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Electrogenerated Zinc as the Catalyst in the Allylation of Carbonyl Compounds
Direct Synthesis of α-Methylene-γ-Lactones

Y. ROLLIN*[a], S. DERIEN[a], E. DUÑACH[b], C. GEBEHENNE[a] and J. PERICHON[a]

a-Laboratoire d'Electrochimie, Catalyse et Synthèse Organique (L.E.C.S.O.),CNRS,
2, rue Henri-Dunant 94320 THIAIS (France)
b-Laboratoire de Chimie Moléculaire, CNRS, Université de Nice-Sophia Antipolis
06108 NICE CEDEX 2 (France)

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***Abstract** : The electroreduction of a catalytic amount of* $ZnBr_2$ *in acetonitrile provided a active* Zn^**, able to catalyze the reductive coupling of allyl bromides and chlorides with carbonyl compounds with high regioselectivity. Substituted α-methylene γ-lactones were obtained from functionalized allyl derivatives.*

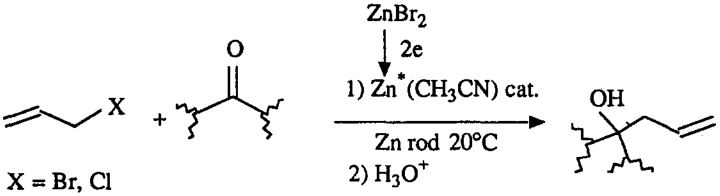
Introduction

Allylic organometallics have seen considerable use in organic synthesis for the formation of C-C bonds[1]. The direct reductive addition of allyl halides to carbonyl compounds avoiding the preparation of organometallic species, the Barbier reaction[2], constitutes an attractive alternative for the synthesis of homoallylic alcohols.

Different methods have been developed based on the direct use of reducing metals such as Mg[2] or Zn[3-5], or on the stoichiometric use of reducing salts, such as SmI_2[6] or $CeCl_3$[7]. The use of zinc presents some advantages : its low reactivity allows the preparation of polyfunctional allylzinc derivatives[8] and the construction of highly functionalized molecules. It avoids the formation of side-products derived from the reductive coupling of the carbonyl compound such as the pinacol condensation, often observed using stronger reducing agents[9]. However, reactive bromides or iodides are generally required, and special care is needed in preparing the active zinc necessary to initiate the reactions. Several methods have been reported to activate zinc such as washing with HCl solutions[10], ultrasound irradiation in the presence of lithium[11], or the use of Zn/Cu couple[12], among others. The preparation of activated Zn by reduction of zinc chloride with alkali metals such as Li, K or C_8C has been described[13], and needs high temperatures and/or long reaction times.

As an outgrowth of research into the reactivity of organozinc compounds[14], we have recently developed a simple and mild method of zinc activation by electrochemistry[15]. We wish to report here the direct reductive allylation of carbonyl compounds catalyzed by electrochemically generated zinc and mediated by non activated zinc or magnesium metal rods (eq. 1). The electrosynthesis of homoallylic alcohols from carbonyl compounds in tin[16] or nickel[17] catalyzed reactions has been reported.

Equation 1 :



Results and Discussion

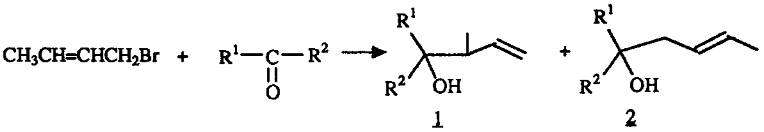
1. Allylation of carbonyl compounds catalyzed by electrogenerated zinc in acetonitrile:

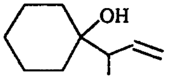
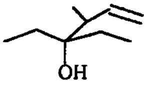
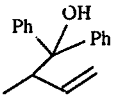
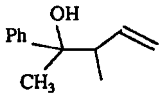
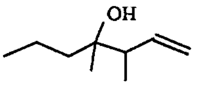
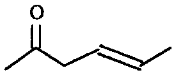
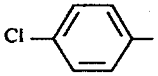
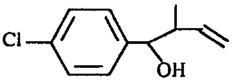
The electrochemically activated zinc was prepared by electrolysis of an anhydrous $ZnBr_2$ solution in acetonitrile, in a one compartment cell fitted with a zinc sheet as the cathode and a consumable zinc rod as the anode. At a constant intensity of 0.1 A (or at a cathode potential of - 0.8 V vs. SCE), 200 Coulomb were passed through the solution, corresponding to the 2e reduction of 1 mmol of $ZnBr_2$. The zinc formed a grey deposit on the cathode surface.

Without any further electrochemical supply, but keeping the zinc rod immersed into the solution, the carbonyl compound (10 mmol) and the allyl bromide (10-12 mmol) were added. The homoallylic alcohols were formed in 1-2 hours at room temperature. In some cases, a short electrolysis of the solution for 100-200 C strongly accelerated the coupling reaction.

Several examples of crotyl bromide addition to carbonyl compounds are gathered in table 1. Good to excellent yield of homoallylic alcohols were obtained, with a high regioselectivity, favoring the branched alcohol. In all cases, the ratio of branched to linear alcohols was 95:5 or higher.

Table 1 : Addition of crotyl bromide to carbonyl compounds catalysed by electrogenerated Zn.[a]

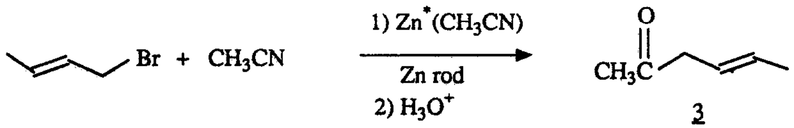


Entry	R^1	R^2	Product (% isolated yield)	Ratio 1 : 2[b]
a	—$(CH_2)_5$—		 1a (85%)	95 : 5
b	Et	Et	 1b (54%)	95 : 5
c	Ph	Ph	 1c (70%)	95 : 5
d	Ph	CH_3	 1d (80%)[c]	95 : 5
e	n-C_3H_7	CH_3	 1e (85%)[c]	95 : 5
f	t-Bu	CH_3	 3 (75%)	—
g		H	 1g (80%)[c]	> 99 : 1

a) For general conditions, see experimental part. 1. b) The ratio of branched to linear alcohols was calculated by GC. c) An aproximate 1:1 ratio of diastereoisomers was obtained.

In the case of sterically hindrered 3,3-dimethyl-2-butanone (entry f), the expected alcohol was formed in less than 20 % yield ; the main product was the unsaturated ketone 3 (eq. 2), isolated in 75 %.

Equation 2 :



3

This ketone results from the reductive allyl coupling with the solvent acetonitrile, and the linear isomer was formed almost exclusively. Ketone 3 was obtained as a by product in other carbonyl allylations in 10-20 % yield. However no aldol or pinacol-type dimerization of the carbonyl compound was observed, even in the case of easily reducible benzophenone or benzaldehyde derivatives.

The nature of the solvent was an important factor for the success of the reaction : nitriles, such as benzonitrile or acetonitrile were efficient, but no homoallylic alcohols were formed in DMF. We have already reported[15] that the reduction of Zn^{2+} to Zn^0 was strongly influenced by the presence of nitriles, these shifting the reduction potential to less negative values.

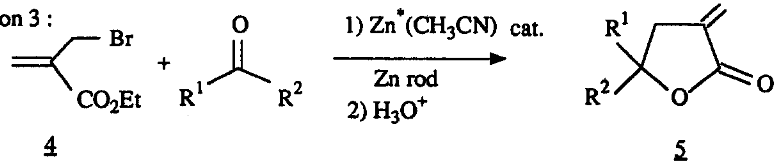
The carbonyl-allyl coupling did not occur in the absence of the freshly deposited zinc. The electrogenerated active $Zn^*(CH_3CN)$ species (Scheme 1) were present in catalytic amount with respect to the allyl halide and the carbonyl compound. The reaction is chemically (and not electrochemically) mediated by a commercial, non-activated, zinc rod drawn into the solution. The same rod served as the anode during the catalyst formation. No homocoupling products were produced under these conditions, and the new carbon-carbon bond was formed from the most substituted end of the allylic system.

2. Synthesis of α-methylene-γ-lactones from functionalized allyl bromides.

The synthesis of α-methylene-γ-butyrolactones remains of interest in view of their remarkable pharmacological properties[18]. Various synthetic routes to these derivatives have been proposed[19]. Among them, the condensation of carbonyl compounds with organometallic derivatives of 2-bromomethyl propenoates with metals such as Cr[20], Sn[21], Si[22], Ni[23] or Zn[19a, 24]. However, these reactions often proceed in two steps, with the intermediate preparation of the allyl-metal species.

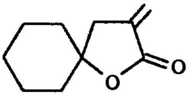
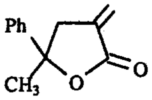
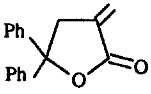
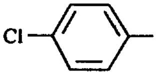
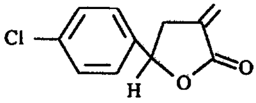
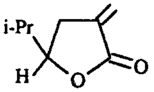
As a functionalized allyl synthon we tested the reactivity of ethyl 2 -bromomethyl acrylate, 4 , with a series of carbonyl compounds (eq. 3).

Equation 3 :



The reductive cyclization was catalyzed by electrogenerated Zn* in the presence of a zinc rod, and led to the synthesis of α-methylene-γ-butyrolactones 5 in a single step under mild conditions. Table 2 presents these results. Both aldehydes and ketones afforded good yields of lactones, the reaction being very sensitive to the steric hindrance of the carbonyl group. Thus, under the standard reaction conditions (vide supra) aldehydes were totally converted, but acetophenone and benzophenone were converted in 60 and 10% respectively. No rearrangement of the α-methylene lactones to the corresponding endocyclic butenolides was observed.

Table 2 : Reductive cyclisation of 4 with carbonyl compounds, catalysed by electrogenerated Zn

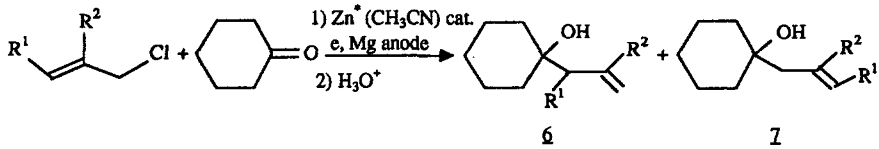
Entry	R^1	R^2	Ketone conversion	Product 5 (isolated yield)[a]	
a	—$(CH_2)_5$—		85		(82%)
b	Ph	CH_3	60		(67%)
c	Ph	Ph	10		(60%)
d		H	100		(90%)
e	$(CH_3)_2CH$	H	100		(88%)

a) Yield calculated as isolated lactones with respect to the reacted ketone

3. Use of allyl chlorides in the regioselective allylation of carbonyl compounds.

One of our goals was the activation and further coupling of less reactive allyl chlorides in electrogenerated Zn*(CH3CN)-catalyzed reactions. The reaction of crotyl chloride with cyclohexanone under the general conditions described in 1 was very slow and led to low yield of homoallylic alcohol. The continuous electrolysis of the solution with a zinc rod as the anode neither accelerated the coupling nor enhanced the reactivity of the chloride : mainly, Zn was oxidized into Zn^{2+} at the anode and Zn^{2+} ions in solution were reduced at the cathode (at a potential of - 0.8 to - 0.7 V vs. SCE). However, if after the Zn*(CH3CN) electrodeposition and the reactant addition, the zinc rod was replaced by a magnesium rod, the electrolysis proceeded at -1.3 to - 1.4 V with the formation of the allylic alcohols, as shown in Table 3. In the presence of the zinc catalyst, high regioselectivities favoring the branched alcohol were obtained.

Table 3 : Electrosynthesis of homoallyl alcohols from allyl chlorides and cyclohexanone catalysed by electrogenerated Zn*.



Entry	Molar % Zinc catalyst (respect to ketone)	R^1	R^2	isolated yield of 6+7	Ratio 6 : 7 $^{a)}$
a	10%	CH_3	H	65%	95 : 5
b	10%	H	CH_3	60%	—
c	10%	Ph	H	57%$^{b)}$	95 : 5
d	—	CH_3	H	20%	20 : 80

a) Ratio 6 / 7 calculated by GC. b) For a ketone conversion of 70%.

The presence of Zn* was necessary ; in its absence the formation of alcohols was only of 20 % (entry d, Table 3) under the same conditions. More surprisingly, the ratio of branched to linear alcohols was reversed, and went from 95/5 to 20/80 in the presence or absence of Zn* species, respectively. This constitutes a further example of the strong influence of the cation on the regiochemical outcome of the reaction[25]. The electrosynthesis of homoallylic alcohols using a Zn anode combined with a nickel catalysis has been reported to afford mainly the branched isomer[17].

The coupling with allyl chlorides needed the continuous electrolysis of the solution for the complete consumption of the halide. The electrolysis was carried out in single compartment cells fitted with a sacrificial magnesium anode. The convenient use of sacrificial anodes in electroreductive coupling of organic halides has been recently reported[26], and similarities to classic organometallic synthesis have been outlined.

No reaction occurred in the absence of current, even in the presence of a magnesium rod immersed to the solution. It is noteworthy that the preparation of the Zn* catalyst needed the electroreduction of $ZnBr_2$ in the presence of a Zn anode (Scheme 1). Replacing the zinc by a magnesium rod during the catalyst formation did not lead to formation of a zinc deposit, and did not afford any coupling product.

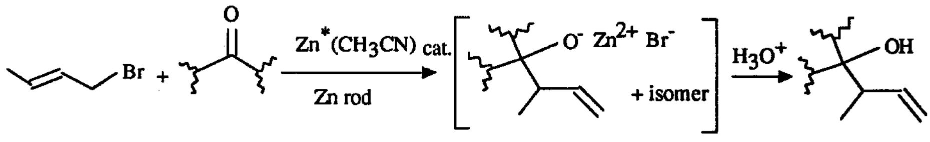
Scheme 1

- Electrochemical preparation of the catalytic species :

Anode : $Zn \rightarrow Zn^{2+} + 2e$

Cathode : $ZnBr_2 + 2e \xrightarrow[CH_3CN]{} \downarrow Zn^*(CH_3CN), 2\ Br^-$

- Coupling reaction :



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Conclusion

The electroreduction of a catalytic amount of $ZnBr_2$ in acetonitrile in the presence of a zinc anode led to the formation of an active $Zn^*(CH_3CN)$ species, able to catalyze the reductive coupling of allyl bromides with carbonyl compounds. Homoallyl alcohols were isolated in good yields and excellent regioselectivities, in a coupling reaction mediated by a rough metal that did not need any other activation.

Moreover, the mild conditions in which the active zinc oxidatively added to allylic bromides allowed the presence of various functionalities, and provided a direct route to α-methylene-γ-lactones.

The carbonyl coupling with less reactive allyl chlorides was carried out by the Zn* catalyzed electrolysis in the presence of a magnesium anode.

The method of zinc electroactivation complements, and constitutes an efficient alternative to other zinc activation methods, by virtue of the mildness of the reaction conditions and the high regioselectivity. The new C-C bond was formed on the most substituted end of the allylic unit.

No excess of halide and of reducing agent is needed, and the electrochemical set-up is very simple. The reaction is carried out in one step with the simultaneous addition of the allyl derivative and the carbonyl compound, without previous preparation nor isolation of the intermediate organozinc compounds.

Experimental

Acetonitrile was reagent grade. The supporting electrolyte, $n\text{-}Bu_4N^+BF_4^-$ and zinc bromide were dried under vacuum (0.1 mm Hg) at 50° C overnight before use. A stabilized constant current supply (Sodelec, EDC 36.07) was used for electrolyses.

- General procedure for zinc activation and allyl bromide coupling : in an electrochemical, one compartment cell, similar to that described in ref. 26, equipped with a zinc sheet cathode (40 cm^2) and a zinc rod (immersed to 3 cm) anode, were introduced acetonitrile (40 ml), anhydrous $ZnBr_2$ (2 mmol) and $n\text{-}Bu_4N^+BF_4^-$ (0.2 mmol). An electrolysis at $i = 0.1$ A or at - 0.8 vs SCE at room temperature, under argon, for 200 Coulomb, was followed by the addition of the bromide (10 mmol) and the carbonyl compound (10 mmol). Without further electrolysis but keeping the zinc anode immersed into the solution, the reaction was followed by GC until disappearance of the halide (1-2 hours). The solution was hydrolyzed with 0.1 N HCl and extracted with ether, the organic layer washed with water, dried and the solvent evaporated. The products were purified by flash column chromatography on silicagel with pentane/ether mixtures as eluent. The compounds were analyzed by NMR (^1H and ^{13}C), IR and mass spectrum.

- General procedure for the coupling of allyl chlorides : following the same $ZnBr_2$ reduction as described above, the allylic chloride (10-12 mmol) and the ketone (10 mmol) were introduced and the zinc rod replaced by a magnesium rod. The solution was electrolyzed at - 1.3 to -1.4 V vs. SCE at room temperature until disappearance of the chloride (by GC), approx. 3 hours. The same reaction can be carried out using a gold cathode. The same work-up as described before afforded the allylic alcohols with the isolated yields reported in Table 3.

The compounds reported in tables 1-3 were identified by comparison of their physical and spectral data with those given in the cited references : 1a[27], 1c[28], 1d[29], 1e[30], 1g[31], 3[32], 5a[23], 5b[23], 5c[33], 5d[34], 5e[34], 7a[35], 6c[35].

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