Tetrahedron Letters, Vol. 33, No. 8, pp. 993-996, 1992
Printed in Great Britain

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

THE SYNTHESIS AND CHEMISTRY OF FUNCTIONALIZED FUROCHROMONES.4.[1] ADDITION OF NITRONATE ANIONS TO 3-BROMOCHROMONE AND 6-BROMOFUROCHROMONE. AN EXPEDIENT ROUTE TO FURO(3',2':6,7)-BENZOPYRANO(2,3-d)-ISOXAZOLONES AND CHROMONO(2,3-d)ISOXAZOLONES.

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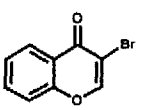
Abstract: Addition of nitronate anions to 3-bromochromone **1** and 6-bromofurochoromone **2** results in the efficient generation of 3-hydroxy-2-(1-(hydroxyimino)alkyl,aryl or carboalkoxy) substituted chromones and the corresponding 6,7-disubstituted furochromones. These compounds are efficiently converted to furo(3',2':6,7)benzopyrano(2,3-d)isoxazoles and chromono(2,3-d)isoxazoles, respectively, with N,N-dimethylformamide dimethylacetal (DMF-DMA).

Our interest in the addition of nucleophilic species to 3-bromochromone 1 and 6-bromofurochromone **2**[2] stems from the pharmacological activity associated with these classes of compounds.[3]



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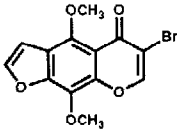

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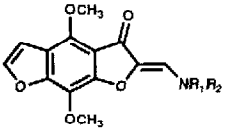
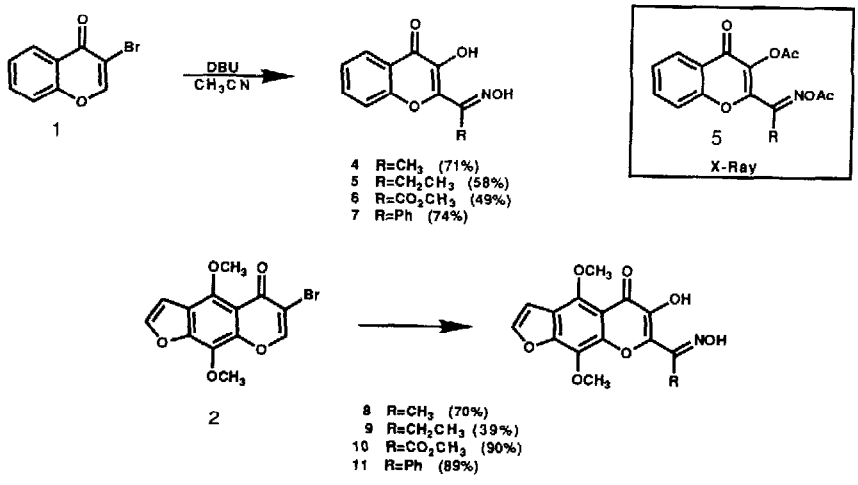


3

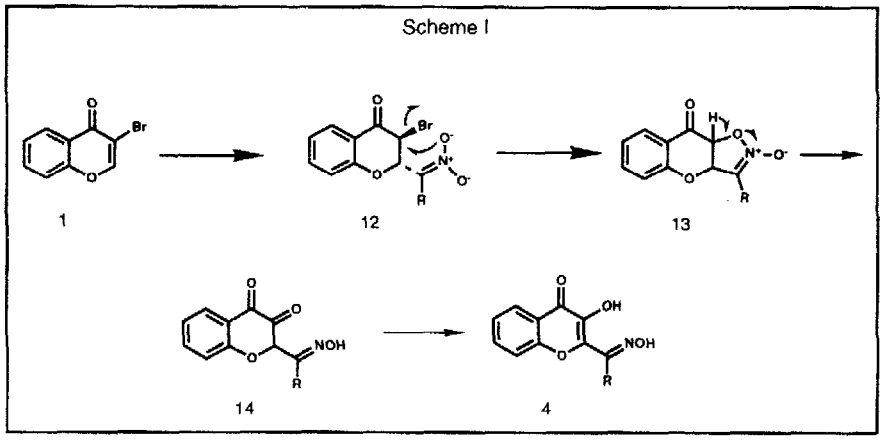
We have continued our efforts to find reactions (of **1** and **2**) which yield a uniquely substituted δ-pyrone ring[4] and reactions which result in replacement of the δ-pyrone ring with another heterocyclic system. An example of this latter strategy is illustrated by conversion of **2** to the benzodifuran **3** upon treatment of **2** with amines.[4b] It is important to note that the product profile resulting from addition of a nucleophilic species to **1** and **2** are often quite different, likely reflecting steric and electronic differences about the δ-pyrone ring. In this letter we report the results of adding the ambident nitronate anion to compounds **1** and **2**.

Dropwise addition of 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU; 3 equiv./CH_3CN/RT) to an acetonitrile solution of **1** and nitroethane (1.1 equiv.) resulted in the smooth conversion of **1** to the 3-hydroxy-2-(1(hydroxyimino)methyl)chromone **4**[5,11] in 71% yield. The structure of **4** was determined by single crystal x-ray analysis on the diacetate **5** (MP 117.9-120.0°C)[6]. As illustrated, addition of nitropropane, α-nitroacetate and α-nitrotoluene likewise added smoothly to **1** to afford **5**, **6**, and **7**, respectively, in good

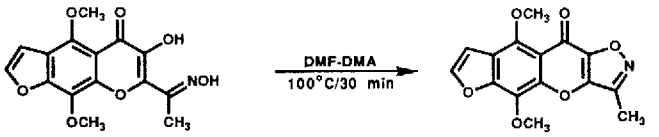
yield.[7] The use of less than three equivalents of DBU resulted in lower yields and somewhat more complex reaction mixtures as did the use of chlorocarbon solvents. The reaction was readily extended to furochromone **2** and provided the novel 6,7-disubstituted analogues.[5]



A plausible mechanism for this reaction is outlined below. Michael addition of nitroethane to **1** likely yields a *trans*-nitronate intermediate **12**.[8,9] That intermediate can then undergo intramolecular o-alkylation to afford **13** which subsequently suffers fragmentation to yield **14**.[10] Tautomerization of **14** yields the observed product **4** (R=CH_3).

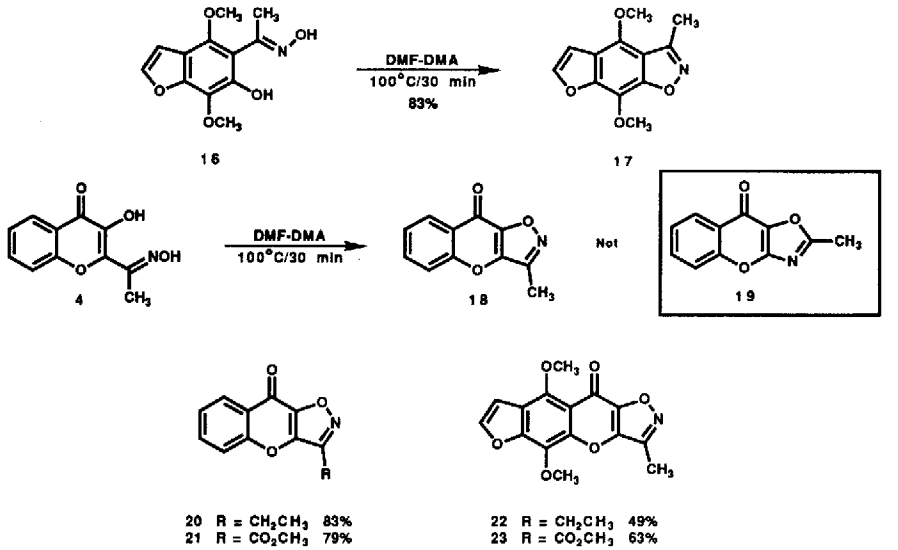


In searching for new ways of dehydrating the o-hydroxyoximino system we discovered that treatment of **8** with DMF-DMA (neat, 100°C, 30 minutes) cleanly afforded the isoxazole isomer **15** in 79.6% yield.[12] There was no evidence of Beckmann rearrangement and thus formation of the oxazole isomer under these reaction conditions was completely suppressed.[13]



8 15

To further survey this reaction, we treated khellinone oxime **16** with DMF-DMA under identical reaction conditions and obtained the known isoxazole **17** in 83% yield.[14] In a similar manner, treatment of chromone **4** with DMF-DMA afforded isoxazole **18** in 76% yield and not the known oxazole isomer **19**.[15] As illustrated, isoxazole analogues from both the chromone and furochromone series are readily available using this procedure.



16 17

4 18 19

20 R = CH_2CH_3 83%
21 R = CO_2CH_3 79%

22 R = CH_2CH_3 49%
23 R = CO_2CH_3 63%

Acknowledgement. We would like to acknowledge Physical and Analytical Chemistry for spectral determinations and Mary Ferriell for the preparation of this manuscript.

References and Notes

1. For part 3 see: Gammill, R.B. and Nash, S.A. *Tetrahedron Letters* **1984**, *25*, 2953.
2. 6-Bromofurochromone **2** was prepared according to the method described in *Synthesis* **1979**, 901.
3. Gammill, R.B.; Day, C.E.; Schurr, P.E. *J. Med. Chem.* **1983**, *26*, 1672. Gammill, R.B.; Bell, F.P.; Bell, L.T.; Bisaha, S.N.; Wilson, G.J. J. Med. Chem. (1990) **33**, 2685.
4. a) Gammill, R.B. *J. Org. Chem.* **1984** *49*, 5035. b) Gammill, R.B.; Nash, S.A.; Mizsak, S.A. *Tetrahedron Letters* **1983**, *24*, 3438.
5. a) All compounds displayed satisfactory H-NMR, C-NMR, IR, UV, C, H and N combustion analysis and mass spectra consistent with the assigned structures. b) Representative physical and spectral data of representative compounds. **4**; MP 244°C; ^{1}H-NMR (DMSO-d_6) 8.15 (dd, 1H, C-5H aromatic, J=1.5 and 8 Hz), 7.70 (m, 3H, aromatic), 2.30 (s, 3H, -CH_3), UV (EtOH) 209 (12,950), 239 (12,900), 251 (11,050), 294 (8,900), 343 (10,400), 355 (8,400). **5**; MP 214-5°C; ^{1}H-NMR (DMSO-d_6) 8.20 (dd, 1H, C-5H aromatic, J=1.5 and 8 Hz), 7.70 (m, 3H, aromatic), 2.85 (q, 2H, J=6 Hz), 1.20 (t, 3H, J=6 Hz). **6**; MP 176-7°C. **7**; MP 214-8°C. **8**; MP 250°C; ^{1}H-NMR (DMSO-d_6) 8.15 (d, 1H, J=2 Hz), 7.30 (d, 1H, J=2 Hz), 4.20 (s, 3H, methoxyl), 4.05 (s, 3H, methoxyl), 2.35 (s, 3H, methyl). **9**; MP 220-3°C. **11**; MP 21-4°C. **15**, MP 253-6°C; ^{1}H-NMR ($CDCl_3$) 7.70 (d, 1 H, J = 2 Hz), 7.15 (d, 1 H, J = 2 Hz), 4.20 (s, 3H, -OCH_3), 4.10 (s, 3H, -OCH_3), 2.62 (s, 3H, -CH_3); IR (mull) 2953, 2869, 1674, 1644, 1613, 1518, 1471 cm^{-1}; UV (max) 209 (20,450), 219 (20,650), 258 (30,050), 298 sh (5,000). **18**, MP 180-1°C; ^{1}H-NMR (DMSO-d_6) 8.3 (dd, 1H, J = 1.5 and 6.0 Hz), 7.5-8.1 (m, 3H, aromatic), 2.6 (s, 3H, -CH_3); IR (mull) 2954, 2870, 1683, 1673, 1602, 1517, 1458, 1390 cm^{-1}; UV [EtOH] (max) 223 (14,450), 236 (16,550), 274 (10,250), 314 sh (7.350). **20**, MP 109-11°C; **21**, MP 191-3°C; **22**, MP 189.8-90.2°C; **23**, MP 239.8-44.5°C;
6. Space group PT, Z=2, a=8.394(2)A, b=8.732(1)A, c=11.244(2)A, α=109.13(1)°, ß=101.53(2)°, =96.53(2)°, 2490 reflections, CuKα, $C_{16}H_{15}NO_6$, Final R=0.048. Coordinates deposited in Cambridge Crystallographic Databank.
7. For a review on the addition chemistry of nitro compounds see: Baer, H.H. and Urbas, L., The Chemistry of the Nitro and Nitroso Groups, H. Feuer, Ed., Part 2, Wiley-Interscience, New York, 1970, p.75.
8. For an example of the conjugate addition of a nitronate anion to an α-bromounsaturated ketone resulting in the formation of a cyclopropane see: Shapiro, E.L.; Gentles, M.J.; Weber, L.; and Page, G. *Tetrahedron Letters* **1977**, 3557.
9. An example of conjugate addition by a resonance stabilized nitroacetate anion can be found in: Richards, R.W.; Rodwell, J.L.; Schmalzl, K.J. *J. Chem. Soc. Chem. Commun.* **1977**, 849.
10. This type of fragmentation has been reviewed; see Erashko, V.I.; Shevelev, S.A.; Fainzil'berg, A.A. *Russian Chemical Reviews* **1966**, *39*, 719.
11. Experimental Procedure (**10**). To an acetonitrile solution (300 mL) of **2** (13.0 g, 40.0 mmol) and ethyl nitroacetate (5.85 g, 44.0 mmol) cooled to O°C and under an atmosphere of nitrogen was added an acetonitrile solution (60 mL) of DBU (18.24 g, 120 mmol) dropwise over 5 minutes. After complete addition of DBU, the reaction was stirred at room temperature for 24 hours. The solvent was then evaporated *in vacuo* and the resulting solid thoroughly washed with 6N HCl, water, and methanol. The product was then collected on a filter to yield 13.38 g (88.7%) of pure product (**10**). MP 198-9°C; IR (mull) 3320, 2952, 1747, 1610, 1596, 1486 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 8.20 (d, 1H, J=2 Hz), 7.30 (d, 1H, J=2 Hz), 4.30 (q, 2H, J=6 Hz), 4.15 (s, 3H, methoxyl), 4.04 (s, 3H, methoxyl), 1.25 (t, 3H, J=6 Hz); UV (EtOH) 216 (29,450), 264 (27,950), 317 (8,100), 375 (6,300).
12. An excellent method for direct conversion of salicylaldehyde to the parent 1,2-benzisoxazole is effected by treating the hydroxy aldehyde with hydroxylamine-O-sulfonic acid under phase transfer conditions as described by Kemp, D.S. and Woodward, R.B. *Tetrahedron* **1965**, *21*, 3019 [also see Grashey, R. and Gaumann, M. *Tetrahedron Letters* **1972**, 2947 and *Ibid., Angew. Chem. Internat. Edn.* **1969**, *8*, 133. Our attempts to activate the hydroxy group of the oxime via addition of mesyl chloride under a variety of reaction conditions gave a low yield mixture of isoxazole and oxazole.
13. For a discussion of this problem see: Begtrup, M. and Pedersen, C. *Acta. Chem. Scand.*, **1967**, *21*, 633. Begtrup, M. *J. Chem. Soc. Chem. Commun.* **1975**, 334. Ollis, W.D. and Ramsden, C.A. J. Chem. Soc. Perkin I, **1974**, 633.
14. Hishmat, O.H.; Khalil, K.M.; El-Ebrashi, N.M.A.; and Khodoir, N.M. *Z. Naturforsch*, **1938**, *336*, 1491.
15. Eiden, F. and Dolcher, D. *Arch. Pharm.*, **1972**, *305*, 698.

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