Dehydroacetic acid and its derivatives in organic synthesis: Synthesis of some new 2-substituted-4-(5-bromo-4-hydroxy-6-methyl-2H-pyran-2-one-3-yl)thiazoles

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Synthesis of 3β,3β,5-tribromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one 2 from the bromination of DHA 1 in chloroform has been reported. The reaction of 2 with various thioureas/thioamides leads to an efficient synthesis of new 2-substituted-4-(5-bromo-4-hydroxy-6-methyl-2H-pyran-2-one-3-yl)thiazoles.

Keywords: Dehydroacetic acid, bromination, thioamides, thioureas, thiazoles

As part of the ongoing studies on the chemistry of 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (dehydroacetic acid, DHA, 1) and its derivatives, the synthesis of a new product 3β,3β,5-tribromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one (Tribromo DHA, 2) from the bromination of 1 involving 2.5 equivalent of Br2 containing catalytic amount of I2 in CHCl3 has been reported earlier. In view of the fact that 2 bears α,α-dibromoketone functionality and the compounds possessing such functionality have offered superior alternatives to α-bromoketones in organic syntheses especially in Hantzsch thiazole synthesis, it was considered worthwhile to investigate the reaction of 2 with various thioureas/thioamides for obtaining new pyranylthiazole derivatives of potential biological interest.

Results and Discussion

Tribromo DHA 2 was prepared by bromination of DHA 1 employing an improved procedure. The reaction of 2 was carried out with phenylthiourea in ethanol at RT. A solid separated out of the reaction mixture within 10 min, which was characterised as the expected 4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-aminophenylthiazole 3a as evidenced by spectral and analytical (CHN) data. To assess the generality of the method, a variety of thioureas were treated with 2 in a similar manner to afford 2-arylamino-4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)thiazoles 3a-e. On replacing thioureas by thioamides, the reaction yielded corresponding 2-aryl-4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)thiazoles 4a-c (Scheme I). The results are summarized in Table I.

The advantages of the synthesis of new pyranylthiazoles 3a-e and 4a-c involving α,α-dibromoketone 2 can be summarized as: (i) The reaction conditions are mild and the reaction time is very short. (ii) The yields are high, the isolation of the products is convenient and crystalline solids obtained
Table 1 — Physical characterization data of pyranylthiazoles

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C₆H₅</td>
<td>240-41</td>
<td>74</td>
</tr>
<tr>
<td>3b</td>
<td>p-Cl</td>
<td>256</td>
<td>75</td>
</tr>
<tr>
<td>3c</td>
<td>p-F</td>
<td>250</td>
<td>72</td>
</tr>
<tr>
<td>3d</td>
<td>p-CH₃</td>
<td>245</td>
<td>71</td>
</tr>
<tr>
<td>3e</td>
<td>p-OCH₃</td>
<td>230-31</td>
<td>70</td>
</tr>
<tr>
<td>4a</td>
<td>C₆H₅</td>
<td>190-91</td>
<td>66</td>
</tr>
<tr>
<td>4b</td>
<td>p-Cl</td>
<td>212-13</td>
<td>70</td>
</tr>
<tr>
<td>4c</td>
<td>p-CH₃</td>
<td>180-81</td>
<td>68</td>
</tr>
</tbody>
</table>

do not require purification. (iii) There is no evolution of HBr, unlike Hantzsch thiazole synthesis and therefore acid sensitive moiety i.e. pyranyl moiety of DHA remains intact in the reaction. (iv) Basification needed in the workup of Hantzsch thiazole synthesis is avoided.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ¹H NMR spectra were recorded on a Brucker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer-2400 instrument using TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrometer. Elemental analyses were carried out in a Perkin Elmer-2400 instrument and mass spectra were recorded on Kratos MS-50 mass spectrometer. Common chemicals such as dehydroacetic acid, bromine, etc. were obtained from commercial suppliers.

3β,3β,5-Tribromoacetyl-4-hydroxy-6-methyl-2H-pyran-2-one, ²

To a solution of 3.36 g of dehydroacetic acid in chloroform (20 mL) was added a solution of 2.58 mL of Br₂ in chloroform (20 mL) at RT. The solution was stirred overnight and then it was washed with 5% sodium bisulphite solution, dried with anhydrous sodium sulphate, concentrated and purified by recrystallization from ethanol to give 5.9 g (74%) of ².

General procedure for the synthesis of 2-substituted-4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-thiazoles

To a solution of 2 (10 mmol) in ethanol (10 mL) was added thiourea or thioamide (10 mmol) and the reaction mixture was stirred for 10-20 min. The solid that separated out was filtered and washed with ethanol to give 3 or 4 respectively.

Spectral and analytical characterization data of the products are as follows

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-aminothiazole, 3a: ¹H NMR (CDCl₃): δ 2.44 (s, 3H, CH₃), 7.35-7.41 (m, 5H, Ar), 8.03 (s, 1H, C₂-H), 10.81 (s, 1H, NH); IR (KBr): 1703 cm⁻¹ (C=O); MS: m/z M⁺ (378), M⁺+2 (380). Anal. Found: C, 47.55; H, 2.89; N, 7.35. C₁₅H₁₂Br₂N₂O₂S requires: C, 47.61; H, 2.91; N, 7.40%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(4'-chlorophenyl)thiazole, 3b: ¹H NMR (CDCl₃): δ 2.40 (s, 3H, CH₃), 7.34-7.50 (m, 4H, Ar), 7.51 (s, 1H, C₂-H), 10.91 (s, 1H, NH); IR (KBr): 1701 cm⁻¹ (C=O); MS: m/z M⁺ (412), M⁺+2 (414). Anal. Found: C, 43.64; H, 2.22; N, 6.77. C₁₅H₁₀BrClN₂O₂S requires: C, 43.68; H, 2.42; N, 6.79%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(4'-fluorophenyl)thiazole, 3c: ¹H NMR (CDCl₃): δ 2.39 (s, 3H, CH₃), 7.27-7.36 (m, 4H, Ar), 7.39 (s, 1H, C₂-H), 10.82 (s, 1H, NH); IR (KBr): 1700 cm⁻¹ (C=O); MS: m/z M⁺ (392), M⁺+2 (394). Anal. Found: C, 45.38; H, 2.49; N, 6.99. C₁₅H₁₀BrFClN₂O₂S requires: C, 45.45; H, 2.52; N, 7.07%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(4'-methyl)phenyl)thiazole, 3d: ¹H NMR (CDCl₃): δ 2.30 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 7.24-7.38 (m, 4H, Ar), 8.12 (s, 1H, C₂-H), 10.71 (s, 1H, NH); IR (KBr): 1704 cm⁻¹ (C=O); MS: m/z M⁺ (412), M⁺+2 (414). Anal. Found: C, 48.84; H, 3.27; N, 6.99. C₁₅H₁₁BrN₂O₂S requires: C, 48.97; H, 3.31; N, 7.14%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-amino-(4'-methoxyphenyl)thiazole, 3e: ¹H NMR (CDCl₃): δ 2.37 (s, 3H, CH₃), 3.77 (s, 3H, OCH₃), 7.01-7.28 (m, 4H, Ar), 7.32 (s, 1H, C₂-H), 10.71 (s, 1H, NH); IR (KBr): 1695 cm⁻¹ (C=O); MS: m/z M⁺ (408), M⁺+2 (410). Anal. Found: C, 47.02; H, 3.17; N, 6.84. C₁₆H₁₃BrN₂O₄S requires: C, 47.05; H, 3.18; N, 6.86%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-phenylthiazole, 4a: ¹H NMR (CDCl₃): δ 2.51 (s, 3H, CH₃), 7.49-7.91 (m, 5H, Ar), 8.33 (s, 1H, C₂-H); IR (KBr): 1706 cm⁻¹ (C=O); MS: m/z M⁺ (363), M⁺+2 (365). Anal. Found: C, 49.44; H, 2.73; N, 3.79. C₁₅H₁₀BrNO₂S requires: C, 49.58; H, 2.75; N, 3.85%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-(4'-chlorophenyl)thiazole, 4b: ¹H NMR (CDCl₃): δ 2.51 (s, 3H, CH₃), 7.49-7.89 (m, 4H, Ar), 8.34 (s, 1H, C₂-H); IR (KBr): 1705 cm⁻¹ (C=O); MS: m/z M⁺ (397), M⁺+2 (399). Anal. Found: C, 45.24; H, 2.22; N, 3.50. C₁₅H₁₀BrClNO₂S requires: C, 45.34; H, 2.26; N, 3.52%.

4-(5-bromo-4-hydroxy-6-methyl-2-pyran-3-yl)-2-(4'-methyl)phenylthiazole, 4c: ¹H NMR (CDCl₃): δ 2.38 (s, 3H, CH₃), 2.50 (s, 3H, CH₃), 7.38-7.87 (m,
4H, Ar), 8.29 (s, 1H, C₅-H); IR (KBr): 1703 cm⁻¹ (C=O); MS: m/z M⁺ (377), M⁺+2 (379). Anal. Found: C, 50.80; H, 3.16; N, 3.67. C₁₆H₁₂BrNO₃S requires: C, 50.92; H, 3.18; N, 3.71%.

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References

9 DHA and its derivatives are known to undergo cleavage or rearrangement in presence of acid. For relevant details see reference 10-12.