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Regiocontrol in the Synthesis of Naphthoquinones. Regiospecific Synthesis of Lomandrone and Aristolindiquinone

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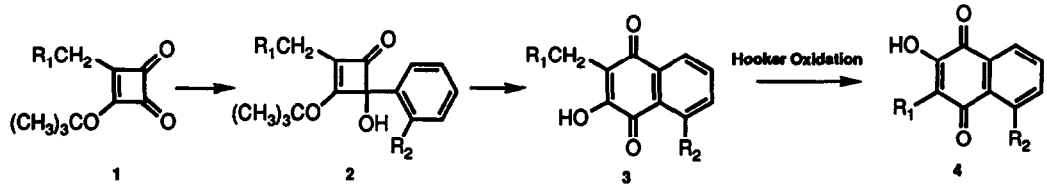
Summary: Combination of the ring expansion of 3-t-butoxy-4-aryl-4-hydroxycyclobutenones to hydroxynaphthoquinones with the Hooker Oxidations of hydroxyquinones provides powerful methodolgy for the regiospecific synthesis of highly substituted naphthoquinones and related compounds. This combination is employed for the synthesis of the natural naphthoquinones, lomandrone and aristolindiquinone.

Reported here is a useful synthetic method for the regiospecific construction of highly substituted naphthoquinones (Scheme-1). This involves the previously reported regiospecific addition of an aryl lithium reagent to the more reactive carbonyl group of t-butoxycyclobutenediones **1** to give the cyclobutenones **2**. Thermolysis of **2** followed by mild oxidation (Ag_2O) of the resulting hydroquinones give the corresponding t-butoxy-1,4-nathphoquinones which undergo facile hydrolytic de-t-butylation (TFA) to the hydroxynaphthoquinones **3**.[1,2] Treatment of **3** with MnO_4^-/OH^- or $H_2O_2/Na_2CO_3;CuSO_4$ in aqueous solution induces a remarkable rearrangement (Hooker Oxidation) to **4**.[3] *Thus, the ring expansion of 2 not only provides a regiocontrolled route to 3, but when combined with the Hooker Oxidation the regioisomeric lower homolog 4 is also available.* Illustrations of the synthetic potential of these combined methods are outlined here for the synthesis of the naturally occurring naphthoquinones, lomandrone (Scheme-2) and aristolindiquinone (Scheme-3).[4]

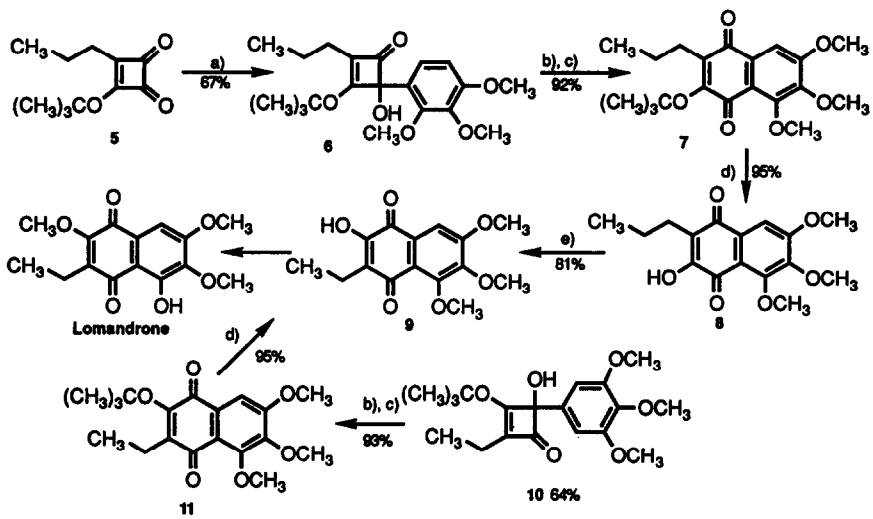
Scheme-1



1 2 3 4

The aryl lithium reagent required for the synthesis of lomandrone using the combined methods was generated directly from commercially available 1,2,3-trimethoxybenzene upon treatment with butyllithium. Regiospecific addition of this reagent to the cyclobutenedione **5** gave the cyclobutenone **6** (67%) which was converted to the naphthoquinone **7** (92%) upon thermolysis in refluxing toluene for 2 h followed by Ag_2O oxidation.[5] De-t-butylation of **7** (TFA) gave **8** (95%) which was converted to **9** (81%, m.p., 168-169 °C, lit.[6a] m.p., 169-170.5 C) when subjected to Hooker Oxidation conditions (MnO_4^-/OH^-, H_2O). The synthesis of **9** constitutes a formal synthesis of lomandrone since it has previously been converted to the natural product by peri-demethylation (HBr) and subsequent methylation (CH_2N_2) of the quinone hydroxyl group.[6]

Scheme-2



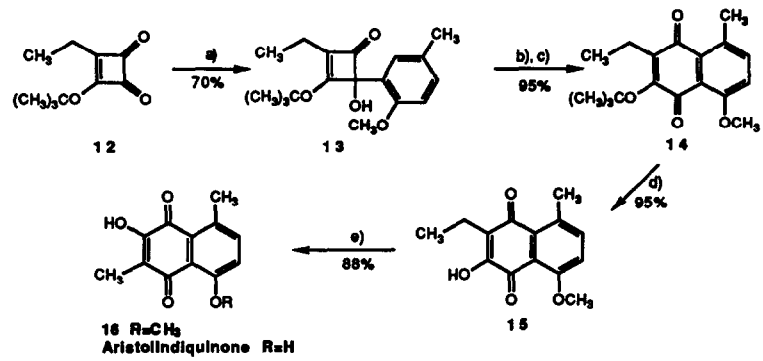
a) 1-Lithio-2,3,4-trimethoxybenzene/Hexanes, -78°C; b) Toluene, 110 °C, 2h; c) Ag_2O; d) TFA, 0 °C; e) $KMnO_4/OH^-$

Previous studies concerning the Hooker Oxidation have been limited to relatively simple 2-alkyl-3-hydroxy-1,4-naphthoquinones. *Thus the conversion of 8 to 9 is noteworthy since it reveals generality to the reaction and documents its use for hydroxyquinones bearing a number of electron donating groups.*

For comparison, **9** was also prepared in an independent fashion starting with 2-t-butoxy-3-ethylcyclobutenedione **12**. This gave the cyclobutenone **10** (64%) upon treatment with 1-lithio-3,4,5-trimethoxybenzene.[7] Thermal ring expansion followed by Ag_2O oxidation gave **11** (93%) which was converted to **9** (95%) upon treatment with TFA. This compound was identical in all respects to the product obtained from the Hooker oxidation of **8**.

The availability of the required aryl lithium reagent plays a key role in the choice of either the cyclobutenone ring expansion alone or its use in combination with the Hooker Oxidation. A further example of this is illustrated in Scheme-3 which outlines the synthesis of aristolindiquinone. Here, as in the lomandrone synthesis, the combined methodology is desired since heteroatom directed lithiation is usually favored over halogen exchange reactions.[8] Thus, treatment of 1-methoxy-4-methylbenzene with butyllithium generated the required aryl lithium reagent which adds to **12** to give the cyclobutenone **13** in 70% isolated yield. Ring expansion of **13** to the quinone **14** (95%) and de-t-butylation to the hydroxynaphthoquinone **15** proceeded in nearly quantitative yield. Finally, Hooker Oxidation ($H_2O_2/Na_2CO_3;CuSO_4$)[3f] of **15** gave **16**, the methyl ether of aristolindiquinone in 88% isolated yield. Although the melting point of **16** (140-141°C) differed from that reported in the literature[9c] (130°C), its ^1H NMR and IR spectral data closely compared to the literature values. Furthermore, **16** was observed to undergo known[9c] peri-demethylation in 88% yield upon treatment with HBr, and the spectral properties of the product (m.p., 186-187 °C; lit. m.p., 190 °C[9a,c]; 176-178 °C[9d]) are essentially identical with those reported for the natural product.

Scheme-3



a) 1-Lithio-2-methoxy-5-methylbenzene/Hexanes, -78 °C; b) toluene, 110 °C, 2h; c) Ag_2O; d) TFA; e) H_2O_2/Na_2CO_3, $CuSO_4$

In conclusion, the following significant points are noted: 1) Until now the Hooker Oxidation has been more a mechanistic curiosity than a viable reaction in the synthetic arsenal. Indeed, it has received little attention for nearly 40 years and its synthetic scope has been limited to relatively simple examples. 2) The examples presented here and elsewhere of the ring expansion of 3-t-butoxy-4-aryl-4-hydroxycyclobutenones further illustrates this rearrangement to be a general and predictable regiospecific route to hydroxynaphthoquinones. 3) Combination of the cyclobutenone ring expansion and the Hooker Oxidation provides a powerful strategy for the regiospecific synthesis of a number of highly substituted hydroxynaphthoquinones and related compounds. Synthesis of 2,5-dihydroxy(or alkoxy)-1,4-naphthoquinones would be particularly amenable to this combined methodology. Examples of natural products in this class include fibrostatin, droserone, 2-hydroxyjuglone, trichione, homotrichione, 2-methoxystypandrone, 6-ethyl-2,7-dimethoxyjuglone, 6-(1-hydroxyethyl)-2,7-dimethoxyjuglone, demethoxylomandrone and 3,5-dihydroxy-6-methoxydehydro-iso-α-lapachone.[10, 11]

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