Facile thermal rearrangement of Lorazepam and Oxazepam

Maravanahalli S Siddegowda,
Hemmige S Yathirajan* & Ramesha A Ramakrishna*
Research and Development Division, R L Fine Chem., No. 15,
KHB Industrial Area, Yelahanka New Town,
Bangalore 560 106, India

*Department of Studies in Chemistry, University of Mysore,
Manasagangotri, Mysore 570 006, India

E-mail: ramesha63@hotmail.com

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Lorazepam 1, a very well known anti-convulsant undergo facile thermal rearrangement at about 110°C to 6-chloro-4-(o-chlorophenyl)-2-Quinazolinecarboxaldehyde 10 in almost quantitative yield. Oxazepam 2 which is structurally similar, require higher temperature for the similar rearrangement to give 6-chloro-4-phenyl-2-quinazolinecarboxaldehyde 11. However, structurally similar temazepam 3 did not undergo this rearrangement.

Lorazepam 1, oxazepam 2 and temazepam 3 are very well known pharmaceutically active benzodiazepine class of compounds having similar structure. The structural difference between 1 and 2 is a chlorine atom attached to one of the benzene ring (Figure 1), whereas, temazepam 3 is N-methylated form of 2.

These compounds 1, 2, 3 have been invented about 4 decades ago 1-3 and have been used regularly as effective anti-convulsant. All these compounds have unstable hemi-acetal imino functional group and therefore unstable under both acidic and basic conditions 4. Lorazepam 1 on acid hydrolysis gives mainly corresponding benzophenone 4 and quinazoline aldehyde 10 in about 22% yield 4,5. Whereas under basic condition, it rearranged to diamido product 5 (Scheme I).

Similarly oxazepam 2 on acid hydrolysis 6,7 gives corresponding benzophenone 6. Under basic condition it gives quinazoline carboxylic acid 7 (Scheme II) as the major product.

Ring expansion, ring contraction and rearrangement of other benzodiazepine molecules have been very well documented in the literature 5,8-10. While considerable amount of work has been done about the acid and base catalyzed reactions of these compounds, there is not much information available on the thermal rearrangements of these compounds under neutral conditions 10c. Compounds 10 and 11 are known pharmacopeia impurity of lorazepam and oxazepam 10b and therefore there is a need to develop a convenient procedure for the synthesis of 10 and 11.

In this context, it was decided to explore the possibility of synthesis of 10 and 11 by thermal methods.

Results and Discussions

Initial attempts to synthesize 10 from the known literature procedures 4,5 gave low yield and impure product. Since quinazoline aldehyde 10 is dehydrated form of lorazepam 1, it was decided to see whether it can be rearranged/dehydrated to get 10 under thermal condition. Thus when 1 was refluxed in toluene for 24 hr, it rearranged completely to 10 (entry 1, Table I) in almost quantitative yield (Scheme III) with a loss of water molecule.

Based on the structural similarity of lorazepam 1 and oxazepam 2, we expected 2 also to undergo this rearrangement under identical conditions. However, it was surprising that 2 did not undergo rearrangement under identical toluene reflux condition (entry 2, Note

Figure 1 — Structure of Lorazepam, Oxazepam and Temazepam
Table I). The remote effect of chlorine atom of 1 which was driving the rearrangement was puzzling. At this point of time, it was difficult to conclude that steric factor alone is responsible for this rearrangement and therefore, it was postulated that it could be either weak hydrogen bond between Cl and OH of 1 or the electronic effect from the chlorine atom is responsible for thermal rearrangement. However the X-ray data of single crystal of lorazepam\textsuperscript{11-13} did not show any information on the hydrogen bonding. Therefore, it was decided to force the thermal rearrangement of oxazepam 2 under higher temperature by refluxing in xylene. When 2 was refluxed in xylene for 24 hr, it underwent clean thermal rearrangement to the quinazoline aldehyde 11 in almost quantitative yield (entry 3, Table I).

Temazepam 3 (entry 4, Table I) did not undergo thermal rearrangement neither in toluene nor in xylene under reflux condition for even after 24 hr (entry 4, Table I).
Scheme III — Rearrangement of Lorazepam and Oxazepam

Table I — Thermal rearrangement of Lorazepam and Oxazepam and their acetates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction condition</th>
<th>Time (hr)</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lorazepam</td>
<td>Quinazoline aldehyde, $X=Cl$, 10</td>
<td>Reflux in toluene</td>
<td>24</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>No reaction</td>
<td>Reflux in toluene</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Oxazepam</td>
<td>Quinazoline aldehyde, $X=H$, 11</td>
<td>Reflux in Xylene</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>No reaction</td>
<td>Reflux in toluene /xylene</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No reaction</td>
<td>Reflux in toluene /xylene</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>No reaction</td>
<td>Reflux in toluene /xylene</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*aYield refers to isolated yield.
To see whether this reaction proceeds if the hydroxyl group is protected, acetyl lorazepam 8 (entry 5, Table I) and acetyl oxazepam 9 (entry 6, Table I) were subjected to reflux under identical condition in toluene and xylene. As expected there was no rearrangement and the starting material recovered in both the cases. Therefore, it is evident that hydroxyl group is essential for the rearrangement of these compounds under thermal condition.

The possible mechanism of this facile rearrangement is explained in the Scheme IV. This mechanism is further supported by the fact that temazepam 3, which is having an N-Methyl group, does not undergo this rearrangement. We believe the favourable rearrangement of lorazepam and oxazepam could be due to the easy formation of stable six-membered heterocyclic ring.

**Experimental Section**

All solvents and reagents were purchased from suppliers and used without further purification. Yields reported are for isolated yield unless otherwise stated. \(^1^H\) NMR (300 MHz) and \(^{13}\)C NMR (75 MHz) spectra were recorded in CDCl\(_3\) on a spectrometer at RT. The chemical shift is based on internal TMS. Analytical TLC was performed on Merck silica gel (60 GF\(_{254}\)) plates (0.25 mm) and components were visualized with ultraviolet light (254 nm wavelength) and iodine vapours.

Lorazepam, oxazepam and temazepam and their acetates were prepared as per the procedure described in the literature\(^1^3\).

**Synthesis of 6-chloro-4-(o-chlorophenyl)-2-quinazoline carboxaldehyde, 10**

Lorazepam (10 g, 31.15 mmol) was added to toluene (50 mL) in a 250 mL Dean stark apparatus under nitrogen atmosphere. Reaction mixture was refluxed and the progress of the reaction was monitored by TLC. After 24 hr, the reaction mixture was cooled to 5-8°C and the white crystals thus obtained were filtered and dried under vacuum for 6 hr at 70-75°C to get 10 as white crystalline product (9.23 g, 97.8%) which is pure compound confirmed by NMR studies and does not require any further purification. m.p. 176-78°C, (Lit\(^5\) 177-78°C); IR (KBr): 1721, 1385, 823 cm\(^{-1}\); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 10.31 (s, 1H), 8.30 (d, \(J = 6.7\) Hz, 1H), 7.99 (dd, \(J = 6.6, 1.6\) Hz, 1H), 7.72 (d, \(J = 1.7\) Hz, 1H), 7.52-7.48 (m, 4H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 191.3, 167.9, 155.3, 149.1, 136.6, 136.1, 134.8, 132.7, 131.7, 131.4, 130.9, 130.2, 127.3, 126.0, 124.8.

**Synthesis of 6-chloro-4-phenyl-2-quinazoline carboxaldehyde, 11**

Oxazepam (10 g, 34.87 mmol) was added to toluene (50 mL) in a 250 mL Dean stark apparatus under nitrogen atmosphere. Reaction mixture was refluxed and the progress of the reaction was monitored by TLC. After 24 hr, the reaction mixture was cooled to 5-8°C and the white crystals thus obtained were filtered and dried under vacuum for 6 hr at 70-75°C to get 11 as white crystalline product (8.99 g, 96%) which is pure compound confirmed by NMR studies and does not require any further purification. m.p. 176-78°C, (Lit\(^5\) 177-78°C); IR (KBr): 1722, 1481, 854, 817 cm\(^{-1}\); \(^1^H\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 10.31 (s, 1H), 8.28 (d, \(J = 6.7\) Hz, 1H), 8.20 (d, \(J = 6.6, 1.29\) Hz, 1H), 7.96 (dd, \(J = 6.7, 1.5\) Hz, 1H), 7.83-7.62 (m, 2H), 7.63-7.60 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 191.3, 167.9, 155.3, 149.1, 136.6, 136.1, 134.8, 132.7, 131.7, 131.4, 130.9, 130.2, 127.3, 126.0, 124.8.\(\text{HRESI-MS: } m/z\) M\(^+\) + Na, found 291.0302. C\(_{15}\)H\(_8\)ClN\(_2\)O\(_2\)Na requires 291.0301.
Conclusion

In a nut shell, it has been possible to bring about the thermal rearrangement of lorazepam 1 and oxazepam 2 in almost quantitative yield in pure form. This method provides an easy access to pure quinazoline aldehyde 10 and 11, which are known pharmacopeia impurities.

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Supporting Information Available

Spectral characterization data, $^1$H and $^{13}$C NMR spectra are available.

References