Indian Journal of Chemistry
Vol. 46B, January 2007, pp. 170-172

Alterntnate routes for the synthesis of ibuprofen piconol

C M Haricharan Raju[a], C Vijay Anand[a], P K Dubey[b] & Palle V R Acharyulu[c]*

[a]Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories, Bollaram Road, Miyapur, Hyderabad 500 050, AP, India

[b]Department of chemistry, college of Engineering, JNT University, Kukatpally, Hyderabad, 500072, AP, India

[c]Oncology Operations, Branded Formulations-II, Dr Reddy's Laboratories, Survey Nos 42, 45 & 46, Bachupalli, Qutubullapur, R R Dist. 500 072, AP, India

E-mail: raghupv@drreddys.com

Received 13 September 2005; accepted (revised) 18 September 2006

New, improved and alternate methods for the synthesis of ibuprofen piconol from ibuprofen and pyridine-2-methanol have been demonstrated with different carboxyl activating groups.

Keywords: Ibuprofen, piconol, NSAID, carbodiimide, chloroformate, hydroxybenzotriazole, dimethylaminopyridine

IPC: Int.Cl.[8] C07C

Arylpropionic acid derivatives ibuprofen, flurbiprofen etc., are class of compounds extensively used in anti-inflammatory and analgesic effects. They are distributed over the counter and their analogues act by (non-selective) inhibition of cyclooxygenase (COX) enzyme that is responsible for the biosynthesis of prostaglandins (PGs) and certain related autacoids. Ibuprofen is the most sought agent from this class of nonsteroidal anti-inflammatory drugs (NSAIDs). Ibuprofen piconol **3**, the pyridin-2-methanol ester of ibuprofen is very effective as topical anti-inflammatory agent in acne treatment[1-4] (**Chart 1**).

Literature method[5] for the synthesis of ibuprofen piconol involves preparation of acid chloride 4, using thionyl chloride followed by treatment with pyridine 2-methanol to furnish ibuprofen piconol **3** **(Scheme I)**.

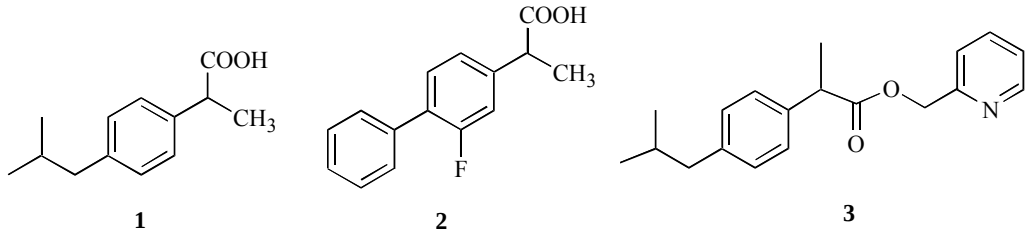
Recently, another route for the synthesis of ibuprofen piconol **3** appeared in literature[6] involving direct condensation of ibuprofen **1** and pyridine 2-methanol in presence of catalysts like clay and ion-exchange resin with improved atom economy.

Herein, we report alternate routes for the synthesis of Ibuprofen piconol **3**, employing activation of the carboxyl group of ibuprofen **1**, with different activating agents like carbodiimide, chloroformates etc., followed by treatment with pyridine 2-methanol, **Scheme II**. Reaction of ibuprofen **1** with pyridine 2-methanol in presence of dicyclohexylcarbodiimide delivered ibuprofen piconol **3** in very low yields. Formation of the biproduct, *N*-acyl urea **6** through the intermediary of **5** is identified as the major product. The reaction is observed to be very sluggish leading to the formation of the bi product **6** and the competitive reaction could be avoided by using suitable catalysts like 1-hydroxybenzotriazole (HOBT), dimethylaminopyridine (DMAP) etc. Subsequent reactions of ibuprofen and pyridine 2-methanol with dicyclohexylcarbodiimide (DCC) in presence of 1-hydroxybenzotriazole (HOBT), 4-dimethylaminopyridine (DMAP) observed to be fast resulting in the exclusive formation of ibuprofen piconol **3** in good yield.

The carboxyl functionality of ibuprofen could also be activated using mixed anhydride approach using isobutyl chloroformate, ethyl chloroformate etc. Reaction of ibuprofen and piconol with isobutylchloroformate or ethyl chloroformate furnished ibuprofen piconol in excellent yields. The spectral data of the isolated product is compared and concurrent with that of standard product.

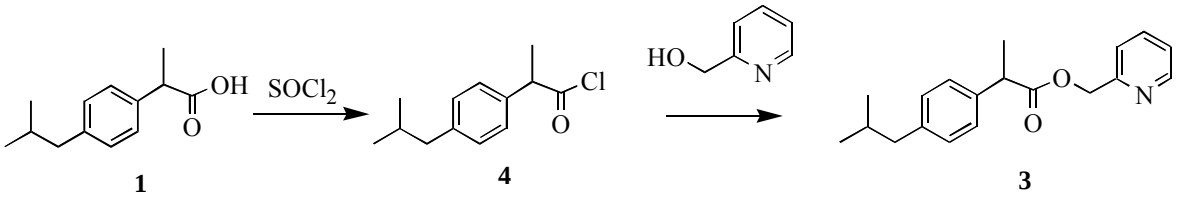
Experimental Section

Melting points were recorded on a Buchi Melting point apparatus in open capillary tubes and are uncorrected. TLC checking was done using pre-



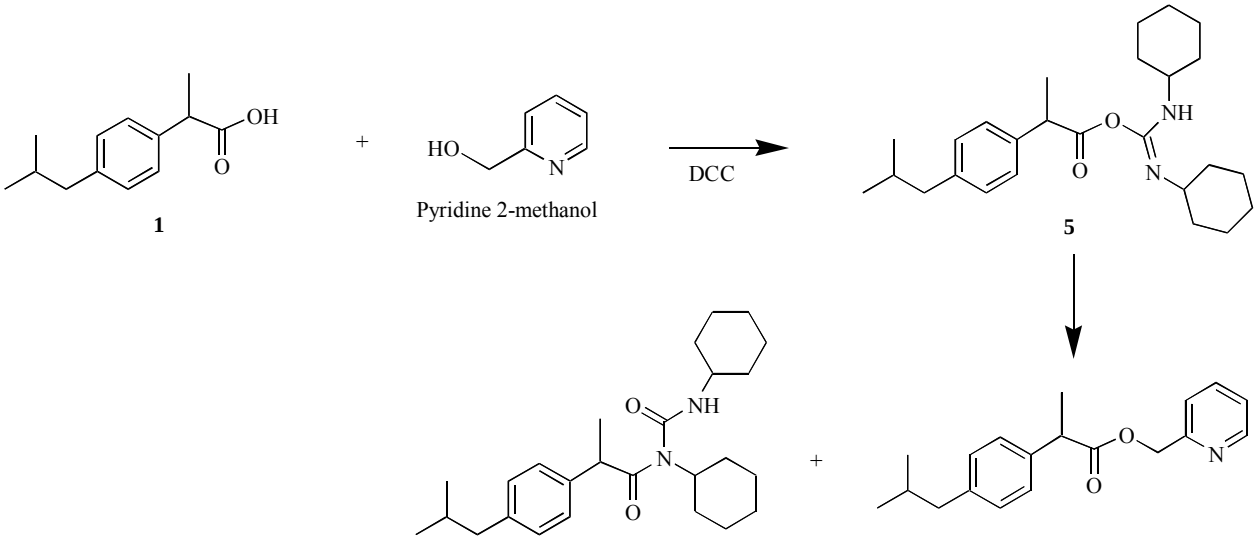
1 **2** **3**

Chart 1



1 **4** **3**

Scheme I



1 **5**

6 **3**

Scheme II

coated silica gel sheets obtained from Merck, Germany. ^{1}H NMR spectra were obtained on a Varian Gemini 2000 model 200 MHz instrument. (Chemical shift in δ, ppm) with TMS as internal standard; and mass spectrum run on HP5989 spectrometer.

Synthesis of ibuprofen piconol using DCC. To a cooled mixture of ibuprofen (0.0097 moles, 2 g), dichloromethane (20 mL) was added DCC (0.0097 moles, 1.99 g) followed by freshly distilled pyridine 2-methanol (0.0097 moles, 1.05 g) under stirring. The progress of reaction was monitored by TLC. After completion of reaction, the solid mass was filtered and washed with dichloromethane (10 mL) to separate urea. The filtrate was concentrated, purified by column chromatography to give *N*-acyl urea **6** (2.1 g, 53%); m.p. 158-61ºC; ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.9-1.0 (d, 6H, -CH_3), 1.4-1.5 (d, 3H, -CH_3-CH), 0.9-2.0 (m, 21H) 2.4-2.5 (d, 2H, -CH_2-CH), 3.5-3.7 (m-1H) 3.8-4.0 (m, 2H), 7.0-7.2 (m, 4H, Ar-H); ^{13}C NMR (200 MHz, $CDCl_3$, δ): 174.7, 154.0, 140.3, 138.8, 129.5, 126.8, 56.0, 49.6, 45.5, 44.9, 32.6, 32.4, 30.9, 30.3, 30.1, 26.3, 26.1, 25.4, 25.2, 24.6, 22.2, 22.1 and 20.9; ES-MS: 413(M+1); ibuprofen piconol **3** (10%, 0.28 g); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.9-1.0 (d, -6H, -CH_3), 1.4-1.5 (d, 3H-CH_3-CH), 1.7-2.0 (septet, 1H, -CH-(CH_3)$_2$), 2.4-2.5 (d, 2H, -CH_2-CH), 3.7-4.0 (q, 1H,-CH-CH_3), 5.2 (s, 2H-O-CH2-Ar), 6.9-7.2 (d, Ar-2H), 7.2-7.4 (dd, Ar-4H), 7.5-7.7 (t, Ar-1H), 8.4-8.6 (d, Ar-1H). ^{13}C NMR (200 MHz, $CDCl_3$: δ 173.8, 155.8, 148.9, 140.3, 137.2, 136.2, 129.1, 127.0, 122.3,

120.7, 66.4, 44.8, 44.7, 29.9, 22.1 and 18.1; ES-MS: 298(M+1); Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71; O, 10.76. Found: C, 76.64; H, 8.68; N, 4.47; O, 10.21%.

Synthesis of ibuprofen piconol using DCC/DMAP. To a mixture of ibuprofen (0.0097 moles, 2 g), dichloromethane (20 mL), DCC (0.0097 moles, 1.99 g) was added DMAP (0.0003 moles, 47 mg) at 10-15°C followed by freshly distilled pyridine 2-methanol (0.0097 moles, 1.05 g). The reaction mixture was stirred at room temp. After completion of the reaction, precipitated dicyclohexylurea was filtered and filtrate was washed with dilute hydrochloric acid, 10% $NaHCO_3$ and brine solution. The organic layer was concentrated to yield compound 3 (2.4 g, 83%)

Synthesis of ibuprofen piconol using DCC/HOBT. To a mixture of ibuprofen (0.0097 moles, 2 g), dichloromethane (20 mL), added DCC (0.0097moles, 1.99 g) and HOBT (0.0003 moles, 40 mg) at 10-15°C followed by slow addition of freshly distilled pyridine 2-methanol (0.0097 moles, 1.05 g) at 10-15°C and the reaction mixture was stirred at room temp. Reaction completed in 2 hr was confirmed by TLC. After completion of the reaction, precipitated dicyclo-hexylurea was filtered and filtrate was washed with dilute hydrochloric acid, 10% $NaHCO_3$ and brine solution, organic layer was concentrated to give product **3** (2.0 g, 70%).

Synthesis of ibuprofen piconol using ethyl-chloroformate. To a solution of ibuprofen (0.0145 moles, 3 g) in DCM (30 mL) was added TEA (0.0291 moles, 4 mL) at -10-15°C followed by ethyl-chloroformate (0.0189 moles, 1.8 mL) and pyridine 2-methanol (0.0145 moles, 1.58 g). After the completion of the reaction, the reaction mass was quenched with water and the organic layer was with 5% HCl, 10% $NaHCO_3$, water and brine solution. The organic layer was concentrated to give the product **3** (2.8 g, 97%)

Synthesis of ibuprofen piconol using isobutyl-chloroformate. To a solution of ibuprofen (0.0145 moles, 3 g) in dichloromethane (30 mL), between -10-15°C was added TEA (0.0291 moles, 4 mL), isobutylchloroformate (0.0189 moles, 1.8 mL) followed by pyridine 2-methanol (0.0145 moles, 1.58 g). The reaction mixture was stirred at room temp. and after the completion of the reaction, the reaction mass was quenched with water and the organic layer was with 5% HCl, 10% $NaHCO_3$, water and brine solution. The organic layer was concentrated to give the product **3** (2.5 g, 86%)

Acknowledgement

We thank the management of Custom Pharmaceutical Services, Dr. Reddy's Laboratories for permission to publish this work. Cooperation extended by all the colleagues of analytical research and development is highly appreciated.

References

1 Stewert S A & John S N, Compositions and method for treating symptoms of inflammation, pain and fever, *US Patent* 3,228,831, **1966**.

2 Stewert S A & John S N, Phenyl propionic acids, *US Patent* 3,385,886, **1968**.

3 Shiori T & Kawai N, *J Org Chem*, 43, **1978**, 2936.

4 Pinhey J T & Rowe B A, *Tetrahedron Lett*, 21, **1980**, 965.

5 Ishikura Y & Tosu S, Phenylacetic acid ester derivative, *DE Patent*, 2658610, **1977**.

6 Haricharan Raju C M, Nagalakshmi P, Srinivas Ch, Om Reddy G & Acharyulu P V R, *Synthetic Communications*, 35, **2005,** 209.