Synthesis of Precursor of Anti-cancer Drugs

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Abstract

Highly reactive electrogenerated zinc metal (EGZn/Naph) was readily prepared by electrolysis of a DMF solution containing naphthalene and a supporting electrolyte in a one-compartment cell fitted with a platinum cathode and a zinc anode. This reactive zinc was used for efficient transformation of ethyl 2-bromoacrylate into the corresponding organozinc compound, which was reacted with various aryl halides in the presence of palladium catalyst to give the corresponding cross-coupling products, ethyl 2-arylpropenoates, in high yields. These cross-coupling reactions were successfully applied to a synthesis of the precursors of non-steroidal anti-inflammatory drugs such as ibuprofen, ketoprofen and loxoprofen, which recently, have been shown to decrease the risk of cancer.

Keywords: electrolysis, reactive zinc, alkylbromide, cross-coupling, palladium catalyst

Introduction

During the last three decades the development of non-steroidal anti-inflammatory drugs (NSAIDs) has shown to be one of the major advances in chemotherapeutical research [1]. Recently, H. Timothy reported that non-steroidal anti-inflammatory drugs, including the common pain relievers; aspirin and ibuprofen inhibit the action of both Cox-1 and Cox-2 enzymes and have been shown to decrease the risk of cancer [2]. Since they are very interesting in the therapeutic and agricultural fields, many synthetic strategies have been developed for the preparation of these acids especially for their derivatives: e.g. a cross-coupling of α-stannyl acrylate with the corresponding aryl iodides or triflates [3], a cyanation or carboxylation of 1-aryl-1-haloethanes [4], an introduction of aryl group into the α-position of propanoic acids [5] and electrochemical carboxylation of vinyl bromides [6]. However, almost all of these synthetic approaches have some troublesome work during the reaction and require long steps and reaction times. Furthermore, the yields of the products were not so reasonable to apply in commercial use. Therefore, the author intended to develop another alternative method in the hope that more efficient route leading to the precursor of anti-inflammatory agents might be invented.

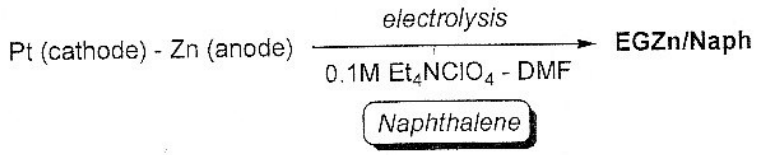
We have already reported a new electrochemical method for preparation of more highly reactive zinc (EGZn/Naph) by using naphthalene as a mediator and its use in cross-coupling reactions of bromoalkanes with aryl iodides [7]. As an extension of the use of EGZn/Naph in organic synthesis, the author attempted to prepare organozinc compound of ethyl 2-bromoacrylate by using EGZn/Naph, and to apply the organozinc compound thus prepared to a palladium-catalyzed cross-coupling reactions with various aryl halides in order to synthesis ethyl 2-arylpropenoates, which would be one of several approaches to a synthesis of the precursor of

non-steroidal anti-inflammatory agents. In this paper, we report the successful use of EGZn/Naph in efficient cross-coupling of ethyl 2-bromoacrylate with aryl iodides or aryl bromides and in facile synthesis of the precursor of anti-inflammatory agents.

Result and Discussion

Electrochemical preparation of highly reactive zinc (EGZn/Naph)

Electrogenerated highly reactive zinc (EGZn/Naph) was readily prepared by electrolysis of a DMF solution containing 0.1M Et_4NClO_4 in the presence of naphthalene as a mediator in a one-compartment cell fitted with a platinum plate cathode (2x2 cm^2) and a zinc plate anode (2x2 cm^2).

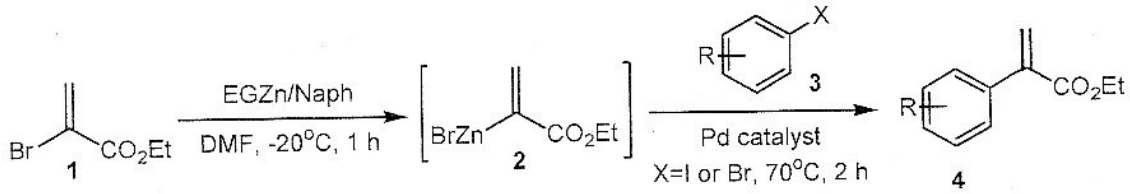


Scheme 1

Electrolysis at -10°C at a constant current of 60 mA/cm^2 in a nitrogen atmosphere was found to give highly reactive zinc metal, EGZn/Naph (Scheme 1).

Cross-coupling of ethyl 2-bromoacrylate with aryl halides using EGZn/Naph

A DMF solution containing EGZn/Naph was readily used in the preparation of organozinc compounds after the zinc anode was removed from the electrochemical cell. The reaction of ethyl 2-bromoacrylate (**1**) with the EGZn/Naph thus prepared (1.2 equivalents) at -20°C for 1 h gave quantitatively the corresponding organozinc bromide (**2**), which was confirmed by the quantitative formation of ethyl acrylate upon acid treatment.



Scheme 2

The reaction of **2** with aryl iodides **3** at 70°C for 2 h in the presence of 5 mol% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ gave the corresponding cross-coupled products **4** in high yields (Scheme 2). Similar reaction of **2** with aryl bromides occurred to give **4** in high yields when THF, instead of DMF, was used as a solvent. These results are summarized in Table 1.

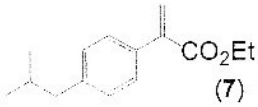
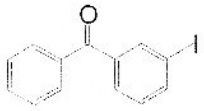
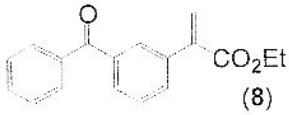
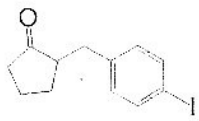
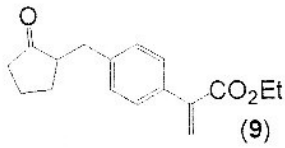
The present cross-coupling reaction using EGZn/Naph was successfully applied to an efficient synthesis of the precursor of various anti-inflammatory agents such as ibuprofen (7), ketoprofen (8) and loxoprofen (9) (Table 2).

Table 1. Synthesis of ethyl 2-arylpropenoates (4) by palladium-catalyzed cross-coupling of aryl halides (3) with organozinc bromide 2 prepared from EGZn/Naph and ethyl 2-bromoacrylate[a)]

entry	R of 3	Product	Yield of 4 (%)[b)] X = I	X = Br
1	H	4a	98	-
2	4-OCH_3	4b	98	99
3	4-CH_3	4c	98	99
4	3-CH_3	4d	96	-
5	2-CH_3	4e	84	-
6	4-CN	4f	97	98
7	4-CO_2Et	4g	98	93
8	2-CO_2Et	4h	51	-
9	4-Br	4i	96	-

a) Bromides **2**, prepared from ethyl 2-bromoacrylate (**1**, 3 mmol) and EGZn/Naph (6 mmol), in DMF was reacted at 70°C with aryl iodides (**3**, X=I, 2 mmol) in the presence of 5 mol % $Pd(P(o\text{-}Tol)_3)_2)Cl_2$. In the cross-coupling with aryl bromides (**3**, X=Br), the reaction was carried out in THF at refluxing temperature.
b) Isolated yields based on aryl halides employed.

Table 2. Synthesis of the precursor of anti-inflammatory agents by cross-coupling of organozinc bromide 2 with aryl iodides[a)]

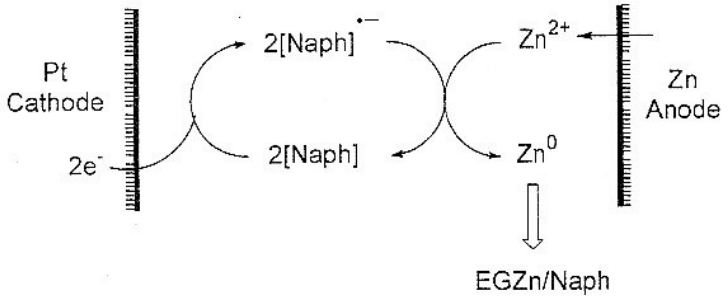
ArI	Products	Yield (%)[b)]
	 CO_2Et (**7**)	93
	 CO_2Et (**8**)	92
	 CO_2Et (**9**)	96

a) The reaction was carried out in the same way as that of the footnote a) of Table 1.
b) Isolated yields.

Reaction pathways

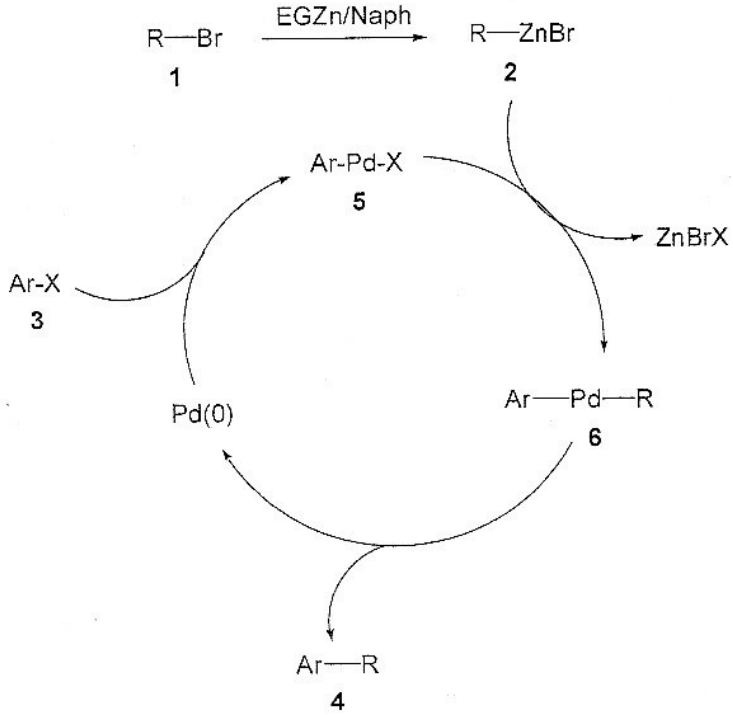
Probable reaction pathway for the formation of EGZn/Naph is shown in Scheme 3. At the cathode, a one-electron reduction of naphthalene molecule readily occurred to give naphthalene radical anion preferentially. The formation of the naphthalene radical anions was shown by the

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 EGZn/Naph.



Scheme 3

Probable reaction pathways of the present cross-couplings are shown in Scheme 4. Oxidative addition of Pd(0) to aryl halides would give Ar-Pd-X (**5**), which undergoes metal exchange reaction with organozinc bromide **2** to give an intermediate **6**. Reductive elimination of **6** would give the cross-coupling product, **4**.



Scheme 4

Conclusion

We developed a new electrochemical method for the preparation of highly reactive zinc (EGZn/Naph) by using naphthalene as a mediator in the electrolysis. The corresponding organozinc bromide could readily be prepared under mild conditions by the reaction of ethyl 2-

bromoacrylate with EGZn/Naph. Subsequent cross-coupling reaction of the organozinc bromide with various aryl iodides readily took place in the presence of a palladium catalyst to give the corresponding cross-coupled products, ethyl 2-arylpropenoates, in high yields. It was also found that this cross-coupling reaction could be applied to a synthesis of the precursor of anti-inflammatory agents such as ibuprofen, ketoprofen and loxoprofen.

Acknowledgement

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