New Efficient Preparation of Functionalized Arylzinc or Thienylzinc Compounds from Aryl or Thienyl Chlorides Using Cobalt Catalysis

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Abstract: A new chemical method is described for the preparation of aryl or thienyl zinc intermediates from their corresponding aromatic or thienyl chlorides in a mixture of acetonitrile–pyridine, using cobalt catalysis. This procedure allows for the synthesis of a variety of functionalized arylzinc species from reactive arylchlorides or chlorothiophenes in good to excellent yields. Some of these arylzinc compounds have been coupled with aromatic bromides using palladium catalysis.

Key words: cobalt halide, catalysis, zinc, thiophenes, aromatic chlorides

The utility of arylzinc compounds in organic synthesis has been recognized for a long time. Their remarkable functional group tolerance allows the synthesis of functionalized cross-coupling products without the need for protecting groups. These polyfunctional zinc reagents can be readily prepared either by direct insertion of zinc¹ or by nucleophilic catalysis of the iodine-zinc exchange reaction from aryl iodides.² From aryl chlorides or bromides, the preparation of these organozinc species was formerly possible though transmetallation of organolithium³ or Grignard reagents⁴ using zinc halides. However, such a procedure could only be applied to compounds bearing reactive functional groups (CO, CN, COOR etc.), provided that the reaction was carried out at low temperature. This drawback was circumvented by synthesizing the organozinc species from aryl bromides using activated zinc (Rieke's zinc),⁵ but the difficulty of handling this reagent makes this procedure very sensitive to reaction conditions.

In our laboratory, several years ago, we successfully synthesized functionalized arylzinc compounds from aryl halides, bromides as well as chlorides, using simple electrochemical methods. These electrosynthetic methods involve a nickel⁶ or more recently a cobalt⁷ catalyst associated with the electroreduction of aromatic halides in an undivided cell using the sacrificial anode process under mild conditions. The use of cobalt allowed us to achieve both the synthesis of organozinc reagents using a wide variety of solvents and to use a less toxic catalyst than nickel. More recently, we have established that readily available cobalt halide and zinc dust are convenient for the facile chemical preparation of arylzinc species from the corresponding bromides or iodides in acetonitrile.⁸ This new and versatile process favourably compares with known chemical processes and could be applied to the preparation of 3-thienylzinc bromide in a single operation from 3-bromothiophene. However, the results obtained with aryl-chlorides were disappointing.

Here, we wish to report a new chemical reaction aimed at preparing aromatic zinc species from aromatic or thienyl chlorides. Aromatic chlorides are generally inexpensive and readily available substrates compared to the corresponding bromides and iodides.

In acetonitrile, the reduction of CoBr₂ leads to a Co(I) species which does not react with the C-Cl bond at room temperature. At 50 °C, ArCl is partially converted into ArZnCl; the entire starting compound does not react due to the disproportionation of Co(I). The effect upon addition of various ligands on the aryl chloride/arylzinc conversion has been examined in order to decrease the rate of disproportionation. In fact, some recent electrochemical studies have shown that the use of additives, such as vinyl acetate and methyl vinyl ketone, stabilize the electrogenerated Co(I) in acetonitrile-pyridine.9 Unfortunately, these ligands as well as adiponitrile do not stabilize Co(I) in acetonitrile. Nevertheless, the formation of chemical arylzinc compounds from aryl chlorides was successful using CoBr₂ in a mixture of acetonitrile-pyridine as described in our electrochemical process (just aryl bromide or iodide could react in acetonitrile). The presence of pyridine is required to avoid the fast disproportionation of Co(I) and allow its oxidative addition into the C–Cl bond. Under these conditions (in the presence of pyridine), yields are higher at room temperature or at 50 °C than in pure acetonitrile even at 50 °C. These yields and the consumption of ArCl depend on the amount of pyridine. It has been shown that an acetonitrile-pyridine ratio of 12:8 has given the best yields. In these conditions, yields of ArZnCl depend on the amount of catalyst, the reaction temperature and solvents. The study was performed with p-CNC₆H₄Cl (Equation 1, Table 1).

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$$\begin{array}{c} \text{CoBr}_2 + \text{Zn} \\ (0.1 \text{ equiv}) + (3 \text{ equiv}) \end{array} \xrightarrow{1) \text{AllyICI (0.3 equiv), MeCN, CF}_3CO_2H, r.t., 3 \text{ min}} \\ \hline 2) \text{ py, CoBr}_2 (0.03 \text{ or } 0.23 \text{ equiv}), T \text{ °C}, \\ \hline NC - CI \quad (1 \text{ equiv}) \end{array}$$

Equation 1

Table 1 Influence of Various Parameters on the Formation of p-CNC₄H₆ZnCl

Entry	Solvent (12:8)	Amount of CoBr_2 (mol%)	Temperature	Reaction time (h)	GC yield of ArZnCl (%)
1	CH ₃ CN–Pyridine	13	r.t.	23	78
2	CH ₃ CN–Pyridine	13	50 °C	6	54 (ArH = 35)
3	CH ₃ CN–Pyridine	33	r.t.	4	82
4	CH ₃ CN–Pyridine	33	50 °C	2	60 (ArAr = 20)
5	DMF-Pyridine	33	r.t.	24	traces

Reaction times depend both on the amount of CoBr_2 and temperature. At the same temperature, an increased of amount of CoBr_2 decreases the reaction time (Table 1, entries 1 and 3 or entries 2 and 4) and results in a slight improvement in the yields. Increasing the temperature decreases the reaction time but lower yields are obtained. Acetonitrile was also replaced by DMF, however, only traces of the corresponding arylzinc species are observed after 24 hours at room temperature (Table 1, entry 5). This was not surprising considering that reduction of CoBr_2 in acetonitrile–pyridine led to a Co(I) species about twice as stable as in DMF–pyridine.⁹ As a consequence, the rate of disproportionation of Co(I) as well as the rate constant between the electrogenerated Co(I) and aryl halides were lower. Therefore, reactions are carried out in acetonitrile– pyridine from various functionalized aryl chlorides with 33 mol% of CoBr₂ at room temperature, in order to ensure moderate reaction rates and to improve the yields (Equation 2, Table 2).

Arylzinc chlorides are readily prepared by the reaction of aryl chlorides with commercially available zinc dust activated by traces of acid (CF₃COOH) in the presence of

$$\begin{array}{c} \text{CoBr}_2 \\ (0.1 \text{ equiv}) \end{array} + \begin{array}{c} \text{Zn} \\ (3 \text{ equiv}) \end{array} \end{array} \underbrace{\begin{array}{c} 1) \text{ AllyICI (0.3 equiv), MeCN, CF_3CO_2H, r.t., 3 min}}_{2) \text{ py, CoBr}_2 (0.23 \text{ equiv), r.t.,}} FG (1 \text{ equiv}) \end{array} }_{CI} FG (1 \text{ equiv}) \\ \end{array}$$

Equation 2

 Table 2
 Formation of Organozinc Species from Functionalized Aryl Chlorides

Entry	FG-C ₆ H ₄ Cl FG	ArZnCl (%)	ArCl recovered (%)	Reaction time (h)	ArH	ArAr
1	Н	95	0	22	5	0
2	<i>p</i> -MeO	45	0	31	55	0
3	<i>p</i> -CN	82	0	4	11	7
4	<i>m</i> -CN	78	0	5	13	9
5	o-CN	84	0	2	16	0
6	<i>p</i> -CF ₃	69	0	23	17	7
7	<i>p</i> -MeCO	75	0	4	18	7
8	o-MeCO	0	0	4	13	87
9	<i>p</i> -MeCO ₂	81	0	4	14	5
10	<i>p</i> -MeSO ₂	91	0	4	9	0

 $CoBr_2$ (0.33 equiv) in acetonitrile–pyridine at room temperature. As described in our previous work, addition of allyl chloride in a preliminary step makes the introduction of hydroscopic ZnBr₂ unnecessary, Zn²⁺ salts being generated in situ in this preliminary step. The resulting organozinc species are converted into aromatic iodide by the addition of iodine. The amount of aromatic iodide is measured by GC using an internal reference (alkane).

This new method generally gives the expected organozinc species in good to excellent yields with aryl chlorides substituted by an electron-withdrawing group (Table 2, entries 3, 4, 5, 6, 7, 9, 10). Even with unactivated chlorobenzene derivatives the corresponding organozinc compound is detected, which is contrary to our electrochemical methods (Table 2, entries 1-2); however, the reaction times are increased. This indicates that Co(I) reacts too slowly with unactivated chlorobenzene derivatives under these conditions. Moreover, no organozinc compound is detected with o-chloroacetophenone (Table 2, entry 8), surprisingly, o-chloroacetophenone resulted in a dimerized adduct. The complexation of cobalt with the carbonyl group should avoid the transmetallation reaction. With other reagents, it can be pointed out that the position of the substituent has again a slight influence on the yields as revealed in Table 2 (entries 3–5). However, the reaction rate decreases when a substituent is placed at the ortho-position. This method also allows for the formation of arylzinc species from aryl bromides in the same yields as obtained in pure acetonitrile. Unfortunately the reaction time increases; for instance, ethyl *p*-bromobenzoate gives 80% yield of the corresponding arylzinc in 15 minutes in acetonitrile whereas 81% yield of ArZnBr is obtained in three hours in a mixture of acetonitrile-pyridine.

Some aromatic organozinc species mentioned in Table 2 have been cross-coupled with different activated aryl bromides (1 equiv vs. ArCl) in the presence of a catalytic amount of PdCl₂(PPh₃)₂. The organozinc species obtained from methyl p-chlorobenzoate (Table 2, entry 9) was coupled with *p*-bromobenzonitrile at room temperature in 77% yield. Conversely, the coupling between p-CN-PhZnCl (Table 2, entry 3) and ethyl p-bromobenzoate gave only a 25% yield under the same conditions. In fact, the organozinc species from *p*-ethyl bromobenzoate was formed. On the other hand, a 48% yield of coupled product was isolated from o-CNPhZnCl (Table 2, entry 5) and ethyl p-bromobenzoate. In conclusion, the amount of coupling product depends on the nature of the arylzinc chloride and in some cases, this coupling could be quantitative. Some studies are in progress to achieve the cross-coupling of such arylzinc compounds with various aromatic halides.

In the following series of experiments, we tried to apply the standard method described for aromatic chlorides to chlorothiophenes (Equation 3).

The results concerning chlorothiophenes are reported in Table 3 and show that the preceding method affords organozinc species in good to excellent yields (Table 3, entries 1, 3). Chlorothiophenes were reactive towards Co(I) at room temperature but the reaction is particularly long especially with 3-chlorothiophene. In fact, this last compound is less reactive than 2-chlorothiophene. However to improve the reaction times, the medium was heated at 50 °C. Under these conditions, yields were good to excellent (Table 3, entries 2, 4).

In order to confirm our estimated yields of thienylzinc species, we have coupled these compounds with ethyl *p*-

Equation 3

 Table 3
 Formation of Organozinc Species from Chlorothiophenes

Entry	Chlorothiophene	Temperature	Reaction time (h)	ThiopheneZnCl	Cl-Thiophene recovered (%)
1	CI	r.t.	7	80	0
2	CI	50 °C	2	88	0
3	S Cl	r.t.	24	67	5
4		50 °C	4	80	0

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bromobenzoate using $PdCl_2(PPh_3)_2$ as catalyst. Starting from 2- or 3-thienylchloride, the corresponding biaryls are obtained in 74% yield in the two cases when the corresponding thienylzinc species are prepared at 50 °C (Table 3, entries 2, 4).

To our knowledge, there is no example of any direct versatile chemical synthesis of thienylzinc compounds from chlorothiophenes.

These results show that this new chemical method gives the expected organozinc species in good yields from aryl or thienyl chlorides. With chloropyridines, the corresponding zinc species have unfortunately been obtained in only low yields up to now. Some studies are still in progress to extend the process to these compounds.

In conclusion, we have established that cobalt(II) bromide associated with pyridine can be used for the simple, highyielding preparation of a broad range of functionalized aryl or thienyl zinc species starting from readily available corresponding chlorides, these species being so far obtained by transmetallation.

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References

- (1) Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. J. Org. Chem. 2003, 68, 2195.
- (2) Kneisel, F. F.; Dochnahl, M.; Knochel, P. Angew. Chem. Int. Ed. 2004, 43, 1017.
- (3) Tucker, C. E.; Majid, T. N.; Knochel, P. J. Am. Chem. Soc. 1992, 114, 3983.
- (4) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
- (5) (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. J. Org. Chem. 1991, 56, 1445. (b) Rieke, R. D. Aldrichimica Acta 2000, 33, 52.
- (6) (a) Sibille, S.; Ratovelomanana, V.; Périchon, J. J. Chem. Soc., Chem. Commun. 1992, 283. (b) Gosmini, C.; Nédélec, J.-Y.; Périchon, J. Tetrahedron Lett. 1997, 38, 1941.
- (7) (a) Gosmini, C.; Rollin, Y.; Nédélec, J.-Y.; Périchon, J. J. Org. Chem. 2000, 65, 6024. (b) Fillon, H.; Gosmini, C.; Nédélec, J.-Y.; Périchon, J. Tetrahedron Lett. 2001, 42, 3843. (c) Fillon, H.; Le Gall, E.; Gosmini, C.; Périchon, J. Tetrahedron Lett. 2002, 43, 5941.
- (8) (a) Fillon, H.; Gosmini, C.; Périchon, J. J. Am. Chem. Soc.
 2003, 125, 3867. (b) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. Tetrahedron Lett. 2003, 44, 6417.
- (9) Buriez, O.; Nédélec, J.-Y.; Périchon, J. J. Electroanal. Chem. 2001, 506, 162.