Three Syntheses of 3,8-Dimethyl-1*H*-pyrano[4,3-*b*][1]benzopyran-10-one, a Model for the Synthesis of the Fungal Metabolite, Fulvic Acid

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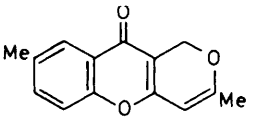
Compounds with the 1*H*-pyrano[4,3-*b*][1]benzopyran-10-one nucleus characteristic of fulvic acid have been prepared by three methods from chromone precursors; the characteristic steps are (i) the acetylation of the 2-methyl group of 3-methoxymethyl-2,6-dimethylchromone by acetyl chloride and lithium di-isopropylamide at −70 °C, (ii) the acetylation of the 2-methyl group of 3-chloromethyl-2,6-dimethylchromone by *N,N*-dimethylacetamide in phosphoryl chloride followed by acid hydrolysis, and (iii) (the best route) the reverse Diels–Alder addition of 2-methoxypropene to 3-formyl-6-methylchromone and the rhodium-catalysed isomerisation of the product to regain the chromone nucleus.

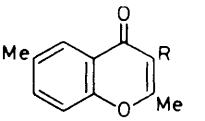
The heterocyclic system in the pyranopyran derivative (**1**) has not been studied much although it is characteristic of metabolic products from micro-organisms, *e.g.*, fulvic acid[1] and radicinin.[2] A synthesis of the pyranopyran derivative (**1**) by standard methods proved ineffective when applied to fulvic acid itself so we have devised two further methods one of which is better suited to elaboration.

In the standard sequence, 2,6-dimethylchromone (**2**) gave upon chloromethylation the 3-chloromethyl derivative (**3**) converted by methanol and base into the analogous 3-methoxymethyl compound (**4**). Although chromones have not been acetylated at the 2-methyl group, this is known to lose a proton to bases[3] and the 3-methoxymethyl group should promote lithiation. In practice lithiation (lithium di-isopropylamide in tetrahydrofuran at −70 °C) was effective, but acetylation was poor (acetyl chloride was better than alkyl acetates or acetic anhydride) and the diacylated product (**5**) accompanied the desired 2-acetonylchromone (**6**), m.p. 109—110 °C, ν_{max} 1 705 (acyclic C:O), 1 640, 1 608, and 1 592 cm^{-1} (chromone pattern), δ ($CDCl_3$) 2.3 (3H, s, Ac), 2.46 (3H, s, ArMe), 3.34 (OMe), 3.92 (2H, s, CH_2Ac), and 4.50 (2H, s, CH_2OMe). Hydrolysis of this product with damp trifluoroacetic acid under reflux replaced the OMe by OH giving (**7**) thus permitting cyclisation to a cyclic hemiacetal. Dehydration occurred spontaneously and led directly to the desired 3,8-dimethyl-1*H*,10*H*-pyrano-[4,3-*b*][1]benzopyran-10-one (**1**), m.p. 155 °C, *m/z* 228, ν_{max} 1 655, 1 610, and 1 592 cm^{-1} (chromone pattern), δ ($CDCl_3$) 2.00 (3H, s, 3-Me), 2.42 (3H, s, 8-Me), 5.29 (2H, s, ring CH_2), 5.42 (1H, s, vinylic H), 7.23 (1H, d, *J* 8.0 Hz, 6-H), 7.36 (1H, dd, *J* 8.0, 2.3 Hz, 7-H), and 7.92 (1H, d, *J* 2.3 Hz), in yields of 34% from (**4**).

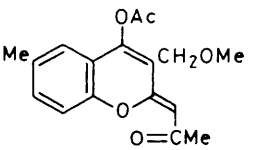
The next approach was suggested by a separate study in which we had found that the Vilsmeier–Haack reagent (*N,N*-dimethylformamide in phosphoryl chloride) attacks the 2-methyl group of chromones. Since an acetyl group was to be introduced, we used *N,N*-dimethylacetamide, a known but unusual practice.[4] In phosphoryl chloride at 110 °C, this reagent converted 3-chloromethyl-6-methylchromone (**3**) into an iminium salt which was converted by controlled hydrolysis into the yellow chlorochromene (**8**), m.p. 173—175 °C (decomp.), *m/z* 286, 284, and 282, δ ($CDCl_3$) 2.36 (3H, s, ArMe), 2.45 (3H, s, Ac), 4.48 (2H, s, CH_2Cl), and 5.55 (1H, s, vinylic H). Only the geometrical isomer shown in (**8**) was produced, although if there is no 3-substituent both isomers result. Hydrolytic removal of halogen by damp trifluoroacetic acid under reflux resulted in the required pyranopyran (**1**), but in only 20% yield from the chloromethylchromone (**3**). The carbonyl stretching frequency of (**8**) seemed to lie at 1633 cm^{-1}, an unusually low frequency that could reflect an exceptional release of electron density into the carbonyl group from the ring oxygen atom which thereby attains the (aromatic) pyrylium state [as indicated by arrows in (**8**)].



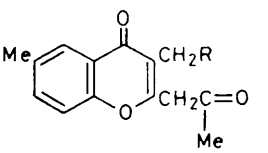
(1)



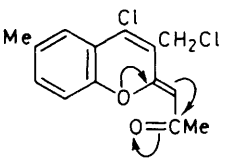
(2) R = H
(3) R = CH_2Cl
(4) R = CH_2OMe



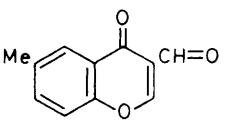
(5)



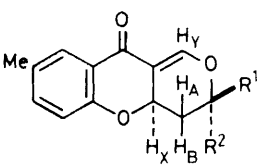
(6) R = OMe
(7) R = OH



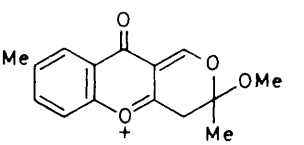
(8)



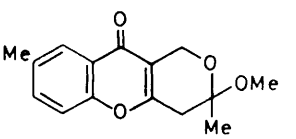
(9)



(10) R^1 = OMe
R^2 = Me
(11) R^1 = Me
R^2 = OMe



(12)



(13)

The third synthesis of the pyranopyran (**1**) was based upon a reversed Diels–Alder reaction of the kind explored by Snider.[5,6] Addition of 3-formyl-6-methylchromone (**9**) to 2-methoxypropene at 18 °C gave the single isomer (**10**), m.p. 116—118 °C, *m/z* 260.10218, $C_{15}H_{16}O_4$ requires *m/z* 260.10485, ν_{max} (KBr) 1665 and 1620 cm^{-1} (br.), δ ($CDCl_3$) 1.47 (3H, s, Me), 2.29 (3H, s, ArMe), 3.41 (3H, s, OMe), 7.55 (1H, d, J_{XY} 1.8 Hz, H_Y), 2.31 (1H, dd, J_{AB} 14, J_{AX} 7 Hz, H_A), 2.45 (1H, dd, J_{AB} 14, J_{BX} 9, H_B), 5.02 (1H, ddd, J_{AX} 7, J_{BX} 9, J_{XY} 1.5 Hz, H_X), 6.82 (1H, d, *J* 8 Hz, 6-H), 7.23 (1H, dd, *J* 8, 2.5 Hz, 7-H), and 7.73 (1H, d, *J* 2.5 Hz, 9-H). The

alternative diastereoisomer (**11**) was procured by removing hydride ion from (**10**) with triphenylcarbenium perchlorate[7] to form the cation (**12**) (not characterised) and selectively reducing it with sodium borohydride in methanol; isomer (**11**) was very similar to the original, the only clear differences being in certain chemical shifts, thus: δ 1.54 (Me), 3.25 (OMe), 2.04 (H_A), 2.54 (H_B), and 5.13 (H_X). In contact with various rhodium catalysts,[8] the original adduct (**10**) isomerised to the chromone (**13**), δ ($CDCl_3$) 1.54 (3H, s, Me), 2.44 (3H, s, ArMe), 3.31 (3H, s, OMe), 2.73 and 2.88 (2H, AB q, *J* 18 Hz, 4-CH_2), 4.47 and 4.78 (2H, AB q, *J* 16 Hz), 7.26 (1H, d, *J* 8 Hz, 6-H), 7.41 (1H, dd, *J* 2, 8 Hz, 7-H), and 7.94 (1H, d, *J* 2 Hz, 9-H). Although both the cycloaddition and the double bond migration steps are slow, they are clean and afford high conversions. Moreover, they are less affected by substituents in the benzene ring than are the essential steps in the two other routes, so the third route is the one preferred for a projected synthesis of fulvic acid itself. As before, trifluoroacetic acid readily converted chromone (**13**) into the pyranopyran (**1**).

Received, 25th February 1983; Com. 262

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