Synthesis of aromatic and heteroaromatic annelated [1,4]diazepines

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Dedicated to Professor R.A. Abramovitch on the occasion of his 70th birthday
(received 24 Apr 01; accepted 06 Nov 01; published on the web 14 Nov 01)

Abstract
4-Chlor-3-coumarincarbaldehyde 2 or 4-azido-3-coumarincarbaldehyde 3 are converted into 1,4-benzodiazepines 9–12 by nucleophilic substitution with diamines 4–7 and subsequent cyclization with good yields. Following the same methodologies, carbaldehydes 2 or 3 when treated with 2-aminophenol 8 afforded 4-(2'-hydroxyphenyl)-amino-3-coumarincarbaldehyde 13 in good yields.

Keywords: Annelated [1,4]diazepines 4-substituted-3-coumarincarbaldehyde, diamines, 2-aminophenol

Introduction

1,4-Benzodiazepines have been the object of intense studies since the early 1960s because of their value in psychotherapy. An impressive number of synthetic routes have thus been described.1 Recently the attention has been concentrated on the synthesis of analogs having heterocycles in place of the benzene ring and on compounds having additional fused heterocyclic rings.

Our target was the synthesis of new compounds possessing 7–membered rings with two heteroatoms a 1,4-diazepines and 1,4-oxazepines having fused heterocyclic ring of coumarin such as 9–12 as depicted in figure 1 and 6-oxo-benzo[b]benzopyrano[3,4-f][1,4]oxazepine 15 (Figure 1, Scheme 2).

Two methods were used for the preparation 9–12:
- a first one involving the transformation of 4-chloro compound 2 into 4-azido-3-coumarincarbaldehyde 3, its reaction with o-arylenediamines 4–7 and subsequent cyclisation
(method A),
- an alternative one by reacting directly the 4-chlor-3-coumarincarbaldehyde 2 with the same o-
arylenediamines 4–7, followed by ring closure to get 1,4-diazepines 9–12 (method B).

**Results and Discussion**

The compound 2 was prepared from 4-hydroxycoumarin 1 under Vilsmeier conditions (POCl₃/DMF). We studied three procedures described in the literature: chloroformylation of 1 carried out with an equimolecular mixture of POCl₃ and DMF in trichlorethylene (yield = 97%)² or in chloroform (65%)³ or in a mixture of POCl₃ and excess of DMF (85%).⁴

Literature²,⁴ claims high yields of carbaldehyde 2 and 4-chlorocoumarin without any indication of their ratio. Steinfeld and al.³ proved that the reaction mixture contained a mixture of 4-chlor-3-coumarincarbaldehyde 2 (65%) with 4-chlorocoumarin as a side product (20%). After further optimization, we could obtain up to 72% of the carbaldehyde 2, the undesired chlorocoumarin having been easily separated inside Soxhlet apparatus.

We prepared 4-azido-3-coumarincarbaldehyde 3 from the 4-chloro-3-coumarincarbaldehyde 2 by reaction with NaN₃ in aqueous acetone. In comparable reaction times, we could at room temperature achieve better yields (up to 87%) than those described in the literature.³ The compounds 3 could be separated from the reaction mixture by simple filtration.

Steinfeld and coll.³ presented 4-azido-3-coumarincarbaldehyde 3 as an useful starting material for synthesis of a variety heterocycle–fused coumarins, i. e. for the preparation of the product 9 (36%).

The reaction between azidocarbaldehyde 3 and diamines 4–7 was tested as possible route to the title 1,4-diazepines 9–12. Under reaction conditions described in literature³ (DMF, 4 h, method A), followed by column chromatography and crystallization from acetonitrile, pure compounds 9–12 were obtained (Scheme 1).

We carried out the preparation of derivatives 9–12 starting from 4-chloro-3-
ocoumarincarbaldehyde 2, and treating it successively with diamines 4–7 under mild basic conditions (triethylamine in ethanol, method B). Method B (one step shorter than method A) leads to satisfactory yields of derivatives 9–12. When diamine 4 reacted with carbaldehyde 2 an intermediate 16 could be isolated.

TLC was used to monitor the progress of the reaction, the structures of products were assessed by MS, IR and/or NMR method. The spectroscopic data MS, IR and ¹H-NMR are in agreement with the structure of 4-chlorocoumarin.⁵

The reaction with 2-aminophenol 8 is a possible route to get the 1,4-oxazepine ring. The reaction failed to deliver the desired product 15, since the aminophenol 8 replaced the chlorine atom or azido group, giving access to 13 instead of the desired oxygen–bridged product 15 (Scheme 2).

In conclusion, new practical and efficient synthetic methodology of preparation of 6-oxo-
13H-benzo[b]benzopyrano[3,4-f][1,4]diazepine 9, 6-oxo-13H-10-methylbenzo[b]benzopyrano[3,4-f][1,4]diazepine 10, 11-oxo-5H-benzopyrano[3,4-f]pyrido[3,2-b][1,4]diazepine 11, 9-oxo-3H-benzopyrano[3,4-f]pyrido[3,4-b][1,4]diazepine 12 have been described. The products could be prepared in appreciable yields using method A and method B. Finally, this study has contributed to finding an efficient production of new compounds belonging to the family of substituted 1,4-diazepines.

**Figure 1**

Scheme 1. (a) POCl₃/DMF; (b) NaN₃, acetone–water; (c) 4–7, DMF; (d) 4–7, Et₃N, EtOH, reflux, 3.5 h; (e) 4–7, Et₃N, EtOH, reflux, 1 h.
Scheme 2. (a) aminophenol 8, DMF; (b) aminophenol 8, Et₃N, EtOH, reflux, 3.5 h.

Table 1. Synthesis of substituted 1,4-diazepines 9–12 and 4-(2'-hydroxyphenyl)amino-3-coumarincarbaldehyde 13

<table>
<thead>
<tr>
<th>Diamine 4–7 / Hydroxyamine 8</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Method</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>9</td>
<td>68</td>
<td>A</td>
<td>239–243</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64</td>
<td>B</td>
<td>(lit.³ 238–240)</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>81</td>
<td>A</td>
<td>243–246</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>57</td>
<td>A</td>
<td>235–238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>52</td>
<td>A</td>
<td>239–243</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>81</td>
<td>A</td>
<td>190–192</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>
Experimental Section

General Procedures. Flash chromatography was carried out on 0.04−0.063 mm (Merck) silica gel, thin layer chromatography was carried out on aluminium backed silica plates by Merck and plates were revealed using a UV 254 light. $^1$H-NMR (300 MHz) and $^{13}$C-NMR (75 MHz) spectra were recorded on a Varian VXR 300 instrument at 293 °K in CDCl$_3$ or DMSO d-6. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), some combinations of these were made by DEPT editing of the spectra. The IR-spectra were recorded on a Philips Analytical PU 9800 spectrometer. The MS-spectra were recorded on a AEI MS 902 S electron ionization spectrometer (EI = 70 eV). The elemental analyses were recorded on a Perkin−Elmer 2400 spectrometer.

Materials. The 4-hydroxycoumarin 1, aromatic and heteroaromatic diamines 4−7 and 2-aminophenol 8 were purchased from Fluka, DMF were purified, dried and distilled over CaH2 prior to use.

4-Chloro-3-coumarincarbaldehyde (2). To a stirred mixture of 4-hydroxycoumarin 1 (9.72 g, 0.06 mol) in anhydrous DMF (46.2 mL, 0.6 mol) were added dropwise POCl$_3$ (27.6 g, 0.18 mol) at −10° to −5 °C. The reaction mixture was then stirred for 1 h at room temperature and heated and stirred for 2 h at 60 °C. After the reaction completed, the mixture was poured onto crushed ice (200 g) under vigorous stirring. After storing the mixture overnight at 0 °C the pale yellow solid was collected by filtration and washed successively with Na$_2$CO$_3$ (5%) and water, and then was air−dried. 4-chlorocoumarin 2a (2.50 g, 20%) was separated by Soxhlet extraction as the second product. Recrystallization from acetone gave 8.99 g (72%) of 2 as a pale yellow powder with mp 115−120 °C (lit. 130 °C, $^2$ 125−127 °C, $^3$ 120−122 °C$^4$); $^1$H-NMR δ 10.39 (1H, s, CH=O), 8.19−7.40 (4H, m, ar-H); $^{13}$C-NMR δ 186.81 (11-C), 158.44 (2-C), 153.28 (4-C), 153.27 (9-C), 135.68 (7-C), 127.65 (5-C), 125.56 (6-C), 118.39 (10-C), 118.22 (3-C), 117.20 (8-C); IR ν 2920, 2874, 1720, 1702, 1603, 1587, 1541 cm −1; MS m/z: 208 (MH +, 11), 182 (31), 180 (100), 154 (31), 152 (91), 124 (20), 101 (11), 89 (80), 63 (37), 62 (31), 61 (14), 39 (17), 36 (31), 32 (14), 28 (80).

4-Chlorocoumarin. $^5$ $^1$H-NMR δ 7.88−7.30 (4H, m, ar-H), 6.62 (1H, s, 3-H); IR ν 3098, 3069, 3040, 1754, 1721, 1611, 1538, 1449, 1348, 1273, 1177 cm$^{-1}$; MS m/z: 182 (12), 180 (MH +, 40), 154 (16), 152 (52), 89 (44), 63 (24), 62 (16), 39 (10), 32 (20), 28 (100).

4-Azido-3-coumarincarbaldehyde (3). A solution of 4-chlor-3-coumarincarbaldehyde 2 (0.2 g, 1 mmol) in acetone (5 mL) was stirred and ice−cooled. The solution of NaN$_3$ (0.13 g, 2 mmol) in water (1 mL) was added dropwise in the solution and this mixture was stirred for 0.75 h at room temperature. After evaporation of acetone, the crude product was separated by filtration and recrystallized from dichlormethane. We have obtained 0.18 g (87%) of 3 as white solid with mp 122−130 °C (lit. $^3$ 120−130 °C); $^1$H-NMR δ 10.13 (1H, s, CH=O), 8.05−7.46 (4H, m, ar-H); $^{13}$C-NMR δ 189.27 (11-C), 160.60 (2-C), 153.70 (4-C), 153.33 (9-C), 135.61 (7-C), 125.85 (5-C),
125.21 (6-C), 116.94 (8-C), 115.84 (10-C), 109.80 (3-C); IR ν 3071, 3047, 2170, 1716, 1674, 1525, 1485, 1359 cm⁻¹; MS m/z: 215 (MH⁺, 7), 187 (78), 159 (12), 143 (39), 130 (12), 115 (39), 104 (22), 103 (100), 91 (12), 76 (56), 63 (24), 50 (17), 39 (17), 28 (22).

[1,4]Diazepines 9–12. General procedure A
4-azido-3-coumarincarbaldehyde 3 (0.2 g, 1 mmol) was suspended in 4 mL of DMF, then aromatic or heteroaromatic diamine 4–7 (1 mmol) was added. The mixture was stirred for 4 h at room temperature, then heated at 70 °C for 25 min and 110 °C for 10 min. After cooling the mixture was poured onto crushed ice, the precipitated [1,4]diazepines were filtered off, washed with water and dried. General procedure B. A mixture of 4-chlor-3-coumarincarbaldehyde 2 (0.2 g, 1 mmol), aromatic or heteroaromatic diamine 4–7 (1.1 mmol) and Et₃N (2 mmol) in 98 % EtOH (10 mL) was heated under reflux for 3.5 h. The reaction mixture was cooled and the formed solid was collected by filtration and dried.

6-Oxo-13H-benzo[b]benzopyran[3,4-f][1,4]diazepine (9). Purification by column chromatography (SiO₂, chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave the product 9 with mp 239–243 °C (lit.³ 238–240 °C) in the yield indicated in the Table 1; ¹H-NMR δ 9.28 (1H, s br, 7-H), 8.34–6.09 (8H, m, ar-H); IR ν 3448, 3267, 3067, 1686, 1640, 1609, 1583, 1488, 1481, 1459, 1382 cm⁻¹; MS m/z: 263 (23), 262 (MH⁺, 100), 261 (16), 234 (9), 206 (9), 205 (15), 179 (9), 39 (9), 28 (16). Anal. Calcd for C₁₆H₁₀N₂O₂: C, 73.28; H, 3.82; N, 10.69; O, 10.69. Found: C, 72.79; H, 3.91; N, 10.63; O, 11.03. O, 12.01.

6-Oxo-13H-10-methylbenzo[b]benzopyran[3,4-f][1,4]diazepine (10). Purification by column chromatography (SiO₂, chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave the product 10 with mp 243–246 °C in the yield indicated in the Table 1; ¹H-NMR δ 9.32 (1H, sbr, 7-H), 8.04–6.87 (8H, m, ar-H), 2.25 (3H, s, CH₃); IR ν 3287, 3113, 1685, 1638, 1605, 1576, 1480, 1364 cm⁻¹; MS m/z: 277 (18), 276 (MH⁺, 100), 275 (16), 247 (9), 44 (9). Anal. Calcd for C₁₇H₁₂N₂O₂: C, 73.91; H, 4.35; N, 10.14; O, 11.59. Found: C, 73.84; H, 4.46; N, 10.39; O, 11.78.

11-Oxo-5H-benzo[3,4-f]pyrido[3,2-b][1,4]diazepine (11). Purification by column chromatography (SiO₂, chloroform/acetonitrile 5:2) and recrystallization from acetonitrile gave the product 11 with mp 235–238 °C in the yield indicated in the Table 1; ¹H-NMR δ 9.43 (1H, sbr, NH), 7.89–6.73 (7H, m, ar-H), 6.75 (1H, s, 12-H); ¹³C-NMR δ 162.10 (12-C), 161.47 (11-C), 159.74 (11f-C), 153.32 (9A-C), 149.55 (4b-C), 145.26 (2-C), 139.46 (8-C), 138.17 (4a-C), 133.66 (6-C), 125.55 (4-C), 124.04 (3-C), 123.98 (7-C), 120.19 (9B-C), 116.70 (9-C), 101.02 (11e-C); IR ν 3440, 3285, 3160, 3110, 1680, 1620, 1595, 1550, 1400, 1340 cm⁻¹; MS m/z: 265 (12), 264 (35), 263 (MH⁺, 100), 262 (17), 236 (33), 235 (76), 234 (17), 208 (11), 206 (28), 179 (13), 67 (23), 104 (12), 89 (9). Anal. Calcd for C₁₅H₁₀N₃O₂: C, 68.44; H, 3.42; N, 15.96. Found: C, 68.21; H, 3.28; N, 15.99.

9-Oxo-3H-benzo[3,4-f]pyrido[3,4-b][1,4]diazepine (12). Purification by column chromatography (SiO₂, chloroform/acetonitrile 10:1) and recrystallization from acetonitrile gave
the product 12 with mp 239–243 °C in the yield indicated in the Table 1; \(^1\)H-NMR \(\delta\) 9.10 (1H, \(s_{br}\), NH), 7.90–6.70 (8H, m, ar-H, 10-H); IR \(\nu\) 3448, 3089, 1689, 1635, 1607, 1555, 1480 cm\(^{-1}\); MS \(m/z\): 264 (21), 263 (MH\(^+\), 100), 262 (24), 236 (26), 235 (9), 234 (12), 206 (11), 89 (8), 76 (11), 63 (17), 51 (13), 50 (13), 41 (13), 39 (16), 28 (39). Anal. Calcd for C\(_{15}\)H\(_9\)N\(_3\)O\(_2\): C, 68.44; H, 3.42; N, 15.96; O, 12.16. Found: C, 68.07; H, 3.59; N, 16.04; O 12.31.

4-(2'-Hydroxyphenyl)amino-3-coumarincarbaldehyde (13). The reaction of 2 or 3 with 2-aminophenol 8 in similar conditions to the general procedures A and B. Purification by column chromatography (SiO\(_2\), chloroform/acetonitrile 20:1) and recrystallization from acetonitrile gave the product 13 with mp 190–192 °C in the yield indicated in the Table 1; \(^1\)H-NMR \(\delta\) 12.76 (1H, \(s_{br}\), OH), 10.30 (1H, \(s_{br}\), N-H), 10.05 (1H, s, CH=O), 7.65-6.91 (8H, m, ar-H); \(^{13}\)C-NMR \(\delta\) 191.32 (11-C), 161.68 (2-C), 157.98 (4-C), 154.43 (9-C), 151.67 (2'-C), 135.00 (7-C), 129.58 (5-C), 126.78 (6-C), 126.38 (8-C), 125.38 (1'-C), 119.96 (4'-C), 118.03 (3'-C), 116.85 (5'-C), 113.63 (10-C), 97.21 (3-C); IR \(\nu\) 3485, 3400, 1720, 1686, 1657, 1630, 1613, 1563, 1501, 1450 cm\(^{-1}\); MS \(m/z\): 281 (MH\(^+\), 62), 280 (100), 265 (12), 264 (55), 252 (43), 236 (10), 211 (14), 181 (14), 165 (8), 120 (10), 89 (12), 77 (10), 65 (14), 63 (14), 51 (10), 39 (17), 32 (14), 28 (64). Anal. Calcd for C\(_{16}\)H\(_{11}\)NO\(_4\): C, 68.33; H, 3.94; N, 4.98. Found: C, 68.58; H, 3.99; N, 4.98.

4-(2'-Aminophenyl)amino-3-coumarincarbaldehyde (16). The product 16 was prepared according to a general procedure B in refluxing EtOH for 1 h. Recrystallization from chloroform–diethyl ether gave 0.22 g (84%) of the solid with mp 192–195 °C; \(^1\)H NMR \(\delta\) 10.28 (1H, s, NH), 10.05 (1H, s, CH=O), 7.70-6.91 (8H, m, ar-H); \(^{13}\)C NMR \(\delta\) 191.40 (11-C), 161.70 (2-C), 158.00 (4-C), 154.60 (9-C), 151.80 (2'-C), 158.00 (5-C), 127.00 (6-C), 126.50 (8-C), 126.00 (6'-C), 120.10 (4'-C), 118.10 (3'-C), 117.00 (5'-C), 97.30 (3-C); IR \(\nu\) 3421, 3234, 1728, 1707, 1619, 1565 cm\(^{-1}\); MS \(m/z\): 281 (68), 280 (MH\(^+\), 100), 264 (56), 252 (44), 236 (9), 211 (16), 183 (9), 181 (15), 165 (9), 120 (9), 89 (12), 65 (15), 63 (12), 51 (9), 39 (15), 28 (62).

Acknowledgements

The authors wish to thank the Slovak Grant Agency, Slovak republic for their financial support of this work (Grant No: 1/8109/01).

References