An Efficient Synthesis of 1,3–Benzodiazine–2,4–diones Analogs

Fredryk Mandey

Department of Chemistry – Hasanuddin University
Jl.Perintis Kemerdekaan Km.10, Makassar – 90245
Ph. (0411) 586016, Fax. (0411) 588551

ABSTRACT

An investigation of base promoted reaction of phenylanthranilate and isocyanate has been carried out. The reaction between phenylanthranilate (11) and phenylisocyanate and n-butylisocyanate gave remarkable yields of corresponding 1,3–Benzo-diazine–2,4–diones (12a) and (12b).

Keyword: one-pot synthesis, heterocyclic compound.

INTRODUCTION

Puniani and Perlmutter [1] have reported successful results in preparing of an oxo–acetal type compound by reacting salicylates (1) with a variety of aldehydes (2) under base catalysis in high yields (Scheme 1).

\[
\begin{align*}
\text{(1)} & \quad \text{O} & \quad \text{Ph} & \quad + & \quad \text{R} & \quad \text{DABCO} & \quad \rightarrow & \quad \text{(3)} \\
\text{(2)} & \quad \text{OH} & \quad \text{O} & \quad \text{O} & \quad \text{R} & \quad \text{O} & \quad \text{O} & \quad \text{R} \\
\end{align*}
\]

Scheme 1

Under the same reaction condition Puniani [2] also found that 1,3–naphthoxazine–4–on (5) also could be prepared by simply reacting Phenylnaphthoate (4) and an aldehydes (Scheme 2).

\[
\begin{align*}
\text{(4)} & \quad \text{Ph} & \quad + & \quad \text{R} & \quad \text{DABCO} & \quad \rightarrow & \quad \text{(5)} \\
\text{(2)} & \quad \text{OH} & \quad \text{O} & \quad \text{O} & \quad \text{R} & \quad \text{O} & \quad \text{O} & \quad \text{R} \\
\end{align*}
\]

Scheme 2

More recently, Boontheung and Perlmutter [3] reported a highly efficient synthesis of 1,3–benzoxazine–2,4–diones (6), a typical oxo–aza cyclic systems, by reacting salicylic esters (1) with an alkyl and arylisocyanates under base catalysis. (Scheme 3)

\[
\begin{align*}
\text{(1)} & \quad \text{O} & \quad \text{Ph} & \quad + & \quad \text{RNCO} & \quad \text{Et}_3\text{N/DMAP} & \quad \text{DMF} & \quad \rightarrow & \quad \text{(6)} \\
\end{align*}
\]

Scheme 3

Synthesis of an oxo–aza cyclic system

An oxo–aza system was a type of six member ring heterocyclic analogs containing one oxygen and one nitrogen in its cyclic structure (7). (Figure 1)

\[
\begin{align*}
\text{(7)} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

Figure 1

Some of this ozaxine type molecules was found to be interesting because it posses several biological activities and practical application. This include antibiotics, anti-tuberculosis, anti-tumour, bactericidal and pesticide agents and as a dyes stuffs [4].

First convenient methods for making 1,3–oxazine derivatives (7a) was a ring closure of aminopropanol with an aldehydes or keton [5]. (Scheme 4)

\[
\begin{align*}
\text{HO} & \quad \text{NH}_2 & \quad + & \quad \text{R} & \quad \rightarrow & \quad \text{(7a)} \\
\end{align*}
\]

Scheme 4

Urbanski [6] also successfully prepared 5–nitro substituent of 1,3–oxazine (7b) by condensing propanediols with a
primary amine or ammonia and formaldehyde. (Scheme 5)

Scheme 5

Synthesis of a di-aza cyclic system

Several methods have been developed previously in synthesised 1,3-benzodiazine, an example of di-aza cyclic system. N3-substituted–2,4(1H,3H)–quinazolinediones (9) was formed when o-(ethoxycarbonylamino)–benzoic esters are heated together with a primary amine. (Scheme 6)

Scheme 6

Another example can be seen in the synthesis of quinazoline. Undergoes Hoffman degradation, phthalic acid diamides can be transformed into quinazolinediones (10) by heated with NaOCl via an isocyanate intermediate. (Scheme 7)

Scheme 7

Base Promoted synthesis of 1,3-Benzodiazine–diones

Substituted 1,3-benzodiazine–2,4–di-ones was found to be interesting because it possesses several biological activities such as anti-hypertensive agents [7]. Only few methods already developed in synthesising this particular type of molecules. In this research we proposed an efficient and simple methods of making this corresponding 1,3-benzodiazine–2,4–diones (12) by simply condensing Phenylanthranilic (11) and an isocyanate under base catalysis. (Scheme 8)

EXPERIMENTAL

Preparation of 3-Phenyl–1,3– benzodiazine–2,4–diones (12a)

A solution of phenyl-anthranilates (149.28 mg, 0.7 mmol), phenylisocyanate (166.76 mg, 1.4 mmol), Et3N (0.1 ml, 0.7 mmol), and DMAP (8.7 mg, 0.07 mmol) in DMF (1 ml) was stirred at 100°C. Reaction was stopped after 5 days (indicate by t.l.c which shown no starting material left) and continuing with the work-up by dissolving in 20 ml of diethyleter. The yellow precipitates, which formed, were filter off and the filtrate was evaporated to remove the solvent. The crude results were then recrystallized with diethyleter to give a pale brown product in a very good yields (0.134 gr, 80 %), m.p 289 – 292°C

FTIR (Nujol) : 3192.8 m, 3142.7 w, 3062 w, 1734.6 s (C=O), 1490.7 w, 1400.4 w, 1341.4 s, 1275 s, 1243.5 m, 1169.3 s, 966.4 s, 869.2 m, 800 s, 756.8 w, 722.1 w, 702.5 s cm−1

1H NMR (300MHz, CDCl3) δ 8.05 (dd, J 1.5 Hz, 7.8 Hz, 1H, H5), (ddd, J 1.8 Hz, 15.6 Hz, 1H, H6), 7.10 – 7.20 (m, 5H, N–Ar), 7.22 – 7.30 (td, J 1.06 Hz, 7.93 Hz, 1H, H8); 1.35 (t, J 7.04 Hz, 3H, –CH3)

Mass-spectrum : Calc’d for C14H10N2O2; m/z 238.0742 found : 261.0628 [M+Na+]

Preparation of 3-n-buthyl–1,3– benzodiazine–2,4–diones (12b)

A solution of phenylanthranilates (149.28 mg, 0.7 mmol), n-buthylisocyanate (138.78 mg, 1.4 mmol), Et3N (0.1 ml, 0.7
mmol), and DMAP (8.7 mg, 0.07 mmol) in DMF (1 ml) was stirred at 100 °C. Reaction was stopped after 19 days (t.l.c shown no starting material left) and continuing with the work-up by dissolving in 20 ml of diethyleter. The yellow precipitates that formed were filter off and the filtrate was evaporated to remove the solvent. The crude result was then recrystallized with diethyleter to give a bright yellow solids product in a very good yields (0.144 gr, 94 %), m.p 153 – 154 °C.

FTIR (Nujol) : 3360.9 w, 1712.1 s (C=O), 1588 w, 1408.9 s, 1278.7 m, 1239.7 s, 1199.9 s, 1077.8 s, 1047.2 s, 763.0 m, 748.3 m, 722.2 m, 692.1 s cm⁻¹

¹HNMR (300MHz, CDCl₃) δ 8.12 (dd, J 1.2 Hz, 8.1 Hz, 1H, H5), 7.60 (td, J 1.8 Hz, 8.7 Hz, 1H, H6), 7.20 (m, 4H, −Ar), 7.10 (td, J 4.8 Hz, 13.5 Hz, 1H, H7), 4.10 (t, J 7.5 Hz, 1H, −NH), 3.30 (t, J 6.6 Hz, 2H, −CH₂−), 1.60 (sextet, 2H, −CH₂−), 1.40 (sextet, 2H, −CH₂−), 1.0 (q, 3H, CH₃).

Mass-spectrum : calc’d for C₁₀H₉N₂O₂; m/z 230.0252 found : 231.1643 [M+H⁺]

RESULT AND DISCUSSION

In attempting the corresponding 1,3−Benzodiazine−diones, phenylanthranilates and isocyanate was mixed together with base catalyst under reflux condition in the ratio of phenylanthranilate : isocyanate : Et3N : DMAP = 1 : 2 : 1 : 0.1 (Scheme 8 ). A result of this reaction was stated in Table 1.

As it seen in Table 1, the yields were remarkably good even it took longer time to be completed. The longer reaction time is causing by two main factors which are, a tendency of slow reaction of phenylanthranilate to be deprotonated by the base catalyst in order to form the phenoxide intermediate and a possibility of the adduct to form an aza-carbamate instead of forming the desired product. A plausible mechanism for this transformation can be seen in Figure 2.

![Figure 2](image-url)

Initially phenylanthranilate is deprotonated to produce an intermediate A. This intermediate A then was added to the isocyanate in a reversible step to provide the adduct B. Finally the adduct B then cyclizes to the cyclic intermediate C followed by a loss of phenoxide ion to give the desired product.

Table 1. Result from base promoted reaction of phenylanthranilates and isocyanate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RNCO (R)</th>
<th>Product</th>
<th>Temp (°C)</th>
<th>Reaction time (days)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phenyl</td>
<td>12a</td>
<td>100</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>n-butyl</td>
<td>12b</td>
<td>100</td>
<td>19</td>
<td>94</td>
</tr>
</tbody>
</table>

CONCLUSION

This research have demonstrated one-pot synthesis of particular heterocyclic molecule analogs, 1,3−benzo-diazine−2,4−diones, with a fashionable yields. These results in the future could lead to the synthesis of other heterocyclic molecules with a similar core structure.

REFERENCES