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A NEW SYNTHESIS OF THIOFLAVONES

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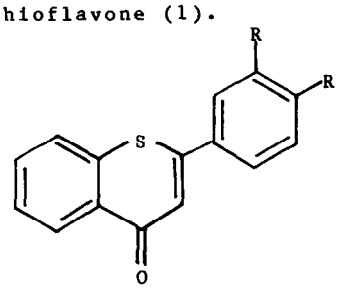
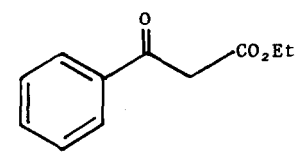
Abstract: A new synthesis of thioflavones from β-keto sulphoxide (12) is described.

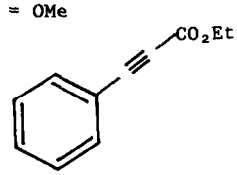
Recently, we have been interested in assessing the antifungal activity of a series of substituted derivatives of thioflavone (1)[1]. In general, thioflavones are readily synthesised by two methods; either the direct condensation of a β-keto ester (e.g. 3) with a thiophenol in polyphosphoric acid,[2] or the cyclisation of a β-substituted cinnamate (e.g. 5), itself derived from the constituent thiophenol and an appropriate propiolate (e.g. 4).[3] We have prepared a number of substituted thioflavones using these methods, but were unable to thus obtain certain target molecules, in particular thioflavones with strongly activated B-rings, e.g. 3',4'-dimethoxy thioflavone (2).[4] Instead, we have developed an alternative thioflavone synthesis which both allows the preparation of thioflavone (2) and should have more general applicability as demonstrated by the synthesis of the parent thioflavone (1).



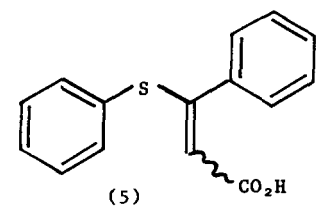
(1) R = H
(2) R = OMe



(3)

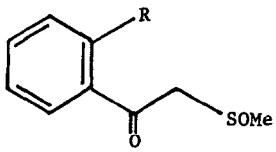


(4)

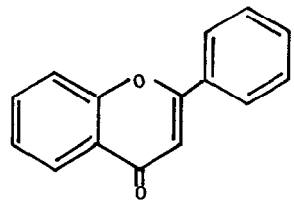


(5)

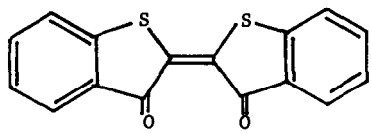
Von Strandtmann et al[5] have reported the condensation of the o-hydroxy β-keto sulphoxide (6) with benzaldehyde to give flavone (8) in 45% yield. However, the corresponding o-thiol (7) is an unsatisfactory source of thioflavones because it is unstable, readily eliminating methanesulphenic acid and further reacting to give thioindigo (9). We have now modified the above synthetic approach to flavones into a practical synthesis of thioflavones in which the key step is the release of the pre-protected thiol group of an enone (e.g. 14), which then spontaneously cyclises to the thioflavanone (e.g. 16).



(6) R = OH
(7) R = SH



(8)



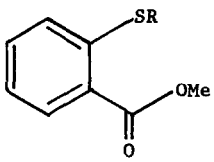
(9)

The cyclisation precursor (14) was prepared in three steps from methyl 2-mercapto benzoate (10). Thus, alkylation of the thiolate anion of (10) with 4-methoxybenzyl chloride (NaH, THF, 60°C, 1h) gave the S-protected ester (11) (96% yield). This was treated with sodium methylsulphinylmethide (THF, room temperature, 1h) giving β-keto sulphoxide (12) (68% yield). Condensation of (12) with 3,4-dimethoxy benzaldehyde (piperidine, toluene, 110°C: Dean-Stark; 1h) furnished the required enone (14) as a mixture of Z:E isomers in an 8:1 ratio (62% yield).[6]

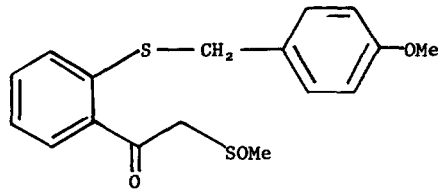
The Z isomer of (14) was separated by fractional crystallisation from ethanol (m.p. 155-157°C) and its stereochemistry was established by nuclear Overhauser effect experiments.

Deprotection of the isomeric mixture of thioethers (14) with formic acid (5°C, 30 min) afforded the thioflavanones (16) as a mixture of diastereoisomers in 45% yield. Thermal elimination of methanesulphenic acid from (16) (toluene, 110°C, 2h) then gave 3',4'-dimethoxy thioflavone (2) (90% yield).

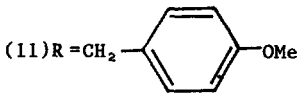
A similar reaction sequence converted β-keto sulphoxide (12) to thioflavone (1) via isomeric enones (13) and thioflavanones (15).

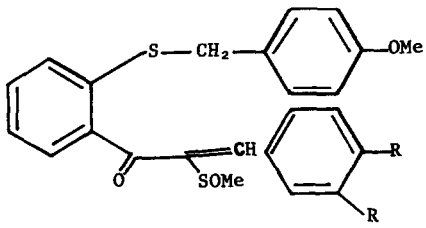


(10) R = H

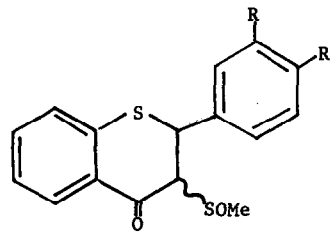


(12)



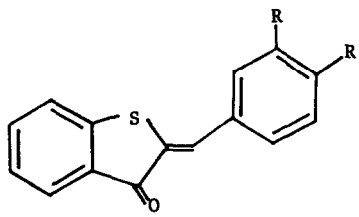


(13) R = H
(14) R = OMe



(15) R = H
(16) R = OMe

It should be noted that when enones (13) and (14) were exposed to the more usual 4-methoxybenzyl thioether deprotection conditions of trifluoroacetic acid:0°C:5 min,[7] the thioaurones (17)[8] and (18) were the only isolated products (72% and 40% yield respectively). However, these substances were not observed after the formic acid treatment described above.



(17) R = H
(18) R = OMe

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References and notes:

1. c.f. H. Nakazumi, T. Ueyama and T. Kitao, J. Heterocyclic Chem., 22, 1593 (1985).
2. F. Bossert, Annalen., 680, 40 (1964).
3. W.E. Truce and D.L. Goldhamer, J. Amer. Chem. Soc., 81, 5795 (1959).
4. c.f. D.H. Wadsworth and M.R. Detty, J. Org. Chem., 45, 4611 (1980).
5. M. von Strandtmann, S. Klutchko, M.P. Cohen and J. Shavel, Jr., J. Heterocyclic Chem., 9. 171 (1972).
6. All the compounds described were characterised by nuclear magnetic resonance, infra red and mass spectral data. Selected physical data are as follows:
(14): Z Isomer; ν_{max} (KBr) 1630 and 1025 cm^{-1}; δ_H ($CDCl_3$) 2.82 (3H, s, $SOCH_3$), 7.50 (1H, s, vinyl-H).
(16): Diastereoisomer A (32%); m.p. 125-127°C (from ether); ν_{max} (KBr) 1656 and 1056 cm^{-1}; δ_H ($CDCl_3$) 4.14, 5.02 (2H, 2d, J 3.2Hz, 2-H and 3-H). Diastereoisomer B (13%); oil; δ_H ($CDCl_3$) 4.53, 5.07 (2H, 2d, J 4.8 Hz, 2-H and 3-H).
(2): m.p. 146-147°C (from EtOH); ν_{max} (KBr) 1610 cm^{-1}; δ_H ($CDCl_3$) 3.96, 3.98 (6H, 2s, 2-OCH_3), 7.23 (1H, s, 3-H).
(18): m.p. 115-117°C (from ether); ν_{max} (KBr) 1663 cm^{-1}; δ_H ($CDCl_3$) 3.96, 3.99 (6H, 2s, 2-OCH_3), 7.93 (1H, s, vinyl-H).
7. O. Nishimura, C. Kitada and M. Fujino, Chem. Pharm. Bull., 26, 1576 (1978).
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