An improved and scalable process for the synthesis of a key intermediate for Etodolac, a non-steroidal anti-inflammatory drug

M Chandra Sekharayya\textsuperscript{a}, G Venkata Narayana\textsuperscript{b}, Satish Nigam\textsuperscript{c} & G Madhusudhan\textsuperscript{a}*

\textsuperscript{a}Department of Research & Development
\textsuperscript{b}Department of Analytical Research & Development

Ingent Laboratories Private Limited, A GVK BIO Company, 28A, IDA, Nacharam, Hyderabad 500 076, India

E-mail: madhusudhan.gutta@ingent.com; madhusudhan.gutta@yahoo.com

Received 1 August 2011; accepted (revised) 14 August 2012

An improved and scalable method is developed for the synthesis of 7-ethyltryptophol, a key intermediate for Etodolac, a non-steroidal anti-inflammatory drug (NSAID) starting from commercially available 2-ethylphenyl hydrazine and dihydrofuran with H\textsubscript{2}SO\textsubscript{4} as a catalyst in N,N-dimethylacetamide (DMAc)-H\textsubscript{2}O (1:1) as a solvent in 69% yield. The method is easy, inexpensive and reproducible and the process is clean, high yielding and operationally simple.

**Keywords:** Etodolac, 7-ethyltryptophol, 2-ethylphenylhydrazine hydrochloride, anti-inflammatory drug N,N-dimethylacetamide

Tryptophols (Figure 1) are derivatives of 2-(1H-indol-3-yl)ethanol (indole class which contain a C-3 hydroxyethyl chain). Tryptophol and its derivatives are generally extracted from various natural sources\textsuperscript{1} and some of these derivatives exhibit biological activity. Esters of 5-methoxytryptophol possess anticholinergic activity whereas 5-methoxytryptophol and other tryptophols have little or no activity\textsuperscript{2}. The production of tryptophol (tryptophan metabolism) has been implicated as one of the pathophysiological mechanisms that provoke sleeping sickness upon infection by trypanosomes\textsuperscript{3}. 7-Ethyltryptophol 1 is one of the important chemical entities and also has pharmaceutical importance, mainly used for the synthesis of Etodolac (Figure 1)\textsuperscript{4}.

Etodolac belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAID)\textsuperscript{5}. It has been released in the USA for the treatment of osteoarthritis in the dog. Etodolac has been shown to inhibit PGE2 synthesis by macrophages, but is even more effective in inhibiting PGE2 biosynthesis by chondrocytes and synoviocytes\textsuperscript{6}. A recent clinical trial demonstrated that etodolac was effective in improving rear limb function in dogs with chronic osteoarthritis secondary to hip dysplasia\textsuperscript{7}.

7-Ethyltryptophol 1, chemically designated as 2-(7-ethyl-1H-indol-3-yl)ethanol, is the key intermediate for Etodolac. The preparation of 7-ethyltryptophol 1 has been reported by two methods. One of which involves the reaction of 2-ethylaniline with 2,2,2-trichloroethane-1,1-diol gave the corresponding aldehyde which on further treatment with hydroxylamine hydrochloride obtained 7-ethylysinat. This 7-ethylysinat intermediate is elaborated to final product, 7-ethyltryptophol 1 in three steps via 7-ethyl-3-indolylglyoxylate\textsuperscript{8}. The second method includes the Fischer indole synthesis of 2-ethylphenylhydrazine hydrochloride and 4-hydroxybenzaldehyde\textsuperscript{9} or 2,3-dihydrofuran\textsuperscript{10}. The later synthetic approach reported for 7-ethyltryptophol 1 is described in numerous research articles including minor process modifications with varied yields ranging from 18 to 60% (Ref 9,10). The reaction is generally carried out in a water miscible ethereal solvent such as 1,4-dioxane, THF, glyme, diglyme or ethylene glycol monomethyl ether. However, upon attempting to repeat the reported procedure\textsuperscript{9,10}, we encountered some difficulties. While preparing the title compound by the reported method, we observed the inconsistency in the process, low purity and low yield, formation of various impurities, tedious work-up and difficulty in isolation.

**Results and Discussion**

As a part of the ongoing research programme on improving synthetic process for pharmaceutically important intermediates\textsuperscript{11}, we report herein the improved and scalable process of 7-ethyl tryptophol 1, a key intermediate for Etodolac (Scheme I).

In the preliminary study, the reaction of 1-(2-ethylphenyl)hydrazine hydrochloride 2 with dihydrofuran (DHF) 3 was tested with different acid catalysts such as HCl, H\textsubscript{2}SO\textsubscript{4}, CH\textsubscript{2}COOH, Amberlyst-15 and Amberlite-120 in 1,4-dioxane-H\textsubscript{2}O (1:1) at 80°C for 2 hr (Table I).
It was found that H$_2$SO$_4$ was superior to all the other catalysts examined and gave a good reaction conversion. During all reactions while preparing 7-ethyltryptophol, formation of a major impurity was observed (20-66% by HPLC), isolated by column chromatography and identified by LC-MS as 4,4-bis(7-ethyl-3-(2-hydroxyethyl)-1H-indol-2-yl)butan-1-ol (Figure 2). In aqueous system, the product and dihydrofuran were insoluble creating a highly concentrated ‘organic layer’ that resulted in formation of the triol by-product.

Encouraged by this result, the scope of this reaction in other solvents such as 50% aqueous acetonitrile, THF, 2-methyl THF, Monoglyme, DMF and N,N-dimethyleacetamide (DMAc) was investigated (Table II). It was found that the reaction proceeded smoothly and gave an excellent reaction conversion (78.68% of 7-ethyltryptophol by HPLC) using H$_2$O-DMAc (1:1) as solvent. It is also worthwhile to mention that under these conditions the formation of impurity was observed as low as 6% (by HPLC).

A tentative mechanism to rationalize the formation of the products is shown in Scheme II. The cyclic enol ether can be hydrated easily in the presence of the acid catalyst in water to give 5 which then undergoes facile ring opening in water to produce 6. The condensation reaction between 1-(2-ethylphenyl)hydrazine hydrochloride 2 and DHF under the present reaction conditions afforded 69% yield of the 7-ethyltryptophol.

In summary, a simple and general method for the synthesis of 7-ethyltryptophol, which offers several advantages including good yield has been developed.

**Experimental Section**

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron.
1H and 13C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d6 and CDCl3 as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.
Table II — Effect of solvent on the reaction of 2-ethylphenylhydrazine hydrochloride with dihydrofuran in the presence of H$_2$SO$_4$ at 80°C

<table>
<thead>
<tr>
<th>Entry No.</th>
<th>Solvent</th>
<th>Conversion by HPLC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O-CH$_3$CN (1:1)</td>
<td>24.60</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$O-THF (1:1)</td>
<td>67.34</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$O-2-MeTHF (1:1)</td>
<td>38.14</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$O-Monoglyme (1:1)</td>
<td>54.33</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$O-DMF (1:1)</td>
<td>48.03</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$O-DMAc (1:1)</td>
<td>78.68</td>
</tr>
</tbody>
</table>

HPLC (gradient mode) chromatograms were measured with the Alliance HPLC device with photodiode array (PDA) detector. Stationary phase: Zorbax SB-Phenyl, 4.6 mm × 250 mm, 5 µm was used for the analyses; column temperature was 40°C. The mobile phase A comprised of mixture of buffer solution pH 7.0 and methanol in proportion (80:20 v/v) and mobile phase B comprised of mixture of methanol and buffer solution pH 7.0 in proportion (80:20 v/v). The buffer solution was 0.05 M KH$_2$PO$_4$ solution adjusted to pH 7.0 with potassium hydroxide. Gradient mode with the flow rate of mobile phase 1.5 mL/min was used. Run time 40 min. Detection at the wavelength of 225 nm was used. Methanol was used as the solvent for the preparation of the samples; 20 µL of the solution was used for the injection. The gradient HPLC method was used for checking the analysis of compounds 1 and 3.

Preparation of 7-ethyltryptophol, 1. To a stirred solution of 1-(2-ethylphenyl)hydrazine hydrochloride 2 (100 g, 0.581 mol), H$_2$SO$_4$ (39.8 g, 0.407 mol) and DMAc-H$_2$O (2000 mL, 1:1), drop wise was added 2,3-dihydrofuran (40.7 g, 0.581 mol) at 80°C. After completion of the addition, the reaction mixture was maintained at the same temperature for 2-3 hr. The completion of reaction was monitored by HPLC. After completion of the reaction, reaction mixture was allowed to cool to RT and extracted with EtOAc (3 × 1000 mL). The combined organic layer was washed with water, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure gave the crude compound 1. The crude compound was further purified by fractional distillation at 160-70°C at 2 mmHg to give 1 as a light yellow color semi-solid (75.6 g); yield 69%; m.p. 42-45°C; HPLC purity 97.3%; $^1$H NMR (CDCl$_3$): δ 1.3 (t, 3H, J = 7.7 Hz), 1.6 (s, 1H, OH), 2.8 (q, 2H, J = 7.9, 15.5, 23.0 Hz), 3.0 (t, 2H, J = 6.0 Hz), 3.9 (t, 2H, J = 6.4 Hz) 7.0 (m, 3H), 7.4 (d, 1H, J = 8.0 Hz), 8.0 (broad s, 1H, NH); $^{13}$C NMR (CDCl$_3$): δ 13.9, 24.1, 28.9, 62.6, 112.5, 116.4, 119.6, 120.6, 122.0 126.5, 127.0, 135.1; ESI-MS: m/z (M$^+$−1) 188; IR (KBr): 3536, 3409, 1442, 1046, 751 cm$^{-1}$.

Acknowledgement
The authors thank Inogen Laboratories Private Limited (A GVK BIO Company) for the financial support and encouragement.

References