

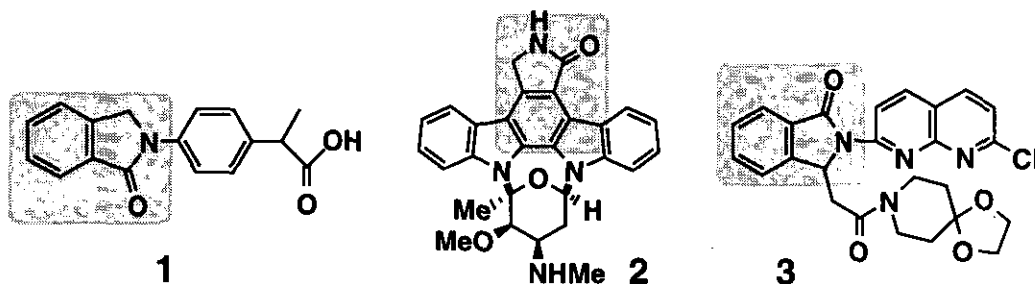
**APPLICATION OF THE PHTHALIMIDINE SYNTHESIS WITH
USE OF 1,2,3-1H-BENZOTRIAZOLE AND 2-MERCAPTO-
ETHANOL AS DUAL SYNTHETIC AUXILIARIES. PART 1.
A SIMPLE SYNTHESIS OF (±)-INDOPROFEN**

Ichiro Takahashi,* Etsushi Hirano, Teruki Kawakami, and
Hidehiko Kitajima

Department of Applied Chemistry and Biotechnology, Faculty
of Engineering, Fukui University, Bunkyo, Fukui 910, Japan

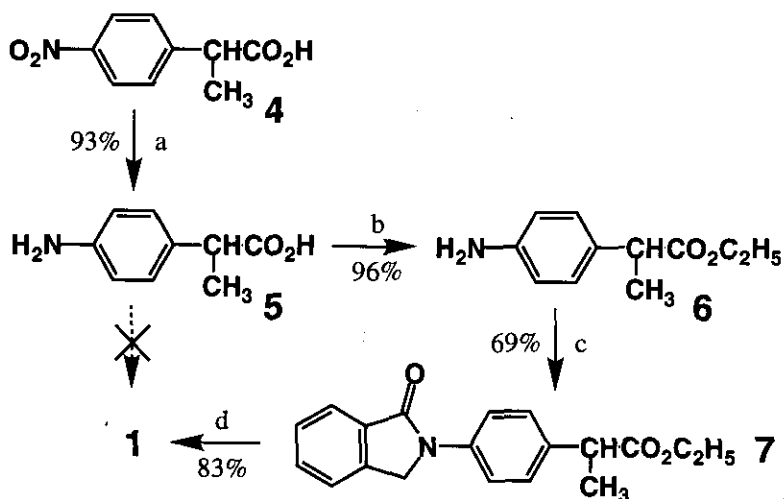
Abstract - A representative nonsteroidal anti-inflammatory drug *indoprofen* is prepared in 4 steps from the commercially available 2-(4-nitrophenyl)propanoic acid. The key step is the mild phthalimidine synthesis by the double Mannich condensation of *o*-phthalaldehyde with ethyl 2-(4-aminophenyl)propanoate with use of 1,2,3-1H-benzotriazole and 2-mercaptoethanol as dual synthetic auxiliaries.

Heterocyclic compounds possessing phthalimidine (2,3-dihydroisoindol-1-one) skeleton have attracted considerable synthetic interest in recent years, because a number of fascinating bioactive compounds such as indoprofen (**1**; anti-inflammatory agent), staurosporine (**2**; protein kinase C inhibitor), and DN-2327 (**3**; anxiolytic agent formerly known as pazinaclone) are involved.¹⁻³



Among them, **1** belongs to the "-profen" type nonsteroidal anti-inflammatory drugs (NSAID's),¹ and has been evaluated not only in clinical uses but also in bio-organic experiments, since phthalimidine derivatives are fluorescent.⁴ The industrial synthetic methods of **1**, however, involve multistep conversions of side chains (e.g., $-\text{COCH}_3 \rightarrow -\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$) after phthalimidine skeleton is complete, since the past phthalimidine syntheses were problematic due to severe reaction conditions or unseparable impurities.

In this report, we describe a short-step synthesis of (\pm)-**1** applying the recently unveiled mild phthalimidine synthesis.⁵ The key step is the double Mannich condensation between *o*-phthalaldehyde and an appropriately substituted aniline derivative, with use of 1,2,3-*H*-benzotriazole (Bt-H) and 2-mercaptoethanol as dual synthetic auxiliaries.



- a) H_2 (50 kg/cm²), 5% Pd-C, EtOH, room temperature, 45 min;
 b) EtOH, toluene, *p*-TsOH (1 eq.), reflux, 18 h;
 c) *o*-phthalaldehyde (1 eq.), Bt-H (1 eq.), 2-mercaptoethanol (8.6 eq.), MeCN, borate buffer (pH 9.6), room temperature, 13 h;
 d) KOH, 95% EtOH, 70 °C, 3 h.

Scheme 1

Our strategy is shown as Scheme 1,⁶ where commercially available 2-(4-nitrophenyl)propanoic acid (**4**)⁷ was chosen as the starting material. Thus, the catalytic hydrogenation of **4** [H_2 (50 kg/cm²), 5% Pd-C, EtOH, room temperature, 45 min] gave the corresponding amino acid (**5**) in 93 % yield (mp 133-134 °C). However, the prompt phthalimidine synthesis using **5** was

unsuccessful.⁸ Then, **5** was esterified by azeotropic dehydration (*p*-TsOH (1 eq.), EtOH reflux, 18 h) to afford **6** in 96 % yield (oil). The phthalimidine synthesis using amino ester (**6**) under the standard condition [*o*-phthalaldehyde (1 eq.), Bt-H (1 eq.), 2-mercaptoethanol (8.6 eq.), in MeCN-borate buffer (pH 9.6), room temperature, 13 h]⁵ gave indoprofen ethyl ester (**7**) in 69 % yield (mp 105-107 °C). Alkaline hydrolysis of **7** (KOH, 95% EtOH, 70 °C, 3 h) afforded (±)-**1** (mp 205-207 °C;⁹ lit., mp 213-214 °C^{1b}) in 83 % yield.

In summary, our phthalimidine synthesis is tolerate to the "-profen" moiety (-CH(CH₃)CO₂H), allowing the obtention of (±)-**1** from **4** in 51 % overall yield in 4 steps. Application to other bioactive skeletons are now underway.

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6. All (new) compounds exhibited satisfactory spectral data and physical constants (including CHN analyses and/or HRms measurements), respectively.
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8. This result is attributable to the existence of $-CO_2H$ moiety in **5**, which not only decreases the nucleophilicity of amino group, but also chelates instead of Bt^- , making the tethered ion pair intermediate (ref. 5) less reactive. As its proof, with use of *p*-toluidine as primary amine, we confirmed the phthalimidine synthesis to proceed under standard conditions using pivalic acid ($tBu-CO_2H$) instead of $Bt-H$, but in a low isolated yield (20%).
9. Different from ref. 1b, recrystallization from EtOH gave 1·1/3H₂O.

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