Tetrahedron Letters,Vol.28,No.42,pp 5045-5046,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

A SHORT AND EFFICIENT SYNTHESIS OF (±) O-METHYLPEREZONE BASED ON A NOVEL OXIDATIVE DEGRADATION APPROACH

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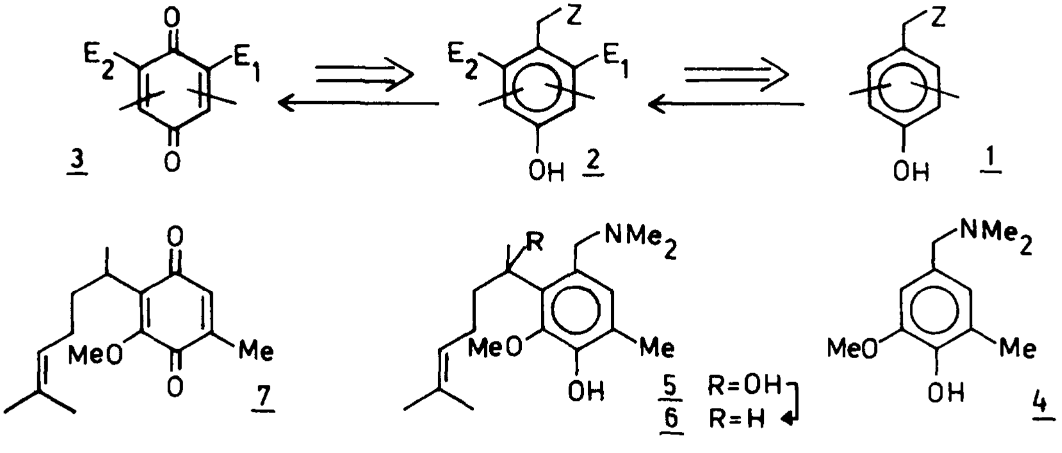
Abstract: *A short synthesis of (±) O-methylperezone based on a novel oxidative degradation* approach (ODA) has been achieved. Distinguished features are : the direct metalation of a phenolic benzylamine and its oxidative degradation to the corresponding 1,4-benzoquinone by the action of Fremy's salt.

The synthesis of naturally occurring quinones[1] is a steady growing area of research interest due to the pharmacological activity associated with many of them[2].

In regard with an ongoing research project, we have recently developed a new entry to the quinone functionality based on the so-called oxidative degradation approach (ODA)[3].A salient feature of this newly developed protocol for the synthesis of p-benzoquinones (Scheme 1), is that quinone synthons[4] 1 (Z= OMe or NMe$_2$) are expected to be amenable to regioselective metalation without resorting to the classical protection/deprotection methodology, provided there is an appropriately located electron-withdrawing group attached to the ring[5].



Scheme 1

In an effort to fully demonstrate the validity of this unsophisticated protocol, we would like here to report a short and efficient synthesis of (±) O-methylperezone 7[6] which according to the straightforward retrosynthetic analysis shown (Scheme 1) could be simply derived from Mannich base 4[7].

In the event it was found that the required carbon chain appendage could be attached regioselectively by treatment of the dianion[8] (in diethyl ether) of N,N-dimethyl-3-methoxy-4-hydroxy-5-methylbenzylamine 4 (prepared uneventfully from orthovanillin[9]) with commercial 6-methyl-5-hepten-2-one at -60ºC, thus furnishing the expected alcohol 5[7] in good isolated yield (64%). Extensive protonation of the dianion was observed when operating at higher temperatures (0ºC or -30ºC). Contrary to our expectations, however, the reduction of 5 to 6 was somewhat troublesome. In fact, neither transfer hydrogenation[10] under several reaction conditions ($\Phi_3SiH/(CF_3CO)_2O$; $\Phi_3SiH/BF_3.Et_2O$; $Et_3SiH/BF_3.Et_2O$), nor borohydride reduction[11] ($BH_4Na/(CF_3CO)_2O$ of 5 yielded the desired 6, the starting material being recovered unchanged in all the above cases. Fortunately, sodium in liquid ammonia reduction of the disilyl ether[12] of 5 (prepared by reaction of 5 with $ClSiMe_3/HN(SiMe_3)_2$ in THF), provided 6[7] on aqueous workup (80% yield from 5). Finally, treatment of a chloroform solution of 6 with Fremy's salt in a buffered aqueous solution (pH=6.1) yielded (±) O-methylperezone 7[7] as a yellow oil in 90% yield. The synthetic material showed identical spectroscopic properties to those reported[13].

Further work now in progress will try to prove the general interest of our strategy for the synthesis of complex quinones.

Acknowledgments.- We gratefully acknowledge financial support by the CAICYT (Project 1073/84).

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7.-All compounds gave correct spectroscopic and/or analytical data.

8.-Typical procedure: To a cooled (0ºC) solution of 4 (2 mmol) in anhydrous diethyl ether (45 ml), under argon atmosphere, a solution (0.8 M) on nBuLi in hexanes (7.5 ml, 6 mmol) was added dropwise (5 min) with stirring. The resulting colorless solution slowly turned yellow on stirring at room temperature (overnight). To the resulting yellow solution of the dianion cooled to -60ºC, the unsaturated ketone 6-methyl-5-hepten-2-one (6 mmol) was added. The resulting solution was mantained at c.a. -60ºC for 48 hours with stirring (not optimized). Standard workup yielded 5 as a crystalline solid (64%) which sublimed, m.p. 125-6 ºC, together with unreacted starting amine 4 (25%).

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(Received in UK 31 July 1987)