SYNTHESIS OF TETRAHYDRO-β-CARBOLINE ALKALOIDS

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ABSTRACT
Tetrahydro-β-Carboline alkaloids are formed from tryptamine and β-oxothioesters. InCl₃ catalyses the two component reaction afforded a condensed intermediate which further undergoes cyclisation in presence of TFA in DCM medium.

INTRODUCTION
Indole alkaloids are a class of alkaloids containing a structural moiety of indole; many of them include isoprene groups. It is one of the largest classes of alkaloids containing more than 4100 known compounds. They possess significant physiological activity and some of them are used in medicine. The amino acid tryptophan is the biochemical precursor of indole alkaloids.3

PREPERATION OF TETRAHYDRO-β-CARBOLINE USING β-OXODITHIOESTER AND TRYPTAMINE
A literature survey indicates that there is no strategies so far developed for the construction of the tetrahydro-β-carboline skeleton starting from β-oxodithioesters, whereas ketene N,S-acetals and dithioesters having electron withdrawing groups are known to produce 1,2,3,4-tetrahydro-β-carbolines on reaction with tryptamine through Bischler-Napieralski type cyclization.9 It was anticipated that the treatment of β-oxodithioesters with tryptamine in the present condition would afford the 1,2,3,4-tetrahydro-β-carbolines in single step, but tetracyclic [6,5,5,6] indole derivatives were obtained.12 We were interested to reexamine the work by isolating the intermediate thioamide and further cyclization. Herein, we report the preparation of 1,2,3,4-tetrahydro-β-carbolines from β-oxodithioesters in two steps(Scheme 1).

RESULTS AND DISCUSSIONS
In a typical experiment, a mixture of β-oxodithioester 1 (0.42g, 2.0 mmol), tryptamine 2 (0.32g, 2.0 mmol) and DCM (10 mL) was refluxed in a round bottom flask. The heterogeneous reaction mixture containing the solid tryptamine was refluxed for 2 hours, β-oxodithioester and tryptamine dissolves rapidly as the reaction proceeds, after 2 hours, the mixture turns to be clear oil, as indicated by TLC. The resulting mixture was quenched with water (25 ml) and extracted with ethylacetate (15
ml). The combined organic bilayer was separated using separating funnel and dried in NaSO₄. The resulting organic layer was then concentrated and separated by column chromatography on silica gel (EtOAc-Hexane, 1:9). The separated solid was recrystallized from warm EtOH. The structure of the 4-(2-(1H-indol-3-yl)ethylamino)-1-phenyl-1-thioxobutan-1-one (3) was fully confirmed by examining its properties with M.P., I.R. and N.M.R. As an extensive investigation, we have elaborated the synthesis of thioamide using catalytic amount of InCl₃ (10 mol%) under different solvents, Table 1.

Table 1. Synthesis of thioamide 11a under different conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time(hours)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Ethyl Acetate</td>
<td>12</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Reaction conditions: 1(0.5 mmol), 2( 0.5 mmol), InCl₃ (10 mol %) and solvent(15 mL)

The reaction under refluxing condition in other solvents such as ethanol, dichloroethane, chloroform and ethyl acetate were carried out. The reaction did not proceed in ethyl acetate but the reaction under dichloroethane affords good yield (80%). However, this condition also requires more time (3 hours) compare to DCM condition which needs less time with good yield (85%) in compared to the former. But, the reaction was far much better in dichloromethane (DCM).

In order to evaluate the scope of this catalytic system, the effect of different Lewis acids on the preparation of (3) under refluxing with DCM are shown in (Table-2). It was observed that FeCl₃, SnCl₄ gave moderate yields, but the reaction mixture showed multi spot as indicated by TLC. The best result was found with InCl₃ (10 mol %) and DCM (Table-1).

Table 2: The feasibility of different Lewis acids on the preparation of 25a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>FeCl₃ (10 mol %)</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>2.</td>
<td>SnCl₄ (10 mol %)</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>3.</td>
<td>InCl₃ (10 mol %)</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>4.</td>
<td>CuCl₂ (10 mol %)</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>5.</td>
<td>No catalyst</td>
<td>12</td>
<td>45</td>
</tr>
</tbody>
</table>

Reaction conditions: 1(0.5 mmol), 1( 0.5 mmol) and solvent(15 mL)

The same process was successfully extended to a range of structurally varied β-oxodithioester, and the corresponding thioamides were obtained in good yields (Table-3). Table 3. Synthesis of thioamide under refluxing condition.
The electron deficiency and the nature of the substituents on the aromatic ring affect the conversion rate; aromatic aldehydes having electron withdrawing groups on the aromatic ring (i.e. Cl) react faster than benzaldehyde and an electron-donating substituents (i.e. CH$_3$) deactived aryl aldehydes remarkably. Further, the isolated thioamides were further reacted for cyclization using TFA in DCM for 4 hours. The yield obtained after cyclization reaction for 3 was 83% which was confirmed using spectroscopic analysis and elemental analysis. The cyclization was also conducted using TsOH and benzene but the reaction time are far more greater than TFA and DCM combination, (Table 4).

Table 4. Synthesis of tetrahydro-β-carbolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$_1$</th>
<th>Time(hrs)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>C$_6$H$_5$</td>
<td>2</td>
<td>11a</td>
<td>78</td>
<td>120</td>
</tr>
<tr>
<td>2.</td>
<td>2-ClC$_6$H$_5$</td>
<td>2</td>
<td>11b</td>
<td>82</td>
<td>115</td>
</tr>
<tr>
<td>3.</td>
<td>4-ClC$_6$H$_5$</td>
<td>2</td>
<td>11c</td>
<td>87</td>
<td>118</td>
</tr>
</tbody>
</table>

Reaction conditions: 1d(0.5 mmol), 1(0.5 mmol), InCl$_3$(10 mol%) and DCM(15 mL).

In the $^1$H NMR spectrum of 11 a singlet at δ 2.45 was observed, which could be assigned to the –CH$_2$ lying between –C=S and –C=O. In the $^{13}$C NMR spectrum, the signals at δ 187.1 and 170.5 corresponds to –C=S and –C=O respectively. From the IR, the C=S stretching of 11 shows absorption at 1055 cm$^{-1}$. Whereas, in the $^1$H NMR spectrum of 12 a singlet at δ 2.45 was not observed for –CH$_2$ lying between –C=S and –C=O in thioamide, instead shown a peak in aromatic region for -CH. In the $^{13}$C NMR spectrum, the signal at δ 189.5 corresponds to –C=O was observed.

EXPERIMENTAL DETAILS

General:
All the reagents were commercial and purchased from Merck, Sigma Aldrich and were used as received. All $^1$H and $^{13}$C NMR spectra were recorded on Bruker 300 FT-NMR spectrometer. Chemical shifts are given as δ value with reference to tetramethylsilane (TMS) as the internal standard. The IR spectra were...
recorded on Shimadzu FT-IR spectrophotometer. All the reactions were monitored by TLC with precoated sheets of silica gel (Silica gel G) using I$_2$ Chamber for visualization and separated through column chromatography (Silica Gel 60-120 Mesh). Melting points were determined with Veego (VMP-1) melting point apparatus and are uncorrected.

**Preparation of Tetrahydro-$\beta$-carboline:**

To a round bottom flask, thioamide (2 mmol) was taken and 5 mL of dichloromethane was added. Catalytic amount of trifluoroacetic acid (20 mol %) was added to the mixture and was stirred for 4 hours (monitored by TLC). The reaction mixture is quenched in water (25 ml) and extracted with ethyl acetate (15 ml). The combined organic layer was separated and dried (Na$_2$SO$_4$), distilled and the product was purified by Column Chromatography on silica gel (EtOAc/Hexane, 1:9) to get pure tetrahydro-$\beta$-carboline (5d).

**Physical and analytical data of 5d**

(5d) obtained as yellow crystals (88%), mp 115 ̊C. IR (KBR); v=1633(C=O), v=3408(O-H), 1523 cm$^{-1}$.$^1$H NMR (CDCl$_3$) $\delta$=10.63(brs, NH,1H), 8.86(brs, NH,1H), 7.62-7.53(m, 6H), 7.37-7.34 (m, 2H), 7.19(s,1H), 3.69(s, 2H), 3.10(s, 2H). $^{13}$C NMR (CDCl$_3$) $\delta$=189.5, 165.1, 152.6, 141.4, 137.8, 130.7, 129.8, 129.0, 127.1, 126.5, 125.2, 120.4, 119.7, 117.4, 90.0, 40.1, 20.2 ppm.

**Spectral Data**

$^1$HNMR SPECTRA OF 5d:

![](image1)

$^{13}$CNMR SPECTRA OF 5d:

![](image2)
IR SPECTRA of 5d:

CONCLUSION
We have described a novel and facile synthetic procedure for the synthesis of tetrahydro-β-carblines by treating β-oxodithioesters and tryptamine in two steps. The procedure offers several advantages including mild conditions, cleaner reaction, and no side product, high yields of products as well as simple experimental and isolation procedures which make it a useful and attractive process for the synthesis of these compounds.

In these reactions, at least 3 different active sites are involved; one C-N bond, one C-C bond and one new ring are constructed with all reactants efficiently utilized in the chemical transformation. To the best of our knowledge, no report on the use of β-oxodithioesters as starting materials for the synthesis of tetrahydro-β-carblines systems is known.

REFERENCES