

Heterocyclic Syntheses with β -Ketosulfoxides. I. New Syntheses of Chromones, Flavones, Thioindigo and Thioflavones.

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Sir:

This communication is the first of a series concerned with the synthetic uses of *ortho*-substituted β -ketosulfoxides. In particular, it deals with new syntheses of chromones, flavones, thioflavones and thioindigo.

Extension of our work on the addition of dimethylsulfoxide anion to various electrophilic reagents (1) led to the consideration of *ortho*-substituted β -ketosulfoxides as intermediates in heterocyclic synthesis.

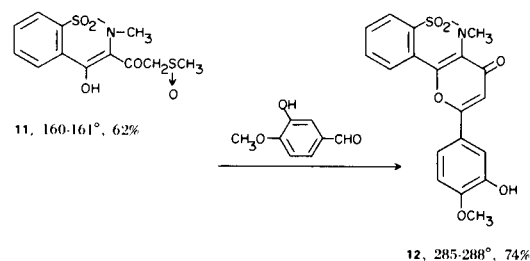
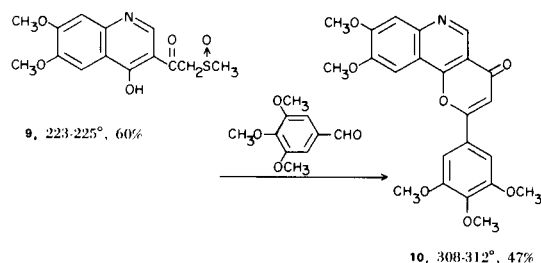
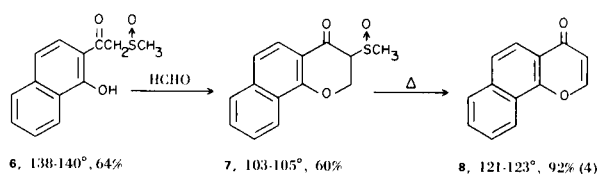
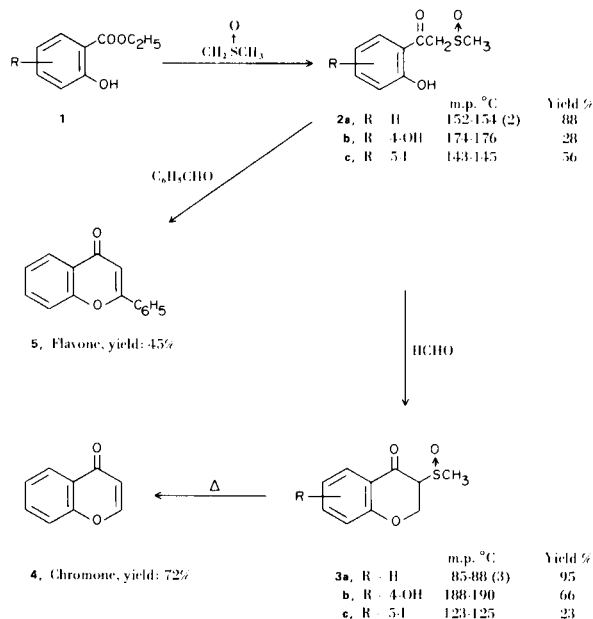
Modification of a reported reaction (2) of dimethylsulfoxide anion with methyl salicylate resulted in yield improvement that made this approach attractive.

Addition of salicyclic esters (1) to a threefold excess of sodium methylsulfinylmethide in dimethylsulfoxide-benzene solution at 35-50° gave *o*-hydroxy- ω -(methylsulfinyl)acetophenones (2) in good to excellent yields. These were readily cyclized with one mole of formaldehyde to 3-(methylsulfinyl)chromanones (3). The cyclizations were carried out in methanol at reflux temperature for 15 minutes in the presence of catalytic amounts of piperidine. Upon refluxing in toluene, 3-(methylsulfinyl)chromanone (3a) lost the elements of

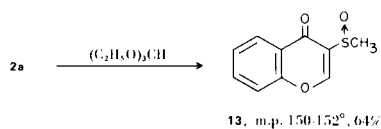
CH₃SOH and was converted to chromone (4).

Condensation with benzaldehyde, achieved by refluxing in toluene in the presence of piperidine for 2 hours, yielded flavone (5).

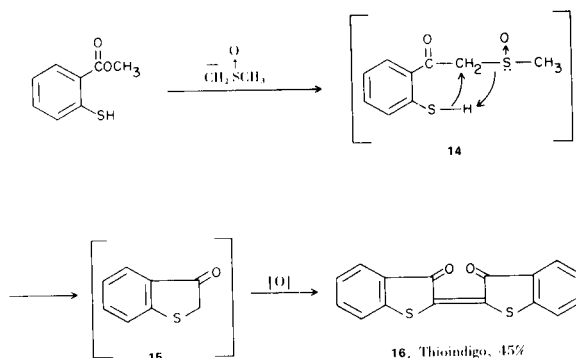
Polycyclic and heterocyclic salicyclic type esters gave analogous results (6-12):



Heating of *o*-hydroxy- ω -(methylsulfinyl)acetophenone (2a) in ethyl orthoformate solution, at 115-125° in the presence of equimolar amounts of piperidine, gave 3-(methylsulfinyl)chromone (13).

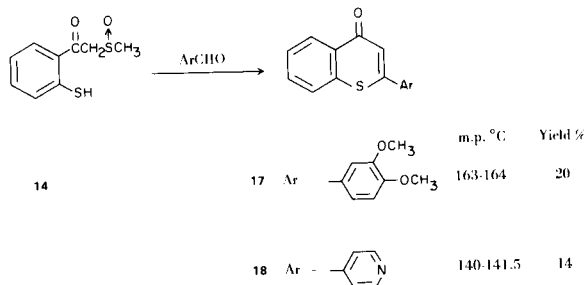


Methyl thiosalicylate behaved analogously to salicylates except that the resulting *o*-mercapto- ω -(methylsulfinyl)-acetophenone (**14**) is unstable (5). It rapidly eliminated CH_3SOH and formed the thio-analog of indoxyl (**15**) which spontaneously oxidized to give thioindigo (**16**) in 45% overall yield. Oxidation proceeded readily even in nitrogen atmosphere, thus the oxygen was probably derived from the sulfoxides present in the reaction mixture.



In spite of the fast rate of thioindigo formation, the reaction can be used for the preparation of thioflavones (**17**, **18**), provided that the arylaldehyde is added shortly after formation of the methylsulfinyl ketone:

Satisfactory spectral data and elemental analyses within 0.3% of calculated values were obtained for all compounds described (6).



REFERENCES

- (1) M. von Strandtmann, S. Klutchko, D. Connor and J. Shavel, Jr., *J. Org. Chem.*, **36**, 1742 (1971).
- (2) H. D. Becker, G. J. Mikol and G. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).
- (3) This is a mixture of diastereoisomers. Recrystallization to the constant melting point gave a 40% yield of a product melting at 104-106°.
- (4) P. Pfeiffer and J. Grimmer, *Ber.*, **50**, 911 (1917).
- (5) Due to lability of this compound, no elemental analysis was obtained. M.p. of the crude: 90-95°.
- (6) The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular, we wish to thank Dr. C. Greenough for the spectral data and Mrs. U. Zeek for analytical determinations. We also wish to thank the Chemical Development Department under the Supervision of Dr. A. W. Ruddy for the large-scale preparation of intermediates.