New Preparation Method of Highly Reactive Electrogenerated Zinc and its Use in Cross-coupling Reaction of Functionalized Organic bromides with Aryl Halides by Using Electrochemical Method

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Abstract

A new highly reactive zinc metal was readily prepared by electrolysis of a DMF solution containing polyaromatic compounds (PA) as a mediator and a supporting electrolyte in a one-compartment cell fitted with a platinum cathode and a zinc anode. This reactive zinc (EGZn/PA) was used for transformation of organic bromides into the corresponding organozinc bromides, which can not be achieved by the use of either reactive zinc (EGZn) or usual zinc metals. Reaction of the organozinc compounds thus prepared with various aryl iodides in the presence of 5 mol% of palladium catalyst gave the corresponding cross-coupling products in high yields. Arylzinc halides were also prepared by the use of EGZn/PA, and they were reacted with other aryl halides to give the corresponding cross-coupled biaryl in good yields.

Keywords:
Electrolysis, highly reactive zinc, organo Zinc bromide, cross-coupling, palladium catalyst

Introduction

Organozinc compounds are very useful organometallic compounds for the forming reaction of carbon-carbon bonds [1]. Organozinc halides can usually be prepared by direct insertion of zinc metal into organic halides [1-2], but commercially available zinc metal is generally poorly reactive. Therefore, activation of the metal is necessary for the preparation of organozinc halides. Various methods of zinc activation, such as the reduction of zinc halide with alkaline metal or alkaline metal naphthalenide, have been reported [3-4]. These methods, however, require high temperature and long reaction times, or vigorous stirring during the reaction.

We previously reported a new method for the preparation of reactive zinc by electrolysis of a DMF solution containing 0.1M Et₄NClO₄ with a platinum cathode and a zinc anode (Scheme 1) [5]. It was shown that this electrogenerated reactive zinc (EGZn) was an aggregation of very fine crystalline zinc particles with a large surface area [6].

\[
\text{electrolysis} \quad \text{0.1M Et}_4\text{NClO}_4 \quad \text{DMF} \quad \text{Pt}(-) \rightarrow \text{Zn}(+) \quad \text{Zn}^+(\text{EGZn})
\]

\[
\text{electrolysis} \quad \text{0.1M Et}_4\text{NClO}_4 \quad \text{DMF} \quad \text{Naphthalene} \quad \text{Zn}^+(\text{EGZn/Naph})
\]

Scheme 1 - Preparation of reactive zinc

It was very reactive and was successfully used in isoprenylation [5] and allylation [6-7] of aldehydes and ketones. We have also reported a facile preparation of organic compounds from functionalized alkyl iodides by using EGZn and their cross-couplings with aryl halides (Scheme 2) [8].

\[
\begin{align*}
\text{I} & \quad \text{CO}_2\text{Et} \\
0^\circ \text{C}, 10\text{ min} & \quad \text{Zn}^+(\text{EGZn}) \\
\text{Ar-X} & \quad \text{Pd(II) cat.} \\
\text{Pd(II) cat.} & \quad \text{Ar}^+ \quad \text{CO}_2\text{Et}
\end{align*}
\]

Scheme 2 - Cross-coupling reaction of organozinc iodide with aryl halide

However, organozinc bromides were rarely obtained or were only obtained in very low yields from the corresponding organic bromides, even if the reactive EGZn was used. Recently, we developed a new electrochemical method for the preparation of more highly reactive zinc (EGZn/Naph) by using naphthalene as a mediator (Scheme 1). This more highly reactive zinc...
successfully transformed bromoalkanes into the corresponding organozinc bromides, which can not be achieved by the use of usual zinc metals, or even if the reactive EGZn was used. The subsequent cross-coupling of corresponding organozinc bromides with various aryl iodides in the presence of palladium catalyst gave the corresponding cross-coupling products high yields (unpublished results).

However, no cross-coupling reaction occurred under these conditions when aryl bromide, which would be more desirable in the cross-coupling reaction, was used as one of the coupling components. We examined various reaction conditions and found that the cross-coupling using aryl bromides could undergo for tetrahydrofuran (THF), instead of DMF, was used as a solvent. In this paper, the authors report a facile cross-coupling reactions of organozinc bromide derived from bromoalkanes prepared by EGZn/Naph with various aryl bromides in the presence of palladium catalyst in tetrahydrofuran.

**Methodology**

**Electrochemical preparation of highly reactive zinc (EGZn/Naph)**

A normal one-compartment cell equipped with a magnetic stirrer and a serum cap was used. Electrogenerated highly reactive zinc (6 mmol) was prepared by the electrolysis of a DMF solution (10 ml) containing 0.1 M Et₄NClO₄ (230 mg) and naphthalene (12 mmol) in a one-compartment cell fitted with a platinum plate cathode (2x2 cm²) and a zinc plate anode (2x2 cm²). Electrolysis was carried out at -10°C at a constant current of 60 mA/cm² under nitrogen atmosphere. The quantity of electricity passed was 0.012 F, which corresponded to 2 F per mol of zinc metal. The amount of EGZn/Naph was calculated from the weight of dissolved zinc anode metal. A solution containing EGZn/Naph was directly used for the preparation of organozinc compound after the zinc anode was removed from the electrolysis cell.

**General procedure for cross-coupling reaction using EGZn/Naph**

To a DMF solution containing EGZn/Naph was added ethyl 4-bromobutanoate (1a) (5 mmol) and the mixture was stirred at 50°C under nitrogen atmosphere for 1 h. DMF solution (5 ml) of aryl bromide (4 mmol) and Pd(PPh₃)₄Cl₂ (0.11 mmol) was added, and the reaction mixture was refluxed for 3 h. The resulting mixture was quenched with HCl solution and filtered. The filtrate was extracted with diethyl ether (50 ml x 3) and the combined organic layers were washed with water (100 ml x 3), saturated Na₂SO₃ solution (100 ml x 1) and saturated NaCl (100 ml x 1) and dried over MgSO₄. After evaporation of diethyl ether, the crude product was purified by column chromatography on silica gel with ethyl acetate-hexane (1:4) to give ethyl 4-phenylbutanoate 4.

**Results and Discussion**

**Electrochemical preparation of highly reactive zinc (EGZn/Naph)**

At the cathode, a one-electron reduction of naphthalene molecule readily occurred to give naphthalene radical anion preferentially. The formation of the naphthalene radical anions was shown by the dark green color which appeared on the surface of the cathode. On the other hand, at the anode, dissolution of the zinc metal occurred to give zinc ions, which were reduced by the naphthalene radical anions to give zero-valence highly reactive zinc, EGZn/Naph (Scheme 1). Probable reaction pathways for the formation of EGZn/Naph is illustrate in Scheme 3.

![Scheme 3 - Probable reaction pathways for the formation of EGZn/Naph](image)

However, the true nature and structure of this EGZn/Naph are not clear at the present stage, but it was found to be very reactive towards an oxidative addition to organic bromides. A solution containing EGZn/Naph was directly used in a preparation of functionalized alkylzinc bromide after the zinc anode was removed from the electrochemical cell. The high reactivity of EGZn/Naph was shown from the transforming reaction of ethyl 4- bromobutanoate 1a at 50°C for 1 h which gave the corresponding organozinc bromide 2a an almost quantitative yield (Scheme 4), whereas the use of commercially available zinc powder (Rare Metalic) in DMF containing naphthalene gave no organozinc compound at all.

![Scheme 4 - Transformation of ethyl 4-bromobutanoate into the corresponding organozinc bromide using EGZn/Naph](image)

Even when the EGZn was used in the presence of naphthalene after the electrolysis, the organozinc compound had only 37% yield. These results show that the use of commercially available zinc or EGZn with the addition of naphthalene was not effective in terms of
reactivity and that the presence of naphthalene molecules in the electrochemical reduction step is required for the preparation of more highly reactive zinc.

Recently, we found that the use of pyrene instead of naphthalene as a mediator turns out much more better result in preparing organozinc compound that show in Scheme 4. Catalyst amount of pyrene is more enough to convert ethyl 4-bromobutanolate into the corresponding organozinc compound. Further results are in progress.

Cross-coupling of Functionalized Bromoalkanes with Aryl Bromides using EGZn/Naph

A DMF solution of alkylzinc bromide 2a was transferred into a THF solution containing aryl bromide (3a-3d) and 5 mol% Pd(P(o-Tol)_3)Cl catalyst, and the reaction mixture was refluxed for 2 h to give the corresponding cross-coupled product (4a-4m), in high yields (Scheme 5). The results are summarized in Table 1.

\[
\begin{align*}
\text{Br} & \rightarrow \text{CO}_2\text{Et} & \text{EGZn/Naph} & \stackrel{50^\circ \text{C}, 1 \text{ h}}{\longrightarrow} & \text{BrZn} & \rightarrow \text{CO}_2\text{Et} \\
1\text{a} & & 2\text{a} & & 4\text{a} & & 4\text{m}
\end{align*}
\]

Scheme 5 - Cross-coupling reaction of organozinc bromide with aryl bromide

Cross-coupling of 2a with bromobenzene (3a) at 70°C for 2 h in the presence of 5 mol% Pd(P(o-Tol)_3)Cl catalyst gave the corresponding cross-coupled products 4a 96% isolated yields (Table 1, entry 1). Similar reaction of 2a with 4-acetyl bromobenzene (3b), 4-methoxybromobenzene (3c) and 1-bromo-3,4-methylenedioxybenzene (3d) also took place efficiently to give the corresponding cross-coupled products 4b, 4c and 4d 80%, 92% and 83% isolated yields, respectively (Table 1, entries 2-4).

4-Bromobutane (1b) and bromohexane (1c) could also be converted into the corresponding organozinc bromides 2b and 2c by their reaction with EGZn/Naph. Palladium (II) catalyzed reaction of 2b and 2c with aryl bromide carrying electron-withdrawing or electron-donating substituents gave the corresponding cross-coupled product (4e-4j) mostly high yields (Table 1, entries 5-10).

The reaction of a secondary-alkyl bromide such as bromocyclohexane (1d) with EGZn/Naph also efficiently gave the corresponding alkylzinc bromide, which was reacted with aryl bromides in the presence of Pd(II) catalyst to give the corresponding cross-coupled products (4k-4m) good yields (Table 1, entries 11-13).

Aryl-aryl Cross-coupling using EGZn/Naph

Aryl iodides carrying a p-acetyl, p-methoxy, or p-cyano group (5) can readily be transformed into the corresponding arylnzine iodides (6) by reaction with EGZn/Naph. Preparation of arylzine compound is not readily achieved when usual zinc metal is used. This fact shows that the electrochemically generated EGZn/Naph has a very high reactivity. The reaction of arylzine iodides (6) with other aryl iodides gave the cross-coupled biaryls (7) in good yields (Scheme 6).

\[
\begin{align*}
\text{X} & \rightarrow \text{Y} & \text{EGZn/Naph} & \stackrel{80^\circ \text{C}, 2 \text{ h}}{\longrightarrow} & \text{Z} & \rightarrow \text{H} & \rightarrow & \text{EGZn/Naph} & \stackrel{80^\circ \text{C}, 2 \text{ h}}{\longrightarrow} & \text{ZnI} \\
\text{Y} & \rightarrow & \text{Z} & \rightarrow & \text{H} & \rightarrow & \text{EGZn/Naph} & \stackrel{80^\circ \text{C}, 2 \text{ h}}{\longrightarrow} & \\
\text{X} & \rightarrow & \text{Y} & \rightarrow & \text{Z} & \rightarrow & \text{H} & \rightarrow & \text{EGZn/Naph} & \stackrel{80^\circ \text{C}, 2 \text{ h}}{\longrightarrow} & \text{ZnI}
\end{align*}
\]

Scheme 6 - Aryl-aryl cross-coupling using EGZn/Naph

Probable reaction pathways of the present cross-couplings are shown in Scheme 7. Oxidative addition of Pd(0) to aryl halides 5 would give Ar-Pd-X, which undergoes metal exchange reaction with organozinc bromide 2a to give an intermediate Ar-Pd-R. Reductive elimination of Ar-Pd-R would give the cross-coupling product, ethyl 2-arylpiperoxaone 4.

\[
\begin{align*}
\text{R} & \rightarrow \text{Br} & \text{EGZn/Naph} & \stackrel{80^\circ \text{C}, 2 \text{ h}}{\longrightarrow} & \text{Ar-Pd-X} & \rightarrow & \text{ZnBr} \\
\text{Ar-Pd-X} & \rightarrow & \text{ZnBr} & \rightarrow & \text{Ar-Pd-X} & \rightarrow & \text{ZnBr}
\end{align*}
\]

Scheme 7 - Probable reaction pathways of cross-coupling reactions

Conclusion

We developed a new electrochemical method for the preparation of highly reactive zinc (EGZn/PA) by using polyaromatic compound as a mediator in the electrolysis. The corresponding organozinc bromide could readily be prepared under mild conditions by the reaction of
bromoalkanes with EGZn/Pd. Subsequent cross-coupling reaction of the organozinc bromide with various aryl bromides readily took place in the presence of a palladium catalyst to give the corresponding cross-coupled products in high yields.

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References


Table 1 - Cross-coupling reactions of functionalized alkyl bromides with various aryl bromides using EGZn/Naph²

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromide</th>
<th>Arl</th>
<th>Product</th>
<th>Yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br(CH₂)₂CO₂Et (1a)</td>
<td>C₆H₆Br (3a)</td>
<td>C₆H₄(CH₂)₂CO₂Et (4a)</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Br(CH₂)₂CO₂Et (1a)</td>
<td>p-CH₃CO₂C₆H₅Br (3b)</td>
<td>p-CH₃CO₂C₆H₄((\text{CH}_2))₂CO₂Et (4b)</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Br(CH₂)₂CO₂Et (1a)</td>
<td>p-CH₃OC₆H₅Br (3c)</td>
<td>p-CH₃OC₆H₄((\text{CH}_2))₂CO₂Et (4c)</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Br(CH₂)₂CO₂Et (1a)</td>
<td>(3,4-OCH₂O-)C₆H₄Br (3d)</td>
<td>(3,4-OCH₂O-)C₆H₄((\text{CH}_2))₂CO₂Et (4d)</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Br(CH₂)₂CN (1b)</td>
<td>C₆H₆Br (3a)</td>
<td>C₆H₄(CH₂)₂CN (4e)</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>Br(CH₂)₂CN (1b)</td>
<td>p-CH₃CO₂C₆H₅Br (3b)</td>
<td>p-CH₃CO₂C₆H₄((\text{CH}_2))₂CN (4f)</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>Br(CH₂)₂CN (1b)</td>
<td>p-CH₃OC₆H₅Br (3c)</td>
<td>p-CH₃OC₆H₄((\text{CH}_2))₂CN (4g)</td>
<td>92</td>
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<tr>
<td>8</td>
<td>Br(CH₂)₂CH₂ (1c)</td>
<td>C₆H₆Br (3a)</td>
<td>C₆H₄(CH₂)₂CH₂ (4h)</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>Br(CH₂)₂CH₂ (1c)</td>
<td>p-CH₃CO₂C₆H₅Br (3b)</td>
<td>p-CH₃CO₂C₆H₄(CH₂)₂CH₂ (4i)</td>
<td>75</td>
</tr>
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<td>10</td>
<td>Br(CH₂)₂CH₂ (1c)</td>
<td>p-CH₃OC₆H₅Br (3c)</td>
<td>p-CH₃OC₆H₄(CH₂)₂CH₂ (4j)</td>
<td>87</td>
</tr>
<tr>
<td>11</td>
<td>C₆H₆Br (1d)</td>
<td>C₆H₆Br (3a)</td>
<td>C₆H₄(CH₂)₄H₂ (4k)</td>
<td>64</td>
</tr>
<tr>
<td>12</td>
<td>C₆H₆Br (1d)</td>
<td>p-CH₃CO₂C₆H₅Br (3b)</td>
<td>p-CH₃CO₂C₆H₄(CH₂)₄H₂ (4l)</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>C₆H₆Br (1d)</td>
<td>p-CH₃OC₆H₅Br (3c)</td>
<td>p-CH₃OC₆H₄(CH₂)₄H₂ (4m)</td>
<td>74</td>
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