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A Novel Three-Step Synthetic Route to 1,4-Anthraquinones

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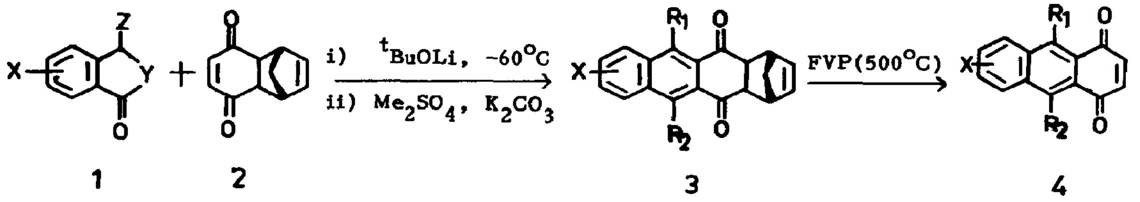
Abstract : The anionic [4+2] cycloaddition (1→3) and the retro [4+2] cycloaddition (3→ 4) are coupled to evolve a general and high yielding three-step synthesis of 1,4-anthraquinones.

1,4-Anthraquinones have received much attention as pivotal building blocks in the synthesis of linear fused polycyclic systems related to anthracyclines,[1a] tetracenomycins,[1b] organic metals[1c] and cyclacenes.[1d] Their cycloadditions leading to tetracyclic structures have been shown to proceed in high diastereoselectivity (98%).[1e] However, the progress in this area is severely impeded by the lack of efficient methods for the synthesis of 1,4-anthraquinones. While 2,3-disubstituted 1,4-anthraquinones could be readily obtained by functional group manipulation of the parent system, other substituted 1,4-anthraquinones are much more difficult to prepare, due to their propensity to oxidation or isomerisation to more stable 9,10-anthraquinones. The problem has been discussed in detail by Paredes et al[1a] and Barranco et al.[1c] For instance, 9,10-dimethoxy- 1,4-anthraquinones **4a**[2] is prepared by a linear sequence of six steps starting from 2-cyclohexenone.



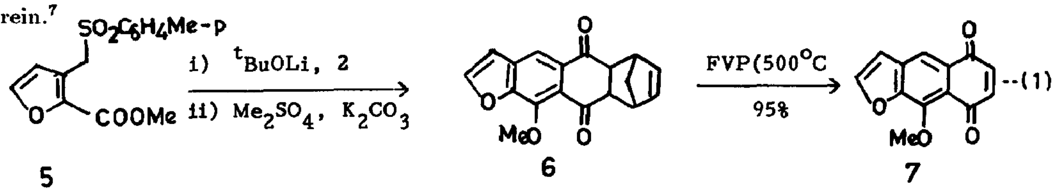
1 **2** **3** **4**

a: X=H,Y=O,Z=SO_2Ph
b: X=7-OMe,Y=O,Z=SO_2Ph
c: X=4,6-di-OMe,Y=O, Z=SO_2Ph
d: X=Z=H,Y=S
e: X=H,Y=S,Z=SPh

a: X=H,R_1=R_2=OMe
b: X=7-OMe, R_1=R_2=OMe
c: X=7,9-di-OMe R_1=R_2=OMe
d: X=R_1=H,R_2=OMe
e: X=H,R_1=SMe,R_2=OMe

a: X=H,R_1=R_2=OMe
b: X=5-OMe, R_1=R_2=OMe
c: X=5,7-di-OMe R_1=R_2=OMe
d: X=R_1=H,R_2=OMe
e: X=H,R_1=SMe,R_2=OMe

Our approach to solve this problem involves retrocycloaddition of **3**, and preparation of **3** by the successful application of the crucial anionic [4+2] cycloaddition of 1,4-dipolar reagents [3] **1a-e** to the readily available protected p-benzoquinone[4] **2**. As apprehended,[5] the attempted annulation of **1a** with p-benzoquinone in the presence of ^{t}BuOLi at -60°C afforded an unamenable mixture of products. On the other hand, the ene-dione **2** on reaction with **1a-e** under similar conditions gave the corresponding annulated products which after O-methylation furnished **3**. It may be noted that no method for the synthesis of **3** was available in the literature. Flash vacuum pyrolysis (500°C, 0.5 torr.) of **3** underwent smoothly to furnish the quinones **4** in 90-100 % yields. Solution phase (toluene) pyrolysis of **3** was found to be less satisfactory. In order to provide a facile entry to hitherto unreported D-ring furan analogue of adriamycin,[1a] the reactions shown in eq. 1 were executed to obtain **7**, further elaboration of which is underway. In conclusion, a concise and synthetically viable route to 1,4-anthraquinones is presented herein.[7]



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7) Selected Physical Data : **4a**: m.p. 189-192°C (lit.[2] m.p. 192-195°C). **4b**: m.p. 135-136°C; IR(cm^{-1}) 1652,1607; ^{1}H NMR($CDCl_3$) 7.99(d,1H,J=8.3) 7.63(t,1H,J=8.0), 7.09(d,1H,J=8.0), 6.84(s,2H), 4.02(s,3H), 3.99(s,3H) and 3.94(s,3H). **4c**: m.p. 181°C; IR(cm^{-1}) 1654, 1604; ^{1}H NMR($CDCl_3$) 7.31(d,1H, J=2.2), 6.83(ABq,2H), 6.70(s,1H,J=2.2), 4.00(s,6H), 3.98(s,3H) and 3.93(s,3H). **4d**: m.p. 183°C (lit.[6] m.p. 184°C). **4e**: m.p. 115-116°C; IR(cm^{-1}) 1656,1613; ^{1}H NMR($CDCl_3$) 8.91(dd,1H,J=1.6,8.0), 8.42(dd,1H, J=1.6,8.0), 7.84(m,2H), 6.95(ABq,2H,J=10), 4.09(s,3H) and 2.47(s,3H). **7**: m.p.193-194°C; IR(cm^{-1}) 1655,1596; ^{1}H NMR($CDCl_3$), 8.11(s,1H), 7.83(d,1H,J=2.0), 6.96(d,1H,J=2.0), 6.89(s,2H) and 4.35(s,3H).
Yields : **3a**, 64%; **3b**, 45%; **3c**, 38%; **3d**, 55%; **3e**, 78%; **6**, 59%

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