Determination of Structure of Precursor of Ibuprofen:  
Purification and Analysis

Aishah Abdul Jalil1, Kurono Nobuhito2 and Tokuda Masao2

1Department of Chemical Engineering, Faculty of Chemical & Natural Resources Engineering,  
Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia.  E-mail: aishah@fkkksa.utm.my  
2Laboratory of Organic Synthesis, Division of Molecular Chemistry,  
Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Abstract

(S)-2-(p-isobutylphenyl)propanoic acid, so called ibuprofen, is one of the most popular anti-inflammatory agents. An efficient cross-coupling reaction of organozinc compound of ethyl 2-bromooctacylate, prepared by the reaction of highly reactive zinc was carried out with aryl iodide to synthesize 2-(4-isobutylphenyl)propanoate, a precursor of ibuprofen. Highly reactive 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. The synthesized precursor of ibuprofen was purified by thin layer chromatography on silica gel and its structure was confirmed by elemental analysis, mass, IR, H NMR and C NMR spectroscopic analysis.

Keywords: reactive zinc, organozinc compound, ibuprofen, thin layer chromatography

Introduction

(S)-Ibuprofen is one of the most popular anti-inflammatory agents and one of the ingredients of mostly used medicine for a cold due to its high potency. Therefore, an asymmetric synthesis of (S)-ibuprofen is an extremely important study. The author applied the efficient cross-coupling reaction of organozinc compound of ethyl 2-bromooctacylate, prepared by the reaction with EGZn/Naph, with aryl iodides in the presence of palladium catalyst [1] to a synthesis of ethyl 2-(4-isobutylphenyl)propanoate (4), a precursor of ibuprofen. Zhang et al. have already reported an asymmetric hydrogenation of 2-(p-isobutylphenyl)propenoic acid with Ru(S)-BINAP gave (S)-ibuprofen in a high enantioslectivity (Scheme 1) [2].

![Scheme 1](image-url)
Result and Discussion

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 (Scheme 2) [2]. The EGZn/Naph thus prepared can readily convert ethyl 2-bromo-2-acylate (1) to the corresponding organozinc compound (2) in an almost quantitative yield. Subsequent cross-coupling reaction of 2 with 1-iodo-4-isobutylbenzene (3) in the presence of 5 mol% Pd(P(o-Tol)₃)Cl₂ catalyst gave the crude product of ethyl 2-(4-isobutylphenyl)-propenoate (4) (Scheme 3).

\[
\begin{align*}
\text{Pt cathode - Zn anode} & \quad \xrightarrow{\text{electrolysis}} \quad \text{EGZn/Naph} \\
0.1 \text{M Et₄NClO₄ - DMF} & \quad \xrightarrow{\text{Naphthalene}} \\
\text{Scheme 2} \\
\end{align*}
\]

The synthesized crude product was purified by thin-layer chromatography on a Merck Kieselgel 60 PF₂₅₄ with ethyl acetate-hexane (1:5) to give 4, the precursor of ibuprofen in 93% yield. The structure of this ibuprofen was confirmed by IR, \(^1\)H NMR, \(^13\)C NMR, mass spectroscopic analysis and elemental analysis. Spectral data of 4 is shown below.

Colorless oil. IR (neat, cm⁻¹): 1720, 1615, 1512, 1466, 1367, 1199, 1181, 1089, 850, 806. \(^1\)H NMR (CDCl₃) δ: 7.34 (d, 2H, J=8.3 Hz), 7.13 (d, 2H, J=8.3 Hz), 6.28 (d, 1H, J=1.3 Hz), 5.87 (d, 1H, J=1.3 Hz), 4.29 (q, 2H, J=7.3 Hz), 2.48 (d, 2H, J=6.9 Hz), 1.87 (m, 1H), 1.33 (t, 3H, J=7.3 Hz), 0.91 (d, 6H, J=6.9 Hz). \(^13\)C NMR (CDCl₃) δ: 163.99, 142.41, 141.37, 130.91, 128.75, 125.45, 118.98, 60.90, 44.94, 30.01, 22.28, 13.95. EIMS m/z (relative intensity) 232(63), 189(100), 161(16), 145(15), 115(28). HRMS Calcld for C₁₅H₂₀O₂: m/z 232.1463. Found m/z 232.1472. Anal. Calcld for C₁₅H₂₀O₂: C, 77.55; H, 8.68. Found: C, 77.68; H, 8.83.

References