Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6417–6420

TETRAHEDRON
LETTERS

New progress in the cobalt-catalysed synthesis of aromatic organozinc compounds by reduction of aromatic halides by zinc dust

Igor Kazmierski,[a] Corinne Gosmini,[a,*] Jean-Marc Paris[b] and Jacques Périchon[a]

[a]*Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582, Université Paris XII-CNRS, 2, Rue Henri Dunant, 94320 Thiais, France*
[b]*Rhodia, Research Center of Lyon, 85, rue des Frères Perret, BP 62, 69192 Saint-Fons Cedex, France*

Received 27 May 2003; revised 26 June 2003; accepted 26 June 2003

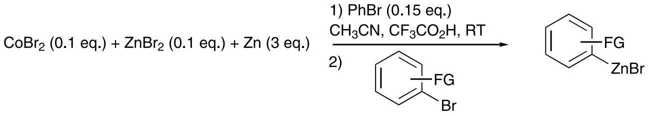
Abstract—The experimental conditions of the cobalt-catalysed synthesis of aromatic organozinc species from the corresponding bromides have been optimised. The preparation of numerous aromatic organozinc reagents under these optimised conditions is reported, with yields between 67 and 99%.

Organozinc species, especially in the aromatic series, are useful reagents for the synthesis of polyfunctional compounds when used in conjunction with the proper transition-metal catalyst, because of their broad spectrum of tolerated functional groups.[1] However, their preparation from aromatic halides requires mild methods when the aromatic ring bears sensitive functions, among which nitriles, ketones or esters. These methods are based on the use of an activated zinc as the reducing agent. Whereas aryl iodides can readily react with zinc dust in polar[2] or ethereal[3] solvents, the conversion of the less reactive aryl bromides to their organozinc counterparts must be realised with a more active zinc, prepared by the reduction of zinc(II) halides by naphtalene/lithium (the Rieke zinc[4]). Still another method has recently been described by Knochel and co-workers:[5] the aromatic organozinc species is prepared by a metal–halogen exchange between an aryl bromide and isopropylmagnesium chloride, subsequently forming the organozinc species by transmetallation with a zinc(II) halide, at low temperature.

Research in our laboratory has focused in the past few years on electrochemical methods of synthesis of organozinc species from aromatic bromides or chlorides, catalysed either by nickel complexes in dimethylformamide,[6] or less harmful and cheaper cobalt halides in DMF–pyridine or acetonitrile–pyridine mixtures.[7] Moreover, a process using pure acetonitrile as solvent and cobalt(II) bromide as catalyst has been developed, permitting the efficient electrosynthesis of organozinc species from aryl bromides.[8]

These last electrochemical processes have enabled the discovery of an easy, reproducible chemical synthesis of aromatic organozinc compounds from functionalised aryl bromides or iodides (Ar–X).[9] These aromatic halides are reduced in pure acetonitrile by zinc dust activated by a small quantity of trifluoroacetic acid, in the presence of a cobalt(II) halide as catalyst. In the same study, it has been evidenced that proportions of by-products Ar–H and Ar–Ar can be significatively reduced when, in a 'pre-treatment' preliminary step, a catalytic quantity of bromobenzene as an additive reacts with the activated zinc dust and the cobalt(II) catalyst (Scheme 1).

The current work is devoted to the optimisation of this reaction, including investigation of the effect of other halides than bromobenzene in the preliminary step in



Scheme 1. Chemical synthesis of functionalised organozinc species (Ref. 9).

---

* Corresponding author. Fax: +33-(0)1-4978-1148; e-mail: gosmini@glvt-cnrs.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01595-8

order to further reduce the proportion of by-products, concentration of catalyst, quantity of zinc dust and the effect of the presence of zinc(II) halide.

Results and discussion

The reactions have been carried out using the procedure described earlier[9] and *p*-bromoanisole as test-compound. The results of the optimisation of the reaction are reported in Table 1.

The effect of the additive has been checked out by comparing preliminary steps with (entry 2) and without PhBr (entry 1). Indeed, using an additive decreases the quantity of the reduction by-product ArH, PhBr being converted to PhH. However, as previously reported,[9] with a higher proportion of PhBr the reaction tends to slow down and a significative amount of PhZnBr is formed. It thus occured to us that PhBr was not reactive enough to act as an additive, and that the by-products of the preliminary step could disturb further coupling reactions. Other additives, such as benzyl chloride, α-chloroacetyl propionate and allyl bromide or chloride have consequently been tried. Among these, allyl chloride has proved to be the most interesting in terms of reactivity and by-products, being fully converted into propene, 1,5-hexadiene and the addition product of allylzinc species on acetonitrile,[10] all of those compounds being easily separated from aromatic or heteroaromatic coupling products. The result is that organozinc synthesis using AllylCl (entry 3) proceeds faster and with a slightly better yield than with PhBr. It is also possible to increase the proportion of AllylCl (entry 4) and thus to further increase the yield of the reaction, diminishing the total of by-products to less than ten percent of the final yield.

Another worry was the addition of zinc(II) bromide, which is a very hygroscopic salt and can therefore increase the ArH yield. However, addition of this salt was found necessary to the reaction.[9] As it has already been pointed out, the organic halide used as the additive presumably reacts in our medium following the same sequence as the aryl bromide. The probable reaction mechanism, as it has been described earlier,[9] is shown in Scheme 2.

Zn(II) salts are formed in situ by the oxydation of zinc dust, and are afterwards engaged in the transmetallation reaction with the organocobalt(II) species. In the case of allyl chloride, the allylzinc species readily reacts with the solvent, thus liberating zinc(II) ions. Our hypothesis therefore was that with 0.3 equiv. of AllylCl, no further addition of $ZnBr_2$ is necessary. This was verified (entry 5) as results are very similar whether $ZnBr_2$ is used or not.

We then wondered if a preliminary step of 30 min was needed when using AllylCl as the additive, as it is more reactive than PhBr. After checking that the one-step reaction (entry 6) results in a slightly worse yield and more by-products, different lengths were tried (entries 7 and 8). It appeared that a 5 min preliminary step (entry 7) was sufficient in order to obtain high yields and reasonable by-product proportions. The next step was to try and reduce the proportion of the cobalt catalyst,

Table 1. Optimisation of the reaction with 4-bromoanisole (GC yields)

Entry	Additive (equiv.)	Prel. step (min)	Zn (equiv.)	$CoBr_2$ (equiv.)	$ZnBr_2$ (equiv.)	Reaction time (min)	ArZnBr (%)[a]	ArH (%)	ArAr (%)	Conv. (%)
1	–	30	3	0.1	0.1	15	73	26	1	100
2	PhBr 0.15	30	3	0.1	0.1	20	78	16	5	100
3	AllylCl 0.15	30	3	0.1	0.1	15	83	9	8	100
4	AllylCl 0.3	30	3	0.1	0.1	20	91	7	2	100
5	AllylCl 0.3	30	3	0.1	–	25	91	6	3	100
6	AllylCl 0.3	0	3	0.1	–	10	86	4	10	100
7	AllylCl 0.3	5	3	0.1	–	14	89	6	6	100
8	AllylCl 0.3	20	3	0.1	–	25	88	8	4	100
9	AllylCl 0.3	5	3	0.05	–	4	83	12	5	100
10	AllylCl 0.15	5	3	0.05	–	25	89	7	3	99
11	AllylCl 0.15	5	1.5	0.05	–	60	83	13	4	100
12[b]	AllylCl 0.15	5	1.5	0.05	–	40	89	5	6	100

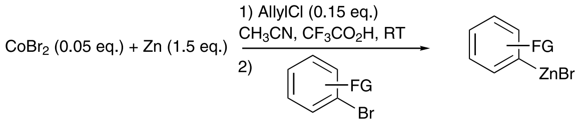
[a] The obtained arylzinc halides are converted into the corresponding aryl iodide by addition of iodine.

[b] Conc. of ArBr = 1 M.

$$(1)\ Co^{II}Br_2 + \tfrac{1}{2}\,Zn \longrightarrow Co^{I}Br + \tfrac{1}{2}\,Zn^{II}Br_2 \qquad (3)\ Ar\text{-}Co^{III}\text{-}Br_2 + \tfrac{1}{2}\,Zn \longrightarrow Ar\text{-}Co^{II}\text{-}Br + \tfrac{1}{2}\,Zn^{II}Br_2$$

$$(2)\ Co^{I}Br + Ar\text{-}Br \longrightarrow Ar\text{-}Co^{III}\text{-}Br_2 \qquad (4)\ Ar\text{-}Co^{II}\text{-}Br + Zn^{II}Br_2 \longrightarrow Ar\text{-}Zn^{II}\text{-}Br + Co^{II}Br_2$$

Scheme 2. Supposed reaction sequence of the synthesis of organozinc species from aryl bromides (Ref. 9).



Scheme 3. Chemical synthesis of functionalised organozinc species with optimised conditions.

but when using 5% of $CoBr_2$ instead of 10% (entry 9), the reaction was considerably slowed down. Consequently, the proportion of AllylCl was adapted to that of the cobalt catalyst by bringing it to 3 equiv. versus $CoBr_2$ (entry 10), and the reaction then proceeded smoothly, and surprisingly nearly as fast as with 10% $CoBr_2$.

The last step was to diminish the proportion of zinc dust, as it was used in large excess versus aryl bromide. It was also decided that this proportion would be based upon the total quantity of halogenated compounds (aryl bromide and allyl chloride), as it would permit further modification of the proportion of $CoBr_2$ and/or AllylCl while always keeping the same amount of zinc dust for the formation of the organozinc species. After a few attempts, it was found that the minimal proportion of zinc that can be used is 1.3 equiv. versus the total quantity of halogenated compounds, which amounts, in the case of entry 11, to 1.5 equiv. versus aryl bromide. It is supposed that the 0.3 overstoichiometric equivalents of zinc dust are the part which cannot be activated by our method. The reaction still proceeded with a good yield, but slower than in the case of 3 equiv. of zinc dust. This prompted us to try and work at a somewhat higher concentration of aryl bromide, switching from 0.75 to 1 M (entry 12). In these conditions, both the rate of the reaction and the yield in ArZnBr were satisfying.

The reaction conditions of entry 12 were consequently applied to various aromatic bromides bearing a wide array of functional groups (Scheme 3). Results are reported in Table 2.

It is of interest to notice that in the *para* series of aromatic compounds (entries 13–19), no clear difference in kinetics or yield (86–94%) are observed except for 4′-bromoacetophenone (entry 19), which reacts faster and gives rise to more dimeric product. The synthesis of organozinc species can also be achieved in the *meta* and *ortho* series, as the two examples of 3-bromobenzonitrile (entry 20) and 2-bromobenzonitrile (entry 21) show. This last aryl bromide reacts faster than its *meta* and *para* counterparts. With a poorly reactive heteroaromatic bromide such as 3-bromothiophene (entry 22), however, the starting product could not be entirely converted into the corresponding organozinc reagent. Strangely enough, carrying the reaction with a greater proportion of catalyst (10% instead of 5%) with the appropriate changes in AllylCl and zinc dust quantities resulted in a faster 3-bromothiophene conversion but availed no change in yield.

Other compounds of a special interest to us are the diorganozinc species formed by the reaction of dibromoaromatic compounds. These syntheses have already been achieved by electrochemical methods[11] as well as with the initial reaction conditions.[9] It has thus been tried to apply the optimised conditions from entry 12 to the synthesis of the diorganozinc compound of 1,4-dibromobenzene (Table 3).

Table 2. Synthesis of mono organozinc species from aryl bromides and 3-bromothiophene using optimised conditions (GC yields)

Entry	ArBr	Reaction time (min)	ArZnBr (%)[a]	ArH (%)	ArAr (%)	Conv. (%)
13	Ph-Br	40	86	10	6	100
14	*p*-MeOPhBr	40	89	5	6	100
15	*p*-FPhBr	60	94	4	2	100
16	*p*-NCPhBr	60	86	5	6	97
17	*p*-EtO_2CPhBr	40	94	0	6	100
18	*p*-CF_3PhBr	60	91	2	2	95
19	*p*-MeCOPhBr	15	69	5	26	100
20	*m*-NCPhBr	60	96	2	1	99
21	*o*-NCPhBr	30	99	0	1	100
22	3-Bromothiophene	60	67	5	5	77

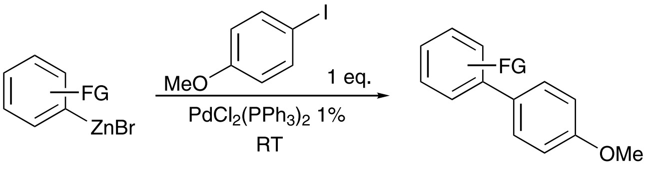
[a] The obtained arylzinc halides are converted into the corresponding aryl iodide by addition of iodine.

Table 3. Synthesis of diorganozinc species from 1,4-dibromobenzene (GC yields)

Entry	Zn (equiv.)	Reaction time (h)	BrZnPhZnBr (%)[a]	BrPhZnBr (%)[a]	PhZnBr (%)[a]	BrZnPh–PhZnBr (%)[a]	Conv. (%)
23	1.5	3[b]	30	23	4	5	66
24	2.8	3	78	6	6	5	99

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

[b] No conversion beyond 1 h.



Scheme 4. Cross-coupling reactions of organozinc bromides with 4-iodoanisole.

With 1.5 equiv. of zinc (entry 23), only 66% of the original dibromide is converted, and the diorganozinc species BrZnArZnBr is formed along with the mono organozinc compound BrArZnBr. The only by-products of a significant amount are the dimeric diorganozinc species BrZnAr–ArZnBr and the semi-reduced ArZnBr, whose formation had already been reported earlier. As it was clear that there was not enough zinc dust to form predominantly the diorganozinc compound, another experiment was carried out with additional 1.3 equiv. zinc dust versus aryl bromide (entry 24), the other parameters remaining unchanged. In this case, the starting molecule is fully converted, yielding 78% of the expected diorganozinc compound in 3 h.

As an application of the synthesis of aromatic organozinc species, we also chose to realise the palladium-catalysed cross-coupling reactions of the organozinc species obtained from 3- and 4-bromobenzonitrile (entries 16 and 20) with 4-iodoanisole (1 equiv. versus starting aryl bromide), in the optimised conditions of entry 12[12] (Scheme 4). The corresponding biaryls, 4′-methoxy-3-cyanobiphenyl[13] and 4′-methoxy-4-cyanobiphenyl[13] were isolated in 70 and 64% yield, respectively.

The conclusion of this work is that aromatic bromides can be efficiently converted into the corresponding organozinc species in acetonitrile using cobalt(II) bromide and zinc dust, under more inexpensive conditions than those described in a previous work. It has been proved that the use of a slight excess of zinc dust and a small quantity of catalyst, along with a short preliminary step requiring allyl chloride as an additive and a somewhat higher concentration, can lead to good to excellent yields in organozinc species. Furthermore, these functionalised organometallics can be readily coupled with aryl iodides using a palladium(II) catalyst. New applications of this synthetic process are being currently developed and will be reported in further works.

Acknowledgements

We gratefully acknowledge the financial support provided by Rhodia. I. Kazmierski thanks Rhodia for a scholarship.

References

1. (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (b) Knochel, P.; Almena Prea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319.
2. Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413–4416.
3. Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2003**, *68*, 2195–2199.
4. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1994**, *56*, 1445–1453.
5. Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435.
6. Sibille, S.; Ratovelomanana, V.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1992**, 283–284.
7. Gosmini, C.; Rollin, Y.; Nédélec, J. Y.; Périchon, J. *J. Org. Chem.* **2000**, *65*, 6024–6026.
8. Fillon, H.; Le Gall, E.; Gosmini, C.; Périchon, J. *Tetrahedron Lett.* **2002**, *43*, 5941–5944.
9. (a) Fillon, H.; Gosmini, C.; Périchon, J. *J. Am Chem. Soc.* **2003**, *125*, 3867–3870; (b) Fillon, H.; Gosmini, C.; Périchon, J. Patent Application 01/08880, France, July 4, 2001.
10. This property of allylzinc species has been reported earlier. See: (a) Blaise, E. E. *C. R. Acad. Sci.* **1904**, *138*, 284–286; (b) Rollin, Y.; Derien, S.; Dunach, E.; Gebehenne, C.; Périchon, J. *Tetrahedron* **1993**, *49*, 7723–7732.
11. Fillon, H.; Gosmini, C.; Nedelec, J. Y.; Périchon, J. *Tetrahedron Lett.* **2001**, *42*, 3843–3846.
12. General procedure for the synthesis of aromatic organozinc species (entry 20) and their palladium-catalysed cross-coupling with 4-iodoanisole: (a) *Preliminary step*: zinc dust <10 μm (1.47 g; 1.49 equiv.) and $CoBr_2$ (164 mg, 0.05 equiv.) are introduced under argon in a reaction vessel. 15 mL Of acetonitrile, allyl chloride (0.185 mL; 0.15 equiv.), dodecane (0.2 mL; reference for GC) and 50 μL trifluoroacetic acid are added and the reaction is stirred for 5 min. (b) *Synthesis of the organozinc reagent*: 3-bromobenzonitrile (2.73 g; 15 mmol) is added to the reaction, which is carried over a 1 hour period, until complete conversion of the starting aryl bromide. (c) *Cross-coupling*: 4-iodoanisole (3.51 g; 1 equiv.) and $PdCl_2(PPh_3)_2$ (105 mg; 0.01 equiv.) are introduced in the reaction vessel, and the reaction is stirred until complete conversion of the organozinc reagent (1 h). The reaction is then quenched with 40 mL HCl 1.5 M and extracted with 3×40 mL ether. The crude product is purified by flash chromatography on silica gel, eluted with pentane/ether 97/3 to 96/4, yielding 2.20 g (70%) of 4′-methoxy-3-cyanobiphenyl (identified by GC/MS and NMR by comparison to Ref. 13).
13. GC/MS and NMR analyses were compared to those found in the following reference: Hassan, J.; Hathroubi, C.; Gozzi, C.; Lemaire, M. *Tetrahedron* **2001**, *57*, 7845–7855.