Tetrahedron Letters No. 29, pp 2559 - 2562.

0040-4039/78/0715-2559$02.00/0

THE USE OF DIRECTED METALATION REACTIONS IN THE SYNTHESIS OF UNSYMMETRICAL ANTHRONES AND ANTHRAQUINONES. SYNTHESIS OF ANTHRACYCLINONE PRECURSORS

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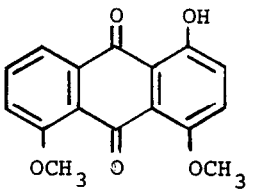
(Received in USA 4 May 1978; received in UK for publication 25 May 1978)

Herein we report a reaction sequence by which unsymmetrical anthrones and anthraquinones can be produced in a regiospecific manner. This method is exemplified by the synthesis of (1) an intermediate used in an approach to the total synthesis of the anthracycline antibiotics daunomycin (2) and adriamycin (3).



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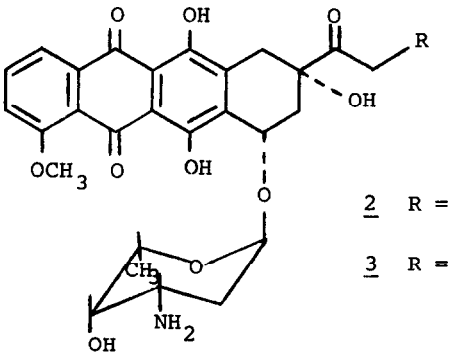
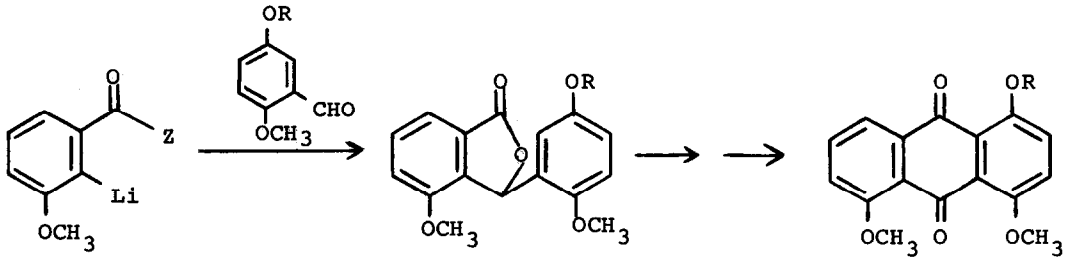


2 R = H

3 R = OH

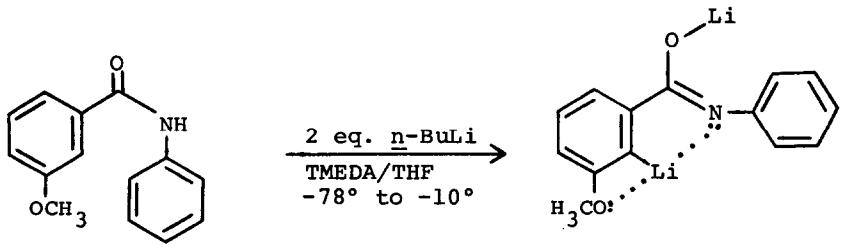
The ortho-metalation of benzene derivatives is a well established reaction.[2] It has also been shown in a few cases that m-disubstituted benzene derivatives metalate (with RLi reagents) at the ortho-position common to each substituent.[3,4] In our method addition of an organometallic reagent, obtained by the directed metalation of an anisic acid derivative, to an appropriately

substituted aldehyde would give after workup a phthalide. This could be cyclized and further oxidized to an anthraquinone (Scheme 1).



Scheme 1

For our purposes N-phenyl-m-anisamide (4) was found to be most suitable. Indeed, metalation (2 eq. n-BuLi/TMEDA) in THF (-78°to -10°) gave virtually quantitative production of the dianion (5) (eq 1).

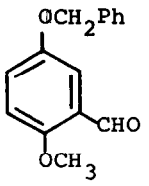


(1)

4 5

When treated with the aldehyde (6) (-78° to RT) followed by acidic workup the phthalide (7) was obtained in 97% yield (mp 156-157°); IR ($CHCl_3$) 1775 cm^{-1}; NMR (d_6-acetone) δ 7.77-6.85 (m, 6H), 7.47 (s, 5H), 6.62 (br. s, 1H), 5.03 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H).[5] We could detect none of the products resulting from metalation of either of the other two o-positions in the amide indicating that metalation had occurred exclusively at the common o-position.

Reduction of 7 (act. Zn/KOH/H_2O/pyr.)[6] gave the o-benzylbenzoic acid derivative (8) in quantitative yield (mp 203-204.5°); IR (KBr) 1690 cm^{-1}; NMR (d_5-pyr.) δ 8.50 (s, 1H), 7.80-6.90 (m, 6H), 7.43 (s, 5H), 5.08 (s, 2H), 5.03 (s, 2H), 3.80 (s, 3H), 3.63 (s, 3H). The benzyl group was then removed (H_2/10% Pd-C/CH_2Cl_2/TFA) to give the phenol-acid (9) in 94% yield (mp 182-184°);



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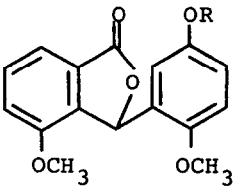
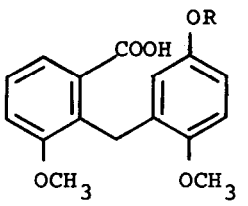


7 R = CH_2Ph

10 R = H



8 R = CH_2Ph

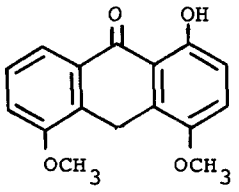
9 R = H

IR (KBr) 1680 cm^{-1}; NMR (d_6-acetone) δ 7.80-6.17 (m, 6H), 4.37 (s, 2H), 3.80 (s, 3H). Alternatively, the lactone-phenol (10), produced by a similar reduction of 7 in 98% yield (mp 204-205°); IR (KBr) 1720 cm^{-1}; NMR (d_6-acetone) δ 8.15-6.83 (m, 6H), 6.52 (br. s, 1H), 3.87 (s, 6H), 3.00 (br. s, 1H), also gave the phenol-acid 9 although this pathway proved to be less useful.

Cyclization of 9 (conc. H_2SO_4, RT) gave the anthrone (11) in 49% yield (mp darkens > 200°); IR ($CHCl_3$) 1635 cm^{-1}; NMR ($CDCl_3$) δ 12.13 (s, 1H), 8.00-6.83 (m, 5H), 3.90 (s, 3H), 3.88 (s, 3H). Direct oxidation of 11, to the desired anthraquinone 1 was unsuccessful, however, the diacetate (12) obtained from acetylation of 11 (Ac_2O/pyr.) in 82% yield (mp 192-194°); IR ($CHCl_3$) 1770 cm^{-1}; NMR ($CDCl_3$) δ 7.63-6.58 (m, 6H), 4.03 (s, 6H), 2.50 (s, 3H), 2.43 (s, 3H) could be oxidized (CrO_3/Ac_2O/HOAc/H_2O) to give the anthraquinone acetate (13) in 52% yield (mp 194-195°); IR ($CHCl_3$) 1750, 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.87-7.10 (m, 5H), 4.00 (s, 6H), 2.42 (s, 3H).[7] This was then hydrolyzed to 1 (KOH/H_2O/pyr.) in 96% yield (mp 177-178°); IR ($CHCl_3$) 1665, 1635 cm^{-1}; NMR ($CDCl_3$) δ 12.20 (s, 1H), 8.00-7.10 (m, 5H), 4.03 (s, 3H), 3.98 (s, 3H).

Although yields have not been optimized, the sequence of amide → phthalide → anthrone → anthraquinone is an efficient one. By proper choice of substitutents on the benzamide or benzaldehyde derivatives, a wide variety of unsymmetrical anthrones and anthraquinones can be synthesized. The utility of

the directed metalation reaction and a further report on the production of anthracyclinones shall be presented subsequently.



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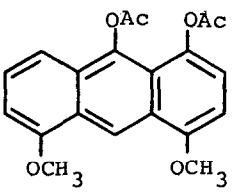

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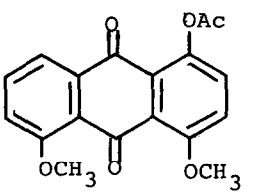

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References and Notes

1. Fellow in Cancer Research supported by Grant DRG-83-F of the Damon Runyon-Walter Winchell Cancer Fund, 1976-1978.

2. For a review see D.W. Slocum and D.I. Sugarman, Adv. Chem. Ser. 130, 122 (1974).

3. P. Beak and R.A. Braun, J. Org. Chem., 42, 1823 (1977) and references therein.

4. D.W. Slocum and C.A. Jennings, J. Org. Chem., 41, 3653 (1976) and references therein.

5. All new compounds gave spectra consistent with their structure; mps are uncorrected.

6. M.S. Newman, V. Sankoran, and D.R. Olson, J. Amer. Chem. Soc., 98, 3237 (1976).

7. D.W. Cameron, J.S. Edmonds, and W.D. Raverty, Aust. J. Chem., 29, 1535 (1976)

8. We thank the National Science Foundation and the National Institutes of Health for financial support.