Diels-Alder reaction of pyran-2(H)-ones: Part VI—Preparation and investigation of the Diels-Alder reaction of 4,6-disubstituted thiopyran-2(H)-ones with 1,4-naphthoquinone and N-phenylmaleimide

Ruchira R Pai, Deven S Bendre & Shriniwas D Samant*
Organic Chemistry Research Laboratory, University Department of Chemical Technology, N M Parikh Marg, Matunga, Mumbai - 400 019, India

Received 10 November 1999; accepted (revised) 22 January 2001

4,6-Disubstituted pyran-2(H)-ones 1 when treated with P4S10 the corresponding pyran-2(H)-thiones 2 are obtained. 2 on boiling in aq. methanol in the presence of Na2CO3 give the corresponding thiopyran-2(H)-ones 3. The mechanism for this reaction has been proposed, which is supported by the AM1 calculation results and the spectral data. The Diels-Alder reactions of 2 and 3 with N-phenylmaleimide and 1,4-naphthoquinone have been studied.

We have earlier reported the Diels-Alder reaction of 4,6-disubstituted pyran-2(H)-ones 1 and the corresponding pyran-2(H)-thiones 2 with 1,4-naphthoquinone (NQ) and N-phenylmaleimide (NPMA) and found that the diene reactivity of 2 was considerably less than that of 1. In the present paper we would like to report the preparation and Diels-Alder reaction of 4,6-disubstituted thiopyran-2(H)-ones 3 which are isomeric with 2. Sulphur being a good deal softer than oxygen, the rearrangement of 2 to 3 was expected to change the diene reactivity of the pyrone system (Scheme I). So far there is no report on the Diels-Alder reaction of thiopyran-2(H)-ones.

Preparation of pyran-2(H)-thiones 2

We had earlier prepared 2 by reacting 1 with P4S10 in benzene1. P4S10 is commonly being used for the thionation of pyrones2-6. Due to different drawbacks in this procedure, the reaction was studied further. Benzene was not found to be a good solvent for a large scale reaction and even after prolonged heating (10-12 hr), complete conversion of 1 was not observed. When chloroform was used as a solvent, due to greater solubility of 1 in it, slightly better yield of 2 was obtained in a shorter time. However, dioxan was found to be the best solvent for the reaction. 1 and P4S10 were almost insoluble in it at ambient temperature, but almost soluble at its boiling temperature. On the other hand, 2 was almost soluble in dioxan at ambient temperature; thus the separation of 2 was facilitated. Hence, 1 was thionated using P4S10 in dioxan (Table I). Ultrasound was neither found to have any beneficial effect on the heterogeneous reaction in benzene nor the homogeneous reaction in dioxan.

Rearrangement of 2 to 3

Thione esters rearrange into thiol esters in the presence of Lewis acids7, amines2-3, and alkalies4. The

---

1 For Part V see Indian J Chem, 39B, 2000, 270
The mechanism of reaction of 2b with a primary amine has been proposed in which the attack of the nitrogen of the amine is shown to take place at the C6 rather than C2 of 2b; thinking that the C6 shared the electron deficiency with C5 by vinylology. This was thought to be untenable on the following grounds. (i) The 2p-orbital of sulphur being larger than the 2p-orbital of carbon, the thione group is expected to be more polar than the C=O group. (ii) The thione group (C=S) is also expected to be more polarizable than the carbonyl group (C=O) under the influence of a nucleophile and hence undergo a nucleophilic attack at the carbon atom. (iii) To compare the electrophilicity of the two carbon atoms, viz., C2 and C6 in 1, 2 and 3, AM1 calculations were carried out. AM1 calculations on 1a/b, 2a/b and 3a/b (Table II), showed that in all the cases, C2 was more positively charged as compared to C6. Further, the electron density on C6 is significantly more as compared to C2 and hence C6 is obviously less susceptible to nucleophilic attack. Thus, in the case of 2a/b, C2 is substantially electron deficient and hence expected to undergo the nucleophilic attack of OH−. From the Table III, it can be seen that there is a large difference in the 13C NMR peak positions of C2 and C6 in these compounds. In the 13C NMR of 2a the C2 appeared at 196.42, considerably downfield as compared to C2 in 1a and 1b appearing at 163.04 and 163.50, respectively. It can also be seen that the 1H NMR shifts of C2H and C5H are sensitive with respect to X and Y (in 6). The conversion of pyrone to thione led to a remarkable downfield shift in the peak position of C2H. This was due to enhanced paramagnetic anisotropy around the proton due to the thione group. The possible mechanism of conversion of 2 to 3 based on these observations is given in Scheme II.

**Diels-Alder reaction of 3**

The reaction of 3 with NQ and NPMA in boiling nitrobenzene gave 4 and 5 (Scheme III, Table IV) respectively. With both the dienophiles the reaction was found to give poor yield of the product. Thus,
both pyran-2(H)-thiones 2 and thiopyran-2(H)-ones 3 were found to be poor dienes as compared to the parent pyran-2(H)-ones 1. It is endorsed by the fact that large volume of literature is available on the Diels-Alder reaction of pyran-2(H)-ones. Against this the Diels-Alder reactions of pyran-2(H)-thiones and related pyridin-2(H)-ones are scanty. In fact, the first example of the Diels-Alder reaction of pyran-2(H)-thiones involved inverse electron demand Diels-Alder reaction with ketene acetal. The present Diels-Alder reactions are Normal Diels-Alder reactions.
Table IV — Diels-Alder reaction of 2 and 3 with NQ and NPMA

<table>
<thead>
<tr>
<th>Diene</th>
<th>Dienophile</th>
<th>Product</th>
<th>Dienophile/ Diene</th>
<th>Time (hr)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>NQ</td>
<td>4a</td>
<td>2</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>2a</td>
<td>NQ</td>
<td>4a</td>
<td>1</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>2a</td>
<td>NPMA</td>
<td>5a</td>
<td>2</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>2b</td>
<td>NQ</td>
<td>4b</td>
<td>2</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>2b</td>
<td>NPMA</td>
<td>5b</td>
<td>2</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>3a</td>
<td>NQ</td>
<td>4a</td>
<td>1</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>3a</td>
<td>NPMA</td>
<td>5a</td>
<td>2</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>3b</td>
<td>NPMA</td>
<td>5b</td>
<td>2</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>1a</td>
<td>NQ</td>
<td>4a</td>
<td>1</td>
<td>4</td>
<td>69&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NQ - 1,4-naphthoquinone; NPMA - N-phenylmaleimide

Experimental Section

The melting points were taken in open capillaries on a Campbell precision melting point apparatus. IR spectra were recorded on Perkin-Elmer 397 spectrophotometers and the peak positions are expressed in wavenumbers (cm<sup>-1</sup>). <sup>1</sup>H NMR and <sup>13</sup>C-NMR spectra were recorded on Varian T-60 spectrometer (60 MHz) and Varian XL-300 standard spectrometer (300 MHz) with TMS as internal standard and the chemical shifts are reported in δ units (ppm). The elemental analyses were found to be satisfactory within ±0.4 of the calculated values. Sonication was done in a Julabo ultrasound apparatus (model USR 3). The semi-empirical calculations (AM 1) were carried out on a Pentium-II computer using MOPAC (version 6.49). Compounds 1<sub>a</sub> and 1<sub>b</sub> were prepared and characterised as per the reported procedures<sup>13</sup>-14.

**General procedures for the preparation of 2 from 1**

**Method A: Reaction in benzene.** 1 (0.01 mole) and P<sub>4</sub>S<sub>10</sub> (0.01 mole) in dry benzene (40 mL) were refluxed with stirring for 4 hr and the solution filtered. The residue was washed with boiling benzene (4 × 25 mL) and the combined filtrate was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub>. Benzene was removed by distillation when crude 2 was obtained, which was crystallised from pet. ether-benzene mixture (40/60 v/v).

**Method B: Reaction in dioxan.** 1 (0.01 mole) and P<sub>4</sub>S<sub>10</sub> (0.01 mole) in dioxan (25 mL) were refluxed for 0.5 hr and the solution was filtered. The filtrate was diluted with water, when crude 2 was obtained, which was crystallised from pet. ether-benzene mixture (40/60 v/v).

**Method C: Reaction in the presence of ultrasound.** 1 (0.01 mole) and P<sub>4</sub>S<sub>10</sub> (0.01 mole) in benzene (40 mL) were sonicated at room temperature for 3 hr. The solution was filtered and the residue was washed with boiling benzene (4 × 25 mL). The combined filtrate was dried over anhyd. Na<sub>2</sub>SO<sub>4</sub>, benzene removed by distillation when crude 2 was obtained, which was crystallised from pet. ether-benzene mixture (60/40).

2<sub>a</sub>: Yield 61%, m. p. 164-65°C. Anal. Found: C, 70.30; H, 4.90; S, 9.80. Calcd for C<sub>19</sub>H<sub>16</sub>0<sub>3</sub>S: C, 70.40; H, 5.00; S, 9.90 %. IR (KBr): 1610 (C=C), 1520, 1419, 1250 (Ar-O-CH<sub>3</sub>), 1210, 1190, 1120, 1110 (thione CS); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz): 3.83 (6H, s, Ar-OCH<sub>3</sub>), 6.93-7.00 (5H, 2d, J<sub>ortho</sub> = 8.0 Hz, Ar-H and C<sub>s</sub>-H), 7.30 (1H, s, C<sub>3</sub>-H), 7.60 (2H, d, J<sub>ortho</sub> = 8.0 Hz, Ar-H), 7.83 (2H, d, J<sub>ortho</sub> = 8.0 Hz, Ar-H).

2<sub>b</sub>: Yield 73%, m. p. 141-42°C. Anal. Found: C, 67.40; H, 5.20; S, 13.70. Calcd for C<sub>13</sub>H<sub>12</sub>0<sub>2</sub>S: C, 67.20; H, 5.20; S, 13.80 %. IR (KBr): 1630 (C=C), 1520, 1419, 1250 (Ar-O-CH<sub>3</sub>), 1210, 1190, 1120, 1110 (thione CS); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 60 MHz): 2.40 (3H, s, C<sub>6</sub>-CH<sub>3</sub>), 3.87 (3H, s, Ar-OCH<sub>3</sub>), 6.57 (1H, s, C<sub>s</sub>-H), 6.90 (2H, d, J<sub>ortho</sub> = 8.0 Hz, Ar-H), 7.30 (2H, d, J<sub>ortho</sub> = 8.0 Hz, Ar-H).

**Rearrangement of 2 to 3**

A mixture of 2 (0.01 mole), aq. Na<sub>2</sub>CO<sub>3</sub> (10% aq., 10 mL) in methanol (40 mL) was refluxed for 3 hr. Methanol was removed by distillation, when crude 3 was obtained.
Diels-Alder reactions of 2/3 with dienophiles

Diene 2/3 (0.0025 mole) and dienophile were refluxed in nitrobenzene (15 mL) for 4 hr. Nitrobenzene was removed by steam distillation. The solid obtained was chromatographed over silica gel using benzene as an eluent to obtain 4/5.

4a: m.p. 199-200°C. Anal. Found: C, 80.12; H, 4.76. Calcd for C25H26N2O5: C, 80.00; H, 4.76%. IR (KBr): 1680 (quinone CO), 1600 (C=C), 1560, 1520, 1470, 1440, 1350, 1180, 1030; 1H NMR (CDCl3, 60 MHz): 3.82 (6H, s, Ar-OCH3), 6.70-7.40 (6H, m, Ar-H), 7.46-7.80 (5H, m, Ar-H), 8.00-8.36 (2H, m, Ar-H), 8.50 (1H, s, peri Ar-H).

4b: m.p. 178-79°C. Anal. Found: C, 80.46; H, 4.89. Calcd for C25H26N2O5: C, 80.47; H, 4.91%. IR (KBr): 1680 (quinone CO), 1600 (C=C), 1520, 1340, 1310, 1280, 1250 (Ar-O-CH3), 1190, 1160, 1040; 1H NMR (CDCl3, 100 MHz): 2.92 (3H, s, CH3), 3.90 (3H, s, Ar-OCH3), 6.98 (2H, d, J = 8.0 Hz, Ar-H), 7.62-7.94 (5H, m, Ar-H), 8.26-8.36 (2H, m, C7-H, C8-H), 8.45 (1H, d, J = 2.0 Hz, C9-H).

References