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REGIOSPECIFIC FRIEDEL-CRAFTS ACYLATION OF 6-ALKOXY-2-PYRONES: PREPARATION OF SUBSTITUTED AROMATICS AND ANTHRAQUINONES.

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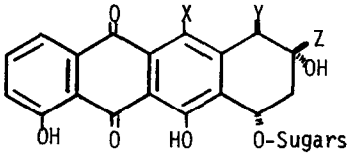
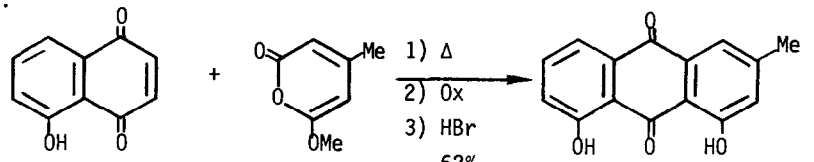
Abstract: Friedel-Crafts acylation of 6-alkoxy-2-pyrones gives high yields of the 5-acyl-2-pyrones which undergo regioselective cycloaddition with various dienophiles.

Adriamycin 1 and daunorubicin 2 are the anthracycline antitumor agents used most extensively in cancer chemotherapy today.[2] Their use is limited by their severe cumulative cardiotoxicity.[2] Several 11-desoxyanthracyclines have been isolated in the last few years, e.g., aclacinomycin 3 and 11-desoxyadriamycin 4, which exhibit good antitumor properties and, more importantly, show lower cardiotoxicity.[3]



1 R=Me X=OH Y=H Z=$COCH_2OH$
2 R=Me X=OH Y=H Z=$COCH_3$
3 R=H X=H Y=COOMe Z=CH_2CH_3
4 R=Me X=H Y=H Z=$COCH_2OH$

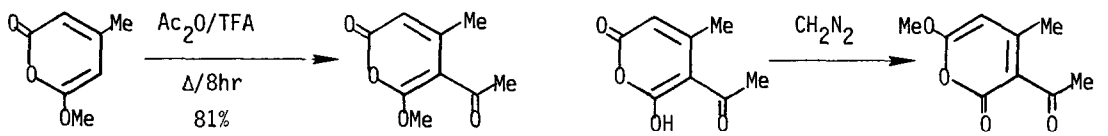
Recently, we reported the results of a synthetic approach to these molecules which permitted the facile preparation of tricyclic analogues of the anthracyclines,[4] namely reaction of juglone 5 with 4-methyl-6-methoxy-2-pyrone 6 followed by oxidation and hydrolysis gave chrysophanol 7 as the only product in 62% overall yield. However, in order to apply this general method to the synthesis of the 11-desoxyanthracyclines, it was necessary to prepare a 4,5-disubstituted pyrone corresponding to 6. We report here our results on the Friedel-Crafts acylation of pyrones which have led to a regiospecific preparation of 5-acyl-2-pyrones. We also describe the utility of the products in Diels-Alder approaches to various substituted aromatic systems and quinones, including the natural product 2-acetylemodin.



5 6 7

As one of several methods[5] for the preparation of specific 4,5-disubstituted-6-alkoxypyrones, we decided to investigate the Friedel-Crafts acylation of pyrones such as 6. We reasoned that substitution should occur at C5 rather than at C3 because of the much higher electron density at C5 than at C3 (see ^{13}C NMR data). However, it was questionable whether any Friedel-Crafts reactions of pyrones

would occur since one might expect the pyrone to be transformed completely into a 2,6-dioxygenated pyrylium salt in the presence of strong electrophiles or Lewis acids and thereby rendered inert to electrophilic substitution.[6] In the event, when the crystalline pyrone 6 was treated with 1.2 eq of acetic anhydride in refluxing trifluoroacetic acid (TFA) for 8 h, the desired 5-acetylpyrone 8 (^{1}H NMR: δ 6.02, 1H, bs; 3.88, 3H, s; 2.40, 3H, s; 2.22, 3H, bs) was produced in 81% yield.[7] Presumably the protonation of the carbonyl oxygen of the pyrone 6 to give the corresponding hydroxypyrylium salt is reversible and thus some of the free pyrone is always available for substitution. It was determined that the product has structure 8, namely that substitution had occurred at C5, by both spectroscopic and chemical evidence. In the ^{13}C NMR spectra (Figure), the signal corresponding to C5 in 6 has moved downfield by 29 ppm in 8 while the signal for C3 has experienced a downfield shift of only about 9 ppm, indicating that substitution had occurred at C5. We decided to prepare the opposite 3-acetyl isomer by another route for comparison. As we had shown in the bicyclic pyrone series,[5] methylation of a glutaconic anhydride provides mainly the less-hindered 6-methoxy-2-pyrone. Thus, it was not surprising that treatment of 3-acetyl-4-methyl-2-pyrone 9[8] with diazomethane produced the 3-acetyl pyrone 10 (^{1}H NMR: δ 5.41, 1H, s; 4.01, 3H, s; 2.54, 3H, s; 2.40, 3H, s) as the major product. The ^{13}C NMR of 10 has a signal at about 87 ppm, corresponding to C5 (Figure). In addition, chemical evidence confirmed the structural assignment for 8. Diels-Alder cycloaddition of 8 with methyl propiolate produced an 84% yield of a 2:1 mixture of methyl 3-acetyl-2-methoxy-4-methylbenzoate 11, in which the two aromatic protons exhibited typical ortho coupling (J = 7 Hz), and the isomeric methyl 4-acetyl-3-methoxy-5-methylbenzoate 12 (aromatic protons accidentally equivalent). Other Diels-Alder reactions of 8 with other dienophiles were also successful: dimethyl acetylenedicarboxylate produced the phthalate 13 (93%) while ethyl β-nitroacrylate gave predominately the benzoate 14 (55%) after treatment with DBU.[9]

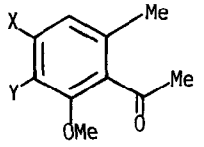


6 8 9 10

^{13}C NMR Data: Chemical Shift, Multiplicity, and Assignment

Compound 6		Compound 8		Compound 10	
164.28 s	C2,C4,C6	165.93 s	C2,C4,C6,COCH$_3$	197.87 s	COCH$_3$
160.84 s		165.01 s		165.26 s	C2,C4,C6
160.76 s		160.54 s		164.67 s	
103.12 d	C3	154.43 s		159.21 s	
83.74 d	C5	112.90 s	C5	113.30 s	C3
55.96 q	OCH$_3$	111.88 d	C3	87.61 d	C5
22.03 q	CH$_3$	52.33 q	OCH$_3$	55.97 q	OCH$_3$
		21.25 q	COCH$_3$	31.10 q	COCH$_3$
		19.67 q	CH$_3$	22.09 q	CH$_3$

Figure

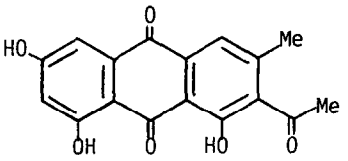


11 X=H Y=COOMe

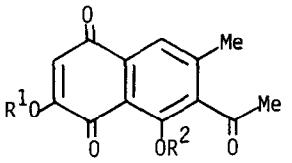
12 X=COOMe Y=H

13 X=COOMe Y=COOMe

14 X=COOEt Y=H



15



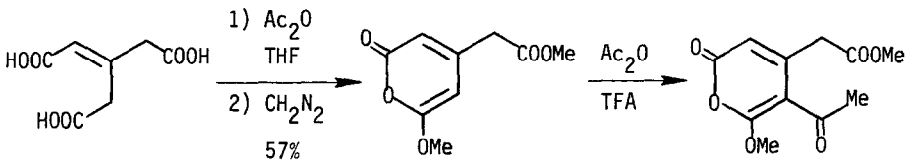
16 R^1=Me R^2=Me

17 R^1=Me R^2=H

18 R^1=H R^2=H

We also have carried out the cycloaddition of 8 with various quinones as a model for the eventual preparation of the desired anthracyclines. Reaction of 8 with 5,7-dihydroxynaphthoquinone[10] followed by oxidation and hydrolysis produced the natural product 2-acetylemodin 15 shown to be identical with an authentic sample.[11] Reaction of 8 with methoxyquinone followed by oxidation gave in 60% yield a single product to which we have assigned structure 16.[12] Monodemethylation (BCl_3, 0°C,1 h) afforded a monomethyl ether assigned structure 17. This same compound is also produced by methylation (Me_2SO_4, K_2CO_3, acetone) of the dihydroxy compound 18 produced by complete demethylation of 16 (BBr_3, 0°C, 1 h). Structure 17 has been assigned to the natural product orientalone based on spectroscopic studies.[13] However, the proton NMR for compound 17 (δ 7.89, 1H, s; 6.1, 1H, s) does not match that reported for orientalone (δ 7.65, 1H, s; 6.2, 1H, s). Unfortunately, it was impossible to obtain natural orientalone or its spectra for comparison purposes.[14]

Finally, the more functionalized pyrone 20 was prepared from the known triacid 19[15] by cyclization (Ac_2O, warm THF) followed by treatment with diazomethane. Acetylation of 20 (NMR: δ 5.75, 1H, m; 3.83, 3H, s; 3.68, 3H, s; 3.34, 2H, s) afforded the corresponding 5-acetyl compound 21 in good yield (^{1}H NMR: δ 6.03, 1H, bs; 3.77, 3H, s; 3.65, 3H, s; 3.62, 2H, s; 2.45, 3H, s).



19 20 21

Further conversion of compounds such as 8 and 21, as well as other substitution reaction of pyrones 6 and 20 are currently under investigation.

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6. Although the Friedel-Crafts chemistry of 4-pyrones has been extensively studied [L. L. Woods, J. Org. Chem. 27, 696 (1962) and references therein], similar reactions with 2-pyrones have not, although 2-pyrone itself afforded 5-nitro-2-pyrone on treatment with nitronium fluoroborate [W. H. Pirkle and M. Dines, J. Heterocycl. Chem., 6, 313 (1969)]. Thus the pyrone electronic structure is compatible with electrophilic substitution reactions.

7. All new compounds possessed spectroscopic data (NMR, IR, mass spectra) in complete accord with the structures assigned. Moreover, crystalline compounds gave correct elemental analyses.

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