New Chemical Synthesis of Functionalized Arylzinc Compounds from Aromatic or Thienyl Bromides under Mild Conditions Using a Simple Cobalt Catalyst and Zinc Dust

Hyacinthe Fillon, Corinne Gosmini,* and Jacques Périchon

Contribution from the Laboratoire d'Electrochimie, Catalyze et Synthèse Organique, UMR 7582 CNRS-Université Paris 12 2, rue Henry-Dunant 94320 Thiais, France

Received October 15, 2002; E-mail: gosmini@glvt-cnrs.fr

Abstract: A new chemical method for the preparation of arylzinc intermediates is described in acetonitrile, on the basis of the activation of aryl bromides by low-valent cobalt species arising from the reduction of cobalt halide by zinc dust. This procedure allows for the synthesis of a variety of functionalized aryl- and thienylzinc species in good to excellent yields. The versatility and the simplicity of that original method represent an alternative to most known procedures.

Introduction

The preparation of functionalized organometallic compounds has been the subject of increased research activity over the past decades,[1] due to the versatility of such key intermediates in organic synthesis. Indeed, organozinc species have received much attention because of their mildness resulting in high functional group compatibility.[2] Numerous methods devoted to carbon−zinc bond formation have been developed. Prior to the discovery of Rieke zinc,[3] zinc was found unreactive toward alkyl, vinyl, and aryl bromides or chlorides except in the well-known Reformatsky reaction.[4] The preparation of these organozinc compounds was formerly achieved only by a transmetalation reaction of a zinc halide from preformed organolithium or magnesium counterparts. Although some functionalized magnesium reagents have been prepared via an iodine−magnesium exchange,[5] they need to be transmetalated with copper or zinc to undergo the cross-coupling reaction. Organolithium compounds can also bear a reactive group, providing they are prepared at low temperature.[6] Alternatively, Rieke reported on a general approach for preparing highly reactive metals such as zinc by reducing the corresponding metal halide.[7] This Rieke zinc is generally reactive toward aryl or heteroaryl bromides at elevated temperature but reacts neither on aryl chlorides nor on some aryl bromides (e.g., 3-bromothiophene). Despite its indisputable synthetic utility, the use of such activated zinc requires specific conditions together with careful handling.

Among the numerous topics developed in our laboratory, the synthesis of organozinc reagents is of current interest. In the past few years, arylzinc compounds have been successfully synthesized from aryl bromides or chlorides in high yields under mild conditions by two electrochemical procedures. The former one was based on the catalytic activity of a nickel complex in DMF as solvent.[8] More recently, we have developed a simpler catalytic system involving cobalt halides in DMF or acetonitrile associated to pyridine.[9] The use of cobalt allowed us both to achieve the synthesis of organozinc reagents using the sacrificial anode process with a wide variety of solvents and to use a less toxic catalyst. To develop a pyridine-free process, the last electrochemical process has been carried out in pure acetonitrile from aryl bromides.[10] These electrochemical methods favorably compare with known chemical processes. Yet all of the electrochemical reactions are generally considered as being more difficult to handle than conventional chemical methods. Thus, electrochemical syntheses are poorly applied by organic chemists, and, although they were found successful on the laboratory scale, they are not used on a larger (industrial) scale.
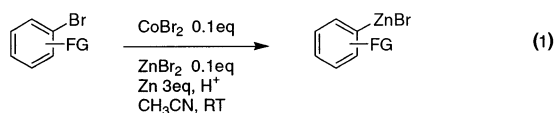
Given the importance of arylzinc species in chemical synthesis, we developed a new chemical reaction aimed at preparing aromatic zinc species. This process relies on our recent discoveries and demonstrates that in some cases a purely chemical reaction could be extended from our initial electrochemical process. Indeed, we have established that chemical reducing agents could advantageously replace electricity for the preparation of arylzinc compounds catalyzed by cobalt in acetonitrile.[11] The low-valent cobalt generated from the chemical

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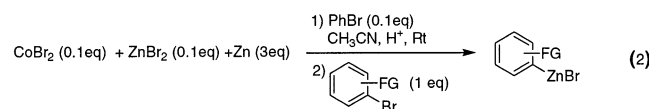
reduction of cobalt halide can unprecedentedly activate aryl bromides in acetonitrile.

Herein, we describe that, in the presence of zinc bromide and zinc dust, the cobalt catalyst is also suitable for the efficient chemical conversion of various aryl bromides to the corresponding arylzinc intermediates (eq 1).

$$\text{(1)}$$

Results and Discussion

Arylzinc bromides are readily prepared by the reaction of aryl bromides with commercially available zinc dust activated by traces of acid in the presence of cobalt halide (0.1 equiv) and zinc halide (0.1 equiv) in acetonitrile at room temperature. The conversion is complete after a reaction time of ca. 30 min, affording the corresponding organozinc species. The resulting organozinc species are converted into aromatic iodide by addition of iodine. The amount of the aromatic iodide is measured by GC using an internal standard (alcane). In the beginning of the reaction, ArH is formed. To decrease the amount of the reduction product, a catalytic amount of bromobenzene (10% vs ArX) is added in the solution before the introduction of the functionalized aryl bromide, allowing this side reaction to proceed on bromobenzene rather than on more functionalized aryl halides used as substrates. Bromobenzene is readily converted into the reduced product, no corresponding organozinc is detected, and only benzene is formed. The aryl bromide is added in a second time (eq 2). An inert atmosphere is not required in this process as long as ArZnX is consecutively engaged in a coupling reaction.

$$\text{(2)}$$

Different aryl bromides have been tested in the first step instead of bromobenzene, such as p-Br–Ph–COOEt, p-Br–Ph–CN, m-Br–Ph–CF$_3$, p-Br–Ph–Me, and 3-bromo pyridine, giving similar results; only the reduction product appears. However, with an aryl bromide substituted in the ortho position, such as o-Br–Ph–CN, the corresponding organozinc compound is detected. For greater convenience, bromobenzene was used. In this protocol, PhBr and CoBr$_2$ are introduced in equimolar amount. If the PhBr/CoBr$_2$ ratio is increased, the organozinc PhZnBr is formed and does not affect the yield in ArZnBr. The large excess of zinc dust enhances the rate of the reaction, but a slight excess is sufficient to consume all of the starting product. Using 2 or 3 equiv of Zn dust has no effect on the yields. The results are similar when the zinc dust is activated either by CF$_3$-COOH or by CH$_3$COOH. Replacement of these Brönsted acids by iodine was attempted but led to poorly reproducible results. CoCl$_2$ can be used instead of CoBr$_2$. A few years ago, we described an electrochemical method catalyzed by nickel, but no organozinc compound was detected when CoBr$_2$ was replaced by NiCl$_2$ in this protocol. At the beginning of the reaction, the presence of ZnBr$_2$ which undergoes transmetalation with ArCoBr is not required according to the mechanism which will be discussed later on. Nevertheless, a little amount of freshly

Table 1. Preparation of Aryl–Zinc Compounds Substituted by Electron-Donating Groups

entry	FG–C$_6$H$_4$–FG	X	% ArZnX	% ArH	% Ar–Ar	conv. %
1	H	Cl	0	0	0	0
2	H	Br	77	8	15	100
3	p-CH$_3$O	Br	86	8	6	100
4	m-CH$_3$O	Br	70	7	23	100
5	o-CH$_3$O	Br	93	7	0	100
6	p-CH$_3$O	I	88	8	3	100
7	p-CH$_3$	Br	71	9	20	100
8	p-NH$_2$	Br	40	52	0	100
9	p-N(Me)$_2$	Br	65	16	19	100
10	p-OH	Br	6	94	0	100
11	p-OCOMe	Br	80	13	7	100

dried ZnBr$_2$ leads to a slight decrease in dimer ArAr formation. ZnBr$_2$ stabilizes cobalt(I) as reported before in an electrochemical study[12] and by electrochemical synthesis of arylzinc compounds from aryl bromides.[10] In the chemical synthesis described herein, ZnBr$_2$ is generated by chemical reduction of cobalt halide with zinc dust. Several other parameters such as the nature of the solvent or the presence of a cosolvent have been studied. The use of dimethylformamide (DMF), dimethylacetamide (DMAC), or tetrahydrofuran (THF) instead of acetonitrile does not lead to organozinc formation. Considering the fact that in the presence of pyridine, the rate of formation of organozinc compounds is very low and could have negative effects in some coupling reaction, we decided to carry out the reactions without any ligand in the following synthesis. The optimized conditions developed for aromatic bromides bearing either electron-donating or electron-withdrawing groups have been applied to the conversion of heteroaromatic bromides into the corresponding organozinc species. In some cases, the arylzinc species has been coupled with aryl iodide using PdCl$_2$-(PPh$_3$)$_2$ as catalyst. The resulting product has been isolated.

The results obtained in acetonitrile from phenyl halides substituted by an electron-donating substituent are reported in Table 1.

These results show that this new original chemical method gives the expected organozinc species in high yields with aromatic bromides (entries 2–5, 7–9, 11) and iodides (entry 6). However, as already observed in the electrochemical process in pure acetonitrile, no organozinc compound could be detected from chlorobenzene (entry 1), which was not consumed. This indicates that Co(I) reacts too slowly with aryl chlorides. Bromophenol (Table 1, entry 10) reacts with Co(I), but the complexation of the alcoholate to the zinc proceeds so fast that transmetalation is no longer observed, leading to the formation of the reduction product. However, the corresponding protected alcohol (Table 1, entry 11) affords the organozinc species in good yield. On the contrary, p-bromoaniline (entry 8) can be converted in moderate yield without protecting the amino group.

The results obtained with aromatic halides substituted by an electron-withdrawing group are reported in Table 2.

These results show that the yields obtained in the standard reaction conditions described above are good to excellent with aromatic bromides substituted by COOEt, CF$_3$, X, or CN (entries 14–22) in the ortho, meta, or para position except when FG is a carbonyl group (Table 2, entries 23 and 24). With these last substituents, poor yields are obtained under these conditions.

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Table 2. Preparation of Aryl–Zinc Compounds Substituted by Electron-Withdrawing Groups
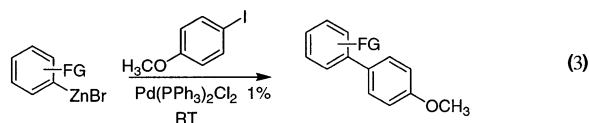
entry	FG–C$_6$H$_4$–FG	X	% ArZnX	conv. %	% ArH	% ArAr
12	*p*-CH$_3$SO$_2$	Cl	41	63	23	0
13	*p*-C$_2$H$_5$OCO	Cl	6	29	23	0
14	*p*-C$_2$H$_5$OCO	Br	80	100	6	13
15	*p*-C$_2$H$_5$OCO	I	75	100	11	14
16	*p*-CF$_3$	Br	86	100	4	10
17	*m*-CF$_3$	Br	80	100	12	3
18	*p*-Cl	Br	89	100	6	5
19	*p*-F	Br	70	100	9	21
20	*p*-CN	Br	95	100	3	2
21	*m*-CN	Br	96	100	4	0
22	*o*-CN	Br	100	100	0	0
23	*p*-CHO	Br	22	100	13	65
24	*p*-CH$_3$CO	Br	52	100	10	38

Table 3. Formation of Organozinc Species from Bromothiophenes

entry	ArBr	%Co	%ArBr	%ArH	%ArAr	%ArZnBr
25		10	22	11	0	67
26		20	0	11	6	83
27		10	0	45	4	50
28		20	0	10	18	72

Surprisingly, these organozinc species quickly evolve, resulting in dimer formation. It can be pointed out that the position of the substituent has again a slight influence on the yields as revealed in entries 16 and 17 or 20–22. When the halogen on ArX is chlorine instead of bromine, the consumption of the aryl chloride is partial even if the aromatic nucleus is substituted by an electron-withdrawing group (Table 2, entries 12 and 13). Such compounds were found to be poorly reactive toward zinc.
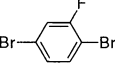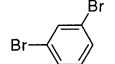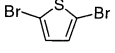
Some aromatic organozinc species mentioned in Table 2 (entries 14, 20, 22) have been coupled with iodo anisole (1 equiv vs ArX) in the presence of a catalytic amount of PdCl$_2$(PPh$_3$)$_2$ (eq 3).

$$\text{(3)}$$

Starting from ethyl 4-bromobenzoate, 4-bromobenzonitrile, and 2-bromobenzonitrile, the corresponding biaryls are obtained in 66, 76, and 61% vs ArX, respectively. The last yield increases when 2 equiv of iodo anisole is introduced in the medium (74%).

In the following series of experiments, we tried to apply this method to heteroaromatic halides. The results are reported in Table 3 and show that the method affords the formation of heteroarylzinc compounds such as bromothiophene. Unfortunately, results were disappointing with bromo pyridine, because all of the reactant ArX is converted into the reduction compound ArH. On the other hand, the thienylzinc bromide can be generated from bromothiophene.

Table 4. Formation of Dizinc Species from Dibromobenzenes

Entry	BrArBr	BrZnArZnBr	ArZnBr	BrZnAr-ArZnBr
		%	%	%
29		77	15	4
30		78	12	10
31		43	8	36
32		67	11	5

To our knowledge, there is no example of any direct versatile chemical synthesis of thienylzinc species from bromothiophene. 3-Thienyl organozinc reagents can be prepared by direct oxidative addition of active zinc to 3-iodothiophene.[13] However, 3-iodothiophene is rather difficult to prepare. A few years ago, we reported the first direct preparation of 3-thienylzinc bromide from 3-bromothiophene by a simple electrochemical method using nickel catalyst and the sacrificial anode process.[14]
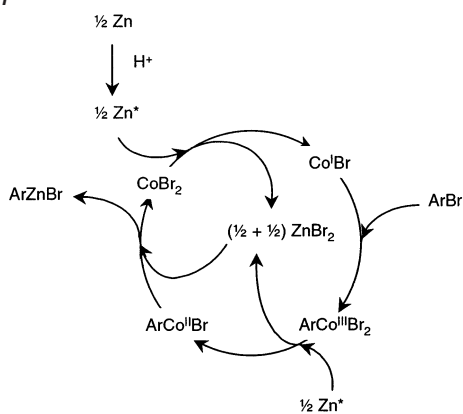
In the standard conditions described for aromatic bromides, the arylzinc species is obtained in 67 or 50% yield from 3- or 2-thienyl bromide, respectively. 3-Thienyl bromide is partially consumed, and 2-thienyl bromide, which is more reactive, gives a large amount of the reduction product. To increase these yields, 20% of CoCl$_2$ was used instead of the standard reaction condition (entries 26 and 28). These results are similar to those obtained previously using our electrochemical process, using more simple conditions. The 3-thienylzinc bromide can be coupled with aromatic halides in the same medium using the classical catalyst PdCl$_2$(PPh$_3$)$_2$. The coupling was found efficient with iodobenzene (70% isolated vs 3-thienyl bromide) or with ethyl 4-iodobenzoate (68% isolated vs 3-thienyl bromide), underlining the high efficiency of the thienylzinc bromide formation.

Therefore, this new method has also been applied to the formation of organodizinc compounds from aromatic or heteroaromatic dibromides. We have already described that these compounds can be synthesized using a cobalt catalysis by our electrochemical process in acetonitrile or DMF associated to pyridine.[15] These compounds are of interest in the preparation of π-conjugated alternating copolymers, which has already been carried out from electrochemically prepared aryldizinc species.[16] In Table 4, we have reported the results obtained with various aryl or heteroaryl dibromides.

The corresponding organozinc species were iodolyzed for GC titration of the resulting aryl diiodide using an internal standard (alcane). In all cases, the analysis of the solution showed the formation of a mixture of the desired organodizinc compound (BrZnArZnBr), the monoorganozinc corresponding to the reduction product (ArZnBr), and the organodizinc species of the dimer (BrZnAr–ArZnBr). The latter product was never observed by

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Scheme 1

electrosynthesis. The reaction conditions are the same as those described for the monozinc compounds, but the reaction time is longer, ca. 1h 30 min.

We observed that all carbon–bromine bonds are reactive, even those arising from the resulting dimer, which was not observed with the electrochemical method. However, yields are similar for the desired diorganozinc compound (BrZnArZnBr). This behavior was expected, considering the higher reaction rate in the chemical reaction, and is consistent with the fact that all of the products are converted into organozinc species. This discovery prompted us to apply this procedure to 2,5-dibromothiophene (Table 4, entry 32).

From a mechanistic point of view, we based our procedure on the mechanism described recently in the case of the electrochemical conversion of aryl halides to arylzinc compounds by cobalt catalysis in DMF/pyridine.[12] The catalytic cycle is initiated by the reduction of $CoBr_2$ by zinc dust, which needs to be activated previously by acid traces. The resulting Co^IBr undergoes an oxidative addition with aryl halides to afford the trivalent cobalt complex $ArCo^{III}Br_2$. That latter species is reduced into $ArCo^{II}Br$ by the excess of zinc dust. The cycle is completed by a transmetalation reaction between $ArCo^{II}Br$ and $ZnBr_2$ formed in the previous steps, leading to the arylzinc compound and regenerating divalent cobalt (Scheme 1).

In summary, we have established that readily available cobalt halide and zinc dust are convenient for the facile preparation of arylzinc species from the corresponding bromides in acetonitrile. This new and versatile process can be applied to the preparation of 3-thienylzinc bromide in a single operation from 3-bromothiophene. The efficient preparation of these organozinc compounds makes this new chemical method an excellent alternative to our electrochemical processes. The cobalt-catalyzed chemical conversion of aryl or thienyl bromides to arylzinc species generally gives excellent yields. The zinc dust acts as the reducing agent, providing the required zinc salt by reaction with the CoX_2. This chemical synthesis using a cobalt catalyst must now be extended to aryl chlorides, and the mechanism requires a thorough study to be clearly elucidated. Currently, studies of the reactivity of these organozinc species are in progress.

Experimental Section

GC analysis was carried out using a 25 m DB-1 capillary column. Mass spectra were recorded with an ITD spectrometer coupled to a gas chromatograph (DB1, 30 m). Column chromatography was performed on silica gel 60, 70–230 mesh. ^{1}H, ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz with TMS as an internal standard.

Unless indicated, all solvents and reagents were purchased and used without further purification. Acetonitrile was stored under argon.

Cobalt bromide and zinc bromide were used as obtained commercially.

General Procedure for the Preparation of Arylzinc Halide. A dried 100 mL three-necked flask is charged with acetonitrile (20 mL), cobalt bromide (330 mg, 1.5 mmol), zinc bromide (340 mg, 1.5 mmol), phenyl bromide (0.16 mL, 1.5 mmol), zinc dust (3.25 g, 50 mmol), and 50 μL of trifluoroacetic acid. The mixture is stirred at room temperature until PhBr is consumed (ca. 15 min). The functionalized aromatic bromide (15 mmol) is then added to the solution, and the reaction mixture is allowed to stir at room temperature. The formation of the arylzinc species is monitored by GC by addition of iodine and is run until whole consumption of the aromatic halide (ca. 30 min). The amount of the corresponding aryl iodide is measured by GC using an internal reference and compared with the commercial product. Some arylzinc species are directly used for the cross-coupling reactions with aryl iodide.

General Procedure for the Preparation of Thienylzinc Halide. A dried 100 mL three-necked flask is charged with acetonitrile (20 mL), cobalt bromide (660 mg, 3 mmol), zinc bromide (340 mg, 1.5 mmol), anisole bromide (0.2 mL, 1.5 mmol), zinc dust (3.25 g, 50 mmol), and 50 μL of trifluoroacetic acid. The mixture is stirred at room temperature until MeOPhBr is consumed (ca. 15 min). Thienyl bromide (15 mmol) is then added to the solution, and the reaction mixture is allowed to stir at room temperature. The formation of the thienylzinc species is monitored by GC by addition of iodine and is run until the bromothiophene was totally consumed (ca. 1 h). The thienyl iodides are measured by GC using an internal reference and are directly used for the cross-coupling reactions with aryl iodide.

General Procedure for Coupling with Phenyl Iodide. After consumption of the aryl bromide, aryl iodide (15 mmol, i.e., in a 1:1 ratio vs initial aryl bromide) and $PdCl_2(PPh_3)_2$ (110 mg, 0.15 mmol) are added at room temperature. The reaction is monitored by GC and is run until the consumption of aromatic zinc halide (ca. 2 h). The reactions are then quenched with 1 N HCl and extracted with diethyl ether (3 × 40 mL). The extracts are dried over $MgSO_4$, and the solvent is removed under reduced pressure. The product was isolated by silica gel column chromatography eluted with 95:5 or 90:10 pentane/diethyl ether.

The following compounds are identified by comparison of their physical and spectral data with those given in the cited references: 4-methoxy-biphenyl-4-carboxylic acid ethyl ester,[17a] 4-methoxy-biphenyl-4-carbonitrile,[17b] 4-methoxy-biphenyl-2-carbonitrile,[17a] and 3-phenylthiophene.[17c]

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