Reaction of Thiols with formaldehyde in Presence of succinimid and Reduction of Phenyl Tetrazole Derivative with Hydrogen and Borohydride

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Abstract: One of most the important compounds which have active hydrogen (substrate) is the thiols which used in a wide field in preparation of Mannich bases.

\[ R - \text{SH} + \text{CH}_2\text{O} + \text{H} - \text{N} \xrightarrow{\text{H}_2\text{O}} R - \text{S} - \text{CH}_2 - \text{N} \]

\[ R = \text{R - CH}_3 , \text{C}_2\text{H}_5 , \]

A large number of Mannich bases have been prepared as a biologically active compound (pharmacological, pesticides, bactericidal, fungicidal and tuberculostatic) and in order to correlate their structure and reactivity with their pharmacological activity such as.

\[ \begin{array}{c}
\text{NR}_2 - \text{CH}_2 \\
\text{Ar}
\end{array} \]

It has been reported that the reaction is easily proceeded by using primary and secondary amine beside formaldehyde. But when we tried the reaction of thiols as substrate and formaldehyde and succinimide instead of amine, the reaction did not proceed to give Mannich base but product were methylenene - bis - sulfide.

\[ 2R - \text{SH} + \text{CH}_2\text{O} \xrightarrow{\text{SUCCINIMIDE}} R - \text{S} \text{CH}_2 - \text{S} - R \]

Mannich base can go farther reaction such as (addition, substitution, cleavage, polymerization, hydrogenation) to produce numerous numberbof compound so we tried to hydrogenation tetrazole derivative which gave different product which depened on type of hydrogen on reagent.

Reduction of 2 - ethyl benzoyle - phenyl tetrazole which performed with hydrogen gas in methanol solution in presence palladium on carbon as catalyst, the tow products were separated by column chromatography.

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Reduction of 2 - methyl - 2 (2 - cycloheptane) - 5 - phenyl tetrazole.

The methanolic solution the ketone was refluxed with equimolar amount of potassium borohydride and the product is isolated and purified to give.

\[
\begin{align*}
\text{8} & \rightarrow \text{9} \\
\end{align*}
\]

and identified by C.H.N analysis and NMR spectra.

**Key words: Phenyl Tetrazole, Reaction, formaldehyde, Thiols, succinimid**

**Introduction:**

Mechanism of Mannich reaction:

The mechanism of Mannich reaction has been well investigated in different pH media, because the reaction can be carried out in basic or acidic condition and the used substrate and the amine reactant decide what condition is preferred.

\[
\begin{align*}
\text{10} & \rightarrow \text{11} \\
\end{align*}
\]

**Base – catalyzed reaction:**

The base – catalyzed reaction appears to involve the reaction of a carbonion (derived from the active hydrogen compound) with the aminomethylol by an SN\textsubscript{2} mechanism. The rate increase at higher pH – value.

\[
\begin{align*}
\text{12} & \rightarrow \text{13} \\
\end{align*}
\]

The reaction in acid media appears to involve the reaction of carbonium ion (derived from aminomethylol) with the active hydrogen compound. The rate is slower than for the reaction in basic media and is independent of pH at low pH values.

It has been reported than various thiophenols were used as the substrate in S – aminomethylation reaction carried out with ammonia and the primary or secondary and tertiary Mannich bases (10).

\[
\begin{align*}
\text{R - SH + CH}_2\text{O} + \text{H - N}_2\text{R'} & \rightarrow \text{R - S - CH}_2\text{ - N}_2\text{R'} \\
\end{align*}
\]

the most frequently used for the reaction were thiophenole and thionaphthol derivative [ 1,2 ].

Similar results were obtained with thiols. The Mannich bases were usually prepared by refluxing a mixture of thiols with formaldehyde and secondary amines for 30 min. secondary amine and formaldehyde in methanol yielding Benzylthiols (methylene –N– dyaikyl ) Thiol.[3,4].

An attempted synthesis of Mannich bases from thiols, formaldehyde and secondary amine we found the reaction give methylene – bis – sulfide instead of Mannich bases.
The know procedure for ethylene – bis phenyl sulfide preparation involve reaction of methylene chloride with reaction of thiol and formaldehyde.

According to the literature strong acid of hydrochloric acid is recommended and the mechanism of the reaction with succinimide is different. Here also a primary Mannich base formed from the thiol, formaldehyde and succinimide can react with excess of the thiol yielding the methylene – bis – sulfide [5,6,7,8].

Material; and Methods

1- Preparation of methylene – bis – sulfide

General procedure for the reaction of thiols with formaldehyde in presence of succinimide. 0.08 mole of formaldehyde and 0.08 mole of succinimide or methylacetamide were suspended in 50 ml of appropriate thiols. The mixture refluxed for 10 hours, the excess of thiols was evaporated under reduced pressure to dryness. The residue was purified and recrystallized with hexane.

Results:

2 R - SH + CH₂O → R - S - CH₂ - S - R

The following Table 1 shows the synthesized methylene – bis – sulfide (16).

<table>
<thead>
<tr>
<th>No.</th>
<th>Molecular formula</th>
<th>R</th>
<th>Yield</th>
<th>m.p°C</th>
<th>C</th>
<th>H</th>
<th>HNMR CoCl₂ S (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₄H₈S₂</td>
<td>C₄H₈CH₂</td>
<td>87</td>
<td>53</td>
<td>69.23</td>
<td>69.16 (S, 2H)</td>
<td>7.26 (m, 10H)</td>
</tr>
<tr>
<td></td>
<td>calc foun</td>
<td></td>
<td></td>
<td></td>
<td>6.15</td>
<td>6.31 (S4H)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>C₄H₈S₂</td>
<td>C₄H₈</td>
<td>72</td>
<td>40</td>
<td>67.24</td>
<td>67.46 (S, 2H)</td>
<td>7.3 (m, 10H)</td>
</tr>
<tr>
<td></td>
<td>calc foun</td>
<td></td>
<td></td>
<td></td>
<td>5.10</td>
<td>5.26 (S4H)</td>
<td></td>
</tr>
</tbody>
</table>

2- Reduction of 2 – ethylbenzoyl – S – phenyltetrazole:

3- It has been reported in literature that two types of product can be formed by reduction of ketonic Mannich bases with different types of reducing agent – besides the usual regent (hydrogen and catalyst , zinc and acid) some novel reducing agent have been recently introduced including the borohydride in an acidic medium, some borohydride and tri – butyltin hydride [9,10,11,12].

Excellent results were obtained by using sodium borohydride in alcohol as a reducing agent. Thus 2 – primary and secondary ethylaryl ketone were converted into the corresponding β – aminoalcohols by sodium borohydride (17).
aluminum hydride yielding allymine [13,14,15].

If reduction of acetylenic Mannich bases methyl iodide carried out with a metal hydride an alien is produced (19).

\[
\text{R - C} = \text{C - CH}_2 - \text{N} = R \quad \text{diisobulyl aluminum hydride} \quad \text{R - CH} = \text{C - CH}_2 - \text{N} = R
\]

The reduction of 2 – ethylbenzoyl – 5 phenyl tetrazole [16 , 17] which performed in methanol solution in the presence of palladium on carbon as a catalyst. The mixture was shacked under 40 ps hydrogen pressure for 6 hrs. The resultant reaction mixture showed two product on TLC – plate. After separation by Colum chromatography the product were defined.

Table 1: Yield and properties the product methl [(2-y) cyclohexane]-5-phenyl tetrazole.

<table>
<thead>
<tr>
<th>No.</th>
<th>Molecular formula</th>
<th>R</th>
<th>analysis</th>
<th>HNMR CoCl_3 (S/ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>C_{10}H_{16}N_{0}</td>
<td>OH</td>
<td>calc.</td>
<td>68.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>foun.</td>
<td>68.12</td>
</tr>
<tr>
<td>2</td>
<td>C_{10}H_{16}N_{1}</td>
<td>OH</td>
<td>calc.</td>
<td>67.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>foun.</td>
<td>67.46</td>
</tr>
</tbody>
</table>

Reduction of 2 – methyl (2 – y 1 – 1 cycloheptanone) – 5 phenyltetrazole by potassium borohydride.

An attempted catalytic hydrogenation of 2 – methyl (2 – y) – 1 – cycloheptanone) - 5 phenyltetrazole. Under the same condition failed. Neither increase of the hydrogen pressure nor extension of the reaction time did not give the positive result. In this case the borohydride reduction was method of choice. The methanolic Solution of the starting ketone was refluxed with equimolar amount of potassium borohydride for eight hours a typical work up the resulting alcohol was obtained.
References:
تفاعل الثابولات مع الفورملهيد بوجود السكتناياماد واختزال مشتقات الفنيل
تترازول مع الهدروجين وهيريد البورون

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الخلاصة:

ان المواد التي تم تحضيرها للمقدمة والتي تحتوي على الهدروجين فعل في تحضير (قاعدة مانخ) في الثابولات وتم فصلها بنجاح بواسطة الفورمةلة الهايدام وامين بالإضافة الى الاستغلال والثائدة ونشرت بعضة من الثبت ظلة (25).

R - SH + CH₂O + H - N → R - S - CH₂ - N - H₂O

R - S - CH₂ - S - R

وفي البحث هذا عندما اردن استعمال الثابول يوصى بوضع مادة أساسية وامينة السكناميد بيلا الامينات methylenene – واضافة الفورمةلة الهايدام لم تحلق على (قاعدة مانخ) وان كان النتيج هو (26).  

2R - SH + CH₂O → R - S - CH₂ - S - R

وضم_reduction

وتم تحضير مجموعة من هذه المشتقات والتأكد منها بناء التحالل المختلفة. إنهم منتصوب به (قاعدة مانخ) في القابلية على التفاعلات المختلفة ومنها (الاضافة، الاستبدال، الكسر، الهدروجة البديلة) لاطبقها لمواد جديدة لا يمكن تحضيرها بالطرق التقليدية. وقد تم تمت التحالل التي تترازول في هذا البحث واتخذت نتائج مختلفة اعتمادا على المادة المستعملة بالهدروجة (الهدروجين مع عامل مساعد أو KH₄BH₃) وقد فصلت المواد الناتجة وتقيمة واختيئت عند القيام بهدروجة (27) - ethyl benzoyl – phenyl tetrazole ووجود عامل مساعد اعملت خليط من مادتين [28, 29].

N - CH₂ - CH₂ - CH - ph

28

وتم فصل المادتين بوساطة جهاز Column chromatography بوصفه مثبناً وتم اجراء التحالل اللازمة. وكذلك تم تمت التحالل (30) -2 methylcycloheptan - 1 – one - 5 – phenyltetrazole، أدأ فشلت الهدروجة بوساطة الهدروجين والعامل المساعد حتى في زيادة وقت التفاعل ولكن باستخدام مادة تمت التحالل بسهولة وقد تم فصل النتائج والتأكد منه بوساطة التحالل المختلفة.

N - CH₂ - CH₂ - CH - ph + KBH₄ → N - CH₂ - CH₂ - OH

N - CH₂ - CH₂ - CH - ph

30

31

393