Synthesis of Precursor of Anti-inflammatory Agents by Using Highly Reactive Zinc

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ABSTRACT

Highly reactive zinc metal was prepared by electrolysis of a *N,N*-dimethylformamide (DMF) solution containing naphthalene and a supporting electrolyte in a one-compartment cell fitted with a platinum cathode and a zinc anode. This highly reactive electrogenerated zinc (EGZn/Naph) was used for transformation of ethyl 2-bromoacrylate into the corresponding organozinc compound, which can not be achieved by the use of usual zinc metals. Reaction of the organozinc compounds thus prepared with various aryl halides in the presence of 5 mol% of palladium catalyst gave the corresponding cross-coupling products in high yields. These cross-coupling reactions were successfully applied to a synthesis of the precursor of anti-inflammatory agents such as ibuprofen, naproxen, cicloprofen and suprofen.

INTRODUCTION

2-Arylpropanoic acids represent an important class of therapeutically valuable non-steroidal anti-inflammatory agents and the physiological activity resides in the (*S*)-isomer, which relieves inflammation by inhibiting cyclooxygenase and therefore interdicting the arachidonic acid cascade (1). The asymmetric synthesis of anti-inflammatory agents has recently been studied extensively. One of the

most promising routes should be the one, which involves asymmetric hydrogenation of 2-arylpropenoic acids using a chiral transition metal catalyst (2). Therefore, our attention has been directed to an efficient preparation of 2-arylpropenoic acids or their derivatives.

Recently, we developed very efficient method for the synthesis of ethyl 2-arylpropenoates by cross-coupling reaction of organozinc compound, derived from ethyl 2-bromoacrylate and electrogenerated highly reactive zinc, with aryl iodides (3) or bromides (4) in the presence of a Pd(II) catalyst. In this paper, we report a successful application of these cross-coupling reactions to an efficient synthesis of the precursor of various anti-inflammatory agents such as ibuprofen, naproxen, cicloprofen and suprofen.

RESULT AND DISSCUSSION

Electrochemical Preparation of Highly Reactive Zinc (EGZn/Naph)

Highly reactive zinc was readily prepared by electrolysis of a DMF solution containing naphthalene and 0.1M Et_4NClO_4 in a one-compartment cell fitted with a platinum cathode and a zinc anode. Electrolysis at -10°C at a constant current of 60 mA/cm2 in a nitrogen atmosphere was found to give highly reactive zinc (EGZn/Naph). In this electrolysis, a one-electron reduction of naphthalene molecule gives naphthalene radical anions, which reduce zinc ions, generated by anodic dissolution of the zinc metal, to give zero-valent EGZn/Naph.

Cross-coupling Reaction Using EGZn/Naph

The reaction of EGZn/Naph with ethyl 2-bromoacrylate **1** gave efficiently the corresponding organozinc bromide **2** and the subsequent cross-coupling reaction with various aryl iodides **3** in the presence of palladium catalyst proceeded

efficiently to give ethyl 2-arylpropenoates **4** in almost quantitative yields (3) (Scheme 1).

We applied these efficient cross-coupling reactions to a synthesis of the precursor of anti-inflammatory agents. Cross-coupling reaction of organozinc bromide **2** with 4-isobutyliodobenzene **3a** gave the precursor of ibuprofen **4a** in 93% yield. Similar one-pot reactions of **2** with aryl iodides **3b-d** afforded the precursor of naproxen **4b**, cicloprofen **4c** and suprofen **4d** in high yields, respectively. Results are summarized in Table I.

ACKNOWLEDGEMENT

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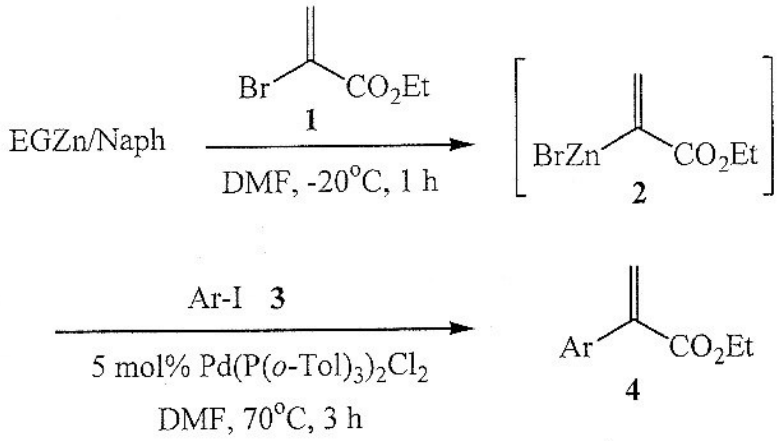
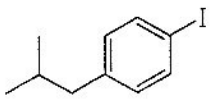
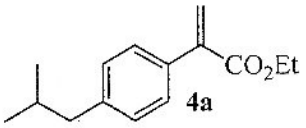
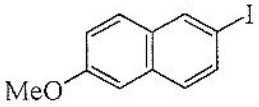
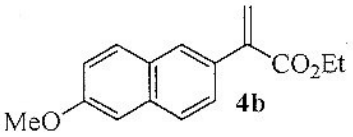
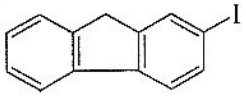
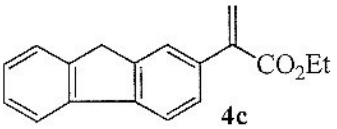
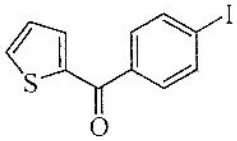
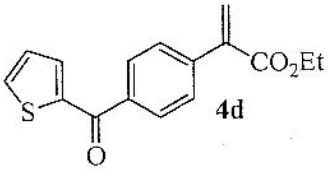


Scheme I

Table I. Synthesis of the Precursor of Anti-inflammatory Agents[a]

Aryl Iodide **3**	Product **4**	Yield (%)[b]
	 **4a**	93
	 **4b**	95
	 **4c**	87
	 **4d**	72

[a] Organozinc bromide **2**, prepared from ethyl 2-bromoacrylate **1** (3 mmol) and EGZn/Naph (6 mmol) in DMF was reacted at 70°C for 3 h with aryl iodides **3** (2 mmol) in the presence of 5 mol% of $Pd(P(o\text{-}Tol)_3)_2Cl_2$.

[b] Isolated yields based on aryl iodides.