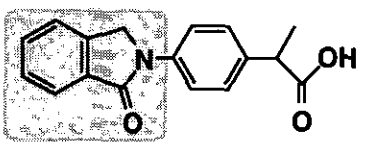
APPLICATION OF THE PHTHALIMIDINE SYNTHESIS WITH USE OF 1,2,3-1*H*-BENZOTRIAZOLE AND 2-MERCAPTOETHANOL AS DUAL SYNTHETIC AUXILIARIES. PART 1. A SIMPLE SYNTHESIS OF (±)-INDOPROFEN

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

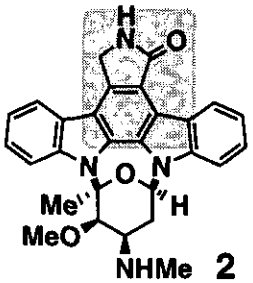
Department of Applied Chemistry and Biotechnology, Faculty of Engineering, Fukui University, Bunkyo, Fukui 910, Japan

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 1,2,3-1*H*-benzotriazole and 2-mercaptoethanol as dual synthetic auxiliaries.

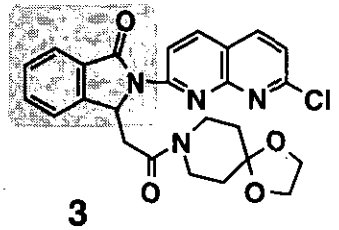
Heterocyclic compounds possessing phthalimidine (2,3-dihydroisoindol-1-one) skeleton have attracted considerable synthetic interest in recent years, because a number of fascinating bioactive compounds such as indoprofen (**1**; anti-inflammatory agent), staurosporine (**2**; protein kinase C inhibitor),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



1



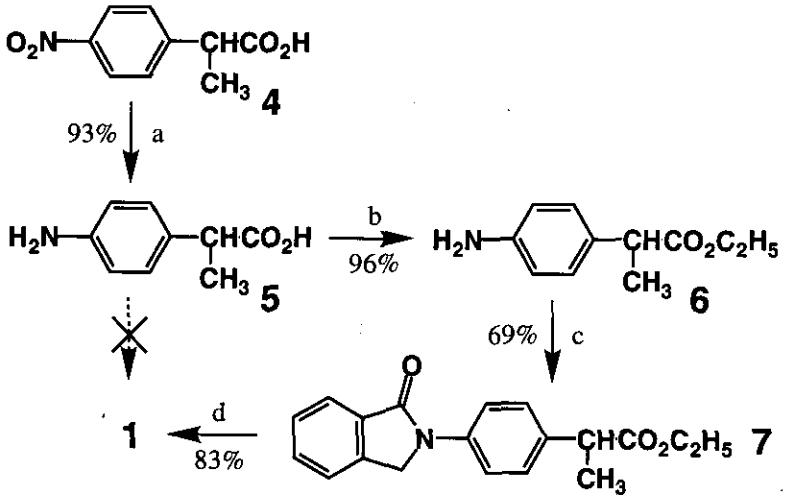
2



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.*, $-COCH_3 \rightarrow -CH(CH_3)CO_2H$) 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 (±)-**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 1,2,3-1*H*-benzotriazole (Bt-H) and 2-mercaptoethanol as dual synthetic auxiliaries.



a) H_2 (50 kg/cm^2), 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/cm^2), 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 (-$CH(CH_3)CO_2H$), allowing the obtention of (±)-**1** from **4** in 51 % overall yield in 4 steps. Application to other bioactive skeletons are now underway.

Authors are grateful to Dr. Kenji Koga (University of Tokyo) and Dr. Kimio Isa (Fukui University) for the courtesy of microanalyses and mass spectral measurements, respectively. We also thank Dr. Minoru Hatanaka (Fukui University) for useful discussions.

REFERENCES

1. (a) G. Nannin, P. N. Griraldi, G. Molgora, G. Biasoli, F. Spinelli, L. Logemann, E. Pradi, G. Zanni, A. Buttinoni, and R. Tommasini, *Arzneim-Forsch.*, 1973, **23**, 10. (b) T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, S. Haga, and K. Shirayama, *J. Heterocycl. Chem.*, 1978, **15**, 369. (c) K. Kigasawa, M. Hiiragi, H. Ishimaru, S. Haga, and K. Shirayama, *Japan Kokai Tokkyo Koho*, 1978, 78149970 (*Chem. Abstr.*, 1979, **90**, 186785w). (d) *idem*, *ibid.*, 1980, 7992954 (*Chem. Abstr.*, 1980, **92**, P76287u). (e) Hisamitsu Pharmaceutical Co. Inc., *Japan Kokai Tokkyo Koho*, 1980, 80149257 (*Chem. Abstr.*, 1981, **94**, 174879z). (f) S. Li, X. Wang, H. Guo, and L. Chen, *Yiyao Gongye*, 1985, **16**, 543 (*Chem. Abstr.*, 1986, **105**, 6378n). (g) M. C. Jiménez, M. A. Miranda, and R. Tormos, *Tetrahedron*, 1995, **51**, 2953.

2. (a) S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi, and R. Masuma, *J. Antibiot.*, 1977, **30**, 275. (b) T. Tamaoki, H. Nomoto, I. Takahashi, Y. Kato, M. Morimoto, and F. Tomita, *Biochem. Biophys. Res. Commun.*, 1986, **135**, 397.

(c) N. Funato, H. Takayanagi, Y. Konda, Y. Toda, and Y. Harigaya, *Tetrahedron Lett.*, 1994, **35**, 1251. (d) J. T. Link, S. Raghavan, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 552.

3. (a) T. Wada, R. Nakajima, E. Kurihara, S. Narumi, Y. Matsuoka, G. Goto, Y. Saji, and N. Fukuda, *Jpn. J. Pharmacol.*, 1989, **49**, 337. (b) Z. Hussein, D. J. Mulford, B. A. Bopp, and G. R. Granneman, *Br. J. Clin. Pharmacol.*, 1993, **36**, 357. (c) G. Goto and N. Fukuda, *Eur. Pat. Appl.*, 1994, EP602814 (*Chem. Abstr.*, 1994, **121**, 134102k). (d) H. Matoba, H. Koyama, and J. Kikuta, *Eur. Pat. Appl.*, 1994, EP610854 (*Chem. Abstr.*, 1994, **121**, 72998w).
4. Y. Tsuruta, Y. Date, and K. Kohashi, *J. Chromatogr.*, 1990, **502**, 178.
5. I. Takahashi, E. Hirano, T. Kawakami, H. Yokota, and H. Kitajima, *Synlett*, 1996, 353; references concerning past phthalimidine syntheses are cited therein.
6. All (new) compounds exhibited satisfactory spectral data and physical constants (including CHN analyses and/or HRms measurements), respectively.
7. (a) P. Trinius, *Ann. Chem.*, 1884, **227**, 262. (b) S. Opolski, Z. Kowalski, and J. Pilewski, *Ber.*, 1916, **49**, 2276. (c) M. Perchinunno, A. Guerrato, and F. Pregnolato, *Org. Prep. Proced. Int.*, 1977, **9**, 303. (d) G. P. Stahly and B. C. Stahly, *U. S. Patent*, 1984, USP4476315 (*Chem. Abstr.*, 1984, **102**, 5953x).
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**·1/3H_2O.

Received, 24th July, 1996