β-Deprotonation by Lithium Di-isopropylamide. Vinyl Carbanions from Oxygen Heterocycles in the Synthesis of Carboxylic Acids in the Benzofuran, Flavone, and Coumarin Series and in the Regiospecific Acylation of 2,6-Dimethylchromone

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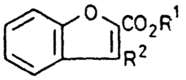
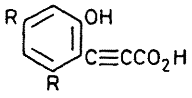
Summary Lithium di-isopropylamide at −70 °C can remove the α-proton from benzofuran in the absence of activating groups and the β-proton if such groups are present, in flavone and 4-methoxycoumarin β-deprotonation occurs readily and the carbanions are easily carboxylated giving acids not previously accessible, while in 2,6-dimethylchromone β-deprotonation is kinetically favoured allowing 3-acylation to be achieved separately from the conventional acylation at the 2-methyl group

LITHIUM DI-ISOPROPYLAMIDE (LDA) is a strong, yet relatively non-nucleophilic, base in widespread use for making carbanions from 'active methylene' compounds[1] although removal of vinylic hydrogen (α-deprotonation) has been observed in vinylic sulphides[2] and halogenated thiophenes [3] It is also known that furans suffer selective α-deprotonation if activating groups assist it[3-5] and that they can even form bis-α-anions [5]

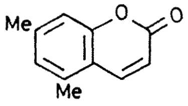
We report that, even in the absence of an activating group, benzofuran suffers α-deprotonation by LDA in tetrahydrofuran at −70 °C almost as readily as by butyllithium,[6] carbon dioxide yielding the 2-carboxylic acid (coumarilic acid) (**1**) in 75% yield To obtain the less accessible β-carbanions it has been usual to employ anionic exchange with bromo-derivatives,[7,8] but even here LDA is successful if assisted by a substituent Thus, coumarilic



(1) $R^1 = R^2 = H$
(2) $R^1 = H$; $R^2 = CO_2H$
(3) $R^1 = Me$; $R^2 = H$
(4) $R^1 = Me$; $R^2 = CO_2H$



(5) R = H
(6) R = Me



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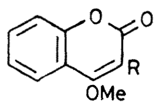
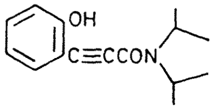
acid (**1**) (with 2 equiv. of base) supplies the dicarboxylic acid (**2**), m.p. 248 °C (decomp.), orientated by the absence of a proton n.m.r. signal near δ 7·5. A little of the acetylenic acid (**5**) (ν_{max} 2195 cm^{-1}) is also formed. Thermal opening of β-carbanions of cyclic vinyl ethers is observed above −90 °C in other series,[8] and substituents may have some influence since 4,6-dimethylcoumarilic acid gave almost entirely the acetylenic acid (**6**). Applied to (**6**), semihydrogenation gave, nearly quantitatively, the known coumarin derivative (**7**).[9] This sequence is virtually a reversal of the celebrated conversion of coumarins into benzofurans (coumarans) discovered by Perkin more than one hundred years ago.[10] The ester group provides less clean results than carboxylate, but the mixed ester–acid (**4**) can be obtained from methyl coumarilate (**3**).

In general, coumarins do not react readily; LDA attacks mainly the ester link of 3-phenylcoumarin giving the corresponding amide. Surprisingly, however, 4-methoxycoumarin (**8**) smoothly provides the carboxylic acid (**9**), m.p. 154 °C, lacking a proton singlet resonance near δ 5·76, in high yield. Such acids are not easily obtained by other methods; there is only one previous reliable synthesis of 4-hydroxycoumarin-3-carboxylic acid,[11] and it cannot be adapted to yield ethers such as (**9**). If treatment with carbon dioxide is delayed, the acetylenic amide (**10**) (ν_{max} 2195 cm^{-1}) becomes the main product; it was characterised by hydrogenation to the corresponding 3-arylpropionic amide derivative.



(8) R = H
(9) $R = CO_2H$



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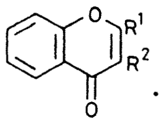
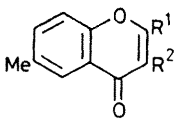


(11) $R^1 = H$, $R^2 = Ph$
(12) $R^1 = CO_2H$, $R^2 = Ph$
(13) $R^1 = Ph$, $R^2 = CO_2H$
(14) $R^1 = Ph$, $R^2 = H$
(15) $R^1 = Ph$, $R^2 = CO_2Et$

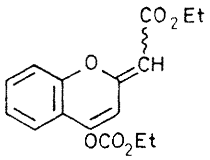


(16) $R^1 = Me$, $R^2 = H$
(17) $R^1 = Me$, $R^2 = CO_2Et$
(18) $R^1 = CH_2CO_2Et$, $R^2 = H$

Chalcones and aurones yield only ill-defined mixtures. For example, 6-methoxyaurone gave highly coloured products along with a small amount of an acetylene from ring opening. Moreover, isoflavone (**11**), in which the 2-proton might be regarded as parallel to that in benzofuran, gave a mixture containing but little (6%) of the acid (**12**). Such acids are better obtained in other ways.[12]

In marked contrast, flavone-3-carboxylic acid (**13**) has never before been made as far as we can tell, probably because most standard flavone syntheses produce intermediates that cyclise in an alternative fashion leading to the corresponding 3-aryl-4-hydroxycoumarins.[13] Obtained in 53% yield by treating flavone (**14**) with LDA and carbon dioxide, this acid had m.p. 178 °C and lacked a proton singlet resonance near δ 6·82; with diazoethane it gave the ester (**15**) also obtained by using ethyl chloroformate in the acylation step.

These results imply a degree of activation in an alkene, whether by the carbonyl group or the ring oxygen atom, or both, that seems to have been overlooked. We have therefore examined 2,6-dimethylchromone because it offers a competition between vinylic deprotonation and the classical deprotonation of 'active methylene'. When this chromone (**16**) was treated with LDA and then ethyl chloroformate the main product was the acetic ester derivative (**18**), m.p. 97 °C, δ 2·44 (ArCH_3), 3·64 (CH_2-CO_2Et), and 6·28 (3-H). The minor product was a mixture of geometrical isomers corresponding to the diacylated chromone (**19**). Other acid chlorides behaved similarly, thus identifying the carbanion as the conventional hybrid (**20a**—**c**) reacting at the methylene terminus (the dienolate γ-position). Most dienolates react at their α-position,[14] but some,[15] and always those with an additional hetero-atom,[16] are known to react selectively at the dienolate γ-position instead, possibly in order to preserve the very important vinylogous ester resonance. Chromones fall into this class, so acylation of the 2-methyl group is indeed the expected reaction.



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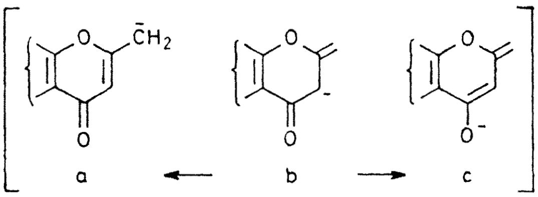

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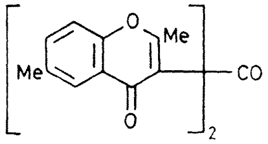
The same procedure with ethyl carbonate instead of ethyl chloroformate failed to result in any acylation Since ethyl carbonate is a particular unreactive ester, however, and is only slowly attacked by LDA at −70 °C, we were able to invert the customary procedure and add the chromone to an excess of a preformed mixture of LDA and ester Acylation now proceeded well, but the product was a new isomer, the 3-carboxylate (**17**), m p 82 °C, δ 2 43 (ArCH_3) and 2·49 (2-Me) Also isolated was the ketone (**21**), m p 203 °C, ν_{max} 1662, 1640, 1614, and 1560 cm^{-1}, formed because the chromone ester (**17**) competes for the intermediate carbanion Acylation with ethyl benzoate gave a 3-benzoylchromone as the only acylation product



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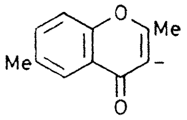

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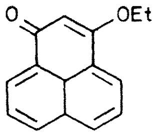

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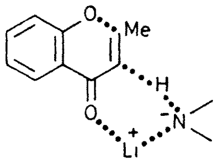

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We reject explanations of the regiospecificity based upon the one carbanion (**20**) It is difficult to see how this could react solely in one form in one case and solely in another form in the other case Even if carbon–lithium bonds are mainly covalent, thus theoretically distinguishing between (**20a**) and (**20b**), the speed at which aggregation occurs would largely obliterate the difference in practice [17] Moreover, carbanion (**20**) has three anionic sites, and any explanation must show why they are distinct, acylation occurring together at oxygen and the methyl group or, quite separately, at the 3-position

On the basis of this evidence therefore, we prefer the idea that LDA first removes the vinylic proton from the chromone giving the 3 carbanion (**22**) under kinetic control The 3-carbanion is reactive enough to be trapped by ethyl carbonate but it changes in a short time into the thermodynamically more stable carbanion (**20**) Since this is correspondingly rather unreactive it requires an acyl halide for acylation which occurs specifically at the γ-site (methylene group) in accordance with precedent as noted above

It appears at present that all easy β-deprotonations have the ether (cyclic) oxygen atom in the antiperiplanar orientation The importance of such an arrangement is emphasised by the phenalenone derivative (**23**) which is recovered completely from the conditions used for carboxylating the chromone (**16**) It seems, therefore, that β-deprotonation may be significantly aided by a redistribution of electronic density within the σ-framework corresponding to a through-bond orbital stabilisation[18] and as indicated in (**24**) Progress along this reaction co-ordinate eventually leads to the ring fission and alkyne formation characteristic of the β-carbanions of vinyl ethers †

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† Selective deprotonation in monocyclic 2-pyrones occurs adjacent to carbonyl We thank Dr J Staunton for this and other information prior to publication

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