactions between these organozinc reagents and acetyl chloride were realized using palladium(II) catalyzed, or copper(I) mediated, classical conditions.

Recently, electrochemical studies carried out in our laboratory have shown that the addition of vinyl acetate or methyl vinyl ketone as ligand to a mixture of acetonitrile and pyridine could enhance Co(I) stability.[9] It has been noticed that in our previously described conditions[7] of electrosynthesis of aromatic organozinc species, the presence of pyridine remained crucial even in the presence of those ligands. Aiming to discard pyridine in our electrosynthesis reaction mixtures, its nucleophilic properties being in some cases a drawback when electrophilic species are added to electrolyses mixtures, other reaction conditions have thus been studied. It has been possible to show, towards several electrochemical studies, that the presence of a stoichiometric amount of zinc bromide, which was electrogenerated, had a very promising effect on Co(I) lifetime. Thus, because the Co(I) lifetime is considered the key point in the catalytic process of aromatic organozinc compounds formation,[10] we thought that we could eliminate pyridine if zinc bromide was present in sufficient amount in the reaction mixture. Several electrosynthesis attempts were realized[11] (Scheme 1).

First, using acetonitrile as a solvent, we chose to examine the effect of the addition of various ligands on the formation of the organozinc species stemming from ethyl 4-bromobenzoate. Results are reported in Table 1.

The main point to note is that the use of an additional ligand is useless because similar yields are obtained in entries 4–6. Moreover, the reaction yield seems to be very sensitive to ligand amount as shown by comparison of entries 3 and 4. Considering the fact that the presence of an additional ligand does not raise the reaction yield and could have negative effects if the optimal amount is not present in the reaction mixture, we decided to work without any ligand in the following electrosyntheses.

Several other parameters such as solvent, cathode nature, halide in the cobalt salts and amount of catalyst have been studied. The use of dimethylformamide (DMF) or dimethylacetamide (DMAC) instead of acetonitrile does not lead to organozinc species formation when these solvents are used without addition of pyridine. When a nickel foam cathode is used instead of a stainless steel grid, a part of the starting material remains unconverted and the organozinc yield decreases in about 10%. The use of cobalt chloride instead of cobalt bromide leads to a lower yield (65%) and again to a partial consumption of the aromatic halide. We have shown that 15% amount of cobalt bromide was the lower range in order to obtain an efficient conversion to the organozinc species since using 10% amount of this salt gives rise to the preferential formation of the hydro-dehalogenation product of the starting material (ArH, 70%).

Then we used the optimized conditions described above to convert aromatic halides bearing electron donating groups to the related organozinc species.

It is noteworthy that in all cases yields vary from moderate to good. The position of the substituent has only a slight influence on yields and in all cases, the sole byproduct is the hydro-dehalogenation product of the starting aromatic halide (ArH), the dimerization product (Ar–Ar) being always absent. Such a behaviour has previously been reported when reactions are carried out with such donating groups.

Our study was then extended to aromatic halides bearing electron withdrawing groups. The results are summarized in Table 2.

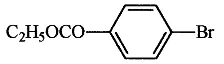
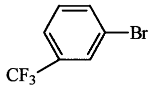
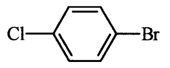
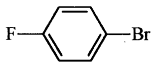
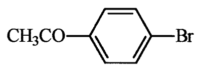
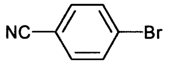
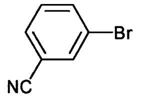
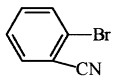
It can be pointed out that the position of the substituent has again a slight influence on yields as revealed by assays in entries 13–15. Yields are fairly good except for *p*-fluoro-bromobenzene which leads to a 43% yield but in that case, the starting material is not totally consumed (entry 11). Curiously, no dimerization products are detected when a nitrile group is connected to the phenyl moiety while in the presence of pyridine, a non negligible part of the self coupling product is obtained.[7] An interesting effect resulting from the absence of pyridine in the electrolysis medium can be observed when *p*-chloro-bromobenzene is used as starting compound. Indeed, electrolyses of 2-chloro-bromobenzene, conducted in the acetonitrile/pyridine mixture, had afforded mono- and dizincation products after a charge of 2 and 4 F per mol of substrate was passed, respectively, the carbon–bromide bond being metallated first.[12] When acetonitrile is solely used, this carbon–bromide bond remains reactive as attested by the formation of the monozincation compound (entry 10) but no dizincation product could be observed when an additional charge of 2 F per mol of substrate was passed. This behaviour could be generalized to aro-

Table 1. Influence of the nature of additive associated with 45 mL of acetonitrile

Entry	Additive	ArZnX (%)[a]	ArH (%)	ArAr (%)	Conv. (%)
1	Phenylsulfonyl acetonitrile 1 equiv./$CoBr_2$	52	34	0	86
2	Adiponitrile 1 equiv./$CoBr_2$	61	37	0	100
3	Vinyl acetate 1 equiv./$CoBr_2$	48	28	0	76
4	Vinyl acetate 2 equiv./$CoBr_2$	75	25	0	100
5	Methyl vinyl ketone 0.5 equiv./$CoBr_2$	77	17	7	100
6	–	76	17	7	100

[a] The obtained arylzinc halides are converted into the corresponding aryl iodide by addition of iodine.

Table 2. Preparation of aryl-zinc compounds substituted by electron-withdrawing groups

entry	ArX	ArZnX %[a]	ArH %	ArAr %	conv. %
8		**76**	17	7	100
9		**90**	4	6	100
10		**76**	24	0	100
11		43	19	0	63
12		77	17	6	100
13		84	16	0	100
14		80	20	0	100
15		80	20	0	100

[a] The obtained arylzinc halides are converted into the corresponding aryl iodide by addition of iodine

matic chlorides bearing electron withdrawing groups. Such compounds proved to be unreactive to zincation while in the presence of pyridine, related organozinc species had been obtained in satisfactory yields.

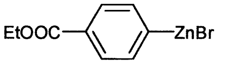
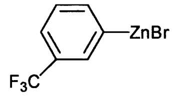
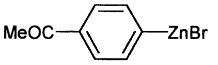
In a following series of experiments, we tried to apply this method to heteroaromatic halides, insofar as electrosyntheses conducted in the presence of pyridine had afforded related organozinc compounds in good yields.

Unfortunately, results were disappointing. Indeed, only 27% yield was obtained starting from 3-bromothiophene, 38% of this compound remaining unconsumed after a charge of 1450 C (2 F per mol) was passed.

Considering that our reaction conditions were sufficiently optimized to insure satisfactory organozinc yields, we focused our work on coupling these compounds with acetyl chloride. Indeed, the coupling of acyl chlorides with organometallic reagents constitutes an efficient and useful method for the synthesis of various ketones. We first tried to activate the organozinc species using a mixture of cuprous cyanide and lithium chloride as previously described in the literature[13] but these assays led quantitatively upon work-up to the hydro-dehalogenation product (ArH).

Therefore, we tried to realize a Negishi coupling reaction between electrogenerated organozinc species and acyl chlorides using a palladium(II) catalysis.[14] Results are reported in Table 3.

Table 3. Coupling between ArZnBr and CH_3COCl via a Pd catalyst

entry	ArZnBr	ArZnX %	isolated $ArCOCH_3$ vs initial ArBr %
16		76	64
17		90	76
18		77	72

Using this procedure, the coupling step appears to be almost quantitative, yields ranging from 85 to 95%. Overall yields and subsequently isolated yields are good (64–76%).

In conclusion, the overall procedure appears to be a useful and mild method for the synthesis of various aromatic ketones. Indeed, aromatic organozinc compounds which are electrogenerated without using pyridine as cosolvent can be coupled efficiently with acetyl chloride in the presence of a catalytic amount of palladium(II). It should be noted that such procedures could not be utilized in the presence of pyridine since such a nucleophile reacts rapidly with acyl chlorides to form pyridinium salts. Thus, the versatility of our new electrochemical method of organozinc compounds formation allows us to be full of hope concerning the extension of the coupling step to many other electrophilic substrates.

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11. All the reactions were carried out in an undivided cell fitted using a consumable zinc anode and a stainless steel cathode. In a mixture of solvent (acetonitrile 45 mL and various cosolvent or not) containing 7.5 mmol of ArX (0.16 M), 1 mmol of $CoBr_2$ (0.02 M) and 9 mmol of $ZnBr_2$ (formed by electroreduction of 1,2-dibromoethane in the presence of a zinc anode) we applied a constant current intensity of 0.2 A (0.01 A/cm^2) at room temperature. The reactions are stopped after consumption of 2 F per mol of ArX.
12. Fillon, H.; Gosmini, C.; Nedelec, J.-Y.; Périchon, J. *Tetrahedron Lett.* **2001**, *42*, 3843–3846.
13. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390–2392.
14. *Typical coupling procedure*: To the solution of the organozinc compound resulting from the electrolysis of the related aromatic bromide was added 1% bis-(triphenylphosphine)palladium chloride (53 mg, 7.5×10^{-2} mmol) and a slight excess of acetyl chloride (1 mL, 12.5 mmol) at room temperature. The solution is stirred until total consumption of the organozinc compound (1–3 h) and quenched by addition of a 2 M HCl solution. The organic materials are then extracted with diethyl ether and the organic layer washed with brine, dried with magnesium sulfate and evaporated under reduced pressure. The resulting crude oil is purified over silica gel using a pentane/diethyl ether mixture (90/10) as an eluent.