Tetrahedron Letters No. 51, pp 5103 - 5106.

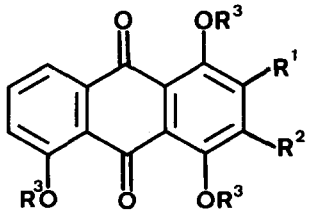
0040-4039/78/1215-5103$02.00/0

DIRECTED LITHIATION OF N,N-DIETHYLBENZAMIDES. REGIOSPECIFIC ROUTES TO UNSYMMETRICAL ANTHRAQUINONE NATURAL PRODUCTS

S. Osmund de Silva and Victor Snieckus*

Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo
Waterloo, Canada, N2L 3G1

In the preceding Letter,[1] we delineated the scope and utility of the directed lithiation reaction of N,N-diethylbenzamides for the regiospecific construction of contiguously tri- and tetra-substituted alkoxybenzene derivatives many of which are vital building blocks for anthraquinones, anthracyclines, and benzylisoquinoline alkaloids. Herein we demonstrate the efficacy of this strategy[2] for the regiospecific construction of unsymmetrical anthraquinone natural products 1 and 2 while in the following Letter[3] we describe its application to phthalideisoquinoline alkaloid synthesis.

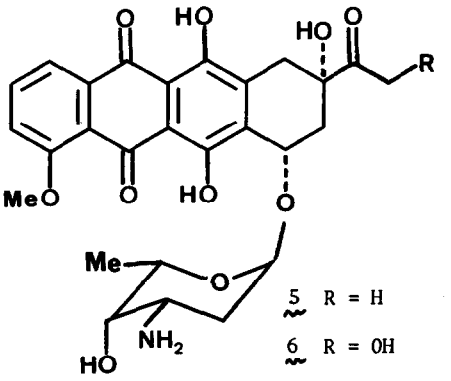


1 R^1 = Me, R^2 = R^3 = H

2 R^1 = R^3 = H, R^2 = Me

3 R^1 = R^3 = Me, R^2 = H

4 R^1 = H, R^2 = R^3 = Me

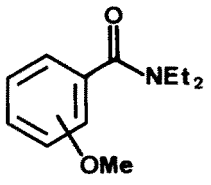


5 R = H

6 R = OH

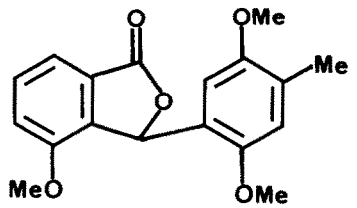
The burgeoning synthetic activity[4] in the area of the antineoplastic anthracycline antibiotics[5] daunomycin (5) and adriamycin (6) has provoked a renaissance in anthraquinone chemistry. For unsymmetrically oxygenated anthraquinones as well as anthracycline intermediates, the classical Friedel-Crafts condensation of phthalic anhydrides with phenols[6] is compromised by lack of regiocontrol,[7,8] and therefore efficiency, and by the perplexing Hayashi rearrangement[6,9] of intermediate o-benzoylbenzoic acids.[10,11] Consequently, major efforts have been focused on the development of alternate regiospecific routes to these substances.[4c,e,10-14] Our conceptually different solution[2] of this problem features

coupling of specifically lithiated benzamides 7,8 with a single p-tolualdehyde to give phthalides 9,14 suitable for elaboration into anthraquinones 3,4.[15] This strategy has led to short, unambiguous syntheses of islandicin trimethyl ether (3) and digitopurpone trimethyl ether (4).



7 3-OMe

8 2-OMe



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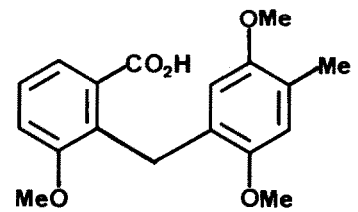

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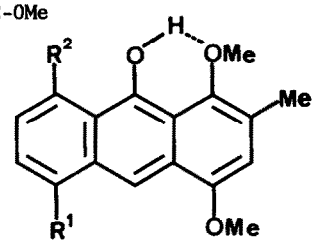
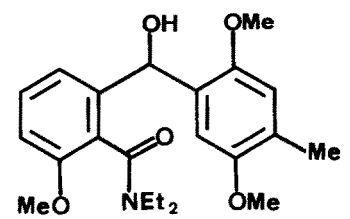


11 R^1 = OMe, R^2 = H

12 R^1 = H, R^2 = OMe



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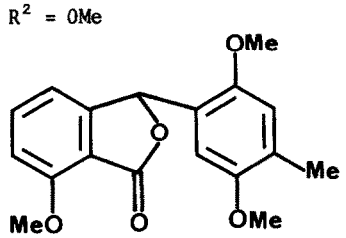

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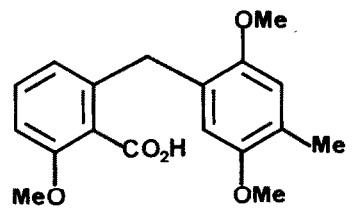

15

Lithiation (1 equiv. sec-BuLi/Et_2O[16]/-78°/1 h) of the m-anisamide 7[17] followed by treatment with 2,5-dimethoxy-p-tolualdehyde[18] (1 equiv./-78° → rt/4 h) and chromatography gave directly the phthalide 9 [68%; mp 176°(MeOH); ν 1770 cm^{-1}; δ 2.23,s,3H, 3.60,s,3H, 3.76,s,3H, 3.80, s,3H, 6.32,s,1H, 6.78,s,2H, 6.97-7.58,m,3H]. The highly acidic methyl hydrogens in the p-tolualdehyde appear to be inconsequential for the success of the condensation. Hydrogenolysis (H_2/Pd/C/HOAc/80°/6 h)[19] of 9 afforded the o-benzylbenzoic acid 10 [95%; mp 201°, lit.[10] mp 191-192°; ν(Nujol) 1690 cm^{-1}; δ(DMSO-d_6) 2.10,s,3H, 3.50,s,3H, 3.73,s,3H, 3.76,s, 3H, 4.20,s,2H, 6.31,s,1H, 6.53,s,1H, 7.13-7.43,m,3H] which upon Friedel-Crafts cyclization[20]

[$(CF_3CO)_2O/CHCl_3$/rt/3 h)][21] and basic work up (Na_2CO_3/MeOH-H_2O/reflux/2 h) provided the yellow anthrol 11 [mp 173° (MeOH); ν 3300 (br), 1635 (w, anthrone) cm^{-1}; δ 2.42,s,3H, 3.93,s,3H, 4.0,s,3H, 4.05,s,3H, 6.37-8.64,m,5H, 10.47,s,1H (OH)]. Since 11 underwent partial oxidation to the corresponding anthraquinone 3 during the Na_2CO_3 treatment, it was expedient to oxidize (CrO_3/HOAc-H_2O/rt/4 h)[22] the crude product directly into islandicin trimethyl ether (3), 63% overall from 10, mp 162°, lit.[12] mp 161-161.5°, mixture mp undepressed with an authentic sample,[23] ir and nmr identical to published values.

Similar condensation of lithiated o-anisamide 8[17] with 2,5-dimethoxy-p-tolualdehyde[18] resulted in the isolation of the hydroxyamide 13 [63%; mp 154° (MeOH); ν 3400, 1600cm^{-1}; δ 1.20, two overlapping t, 6H, 2.25,s,3H, 3.20-3.93, two overlapping q, 4H, 3.55,s,3H, 3.81,s,3H, 3.85,s,3H, 5.97,s,1H, 6.43-7.37,m,5H] rather than the corresponding phthalide 14 presumably due to the less crowded environment of the hydroxybenzyl moiety in 13 compared to the precursor of 9. Cyclization (TsOH/PhMe/reflux/6 h) gave the phthalide 14 [98%; mp 168°(MeOH); ν 1760 cm^{-1}; δ 2.23,s,3H, 3.70,s,3H, 3.90,s,3H, 4.03,s,3H, 6.59,s,1H, 6.77-7.75,m,5H] which was transformed by hydrogenolysis into 15 [95%; mp 177° (EtOH); ν(Nujol)1690 cm^{-1}; δ(DMSO-d_6) 2.13,s,3H, 3.63,s,3H, 3.70,s,3H, 3.77,s,3H, 3.83,s,2H, 6.53-7.27,m,5H]. Treatment with $(CF_3CO)_2O$ gave the anthrol 12 [mp 182° (MeOH); ν 3320, 1630 (w) cm^{-1}; δ 2.45,s,3H, 3.90,s,3H, 4.03,s,3H, 4.10,s,3H, 6.50-8.23,m,5H, 11.90,s,1H (OH)] which, as above, was preferably not isolated but directly oxidized with CrO_3 to give digitopurpone trimethyl ether (4), 67% overall, mp 166-167°, lit.[10] mp 163-164°, identical with an authentic sample[23] by mixture mp and spectral (ir, nmr) comparison.

Since 3 and 4 have been converted[10,12] by BBr_3 demethylation into islandicin (1) and digitopurpone (2) respectively, this concludes formal syntheses of these natural products.

This and the related[2] work demonstrate the utility of ortho-lithiated benzamides for the efficient and regiospecific entry into unsymmetrical anthraquinones. The $CONEt_2$ > OMe order in directing ortho lithiation and the untroubled condensation with the p-tolualdehyde suggest the synthesis of a variety of naturally occurring anthraquinones[7] by simple retrosynthetic recognition of the strategic bonds in the quinone ring. Efforts in this and other[3] directions are in progress.[24,25]

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23. Provided generously and swiftly by Professor A.S. Kende to whom we express our gratitude.

24. All new compounds show satisfactory analytical and/or mass spectral data. Mp's are uncorrected. Ir ($CHCl_3$) and nmr ($CDCl_3$) were recorded unless otherwise indicated.

25. This work was supported by the National Research Council of Canada.

(Received in USA 7 September 1978)