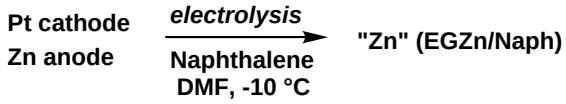
Use of Electrogenerated Highly Reactive Zinc in Facile Synthesis of 2-Arylpropenoic Acid Esters and Anti-inflammatory Agents

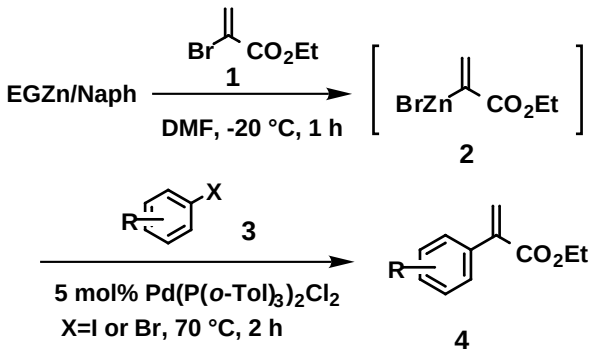
Masao Tokuda, Aishah A. Jalil, and Nobuhito Kurono

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University
Sapporo 060-8628, Japan

We have already reported a new method for preparation of reactive zinc (EGZn) by electrolysis[1-3] and its use in isoprenylation[1] and allylation[2,3] as well as cross-coupling of functionalized alkyl iodides with aryl halides.[4] @Recently, we further developed a new electrochemical method for preparation of more highly reactive zinc (EGZn/Naph) by using naphthalene as a mediator and used it in cross-coupling reaction of bromoalkanes with aryl halides.[5] 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 precursors of anti-inflammatory agents.



Highly reactive zinc (EGZn/Naph) 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.[5] The reaction of EGZn/Naph with ethyl 2-bromoacrylate (**1**) in DMF at –20 °C gave quantitatively the corresponding organozinc bromide **2**, which was confirmed by the quantitative formation of ethyl acrylate upon acid treatment. The reaction of **2** with aryl iodides at 70 °C for 2 h in the presence of 5 mol% of $Pd(P(o\text{-}Tol)_3)_2Cl_2$ gave the corresponding cross-coupled products **4** in high yields (Scheme 1). 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.



Scheme 1

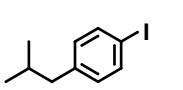
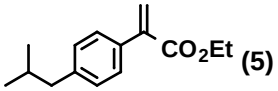
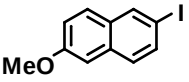
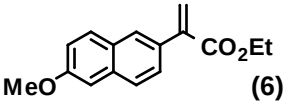
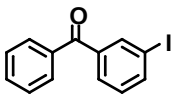
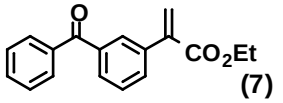
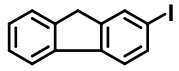
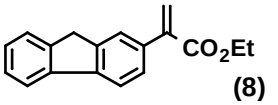
The present cross-coupling reaction using EGZn/Naph was successfully applied to an efficient synthesis of the precursor of various anti-inflammatory agents such as ibuprofen (**5**), naproxen (**6**), ketoprofen (**7**), and cicloprofen (**8**) (Table 2).

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) Organozinc bromide (**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% $Pd(P(o\text{-}Tol)_3)_2Cl_2$. 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)]
	 **(5)**	**93**
	 **(6)**	**95**
	 **(7)**	**92**
	 **(8)**	**87**

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

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4) Kurono, N.; Sugita, K.; Takasugi, S.; Tokuda, M. *Tetrahedron*, **1999**, *55*, 6097.
5) Tokuda, M.; Kurono, N.; Takasugi, S.; Jalil, A. A. "New Directions in Organic Electrochemistry" ed. by Fry, A. J. and Matsumura, Y. The Electrochemical Society, **2000**, 80.