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Directable Regiochemistry in Naphthazarins *via* the Use of Masked Derivatives

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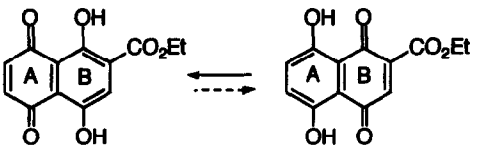
Abstract: The carboethoxynaphthol **3d** was converted *via* salcomine oxidation to the masked carboethoxynaphthazarin **4b** which could undergo nucleophilic addition or, if unmasked, transfer quinone reactivity to the alternative ring in form **5**. The latter should undergo regiospecific Diels-Alder reactions.

The present communication describes the synthesis of a masked form of the less stable isomer **2** which, unlike previous synthons, may react regiospecifically with nucleophiles in ring B and the reactivity then directed to ring A by unmasking to produce form **1**. Incorporation of chlorine assures regiospecificity in ring A as well thus complementing the studies noted below. Functionalized naphthazarins **1** are of interest as synthons due to their widespread occurrence as chromophores in polyketide natural products, including the anthracyclines.[1] Successful applications of naphthazarins to anthracyclinone syntheses require that the regiochemistry be controlled at both ends of the molecule. Perhaps the most successful studies along these lines are those of Kelly[2] which introduced regiospecificity into the parent naphthazarin *via* the *p*-nitrobenzyloxycarbonyl derivative and those of Fariña and Echavarren based on dichloronaphthazarins.[3] The former studies took advantage of two Diels-Alder reactions, of which the latter reaction utilized a less favorable isomer.



1 **2**

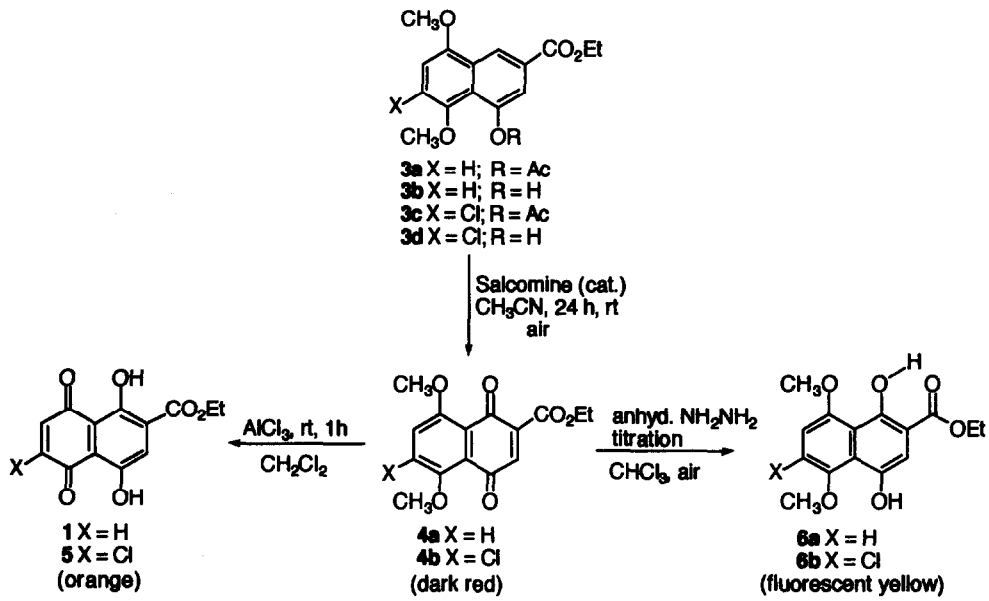
The effect of an electron-withdrawing substituent on the naphthazarin ring is well documented. In the example shown above, we would expect the isomer **1** to exist to the virtual exclusion of isomer **2** as it does in the corresponding methyl ketones.[4] The isomer **2** would be of interest since nucleophilic addition to quinones with electron-withdrawing groups is also well known. A noteworthy example includes the addition of stannanes to 2-acetyl-1,4-naphthoquinone derivatives.[5] It had been our experience, as well as others, that methoxy groups could be demethylated easily with aluminum chloride[6] at room temperature if adjacent carbonyls were present. We selected that group to be the masking group especially as we had in hand the corresponding masked juglone derivatives **3a** and **3c** (**Scheme: 1**) which had been prepared in connection with anthracycline analog studies.[7]

Some existing methods for the preparation of functionalized naphthazarins, for example, have involved Friedel-Crafts reaction of a hydroquinone or its ether with maleic anhydride[8] or an acrylic acid derivative[9] under relatively harsh reaction conditions (e.g. aluminum chloride/sodium chloride melt at 140-180°C) with yields

which were frequently poor. In addition, when the reactants were unsymmetrically substituted mixtures of regioisomers or isomerized products were often produced.

Even under relatively mild conditions such as the Diels-Alder reaction of benzoquinones with 1,4-diacetoxybutadiene[10] the adducts tended to give undesireable eliminations to simple 1,4-naphthoquinones. Similar synthons such as 1,1,4-trimethoxybutadiene[11] were not very easily prepared. Again, yields of the naphthazarins tended to be extremely low.

Scheme: 1

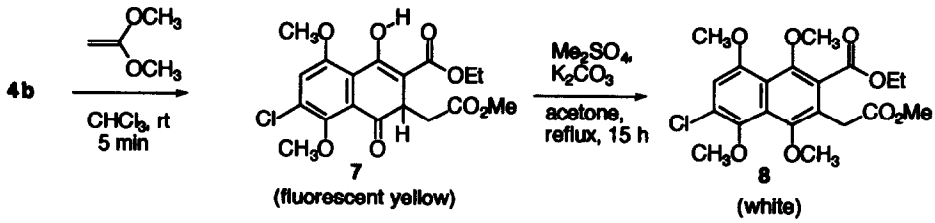


The acetates **3a** and **3c** were readily obtained from the Stobbe condensation[12] of 2,5-dimethoxybenzaldehyde (or its 4-choro derivative[13]) with diethylsuccinate followed by acetic anhydride cyclization.[12] Hydrolysis of the acetates **3a** and **3c** to the corresponding naphthols **3b** and **3d** was accomplished in 85% yield by refluxing in acidic ethanol.[14] Application of the ceric ammonium nitrate (CAN) oxidation which had been used previously to oxidize 5-methoxy-1-naphthol to the juglone methyl ether produced a brick red solid which could not be characterized.[15] Fortunately, the naphthols could be cleanly and efficiently converted to the brilliant red quinones **4a** and **4b** by salcomine catalyzed aerial oxidation in acetonitrile.[16] None of the corresponding 1,2-quinones could be detected in the reaction mixture.

This experimental result is interesting in that we have oxidized the ring with the higher oxidation potential to produce a masked form of the less stable isomer. This was easily demonstrated by demethylation of quinones **4a** and **4b** by aluminum chloride in dichloromethane whereby high yields of the naphthazarins **1** and **5** were obtained.[7,17]

Thus, we were able to switch the potential reactivity cleanly from one ring to the other. Regiospecific synthetic manipulation may be carried out on the initial quinone taking advantage of the electrophilic effect of the

carboethoxy group. As a simple demonstration, we reacted the chloroquinone **4b** (1mmol) with 1,1-dimethoxyethene (1mmol) to afford the adduct **7** (quantitative) by nucleophilic addition under very mild conditions (5 min at ambient temperature in chloroform).[18] This structure is apparently favored over the aromatic tautomer because of steric effects of the bulky ester groups adjacent to each other. Although similar structures have been observed with the addition of stannanes to quinones,[5] tetralone **7** was not anticipated with the addition of 1,1-dimethoxyethene since all other reported cases produced cyclic ortho esters.[19] The fully aromatic system **8**[20] may be obtained upon simple methylation under unexceptional conditions.[5]



The masked leuconaphthazarins **6a** and **6b** were obtained quite serendipitously in an attempt to exploit synthons **4a** or **4b** in heterocyclic syntheses. The dropwise addition of anhydrous hydrazine to a chloroform solution of either synthon **4a** or **4b** resulted in an immediate color change from bright red to fluorescent yellow producing the hydroquinones **6a** and **6b** in quantitative yield.[21] Taken together, the room temperature salcomine catalyzed air oxidation followed by the unprecedented use of hydrazine titration[22] to reduce the resulting quinoine represents an extremely mild method for the regiospecific *para*-hydroxylation of carboethoxynaphthols. In addition, the hydroxyl groups are, in theory, regiochemically differentiated due to hydrogen bonding with the carboethoxy group. We are currently investigating the application of the naphthols in the series **6a** and **6b** for the synthesis of tricyclic oxygen heterocycles and C-allyl naphthazarin derivatives.

Based on the studies of Fariña and Echavarren noted above, we would expect our chloronaphthazarin **5** to be capable of regiospecific reaction with dienes to produce anthracyclinone synthons. The sequence of nucleophilic substitution, unmasking/isomerization, and Diels-Alder reaction should provide a potentially useful alternative for the construction of polycyclic molecules using naphthazarins.

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14. To a mixture of the acetate **3a** or **3c** (1mmol) dissolved in 95% ethanol (35 mL) was added conc. HCl (10 mmol) and the solution refluxed for 8 h. After cooling, the solution was extracted with ether then washed with water (5 X 100 ml). The ether layer was dried, filtered and evaporated to yield the pure naphthol **3b** (85%) or **3d** (85%).
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16. Adapted from: Wakamatsu, T.; Nishi, T.; Ohnuma, T.; Ban, Y. *Synth. Commun.* **1984**, *14*(12), 1167-1173. To a rapidly stirred solution of the naphthol **3b** or **3d** (1 mmol) in 100 mL of acetonitrile at room temperature was added salcomine hydrate (0.20 mmol). Oxygen was bubbled through the reaction mixture for 5 min then the solution was stirred for an additional 24 h in the air. Removal of the solvent yielded the brilliant red quinones **4a** (88%) or **4b** (84%).^{1}H NMR-300 MHz ($CDCl_3$) of **4b**: δ 8.69 (s, 1H) 7.31(s, 1H); 4.38 (q, 2H, J = 7.2 Hz), 3.98 (s, 3H), 3.92 (s, 3H), 1.40 (t, 3H, J = 7.2 Hz); mp = 223.5°C.
17. To a rapidly stirred solution of quinone **4a** or **4b** (1 mmol) dissolved in 30 mL CH_2Cl_2 and at room temperature and under nitrogen was added $AlCl_3$ (10 mmol) and the solution stirred for 1 h only. Water (30 mL) then conc. HCl (10 mmol) were added cautiously with rapid stirring. The orange solution was extracted with CH_2Cl_2 and the organic layer dried, filtered and the solvent removed to yield naphthazarins **1** (88%) or **5** (83%).^{1}H NMR-300 MHz ($CDCl_3$) of **5**: δ 12.03 (s, 1H), 11.90 (s, 1H), 8.19 (s, 1H), 7.28 (s, 1H), 4.52 (q, 2H, J = 7.2 Hz), 1.49 (t, 3H, J = 7.2 Hz); mp = 203°C.
18. ^{1}H NMR-300 MHz ($CDCl_3$) of **7**: δ 11.52 (s, 1H); 7.16 (s, 1H); 4.50-4.39 (m, 3H); 3.94 (s, 6H); 3.48 (s, 3H); 3.05-2.90 (m, 2H); 1.45 (t, 3H, J = 7.2 Hz); mp = 157°C. In addition, ^{1}H-NMR decoupling experiments as well as the mass spectrum, infrared and elemental analysis supported this structure.
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20. ^{1}H NMR-300 MHz ($CDCl_3$) of **8**: δ 6.76 (s, 1H); 4.45 (q, 2H, J = 7.2 Hz); 4.06 (s, 2H); 4.03 (s, 6H); 3.90 (s, 3H); 3.87 (s, 3H); 3.83 (s, 3H); 1.40 (t, 3H, J = 7.2 Hz); mp = 82-85°C.
21. To a rapidly stirred solution of the quinone **4a** or **4b** (1mmol) in 30 mL of chloroform was added anhydrous hydrazine dropwise (4 drops) until the solution turned fluorescent yellow (5 seconds). An extra drop of hydrazine was added and the solution dumped onto water (50 mL). The layers were separated and the chloroform was washed with water (3 X 50 mL), dried, filtered and then evapoprtaed to yield **6a** or **6b** in quantitative yield. ^{1}H NMR-300 MHz ($CDCl_3$) of **6b**: δ 10.70 (s, 1H); 9.09 (s, 1H); 8.36 (s, 1H); 6.56 (s, 1H); 4.51 (q, 2H, J = 7.2 Hz); 4.04 (s, 3H); 3.99 (s, 3H); 1.49 (t, 3H, J = 7.2 Hz); mp = 236°C.
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