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LETTERS

Synthesis and cycloadditions of 9*H*-furo[3,4-*b*][1]benzo(thio)pyran-9-ones: furan ring formation by a novel hydrolytically induced cycloreversion

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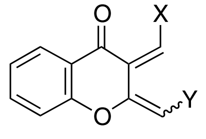
Abstract—C-2 lithiation of acetals **2** followed by trapping with aldehydes gives **3**. Subsequent unmasking of the acetal function provides furobenzo(thio)pyrans **4**, cycloadditions of which have been investigated. © 2002 Elsevier Science Ltd. All rights reserved.



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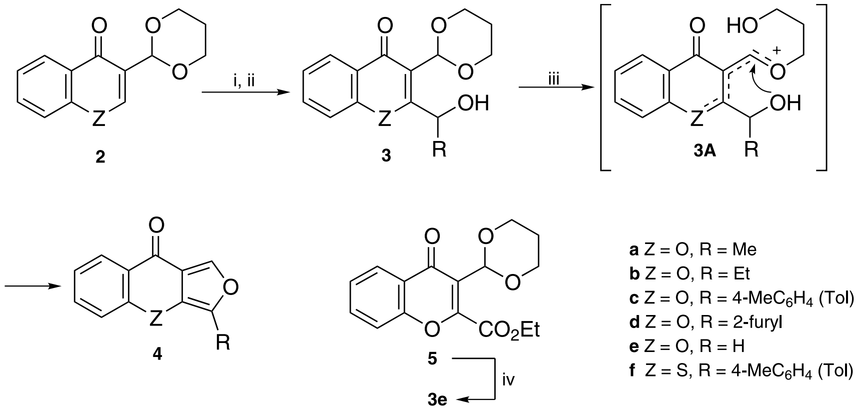
Cycloadditions to 2,3-dimethylidenechroman-4-ones **1** (X, Y = H or substituent) would offer an entry to 2,3-disubstituted 9*H*-xanthen-9-ones and linear fused derivatives. The intermediacy of **1** (X = NH-NMe$_2$, Y = H) is evident in the cycloaddition of 3-(dimethylhydrazonomethyl)-2-methylchromone with *N*-methylmaleimide (NMM),[1] and **1** (X = OH, Y = H) has been



a Z = O, R = Me
b Z = O, R = Et
c Z = O, R = 4-MeC$_6$H$_4$ (Tol)
d Z = O, R = 2-furyl
e Z = O, R = H
f Z = S, R = 4-MeC$_6$H$_4$ (Tol)

Scheme 1. *Reagents and conditions*: (i) LTMP, THF, −78°C; (ii) RCHO; (iii) TsOH (cat.), PhMe, ca. 50°C; (iv) NaBH$_4$ 1 equiv., MeOH.

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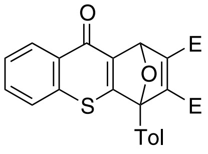
invoked in the base-catalysed deacylative dimerisation of 3-acetylchromone.[2] A more versatile approach to derivatives of **1** would permit access to a wide range of xanthone-containing systems, for which few cycloaddition strategies exist. We sought, therefore, to investigate stable synthetic equivalents of **1** and focussed on derivatives of furo[3,4-*b*][1]benzopyran-9-one. Very few of these compounds are known, and their chemistry remains unexplored.[3] The cycloaddition chemistry of furans and their iso-condensed derivatives represents an area of significant current interest.[4]

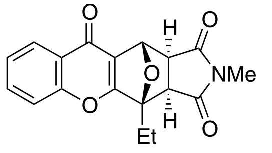
We now report an expedient and versatile synthesis of furo[3,4-*b*][1]benzopyran-9-ones and some of their cycloaddition chemistry. We have shown that the readily available acetal **2** (Z = O) can be metallated with lithium 2,2,6,6-tetramethylpiperidide (LTMP), and the C-2 lithio derivative intercepted with electrophiles.[5] Extension of this chemistry provided **3a**–**d** in useful yields (40–56%).[6] Unmasking of the acetal function proceeded rapidly with a trace of TsOH in warm toluene, with concomitant cyclisation and elimination of propanediol, presumably via the dioxyallyl cation **3A** (Z = O), to give the furobenzopyrans **4a**–**d** (45–67%) (Scheme 1). Attempts to obtain **3e** via anhydrous HCHO failed. However, reduction of **5**[5] proceeded chemospecifically to give **3e** (77%, mp 126–127°C), unfortunately, treatment with TsOH failed to give an identifiable product, even in the presence of a dienophile.

The thiochromone **2** (Z = S) was converted to **4f** (62.5% overall, mp 183.5–184.5°C) by an identical protocol (Scheme 1), in this case the lithiation proceeded more efficiently than **2** (Z = O). Cycloadditions of **4a**–**d** and the furobenzothiopyran **4f** have been investigated. When **4a** was treated with methyl propiolate (MP) (PhMe, rt, 48 h) flash chromatography provided a new compound (43%, mp 228–229°C). Both NMR and HRMS indicated this was a 2:1 adduct of **4a** with MP (Scheme 2). The ^{1}H and ^{13}C NMR spectra were consistent with the *syn exo–endo* adduct **6**, which was proved unequivocally by X-ray crystallography[7] (Fig. 1). The octacycle **6** is remarkable since it represents the first example of a pincer adduct from cycloaddition of an unsymmetrically substituted furan with a propiolic ester,[8] although an intramolecular pincer addition of MP to 1,3-bis(2-furyl)propane has been reported.[9] The *syn* orientation of **6** can be considered as the outcome of 'double *ortho*' regiocontrol. Evidently electronic factors are sufficient to over-ride unfavourable interactions arising between the Me groups in the addition of **4a** to the 1:1 adduct.[10] The stereochemistry of **6** is in accord with both observations and semi-empirical calculations[4,11] that indicate, under kinetic conditions, pincer Diels–Alder reactions of furans lead to *exo–endo* adducts preferentially. We were unable to observe the 1:1 adduct from **4a** and MP; the reaction gave **6** directly. Furan **4c** failed to react with MP, presumably steric factors account for its diminished reactivity.

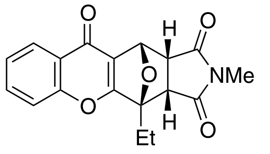
Reaction of **4a** with DMAD gave the 1:1 adduct **7a** as the only characterisable product. However, under the same conditions **4c** gave two compounds the least polar (TLC) of which was **7c** (52%, mp 149.0–149.6°C). The polar compound exhibited very simple ^{1}H and ^{13}C NMR spectra consistent with a highly symmetrical structure whilst CI-HRMS exhibited [MH]$^+$ at *m*/*z* 695.1912 corresponding to $C_{42}H_{30}O_{10}$. This data is only compatible with the C_2 symmetric, *anti exo–exo* adduct **8**[12] (24%, mp 225–226°C). Formation of **8** parallels the behaviour of 2-methylfuran towards symmetrical acetylenes.[9] Surprisingly, we did not observe any of the analogous 2:1 adduct from the cycloaddition of **4f** with DMAD, the only product being **9** (45%, mp 176–177°C). Although **4d** reacted with DMAD it provided a highly complex mixture that we failed to resolve.



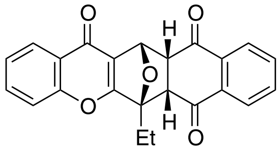
9



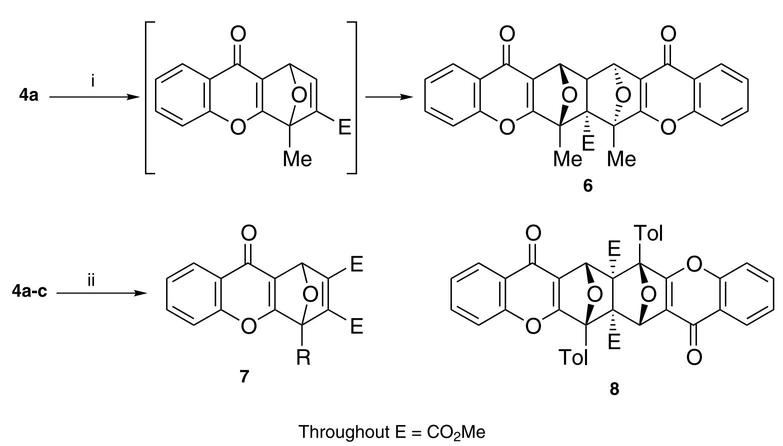
10a



10b



11



Throughout E = CO_2Me

Scheme 2. *Reagents and conditions*: (i) HC≡CCO_2Me, PhMe, rt, 48 h; (ii) $MeO_2CC≡CCO_2Me$, PhMe, Δ, 2 h.

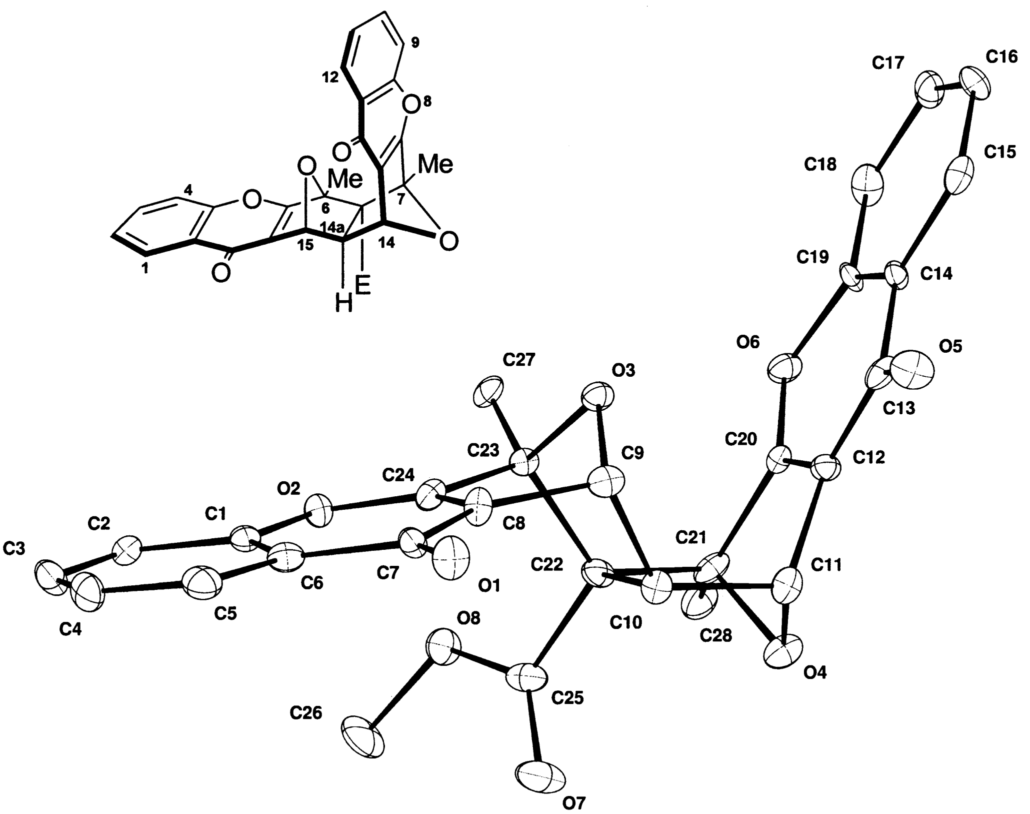
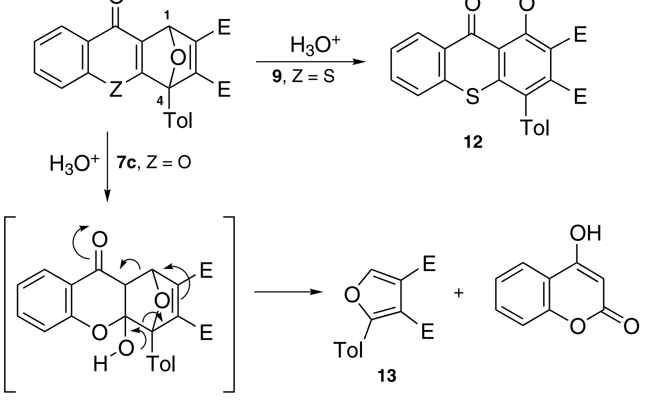


Figure 1. Perspective view and X-ray crystal structure of cycloadduct **6**.

Compound **4b** and NMM (PhMe, rt, 6 h) gave both *exo* **10a** and *endo* **10b** adducts (79% overall, ratio 2.75:1) from which only the former could be obtained pure (mp 257–259°C) by chromatography. In contrast **4b** reacted slowly with 1,4-naphthoquinone and gave the *endo* adduct **11** exclusively.

Dramatically differing behaviour was exhibited in the acid-catalysed aromatisation (aq. HCl, MeOH, Δ) of **7c** and **9** (Scheme 3). Whilst the latter gave the expected hydroxythioxanthone **12** [red needles, 82%, mp 218–220°C, $\delta(\mathrm{CDCl_3})$ 16.65, OH] the former provided, remarkably, the furan diester **13**[13] (68%) together with 4-hydroxycoumarin (77%). This unique and unprecedented pathway formally represents a hydrolytic retro Diels–Alder (RDA) reaction of a 7-oxabicyclo[2.2.1]heptadiene ring. Cleavage of **7c** is triggered by protonation of the chromone carbonyl group that promotes conjugate addition of water to C-4a (Scheme 3); collapse of the intermediate hemiacetal ensues. The hemiacetal may be regarded as the [4+2] adduct of **13** and 2-hydroxychromone, a minor tautomer of 4-hydroxycoumarin. The differing reactivity of **7c** and **9** stems from higher basicity of the carbonyl group in the chromone than in the thiochromone system, due to diminished heteroatom p–π conjugation in the latter. In accord with this, a study of electrostatic potentials predicted that C-2 in chromones is more electrophilic than C-4, and that replacement of ring O by S promotes a reversal in reactivity.[14] The reaction **7c**→**13** is noteworthy since it generates a furan with a new substitution pattern. Other acid promoted RDA reactions of 7-oxabicycloheptadienes are known, but these merely furnish the addends.[15]



Scheme 3.

Acknowledgements

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6. New compounds were characterised by ^{1}H and ^{13}C NMR, HRMS and elemental analysis.
7. *syn* Refers to the disposition of the bridgehead methyl groups. δ_H(CDCl$_3$) 1.82 (3H, s, Me), 1.85 (3H, s, Me), 3.62 (3H, s, CO$_2$Me), 3.80 (1H, d, $J_{14a,15} = 5.1$, 14a-H), 5.09 (1H, s, 14-H), 5.61 (1H, d, $J_{15,14a} = 5.1$, 15-H), 7.55 (6H, m, Ar-H), 8.21–8.28 (2H, m, 1-H, 12-H). Crystal data for **6**: $C_{28}H_{20}O_8$, $M = 484.44$, triclinic, space group $P\bar{1}$, $a = 7.5200(5)$, $b = 13.984(4)$, $c = 21.53(2)$ Å, $\alpha = 102.710(3)$, $\beta = 93.440(8)$, $\gamma = 94.76(2)°$, $U = 2194(2)$ Å^3, $D_c = 1.467$ mg m^{-3}, $Z = 4$, Mo–Kα radiation ($\lambda = 0.71069$ Å), $\mu = 0.108$ mm^{-1}, $T = 150(2)$ K, 5958 measured reflections, 5044 observed reflections ($R_{int} = 0.0722$), $R_1 = 0.0386$ [$I > 2\sigma(I)$], $wR_2 = 0.0643$ (all data). Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 157078.
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12. The presence of one Ar-Me and one OMe signal [δ(CDCl$_3$) 2.48 (6H, s, Ar-Me), 3.49 (6H, s, OMe)] limits the choice from six diastereomeric adducts to two i.e. **8**, or the *anti endo–endo* isomer. The latter is excluded on steric grounds since *endo–endo* adducts have never been observed in furan cycloadditions.[4] *exo–exo* Stereochemistry is normally observed under thermodynamic conditions.[9,11]
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