# AN EFFICIENT SYNTHESIS OF REDUCED FLAVONES *VIA* DIELS-ALDER ADDITION TO 4*H*-PYRAN-4-ONES

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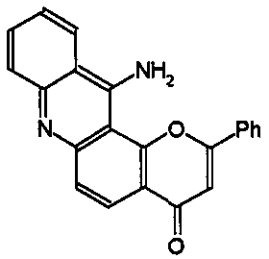
**Abstract** - The 4*H*-pyran-4-one (**4c**) undergoes Diels-Alder cycloaddition with electron-rich dienes to give the reduced flavones (**7**), whereas the pyran-4-one (**4b**) and 2-phenyl-4*H*-pyran-4-one (**4a**) are unreactive. The 3D structure of the adduct **7a** of **4c** with Danishefsky's diene (**6a**) was confirmed by X-ray crystallography.

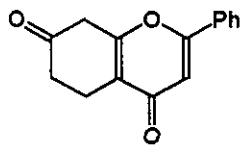
We have recently described the synthesis of a series of pyranoacridinone inhibitors, *e.g.* **1**, of protein tyrosine kinases, which have potential in the treatment of gastric carcinoma.[2] A key intermediate in the synthesis of these pyranoacridinones is 7-oxo-5,6,7,8-tetrahydroflavone (**2**) and, as part of our ongoing investigation into the biological potential of these pyranoacridinones, we have become interested in an alternative, more efficient, synthesis of these compounds. One possible alternative is the Diels-Alder cycloaddition of dienes to pyran-4-ones to give reduced flavones which could subsequently be converted to pyranoacridinones. We wish to report here an efficient synthesis of reduced flavones which involves the Diels-Alder cycloaddition of electron-rich dienes to 4*H*-pyran-4-ones.

The reactivity of 4*H*-benzopyran-4-ones (**3**) in Diels-Alder reactions with electron-rich dienes is well documented[3] and recently high asymmetric induction has been achieved in the reaction of 3-

alkoxycarbonyl substituted chromones (**3** R=OR*) with chiral auxiliaries and Danishefsky's diene by *Ohkata et al.*[4] The 3-formylchromones (**3** R=H) behave as heterodienes in the stereoselective inverse electron demand Diels-Alder reaction with enol ethers[5] and such processes offer a direct route to pyrano[4,3-*b*][1]benzopyrans, whose heterocyclic nucleus occurs naturally in the fungal metabolite fulvic acid.[6] The 3-acylchromones (**3** R=Me) appear to function both as dienes and dienophiles in some dimerisation reactions.[7]

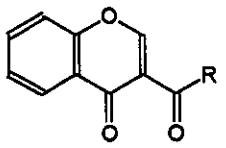



**1**

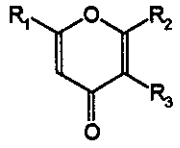



**2**

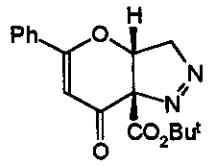
In contrast, little attention has been paid to the cycloaddition reactions of 4*H*-pyran-4-ones (**4**), with the only example being a footnote by *McCombie et al.* in their paper on the preparation of these compounds, in which **4c** readily reacted with diazomethane in a 1,3-dipolar cycloaddition to give the adduct (**5**).[8]




**3**



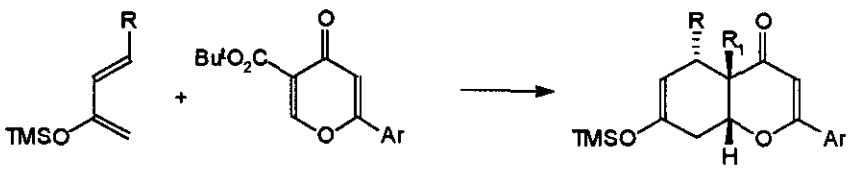

**4a** $R_1$= Ph, $R_2$=$R_3$= H
**4b** $R_1$= Ph, $R_2$= $CO_2Et$, $R_3$= H
**4c** $R_1$= Ph, $R_2$= H, $R_3$= $CO_2Bu^t$
**4d** $R_1$= *p*-$MeOC_6H_4$, $R_2$=H, $R_3$=$CO_2Bu^t$




**5**

We have obtained the pyranones (**4c**) and (**4d**) *via* a modification of the reported method from *t*-butyl acetoacetate in two steps.[8] **4c** was then reacted with an excess of Danishefsky's diene (**6a**) in toluene at 110°C for 6 hours to give **7a** in 54 % yield. The $^1$H-nmr spectrum of the cycloadduct indicates the presence of only one diastereoisomer (**7a**).[9] Important features of the $^1$H-nmr spectrum are; the doublet of doublets at δ 2.5 for H-8 which has coupling constants of 19 Hz (geminal) and 4 Hz (*cis* to H-8a); the doublet at δ 2.69 for H-8′ (*trans* to H-8a), with a coupling constant of 19 Hz; and the doublet at 5.27 for

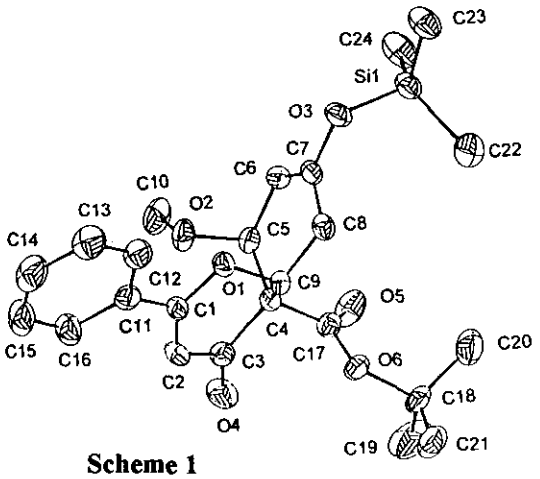
H-8a, with a coupling constant of 4 Hz. The 3D structure of the cycloadduct (**7a**) was determined by X-ray crystallography and shows that the methoxy group at C-5 and the ester group at C-4a are *trans* to one another, with the methoxy group in a *pseudo*-axial position (Scheme 1).[10] Pyranone (**4d**) also reacted with Danishefsky's diene (**6a**) to give the cycloadduct (**7b**).




**6a** R = OMe
**6b** R = H

**4c** Ar = Ph
**4d** Ar = *p*-MeOC$_6$H$_4$

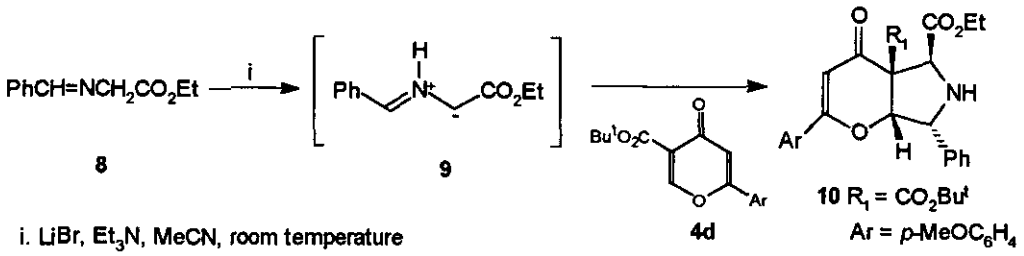
**7a** R = OMe, R$_1$ = CO$_2$Bu$^t$, Ar = Ph
**7b** R = OMe, R$_1$ = CO$_2$Bu$^t$, Ar = *p*-MeOC$_6$H$_4$
**7c** R = H, R$_1$ = CO$_2$Bu$^t$, Ar = Ph




**Scheme 1**

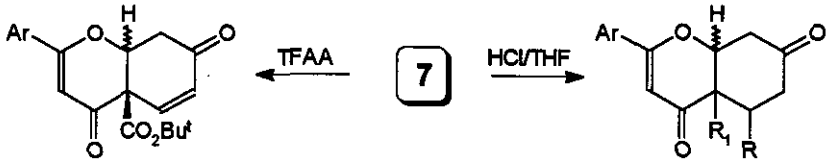
The addition of **4c** to 2-trimethylsilyloxybuta-1,3-diene (**6b**) under the same conditions proceeded more slowly, due to the less reactive diene, and gave the cycloadduct (**7c**) in poor yield (**7c** could not be isolated, only the ketone (**11c**) in 16 % overall yield after treatment of **7c** with 0.01M aqueous HCl/THF followed by chromatography).

It is noteworthy that the pyranone (**4a**),[12] without any electron-withdrawing groups, and more surprisingly, the pyranone (**4b**)[13] were unreactive towards both dienes under similar or forced (neat, 160 °C or Lewis acid catalyst) conditions. Similar observation was madein the case when the ester-stabilized azomethine ylide (**9**) acted as a 4π component in 1,3-dipolar cycloaddition;[14] while **4a** and **4b** were unreactive, in the reaction of **4d** pyrone (**10**) cycloadduct[11] was formed in good yield.




i. LiBr, $Et_3N$, MeCN, room temperature

The tetrahydroflavones (7) were converted by means of 0.01 M HCl/THF to **11**. Brief treatment of **7a** or **7b** with trifluoroacetic anhydride in $CH_2Cl_2$ solution gave **12a** or **12b**. In both the treatment with acid and with TFAA epimerisation of H-8a was observed to give a 1:1 mixture of diastereoisomers. This is unimportant in the synthesis of the pyranoacridinones, *e.g.* **1**, since the groups at the 4a- and 8a-positions will be lost upon aromatisation.




**12a** Ar = Ph
**12b** Ar = *p*-$MeOC_6H_4$

**8a** R = OMe, $R_1$ = $CO_2Bu^t$, Ar = Ph
**8b** R = OMe, $R_1$ = $CO_2Bu^t$, Ar = *p*-$MeOC_6H_4$
**8c** R = H, $R_1$ = $CO_2Bu^t$, Ar = Ph

In conclusion these reaction schemes provide a new, efficient and practical method, for the synthesis of reduced flavone derivatives in four steps and 27-30 % overall yield.

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9. **7a** $^1$H-Nmr (360 MHz, $CDCl_3$) δ: 0.41 (s, 9H, OTMS), 1.48 (s, 9H, OBu$^t$), 2.50 (dd, J= 4 and 19 Hz, 1H, H-8′), 3.23 (s, 3H, OMe), 4.56 (d, J=5.5 Hz, 1H, H-5), 5.27 (d, J=4 Hz, 1H, H-8a), 5.30 (d, J= 5.5 Hz, 1H, H-6), 6.17 (s, 1H, H-3), 7.38-7.47 (m, 3H, Ph), 7.73-7.76 (m, 2H, Ph); ir (nujol, cm$^{-1}$): 1730, 1652, 1598, 1571, 1334, 1251, 1216, 1187, 1162, 1077, 1017, 886, 851.

10. The crystal structure data is available on request from the Cambridge Crystallographic Database.

11. **10** $^1$H-Nmr (360 MHz, $CDCl_3$) δ: 1.32 (t, J= 7.1 Hz, 2H, $CH_2\underline{CH_3}$), 3.85 (s, 3H, OMe), 4.26 (q, J= 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 5.01 (d, J=5.7 Hz, 1H, H-7a), 5.14 (t, J=5.5 Hz, 1H, H-7), 5.27 (d, J=3.7 Hz, 1H, H-5), 6.53 (s, 1H, H-3), 6.91-6.87 (m, 2H, Ar-3′- and 5′H), 7.28-7.17 (m, 5H, Ph), 7.88-7.85 (m, 2H, Ar-2′H and 6′H); ir (nujol, cm$^{-1}$): 1688, 1606, 1585, 1536, 1510, 1308, 1254, 1192, 1176, 1114, 1090, 1022, 998, 913, 866, 837, 798, 775, 698;

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