A Novel Synthesis of New 3-Aryl-7-methylpyrano[4,3-b]pyran-4H,5H-diones Using Hypervalent Iodine(III) Reagents

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Abstract: Oxidation of 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-ones with [hydroxy(tosyloxy)iodo]benzene in CH₂Cl₂ leads to cyclization, thereby providing a new and convenient route for the synthesis of 3-aryl-7-methylpyrano[4,3-b]pyran-4H,5H-diones.

Key words: hypervalent iodine, [hydroxy(tosyloxy)iodo]benzene, oxidation, chalcone, dehydroacetic acid

Research work in our laboratory has been recently concerned with the reactions of dehydroacetic acid (DHA) and its derivatives as a rich source to the synthesis of heterocyclic compounds.¹–³ In our previous two papers, we have reported facile synthesis of benzodiazepines² 2 and bipyrones³ 3 from the reaction of 3-cinnamoyl-4-hydroxy-6-methyl-2H-pyran-2-ones 1 (Figure 1).

Figure 1

A literature survey reveals that in contrast to the several reports on the synthesis of pyranopyrones of the type 3,³,⁴ isomeric compounds of the type 4 remain unknown. In view of these observations and encouraged by earlier results on the use of organoiodine (III) reagents in the synthesis of heterocyclic compounds, especially flavonoids,⁵⁻⁷ it was thought of significant interest to develop I(III)-mediated approach for the synthesis of the title compounds 4.

In principle, two synthetic strategies based on the oxidative rearrangement of flavanones⁸ 5 and o-

hydroxychalcones⁹ 7 to isoflavones 6 could be used for the present purpose. The first one (Equation 1) involves the application of [hydroxy(tosyloxy)iodo]benzene (HTIB), whereas the second one (Equation 2) makes the use of Tl(III) acetate.

Equation 1

Equation 2

In order to attempt strategy one for the synthesis of compound 4, we needed flavanone analogues of DHA (8). Accordingly, we first undertook the preparation of 8 by the cyclization of chalcone¹⁰ analogues of DHA under standard conditions using acids such as HCl–EtOH, HCl–AcOH, H₂SO₄–AcOH, etc. However, all our efforts ended up with the formation of rearranged products, chromones 9 (Figure 2). It is worth mentioning here that compounds of the type 8 have yet not been reported in the literature.

Alternatively, we intended to follow strategy outlined in Equation 2. Since Tl(III) salts required for this procedure are associated with toxic properties, it is always better to avoid the use of such reagents. These observations coupled with the fact that Tl(III) salts and organoiodine(III) compounds behave analogously; it was decided to use organoiodine(III) reagents for this purpose.

Figure 2
Thus, 1a was treated with 1.1 equivalents of PhI(OAc)₂, H₂SO₄ in MeOH by refluxing for four days. The reaction afforded the desired 3-phenyl-7-methylpyrano[4,3-b]pyran-4H,5H-dione (4a; Equation 3). Further experimentation by changing the conditions such as increase in time, temperature, amount of reagent, etc. did not give any significant improvement in the results. Using same method, other chalcone analogues also gave the corresponding 4 in poor yields (10–20%) together with the recovery of unchanged starting material.

Due to the poor yields obtained in the aforementioned conversion, we attempted this oxidative rearrangement by using other I(III) reagents such as (PhIO)n, PhI(OCOCF₃)₂ and HTIB in different conditions. Interestingly, reaction of 1 and HTIB (1.1 equivalent) in CH₂Cl₂ at reflux for 40–50 hours gave the best results (Equation 4, Table 1). The same method was successfully extended to the synthesis of other derivatives. It is to be noted that this is the first report on the direct conversion of o-hydroxychalcone type compounds into isoflavone analogues.

The mechanistic pathway for this conversion probably involves formation of I(III) intermediate which subsequently undergoes 1,2-aryl shift to give 4 (Scheme 1). Mild reaction conditions probably do not allow opening of the pyrone ring as observed in cyclization of 1 under strong acidic conditions. In conclusion, I(III) mediated approach provides a novel and convenient route for the synthesis of new 3-aryl-7-methylpyrano[4,3-b]pyran-4H,5H-diones 4.

The structures of the products were confirmed by their spectral data. Compounds 4a-f exhibited carbonyl absorptions in the regions 1740–1760 and 1630–1640 cm⁻¹, for the 2-pyrone and 4-pyrone rings, respectively. The characteristic signal in the ¹H NMR spectra (TFA) at δ = 7.8 (s) shows the proton of the isoflavone analogue at position 2 in the structure 4.

The ¹H NMR spectra were recorded on a Bruker 300-MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1800 FTIR spectrophotometer. Mass spectrometric data were collected on a Kratos MS-50 mass spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 analyzer.

### General Procedure

To a solution of 1 (0.002 mol) in CH₂Cl₂ (30 mL) was added HTIB (0.86 g, 0.0022 mol). The mixture was refluxed for 2 d. Excess of solvent was distilled off and the gummy material was absorbed on silica gel. Pure isoflavone analogue 4 was obtained by eluting it with hexane–EtOAc (8:2).

### Table 1 Synthesis of Compound 4

<table>
<thead>
<tr>
<th>1, Ar</th>
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<tbody>
<tr>
<td>a C₆H₅</td>
<td>d 2-CH₃C₆H₄</td>
<td></td>
</tr>
<tr>
<td>b 4-CH₃C₆H₄</td>
<td>e 4-CIC₆H₄</td>
<td></td>
</tr>
<tr>
<td>c 4-OCH₃C₆H₄</td>
<td>f 4-(CH₃)₂CHC₆H₄</td>
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The 7-Methyl-3-phenylpyrano[4,3-b]pyran-4H,5H-dione (4a) Yield: 55%; mp 165–166 °C.

IR (KBr): 1760, 1632 (C=O) cm⁻¹.

**1H NMR (300 MHz, CDCl₃):** δ = 2.41 (s, 3 H, CH₃), 5.82 (s, 1 H, C₅¢-H, DHA), 7.91 (s, 1 H, C₂-H), 7.02–7.51 (m, 5 H, arom).

**MS:** m/z = 254.


### Scheme 1

![Scheme 1](image-url)
3-(4-Methoxyphenyl)-7-methylpyrano[4,3-b]pyran-4H,5H-4,5-dione (4c)
Yield: 59%; mp 230–231 °C.
IR (KBr): 1760, 1632 (C=O) cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 2.33 (s, 3 H, CH₃), 3.90 (s, 3 H, OCH₃), 5.85 (s, 1 H, C5'-H, DHA), 7.91 (s, 1 H, C2-H), 7.07 (d, 2 H, arom), 7.42 (d, 2 H, arom).
MS: m/z = 284.

3-(2-Methylphenyl)-7-methylpyrano[4,3-b]pyran-4H,5H-4,5-dione (4d)
Yield: 58%; mp 180–181 °C.
IR (KBr): 1763, 1637 (C=O) cm⁻¹.
1H NMR (300 MHz, CDCl₃): δ = 2.24 (s, 3 H, CH₃), 2.34 (s, 3 H, CH₃), 6.04 (s, 1 H, C5'-H, DHA), 7.66 (s, 1 H, C2-H), 7.01–7.42 (m, 4 H, arom).
MS: m/z = 268.
Anal. Calcd C₁₆H₁₂O₄: C, 71.64; H, 4.48. Found: C, 71.68; H, 4.52.

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References