A convenient method for the preparation of aromatic ketones from acyl chlorides and arylzinc bromides using a cobalt catalysis

Hyacinthe Fillon, Corinne Gosmini* and Jacques Périchon

Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582, Université Paris 12-C.N.R.S, 2, Rue Henri Dunant, F-94320 Thiais, France

Abstract—Aromatic ketones are synthesized efficiently via cobalt catalyzed cross-coupling reaction between arylzinc bromides and acid chlorides. Arylzinc bromides prepared chemically via a cobalt catalysis undergo coupling without additional catalyst unlike their electrochemical analogs.
© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

Many synthetic methods have been developed for the synthesis of aromatic ketones which are important building blocks included in a large number of natural products and active pharmaceutical ingredients. The reaction of acid chlorides with organometallic reagents provides a direct and convenient method for the synthesis of ketones.[1] Although a variety of alkali, alkaline earths, transition metal and main group organometallic reagents react with acid chlorides to give ketones, the most useful synthetic methods generally utilize organocopper reagents or palladium catalyzed routes. In most cases, the organocopper species arise from the reaction of an organolithium or Grignard reagents with an appropriate copper (I) salt.[2] This approach exhibits severe restrictions toward the type of functional groups, except in the case of low temperature iodine magnesium or bromide–lithium exchange reaction.[3] Alternatively, this drawback can be overcome by using a higher reactive zerovalent copper that undergoes fast oxidative addition on the aryl halide.[4] Despite its indisputable synthetic utility, the use of such activated Rieke metal powders requires specific conditions together with careful handling.[5] In the same way, highly reactive manganese prepared by Rieke's method reacts with 3-bromothiophene to yield the corresponding organomanganese reagent.[6] These compounds are very interesting since they can be used to perform various useful synthetic reactions notably acylation without involving any additive. More recently, functionalized organomanganese have also been one-pot synthesized according to a two step procedure, involving halogene–lithium exchange at low temperature followed by lithium-manganese transmetallation[7] and coupling with acyl chlorides with a catalytic amount of CuCl.

Functionalized organozinc species can be transmetalled into organocopper reagents in order to react with acid chlorides.[8] However, like organostannanes[9] and arylboronic acids,[10] arylzinc compounds can also be acylated to produce ketones if the reaction is catalyzed by palladium[11] complexes.

In the past few years, we have successfully synthetized arylzinc compounds from aryl bromides by an electrochemical method using a simple catalytic system involving cobalt halide in acetonitrile as solvent. In a second step, these compounds undergo coupling, with acetyl chloride in quantitative yields using a palladium catalyst (Eq. (1)).[12]

$$(1)$$
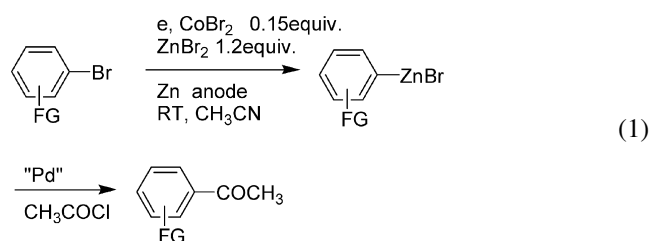
In this paper, we report our investigations on the cobalt-catalyzed coupling reaction of arylzinc compounds with acid chlorides, leading to aromatic ketones in acetonitrile. Indeed, cobalt halides have also been employed as catalyst in the acylation of dialkylzinc reagents by Knochel at 0°C in THF-NMP.[13]

2. Results and discussion

Several new approaches have been developed depending on the preparation of arylzinc species leading to aromatic ketones.

2.1. Coupling of acyl chlorides with electrosynthetized arylzinc compounds using a cobalt catalysis in acetonitrile

A previous report from our laboratory has shown that arylzinc species formed by our electrochemical method could not be activated using a mixture of cuprous cyanide and lithium chloride to form aromatic ketones. In fact, these assays led quantitatively upon work up to the hydro-dehalogenation product (ArH). Therefore, we tried to achieve the coupling reaction between electrogenerated organozinc species and acid chlorides using a cobalt halide as catalyst (Eq. (2)).

$$(2)$$
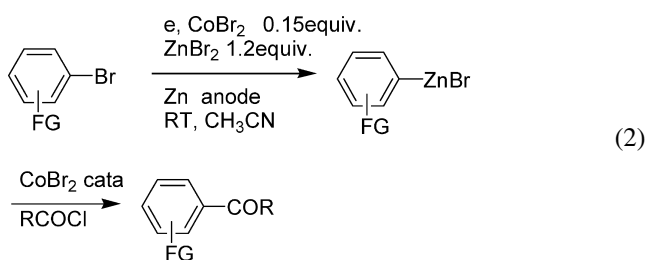
All reactions are carried out in an undivided cell already described[14] fitted with a consumable zinc anode and a stainless steel cathode. The ionic conductivity of the medium is ensured by addition of NBu_4BF_4 as supporting electrolyte. Electrolyses are run at constant current intensity of 0.2 A (0.01 A/cm^2), at room temperature and under inert atmosphere of argon. The consumption of ArX is monitored by GC analysis. Electrolyses are stopped after total consumption of ArX. Then, 0.13 equiv. of $CoCl_2$ and 1 equiv. of RCOCl vs ArX are introduced into the medium at room temperature. The solution is stirred until total consumption of the organozinc compound and formation of the aromatic ketone.

The use of a supplementary amount of cobalt catalyst (0.05 equiv. vs ArX) is sufficient to consume all the starting products in the acylation step. In this case, the reaction is slower than with 0.13 equiv. of catalyst. $CoBr_2$ could replace $CoCl_2$. Acylation of the electrochemically prepared arylzinc species does not occurs in the absence of CoX_2 added in the second step. Results are reported in Table 1.

The yields are moderate to excellent, ranging from 33 to 93%. The overall yields vs initial aromatic bromides are moderate to good (26–77%). These yields decrease when the substituent is in *ortho* position (Table 1, entries 3 and 12). Moreover, an electron-donating or withdrawing group on the aryl bromide does not affect the yield in the coupling reaction. No further optimization of that process has been undertaken, since pure chemical conditions afford the coupling product without supplementary cobalt catalyst, as described in the next paragraph.

Table 1. Coupling of electrochemical aryl zinc compound with acid chlorides


Entry	FG	RCOCl	Yield^a (isolated yield^b)
1	H	MeCOCl	74 (40) [1]
2	*p*-MeO	MeCOCl	87 (68) [2]
3	*o*-MeO	MeCOCl	87 (58) [3]
4	*p*-Me	MeCOCl	69 (51) [4]
5	*p*-EtOCO	MeCOCl	73 (55) [5]
6	*m*-CF$_3$	MeCOCl	67 (60) [6]
7	*p*-Cl	MeCOCl	63 (48) [7]
8	*p*-F	MeCOCl	93 (40) [8]
9	*p*-MeCO	MeCOCl	42 (30) [9]
10	*p*-CN	MeCOCl	69 (58) [10]
11	*m*-CN	MeCOCl	84 (67) [11]
12	*o*-CN	MeCOCl	33(26) [12]
13	*p*-CN	PhCOCl	90 (77) [13]
14	*m*-CN	PhCOCl	49 (39) [14]
15	*p*-EtOCO	PhCOCl	66 (50) [15]

^{a} Yields calculated with respect to ArZnBr (titrated by quenching with I_2).
^{b} Isolated yields obtained for the 2 steps reported with respect to ArBr.

2.2. Coupling of acyl chlorides with aryl zinc compound formed by our chemical process using a cobalt catalysis in acetonitrile

Recently, we have reported a new simple chemical method for the preparation of arylzinc intermediates based on the activation of aryl bromides by low-valent cobalt species arising from the reduction of cobalt (II) halides by zinc dust[15] in acetonitrile as solvent. The versatility and the simplicity of that original method represent an alternative to most known procedures. Moreover, the chemical formation of these aryl zinc compounds proceeds faster than in the case of the electrochemical preparation (Eq. (3)). In these conditions, a supplementary catalyst is not necessary to form the corresponding aromatic ketone. Cobalt (I) produced in the medium, was found effective to catalyze the acylation reaction (Eq. (3)).
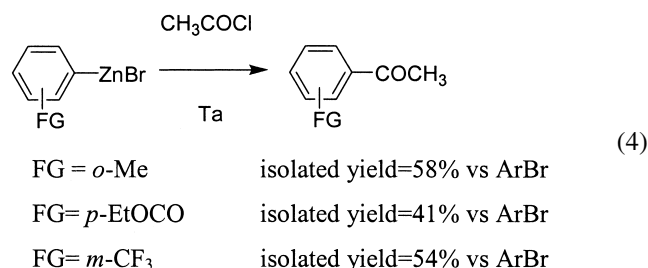

$$(3)$$
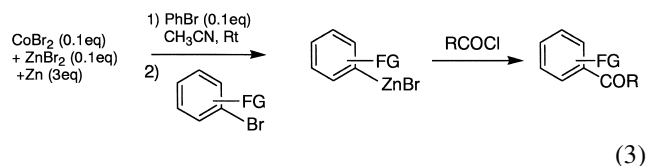
The mechanism of the reaction can be explained from a catalytic sequence already proposed for other metals:[1] oxidative addition of RCOCl to a Co(I) complex formed in the previous step (formation of the arylzinc species) provides RCOCo(III)Cl. Reaction between this acyl cobalt complex and the arylzinc reagent, followed by reductive elimination, affords the expected ketone and regenerates the Co(I) species (Scheme 1).

On the contrary to the acylation of aryl zinc bromides formed by our electrochemical method, no supplementary cobalt catalyst was necessary (Eq. (4)). The rate of the chemical formation of the arylzinc species is faster than the analog electrochemical reaction (20–30 min in comparison with 2 h 30 min). So, the low-valent Co(I) species, which is
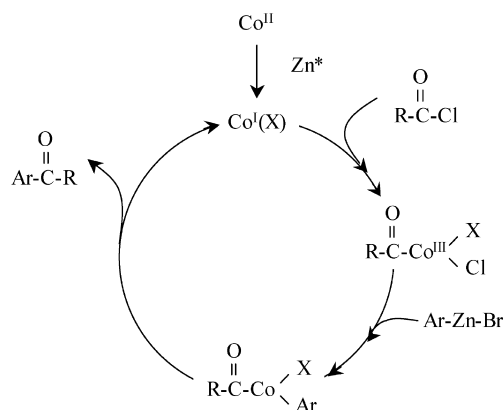
Scheme 1.

necessary for the coupling reaction with acyl chloride, is present in the medium and most likely evolves into a cobalt (III) carbonyl intermediate. In fact, disproportionation of Co(I) occurs in the case of the electrochemical reaction considering the reaction is very slower.

(4)

FG = o-Me   isolated yield=58% vs ArBr

FG= p-EtOCO   isolated yield=41% vs ArBr

FG= m-CF$_3$ isolated yield=54% vs ArBr

These yields in ketone are good but can be improved by adding a catalytic amount of CoBr$_2$ (10% vs ArBr).

In a typical experiment, the suitable acyl chloride (1–1.9 equiv. vs ArBr) and CoBr$_2$ (0.1 equiv. vs ArBr) were added into the solution of the arylzinc reagent formed via a cobalt catalysis in the same solvent at room temperature. After hydrolysis with aqueous HCl, the organic layers, extracted with diethyl ether, give the crude product in good chemical yield. The yields of the corresponding ketone obtained are even higher than those obtained using electrochemically prepared aryl zinc compounds. The preparation of various functionalized ketones is reported in Table 2.

3. Conclusion

We have developed a new cobalt-catalyzed two components cross-coupling reaction between arylzinc species and acyl chlorides. As observed for the palladium catalyzed cross-coupling reaction, cobalt salts also catalyze the cross coupling reaction between an arylzinc species and acyl chlorides. Acylation proceeds in short reaction times (30 min to convert 15 mmol of ArZnBr) and gives good yields in aromatic ketones. Although the yields are increased in the presence of 0.1 equiv. CoBr$_2$, additional cobalt is not necessary to obtain the ketone in good yields when arylzinc species are prepared by the chemical process.

Table 2. Coupling of chemically prepared aryl zinc compound with acid chlorides

Entry	FG	RCOCl	Yield[a] (isolated yield[b])
16	m-MeO	MeCOCl	87 (61) [**16**]
17	o-MeO	MeCOCl	74 (64) [**3**]
18	p-Me	MeCOCl	66 (47) [**4**]
19	p-EtOCO	MeCOCl	83 (63) [**5**]
20	m-CF$_3$	MeCOCl	98 (80) [**6**]
21	p-Cl	MeCOCl	72 (64) [**7**]
22	p-F	MeCOCl	93 (65) [**8**]
23	p-CN	MeCOCl	71 (67) [**10**]
24	m-CN	MeCOCl	66 (63) [**11**]
26	p-CN	C$_8$H$_{17}$COCl	60 (57) [**17**]
27	m-CN	PhCOCl	51(48) [**14**]

[a] Yields calculated with respect to ArZnBr (titrated by quenching with I$_2$).
[b] Isolated yields obtained for the 2 steps reported with respect to ArBr.

4. Experimental

GC analysis was carried out using a 25 m DB1 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 and ^{19}F spectra were recorded in CDCl$_3$ at 200 MHz with TMS as an internal standard.

The electrochemical cell was similar to that described previously.[12] All solvents and reagents were purchased and used without further purification. Acetonitrile was stored under argon.

4.1. General procedure

1-Coupling of aryl zinc compounds formed electrochemically using a cobalt catalysis in pure acetonitrile with acid chlorides. 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) containing 7.5 mmol of ArX (0.16 M), 1 mmol of CoCl$_2$ (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 2F per mole of ArX. The yields of organozinc compounds thus obtained were estimated as follows: samples of the electrolysis solutions were iodinated, then hydrolyzed with sodium thiosulfate and extracted with diethyl ether. Amounts of iodinated compounds were compared to the amounts of starting phenyl bromides via an internal standard by gas chromatography. Then, 1 mmol of CoCl$_2$ and 7.5–14 mmol of RCOCl vs ArX were introduced into the medium at room temperature. The solution was stirred until total consumption of the organozinc compound. The reaction mixture was poured into a solution of 2 M HCl (50 mL) and extracted with diethyl ether (2×25 mL). The combined extracts were dried over MgSO$_4$. Evaporation of ether and purification by column chromatography on silica gel (pentane/ether, 9/1) afforded the aromatic ketones and were characterized by NMR (^{1}H, ^{13}C, ^{19}F) and mass spectrometry.

2-Coupling of aryl zinc compound formed by our chemical process using a cobalt catalysis in pure acetonitrile with acid chlorides. A dried 100 mL three-necked flask is charged with acetonitrile (20 mL), cobalt bromide (1.5 mmol), zinc bromide (1.5 mmol), phenyl bromide (1.5 mmol), zinc dust (50 mmol), 50 μl of trifluoroacetic acid. The mixture is stirred at room temperature until PhBr is consumed (ca. 15 min). Then the functionalized aromatic bromide (15 mmol) is added to the solution and the reactions 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. Then, $CoCl_2$ (1.5 mmol) and acyl chloride (15–20 mmol) were introduced into the medium at room temperature. The solution was stirred until total consumption of the organozinc compound. The reaction mixture was poured into a solution of 2 M HCl (50 mL) and extracted with diethyl ether (2×25 mL). The combined extracts were dried over $MgSO_4$. Evaporation of ether and purification by column chromatography on silica gel (pentane/ether, 9/1) afforded the aromatic ketones and were characterized by NMR (^1H, ^{13}C, ^{19}F) and mass spectrometry.

4.1.1. Registry numbers (provided by the authors) or references. 1-Phenyl-ethanone (**1**), 98-86-2; 1-(4-methoxy-phenyl)-ethanone (**2**), 100-06-1; 1-(2-methoxy-phenyl)-ethanone (**3**), 579-74-8; 1-(4-methyl-phenyl)-ethanone (**4**), 122-00-9; 4-acetyl-benzoic acid ethyl ester (**5**), 38430-55-6; 1-(3-trifluoromethyl-phenyl)-ethanone (**6**); 349-76-8; 1-(4-chloro-phenyl)-ethanone (**7**), 99-91-2; 1-(4-fluoro-phenyl)-ethanone (**8**), 403-42-9; 1-(4-acetyl-phenyl)-ethanone (**9**), 1009-61-6; 1-(4-cyano-phenyl)-ethanone (**10**);1443-80-7; 1-(3-cyano-phenyl)-ethanone (**11**), 6136-68-1; 1-(2-cyano-phenyl)-ethanone (**12**), 91054-33-0; 4-benzoyl-benzonitrile (**13**), 1503-49-7; 3-benzoyl-benzonitrile (**14**), 6136-62-5; 4-benzoyl-benzoic acid ethyl ester (**15**), 15165-27-2; 1-(3-methoxy-phenyl)-ethanone (**16**),586-37-8; 4-nonanoyl-benzonitrile (**17**), 1279928-59-0.

References

1. Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177–4236.
2. Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4414.
3. Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253.
4. Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 4482.
5. Rieke, R. D. *Aldrichimica Acta* **2000**, *33*, 52.
6. Kim, S.-H.; Hanson, M. V.; Rieke, R. D. *Tetrahedron Lett.* **1996**, *37*, 2197.
7. Klement, I.; Stadtmüller, H.; Knochel, P.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 1927.
8. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
9. Arukwe, J.; Undheim, K. *Acta Chem. Scand.* **1991**, *45*, 914.
10. Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109. Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057.
11. Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288. Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
12. Fillon, H.; Le Gall, E.; Gosmini, C.; Périchon, J. *Tetrahedron Lett.* **2002**, *43*, 5941.
13. Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700.
14. Chaussard, J.; Folest, J.-C.; Nédelec, J.-Y.; Périchon, J.; Sibille, S.; Troupel, M. *Synthesis* **1990**, *5*, 369–381.
15. (a) Fillon, H.; Gosmini, C.; Périchon, J. Patent application no 01/08880, July 4, 2001. Fillon, H.; Gosmini, C.; Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870.