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The Addition of Amines to 3-Bromochromone And 6-Bromofurochromone. An Unexpected Ring Contraction of the Pyrone Ring.

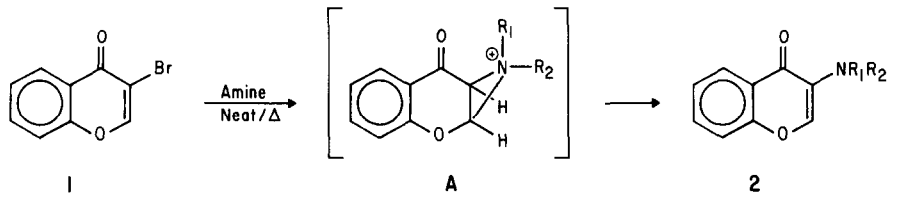
R. B. Gammill,* S. A. Nash and S. A. Mizsak

The Upjohn Company

Kalamazoo, Michigan 49001

Summary: Addition of amines to 3-bromochromone and 6-bromofurochromone results in a novel ring contraction of the pyrone ring.

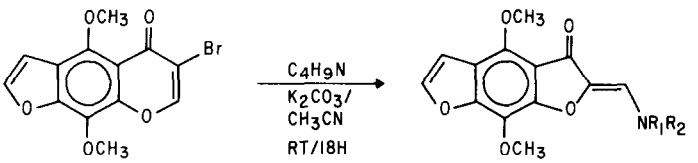
Despite the uniqueness of the reaction, the conversion of bromochromone 1 to the 3-aminochromone 2 has attracted little interest since its discovery by Winter and Hamilton in 1952.[1] Keller[2] has postulated a mechanism for this reaction which involves the aziridium intermediate (A) shown below. The collapse of A, which was not elaborated on by Keller, yields the 3-aminochromone 2.



1 A 2

NR_1R_2 = Pyrrolidine

As a result of the lipid-altering and antiatherosclerotic activity of khellin[3] we were interested in extending the above chemistry to the 6-bromofurochromone 3.[4] Under the reaction conditions of Winter and Hamilton (neat/100°C), the addition of amines to 3 unfortunately yielded extremely complex mixtures.[5] In an attempt to find more suitable reaction conditions we decided to conduct the reaction in acetonitrile rather than neat, at a lower temperature and with added K_2CO_3 to neutralize the HBr formed during the course of the reaction. Under these new reaction conditions (2 eq. amine/1.5 eq. K_2CO_3/CH_3CN/RT/18 H) addition of pyrrolidine to 3 resulted in the formation of the novel ring contraction product 4a[6] (58%). The anticipated 6-aminofurochromone could not be detected.

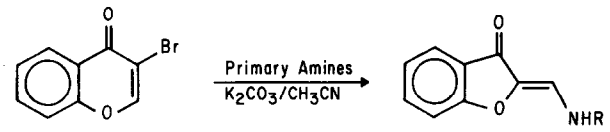


3

4a Pyrrolidine
4b Morpholine
4c Benzylamine
4d Cyclohexylamine

The structure of 4a was quite evident from its IR (1675 and 1625 cm^{-1}) and UV (EtOH, 413 nm, =32,050) spectra.[7] Addition of morpholine, benzylamine and cyclohexylamine to 3 gave the same results, i.e., ring contraction products 4b-d.

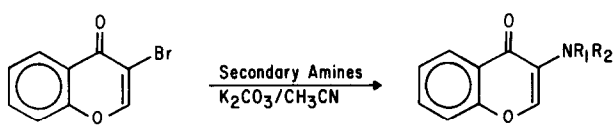
In light of the above results we decided to add several amines to bromochromone 1 under these new reaction conditions to see if this ring contraction process was at all general in nature or simply unique to the khellin system. Addition of butyl, benzyl and cyclohexylamine to 1 yielded the ring contraction products 5a-5c rather than the 3-aminochromone products.[8] As in the case of the furochromones, these ring contraction products exhibited a strong UV absorption in the 395-400 nm range with high molar extinction coefficients (ε=21000-22000).



1

5a R=Butyl 31%
5b R=Benzyl 80%
5c R=Cyclohexyl 96%

To further probe this reaction, we added pyrrolidine and piperidine to 1 using the K_2CO_3 mediated reaction conditions. Addition of these secondary amines to 1 failed to yield the ring contraction products. Instead, only the 3-aminochromones 2 and 6 were obtained. Thus while secondary amines yield the ring contraction product in the khellin series, the substitution product is found in the chromone series.

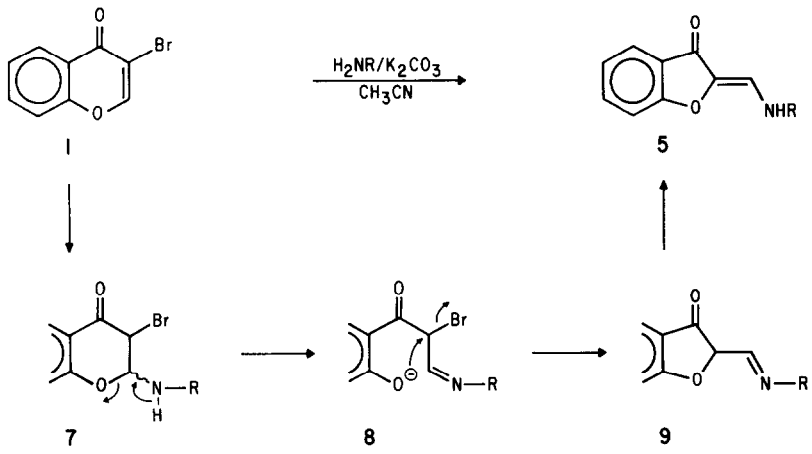


1

2 Pyrrolidine 43%
6 Piperidine 70%

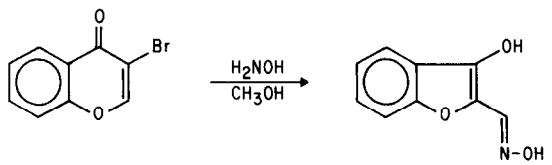
While we do not at this time have a satisfactory explanation for this dichotomy in reaction pathways, we put forward the mechanism shown in Scheme 1 to explain the ring contraction process. Michael addition of the amine to the pyrone ring of 1 yields the α-bromo-β-aminochromone 7. Ring opening[9] (7 to 8) followed by intramolecular o-alkylation at the doubly activated C-3 carbon results in the formation of the benzofuranone 9. Tautomerization of 9 then yields 5.

SCHEME I



1 5 7 8 9

A final example of the generality of this new ring contraction process is found in the addition of hydroxylamine to 1. Treatment of 1 with two equivalents of hydroxylamine in methanol yielded the benzofuran 10[10] in 90% yield. While it is likely that the mechanism for this reaction is somewhat different than that illustrated in Scheme I, it is important to note that it occurs in the absence of carbonate and in a protic solvent.



1 10

Details of this chemistry, both in the chromone and furochromone series, is currently under study and will be reported in due course.

References and Notes

1. C.W. Winter and C.S. Hamilton, J. Amer. Chem. Soc., 74, 3999 (1952). For other reports see reference 2 and the following: J. Colonge and A. Guyot, Bull. Chim. Soc. Fr., 329 (1958); E.K. Orlova, N.S. Tolmecheva, L.M. Meshcheryakova, and V.A. Zagorevshii, Khim. Farm. Zh., 7, 14 (1973); M.K. Tastoge, C. Kamla, R.P. Kapoor, and C.P. Garg, Indian J. of Chem., 16B, 895 (1978).

2. H.H. Auf dem Keller and F. Zymalkowski, Arch. Pharm. (Weinheim), 304, 543 (1971).

3. R.B. Gammill, C.E. Day and P.E. Schurr, J. Med. Chem., submitted for publication.

4. The synthesis of 3 is based on the synthesis of 3-bromochromones reported in: Synthesis, 901 (1978). The full details of the preparation of 3 will be published in the full report of this work.

5. These results are not extremely surprising since aniline hydrochloride is known to very effectively demethylate the C-4 methoxyl of khellin. See: A Schonberg and G. Aziz, J. Amer. Chem. Soc., 75, 3265 (1953).

6. All new compounds exhibited spectral and analytical data consistant with their proposed structures. The stereochemical assignment of the enaminone double bond found in 4 and 5 is based on x-ray data and will be reported in the full account of this work.

7. MP 216-217°C; ^{1}H-NMR ($CDCl_3$,δ) 7.5(d,1H,J=2Hz), 7.19(s,1H,vinyl proton), 6.91(d,1H,J=2Hz), 4.29(s,3H,-OCH_3), 4.12(s,3H,-OCH_3), 3.72(m,4H,-$N(CH_2)$), 1.99(m,4H,-CH_2-CH_2-); Mass Spectrum; ions at m/e (relative intensity) 315(100), 301(13), 300(73), 286(13), 285(14), 231(27), 230(12), 217(12).

8. Our results clearly imply that some of the 3-amino-chromones reported by Winter and Hamilton might, in fact, be ring contraction products. This is particularly true with entry 5c which we, as well as Winter and Hamilton, find as a yellow solid characteristic of the ring contraction products and not the 3-amino-chromone system. We are currently reexamining the amine additions to 1 under the original reaction conditions to fully define the reaction.

9. The formation of ring contraction rather than substitution products could be viewed as suggesting a cis relationship between the amine group and halogen, however, an alternate explanation, involving the aziridium intermediate would be an equilibrium controlled process in which opening of the aziridium ring, either α or β to the carbonyl would determine the product of the reaction. We thank the referee for comments on the mechanism of this reaction.

10. The structure of this compound was established by x-ray analysis. We thank Constance Chidester of the Physical and Analytical Chemistry Department of The Upjohn Company for this determination.

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