

New Synthetic Approaches to 6-Thiophenoxysalicylates, 6-Phenoxy-salicylates and 1-Hydroxy-9-xanthenes

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Abstract A new two step synthetic route to 6-thiophenoxysalicylates and 6-phenoxy-salicylates and a three step route to 1-hydroxy-9-xanthenes which permits the regioselective introduction of a methyl group into the 4-position is reported.

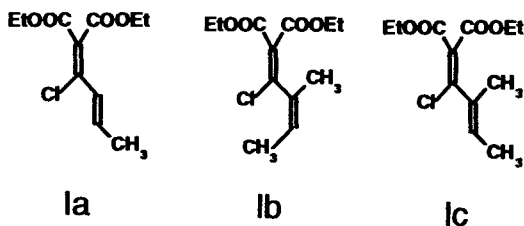
In an earlier study,¹ we have shown that 1-propenyl substituted malonic ester derivatives undergo ready thermolytic ring closure at 240 °C to the corresponding salicylates. Through this cyclization, each of carbon atoms of the malonate system functions as a latent substituent equivalent permitting synthesis of multisubstituted aromatic compounds, cf. **Scheme**. In our recent work 1-propenyl substituted malonates have been employed as latent 6-hydroxyanthranilate equivalents in the synthesis of 1-hydroxyacridones.¹



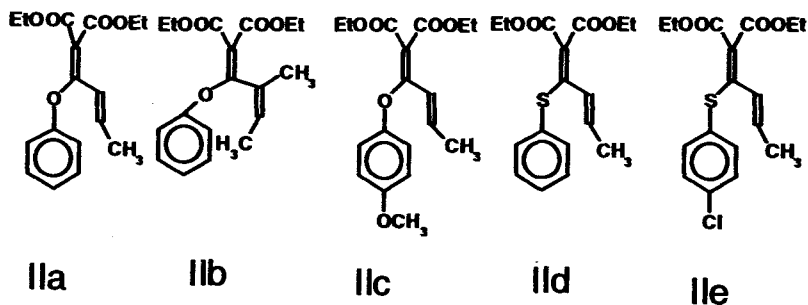
Scheme

The useful biological activity has generated much attention to the synthesis of 1-substituted 9-xanthenes.² 1-Hydroxyxanthenes are also of interest because they constitute a class of naturally occurring compounds.³

We will communicate in this report an extension of the above methodology for the synthesis of various 1-hydroxyxanthenes which permits the regioselective introduction of a methyl group into the 4-position of the xanthone ring system.⁴ Subsequently, we also investigated the synthesis of the thiophenoxysalicylates **III**d and **III**e which can be modified further to give herbicidal salicylate derivatives.⁵

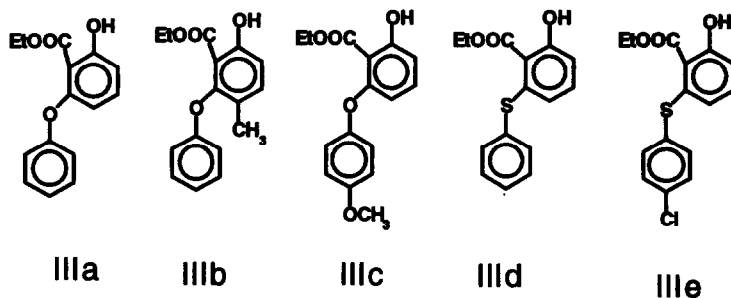


The chloromalonates **I** were available from the acylmalonates and POCl_3 .⁶ A difficulty in the synthesis of **Ib** from tigloyl chloride was that it also afforded the isomerized **Ic** in a ratio of 6 : 4. The two isomers could not be separated using vacuum distillation. The first step in the synthetic sequence was the $\text{S}_\text{N}\text{V}$ -reaction⁷ between the chloromalonate and phenolates or thiophenolates. Attempted $\text{S}_\text{N}\text{V}$ reactions between **I** and phenols or thiophenols using phenols or thiophenols / potassium carbonate / dimethylformamide⁸ (or acetone) were complicated by formation of tarry material and therefore a milder method was employed with triethylamine / chloroform. This approach produced **IIa** (M calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_5$: 304.1311, M^+ found 304.1200) and **Ic** (M calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_6$: 334.1416, M^+ found 334.1399) in 81 % yield and the crude products were sufficiently pure for further transformations. We also made several attempts to apply the triethylamine and potassium *tert.*-butoxide (see below) procedures to the chloromalonate mixture **Ib** - **Ic** but were unable to transform **Ic** to the corresponding **II** (**II** is clearly present in the reaction mixture, GC-MS, M calcd. for $\text{C}_{18}\text{H}_{22}\text{O}_5$: 318.1467, M^+ found 318.1441, 55 % yield based on **Ib**, 33 % based on **Ib** + **Ic**) owing to, so far, unknown resistance of **Ic** to react with the phenolate. It was most convenient to thermolyze the reaction mixture of **Ic** and **IIb** directly to the salicylate **IIIb** (M calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_4$: 272.1049, M^+ found 272.1030) in 29 % yield over the two steps.



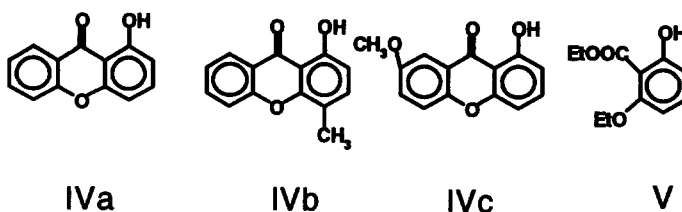
Noteworthy was the air-oxygen induced sulfur - sulfur coupling obtained when the reaction of potassium thiophenolate (produced *in situ* from thiophenol and potassium *tert.*-butoxide) with **Ia** was not

performed under N_2 . A much dirtier reaction occurred and considerable amounts of aromatic disulphides were produced. When these same experiments were repeated under N_2 none of the dimeric sulfur products were observed. No attempts were made to isolate and purify the thiophenoxymalonates **II**d (GC-MS, M calcd. for $C_{17}H_{20}O_4S$: 320.1082, M^+ found 320.1073) and **II**e (GC-MS, M calcd. for $C_{17}H_{19}O_4SCl$: 354.0693, M^+ found 354.0665). Instead they were thermolyzed directly to the thiophenoxysalicylates **III**d (M calcd. for $C_{15}H_{14}O_3S$: 274.0644, M^+ found 274.0635, mp. 48 - 50 °C) and **III**e (M calcd. for $C_{15}H_{13}O_3SCl$: 308.0274, M^+ found 308.0289, mp. 78 - 79 °C) in 43 % and 61 % yield over the two steps respectively.



It was also surprising that attempted thermolysis of phenoxy- and thiophenoxy-malonates **II** without efficient removal of ethanol from the reaction mixture produced **V** (GC-MS). We think that one possible cause for the formation of **V** from **II** is a sequence of reactions initiated by attack of ethanol on **II** followed by replacement of the phenoxy or thiophenoxy group by ethoxide. The resulting ethoxymalonate is then cyclized to **V**.

The utilization of high vacuum conditions has precedent in the thermolysis chemistry.⁹ We found, however, that when we applied high vacuum conditions to **III** considerable amounts of uncyclized **III** distilled from the reaction mixture. The yields of the required **IV** could be enhanced simply by omitting the vacuum. The phenoxysalicylates **III**a (M calcd. for $C_{15}H_{14}O_4$: 258.0892, M^+ found 272.0885) and **III**c (M calcd. for $C_{16}H_{16}O_5$: 288.0998 M^+ found 288.0974) were produced in 75 % and 56 % yield respectively.



The final step in the synthetic sequence **I** -> **IV** was the ring closure of the phenoxymalonates **III**a, **III**b and **III**c to the corresponding hydroxyxanthenes **IV**a (mp. 144 °C, mp. lit.¹⁰ 144 °C), **IV**b (mp. 148

°C, mp. lit.¹¹ 148 °C) and IVc (mp. 125 - 127 °C, mp. lit.¹² 124 - 126 °C) This proved to be easy with polyphosphoric acid at 170 °C (2 h). The yields were in the range 80 - 95 %.

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