Synthesis of Some Substituted Benz/acetamidines

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Received 2006/7/17 Accepted 2005/12/7

ABSTRACT
In the present work the synthesis of substituted acetamidines was achieved. Phthalic anhydride was treated with p-aminobenzoic acid or glycine to give the corresponding acid which then converted to acid chloride with thionyl chloride. The acid chloride was treated with diethyl amine or dibutyl amine to give amides. The amides then converted to final products by their reaction with aniline or its substituents and POCI₃.

The structure of the synthesized compounds was confirmed by IR, UV and physical means.
INTRODUCTION

The synthesis of substituted imidines was studied in recent years as a program to develop new anticoagulants for the treatment of thrombotic disorders.

2-Hydroxy benzamidines have been prepared from 3-amino benzisoxazoles by reductive cleavage of nitrogen-oxygen bond using catalytic hydrogenation\(^{(1)}\). Phosgene was also reacted with 2 moles of acetonilide to give N,N'-diphenyl acetamidine\(^{(2)}\).

The aminolysis of gem-dichloroaziridine provides a convenient synthesis of amidines as compound\(^{(3)}\) (I).

\[
\text{Ph} - \text{C} = \text{N} - \text{Ph} \quad \text{(I)}
\]

Tetrakis (dimethyl amino) titanium reacts with N-mono substituted carboxamides to give trisubstituted amidines as in the following equation\(^{(4)}\).

\[
2 \text{R}_1\text{CONHR}_2 + \text{Ti[N(CH}_3)_2\text{]}_4 \rightarrow 2 \text{R}_1\text{C} - \text{N(CH}_3)_2 + \text{TiO}_2 + 2 \text{(CH}_3)_2\text{NH}
\]

\(\text{R}_1 = \text{CH}_3, \text{C}_6\text{H}_5\)

\(\text{R}_2 = \text{CH}_3\)

Amidines was prepared from nitriles by their reaction with amines or ammonium salts as in the following equations\(^{(5)}\).

\[
\text{PhNH}_2 \rightarrow \text{NH} \quad \text{Ph} - \text{C} - \text{NHPh}
\]

\[
\text{PhCN} \quad \begin{array}{c} \text{NH}_3 / 150^\circ \text{C} \\ \text{NH}_3 \text{Cl} \end{array} \quad \text{Ph} - \text{C} - \text{NH}_2
\]

The reaction of N-methyl benzamide with \(\text{TF}_2\text{O}_2\) in pyridine, then with Grignard reagents at \(-78^\circ \text{C}\) gave compound (I).
Compound (I) oxidized with DDQ/THF to give 2-alkyl pyrimidines.$^6$

Cyclic amidine was also prepared as in the following equation.$^7$

$$\begin{array}{c}
R-\text{NHCH}_2-C-\text{NH}-X-\text{NH}_2 \\
\text{1) 1% NaOH} \\
\text{2) 2N HCl} \\
\rightarrow R-\text{NHCH}_2-\text{N}\text{X} \\
\end{array}$$

$R = \text{NHSO}_2^-$

$X = \text{ethylene diamine, 1-phenylene diamine}$

The treatment of $\alpha,\beta$-unsaturated trifluoroketones with amidines in acetonitrile gave the corresponding 4-hydroxy-4-((trifluoromethyl)-3,5,6-trihydropyrimidines, which was dehydrated with phosphorus oxychloride then oxidation with manganese oxide, producing 2,6-disubstituted-4-(trifluoromethyl) pyrimidines.$^8$

**EXPERIMENTAL**

Melting points were measured using Electrothermal 9300 and are uncorrected. The IR spectra were recorded on Brucker FT-IR Spectrophotometer, Tensor 27, using KBr discs. The UV spectra were recorded on UV-Visible Shimadzu 1601 Spectrophotometer.

**Synthesis of acids (1-2):**

A mixture of p-aminobenzoic acid or glycine (0.01 mole) and phthalic anhydride (0.01 mole) was heated with shaking on a sand bath at (195-200 °C) for 10 min and then left at this temperature for 15 min. The product was solidify on cooling. Water (50 ml) was then added and filtered. The product was recrystallized from water to give white powder.$^9$

<table>
<thead>
<tr>
<th>Comp.</th>
<th>m.p.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>192-194 °C</td>
<td>85%</td>
</tr>
<tr>
<td>(2)</td>
<td>281-283</td>
<td>87%</td>
</tr>
</tbody>
</table>

Lit$^{10}$ 193-196

Lit$^{11}$ 284-286
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Synthesis of acid chlorides (3-4):
The acid (1 or 2) (0.05 mole) was mixed with thionyl chloride (0.05 mole) in a round bottomed flask fitted with condenser and drying tube. The mixture then refluxed for two hours (60-70 °C) with stirring, the excess thionyl chloride was evaporated under reduced pressure to give the products.[12]

| Comp. (3) | m.p. 83-85 °C | Yield 60% |
| Comp. (4) | m.p. 248-250 °C | Yield 70% |

Synthesis of amides (5-8):
Acid chloride (3 or 4) (0.01 mole) was dissolved in dry THF (15 ml), diethyl amine or dibutyl amine (0.01 mole) was added with stirring. The mixture was refluxed for two hours, cool and then water (30 ml) was added to give solid product, which was recrystallized from ethanol[12].

Synthesis of substituted amidines (9-20):
To amides (5-8) (0.37 mole) in dry benzene (50 ml), phosphorous oxychloride (23 g) was added with stirring, the mixture was allowed to stand at room temperature for 18 hrs. Aniline (11.6 g) was added dropwise keeping the temperature at 35 °C, then stirred for 6 hrs, and the mixture was extracted with benzene, then cold sodium hydroxide solution was added until the aqueous solution is basic. The benzene layer was separated and dried, then evaporated to give the product[5].

RESULTS AND DISCUSSION
The synthesis of substituted amidines was studied by many research worker and could be prepared using several methods. One of these methods is the condensation of nitriles with amines in presence of Friedal-Craft catalysts such as AlCl₃, BF₃, ZnCl₂, FeCl₃ and SnCl₄[5]. Other method was adjusted through substitution reaction which involve the reaction of amines with imidate[14] and imidoyl chloride[15].

In this paper some substituted benz/acetamidines were prepared from phthalic anhydride which was treated with p-aminobenzoic acid or glycine to give the corresponding acids (1 and 2), (Scheme 1), the prepared acids were identified by I.R and UV spectrum ν cm⁻¹ (1715-1725) (C=O) and (2935-2985) (O-H), λ_max (374-312) nm.

The acids (1,2) were then converted to the corresponding acid chloride (3,4) by their reaction with thionyl chloride. The acid chlorides (3,4) were treated with diethyl amine or dibutyl amine to give amides (5,6) and (7,8) respectively.
The compounds (5-8) show absorptions at $\nu$ cm$^{-1}$ (1621-1689) (C=O amide) and (1717-1724) (C=O), $\lambda_{\text{max}}$ (313-305) nm.

Final products were obtained by the reaction of amides with POCl$_3$ then with aniline and substituted aniline as in the following mechanism.

The physical spectral and data are listed in Tables (1) and (2).

9,11,13 $\begin{align*} R &= C_3H_5 \\ X &= CH_2 \\ Y &= NO_2, CH_3, H \end{align*}$

10,12,14 $\begin{align*} R &= C_3H_5 \\ X &= C_6H_4 \\ Y &= NO_2, CH_3, H \end{align*}$

15,17,19 $\begin{align*} R &= C_4H_9 \\ X &= CH_2 \\ Y &= NO_2, CH_3, H \end{align*}$

16,18,20 $\begin{align*} R &= C_4H_9 \\ X &= C_6H_4 \\ Y &= NO_2, CH_3, H \end{align*}$
Synthesis of Some Substituted Benz/acetamidines

Scheme (1)

Table (1): Physical and spectral data for compounds (5-8)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Colour</th>
<th>I.R. (KBr) v cm⁻¹</th>
<th>UV (EtOH) λ_max nm</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C=O amide</td>
<td>C=O</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>117-119</td>
<td>68</td>
<td>Brown</td>
<td>1660</td>
<td>1723</td>
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<td>6</td>
<td>137-139</td>
<td>59</td>
<td>Grey</td>
<td>1689</td>
<td>1722</td>
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<td>7</td>
<td>68-70</td>
<td>42</td>
<td>Brown</td>
<td>1668</td>
<td>1724</td>
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<tr>
<td>8</td>
<td>271-273</td>
<td>38</td>
<td>Grey</td>
<td>1621</td>
<td>1717</td>
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Table (2): Physical and spectral data for compounds (9-20)

<table>
<thead>
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<th>Comp. No.</th>
<th>m.p. °C</th>
<th>Yield %</th>
<th>Colour</th>
<th>I.R. (KBr) v cm⁻¹</th>
<th>UV (EtOH) λ_max nm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C=O</td>
<td>C=N</td>
<td>C-N</td>
</tr>
<tr>
<td>9</td>
<td>150-152</td>
<td>73</td>
<td>Yellow</td>
<td>1717</td>
<td>1621</td>
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<tr>
<td>10</td>
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<td>85</td>
<td>Yellow</td>
<td>1719</td>
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<td>1717</td>
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<tr>
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<td>1703</td>
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<td>1716</td>
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<td>20</td>
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<td>60</td>
<td>Brown</td>
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REFERENCES