A DEVELOPED PROCESS FOR THE SYNTHESIS OF 2-ETHYL PHENYL HYDRAZINE HYDROCHLORIDE, A KEY STARTING MATERIAL FOR 7-ETHYL TRYPTOPHOL.

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ABSTRACT:
A developed process for the synthesis of 2-ethyl phenyl hydrazine hydrochloride, a key starting material for 7-ethyl tryptophol. Starting from commercially available 2-ethylaniline. First prepared a diazonium salt of aniline by using HCl and sodium nitrite at lower temperature and then reduced the diazonium salt with sodium sulfite and Cons. H2SO4 within 92% yield. The method is easy, inexpensive, without purification getting pure solid. The process is very clean, high yielding & high quality and operationally simple.

KEY WORDS:7-ethyl tryptophol, 2-ethyl phenyl hydrazine hydrochloride, 2-ethyl aniline, NaNO2, water.

INTRODUCTION:
Tryptophol is a chemical compound that induces sleep in humans1. It is formed in the liver after disulfiram treatment. It is also produced by the trypanosomal parasite in sleeping sickness. tryptophol are derivatives of indole class which contain a C-3 hydroxyethyl chain1,2. Tryptophol and its derivatives are communally extracted from various natural soures3. Some of the tryptophol derivatives exhibit biological activity4. Here 2-ethyl phenyl hydrazine hydrochloride is one of the important chemical moiety and it has a also pharmaceutical importance. 2-ethyl phenyl hydrazine hydrochloride is prepare from 2-ethyl aniline. 7-ethyl tryptophol mainly used for the synthesis of Etodolac5.

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Etodolac is a nonsteroidal anti-inflammatory drug (NSAID). The U.S. Food and Drug Administration approved etodolac in January 1991. Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Its therapeutic effects are due to its ability to inhibit prostaglandin synthesis. It is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. A recent clinical trial demonstrated that etodolac was effective in improving rear limb function in dogs with chronic osteoarthritis secondary to hip dysplasia.

2-ethyl phenyl hydrazine hydrochloride is the key intermediate for the preparation of 7-ethyl tryptophol. Here we are prepare 2-ethyl phenyl hydrazine hydrochloride from 2-ethyl aniline with improve the yield and quality. So we are getting better yield and quality in preparation of 2-ethyl phenyl hydrazine hydrochloride. The 2-ethyl phenyl hydrazine hydrochloride preparation has been reported by several methods. One of the reaction of 2-ethyl aniline prepare a diazonium salt with sodium nitrite and HCl and then reduced the diazonium salt with tin chloride. The second method is reduced the diazonium salt with sodium sulfite with base (sodium hydroxide). The reaction is generally carried out in water. However, upon attempting to repeat the reported procedure. 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.

**EXPERIMENTAL METHOD:**

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 corporation spectrum one), 1H and 13C CMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d6, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadruple mass spectrometer equipped with turbo ion spray interface at 375°C.

**Preparation of 2-ethylphenyl hydrazine hydrochloride,**

To a stirred cooled solution of Conc.HCl (250ml) at 0-5°C. drop wise added 2-ethyl aniline(100gm)in 30-45 mins at same temp. Stirred 15 mins and then further cooled it 0 to -5°C. Added fresh solution of NaNO2 (62.7gm NaNO2 + 85 ml water) in 1.5 hrs at same temp. Maintain the reaction mass for 45 mins at 0 to -5°C & check the presence of excess nitrosonium ion on starch paper. Dissolve 415.8gm sodium sulphite in 780ml water & cool it 0 to 5°C. add prechilleddiazonium salt solution to this white hazy solution at 0 to -5°C and stir for 60 mins at same temp. Heat the reaction mass up to 70-75 and drop wise added Conc. H2SO4 (200ml) and maintain the reaction mass for 15 mins at same temp. Cooled the reaction mass 20-25°C and stir for 60 mins at same temp. filtered the solid and washed the solid with chilled 25ml Conc. HCl. Make the slurry of above wet cake in 350ml Conc.HCl at 20-25C and stir the reaction mass for 120mins and then filtered the slid and washed the solid with chilled 25ml conc. HCl to give a light white powder (130gm), yield 94%, M.P.181-182°C., HPLC Purity : 99.3%, 1H NMR(DMSO): 1.16(t,3H), 2.59(q,2H), 6.94(t,1H), 7.01(d,1H), 7.11-7.18(q,2H), 7.90(s,1H), 10.26(s,2H) , CMR : 13.74,23.43,113.54,122.12,126.76,128.61,130.82,142.94 & IR: 3255, 2869, 2515, 1927, 1507, 1246, 1166, 1061, 927, 848, 796 cm⁻¹. Mass: 168.90
RESULTS & DISCUSSION:

As a part of our research involving synthetic process of 2-ethylphenyl hydrazine hydrochloride improving method for a key intermediate of 7-ethyl tryptophol.

In our study the reaction of 2-ethyl aniline with sodium nitrite was tested with different catalysts such as a Sodium sulfite and sodium hydroxide with sulfur oxide, Sodium sulfite and Conc. H₂SO₄, SnCl₂·H₂O, Zn dust and acetic acid and sodium sulfite at 65-75°C for 3 hrs (table-1).

![Figure 1- chemical structures of tryptophol, 7-ethyl tryptophol, 2-ethylphenyl hydrazine hydrochloride.](image)

Table 1- Reaction of 2-ethylaniline with NaN₂ in the presence of various catalyst.

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Catalyst</th>
<th>Conversion by TLC.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sodium sulfite and sodium hydroxide with sulfur oxide</td>
<td>70-75%</td>
</tr>
<tr>
<td>2.</td>
<td>Sodium sulfite and Conc. H₂SO₄</td>
<td>90-95 %</td>
</tr>
<tr>
<td>3.</td>
<td>SnCl₂·2H₂O</td>
<td>60-62%</td>
</tr>
<tr>
<td>4.</td>
<td>Zn dust and acetic acid and sodium sulfite</td>
<td>70-75%</td>
</tr>
</tbody>
</table>

It was found that H₂SO₄ was superior to all the other catalysts examined and gave a good reaction conversion. During all reaction while preparing 2-ethyl phenyl hydrazine hydrochloride formation of product observed (60-95% by TLC). It was found that the reaction proceeded smoothly and gave an excellent reaction conversion (90-95 % by TLC) using Conc.H₂SO₄ as a reducing catalyst.

In the preliminary study, the reduction stage of diazonium salt, if the sodium sulfite contains excess alkali, a black tar tends to form when the solution is warmed, and very little 2-ethylphenyl hydrazine is obtained.

In summary, a simple and general method for the synthesis of 2-ethyl phenyl hydrazine hydrochloride at 70°C, which offers several advantages including good yield has been developed.
Scheme-1

2-ethylaniline \[\rightarrow\] Diazonium salt \[\rightarrow\] 2-ethylphenyl hydrazine.HCl

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References:


