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REGIOSELECTIVE NUCLEOPHILIC ADDITIONS TO UNSYMMETRICALLY SUBSTITUTED MALEIC ANHYDRIDES

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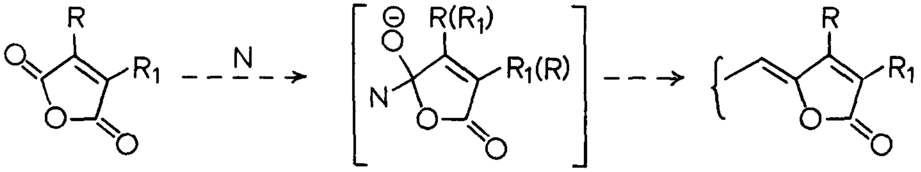
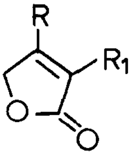
4-Ylidenebutenolides (1) and 4-ylidenetetronic acids (2) are widely distributed in Nature, and many show interesting biological properties.[1] Our studies directed towards the synthesis of' these molecules[2] have led us to examine the selectivity of nucleophilic additions to unsymmetrically substituted maleic anhydrides. Here we report efficient regioselective nucleophilic additions to anhydrides, and a novel dichotomy in the reactivity of anhydrides towards the hydride ion and carbanions



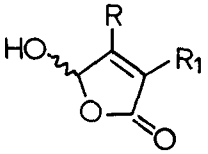
N = Nucleophile

1, $R=R_1$=H,alkyl etc.
2, R=OH; R_1=H,alkyl etc.

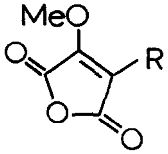
Treatment of 2-methylmaleic anhydride with metal hydride reducing agents [$Li(OBu^t)_3AlH$, $LiAlH_4$] led to a mixture of lactone and lactol products (3→6) (60%) resulting from hydride ion attack at both carbonyl functions in the anhydride. The reduction products were separated by a combination of fractional distillation and preparative layer chromatography and identified by comparison with authentic samples.[3] Inspection of p.m.r. data of crude reduction mixtures showed that the lactones (3) and (4) and the lactols (5) and (6) were formed in the approximate proportions 35:3:9:53. These data showed that attack by the hydride ion was ca 88% selective at the more hindered (C-1) carbonyl function in the anhydride. In similar studies with 2-methoxy-3-methyl (7) and 2-methoxy-3-phenyl (8) maleic anhydrides, the reductions were completely regioselective and led to lactone and lactol products resulting from hydride ion attack at only C-1 in the anhydrides. Thus reduction of anhydride (7) with $Li(OBu^t)_3AlH$ led to a 7.3 mixture (70%) of lactol (9) and lactone (11); further reduction of (9) with $NaBH_4$-NaOH also gave (11). The structure of lactone (11) followed from comparison with an authentic specimen prepared from 2-methylacetoacetate.[2] The regioselectivity of reduction of 2-methoxy-3-phenylmaleic anhydride (8) could not



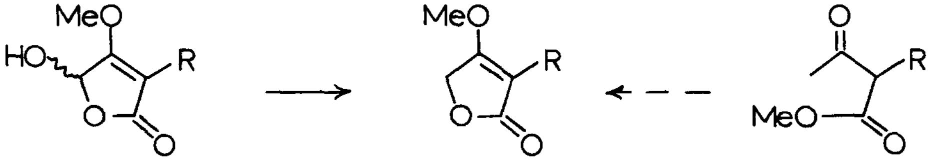
3, R=Me, R_1=H
4, R=H, R_1=Me



5, R=Me, R_1=H
6, R=H, R_1=Me



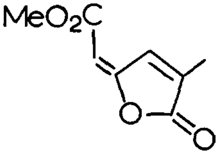
7, R=Me
8, R=C_6H_5



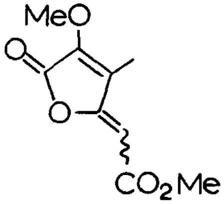
9, R=Me
10, R=C_6H_5
11, R=Me

be established unambiguously from spectral data and instead followed from X-ray measurements on the lactol reduction product. The lactol, m.p. 133-134°, $C_{11}H_{10}O_4$ crystallised from ethyl acetate in the space group $P2_1/c$ with $\underline{a}$=13.79, $\underline{b}$=7.81, $\underline{c}$=10.38 Å and β=114.4°, $\underline{Z}$=4. Intensity data were collected with Mo-K_α radiation using an automatic four-circle diffractometer, and 1388 reflections were considered observed The structure was then solved by direct methods using the Multan program, and refined by block-diagonal least squares to a current $\underline{R}$ index of 7.0%. These data clearly established the structure of the lactol as (10).

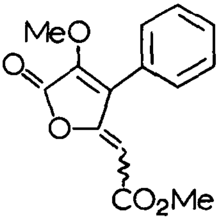
By contrast, condensations between the anhydrides above and carbomethoxymethylenetriphenylphosphorane took a completely different course, and led to ylidenebutenolides resulting from nucleohilic additions to the carbonyl functions (C-4) largely not affected in the hydride ion reductions of the anhydrides. Thus, reaction between 2-methylmaleic anhydride and the phosphorane, which has been reported previously,[4] produced largely butenolide (12), the regioselectivity corresponding to *ca* 90% in favour of carbanion attack at C-4 in the anhydride. Similar Wittig reactions with anhydrides (7) and (8) were completely regioselective and led to *Z*-*E*-isomeric mixtures of butenolides (13) and (14) respectively. The structures and geometries of butenolides (12→14) followed largely from comparative ultraviolet and p.m.r. shift data, details of which will be published in the full paper.



(12)

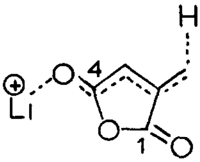


(13)



(14)

Although steric and electronic effects of substituents play complementary roles in determining the regioselectivity of nucleophilic additions to unsymmetrical anhydrides, it seems likely that in the case of phosphorane addition to 2-methylmaleic anhydride, the addition is largely under steric control, since the less hindered carbonyl function is attacked preferentially. In similar Wittig reactions with anhydrides (7) and (8) effects in addition to steric effects are probably important.[5] Selective hydride ion addition to the more hindered (C-1) carbonyl group in 2-methylmaleic anhydride can be rationalised by invoking hyperconjugative interaction between the methyl group and the enone system in the anhydride (see 15); this interaction places electron density at C-4 making it less susceptible to nucleophilic attack. An alternative rationale can be found based on initial formation of a cationic complex(*viz* 16) between the reducing agent and the less hindered(C-4) carbonyl oxygen in the anhydride;[6] this would make C-4 less accessible towards attack, and hydride ion addition takes place preferentially at C-1. The regioselective reductions of anhydrides (7) and (8) can be accommodated by an



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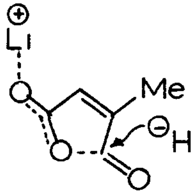

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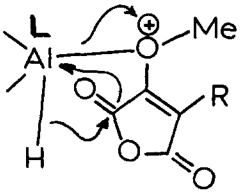

(17) R=Me,aryl

intramolecular 4-centre mechanism involving intermediate formation of an oxonium ion (viz 17).

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5. In anhydride (8), the C-4 carbonyl function is sterically more accessible, when the aryl ring is out-of-plane.

6. cf J.J. Bloomfield and S.L. Lee, J. Org. Chem., 32, 3919 (1967)