Synthesis of Grisa-2′,5′-dien-3,4′-diones by Intramolecular *ipso*-Substitution

By Melvyn V. Sargent

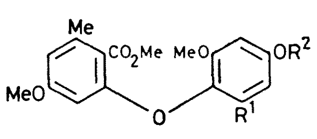
(*Department of Organic Chemistry, University of Western Australia, Nedlands, W.A.* 6009, *Australia*)

Summary Appropriately substituted *o*-phenoxybenzoic esters on treatment with dry hydrogen chloride and titanium(IV) chloride in dichloromethane yield grisa-2′,5′-dien-3,4′-diones by intramolecular *ipso*-substitution.

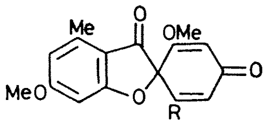
Grisa-2′,5′-dien-3,4′-diones, particularly dehydrogriseofulvin, have usually been synthesized by oxidative coupling of benzophenones,[1] or by annulation of β-coumaranones.[2] I now report that they are readily obtained in high yield from *o*-phenoxybenzoic esters by intramolecular *ipso*-substitution.

Thus treatment of the ester (**1**)† in dry dichloromethane containing dry hydrogen chloride with an excess of titanium(IV) chloride at 0—25 °C for 12 h gave exclusively the grisadiendione (**4**). The structure (**4**) was supported by the i.r. [ν_{max} ($CHCl_3$) 1714 (coumaranone C=O) and 1664 (dienone C=O) cm^{-1}] and u.v. spectra [λ_{max} (EtOH) 236, 278, and 313 nm (log ϵ 4·42, 4·44, and 4·08)]. Compound (**4**) was differentiated from the isomeric dienone (**6**) since the dienone olefinic protons resonated as a singlet at δ 5·52 in the n.m.r. spectrum, and it was thermally stable.[3] Additional evidence for structure (**4**) was provided by the following reactions. Treatment of the dienone (**4**) with sodium methoxide in boiling methanol effected vinylogous β-diketonic fission and the phenol (**2**) resulted; this on methylation gave the starting material (**1**). Reduction of the dienone (**4**) with zinc and acetic acid gave the benzophenone (**7**) which was oxidized back to the dienone (**4**) with potassium hexacyanoferrate(III) in aqueous potassium carbonate solution. Partial methylation of (**7**) yielded (**8**) which on boiling with dilute ethanolic potassium hydroxide[4] gave the xanthone (**9**). Treatment of (**9**) with boron trichloride gave lichexanthone (**10**),[5] identical with an authentic sample.[6]

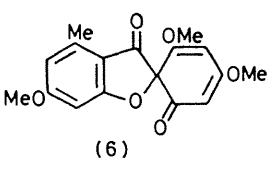
The *o*-phenoxybenzoic esters (**3**),[7] (**11**), and (**12**) on treatment as above gave the grisadiendiones (**5**), (**13**), and (**14**). These *o*-phenoxybenzoic esters would readily give an acylium ion, *e.g.* (**15**) (presumably complexed with the Lewis acid) by an $A_{AC}1$ type mechanism because of the steric acceleration and stabilization of the positive charge provided by the adjacent electron donating substituents. *ipso*-Substitution would then yield a Wheland intermediate, *e.g.* (**16**) which would undergo S_N2 attack by chloride at the least hindered methoxy group thus yielding the cross-conjugated dienone.

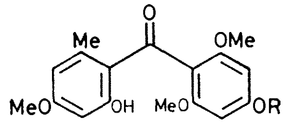


(1) R^1 = OMe, R^2 = Me
(2) R^1 = OMe, R^2 = H
(3) R^1 = R^2 = Me

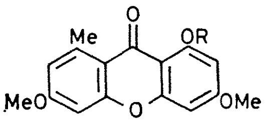


(4) R = OMe
(5) R = Me

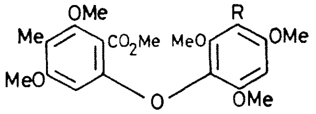




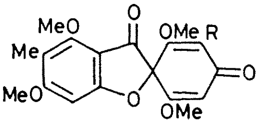
(7) R = H
(8) R = Me



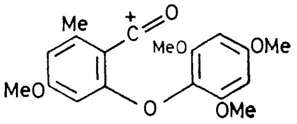
(9) R = Me
(10) R = H



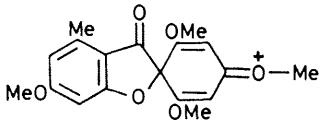
(11) R = H
(12) R = Me



(13) R = H
(14) R = Me



(15)



(16)

ipso-Nitration and halogenation[8] of phenols and their derivatives are well documented. The present intramolecular *ipso*-acylations appear to be entirely novel.

I thank the Australian Research Grants Committee for financial support.

(*Received*, 15*th January* 1980; *Com.* 039.)

---

† All new compounds gave satisfactory elemental analyses.

[1] A. I. Scott, *Proc. Chem. Soc.*, 1958, 195; A. C. Day, J. Nabney, and A. I. Scott, *J. Chem. Soc.*, 1961, 4067; D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, 1963, **19**, 1; D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, 1963, **28**, 2752, 3344.
[2] M. Gerecke, E. Kyburg, C. v. Planta, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 2241 and earlier papers.
[3] *Cf.* T. Sala and M. V. Sargent, *J.C.S. Chem. Comm.*, 1978, 1043.
[4] D. H. R. Barton and A. I. Scott, *J. Chem. Soc.*, 1958, 1767.
[5] Y. Asahina and H. Nogami, *Bull. Chem. Soc. Japan*, 1942, **17**, 202.
[6] J. A. Elix, H. W. Musidlak, T. Sala, and M. V. Sargent, *Austral. J. Chem.*, 1978, **31**, 145.
[7] T. Sala, M. V. Sargent, and J. A. Elix, *J.C.S. Chem. Comm.*, 1978, 1041.
[8] R. B. Moodie and K. Schofield, *Accounts Chem. Res.*, 1976, **9**, 287; S. R. Hartshorn, *Chem. Soc. Rev.*, 1974, **3**, 167.