A New Synthesis of Anthraquinones

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Methoxy substituted benzyl magnesium chlorides formed by the use of a magnesium anthracene complex smoothly displace the *ortho*-methoxy group from (*o*-methoxyaryl)dihydro-oxazoles (oxazolines); the resultant masked *o*-benzylbenzoic acids are easily converted into anthraquinones.

There has recently been a resurgence of interest in methods for the synthesis of anthraquinones and we now describe a simple and convenient method based on the nucleophilic displacement of the *ortho*-methoxy group from an (*o*-methoxyaryl)dihydro-oxazole by a benzylic Grignard reagent and subsequent steps. Benzylic halides are prone to undergo Wurtz coupling with magnesium and consequently yields in reactions involving them are often reduced. We have found,

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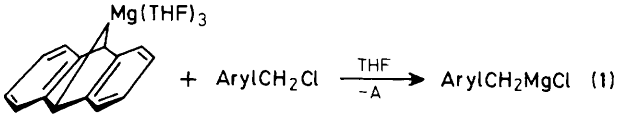
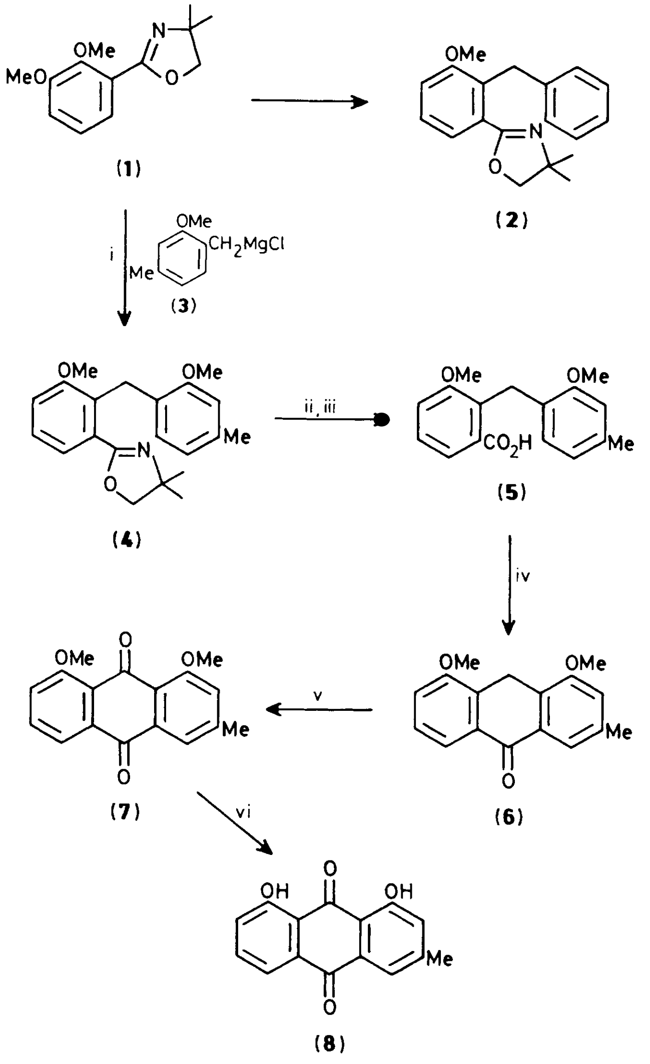
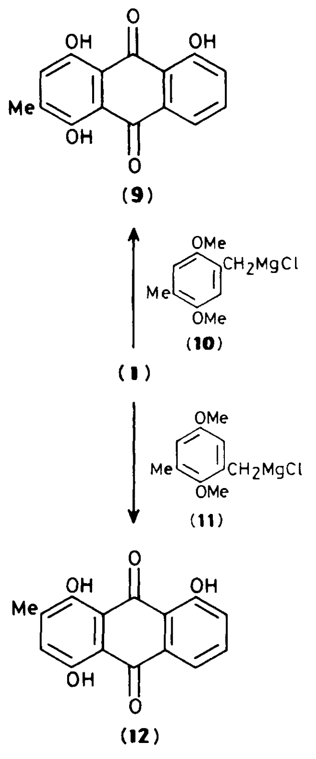


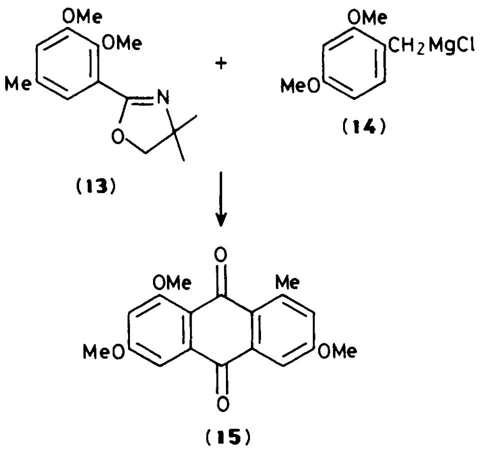


Scheme 1. *Reagents and conditions:* i, 1.13 mol. equiv. (**3**), THF, 25 °C, 18 H; II, MeI, $MeNO_2$, 70 °C, 18 h; iii, 20% aq. NaOH, MeOH, reflux, 44 h; iv, TFAA, CH_2Cl_2, 0 °C, 30 min; v, CrO_3, AcOH, 90 °C, 15 min; vi, HBr, AcOH, reflux, 0.5 h.

however, that when benzylic Grignard reagents are generated at 0 °C from 0.1 M solutions of benzyl chlorides in tetrahydrofuran (THF) using the magnesium anthracene (A) complex, $Mg(A)(THF)_3$,[1] as a source of magnesium (equation 1), then no Wurtz coupling can be detected. Meyers and his coworkers[2] found that when the dihydro-oxazole (**1**) (Scheme 1) was treated with a slight excess of benzyl magnesium bromide at 25 °C only a 6% yield of the substitution product (**2**) was obtained. We have found that this yield can be considerably increased (80%) by using an excess of benzyl magnesium chloride generated by the above method. We have therefore used this method in the synthesis of a number of variously oxygenated naturally occurring anthraquinones or their derivatives. Thus the Grignard reagent (**3**) (Scheme 1) was allowed to react with the dihydro-oxazole (**1**). The product (**4**) (86%), m.p. 155—156.5 °C, on deprotection provided the benzylbenzoic acid (**5**) (90%), m.p. 175—176.5 °C, which underwent ring-closure on treatment with trifluoroacetic anhydride (TFAA) thereby supplying the anthrone (**6**) (91%), m.p. 187.5—189 °C. Oxidation of the anthrone (**6**) yielded the anthraquinone (**7**) (85%), m.p. 191—191.5 °C (lit.[3] 190 °C), which on demethylation gave chrysophanol (**8**) (94%), m.p. 194—195 °C (lit.[3] 190 °C).

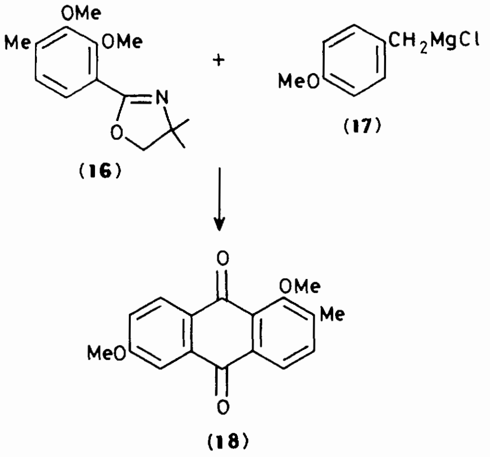


Scheme 2



Scheme 3

Islandicin (**9**)[4] (Scheme 2) and digitopurpone (**12**)[5] were prepared in a similar fashion using the dihydro-oxazole (**1**) and the benzylic Grignard reagents (**10**) and (**11**), respectively. Tri-*O*-methylemodin (**15**) (Scheme 3), identical with an authentic sample,[6] resulted from a sequence employing the dihydro-oxazole (**13**) and the benzyl magnesium chloride (**14**), whilst di-*O*-methylsoranjidiol (**18**)[7] (Scheme 4) resulted from the dihydro-oxazole (**16**)[8] and the benzyl magnesium chloride



Scheme 4

(**17**). These examples amply demonstrate the utility and versatility of this method of anthraquinone synthesis.

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