Tetrahedron Letters, Vol. 33, No. 8, pp. 997-1000, 1992
Printed in Great Britain

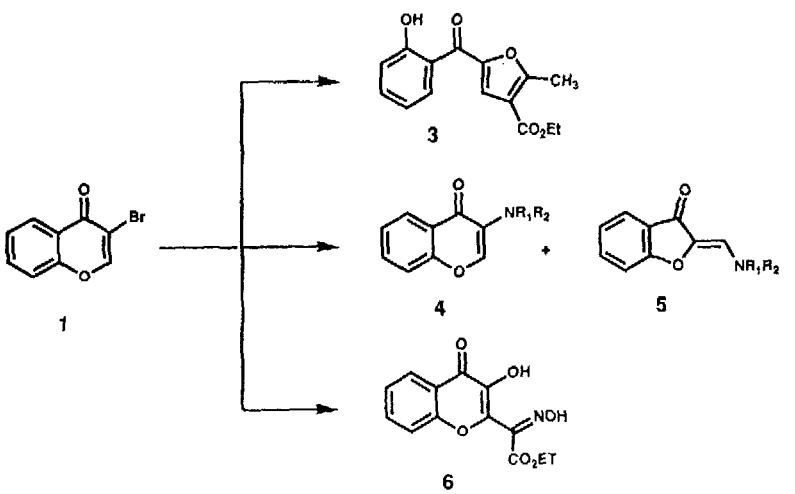
0040-4039/92 $3.00 + .00
Pergamon Press plc

A NOVEL ENTRY TO SUBSTITUTED CHROMONES AND FUROCHROMONES THROUGH CYCLOPROPANE INTERMEDIATES.[1]

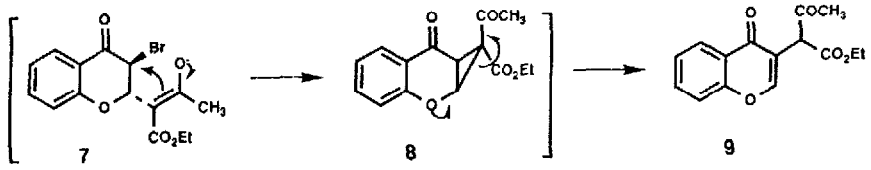
Ronald B. Gammill*, Sharon A. Nash, Larry T. Bell and William Watt
The Upjohn Laboratories
The Upjohn Company, Kalamazoo, MI 49001

Abstract: Addition of several carbon nucleophiles to 3-bromochromone **1** and 6-bromofurochromone **2** yield interestingly substituted δ-pyrone ring analogues.

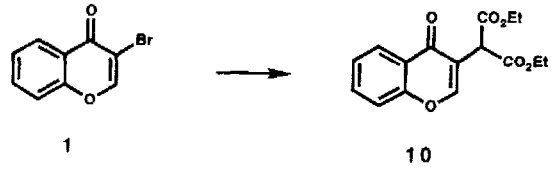
The addition of carbon and nitrogen nucleophiles to chromones generally results in the rupture of the δ-pyrone ring leading to the formation of substituted aryl systems.[2] We are interested in reactions of both 3-bromochromone **1** and 6-bromofurochromone **2**[3a] which generate a uniquely functionalized pyrone ring, or, those in which the pyrone ring is replaced by a completely new heterocyclic ring. For example, we have previously reported that addition of ß-ketoesters to **1** results in the rupture of the pyrone ring leading to a substituted furan (**3**).[1] Addition of amines to **1**, however, can lead to either a 3-substituted chromone (**4**), or a ring contracted product (**5**).[3b] Due to our continued interest in chromones and furochromones as medicinal agents, our interest in the utilization of **1** and **2** as intermediates leading to uniquely substituted analogues of these systems has progressed.[4]

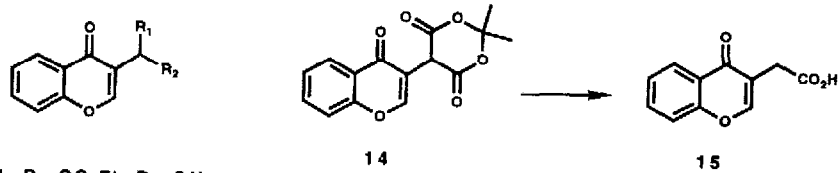


While studying the addition of ß-ketoesters to **1** we postulated that products arising from a cyclopropane intermediate such as **8** might be possible. We felt that an intermediate such as **8** should very cleanly open to a 3-substituted chromone (i.e., **9**) due to the anachimeric assistance that should be available via the adjacent oxygen. To circumvent the O-alkylation experienced in the case of ß-ketoesters, we investigated the addition of a number of substrates to **1** which would naturally favor C-alkylation subsequent to the Michael addition (**7**→**8**), thus forcing the involvement of cyclopropane intermediates which ultimately should yield 3-substituted chromones.[5]

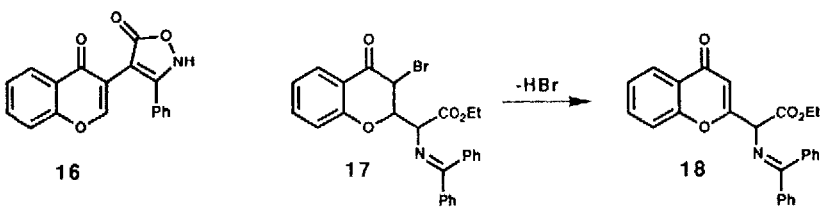


In contrast to ß-diketones and ß-ketoesters, we found that addition of diethyl malonate to **1** (3 equiv. DBU/CH_3CN/RT) afforded the 3-substituted chromone **10** in 68% yield.[6] The structure of **10** was readily established in the following manner. The UV (max 225 nm; ε=21,000) and IR (1744, 1734, 1636 cm^{-1}) of **10** was characteristic of the chromone nucleus and the intact malonate unit. The ^{1}H-NMR contained a sharp singlet at δ 7.8 typical of the C-2 proton and at δ 4.5, typical of the methine bearing the malonate moiety at C-3. Addition of ethyl and t-butyl cyanoacetate and methyl sulfonyl acetonitrile likewise smoothly afforded **11**, **12**, and **13**, respectively, in the yields shown. The structural integrity of these compounds was established through conversion of the Meldrum acid adduct **14** to the known acid **15**[7] and through single crystal x-ray analysis of the 3-(methylsulfonyl)acetonitrile benzopyrone **13**.[8]



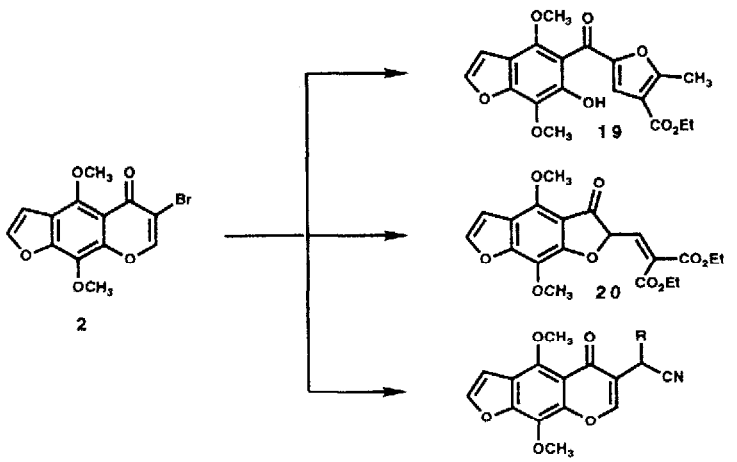


In a similar fashion, addition of 4-phenyl-5H-oxazole to **1** afforded the isoxazolone **16** in 75.7% yield. The structure of **16** was confirmed by single crystal x-ray analysis.[8] Interestingly, addition of ethyl N-(diphenylmethylene) glycine afforded the C-2 substituted product **18** in 56% yield. This latter product presumably results from elimination of HBr from a protonated Michael adduct (i.e., **17**). The change in reaction pathway is likely a consequence of the increased steric demand of the diphenylimine moiety preventing the formation of a cyclopropane intermediate. The pyrone ring rupture observed in the case of ß-diketones and ß-ketoesters can thus be avoided by utilizing stabilized enolate systems that favor a second carbon alkylation rather than O-alkylation.



16 17 18

Consistent with our earlier results in the chromone series,[2] addition of ethyl acetoacetate to furochromone **2** afforded **19**, the product resulting from rupture of the pyrone ring, in 95% yield. However, addition of diethyl malonate to **2** afforded the ring contraction product **20** and not the expected 6-substituted product. The structure of **20** was confirmed by single x-ray crystallography.[8] Addition of both ethyl and t-butyl cyanoacetate to **2** afforded the 6-substituted products **21** and **22**, respectively. The dichotomy in the addition of diethyl malonate to **2**, to afford the unexpected ring contracted product **20**, must reflect the difference in the electronic nature of the enolates.[9]



2 19 20

21 R=CO_2Et
22 R=CO_2t-Bu

This methodology makes available a number of heretofore inaccessible 3-substituted chromones, 6-substituted and ring contracted furochromones for biological and chemical investigation.

Acknowledgements: We would like to acknowledge Physical and Analytical Chemistry for spectral data and Mary Ferriell for preparation of this manuscript.

References and Notes

1. Part 5 in a series on the synthesis and chemistry of functionalized furochromones. For Part 4 see preceding letter in this issue.
2. Gammill, R.B. *J. Org. Chem.*, **1979**, *44*, 3988; and references therein.
3. a) Furochromones such as **2** have been shown to have antiatherosclerotic activity. For leading references see: Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672. b) Gammill, R.B.; Nash, S.A.; and Mizsak, S.A. *Tetrahedron Letters* **1983**, 3435.
4. Gammill, R.B.; Nash, S.A.; and Williams, W. *Tetrahedron Letters*, preceding article in this issue.
5. For example see: Takei, I; Fukuda, Y; Sugaya, K; Taguchi, T; Kawara, T. *Chem. Lett.* **1980**, 1307.
6. a) All compounds displayed satisfactory H-NMR, IR, UV, C,H, and N combustion analysis and mass spectra consistent with their assigned structures. b) Melting points: **10**, 86.9-8°C; **11**, 97.5-9°C; **12**, 135-7°C; **13**, 148.9-9.2°C; **14**, 160°C; **15**, 223-225°C; **16**, 204-10°C; **18**, 147.5-154°C; **19**, 135-6°C; **20**, 91-7.5°C; **21**, 127°C; **22**, 167-70°C.
7. Klutchko, S.; Cohen, M.P.; Shavel, J. and von Strandtmann, M. *J. Heterocyclic Chem.*, **1974**, *11*, 183.
8. Atomic coordinates, thermal parameters, coordinate parameters for isotropic hydrogen atoms, bonding distances, bond angles, torsion angles and intermolecular distances have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, CB2,1EW.
9. This change in reaction pathway has also been observed in the addition of amines to both **1** and **2** (see reference 3b). Frequently, addition of amines to **1** yields a 3-substituted product whereas addition of the same amine to **2**, under identical reaction conditions, yields a ring contraction product.

(Received in USA 20 November 1990; accepted 4 November 1991)