A FLEXIBLE NEW SYNTHESIS OF BENZO-1,3-DIOXAN-4-ONES

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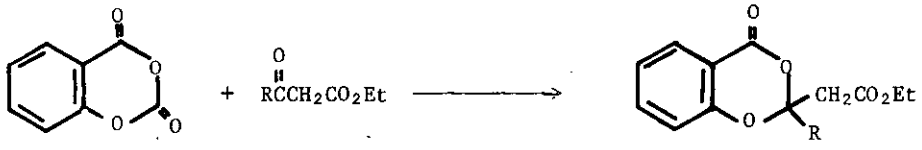
As an outgrowth of our synthetic studies on furoquinoline alkaloids (1) we developed an efficient general synthesis of 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid antibacterial agents based upon appropriately substituted isatoic anhydrides (2). A proposed extension of this work using salicylic carbonate (I), readily prepared from the disodium salt of salicylic acid and phosgene,(3) led instead to a convenient synthesis of benzo-1,3-dioxan-4-ones (II), a class of compounds of potential value as analgesics and antiinflammatory agents (4) and very difficult to prepare with two different carbon



(I)

(IIa, R = H)
(IIb, R = CH_3)

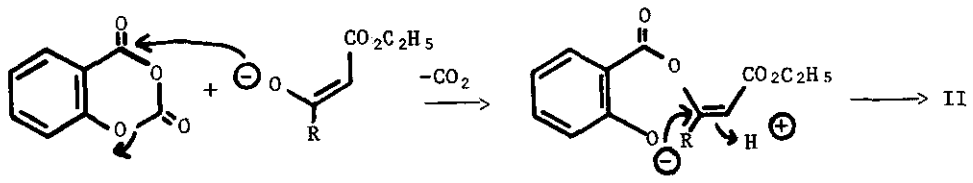
Dedicated to Professor Tetsuo Nozoe with congratulations on the occasion of his 77th birthday

substituents at the C_2 position using existing methods. Such methods involve Friedel-Crafts reactions of acetyl salicyloyl chlorides, (5) reaction of Grignard or organocadmium reagents with salicyloyl chlorides, (6,7) the nucleophilic displacement of acetyl salicyloyl chlorides with alcohols, phenols, peroxides and thiols, (8) or the vinyl ester exchange of salicylic acid followed by acid treatment or by formation of intermediate 1,3-benzodioxanes followed by oxidation. (9,10).

The contrasting simplicity and flexibility of our new procedure is illustrated by the following examples. In an inert atmosphere, 250 mg of salicylic carbonate (I, m.p. 118-121° dec. (3)) in 20 ml of dry DMF was added to 231 mg of sodioethylformyl acetate and heated to 110° for one hour. During this time CO_2 evolved. The reaction mixture was cooled, evaporated in vacuo to dryness, and partitioned between water and chloroform. The residue from the dried chloroform layers was purified by silica gel chromatography to yield ethyl 1,3-benzodioxane-4-one-2-acetate (IIa), 263 mg (74%), as a yellow oil; ir(neat) 1750, 1720, 1420, 1410, 1300, 1240, 1180, 760, 700 cm^{-1}; pmr ($CDCl_3$) 1.30 δ(3H, t, J = 7Hz, $OCH_2\underline{CH_3}$), 3.05(2H, d, J = 6Hz, $-\underline{CH_2}CO_2Et$), 4.27(2H, q, J = 7Hz, $OCH_2\underline{CH_3}$), 6.00(1H, t, J = 6Hz, $\underline{H_2}$), 6.95-8.00(4H, m, ArH); eims m/e 236 (1.2%=M^+), 208(4%), 149(12%), 120(100%) and 92(19%); anal., C,H.

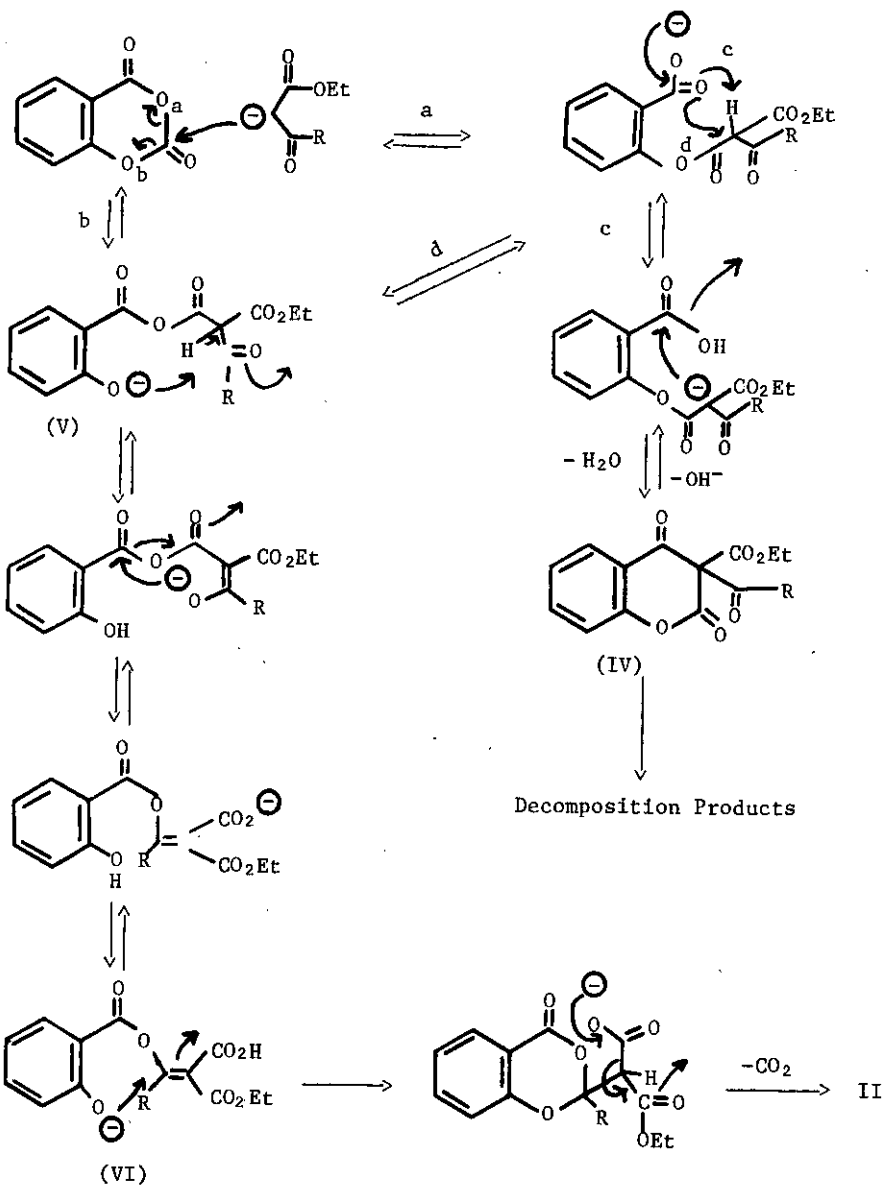
Using the same reaction conditions, 250 mg of salicylic carbonate and 210 mg of sodioethylacetoacetate produced 132 mg (34%) of ethyl 1,3-benzodioxane-4-one-2-methyl-2-acetate (IIb) as a clear oil; ir(neat) 1750, 1720, 1420, 1405, 1310, 1245, 1180, 760 and 700 cm^{-1}; pmr ($CDCl_3$) 1.30δ(3H, t, J = 7Hz, $OCH_2\underline{CH_3}$), 1.87(3H, s, $\underline{CH_3}$), 3.00(2H, s, $\underline{CH_2}CO_2Et$), 4.17(2H, q, J = 7Hz, $OCH_2\underline{CH_3}$), 6.82-7.97(4H, m, Ar$\underline{H}$); eims m/e 250(2.9% = M^+), 163(8%), 120(100%) and 92(19%); anal., C,H.

The simplest mechanism to explain this otherwise unusual base catalyzed ketalization reaction would be to invoke oxygen anion attack on the ester-like carbonyl of I followed by a Michael addition (via III) to give II. We believe, however, that the reaction is more complex. The carbonate-like



(I) (III)

carbonyl group should be the more reactive due to the electron releasing character of the two appended oxygens. Further, use of chelating bases such as magnesium ethoxide and thalium ethoxide, which should favor carbon rather than oxygen attack, (11,12) led to the same result. The use of of a non-reversible base such as methyl Grignard reagent led to recovery of salicylic acid rather than 2-hydroxyacetophenone or degradation products of the unstable corresponding tertiary carbinol which would be formed by attack on the ester-like carbonyl. We believe, therefore, that carbanion attack on the carbonate-like carbonyl group sets up a series of possible equilibria as illustrated in the following scheme:



Cleavage of bond a would lead to IV via path c and a dehydration. Compound IV is unlikely to be stable in the basic condition of the reaction having no less

than four carbonyl groups, three of which are non-enolyzable, attached to carbon-3. The alternate cleavages (b and d) would lead to mixed anhydride V which, by the illustrated prototropic shifts and an intramolecular transesterification involving a 6-membered transition state, would lead to VI and this would be followed by the only non-reversible step in this sequence, the loss of CO_2, which presumably provides the driving force for the reaction.

Whatever the mechanism, we are now in possession of a powerful new synthesis of this interesting heterocyclic ring system and a detailed paper will discuss its elaboration.

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