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A NEW COUMARIN SYNTHESIS BASED ON THE AROMATIC METALATION REACTION

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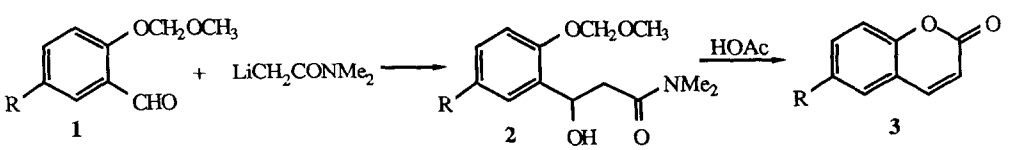
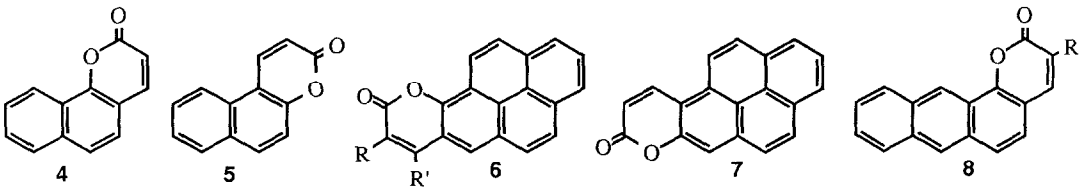
Summary: A convenient synthetic approach to coumarins and polycyclic coumarins based on the aromatic metalation reaction is described. Several polycyclic coumarins exhibit strong anticarcinogenic activity.

Coumarins constitute an important class of natural products many of which exhibit useful drug activity. Coumarin analogs have also been shown to inhibit induction of polycyclic hydrocarbon-induced tumorigenesis in rodents.[1,2] However, systematic investigations of the effects of structural modifications on anticarcinogenic activity have not been conducted. As part of a program with this objective, we undertook to synthesize a series of polycyclic coumarin derivatives. The latter were chosen for specific study on the basis of evidence which suggested that coumarin derivatives structurally related to the carcinogenic polycyclic hydrocarbons benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene may be more effective in blocking tumor induction than their analogs having smaller aromatic ring systems. Although many synthetic routes to coumarins are known,[3-5] these methods were generally unsuitable for our purpose due to the likelihood of substitutions at multiple ring positions with the reagents and relatively harsh conditions required.

We now report a new synthetic approach to coumarins which does not suffer from these limitations and is readily adaptable to the preparation of polycyclic coumarin derivatives. The method is based upon ortho-methoxymethyl aryl aldehydes (**1**) obtainable by regiospecific ortho-lithiation of the related methoxymethylphenolic ethers with alkyllithium reagents followed by reaction with dimethylformamide.[6,7] Addition of α-lithio-N,N-dimethylacetamide[8] to **1** yields **2** which on heating in refluxing acetic acid undergoes smooth conversion directly to the coumarin derivative **3**. Deprotection of the phenolic group, cyclodehydration, and dehydration apparently all take place in this final step. While no attempt was made to optimize yields, they were generally good in both steps, independent of the nature of the groups present in the aldehyde component (**1**: R = H, Cl, CH_3, phenyl) or the number of fused aromatic rings present. Compounds synthesized by this method include several coumarin derivatives (**3**: R = H, Cl, CH_3, phenyl) and the polycyclic coumarin analogs **4-8** (R = H, CH_3; R' = H, CH_3).



The success of the cyclization step was markedly dependent upon the acid employed. With acids stronger than acetic acid, such as polyphosphoric or p-toluenesulfonic acid, tarry products and markedly



4 5 6 7 8

diminished yields resulted. Attempted synthesis of 3 by Reformatski reaction of 1 (R = H) or the free phenol followed by HCl treatment gave resinous products from which significant yields of 3 could not be isolated. The unique efficacy of acetic acid apparently lies in its relative inefficiency as a dehydrating agent in relation to its ability to catalyze removal of the methoxymethyl group and subsequent cyclization. This allows intramolecular cyclization of the saturated amide to compete effectively with dehydration to the more rigidly constrained unsaturated amide, cyclization of which is less favorable.[9]

Typical experimental procedures are as follows: A solution of α-lithio-N,N-dimethylacetamide (62.5 mmol based on CH_3CONMe_2) was prepared from reaction of n-BuLi, i-Pr_2NH, and CH_3CONMe_2 in hexane (50 ml) by the method of Woodbury and Rathke.[8] This solution was cooled to -78°C, and a solution of 1 (R = CH_3)[7] (7.2 g, 40 mmol) in THF (50 ml) was added. Stirring was continued for 3 hr at -78°C, then reaction was quenched by addition of 50 ml of 1M HOAc and worked up conventionally to yield 2 (R = CH_3) (10.3 g, 99%) which was employed directly in the next step. A solution of 2 (R = CH_3) (3 g, 11.4 mmol) was heated in refluxing acetic acid (25 ml) for 6 h, then worked up in the usual manner to furnish 3 (R = CH_3) (1.53 g, 90%).[11] Chromatography on silica gel followed by recrystallization from benzene-hexane gave pure 6-methylcoumarin 3 (R = CH_3) (1.23 g, 72%, mp 73-74°C, lit.[11] 73-74°C).

The present coumarin synthesis offers significant advantages over older methods for the preparation of polycyclic coumarins in that it employs convenient reagents and mild conditions, entails few steps, and affords relatively high yields of pure products. In contrast, the most widely employed coumarin synthesis, the von Pechmann method,[3] requires strongly acidic conditions and often affords low and erratic yields. Thus, the yields of **3a-c** obtained via the latter route[3] were "poor", 3%, and 32-50%, respectively, whereas the overall yields of these pure compounds from 1 by the present procedure were in excess of 70%.

Preliminary bioassays confirm the anticarcinogenic activity of the polycyclic coumarins.[12,13]

References and Notes

1. G. Feuer, J. A. Kellen, and K. Kovacs, Oncology, 33, 35 (1976).
2. L. W. Wattenberg, L. K. Lam, and A. V. Fladmoe, Cancer Res., 30, 1922 (1970).
3. S. Sethna and R. Phadke, Org. Reactions, 7, 1 (1953).
4. R. Livingstone, In "Rodd's Chemistry of Carbon Compounds", Vol. IV, Part E, S. Coffey, Ed., Elsevier, Amsterdam, (1977) pp. 51-221.
5. S. Wawzonek, In "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, (1951) pp. 173-216.
6. C. A. Townsend and L. M. Bloom, Tetrahedron Lett., 22, 3923 (1981).
7. H. Christensen, Syn. Commun., 5, 65 (1975).
8. R. P. Woodbury and M. W. Rathke, J. Org. Chem., 42, 1688 (1977).
9. Cyclization of the unsaturated amide requires the sterically less favorable cis configuration, whereas the saturated amide is relatively free to adopt a favorable conformation for cyclization.
10. All new compounds were fully characterized by m.p., high resolution NMR and UV spectra, mass spectra, and/or microanalysis.
11. T. J. Thompson and R. H. Edie, J. Am. Chem. Soc., 47, 2558 (1925).
12. **7b** exhibits highest activity, showing strong potency as an inhibitor of DMBA-induced skin tumors in mice and as an inducer of the aryl hydroxylase enzyme.
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