Determination of Structure of Precursor of *Ibuprofen*: Purification and Analysis

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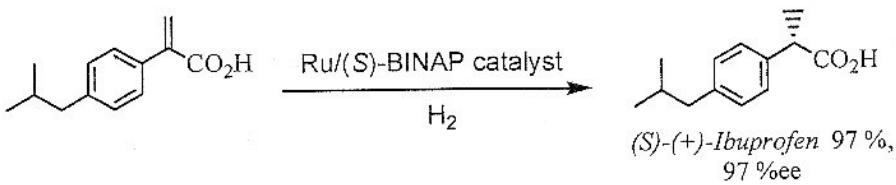
Abstract

(*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-bromoacrylate, prepared by the reaction of highly reactive zinc was carried out with aryl iodide to synthesize 2-(4-isobutylphenyl)-propenoate, 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, ^{1}H NMR and ^{13}C NMR spectroscopic analysis.

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

Introduction

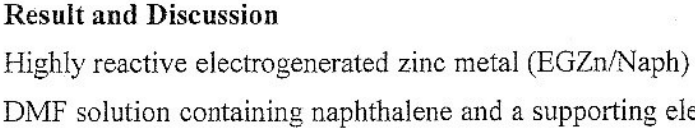
(*S*)-Ibuprofen is one of the most popular anti-inflammatory agents and one of the ingredients of mostly used medicine for a cold due to its high potency. Therefore, an asymmetric synthesis of (*S*)-ibuprofen is an extremely important study. The author applied the efficient cross-coupling reaction of organozinc compound of ethyl 2-bromoacrylate, 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)propenoate (**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 enantioselectivity (Scheme 1) [2].



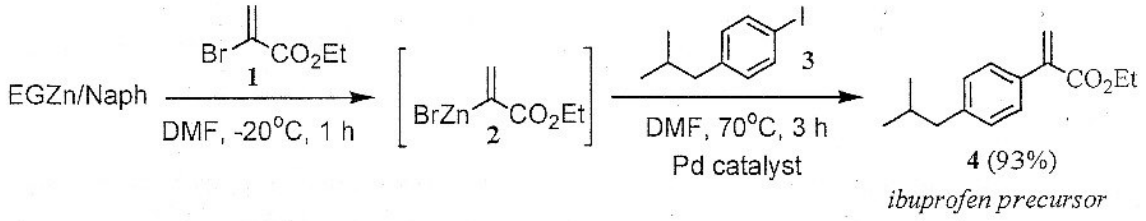
Scheme 1

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-acrylate (**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% $Pd(P(o\text{-}Tol)_3)_2Cl_2$ catalyst gave the crude product of ethyl 2-(4-isobutylphenyl)- propenoate (**4**) (Scheme 3).



Scheme 2



Scheme 3

The synthesized crude product was purified by thin-layer chromatography on a Merck Kieselgel 60 PF_{254} 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, ^1H NMR, ^{13}C NMR, mass spectroscopic analysis and elemental analysis. Spectral data of **4** is shown below.

Colorless oil. IR (neat, cm^{-1}) ν: 1720, 1615, 1512, 1466, 1367, 1199, 1181, 1089, 850, 806. ^1H NMR ($CDCl_3$) 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 ($CDCl_3$) 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 Calcd for $C_{15}H_{20}O_2$ *m/z* 232.1463. Found *m/z* 232.1472. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.68; H, 8.83.

References

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2. X. Zhang, T. Uemura, K. Matsumura, N. Ayo, H. Kumobayashi, H. Takaya, *Synlett* 501, (1994).