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A New, Simple, Efficient Electrosynthesis of Functionalized Benzylic Zinc Species and Their Reactivity Toward Aromatic Aldehydes

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Abstract : *Various stable substituted benzylic zincs are formed in acetonitrile upon reaction of the bromide derivatives, in good yields , using a catalytic electrogenerated zinc species associated with massive zinc. In the presence of chlorotrimethylsilane, these organozincs react instantaneously with functionalized aromatic aldehydes* .

Organozinc compounds are of great interest in organic synthesis since they undergo efficient and selective carbon-carbon bond formation. Furthermore, they can bear various functional groups. Thus, considerable effort has been devoted to their preparation[1]. Unfortunately, functionalized organozinc compounds are weakly reactive toward organic electrophiles. Catalytic amounts of transition metals such as Pd[2], Cu[3] or Ni[4] are needed to enhance reactivity via a transmetallation reaction. We have recently reported a simple and mild method for zinc activation using an electrochemical process[5]. Indeed, a catalytic amount of electrogenerated zinc deposit readily induced activation of zinc metal toward allylic - halides(X= Br or Cl) and α-bromoesters. The subsequent organozincs coupled with various electrophilic compounds[6,7]

We explore in this paper the scope of this electrochemical procedure in the field of benzylic halides, and derivatives. The benzylic zincs formed are used in the cross - coupling with aromatic aldehydes .

Experimental procedure : In a first step, a catalytic amount of activated zinc (Zn* - 0,5 - 1 mmol) is deposited on a zinc plate cathode by electroreduction of zinc bromide The anode is composed of a zinc rod, and the solvent is acetonitrile. Electrolysis is carried out in an undivided cell under a constant current (0.1 - 0.2 A) at room temperature. When Zn deposition is achieved, the electrolysis is stopped. Keeping the metal into the solution, the benzyl bromide is then added (5 - 40 mmol). Organozincs formation is monitored by capillary GLC analysis of a hydrolyzed aliquot of the solution. In a second step, one equivalent of functionalized aldehyde is added to the solution. No coupling occurs but, in the presence of one equivalent of chlorotrimethylsilane, the corresponding alcohol is obtained instantaneously.

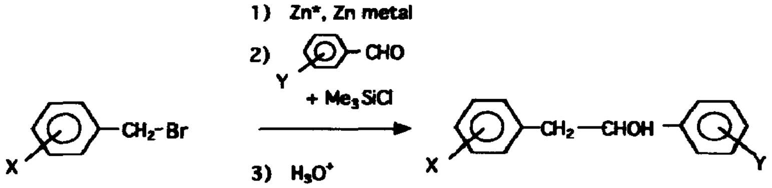
Results and Discussion : In our previous work devoted to allylic - halides and α-bromoesters[5] the zinc derivative could not be isolated. On the contrary, it is noteworthy that benzylic zincs are generated in over 80 % yield with 2 to 4 hours of reaction time. (A low additionnal reduction current allows a diminishing of this time). In most cases, the Wurtz coupling does not exceed 5 % (Table I, entries 1 - 13). Surprisingly, this side product rises to 10 - 20 % when the organozinc is substituted by a methyl substituent on ortho or para position

(entries 14 -15). Another noticeable feature is that the benzylic zinc electrochemically prepared, exhibit a high stability in MeCN. Solutions can be stored for several days, at room temperature under argon atmosphere with no detectable damage of the organozinc.

Despite this stability, the further addition of one equivalent of chlorotrimethylsilane yields an instantaneous coupling with aromatic aldehydes (reaction I). Actually, Me_3SiCl is known to activate the carbonyl function[8]. The resulting alcohols are obtained in good to excellent yields (Table I).

The direct oxidative addition of activated zinc metal to benzylic halides has been already described by Knochel[9]. However the author used THF as solvent and activated zinc metal at 5°C. Recent papers deal with a new methodology using metal-halogen exchange between benzylic halides and diethylzinc in the presence of a catalytic amount of transition metals[10]. Knochel *et al*[11] showed that the conversion of these organozincs into their copper analogues leads to the enhancement of their reactivity. Comparatively, our electrochemical process appears to be milder and quite simple.

Reaction I :

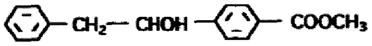
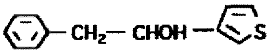
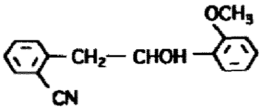
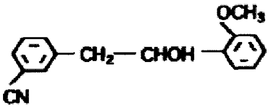
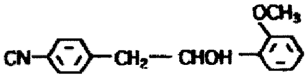
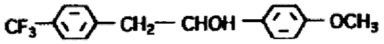
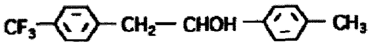
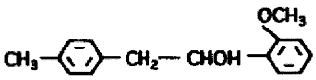
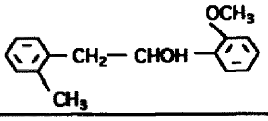


As a part of general studies on the scope and limitations of this process, the reactivity and compatibility of aromatic and heteroaromatic aldehydes (entry 7) bearing a variety of electrophilic functionnal groups (CN, Br, OCH_3, CO_2R, SCH_3) were examinated. In all cases, the sensitive groups remain intact after the reactions,and cross - coupling is successful.

When the benzylbromide is substituted by a methyl - group on ortho or para - position, the corresponding zinc derivative is obtained in good yield.To your disapointement, coupling of ortho benzyl bromide with ortho - methoxybenzaldehyde result in low yield (10 %) of desided product. No explanation has been yet found for this matter.

It is interesting to notice that with E - cinnamaldehyde, the 1, 2 - addition product is isolated with a good yield (70 %).

Table I : Reaction of Aromatic aldehydes with functionalized Benzylic zincs

Entry	X	Y	Product	Isolated yield % (a)
1	H	4 - CN		77
2	H	4 - Br		76
3	H	4 - OCH_3		70
4	H	4 - $COOCH_3$		70
5	H	4 - SCH_3		60
6	H	4 - CHO		32
7	H	(b)		70
8	2 - CN	2 - OCH_3		70
9	3 - CN	2 - OCH_3		72
10	4 - CN	4 - OCH_3		74
11	4 - CN	2 - OCH_3		77
12	4 - CF_3	4 - OCH_3		70
13	4 - CF_3	4 - CH_3		65
14	4 -CH_3	2 - OCH_3		66
15	2 -CH_3	2 - OCH_3		10

(a) : Isolated yields based on initial functionalized benzyl bromide. All compounds were caracterized by ^1H, ^{13}C, NMR, IR and GC / MS analysis. (b) : 3-Thiophene aldehyde

It has been recently reported that 2-methoxybenzaldehyde was highly reactive toward diethylzinc, while the corresponding 4 - methoxy substituted compound was not reactive[12]. Our experimental procedure allows alcohol formation in both cases (entries 3, 10, 12). However, when an equimolecular mixture of A, B, C, is engaged in our workup (reaction II), D is isolated (80 %) while A is entirely recovered.

Reaction II :

$$\text{4-CH}_3\text{OPhCHO} + \text{2-CH}_3\text{OPhCHO} + \text{"NCPhCH}_2\text{Zn"} \xrightarrow{(\text{CH}_3)_3\text{SiCl}} \text{2-CH}_3\text{OPhCH(OH)-CH}_2\text{-CH}_2\text{PhCN} + \text{A}$$

A = 5 mmol B = 5 mmol C = 5 mmol D = 4 mmol 5mmol

Concerning the reaction of benzylic zinc with terephthalaldehyde, both the mono and the bis coupling product (entry 6) are obtained (reaction III). Their proportions depend on the experimental conditions.

Reaction III :

$$\text{PhCH}_2\text{Br} + \text{4-OHCPhCHO} + (\text{CH}_3)_3\text{SiCl} \longrightarrow \text{PhCH}_2\text{-CH(OH)-PhCHO} + (\text{PhCH}_2\text{CH(OH)})_2\text{Ph}$$

1 eq.	1 eq.	1eq.	32%	10%
2 eq.	1 eq.	2 eq.	10%	60%

The scope and the extension of this methodology will be published later.

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