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New Synthetic Approaches to 6-Thiophenoxysalicylates, 6-Phenoxysalicylates and 1-Hydroxy-9-xanthones

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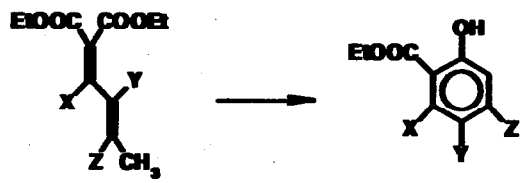
Abstract A new two step synthetic route to 6-thiophenoxysalicylates and 6-phenoxysalicylates and a three step route to 1-hydroxy-9-xanthones which permits the regioselective introduction of a methyl group into the 4-position is reported.

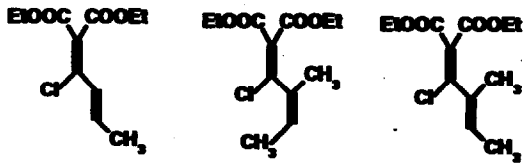
In an earlier study,[1] we have shown that 1-propenyl substituted malonic ester derivatives undergo ready thermolytic ring closure at 240 °C to the corresponding salicylates. Through this cyclization, each of carbon atoms of the malonate system functions as a latent substituent equivalent permitting 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

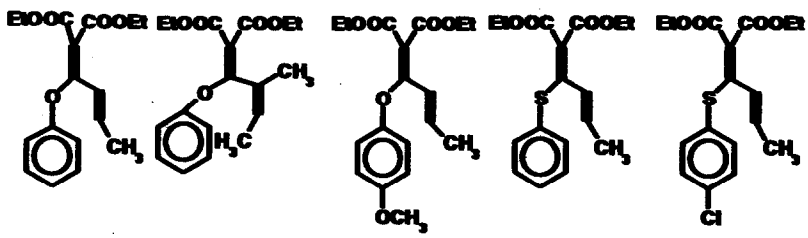
The useful biological activity has generated much attention to the synthesis of 1-substituted 9-xanthones.[2] 1-Hydroxyxanthones are also of interest because they constitute a class of naturally occurring compounds.[3]

We will communicate in this report an extension of the above methodology for the synthesis of various 1-hydroxyxanthones 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 IIId and IIIe which can be modified further to give herbicidal salicylate derivatives.[5]



Ia Ib Ic

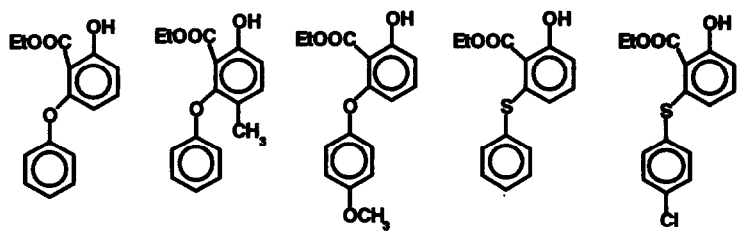
The chloromalonates I were available from the acylmalonates and $POCl_3$.[6] A difficulty in the synthesis of Ib from tigloyl chloride was that it also afforded the isomerized Ic in a ratio of 6 : 4. The two isomers could not be separated using vacuum distillation. The first step in the synthetic sequence was the S_NV-reaction[7] between the chloromalonate and phenolates or thiophenolates. Attempted S_NV reactions between I and phenols or thiophenols using phenols or thiophenols / potassium carbonate / dimethylformamide[8] (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 $C_{17}H_{20}O_5$: 304.1311, M^+ found 304.1200) and IIc (M calcd. for $C_{18}H_{22}O_6$: 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 $C_{18}H_{22}O_5$: 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 $C_{16}H_{16}O_4$: 272.1049, M^+ found 272.1030) in 29 % yield over the two steps.



IIa IIb IIc IId IIe

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

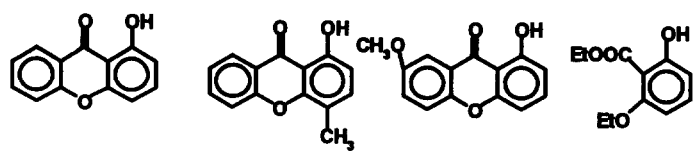
performed under N_2. A much dirtier reaction occurred and considerable amounts of aromatic disulphides were produced. When these same experiments were repeated under N_2 none of the dimeric sulfur products were observed. No attempts were made to isolate and purify the thiophenoxymalonates **IId** (GC-MS, M calcd. for $C_{17}H_{20}O_4S$: 320.1082, M^+ found 320.1073) and **IIe** (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 **IIId** (M calcd. for $C_{15}H_{14}O_3S$: 274.0644, M^+ found 274.0635, mp. 48 - 50 °C) and **IIIe** (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.



IIIa IIIb IIIc IIId IIIe

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 **IIIa** (M calcd. for $C_{15}H_{14}O_4$: 258.0892, M^+ found 272.0885) and **IIIc** (M calcd. for $C_{16}H_{16}O_5$: 288.0998 M^+ found 288.0974) were produced in 75 % and 56 % yield respectively.



IVa IVb IVc V

The final step in the synthetic sequence **I** -> **IV** was the ring closure of the phenoxymalonates **IIIa**, **IIIb** and **IIIc** to the corresponding hydroxyxanthones **IVa** (mp. 144 °C, mp. lit.[10] 144 °C), **IVb** (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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