EFFECT OF MEDIATOR ON PREPARATION OF HIGHLY REACTIVE ELECTROGENERATED ZINC AND ITS USE IN CROSS-COUPLING REACTION

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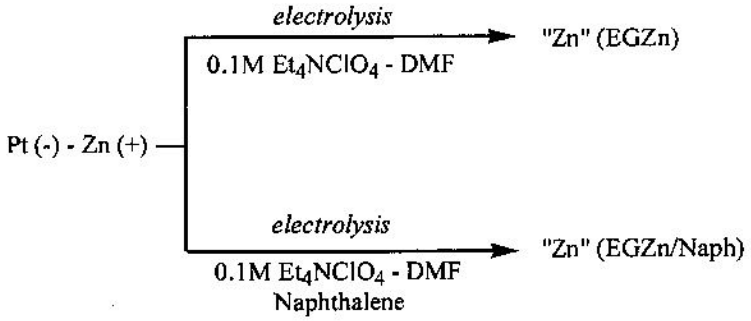
Abstract

A new highly reactive zinc metal was readily prepared by electrolysis of a DMF solution containing polyaromatic compounds (PA) such as naphthalene and pyrene 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.

Introduction

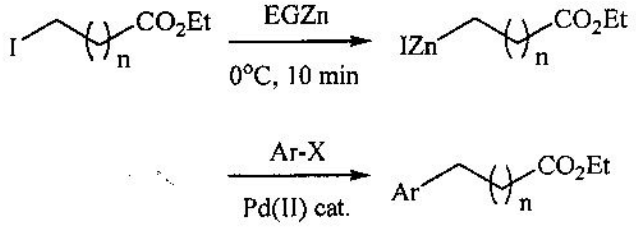
Organozinc compounds are very useful organometallic compounds for the forming reaction of carbon-carbon bonds [1]. Organozinc halides can usually be prepared by direct insertion of zinc metal into organic halides [1-2], but commercially available zinc metal is generally poorly reactive. Therefore, activation 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 alkali 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 Et_4NClO_4 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].

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].



***Scheme 1**: Preparation of reactive zinc*

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).



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

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). Reaction of EGZn/Naph with ethyl 2-bromoacrylate efficiently gave the corresponding organozinc bromide, which could be successfully used for palladium-catalyzed cross-coupling reactions with various aryl iodides to give ethyl 2-arylpropenoates [9].

As an extent of our study, we attempted an alternative route on preparation of highly reactive electrogenerated zinc by adding pyrene, instead of naphthalene as a mediator. In this paper, we report those results and also the results on palladium-catalyzed cross-coupling reactions of organozinc bromides with aryl iodides and bromide.

Experimental

Electrochemical preparation of highly reactive zinc (EGZn/Py)

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 0.1M Et_4NClO_4 (230 mg) and pyrene (6 mmol) in a one-compartment cell fitted with a platinum plate cathode (2x2 cm^2) and a zinc plate anode (2x2 cm^2). Electrolysis was carried out at -10°C at a constant current of 60 mA/cm^2 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/Py was calculated from the weight of dissolved zinc anode metal. A solution containing EGZn/Py was directly used for the preparation of organozinc compound after the zinc anode was removed from the electrolysis cell.

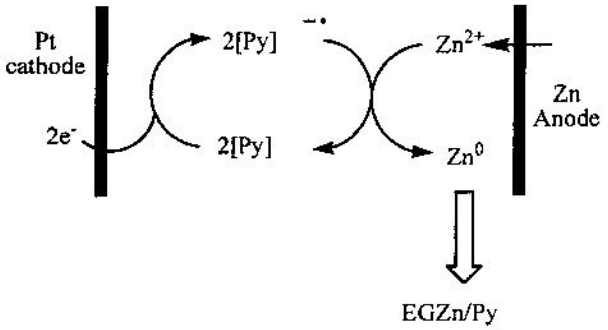
General procedure for cross-coupling reaction using EGZn/Naph

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 $Pd(P(o\text{-}Tol)_3)_2Cl_2$ (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 $Na_2S_2O_3$ solution (100 ml x 1) and saturated NaCl (100 ml x 1) and dried over $MgSO_4$. After evaporation of diethyl ether, the crude product was purified by column chromatograph 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/Py)

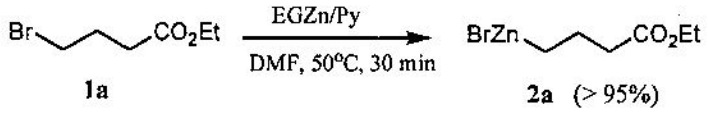
At the cathode, a one-electron reduction of pyrene molecule readily occurred to give pyrene radical anion preferentially. The formation of the pyrene radical anions was shown by the dark brown color which appeared on the surface of the cathode. On the other hand, at the anode, dissolution of the zinc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



***Scheme 3:** Probable reaction pathways for the formation of EGZn/Py*

However, the true nature and structure of either EGZn/Naph or EGZn/Py 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/Py 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/ Py was shown from the transforming reaction of ethyl 4-bromobutanoate **1a** at 50°C for 30 min which gave

the corresponding organozinc bromide **2a** in almost quantitative yield (Scheme 4), whereas the use of commercially available zinc powder (Rare Metallic) in DMF containing naphthalene gave no organozinc compound at all.



1a **2a** (> 95%)

***Scheme 4**: Transformation of ethyl 4-bromobutanoate into the corresponding organozinc bromide using EGZn/Py*

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 turn out much more better result in preparing organozinc compound that show in Scheme 4. As shown in Table 1 when EGZn/Naph generated by using 2 equivalent of naphthalene to zinc metal was used, **1a** could be converted into **2a** in 98% yield within 20 min of reaction (entry 2). However, its reactivity decreased when EGZn/Naph was prepared by using 1 equiv of naphthalene (entry 3). Entry 4-7 shows that pyrene gave the best results in preparing highly reactive electrogenerated zinc which catalyst amount of pyrene is more enough to convert **1a** into **2a** in high yield.

***Table 1**: Effects of polyaromatic compounds on the reactivity of EGZn/PA*

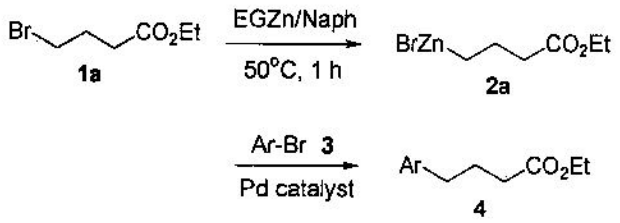
Entry	Polyaromatics	Equivalent[a]	Reaction Time (min)	Conversion (%)[b]
1	None	-	60	25
2	Naphthalene	2	20	98
3		1	20	88
4	Pyrene	1	20	97
5		0.5	20	98
6		0.25	30	94
7		0.1	90	95
8		0.05	130	82

[a] Equivalent of mediator to zinc ion (6 mmol) by dissolution from zinc anode.
[b] Conversions of **1a** into **2** a were estimated by GC of unreacted **1a**.

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% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ 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 2.

Cross-coupling of **2a** with bromobenzene (**3a**) at 70°C for 2 h in the presence of 5 mol% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ catalyst gave the corresponding cross-coupled products **4a**



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

96% isolated yields (Table 1, entry 1). Similar reaction of **2a** with 4-acetylbromobenzene (**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-Bromobutanenitrile (**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).

Table 2: Cross-coupling reactions of functionalized alkyl bromides with various aryl bromides using EGZn/Naph

Entry	Bromide	Arl	Product	Yield (%)[b]
1	$Br(CH_2)_3CO_2Et$ (**1a**)	C_6H_5Br (**3a**)	$C_6H_5(CH_2)_3CO_2Et$) (**4a**)	96
2	$Br(CH_2)_3CO_2Et$ (**1a**)	*p*-$CH_3COC_6H_4$ Br (**3b**)	*p*-$CH_3COC_6H_4(CH_2)_3CO_2Et$ (**4b**)	80
3	$Br(CH_2)_3CO_2Et$ (**1a**)	*p*-$CH_3OC_6H_4Br$ (**3c**)	*p*-$CH_3OC_6H_4(CH_2)_3CO_2Et$ (**4c**)	92
4	$Br(CH_2)_3CO_2Et$ (**1a**)	(3,4-OCH_2O-)C_6H_3Br (**3d**)	(3,4-OCH_2O-)$C_6H_3(CH_2)_3CO_2Et$ (**4d**)	83
5	$Br(CH_2)_3CN$ (**1b**)	C_6H_5Br (**3a**)	$C_6H_5(CH_2)_3CN$ (**4e**)	82
6	$Br(CH_2)_3CN$ (**1b**)	*p*-$CH_3COC_6H_4Br$ (**3b**)	*p*-$CH_3COC_6H_4(CH_2)_3CN$ (**4f**)	87
7	$Br(CH_2)_3CN$ (**1b**)	*p*-$CH_3OC_6H_4Br$ (**3c**)	*p*-$CH_3OC_6H_4(CH_2)_3CN$(**4g**)	92
8	$Br(CH_2)_5CH_3$ (**1c**)	C_6H_5Br (**3a**)	C_6H_5 $(CH_2)_3CH_3$ (**4h**)	84
9	$Br(CH_2)_5CH_3$ (**1c**)	*p*-$CH_3COC_6H_4Br$ (**3b**)	*p*-$CH_3COC_6H_4(CH_2)_3CH_3$ (**4i**)	75
10	$Br(CH_2)_5CH_3$ (**1c**)	*p*-$CH_3OC_6H_4Br$ (**3c**)	*p*-$CH_3OC_6H_4(CH_2)_3CH_3$ (**4j**)	87
11	$C_6H_{11}Br$ (**1d**)	C_6H_5Br (**3a**)	$C_6H_5C_6H_{11}$ (**4k**)	64
12	$C_6H_{11}Br$ (**1d**)	*p*-$CH_3COC_6H_4Br$ (**3b**)	*p*-$CH_3COC_6H_4C_6H_{11}$ (**4l**)	98
13	$C_6H_{11}Br$ (**1d**)	*p*-$CH_3OC_6H_4Br$ (**3c**)	*p*-$CH_3OC_6H_4C_6H_{11}$ (**4m**)	74

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/PA. 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 high yields.

Acknowlwdgements

This work was supported by a Grant-in-Aids for Scientific Research (B) (No. 11450342) from The Ministry of Education, Science, Sports and Cultures of Japan and The SAGA Grant (Vot : 73704) from Academic Science Malaysia. The authors would like to thank The Hitachi Scholarship Foundation for their financial support for gas chromatography instruments.

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